Figure 19.10. (a) Myocilin by western blot in normal and POAG in Beagle (early, moderate, and advanced stages). (b) Myocilin by western blot in other breeds with the primary glaucomas and primary cataract formation. (c) Myocilin localization (arrows) in the trabecular meshwork (original magnification 400×) and nonpigmented ciliary epithelium (original magnification 400×) of a moderate POAG Beagle. (d) CD-44 localization (arrows) in the nonpigmented epithelium of the ciliary body (original magnification 400×). (Photographs A and B courtesy of Edward MacKay, and C and D courtesy of Don Samuelson).
the myocilin gene appears normal in, at least, primary narrow- or angle-closure glaucoma in the Shiba Inu and POAG in Beagle (Gelatt & Wallace, 2004; Kato et al., 2006a, 2006b, 2007, 2009b; Storey et al., 2008). The CYP1B1 gene has also been eliminated as a candidate gene in the POAG Beagle (Kato et al., 2009a).

Fortunately a mutation of the ADAMTS10 gene was been associated with POAG in the Beagle (Kuchtey et al., 2010), and specific studies are in progress to explore the biochemical events which lead to increasing the trabecular meshwork resistance and elevation in IOP. The ADAMTS10 mutation results from a glycine substitution of arginine (Gly661Arg) within the cysteine-rich domain of the ADAMTS10 gene in canine 20 chromosome and may affect folding of the protein causing microfibril defects.

As a member of the ADAMTS family which participates in collagen processing and proteoglycans degradation within the ECM, the substrate for ADAMTS10 is not known. However, the mutation ADAMTS10 is expressed in high levels within the Beagle POAG trabecular meshwork (Kuchtey et al., 2010). In selected other breeds with the primary glaucomas, the mutation ADAMTS10 has not been demonstrated (Kuchtey et al., 2012).

Like the myocilin gene, the ADAMTS10 gene occurs in at least 38 animal species, including man and dog, ranging from the lamprey to man (Kuchtey et al., 2010), and thus appears highly conserved. All ADAMTS family members share a common structural organization including a metalloproteinase domain followed by a disintegrin-like module, a thrombospondin repeat unit, a cysteine-rich domain, and a spacer region. The Beagle POAG 4 Mb on the canine chromosome 20 locus (base pair positions: 55,881,144 to 59,844,869) is syntenic with the human quantitative trait locus for IOP, and maps to the short arm of the human 19 chromosome (base pair positions 2,389,784 to 8,841,863). Mutations of the ADAMTS10 gene in man have been expressed clinically as the autosomal recessive Weill–Marchesanie syndrome, a relatively rare condition, with short stature, and stubby hands and feet as well as glaucoma. Because of limited numbers of these patients, the mechanism for elevated IOP is not well studied. In the autosomal dominant form of the Weill–Marchesanie syndrome (which clinically is indistinguishable from the autosomal recessive form), a mutation in the type 1 fibrillin has been reported.

The mutation ADAMTS10 in man has been associated with an abnormal type 1 fibrillin as well as short stature, stubby hands and feet. Another member of the ADAMTS family of secreted metalloproteinases is the ADAMTS17 mutation, which has been associated recently with lens luxations in three breeds of dogs (Farias et al., 2010).

**CLINICAL STAGES OF THE PRIMARY GLAUCOMAS**

Both POAG and PACG have different clinical stages or phases based on the level of IOP elevation and the duration of the ocular hypertension. In the breeds with POAG, the increase in IOP is gradual and progressive, and the clinical signs develop from barely noticeable to advanced over a few (2–4) years (Miller, 2005). In the early and moderate stages of the disease, IOP is generally between 25 and 40 mmHg, and there is mydriasis, variable corneal edema, and episcleral congestion. Vision is present. The dog’s eye is not appreciated as abnormal, and the dog is not usually presented to the veterinarian.

As POAG advances and the IOP climbs further, globe enlargement (megaloglobus, buphthalmos) occurs, and lens instability results from the damage to the zonules and directly contributes to abrupt increases in IOP. Episcleral congestion, corneal edema, mydriasis, lens subluxation or total luxation, optic disc and retinal degeneration, and blindness result. Lens instability leads to more variable IOP, with frequent pupillary blockage by lens and/or vitreous abrupt high IOP (50–60 mmHg). Often this is when the dog is first presented to the veterinary ophthalmologist.

The clinical stages of the PACG dogs is different and characterized by abrupt increases in IOP, which are initially transient and self-controlled, but eventually, the elevation in IOP persists and necessitates presentation to the veterinary ophthalmologist (Miller, 2005). These abrupt IOP changes are apparently the result of pupillary blockage to aqueous humor from posterior chamber to anterior chamber and the forward displacement of the basal iris with narrowing to closure of the iridocorneal angle and cleft. These abrupt increases in IOP initially are in the 30 mmHg or higher range, but as the angle narrowing and closure advance, the increase can reach 50 mmHg or higher and produce clinical signs that merit presentation to the veterinarian. Eventually (sometimes within days), this appositional narrowing and closure of the iridocorneal angle and sclerociliary cleft develops peripheral anterior synchiae, “zipping” the outflow pathways close, and rending the glaucoma refractory to pressure-lowering drugs. However, the Basset Hound is thought to belong to this group of pectinate ligament dysgenesis PACGs, but recent studies with periodic applanation tonometry suggest a chronic and progressive elevation in IOP (Grozdanic et al., 2010). During the next decade or so, the PACG breeds will hopefully be characterized further and the genesis of their glaucomas documented. The increased occurrence of the disease with the females of many of these breeds will complicate the search for mode of inheritance as well as the causative gene!

The stages of canine PACG can be divided clinically into latent or predromal; intermittent glaucoma; acute congestive or high-pressure glaucoma; postcongestive; and chronic glaucoma, as proposed by Miller (Table 19.3) (Miller, 2005). Each stage of PACG has certain clinical characteristics that can help in the determination of the stage and serve as a guide for therapy. Because the acute congestive stage of PACG is usually the first stage presented to the veterinarian, it is not surprising that nearly 50% of these eyes are blind and medical therapy of this stage has limited success and for a short duration. In the Basset Hound with primary chronic closed-angle
Table 19.3  The Different Stages of Primary Angle-Closure Glaucoma in the Dog

<table>
<thead>
<tr>
<th>Stage</th>
<th>History</th>
<th>IOP at Exam</th>
<th>AC Depth</th>
<th>Gonioscopy</th>
<th>High-Resolution Ultrasonography</th>
<th>Clinical Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latent</td>
<td>Breed-predisposed</td>
<td>Normal</td>
<td>Shallow</td>
<td>Narrow; occludable</td>
<td>Sigmoidal iridal</td>
<td>None; watch for configuration; progression; consider prophylactic therapy</td>
</tr>
<tr>
<td>Intermittent</td>
<td>Transient corneal edema</td>
<td>Normal</td>
<td>Shallow</td>
<td>Narrow to nearly narrow/ appositional</td>
<td>Cleft closed</td>
<td>Bouts of partial mydriasis and corneal edema; other glaucoma signs variable. Prophylactic therapy</td>
</tr>
<tr>
<td>Congestive</td>
<td>Possible previous ‘attacks’</td>
<td>Elevated; Shallow marked</td>
<td>Closed Appositional to PAS</td>
<td>Cleft closed</td>
<td>Cleft closed</td>
<td>High IOP with mydriasis; corneal edema; episcleral congestion; other signs</td>
</tr>
<tr>
<td>Post-congestive</td>
<td>Glaucoma history</td>
<td>Normal</td>
<td>Shallow</td>
<td>Closed PAS</td>
<td>Cleft closed</td>
<td>Normal to low IOP due to decrease aqueous humor production. Signs of glaucoma</td>
</tr>
<tr>
<td>Chronic glaucoma</td>
<td>Glaucoma history</td>
<td>Increased</td>
<td>Shallow</td>
<td>Closed with PAS</td>
<td>Cleft closed</td>
<td>Buphthalmia. Other signs of glaucoma. Optic disc and retinal degeneration. Blindness</td>
</tr>
</tbody>
</table>

Glaucoma in the American Cocker Spaniel

Prevalence of the glaucomas in the ACS varies from 1.39% (1964–1973), 2.07% (1974–1983), 3.95% (1984–1993), to 5.52% (the highest for any breed) (Gelatt & MacKay, 2004a). In the first ACS report of 25 animals with glaucoma, 7 were males and 18 were females (1:2.6) (M agrane, 1956, 1957b). The mean age of affected animals was 6.33 ± 1.46 years. Subsequent reports described glaucoma in the ACS in additional dogs: America, 3 dogs (Lovekin & Bellhorn, 1968), and the Netherlands, 19 dogs (Boevé & Stades, 1985a, 1985b). In the North America survey of the 1982 glaucomatous cockers, 665 were males and 1331 were females (1:2). The mean ± SD for affected animals was 6.72 ± 1.13 years. The presentation of primary glaucoma in the ACS is highest in middle- to old-age dogs. For 1994 through 2002, the prevalence of affected dogs was 0.63% (1–2 years old); 1.07% (2–4 years old); 4.3% (4–7 years old); 7.03% (7–10 years old); 8.39% (10–15 years old); and 5.32% (15+ years old). Narrow-angle glaucoma in the ACS continues to be the most frequent primary glaucoma presented to U.S. veterinary ophthalmologists (Gelatt & MacKay, 2004c; M agrane, 1956, 1957b). This breed also continues to be one of the most popular in the United States. Primary glaucoma has also been reported for this breed in other countries. More females in the ACS breed are affected with glaucoma than the males (1:1.3).

The usual history of PCAG or narrow-angle glaucoma in the ACS contains few classic clinical signs of glaucoma, but occasional histories report the presence of conjunctival hyperemia and even transient corneal edema. Most affected dogs present with either classic clinical signs of unilateral, acute congestive glaucoma of a few days’ duration or with chronic, advanced glaucoma with buphthalmia, lens changes, retinal and ONH degeneration, and blindness (Fig. 19.11A–C, Fig. 19.12, and Fig. 19.13). Often, the condition becomes bilateral within several months. In M agrane’s series, the ratio of males to females was 1:3, the left eye was initially affected twice as often as the right eye, the mean age of affected dogs was 6 years (range, 3–10 years), and the second eye was usually affected within 12 months (M agrane, 1957b).

Both the history and clinical course suggest this glaucoma may be a series of acute IOP attacks, with the subsequent magnitude of the IOP elevation gradually increasing. Tonomographic measurements are usually within normal limits in dogs with narrow iridocorneal angles, but they are lower than normal (≤0.10–0.15 µL/min/mmHg) in dogs with very narrow and closed (due to synechial formation) iridocorneal angles and clefts. Tonometry of the acute congestive glaucomas often yields IOPs as great as 50–70 mmHg, and the corneal edema that parallels the elevation in IOP after approximately 40 mmHg usually prevents gonioscopy. Gonioscopy of the ACS with ocular hypertension usually reveals a narrow to closed iridocorneal angle and reduced ciliary clefts; as the glaucoma progresses, angle closure and ciliary cleft collapse with peripheral anterior synechial formation are common. More recently, pectinate ligament dysplasia in the ACS has also been reported, but it does not appear to occur frequently in our experience (Smith et al., 1993).

Changes of the ocular fundus in the ACS may not correlate well with the duration and magnitude of the elevated IOP because of the wide difference in the levels of elevated IOP.
Figure 19.11. (a) Hypothesis for the development of narrow and closed iridocorneal angle glaucoma and ciliary cleft collapse in the American Cocker Spaniel. Tight apposition of the pupillary aspects of the paracentral iris slightly increases the pressure within the posterior chamber, which in turn causes forward displacement of the basal iris. Eventually, the basal iris narrows the iridocorneal angle and opening of the ciliary cleft (arrows). (b) High-resolution or ultrasound biomicroscopy of the iridocorneal angle and ciliary cleft in a normal dog, and (c) an American Cocker Spaniel with iridocorneal angle closure and collapse of the ciliary cleft (Photographs B and C are courtesy of Ursula Dietrich, 2007). (C, cornea; S, sclera; I, iris; PL, pectinate ligament; CC, ciliary cleft; and A, Iridocorneal angle).

Figure 19.12. Narrow-angle and cleft glaucoma in an American Cocker Spaniel. (a) Both corneal edema and striae are present, and the IOP is 52 mmHg. (b) Gonioscopy reveals a closed iridocorneal angle and cleft.
It is not unusual for an ACS to present with a very high IOP (70–80 mmHg) and a history of signs of glaucoma being present for less than 1 week, yet after lowering the IOP to less than 20 mmHg, the dog does not recover its vision. Ophthalmoscopically, the ocular fundus cannot be visualized until the IOP is lowered and the corneal edema reduced. The optic nerve and retina may initially appear to be normal, although some vascular attenuation may be present. With the IOP maintained within the normal range after these acute increases, additional retinal and ONH degeneration may become apparent within a few weeks.

In some of these dogs, the retinal degenerations may affect only limited areas, appearing as radiating or fan-shaped zones from the ONH and representing areas of retinal and choroidal degeneration caused by ischemia from the occlusion of individual short posterior ciliary arteries apparently with high IOP levels. Because this breed often presents with its first affected eye with very high IOP and often irreversibly blind, prophylactic therapy of the fellow eye is very important.

**Glaucoma in the Basset Hound**

In the Basset Hound, the reports of glaucomatous dogs have consisted of four animals (mean ± SD 5.0 ± 2.3 years old) (Martin & Wyman, 1968); six animals in a colony of 224 animals (Wyman & Ketring, 1976); four dogs in the Netherlands (Boeve & Stades, 1985a); and five animals in England (mean age 7.8 years) (Bedford, 1975). In the recent North American survey, 545 glaucomatous dogs were diagnosed with glaucoma; the mean ± SD was 6.3 ± 1.30 years of age at first presentation for glaucoma. Prevalence has increased in the Basset Hound from 3.08% (1964–1973) to 5.44% (1994–2002) (Gelatt & MacKay, 2004a). More recently, a new colony of glaucomatous Basset Hounds has been established again (Grozdanic et al., 2010) and more timely information reported.

Prevalence of glaucoma in the Basset Hound appears to increase with age. In one report on the glaucomatous Basset Hound (n = 552), the prevalence and age groups affected during the 1964–1973 interval were as follows: 0.20% (2–6 months); 0.48% (6–12 months); 0.74% (1–2 years); 2.03% (2–4 years); 5.96% (4–7 years); 5.81% (7–10 years); and 8.62% (10–15 years). From 1974 to 1983, the prevalence was 0.48% (2–6 months); 0.35% (6–12 months); 0% (1–2 years); 3.26% (2–4 years); 5.71% (4–7 years); 5.99% (7–10 years); and 5.78% (10–15 years). From 1984 through 1993, the glaucoma prevalence was 0.95% (2–6 months); 0.29% (6–12 months); 0.78% (1–2 years); 2.21% (2–4 years); 6.52% (4–7 years); 6.88% (7–10 years); 4.53% (10–15 years); and 2.63% (15+ years). In 1994–2002, the glaucoma prevalence was 0.47% (2–6 months); 0.37% (6–12 months); 0.36% (1–2 years); 4.19% (2–4 years); 6.74% (4–7 years); 6.95% (7–10 years); and 6.81% (10–15 years). The mean ± SD age of initial presentation with glaucoma in the Basset Hound was 6.33 ± 1.30 years. The gender ratio differs with more females affected than males (1:2.4).

Narrow- and closed-angle glaucoma with pectinate ligament dysplasia (i.e., mesodermal dysgenesis) was documented in Basset Hounds during the late 1960s and investigated during the early 1970s (Martin & Wyman, 1968; Wyman & Ketring, 1976). In these reports, 63% of Basset Hounds had some degree of pectinate ligament dysplasia, but fewer than 3% had glaucoma. Bedford’s study of the Basset Hound and the English Cocker Spaniel reported the gonioscopic results in these two breeds were quite similar (Bedford, 1975). Serial gonioscopy of some glaucomatous Basset Hounds suggests a gradual increase in the extent of pectinate ligament dysplasia with aging, suggesting possible formation of peripheral anterior synechiae.

More recently a colony of glaucomatous Basset Hounds has been established again and the glaucoma classified as chronic angle-closure glaucoma animal model (Grozdanic et al., 2010). Primary chronic angle-closure glaucoma in man is characterized by positions of the anterior chamber angle becoming closed permanently closed by the formation of peripheral anterior synechiae (Ritch & Lowe, 1996a, 1996b). The key for this study to be successful will be producing affected animals! Unlike the simple autosomal recessive inheritance pattern in the Beagle and equal gender ratio, the heredity of Basset Hound glaucoma may be more complex, as the male to female ratio is about 1:2 or 1:3.

This form of glaucoma usually presents clinically as either a unilateral, acute, congestive, closed-angle glaucoma or as chronic narrow-angle-closure glaucoma with buphthalmia and eventual blindness (Fig. 19.14A, B). In a study using periodic applanation tonometry, a gradual rise in IOP occurred in glaucomatous Basset Hounds starting at 14 mmHg (8-month-old dogs), 15.5 mmHg (15-month animals), 17.5 mmHg (18-month-old dogs), 24 mmHg (24-month-old animals), and 36 mmHg (30-month-old dogs) (Grozdanic et al., 2010). This suggests progressive changes in the aqueous humor outflow pathways, probably within the trabecular meshwork, develop...
reveals a narrow to closed iridocorneal angle, and the opening of the ciliary cleft is spanned by varying sizes and numbers of consolidated thickened pectinate ligaments or mesodermal remnants, with varying numbers of “flow holes.” There are usually some gaps in the regions of pectinate ligament dysplasia, where the pectinate ligaments appear normal, and the gaps permit direct inspection of the trabecular meshwork and the ciliary cleft opening. Gonioscopy of Basset Hounds which eventually develop glaucoma suggest the pectinate ligament dysplasia may become more extensive over time and with progressive narrowing the iridocorneal angle.

Figure 19.14. (a) Basset Hound with bilateral advanced glaucoma. (b) Scleral thinning near the equator may be evident, often signaling previous very high levels of IOP (chronic glaucoma scleral thinning file). (c) At gonioscopy, large, persistent mesodermal bands, rather than the distinct, individual pectinate ligaments, are often visible. With extensive involvement, flow holes are present in these dysplastic pectinate ligaments. Because iridocyclitis is often present, these pectinate ligament anomalies must be differentiated from progressive, peripheral anterior synechiation of the aqueous outflow pathways in this type of glaucoma.

Before IOP exceeds normal levels, anterior uveitis, with at least some of the corneal edema related to this inflammation, is present, which is unusual among breed-related canine glaucomas. It is not known if the glaucoma precipitates the uveitis or if the uveitis develops in the inflammatory response to the marked elevations in IOP and tissue damage. This inflammation complicates greatly the medical and surgical treatments of this form of glaucoma and requires concurrent topical and systemic corticosteroid therapy.

High-frequency ultrasonography (HFU) indicates complete collapse of the iridocorneal angle in dogs of about 20 months old (Grozdanic et al., 2010). In the opposite, normotensive eye, and in the affected eye, gonioscopy usually reveals a narrow to closed iridocorneal angle, and the opening of the ciliary cleft is spanned by varying sizes and numbers of consolidated thickened pectinate ligaments or mesodermal remnants, with varying numbers of “flow holes.” There are usually some gaps in the regions of pectinate ligament dysplasia, where the pectinate ligaments appear normal, and the gaps permit direct inspection of the trabecular meshwork and the ciliary cleft opening. Gonioscopy of Basset Hounds which eventually develop glaucoma suggest the pectinate ligament dysplasia may become more extensive over time and with progressive narrowing the iridocorneal angle.

From the traditional provocative tests used for the glaucomas (water; corticosteroid; and mydriatic or darkroom),
affected dogs treated with topical tropicamide (1%) or atropine (1%) caused significant elevations in IOP (35% and 50%, respectively). While scotopic and photopic electroretinography did not reveal significant deficits, pattern electroretinography indicated significant reduced amplitudes. These reduced PERGs can occur in dogs as young as 18 months of age, and gradually declined from 3.5 ± 0.42 µV (18-month-old dogs) to 1.84 ± 1.06 µV (30-month-old dogs). There appeared to be a significant correlation between IOP levels and pERG amplitudes. This also suggests functional vision deficits may precede significant elevations in IOP (Grozdanic et al., 2010).

Results of histopathologic examinations of these affected eyes mainly involved the advanced form of the glaucoma. Short, stout pectinate ligaments span the collapsed ciliary cleft and, in the advanced glaucomas, are often in direct contact with the peripheral cornea, with the opening to the ciliary cleft being collapsed. The termination of Descemet’s membrane in advanced cases is often enlarged, divided, and bulbous. Descemet’s membrane and corneal endothelial cells may extend posteriorly along the trabecular beams. Specific changes within the trabecular meshwork in the early stages of this disease are unknown.

Schiotz tonographic measurements in two Basset Hounds with glaucoma were 0.05 µL/min/mmHg (one dog with bilateral glaucoma), and in another Basset Hound, this value was 0.03 µL/min/mmHg in an eye with unilateral glaucoma and 0.10 µL/min/mmHg in the “normal” eye, which developed glaucoma 1 year later. Other Basset Hound data from the Ohio State University colony had both normal and low outflow values (range, 0.03–0.38 µL/min/mmHg), but whether any of these animals developed glaucoma later was not reported (Helper et al., 1974).

Medical treatment of Basset Hound glaucoma is difficult because of the often acute and very high elevations of IOP, and the clinical signs of combined angle-closure glaucoma and iridocyclitis. Often, the first presenting eye is moderately enlarged, the lens subluxated, the ONH cupped, and vision has been lost.

**Glaucoma in the Beagle**

In the 2002 North America survey, the prevalence of glaucoma in the Beagle is 1.01% in 1984–1993 and 1.10% in 1994–2002 (Gelatt & MacKay, 2004a). The prevalence of glaucoma in the Beagle (n = 189) was selected to compare to the glaucomatous Beagle colony established over 40 years ago. In 1994 through 2002, the prevalences of the glaucomatous dogs were 0.25% (2–6 months); 0.28% (6–12 months); 0.24% (1–2 years); 1.06% (2–4 years old); 1.61% (4–7 years); 0.75% (7–10 years); and 1.58% (10–15 years). Beagle glaucoma is presented clinically in middle-age and older dogs; the mean ± SD age of initial presentation with glaucoma was 6.24 ± 1.31 years old. In the Utrecht University study, several glaucomatous Beagles were reported in 1982. The Beagle breed is thought to be a very old breed (called Begles), having its genesis in both England and France.

Inherited glaucoma in Beagles was first reported in 1971 (Gelatt, 1972), and a colony of affected dogs was established shortly thereafter to permit long-term investigation of this spontaneous disease (Gelatt et al., 1977b, 1981b). The initial nine Beagles that presented with bilateral primary glaucoma had either an initial open iridocorneal angles in the early glaucoma eyes or later iridocorneal angle closure and ciliary cleft collapse with enlargement of the globe in eyes with advanced glaucoma. During the past 40 years, POAG in the Beagle has been investigated in considerable detail compared with the other breeds; clinical reports included 9, 37, and 55 glaucomatous dogs, but nearly 200 glaucoma dogs have been investigated over four decades. In the North America survey, the glaucomatous dogs presented for first diagnosis at 6.24 ± 1.31 years of age. In the closed colony of glaucomatous Beagles, the ocular hypertension begins between 1 and 2 years of age but becomes first noticeable by owners when secondary globe enlargement, mydriasis, and lens subluxation develop much later usually at 4–6 years of age.

The elevation in IOP becomes apparent at tonometry in Beagles between 8 and 16 months of age, but the clinical signs of glaucoma are delayed until 2–5 years (Fig. 19.15). The increase in IOP and decline in facility of outflow, as measured by Schiotz tonography, pneumotonography, and constant-pressure perfusion of the anterior chamber, develop slowly (Gelatt et al., 1977a; Peiffer et al., 1980). In affected dogs, the pneumotonographic outflow declines from 0.19 ± 0.07 µL/min/mmHg (3–6 months of age) to 0.07 ± 0.05 µL/min/mmHg (43–48 months of age) (Gelatt et al., 1996). The pneumotonographic outflow measurements of genetic carrier dogs are between the affected and normal dogs. The mean episcleral venous pressure of both normal and glaucomatous dogs is 10–12 mmHg (Gelatt et al., 1982).

The iridocorneal angle and sclerociliary cleft are initially open and devoid of any abnormalities (Fig. 19.16). The IOP in early glaucomatous dogs slowly increases from the mean normal IOP of 16–18 mmHg. Animals from 2 to 5 years old have IOPs in the range of 25–40 mmHg. Diurnal IOP variations (8–12 mmHg) as well as IOP differences between fellow eyes of individual dogs are greater in affected dogs, with the highest IOP in the morning (Gelatt et al., 1981a). Results of serial A-scan ultrasonography indicate the increased IOP produces slight enlargement (1–2 mm) of the axial length of the globe, which in turn results in lens subluxation and narrowing of the iridocorneal angle and collapse of the sclerociliary cleft in dogs between 1 and 4 years. Lens removal prior to the onset of ocular hypertension in Beagles bred for POAG did not delay the onset of glaucoma (Fig. 19.17) (Gelatt & Samuelson, 1988).

Eventual iridocorneal angle and sclerociliary cleft closure result in animals from 4 to 6 to as much as 8–10 years of age (Gelatt et al., 1977b, 1981b). POAG is inherited in Beagles as an autosomal-recessive trait (Gelatt & Gum, 1981) and...
Figure 19.15. Progression of primary open-angle glaucoma in a Beagle with monitoring of IOP (applanation tonometry), aqueous humor resistance to outflow (C: tonography), position of the lens, appearance of the iridocorneal angle and ciliary cleft (gonioscopy), and A-scan ultrasonography (axial globe length). With globe enlargement, secondary iridocorneal angle and ciliary cleft closure as well as lens luxation with zonular disinsertion occur.

Figure 19.16. Gonioscopic view of the iridocorneal angle and opening of the ciliary cleft in a Beagle with early primary open-angle glaucoma.

Figure 19.17. Effect of unilateral lens removal in 6-month-old Beagles bred for inherited glaucoma. Comparison of IOP results between the aphakic and fellow eyes did not prevent the onset of ocular hypertension bilaterally.
recently associated with the ADAMTS10 gene (Kuchey et al., 2010). The ADAMTS10 mutation has not only been identified in this colony of glaucomatous Beagles but also in clinical patients. In some of the original dogs, the glaucoma presented either as fairly high IOP and blindness by 4 years of age; however, in some dogs, there is a gradual increase in IOP (usually in the 30-35 mmHg level), and these affected animals as old as 8–10 years old can still be visual. The male: female ratio for POAG in the Beagle is 1:1.

Oral administration of water and topical administration of corticosteroids produce abnormal increases in the IOP of glaucomatous Beagles. In normal dogs, oral administration of water (50 mL/kg) increased the IOP by 3.1–8.6 mmHg, whereas in glaucomatous Beagles, the rise in IOP ranged from 7.3 to 19.9 mmHg (Gelatt et al., 1976). Elevated serum cortisone levels occur in glaucomatous Beagles and appear to be cyclical with the diurnal IOP changes (Chen et al., 1980). After 10–14 days of either unilateral or bilateral 0.1% dexamethasone administered four times a day in glaucomatous Beagles, the IOP increases by approximately 5 mmHg (Gelatt & MacKay, 1998b).

Visual resolution as measured by PERG in both normal and glaucomatous Beagles has been compared (Ofri et al., 1993a, 1993b, 1993c, 1994). The visual resolution limit of normal dogs was determined to be 6.9 ± 2.6 minutes of arc per phase in the central 15° of the retina and 11.8 ± 2.3 minutes of arc per phase in the toroidal 15° of the retina. In dogs with early glaucoma, the respective results were 7.8 ± 2.1 and 13.0 ± 3.1 minutes of arc per phase. For both groups, the resolution limit of the central 15° was significantly higher (P < 0.0005) than that of the more peripheral, toroidal 15° of the retina. There was no significant difference (P > 0.29) between the resolution limit of normal and that of early glaucomatous dogs for either the central or toroidal fields. One interesting finding, however, was identified with the injection of thiamyal sodium in the glaucomatous dogs. Analyses of PERG results obtained 30 minutes after and 2 hours after the injection of thiamyal sodium revealed that the second stimulation of the toroidal 15° of the retina was remarkably larger than the first stimulation only in the glaucoma dogs and that it occurred with only the larger (>48 minutes of arc per phase) gratings. Thiamyal sodium in a glaucomatous dog produced an initial 66% decline in signals from the central 30° of the retina and an 88% decline in those from the more peripheral toroidal 15° of the retina 30 minutes after the injection. Two hours after the injection, signals from the peripheral 15° of the retina again were increased above the first signal, with the central 15° being unaffected. One possible explanation for this may be local effects from this barbiturate anesthetic on the larger RGCs within the less vascular toroidal retina. Barbiturates are known to increase retinal excitability, and perfusion deficits found in glaucoma might delay the drug reaching the retinal cells or prolong the presence of drug metabolites (Ofri et al., 1993c, 1994).

Results of preliminary studies using OCT of the superior and inferior neural rims of the ONHs in dogs indicated the mean thickness of the retinal NFL ranged from 278±5 mm in one normal dog, 361±5 mm in one dog with early glaucoma, and 211±65 mm in six eyes with advanced glaucoma (Dawson et al., 1995, 1996). Mean histopathologic retinal NFL measurements in similar dogs produced values of 242±158 mm in eight normal eyes and 90.5±50.3 mm in the glaucomatous dogs. One possible explanation for this increased peripapillary retinal thickness in dogs with the early glaucoma may be the presence of enlarged RGC axons from impaired axoplasmic flow.

Results of color Doppler imaging of normal Beagles and those with inherited glaucoma in which the IOP was not medically controlled indicate significant differences in several specific blood flow parameters of many ophthalmic and orbital blood vessels (Gelatt et al., 2003; Gelatt-Nicholson et al., 1999). Differences in blood flow parameters on color Doppler imaging affected the exterior and internal ophthalmic arteries, anterior ciliary arteries, and short posterior ciliary arteries, all of which exhibited significant differences, but the parameters of the primary retinal arteries were not affected. Results of color Doppler imaging also demonstrate characteristic spectral waveforms for several of these blood vessels, as well as further differences when dogs with early, moderate, and advanced glaucoma are compared. Of interest, initial changes in the color Doppler measurements of most of the orbital blood vessels in the glaucoma dogs developed prior to the onset of ocular hypertension.

Results of light microscopic examinations of the aqueous outflow indicate no abnormalities in the animals affected early in life (Peffer & Gelatt, 1980). By transmission-electron microscopy (TEM), however, abnormalities were first detected in 12-month-old dogs (Samuelson et al., 1989). Clustered basement membrane-like material was scattered throughout the outer corneoscleral trabecular meshwork (Fig. 19.18A-D). Elastin-like fibers appeared to be more numerous and to be arranged less regularly than those in normal dogs, and small clusters of serratated, opaque rods were present within the cytoplasm of the trabecular cells within the corneoscleral meshwork. In the more advanced stages of the disease, these changes were more extensive and generalized within the corneoscleral meshwork. The trabeculae became more compressed and disorganized, with the concomitant accumulation of extracellular materials.

Perfusion of the anterior chamber in normal dogs with bovine testicular hyaluronidase increases the constant-pressure perfusion rate beyond that of control dogs (Gum et al., 1992; Samuelson et al., 1987). Perfusion of glaucomatous dogs with hyaluronidase, however, did not increase the constant-pressure perfusion rates. Histochemical localization of the GAGs within the corneoscleral beams and juxtaocular zone in normal dogs reveals that chondroitin sulfate is the major component, with lesser amounts of hyaluronic acid, dermatan sulfate, and heparin sulfate (Gum et al., 1986, 1987, 1989, 1993; Gum & Gelatt, 1988). In glaucomatous dogs, the amount of chondroitin sulfate decreases as the disease advances, and a GAG hyaluronidase-resistant material develops (Gum & Gelatt, 1988; Gum et al., 1993c).
Retinal and optic nerve changes in affected dogs have also been studied. Anterior movement of the scleral lamina cribrosa can initially be detected at scanning laser ophthalmoscopy, which is followed by posterior displacement of the multilayered lamina cribrosa (Brooks, 1996). Cupping of the canine ONH develops as the disease progresses. Such cupping is difficult to use as a clinical guide to glaucoma progression, however, because the rate of cup progression is variable. The retinal blood vessels, especially the small, peripapillary retinal arterioles and veins, gradually disappear. The optic discs become round with the loss of myelin, depressed, and atrophied. Results of short-term studies measuring orthograde rapid axoplasmic flow with tritiated leucine in normal dogs at perfusion pressures (i.e., diastolic blood pressure + 1/3 [systolic-diastolic blood pressure] – IOP) of 12-100 mmHg (IOP, 6-100 mmHg) revealed a pressure-related label accumulation at the scleral lamina cribrosa (Williams et al., 1983). The same effect also occurs in glaucomatous dogs (Samuelson et al., 1983).

Trypsin and detergent digests reveal a well-developed scleral lamina cribrosa in the dog (Brooks, 1998). Slight posterior distortion or bowing of the scleral lamina cribrosa occurs before ophthalmoscopic changes to the optic disc can be observed. Posterior displacement and compression of the...
scleral lamina occurs regularly in moderate stages of the disease. In advanced glaucomatous eyes, extreme posterior displacement of the scleral lamina, marked distortion of the lamina pore space, compression of the lamina, and disturbances of the congruent laminar pores are observed. Vascular casts of the optic nerve microirculation did not reveal any differences between normal and glaucomatous Beagles (Brooks et al., 1989a). Results of ultrastructural examination of the optic nerve capillaries revealed many spherical, membrane-bound, electron-dense inclusions that closely resemble Weibel–Palade bodies in the pericytes and endothelial cells of affected Beagles at all stages of the disease; the Weibel–Palade bodies have been associated with microcirculatory abnormalities in both humans and diabetic dogs (Brooks et al., 1989a).

The ultrastructural changes of the optic nerve axons at the ONH in glaucomatous dogs are prominent (Samuelson et al., 1983). In dogs with early glaucoma, the optic nerve axons vary in diameter, are irregularly swollen, have various stages of demyelination, and contain occasional swollen mitochondria, dense bodies, and vesicles. Within most of the prelamina, choroidal, and scleral lamina cribrosa, the axonal mitochondria frequently possess irregular, electron-dense bodies. In globes with moderate and advanced glaucoma, the optic nerve has more extensive pathologic changes. The myelinated axons are widely separated by demyelinated axons, hypertrophied or hyperplastic glial cells (i.e., astrocytes, oligodendrocytes, microglia), and edema. Dense, multilaminar myelin structures with shrunken, degenerated axons occur frequently within the prelaminar regions. Axons in the scleral lamina are extremely swollen with mitochondria and other cytoplasmic organelles, including various types of opaque inclusions and smooth-surfaced vesicles. Frequently, axoplasmic debris fills the spaces between the axons and the glial cells.

Histomorphometry of the optic nerves in age-matched normal and glaucomatous dogs indicate significant differences (Brooks, 1998; Brooks et al., 1993, 1995a). The mean total optic nerve axon count in normal dogs is nearly 150,000. The mean optic nerve axon diameters in normal, early glaucomatous, and advanced glaucomatous eyes are 1.53, 1.25, and 1.13 μm, respectively. The counts of optic nerve axons 2.0 μm or greater in diameter were reduced by up to 60% in the central regions of the optic nerves of affected dogs (Brooks et al., 1995a). These findings suggest that, as with POAG in humans and laser-induced experimental glaucoma in nonhuman primates, the large-diameter optic nerve axons are more susceptible than the smaller-diameter fibers to damage and disappear first in glaucomatous Beagles. Smaller-diameter axons are extensively damaged later such that only “resistant” ganglion cell axons are present late in the disease. The dog RGCs have been assigned to the morphologic classes α, β, and γ, which are equivalent to the neurophysiologically classified RGC types Y, X, and W reported in other species. The large RGCs have fast conduction velocities, large retinal receptive field surface areas, large-diameter axons, and preferentially project to layers A and C of the carnivore (i.e., magnocellular layers) lateral geniculate body.

Because several glycoproteins have been identified as the source of the increased resistance to aqueous humor outflow in the Beagle, we have focused initially on the gene and protein myocilin, the first gene associated with several types of early- and late-onset glaucomas in humans. The gene myocilin was reported in the normal dog genome in the summer of 2003. In the same year, we identified the protein myocilin in the aqueous humor of normal laboratory-quality Beagles, and in POAG in the Beagles, myocilin aqueous humor levels were increased (Mackay et al., 2004, 2008b). As POAG progressed in these Beagles, the aqueous humor myocilin levels increased further. Myocilin was also localized in the normal and glaucomatous Beagle trabecular meshwork and nonpigmented ciliary body epithelium (Samuelson et al., 2005). As with the aqueous myocilin levels, the glaucoma animals had increased amounts of myocilin in these tissues, and it increased further in the older glaucomatous dogs (see Fig. 19.10).

As a result of several studies, the MYCO gene in Beagles with POAG was determined normal (Gelatt & Wallace, 2004; Kato et al., 2009b; Storey et al., 2008), even though both the myocilin and CD44 proteins were elevated in aqueous humor, the trabecular meshwork, and nonpigmented ciliary body epithelium (Källberg et al., 2006; Mackay et al., 2008a, 2008b). Another candidate gene, CYP1B1, was also normal (Kato et al., 2009a). Fortunately a mutation in the ADAMTS10 gene, caused by the substitution by glycine for arginine (gly661/arg) within a single 4 Mb locus on the canine chromosome 20 was documented which appears to affect the folding of the DNA, possible collagen processing, and proteoglycans degradation. This gene is also associated with fibrillin mutations, and is important in microfibril formation and function (Kuchtey et al., 2010).

**Glaucoma in the Boston Terrier**

The prevalence of glaucoma is also increasing in the Boston Terrier, ranging from 0.97% (1964–1973), 1.82% (1974–1983), 2.60% (1984–1993), to 2.88% (1994–2002) (Gelatt & Mackay, 2004). The prevalence of the glaucoma in the Boston Terrier (n = 255) was consistently in the highest 10 breeds for the past 38 years. In 1994–2002, the glaucoma prevalences were 0.88% (2–6 months); 0.52% (6–12 months); 0% (1–2 years); 1.16% (2–4 years); 1.99% (4–7 years); 4.08% (7–10 years); 5.64% (10–15 years); and 12.5% (15+ years). Glaucoma presents in the middle-age and predominately old-age Boston Terrier, and mean ± SD age of initial presentation was 7.02 ± 1.24 years old. The male/female ratio is 1:1. There is no clinical report on glaucoma in this breed to date.

**Glaucoma in the Bouvier des Flandres**

In the Bouvier des Flandres, two reports of pectinate ligament dysplasia and narrow-angle glaucoma included 35 and 36 glaucoma animals (Boëvé & Stades, 1985a, 1985b, 1985c;
Van Der Linde-Sipman, 1987). Both reports were based on dogs in the Netherlands, where the breed is the most frequently affected purebred dog with glaucoma. In America, the Bouvier des Flandres is a relatively new breed of dog, and the number of glaucomatous animals in the survey report was limited to 23 animals (mean ± SD age of 5.43 ± 1.70 years old) (Gelatt & MacKay, 2004a). The male:female ratio of affected dogs is 1:1.

In addition to pectinate ligament dysplasia and narrow iridocorneal angle and ciliary cleft, histopathology of the affected secondary pectinate ligaments and trabecular meshwork contained significant amounts of PAS material, which may also affect aqueous humor outflow (Van Der Linde-Sipman, 1987). An HRUS study on this breed is focusing on angle and cleft width, pigmentation, and other ocular abnormalities (Miller et al., 2004).

**Glaucoma in the Chow Chow**

In the Chow Chow breed, the first report of glaucoma consisted of 18 glaucomatous animals (13 females and 5 males) with a mean ± SD of 6.2 ± 2.2 years of age on first presentation for glaucoma (Corcoran et al., 1994). In the prevalence survey in North America, 223 glaucomatous dogs were recorded with the mean ± SD age of 6.45 ± 1.07 years on first presentation for glaucoma (Gelatt & MacKay, 2004a). During nearly 40 years in North America, glaucoma was diagnosed infrequently: 2.05% (1984–1993) and 4.70% (1994–2002). Glaucoma in this breed predominantly affects the older dog. During the period 1994 through 2002, the glaucoma prevalences were 0.46% (2–6 months); 1.04% (6–12 months); 0.35% (1–2 years); 0.86% (2–4 years); 5.92% (4–7 years); 9.69% (7–10 years); and 5.22% (10–15 years). The mean ± SD age of initial presentation with glaucoma in the Chow Chow was 6.45 ± 1.07 years old. The male:female ratio in primary glaucoma in this breed is about 1:2.

Primary glaucoma in the Chow Chow has been associated with iridocorneal angle closure and limited pectinate ligament dysplasia (Corcoran et al., 1994). Most animals presented with bilateral, acute congestive glaucoma. Results of gonioscopy, when possible, revealed narrow to closed iridocorneal angles, with short, stout pectinate ligaments. Pectinate ligament dysplasia, appearing as focal areas of solid pigmented sheets, was usually quite limited (<1/16 the circumference of the angle). On the basis of clinical observations regarding the extent of pectinate ligament dysplasia, the genesis of this form of primary glaucoma appears to be of the narrow- and closed-angle type.

Histopathologic results of a dog that had glaucoma for 18 months, as well as of four globes from three other Chow Chows with chronic glaucoma, revealed extensive retinal degeneration as well as deep cupping and gliosis of the optic discs. The pathology of the outflow pathways indicated collapse of the ciliary clefts and compression of the trabeculae. Endothelial cells and PAS-positive basement membrane material spanned the pectinate ligaments and occurred within the trabecular meshwork. The termination of Descemet's membrane had irregularities and nodular terminations. The Chow Chow is another breed with primary glaucoma that often retains functional vision until late in the disease, often with profound optic disc cupping. This is despite elevated IOP, buphthalmia, and obvious, extensive ONH cupping and degeneration.

**Glaucoma in the English Cocker Spaniel**

Glaucoma in the English Cocker Spaniel may be more common in the United Kingdom, and the single report included 16 glaucomatous dogs with a mean age of 9.8 years old (Bedford, 1980b). The prevalence of glaucoma in the English Cocker Spaniel in North America was fairly constant (1.16% in 1974–1983; 1.59% in 1984–1993; and 1.35% in 1994–2002) and primarily affected middle-aged and older dogs (Gelatt & MacKay, 2004a). For the English Cocker Spaniel (n = 37) in North America, the prevalence of the glaucomatous dogs by age group from 1994 to 2002 were 0% (2–6 months); 0% (6–12 months); 2% (1–2 years); 0% (2–4 years); 0.66% (4–7 years); 1.44% (7–10 years); and 3.36% (10–15 years). The mean ± SD age of initial presentation with glaucoma in the English Cocker Spaniel was 6.83 ± 1.34 years old. The male:female ratio for this breed's glaucoma is 1:2 females. Bedford reported both narrow and closed iridocorneal angles and clefts as well as pectinate ligament dysplasia in this breed (Bedford, 1977b).

**Glaucoma in the English Springer Spaniel**

The prevalence of primary glaucoma in this breed in North America is low (0.48% in 1974–1983); only 25 dogs were affected (15 males; 12 females) (Gelatt & MacKay, 2004a). The age of initial diagnosis of primary glaucoma varied from 0.48% (2–4 years); 0.28 (4–7 years); and 0.72% (7–10 years); to 1.40% (10–15 years). Primary glaucoma, characterized as narrow iridocorneal angle and pectinate ligament dysplasia, was reported in 14 (5 males and 9 females) of 279 English Springer Spaniels in Norway (Bjerkaas et al., 2002). While narrowing of the iridocorneal angle in the hypertensive dogs seemed somewhat constant, the degree of pectinate ligament dysplasia was more variable with affected dogs generally more severely affected, and more frequent in older dogs. Similar age-related changes in pectinate ligament dysplasia have been made in the Basset Hound; could this be synchetical narrowing and eventual angle closure? About 25% of the normotensive Springers had some degree of pectinate ligament changes. Grades (based on 1/16 of angle circumference involved with pectinate ligament dysplasia) for the normal dogs were normal (74.5%); grade 1 (15.8%); grade 2 (6.8%); grade 3 (1.8%); and grade 4 (1.1%). Also in the normal dogs, 17.9% had some narrowing of the iridocorneal angle. This breed-related glaucoma appears to be inherited because related dogs were affected, and this possibility should be investigated more thoroughly. Important studies to elucidate further the
Glaucoma in the Flat-Coated Retriever

Primary glaucoma also affects Flat-Coated Retrievers from England, but the condition has not been reported among those from the United States (Read et al., 1998; Wood et al., 1998). Flat-Coated Retrievers with the more extensive forms of pectinate ligament dysplasia are predisposed to glaucoma. In one study, 16 had glaucoma (62.5%–100.0% of the iridocorneal circumference affected), and 11 were normotensive (62.5%–87.5% of the circumference affected) (Read et al., 1998). The onset of glaucoma was proposed as corneal endothelial basement membrane deposition within the ciliary cleft, or as gradual closure of the compromised cleft from lenticular enlargement with aging, but no histopathologic results were described. The possible relationship between the corneal endothelium and the trabecular meshwork endothelia within the ciliary cleft in the pathogenesis of this glaucoma is unclear but interesting. Many other aspects of this type of glaucoma need to be investigated.

Glaucoma in the Great Dane

Primary glaucoma affects Great Danes from England (Barrett & Mason, 1993; Wood et al., 2001). Eighteen dogs (11 females and 7 males) have been affected, with an age range of 1–9 years (mean age, 4 years). Most dogs presented with unilateral acute congestive glaucoma, with 3- to 24-month intervals between binocular involvement. Gonioscopy of the initially affected eyes, as well as of the opposite, normotensive eyes, revealed narrow to closed iridocorneal angles with pectinate ligament dysplasia. No tonographic or histopathologic examinations of affected eyes have been reported.

A subsequent study of 180 Great Danes (30 with ocular ultrasonography) compared depth of anterior chamber, goniodysgenesis (pectinate ligament dysplasia), development of glaucoma, and inheritance of goniodysgenesis (Wood et al., 2001). The estimated heritability of the degree of goniodysgenesis was 0.52, and there was a significant relationship between the angle abnormalities in the parents and their offspring. An anterior chamber depth of <3.7 mm was also a predictor of glaucoma. If both parents had extensive goniodysgenesis (<70%), the occurrence of glaucoma was estimated at <4/1000. Hence, shallow anterior chambers and extensive pectinate ligament dysplasia appear to be risk factors in this breed.

Glaucoma in the Shiba Inu in Japan

The Shiba Inu is a relatively new breed in America and does not have a large number of registered dogs at this time. However, the Shiba Inu is a popular breed in Japan and demonstrates glaucoma with iridocorneal angle narrowing and thickening of pectinate ligaments (Kato et al., 2006a, 2006b, 2007). The thickened pectinate ligaments range from very broad strands, small sheets, and broad solid sheets with or without flow holes.

In a population of 1244 animals, 127 dogs were diagnosed with primary and secondary glaucomas. In these glaucomatous dogs, primary glaucoma was diagnosed in 129 eyes and secondary glaucoma in 33 eyes (Kato et al., 2006b). Of the primary glaucoma dogs, the Shiba Inu breed had the highest incidence (42 dogs; 33%), followed by Shih Tzu breed (21 dogs; 16.5%) (Kato et al., 2006b). Most Shiba Inu patients present with acute high IOP elevations, mydriasis, corneal edema, scleroconjunctival congestion, pain, and often loss of vision.

The Shiba Inu breed in Japan may be predisposed to hereditary glaucoma. In a study involving glaucomatous, nonglaucomatous with open iridocorneal angle, and nonglaucomatous with closed iridocorneal angle Shiba Inu dogs, the exons of the canine myocilin gene were amplified and sequenced. A healthy Beagle dog was the control. Myocilin RNA was present in the ciliary body and trabecular meshwork, but the myocilin gene in this breed appeared normal (Kato et al., 2007).

Glaucoma in the Toy and Miniature Poodle

Although the glaucoma is not highly frequent in North America (Miniature Poodle: 1.49% in 1984–1993, and 1.68% in 1994–2002; and Toy Poodle: 1.06% in 1984–1993, and 1.20% in 1994–2002) (Gelatt & Mackay, 2004a), the popularity of these breeds results in larger number of glaucomatous animals. The prevalence of the glaucomas in North America in the Toy and Miniature Poodle were combined and involved a large number of affected dogs (n = 573). During the period 1994 through 2002, the glaucoma prevalence by age groups for the Miniature Poodle were 0% (2–6 months); 0% (6–12 months); 0% (1–2 years); 0% (2–4 years); 0.42% (4–7 years); 2.00% (7–10 years); 2.37% (10–15 years); and 3.78% (15+ years). From 1994 to 2002, the glaucoma prevalence for the Toy Poodle were 0% (2–6 months); 0.44% (6–12 months); 0% (1–2 years); 0.45% (2–4 years); 1.07% (4–7 years); 1.19% (7–10 years); 1.79% (10–15 years); and 2.34% (15+ years). The mean ± SD age of initial presentation with glaucoma in the Miniature Poodles was 7.31 ± 1.23 years. The glaucomas in the Toy and Miniature Poodle breeds appeared to be increasing slightly. The affected male to female ratio for this breed is 1:1.4.

Glaucoma in the Norwegian Elkhound

The prevalence of glaucoma in the Norwegian Elkhound is 2.96% (1974–1983), 2.34% (1984–1993), and 1.98% (1994–2002). POAG was originally described in 29 Norwegian Elkhounds from Norway (Bjerkås et al., 1994; Ekesten et al., 1997). The 15 glaucomatous dogs (1 female and 14 males) ranged in age from 3.9 to 13.0 years (median age, 6.6 years). The male to female ratio of affected dogs is 1:1.3.
Glaucoma in the Samoyed

In the Samoyed, the first report of narrow-angle or angle-closure glaucoma was in Europe and included 12 glaucomatous animals (mean age ± SD: 6.6 ± 2.8 years) and 179 normotensive dogs (Ekesten, 1993; Ekesten & Narfström, 1991, 1992; Ekestan & Torrang, 1995). In the North America survey, there were 148 glaucomatous dogs with the age (mean ± SD) at first presentation at 6.16 ± 1.39 years (Gelatt & MacKay, 2004a). Prevalence in North America is relatively stable (1.43% in 1974–1983; 1.57% in 1984–1993; and 1.59% in 1994–2002). From 1994 to 2002, the glaucoma prevalences were 0% (2–6 months); 0% (6–12 months); 0% (1–2 years); 1.02% (2–4 years); 3.15% (4–7 years); 2.15% (7–10 years); and 0.61% (10–15 years). In the Samoyed breed, glaucoma is presented in middle-aged and older dogs, and the mean ± SD age of initial presentation with glaucoma was 6.16 ± 1.39 years old. The ratio of males to females in the breed is 1:2.23.

Narrow- or closed-angle glaucoma in Samoyeds has been investigated clinically in Sweden (Ekesten, 1993; Ekesten & Narfström, 1991, 1992; Ekestan & Torrang, 1995). This breed is an excellent example of the members that with IOPs in the mid 30mmHg, and ONH cupping that involves the entire nerve head, the animal can still see. An additional retrospective histopathologic study of 9 clinically normal and 22 glaucoma eyes showed open-angle and closed-cleft glaucoma with pectinate ligament dysplasia (2 normal and 18 glaucoma eyes), ciliary cleft abnormalities (hypoplasia or collapse), and linear deposition of PAS-positive basement material within the uveal trabecular meshwork (in 19 glaucoma eyes). TEM demonstrated thickening of uveal trabecular beams by poorly staining large collagen fibrils and irregular deposition of excess basement material. Affected dogs were 5.5–8 years old, and there were 7 males and 2 females, and gender was unknown for 3 animals (Oshima et al., 2004).

This breed also exhibits primary glaucoma in the United States, but it has not been studied in detail. We have noticed these dogs can tolerate fairly high IOP for months, be quite buphthalmic, and yet retain some functional vision. In the study of prevalence of the primary or breed-related glaucomas in this breed in North America, the prevalence varied from 2.96% (1974–1983); 2.34% (1984–1993), and 1.98% (1994–2002). The number of affected dogs was 99; the male to female ratios were 1:1.39 (1974–1983); 1:0.43 (1984–1993); and 1:1.32 (1994–2002); and mean ± SD age of 6.9 ± 0.8 years at initial presentation (Gelatt & MacKay, 2004a). Most glaucoma patients presented in the 4- to 7- and 7- to 10-year age groups.

Glaucoma in the Shar Pei

A relatively new breed to North America, the Shar Pei exhibits its primary or breed-related glaucoma (1.53% in 1984–1993 and 4.40% in 1994–2002) in later life (Gelatt & MacKay, 2004a). The breed has also been reported with hereditary lens luxation (Lazarus et al., 1998), and how these two breed-related diseases interrelate remains to be defined. In the glaucoma study, the male to female ratios were about the same: 1:1.18 (1984–1993) and 1:0.89 (1994–2002). From 1994 to
2002, the prevalence of glaucoma based on age was 0% (2–6 months); 0% (6–12 months); 0% (1–2 years); 1.49% (2–4 years); 7.58% (4–7 years); 7.42% (7–10 years); and 3.17% (10–15 years). The male to female ratio of glaucomatous dogs was 1:0.89. In the dogs with PLLs, the mean age of affected animals was 4.9 years (range of 3–6 years). This breed is another example of the members that with IOPs in the mid 30 mmHg, and ONH cupping that involves the entire nerve head, the animal can still see.

Glaucoma in the Siberian Husky

The prevalence of glaucoma in the Siberian Husky (1.13% in 1984–1993 and 1.88% in 1994–2002) reflects the increased popularity of the breed in North America. Pectinate ligament dysplasia and progressive narrowing of the iridocorneal angle have been related to this form of ocular hypertension. Nell and colleagues reported that pectinate ligament dysplasia in this breed may be inherited, but the mode of inheritance could not be ascertained. She also reported the pectinate ligament dysplasia was observed more frequently in the female and in blue irides (Nell et al., 1993). In these normotensive dogs, there was no relationship between the amount of pectinate ligament dysplasia and IOP.

The prevalence of Siberian Husky glaucoma in North America (n = 177 for 1964–2002) by age group in 1994 to 2002 was 1.75% (from 2 weeks to 2 months); 1.24% (2–6 months); 1.42% (6–12 months); 1.0% (1–2 years); 1.69% (2–4 years); 2.59% (4–7 years); 2.01% (7–10 years); and 0.86% (10–15 years) (Gelatt & MacKay, 2004a). Glaucoma in this breed affects mainly young and middle-aged dogs; the mean ± SD age of initial presentation with glaucoma was 5.27 ± 1.64 years old. In the Husky, the ratio of affected males to females is 1:1.88.

Glaucoma in the Welsh Springer Spaniel

Twenty-eight cases of primary angle closure have been reported in Welsh Springer Spaniels from England (Cottrell & Barnett, 1988). Females were affected more frequently than males (ratio, 4.2:1). A age of onset ranged from 10 weeks to 10 years (mean age, 2 years and 9 months). Four dogs were affected before 1 year of age. Time from the onset of glaucoma in the first eye to that in the second eye ranged from 6 days to 3 years.

Clinical signs were either those of acute congestive glaucoma with pain, dilated and unresponsive pupils, episcleral congestion, corneal edema, and IOP as high as 80–100 mmHg, or those of chronic angle-closure glaucoma with enlarged globes, Haab’s striae, lens subluxation and cataract formation, and advanced retinal and ONH degenerations. Gonioscopy of the affected dogs revealed eyes with regions of narrow and regions of closed iridocorneal angles and ciliary clefts, as well as other eyes with the angles totally closed. The Welsh Springer Spaniel has sparse and “wispy” pectinate ligaments. Scanning-electron micrographs of the outflow pathways revealed closure of the iridocorneal angle, complete absence of the pectinate ligaments, the iris root merging with the corneal endothelium, and partial collapse to complete closure of the ciliary cleft.

This form of glaucoma was familial, and the mode of inheritance appeared to be dominant. Selected matings, however, were not performed. The affected animals with the partially open and closed angles were thought to be heterozygous, and those with the eyes having completely closed angles were thought to be homozygous. The defect may show variable expression as well.

Other Breeds

Additional breeds also develop the primary glaucomas (see Table 19.1), but most breeds have not been investigated. PNA occurs in Golden Retrievers from England; angle closure, cleft collapse, and pectinate ligament dysplasia have been observed. Secondary glaucoma associated with pigmented dispersion and anterior uveal cysts also occurs in this breed (see Chapter 20, “Diseases and Surgery of the Canine Anterior Uvea”). Additional clinical studies using HRUS (20 MHz), UBM (50–60 MHz), OCT, ultrasound ocular measurements, and IOP diurnal recordings will hopefully document these glaucomas and their pathogenesis during the onset and early stages of these diseases. Once families of affected dogs are identified, DNA tests may reveal the causative genes.

SECONDARY GLAUCOMAS

The secondary glaucomas consist of diseases with increased IOP, open to closed iridocorneal angles and ciliary clefts, and detectable impairment of aqueous humor outflow. Both the medical and surgical management of secondary glaucomas in the dog has been overshadowed by those of the primary glaucomas. Clinical management of these secondary glaucomas is often more clear-cut because the cause of the increased IOP can usually be ascertained (Table 19.4), and the prognosis for the glaucoma progression ascertained.

Medical or surgical treatment of the secondary glaucomas is directed toward removing the cause of the elevated IOP. There may be additional or secondary changes (e.g., peripheral anterior synechiae) that may require application of the standard glaucoma filtering or cyclodestructive procedures. The most frequent causes of secondary glaucoma in the dog requiring surgery is lens displacement, which is demonstrated as subluxation, anterior luxation, or posterior luxation and cataract formation. Uveitis and intraocular tumors are also associated with secondary glaucoma in the dog.

Risk Factors of the Canine Secondary Glaucomas

Epidemiology Study of North America

Secondary glaucoma associated with five major risk factors was analyzed in the veterinary schools of North America from
Chapter 19: The Canine Glaucomas

SECTION III

The prevalence of canine secondary glaucomas ranged from 0.25% (1964–1973), 0.46% (1974–1983), 0.79% (1984–1993), to 0.80% (1994–2003) and were as frequent as the primary or breed-related glaucomas (0.9%).

University of California Study

A recent 5-year study from the University of California-Davis reported secondary glaucoma occurred in 156 of 2257 (6.9%) dogs examined because of ophthalmic disease and affected both eyes in 33 (21.2%) of these dogs (Johnsen et al., 2006). The most common causes of secondary glaucoma were non-surgical anterior uveitis (44.9%), anterior uveitis associated with prior phacoemulsification (15.8%) and lens dislocation (15.2%). Certain breeds were predisposed to the secondary glaucoma and included Parson Russell Terriers, Poodles, Boston Terriers, ACSs, Rhodesian Ridgebacks, and the Australian Cattle Dogs. No significant effects of gender and neuter status, age, or laterality on the cause of secondary glaucoma were detected.

THE LENS AND THE GLAUCOMAS

Removal of the lens, though not commonly considered to be a surgical procedure for treatment of glaucoma, may be necessary in treatment of many of the canine lens-induced glaucomas. Lens removal may be indicated for secondary glaucomas associated with lens-induced uveitis and cataract resorption, intumescent cataracts, anterior and posterior lens luxations, and subluxations. When the lens is displaced from its patella fossa in a glaucomatous eye, maintenance of IOP within normal limits by surgical, medical, or some combination of these treatments may be impossible without lens removal.

Subluxated Lenses and Anterior and Posterior Lens Luxations

Lens luxations are the most frequent cause of secondary glaucoma in the dog, but they also occur secondary to buphthalmia in the primary glaucoma. Enlargement of the globe causes progressive stretching of the zonules, which eventually breaks their attachments to the equatorial lens capsule, or infrequently, causes disinsertion of their attachments to the ciliary body. In the dog with bilateral buphthalmia and lens subluxation/luxation, it may be impossible to determine if the lens luxations are primary or secondary; the breed, age of onset, and presence or absence of cataract development may aid in making this determination. Total luxation with normalized globes is more common in primary luxation syndromes, with subluxations more commonly caused by the buphthalmia from glaucoma. Lens luxations in Terriers are common (Table 19.5), and these dogs may present with either unilateral or bilateral and acute or chronic secondary glaucoma (Curtis, 1990).

In our study on the prevalence of primary or breed-related and secondary glaucomas in the Wirehaired Fox Terrier, this
breed was diagnosed with both the primary and secondary glaucoma types (Gelatt & MacKay, 2004a, 2004b). It is obvious many veterinary ophthalmologists have difficulty establishing whether the initial ocular hypertension is primary or related to lens displacement in this breed. In the Wirehaired Fox Terrier, Formston first associated lens luxation to the glaucoma in 90 animals with a mean ± SD age of 4.96 ± 1.43 years of age. None of the dogs were less than 3 years old (Formston, 1945).

Of the 193 dogs presented with glaucoma without lens luxation in the North America survey, the mean ± SD age was 6.56 ± 0.93 years old (Gelatt & MacKay, 2004a). From 1994 to 2002, the prevalence of the glaucomatous dogs by age group was 0% (2–6 months); 0% (6–12 months); 0.99% (1–2 years); 2.42% (2–4 years); 2.67% (4–7 years); 2.56% (7–10 years); and 3.5% (10–15 years old) for a total of 2.28%. In a study on lens luxation in dogs, Curtis and Barnett reported the terrier breeds with lens luxation were younger; in their report of 100 dogs, 57 were Jack Russell Terriers with a mean age of 4.7 years old (Curtis et al., 1983). The PLLs occurred in dogs between 3 and 5 years old; while the secondary lens luxations occurred in dogs over 8 years old (Curtis et al., 2008). In this breed, the cataracts and the PLL were genetically correlated.

Genomewide association analysis and fine mapping by homozygosity were used to demonstrate the ADAMTS17 splice donor site mutation in the three breeds of dogs with primary lens luxations (Farias et al., 2010). The breeds affected included Miniature Bull Terrier, Jack Russell Terrier, and the Lancashire Heelers. The PLL locus was mapped to a 664-kb region of canine chromosome 3 containing the regional candidate gene ADAMTS17. Resequencing ADAMTS17 revealed a GT→AT splice-donor site mutation at the 5' end of intron 10. The predicted exon 10 skipping and resultant frame shift were confirmed with RNA derived from affected dogs. ADAMTS17 is one of 19 known mammalian members of the ADAMTS family of genes that encode secreted metalloproteases that proteolytically modify extracellular structural proteins. The exact mechanism(s) by which the ADAMTS17 mutation affects the lens zonules remains to be determined. The non-pigmented (inner) ciliary body epithelium produce and secrete fibrillin 1, which is the important component of the zonules.

The glaucoma may be associated with iridocyclitis from microtrauma between the unstable lens and iris, with resultant increases of aqueous humor fibrin, proteins, and inflammatory cells, which can themselves interfere with aqueous drainage, and it also may aid in formation of pre-iridal fibropupillary membranes as well as anterior and posterior synechiae, which further compromise aqueous humor drainage (Fig. 19.19). Anterior lens movement can mechanically impair passage of aqueous humor through the pupil, thereby causing increased posterior chamber pressure, which in turn causes anterior ballooning of the peripheral iris and reduction in the area of the iridocorneal angle outflow pathways. Such movement of the iris also contributes to formation of permanent peripheral anterior synchiae, and posterior synchiae which cause a condition known as iris bombé.

The completely luxated lens can remain in the patella fossa, luxate into the anterior chamber, or move posteriorly through the torn anterior vitreal face and into the vitreous (Fig. 19.20). One report suggests that ocular hypertension occurs in 73% of canine eyes with anterior lens luxations, in 43% of those with subluxations, and in 38% of those with posterior lens luxations (Glover et al., 1995a). With anterior displacement of the lens from the patella fossa, vitreous adhering to the posterior lens capsule may occlude the pupil, thereby preventing pupillary flow of aqueous humor and ballooning the base of the iris, which in turn causes iridocorneal angle and sclerociliary cleft closure. This type of iris bombé often masks the basal iridal and filtration angle changes.

With posterior or vitreal luxation of the lens, the torn anterior vitreal membrane allows both liquid and formed (i.e., gel) vitreous access into the pupil and the anterior chamber. Formed vitreous may cause pupillary blockage and secondary glaucoma. It can also adhere to the posterior cornea and

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<td>West Highland White Terrier</td>
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<td>Tibetan Terrier</td>
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<td>Wirehaired Fox Terrier</td>
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In Table 19.5, Inherited and Breed Predisposition to Lens Luxation in the Dog is presented.

In another report in the Jack Russell Terrier with cataracts and PLL, possible involvement of an HSF4 mutation with cataracts was determined by DNA sequencing (Oberbauer et al., 2008). In this breed, the cataracts and the PLL were genetically correlated.
iridocorneal angle. Blockage of the iridocorneal angle with formed vitreous sufficient to increase IOP is infrequent, but blockage of the pupil from vitreous sufficient to increase IOP is more common.

Lens subluxation is first apparent with a variable size aphakic crescent (Fig. 19.21). With loss of the zonular support, the lens becomes unstable (phakodenesis) as does the iris (iridodenesis). The vitreous may protrude through the aphakic crescent to variable amounts. Possible mechanisms that these unstable lenses may produce ocular hypertension include microtrauma and iridocyclitis; peripheral anterior and posterior synechiae; formation of pre-iridal and iridocorneal angle inflammatory membranes; pupillary blockage of aqueous humor flow; vitreous pupillary blockage; and other factors.

Cataractous versus “Clear” Lens

Lens luxation may involve normal as well as cataractous lenses, with the mechanism for the zonular disinsertions that occur in luxated lens or cataracts differing. In terriers, Tibetan Terriers, and Border Collies, the zonules appear to possess structural malformations, and bilateral lenticular displacement occurs in dogs only a few years of age having clear lenses. IOP can remain normal or be associated with abrupt elevations (Curtis, 1990; Curtis & Barnett, 1980; Curtis et al., 1983;
Foster et al. 1986; Willis et al., 1979). In contrast, luxations of cataractous and often hypermature lenses tend to occur with inherited cataracts in older dogs of the nonterrier breeds. The zonular degenerations with advanced cataractous lenses produce subtle to overt degrees of subluxation/luxation, and they appear to relate to the capsular changes associated with cataract hypermaturity and lens-induced uveitis. With focal zonular degenerations, small aphakic crescents develop, and partially liquefied vitreous may protrude through a defect in the anterior hyaloid membrane and into the pupil. This vitreous may also display pigment spots.

Early removal of displaced lenses, particularly in terriers, has the highest possibility of success for retention of vision and prevention of secondary glaucoma. The primary objective of lens extraction is to prevent secondary glaucoma, to diminish inflammation, or to treat the secondary glaucoma. Delayed medical or surgical treatment of eyes with displaced lenses can result in secondary glaucoma. Surgical removal of subluxated lenses, anterior luxated lenses, and the posterior luxated (i.e., intravitreal) lenses is accomplished by the extracapsular, phacoemulsification, or intracapsular techniques combined with sulcus intraocular lens fixation (Glover et al., 1995a; Nasisse & Glover, 1997; Stuhr et al., 2009; see Chapter 22, “Surgery of the Canine Lens”). We prefer a very careful phacoemulsification technique avoiding lens motion and further displacement. In contrast to the high success rate of cataract surgery in dogs by phacoemulsification, the removal of luxated lenses has a much higher risk of serious postoperative complications including glaucoma and retinal detachment. A medical approach is long-term therapy with demecarium bromide in those eyes with very little gel vitreous and posterior luxated lens, often attached to the ventral retina (Binder et al., 2007).

A recent study evaluated zonular fiber morphology by light microscopy and special stains in dogs with glaucoma (Morris & Dubielzig, 2005). Zonular fibers are composed of microfibrils, whose primary components are the glycoproteins fibrillin-1 and fibrillin-2. In 63 dogs diagnosed with glaucoma secondary to lens luxation, two distinct forms of abnormal zonular fiber morphology were recognized and designated as zonular fiber dysplasia and zonular fiber collagenization. The dysplastic form had zonular protein tightly adherent to the nonpigmented ciliary body epithelium, exhibited a distinct lamellar and cross-hatched pattern which was strongly positive to PAS and trichrome stains and staining negative to elastin stains. In the second form of zonular fiber collagenization, the abnormality was prevalent in the terrier breeds and Shar Pei breed, and characterized by excessive zonular fiber that was not tightly adherent to the nonpigmented ciliary body epithelium and positive with PAS, trichrome (blue for collagen), and elastin stains. The age of onset of the secondary glaucoma in these dogs also varied between the zonular fiber dysplasia (mean age 5.2 years old) and zonular fiber collagenization (mean age 8.9 years), suggesting the group with zonular fiber dysplasia having a possible heritable disease.

Phacomorphic Glaucoma and Intumescent Cataract

The intumescent (i.e., swollen) cataract has been associated with an acute pupillary block, phacomorphic glaucoma in the dog. This phenomenon occurs most frequently in the dog with diabetic cataracts, which may also develop anterior and equatorial capsular tears. The enlarged lens displaces the iris forward, thus increasing the posterior chamber pressure and causing the base of the iris to shift forward. This in turn narrows the iridocorneal angle and impinges on the ciliary cleft opening. If iridocyclitis is also present, peripheral anterior synechia may form. Treatment of this form of secondary glaucoma is by phacoemulsification extraction of the cataract.

Phacolytic Glaucoma/Resorbing Hypermature Cataracts and Lens-Induced Uveitis

Rupture of the lens capsule from ocular trauma and lens-induced uveitis from resorbing hypermature cataracts can cause the phacolytic form of open-angle glaucoma in the dog (Davidson et al., 1991a; Rubin & Gelatt, 1968). If the lens-induced uveitis is not carefully monitored and controlled medically, the filtration angle can eventually become obstructed with inflammatory cells, protein-rich aqueous humor, fibrin, and macrophages filled with lens-like material. With chronic lens-induced uveitis, formation of anterior and posterior synechia, peripheral anterior synechia, and iris bombé may cause this phacolytic form of secondary glaucoma. The definitive treatment for phacolytic glaucoma is cataract extraction to eliminate the source of the lens protein obstructing the aqueous outflow pathways. Medical therapy with β-blockers, carbonic anhydrase inhibitors (CAIs), and hyperosmotic agents is useful for reducing IOP in preparation for surgery.

THE APHAKIC GLAUCOMAS

The frequency of aphakic and pseudophakic glaucomas in humans after cataract surgery has gradually declined as surgical techniques have improved. In the 1950s and 1960s, the incidence of these glaucomas in humans was reported to be from 0.7% to 7.0%, and even as high as 12%. In 1965, secondary glaucomas after cataract extraction were the most common cause for enucleation in humans (35% in 1954 and 31% in 1965) (Tomey & Traverso, 1991; Vuori & Ali-Melkkila, 1993).

With the increased frequency of extracapsular and phacoemulsification cataract surgery and the intracapsular lensectomy for luxated lens in the dog, aphakic and pseudophakic glaucomas are becoming more frequent as well (Biros et al., 2000; Davidson et al., 1991b; Lanke & Miller, 2001; Paulson et al., 1986). In one report, the incidence of aphakic glaucomas after cataract surgery was estimated to be 3% (Davidson et al., 1991b). In another study, in which extracapsular cata-
Intravenous mannitol can be administered rapidly to reduce IOP, but its effects may be muted from increased permeability of the blood–aqueous barrier (BAB) because of the iridocyclitis. Intracameral tissue-plasminogen activator (TPA), 25–50 μg, can readily assist in resolution of fibrin occlusion of the pupil of less than 2 weeks’ duration (Martin et al., 1993).

If pupillary flow of aqueous humor is not possible, the occluded pupil can be opened by dissection with a sharp blade or hypodermic needle, laser iridotomy, iridectomy, or iridencleisis. Our preference is usually the latter procedure. Unsuccessful resolution of an occluded pupil and iris bombé results in chronic buphthalmia and blindness. Intraocular hemorrhage should be anticipated in these procedures, because the inflamed canine iris is highly vascular. During iridectomy, a radial (i.e., complete) or basal (i.e., peripheral) section of the iris is excised; unless they are large, these sites will eventually close with iridal scarring and inflammatory membranes. The Nd:YAG laser may be used to produce full-thickness iris holes (i.e., laser iridotomy); however, these holes will unfortunately usually close within a few days.

Our impression is that aphakic glaucomas secondary to pupillary occlusion tend to occur early in the postoperative recovery period. The form of aphakic glaucoma characterized by angle closure, ciliary cleft collapse, and formation of peripheral anterior synchiae develops in the dog several months or even years after successful cataract surgery. The onset of this glaucoma is usually slow and insidious, which is another reason for long-term monitoring of these patients after cataract surgery. Clinical signs may be either acute or chronic, but the elevations in IOP usually occur over several weeks. Gonioscopic examination reveals large areas of peripheral anterior synchiae. Aggressive, long-term anti-inflammatory therapy may reduce the concurrent iridocyclitis and lower the IOP. Topical β-blockers as well as topical and systemic CAIs...
can temporarily lower the IOP, but eventually, an antiglaucoma surgical procedure will be necessary. Aphakic glaucomas caused by either of these mechanisms may be difficult to reverse with intensive medical therapy; more often, they will require further surgery to relieve the pupillary occlusion and angle blockage.

**Acute Postoperative Hypertension**

Increases in IOP during the immediate postoperative period after cataract removal have been recognized for several years in both humans and the dogs. In one report involving humans, the frequency of postoperative hypertension (POH) 5 hours after surgery was 75% for an IOP of 30 mmHg or greater and 21% for an IOP of 40 mmHg or greater (Vuori & Ali-Melkkila, 1993). In a clinical study involving 88 dogs that received cataract surgery, the incidence of postoperative hypertension of 25 mmHg or greater was 49%, of 30 mmHg or greater was 34%, of 40 mmHg or greater was 20%, and of 50 mmHg or greater was 6% (Smith et al., 1996). Other studies have confirmed consistently ocular hypertension following lens removal: perhaps the most important variable is the times and frequencies of the postoperative applanation tonometry (Chahory et al., 2003; Miller et al., 1997b). The average onset for POH of 25 mmHg or greater was 4.9 hours. The incidence of POH was not affected by either extracapsular or phacoemulsification techniques; however, those eyes operated on by phacoemulsification demonstrated a more rapid increase in IOP (mean, 3.9 hours) than those eyes operated on by extracapsular techniques (mean, 8.4 hours). The incidence of postoperative ocular hypertension is also directly related to the frequency, times, and duration of the postoperative tonometry. Tonometry started 6-12 hours after cataract surgery will miss the majority of ocular hypertension occurrences. Intracocular lens placement may also cause a more rapid increase in postoperative IOP. Both older dogs and longer phacoemulsification times increase the likelihood of POH. Factors not found to correlate with development of POH included sex, stage of cataract, type of surgical procedure used, intracocular lens placement, preoperative lens-induced uveitis, posterior capsular tears, and anterior vitrectomy (Biros et al., 2000).

The cause of POH is not specifically known, but it may result from several factors. It is also unknown if dogs which develop postoperative ocular hypertension will, at a future date, develop glaucoma. In an experimental study of normal dogs that underwent phacoemulsification, IOP peaked at the third postoperative hour, with a mean IOP of 49.9 ± 5.0 mmHg (Miller et al., 1997b). Use of a viscoelastic agent, 2% hydroxypropyl methylcellulose, did not affect the peak or the duration of POH. Results of computer-aided morphologic analysis indicated the increased IOP immediately after surgery may result from a significant reduction in the ciliary cleft cross-sectional area and width.

Results of both of these studies confirm the value of postoperative tonometric monitoring in the dogs undergoing postoperative cataract and lens removal. If the IOP exceeds “safe limits,” topical or systemic CAIs (or both) or β-blockers (or some combination of these) are recommended, because they reduce the rate of aqueous humor formation but do not affect pupil size or increase the amount of iridocyclitis. Carbachol injected intracamerally during cataract surgery has been reported to prevent POH in the dogs (Stuhr et al., 1998); however, the relative risk and benefits of a miotic agent to prevent this increase in IOP versus the intensification of postoperative uveitis must be weighted. When IOP exceeds 40 mmHg and is refractory to topical therapy and IV mannitol, anterior chamber paracentesis may be necessary.

**MALIGNANT GLAUCOMA (AQUEOUS MISDIRECTION)**

Malignant glaucoma is a variation of pupillary block aphakic glaucoma, and it may develop after extracapsular/phacoemulsification, intracapsular cataract, or lens extraction surgery (Denis, 2002; Strubbe, 2002). The pupil is usually of medium size and is obstructed with inflammatory membranes, combined with either the posterior lens capsule and anterior vitreous face (with extracapsular/phacoemulsification) or the organized anterior vitreal face or membrane. The iris bombé is more limited centrally but is nearly against the corneal endothelium peripherally. If the pupil is small, aqueous misdirection glaucoma cannot be detected except by ultrasonography.

Rather than remaining in the enlarged posterior chamber behind the iris bombé, the aqueous humor is either misdirected or redirected into the vitreous body through a tear in its anterior face (Fig. 19.23). As aqueous humor formation continues and the IOP rises, the aqueous humor is now misdirected into the vitreous body, thereby pushing the organized or formed vitreous further into the occluded pupil. This is a surgical condition in which the impermeable pupillary membranes are removed by incisions with iridal scissors and an anterior vitrectomy is performed. Once these impediments are removed, pupillary flow of aqueous humor is reestablished. Because peripheral anterior synchia may develop quickly with this disorder, however, an iridencleisis is another consideration.

**TRAUMATIC GLAUCOMAS**

Traumatic glaucomas, which occur secondary to blunt and penetrating trauma, are infrequent in the dog. Complete acute hyphema in the dog is usually associated with uveal inflammation and low IOP; chronic or repeated intraocular hemorrhage in the dog is more apt to increase IOP. Direct damage to the trabecular meshwork and angle recession, which occurs in humans and results in glaucoma months to years after the traumatic incident, has not been reported in the dog. Traumatic glaucomas in the dog are usually associated with intense iridocyclitis and are best managed clinically, with aggressive treatment of the inflammation, prevention of peripheral anterior synchia, and control of the IOP (with CAIs). If peripheral
Recenty discovered pigmentary dispersion and cyst formation in Golden Retrievers and Great Danes can occur as chronic intraocular inflammations. Their serious long-term complications are frequently cataract formation and secondary glaucoma (Deehr & Dubielzig, 1998; Sapienza et al., 2000; Spiess et al., 1998).

Several factors appear to be important in the pathogenesis of uveitic glaucomas (Moorthy et al., 1997). The trabecular meshwork may be plugged with inflammatory cells, fibrin, blood, and large molecular proteins, or it may be directly involved in the inflammation. The inflammatory cells within the trabecular meshwork may release cytotoxic substances such as arachidonic acid metabolites, cytokines, proteolytic enzymes, and oxygen metabolites (i.e., oxygen free radicals). Endogenous prostaglandins lower the IOP by increasing the uveoscleral outflow of aqueous humor through the ciliary cleft during the first hours of an intraocular inflammation, but the prostaglandin-induced breakdown in the BAB may briefly increase the IOP. Peripheral anterior synechiae may eventually occlude the filtration angle and the ciliary cleft. Posterior synechia that encircles the pupil produces rapid development of iris bombé, which is caused by the lack of transpupillary aqueous humor flow, and increased IOP within the posterior chamber and segment. And lastly, chronic uveitis is a very important risk factor.

Clinical signs of uveitic glaucoma are a combination of iridocyclitis and either acute or chronic glaucoma. The pupil may be normal in size, thus representing a balance between the iridal inflammation and the IOP. Episcleral venous congestion, which is often present in the glaucoma, is partially masked by the conjunctival hyperemia (or ciliary flush) associated with the anterior segment inflammation. Likewise, corneal edema may represent a combination of the intensity of the iridocyclitis and the IOP.

Figure 19.24. Secondary glaucoma from angle closure and formation of extensive peripheral anterior synechiae and pre-iridal rubeosis in an Akita with uveodermatologic syndrome (Vogt–Koyanagi–Harada syndrome). Secondary glaucoma associated with uveitis is most likely to be associated with chronic uveal inflammations.
Elevations in IOP may be acute or may gradually elevate over several weeks or months. Aplanation tonometry is an important diagnostic procedure for uveitis. Most often, iridocyclitis causes decreased IOP; however, the onset of acute iridocyclitis, within the first hours, actually produces a transient elevation in IOP associated with the release of prostaglandins from the iris. Clinical signs of iridocyclitis with a normal IOP may signal early formation of peripheral anterior synchiae.

The treatment of uveitic glaucomas occurring secondary to peripheral anterior synchiae in phakic eyes is targeted at the underlying uveitis and at controlling the IOP; thus, retinal and ONH damage are minimized. High levels of topical and systemic corticosteroids and nonsteroidals are indicated. Because neither miosis nor mydriasis is desired, short-term mydriatics may be used to intermittently move the inflamed iris and pupil and to discourage formation of posterior synchiae. Topical and systemic antibiotics may also be indicated if an infectious process is present. Topical and systemic CAIs are administered to, hopefully, maintain the IOP within normal limits. Surgical treatments, such as laser cyclophotocoagulation and anterior chamber shunts, may also be attempted. As in humans, however, lower success rates in uveitic glaucomas versus other types of glaucoma occur in the dog because of the inflammation and protein-rich aqueous humor.

**OCULAR MELANOSIS AND MELANOCYTIC GLAUCOMA**

Originally described as pigmentary glaucoma in the Cairn Terrier by Covitz et al. (1984) and then by Petersen-Jones (Petersen-Jones, 1991; Petersen-Jones et al., 2007, 2008), the preferred term melanocytic glaucoma now seems to be more appropriately associated with ocular melanosis. Pigmentary glaucoma or pigmentary dispersion glaucoma in humans is characterized by a 360-degree, dense band of pigmentation on the trabecular meshwork; slit-like transillumination defects in the midperiphery of the iris; and a vertical band of pigment deposits on the central corneal endothelium (i.e., Kruckenberg spindle). In humans, the source of the pigment granules appears to be the posterior iridal pigmented epithelium. In the dog, the pigmentation appears to relate primarily to the uveal melanocytes and melanophages, not the extracellular melanin granules. Although the glaucoma in the Cairn Terrier surfaced in our breed-related prevalence study, melanosis (also called pigmentary glaucoma) of the globe has been associated with this form of secondary ocular hypertension. Glaucoma in this breed in North America has a prevalence of 1.33% (1984–1993) and 1.82% (1994–2002) (Gelatt & MacKay, 2004b).

This unique glaucoma affects middle-aged to older Cairn Terriers, and it may affect one or both eyes (Fig. 19.25). It has also been reported in the Boxer and Labrador Retriever (Van De Sandt et al., 2003). In these eyes, large aggregations of melanocytes and melanophages occur within the filtration angle, episcleral and subconjunctival tissues, tapetal ocular fundus, and even in the meninges about the ONH. What initiates the unchecked proliferations of these melanocytes is unknown, but the condition may represent a diffuse type of benign iris melanin cell proliferation.

Two most recent reports focused on ocular melanosis and have provided considerably more insight (Petersen-Jones et al., 2007, 2008). There were 114 Cairn Terriers affected (44 males, 67 females and 3 dogs gender unknown). Age of onset was quite variable, and the first noticeable clinical sign was a dark-colored thickening of the basal iris. This was followed by the development of distinct episcleral and scleral pigment plaques, the release of pigment into the anterior chamber and aqueous humor, and the deposition of pigment into the aqueous humor outflow pathways (especially ventrally). Secondary glaucoma developed in the most severely affected dogs. A slow progression of pigmentation of the tapetal fundus occurred, probably from the posterior uveoscleral outflow of aqueous humor. In some dogs, pigmentation adjacent to the ONH also developed. Pedigree analysis indicated a possible autosomal dominant mode of inheritance. Three affected Cairn Terriers eventually developed ocular melanomas and one mass metastasized widely. In the second report, 49 globes from Cairn Terriers with ocular melanosis were examined histologically, some by immunohistochemistry and others by TEM. Large, round pigment-laden cells were present within the anterior uvea, drainage angle, and within the sclera and episclera. In 39 of the 49 globes (80%), the structures of the iridocorneal angle were obliterated by the infiltrating pigment
cells. Some of these cells were also within the posterior segment (choroid, 78%, and retina, 28%), optic nerve meninges, and periphery of the ONH. The posterior iridal epithelium was present and did not appear to be involved in the proliferative process. About 20% of the affected globes also had a lymphocytic-plasmacytic infiltration of the anterior uvea and formation of pre-iridal fibrous vacuolar membranes. Ultrastructurally, the pigment cells were mainly melanocytes with some cells which appeared as macrophages. Many of the pigmented cells were immunoreactive to HMB45 (antibody for gp100 localized in stages II and III melanosomes), and some were microphthalmia-associated transcription factor (MITF) and vimentin positive.

Onset of the chronic glaucoma appears to be slow and to be associated with the accumulation of pigmented cells within the filtration angle and scleral venous plexus. Some free melanin granules occur and are phagocytized by the wandering macrophages and trabecular endothelia within the outflow pathways. Medical and surgical treatment of this secondary glaucoma has not been successful in the long term because the proliferating melanocytes and melanophages eventually completely obstruct any surgical anterior chamber bypass.

**PIGMENTARY AND CYSTIC GLAUCOMA**

An angle closure/occlusion secondary glaucoma has been associated with pigment dispersion, iris, and ciliary body cysts in Golden Retrievers (Deehr & Dubielzig, 1998; Esson et al., 2009; Sapienza et al., 2000). The mean age of the affected dogs is 7.6 years. Affected eyes, early in the disease, demonstrate iridal hyperpigmentation, pigment deposition on the anterior lens capsule, cataract formation, and web-like strands of opaque material within the anterior chamber. The clinical syndrome is characterized by the formation of thin-walled cysts within the posterior chamber, proteinaceous exudation and pigment dispersion, which appears to cause the glaucoma and cataract formation. These cysts are typically light brown and red; some appear collapsed within the posterior chamber. The pigment dispersion was deposed on the lenticular, iridal, and corneal endothelial surfaces. The time from diagnosis of the syndrome to glaucoma is about 5 months. All affected globes had free pigment within the trabecular meshwork.

The anterior uveal cysts were histopathologically lined by thin cuboidal or simple squamous epithelium, PAS-positive basement membrane-like protein, and sometimes collagen (some may contain hyaluronic acid). Affected globes had little or no evidence of inflammation. Nearly all cysts remain in the posterior chamber. The thin cellular wall of the cysts stained positive with vimentin, neuron-specific enolase (NSE), and S-100 in all globes. This staining pattern is consistent with a ciliary body epithelial cellular origin; however, one-third of the cysts also stained weakly positive for cytokeratin, which could rule out an iridociliary epithelial origin. They may be stretched across of the anterior face of the vitreous and some were attached to the anterior lens capsule. Peripheral anterior synechiae formation occurred in about 30% of the globe; posterior synechiae were noted in about 50% of the globes. Pre-iridal fibrovascular membranes were present in about 50% of the globes.

The pigment dispersion seems to cause the elevation in IOP. The cysts may compress focally the iridocorneal angle and ciliary cleft, or by releasing their own contents to cause angle closure by mechanical and inflammatory means. The toxic effects of the contents within the iridociliary cysts upon the trabecular meshwork are unknown. Medical and/or surgical treatment of this syndrome may lower IOP and prolong vision for a short period of time, but may eventually fail. A secondary glaucoma in the Great Dane dog is similar but not identical to the disease in the Golden Retrievers (Spiess et al., 1998). Additional information on this syndrome can be found in Chapter 20.

**INTRAOCULAR NEOPLASMS AND GLAUCOMA**

The most frequently occurring primary intraocular neoplasms in the dog are melanomas (Wilcock & Peiffer, 1986) and adenomas and adenocarcinomas of the ciliary body and iris. Not infrequently, the presenting clinical signs of these anterior segment tumors are secondary glaucoma, iridocyclitis, hyphema, or some combination of these (Fig. 19.26). Metastatic intraocular neoplasms, which are most often adenocarcinomas, also frequently involve the iris and ciliary body. Lymphoma or lymphosarcoma may also affect the anterior uvea.

Glaucomas secondary to these neoplasms usually result from direct infiltration of the filtration angle, obstruction of the angle by tumor-associated inflammatory products and peripheral anterior synechiae, or secondary pre-iridal membrane formation. Rapidly growing neoplasms often produce
glaucoma, and tumor-related necrosis may produce a secondary iridocyclitis.

In the clinical management of these patients, gonioscopy, indirect ophthalmoscopy of the peripheral ocular fundus, and ultrasonography are used to carefully define the borders of the neoplasm. A systemic medical workup is performed to rule out any metastases. Most of these tumor-induced glaucomas are treated with enucleation, but local iridocyclectomy, either with or without scleral grafts, may successfully remove the smaller neoplasms and preserve vision.

GLAUCOMAS SECONDARY TO SILICONE OIL AND RHEGMATOGENOUS RETINAL DETACHMENTS

New glaucomas recently reported or observed in the dog are those occurring secondary to silicone oil in the anterior chamber and secondary to rhegmatogenous retinal detachments. Silicone oil is used in the repair of canine retinal detachments to tamponade the detached retina into contact with the retinal pigment epithelium. Shifting of the oil from the vitreous into the anterior chamber, which occurs frequently in both aphakes and pseudophakes, increases the IOP by physically obstructing most of the aqueous outflow pathways. Treatment consists of removing the oil from the anterior chamber.

The association between rhegmatogenous retinal detachments and elevated IOP in humans was described in 1972 (Netland et al., 1994) and reported in the dog (Smith et al., 1997). Nonrhegmatogenous retinal detachments in the dog are usually associated with normal or low IOP (i.e., ocular hypotony), presumably resulting from increased uveoscleral aqueous humor outflow. Canine rhegmatogenous detachments, however, especially in those dogs with giant retinal tears, may release rod and cone outer segment fragments into the subretinal fluids and vitreous, which eventually enter the anterior chamber (Smith et al., 1997). This cellular debris accumulates in the aqueous humor outflow pathways and elevates the IOP. Rod and cone outer segments may be demonstrated in the aqueous humor at the trabecular meshwork. Reattachment of these giant tears prevents further anterior movement of the outer segments and lowers the IOP.

CONGENITAL GLAUCOMAS

Extensive goniodysgenesis or trabecular maldevelopment is rare in the dog. When present, however, it may be unilateral or bilateral, and it occurs as an isolated defect or with other systemic anomalies. When present, elevations of IOP occur early in the puppy’s life (usually 3–6 months of age), and the primary complaint is one of rapid and often dramatic globe enlargement (Fig. 19.27). This often-severe buphthalmia occurs because of the abundance of elastin fibers within the immature sclera, and if the IOP can be rapidly reduced to a normal level, the globe may return to near-normal size. The longer the buphthalmia persists, however, the less likely an approximately normal globe size will result. This rapid buph-

Figure 19.27. Advanced unilateral congenital glaucoma in a Welsh Corgi puppy. The cause was not determined.
12.2/100,000 per year in those persons aged 30 years or older. In America, PACG is a very uncommon diagnosis. While medical therapy of POAG in humans is generally quite successful initially, treatment of PACG in humans is far less rewarding because, as in the dog, vision is often impaired or lost on the initial presentation to the ophthalmologist (Aung et al., 2004). In one report, 17.8% of the PACG patients were blind in the initially affected eye and 59% had best-corrected vision worse than 6/9 (Aung et al., 2004). In patients in Singapore followed 6.3 years after the original diagnosis, more women were affected (68%) with an average age of 62 years old. A bout 18% of patients were blind in the attack eye with about 50% having glaucomatous optic nerve damage; half of these blind eyes could be related to PACG. A bout 58% of the patients had corrected vision worse than 6/9 with cataract formation involving about one-half of these patients at the last eye exam. It is generally believed that PACG is a much more serious disease than POAG in man (Ritch & Lowe, 1996a, 1996b), with considerable loss of vision in the presenting eye, and a poor response to both medical and surgical treatments. The same is apparent in the dog!

Chronic angle-closure glaucoma in man is difficult to control with medications when a significant part of the drainage angle becomes closed by peripheral anterior synechiae (Lai et al., 2005). Primary surgical options include trabeculectomy and goniosynechialysis with or without combined clear or cataract lens extraction. Trabeculectomy in these eyes with shallow anterior chambers poses the risk of further shallowing of the anterior chamber or precipitating malignant glaucoma by aqueous misdirection. The efficacy of goniosynechialysis in chronic angle-closure eyes remains unknown. Clear lens extraction is not well established or accepted at present. The efficacy of clear lens extraction as a means to prevent chronic angle-closure glaucoma remains to be documented. Diode laser transcleral cyclophotocoagulation in chronic angle-closure glaucoma in man has very limited success, and nearly always is combined with concurrent two or more topical medications.

**TARGET, SAFE, AND DIURNAL IOP**

Intraocular pressure has been firmly established as the primary risk factor for development of GON in the dog. Other factors are also important, but the higher the IOP, the greater the risk and severity of optic nerve damage. We believe that lowering the IOP is critical for maintaining both vision and quality of life of our canine glaucoma patients. A fundamental question that arises whenever therapy is initiated, however, is the amount of IOP reduction necessary to prolong vision. By setting a target pressure, we provide an operational answer to this question. Because we are presently unable to assess the true health of the optic nerve ophtalmoscopically, we have no practical end point for IOP reduction unless we set a target pressure. Establishing a “target” or “safe” IOP for each canine eye implies an IOP reduction to levels that reduce the RGC loss from glaucoma to normal, age-related levels of RGC loss and achieving an IOP that maintains the threshold number of RGCs necessary for vision (Jampel, 1997). Target IOP can be set by lowering the pressure to a given IOP, or it can be reduced by a given percentage. The greater the likelihood of future damage from glaucoma, the lower the target IOP should be set. The greater the amount of preexisting damage from glaucoma, the lower the target IOP should be set. We also believe the target IOP should take into account the side effects of medical and surgical treatment. The target IOP should relate to the maximum quality of life to be derived from preserving vision and not experiencing side effects of therapy. A weakness of the target IOP concept is that because we are only able to obtain single, infrequent IOP tonometric measurements in the dog, we do not know the true IOP level that may be present at other times throughout the day. We also do not understand the significance of mean IOP, maximum IOP, and liability of IOP in terms of the overall risk of IOP causing optic nerve damage and thus may be evaluating the wrong IOP parameter. It is also possible that the optic nerve may become damaged by not setting the target or safe IOP low enough. In the dog setting the “target IOP pressure” at 21 mmHg is reasonable, but with progressive loss of vision should be lower.

In the dog, setting a target range for the IOP may make the most sense. The target range provides a workable framework for therapeutic goals and should be reevaluated periodically by ophthalmic examination that includes tonometry. A reasonable population distribution of IOP (mean ± 2 SD) in the normal dog based on the two largest studies is 8–30 mmHg and, on clinical experience, is 12–25 mmHg (Gelatt & MacKay, 1998a; Miller et al., 1991). The mean and SD of IOP in the normal dog represent the real variation in IOP, variations in tonometers, and the daily (i.e., diurnal) variation. Previous results in normal dogs indicate that diurnal IOP fluctuates by 2–4 mmHg, with the higher IOP occurring in the morning and the lower IOP in the early evening; in dogs with POAG, however, these diurnal IOP variations are greater, often ranging from 6–10 mmHg (Gelatt et al., 1981a).

**WHAT IS A “SAFE” IOP?**

The scleral lamina cribrosa is a zone of pressure transition for the optic nerve axons. The IOP largely affects optic disc tissue pressure over the most anterior 100 µm of the ONH tissue. The axoplasmic flow of these axons is tenuous at even normal IOPs! The axons leave the eye under the influence of the IOP and pass through the decreasing tissue pressures of the lamina to come under the influence of the retrolaminar tissue pressure (RLTP). The RLTP (mean canine RLTP, 7 mmHg) directly relates to the cerebrospinal fluid pressure in the dog (Morgan et al., 1995). The normal canine retina begins to show electrophysiologic evidence of effects from elevated IOP at 33 mmHg (under general anesthesia, the baseline IOP is usually 10–12 mmHg) (Hamor et al., 2000), and oscillatory potential parameters show changes in latency and amplitude at this IOP as well. Results of ONH autoradiography of normal dogs indicate that 10% of the axons have mildly obstructed...
axoplasmic flow at an IOP of 25 mmHg (Williams et al., 1983), and this increases to near 100% at an IOP of 50 mmHg. Thus, the optic nerve axons are in a precarious functional state even at relatively normal IOPs in normal dogs. Beagles with hereditary glaucoma have mild to moderate obstruction of the axoplasmic flow of 87% of their optic nerve axons at an IOP of 30–35 mmHg (Samuelson et al., 1983). Trying to achieve a goal of 30 mmHg in a glaucomatous eye will not often prevent damage to the optic nerve axons. It may make the eye less painful, but if you are trying to save vision, the IOP must be reduced much further than this to protect the canine optic nerve. Once an optic nerve is damaged, the remaining axons appear to be more sensitive to further pressure insults. Unfortunately, the exact “safe” IOP for the dog is not known, but it must be much less than 30 mmHg—and possibly somewhat less than 20 mmHg—for a glaucomatous eye.

MEDICAL THERAPY FOR IOP CONTROL

Therapy for canine primary glaucomas is difficult to rationalize and apply when we do not yet understand the initiating events that result in compromised outflow of aqueous humor, the mechanisms by which these events lead to aqueous outflow obstruction, or even the nature of the obstruction itself. Thus, it follows that we have, at present, no means of detecting the initiating events in clinical patients, nor do we have treatments to prevent the outflow obstruction and optic nerve atrophy. Therefore, at present, there is no true treatment for the glaucomas. To treat the optic nerve damage in the glaucomas, we would have to reverse the visual field defects. Thus, is glaucoma therapy useless? We think not, but this is a question for which answers are changing constantly as we obtain more information about these diseases.

Treatment of the different types of canine glaucoma has, as the paramount purpose, maintenance of vision and IOP within the normal range after the condition has been diagnosed and prevention of further damage to the optic nerve and retina. Unfortunately, most canine glaucomatous patients present with the condition at an advanced stage in at least the first eye, and the therapeutic goal may simply be a pain-free eye that requires little to no medical care.

No single treatment regimen for canine glaucoma is possible because of the many different types of glaucoma (Table 19.6). In the secondary glaucomas, the initiating cause is identified and, if possible, either removed or suppressed. Medical treatment of canine glaucoma is a most important aspect, because surgical procedures often still require concurrent medical therapy. Medical therapy for the narrow- and closed-angle glaucomas is usually short term when employed alone, because eventually, the outflow becomes so impaired that drug-associated changes in formation and outflow are inadequate. A filter anterior chamber bypass surgeries, however, some medical therapy may be necessary to maintain the IOP at less than 20 mmHg.

As with cataract surgery in the dog, results of some clinical studies suggest that the earlier in the glaucoma process the surgery is performed, the higher the long-term success rate at controlling IOP and maintenance of vision for as long as possible (Jampel, 1997). Medical therapy for the glaucomas can also be quite expensive. Medical treatment of the primary glaucomas often includes short-term administration of a single drug, or a combination of drugs, to maintain the IOP within normal limits (usually 21 mmHg or less), and the long-term administration of combinations of drugs to supplement the available filtering surgeries and cyclodestructive procedures. Prophylactic treatment of fellow eyes in dogs presenting with unilateral primary glaucoma appears to delay the onset of glaucoma in these eyes for several months or longer, and is highly recommended (Miller et al., 2000).

Table 19.6 Treatment of the Primary Glaucomas

<table>
<thead>
<tr>
<th>A Initial Medical IOP Control: Is the Eye Blind or Visual?</th>
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<tbody>
<tr>
<td>IV Mannitol; AC paracentesis if mannitol fails to reduce IOP</td>
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<tr>
<td>Prostaglandins</td>
</tr>
<tr>
<td>Miotics</td>
</tr>
<tr>
<td>Adrenergics-beta blockers</td>
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<tr>
<td>IV acetazolamide</td>
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<tr>
<td>Corticosteroids possibly</td>
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<td>Neuroprotective drugs</td>
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<th>B Short-Term IOP Control</th>
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<tr>
<td>Prostaglandins</td>
</tr>
<tr>
<td>Miotics</td>
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<tr>
<td>Adrenergics-beta blockers</td>
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<tr>
<td>CAI-topical and parenteral</td>
</tr>
<tr>
<td>Neuroprotective drugs</td>
</tr>
<tr>
<td>Surgery/laser</td>
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<tr>
<th>C Long-Term IOP Control (To improve Outflow)</th>
</tr>
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<tbody>
<tr>
<td>Surgery-usually AC shunt/laser cyclophotocoagulation</td>
</tr>
<tr>
<td>Supplement with medical control:</td>
</tr>
<tr>
<td>Miotics/prostaglandins</td>
</tr>
<tr>
<td>Adrenergics</td>
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<tr>
<td>CAI-topical/systemic</td>
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<td>Neuroprotective Drugs</td>
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TOPICAL AND SYSTEMIC MEDICATIONS FOR TREATMENT OF THE GLAUCOMA

Control of elevated IOP associated with glaucoma can be achieved through medical and/or surgical therapy. Medical treatment of glaucoma is almost always directed at lowering the existing IOP and relies on topical or systemic administration of pharmacologic agents which can be grouped into three categories on the basis of their IOP lowering effect: (1) those that reduce the rate of aqueous humor production; (2) those
that increase aqueous humor outflow without affecting its formation; and (3) those that affect both aqueous humor outflow and formation. Many pharmacologic agents are available, including parasympathomimetic and adrenergic agents, as well as CAIs, prostaglandins, and osmotic diuretics. Because of their unique mode of action, these drugs are used as monotherapy or as unfixed or fixed combinations to decrease IOP to levels supposed to prevent the progressive loss of vision associated with the disease processes (Willis, 2004; Willis et al., 2002). If IOP lowering still remains the mainstay treatment of glaucoma, alternative neuroprotective therapies targeting RGCs have been developed during the last decade, and will probably emerge as potential strategies to prevent apoptosis of RGCs in the glaucomatous eye in the near future (Danesh-Meyer, 2011).

Cholinergic Agonists (Miotics)

Also known as parasympathomimetics or cholinomimetics, because they produce biologic responses similar to those of acetylcholine, these agents are divided according to their mechanism of action as direct acting and indirect acting. Drugs in the former class stimulate cholinergic receptors directly while drugs in the latter class are inhibitors of acetylcholinesterase, permitting acetylcholine to accumulate at the cholinoreceptive sites (Bartlett et al., 2008).

Effects on the Eye

Topical application of a parasympathomimetic compound on the eye results in miosis and lowering of IOP. In human and nonhuman primate eyes, contraction of the longitudinal fibers of the ciliary muscle with widening of the scleral spur is the likely mechanism by which parasympathomimetics decrease resistance of aqueous humor passage through outflow pathway (Kaufman & Gabelt, 1997). In nonhuman primate and human eyes, an increase in the number of giant vacuoles in the endothelium of Schlemm’s canal may also participate in improved aqueous outflow (Kaufman & Gabelt, 1997). In small animals, the contribution that contraction of ciliary muscle makes on aqueous removal has not been determined and thus, mechanism by which parasympathomimetics lower the IOP is not established. Nevertheless, a cholinergic activity has been identified in the ciliary body musculature of the canine eye, indicating that there is the potential for modulation of outflow facility by the cholinergic nervous system (Gwin et al., 1979). Further evidence supporting such a hypothesis were observations that either intracameral injection of pilocarpine or N-demethylated carbachol (Chiou et al., 1980), as well as topical application of pilocarpine in canine eyes (Gum et al., 1993a), induce a substantial increase in the conventional outflow facility.

Direct-Acting Parasympathomimetics

Pilocarpine is a natural alkaloid obtained from the leaves of South Africa shrubs of the genus Pilocarpus. The drug is used as a nitrate or a hydrochloride and is available in concentrations of 0.5%-8% in methylcellulose or polyvinyl alcohol vehicles. Most commercial pilocarpine eyedrops are in solutions with a pH range of 4.5–5.5, to preserve the drug from hydrolysis. Pilocarpine hydrochloride 4% in a high-viscosity acrylic gel has been introduced to prolong drug-eye contact time (Kaufman & Gabelt, 1997). Studies in glaucomatous (open-angle) and normotensive beagles indicate that a single instillation of 0.5–8.0% pilocarpine hydrochloride reduces IOP by 30%-40% for at least 6 hours (Gwin et al., 1977; Whitley et al., 1980). In these animals, a single drop instillation of pilocarpine (1%, 2%, or 4%) increased the coefficient of tonographic outflow facility from 0.33±μl/min/mmHg prior treatment up to 0.61±μl/min/mmHg after treatment in normal eyes and from 0.15±μl/min/mmHg prior treatment up to 0.38±μl/min/mmHg after treatment in glaucomatous eyes (Gum et al., 1993a). Glaucomatous beagles responded with a greater reduction of IOP than normotensive dogs and no significant difference in the hypotensive response was found among the different concentrations. Miosis occurred within 10–15 minutes and lasted for 6–8 hours (Gwin et al., 1977). Therapeutic additivity of pilocarpine with adrenergic agents or CAIs, has been demonstrated in human eyes (Kaufman & Gabelt, 1997). The combination of 1% epinephrine and pilocarpine hydrochloride (1%, 2%, 3%, 4%, and 6%) produced a significant IOP-lowering effect in glaucomatous (open-angle) and normotensive beagles. Following a single instillation of these combinations, the drop in IOP lasted for at least 8 hours and was not dose-related (Gelatt et al., 1983). Surprisingly, combined administration of 1% epinephrine with either 1%, 2%, or 4% pilocarpine did not increase tonographic outflow facility in these eyes in comparison to pilocarpine 4% used alone (Gum et al., 1993a).

In normotensive female horses, once-daily or twice-daily topical application of 2% pilocarpine hydrochloride was not associated with significant decrease in both IOP and vertical pupil size (van der Woerd et al., 1998). The lack of pharmacologic effect of pilocarpine on IOP was attributed most likely by a decrease in aqueous outflow resulting from ciliary muscle contraction. Dilution of the drug in the large equine tear volume leading to subtherapeutic concentration that penetrates the eye might also contribute to low availability of the drug (van der Woerd et al., 1998).

Carbachol is the carbamyl ester of choline. Because the drug is not lipid-soluble at any pH and penetrates the intact corneal epithelium poorly, it must be combined with a surfactant, such as benzalkonium chloride, to facilitate its penetration through the corneal epithelium (Kaufman & Gabelt, 1997). Carbachol is stable in solution and is available for topical use in concentrations of 0.75%-3%. A 0.01% solution is used for intracameral administration at completion of an intraocular surgery, to induce rapid miosis and inhibit postoperative ocular hypertension (Kaufman & Gabelt, 1997). At concentrations of 0.75%, 1.5%, 2.25%, and 3%, carbachol reduced IOP in normotensive and early glaucomatous (open-angle) beagles. The reduction in IOP was clearly evident
within 1 hour and peaked 2–7 hours after instillation (Gelatt et al., 1984). A minimum concentration of 0.75% carbachol was recommended in the management of open-angle glaucoma in the beagle (Gelatt et al., 1984). In an initial report, 0.01% solution injected into the anterior chamber of dogs at the end of cataract surgery was found to prevent the postoperative increase in IOP associated with phacoemulsification (Stuhr et al., 1998). This preventive effect on the development of acute POH was not further confirmed by an investigation in which dogs treated with intracameral administration of 0.3 mL of 0.01% carbachol immediately after phacoemulsification had significantly higher IOP than the controls (no treatment) 2 hours after administration, and had a number of POH peaks not significantly different from that observed in the controls (Crasta et al., 2010).

Indirect-Acting Parasympathomimetics
The anticholinesterases are divided into the carbamate inhibitors, which bind to the acetylcholinesterase in a reversible manner, and the organophosphorus inhibitors which irreversibly inhibit the enzyme by forming a stable complex.

Demecarium bromide is a potent carbamate inhibitor, no longer commercially available, but which can be compounded in 0.125% and 0.25% solutions for veterinary use. The drug remains stable for extended periods, and does not require refrigeration (Kaufman & Gabelt, 1997). A single drop of demecarium bromide in human eye provided a significant reduction of IOP starting a few hours after instillation and lasting for more than 3 days (Shihab, 1987). The accompanying miosis lasted for up to 10 days (Shihab, 1987). Investigations using single-drop application of either 0.125% or 0.25% topical demecarium bromide and conducted in normal and glaucomatous (open-angle) beagles revealed that both formulations induce long-term miosis (up to 77 hours) and IOP lowering effect that lasts up to 55 hours (Gum et al., 1993b). The mean decrease in IOP is about the same magnitude as that observed with pilocarpine solution and gel as well as with carbachol solution, but is more prolonged (Gum et al., 1993b).

Echothiophate iodide (or phospholine iodide) is another long-acting organophosphorus compound, available in 0.03%, 0.125%, and 0.25% solutions (Ellis, 1997). The refrigerated solution remains stable for at least 1 month after reconstitution. Instillation of one drop echothiophate iodide 0.125% or 0.25% results in decrease in IOP of about 10 mmHg and about 13 mmHg in normotensive and glaucomatous (open-angle) beagle eyes, respectively (Gum et al., 1993b). Reduction in IOP persists for 25–53 hours. Associated miosis becomes maximal within 1–3 hours and persists for 49–55 hours (Gum et al., 1993b). Thus, echothiophate iodide appears as potent as demecarium bromide in the dog.

Clinical Use
The major use of parasympathomimetic drugs has been the long-term treatment of open-angle glaucoma in the dog. Use of these agents in combination with adrenergic drugs or CAIs would also be of help for initial therapy in most early glaucomas. However, once glaucoma is advanced, parasympathomimetic therapy has little beneficial effect, because the filtration angle is usually obliterated by extensive peripheral anterior synechiae (Gaarder, 2000). Parasympathomimetic agents should be avoided in secondary glaucoma associated with iridocyclitis, and used with caution in dogs with subluxated or luxated lens, because the miosis predispose to synechia formation and may induce a pupillary block, respectively.
Pilocarpine solution should be prescribed three to four times daily (Gaarder, 2000), while pilocarpine gel, that reduced IOP by 25%–30% for at least 24 hours in glaucomatous canine eyes, is applied once daily (Carrier & Gum, 1989). Although demecarium bromide is a long-acting hypotensive ocular agent, its instillation has been recommended in the dog on a twice-daily basis, to regulate IOP and avoid occasional peaks that may be destructive for the glaucomatous eye (Gum et al., 1993b). In order to determine the ability of prophylactic anti-glaucoma treatment to prevent or delay onset of glaucoma in the second eye of dogs with unilateral closed-angle glaucoma, a combination of 0.25% demecarium bromide and a topical corticosteroid (DB/GB) was compared with topical 0.5% betaxolol in a multicenter clinical trial (Miller et al., 2000). Untreated control eyes developed glaucoma significantly sooner (median 8 months) than eyes treated either with betaxolol (median 30.7 months) or DB/GB (median 31 months). Although both treatment protocols similarly delayed the onset of glaucoma in the fellow eye, DB/GB would be preferable to betaxolol in preventing closed-angle glaucoma because of less frequent dosing (Miller et al., 2000). Pilocarpine is also used topically or orally (well mixed with food) in small animal ophthalmology to stimulate tear production in patients with keratoconjunctivitis sicca, and to improve the ocular and digestive signs of feline dysautonomia.

Side Effects
Because of the low pH (4.5–5.5) of its ophthalmic solutions, pilocarpine may cause local irritation manifested by blepharoospasm, prolapsed nictitans, epiphora, and conjunctival hyperemia which are observed within the first 15 minutes and may last for up to 6 hours (Martin & Wyman, 1978; Whitley et al., 1980). These signs are most prominent for the first 72 hours of treatment. Use of a special droptainer with a buffer system in its tip to adjust the pH of the pilocarpine solution to a level close to the physiological pH was evaluated in glaucomatous beagles (Gelatt et al., 1997). One and two percent pilocarpine solutions instilled by buffer-tip droptainer (pH 7) showed excellent pharmacological effects determined by miosis and ocular hypotension and were well tolerated (Gelatt et al., 1997). Topical application of pilocarpine transiently increases the permeability of the BAB, but does not result in short- or long-term changes (Krohne, 1994). In the dog, systemic side effects are unlikely after topical administration of pilocarpine 0.5%–8% solution or 4% gel (Carrier & Gum, 1989; Whitley et al., 1980).
Ocular and systemic side effects may occur with topical application of indirect-acting parasympathomimetics. Since they potentiate the action of acetylcholine on muscles, they produce more severe ciliary and iridal spasms than does pilocarpine. Decreased vision resulting from miosis and induced myopia is the most adverse reaction reported in human ophthalmology (Kaufman & Gabelt, 1997). A transient increase in BAB permeability, resulting in increase in aqueous humor flare, occurs in the canine eye after topical application of pilocarpine and demecarium bromide, and may represent a potentially adverse effect in dogs with glaucoma (Krohne, 1994). An experimental investigation in dogs demonstrated that miosis and increased flare caused by topical pilocarpine were inhibited by both proparacaine and nonsteroidal anti-inflammatory drugs (NSAIDs), such as flurbiprofen, suprofen, and diclofenac, while IOP was decreased only in proparacaine-treated eyes and increased in NSAID-treated eyes (Krohne et al., 1998). A transient increase in aqueous humor flare, probably secondary to nerve changes, occurs in eyes treated with pilocarpine and demecarium bromide, and may represent a potentially adverse effect in dogs with glaucoma (Krohne, 1994). At the light of these observations, the investigators’ conclusion was that miosis and increased aqueous humor caused by pilocarpine are prostaglandin-mediated events (i.e., substance P or calcitonin gene-related peptide) from antidromic stimulation (Krohne et al., 1998). In addition, the pilocarpine IOP-lowering effect observed in the eyes additionally treated with proparacaine was of a comparable amount to that previously reported for eyes treated only with pilocarpine, indicating that this pharmacologic effect is not affected by BAB breakdown (Krohne, 1994; Krohne et al., 1998). Another relevant conclusion of this investigation was that NSAID should not be used in glaucomatous dogs because it interferes with pilocarpine-induced decrease in IOP (Krohne et al., 1998). Systemic toxicity may develop with any cholinesterase inhibitor and may include salivation, vomiting, diarrhea, and abdominal cramps. To minimize the risk of toxicity, indirect-acting parasympathomimetics should be avoided in subjects treated with fleas containing organophosphates (Gum et al., 1993b). When signs are severe, atropine (0.2 mg/kg IV or IM) and pralidoxime chloride (20 mg/kg IV) are administered to block the action of acetylcholine. In humans, their long-term use may result in cataract formation, development of iris cysts (Ellis, 1997; Kaufman & Gabelt, 1997).

**Drugs Acting on Adrenoceptors**

Drugs that stimulate or block the activity of the ocular sympathetic nervous system may be used to lower IOP. Pharmacologically, their mechanisms of action are still unresolved and continue to be the subject of considerable study.

**Epinephrine and Dipivefrin**

Epinephrine, or adrenaline, is classified as a nonspecific adrenergic agonist which stimulates α and β types of membrane receptors. Dipivefrin, or dipivalyl epinephrine, is an epinephrine prodrug produced by the addition of two pivalic acid groups to the parent compound. The lipophilic prodrug penetrates the corneal epithelium barrier, where it is converted by esterases (acetylcholinesterase, cholinesterase, and arylesterase) to its parent drug, epinephrine, which is absorbed in the anterior segment (Nakamura et al., 1993; Wei et al., 1978). Epinephrine has been used for many years to treat glaucoma in humans but knowledge of its mechanism of action is still incomplete. Currently, it is believed that its ability for lowering IOP is manifested both by reduction in the formation of aqueous humor and increase in aqueous outflow. Investigations in monkeys and men indicate that epinephrine and dipivefrin reduce aqueous humor formation most likely by decreasing blood flow in the ciliary body, due to their vasoconstrictive action upon the vasculature of the ciliary body (Alm, 1980; Michelson & Groh, 1994). Improvement in conventional facility of aqueous outflow by adrenergic drugs has also been clearly identified in nonhuman primate and human eyes (Erickson-Lamy & Nathanson, 1992; Erickson et al., 1978; Neufeld, 1984). It was also found in the human eye that increase in aqueous outflow is mediated by β-2 adrenergic receptors and is correlated with increased cyclic adenosine monophosphate (cAMP) production by the trabecular meshwork (Erickson et al., 1978; Erickson-Lamy & Nathanson, 1992).

Concentrations of 1% and 2% topical epinephrine were effective in reducing IOP in glaucomatous (open-angle) and normotensive Beagles (Gwin et al., 1978). In these animals, the 0.5% solution of dipivefrin manifested hypotensive and mydriatic effects similar to those of the 2% solution of epinephrine (Gwin et al., 1978). Topical epinephrine or dipivefrin, alone or in combination with other antiglaucoma drugs such as direct-acting parasympathomimetics, β-blockers, and CAIs, is its main indication in the management of open-angle glaucoma. Various local and systemic side effects have been reported in man with the ocular instillation of epinephrine and dipivefrin (Fang & Kass, 1997). The most common side effects include local intolerance, formation of adrenochrome deposits in the conjunctiva and cornea, loss of eyelashes, and macular edema in aphakic eyes (Fang & Kass, 1997). Incidence of conjunctival and corneal staining in veterinary ophthalmology is unknown. Local irritation consisting of mild conjunctivitis and tears has been reported in the dog with the 0.5% solution of dipivefrin (Gwin et al., 1978). Some of the corneal esterases that convert dipivefrin to epinephrine are inhibited by anticholinesterase drugs, combined use of long-acting miotic and dipivefrin is contraindicated (Abramovsky & Mindel, 1997).

**Alpha₂-Adrenergic Agonists**

The mechanism by which α₂-adrenergic agonists lower IOP is not fully understood. Studies in human eyes have clearly demonstrated that these drugs decrease aqueous formation, but gave conflicting results as regards their effect on outflow facility (Lee et al., 1984a). From different investigations, it
appears that α2-adrenergic agonists most likely decrease aqueous humor formation by interfering with presynaptic (nerves) and postsynaptic (nonpigmented epithelial cells) α2-adrenoceptors at the sympathetic nerve-ciliary body junction (Lee et al., 1984a; Ogidigben et al., 1994; Toris et al., 1995a). Activation of the presynaptic α2-receptors inhibits norepinephrine release, thereby blocking the tonic adrenergic stimulation of the secretory ciliary epithelium by endogenous norepinephrine. Activation of the postsynaptic ciliary body α2-receptors, coupled to a G protein, suppresses the activity of adenylate cyclase and reduces the intracellular concentration of cAMP in the ciliary body epithelium. The net effect is also a decrease in aqueous humor formation (Ogidigben et al., 1994).

Apraclonidine (p-aminoclonidine), a derivative of cloni- dine with comparable IOP lowering effect and minimal cardiovascular effects, has been developed for use in humans (Toris et al., 1995b). It is available as a topical 0.5% solution. The IOP lowering ability of apraclonidine has been evaluated in normal dogs and cats. Single topical administration of 0.5% apraclonidine in canine eyes resulted in a 3.0 mmHg (16%) IOP decrease 8 hours after treatment (Miller & Rhaesa, 1996). In the cat, apraclonidine-treated eyes showed mean IOP decrease of 4.8 mmHg (24%) 6 hours after treatment (Miller et al., 1996). The topical application of apraclonidine resulted in ocular and nonocular side effects both in dogs and cats. Mydriasis occurred in 29% of the treated canine eyes and at the opposite pupillary diameter was reduced a mean 46% in the feline-treated eyes (Miller et al., 1996, 1996). Reduction in heart rate was more marked in cats than in dogs and undesirable gastrointestinal effects, such as salivation and vomiting, occurred in most cats (Miller et al., 1996, 1996). Thus, it appears that apraclonidine is not a first-line antiglaucomatous agent in the dog and is too toxic to be used in the cat. Nonocular side effects most likely result from systemic absorption of the topical drug. This is consistent with the finding that conjunctival/scleral route is the main pathway for apraclonidine absorption after topical application (Chien et al., 1990).

Brimonidine tartrate, a highly selective α2-agonist, has been introduced for treating acute and chronic elevations of IOP in human beings (Walters, 1996). Its hypotensive effect in human glaucoma patients was found to be similar to that of timolol and was not associated with any systemic side effects (Katrz, 1999). Current data indicate that brimonidine reduces IOP in human eyes by a dual mechanism, decreasing aqueous inflow and increasing uveoscleral outflow (Toris et al., 1995a). Ocular effects of single and multiple doses of topical 0.2% brimonidine was recently evaluated in glaucomatous beagles (Gelatt & MacK ay, 2002b). After application, a trend to reduction in IOP was observed but not at statistical significance (Gelatt & MacKay, 2002b). As a result, the authors advised to use brimonidine as additive therapy and not as monotherapy in glaucomatous dogs. Side effects observed with brimonidine treatment in dogs included miosis and decrease in heart (Gelatt & MacKay, 2002b). A survey conducted in a poison control center documented the clinical signs associated with ingestion of brimonidine ophthalmic solution by dogs (Welch & Richardson, 2002). Severe cardiovascular effects (hypotension, bradycardia) and central nervous system depression can ensue the ingestion of brimonidine, depending of the amount of drug ingested. Supportive care, as well as yohimbine or atipamezole as α2-antagonist, is helpful to reverse the signs of the toxicosis (Welch & Richardson, 2002).

Beta-Adrenergic Antagonists (Beta-Blockers)

Topical β-blockers have become the most widely used medications for the control of ocular hypertension in humans. In 1967, it was observed that propranolol caused a reduction in IOP after intravenous or topical administration. A number of other β-blockers used for cardiovascular disease (i.e., proctalo-l, oxprenolol, and atenolol) then were investigated as antiglaucoma agents, but adverse side effects limited their ocular use. It was not until 1977 that timolol was found to be a safe and effective agent for lowering IOP in human glaucoma patients. Since the drug was first marketed in 1978, levobunolol, betaxolol, metipranolol, and more recently, carteolol, have also been released as antiglaucoma medications. All but betaxolol are nonspecific β-blocking agents (i.e., they block both β1 and β2 receptors). Betaxolol is a β1-selective ophthal-mic β-blocker. Carteolol is the only compound which possesses intrinsic sympathetic activity when bound to the beta-adrenergic receptors (Frishman et al., 1994; Juzycz & Zimmerman, 1997; Zimmerman, 1993). Many investigations have convincingly demonstrated that topical β-blockers reduce IOP by decreasing formation of aqueous humor (Coakes & Brubaker, 1978; Helal et al., 1979; Liu et al., 1980; Vogh et al., 1989). A single drop of 0.5% timolol solution suppresses aqueous formation in the range of 13%-48% in normal human eyes (Coakes & Brubaker, 1978). In cat eyes, the rate of aqueous humor formation is reduced 28%, 56%, and 71% by 0.005%, 0.025%, and 0.15% intracameral injected timolol solution, respectively (Liu et al., 1980).

Topical 0.5% timolol given to normal rabbit eyes decreases aqueous flow by 35% as measured by sulfacetamide clearance from aqueous humor (Vogh et al., 1989). However, their mechanism of action is still uncertain, and three possibilities have been suggested: (1) they may block beta-receptors in the ciliary body processes; (2) they may inhibit active transport and ultrafiltration related to Na+/K+-adenosine triphosphatase (ATPase); or (3) they may act through a vasoactive mechanism. According to the classical view, β-blocking agents lower aqueous humor flow by altering the adrenergic neuronal control of aqueous humor formation by blockade of the β-receptors in the ciliary body processes (Frishman et al., 1994). β2-adrenergic receptors seem to be predominant in the ciliary body processes (Nathanson, 1981; Trope & Clark, 1982), and experimental findings indicate that β-adrenergic receptors mediating pressure changes in the anterior segment of the cat eye are predominantly β2 (Colasanti & Trotter, 1981). It has been postulated that occupation of the β-adrenoceptors of the
ciliary body epithelium inhibits the tonic influence of norepinephrine released by the sympathetic nerves, thereby inducing a decrease of cAMP levels in the ciliary body epithelium and hence a reduction of the secretory function of the ciliary body epithelium (Juzycz & Zimmerman, 1997). However, in vivo and in vitro findings indicated that the correlation between aqueous humor formation and ciliary body epithelial cAMP content was unclear and that β-blocking drugs might act through mechanisms unrelated to β-adrenergic blockade in the ciliary body epithelium (Boas et al., 1991; Shahidullah et al., 1995). Since plasma membrane ATPases of the ciliary body epithelium are involved in aqueous humor formation, the potential relationship between inhibition of ciliary ATPases and the IOP-lowering effect of the β-blockers was investigated. Studies provided support to a mechanism for β-adrenergic antagonist inhibition of ciliary Na⁺-K⁺-ATPase activity in vitro and in vivo (Rittenhouse & Pollack, 1999; Whikehart et al., 1992). At the opposite, other studies in rabbits demonstrated that neither Na⁺-K⁺-ATPase nor Mg²⁺-ATPase was inhibited by timolol, and showed that the IOP-lowering effect of the drug was related to a significant reduction of blood flow in the iris root-ciliary body, related to a significant reduction in dopamine concentrations in this tissue (Watanabe & Chiou, 1983). Beta-blockers have no effect on aqueous outflow (Juzycz & Zimmerman, 1997).

Topical timolol is available as a 0.25% and 0.50% solution of the maleate salt. In the United States, the drug is also supplied as a 0.25% and 0.50% hemihydrate salt, which has an ocular hypotensive effect similar to that of the maleate salt in humans (Bartlett et al., 2008). In 1993, timolol maleate became also available in an anionic heteropolysaccharide gellan gum (Gelrite), which gels in contact with the cations in the tear fluid. This in situ gel-forming formulation allows increased bioavailability and is administered once daily. Diverging results have been obtained in normotensive dogs after single and repeated instillation of 0.5% timolol maleate. In an early investigation, a mean reduction in IOP of 2.5 mmHg (16%) was observed within 2–4 hours postdosing (Wilkie & Latimer, 1991a), while in two other reports the 0.25% and 0.5% timolol formulations were found ineffective at reducing IOP in normal dogs (Gum et al., 1991b; Smith et al., 2010). In clinically healthy cats, a single application of 0.5% solution induced a mean reduction in IOP of 4.1 mmHg (22%), with the maximum IOP reduction occurring within 6–12 hours after instillation (Wilkie & Latimer, 1991a, 1991b). A contralateral decrease in IOP also occurred in nontreated eyes, both in dogs and cats (Wilkie & Latimer, 1991a, 1991b). A dose–response study of timolol maleate employing single- and multiple-drop instillations in glaucomatous (open-angle) beagles found that 0.25% and 0.5% timolol lowered IOP by approximately 4–5 mmHg (Gum et al., 1991b). A dose-related reduction in IOP was observed in normotensive dogs, with concentrations of 2%–8% (Gelatt et al., 1995). In eyes with open-angle glaucoma, decrease in IOP ranging from 8 to 14 mmHg was observed for up to 6 hours after administration of 4%, 6%, and 8% concentrations (Gelatt et al., 1995). Once-daily instillation of timolol maleate 0.5% gel-forming ophthalmic solution in healthy beagles was found to induce a mean reduction in IOP of 5.4 mmHg (Takiyama et al., 2006). The hypotensive effect persisted for 24 hours after the instillation (Takiyama et al., 2006). The effect of topical application of timolol on IOP has been evaluated in female horses with normotensive eyes (van der Woerd et al., 2000). A significant mean decrease of approximately 4–5 mmHg was observed 8 hours after single-dose application, and the pressure-lowering effect was present throughout the 5-day multiple-dose study with a maximum reduction in IOP of 27% (van der Woerd et al., 2000). No ocular side effects were noted with the exception of 11% reduction in the pupil size. These results indicate that timolol could be of benefit in the management of glaucoma in horses (van der Woerd et al., 2000).

In people, carteolol, metipranolol, and levobunolol have similar potency to that of timolol for decreasing IOP (approximately 20%–30%) (Zimmerman, 1993). The IOP-lowering effect of blockers in man is generally additive to that of the other antiglaucomatous agents, such as parasympathomimetics, epinephrine, and dipivefrin (Juzycz & Zimmerman, 1997). Typically, such combinations provide an additive effect by using two drugs that together affect aqueous inflow and outflow. For instance, pilocarpine is often used in combination with β-blockers. In glaucomatous beagles (open-angle), the response to either 4% or 6% timolol was enhanced by combination with 2% pilocarpine (Gelatt et al., 1995). When two topical antiglaucomatous medications are combined during the same dosing episode, at least 5 minutes should pass between applying the two formulations since coadministration reduces their ocular bioavailability. Pharmacokinetics data in rabbits demonstrate that when timolol is coadministered with either pilocarpine or epinephrine, its ocular absorption is reduced by 20%–70% (Lee et al., 1991). In people, the topical β-blockers are indicated in primary glaucoma (open-angle and closed-angle), many types of secondary glaucomas, and various conditions with ocular hypertension (Juzycz & Zimmerman, 1997; Zimmerman, 1993). They are also commonly used in small animal veterinary ophthalmology, although their effectiveness has never been documented by controlled clinical trials. Nevertheless, experimental data suggest that topical timolol could be potentially effective for controlling glaucoma when applied twice daily at a concentration of 0.5% in cats and at concentrations ranging from 4% to 8% in dogs. The latter are not available commercially and would probably induce systemic side effects. Combination of timolol and pilocarpine also may be useful in some glaucomatous dogs. As mentioned previously, topical 0.5% betaxolol is an alternative to demecarium bromide to prevent or delay the onset of hypertension in an eye predisposed to PCAG (Miller et al., 2000). The most common ocular side effect of topical β-blocking agents is local intolerance (i.e. stinging, burning) on ocular instillation (Juzycz & Zimmerman, 1997). Photophobia, ptosis, blepharoconjunctivitis, and superficial keratitis are other potential ocular side effects of these drugs (Juzycz & Zimmerman, 1997). Changes of the ocular surface observed
during treatment with timolol have been associated with a significant reduction in tear production and turnover (Shimazaki et al., 2000). It seems that carteolol has better ocular tolerability than the other compounds (Zimmerman, 1993). In human beings, topical timolol has minimal effect on pupillary diameter. On the contrary, significant reduction in the pupil size is observed in the canine and feline-treated eyes (Gelatt et al., 1995; Wilkie & Latimer, 1991a, 1991b). Reduction of pupillary diameter is more marked in cats than in dogs with a maximum duration of 1 week after treatment (Wilkie & Latimer, 1991a, 1991b). Timolol has been shown to be more toxic to regenerating corneal epithelium than levobunolol and betaxolol in rabbit eyes (Trope et al., 1988), and therefore may not be the drug of choice in animals with glaucoma and corneal epithelial defects. In people, topical β-blockers are contraindicated in patients with severe heart failure and bronchial asthma due to their potential cardiopulmonary adverse effects resulting from systemic absorption. It is possible that the partial agonist activity of carteolol may reduce its cardiopulmonary and bronchopulmonary adverse effects by lessening systemic β-blockade effect (Frischman et al., 1994; Zimmerman, 1993). Significant decrease in pulse rate was observed in normotensive and glaucomatous beagles treated with topical timolol at concentrations ranging from 2% to 8% (Gelatt et al., 1995; Gum et al., 1991b). A contralateral effect on IOP and pupillary diameter was also identified in the nontreated eyes when timolol was topically given to dogs and cats (Wilkie & Latimer, 1991a, 1991b). These effects likely result from systemic uptake via transconjunctival route and nasolacrimal duct pathway. A systemic activity of topically applied timolol has been demonstrated in an experimental dog model (Svec & Strosberg, 1986). To prevent occurrence of deleterious cardiovascular effects secondary to systemic absorption, suggestion of using 0.25% timolol in cats as well as dogs weighing less than 20lbs, and 0.5% timolol in dogs with body weight above 25lbs, is given in the literature (Willis, 2004).

Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors (CAIs) that belong to the class of nonbacteriostatic sulfonamide-related compounds were used in ophthalmology as early as 1954 with the introduction of acetazolamide. Methazolamide and dichlorphenamide were released subsequently. These agents have been widely used ever since, but as their clinical usefulness is limited by various systemic side effects, topical CAIs have been developed in the last decade.

Mechanism of Action

The ciliary body process epithelium contains enzyme systems, such as NA,K-ATPase and carbonic anhydrase, that are involved in aqueous humor formation. Carbonic anhydrase is a ubiquitous enzyme for which seven isoenzymes have been identified. CA I, CA II, CA III are located in the cytosol, CA IV is membrane bound, CA V is present in mitochondria, and CA VI and CA VII are only found in salivary glands (Jampel et al., 1997). Only CA II, CA III, and CA IV are present in significant amounts in pigmented and nonpigmented ciliary body epithelial cells to catalyze the reversible hydration of carbon dioxide (Jampel et al., 1997). Aqueous humor formation depends on the production of bicarbonate (HCO₃⁻) from CA II, the isoenzyme found in the nonpigmented ciliary body epithelium. Chemically, the enzymatic effect of carbonic anhydrase is to catalyze carbon dioxide (CO₂) hydration to carbonic acid (H₂CO₃) which dissociates spontaneously into protons and bicarbonate ions according to the equation:

\[ \text{H}_2\text{O} + \text{CO}_2 \leftrightarrow \text{HCO}_3^- + \text{H}^+ \]

Newly formed bicarbonate ions are neutralized by sodium and other cations and transferred to the intercellular channels and the posterior chamber (Fig. 19.28). Water is then osmotically attracted from the vessels of the ciliary stroma to aqueous humor formation (Derick, 1994).

**Figure 19.28.** Contribution of carbonic anhydrase to aqueous humor formation in the pigmented and nonpigmented ciliary body epithelium.
aqueous flow from 9 μL/min prior treatment to 6.4 μL/min after treatment (Friedland & Maren, 1984). In general, sulphonamide CAIs inhibit the enzyme with high specificity, meaning that they have no inhibitory activity against other enzymes, and in a noncompetitive and reversible manner.

Although systemic CAIs are diuretics, it is currently believed that their ocular hypotensive effect does not depend on diuresis. There is, however, some indication that the systemic acidoses induced by these agents also inhibits aqueous humor formation and enhances their pressure-lowering effect (Friedland & Maren, 1984). In addition to their IOP-lowering effect, CAIs have also been shown to affect the ocular circulation. Carbon dioxide is a potent vasodilator involved in autoregulation of blood flow in the eye and elsewhere in the body. Blockade of carbonic anhydrase in local tissues by CAIs results in increased levels of CO₂ and/or lower tissue pH that can act on blood vessels and produce vascular dilation and increased blood flow (Rassam et al., 1993; Taki et al., 1999).

However, the recent observation that the vasodilation induced by these drugs on retinal arterioles is increased by the perivascular retinal tissue, by acidosis, but not by hypercapnia, suggest that mechanisms other than carbonic anhydrase inhibition might also be involved in the vasodilating effect of CAIs, although a contributing action of the enzyme cannot be excluded (Torringer et al., 2009). According to the authors, alternative mechanisms of action could include an effect through voltage-gated K⁺ channels or an effect mediated by NO (Torringer et al., 2009). An increase in ocular blood flow in the retinal circulation has been demonstrated in human eyes following application of topical CAIs, and is expected to be beneficial to patients with glaucoma (Siesky et al., 2009). In rabbits, acute topical dorzolamide vasodilates the ciliary body circulation, increasing ciliary blood flow by 18%, but does not alter the choroidal hemodynamics (Reitsamer et al., 2009). This mechanism is in contrast with those of drugs that decrease aqueous formation indirectly by constricting the ciliary body circulation (i.e., epinephrine, β-blockers) (Reitsamer et al., 2009).

Systemic Carbonic Anhydrase Inhibitors

A cetazolamide, the first drug in this group to be synthesized, can be administered either orally or intravenously. It is supplied in tablets of 125 and 500 mg as well as in time-release capsules of 500 mg. A single oral administration of a dose ranging from 10 to 75 mg/kg significantly lowers IOP in normotensive and glaucomatous beagles for at least 8 hours (Gelatt et al., 1979). A dosage of 4–8 mg/kg two to three times daily is usually recommended for treatment of canine glaucoma (Gaarder, 2000). In the cat, doses ranging from 10 to 25 mg/kg are effective in lowering the IOP in glaucomatous animals. The hypotensive effect lasts about 5 hours (Othman & Samy, 1987). A cetazolamide is also available for intravenous injection as a lyophilized powder (500 mg/vial). Intravenous acetazolamide at a dose of 5–10 mg/kg is useful as adjunctive therapy in the management of acute glaucoma.

Dichlorphenamide has been withdrawn from the market, but is available as generic forms in the United States. The oral dose rate in the dog ranges from 2 to 4 mg/kg, two to three times daily (Gaarder, 2000). In glaucomatous beagles, the maximal effect occurs at a dose of 10 mg/kg, 3 hours after administration (Gelatt et al., 1979). Single oral administration of dichlorphenamide in the cat in doses ranging from 0.5 to 2 mg/kg significantly reduced IOP for 4 hours (Othman & Samy, 1987).

Methazolamide is supplied in 50-mg tablets. After oral administration of 25 or 50 mg methazolamide to healthy beagle dogs, a significant IOP decrease of 18%–21% was observed 3–6 hours after administration depending on the dose, but thereafter, IOP increased to levels above the control baseline values (Skorobohach et al., 2003). The lowering effect on IOP was accounted for by a mean 28% reduction in aqueous humor formation (Skorobohach et al., 2003). The rebound effect was ascribed to a possible upregulation of CA after treatment ceased, and it should be kept in mind in clinical setting when administration of methazolamide is stopped (Skorobohach et al., 2003). In a study of the systemic CAIs in normal and glaucomatous dogs, results suggested that methazolamide decreases IOP at dosage levels lower than acetazolamide, dichlorphenamide, and ethoxzolamide (Gelatt et al., 1979). In glaucomatous dogs, the IOP decreasing effect of oral methazolamide (5 mg/kg twice daily) was comparable to that achieved with topical dorzolamide instilled twice of three times daily (Gelatt & MacKay, 2001b). When coadministered, the drugs did not produce an additional reduction in IOP (Gelatt & MacKay, 2001b).

Topical Carbonic Anhydrase Inhibitors

Systemic complications associated with chronic use of oral CAIs in man inspired many attempts at developing formulations that would allow for topical administration of CAIs. In the last 15 years, a large number of studies have focused on the development of topical CAIs as potent as systemic agents and with fewer systemic adverse effects. Dorzolamide was the first of these drugs to be marketed in 1995, and brinzolamide was launched on the market a few years later. The history of the design and development of the topical CAIs has been extensively reviewed (De Santis, 2000; Higginbotham, 1989; Kass, 1989).

Dorzolamide and brinzolamide are most potent against CA II, with less activity against CA IV (De Santis, 2000; Maren et al., 1997). Experimental data in rabbits indicate that topical dorzolamide and brinzolamide readily penetrate the eye by both the corneal and scleral routes (Maren et al., 1997; De Santis, 2000). After topical application on canine eyes, the dorzolamide concentrations achieved in the ciliary body were much higher than those reached in the aqueous humor, suggesting that in the dog, the cornea/scleral route has also a role in the intraocular penetration of the drug (Cawrse et al., 2001). In healthy dogs, administration of a single dose of 2% dorzolamide was associated with a mean reduction in IOP of
Topical dorzolamide was also found to lower IOP when applied to normotensive feline eyes every 12 hours (Rainbow & Dziezyc, 2003). The amplitude of IOP decrease observed in cats after twice daily applications of dorzolamide was almost the same as that observed previously in dogs with three times daily applications (Cawrse et al., 2001; Rainbow & Dziezyc, 2003).

Topical dorzolamide seems to influence IOP in horses less than it does in small animals, since its twice daily application to normotensive equine eyes only reduced IOP by an average of 2 mmHg (Willis et al., 2001b). At the light of these findings, the authors’ suggestion was that topical dorzolamide can only be recommended as adjunctive therapy in glaucomatous horses.

The effect of topical administration of 1% brinzolamide on the IOP has been evaluated in small and large animals. In a preliminary study in healthy dogs, 1% brinzolamide instilled twice a day (i.e., every 12 hours) significantly reduced IOP with the peak effect observed between 5 and 6 hours post medication. The amplitude of the IOP reduction was similar to that induced by topical dorzolamide, but lower than that resulting from oral administration of 5 mg/kg of methazolamide (Whelan et al., 1997). Mean IOP returned to baseline value about 10−11 hours following treatment, indicating that administration every 8 hours would be more appropriate than every 12 hours for optimal pharmacologic effect (Whelan et al., 1997). Contrary to dorzolamide, brinzolamide topically applied every 12 hours was unable to significantly influence IOP of normotensive feline eyes (Gray et al., 2003). Possible reasons for this unexpected result might include the small population sample, the method of drug administration (privately owned cats medicated by their owners), the drug concentration, and frequency of administration (Gray et al., 2003). Further studies using three time-daily administrations would be warranted to assess if this dosage regimen would be effective to reduce IOP in feline eyes. In horses, topical application of 1% dorzolamide was well tolerated, and the mean IOP reduction achieved with once- and twice-daily administration was 3.1 mmHg and 5.0 mmHg, respectively (Germann et al., 2008), which represents a higher IOP-lowering effect than that previously reported with dorzolamide in equine patients (Willis et al., 2001b). This finding seems to indicate that monotherapy or adjunctive therapy with 1% brinzolamide may represent a valuable option for the treatment of equine glaucoma (Germann et al., 2008).

Clinical Use

Because they diminish aqueous humor formation, CAIs can be employed in the treatment of practically all types of glaucoma. Short-term administration of systemic or topical CAIs may be effective in the management of acute increases in IOP resulting from primary or secondary glaucoma. On the basis of findings in normal and glaucomatous dogs, combined administration of topical and systemic CAI has no additional IOP-decreasing effects over dorzolamide or brinzolamide alone that would warrant its use in dogs with acute glaucoma (Dziezyc, 2003). Further studies using three time-daily administrations of drugs might be warranted to assess if this dosage regimen would be effective to reduce IOP in equine eyes. In horses, topical and systemic CAIs are less likely (Gelatt & MacKay, 2001b; Whelan et al., 1997). Theoretically, CAIs can be used in combination with other antiglaucoma agents as their effect is usually additive, reducing IOP more than any single agent. In the dog, the combined use of dorzolamide and latanoprost may be appropriate for the management of chronic glaucoma, since dorzolamide given every 8 hours and latanoprost instilled once in the morning were demonstrated to have an additive effect on decreasing IOP (Kennard & Whelan, 2001). The additivity of topical CAIs to topical β-blockers regarding the decrease in aqueous humor outflow has also been documented in normotensive human eyes. In healthy eyes, 18% and 47% reduction in aqueous flow is observed following topical combination treatment with dorzolamide and timolol, respectively. Topical administration of unfixed combination of both drugs leads to an incremental 55% decrease flow (Wayman et al., 1997). A fixed combination of 2% dorzolamide and 0.5% timolol is currently available. Its administration twice daily in glaucomatous human patients has an IOP-lowering effect similar to that obtained with dorzolamide alone instilled three times daily (Hutzelmann et al., 1998). In glaucomatous beagles, the combination product has been compared with monotherapy with either 0.5% timolol or 2% dorzolamide three times daily. After 4 days of treatment, the mean reduction in IOP was −7.50 mmHg, −3.75 mmHg, and −8.40 mmHg for the dorzolamide, timolol, and combination product, respectively (Plummer et al., 2006). Thus, the fixed combination of dorzolamide-timolol seems more effective at decreasing the IOP in dogs with glaucoma than is either dorzolamide or timolol alone (Plummer et al., 2006). By contrast, data indicate that in horses this combination may not have additional IOP-lowering effects over dorzolamide alone (Willis et al., 2001b).
bances (anorexia, vomiting, diarrhea), and possibly, increased respiratory rate secondary to metabolic acidosis. Cats appear to be more susceptible to these drugs and should be observed very closely. The dose should be decreased or therapy discontinued if signs of toxicity are observed. Except for acetazolamide, little is known about either the short- or long-term effects of the other CAIs on blood chemistry in the dog. In this species, the intravenous and oral administrations of acetazolamide were found to cause significant metabolic acidosis that achieved a steady state after 1–5 days of treatment (Haskins et al., 1981; Rose & Carter, 1979). This effect, attributed to increased bicarbonaturia, was associated with an increase in PO₂, and a decrease in PCO₂, indicative of compensatory hyperventilation. All dogs given acetazolamide had an increase in plasma chloride. A decrease in plasma potassium also develops, reaching its maximum between the second and fifth day of treatment, presumably as a result of increased kaliuresis. Normal food intake usually obviates any serious potassium depletion, but care must be taken in patients with anorexia or preexisting hypokalemia (Haskins et al., 1981; Rose & Carter, 1979). When acetazolamide administration is discontinued, complete recovery of acid-base and blood electrolyte disorders occurs within 36 hours, because of the short half-life of the drug (Haskins et al., 1981). The ophthalmic formulation of 2% dorzolamide has a pH of 5.6, and its instillation may be associated with symptoms of ocular discomfort (i.e., burning, stinging) on instillation in people (Strahlman et al., 1996). By comparison, 1% brinzolamide is formulated as an ocular suspension with a pH of 7.5 which compares favorably to the pH of the tear fluid, and is better tolerated by human patients (Silver & The Brinzolamide Comfort Study Group, 2000). In dogs, topical administration of 2% dorzolamide has been associated with blepharitis which resolved following discontinuation of the drug (Willis et al., 2002). In short-term studies of topical CAIs in the dog, cat, and horse, no local or systemic side effects were reported (Cawrse et al., 2001; Rainbow & Dziezyc, 2003; Willis et al., 2001b). Moreover, the topical CAIs have the advantage over parasympathomimetics and prostaglandin analogs of not causing miosis, and they have the advantage over β-blockers to be less problematic for animals with cardiac or pulmonary disease.

Prostaglandin Analogues

History and Chemistry

The prostaglandins (PGs) are a family of biologically active lipids with a wide spectrum of possible pharmacologic activity. Since early studies showed that low doses of PGF₂α can decrease IOP, it has been established that most of the naturally occurring PGs, as well as some of their analogues and esters, are potent ocular hypotensive agents in both animals and humans (Alm, 1998; Bito, 1984). The PG derivatives currently approved for the reduction of IOP in humans and animals were all developed through chemical modification of PGF₂α. Latanoprost and isopropyl unoprostone first emerged as a result of active screening programs. Unoprostone was available in Japan in 1994, and was marketed in 2000 in the United States. It is presently seldom used because it has limited efficacy compared with the other PG analogues (Bean & Camras, 2008). Latanoprost was marketed in 1996, and then two other PG analogues, travoprost and bimatoprost, were approved for use in 2001 (Bean & Camras, 2008; Bito, 1984, 1986). They are instilled as ophthalmic solutions, and it was demonstrated that the latanoprost 0.005% solution remains stable at room temperature for up to 6 weeks (Varma et al., 2006). As the naturally occurring PGs are hydrophilic molecules due to their carboxylic acid moiety and several hydroxyl groups, they penetrate the membranes poorly. Thereby, all the commercially available PG analogues used for their IOP-lowering activity are esterified prodrugs of the PGF₂α, more lipophilic, and designed to facilitate penetration through the ocular membranes (Bean & Camras, 2008). Latanoprost is the right-handed epimer of a phenyl-substituted analogue of PGF₂α, while unoprostone is an isopropyl ester of the 20-ethyl derivative of PGF₂α. Travoprost and bimatoprost are structurally similar to other PGF₂α analogues (Fig. 19.29) (Eisenberg et al., 2002). After topical application, the prodrug is enzymatically hydrolyzed during its passage through the corneal epithelium to release the active molecule (the carboxylic acid) which is then delivered to the anterior segment of the eye (Bito, 1986; Bito & Baroody, 1987). The major intracocular metabolite that is expected to act on target tissues is 17-phenyl-PGF₂α for latanoprost, bimatoprost, and travoprost (Bito & Baroody, 1987; Davies et al., 2003), and a free acid of isopropyl unoprostone for unoprostone (Numaga et al., 2005). It has been established that human and canine ocular...
tissues have a similar profile of PGF$_{2\alpha}$ prodrug hydrolysis (Woodward et al., 1996).

**Mechanism of Action**

A common feature of the biologically active forms of latanoprost, bimatoprost, travoprost, and unoprostone is the high affinity and selectivity for the prostanooid FP receptors, and investigation revealed that the IOP-lowering action of these PG derivatives is mediated through the binding of their free acid (the active molecule) to FP receptors in humans (A nthony et al., 1996), monkeys (Lee et al., 1994b), and presumably in dogs (Gum et al., 1991a). Despite their differences in potency at the FP receptor, the free acids of latanoprost, travoprost, and bimatoprost fully activate the receptor relative to the natural occurring PGF$_{2\alpha}$ (Bean & Camras, 2008). The pivotal role of FP receptors in the ocular hypotensive effects of the PGF$_{2\alpha}$ analogs has also been demonstrated with the use of FP-receptor deficient (FPKO) mice (Ota et al., 2005). The IOP-lowering action of PGs in the feline species reportedly works through EP$_1$ receptors and not FP ones (Bhattacherjee et al., 1999; Lee et al., 1984b). In the dog, EP receptors mediating PGE$_2$ action also can alter aqueous humor dynamics as demonstrated with a potent and selective EP4-PGE$_2$ agonist which was able to lower IOP by 5–7 mmHg in healthy beagles when given topically (A guirre et al., 2009). The mechanism by which this EP4-receptor agonist lowers IOP is currently unknown but may involve trabecular outflow and not uveoscleral outflow (A guirre et al., 2009).

In man and animal species studied so far, it has been well established that increase in uveoscleral outflow is the primary mechanism by which PGs reduce IOP (Hurwitz et al., 1991). Increased uveoscleral outflow has been reported in humans, monkeys, rabbits, and dogs treated with PGF$_{2\alpha}$ or its analogues (Gabelt & Kaufman, 1990; Gum et al., 1991a; Payer et al., 1992; Toris et al., 1993), and in cats treated with PGA$_2$ (Toris et al., 1995c). However, data in the current literature indicate that latanoprost, bimatoprost, and unoprostone also affect the pressure-dependent conventional outflow pathway (Taniguchi et al., 1998; Richter et al., 2003). The mechanisms by which activation of FP receptors lead to an increased uveoscleral outflow are still under investigation, but there is scientific evidence that MMP-mediated remodeling of the ECM of the ciliary body muscle contribute to this pharmacological effect. This concept is based on in vitro and in vivo observations that after several days of treatment with PGF$_{2\alpha}$, the MMP-1, -2, and -3 are increased within uveoscleral outflow tissues (Gaton et al., 2001; Weinreb et al., 1997), while collagen types I, III, and IV are decreased (Sagara et al., 1999). In human ciliary body tissue, the transcription of the genes for MMP-3 and -17 is increased after topical treatment with latanoprost (Oh et al., 2006). MMP-9 is also present and may contribute to the ECM changes, while tissue inhibitor of metalloproteinase 3 (TIMP-3) is upregulated and may compensate for the increase in MMPs (Oh et al., 2006). The amount of myocilin, an intra- and extracellular protein of the ciliary body muscle which may contribute to outflow resistance also is reduced after topical PGF$_{2\alpha}$ treatment (Lindsey et al., 2001, 2002). Ultrastructurally, remodeling of ECM components within uveoscleral outflow pathway was characterized as lysis of ECM between ciliary body muscle bundles and widening of the intermuscular spaces in monkey eyes treated with PGF$_{2\alpha}$ (Lütjen-Drecoll & Tamm, 1988), latanoprost, or bimatoprost (Richter et al., 2003). In addition to the changes induced within the uveoscleral outflow pathway, various experimental data argue for an effect of PG analogs on alteration of aqueous outflow through the trabecular meshwork. Among these are the identification of FP receptors in human trabecular meshwork and increased expression of different MMPs and TIMPs by trabecular meshwork cells in culture treated with latanoprost (Toris et al., 2008). Long-term treatment with latanoprost or bimatoprost also led to morphologic changes in the trabecular meshwork perhaps in agreement with increased conventional outflow facility (Richter et al., 2003). Increase in both uveoscleral and trabecular outflow has been observed in monkeys given topical tafuroprost, the new fluoroprostaglandin F$_{2\alpha}$ (Takagi et al., 2004). If stimulated induction of MMPs within the ciliary body muscles is the most thoroughly understood effect of PG treatment, it also appears certain that endogenous PGs are released in iris and ciliary body muscles secondarily to topical administration of PGF$_{2\alpha}$ analogues and may contribute to the observed hypotensive effects (Yousufzai et al., 1996). Endogenous PGE$_2$, PGD$_2$, PGF$_{2\alpha}$ are produced via phospholipase A2 stimulation and release of arachidonic acid for PG synthesis (Yousufzai et al., 1996; Toris et al. 2008). Inhibition of the latanoprost-induced reduction of IOP in humans by ophthalmic NSAID bromfenac, (Chibac et al., 2006), and in dogs by topical prednisolone and flurbiprofen (Pirie et al., 2006, 2011) suggest that the IOP-lowering response to topical latanoprost is mediated in part through formation of endogenous PGs both in men and dogs. In what manner the endogenous released PGs act to alter aqueous outflow is unclear. Widening of the connective tissue-filled spaces among the ciliary muscle bundles, caused by relaxation of the ciliary muscle, and with subsequent reduction in outflow resistance via the uveoscleral pathway, has been suggested as responsible for the reduction in IOP induced by PGE$_2$ (Poyer et al., 1995). Investigations demonstrated that scleral permeability is enhanced with exposure to PGs or PG analogues, such as latanoprost (Aihara et al., 2001; Kim et al., 2001), and that these changes are associated with increased intrascleral MMP-1, MMP-2, and MMP-14 expression (Lindsey et al., 2007). PG-induced changes in the sclera also may be important in the regulation of the uveoscleral outflow (Toris et al., 2008), and suggest that the prospect of increasing transcleral permeability by PG cotreatment might allow sufficient transcleral transport to provide delivery of high-molecular-weight substances to the posterior segment of the eye (Aihara et al., 2001; Kim et al., 2001).

Experiments in humans, monkeys, and rabbits indicate that in addition to its IOP-reducing effect, latanoprost increases blood velocity in the ONH or dilates the vessels supplying the
In normotensive canine eyes, 0.005% latanoprost instilled in the evening, morning, as well as twice daily induced an average decline in IOP of about 25%, while in glaucomatous eyes, it produced a mean decline in IOP of about 50% (Gelatt & MacKay, 2001a; Studer et al., 2000). In glaucomatous dogs, a comparable IOP-lowering action was observed with once or twice daily application of 0.03% bimatoprost (Gelatt & MacKay, 2002b) (Fig. 19.30), and 0.004% travoprost (Gelatt & MacKay, 2004c). In normal dogs, the ONH because of its pharmacologic effect on the vessels (Ishii et al., 2001). Increased nerve head perfusion may be important for preservation of visual function in glaucomatous eyes.

**Clinical Pharmacology**

Experimental studies have demonstrated that topical application of 0.005% latanoprost significantly reduces IOP in normotensive and glaucomatous canine eyes (Studer et al., 2000).
amplitude and duration of the IOP-lowering effect of a single application of 0.12% unoprostone isopropyl were found to be similar with those observed after a single application of 0.005% latanoprost (Gelatt & MacKay, 2002a; Ofri et al., 2000). By contrast, neither once daily application of 0.005% latanoprost (Studer et al., 2000), and 0.03% bimatoprost (Bartoe et al., 2005), nor twice daily applications of 0.03% bimatoprost (Regnier et al., 2006), and 0.12% unoprostone (Bartoe et al., 2005) significantly lowered the IOP of normal cats. These observations are in agreement with the fact that FP receptor signaling does not play a crucial role in the IOP response to PGs or PG analogues in cats (Bhattacherjee et al., 1999; Lee et al., 1984b).

The potential of 0.005% latanoprost for lowering IOP has also been evaluated in normotensive equine eyes (Willis et al., 2001a). In clinically normal horse, a once daily application of 0.005% latanoprost resulted in a mean decrease in IOP of 20 mmHg or about 5% in males, and 30 mmHg or about 17% in females (Willis et al., 2001a). The reason for the gender effect in the response of the equine eye to topical 0.005% latanoprost has not been determined (Willis et al., 2001a).

Clinical Use

In a short time, PG derivatives have reached extensive clinical use in human beings with ocular hypertension and POAG (Soltau, 2002). Several studies documented their IOP-lowering effect in people, but latanoprost has mostly been evaluated as either monotherapy or an adjunctive agent added to another antiglaucoma agent (Alm, 1998). In patients with either ocular hypertension or POAG, latanoprost, bimatoprost, and travoprost administered once daily in the evening induce a higher reduction in IOP than 0.5% timolol applied twice daily (Alm & Stjernschantz, 1995; Mishima et al., 1996; Sherwood & Brandt, 2001). Latanoprost twice daily is less effective than once daily in human glaucoma patients (Lindén & Alm, 1998). This reduction of efficacy possibly may result either from desensitization or downregulation of the FP-receptor with twice daily administrations (Lindén & Alm, 1998). In glaucomatous people who are no longer regulated on one antiglaucomatous drug alone, a combination of two drugs is common. In addition to their use as monotherapy, PGF2α-related drugs became first-line prescriptions as combination therapies in humans because about half of the patients require more than one antiglaucoma agent for IOP reduction (Bean & Camras, 2008). Beta-blockers, topical CAIs, and alpha-adrenergic agonists are the most common antiglaucoma agents used in addition to PGs analogues in glaucomatous humans (Tabet et al., 2008). Three fixed combinations of timolol 0.5% with either latanoprost 0.005%, travoprost 0.004%, or bimatoprost 0.03% have been evaluated in humans with primary glaucoma, and almost all published data indicate that each fixed combination has a greater IOP-lowering effect than the monotherapy with either timolol or the PG analogue (Tabet et al., 2008). Used in unfixed combinations, latanoprost proved efficacious when added either to timolol or pilocarpine (Stewart et al., 2000; Toris et al., 2001). When added to beta-blockers, latanoprost compared favorably in IOP-lowering efficacy and was similar in safety to brimonidine and dorzolamide (Stewart et al., 2000). In the dog, the PG derivatives are mostly indicated for the treatment of primary glaucoma, and may replace mannitol and/or acetazolamide as first-line drugs in the emergency management of acute closed-angle primary glaucoma (Willis, 2004).

Investigations using high resolution imaging of the anterior segment of dogs with primary glaucoma suggested that latanoprost may rapidly lower IOP in PCAG by inducing miosis which breaks the pupillary block, and by opening the collapsed ciliary cleft in POAG (Miller et al., 2003). Topically applied to normotensive canine eye, the latanoprost 0.005%-timolol 0.5% fixed combination caused the IOP to decrease by 1–2 mmHg more than the decrease for latanoprost alone, while no ocular hypotensive effect was observed with 0.5% timolol alone (Smith et al., 2010). Although latanoprost, bimatoprost, and travoprost are instilled once daily in humans, experimental data in glaucomatous dogs suggest that twice daily instillation of these drugs should be recommended in the dog to result in less daily IOP fluctuations (Gelatt & MacKay, 2002b, 2004c). Latanoprost instilled immediately after phacoemulsification in dogs was found to have no significant effect on the number of POH peaks compared with control untreated dogs (Crasta et al., 2010). Primary or secondary intraocular inflammation is often associated with glaucoma in dogs, and therefore ophthalmic anti-inflammatory drugs sometimes are administered concurrently to antiglaucoma agents. As mentioned in a previous section, topical prednisolone and flurbiprofen were shown to significantly inhibit the IOP-lowering effect of latanoprost in dogs (Pirie et al., 2006, 2011). This potential interaction should be taken into account when prescribing ophthalmic anti-inflammatory drugs to glaucomatous dogs treated with PGF2α-related agents.

Side Effects

Side effects most commonly encountered in glaucomatous human eyes treated with PGF2α analogues include conjunctival hyperemia, iris darkening, and eyelash changes (Alm et al., 2008). The secondary effects of elongation and thickening of the human eyelashes after latanoprost therapy has resulted in a new commercial use for this drug in man. Current evidence indicates that these represent only cosmetic concerns with no apparent consequences (Alm et al., 2008). Other potential and relatively rare complications of this therapy include cystoid macular edema, anterior uveitis, iris cysts, herpes simplex reactivation, periocular skin darkening, and headaches (Alm et al., 2008; Schumer et al., 2002). Several PG derivatives used for the treatment of glaucoma cause increased pigmentation of the iris in man, but most of the data have been obtained with latanoprost (Sjörmanschantz et al., 2002). Increased iris pigmentation was observed in about 5% of the patients during 2 years of treatment with latanoprost, and it appeared that
individuals with hazel or heterochromic eye color were at risk of developing this side effect (Stjernschantz et al., 2002). As PGF$_2\alpha$ analogues are selective agonists of FP receptors, it is likely that FP receptor activation is involved in this phenomenon. Results of different studies suggested that latanoprost can stimulate tyrosinase gene transcription in the iris (Lindsey et al., 2001), and that latanoprost-induced melanogenesis most likely results from stimulation of iridal melanogenesis rather than melanocyte proliferation (Alm & Stjernschantz, 1995; Stjernschantz et al., 2002). Endogenous PGE$_2$ produced by iridal melanocytes exposed to latanoprost might also contribute to the increased melanogenesis (Bergh et al., 2002). Iris darkening in humans has raised concerns about the possibility of development of precancerous lesions or pigmentary glaucoma in some individuals, but presently no evidence of harmful consequences of this phenomenon has been reported (Grierson et al., 2002; Stjernschantz et al., 2002). In addition, a recent study showed that there are no histopathological features suggesting premalignant changes in human latanoprost-treated darkened irides (Aibert et al., 2008). Darkening of the latanoprost-treated irides is associated with a thickening of the anterior border layer and an increased amount of melanin in this layer and within the stromal keratocytes (Aibert et al., 2008). As reported in humans, conjunctival hyperemia has been observed in dogs treated with latanoprost (Studer et al., 2000), which also induced epiphora, blepharospasm, and blepharedema when instilled in equine eyes (Willis et al., 2001a). The mechanism behind the vaso-dilation of the conjunctival vessels predominantly seems to involve NO release (Alm et al., 2008). Decreased stromal collagen density has been identified in latanoprost-treated conjunctival specimens by histopathologic evaluation (Terai et al., 2008). This reduction in the ECM of the conjunctival stroma might result from marked upregulation of MMP-2, MMP-3, and MMP-9 along with a decrease in TIMP-1 in epithelial cells and on the ocular surface as observed in eyes treated with latanoprost (Honda et al., 2010; Terai et al., 2008). This MMP enhancement observed in the conjunctival matrix and at the ocular surface was said to potentially have a favorable effect on the outcome of glaucoma filtering surgery by decreasing the risk of local fibrosis (Terai et al., 2008), but at the opposite, it also may have the disadvantage to contribute to lysis of the corneal stroma (Honda et al., 2010). For the latter reason, use of topical latanoprost is not recommended in human patients with keratoconus or after laser-assisted in situ keratomileusis (Honda et al., 2010), and by extension should be used with great care in glaucomatous dogs with corneal defects.

A moderate to marked miosis is usually present in dogs treated with the PGF$_2\alpha$ derivatives (Gerlett & MacKay, 2001b, 2002b; Studer et al., 2000). The pupillary constriction is more limited when the drug is instilled only in the evening (Gerlett & MacKay, 2001a, 2001b, 2002b; Gerlett & MacKay 2002b). The occurrence of miosis reflects the sensitivity of the canine iridal sphincter muscle to the PGF$_2\alpha$, which appears to act directly rather than through the release of adrenergic neu-rotransmitters (Yoshitomi & Ito, 1988). Reports have also described miosis in cats and horses receiving latanoprost (Studer et al., 2000; Willis et al., 2001a), as well as in cats treated with bimatoprost (Regnier et al., 2006). A consequence of the miotic effect of PGs derivatives in companion animals is their contraindication in glaucoma secondary to subluxation or anterior luxation of the lens, because of the potential pupillary block that may result from vitreous entrapment (Willis, 2004). Prostaglandins at high concentrations are well-known to induce breakdown of the B A B (Alm et al., 2008). Although PG analogues developed for glaucoma treatment are used at very low concentrations, they retain the potency to enhance BAB breakdown. An experimental study with topical latanoprost showed a significant enhancement in BAB disruption in healthy dogs, compared with topical treatment with a fixed 0.5% timolol-2% dorzolamide combination (Johnsen-McLean et al., 2008). For this reason, PG derivatives should be used cautiously in glaucomatous dogs with intraocular inflammation (Seki et al., 2005), and also in aphake or pseudophake subjects because they may increase the existing BAB breakdown in these subjects (Arcieri et al., 2005). Although anterior uveitis is a rare but real potential side effect in human patients treated with topical PG analogues (Alm et al., 2008), recent clinical data observed in human patients with uveitis indicate that there is no significant difference in the frequency of anterior uveitis between the patients treated with PG analogues and those treated with non-PG agents (Chang et al., 2008). Nevertheless, because most horses with secondary glaucoma appear to be at risk for recurrent uveitis, PG analogues are considered to have the potential to exacerbate the inflammatory process and should be used with caution in these animals (Willis et al., 2001a).

### Osmotic Agents

Osmotic agents are another group of antiglaucoma drugs. They are almost always used in combination with other drugs and usually for very short-term. They are most often administered in the therapy of high pressure glaucoma.

### Mechanism of Action

After oral or intravenous administration, osmotic agents (also called hyperosmotic agents) are distributed in the extracellular fluids (primarily plasma), thereby contributing to a substantial increase in their osmolality. This increase creates an osmotic gradient in which the extracellular fluids are hypertonic to intraocular fluids (i.e., aqueous and vitreous humors), from which they are separated by semipermeable membranes (i.e., blood-aqueous and blood-vitreous barriers). This osmotic gradient favors the diffusion of water from the intraocular fluids back into the plasma (Craig, 1994; Dugan et al., 1989). This fluid shift has two effects on the eye. First, it inhibits the ultrafiltration process that contributes to aqueous humor formation, and second, it reduces the volume of the vitreous body. Shrinkage of the vitreous displaces the iris-lens plane...
posteriorly and subsequently opens the iridocorneal angle, allowing for better drainage (Gwin, 1980). As a final result, IOP is reduced. For the pharmacologic effects of osmotic agents to occur, they should not cross the blood-aqueous and blood-vitreous barriers. If for any reason the integrity of either barrier is compromised, as in ocular inflammation, the osmotic agent may leak in the intraocular fluids, and the extent of osmosis as well as of ocular hypotension will be reduced (Brooks, 1990). Because of its large molecular weight, mannitol penetrates in the eye less than other osmotic agents in presence of ocular inflammation (Singh & Krupin, 1997). Other factors important in the establishment of an adequate osmotic gradient between plasma and intraocular fluids include the dosage of the drug, its molecular weight, and its systemic bioavailability (rate of absorption for oral route and rate of elimination). Water deprivation for up to 4 hours following the use of an osmotic agent will reduce the extracellular fluid volume and will enhance the increase in blood osmolality and the resulting hypotensive ocular effect (Craig, 1994).

**Products Available**

Mannitol, a six-carbon sugar, is poorly absorbed from the gastrointestinal tract and must, therefore, be administered intravenously. It is available in concentrations of 5%–25%, but the 20% solution is most often used in ophthalmology (Craig, 1994). The dose for the lowering of IOP in dogs ranges from 1 to 2 g per kilogram, infused over a period of 20–30 minutes (Gwin, 1980; Lorimer et al., 1989). To increase the effectiveness of the drug, one fifth of the total dose can be administered rapidly over the first 2–5 minutes (Gwin, 1980).

Following intravenous administration of 1.5 g/kg mannitol, IOP of normal canine eyes decreases from baseline values in times ranging from 0.25 to 5.5 hours. A mean maximal depression of 9 mmHg occurs 1.5 hours after administration (Lorimer et al., 1989). It has been assumed that in patients with acute glaucoma, mannitol is a most effective hyperosmotic agent, reducing IOP within 0.5–1 hour, with the effect lasting for some 6–10 hours (Bedford, 1980a). Mannitol is not metabolized, but is filtered across the glomerulus and excreted in the urine without reabsorption by the renal tubules, causing a marked diuresis. If mannitol is infused during surgery, bladder catheterization is advisable to prevent uncontrolled urination during the recovery period.

Saline hypertonic hydroxyethyl starch (HES), used in humans for the treatment of hemorrhagic shock and intracranial pressure, has been evaluated for its effects on IOP in dogs (Volopich et al., 2006). In healthy normotensive dogs, the IOP-lowering effect of intravenous HES (7.5%/6%) was comparable to that of mannitol 20%, but was shorter in duration. Used in a small series of dogs with acute primary glaucoma, intravenous hypertonic HES induced an average maximum decrease in IOP of 24% from baseline values in most subject dogs (Volopich et al., 2006). Major potential side effects of HES include hypernatremia and hypokalemia, particularly in patients with preexisting dehydration.

Glycerin, or glycerol, is a trihydric alcohol that is rapidly absorbed from the gastrointestinal tract after oral administration. The drug is marketed as flavored commercial preparations of 50 and 75% glycerin. Glycerin USP, which contains approximately 1.25 g of glycerin per milliliter, may also be used and mixed in milk or syrup to improve palatability (Singh & Krupin, 1997). Glycerin is administered per os or in food in a daily dose of 1–2 g/kg (Gwin, 1980). Occasionally, animals may experience nausea or vomiting after ingestion of the drug. The incidence of vomiting appears to be dose-dependent, occurring the most frequently with doses higher than 2 g/kg (Gwin, 1980; Lorimer et al., 1989). Aminoglycosides of 1.44 g/kg glycerin in healthy dogs led to a significant ocular hypotensive effect, occurring within 1 hour and lasting about 10 hours (Lorimer et al., 1989). Glycerin is metabolized into glucose, so hyperglycemia and glycosuria may ensue (Dugan et al., 1989). Weight gain may be another consequence of glycerin metabolism if the drug is administered for a prolonged period. As this agent is readily metabolized, it induces less diuresis than mannitol.

Isosorbide is a dihydric alcohol that resembles mannitol in chemical structure and can be given orally. It is available as a 45% flavored solution (Singh & Krupin, 1997). Unlike glycerin, it is totally inert and does not produce elevated blood glucose. In humans, a dose of 1.5–2.0 g/kg induces an ocular hypotensive effect similar to that of 1–1.5 g/kg glycerin (Craig, 1994). A daily dose of 1.5 g/kg is recommended in the dog (Dugan et al., 1989), although there is currently no published study documenting its effect on IOP in this species.

**Clinical Use**

Osmotic agents are used mainly in the emergency treatment of acute glaucoma (Brooks, 1990; Gaarder, 2000; Gwin, 1980). These compounds are employed for short-term control of IOP since they are not practical for prolonged therapy (Singh & Krupin, 1997). Rapid reduction of IOP is usually achieved with mannitol rather than with glycerin. Both drugs, however, can be used in combination for maintenance of normal IOP. Mannitol is infused first; 6–8 hours later, glycerin can be administered and repeated as necessary for maintenance (Brooks, 1990). Osmotic agents are also indicated to reduce IOP in patients with hyphema, but their value in facilitating the resorption of anterior chamber hemorrhage is not clearly established. Mannitol may be employed preoperatively or intraoperatively to lower IOP and reduce vitreous volume (Singh & Krupin, 1997). This drug may also be used both before and during surgical procedures on the lens (i.e., cataract surgery, removal of a luxated or subluxated lens), because shrinkage of the vitreous body reduces the incidence and severity of vitreous prolapse. Finally, osmotic agents are indicated after intraocular surgery to relieve ciliary body block glaucoma (Singh & Krupin, 1997).
Side Effects and Contraindications

The major potential toxicity of intravenous osmotic agents is related to their effect on the volume and distribution of body fluids. Mannitol may quickly expand extracellular fluid volume and subsequently overload the cardiovascular system (Craig, 1994; Dugan et al., 1989; Singh & Krupin, 1997). This acute expansion of extracellular fluid volume may precipitate pulmonary edema in patients with cardiac failure or who are under general anesthesia. Deaths due to pulmonary edema occurred in a few dogs and cats that underwent ophthalmic surgery and were given mannitol while anesthetized with methoxyflurane in oxygen (Brock & Thurmon, 1979). Subsequent studies have shown that infusion of 2.2 g/kg of 20% mannitol in healthy dogs, under the same anesthetic regimen of methoxyflurane with oxygen maintenance, increases central venous pressure enough to produce pulmonary perivascular and interstitial edema (Brock et al., 1985). Infusion of a lower dose (0.25 g/kg) of 25% mannitol in dogs anesthetized with halothane does not induce significant changes in cardiovascular variables, but has no effect on IOP (Gilroy, 1986). Mannitol does not cross the blood–brain barrier and thus extracts water from cerebral fluid and tissue. Cerebral dehydration induced during the phase of maximal plasma hyperosmolalization has been found in association with side effects such as nausea, vomiting, and changed consciousness. Shrinking the brain could also promote subdural hematoma formation (Craig, 1994). Mannitol should be avoided in patients with renal failure. Glycerin should be avoided in patients with diabetes mellitus because the drug is converted to glucose (Singh & Krupin, 1997).

Neuroprotective Therapy in Glaucoma

Glaucoma is a vision-threatening disease because several processes involved in its pathophysiology lead to progressive loss of RGCs and their axons in the optic nerve. Therefore, glaucoma is currently considered as an optic neuropathy, referred to as GON (Ofri & Narfström, 2007). There is no doubt that IOP is an important risk factor for the development of optic nerve damage at the level of the lamina cribrosa, but other factors may act in combination to cause atrophy and loss of RGCs (Abbasoglu & Kooner, 1997; Quigley, 1996). The goal of glaucoma treatment in humans is to preserve the visual field and prevent the loss of visual function that is associated with the disease. The conventional treatment of glaucoma has been directed toward controlling IOP, because there is scientific evidence that lowering IOP in patients with glaucoma is beneficial to decrease the rate of RGC loss in most of them (Goldberg, 2003). However, clinical trials showed that even with excellent control of IOP, some patients have worsening visual field resulting from progressive RGC loss. The rationale for a therapeutic strategy, independent of IOP reduction and directed at keeping RGCs alive and functional when lowering IOP is not enough, or is difficult to achieve, therefore derived from these clinical observations. The concept of neuroprotection emerged with recent advances in understanding of glaucoma pathophysiology which allow investigators to develop pharmacological approaches aimed at preventing loss of RGCs and damage to the optic nerve by interfering with neuronal death pathways (Ofri & Narfström, 2007). There is current evidence that RGCs die in glaucoma via apoptosis which might have several causes, including compromised blood flow to the optic nerve, blockade of retrograde axonal transport of neurotrophic factors that facilitate RGC survival, excitotoxic injury to the nerve cell, oxidative stress, inflammation, and mitochondrial dysfunction (Baltmr et al., 2010; Goldberg, 2003; Levin, 2003; Naskar & Dreyer, 2001; Quigley, 1996). Treatments that aim to directly protect the RGC against glaucomatous damage, therefore, may be achievable through correction of compromised blood flow through the use of vasoactive agents or reduction of IOP, use of neuroprotective factors to influence the survival of injured RGCs, and prevention of excitotoxic RGC death. These therapeutic approaches have been reviewed in recent articles (Baltmr et al., 2010; Danesh-Meyer, 2011; Vasudevan et al., 2011).

Excitotoxicity refers to the pathophysiologic condition in which excitatory amino acids (EAAs), such as glutamate and aspartate, excite the neurons excessively, resulting in neurotoxicity and neural death (Abbasoglu & Kooner, 1997). A variety of findings in humans with glaucoma and animals with experimental ocular hypertension have suggested that an increase in glutamate levels may be involved in glaucomatous RGC loss by overactivation of N-methyl-D-aspartate (NMDA) receptors on RGC cell bodies (Osborne et al., 1999). A large variety of agents may potentially prevent excitotoxicity such as Ca++ channel blockers, EAA receptor antagonists, NO inhibitors, and free radical scavengers (Abbasoglu & Kooner, 1997; Osborne et al., 1999). NMDA receptor antagonists have been explored in several animal models of experimental glaucoma, but their evaluation in glaucomatous humans led to limited success. For example, memantine, a neuroprotective agent approved for Alzheimer’s disease, failed to demonstrate neuroprotection in phase III clinical trials in humans (Danesh-Meyer, 2011). Neurotrophic growth factors, including neurotrophin, nerve growth factor (NGF), and BDNF, are acquired by retrograde axoplasmic transport to regulate RGC metabolism. Blockade of axonal transport in glaucoma hence results in neurotrophic withdrawal. Most of the studies in animal models have been focused on BDNF and have remained inconclusive (Vasudevan et al., 2011). However, NGF topically administered as eye drops was demonstrated to significantly inhibit RGC loss in a murine glaucoma model, and to improve parameters of visual functions in a small series of glaucomatous humans (Lambiasi et al., 2009).

Neuroprotection also has been demonstrated in animal models of glaucoma with currently available antiglaucoma agents such as brimonidine, various β-blockers, and prostaglandin analogues (Ofri & Narfström, 2007; Seki et al., 2005; WoldeMussie et al., 2001). It is established that these agents
are neuroprotective to RGCs not only by their IOP-lowering effect but also by blocking calcium and sodium influx into neurons, which in turn reduces NMDA-stimulated calcium influx, or by impeding glutamate and hypoxia-induced apoptosis, for β-blockers, and prostaglandin analogues, respectively (Vasudevan et al., 2011).

Although new, emerging research has established the rationale for neuroprotection in glaucoma, long-term controlled trials are needed to determine whether or not neuroprotective agents may be beneficial in the management of human POAG. However, it is also evident that the pharmacologic approaches for neuroprotection represent an exciting development in the search for drugs that not only decrease IOP but also prevent RGC apoptosis.

**PATIENT SELECTION FOR GLAUCOMA SURGERY**

The optimal canine candidates for antiglaucoma surgery are visual patients with early glaucoma, no iridocyclitis or lens subluxation, and normal-appearing optic discs. Patients with vision and with IOP that is increasing despite maximum levels of medical therapy are also good candidates. Surgical treatments for advanced glaucomas not under adequate medical control and often without the possibility of restoration of vision require different strategies.

**REASONS TO OPERATE EARLY**

Higher success rates may result when the filtering techniques and gonioimplants for the canine glaucomas are employed early in the disease process. Reasons for this apparently higher success rate include:

1. Some aqueous humor outflow still remains.
2. Damage to the retina and ONH is not advanced, and vision is present.
3. The likelihood of lens subluxation, buphthalmia, peripheral anterior synchiae, and ciliary cleft collapse is reduced.
4. The incidence of the complications of concurrent iridocyclitis, pre-iridal rubeosis, and vitreous within the posterior or anterior chamber (or both) is reduced.
5. There is preliminary evidence that surgical treatment of early glaucomatous globes is more successful than for the advanced stages.

In addition, the aqueous humor of humans with primary glaucoma, as well as of those with uveitic glaucoma, seems to stimulate proliferation of the subconjunctival and sub-Tenon’s fibroblasts more than normal aqueous humor does. This may relate to higher levels of growth factors and glycoproteins/GAGs in chronically affected and perhaps inflamed eyes.

**AVAILABLE SURGICAL PROCEDURES**

Surgical procedures for treatment of the primary glaucomas in the dog are divided into two types: those that construct alternate pathways of drainage within or to the outside of the eye and those that decrease the formation rate of aqueous humor by destroying part of the ciliary body (Gelatt & Gelatt, 2011). Procedures to increase aqueous humor outflow include iridencleisis, corneoscleral trephination, cyclodialysis, combined iridencleisis and cyclodialysis, posterior sclerectomy, and anterior chamber shunts (i.e., gonioimplants). Techniques to reduce aqueous humor formation by partial destruction of the ciliary body include cyclocryotherapy, cyclodiathermy, and transscleral cyclophotocoagulation. The most frequently used procedures are anterior chamber shunts (i.e., gonioimplants) and destruction of the ciliary body processes by cryotherapy or laser photocoagulation. All of these surgical procedures have been recently summarized in the veterinary literature (Cook, 1997; Garcia et al., 1998); therefore, only those techniques most frequently used at the time of this writing (i.e., anterior chamber shunts, laser cyclophotocoagulation, cyclocryotherapy) are discussed here.

**PREOPERATIVE TREATMENT**

Preoperative considerations in treatment of the primary glaucomas include:

1. Preoperative control of IOP to a near-normal level
2. Suppression of any concurrent anterior segment inflammation with corticosteroids and nonsteroidal agents
3. Maintenance of desired pupil size
4. Dehydration and reduction in size of the vitreous with osmotic agents

The IOP must be reduced to the low-normal range in patients before glaucoma surgery. Medical therapy and paracentesis may be necessary to lower the IOP to between 10 and 20 mmHg. If the IOP is 30 mmHg or greater after intensive antiglaucoma medical therapy, anterior chamber paracentesis is recommended to prevent further damage to the ocular tissues (Fig. 19.31).

Many types of canine glaucoma also exhibit concurrent iridocyclitis, which may also be a primary factor or secondary factor in the genesis of the glaucoma. Both topical and systemic corticosteroids and nonsteroidal anti-inflammatory agents are indicated to suppress inflammation and to reduce the levels of inflammatory cells and proteins in the aqueous humor. This inflammatory debris may compromise both short- and long-term, existing aqueous humor outflow pathways as well as the new surgical site.

**CURRENT STRATEGIES FOR SURGICAL TREATMENT OF THE GLAUCOMAS**

Two newer treatment modalities, laser transscleral cyclophotocoagulation and anterior chamber shunts (i.e., gonioimplants), have shown promise in the clinical management of canine primary glaucomas. Hence, a treatment strategy for canine primary glaucomas is evolving that includes initial surgical implantation of an anterior chamber shunt (i.e,
Section III

Chamber shunts in limited numbers of normal dogs as well as in dogs with the primary glaucomas (Fig. 19.32) (Gelatt & Gelatt, 2011; Glover et al., 1995b). More recent reports with higher success rates evaluated alternate drainage sites as well as combined gonioshunts and either diode laser cyclophotocoagulation or cryothermy (Bentley et al., 1999; Cullen et al., 1998; Sapienza & van der Woerd, 2005). In humans, the gonioshunts are used for the medically refractory glaucomas and when vision loss continues in spite of maximum medications (Hong et al., 2005).

Gonioimplants are divided into those with unidirectional valved systems, which are designed to permit passage of aqueous humor at approximately 10–12 mmHg, and those with bidirectional nonvalved systems, which have no pressure-regulatory devices except for the limited resistance in the shunt’s tubing (Table 19.7) (Gelatt & Gelatt, 2011; Gelatt et al., 1992; Hong et al., 2005). Typically with the valved implants, IOP immediately after surgery is about 10–12 mmHg; with the nonvalved implants, IOP is often below 5 mmHg.

With fibrosis around the implant, which develops approximately 3–6 weeks postoperatively, the resistance for aqueous outflow with both types of implants is the same. The Ahmed valve has been evaluated in an in vitro system at flows approximating the rate of aqueous turnover in the dog (Strubbe et al., 1997). Very low levels of IOP postoperatively in the dog can result in excessive fibrin in the anterior chamber, occasional hemorrhage, and even retinal detachments. To limit postoperative hypotony and shallow anterior chambers in the nonvalve systems, the anterior chamber tubing can be temporarily occluded intraoperatively with a nonabsorbable suture inside the tubing, a ligature (either absorbable or non-absorbable suture) around the tube, or other techniques.

Anterior Chamber Shunts (Gonioimplants)
The first report of anterior chamber shunts or gonioimplants in the dog was published in 1942, when the lacrimal canaliculi were transposed into the limbus of normal dogs as a new exit for aqueous humor from the anterior chamber (Gibson, 1942). In 1970, insertion of a Silastic Dacron tube through the limbus was attempted in normal dogs (Pritchard & Hamlet, 1970). In the early 1980s, the original Krupin-Denver valve was evaluated in normal Beagles as well as in Beagles with inherited glaucoma (Gelatt et al., 1987; Gum et al., 1981). This small scleral implant consisted of a small tube placed in the anterior chamber, a valve mechanism, and a short tube that extended only a few millimeters into the subconjunctival spaces. Without a broad area for reabsorption of the aqueous humor to occur, the exit of this implant became scarred and occluded in 50% of the dogs at 6 months.

A modified (i.e., nonvalved) Joseph implant was evaluated in 15 dogs (21 eyes) with primary glaucoma, and encouraging results were reported (Bedford, 1988, 1989). Additional reports have evaluated Ahmed, Baerveldt, and other anterior chamber shunts in limited numbers of normal dogs as well as in dogs with the primary glaucomas (Fig. 19.32) (Gelatt & Gelatt, 2011; Glover et al., 1995b). More recent reports with higher success rates evaluated alternate drainage sites as well as combined gonioshunts and either diode laser cyclophotocoagulation or cryothermy (Bentley et al., 1999; Cullen et al., 1998; Sapienza & van der Woerd, 2005). In humans, the gonioshunts are used for the medically refractory glaucomas and when vision loss continues in spite of maximum medications (Hong et al., 2005).

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Surgical Procedure for Anterior Chamber Shunts
The surgical procedures for gonioimplants is about the same for all of the episcleral devices. A 120-degree to 140-degree...
**Postoperative Management**

General postoperative management includes:

1. Control and resolution of the iridocyclitis with use of topical and systemic corticosteroids and nonsteroidal anti-inflammatory agents
2. Moderate pupillary dilatation and encouragement of pupil movement with careful use of mydriatics (e.g., 1% tropicamide)
3. Prevention of infection with use of topical and systemic antibiotics
4. Maintenance of normal IOP levels using CAIs and, if necessary, β-blocker adrenergics (miotics may be contraindicated because of their effects on the episcleral fibroblasts and increased aqueous humor flare)
5. Maintenance of a patent anterior chamber tubing and valve system; if IOP increases in excessive of 12–15 mmHg in the first week postoperatively, the valve mechanism may be plugged with fibrin, and an intracameral injection of 25 mg of TPA usually resolves the problem (Sidoti et al., 1995)
6. The bleb and the gonioimplant can be imaged with ultrasonography, and the blebs characterized as small, medium and large (Lloyd et al., 1993). The aqueous humor within the bleb appears as an echolucent area and the gonioplate appears as an echodense area. Although bleb size does not necessarily correlate with the levels of IOP control, it does confirm that the implant’s tube is patent.
7. Continued topical medications which may lower IOP as well as control inflammation may be important postoperatively. Prednisolone acetate (1%) was recommended in one clinical series to reduce any inflammation and control the fibroblasts within the bleb surrounding the extra-scleral implant (Westermeyer et al., 2011).

Successful anterior chamber shunts will provide an IOP immediately after surgery of approximately 5 mmHg with

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### Table 19.7  Anterior Chamber Shunts Reported in the Dog

<table>
<thead>
<tr>
<th>Implant</th>
<th>AC Tubing</th>
<th>Scleral Explant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonvalved:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“T”-implant</td>
<td>Silicone-7 × 30 mm</td>
<td>Silicone, 420 mm²</td>
</tr>
<tr>
<td>ID 0.3 mm</td>
<td>OD 0.6 mm</td>
<td>c valve</td>
</tr>
<tr>
<td>Ahmed</td>
<td>Silicone</td>
<td>5-sided polypropylene</td>
</tr>
<tr>
<td>ID 0.3 mm</td>
<td>OD 0.6 mm;</td>
<td>Valve opens</td>
</tr>
<tr>
<td>Valve-slit (side)</td>
<td>8 to 10 mmHg</td>
<td>Bedford- used as nonvalve in dogs</td>
</tr>
<tr>
<td>Joseph</td>
<td>Silicone</td>
<td>Silicone strap-1 × 9 mm</td>
</tr>
<tr>
<td>ID 0.3 mm</td>
<td>OD 0.64 mm</td>
<td>Valve-slit</td>
</tr>
<tr>
<td>Valve-slit (side)</td>
<td>4–20 mmHg</td>
<td>Bedford- used as nonvalve in dogs</td>
</tr>
<tr>
<td>Krupin</td>
<td>Silastic</td>
<td>Later #220 episcleral explant,</td>
</tr>
<tr>
<td>ID 0.3 mm</td>
<td>OD 0.64 mm</td>
<td>Valve-slit</td>
</tr>
<tr>
<td>Open at 11 mmHg;</td>
<td>Closes-9 mmHg</td>
<td>Bedford- used as nonvalve in dogs</td>
</tr>
</tbody>
</table>

*Implant dimensions are calculated for the entire surface areas of each implant.

fornix-based, dorsal bulbar conjunctival flap is prepared, with 5 mm of bulbar conjunctiva left to manipulate the globe (Fig. 19.33A–E). The implant is usually positioned at or just posterior to the equator, with its rostral end approximately 10–12 mm from the limbus. The anterior border of the implant should be posterior to the extraocular muscle insertions. All anterior chamber shunts are checked before placement for both function and patency. A 25- to 27-gauge hypodermic needle is cannulated into the end of the anterior chamber tubing, and sterile balanced salt or lactated Ringer’s solution is injected. Once the device is properly positioned, it is secured to the sclera and Tenon’s capsule with two to four nonabsorbable 7-0 to 9-0 sutures, which are usually placed at the anterior border and near the extraocular muscle insertions. In some dogs with glaucoma, the sclera may be very thin in this area, and sutures with good holding abilities may be difficult to achieve. The overall length of the anterior chamber silicone tubing is carefully estimated by laying the tubing directly onto the cornea. Once in the anterior chamber, the tubing should not touch either the iris or the cornea, and it should avoid crossing the center of the pupillary axis. The tip is usually cut in a slightly beveled position to facilitate insertion into the anterior chamber; a beveled opening may be less subject to plugging with fibrin postoperatively as well. When the tubing end is beveled at 45° or less, however, it may be more easily plugged if contact with the corneal endothelium occurs.

A limbal-based, partial-thickness scleral hinge of 5 by 8 mm or a beveled hypodermic tunnel into the anterior chamber is prepared for the tubing to be inserted into the anterior chamber. The bend of the tubing as it enters the anterior chamber must be covered with scleral homografts or angled in the scleral tunnel to prevent its erosion through the bulbar conjunctiva in dogs “tight eyelids.” Once the tubing is positioned in the anterior chamber, aqueous humor will generally be noted flowing through the device. The conjunctival flap wound is apposed using several simple, interrupted or a continuous 6-0 to 7-0 absorbable suture. To treat any fibrin both in the aqueous humor and within the implant intraoperatively, 25 mg of TPA is usually injected into the anterior chamber at the limbus.
Figure 19.33. Surgical placement is similar for all the various anterior chamber shunts. (a) Either the dorsolateral or dorsolateral quadrant is approached by scissor dissection under a fornix-based conjunctival flap. A space adequate to accommodate the episcleral base of the shunt between the dorsal rectus muscle and either the medial or lateral rectus muscle is prepared. (b) The anterior chamber shunt must be primed with balanced salt solution before implantation. (c) The anterior chamber shunt is positioned between the adjacent rectus muscles and, with some implants, under the rectus muscles. It is secured with simple interrupted nonabsorbable sutures. (d) After limbal puncture with a 20- to 22-gauge hypodermic needle and creation of the proper length and beveled end for the tube, the silicone tubing is inserted into the anterior chamber. The scleral aspect of this tube should be covered with either autogenous or homologous sclera to protect the overlying bulbar conjunctiva. (e) Sagittal, postoperative view shows the proper position of the anterior chamber shunt, with its leading edge approximately 10- to 14-mm posterior of the limbus. (Modified from Gelatt, K.N. & Gelatt J.P. (2011) Surgical procedures for treatment of the glaucomas. In: Veterinary Ophthalmic Surgery, New York: Saunders-Elsevier, 263–303.)
nonvalved systems and of 8–12 mmHg with valved systems (Fig. 19.34A, B). Occasional spikes of 5 or 10 mmHg may develop in the first few weeks if the shunt is temporarily plugged with fibrin. With development of the fibrous capsule about the base of the shunt in 3–6 weeks, IOP will gradually increase to 12–20 mmHg several weeks postoperatively. Ultrasonography through the upper eyelid over the area of the shunt can demonstrate no surrounding aqueous humor “pool” if the tube or valve is occluded (Lloyd et al., 1993) or a very large bleb if the fibrosis around the implant has become resistant to aqueous exit. Topical corticosteroids (e.g., 1% prednisolone) are recommended postoperatively for several months to impede capsule formation about the base of the anterior chamber shunt. Needling or partial excision of the dorsal fibrotic capsule as well as the injection of 5-fluorouracil are used to address implant failure several months postoperatively (Sherwood, 1990).

**Complications of Anterior Chamber Shunts**

Failures of anterior chamber shunts may be grouped into three types (Sherwood, 1990). The immediate postoperative iridocyclitis can usually be controlled by the routine anti-inflammatories; any fibrin or blood in the anterior chamber that may occlude the tubing or valve usually resolves with one or two injections of TPA (Sidoti et al., 1995).

Long-term failure of anterior chamber shunts is usually associated with development of an impermeable capsule about the episcleral base of the device. More effective anti-fibrosis drugs are needed to markedly impede or totally prevent capsule formation about the extrascleral base of these implants. These drugs may be injected or inserted as time-release medications into the retrobulbar space either intraoperatively or 1–2 months postoperatively after some capsule has formed about the implant and healing is complete.

**Surgical Results**

Strategies for placing anterior chamber shunts in the dog are still evolving. The current anterior chamber shunts drain aqueous humor into the subconjunctival and retrobulbar spaces, but alternate sites, including the frontal sinus and other areas, have been attempted in the dog (Cullen et al., 1998; Gelatt & Gelatt, 2011; Håkanson, 1996).

The success rate for anterior chamber shunts has progressively improved with the refinement in the gonioimplant, surgical procedure, and postoperative clinical management. In 1989, a report involving 21 eyes in 15 dogs with the primary glaucomas that received the modified Joseph shunt, 20 eyes were normotensive at 4 weeks, and 17 eyes were still normotensive at 9–15 months (Bedford, 1989) with about 50% of these eyes receiving oral dichlorphenamide, 1.6–2.5 mg/lb daily. Of the nine eyes with vision preoperatively, eight were still visual at 9 months.

A larger series of studies in 1993, 1995, and 1998, involving 83 eyes in 65 dogs, compared three different anterior chamber shunts for treatment of primary glaucoma (Garcia et al., 1998; Garcia et al., 1993, 1995). The criteria for success were maintenance of vision and IOP levels of 20 mmHg or less. The median time at which the IOP began to increase postoperatively depended on the shunt and ranged from 4 to 10 to 15 months. The median time for vision loss to develop postoperatively again varied by shunt and ranged from 4 to 6 to 9 months. Fifteen of the 22 eyes with an IOP of 20 mmHg or less were still visual at 1 year. The most promising shunt was the large Ahmed shunt attached to a silicone band (10 = 30 = 0.4 mm).

More recent reports have combined the gonioimplant with cyclophotocoagulation or cryotherapy. Bentley et al. reported on 18 glaucomatous dogs (19 eyes) treated with cycloablation and Ahmed gonioimplantation (7 eyes were treated with a
diode laser and 12 were treated with cyclocryoablation) (Bentley et al., 1996). One year after surgery, 11 of 19 eyes (60%) had vision, and 14 of 19 eyes had IOP lower than 25 mmHg. The implant can prevent the IOP spikes that follow the cycloablation as well as reduce the amount of energy or freezing for cryoablation. Sapienza and van der Woerdt reported their results using a combined diode laser cycloablation and the Ahmed gonioimplant in 48 dogs (51 eyes). Good control of IOP was achieved in 39 of 51 (76%) of the eyes, and IOP was poor or uncontrolled in 12 of 51 (24%) of the eyes. Twenty of 41 (49%) eyes maintained vision after 6 months, and 12 of 29 (41%) of the eyes had vision after 12 months (Sapienza & van der Woerdt, 2005).

In another series, temporalis muscle fascia or porcine intestinal submucosa grafts were used to cover the tube from the implant’s base to the limbus, and topical 1% prednisolone acetate was instilled daily to control any intraocular inflammation as well as to submit fibroblastic activity within the bleb’s walls (Westermeyer et al., 2011). Mitomycin (0.25–0.50 mg) was administered by a trimmed cellulose sponge in the operative pocket for 5 minutes before implant insertion. The sides of the overlying conjunctival incision were not touched with the mitomycin solution-soaked sponge, and the entire area was rinsed with copious amounts of balanced solution for 5 minutes. Bleb revision was occasionally necessary and was performed by an incision on the top of the bleb. The fibrous tissue was excised, and aqueous humor flow immediately returned. The bleb was then again treated with mitomycin again using the same protocol. As an alternate approach, 5-fluorouracil (5 mg) was injected directly into the bleb twice at a 2-week interval. At 12 months postoperatively, 8 of the 9 dogs were still visual.

**CYCLODESTRUCTIVE TECHNIQUES**

Several noninvasive cyclodestructive procedures have been developed to treat the different primary glaucomas in small animals by decreasing aqueous humor formation through partial destruction of the ciliary body processes. Excessive heat, as with diathermy or lasers, or extreme cold, as with cryotherapy, is directed through the overlying sclera to the ciliary body processes. Proper positioning of the cryo and laser probes is critical; these probes must be directly over the ciliary body processes. In the dog, this area is approximately 5 mm from the limbus in the dorsal aspects of the globe. With globe enlargement, the ciliary processes of the pars plicata may shift an additional 0.5–1.0 mm posteriorly. Cyclodestructive procedures require some functional aqueous humor outflow to have an optimal IOP-reducing effect, because only partial destruction of the ciliary body will allow some level of minimal aqueous humor formation, which will continue to result in normal to subnormal IOP. Traditional cyclodestructive procedures can be refined only so much, in part because of the less-than-predictable regeneration of the ciliary body epithelium. Excessive application of these energies result in phthisis bulbii, with irreversible destruction of the ciliary body and permanent ocular hypotony.

**Cyclocryotherapy**

Cyclocryotherapy is employed primarily in advanced glaucomatous eyes to reduce IOP in the presence of persistent pain or to induce phthisis bulbii, which may be more cosmetically acceptable than a buphthalmic eye (Merideth & Gelatt, 1980; Roberts et al., 1984). This technique is also used in permanently blind glaucomatous eyes that are nonresponsive to intensive medical treatments. Cyclocryotherapy is used infrequently in visual eyes, because prolonged periods of elevated IOP may follow the procedure.

The nitrous oxide or liquid nitrogen, 2.0- to 3.0-mm cryo-probe is applied 5 mm from the limbus directly onto the dorsal bulbar conjunctiva. Four to eight sites in the dorsal half of the eye are frozen for 120 seconds, each with the temperature of the cryoprobe reaching −60°C to −80°C. The three- and nine-o’clock positions are avoided to prevent direct damage to the long posterior ciliary blood vessels (Brightman et al., 1982; Vestre & Brightman, 1983a, 1983b).

**Transscleral Laser Photocoagulation**

Transscleral cyclophotocoagulation uses energy developed by different types of lasers to destroy the ciliary body and to reduce aqueous humor formation. Both noncontact and contact Nd:YAG and diode lasers have been used in different animal species and, though costly, are promising treatments of canine glaucoma.

Laser cyclophotocoagulation has been evaluated in the normal dog using the Nd:YAG and diode lasers (Nadelstein et al., 1997; Nasisse et al., 1988; Quinn et al., 1994; Sapienza et al., 1992). Using a noncontact Nd:YAG laser in 25 normal dogs, either 100 J or 238 J were delivered 5 mm posterior to the limbus to the canine ciliary body. In the 100-J group, IOP declined by 6 mmHg but returned to prelaser levels within 7 days (Nadelstein et al., 1997). In the 238-J group, IOP declined by 10 mmHg throughout the 7 and 28 days of observation. Seven days after laser treatment, ciliary hemorrhage and ciliary necrosis were prominent. Twenty-eight days after treatment, ciliary atrophy and fibrosis were the primary histopathologic findings, though one eye developed extensive intraocular hemorrhage and phthisis bulbus.

With the total pulse energy delivered 5 mm posterior to the limbus and varied at 126, 154, and 212 J, contact Nd:YAG laser cyclophotocoagulation in normal dogs produced a 1-month decline in IOP, except in the high-energy group, in which ocular hypertension developed 5–10 days after treatment (Sapienza et al., 1992). As the energy dose increased, the intensity of iridocyclitis and the possibility of acute iatrogenic glaucoma also increased. Focal cataract formation occurred in 75% of laser-treated eyes.

The diode laser was evaluated in a study of five normal dogs undergoing contact transscleral cyclophotocoagulation...
3 mm posterior to the limbus (Nadelstein et al., 1997). The energy was delivered to 35 spots using 1.5 W at a duration of 1.5 seconds (i.e., 78.7 J per eye at 2.25 J/spot) and avoiding the nine- and three-o’clock positions. Clinically, aqueous flare, conjunctival hyperemia, fibrin in the aqueous, miosis, limited hyphema, and in one dog, intravitreal hemorrhage developed. IOP declined within 12–24 hours after treatment and remained low for the 28 days of observation. One dog’s IOP spiked a single reading of 30 mmHg at 1 hour after laser treatment. One hour after laser treatment, the treated areas in the dog appeared as white, blisterlike lesions, with adjacent hemorrhage, fibrin strands, and inflammatory debris; by 28 days, these areas appeared as depigmented and slightly atrophied areas.

In another study, thermography was compared using the Nd:YAG and semiconductor diode laser among in vitro, normal canine eyes (Quinn et al., 1994). Histopathologic findings at the treated areas included a poorly demarcated, circular, hypereosinophilic focus of tissue coagulation that straddled the scleral–ciliary body interface. In this study, the Nd:YAG and diode lasers produced similar cyclodestructive effects.

In a study using the noncontact Nd: YAG laser in 56 eyes of 37 dogs with glaucoma, promising results were obtained (Nasisse et al., 1990). Forty-four eyes had preexisting glaucoma, and 12 fellow eyes were treated prophylactically. The mean number of laser-treated spots were 35 ± 10. The mean energy per burst was 7.1 ± 2.6 J, and the mean total energy delivered to each eye was 228 ± 81 J. Treatment success was defined as an IOP of 25 mmHg or less. Information on vision was not reported. In the 44 treated glaucoma eyes, IOP was reduced to 25 mmHg or less in 83%. Three of the four failures were eyes devoid of uveal pigmentation (Nasisse et al., 1990). In lightly or nonpigmented eyes, such as those in the Siberian Husky or Old English Sheepdog, laser cyclophotocoagulation was not nearly so successful. Hyphema developed in 16% of those eyes, but it resolved without complications in all but two. Cataract formation occurred in approximately 37% of treated dogs (i.e., 12 of 32 eyes) (Nasisse et al., 1990).

A larger study using diode laser transscleral cyclophotocoagulation involved 176 eyes in 144 dogs with clinical primary glaucoma (Cook et al., 1997). The different breeds with these primary glaucomas were not analyzed separately, but approximately 50% were ACS. Laser treatments were administered 3–4 mm posterior to the limbus at 30–40 sites, for a mean dose of 85 J per eye. An immediate posttreatment IOP elevation of 11.3 ± 7.8 mmHg occurred (pretreatment IOP, 45 ± 10 mmHg) and was treated by anterior chamber paracentesis. This immediate spike in IOP occurred in four eyes was associated with the loss of vision. An IOP of 30 mmHg or less occurred in 110 of 136 eyes at 8 weeks, 69 of 106 eyes at 6 months, and 45 of 88 eyes at 1 year. Major complications included corneal ulcerations, cataract formation, intraocular hemorrhage, retinal detachments, and phthisis bulbi. Using the menace response as a test of vision, positive results were obtained in 21 of 37 eyes (57%) at 8 weeks, 11 of 30 eyes (37%) at 6 months, and 11 of 19 eyes (53%) at 1 year. Of the 45 eyes that tested positive with the menace test before laser therapy, only 10 (5.5%) were still evaluated as being visual at 12 months. The results of this study suggest diode laser cyclophotocoagulation may be effective at lowering IOP for as long as 1 year (50% of the eyes) but is less effective at maintaining vision (22%).

In two studies from Australia, transscleral cyclophotocoagulation with the diode laser was evaluated in dogs with glaucoma following intracapsular lens extraction for displaced lenses and for the primary glaucomas (Hardman & Stanley, 2001; O’Reilly et al., 2003). Approximately 16% of 99 patients with intracapsular lens removal for displaced lenses developed glaucoma. The diode laser probe with a spot size of 600 µm was applied perpendicularly (causing slight scleral indentation) to the globe in 20–25 sites 4 mm posterior to the limbus. A power of 1000 mW for 5000 ms delivered an average of 125 J per eye. Diode laser cyclophotocoagulation produced adequate control of IOP in 15 of 20 eyes (75%) without medications at 1 month posttherapy. After 12 months, 8 of 15 eyes (53%) had vision, and 7 of 15 eyes (47%) were nonvisual.

Our present recommendation in visual eyes receiving contact diode laser cyclophotocoagulation is 1.2 W per site at a duration of 1.2 seconds with 35 sites (20 dorsal and 15 ventral), for a total of 50 J per eye (Fig. 19.35). The energy is delivered 3–4 mm posterior to the limbus. More energy can be delivered in eyes that are permanently blind. Medical treatment of glaucoma and anti-inflammatory therapy for posttreatment iridocyclitis should continue until the IOP is reduced and the inflammation subsides.

Diode Endoscopic Cyclophotocoagulation

Diode endoscopic cyclophotocoagulation has been recently reported for therapy of the canine glaucomas (Bras et al., 2005) and offers the advantage of highly selective laser ablation of the pigmented ciliary body epithelium while under direct observation. The microendoscope has three divisions:
humor formation. In the original technique, 0.5–0.6 mL of liquefied vitreous was aspirated, and 25 mg of gentamicin sulfate and 1 mg of dexamethasone were injected into the vitreous space (Vainisi et al., 1983). In one recent study, both anterior chamber and intravitreal injections were attempted (Bingaman et al., 1994). The dose of gentamicin should not exceed the patient’s total daily dose for this drug. This technique seemed to work best when the preinjection IOP was less than 20 mmHg. Eyes treated with doses of gentamicin higher than 20 mg had a significantly lower IOP after injection.

Pharmacologic ablation of the ciliary body was successful in lowering the IOP in 65% of patients for treatment of absolute and blind glaucomatous eyes. Fifty percent of eyes that do not respond to the first injection of gentamicin fail again to respond after the second injection, and approximately 10% of the eyes will be phthisical after this method.

If cost is not a limitation, our preference is for evisceration and intrascleral prosthesis. This procedure treats the pain associated with absolute glaucoma, limits the corneal exposure from enlarged globes, and eliminates the need for antiglaucoma treatments. The average prosthesis is 20–22 mm in diameter. The overall result is more predictable, and phthisis bulb is not possible. Some corneal edema and pigmentation occur postoperatively.

The most serious short-term complications are the development of central corneal ulcerations and infections postoperatively. The most common long-term complication is the development of keratoconjunctivitis sicca (Lin et al., 2007). As these dogs often do not blink well in the immediate postoperative period, a routine temporary tarsorrhaphy is recommended for 10–14 days for all patients. If corneal ulceration occurs, a pedicle conjunctival graft can also be applied because the corneal healing in these patients is slow. The overall
success rate with intrascleral prosthesis is approximately 85%-95%.

THE FUTURE-GENE THERAPY FOR THE CANINE PRIMARY GLAUCOMAS

The future therapy for the selected primary glaucomas in man as well as in animals may well include gene therapy (gene transfer; gene recovery; and gene protection) (Borrás, 2012). Gene therapy for retinal diseases first involved the dogs (Biard breed) with inherited Leber retinopathy and was highly successful; these same methods are now in experimental clinical trials in man affected with Leber retinopathy. Part of the rationale is the dog shares many inherited eye diseases similar to man, and many of the basic pathologic mechanisms are identical. In addition, the eye size in these “large laboratory animals” is about the same as man. Hence, it is logical when specific genes are identified for the different canine breeds with the inherited glaucomas, the feasibility of gene transfer should be investigated, thereby benefiting both man and his best friend—the dog!

Goals for Gene Transfer in the Anterior Segment

The eye seems one of the best tissues for gene transfer because its accessibility facilitates relatively simple techniques for injections into the anterior and posterior segments of the eye and the anterior chamber’s immune privilege (Demetriades, 2011; Liu et al., 2009; McKinnon, 2009; Tamm, 2002). Gene transfer for therapy of the primary glaucomas may target either the aqueous humor outflow tissues (mainly the trabecular meshwork) or neuroprotection of the RGCs and the optic nerve cells. Several systems are already developed using pathogenic viruses to deliver specific genes (transfer genes) to target specific ocular tissues. The first virus employed as a vector for gene transfer is the adenovirus (which in man has been associated with respiratory and ocular infections in man). Other viruses investigated include adeno-associated viruses (AAVs) and the retroviruses, including the lentivirus. The optimal virus vector delivers the transfer gene successfully to the target cells and causes very limited or no secondary inflammatory response from the host (McKinnon, 2009). The animal species investigated to date are primarily the mouse, rabbit, rat, and dog (Buie et al., 2010); the canine species offers the animal species with the highest number of breeds with spontaneous and inherited glaucomas. As idiosyncratic immune responses leading to human deaths have been reported, nonviral methods using cationic lipid delivery systems (lipofection) and electric current (electroporation) have been reported to deliver DNA sequences to the different target cells.

Possible Vectors for Anterior Segment Gene Transfer

The AAV group (currently more than 10 AAV different serotypes) does not possess the Rep and Cap viral sequences, and there is no viral protein synthesis transduction which limits the amount of foreign protein which triggers the host’s inflammatory response. The AAV group also can infect both dividing and nondividing cells. The AAV also depend on coinfection with a helper virus for efficient replication. Using postmortem human eyes, an adenoviral reporter gene transfer to the human trabecular meshwork did not alter aqueous humor outflow using anterior chamber perfusion studies of 3 days duration (Borrás et al., 1999). A denovirus-mediated gene transfer was evaluated in canine eyes for gene therapy of the human uveal melanoma (Andrawiss et al., 2001). The injection of the anterior chamber in two normal beagle controls with the replication-defective adenoviral vector with human angio- statin (AdK3) resulted in strong cellular local and humoral immune responses. As there are several reports using the AAV vector in dogs, this is probably the best vector, to date, to begin investigations for the glaucomatous dog.

The lentiviruses are the RNA type and use a unique type of replication. These viruses include the human immunodeficiency virus (HIV) and the feline immunodeficiency virus (FIV), and have the advantage of stable incorporation into both dividing and nondividing cell genomes. The group includes currently five serotypes. Lentiviral vector studies have been reported in cats using the dual-gene FIV vectors to induce open-angle glaucoma by modulating the aqueous humor outflow pathways (Khare et al., 2008) with myocilin proteins and the protein fluorescein. Although the myocilin and a juvenile glaucoma-associated mutant myocilin transgene expression did not elevate IOP, the dual-gene expression of the green fluorescent protein, which was expressed in the trabecular meshwork for as long as 1.2–2.3 years, could be monitored and photographed by digital photography using gonioscopy and a microscopy camera (DXM 1200; Nikon, Melville, NY) and an automatic camera tamper image capture software (ACT-1, Nikon) noninvasively. Other potential methodologies include modulation of programmed cell death (apoptosis) and intracellular signaling pathways. Hopefully, gene transfer methodology for the anterior segment can utilize, at least, some of the experiences and studies from the posterior segment.

The success of gene transfer therefore includes transfection of the target host cell by the vector–transgene combination and the host cell being reprogrammed to modulate release of the new gene’s proteins. Also, downregulation of gene expression using antisense oligonucleotides and siRNA is another approach to target mRNA and lower specific protein production.

Effects on the Trabecular Meshwork and Outflow Pathways

The modulation of aqueous humor outflow pathways (ie, the trabecular meshwork cells), which has targeted the ECM, trabecular meshwork, and cytoskeleton proteins, has used all available methodologies including adenoviral and lentiviral vectors as well as siRNA. Injections have been usually directly
into the anterior chamber. Using enucleated globes, perfusion studies can be injected with these different transgenes and outflow measured to determine short-term effects. Tissue culture can also reveal mechanisms of action and biochemical effects at the cellular level.

In addition to possible modulation of aqueous humor outflow through the aqueous outflow trabecular and uveoscleral pathways by gene transfer, injections into the posterior vitreous (almost directly next to the RGCs) or subretinally have used the AAV vectors. First investigated was the neurotropins for retinal neuroprotection. Fortunately, the AAV vectors induce a very limited to no inflammatory chorioretinal response.

**Potential Outcomes**

In the past and presently, glaucoma medical therapy is based on the nonspecific reduction in aqueous humor formation rates and the enhancement of aqueous humor flow through the trabecular and uveoscleral pathways. The exact cause of the glaucoma is not addressed therapeutically, and over time, the glaucoma process become worse, requiring additional medicines and even surgery. The usual outcome is overtime blindness! Although gene transfer for the canine glaucomas is still in its infancy, identification of specific gene mutations in the different breeds of dogs with the primary glaucomas will be critical to target the trabecular cells and the ECM and alter the effects of these mutations. There also will be secondary events, in which certain DNA, RNA, and the related proteins respond to only increased IOP, and thereby worsen the glaucoma. These effects may also altered by gene transfer. In reality, gene transfer represents the potential of not only lowering IOP, but also correcting the defective gene and its products, and curing the disease!

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The uvea includes the iris, ciliary body, and choroid. The anterior uvea refers to the iris and ciliary body. The iris, because of the pupil, is responsible for regulating light entering the globe, and it is also important for normal esthetics. The ciliary body is contiguous with the choroid at its posterior aspect and is responsible for aqueous production and lens accommodation. The anterior uvea is also the site of the blood-aqueous barrier, which normally prevents large, high-molecular-weight proteins from entering the aqueous humor. The rich blood supply and immunosensitivity of the anterior uvea make it the source for most of the inflammatory responses in the eye.

A complete ophthalmic examination, especially with the use of magnification as that given with a slit-lamp biomicroscope, can reveal much information in an eye with uveal disease. The size of the pupil can vary tremendously, and abnormalities in its size, shape, color, or responsiveness may indicate ocular or neurologic disease. Diseases such as anterior uveitis, glaucoma, retinal detachment and degeneration, and lesions along the afferent and efferent pupillary pathways can alter pupil size and function. Inflammation of the anterior uvea, termed anterior uveitis, is very common with both ocular and systemic diseases and may cause intense intraocular pain, alter pupillary function, and lead to blindness. Intraocular neoplasia is not unusual in dogs and varies in its appearance. In addition to inflammatory and neoplastic disorders, developmental, degenerative, and traumatic disorders can all affect the anterior uvea. This chapter focuses on diseases that primarily involve the iris and ciliary body, but because the anterior uvea is contiguous with the choroid (or posterior uvea), several of the diseases may concurrently affect the posterior segment.

### DEVELOPMENTAL CONDITIONS

Developmental abnormalities of the canine anterior uvea include disorders of incomplete development (e.g., coloboma), maldevelopment (e.g., anterior segment dysgenesis), and incomplete regression of embryonal tissues (e.g., persistent pupillary membranes [PPMs]). Most anterior uveal anomalies in the dog occur sporadically, but some are heritable.

Normal anterior uveal development during embryogenesis occurs by invagination of the optic cup resulting in a bilayered medullary epithelium. Continued differentiation of the innermost (i.e., more vitreal) layer forms the inner pigmented epithelium of the iris, the nonpigmented ciliary body epithelium, and the neurosensory retina. Differentiation of the outermost (i.e., scleral) layer forms the outer pigment epithelium (and dilator and sphincter muscles) of the iris, the pigmented epithelium of the ciliary body, and the retinal pigment epithelium. Because normal ocular embryogenesis depends on initial development of the pigmented layers of the eye, several congenital defects relate directly to ocular color dilution and specifically to the merling gene. However, there is considerable variation of anterior uveal pigmentation in normal dogs, which accounts for the marked differences in eye color both within and among breeds.

### Color Variants

#### Subalbinism

Subalbinism refers to dilution of ocular pigmentation. In contrast to complete albinism, in which the eye lacks all pigment, subalbinism is seen as a blue iris with a red fundus reflex. The neuroectodermal layer of the iris has normal pigmentation;
however, the overlying stroma lacks pigment. These animals have a nonpigmented fundus that allows the visualization of choroidal vessels. Presence of a tapetum is variable. Complete albinism results in a translucent iris with visible iris vessels, which gives a reddish hue to the iris stroma. Complete ocular albinism has not been reported in the dog.

**Heterochromia Iridis**

Heterochromia iridis refers to different colors within one iris or between the two irides. In the heterochromic eye, the iris is characterized by at least two distinct, solidly colored areas or by differently colored patches or spots (Fig. 20.1). Alternatively, each iridis may be a different color. Lay terms for this condition include “watch eye” and “china eye.”

Heterochromia iridis may be the sole manifestation of ocular color dilution in many breeds, including the Old English Sheepdog, Siberian Husky, American Fox Hound, American Cocker Spaniel, Malamute, and Shih Tzu. Apart from the variation in appearance, simple heterochromia iridis has no significance. Heterochromia iridis can be a component of ocular merling and may be accompanied by multiple ocular anomalies such as dyscoria, corectopia, iris hypoplasia, PPMs, staphylomas, cataract, and retinal detachment (Gelatt & McGill, 1973; Gwin et al., 1981).

**Iridal Changes Associated with Merling**

Multiple ocular anomalies including iris anomalies occur in breeds affected by the merle gene (e.g., Australian Shepherds, Great Danes, Collies, and Dachshunds) (Bertram et al., 1984; Gelatt & McGill, 1973; Gelatt et al., 1981). The most severe ocular anomalies occur in homozygous merles with excessive white hair coat involving the head region. Affected animals also have varying degrees of congenital deafness (Gwin et al., 1981). Anterior uveal manifestations of the merling gene may include heterochromia irides, iris hypoplasia, a black-rimmed pupil from prominent iridal pigmented epithelium, and an eccentric pupil (i.e., corectopia). Both typical and atypical iris colobomata (Fig. 20.2 and Fig. 20.3) and mild to severe PPMs are also common findings in merle dogs (Gelatt & McGill, 1973).

Anomalies caused by the merle gene have been studied most extensively in the Australian Shepherd (Bertram et al., 1984; Gelatt & McGill, 1973; Gelatt et al., 1981). Multiple ocular anomalies, including microphthalmia, irregular pupils, cataracts, equatorial staphylomas, retinal dysplasia, and retinal degeneration, occur as an autosomal-recessive trait in this breed (Bertram et al., 1984; Gelatt et al., 1981). Severity of ocular lesions correlates with the amount of white in the hair coat (Bertram et al., 1984; Gelatt et al., 1981). While the ocular disease is recessively inherited, the inheritance of merling appears to be dominant (Gelatt et al., 1981).
Persistent Pupillary Membranes

The pupillary membrane is a primitive mesodermal tissue present during fetal development that forms a layer on the anterior face of the iris. This membrane consists of fine blood vessels and connective tissue. Normally, the central vascular arcades regress first, beginning during the sixth week of canine development. The peripheral arcades that have their origins at the collarette of the iris regress last (Aguirre et al., 1972; Roberts & Bistner, 1968). This process continues through the final 3 weeks of fetal development and into the immediate postnatal period. In most puppies, the pupillary membranes completely atrophy by 6 weeks after birth. The rate of pupillary membrane dissolution varies, however, and it may not be complete for several months (Roberts & Bistner, 1968). Incomplete resorption of embryonal vasculature and mesenchymal tissues results in retained iris strands in both juvenile and adult dogs. These uveal remnants, which are termed persistent pupillary membranes, or PPMs, attach at the collarette region of the iris and usually retain the color of the adjacent iris. Total persistence of the fetal pupillary membrane with absence of the pupil is quite rare; when present, it is associated with other severe ocular anomalies (Martin & Leipold, 1974).

PPMs occur commonly in the dog and are usually an incidental finding. Iris-to-iris strands that bridge over the iris surface or cross the pupil and remnants with a single iris attachment that occur as small, free-floating tags are benign (Fig. 20.4). Forms of PPMs that can result in significant ocular opacification are iris-to-cornea strands and iris-to-lens strands. Resultant corneal or lenticular opacities may compromise vision. Because contact of the pupillary membrane with the lens and cornea is not normal, it is more correct to classify pupillary membranes that contact these tissues as “dysplastic” rather than persistent (Grahn & Peiffer, 2007). PPMs may be present either unilaterally or bilaterally, and different forms may be seen in the same dog.

Dysplastic pupillary membranes are observed as iridocorneal or iridolenticular adhesions that can result in significant ocular opacification (Fig. 20.5). Iridocorneal adhesions are associated with corneal edema, fibroplasia, and changes in Descemet’s membrane causing a clinical leukoma (Roberts & Bistner, 1968). The corneal opacities may remain as the only sign of dysplastic pupillary membranes. Additionally, iridolenticular strands may extend from the iris collarette to the anterior lens capsule, with the adhesions resulting in capsular opacities or anterior polar subcapsular cataracts.

Dysplastic pupillary membranes can be differentiated from anterior or posterior synechia by observing the origin of a pupillary membrane at the iris collarette and the origin of a synechia at the pupillary margin. PPMs within the width of the iris are seen most easily when the pupil is constricted. Visualization of iris-to-iris PPMs that span the pupil is accomplished more easily with mydriasis as the strands are pulled taut (Barnett & Knight, 1969). Magnification may be required to appreciate small PPMs.

Heritable, clinically significant PPMs occur in the Basenji (Barnett & Knight, 1969; Bistner et al., 1971; Roberts & Bistner, 1968). The incidence of PPMs in this breed is high, and the severity varies considerably. Examination for PPMs should be performed before pharmacologic dilation of the pupils. The most common manifestation is small, iris-to-iris PPM remnants. Mild forms appear as small, linear, or Y-shaped strands originating from the iris collarette. These minor lesions may spontaneously disappear by 8 months of age. Such lesions have no clinical significance, but they do present a problem regarding genetic control of the disease (Rubin, 1989).

The more severe form of PPM in the Basenji manifests as cobweb-like strands of iridal tissue that cross the pupil opening, with or without attachments to the cornea or lens. In
severe cases, corneal opacities are present axially or periaxially secondary to disruption of the endothelium by the pupillary membrane attachment. Corneal opacities vary in size from discrete white dots to long, linear, or broad circular opacities. Slit-lamp biomicroscopy reveals an irregular and optically denser posterior polar cataracts (Barnett & Knight, 1969; Roberts & Bistner, 1968). The deep stroma can also be affected. Multiple membranes inserting on the central or para-central lens capsule may result in multifocal or diffuse anterior polar cataracts (Barnett & Knight, 1969; Roberts & Bistner, 1968). With extensive pupillary membranes, puppies may be blind with searching nystagmus (Roberts & Bistner, 1968). The mode of inheritance has not been determined, but it does not appear to be a simple recessive or dominant trait (Bistner et al., 1971).

Histopathologically, PPMs are nests of connective tissue cells, some of which are pigmented. Areas of corneal opacification seen clinically correlate with defects in Descemet’s membrane and endothelium. Fibrous membranes in the area of the anterior lens capsule and disrupted, liquefied lens fibers are present in areas corresponding to anterior polar cataracts (Roberts & Bistner, 1968). With extensive pupillary membranes, pupils may be blind with searching nystagmus (Roberts & Bistner, 1968). The mode of inheritance has not been determined, but it does not appear to be a simple recessive or dominant trait (Bistner et al., 1971).

Familial PPMs occur in the Pembroke Welsh Corgi, Basenji, Chow Chow, and Mastiff breeds; breeding affected animals is not recommended (Genetics Committee of the American College of Veterinary Ophthalmologists, 2010; Rubin, 1989). PPMs and congenital cataracts of varying densities occur in the English Cocker Spaniel (Strande et al., 1988). Test matings have not been conclusive but suggest a complex mode of inheritance. PPMs, cataracts, entropion, wandering nystagmus, microphthalmia, and multifocal retinal folds have been observed in a closely inbred line of Chow Chows (Collins et al., 1992). Generalized corneal opacities resulting from dysplastic pupillary membranes have been observed in the Irish Setter (Collins & Moore, 1999). Additionally, both minor and severe PPMs have been noted in many other breeds as well, though the genetic implications have not been determined (Barnett & Knight, 1969; Genetics Committee of the American College of Veterinary Ophthalmologists, 2010; Rubin, 1989).

Therapy is rarely needed for PPMs. Therapy may be beneficial in severely affected eyes, but the number of options is limited. In cases of diffuse corneal opacities with considerable corneal edema, topical instillation of a hyperosmotic agent (i.e., 5% NaCl ointment) may be used 3 times daily for a trial period of 3–4 weeks. If this treatment is helpful, it may be continued indefinitely. Mydriasis is not recommended for dysplastic pupillary membrane-associated opacities because pharmacologic dilation may induce tension on the membrane attachments, thereby aggravating the corneal or lens lesions. Surgically, the membranes attached to the cornea can be excised after entering the anterior chamber, and phacoemulsification can be done for an extensive anterior capsular or subcapsular cataract. In humans, a penetrating keratoplasty is often indicated (Zaidman et al., 2007). Rarely is surgery indicated for PPMs, even in humans, but excision of the membranes with vitreous scissors after elevating the iris from the lens with sodium hyaluronate is effective (Oner et al., 2007; Sari et al., 2008).

Peters Anomaly

Peters anomaly refers to a condition in which a central corneal leukoma is associated with iridocorneal or corneolenticular adhesions that may also be associated with other ocular and systemic malformations (Bhandari et al., 2011; Dubielzig et al., 2010; Zaidman et al., 2007). A Springer Spaniel puppy was seen with a central corneal leukoma with cords of uveal tissue extending from the iris collarette to the posterior cornea. Histopathologic evaluation corroborated the clinical findings and showed disruptions in Descemet’s membrane at the sites of uveal adhesions (Swanson et al., 2001). The more severe form of PPM in the Basenji, which manifests as strands of iridal tissue attachments that disrupt the endothelium leading to corneal opacities, fits the definition of Peters anomaly. In humans, Peters anomaly has been subdivided as Peters anomaly type 1, characterized by a central corneal opacity with iridocorneal adhesions; Peters anomaly type II, characterized by a central corneal opacity with cataracts or corneolenticular adhesions; and Peters plus syndrome, characterized by Peters anomaly with systemic malformations. This condition has been associated with several genetic mutations in humans (Bhandari et al., 2011; Zaidman et al., 2007). Penetrating keratoplasty is often indicated in humans with Peters anomaly (Zaidman et al., 2007).

Aniridia and Iris Hypoplasia

A niridia, iris hypoplasia, and iris coloboma all refer to incomplete iris development. A niridia is a total absence of iris tissue, and it is extremely rare in the dog (Startup, 1966). In instances of apparent aniridia, a rudimentary iris base is usually present and would therefore be properly termed iris hypoplasia. Iris hypoplasia may occur as a partial- or full-thickness defect. Partial-thickness hypoplasia (i.e., incomplete iris coloboma) is a defect of one or more, but not all, layers of the iris. In cases of full-thickness hypoplasia, complete iris coloboma, the ciliary body processes, zonules, and equator of the lens can be visualized (Fig. 20.6). A complete iris coloboma is a result of localized developmental failure of all layers of the iris. These colobomata may be at the pupillary margin (i.e., notch coloboma), at the base of the iris (e.g., iridodiasis), or within the iris body (i.e., pseudopolycoria) (Barnett & Knight, 1969; Startup, 1966). Colobomata in the ventral aspect of the iris occur secondary to failure of closure of the optic fissure and are referred to as typical colobomata. Colobomata in other locations are referred to as atypical colobomata and may be caused by primary abnormalities in the outer layer of the optic cup (Cook, 1995). Iris coloboma is a common
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A complete lack of iris is seen clinically at the seven- to nine-o’clock position, revealing the ciliary processes and lens equator. No pupillary light response could be elicited in this dog. Vision and the remainder of the ocular examination were normal.

**Other Congenital Pupillary Abnormalities**

Several congenital pupillary abnormalities exist in dogs and may occur as sporadic abnormalities or in conjunction with previously described anomalies. Polycoria, an iris with more than one pupil with associated musculature, is extremely rare. More often, pseudopolycoria is present. Pseudopolycoria refers to multiple colobomata in the iris body that do not have associated pupillary musculature. Dyscoria is an abnormally shaped pupil, and corectopia is a pupil in an anomalous position. Mircocoria is a congenital miosis resulting from absence of the dilator muscle.

**Miscellaneous Congenital Abnormalities**

Abnormal, lightly pigmented irides occur in beagles with hereditary tapetal degeneration (Burns et al., 1988). The melanosomes in the iris stroma and choroid of affected dogs are fewer in number than those found in the irides of unaffected beagles. The iris and ciliary body pigmented epithelium contain melanosome organelles but no normal melanosomes. In addition, the melanin deposition is patchy and irregular. The condition may result from a defect in synthesis of the matrix component of melanosomes, resulting in absent or abnormal deposition of melanin and initiating autophagy of these organelles (Burns et al., 1988).

In a litter of Springer Spaniel pups, multiple ocular defects, including microphthalmia, PPMs, ciliary body dysplasia, lens luxation, and cataract, were present. The puppies were blind and smaller than normal but were otherwise healthy. Histopathologically, the pars plicata had irregular and thickened margins, and the zonules were well organized but abnormal in length and shape (Dubielzig et al., 1985). Ciliary body hypoplasia has been seen in dogs with multiple ocular defects (Gwin et al., 1981; Martin & Leipold, 1974).

Congenital uveal cysts can occur alone or in conjunction with other ocular anomalies. Additionally, congenital cysts may not be observed until the dog is older, making the diagnosis of “congenital” questionable. One explanation for the development of an iris cyst is failure of fusion of the two layers of the primary optic vesicle because most cysts in dogs form between the two layers of pigmented iris epithelium (Peiffer & Gelatt, 1976). Failure of the two embryonal neuroectodermal layers to fuse allows fluid to accumulate between these otherwise contiguous epithelial layers (Duke-Elder, 1963a). Cysts located at the pupillary margin are associated with a persistent or excessive development of the marginal sinus (Duke-Elder, 1963a). A nther possible explanation for congenital cysts is entrapment of surface ectodermal epithelium, neuroectoderm, and mesodermal tissue during development (Deehr & Dubielzig, 1998; Grutzmacher et al., 1987).

Cysts may enlarge, suggesting that a limited proliferative or secretory activity of the epithelial cells remains (Duke-Elder, 1963b). Histopathologically, the cysts are simply composed of heavily pigmented epithelial cells (Carter & Mausolf, 1970). Cysts may be located caudal to the iris in association with the ciliary body or the posterior epithelium of the iris, at the pupillary margin, or free in the anterior chamber or vitreous. Uveal cysts are particularly common in retriever breeds, but they also occur in other breeds (Corcoran & Koch, 1993; Genetics Committee of the American College of Veterinary Ophthalmologists, 2010; Rubin, 1989; Startup, 1966). Anterior uveal cysts are discussed in more detail under “Degenerative Iridal Changes.”

A anterior segment dysgenesis, which is an anterior chamber-cleavage anomaly syndrome, has been described in Doberman puppies (Andnbjerg & Jensen, 1982; Bergsjo et al., 1984; Lewis et al., 1986; Peiffer & Fischer, 1983). Affected eyes are blind and are characterized clinically by variable microphthalmia and opaque corneas. Malformation of mesodermal, ectodermal, and neuroectodermal tissues is involved. A primary defect in formation of the neuroectodermal optic cup is suspected as the cause (Peiffer & Fischer, 1983). A nterior segment dysgenesis is characterized histopathologically by a thinned corneal epithelium and stroma, absent Descemet’s membrane and endothelium, undifferentiated anterior uveal tissue with lack of iridocorneal angle differentiation, and unencapsulated globules of lens material. Occasionally, rudimentary iris leaflets or elongated ciliary processes are observed. Posterior segment anomalies include hyperplastic primary vitreous, hyaloid artery remnants, retinal dysplasia, and retinal detachments (Andnbjerg & Jensen, 1982; Lewis et al., 1986; Peiffer & Fischer, 1983). The mode of inheritance in Doberman Pinschers is thought to be autosomal recessive (Lewis et al., 1986). Owners of dogs related to affected Doberman Pinschers should be informed about the genetic implications of this anomaly. Unfortunately, there is no treatment. Similar...
DEGENERATIVE IRIDAL CHANGES

Senile Iris Atrophy

Spontaneous, progressive thinning of the stroma or pupillary margin of the iris is a common finding in older dogs and may occur in any breed. Most commonly, the pupillary margin develops a scalloped, moth-eaten appearance (Fig. 20.7). In these animals, atrophy of the pupillary muscles often results in dyscoria and may lead to a reduced or absent pupillary light responses. Therefore, when effenter pupillary abnormalities are present, iris atrophy must be considered as a possible cause.

Senile iris atrophy may also initially manifest as a subtle color change: the natural iris color fades, and foci of hyperpigmentation may be noted as stroma is lost and pigmented epithelium is exposed. As degeneration progresses, additional thinning may result in loss of pigmented epithelial layers. With transillumination, affected areas appear as translucent patches or openings within the iris and are most striking when light is reflected from the tapetal fundus through the areas of affected iris. These full-thickness defects should not be mistaken for congenital iris colobomata (Fig. 20.8). Vision is unaffected by iris atrophy; however, severe cases may result in photophobia.

Secondary Iris Atrophy

Glaucoma and chronic uveitis may cause degenerative changes in the iris resembling those of senile iris atrophy. Signs of preexisting disease such as buphthalmia, lens subluxation, synechiae, or pigment dispersion on the anterior lens capsule may be present, aiding in the diagnosis. As with senile iris atrophy, there is no specific treatment, but any active, concur- rent glaucoma, or uveitis should be treated.

Uveal Cyst

Uveal cysts are frequently seen in dogs. They may arise either from the posterior pigmented epithelium of the iris or from the inner ciliary body epithelium and therefore are neuroectodermal in origin (Carter & Mausolf, 1970; Hildreth et al., 1991; Rush et al., 1982). The cysts can be congenital or acquired. They occur most commonly in Golden Retrievers, Labrador Retrievers, and Boston Terriers (Corcoran & Koch, 1993). Multiple iris cysts have been reported in an English Setter as well (Peiffer & Gelatt 1976).

Cysts may arise from the pupillary margin, the posterior iris face, or the pars plicata of the ciliary body. Examination through a dilated pupil may facilitate visualization of cysts in the posterior chamber. Potential sequelae of larger cysts include vision impairment, corneal endothelial opacities, pigmentation of the anterior lens capsule, mechanical interference with iris function, and aqueous outflow obstruction with secondary ocular hypertension (Bedford, 1980; Deehr & Dubielzig, 1998; Peiffer & Gelatt 1976; Spiess et al., 1998). Most cysts are first noted clinically in adult dogs and may occur spontaneously; however, trauma and inflammation have also been proposed as initiating etiologies. When cysts occur without preexisting eye disease, it is possible that a defect was present at birth, and the cysts were not recognized until several years of age (see “Miscellaneous Congenital Abnormalities”) (Duke-Elder, 1963a).

Uveal cysts are usually benign and are incidental findings in the dog. Iridal or ciliary cysts can be unilateral or bilateral; single or multiple; variably sized; and spherical, oval, or elongated dark or translucent masses (Fig. 20.9). Uveal cysts are usually brown or black, though light brown and amelanotic
Uveal cysts are usually diagnosed on the basis of the clinical appearance described. However, the most definitive diagnostic test is performed by transilluminating the cysts with a bright light source. Cysts should transilluminate, whereas neoplastic masses will not transilluminate. This test may not be reliable for very small cysts or cysts that are not within the pupil, making it difficult to generate a tapetal reflection through the cyst. Ocular ultrasound can be used in questionable cases.

**Uveal Cyst Removal**

Because most uveal cysts are benign and generally do not interfere with vision, they usually do not require treatment. However, attached or free-floating uveal cysts that occlude the pupil and compromise vision or multiple cysts that may lead to angle closure may be aspirated with a small-gauge needle or deflated with a laser. Because these cysts generally arise from the posterior iris pigment layer, they are darkly pigmented and are easily visualized. Poorly pigmented cysts may not be amenable to diode laser therapy. Surgical removal or aspiration of the cysts may prevent progressive angle closure when identified and treated early (Spiess et al., 1998).

The use of semiconductor diode lasers for deflation and coagulation of anterior uveal cysts is effective. Perioperatively, mydriatics and corticosteroids are used topically. The operating microscope attachment and the indirect ophthalmoscope facilitate treatment of these cysts because these two delivery systems emit a converging laser beam appropriate for transcorneal treatment of intraocular cysts and tumors. Topical anesthetic, sedation, or general anesthesia can be used. Discomfort or aqueous flare is not seen postoperatively (Gemensky-Metzler et al., 2004). An Nd:YAG laser may also be used to destroy uveal cysts. Occasionally, remnants of the cyst remain attached to the corneal endothelium.

Alternatively, a straight, 25- or 27-gauge needle attached to a tuberculin syringe can be introduced into the anterior chamber at the limbus. The precise point of entry will vary with the cyst location and should facilitate comfortable hand positioning for the surgeon. The tip of the needle is directed toward the cyst. Because the cyst wall is quite thin, it is readily penetrated by the beveled needle tip. After the cyst wall is punctured, slight negative pressure is exerted on the syringe plunger to collapse the cyst. The needle is then immediately withdrawn. Portions of the collapsed cyst may remain free in the anterior chamber or as a residual layer of pigment on the ventral corneal endothelial or anterior lens capsule. In most cases, uveal cysts do not obstruct vision or cause lens or corneal opacities. Reports describing the association with cysts and glaucoma in both the Golden Retriever and Great Dane have emerged and are described later under “Pigmentary and Cystic Glaucoma (Pigmentary Uveitis).”

**Uveal Inflammation**

Uveitis occurs commonly in conjunction with many intraocular and systemic diseases. Uveitis refers to inflammation of the uveal tissue, which is composed of the iris, ciliary body,
and choroid. Uveitis is common because of the highly vascular nature of the tissue, its immunosensitivity, and its close proximity to other structures. Similar to inflammation elsewhere, inflammation in the uvea consists of three basic events: increased blood supply, augmented vessel permeability, and white blood cell migration to the injury site (Dalma-Weiszhaus & Dalma, 2002). A anterior uveitis is inflammation of the iris and ciliary body, posterior uveitis is inflammation of the choroid, and panuveitis is inflammation of all three portions of the uvea. More specifically, iritis and cyclitis may be used to describe inflammation of the iris and ciliary body, respectively. Anterior uveitis is the term most commonly used, because differentiating between iritis and cyclitis clinically is very difficult and usually both tissues are inflamed simultaneously. Posterior uveitis, or choroiditis, can occur independently from anterior uveitis. A more advanced condition, termed endophthalmitis, is inflammation involving the ocular cavities and adjacent structures. Panophthalmitis is inflammation involving all tunics of the eye, and it may result in signs of orbital disease as well. Chapter 24 discusses posterior segment inflammations.

Etiopathogenesis of Uveitis

Uveitis can occur independently of disease in other ocular structures, or it can occur secondary to lens, corneal, or scleral disease. Additionally, uveitis can be associated with primary ocular disease or be secondary to neoplastic, infectious, or immune-mediated diseases. Elucidating the etiology of uveitis in the dog can be difficult. However, because uveitis can lead to blindness or be a sign of a potentially fatal disease, attempting to define the etiology is always warranted. Uveitis should be approached in a systematic fashion evaluating for the most common diseases based on signalment, historical information including travel, ocular and physical examination findings, and locale.

Many etiologies for uveitis exist in all animal species. Most simply, causes can be divided into endogenous and exogenous. Endogenous causes originate from within the eye or spread to the eye from the bloodstream or from contiguous structures. Endogenous causes account for most cases of uveitis and include infectious, neoplastic, toxic, metabolic, and autoimmune diseases. Immune-mediated and autoimmune disease is the most rapidly growing group of diseases responsible for endogenous uveitis. Several endogenous antigens have been found to be associated with uveitis, including retinal-S antigen, melanin, and lens and corneal proteins (Bellhorn et al., 1988; Morgan, 1989; Parma et al., 1985; Wilcock & Peiffer, 1987). Exogenous causes arise from outside the eye and most commonly involve trauma but also include radiation exposure and chemical injuries (Jamieson et al., 1991). Trauma also includes surgical procedures and both perforating and nonperforating injuries with or without secondary infection.

As stated previously, many diseases and conditions are known to cause uveitis in the dog. Idiopathic uveitis is the most common diagnosis given to dogs with anterior uveitis (Gelatt & MacKay, 2004; Massa et al., 2002). One review found that an etiology for anterior uveitis could not be determined in 47% of the dogs. Infectious disease was diagnosed in 18%, neoplasia in 25%, and uvedermatologic syndrome (UDS) or a vaccine reaction in 10% of the dogs (Massa et al., 2002). This study excluded dogs with anterior uveitis secondary to cataracts or trauma. The more commonly recognized causes of uveitis in the dog are listed in Table 20.1. Several excellent reviews have also addressed uveitis in small animals (Crispin, 1988; Gwin, 1988; Hakanson & Forrester, 1990; Massa et al., 2002; Townsend, 2008).

General Uveal Inflammatory Responses

Most knowledge regarding canine uveitis has been derived from experimental and clinical observations in a variety of animal species, including humans. Clinicians must recognize that species variation exists and that some data may not be applicable and may even be contradictory to mechanisms occurring in the dog. Still, several unique aspects of uveal inflammation do cross species lines and play a role in the uveal response. These include (1) the blood-aqueous barrier, (2) the concentration of ascorbic acid and other antioxidants in the aqueous humor, (3) the anterior chamber-associated immune deviation (ACAID), and (4) the lack of an intrinsic lymphatic system (Rosenbaum et al., 1999).

Uveitis is always initiated by tissue injury. This injury may be incited by trauma, bacteria, fungi, parasites, viruses, or immune-mediated disease. The ensuing clinical signs are attributed to disruption of the blood-ocular barrier and release of various chemical mediators after tissue damage. The blood-ocular barrier is composed of the blood-aqueous barrier anteriorly and the blood-retinal barrier posteriorly. Morphologically, this barrier consists of tight junctions (zonulae occludens) between nonpigmented ciliary body epithelial cells, tight junctions and gap junctions in the iris vascular endothelium, and nonfenestrated impermeable capillaries in the iris (Freddo & Sacks-Wilner, 1989; Gabelt & Kaufman, 2003). Evolutionary divergence in ocular defense mechanisms has resulted in extreme differences of blood-aqueous barrier stability among different mammalian species. Primates have a very stable barrier, whereas the rabbit has an extremely labile barrier, which destabilizes in response to minute ocular irritants (Bito, 1984). Stability of the canine blood-aqueous barrier lies somewhere between these two extremes. Destabilization of the blood-aqueous barrier marks the onset of anterior uveitis.

Three phases of the ocular inflammatory response have been identified: active, subacute, and chronic responses (Peiffer, 1980; Yanoff & Sassani, 2009). A phase with inflammation in other tissues, the acute phase has the five cardinal signs, including redness and heat, which are both caused by increased rate and volume of blood flow; increased mass caused by exudation of fluid and cells; and pain and loss of function, which are both caused by outpouring of fluid and irritating chemicals. Immediately after injury, the arterioles contract for
approximately 5 minutes and then gradually dilate because of histamine release from mast cells and factors released from plasma (kinin, complement, and clotting systems). The chemical mediators, which include histamine, serotonin, kinins, plasmin, complement, prostaglandins (PGs), and peptide growth factors, increase vascular permeability by causing the intercellular tight junctions in the vascular endothelial cells to open, allowing fluid to leak into the tissues. After several hours, the blood flow decreases to below normal because of increased viscosity of the blood resulting from fluid loss. Early after injury, various types of blood vessels marginate (polymorphonuclear neutrophils [PMNs]), then leave the vessels via emigration (PMNs), emperipolesis (PMNs, small lymphocytes, macrophages, and immature erythrocytes), and diapedesis (mature erythrocytes) (Yanoff & Sassani, 2009). In addition, plasma proteins, initially albumin and then larger globulins, leak through the vessel walls (Peiffer, 1980). Reported mean values for aqueous protein in the noninflamed canine eye using different assays range from 21 ± 1.2 mg/dL to 37.4 ± 7.9 mg/dL (Blogg & Coles, 1971; Brightman et al., 1981; Krohne & Vestre, 1987; Olin, 1977). In sharp contrast, aqueous protein values at various intervals after the onset of uveitis range from approximately 1200 mg/dL to as high as 6600 mg/dL in experimental and clinical cases, respectively. Additionally, flaremetry readings in clinically normal canine eyes range from 1.4 to 7.0 photon count (PC)/msec, with actual protein measurements ranging from 5 to 28 mg/dL (Krohne et al., 1995). One eye with uveitis that was considered subjectively to have a 3+ flare had flaremetry readings as high as 246 PC/msec and a protein concentration of 729 mg/dL (Krohne et al., 1995).

The acute phase of the ocular inflammatory response is exudative. There are four types of exudates: serous exudate is composed primarily of protein; fibrinous exudate is composed primarily of fibrin; sanguineous exudate is composed primarily of erythrocytes; and purulent exudate is composed primarily of PMNs and necrotic products. These exudates are seen clinically as aqueous flare, fibrin clot (or plastic aqueous), hyphema, or hypopyon, respectively (Yanoff & Sassani, 2009). In acute inflammation, the PMN is the predominant type of inflammatory cell present (Olin, 1977). The degranulation or death of PMNs causes additional tissue destruction and increases inflammation by inducing the chemotaxis of mononuclear phagocytes characteristic of the subacute stage (Yanoff & Sassani, 2009).

The subacute stage has special significance because during this period the immunologic reactions are initiated, healing occurs, or there is necrosis, recurrence, or chronicity (Yanoff & Sassani, 2009). If the inflammatory response is localized, the PMNs and mononuclear phagocytes can resolve the injury, and healing is possible with minimal scarring. If the inflammation is profound and uncontrolled, however, granulation tissue may result in excessive scarring, with subsequent ocular dysfunction. Granulation tissue is composed of leukocytes, fibroblasts, and proliferating blood vessels, which tend to be leaky when new. If healing ensues, the blood vessels involute,
the leukocytes disappear, and the fibroblasts return to a resting state. If healing does not occur because of the inability to control both acute and subacute inflammatory events, the inability to eliminate the causative agent, or both, the inflammation becomes chronic (Yanoff & Sassani, 2009). Permanent alterations in uveal vascular structure, permeability, or both have been implicated as the cause of recurrent or chronic episodes of uveitis (O’Connor, 1983).

It may be possible to distinguish acute (<4 weeks) from chronic (>4 weeks) uveitis on the basis of aqueous protein and cellular determinations. Dogs with acute uveitis have higher protein values (3.5 g/dL) than those suffering from chronic uveitis (1.8 g/dL). Polymorphonuclear cells are more typical of acute uveitis compared with a predominance of small and large mononuclear cells in those with chronic uveitis (Olin, 1977).

Chemical Mediators of Inflammation

Much effort has been directed toward identifying the chemical mediators of ocular inflammation because their recognition has direct therapeutic implications. While progress is always being made toward understanding inflammation, the variations in species’ responses to inflammation and the varying diseases among species slow the progress.

PGs are the most widely studied mediators of ocular inflammation and are considered to be primary mediators of ocular inflammation (O’Connor, 1983; Wilkie, 1990b). Cyclooxygenase has been identified in all cell types, except for mature red blood cells (Kulkarni & Srinivasan, 1986), and PGs are produced by the irides of all species studied to date (Yoshitomi & Ito, 1988). The most notable pathologic ocular effects of PGs include miosis, hyperemia, changes in vascular permeability, and alterations in intraocular pressure (IOP) depending on the particular PG and species in question. Most of these effects are caused by direct action on the specific tissue. PGs disrupt the tight junctions between nonpigmented ciliary body epithelial cells and, to a lesser extent, the iridal vasculature, thereby allowing protein exudation and aqueous flare (Adler, 1992; Laties et al., 1966). In the dog, PGF₂α is a potent constrictor of the iris sphincter muscle, whereas PGE₁ and PGE₂ have little effect (Dziezyc et al., 1992; Yoshitomi & Ito, 1988). This action is independent of cholinergic or adrenergic innervations (Yoshitomi & Ito, 1988).

PGs also have normal physiologic functions such as moderation of inflammation, hypotensive effects, and other beneficial therapeutic effects (Bito, 1986; Havener, 1983). The PGs involved in uveitis, however, are present in excessive quantities. The eye has limited amounts of PG 15-dehydrogenase, which is the enzyme responsible for inactivation of PGs; therefore, PGs must be removed by active transport through the ciliary body for inactivation elsewhere. When uveitis is present, these active transport mechanisms are diminished (Bito, 1986; Eakins et al., 1974).

PG analogs are used extensively in the treatment of glaucoma in humans and dogs. With their use, several side effects, including iritis, have emerged (Schumer et al., 2002). However, several studies have failed to detect even small changes in the blood-aqueous barrier in normotensive volunteers and in glaucoma patients (Schumer et al., 2002). Transient, low-grade uveitis has been detected in patients receiving latanoprost in excessive doses (Linden & Alm, 2001). One reason for the lack of development of uveitis may be that PG does not have chemotactic properties (Schumer et al., 2002).

A rachidonic acid derivatives appear to play a key role in ocular inflammation. A rachidonic acid is released from damaged cellular membranes through phospholipases acting on cellular phospholipids (Boothe, 1984). It can then enter one of at least three metabolic pathways: the cyclooxygenase, lipoxygenase, or oxidation pathway (Millichamp & Dziezyc, 1991; Wilkie, 1990a). Each of these pathways has been identified in the eyes of various species, but the relative contribution of each in the genesis of uveitis is poorly defined (Collins & Moore, 1999). The cyclooxygenase pathway produces PGs, thromboxane, and prostacyclin, and the lipoxygenase pathway produces leukotrienes, hydroperoxy, and hydroxyeicosatetraenoic acids (Millichamp & Dziezyc, 1991; Wilkie, 1990a).

Leukotrienes are synthesized in the cornea, conjunctiva, anterior uvea, and lens. Species variations exist in the extent and duration of leukotriene production (Dziezyc et al., 1989). Leukotrienes are potent vasoactive substances and chemotactants. Their chemotactic, humoral, and cellular activities are greater than those of PGs (Boothe, 1984). Leukotriene B₄ has almost no vasoconstrictive activity but allows adherence of leukocytes to vascular endothelium; this may be an early mechanism for cell migration into the inflamed uvea (O’Connor, 1983). In a canine model of lens-induced uveitis (LIU), levels of leukotriene B₄ were increased during early inflammation (Dziezyc et al., 1989). In addition, dogs that received systemic lipoxygenase inhibitors did not experience the transient rise in IOP during acute uveitis often attributed to PGs, whereas the control dogs did. In another study that used a mild paracentesis model of uveitis, it was concluded on the basis of similar results in treated and control dogs that leukotrienes are not important mediators of blood-aqueous barrier disruption in dogs (Ward et al., 1992a). Furthermore, it was suggested that leukotriene inhibitors might exacerbate uveitis through shunting of arachidonic metabolites to the cyclooxygenase and epoxygenase pathways.

Substance P, an undecapeptide normally present in sensory nerves, may be important in uveitis, particularly when associated with corneal irritation (O’Connor, 1983). Ulcerative keratitis causes varying degrees of uveitis, but it does so through a poorly understood “axon reflex.” With corneal irritation, antidromic impulses mediated by the trigeminal nerve (ophthalmic branch) reaching the iris and ciliary body are believed to stimulate release of substance P. This causes vascular dilatation and altered permeability as well as PMN chemotaxis. These effects are transient and unlikely to result in permanent uveal changes. The role of substance P in canine uveitis is unclear (O’Connor, 1983; Unger & Tighe, 1984).
SECTION III: Canine Ophthalmology

Also be a secondary component of other ocular diseases, such as corneal ulceration and glaucoma, demonstrating the need for a complete ophthalmic examination. The clinical signs of uveitis are listed in Table 20.2.

<table>
<thead>
<tr>
<th>Anterior Uveitis</th>
<th>Posterior Uveitis</th>
<th>Additional Adverse Sequelae</th>
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<tbody>
<tr>
<td>Aqueous flare</td>
<td>Vitreous opacity</td>
<td>Deep corneal vascularization</td>
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<tr>
<td>Fibrin in anterior chamber</td>
<td>Decreased vision</td>
<td>Ectropion uvea</td>
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<td>Keratic precipitates</td>
<td>Chorioretinal granulomas</td>
<td>Iris atrophy</td>
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<td>Hyphopyon</td>
<td>Retinal detachment</td>
<td>Rubeosis iridis (or pre-iridal fibrovascular membrane)</td>
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<td>Hyphema</td>
<td>Retinal hemorrhage</td>
<td>Secluded pupil and iris bombé</td>
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<tr>
<td>Miosis</td>
<td>Choroidal effusion</td>
<td>Secondary glaucoma</td>
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<td>Decreased intraocular pressure</td>
<td>Optic neuritis</td>
<td>Cataract</td>
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<td>Ciliary flush</td>
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<td>Lens luxation</td>
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<tr>
<td>Corneal edema</td>
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<td>Endophthalmitis/panophthalmitis</td>
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<td>Iris color change (usually darker)</td>
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<td>Phthisis bulbi</td>
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<td>Iris swelling</td>
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<tr>
<td>Pain</td>
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<tr>
<td>Posterior synechiae</td>
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<tr>
<td>Decreased vision</td>
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<td>Conjunctival hyperemia</td>
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One study indicated that PGs play a greater role than substance P in the canine ocular irritative response induced by rapid paracentesis because inhibition of neuropeptide release by topical application of proparacaine did not affect the response of blood–ocular barrier breakdown and miosis (Ward et al., 1992a). However, when topically applied pilocarpine is used as a model for measuring aqueous flare and miosis, pretreatment with proparacaine or with nonsteroidal anti-inflammatory drugs (NSAIDs) inhibits the response equally (Krohne et al., 1998). The variation in results of the two studies may be due to the method of inducing aqueous flare. While the pilocarpine model does increase protein in the aqueous humor, it does not appear to do so by interfering with the blood–aqueous barrier (Freddo et al., 2006).

Numerous other chemical mediators also have contributory, albeit largely undefined, roles in ocular inflammation. Histamine is important in the initiation of many inflammatory processes, and its release from mast cells leads to an increase in vascular permeability (Yanoff & Sassani, 2009), but histamine’s role in canine uveal disease is poorly understood. Reactive oxygen metabolites, angiotensin-converting enzyme, and basic fibroblast growth factor may also play roles in uveitis (Abrams, 1989; Grahn et al., 1992; Mittag, 1984). For information on direct functional impact of immune cells on the ocular microenvironment and mechanisms of ocular immune homeostasis, see Chapter 5.

**Clinical Manifestations and Diagnosis**

Anterior uveitis can manifest with many clinical signs. Some of these signs are specific for uveitis, such as aqueous flare and hyphopyon, while others are general ocular responses, such as blepharospasm and ocular hyperemia. Anterior uveitis can also be a secondary component of other ocular diseases, such as corneal ulceration and glaucoma, demonstrating the need for a complete ophthalmic examination. The clinical signs of uveitis are listed in Table 20.2.

Excessive lacrimation, blepharospasm, and photophobia are readily observed. These signs suggest varying degrees of ocular discomfort not specific to uveitis. Anterior uveitis tends to be more painful than chronic uveitis. The pain is referred to the ocular and periorbital regions. Pain and photophobia are caused by ciliary spasm. Excessive lacrimation is thought to occur secondary to the photophobia (Hogan et al., 1959).

Ciliary flush is hyperemia of the deep, perilimbal, or circumcorneal anterior ciliary vessels and is common with deep corneal and intraocular disease (i.e., uveitis and glaucoma). Congestion of the conjunctival vessels also commonly occurs with uveitis, and in severe cases, uveitis can even lead to chemosis (Hogan et al., 1959). Determination of the presence of ciliary flush is important for diagnostic purposes because it must be distinguished from superficial conjunctival hyperemia, which is commonly seen with extraocular disease such as allergic conjunctivitis. Distinguishing between these vascular patterns may be facilitated by topical application of a sympathomimetic agent (e.g., 1% epinephrine solution). The topical sympathomimetic agent will have a greater immediate vasoconstrictive effect on the superficial conjunctival vessels than on the deeper anterior ciliary vessels (Rubin, 1968). In addition, conjunctival vessels are noted to move on the surface of the globe, whereas the anterior ciliary vessels remain stationary within the sclera during movement of the globe.

Corneal edema with an associated increase in corneal thickness develops with anterior uveitis secondary to both an increase in endothelial permeability and a decrease in Na/K ATPase pump site density (Fig. 20.11) (MacDonald et al.,...
also cause painful spasm of the ciliary body musculature, causing what is described as “brow ache” in humans. Subtle miosis is often more apparent when examining both eyes simultaneously in a darkened room using retroillumination with a penlight or Finoff transilluminator. The comparison of light reflected from the tapetal fundi in this technique readily allows detection of disparities in pupil size, or anisocoria. Iris swelling from edema and cellular infiltrates may also, in conjunction with inflammatory mediators, impede normal pupil mobility. Subclinical uveitis often manifests with a pupil that dilates more slowly after short-acting mydriatic therapy (i.e., 1% tropicamide) compared with the normal eye. This observation is itself diagnostic. Conversely, the pupil may respond sluggishly to light. In addition, the pupil may be nonresponsive because of increased IOP seen with secondary glaucoma or synechia.

Synechia formation is one of the more serious complications of anterior uveitis, and it results from inflammatory cells, fibrin, and fibroblasts leading to adhesions of the iris to the lens or peripheral cornea. Both peripheral anterior synechiae and posterior synechiae occur (Fig. 20.13). Peripheral anterior synechiae form because of shallowing of the anterior chamber as a result of pupillary block, secondary to organization of inflammatory exudates in the angle with gradual attraction of the iris toward the angle structures, and with intense swelling of the root of the iris (Hogan et al., 1959). Posterior synechiae are a consequence of the central portion of the lens extending more anteriorly than the peripheral lens. With miosis, the iris is in more intimate contact with the lens, increasing the surface area for synechia formation. Fibrin and other inflammatory products allow the iris to adhere to the lens capsule. Posterior synechia can cause occlusion of the pupil, leading to loss of sight or seclusion of the pupil and resulting in iris bombe with subsequent acute glaucoma (Fig. 20.14). Synechia can result in a fixed miotic or midrange pupil. With chronic synechiae, pigment often migrates from the surface of the iris onto the

1987). Severe edema may result in bulla formation. Morphologically, edematous endothelial cells with disrupted intercellular junctions and a normal cell density are seen. The exact mechanisms for the damage to the endothelium probably include formation of PG, oxygen-free radicals, and hydrolytic enzymes liberated in part by leukocytes. Persistent corneal edema may be followed by peripheral corneal vascularization. The use of steroids prevents these morphological and physiologic changes. IOP determination is helpful in distinguishing the corneal edema of uveitis from that of glaucoma, but the two often occur together. Peripheral corneal edema can also occur from extension of inflammation from the limbal circulation (Hogan et al., 1959).

Pupillary constriction, or miosis, is a very common sign of anterior uveitis. Miosis occurs in response to PGF, acting directly on the iris sphincter muscle (Fig. 20.12) (Dziezyc et al., 1992; Yoshitomi & Ito, 1988). Inflammatory mediators

Figure 20.11. Severe corneal edema, corneal vascularization, and conjunctival hyperemia are present in this dog with anterior uveitis secondary to blastomycosis.

Figure 20.12. Congestion of iris vessels and miosis are evident in a Pharaoh Hound with anterior uveitis secondary to blastomycosis.

Figure 20.13. Posterior synechiae is the only evidence of previous anterior uveitis in this eye that has a hypermature cataract.
anterior lens capsule, which is more likely to interfere with vision if the pupil is miotic. Pigment clumps on the anterior lens capsule usually indicate previous uveitis; however, the pigment clumps can result from congenital remnants of the pupillary membrane. Lens capsular pigment from uveitis is usually darker than the pigment associated with pupillary membranes, and in the latter instance, pigment is usually confined to the axial lens surface. Prolonged inflammation in the iris epithelium and stroma may eventually result in iris atrophy that may be patchy or diffuse.

Aqueous flare, increased turbidity of aqueous humor, occurs as protein-rich aqueous humor and cellular components accumulate within the anterior chamber after the blood-aqueous barrier has been disrupted. Aqueous flare is visualized when light scattering from particles suspended in the anterior chamber causes a continuous light reflection throughout the chamber. This continuous beam effect is called the Tyndall phenomenon, and it is analogous to shining a flashlight within a smoke-filled room. Observation of the Tyndall phenomenon is indicative of aqueous flare, and aqueous flare is pathognomonic for anterior uveitis (Berliner, 1966). Varying degrees of aqueous flare are possible, and though this scheme is highly subjective, some clinicians attempt to quantitate flare numerically as 1+ to 4+, with higher numerals indicating increased severity (Hogan et al., 1959). One grading scheme describes the severity of flare as follows: 1+ indicates faint flare (barely detectable), 2+ indicates moderate flare (iris and lens details are clear), 3+ indicates marked flare (iris and lens details are hazy), and 4+ indicates intense flare (fixed, coagulated aqueous humor with fibrin) (Fig. 20.15) (Hogan et al., 1959). Flare is best detected with slit-lamp biomicroscopy, but other focal light sources (e.g., the small aperture of a direct ophthalmoscope) in a very dark room may also be useful. Experimentally, laser flaremetry and fluorophotometry are used to assess the amount of protein in the aqueous humor. The flare meter quantitates the level of aqueous humor protein by measuring PC of scattered light, which is proportional to the amount of protein in the anterior chamber (Krohne et al., 1995). In experimental studies of uveitis, fluorophotometry, in which fluorescein concentrations in the anterior chamber are measured after intravenous injection of fluorescein, has also been useful (Ward et al., 1991).

The term fibrinous (or plasmoid) aqueous refers to aqueous humor that has an increased level of aqueous protein approximating that of normal plasma. This condition occurs most commonly in cases of acute, severe anterior uveitis with sudden onset. If fibrinous exudation is severe, fibrin clots may form in the anterior chamber. Lipid-laden aqueous is also possible if the patient has concurrent hyperlipidemia in which the aqueous assumes a milky-white appearance (Fig. 20.16) (Olin et al., 1976). A specific cause-and-effect relationship between hyperlipidemia and uveitis is not well established; however, in most instances, lipids simply enter the chamber.

Figure 20.14. Iris bombé secondary to 360 degrees of posterior syn-echia has caused the iris to balloon forward in this dog. Episcleral injection is also present.

Figure 20.15. The visible haziness in this eye is caused by slight corneal edema and aqueous flare.

Figure 20.16. Lipoid aqueous is visible in the anterior chamber of this Miniature Schnauzer.
with blood–aqueous barrier breakdown, as do other large proteins.

Cells from the inflammatory process pass into the aqueous humor either from diffusion or from active migration from the uvea. They are either manufactured locally or egress through the capillary walls from the blood into the uveal tissue and into the aqueous humor (Hogan et al., 1959). Keratic precipitates (KPs) are accumulations of inflammatory cells, fibrin, and pigment from the iris that are deposited on the corneal endothelium (Fig. 20.17). KPs are usually located inferiorly on the cornea in a triangular shape with the apex located superiorly. Convection currents in the anterior chamber that rise along the warm iris and fall along the cooler cornea create the characteristic formation (Tessler, 1989). KPs can be readily missed, however, if the examiner is not specifically looking for them. Detection of KPs is facilitated by magnification and gently tilting the animal’s head downward, thereby allowing upward rotation of the eye and ready examination of the ventral cornea. In painful eyes with protrusion of the nictitating membrane, KPs can be especially difficult to observe. It is important to note KPs because their presence is always indicative of active or previous uveitis. In early studies, Koepe placed pathognomonic significance on the size, shape, and appearance of certain KPs (Berliner, 1966). In some granulomatous conditions, KPs tend to form as large, waxy-yellow deposits, often called “mutton-fat” deposits. Berliner notes that these deposits are made of plasma cells and macrophages typical of granulomatous inflammation and that they have a greater tendency to agglutinate and adhere to the cornea than do lymphocytes and polymorphonuclear cells, as is typical of nonspecific uveitides (Berliner, 1966). However, lymphocytes and polymorphonuclear cells can also form “nongranulomatous” KPs, which tend to be smaller (Whitcup, 2010). Therefore, the presence of KPs should be noted and the finding incorporated with additional information. Varying amounts of pigment are present in KPs, with larger amounts seen with chronicity.

The deposition of red and white blood cells within the anterior chamber are the most marked examples of blood–uveal barrier breakdown and are termed hyphema and hypopyon, respectively (Fig. 20.18 and Fig. 20.19). In both instances, cellular components typically gravitate toward the ventral anterior chamber and settle in a homogeneous layer. If bleeding was initially extensive or is continuous, complete (i.e., total) hyphema with filling of the entire anterior chamber may occur. Layering in the hyphema may indicate rebleeding. Occasionally, iridal hemorrhage may be seen (Fig. 20.20). Clotted blood may also be observed. The term eight-ball hyphema has been used to describe complete hyphema of 5–7 days’ duration when the blood turns from bright red to bluish black. Blood staining of the cornea can occur, especially with large hyphemas, corneal epithelial damage, and elevated IOP.
Pre-iridal fibrovascular membranes (PIFM s) arise from the anterior border layer of the iris and develop secondary to chronic ocular disease such as uveitis, glaucoma, intraocular neoplasia, endophthalmitis, and retinal detachment (Peiffer et al., 1990). The clinical term for this condition is rubeosis iridis. Clinically, a haphazard array of very small vessels is seen on the iridal surface (Fig. 20.21). These vessels can extend over the lens or pectinate ligaments and are differentiated from normally present but dilated iridal vessels by the haphazard organization as opposed to the radial orientation of normal iridal vessels. PIFM s are always preceded by ocular disease, and their development can lead to hyphema because of the fragility of the vessel walls and to glaucoma because of membrane formation over the iridocorneal angle. Histopathologically, cellular, vascular, and fibrous membranes are observed on the anterior face of the iris. These three types of membranes are thought to represent a continuum of maturation (Peiffer et al., 1990). All PIFM s consist of blood vessels with plump endothelial cells, spindle cells, inflammatory cells (primarily lymphoplasmocytic) and an extracellular matrix. Immunohistochemically, the extracellular matrix stains positive for collagen, mucins, and usually laminin. The vessels, which are CD 31 positive, and spindle cells are both positive for laminin, vimentin, smooth muscle actin, VEGF, and COX-2 (Zarfoss et al., 2010). The pathogenesis of membrane formation is not known but may be related to hypoxia, angiogenic, and fibroblastic stimulatory factors from chronic inflammation and neoplasia (Peiffer et al., 1990; Yanoff & Sassani, 2009). Because of the positivity for VEGF and COX-2 and similarities between all PIFM s regardless of the inciting ocular disease, in the future there may be a way to pharmacologically interfere with PIFM formation.

Cytologic evaluation of aqueous humor, bacterial or fungal culture of the aqueous, vitreous aspirates, or a combination thereof may be beneficial in determining the cause of uveitis. Aqueous aspiration appears to yield useful and positive results, mainly in eyes with visible exudates or in animals suspected of having lymphosarcoma (Olin, 1977). Most commonly, aqueous aspiration yields nonspecific inflammatory cells. Because of the rarity of specific results and the exacerbation of existing uveitis, the procedure is not recommended in most cases. In patients with concurrent posterior uveal involvement, vitreous aspiration is more likely to yield positive results than aqueocentesis (see Chapters 23 and 24). This procedure should be considered for eyes with marked vitreous opacity, exudative retinal detachments, or panophthalmitis. Care must be taken not to puncture the lens. Intraocular hemorrhage following either aqueous or vitreous aspiration is possible.

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In addition to rubeosis iridis, diffuse iris hyperpigmentation can occur with chronic anterior uveitis. This condition is more obvious in eyes with lightly pigmented irides and in cats.

Decreased IOP is one of the earliest and most subtle indications of uveitis. Proposed mechanisms for decreased IOP include both decreased aqueous humor production with breakdown of the blood–aqueous barrier and increased uveoscleral flow mediated in part by PGs (Gabelt & Kaufman, 2003; Millichamp & Dziezyc, 1991; Toris & Pederson, 1987). IOP will vary depending on the duration and severity of uveitis. In acute or subacute uveitis, IOP is usually decreased for the previously mentioned reasons; in chronic uveitis,
fibrosis or atrophy (or both) of the ciliary body may contribute to decreased secretory function with subsequent ocular hypotony. Marked ciliary body dysfunction and hypotony may result in phthisis bulbi.

Secondary glaucoma is a common manifestation of severe or protracted uveitis. The causes of secondary glaucoma include obstruction of the angle by inflammatory debris, iris bombé that occurs with formation of annular posterior synechiae, extensive anterior peripheral synechia, and formation of PIFMs. An IOP of less than 10 mmHg is consistent with uveitis. A difference of more than 5 mmHg in IOP between the two eyes, even if the values obtained are in the normal range, should also be considered significant and may suggest the eye with the lower IOP has uveitis or the higher has impending glaucoma. In one study, nonsurgical anterior uveitis was found to be the most common cause of secondary glaucoma with uveitis secondary to lens surgery being less frequent (Johnsen et al., 2006). In another study, cataract formation, specifically, was found to be the most common cause of secondary glaucoma (Gelatt & MacKay, 2004). Some infectious diseases, such as blastomycosis, frequently lead to secondary glaucoma. Glaucoma can result from intraocular neoplasia; however, it is usually a late manifestation (Gelatt & MacKay, 2004).

Cataracts, especially anterior subcapsular cataracts, occur commonly with chronic anterior uveitis. They are thought to arise from inflammatory mediators in the aqueous humor interfering with normal lens metabolism. Lenticular changes are not specific and include epithelial metaplasia or posterior migration and liquefaction, degeneration, or necrosis of lens fibers (Eagle & Spencer, 1996). Posterior synechia can also result in cataract formation.

Systemic Evaluation

When the diagnosis of uveitis is made, an attempt should be made to identify the etiology. Some causes are readily apparent, such as when anterior uveitis occurs in conjunction with a hypermature cataract. Conversely, extensive diagnostic testing and evaluation frequently do not lead to a specific conclusion. A complete ophthalmic and physical examination are always indicated when a diagnosis of uveitis has been made. Regarding the ophthalmic examination, special attention should be made to the cornea and lens of the affected eye and the fundi of both eyes (e.g., presence of chorioretinitis). Physical examination should include evaluation of the skin, looking for depigmented areas or draining lesions; lymph node palpation, auscultation, and abdominal and possibly rectal (especially in intact male dogs) palpation. A complete blood count and serum panel is usually indicated. Selected titers are run based on the endemic diseases in the dog's location and in areas where the dog may have traveled. Thoracic radiographs are also considered part of the minimal screening protocol when systemic disease is suspected. Radiographs are evaluated for evidence of metastatic or fungal diseases. Additional serologic tests and diagnostics are indicated according to the clinician’s index of suspicion. Refer to the section on selected uveal diseases in this chapter as well as to Chapter 35.1 for further discussion.

Therapy for Anterior Uveitis

Topical anti-inflammatory therapy should be instituted immediately after the diagnosis of anterior uveitis is made, even in those patients with suspected systemic disease. Failure to initiate therapy early in the disease process may result in many adverse sequelae, including synechiae formation, cataract, secondary glaucoma, endophthalmitis, and phthisis bulbi. Topical therapy alone may suffice for mild anterior uveitis, but for severe anterior uveitis, posterior uveitis, and systemic disease, systemic therapy as dictated by the primary disease is also indicated.

Corticosteroids are the primary therapy for the treatment of anterior uveitis. Corticosteroids inhibit phospholipase and the release of arachidonic acid. They decrease cellular and fibrinous exudation and tissue infiltration, inhibit fibroblastic and collagen-forming activity, diminish postinflammatory neovascularization, and decrease vascular permeability (Duke-Elder & Ashton, 1951). Treatment with topical corticosteroids can be initiated in all cases of uveitis pending diagnostics except in those cases with corneal ulceration. Prednisolone acetate, 1% suspension, is the most commonly prescribed ophthalmic corticosteroid because of its potency and availability. Dexamethasone is also a potent steroid; however, in one experimental study, topically applied 1% prednisolone acetate was more effective than dexamethasone sodium phosphate in stabilizing the blood-aqueous barrier (Ward et al., 1992b). Both prednisone acetate and dexamethasone are more potent than hydrocortisone, and are available as ophthalmic preparations either alone or in combination with antibiotics. An initial application frequency of four to six times daily may be required with solutions, compared with three to four times daily as recommended for ointments. Subconjunctival corticosteroids may be administered in select cases as an adjunct to topical therapy, but they are not intended as a substitute. Triamcinolone acetonide and betamethasone are long-acting steroids that may be used for subconjunctival injection. Risks include scleral perforation at the time of injection, granuloma formation, and extraocular muscle atrophy and paralysis (Pappa, 1994). Long-acting steroids should be used judiciously because the effects cannot be reversed in the case of corneal ulceration or infection.

Systemic corticosteroid therapy or treatment with other systemic immunosuppressive drugs should not be initiated until diagnostics have been completed. Systemic infectious disease may require treatment with antibiotics or antifungal drugs. Systemic neoplasia may require treatment with chemotherapeutic agents. Systemic corticosteroids are contraindicated in most cases of infectious systemic disease. When systemic prednisone is indicated, a recommended initial dosage is 1–2 mg/kg per day in divided doses per os, followed by gradual reduction.
Contraindications for the use of topical and systemic corticosteroids differ. In general, topical steroids should not be used on eyes with corneal ulceration because of the inhibition of corneal healing and possible potentiation of infection and collagenolysis (Hendrix et al., 2002; Tolar et al., 2006). Systemic steroids can be used in dogs with simple, superficial, noninfected corneal ulcers; however, caution should be used, and the cornea should be monitored frequently for deterioration and collagenolysis. Systemic corticosteroids should be avoided in diabetic dogs if possible, and though topical therapy may alter an animal’s glucose levels and subsequently its insulin requirements, the clinician must weigh the benefits against the risks. Topical steroids are frequently used to control uveitis after cataract surgery in diabetic animals with very few complications. Additionally, it is well known that systemic steroids suppress the hypophysial–adrenal axis; topical steroids applied frequently will cause a similar suppression (Glaze et al., 1988; Roberts et al., 1984). Therapy with either topical or systemic therapy is gradually reduced as the clinical signs of uveitis resolve and is then maintained at the lowest necessary dose.

Many topical NSAIDs are available for ophthalmic use. NSAIDs prevent intraoperative miosis, control postoperative pain and inflammation after intraocular surgery, control symptoms of allergic conjunctivitis, and alleviate signs of uveitis (Giuliano, 2004; Krohne et al., 1998; Ward, 1996; Ward et al., 1992b; Wilkie, 1990b). Most NSAIDs inhibit PG-mediated inflammation by interrupting the cyclooxygenase pathway (Opremcak, 1994). PGs generated via the cyclooxygenase pathway appear to have a greater effect on the blood–ocular barrier in the dog than do leukotrienes or sensory neuropeptides after anterior chamber paracentesis (Ward et al., 1992a). A different anti-inflammatory action may include suppression of polymorphonuclear leukocyte locomotion and chemotaxis, decrease in the expression of cytokines and mast cell degranulation, and action as a free-radical scavenger (Giuliano, 2004). The anterior chamber paracentesis model showed that flurbiprofen and prednisolone acetate were equally effective in preventing blood–aqueous barrier disruption (Ward et al., 1992b). In a laser capsulotomy model, flurbiprofen was more effective at preventing blood–aqueous barrier disruption than was prednisolone acetate (Dzieycz et al. 1995). Topical NSAIDs may be used either alone or in combination with corticosteroid therapy; the therapeutic effects of using both NSAIDs and corticosteroids are additive. Many ophthalmic NSAIDs are available and include indomethacin, flurbiprofen, suprofen, and diclofenac. A newer ophthalmic NSAID, bromfenac, is effective in human patients when dosed once daily which is in difference to the other ophthalmic NSAIDs which are usually dosed twice a day (QID) or four times a day (Henderson et al., 2011; Silverstein et al., 2011). One study showed that injectable flunixin meglumine (50 mg/mL) administered topically gave similar results to topical dexamethasone in dogs with naturally occurring anterior uveitis (Andrade et al., 2003).

An experimental study evaluating the relative blood–aqueous barrier–stabilizing effects of topical NSAIDs in dogs found that diclofenac and flurbiprofen appear to be more efficacious than suprofen (Ward, 1996). Although topical NSAIDs may delay corneal wound healing, they are commonly used to treat eyes with concurrent uveitis and corneal ulceration in dogs (Hendrix et al., 2002). However, dogs with corneal ulceration should be monitored judiciously because a link with topical NSAID use and collagenolysis has been made in humans. Most cases appear to be associated with increased administration, diabetes mellitus, and the presence of concurrent ocular disease (Gaynes & Fiscella, 2002). The adverse corneal effects may be related to increased matrix metalloproteinase production and alterations in epithelial cell membranes and surface microvilli. Despite the possible adverse effects, the favorable clinical risk–benefit assessment of topical ophthalmic NSAIDs remains. If a favorable response is not noted with treatment, reevaluating the therapeutic approach rather than switching NSAID classes is recommended. In addition, increasing the frequency of administration will not enhance the anti-inflammatory action of NSAIDs, and tapering NSAIDs may help avoid inflammatory rebound (Gaynes & Fiscella, 2002). Topical NSAIDs are applied as often as four times daily.

Relatively little research has been done evaluating the effect of systemic NSAIDs on anterior uveitis. In a repeated anterior chamber paracenteses model, dogs treated with carprofen had lower levels of PGE_2_ than placebo-treated dogs although the levels in both groups were low (Pinard et al., 2011). Results of an aqueoucentesis model of induced anterior uveitis showed that tepoxalin, which is no longer commercially available, decreased aqueous PGE_2_ concentrations significantly more than carprofen and meloxicam, which did not have significantly lower concentrations than the control (Gilmour & Lehenbauer, 2009). Many other systemic NSAIDs are available, but their ocular effects have not been evaluated. Etodolac (EtoGesic, Fort Dodge Animal Health, Fort Dodge, IA) has been associated with the development of keratoconjunctivitis sicca and should be avoided (Klauss et al., 2007). For years, aspirin and flunixin meglumine were the mainstays of systemic NSAID therapy; however, use of these drugs has been replaced with newer and safer systemic NSAIDs. Systemic NSAIDs are not used in conjuction with systemic corticosteroids because of the greater potential for gastrointestinal complications, and their use is contraindicated when hyphema or generalized bleeding tendencies are present.

Immunosuppressive drugs such as azathioprine are commonly employed in cases of uveitis that are deemed immune mediated and are unresponsive to conventional therapy. Azathioprine has been used most commonly in therapy for UDS in the dog (Organ, 1989). Frequent blood and platelet counts as well as liver enzyme determinations are recommended with this therapy because of potential hepatotoxic and myelosuppressive effects (Moore, 2001). One recommended initial dosage is 2 mg/kg per day for 3–5 days, followed by reduction to 1 mg/kg/day for 10 days, then, if needed, 0.5 mg/kg/day as a maintenance dose (Moore, 2001). Cyclosporine is another
immunosuppressive agent that can be used systemically in the treatment of immune-mediated diseases. Cyclosporine primarily affects T-lymphocyte functions. Topical cyclosporine, as used in the treatment of keratoconjunctivitis sicca, has relatively poor intraocular penetration (Kaswan, 1987). While there have been no publications on the use of systemic cyclosporine in veterinary ophthalmology for the treatment of uveitis, it is used commonly in the treatment of atopic dermatitis and other dermal diseases in dogs (Radowicz & Power, 2005; Steffan et al., 2005). Many complications have been reported in conjunction with the systemic use of cyclosporine; therefore, close monitoring of the patient is imperative when this medication is used (Radowicz & Power, 2005; Steffan et al., 2005).

There are few indications for the use of topical antibiotics in the treatment of anterior uveitis both because the intraocular inflammation is rarely bacterial in origin and because the intraocular penetration of topically-administered antibiotics would not be adequate for treatment of an intraocular infection without the concurrent use of systemic antibiotics. Topical antimicrobial therapy is primarily used to prevent bacterial infection of corneal ulcers that may be present concurrently with anterior uveitis. If ulceration occurs during topical steroid therapy, treatment with an ophthalmic antibiotic preparation should be initiated. The topical steroid should be discontinued and initiation of treatment with an ophthalmic NSAID may be indicated. While ophthalmic antibiotics are often combined with corticosteroids, there is little indication for the use of this combination of drugs in the treatment of anterior uveitis. Many times the greatest indication for the use of antibiotic-steroid combinations is when an ointment is needed because ointments that contain only a steroid are unavailable.

Systemic antimicrobial therapy for uveitis may be indicated for treatment of specific systemic diseases or for prophylaxis against infection in the case of corneal perforation or intraocular surgery. The blood-aqueous barrier is normally impermeable to many antibiotics, but during active uveitis, the blood-aqueous barrier is compromised and drug permeability enhanced. Therefore, it is assumed that systemically administered antibiotics will reach the aqueous humor when trauma, infection, or ocular surgery dictates their use. Chloramphenicol penetrates the normal blood-aqueous barrier more effectively than do other antibiotics (Auger, 1994a). Recovery of infectious organisms by microbial culture of aqueous humor is unlikely in most instances, so antibiotic choice should be based on the odds of a certain bacteria causing the disease process (Olin, 1977). Fortunately, bacterial uveitis is extremely rare in the dog. A particular antimicrobial may be indicated in specific instances, such as doxycycline for the therapy of uveitis secondary to rickettsial diseases and itraconazole for the treatment of blastomycosis.

Parasympatholytic agents are important in therapy for uveitis. A tropine is the most efficacious ophthalmic parasympatholytic drug. The two major benefits of parasympatholytic drugs are mydriasis and cycloplegia. Dilating the pupil decreases contact between the iris and lens, thereby minimizing the likelihood of posterior synechiae formation. Dilating the pupil also decreases the possibility of occlusion of the pupil resulting in vision loss. Parasympatholytic agents paralyze the iris (i.e., iridoplegia) and ciliary body (i.e., cycloplegia) musculature (Kachmer-McGregor, 1994). Intraocular pain is primarily derived from ciliary body muscle spasm. A tropine also stabilizes the blood-aqueous barrier by blocking the effect of acetylcholine, which dilates blood vessels (Van Alphen & Macri, 1966). A tropine is contraindicated when IOPs are elevated, with the rare exception of early iris bombe, for which atropine may be beneficial in breaking posterior synechiae. A tropine ointment or solution is the most commonly used parasympatholytic agent and is given to effect with mild uveitis requiring therapy once or twice daily and more severe cases requiring more frequent application (e.g., four to six times daily) initially. The actively inflamed eye reacts much more slowly to atropine than does the normal eye, and the effects are shorter lived. The duration of mydriasis in the normal dog eye is 96–120 hours after administration of topical 1% atropine (Rubin & Wolfes, 1962). If synechiae are present at examination, repeated drops of atropine may break them down. If the synechiae have been present longer than a few days, the continued application of atropine may break them down over several days. The addition of 10% phenylephrine may aid in breaking the synechiae.

Side effects of frequent treatment with topical atropine may include decreased tear production, tachycardia, decreased gut motility, and the potential to precipitate acute glaucoma (Moore, 2001). While the decrease in tear production is statistically significant, the levels do not typically drop below normal (Hollingsworth et al., 1992). However, caution should be used in dogs with borderline tear production and in dogs with ulcerative keratitis.

Tropicamide is a very weak parasympatholytic compared to atropine. It can be useful in treating cases of anterior uveitis in which the IOP is borderline high. Tropicamide can dilate the pupil just enough to prevent synechia and tends to alter the IOP less than atropine does. Tropicamide also has a greater mydriatic effect than cycloplegic effect; therefore, mydriasis does not necessarily indicate cycloplegia (Kachmer-McGregor, 1994).

**UVEAL MANIFESTATIONS OF SELECTED DISEASES**

The following discussion summarizes selected diseases that are documented causes of uveitis in the dog. A complete ophthalmic and physical examination is necessary in all cases of uveitis. Many ophthalmic and systemic diseases can lead to uveitis, and results from ocular and physical examinations in conjunction with ancillary diagnostic tests are necessary to confirm or rule out etiologies. Referral to textbooks on internal medicine and infectious diseases are recommended for detailed discussions of specific disorders, diagnostics, and systemic treatment. Refer also to Chapter 35.1.
Lens-Induced Uveitis

LIU is a common complication of cataract in the dog (Dziezyc et al., 1997; Paulsen et al., 1986; van der Woerd et al., 1992). Historically, LIU was associated with hypermature cataracts, but studies using fluorophotometry, laser flaremetry, and IOP have shown that dogs with all stages of cataracts have evidence of at least subclinical uveitis (Dziezyc et al., 1997; Krohne et al., 1995; Leasure et al., 2001).

Most likely, small amounts of lens protein escape the normal lens and induce T-cell tolerance (Denis et al., 2003). Increased immune system exposure to lens crystallins by lens trauma, spontaneous lens resorption, or cataract extraction may overwhelm this tolerance and induce an intraocular or systemic cell-mediated and/or humoral immune response. A negative association between the presence and maturity of cataract and presence of antilens crystallin serum antibodies has been shown. This negative association may be because of the alteration of lens proteins with maturity of the cataract, affinity maturation of anti-crystallin antibodies, or ACAID (Denis et al., 2003).

Two distinct types of LIU are recognized in the dog (Fischer, 1983; Wilcock & Peiffer, 1987). Phacolytic uveitis occurs in dogs with rapidly developing or hypermature cataracts in which soluble lens protein leaks through an intact lens capsule. This type of LIU is nongranulomatous and is characterized by mild lymphocytic-plasmacytic uveitis, not unlike that occurring with most idiopathic uveitides (Fischer, 1983; Wilcock & Peiffer, 1987). The diagnosis of this type of LIU is presumptive, being made on the observation of cataracts and the absence of other ocular or systemic disease. Phacolytic LIU may develop more rapidly in young dogs after the onset of cataract (van der Woerd et al., 1992). Phacolytic LIU usually responds to conventional therapy; however, one study showed that young dogs may respond more poorly to uveitis therapy, possibly because of higher concentrations of lenticular α-crystallin protein and faster cataract resorption in young dogs (van der Woerd et al., 1992). LIU must be recognized and treated prior to cataract surgery. Long-term success rates of cataract surgery in dogs with LIU may be lower than in dogs without LIU (van der Woerd et al., 1992). LIU also needs to be treated in dogs that are not surgical candidates because the uveitis is painful, and treatment may delay the onset of secondary glaucoma. Granulomatous LIU also occurs in dogs with an intact lens capsule but usually occurs in older dogs with rapidly progressing cataracts, especially Miniature Schnauzers, or long-standing cataracts (Fischer, 1983). These eyes have severe uveitis, often with large KPs, and are less responsive to therapy (Fig. 20.22).

Phacolytic uveitis occurs after lens capsule rupture, which causes sudden exposure of intact lens protein in amounts sufficient to overwhelm the normal low-dose T-cell tolerance to lens proteins (Wilcock & Peiffer, 1987; Davidson et al., 1991). There may be a history of recent ocular trauma; however, lens penetration is rarely suspected. Often, the eye is not examined until late in the course of disease when the cause is not immediately apparent and puncture wounds have healed. Clinically, there is evidence of corneal penetration, varying degrees of anterior uveitis, and exudate or hemorrhage in the anterior chamber. Usually, the corneal wound has sealed and the anterior chamber has reformed. Capsular rents are often difficult to detect, but overlying fibrinous or inflammatory cellular material is suggestive of capsular disruption (Davidson et al., 1991). Histopathologically, phacolytic uveitis is characterized by lymphocytic-plasmacytic anterior uveitis, perilenticular inflammation that varies from supplicative to lymphocytic, intralenticular neutrophils, and perilenticular fibroplasia. With chronicity, the perilenticular fibroplasia causes formation of posterior synechiae and secondary glaucoma, leading to loss of the eye. Granulomatous inflammation is not as typical of lens rupture in the dog as it is in humans (Wilcock & Peiffer, 1987).

Lensectomy using phacoemulsification is the ideal therapy for lens rupture in the dog. One study showed that the average number of days to referral in cases amenable to surgery was 3 versus 10 days in dogs that were not considered surgical candidates. Those cases seen later in the time course of disease had profound uveitis and extensive posterior synechiae. Medical therapy was not successful in dogs with ruptured lenses, and most of those eyes developed phthisis bulbi or required enucleation because of progressive anterior uveitis and secondary glaucoma (Davidson et al., 1991).

Even after cataract surgery, anterior uveitis may persist for months, reducing postoperative success rates. There are many proposed mechanisms, including persistent blood-aqueous barrier breakdown, exposure of the uvea to sufficient amounts of intact lens protein to overwhelm the normal low-dose T-cell tolerance, acquired ability of vascular endothelial cells to express major histocompatibility complex to antigens, and cross-reaction of antilens antibodies with uveal antigens (Strube, 2002). After surgery, uveitis may result in cyclitic membranes, posterior synechiae, or pigment migration across the lens capsule. While long-term success is rare, iridotomy
has been reported to relieve pupillary block glaucoma by reestablishing flow between the anterior and posterior chambers and creating a scleral window for aqueous outflow (Strubbe, 2002).

**Anterior Uveitis Secondary to Corneal and Scleral Disease**

Anterior uveitis occurs commonly secondary to corneal ulceration. This response is much greater in horses and rabbits than in dogs. Miosis is the most common clinical sign of anterior uveitis seen in dogs with corneal ulceration, but decreased IOP and aqueous flare are also seen. The purpose of topical atropine in the treatment of corneal ulceration is to decrease ciliary spasm, thereby decreasing pain. The mechanism for uveitis secondary to corneal disease was described in “Chemical Mediators of Inflammation.”

Nonnecrotizing scleritis in dogs is relatively common and does not typically involve the anterior and posterior segments of the eye. Necrotizing scleritis, however, may cause anterior uveitis, vitritis, subretinal masses, tapetal degeneration, hemorrhage, and edema. Scleral biopsies reveal an infiltration of lymphocytes, plasma cells, and macrophages with few neutrophils. Therapy with immunosuppressive dosages of prednisone and azathioprine is indicated but may not be effective (Grahn et al., 1999).

**Uveodermatologic Syndrome**

UDS, or Vogt-Koyanagi-Harada (VKH)-like syndrome, is a disease of dogs that causes anterior uveitis, chorioretinitis, poliosis, and vitiligo. The syndrome in dogs was initially termed Vogt-Koyanagi-Harada-like syndrome because of similarities to a disease in humans known as VKH syndrome. The term uveodermatologic syndrome has also been adopted to further separate the disease in dogs from that in humans because of the absence of neurological signs in dogs. The disease was first reported in two Akitas in Japan in 1977 (Asakura et al., 1977). Reports of UDS in other breeds have followed (Berg & Riis, 2004; Bussanich et al., 1982; Cottrell & Barnett, 1987; Herrera & Duchene, 1998; Kern et al., 1985; Laus et al., 2004; Morgan, 1989).

The pathogenesis of UDS is not completely understood. VKH in humans is an autoimmune disease directed against melanocytes and is mainly mediated by cellular immune responses (Yamaki et al., 2005). Experimentally, Akitas have been immunized with tyrosinase-related protein, an enzyme involved in melanin formation that is expressed specifically in melanocytes. The Akitas developed some clinical and histologic signs consistent with UDS, supporting the similarities between the canine and human diseases (Yamaki et al., 2005). Additionally, the canine leukocyte antigen DLA-DQA1*00201 has been associated with a significantly higher relative risk for UDS syndrome in American Akitas than other DLA class II alleles (Angles et al., 2005).
melanophages. The anterior chamber often contains many lymphocytes and plasma cells. Retinal detachment, destruction of the retinal pigmented epithelium, subretinal neovascularization, choroidal scarring, and signs consistent with secondary glaucoma are also seen frequently (Bussanich et al., 1982; Carter et al., 2005; Kern et al., 1985; Morgan, 1989). Pigment-containing macrophages and melanophages are a prominent feature (Bussanich et al., 1982; Carter et al., 2005). Histopathologic examination of the skin reveals interface dermatitis with a primarily lichenoid pattern. Large histiocyctic cells, plasma cells, melanophages, and small mononuclear cells are characteristic (Herrera & Duchene, 1998; Kern et al., 1985; Laus et al., 2004).

Results of an immunohistochemical study of two cases showed that most lymphocytes were of the B-cell lineage and suggested that the skin lesions were mediated by T cells and macrophages (Th1 immunity), whereas the ocular lesions were more consistent with a B-cell and macrophage response (Th2 immunity) (Carter et al., 2005).

Immunosuppressive drugs are the mainstay of therapy. Standard therapy for anterior uveitis with topical steroids and atropine (if the IOP is not elevated) is initiated. Oral prednisone at immunosuppressive doses is also used. Subconjunctival injections of steroids, such as methylprednisolone, are used by some (Herrera & Duchene, 1998; Morgan, 1989). Generally, there is a relatively rapid response to therapy. Unfortunately, many dogs have recurrence of clinical signs if the dose of oral prednisone is decreased and have the undesirable side effects of weight gain, polyuria, and polydipsia if they are continued. Therefore, other immunosuppressive drugs, such as azothioprine, are often combined with corticosteroids in the treatment of UDS (Pye, 2009; Sigle et al., 2006). However, even with appropriate therapy, secondary glaucoma is a common sequela.

Mycoses-Associated Uveitis

Disseminated mycotic infections with ocular involvement are relatively common among dogs living in endemic areas. Even though mycotic infections typically involve multiple body systems, ocular disease is often the reason for presentation. Common systemic mycoses include blastomycosis, coccidioidomycosis, histoplasmosis, and cryptococcosis. Less frequently occurring infections are aspergillus and candidiasis (Clercx et al., 1996; Linek, 2004). Inhalation is believed to be the primary route of infection for all the major systemic mycoses, with later hematogenous spread to the eye. Direct animal-to-animal or animal-to-human infection is rare (Wolf, 1989). Ocular involvement may be unilateral or bilateral, and infections of the paranasal sinus, orbit, and optic nerve may affect the eye secondarily.

The diagnosis is made on the basis of concurrent clinical signs, which vary between mycotic organisms; identification of organisms in ocular or other tissue aspirates; or the results of fungal culture, histopathologic examination, or various serologic tests. The typical histopathologic pattern for all mycoses is granulomatous or pyogranulomatous inflammation characterized by variable numbers of neutrophils, lymphocytes, plasma cells, histiocytes, and occasionally, epithelioid cells. Histopathologic identification of organisms is facilitated by special stains, such as Gomori’s methenamine-silver, periodic acid-Schiff, and mucicarmine.

The preferred systemic therapy for each type of mycosis varies. Eyes that are potentially visual should be treated topically with corticosteroids and atropine if hypotensive or normotensive, but a painful, blind eye is best enucleated. Histopathologic evaluation of the enucleated globe may facilitate making the diagnosis as well.

Blastomycosis

Blastomyces dermatitidis is the causative agent of blastomycosis. The endemic distribution is primarily the Mississippi, Missouri, the Ohio River valleys, the mid-Atlantic states, Quebec, Manitoba, and Ontario in North America, but it has been identified in other countries as well (Legendre, 2006). Blastomycosis has a propensity for young, male, large-breed dogs (Albert et al., 1981; Bloom et al., 1997; Buyukmihci, 1982; Buyukmihci & Moore, 1987; Hendrix et al., 2004; Legendre, 2006). Ocular disease occurs in 30%–43% of dogs with systemic blastomycosis (Arceneaux et al., 1998; Brooks et al., 1991; Legendre et al., 1981). Anterior uveitis has been reported as the most common ocular sign, though anterior segment lesions appear secondary to posterior segment lesions (Buyukmihci & Moore, 1987; Peiffer & Wilcock, 1991). Clinically, anterior uveitis, posterior segment disease, or endophthalmitis, with all of their sequelae, are commonly seen (Fig. 20.24; also see Fig. 20.11 and Fig. 20.12). Histopathologically, all tunics of the eye are commonly involved. Infection appears to center in the choriocapillaris of the nontapetal choroid with a relative sparing of the tapetal

Figure 20.24. This mixed-breed dog has blastomycosis. This eye has endophthalmitis with corneal edema, corneal vascularization, conjunctival hyperemia, and chemosis. Aqueous flare was visible on examination.
Coccidioidomycosis

Coccidioidomycosis, caused by Coccidioides immitis, is endemic to the Lower Sonoran life zone, which includes the southwestern United States, Mexico, and areas of Central and South America (Greene, 2006c). One report suggests no breed predilection, but others suggest a predilection for the Boxer and Doberman Pinscher (Angell et al., 1987; Greene, 2006c). Ocular changes include keratitis, granulomatous panuveitis, endophthalmitis, chorioretinitis with retinal detachments, and orbital cellulitis (Angell et al., 1987). Interestingly, 80% of eyes that do not respond to treatment and continue to have uveitis and develop glaucoma are seen to have thriving Blastomyces dermatitidis organisms in the eye and/or may have lens rupture secondary to the severe inflammatory response (Hendrix et al., 2004). These findings may explain why the inflammation is intractable in many dogs.

Fluconazole is less effective and requires a longer treatment time than itraconazole, but the cost is less (Mazepa et al., 2011). Dogs should be monitored for hepatotoxicity with both drugs. Parenteral amphotericin B is also effective, but renal toxicity may be problematic with this drug (Aguirre, 1974). A newer amphotericin B–lipid complex is available and appears to be both safe and effective (Krawiec et al., 1996). Some clinicians have used a combination treatment with itraconazole and amphotericin B–lipid complex successfully in dogs at risk of losing vision from retinal detachment (Collins & Moore, 1999). Intravenously administered amphotericin B does not enter the normal eye, but does penetrate into the severely uveitic globe (Mauger, 1994a). Prior to the common use of itraconazole, ketoconazole was used to treat ocular blastomycosis either alone or in combination with amphotericin B at oral doses ranging from 10 mg/kg per day to 30 mg/kg per day (Bloom et al., 1997; Dunbar et al., 1983).

Studies have evaluated the use of corticosteroids via different routes to augment therapy with systemic antifungals. Oral prednisone has been administered with itraconazole or fluconazole in an attempt to preserve vision. The prednisone dosage ranged from 0.2 mg/kg/day to 1.4 mg/kg/day, and the mean duration was 3 months. The prednisone did not appear to adversely affect the survival rate. All eyes with mild or moderate lesions and half of the dogs with severely affected eyes were visual at their last recorded recheck examination (Finn et al., 2007). However, many clinicians do not advocate systemic corticosteroid treatment in dogs with mycotic infection (Collins & Moore, 1999). However, topical prednisolone acetate should be used in the treatment of anterior uveitis secondary to blastomycosis. Topical atropine should be used in eyes without evidence of secondary glaucoma to increase comfort and decrease synechia formation. If IOP is elevated, dorzolamide and timolol may be used in conjunction with steroids.
dogs in one study had uniocular lesions, and 43% of dogs demonstrated ocular disease alone (Angell et al., 1987). Similar to blastomycosis, anterior segment lesions are thought to be an extension of posterior segment disease.

Several tests are available for use in making a serologic diagnosis (Greene, 2006c). The tube precipitin test measures IgM antibody levels; IgM both appears and disappears early in the course of disease. The complement fixation test measures IgG antibody, which persists longer. The complement fixation titer is indicative of the severity of infection: a titer of 1:64 or greater is indicative of disseminated disease. It is possible to have one test be positive and the other negative depending on the stage of infection; thus, the two tests should be performed in parallel. Latex agglutination, AGID, and ELISA are now also employed by some laboratories (Greene, 2006c). Oral ketoconazole, fluconazole, and itraconazole are all commonly used in the treatment of coccidioidomycosis (Angell et al., 1987; Greene, 2006c).

Cryptococcosis

Cryptococcosis, caused by Cryptococcus neoformans, commonly causes CNS, ocular, respiratory, and cutaneous signs. Fever, lymphadenomegaly, and lameness secondary to lytic bone lesions occur less frequently (Malik et al., 2006). CNS signs usually relate to meningoencephalitis and may include head tilt, nystagmus, facial paralysis, ataxia, mild paresis to complete paralysis, depressed reflexes, circling, and seizures (Berthelin et al., 1994a; Malik et al., 2006). Ocular signs may include optic neuritis, granulomatous chorioretinitis, exudative retinal detachment, anterior uveitis, and occasionally, orbital abscess, cellulitis, or exophthalms (Carlton, 1983; Carlton et al., 1976; Malik et al., 2006). Anterior uveitis, though reported, is not a common finding with cryptococcosis. As with other mycoses, even when anterior uveitis is present, organisms are rarely demonstrated in the anterior uvea. Posterior segment disease is the most common ocular manifestation, and funduscopic examination often reveals chorioretinitis characterized by single or multiple raised, gray, yellow, or white exudative lesions. Rarely, anterior uveitis and retinal detachment occur without the presence of granulomas (Carlton, 1983; Carlton et al., 1976; Wofler et al., 1996). The eye is involved secondary to hematogenous spread or extension from the brain along the optic nerve (Malik et al., 2006).

Cryptococcosis is diagnosed on the basis of clinical signs, identification or culture of the organism in ocular or other tissue aspirates including CSF, results of histopathologic examination, and results of serologic testing (Berthelin et al., 1994b; Malik et al., 2006). The latex cryptococcal agglutination test is considered to be the most reliable serologic test because it can detect the presence of cryptococcal antigen in body fluids, including serum, urine, CSF, aqueous humor, and vitreous (Fujita et al., 1983; Malik et al., 2006). The magnitude of antigen titer tends to correlate with severity of disease and response to therapy (Berthelin et al., 1994b; Malik et al., 2006).

The prognosis for dogs with cryptococcosis is generally poor because of the severity of meningoencephalitis, the difficulty of reaching organisms within large lesions, possible decreased immunity, and poor penetration of some antifungal drugs into the CNS. Variable responses have been obtained with systemic therapy with itraconazole, amphotericin B, fluconazole, ketoconazole, and fluconazole either singularly or in various combinations (Berthelin et al., 1994b; Malik et al., 2006). One dog recovered without medical treatment after enucleation, suggesting localized disease (Berthelin et al., 1994b).

Histoplasmosis

Histoplasma capsulatum is widely distributed in soil in temperate and subtropical regions. In the United States, major endemic areas are associated with the Ohio, Missouri, and Mississippi rivers, but histoplasmosis has been identified in most states (Greene, 2006a). In the dog, clinical signs of disseminated histoplasmosis are most often referable to the gastrointestinal tract or liver. Reports of ocular involvement are relatively rare but usually include chorioretinitis, conjunctivitis, blepharitis, retinal detachment, and optic neuritis (Gwin, 1980; Greene, 2006a). In experimentally infected dogs, peripheral granulomatous choroiditis was the most common finding (5 of 17 dogs) (Salfelder et al., 1965). Because of the cross-reactivity in the urine antigen test for Blastomyces, this test is also recommended for use in diagnosing histoplasmosis. The cross-reactivity is not seen as a problem because the preferred treatment for both mycoses is itraconazole (Spector et al., 2008).

Parasitic Diseases

Ocular Nematodiasis

Intraocular nematodiasis is reported infrequently in domestic animals. Ocular nematodiasis includes two distinct conditions: ocular filariasis and ocular larva migrans (OLM).

Ocular filariasis due to aberrant migration of immature Dirofilaria immitis occurs in dogs and humans. The condition occurs in dogs with and without concurrent microfilaraemia. Uveitis and mild to severe corneal opacity are the predominating signs. Uveitis is commonly attributed to direct mechanical trauma or reaction to metabolic waste products of the parasite. In one case, it was speculated that antigen–antibody complex formation was an additional factor in uveitis when severe corneal scarring and pigmentation occurred after removal of the parasite (Bellhorn, 1973). Typically, one 5- to 10-cm filaria is seen undulating in the anterior chamber; it may migrate freely between the anterior and posterior chambers and vitreous. Light stimulation may increase motility of the filaria and, subsequently, discomfort to the patient. The prognosis is favorable with anti-inflammatory therapy and manual removal of the filaria (Carastro et al., 1992). Delay in surgical removal may increase the likelihood of posterior segment migration, and with continued inflammation, enucleation may
be required (Miller & Cooper, 1987). Presurgical adulticide therapy is not advised because a severe inflammatory reaction to the dead filaria may cause intractable uveitis. Microfilaricide administration caused increased activity of the filaria and transient exacerbation of clinical signs in one case (Lovers, 1968). Angiostrongylus vasorum, a metastrongylid nematode that infects the pulmonary artery and right ventricle, has also been found in the anterior chamber of dogs. This parasite is primarily found in Europe (King et al., 1994; Rosenlund et al., 1991).

OLM generally refers to aberrant ocular migration of Toxocara spp.; Toxocara canis is suspected to be the most commonly involved (Hughes et al., 1987; Rubin & Saunders, 1965). T. canis is of public health significance because the nematode causes OLM and visceral larval migrans (VLM) in children. In dogs and humans, OLM resulting from Toxocara spp. is characterized by inflammation primarily of the retina and vitreous. Ophthalmoscopy reveals areas of hyperreflectivity, hyperpigmentation, and vascular attenuation. Uveal involvement is rare and was appreciated histopathologically in only one study (Hughes et al., 1987). 

Onchocerciasis primarily causes pea- to bean-sized masses in the conjunctiva, nictitans, and sclera (Gardiner et al., 1993; Orihel et al., 1991; Sreret et al., 2002; Szell et al., 2001). However, it may also cause anterior and posterior uveitis, periorbital swelling, exophthalmos, conjunctival congestion, protrusion of niclating membranes, granuloma formation, and localized corneal edema (Komenou et al., 2003; Zarfoss et al., 2005). Histopathologically, a pyogranulomatous or granulomatous reaction with eosinophils is associated with the adult worms. Lymphoplasmacytic uveitis, PIFMs, and evidence of secondary glaucoma are also seen (Zarfoss et al., 2005). Microfilariae are seen in the uteri of females and the surrounding tissues and can be isolated from skin biopsy specimens (Eberhard et al., 2000; Szell et al., 2001). There is debate as to whether the organism is Onchocerca lienalis or Onchocerca lupi (Gardiner et al., 1993; Komenou et al., 2003; Zarfoss et al., 2005). Surgical removal may be curative, but medical therapy is often needed as well (Gardiner et al., 1993; Komenou et al., 2003). Postoperative medical therapy includes prednisolone 0.5 mg/kg PO BID for at least 3–4 weeks and doxycycline 5 mg/kg PO BID for at least 6–8 weeks. Additionally, 2.5 mg/kg of melarsomine is given IM twice within 24 hours 1 week after surgery, followed by ivermectin 50 µg/kg SC and melarsomine 1 month after surgery. Where melarsomine is not available, ivermectin can be effective at 200 µg/kg PO or SQ as a single dose 1 week after surgery and then repeated at 6 months (A. Komenou, personal communication).

**Ophthalmomyiasis**

Ophthalmomyiasis refers not only to aberrant ocular migration of fly larvae, most commonly of the order Diptera, but also the sheep nasal botfly (Oestrus ovis) and the cattle warble (Hypoderma bovis) (Gwin et al., 1984). Both intraocular and extraocular disease occur in domestic animals, but the intraocular disease ophthalmomyiasis interna posterior (OIP) has been reported most often in dogs, cats, and humans. As the name implies, OIP is primarily a disease of the posterior segment. The characteristic lesion has roadmap-like subretinal tracts that may be active or inactive. Active disease may be associated with uveitis, retinal detachment, and hemorrhage. The larva may be visible in active infections; larvae have been identified in the anterior segment with concurrent uveitis. Increased numbers of migratory tracts in the retina may be visualized daily in active infections (Gwin et al., 1984). Inactive infections require no therapy, whereas anti-inflammatory therapy is indicated in active disease. Organophosphates may be administered in an attempt to kill the larva, but a dead larva may exacerbate inflammation. The larva may also spontaneously depart from the globe.

**Protozoal Diseases**

**Leishmaniasis**

Visceral leishmaniasis is most commonly caused by the flagellate organism Leishmania infantum. The disease is endemic along the Mediterranean shore and in parts of East Africa, India, and Central and South America, but it also rarely occurs in North America, especially in foxhounds (Boggiatto et al., 2011; Pena et al., 2000). Domestic and wild members of Canidae serve as reservoir hosts, and the intermediate host is the sandfly (Phlebotomus spp.).

Ocular findings include blepharitis, keratoconjunctivitis, uveitis, retinitis, and endophthalmitis (Ciaramella et al., 1997; Giles et al., 1975; Koutinas et al., 1999; M Connell et al., 1970; Pena et al., 2000; Swenson et al., 1988). Ocular disease may be the only clinical sign in some dogs (M Connell et al., 1970; Pena et al., 2000). The anterior segment is usually more severely involved than the posterior segment. Additional signs include lymphadenopathy, splenomegaly, hepatoomegaly, renal failure, anemia, thrombocytopenia, and varying dermatologic conditions (Ciaramella et al., 1997; Koutinas et al., 1999).

Histopathologically, vasculitis and intense granulomatous inflammatory zones are seen in conjunctiva, fibrous tunic, uvea, optic nerve sheath, lacrimal duct, and both smooth and striated ocular muscles (Garcia-Alonso et al., 1996; Naranjo et al., 2010; Pena et al., 2008). The parasite has been found immunohistochemically in 27% of affected eyes (Pena et al., 2008). Treatment usually consists of pentavalent antimoniols and/or allopurinol. However, the organisms are rarely completely eliminated, the clinical response to therapy is variable, and relapses are common (Baneth, 2006; Pena et al., 2000).

**Toxoplasmosis**

Toxoplasma gondii is a protozoan-obligate intracellular parasite that affects most warm-blooded animals. The cat is
considered the only definitive host and is therefore integral to transmission of the disease. Dogs may be infected via genital transmission or by ingesting sporulated oocysts from cat excreta, ingesting tissue cysts in infected meats, or ingesting a transport host. Infection is usually subclinical (Bussanich & Rootman, 1985; Dubey, 1987), but clinical signs may include neuromuscular, respiratory, gastrointestinal, or ocular disease.

Ocular toxoplasmosis has been reported infrequently in dogs (Bussanich & Rootman, 1985; Dubey, 1987; Piper et al., 1970); when it is present, anterior uveitis, retinochoroiditis, and vitritis can be seen (Piper et al., 1970; Wofier & Grahn, 1996). Hyperplasia of the ciliary epithelium and a pseudocyst of ciliary epithelium without inflammation have also been reported in dogs (Piper et al., 1970). Additional findings may include optic neuritis and extraocular myositis. Even though signs of anterior uveitis may not be seen clinically, histologically, inflammation of the iris may be present (de A breu et al., 2002).

Diagnosis of ocular toxoplasmosis is by clinical signs, serologic testing, and histopathologic examination. Serologic evaluation is beneficial but does not always correlate with clinical disease, as some subclinically affected dogs may have high antibody titers. A test that distinguishes IgM and IgG antibodies is necessary, and convalescent titers should be run (Dubey, 1987). Granulomatous or nongranulomatous inflammation is possible. Clindamycin is the drug of choice for treating toxoplasmosis (Dubey & Lappin, 2006).

Other Protozoal Diseases

Neospora caninum was diagnosed in four litters of puppies from one owner. The most common clinical sign was hindlimb paralysis. Others had generalized encephalomyelitis. Histopathology showed tachyzoites and tissue cysts in the brain and spinal cord. Lesions in the eyes included retinitis, choroiditis, nonspecific iridocyclitis, and myositis of the extraocular muscles (Dubey et al., 1990).

Trypanosoma evansi may cause corneal opacities, conjunctivitis, and anterior uveitis in dogs. Therapy with subconjunctival steroids and intramuscular diminazene aceturate leads to corneal clearing and restoration of vision in affected dogs (Varshney et al., 2003). Parasitemia in peripheral blood smears and aqueous fluid confirms the infection.

Rickettsial Diseases

Ehrlichiosis

Ehrlichia canis is an obligate intracellular parasite transmitted by the brown dog tick, Rhipicephalus sanguineus. Pronounced clinical and laboratory abnormalities often occur with E. canis infections (canine monocytic ehrlichiosis) and include fever, lymphadenopathy, anemia, leukopenia, thrombocytopenia, monoclonal or polyclonal gammopathy, neurologic signs, and generalized bleeding tendencies (Stiles, 2000).

Ocular signs are common, and dogs may have ocular signs with no other apparent clinical signs. Ocular signs are most commonly bilateral and may occur in both the acute and chronic forms of natural or experimentally induced E. canis infections. A anterior uveitis and exudative retinal detachment are reported to be the most common ophthalmic signs (Leiva et al., 2005; Oria et al., 2004). Other signs include conjunctivitis, conjunctival or iridal petechiations, corneal opacity, corneal ulceration, necrotic scleritis, low tear production, orbital cellulitis, panuveitis often with hyphema, diffuse retinitis or vasculitis, retinal hemorrhage, papilledema, and optic neuritis (Bayon et al., 1999; Gould et al., 2000; Harrus et al., 1998; Komenou et al., 2007; Oria et al., 2004; Stiles, 2000). The ocular hemorrhage associated with ehrlichiosis is thought to be related to thrombocytopenia, platelet dysfunction, and/or hyperviscosity (Harrus et al., 1998).

Experimentally, ocular signs consist of papilledema, perivascular retinal infiltrates, retinitis, and anterior uveitis (Swanson & Dubielzig, 1986). The ocular signs are evident 3 weeks after the onset of fever. The most consistent histopathologic finding is a predominantly mononuclear cellular infiltrate of the uveal tract and, to a lesser extent, the retina and optic nerve (Swanson & Dubielzig, 1986). Results of another study indicated that the primary inflammatory response was lymphocytic with fewer monocytes and plasma cells, and the most intense inflammation was located in the ciliary body with lesser inflammation in the iris, choroid, and retina (Panciera et al., 2001).

Diagnosis is made on the basis of clinical signs, hematologic abnormalities, and serologic testing. Multiple intracytoplasmic subunits of E. canis (i.e., morulae) may be seen within monocytes (Stiles, 2000). Serologic diagnosis is by indirect IFA testing (Stiles, 2000). Doxycycline and several other antibiotics are commonly used for systemic therapy (Neer & Harrus, 2006; Stiles, 2000).

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) is an acute infectious disease caused by Rickettsia rickettsii and transmitted by ticks of the Dermacentor spp. Vasculitis is the primary lesion caused initially by direct infection of the vascular endothelium and perithelial smooth muscle, and later by immunologic phenomena. It is postulated that an Arthus-type reaction may be involved (Davidson et al., 1989; Koenen et al., 1977). Common clinical signs include fever, neurologic dysfunction, polyarthritis, thrombocytopenia, nonregenerative anemia, and ocular disease.

Ocular lesions are commonly observed in dogs with serologically confirmed RMSF (Davidson et al., 1989). A anterior segment findings include subconjunctival hemorrhage, iris stromal petechiations, anterior uveitis, and hyphema. Posterior segment findings include retinitis characterized by perivasculitis, focal areas of edema, and petechiation. Because ocular disease may be confined to the retina, ophthalmoscopy should always be done in dogs with suspected
RMSF. Generally, the ophthalmic lesions are mild with RMSF (Davidson et al., 1989).

The histologic appearance of RMSF is different from ehrlichiosis in that the most prominent lesion is one of necrotizing vasculitis with perivascular accumulations of polymorphonuclear and lymphoreticular cells (Davidson et al., 1989; Keenan et al., 1977). Confirmation of the diagnosis of RMSF is made by a demonstration of rising serum IFA titers; therefore, a single titer is nondiagnostic (Davidson et al., 1989; Greene et al., 1985). Doxycycline, tetracycline, chloramphenicol, enrofloxacin, and trovafloxacin are all effective systemic therapies (Breitschwerdt et al., 1991, 1999; Stiles, 2000). Ehrlichia phyllos infection rarely causes anterior uveitis (Glaze & Gaunt, 1986; Harvey et al., 1978). Single intracytoplasmic subunits or morulae may be seen within platelets (Stiles, 2000).

**Viral Diseases**

**Infectious Canine Hepatitis**

Infectious canine hepatitis (ICH) is caused by the canine adenovirus-1 (CAV-1). Natural infection is most common in unvaccinated dogs less than 1 year of age, in which the disease may be fatal. The virus replicates in reticuloendothelial, hepatic parenchymal, and vascular endothelial cells (Aguirre et al., 1975). Clinical findings may include fever, vomiting, diarrhea, abdominal tenderness, hepatitis, or hepatic necrosis, hemorrhagic diathesis, tonsillar enlargement, pneumonia, glomerulonephritis, and CNS and ocular disease (Greene, 2006b).

Nongranulomatous anterior uveitis and secondary corneal edema (so-called blue eye) is reported in approximately 20% of dogs recovering from natural ICH (Aguirre et al., 1975; Curtis & Barnett, 1981). This keratouveitis may be the only abnormality in otherwise subclinically affected dogs (Greene, 2006b). Persistent corneal edema, secondary glaucoma, and phthisis bulbi are possible sequelae of severe keratouveitis. The pathogenesis of ICH keratouveitis is related primarily to immune-complex deposition or to an Arthus-type reaction (Aguirre et al., 1975; Carmichael, 1965; Carmichael et al., 1975; Curtis & Barnett, 1981).

Keratouveitis occurs as a postvaccinal reaction in approximately 0.4% of dogs that receive the CAV-1 vaccine. An increased susceptibility of the Afghan hound to postvaccinal keratouveitis has been suggested (Curtis & Barnett, 1981). The CAV-2 vaccine is thought to cause ocular disease only when experimentally injected into the anterior chamber (Greene, 2006b). However, anecdotal accounts exist of rare keratouveitis following subcutaneous administration of CAV-2 vaccines.

Therapy for dogs suffering from systemic disease with ICH is primarily supportive. Anti-inflammatory therapy of keratouveitis in dogs recovering from natural ICH infection or suffering postvaccinal reaction is debatable, since some consider the keratouveitis self-limiting (Carmichael, 1965). Corticosteroid therapy may be contraindicated and has been implicated in prolongation of corneal lesions and even blindness in dogs suffering postvaccinal reactions (Carmichael, 1965). However, the potential for severe sequelae without therapy may be sufficient justification to treat affected eyes. Anti-inflammatory therapy of postvaccinal keratouveitis may be necessary to prevent severe sequelae and to hasten resolution of ocular disease.

**Bacterial Disease**

Brucella canis is an aerobic, gram-negative coccobacillus that can survive in mononuclear cells (Dziezyc, 2000). Infection is by penetration of the organisms through mucous membranes of the oropharynx, genital tract, and conjunctiva. The concentration of the organism is highest in semen and vaginal discharge in infected dogs (Dziezyc, 2000). Abortion and infertility are common clinical signs that occur in breeding dogs, but neutered dogs may also be affected (Greene & Carmichael, 2006; Ledbetter et al., 2009). Ocular signs occur in ~14% of dogs with brucellosis. The more common ocular findings include endophthalmitis, chronic uveitis, hyphema, and chorioretinitis (Ledbetter et al., 2009; Vinayak et al., 2004). Other signs include diskospondylitis, glomerulopathy, and meningoencephalitis, but overt systemic disease may not occur (Dziezyc, 2000; Greene & Carmichael, 2006; Ledbetter et al., 2009). Diagnosis is made using the slide agglutination test in combination with the A/GID or by positive culture (Dziezyc, 2000). Antimicrobial therapy is complicated and must be continued long term because of the intracellular nature of the organism, but successful treatment has been reported (Ledbetter et al., 2009). Because of the zoonotic potential of brucellosis and the difficulty in eradicating the organism, euthanasia may be elected.

Bartonella vinsonii subsp berkhoffii is one subspecies of a group of intraerythrocytic bacteria most likely transmitted by the brown dog tick, Rhipicephalus sanguineus. Clinical signs in dogs infected with this organism include lethargy, weight loss, muscle and joint pain, hindlimb paresis, endocarditis, myocarditis, lymphadenitis, and fever (Breitschwerdt et al., 2004; Breitschwerdt & Homel, 2006). Various other neurologic and dermatologic signs may also be seen. Ophthalmic signs include anterior uveitis, chorioretinitis, hyphema, and retinal detachment (Breitschwerdt et al., 2004; Michau et al., 2003). Diagnosis is based on serologic testing. Multiple antibiotics have been used in the treatment of this disease (Breitschwerdt et al., 2004).

Leptospirosis is caused by a spirochete, a filamentous bacteria belonging to the genus Leptospira, which includes many species and serovars. Leptospira organisms are most commonly transmitted through urine. Vasculitis and endophthalmitis involving the kidneys, liver, spleen, muscles, CNS, and eyes occur. Ocular lesions are infrequently seen but may include anterior uveitis (Dziezyc, 2000; Lajeunesse & DiFruscia, 1999; Thirunavukkarasu et al., 1995). The leptospira organisms may be cultured from the aqueous humor of some dogs (Greenlee et al., 2004).
Algal Disease
Prototheca zopfii and Prototheca wickerhamii are algae that lack chlorophyll and are known pathogens in dogs and other animals. The primary clinical sign is usually hemorrhagic diarrhea; however, dogs may present with blindness as the initial sign (Schultze et al., 1998; Stenner et al., 2007). Neurologic signs may also occur, and ocular signs may include anterior uveitis, secondary glaucoma, chorioretinitis, and retinal detachment (Fig. 20.26) (Hosaka & Hosaka, 2004). Cytology or culture of vitreal aspirates may be diagnostic (Fig. 20.27) (Rizzi et al., 2006). Prototheca sp. are extracellular, round to oval organisms with thin, unstained walls. Larger cells may contain endospores. Therapy with itraconazole has been attempted but has been unsuccessful long term.

Hyperlipidemia
Dogs with hyperlipidemia resulting from elevations in either cholesterol or triglycerides may have associated ocular abnormalities. Lipid-laden aqueous humor was discussed briefly under “Uveal Inflammation” as occasionally occurring with anterior uveitis (Fig. 20.16). Lipoproteins of dogs range in size from 50 to 350 Å in diameter (Olin et al., 1976). However, the iridal vascular endothelium and nonpigmented ciliary body epithelium normally prevent particles greater than 40 Å from entering the aqueous humor. Breakdown of the blood-aqueous barrier (i.e., anterior uveitis) concurrent with hyperlipidemia may result in lipid-laden aqueous. Lipoid aqueous can be seen in dogs with known uveitis, such as dogs following cataract surgery. However, it is also seen in dogs without a history of ocular disease, suggesting that the lipids may also incite the inflammation.

Additional ocular manifestations of hyperlipidemia may include lipid engorgement of retinal vasculature and infiltration of the perilimbal cornea, conditions referred to as lipemia retinalis and corneal lipidosis (or arcus lipoides corneae), respectively (Cullen & Webb, 2007). Lipoid-laden aqueous and lipemia retinalis are likely to resolve with resolution of the primary disorder (Olin et al., 1976).

Pigmentary and Cystic Glaucoma (Pigmentary Uveitis)
Uveal cysts are usually considered to be benign; however, reports describing an association with cysts and glaucoma in both the Golden Retriever and the Great Dane have emerged. A syndrome that occurs primarily in Golden Retrievers in the United States has been referred to as both pigmentary uveitis, and pigmentary and cystic glaucoma (Esson et al., 2009; Sapienza et al., 2000). Pigment dispersion on the anterior lens capsule in a radial orientation is the most frequently observed early clinical sign (Fig. 20.28) (Esson et al., 2009; Sapienza et al., 2000). Other clinical signs include uveal cysts, spiderweb-like fibrinous debris in the anterior chamber, cataracts, and posterior synechia (Fig. 20.29). Secondary glaucoma occurs in the majority of eyes, and this disease is usually bilateral (Esson et al., 2009; Sapienza et al., 2000).

Common histopathologic features include thin-walled iridociliary cysts and glaucoma. The cysts are lined with attenuated cuboidal epithelium and fill most of the posterior chamber, stretch across the anterior face of the vitreous, or attach to the lens capsule. Iris bombé, PIFMs, trichrome-positive collagen deposition on the lens capsule, peripheral anterior synechiae, posterior synechiae, and free pigment within the trabecular meshwork are also seen (Deehr & Dubielzig, 1998; Esson et al., 2009).

Clinically, many dogs have evidence of uveitis seen as aqueous flare; however, histopathologically, only about half of the eyes have evidence of very mild uveitis (Esson et al., 2009). The clinical appearance of uveitis may be the result of
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has obstructed the trabecular meshwork (Werblin et al., 1983). Glaucoma therapies usually are not efficacious in the syndrome.

The syndrome in Great Danes may not be identical to that in the Golden Retrievers. Consistent findings in Great Danes with ciliary body cysts include multiple cysts in the anterior and posterior chamber and glaucoma. The cysts are variable in size, very poorly pigmented, and usually transparent. The entire posterior chamber is filled with cysts that may push the iris forward (Spiess et al., 1998). Histopathologically, multiple stacked cysts are seen in the area of the pars plicata and between the iris and ciliary body. The cysts originate from the ciliary body epithelium and are composed of a layer of epithelial cells that contain few melanin granules and are irregularly periodic acid-Schiff-positive. Commonly, a PIFM covers the drainage angle and the anterior surface of the iris (Spiess et al., 1998). The mechanism of glaucoma is thought to be anterior displacement of the iris with narrowing of the angle and a possible contribution by the PIFM. Evidence suggests that both glaucoma and ciliary body cysts are inherited in the Great Dane (Spiess et al., 1998).

Solid Intraocular Xanthogranuloma in Miniature Schnauzer Dogs

Solid intraocular xanthogranulomas were identified in four globes from three older Miniature Schnauzers that all had a history of diabetes mellitus, hyperlipidemia, and bilaterally severe uveitis with glaucoma that was believed to be lens-induced. Grossly, all globes were filled with a heterogenous tan mass. Histologically, intraocular contents were effaced by solid sheets of foamy macrophages admixed with hemorrhage, necrosis, and Alcian blue-positive refractile crystalline material in stellate patterns. Additionally, episcleral atherosclerosis was present, as evidenced by foamy macrophages within vessel walls (Zarfoss & Dubielzig, 2007b).

Hyperviscosity Syndrome

Monoclonal gammopathy associated with lymphoproliferative disorders may result in hyperviscosity syndrome (HVS). HVS causes clinical signs referable to multiple organ systems, including the cardiac, renal, hemostatic, ocular, and central nervous systems (Kirschner et al., 1988; Kobayashi et al., 1990; Lane et al., 1993). In the dog, HVS associated with increased serum concentrations of IgG, IgM, and IgA are reported (Center & Smith, 1982; Hendrix et al., 1998; Kirschner et al., 1988; MacEwen et al., 1977). HVS secondary to polycythemia vera has also been reported (Gray et al., 2003). Ocular anterior segment findings have included conjunctival hyperemia, corneal edema, hyphema, and secondary glaucoma, all of which are likely related to concurrent anterior uveitis. However, ocular findings are most often referable to the posterior segment and may include retinal vascular dilatation, tortuosity, microaneurysms, retinal hemorrhage, retinal detachment, chorioretinitis, and papilledema.
Sulfonamide Hypersensitivity

Multiple clinical abnormalities have been described in dogs with sulfonamide hypersensitivity (Giger et al., 1985; Trepanier, 2004; Trepanier et al., 2003). General signs include fever, arthropathy, blood dyscrasias, glomerulonephropathy, hepatocholangitis, skin eruption, retinitis, and keratoconjunctivitis sicca. Uveitis may also occur alone or secondary to intraocular bleeding from thrombocytopenia (Trepanier, 2004).

UVEAL TRAUMA

Ocular trauma may result in clinical signs that vary from mild miosis to disruption of the cornea or sclera. Often, blunt trauma manifests with flare, fibrin or hyphema, corneal edema, or iridial dialysis, but rarely hypopyon. With sharp trauma or extremely severe blunt trauma, fibrin, hemorrhage, uveal prolapse, and perforation of the cornea or sclera can be seen. Uveal prolapse occurs with globe rupture because the sudden decompression of the anterior chamber with aqueous outflow forces the iris into the wound, plugging it (Dalma-Weiszhaus & Dalma, 2002). Intraocular hemorrhage may be in the form of hyphema, iridial stromal hemorrhage, or hemorrhage around the equator of the lens or in the vitreous. In all cases of trauma, careful examination with necessary additional diagnostics should be done to determine the extent of ocular and periocular damage.

If the cornea is intact and the media sufficiently clear to permit examination of intraocular structures, it may be possible to determine the integrity of the iris, lens, vitreous, and retina by direct visualization of these structures. Miosis, fibrin, or hyphema often preclude a thorough examination. In the case of globe rupture, uveal prolapse may be evident on examination if the rupture occurred in the cornea or anterior sclera; however, it may not be evident if the rupture is posteriorly located. When ocular changes preclude a detailed direct examination, ultrasonic imaging is an invaluable tool for assessing the extent of intraocular damage.

Emergency Management of Acute Ocular Trauma

Cases of acute ocular trauma must be handled on an emergency basis. When a dog is presented with ocular trauma, the dog should be restrained or sedated as needed to facilitate an ocular examination. Care must be used to prevent further trauma. If debris, exudates, or hemorrhage are present, they should be gently irrigated from the ocular surface with warm, physiologic saline solution (without preservative). If possible, the clinician should determine whether a laceration or rupture of the globe is present. An assessment of the extent of globe laceration or rupture is not always easy, but it is important as a prognostic indicator. Note that corneal lacerations frequently extend across the limbus under an intact but often hemorrhagic conjunctiva. If the globe is ruptured, further examination to assess the degree of rupture and foreign-body examination should be delayed until the animal has been anesthetized.

However, the appearance of intraocular contents (e.g., lens material or vitreous) within the wound or on the ocular surface is usually seen with minimal effort. It must be determined whether surgical repair is feasible or if enucleation or implantation of an intraocular prosthesis should be advised. This determination is made on the basis of the extent of intraocular damage, the likelihood of preserving vision, and cosmetic concerns. Systemic antibiotics should also be administered if the globe is ruptured. If the globe appears to be intact, topical anesthetic solution should be applied, and the ocular surfaces, including the conjunctival fornices and both sides of the nictitating membrane, should be inspected for foreign bodies.

Ancillary Diagnostic Procedures

Following a thorough ocular examination, additional diagnostics may be required. Radiography of the skull, including oblique views of the orbit or orbits, will confirm or rule out the presence of fractures and establish whether gunshot injury is involved. B-scan ultrasonography is specifically indicated when the normally transparent ocular media are opaque. Integrity of the lens and posterior sclera as well as the position of the lens and retina can generally be determined with B-scan ultrasonography. In traumatized eyes, echo-dense areas in the vitreous cavity usually indicate vitreous hemorrhage. Computed tomography (CT) and magnetic resonance imaging (MRI) may be beneficial in assessing trauma, especially when intraocular foreign bodies (IOFBs) are suspected. Care should be taken with MRI because metallic foreign bodies can incite additional damage.

Treatment of Blunt Injuries

Intense pressure exerted on the globe during blunt trauma may result in vector forces reflecting off the posterior sclera and transferring anteriorly, causing a blow-out rupture of the perilimbal cornea or anterior sclera (Collins & Moore, 1999). Some causes of blunt injuries are impacts by golf balls and baseball bats; commonly, the owner is not aware that the dog is in such close proximity when the accident occurs. A cute traumatic uveitis or hyphema from blunt injury is treated similarly to other causes of anterior uveitis and hyphema (see “Uveal Inflammation” and “Hyphema”). A ruptured globe resulting from blunt trauma is handled similarly to cases of penetrating corneal trauma with uveal prolapse (see Chapter 18). When globe rupture has occurred secondary to forceful trauma, retinal detachment with vitreal hemorrhage is a common complicating factor. Iris bombe, traumatic cataract, endophthalmitis, and phthisis bulbi may also occur. Therefore, the prognosis following severe blunt trauma to an eye is guarded to grave.

Treatment of Penetrating Injuries

Focal punctures of the globe may cause minimal damage to the cornea and may seal spontaneously. If the eye is examined
within a few hours of the injury, it may be difficult to determine whether the cornea was completely penetrated or to determine the extent of intraocular damage. Penetrating corneal injuries that seal spontaneously are treated with topical and systemic antibiotics and topical NSAIDs. Topical corticosteroids are usually not applied until the corneal epithelium has healed unless the uveitis is severe. Systemic antibiotics are administered for a minimum of 10 days. In the absence of an IOFB, the primary concerns after such injuries are focal anterior or posterior synechiae, lens puncture with phacoclastic uveitis, traumatic cataract, secondary glaucoma, and infectious endophthalmitis.

Most penetrating injuries of the globe result in uveal prolapse, which appears as a protrusion of darkly pigmented tissue through the cornea or sclera. A grayish, fibrinous membrane typically covers the prolapsed uvea (Fig. 20.30). Sometimes, the uvea abuts the penetrating wound and exudes fibrin, creating a mass of fibrin on the surface of the cornea. A shallow or absent anterior chamber, pupil loss, and hyphema may also be present (Fig. 20.31). Traumatic uveal prolapse requires surgical repair that involves replacement or amputation of the prolapsed uvea. Specific steps in the repair of uveal prolapse are covered in Chapter 18. The prognosis after uveal prolapse varies depending on the time between injury and treatment, the extent of injury, concurrent infection, presence of a pupil opening, patency of the iridocorneal angle, and integrity of other intraocular structures (e.g., the lens and retina).

Large lacerations or tears of the cornea or sclera with prolapsed uvea, total hyphema, and the presence of vitreous, lens capsule, or lens cortical material within the wound or on the surface of the eye indicate a very poor prognosis. In such cases, enucleation or globe evisceration with a prosthetic silicone implant are recommended alternatives to primary surgical repair. Severely injured eyes that are not repaired or enucleated will usually become phthisical within several days or weeks after the trauma. Even eyes that are repaired surgically may undergo phthisis if the uveal trauma is marked. Severely traumatized globes may become a source of chronic pain to the affected animal, because panophthalmitis and secondary glaucoma are possible sequelae.

**Traumatic Uveitis with Lens Rupture**

Lens capsule rupture is most commonly caused by a penetrating foreign body or a cat claw injury and may lead to phacoclastic uveitis. Lens capsule rupture allows the release of lens cortex into the anterior chamber, which may precipitate fulminating endophthalmitis (Davidson et al., 1991; Wilcock & Peiffer, 1987). There may be a history of recent ocular trauma; however, lens penetration is rarely suspected. Usually, the corneal wound has sealed, and the anterior chamber has reformed by the time of examination. Capsular rents are often difficult to detect, but overlying fibrinous or inflammatory cellular material is suggestive of capsular disruption (Davidson et al., 1991). Medical therapy of phacoclastic uveitis needs to be aggressive with the use of topical and immunosuppressive doses of prednisone and topical atropine. Unfortunately, medical therapy is often inadequate, and endophthalmitis or secondary glaucoma commonly develops. Phacoemulsification may be necessary to treat lens rupture in the dog and when indicated, it must be done early in the disease process (Davidson et al., 1991). Very small rents may seal spontaneously and result in only a focal cataract (Fig. 20.32). For additional information, see the section “Lens-Induced Uveitis.”

**Intraocular Foreign Bodies**

IOFBs are relatively rare in dogs. IOFBs may be characterized by a range of clinical signs. The variability of presenting signs
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results from the type, size, location, point of entry of the foreign material, and the severity of the initial trauma (Schmidt et al., 1975). In humans, the majority of foreign body entrance wounds are corneal, and most foreign bodies are found in the vitreous. Foreign bodies can cause mechanical damage, anterior uveitis, endophthalmitis, and direct toxicity depending upon the composition of the IOFB (Lit & Young, 2002). Organic foreign bodies such as splinters, thorns, pine needles, cactus needles, and porcupine quills may be more likely to cause endophthalmitis than inorganic foreign bodies. Inorganic foreign bodies such as lead, glass, and plastic are non-reactive, while iron and copper foreign bodies are reactive and are the most likely metals to cause direct toxicity to intraocular structures (Lit & Young, 2002; Mester & Kuhn, 2002).

Diagnosing IOFBs can be difficult. A thorough history and a complete ocular examination including biomicroscopy with special attention to evaluation of the lens and inspection of the conjunctival fornices, both sides of the nictitating membrane, and all remaining conjunctival surface are essential.

CT with thin cuts is beneficial in the diagnosis and localization of an IOFB, but fresh wood and certain ceramics and plastics may be difficult to see on CT. MRI may be beneficial as well but should be used only when metallic foreign bodies have been ruled out because MRI can cause metallic foreign bodies to shift, leading to increased intraocular damage. Ultrasound can also be helpful as long as increased trauma can be avoided. Plain films are very poor at localization even when taken in multiple planes and are therefore rarely used (Lit & Young, 2002). When plain films are the only diagnostic modality available, a metal ring (e.g., a Flieringa ring) placed under the eyelids can help with IOFB localization by identifying the anterior aspect of the globe.

Method of removal of IOFBs depends on the location, depth, size, composition of the foreign body, extent of associated tissue damage, and the amount of uveal inflammation. Small, inert foreign bodies may be left alone. In contrast, organic foreign bodies that remain inside the eye stimulate severe, usually nonresponsive endophthalmitis; therefore, every effort should be made to remove all organic foreign material from the globe. Regardless of the type of foreign body, both septic and nonseptic endophthalmitis are sequelae that may necessitate enucleation.

A penetrating foreign body that is tapered, smooth, and relatively small in diameter (e.g., a sewing needle) may be removed directly after administration of general anesthesia. A single suture is placed at the site of penetration to seal the cornea and to prevent aqueous leakage. Rough, jagged, or barbed penetrating foreign bodies may require a full-thickness incision adjacent to or over the top of the foreign body to facilitate removal.

For retained linear foreign bodies that have penetrated the globe tangentially, an oblique, full-thickness corneal or scleral incision directly over the foreign body may be necessary to allow removal. After incising the cornea or sclera with a pointed surgical blade (e.g., a No. 65 Beaver blade), the foreign body is removed, and the wound is irrigated liberally with balanced salt or lactated Ringer’s solution. The defect is sutured with 6-0, 7-0, or 8-0 polyglactin 910. The associated uveitis is treated topically with antibiotics, 1% atropine, and NSAIDs. Some cases require the judicious use of topical corticosteroids. Systemic treatment should include antibiotics and anti-inflammatory agents.

Unless there is a gaping corneal wound or an exceptionally large foreign body, a foreign body located completely within the anterior chamber should be removed from a site distant from the entrance wound to minimize scarring and damage to endothelial cells (Lit & Young, 2002). This positioning allows for visualization of an instrument as it approaches the IOFB and minimizes obscuration from corneal edema if more manipulation is required than expected. The entrance wound should be closed with reestablishment of IOP prior to creating a new surgical wound through which to remove the foreign body. Attempts to dislodge foreign bodies that are located near the angle with saline or viscoelastics may be beneficial. Maintaining the anterior chamber with viscoelastics will aid with visualization.

Lens capsule rupture may occur with penetrating injuries of the globe (Davidson et al., 1991; Wilcock & Peiffer, 1987). When lens cortex is identified in the anterior chamber, lensectomy may be indicated to prevent phacoclastic endophthalmitis. With focal lens punctures in which the capsule seals spontaneously, the affected eye may respond favorably to medical therapy. Small, inert foreign bodies (e.g., lead shot) may lodge within the lens, thereby causing a traumatic cataract. When this occurs, however, the lens capsule may spontaneously seal, and the uveitis may respond to appropriate medical therapy. In this circumstance, the best achievable outcome is usually a quiet, cosmetically acceptable eye that is often visually compromised because of the traumatic cataract. As with other forms of lens rupture, phacoclastic endophthalmitis is also possible.
Poor prognostic indicators in humans include posterior and large entry wounds, posteriorly located foreign bodies, poor initial visual acuity, larger size of foreign body (Bai et al., 2011; Mester & Kuhn, 2002). Foreign-body penetration with extensive intraocular damage, nonresponsive uveitis, and chronic pain are indications for enucleation. Immediate referral to a veterinary ophthalmologist is advised in difficult cases to confirm the diagnosis, offer a prognosis, perform any necessary surgery, or treat any complications, which frequently arise.

**HYPHEMA**

Hyphema, or blood in the anterior chamber, occurs when uveal or retinal vessels are damaged or abnormally formed (see Fig. 20.18). Causes of hyphema in the dog include trauma, neoplasia, retinal detachments, blood dyscrasias, PIFMs, hypertension, infectious disease, severe uveitis, and congenital anomalies (Bayon et al., 2001; Berg & Riis, 2004; Cullen et al., 2000; Gould et al., 2000; Grahn et al., 1997; Gray et al., 2003; Habin & Else, 1995; Heath et al., 2003; Kilrain et al., 1994; Littman et al., 1988; Nelms et al., 1993; Oria et al., 2004; Peiffer et al., 1990; Stades, 1980; Trepanier, 2004; van de Sandt et al., 2004; Vinayak et al., 2004). Retinal detachment is the disease process most commonly associated with hyphema seen at referral institutions (Nelms et al., 1993). Chronic uveitis, chronic glaucoma, neoplasia, and retinal detachments may all lead to the development of PIFMs, which may result in hyphema (Peiffer et al., 1990).

The prognosis for hyphema is dependent on the etiology and presence of posterior segment damage. Hemorrhage from damaged choroidal or retinal vessels frequently moves anteriorly through to the pupil to manifest as hyphema. Vitreous, retinal, or choroidal hemorrhages or retinal detachment indicates severe intraocular disease and a poor visual prognosis. Also, the cause of hyphema influences whether blood clots in the anterior chamber. If the hyphema is secondary to a blood dyscrasia resulting in clotting abnormality, then the hyphema is unlikely to clot. However, hyphema occurring secondary to trauma or iridocyclitis will usually clot. Hemorrhage resulting from neoplastic, retinal detachment or congenital ocular diseases is often recurrent, and the hyphema in these cases may be clotted or unclotted and may form multiple layers within the anterior chamber.

When hyphema is present, a detailed history and complete physical and ocular examinations are essential. In young dogs with no history of trauma, congenital anomalies must be considered. Examining the eyes of littermates and reviewing breed predilections to hereditary congenital ocular disease such as Collie eye anomaly or persistent hyaloid artery may also be helpful in making a diagnosis. Other differential considerations in young adult dogs with spontaneous hyphema but no history of trauma include infections (e.g., ehrlichiosis) and toxic bleeding disorders. Neoplasia and systemic hypertension are causes that must be considered in geriatric animals. Regardless of the animal’s age, both genetic and acquired hemostatic diseases should be ruled out.

A complete ophthalmic examination including fluoroscein staining and IOPs is indicated for all cases of hyphema. A complete physical exam in association with a diagnostic evaluation, including appropriate laboratory tests, may be indicated to rule out systemic disease in animals with atraumatic hyphema (see Chapter 35.1). In many cases of hyphema, the most informative ancillary diagnostic procedure is ocular ultrasonography. Extensive hyphema prevents evaluation of intraocular tissues; therefore, the presence of intraocular masses, vitreous hemorrhage, retinal detachments, or scleral rupture may be detectable only with B-scan ultrasonography. CT or plain-film radiographs of the skull and orbit or may be necessary to diagnose concurrent orbital fractures or foreign bodies. While MRI can be used, additional damage to the globe and contents from intraocular ferromagnetic foreign bodies is a risk with this imaging modality.

Thoughts on the best medical treatment of hyphema vary. Assuming no contraindications, topical dexamethasone or prednisolone acetate with or without systemic prednisone is typically used to reduce and control intraocular inflammation and to reduce the incidence of rebleeding (Brandt & Haug, 2001; Walton et al., 2002). Pupilloactive drugs are often used; however, their use is somewhat controversial. A study in humans showed there was no difference in the outcome of patients treated with mydriatics, miotics, neither, or both (Gharibeh et al., 2011; Rakusin, 1972). Topical 1% atropine may be indicated initially to reduce the possibility of posterior synechiae formation, to decrease ciliary spasm, and to stabilize the blood-aqueous barrier. IOPs may increase with hyphema due to obstruction of the trabecular meshwork by clot, inflammatory cells, or erythrocytic debris, and the use of atropine may exacerbate ocular hypertension (Walton et al., 2002).

Therefore, tonometry should be done regularly to monitor for changes in IOP. If an increased IOP is noted after the initiation of mydriatic treatment, atropine is discontinued immediately and topical timolol and dorzolamide are then initiated (see Chapter 19) to reduce the IOP. Tropicamide (1%) may help prevent synechia formation without having the risk of elevating IOP if used judiciously. Conversely, pilocarpine may be efficacious because it enhances the outflow of aqueous humor, facilitates the removal of blood through the trabecular meshwork, and increases the surface area of the iris (via miosis), thereby enhancing fibrinolysin activity (Havener, 1983). The potential disadvantages of pilocarpine are that miosis predisposes patients to posterior synechiae and, subsequently, to iris bombé, and cholinergic agents may potentiate uveitis (Havener, 1983; Kohne et al. 1998).

Tissue plasminogen activator (TPA) is effective in the treatment of hyphema when large blood clots and fibrin are present in the anterior chamber or the IOP is elevated secondary to fibrin blocking the iridocorneal angle (Gerding et al. 1992; Martin et al. 1993). An injection of TPA into the anterior chamber can lead to rapid dissolution of the clot. TPA is most effective when injected within 72 hours of clot formation, but it may also be effective in dissolving clots of longer duration. The recommended dosage for intracameral injection...
is 0.1 mL of a 25 mg/100 µL solution (Gerding et al. 1992; Martin et al., 1993). TPA should not be injected if recurrent bleeding is likely; however, the risk of rebleeding is low due to clot specificity (Crabbe & Cloninger, 1987). Topical and systemic antifibrinolytics such as aminocaproic acid and tranexamic acid are used in the treatment of traumatic hyphema in humans to prevent rebleeding (Brandt & Haug, 2001; Mauger, 1994b; Walton et al., 2002). However, comparisons on the efficacy of systemic aminocaproic acid and prednisone have not shown a significant difference (Mauger, 1994b). Lastly, confining the dog’s activity to a cage or small room in a quiet area may minimize the possibility of recurrent hemorrhage.

**Establishing a prognosis or elucidating the cause of hyphema may not be possible immediately.** Evaluating the response to medical or surgical therapy (e.g., laceration repair) may be necessary to determine the extent of disease. Uncomplicated hyphema usually clears within 1 week (Walton et al., 2002). In cases of unexplained, nonresponsive, or recurring hyphema, the diagnosis must be reassessed. When intraocular neoplasia is known or strongly suspected to be the cause of hyphema, the affected eye should be enucleated and submitted for histopathologic evaluation. The prognosis for vision is best with cases of small hyphema volumes not associated with retinal detachment, hypertension, or trauma. Chronic hyphema may lead to all of the sequelae observed with chronic uveitis. Ghost cell glaucoma is a common complication of hyphema that may also occur in dogs (Campbell, 1981). The disease appears to be familial and tends to occur in older dogs. This syndrome has been compared with the pigmentary dispersion syndrome reported in humans. Clinically, hyperpigmentation involves the iris, ciliary body, choroid, and filtration angle. Often, the iris appears thickened, and there is pigment dispersed in the aqueous humor. Additionally, patchy pigment deposition around the perilimbal zone of the sclera and progressive pigmentation of the tapetal fundus and secondary glaucoma are seen (Fig. 20.33) (Petersen-Jones et al., 1991; van de Sandt et al., 2003). Affected dogs are poorly responsive to long-term therapy.

Histopathologically, many large, round, pigment-laden cells are seen infiltrating the anterior uvea, sclera, and episclera and obscuring the drainage angle. Fewer cells are present in the posterior segment of the globe, the optic nerve meninges, and periphery of the optic nerve. Many globes have changes secondary to chronic glaucoma, and some have evidence of uveitis (Petersen-Jones et al., 2008). While this disease is not considered to be neoplastic, three dogs in one large study were subsequently diagnosed with uveal melanocytic neoplasms (Petersen-Jones et al., 2007).

**Figure 20.33.** This Cairn Terrier has pigmentary glaucoma. Pigment is dispersed in the aqueous humor and is present on the anterior lens capsule. Additionally, there is pigment deposition in the perilimbal zone of the sclera. Secondary glaucoma has caused buphthalmia and lens subluxation.
Melanocytic Neoplasms

Melanocytic neoplasia (i.e., melanoma) is the most common primary intraocular neoplasm in the dog (Saunders & Barron, 1958; Trucksa, 1983). Unfortunately, the terminology pertaining to melanomas is inconsistent. Some of the inconsistency is due to the variation in clinical behavior of melanomas and location of tumors between species (Yanoff & Fine, 1982; Ryan & Diter, 1984; Trucksa, 1983). Physicians use the term melanoma to imply malignancy. Melanocytoma is used to describe a flat mass near the optic disk, which is an unusual manifestation in dogs (Bussanich et al., 1987). Also, in humans, posterior uveal melanomas are more common than those arising from the anterior uvea and are more likely to metastasize. In veterinary medicine, benign and malignant are often used as qualifiers in the description of a melanoma. The two larger studies of canine ocular melanomas classify canine uveal melanomas as melanocytomas and (malignant) melanomas (Giuliano et al., 1999; Nasisse et al., 1993; Wilcock & Peiffer, 1986). The term melanocytoma refers to benign anterior uveal melanomas, limbal melanomas, and choroidal melanomas. Benign melanocytomas are differentiated from (malignant) melanoma by nuclear pleomorphism, nuclear-to-cytoplasmic ratio, and mitotic index. The tumors are considered malignant if cellular morphology includes prominent nucleoli, a nuclear to cytoplasmic ratio greater than one, and more than two mitotic figures per 10 high-power fields (HPFs) (Giuliano et al., 1999; Wilcock & Peiffer, 1986). Most canine ocular melanomas arise in the anterior uvea, and both the iris and the ciliary body are common sites of origin. With large masses, the tissue of origin is often difficult to determine even histopathologically.

Intraocular melanocytic tumors are most common in older dogs with a mean age of around 9 years, but an age range of 2 months to 17 years has been reported in one large study (Bussanich et al., 1987; Giuliano et al., 1999; Ryan & Diter, 1984; Wilcock & Peiffer, 1986). While German Shepherds and retrievers are the more commonly affected breeds reported in studies, population statistics have not been done to determine if breed is a risk factor (Bussanich et al., 1987; Giuliano et al., 1999; Ryan & Diter, 1984). Inherited iris melanoma has been reported in a family of Labrador Retrievers, but the diagnosis was made on the basis of clinical examination with no histopathologic confirmation (Cook & Lannon, 1997). A sex predilection has not been demonstrated.

A color change or mass effect in the dog’s eye may be the first abnormality observed, or changes may go unnoticed until secondary uveitis or glaucoma develops. Melanomas in dogs tend to produce nodular growth rather than diffuse infiltration, as is seen in cats and humans (Acland et al., 1980). While clinical presentation, melanoma may be focal and confined to the iris, or it may be extensive. Large masses will often bulge through the pupil, displace the iris anteriorly, or cause dyscoria. Iris thickening, an irregular pupil, blindness, and ocular pain are the most common clinical signs (Fig. 20.35) (Dubielzig, 1990). Pigmentation is variable, and amelanotic melanomas can occur but are rare (Dubielzig, 1990). A ditionally, keratitis, anterior uveitis, hypHEMA, secondary glaucoma, buphthalamos, and retinal detachment may be observed (Bussanich et al., 1987; Wilcock & Peiffer, 1986). Anterior uveal melanomas are often locally invasive, and they may extend to involve the choroid, sclera, filtration angle, cornea, and orbit (Ryan & Diter, 1984; Wilcock & Peiffer, 1986). Lens subluxation may also occur because of displacement by the mass.

Primary Neoplasms

ANTERIOR UVEAL TUMORS

Intraocular tumors are relatively uncommon in the dog. The tumors may be primary or secondary from metastatic disease or local invasion. The great majority of primary intraocular tumors have their origin in the anterior uvea. While distant metastasis from primary intraocular tumors is rare, local tissue destruction and secondary glaucoma occur commonly. Tumors must be differentiated from other intraocular masses, including iris cysts, granulomatous lesions, and staphylomas. Tumors must also be considered in any eye with secondary glaucoma or opaque media. Diagnosis is based on findings from complete ophthalmic and physical examinations and whether the masses are unilateral or bilateral, singular or multiple, raised or flat, and stationary or changing in appearance.

Primary Neoplasms

Melanocytic Neoplasms

Slightly elevated mass on the iris face (Fig. 20.34) (Gelatt et al., 1979; Peiffer, 1981). Nevi tend to occur in young dogs. Histopathologically, cells replace the iris stroma, and cystic areas may be present. Mitotic figures are not observed, and the cell population is relatively homogeneous (Gelatt et al., 1979). Nevi may undergo malignant transformation; however, diffuse malignant melanoma of the iris rarely occurs in dogs, in comparison to cats, and usually the iris is thickened concurrently (Peiffer, 1981).

Figure 20.34. An iris nevus is present in the iris of this German Shepherd mix.
Neoplastic melanocytes or melanophages (or both) are often free-floating in the anterior chamber, and their obstruction of the filtration angle may contribute to secondary glaucoma (Wilcock & Peiffer, 1986). Uveal melanomas that penetrate the perilimbic sclera may simulate a limbal (i.e., epibulbar) melanoma.

Diagnosis is usually made by clinical examination. Possible differentials include uveal cysts, staphylomas, and limbal melanocytoma. Clinical distinction is important because the prognosis and therapy are different for iris cysts and melanomas. Iris cysts are identified by transillumination, and limbal melanocytomas are apparent on the external surface of the globe. The use of ultrasound may be helpful when the cornea or ocular media is opaque, to differentiate between cysts and tumors and to help determine the extent of growth of the tumor. Gonioscopy may facilitate in differentiating between uveal and limbal melanocytomas. Uveal melanomas with extraocular extension often invade the filtration angle, whereas limbal melanocytoma, though extending deep into the sclera, may compress but will less commonly invade the angle; still, invasion of limbal melanomas into the filtration angle and anterior uvea has been reported (Bussanich et al., 1987; Wilcock & Peiffer, 1986). Primary choroidal melanoma has been reported infrequently in the dog, and anterior uveal melanomas may infiltrate posteriorly into the choroid (Dubielzig et al., 1985). It is important to rule out metastasis from a distant site by doing a thorough physical examination that includes examining the oral cavity, foot pads, and nail beds.

The histopathologic descriptions of intraocular melanocytic tumors vary. Some authors use quantification of relative proportions of cell types (e.g., spindle, ovoid, epithelioid) to define benign or malignant qualities (Diters et al., 1983; Ryan & Diters, 1984; Wilcock & Peiffer, 1986). However, the criteria for certain cell types vary significantly. Spindle A and epithelioid cells are described by some but not by others (Bussanich et al., 1987; Diters et al., 1983; Dubielzig, 2002; Ryan & Diters, 1984; Trucksa et al., 1985; Wilcock & Peiffer, 1986). Most authors do agree that plump or round pigment cells are a feature of canine uveal and limbal melanomas (Bussanich et al., 1987; Diters et al., 1983; Dubielzig, 2002; Ryan & Diters, 1984; Trucksa et al., 1985; Wilcock & Peiffer, 1986). These cells are typically polyhedral and heavily pigmented. Results of ultrastructural studies have revealed that plump cells are neoplastic melanocytes rather than melanophages (Bussanich et al., 1987; Wilcock & Peiffer, 1986). Plump cells occur with much greater frequency in histopathologically benign melanomas; accordingly, these melanomas tend to be more heavily pigmented and lack mitotic figures (Bussanich et al., 1987; Wilcock & Peiffer, 1986). The plump cell is postulated to be a hypermature spindle cell that is amitotic and prone to lysis, whereas the cell types typical of histopathologically malignant melanomas are thought to represent anaplasia rather than spindle cell maturation (Wilcock & Peiffer, 1986). In cases of a poorly pigmented or differenti-ated melanoma, it may be difficult to make the histopathologic diagnosis, but immunohistochemical staining with Melan A may be beneficial. Additionally, monoclonal antibodies designed to detect melanoma-associated antigens in human tissues have been used with some success to diagnose canine melanomas, and such antibody markers may be useful in these rare instances (Berrington et al., 1994).

Historically, the Callender classification was used in the description of intraocular melanocytic tumors in dogs; this classification was first described in 1931 and is still used for correlating histopathologic features of uveal malignant melanomas with their metastatic potential in humans (Callender, 1931; Ryan & Diters, 1984). However, because many canine tumors are benign, are of the mixed or epithelioid-cell type, or have plump cells not seen in human uveal melanomas, this classification scheme is not deemed appropriate for canine uveal melanomas (Bussanich et al., 1987; Trucksa et al., 1985; Wilcock & Peiffer, 1986).

Severity of intraocular destruction has also been used as a sole indicator of malignancy; however, most canine anterior uveal melanomas, though frequently invasive, do not conform with the strictest definition of malignancy, which includes metastasis having the potential to cause death (Ryan & Diters, 1984; Wilcock & Peiffer, 1986). One large study of primary ocular melanocytic neoplasia showed that 79% of the benign lesions arose from the anterior uvea instead of the limbus or choroid, and 95% of the malignant melanomas were anterior uveal in origin (Giuliano et al., 1999). Regardless of histologic characteristics, approximately the same number of tumors remained inside the sclera (−7%), invaded the sclera (−56%), or had extra scleral extension (−28%) (Giuliano et al., 1999). Most tumors arising from the anterior uvea grow expansively rather than invasively and occupy the filtration angle and deep stroma of the peripheral cornea and sclera (Wilcock & Peiffer, 1986). Malignant melanomas tend to be less pigmented and comprise 20% of intraocular melanocytic tumors (Dubielzig, 2002).

Metastasis occurs hematogenously and typically involves the thoracic and abdominal viscera (Bussanich et al., 1987;
Galan et al., 2009; Giuliano et al., 1999; Ryan & Diters, 1984; Wilcock & Peiffer, 1986). Microscopically, neoplastic cells may be identified in the scleral emissaria or the optic nerve, confirming the egress of neoplastic cells from the globe. Metastasis may be more likely when extraocular extension or glaucoma (or both) is present (Trucksa et al., 1985). Metastasis to the contralateral eye has been reported once (Render et al., 1997). Melanoma can also metastasize to the eye from cutaneous or oral sites; thus, the primary tumor site may be difficult to determine (Ryan & Diters, 1984; Trucksa et al., 1985). Cytologic indices (i.e., mitotic index, nuclear pleomorphism, nuclear–cytoplasmic ratio) are sensitive and accepted indicators of malignant potential in many tumors. For all cases of canine anterior uveal melanomas in which metastasis has been confirmed, the neoplasms have shown morphologic characteristics easily recognizable as being indicative of malignancy (Dubielzig, 1990). Specifically, the mitotic index has been suggested as being the superior criterion for predicting malignancy (Dubielzig, 1990; Wilcock & Peiffer, 1986). A low mitotic index (<2 per 10 HPFs) is typical of melanocytomas. For melanomas in which metastasis was confirmed, however, the mitotic index was higher (>4 per 10 HPFs, and usually much higher) (Bussanich et al., 1987; Wilcock & Peiffer, 1986). Histologic criteria such as necrosis, inflammation, degree of pigmentation, and presence of tumor cells in the cornea, filtration angle, or episclera are not predictive of postsurgical biologic behavior (Wilcock & Peiffer, 1986). Expression of cyclooxygenase-2 was evaluated in normal eyes and in eyes with benign and malignant melanocytic neoplasms. All eyes expressed COX-2 similarly, and therefore COX-2 expression was not useful in differentiating benign from malignant tumors (Paglia et al., 2009).

Dogs with malignant melanoma have shorter survival times than unaffected dogs and dogs with melanocytomas. Tumor extension, tumor size, and mitotic index are not specifically related to survival time (Wilcock & Peiffer, 1986). The metastatic rate for uveal melanomas in dogs has been reported to be 4% and 10% (Bussanich et al., 1987; Wilcock & Peiffer, 1986). One study showed evidence of metastasis with both melanocytomas and malignant melanomas with a lower metastatic rate in the dogs with melanocytomas (∼4%) and a rate of 25% in dogs with malignant melanomas (Giuliano et al., 1999). The overall low risk of metastasis of canine uveal melanomas and unproven efficacy of enucleation at preventing metastasis makes the decision to remove normotensive noninflamed visual eyes difficult (Wilcock & Peiffer, 1986). Additionally, studies in humans with uveal melanomas have shown that dissemination of tumor cells at the time of enucleation may be a major risk for metastasis with small- and medium-sized tumors (McLean et al., 1982; Zimmerman & McLean, 1979).

**Iridociliary Epithelial Tumors**

Iridociliary epithelial tumors are the second-most common primary intraocular tumor in the dog (Dubielzig et al., 1998; Peiffer, 1983a). These tumors arise from either the epithelial cells of the iris or ciliary body (Dubielzig, 2002). Primary iridociliary epithelial tumors are identified by having one of the following criteria: noninvasive epithelial growth extending into the aqueous adjacent to the iris or ciliary body, pigmented epithelial cells, or thick basement membrane structures on the cell surface (Dubielzig et al., 1998).

Iridociliary epithelial tumors are more common in middle-aged to older dogs (mean age, 9.0 years) (Dubielzig et al., 1998; Peiffer, 1983a; Peiffer et al., 1978). They appear clinically as segmental or nonsegmental, solid or papillary, and invasive or noninvasive (Fig. 20.36). The incidences of adenoma (i.e., benign) and adenocarcinoma (i.e., potentially malignant) are approximately equal, and these tumors combined are suggested to have an incidence approximately half that of uveal melanoma (Peiffer, 1983s). Distant metastasis of ciliary body adenocarcinoma has been reported; however, metastasis appears to be highly unusual (Bellhorn, 1971; Dubielzig et al., 1998; Glickstein & Allen, 1974; Peiffer, 1983a; Zarfoss & Dubielzig, 2007a).

The clinical presentation may appear similar to that of melanoma, and distinguishing between the two may be difficult (Peiffer et al., 1978). The tumors may extend through the pupillary or invade the iris, but adenomas are more often limited to the ciliary body. A denocarcinoma, on the other hand, are typically more invasive, may extend through the iris base or pupil, and may metastasize. A cystic adenoma has also been reported (Peiffer et al., 1978). One report described a ciliary body adenoma that appeared to be relatively quiescent until the dog developed a distant malignant tumor at which time rapid growth of the ciliary body tumor was noted (Whittemore et al., 2004).

Histopathologically, the iridociliary epithelial tumors are papillary, solid, or cystic (Dubielzig, 2002; Dubielzig et al., 1998). Adenomas are characterized histopathologically by sheets and cords of well-differentiated epithelial cells with a...
tendency to form adenoidal structures with an eosinophilic secretory substance (Peiffer, 1983b). Adenocarcinomas form fewer adenoidal structures, have less secretory substance, and have variable cellular pleomorphism and numbers of mitotic figures (Peiffer, 1983a, 1983b). The usefulness of correlating cellular morphology with metastatic potential in these tumors is unknown (Dubielzig, 1990). While pigmentation is present in about half of the tumors histopathologically, most have the clinical appearance of being nonpigmented. Invasion into the uvea or sclera is variable, and tumors that extend into the sclera often have cellular features of anaplasia; therefore, they are designated as adenocarcinomas (Dubielzig et al., 1998). One tumor was seen to invade into the lens (Hendrix & Donnell, 2007). Most tumors stain positive for vimentin, S100, and neuron-specific enolase. Secretion of hyaluronic acid, which stains with Alcian blue, is further evidence of iridociliary epithelial origin (Dubielzig, 2002; Dubielzig et al., 1998). Other commonly seen histologic findings are PIFMs, retinal detachment, asteroid hyalosis, intraocular hemorrhage, and evidence of glaucoma (Dubielzig et al., 1998).

Intraocular tumors, primarily of the ciliary body, were induced with intravenously injected $^{226}$Ra and $^{228}$Ra in Beagles. Most of the tumors were thought to represent a unique radium-induced neoplasm arising from the pigment epithelium of the ciliary body. In contrast to melanomas, these tumors were not of neural crest origin. Metastasis was rare (Taylor et al., 1972, 2000).

**Medulloepitheliomas**

Medulloepitheliomas arise from the primitive medullary epithelium or inner layer of the optic cup, before differentiation into adult tissues and are therefore classified as congenital tumors and diagnosed in young dogs (Broughton & Zimmerman, 1978). Although these tumors are reported rarely in dogs (Aleksandersen et al., 2004; Langloss et al., 1976; Peiffer, 1983b; Wilcock & Williams, 1980), historically, diagnoses of retinoblastoma, melanocarcinoma, and intraocular ganglioma in the dog were reevaluated and believed to actually represent medulloepitheliomas (Langloss et al., 1976; Peiffer, 1983b; Wilcock & Williams, 1980). Usually, a white or gray-white mass is present in the pupil or extending through the iris. Secondary glaucoma may be the presenting clinical sign. Tumors typically arise from the ciliary body (Dubielzig, 2002).

Histopathologically, the medulloepithelioma is composed of sheets and cords of primitive neuroectoderm. Rosette formation is frequently observed. Typically, the tumor contains structures resembling normal derivatives of neuroectoderm such as retina, ciliary epithelium, vitreous, and neuroglia (Wilcock & Williams, 1980). Some tumors contain additional tissues not normally present in the globe, such as undifferentiated mesenchyma, cartilage, striated muscle, or tissue resembling brain, and these tumors are called teratoid medulloepitheliomas (Lahav et al., 1976; McGean et al., 1994). Mitotic figures may be frequent. While the vast majority of these tumors have a clinically benign behavior, one case with metastasis to the brain and kidneys has been described (Aleksandersen et al., 2004; Langloss et al., 1976; Wilcock & Williams, 1980). Treatment is enucleation.

**Miscellaneous Primary Neoplasms**

Reports of additional primary intraocular neoplasms are extremely rare. There has been one report of a cavernous hemangioma of the iris, which was successfully excised by iridectomy (Megrane, 1954). Histopathologically, the mass consisted of endothelial-lined blood channels. Ciliary body hemangioma has also been reported, and iridal hemangiosarcoma was confirmed in one other instance following enucleation of the globe (Kirschner et al., 1986; Read, 1993). Metastatic disease was not observed in the latter report. Iridal leiomyosarcoma, presumably arising from the pupillary constrictor muscle, has also been reported on one occasion, and again, metastasis was not observed (Barron & Saunders, 1959). One case of a myxoid leiomyoma appeared clinically as a nonpigmented mass on the peripheral iris. Histologically, predominantly uniform spindle-shaped cells were loosely packed and arranged in a swirling pattern, and the tumor involved the dilator pupillary muscle, possibly arising from these cells (Billson et al., 2003).

Ocular osteosarcomas are extremely rare (Heath et al., 2003; Langenbach et al., 1998; Patnaik, 1990; van de Sandt et al., 2004). Generally, extraskeletal osteosarcoma is a highly aggressive tumor with a high rate of recurrence or metastasis (Langenbach et al., 1998; Patnaik, 1990). However, two dogs that were enucleated did not develop metastasis or recurrence (Heath et al., 2003; van de Sandt et al., 2004). Primaryocular osteosarcoma is diagnosed based on histopathologic evidence of pleomorphic spindle or stellate cells, occasional multinucleated cells resembling osteoclasts, and an abundance of extracellular collagen matrix typical of osteoid (Heath et al., 2003; van de Sandt et al., 2004).

Spindle cell tumors of the anterior uveal tract of dogs present as nodular, nonpigmented masses of the anterior uvea. The majority of affected dogs have blue irides, and the Sibeian Husky is overrepresented (Klauss & Dubielzig, 2001). Histopathologically, the masses occur in the iris with or without ciliary body involvement and are composed of pleomorphic spindle cells showing interdigitation with stromal collagen. Tumor cells show nuclear palisading, with the spindle cells arranged in fascicles and whorls (variable Antoni A and B behavior) (Klauss & Dubielzig, 2001; Dubielzig 2002; Zarfoss et al., 2007). Tumors are positive when immunostained for vimentin and S-100 with variable immunoreactivity to glial fibrillary acidic protein (GFAP) and other stains. These tumors are morphologically and immunohistochemically most consistent with Schwannoma (Zarfoss et al., 2007). Glaucoma and PIFMs are also commonly seen (Klauss & Dubielzig, 2001). Primary (or posttraumatic) ocular sarcoma, as reported in the cat, has not been described in the dog (Dubielzig, 1990).
Secondary Neoplasms

Neoplasms may metastasize hematogenously to the eye from local or distant sites, or they may invade the eye by local extension from the ocular adnexa, cornea, orbit, paranasal sinuses, or nasal cavity. Hematogenous spread accounts for most secondary neoplasms, and of these, intraocular lymphosarcoma is the most common in the dog (Cello & Hutcherson, 1962; Krohne et al., 1994). Other metastatic neoplasms include hemangiosarcoma, cutaneous and oral melanoma, osteosarcoma, malignant histiocytosis, seminoma, transmissible venereal tumor, transitional cell carcinoma of the urinary bladder and urethra, neurogenic sarcoma, rhabdomyosarcoma, anaplastic fibrosarcoma, pheochromocytoma, and adenocarcinoma of mammary gland, thyroid gland, parotid salivary gland, adrenal gland (presumed), nasal, renal, pancreatic, and pulmonary origin (Barron et al., 1963a, 1963b; Bellhorn, 1972; Castellano et al., 2006; Dubielzig, 1990; Esson et al., 2007; Ferreira et al., 2000; Gelatt et al., 1970; Habin & Else, 1995; HogenEsch et al., 1987; Kirschner et al., 1986; Moore, 1984; Moore et al., 1980; Nyska et al., 1992; Pereira et al., 2000; Schmidt, 1981; Szymanski, 1972; Szymanski et al., 1984; Trucksa et al., 1985; Yoshikawa et al., 2008).

Secondary neoplasms often have similar clinical presentations, regardless of the histopathologic type, and may be more likely to occur bilaterally than primary ocular neoplasms. Dogs with secondary ocular neoplasms may have obvious concurrent systemic disease or signs may be referable only to the eye (Lavach, 1984). An intraocular mass may or may not be readily apparent. The uvea appears to be a predilection site for those tumors that metastasize hematogenously (Bellhorn, 1972). Therefore, ocular signs may include anterior uveitis, hyphema, and glaucoma. Hyphema of undetermined etiology may be the presenting sign of a metastatic neoplasm; in those cases, ocular ultrasound may help delineate a mass (Moore et al., 1980). Additionally, signs associated with chronic ocular disease such as secondary glaucoma, keratitis, lens luxation, retinal hemorrhage or detachment, and extraocular extension may be present.

Ocular Lymphosarcoma

Ocular signs are seen commonly with lymphosarcoma. The reported incidence of ocular involvement with lymphosarcoma in one prospective study was 37% (Krohne et al., 1994). The high incidence of ocular signs makes ocular disease the second-most common clinical sign of lymphoma second to lymphadenopathy. With the high incidence of ocular signs and because ocular lymphoma can mimic inflammation, lymphoma should be considered as a differential for anterior uveitis and retinal disease even in the absence of lymphadenopathy or other evidence of systemic disease (Cave & Billson, 2003). Most cases are bilateral. Anterior uveitis with thickening and a lighter color to the iris is commonly seen (Fig. 20.37) (Cello & Hutcherson, 1962; Krohne et al., 1994). Panuveitis is also frequently diagnosed, whereas posterior uveitis alone is uncommon. Additional ocular signs include conjunctival infiltrates, corneal infiltrates, hyphema, hypopyon, intraretinal and subretinal hemorrhages, and glaucoma (Fig. 20.19 and Fig. 20.38). The keratitis occurring with ocular lymphosarcoma is distinctive. It usually begins with corneal edema and vascularization, followed 2–3 weeks later by perilimbal corneal infiltrates of neoplastic lymphocytes, which impart the appearance of a circumcorneal, dense white band (Cello & Hutcherson, 1962). Observation of a distinct intraocular mass is uncommon in the dog (Cave & Billson, 2003; Cello & Hutcherson, 1962; Krohne et al., 1994). Cytology of aqueous humor can be useful in making a diagnosis of lymphoma in dogs with anterior uveitis (Cave & Billson, 2003; Pate et al., 2011). Polymerase chain reaction (PCR) assay for antigen receptor rearrangement on an aqueous humor sample has been used to determine the immunophenotype of lymphosarcoma cells in one case (Pate et al., 2011).
Histopathologically, a diffuse uveal infiltration of neoplastic lymphocytes is present, and the anterior uvea is usually more heavily infiltrated than the choroid. Increased vascularity of the canine iris may be the reason for the increased incidence of anterior uveal involvement in the dog (Cello & Hutcherson, 1962). Extensive tumor growth may also occur in the retina, where lesions may range from mild retinal perivascular infiltrates to complete replacement of the retina by neoplastic cells (Cello & Hutcherson, 1962). Lymphocytic and lymphoblastic lymphosarcoma are the histopathologic types most often reported with ocular involvement, with the lymphoblastic type being slightly more common (Krohne et al., 1994). Intravascular lymphoma, also known as malignant angioendotheliomatosis, may also cause panophthalmitis, iridal swelling, and retinal detachment (Cullen et al., 2000).

Ocular signs are attributable not only to the neoplastic infiltrates but also to associated abnormalities such as anemia, thrombocytopenia, and disseminated intravascular coagulation. These hematologic abnormalities, including leukemic blood profiles, are consistent with bone marrow involvement. Megaloblastic anemia after bone marrow infiltration may be responsible for anemia and thrombocytopenia, and bone marrow involvement is more common in dogs with lymphosarcoma-associated ocular signs than those with lymphosarcoma and no ocular signs (Krohne et al., 1994).

Ocular examination of dogs with lymphosarcoma may be useful in the clinical staging of the disease and as a predictor of longevity. In one study of 94 cases, the life span of dogs with ocular lymphosarcoma was 60%–70% of that of those dogs without ocular involvement after treatment (Krohne et al., 1994). In this same study, all dogs presenting with uveitis and intraocular hemorrhage were considered to be stage V on the basis of other organ involvement and criteria established by the World Health Organization. Therefore, dogs with concurrent lymph node involvement, uveitis, intracocular hemorrhage, or a combination thereof should be considered as clinical stage V. This may be particularly beneficial for immediate staging of those cases in which bone marrow biopsy has been nondiagnostic.

**Diagnosis and Therapy of Uveal Neoplasms**

Uveal neoplasms may present as masses or anterior uveitis. Unilateral disease is more suggestive of a primary neoplasm, whereas bilateral disease is suggestive of secondary or metastatic neoplasia. A complete physical examination, serum biochemical profile, as well as thoracic and possibly abdominal radiography and ultrasound are indicated when an intraocular neoplasm is detected or suspected to determine the presence of metastatic disease. Disseminated neoplasia most commonly indicates that the neoplasm has metastasized from a primary site to the eye rather than a primary tumor in the eye has metastasized.

A primary uveal melanoma is the most common intraocular tumors and are often pigmented. As mentioned previously, transillumination to distinguish uveal cysts from melanoma or gonioscopy to distinguish limbal melanoma from uveal melanoma may be beneficial. Concurrent uveitis, hyphema, glaucoma, and ocular discomfort may be the first indicators of intraocular neoplasia, and neoplasia should be considered in all such cases with an uncertain cause. Primary or secondary uveal neoplasia can mimic inflammation (masquerade syndrome) by shedding cells into the aqueous humor and by increasing the local blood supply or by causing necrosis (Read et al., 2002). Ocular B-scan ultrasonography may be helpful in delineating a mass when opaque ocular media prohibit a thorough intraocular examination.

Histopathologic examination is necessary to confirm any neoplasm. Histopathology should be performed on all enucleated eyes or locally excised neoplasms. Fine needle aspiration of intraocular masses has not been routinely used in veterinary ophthalmology. The technique appears to be beneficial in humans, but the increased vascularity of the canine iris suggests that hyphema would be a more common and serious complication in the dog (Shields et al., 1993).

Treatment of an intraocular neoplasm is based on many factors, including the type of neoplasia, the overall health of the globe and the dog, the presence of metastatic disease, and the financial constraints of the owner. Treatment options may include temporization, local excision, enucleation, orbital exenteration, and possibly euthanasia if metastatic disease is present. Given the seemingly benign biologic behavior of most uveal melanomas, some clinicians elect to simply observe the mass for progression rather than to hastily remove a sighted eye. Removal of a mass localized to the iris and not invading the filtration angle may be attempted by iridectomy. Masses that involve the iris and ciliary body can be excised via iridocyclectomy (see “Uveal Surgery”). A decision to perform local resection is made largely on the basis of clinical preference, the surgeon’s technical proficiency in microsurgery, and the owner’s financial constraints. Diode laser photocoagulation of melanomas is an effective, less invasive treatment and is described in detail in the section “Photocoagulation of Iris Melanoma.” Transectional laser ablation and surgical excision of iris or ciliary body adenocarcinoma combined with chemotherapy using 5-fluorouracil has been reported (Clerc, 1996). In these latter instances, the diagnosis is presumptive because histopathologic confirmation is usually not feasible.

From a practical standpoint, therapy in many instances is limited to enucleation or exenteration. The curative potential of enucleation and the likelihood of inciting metastasis by performing such surgery, however, remain controversial (McLean et al., 1982; Wilcock & Peiffer, 1986). Some clinicians recommend enucleation for primary tumors of any type when distant metastasis is not evident. Concurrent anterior segment inflammation or glaucoma is additional justification for enucleation. Orbital exenteration meant to completely remove the neoplasm is generally reserved for neoplasms that have extended outside the globe.

Enucleation or exenteration may be elected in the case of disseminated neoplasia when the goal is to reach a diagnosis
or treat ocular discomfort. Systemic chemotherapy of secondary tumors may lead to resolution of ocular inflammation and regression of the intraocular mass. Topical corticosteroids alone may cause significant regression of anterior segment infiltrates associated with lymphosarcoma. Euthanasia may be more appropriate than enucleation (or enexenteration) among select cases in which metastasis is present and the patient is debilitated or the owner has declined therapy.

**UVEAL SURGERY**

Uveal surgery is indicated most commonly in the treatment of intraocular neoplasms and in treatment of pupillary abnormalities secondary to inflammation. Two other indications for surgery of the anterior uvea are the repair of globe perforations with prolapsed uveal tissue and the treatment of glaucoma refractory to medical therapy. These important areas of uveal surgery are addressed in Chapters 18 and 19.

**General Concepts of Uveal Surgery**

The anterior uvea is accessed through clear corneal, limbal, or scleral incisions. Entrance location into the anterior chamber is dependent upon the surgical procedure being performed and the location of the lesion within the uvea. Regardless of the entry point, several items need to be remembered. The ora ciliaris retinae, the junction between the pars plana of the ciliary body and the peripheral retina, is located 8 mm caudal to the limbus superiorly and temporally and only 4 mm inferiorly and nasally (Samuelson, 2007). An incision extending caudally to the ora may lead to retinal detachment or massive hemorrhage. The long posterior ciliary arteries enter the globe axially to the major iris blood vessels. The procedure is initiated by making a clear corneal incision adjacent to the iridectomy site. The incision is usually 90–180 degrees. A fiber filling the anterior chamber with viscoelastic, the iris is retracted into the incision using a blunt iris hook. The iris, on both sides of the mass, is incised with iris scissors or cautery. The base is then incised. While there is limited hemorrhage with the radial incisions, more hemorrhage may occur with the base

**Mass Removal Procedures**

**Sector Iridectomy**

Localized masses of the iris may be removed by sector iridectomy although this procedure has largely been replaced with laser photocoagulation. This procedure is optimal for removing well-defined focal lesions of the iris that are located axially to the major iris blood vessels. The procedure is initiated by making a clear corneal incision adjacent to the iridectomy site. The incision is usually 90–180 degrees. A fiber filling the anterior chamber with viscoelastic, the iris is retracted into the incision using a blunt iris hook. The iris, on both sides of the mass, is incised with iris scissors or cautery. The base is then incised. While there is limited hemorrhage with the radial incisions, more hemorrhage may occur with the base
In cases of iris tumor, the possible complications associated with iridectomy must be weighed against both cosmetic and functional loss of the eye as the surgeon considers iridectomy versus laser photocoagulation or enucleation.

Iridocyclectomy

A sector iridocyclectomy may be indicated when the ciliary body is involved in an anterior uveal tumor; however, this surgery is rarely performed. The surgery involves removing a portion of the iris and ciliary body. The ideal candidate has an uninvolved iridocorneal angle and a well-defined lesion confined to the anterior uvea. The presence of uveitis, glaucoma, or extension of the mass into the retina, choroid, or deep sclera jeopardizes the success rate of the surgery (Peiffer et al., 1988). The surgery should be limited to 90 degrees of the iris and ciliary body to minimize the occurrence of phthisis bulbi.

The iridocyclectomy involves making a limbal-based conjunctival graft and a 120- to 180-degree limbal incision over the mass (Gelatt & Wilkie, 2011). A full-thickness block of sclera is then excised over the affected area with a 6400 Beaver blade. Hemorrhage is controlled with point electrocautery. The affected iris and ciliary body are then excised with iris scissors (Fig. 20.40). A homologous graft of tissue 0.5 mm larger than the wound and the limbal defect are sutured using a simple, interrupted pattern with 7-0 or 8-0 polyglactin 910. After the globe is reinflated, the conjunctiva is sutured using a simple, continuous pattern (Gelatt & Wilkie, 2011).

Alternatively, the procedure may be initiated by making fornix-based conjunctival and scleral flaps. Then a perilimbal, clear corneal incision is made for approximately 100 degrees to allow access to the affected iris. A cyclodialysis spatula is used to separate the ciliary body from the sclera. The area of uvea to be removed is initially incised with electrocautery for hemostasis. Iris scissors are then used to complete the incision, allowing the block of affected uveal tissue to be removed. The scleral flap and corneal incision are sutured with 8-0 in a simple, interrupted pattern, and the conjunctival flap is sutured to the limbus in a continuous pattern of 8-0 polyglactin 910 (Collins & Moore, 1999).

Severe uveitis is anticipated postoperatively. Therefore, intensive medical treatment is indicated to prevent a chronic, uncontrolled uveitis, which may result in phthisis bulbi. Other potential postoperative complications include hyphema, secondary glaucoma, and cataract formation. Enucleation is indicated when complications occur that do not respond to medical therapy or if tumor recurrence is noted.

Laser Photocoagulation of Iris Melanoma

Diode laser photocoagulation may be used in the treatment of presumed iris melanoma in dogs (Fig. 20.41). Selection criteria should include lesions isolated to the iris with no evidence of complicating factors. The diode laser delivery system may be used in a continuous mode with either an operating microscope adapter or a laser indirect ophthalmoscope with a 20...
diopter lens. Visualization of the lesion allows the surgeon to assess the surface changes, including shrinkage, surface disruption, and release of pigment cells into the aqueous humor (Fig. 20.42). Treatment is discontinued when no further shrinkage is observed, and surface changes are noted over the entire lesion (Cook & Wilkie, 1999).

Common postoperative findings include pigment dispersion on the anterior lens capsule, dyscoria, and diffuse iris hyperpigmentation. In most cases, the lesion is flattened and reduced in diameter but persists (see Fig. 20.42). Occasionally, iris atrophy and corneal edema may be observed. The postoperative corneal edema is suspected to occur because of collateral damage from heat generated when the laser is damaging the tumor. Some cases may need more than one laser treatment (Cook & Wilkie, 1999).

**Sphincterotomy, Synechiotomy, Pupil Iridotomy**

Occasionally, intraoperative mydriasis is inadequate to allow lens delivery during cataract surgery, or miosis occurs immediately after lens removal. In those cases, iridotomy of the pupillary sphincter (also termed sphincterotomy) may be necessary. Sphincterotomy is done by incising 1–3 mm of the pupil margin, usually at two to four positions in quadrants, with iris scissors. Limited hemorrhage and fibrin formation will follow (Gelatt & Wilkie, 2011).

One chronic postoperative complication of cataract surgery is the extensive formation of pupillary membranes, which is often secondary to progressive posterior synechiae. Extensive formation of pupillary membranes may lead to vision loss by obliterating a functional pupillary opening or lead to iris bombé with secondary glaucoma and resultant vision loss and loss of the eye. A pupil iridotomy may be necessary in these cases. Pupillary membranotomy refers to a pupil iridotomy used in the treatment of postoperative pupillary membranes (Peiffer et al., 1988). Unfortunately, many failures result from reformation of the membranes.

Postoperative pupil iridotomy, or pupillary membranotomy, is performed by making two small corneal stab incisions at the ten- and two-o’clock positions to allow introduction of...
an infusion port and one needle that has its tip bent at a 90-degree angle. After the needle is directed through the stab incision and into the anterior chamber, it is rotated so the tip engages iris tissue near the pupillary margin. The needle is then pulled across a portion of the membrane in either one or two locations, which usually results in an elliptical pupil opening. The anterior chamber is reestablished with physiologic irrigating fluid, and the corneal incision is closed with two interrupted 8-0 polyglactin 910 sutures (Collins & Moore, 1999; Peiffer et al., 1988).

The Nd:YAG laser is a noninvasive means of disrupting posterior synechiae (Brinkmann et al., 1992; Nasisse et al., 1990). This procedure is most effective in cases with limited numbers of clearly identified synechiae. Iris hemorrhage may occur after laser therapy (Nasisse et al., 1990).

After pupil iridotomy, intensive medical therapy for anterior uveitis is initiated with ophthalmic steroids and atropine. Postoperatively, additional pharmacologic mydriasis may further dilate the pupil, thus enhancing the elliptical appearance. Unfortunately, the posterior synechia may recur.

**Iridotomy**

Iridotomies are used for the creation of an alternative pathway for aqueous flow when flow through the pupil is not possible because of extensive annular posterior synechia. By creating holes in the iris peripheral to the synechiae, aqueous flow can bypass the normal route through the pupil and go directly from the posterior chamber to the anterior chamber. Full-thickness iris is incised with iris scissors or laser. After entrance into the anterior chamber via a 90-degree or 140-degree limbal incision, the middle third of the dorsal iris is incised with iris scissors. The middle third is incised to avoid the pupillary sphincter muscle and the greater arterial circle, which are located at the pupillary margin and base of the iris, respectively. Formation of full-thickness holes may be difficult in the inflamed iris. The inflamed iris of the dog is much thicker than the normal iris and frequently has a PIFM that thicken as the adjacent iris contracted into the laser site (Nadelstein et al., 1996).

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Chapter 21
Diseases of the Lens and Cataract Formation
Michael G. Davidson and Susan R. Nelms

INTRODUCTION
The crystallin lens is an avascular, transparent, and highly structured tissue that refracts incoming light rays to a point source on the retina in the normal eye. The fact that lens disorders may be classified into a small list of those affecting embryologic development, transparency, and correct position within the eye is a reflection of its relatively basic anatomic design which includes a zonular fiber support system, external capsule composed of basement membrane, epithelia, and differentiated lens fibers. Despite this simplistic anatomic structure, the lens has a highly refined and elegant series of biochemical processes that must function correctly throughout the life of the animal to maintain clarity. Loss of transparency is an almost invariable common denominator of all lens diseases; due to the prevalence of heritable lens disorders in dogs, cataract is among the most common of all intraocular lesions and a leading cause of vision loss in this species.

CONGENITAL AND DEVELOPMENTAL ABNORMALITIES
The lens is formed by surface ectoderm, and during its embryologic development, a vascular envelope surrounds it. A nomalous development may occur in the lens cells and capsule or may be a result of abnormalities of the surrounding tissues (Eagle & Spencer, 1995). Congenital lens abnormalities may be caused by genetic or exogenous factors, and because proper development of the lens is crucial in the orchestration of intraocular embryogenesis, eyes with lens anomalies often also exhibit multiple ocular defects (Cook, 1995).

Aphakia
Congenital absence of the lens is extremely rare in the dog, and occurs through failure of contact of the optic vesicle with the surface ectoderm during a critical inductive period of embryogenesis, and subsequent failure of lens placode formation (Cook, 1995). In humans, congenital aphakia is classified as primary when no lens induction of the surface ectoderm occurs and secondary when lens development takes place but later is resorbed or expelled in utero (Johnson & Cheng, 1997). Embryonic lens tissues have a major influence on the development of the optic cup, surface ectoderm, anterior segment cleavage, and the vitreous. As a result, aphakia would be expected to cause multiple ocular defects, such as microphthalmia, deformities of the anterior segment (e.g., Peters anomaly), retinal dysplasia, and staphylomas (Coulombre, 1969; Duke-Elder, 1963; Johnson & Cheng, 1997; Mikami et al., 2004; Trabucchi et al., 1997). Several Saint Bernard puppies with aphakia, multiple ocular defects (microphthalmia, retinal dysplasia, absence of anterior chamber, and acorea), and internal hydrocephalus have been reported, and a genetic basis has been proposed (Martin & Leipold, 1974).

Microphakia
Congenital microphakia, an abnormally small lens, may result from optic vesicle derangement during formation of the neural plate. Microphakia has been associated with multiple ocular defects in the Beagle (Rubin, 1971) and Doberman Pincher (Arnbjerg & Jensen, 1982; Bergsjo et al., 1984; Peiffer & Fischer, 1983), with congenital cataract and microphthalmia in the Miniature Schnauzer (Gelatt et al., 1983a, 1983b), and with persistent hyperplastic primary vitreous (PHPV) in a Spanish Pacard (Bayon et al., 2001). Congenitally displaced lenses may be small and spherophakic (small, spherically shaped lens), possibly from an abnormal embryonic lens/zonule relationship (Cook, 1995; Martin & Leipold, 1974). Microphakia may also be a consequence of acquired lens zonular disorders (Fig. 21.1). In humans, microphakia and
Coloboma

Coloboma, a shortened segment of the lens fibers that appears biomicroscopically as a notch in the lens equatorial region (Fig. 21.2), is a rare congenital defect in dogs (Gelatt, 1991). Colobomas can be either typical (6-o’clock position) or atypical (other location), and may be associated with colobomas of the uvea (Duke-Elder, 1963; Martin, 1978; Priester, 1972). The anomaly is thought to arise from a localized zonular defect (Bavbek et al., 1993), although an overt lens zonule defect may not be apparent with atypical colobomas (Eagle & Spencer, 1995). Lenticular colobomas are often associated with some form of cataract, and extensive colobomas may be associated with lens displacement (Grahn et al., 2003).

Lenticulus/Lentiglobus

Congenital deformity of the axial, anterior, or posterior lens surface may result in a circumscribed cone-like (lenticulus) or spherical (lentiglobus) protrusion of variable size. Posterior lenticulus is the most common form and involves protrusion of the posterior cortex and capsular regions into the vitreous body. The defect is thought to occur at the time of primary lens fiber elongation, approximately day 25 of gestation in dogs (Aguirre & Bistner, 1973). The condition may be unilateral or bilateral, and often occurs in conjunction with other ocular anomalies, including congenital cataract, persistent hyaloid vasculature, microphthalmia, retinal dysplasia, and optic nerve hypoplasia (Gelatt, 1991; Narfstrom & Dubielzig, 1984; Van Rensburg & Petrick, 1992). Numerous theories of the pathogenesis have been proposed; the defect may relate to an abnormal embryonic remnant in the epithelial cell proliferation before the lens capsule forms, or a hyperplasia of the lens accompanied by a thinning of the capsule over the defect (Duke-Elder, 1963). Rarely, cases may show rupture of the lens capsule with extrusion of lens cortical material into the vitreous, with varying degrees of secondary inflammation (Narfstrom & Dubielzig, 1984; Venter et al., 1996). Biomicroscopic examination generally reveals an intact posterior lens capsule extending deep into the vitreous commonly with varying degrees of cataractous changes. If biomicroscopy of the posterior lens is not possible because of cataract formation, the condition may also be recognized ultrasonographically. Lenticulus internus occurs when the lens nucleus is abnormally shaped and extends into the posterior cortex (Lavach & Severin, 1977).

Posterior lenticulus has been reported in the Miniature Schnauzer (Aguirre & Bistner, 1973; Gelatt et al., 1983a), Doberman Pinscher (Stades, 1980), Cavalier King Charles Spaniel (Narfstrom & Dubielzig, 1984), Old English Sheepdog (Barrie et al., 1979), Mastiff (Aguirre & Bistner, 1973), Golden Retriever (Lavach & Severin, 1977), Akita (Laratta et al., 1985), Bouvier de Flandres (Van Rensburg & Petrick, 1992), Bloodhound (Venter et al., 1996), and Shih Tzu (Ori et al., 2000). Posterior lenticulus occurs in 19% of Miniature Schnauzers with congenital cataract and microphthalmia, with 1% more severely affected with lentiglobus (Gelatt et al., 1983a). Lenticulus occurs in conjunction with persistent hyperplastic tunica vasculosa lentis/persistent hyperplastic primary vitreous (PHTVL/PHPV) (see later discussion) in Doberman Pinschers (Stades, 1980). Anterior lenticulus has been reported in Bull Terriers with a hereditary nephritis.
resulting from a glomerular capillary basement membrane defect. The defect in the anterior lens capsule may reflect a generalized basement membrane anomaly (Hood et al., 1995).

A heritable basis for this lens defect is suggested in some of these reports where multiple dogs of the same breed are affected. Although it has been proposed the defect may be sporadic without a heritable basis in some dogs (Lavach & Severin, 1977), a prudent approach would be to not use affected animals for breeding purposes.

**Congenital Lens Luxation**

A congenital lens luxation associated with microphakia has been described in a Brittany Spaniel puppy. Scanning electron microscopy demonstrated a lack of zonular fragments attached to the equator; although focal elevations were present at the equator, there was no evidence of prior zonular attachment, suggesting a congenital absence of zonules (Martin, 1978). Presumed congenital, heritable abnormalities in ciliary zonules may result in acquired lens luxations usually at 3–6 years of age (see “Dislocation of the Crystalline Lens”).

**Embryonic Vascular Abnormalities**

The vascular supply of the lens, present during prenatal development, is composed of the anterior and posterior tunica vasculosa lentis. The anterior portion is formed by a pupillary membrane extending from the iris, and the posterior portion is derived from the intravitreal hyaloid vascular system. A trophy of the hyaloid vascular system in the dog begins by day 45 of gestation (Duddy et al., 1983). The anterior pupillary membrane remains until approximately 14 days following birth (Gelatt, 1991).

Persistent pupillary membrane (PPM) is a common congenital ocular anomaly seen sporadically in many breeds, presumably as a nonhereditary trait. Other breeds with a higher prevalence or more severe manifestations of PPM’s, most notably the Basenji, likely have a hereditary predisposition (ACVO Genetics Committee, 2010; Barnett & Knight, 1969; Bistner et al., 1971; Martin, 1978; Priester, 1972; Roberts, 1967; Roberts & Bistner, 1968; Strande et al., 1988). PPM arises from the iris collarette and may extend to the anterior lens capsule causing varying degrees of focal or multifocal lenticular opacities (Barnett & Knight, 1969; Bistner et al., 1971; Grahn & Cullen, 2004; Roberts & Bistner, 1968; Veith & Gelatt, 1970). Other ocular disorders associated with PPM include congenital cataract and microphthalmia (Barnett & Knight, 1969; Strande et al., 1988), anterior capsular, and subcapsular cataract.

Multiple, punctate pigment foci on the central anterior lens capsule are a common incidental finding in many breeds of dogs examined with critical biomicroscopy (Fig. 21.3). Small, punctate anterior capsular opacities, characterized histologically by fibrous tissue and nuclei, sometimes with brown pigment, were reported in 24 out of 1314 laboratory beagles, and were also attributed to remnants of the pupillary membrane (Hirth & Greenstein, 1974). These pigmented foci are presumed to represent remnants of the pupillary membrane and may be distinguished from pigment deposition from acquired posterior synechia secondary to inflammation by generally being axial, punctate, and unassociated with other evidence of intraocular inflammation. In the authors’ experience, the pigment foci are common in Cairn Terrier and Dachshund breeds, and rarely cause clinically apparent visual disturbances.

PHTVL/PHPV, the most severe lesion associated with abnormal development of the embryonic intraocular vasculature, is a congenital eye anomaly leading to cataract in most cases (Boevé et al., 1993). The first documented canine case was reported in a Greyhound (Grimes & Mullaney, 1969), and numerous subsequent case reports in several breeds have been made (Arnbjerg, 1982; Barnett & Grimes, 1973; Boroffka et al., 1998; Cullen & Grahn, 2004; Curtis et al., 1984; Gemensky-Metzler & Wilkie, 2004; Kern, 1981; Leon et al., 1986; Ori et al., 1998; Peiffer et al., 1977; Rebhun, 1976; Verbruggen et al., 1999). Frequent occurrence was noted in the Doberman in the Netherlands, where the clinical aspects of the entity in 90 closely related Dobermans was described (Stades, 1980). Six grades of PHTVL/PHPV have been described based on morphologic severity (Stades, 1980; Van Rensburg & Petrick, 1992): Grade 1: Retrolental fibrovascular pigmented dots alone. Grade 2: Dots in combination with retrolental tissue proliferation attached to posterior lens capsule. Grade 3: Plaque in combination with persistent parts of the hyaloid (tunica vasculosa lentis [TVL]) vascular system (Fig. 21.4). Grade 4: Plaque with lenticonus posterior. Grade 5: Combination of grades 3 and 4. Grade 6: Combinations of former grades associated with lens coloboma, microphakia, and retrolental clots of pigment or free blood.

Abnormalities in the Doberman originate mainly from the TVL and posterior lens capsule. Complete persistent hyaloid
artery was found in 29 out of 180 eyes; incomplete persistence was found in 18. PPMs in 27 dogs appeared mainly as a branch of an equatorial vessel of the TVL to the iris (Stades, 1980). In the Doberman, no ocular or systemic abnormalities other than microphthalmia have been associated. A breed predisposition for the Standard Schnauzer has also been suggested (Slater, 1981). In the Staffordshire Bull Terrier, the disease is similar to the Doberman; however, progressive secondary cataracts were infrequent and PPM or PTVL anterior were not a characteristic feature (Boevé et al., 1988a, 1988b, 1989; Olesen et al., 1976). Bergmeister’s papillae and occasional localized rosettes of retinal dysplasia were present sporadically (van der Linde-Sipman et al., 1983). Histopathologic findings in Staffordshire Bull Terriers were similar to Dobermans; however, there were fewer cataracts, no abnormalities of the posterior lens capsule, and less retinal folds (Leon et al., 1986). Histologic features of a retrolental plaque removed by capsulectomy during phacoemulsification on a Bloodhound puppy revealed dense fibrous connective tissue, blood vessels, free red blood cells, hemosiderin-laden macrophages, a pocket of neural tissue, and perivascular mast cells. Immunohistochemistry of the neural tissue was compatible with astrocytes (Gemensky-Metzler & Wilkie, 2004).

Pathomorphologic studies on prenatal ocular development of fetuses from Dobermans with severe PHTVL/PHPV have been reported (Boevé et al., 1988a, 1988b, 1989; Olesen et al., 1974). No developmental abnormalities were noted until day 30, when the hyaloid TVL system of affected eyes appeared more developed. A retrolental membrane developed that did not attach to the posterior lens capsule until day 35. Cataractous changes were noted at day 37.

The diagnosis of PHTVL/PHPV is based on history, clinical examination with complete mydriasis, and exclusion of other causes of leukocoria. Ocular ultrasonography can be used to confirm the diagnosis of PHTVL/PHPV, and color Doppler imaging can confirm the presence or absence of blood flow in the retina and lens, and assess the likelihood of surgical complications (Boroffka et al., 1998; Verbruggen et al., 1999). The resolution of computed tomography is inadequate for identifying persistent hyaloid artery (Verbruggen et al., 1999).

Surgical success rates for restoration of vision have historically been low, and in the pre-phacoemulsification era, intracapsular lens extraction with anterior vitrectomy and excision of the hyaloid artery surgically has been recommended for cases of bilateral PHTVL/PHPV causing blindness (Stades, 1983). Successful extracapsular cataract extraction by phacoemulsification with primary posterior capsulotomy to remove retrolental plaque and placement of an intraocular lens (IOL) implant has been reported (Gemensky-Metzler & Wilkie, 2004).

**Multiple Ocular Anomalies with Lens Abnormalities**

Australian Shepherds that are homozygous for the merle gene develop congenital ocular anomalies, including microphthalmia, microcornea, colobomas of the iris, retina, choroid and/or sclera, retinal dysplasia with or without detachment, and cataract. This syndrome is referred to as merle ocular dysgenesis and is inherited as an autosomal recessive trait (Bertram...
Cortical vacuolar cataracts may be seen, and progression is variable. A normal retinal pigment epithelium development, noted as early as day 30 of gestation, is the reported cause of the ocular colobomas. Avoiding breeding of two merle animals can reduce the incidence of this condition (Cook et al., 1991).

Three litters of Doberman Pinschers with multiple congenital ocular anomalies, including microphthalmia, aphakia, retinal dysplasia, and retinal detachment, have been reported. No normal lens was recognized microscopically; however, fragments of cataractous lens material were found in the anterior uvea and posterior cornea (Lewis et al., 1986). Two Saint Bernard puppies with congenital defects, including microphthalmia, acoreia, and aphakia, have also been described (Martin & Leipold, 1974).

Congenital cataract with concurrent ocular anomalies have been described in a closely inbred line of Chow Chow dogs (Collins et al., 1992). Clinical appearance of the cataract was variable, ranging from incipient nuclear or capsular lesions to advanced cortical opacity. The lens nucleus was most consistently affected. Concurrent anomalies included wandering nystagmus, entropion, microphthalmia, PPM, and multiple retinal folds. A mode of inheritance could not be established. A litter of English Cocker Spaniels with congenital cataracts, PPM, and microphthalmia have been described (Strande et al., 1988). In the Red Cocker Spaniel, congenital cataracts with PPM, microphthalmia, hypotonia, and nystagmus have been reported (Olesen et al., 1974). Cataracts were anterior subcapsular and nonprogressive. Inheritance was not established.

Congenital lens abnormalities with hereditary retinal dysplasia are seen in the Bedlington Terrier, Sealyham Terrier, Labrador Retriever, and English Springer Spaniel (Ashton et al., 1968; Barnett et al., 1970; Carrig et al., 1977; Meyers et al., 1983; Olesen et al., 1974; Rubin, 1963, 1968). In the Labrador Retriever, appendicular skeletal growth retardation, persistent hyaloid remnants, and rhexis-matogenous retinal detachment may also be seen (Blair et al., 1985; Carrig et al., 1977, 1988). In the Beagle and Old English Sheepdog, cataract, microphthalmia, and retinal dysplasia have been reported (Andersen & Shultz, 1958; Barrie et al., 1979). Short-limbed dwarfism is inherited in the Samoyed breed as an autosomal recessive trait (Meyers et al., 1983). Anterior and posterior cortical cataracts, vitreal liquefaction, hyaloid remnants, and retinal detachment are the associated ocular defects. ADVANCED cataracts and lenticous were described in two unrelated Bloodhound puppies in association with multiple ocular defects including microphthalmia, goniodysplasia, PPM's, PHTVL/PHPV, and retinal dysplasia (Venter et al., 1996). Congenital cataract, microphthalmia, and retinal dysplasia were reported in two litters of Akita dogs (Laratta et al., 1985).

**Congenital Cataract**

Lens growth disruption during primary fiber formation results in fetal nuclear cataract that is generally nonprogressive (Gelatt, 1991), although involvement of the adjacent anterior and posterior cortical regions may concurrently be seen. All opacities of the lens previously discussed under congenital defects are classified as congenital cataracts. Congenital cataracts are inherited in the Miniature Schnauzer, Boston Terrier, Old English Sheepdog, Welsh Springer Spaniel, and West Highland White Terrier breeds (see Table 21.1). In addition, congenital cataracts may be of maternal origin resulting from toxic or infectious agent exposure in utero (Carmichael et al., 1965; Koch & Rubin, 1967).

**PATHOPHYSIOLOGIC CHANGES ASSOCIATED WITH CATARACT FORMATION**

Transparency within the lens is maintained by a number of complex factors, including a low cytoplasm density from a lack of intracellular organelles and cell nuclei in lens fibers, small spatial fluctuations of the refractive index of cytoplasm, and highly organized lattice arrangement of fiber cells. The fluctuations in cytoplasmic refractive index are small compared with the wavelength of light, such that light scattering is minimized. The spatial fluctuations depend on the molecular weight of lens crystallins, the concentrations and volume fraction of intracellular proteins, and the organization of proteins within the cytoplasm. These factors in turn are influenced by cytoplasmic hydration, ionic strength, and other specialized metabolic functions within the lens (Hejmancick & Piatigorsky, 2000; Kuszak et al., 2000). Early events in cataractogenesis, resulting in nontransparency or light scattering, are caused by alterations in one or more of these factors. In humans with senescent cataracts, age-related small changes in the conformation of lens proteins occur prior to proteolysis (Eagle & Spencer, 1995; Siebinga et al., 1992).

At the point that cataracts are evident clinically, and certainly with moderate to advanced cataracts, gross and irreversible alterations in lens metabolism have occurred from a series of events related to protein content of the lens, metabolic pumps, ionic concentrations, and antioxidant activity (Hejmancick & Piatigorsky, 2000; Hurst, 1993; Kuszak et al., 2000). Studies of senescent cataracts in humans, several types of cataracts in laboratory animals, and Miniature Schnauzer dogs (Gelatt et al., 1982) suggest several common biochemical consequences of cataracts in the advanced state. Cataracts are associated with an increase in high molecular weight, insoluble proteins (albuminoids) that normally comprise 15% of the proteins of the lens, and a decrease in the relative amount of soluble proteins (crystallins). Specific types of cataracts may be associated with a shift in the relative concentrations of lens crystallin proteins (Hejmancick & Piatigorsky, 2000). For example, in the Miniature Schnauzer congenital cataract, there is a decrease in alpha- and beta-light crystallins, and an increase in beta-heavy and gamma crystallins (Daniel et al., 1984). Electron microscopic studies in canine cataracts have documented a redistribution and/or loss of these cytoplasmic proteins which contribute to cataract formation.
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A ribonucleoprotein complex responsible for maintaining the ends of chromosomes and for repair of DNA strand breaks (Colitz et al., 1999). Telomerase reverse transcriptase (TERT) is the catalytic subunit of telomerase, and its expression is upregulated and overexpressed in both the nucleus and cytoplasm of cataractous canine LEC compared with normal LEC. Aberrant proliferation and migration of LEC occur during cataractogenesis and posterior capsule opacification (PCO) in a process known as epithelial to mesenchymal transition (EMT). TERT becomes phosphorylated and activated by phosphorylated Akt (pAkt) (Colitz et al., 2009), and pAkt is a survival factor that is upregulated and interacts with TERT in LEC undergoing EMT (Colitz et al., 2004, 2009). Estrogen receptor alpha is also overexpressed in LEC during cataractogenesis and PCO. Estrogen receptor is phosphorylated and activated by pAkt, like TERT, and plays a role in EMT, and may, therefore, be involved in cataractogenesis (Colitz et al., 2009).

These pathologic alterations associated with cataract cascade with progression, and hydrolytic and proteolytic enzyme activity increase, and cell membrane rupture is associated with irreversible damage, loss of low molecular weight proteins, and an increase in water content. The shift in intra-

<table>
<thead>
<tr>
<th>Breed</th>
<th>Inheritance</th>
<th>Age of onset</th>
<th>Initial Anatomic Localization</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghan Hound</td>
<td>Autosomal recessive</td>
<td>6–12 months</td>
<td>Equatorial/posterior cortex</td>
<td>Roberts &amp; Helper (1972)</td>
</tr>
<tr>
<td>American Cocker Spaniel</td>
<td>Autosomal recessive/polygenic</td>
<td>6+ months</td>
<td>Anterior/posterior cortex</td>
<td>Yakely (1978), Yakely et al. (1971)</td>
</tr>
<tr>
<td>Bichon Frise</td>
<td>Autosomal Recessive</td>
<td>2–8 years</td>
<td>Anterior/posterior cortex</td>
<td>Gelatt et al. (2003), Wallace et al. (2005)</td>
</tr>
<tr>
<td>Chesapeake Bay Retriever</td>
<td>Incomplete Dominant</td>
<td>1+ years</td>
<td>Nuclear/cortex</td>
<td>Gelatt (1979)</td>
</tr>
<tr>
<td>Entelbucher Mountain Dog</td>
<td>Autosomal Recessive</td>
<td>1–2 years</td>
<td>Posterior/cortex</td>
<td>Spiess (1994)</td>
</tr>
<tr>
<td>German Shepherd</td>
<td>Autosomal Recessive</td>
<td>8+ weeks</td>
<td>Posterior sutures/cortex</td>
<td>Barnett (1986), von Hippel (1930)</td>
</tr>
<tr>
<td>Norwegian Buhund</td>
<td>Autosomal Dominant</td>
<td>Congenital</td>
<td>Fetal nucleus</td>
<td>Bjerkas &amp; Haaland (1995)</td>
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<tr>
<td>Old English Sheepdog</td>
<td>Autosomal Recessive</td>
<td>Congenital</td>
<td>Nuclear/cortex</td>
<td>Koch (1972a, 1972b)</td>
</tr>
<tr>
<td>Staffordshire Bull Terrier</td>
<td>Autosomal Recessive</td>
<td>6+ months</td>
<td>Posterior sutures/cortex</td>
<td>Barnett (1978)</td>
</tr>
<tr>
<td>Standard Poodle</td>
<td>Autosomal Recessive</td>
<td>1+ year</td>
<td>Equatorial cortex</td>
<td>Rubin &amp; Flowers (1972)</td>
</tr>
</tbody>
</table>

Receptors for advanced glycation end products increase in human cataract but not in dogs with diabetic and inherited cataracts. The same study documented increased levels of markers associated with cell cycle and proliferation dysregulation in diabetic cataract in dogs, possibly explained by their rapid onset (Bras et al., 2007). In vitro studies of lens epithelial cells (LECs) have documented the presence of telomerase, a ribonucleoprotein complex responsible for maintaining the ends of chromosomes and for repair of DNA strand breaks (Colitz et al., 1999). Telomerase reverse transcriptase (TERT) is the catalytic subunit of telomerase, and its expression is upregulated and overexpressed in both the nucleus and cytoplasm of cataractous canine LEC compared with normal LEC. Aberrant proliferation and migration of LEC occur during cataractogenesis and posterior capsule opacification (PCO) in a process known as epithelial to mesenchymal transition (EMT). TERT becomes phosphorylated and activated by phosphorylated Akt (pAkt) (Colitz et al., 2009), and pAkt is a survival factor that is upregulated and interacts with TERT in LEC undergoing EMT (Colitz et al., 2004, 2009). Estrogen receptor alpha is also overexpressed in LEC during cataractogenesis and PCO. Estrogen receptor is phosphorylated and activated by pAkt, like TERT, and plays a role in EMT, and may, therefore, be involved in cataractogenesis (Colitz et al., 2009).
lenticular colloid osmotic pressure causes a further cation concentration shift of the lens toward equilibrium with the extralenticular fluid (increase in sodium content and decrease in potassium). Further degradation of proteins into amino acids and polypeptides allows small products of proteolysis to diffuse from the lens. The loss of water and nitrogenous material may cause the lens to shrink as with a hypermature cataract (Andley et al., 2000; Eagle & Spencer, 1995; Gelatt et al., 1982; Hurst, 1993). With senescent cataracts in humans, cortical cataracts are generally manifested by derangement of electrolyte and water balance, while nuclear cataracts are associated more with protein modification and insolubilization (Beebe, 2003). It should be noted that these consequences are for the most part nonspecific and do not imply an initiating event in cataractogenesis, although some types of cataracts discussed later have defined alterations in one or more of these specific metabolic pathways of the lens.

**HISTOPATHOLOGIC CHANGES ASSOCIATED WITH CATARACT FORMATION**

Specific capsular, epithelial, cortical, and lens nuclear morphologic abnormalities are commonly seen with light microscopy in many types of cataract. Both the anterior and posterior capsules may become thinned with an intumescent lens, and the lens capsule may be wrinkled with an advanced hypermature cataract. Lens capsule perforation or rupture usually causes the edges to curl, and an associated inflammatory response with intralenticular leukocytes is often seen (Fig. 21.5). Lens epithelial abnormalities include the formation of bladder or "Wedl" cells, which are balloon-like, swollen LECs (Fig. 21.6). Migration of lens epithelial past their normal point of termination in the lens bow, and along the posterior capsule, may occur, and these cells may have either a spindle or bladder cell appearance (Fig. 21.7). Myofibroblastic differentiation of these posteriorly migrated cells may result in a plaque which is adherent to the subjacent capsule. Another similar type of epithelial proliferation, with hyperplasia and fibrous metaplasia, forming multilayered spindle-shaped epithelial cells, may also occur beneath the anterior capsule from a variety of insults; the subjacent cortex may also show microscopic cataracts changes (Fig. 21.8A). Advanced cortical and nuclear cataracts often have a paucity or absence of lens epithelium, from degeneration or necrosis. Lens cortical changes may include particle aggregates within the cytoplasm and increased eosinophilia (Fig. 21.8B). Eosinophilic fluid from lytic lens proteins may accumulate in small clefts formed between

**Figure 21.5.** Photomicrograph of a lens capsule perforation 7 days following injury. Note curling of anterior lens capsule, extrusion of cataractous lens fibers past the capsular surface, and intralenticular polymorphonuclear cells. With chronicity, such a wound often exhibits marked fibrous metaplasia of the anterior lens epithelia.

**Figure 21.6.** "Bladder" or Wedl cells are seen as swollen lens epithelial cells with increased particulate matter in the cytoplasm in the lens bow region.

**Figure 21.7.** Migration of lens epithelial cells (arrows) along the posterior lens capsule associated with a posterior cortical cataract. More normal lens fibers are seen more internally.
matrix containing collagen fibrils, often with duplicated or split basement membranes. TGF-beta and alpha-smooth muscle-specific actin are found in most cells and some areas of the extracellular matrix, and fibronectin and tenascin are found in the extracellular matrix (Colitz et al., 2000).

CLASSIFICATION OF CANINE CATARACT

A myriad of classification schemes can be used for canine cataracts, some of which are useful for denoting etiology, likely course or progression, associated visual deficits, and likelihood of concurrent ocular disorders, such as lens-induced uveitis (Gelatt, 1979, 1991; Playter, 1977). Commonly used schemes include: those associated with an etiology (numerous specific causes described later); age of onset of the cataract (congenital-infantile, juvenile, senile); location of incipient stages of the cataract within the lens (Chylack & Khu, 2000), that is, capsular, subcapsular, zonular, cortical, nuclear, sutureal, axial, equatorial; appearance of the cataract (e.g., spike or wedge-shaped, spoke, cuneiform, sunflower, stellate, punctate, and purverulent); and stage of progression of the cataract (incipient, immature, mature, and hypermature). It is often appropriate to use several of these classification schemes concurrently to accurately describe a specific type of cataract. It should be noted that most of these classification schemes do not de facto imply a specific etiology; for example, a congenital or juvenile cataract does not necessarily imply a heritable basis, although this is often the case with these specific examples.

Of all the means of classification, the stage of cataract development is perhaps most useful and most widely used for canine cataract. Incipient cataract refers to early clinically apparent cataractous changes, generally involving less than 10%–15% of the lens volume (Fig. 21.10). They most commonly involve the cortical, subcapsular, or Y-suture regions in the lens and, depending on etiology, may or may not progress. Immature cataracts are the next stage of progression, and
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SECTION III

Although immature cataracts can be osmotically active, resulting in imbibition of fluid into the lens, the formation of large separation clefts, especially in the Y-suture region, and an increase in the overall size of the lens (intumescence), one study has documented a reduction in lens thickness with immature cataract, perhaps through loss of lens protein (Williams, 2004). A mature cataract is one that involves the entire lens structure, totally obscuring a fundic reflection, and large clefts and intumescence, with an increase in lens thickness (Williams, 2004) are common here, too (Fig. 21.12).

Many progressive or advanced canine cataracts continue to the hypermature stage, in which degradative enzymes are presumably released from degenerative and ruptured lens fibers and cause further proteolysis of areas of the lens, most commonly the cortical areas (Fig. 21.13). These lysed lens fibers include any lens involvement with a cataract from the incipient stage to a complete cataract (Fig. 21.11). The hallmark feature is the presence of some areas of less dense cataract formation or normal lens fibers, such that a portion of the tapetal reflection is visible, and the absence of features of a hypermature cataract described later (which can also have tapetal reflection visible).
proteins and water may traverse across the intact lens capsule, causing a reduction in the size of the lens, and a characteristic irregular or wrinkled anterior lens capsule surface. Lens-associated inflammation (discussed elsewhere) is a common sequel (Van Der Woerdt, 2000). With diffuse illumination, cortical regions of hypermature cataracts often have small glistening, crystallin particles from degraded lens fibers and proteins. As previously mentioned, multifocal, subcapsular white plaques are common with hypermature cataracts on both the anterior and posterior capsules. Liquefaction and resorption of the cataract may result in visibility of portions of the tapetal reflection, and an increase in the anterior chamber depth. The lysed cortex generally has a soft and liquidy consistency, and with advanced hypermature cataracts, the lens nucleus may gravitate to the ventral fluid-filled, lens capsular bag, resulting in a Morgagnian cataract. In young dogs (generally less than 12 months), resorption may progress to the extent that most or all of the cataractous material disappears (Clark, 1994; Gelatt, 1970, 1975; Rubin & Gelatt, 1968), leaving an adherent anterior and posterior capsule, often with multifocal capsular plaques.

NUCLEAR OR LENTICULAR SCLEROSIS

A consistent finding in dogs greater than 7 years of age, this senescent change in the lens occurs from progressive lens fiber formation and internal compression of older lens fibers, especially in the lens nucleus. A study of 2000 dogs in the United Kingdom found a C50 (age at which the prevalence of nuclear sclerosis was 50%) for all dogs studied to be 9.6 ± 2.6 years (Williams et al., 2004). The change in the optical properties of the compressed lens fibers cause light scattering, imparting a clinically apparent whitish-blue appearance on diffuse illumination. With retroillumination, a tapetal or fundic reflection is still visible, and the outline or zone of the lens nucleus may be apparent. Funduscopic examination is still possible through the affected lens, although with advanced sclerosis, fine ophthalmoscopic detail is variably obscured. The clinical appearance between dense nuclear sclerosis and early nuclear cataract is often an indistinct one. A characteristic yellow discoloration (brunescence) is often present in the sclerotic human and primate lens or nuclear cataract (Chylack & Khu, 2000; Kuszak et al., 1994). The age-related chromophore pigments responsible for this phenomena (Andley et al., 2000; Cooper & Robson, 1969) are found in a few other diurnal species other than man, but have not been identified in canine lenses.

CLINICAL AND BIOMICROSCOPIC FEATURES OF CANINE CATARACTS

Incipient and immature cataracts may be grossly characterized by retroillumination of the lens with an external light source held at an arm’s distance from the patient and following pharmacological mydriasis, noting the degree of obstruction by the cataract of the tapetal or fundic (in atapetal dogs) reflection. This procedure is also used to distinguish nuclear sclerosis from cataract. Incipient and immature cataracts appear brown to black when viewed against a tapetal background or red reflex, due to obstruction of the reflected light. Immature and more advanced cataracts are recognized clinically as leukemia with a whitish to blue appearance to the lens with diffuse illumination using an unfocused light source. Complete cataracts are characterized by an inability to elicit a fundic or tapetal reflection with retroillumination or with ophthalmoscopy. Hypermature cataracts often exhibit an increase in anterior chamber depth and evidence of lens-induced uveitis, small refractile crystals and subcapsular plaques. Subtle cataractous changes in the lens are associated with specific features that may be best elucidated by the various illumination techniques of slit-lamp biomicroscopy. Importantly, anatomic localization of incipient cataracts with a biomicroscope often aids in determining an etiology or expected course of progression. The normal and pathologic lens may be studied through a widely dilated pupil with diffuse illumination, direct focal illumination, and direct and indirect retroillumination (Berliner, 1966; Martin, 1969a, 1969b). The normal biomicroscopic appearance of the canine lens with direct focal illumination using a parallelepiped or optical section appears as a series of opalescent blocks of light, produced by the surface of zones of discontinuity from the internal lens architecture. These zones include the convex surfaces of the anterior capsule, anterior cortex, anterior adult nucleus, anterior fetal nucleus, and anterior embryonal nucleus; similar concave zones are produced by the posterior situated counterparts of these areas. The fetal and embryonal nucleus are variably visualized, and the zones of discontinuity between the cortex and adult nucleus become more prominent with age, and are sometimes not visible in dogs less than 1 year of age. Y-suture regions are seen as fine white lines within the light block, and may have a central dark zone with high magnification, and are visible near the anterior and posterior capsules (a replication of the Y-sutures is sometimes visible at the nuclear/cortical junction of the zone of discontinuity). On the vitreal aspect of the posterior capsule, Mitendorf’s dot and a white, translucent circular white line representing the anterior extent of Cloquet’s canal (arcuate line of Vogt) are generally visible (Berliner, 1966; Martin, 1969b).

Cataracts cause reflection, refraction, or dispersion of light, depending on their specific structure (Fig. 21.14A–C). With direct focal illumination, most cataractous changes obstruct light and appear whiter (white to bluish white, to bluish green, depending on the nature of the illumination beam) with increased relucency when compared with the normal opalescent of lens blocks. Fluid within the lens, as is seen with vacuoles, clefts, or Morgagnian globules, appears dark or black in focal illumination, as they have lesser optical density than the normal lens fibers (Fig. 21.15). Lens opacities may be anatomicall localized by inspecting and estimating the proximity to the adjacent zones of discontinuity. Biomicroscopic examination with direct retroillumination may be performed
Figure 21.14  A. Posterior cortical cataract seen with direct focal illumination using a parallelepiped directed from left to right. Note opalescent blocks of light as they pass through the cornea, and the internal lens architecture. The cataract is seen as a (white) area of increased relucency within the parallelepiped. B. Same opacity viewed with direct retroillumination using the tapetal reflection and a diffuse light source. The cataract appears as a dark brown opacity. C. Same opacity viewed with indirect retroillumination from the tapetal reflection using a parallelepiped passed from right to left. The opacity appears brightly luminous from reversed illumination.

Figure 21.15. Hypermature cataract viewed with direct focal illumination with optical section passed from right to left. Note increased relucency and glistening refractile property of some lens fibers, with focal pockets of liquefied lens material appearing as areas of decreased relucency.

by reflective light from either the posterior lens capsule or tapetum; the former allows more critical and detailed examination of small opacities, but the latter is often more conveniently performed in the conscious animal using handheld biomicroscopy. The lens is normally nonrelucent (nonlight scattering) in retroillumination, and lens opacities that obstruct light appear dark (yellow-brown, brown, or black) against the reflective background of light. By direct retroillumination, lens vacuoles appear with a dark ring or crescent, with a bright center due to inherent respersive properties. Conversely, with indirect retroillumination, lens vacuoles display unreversed illumination, with the margin of the vacuole nearest the light outlined by a white crescent of light and the opposite side appearing dark. Solid lens precipitates (obstructive) display reversed illumination with indirect retroillumination, with the margin of the opacities away from the light becoming more luminous. Anatomic localization of lens opacities by retroillumination is more difficult than with direct focal illumination, which depends on using focal depth, stereoscopic...
CATARACT WITH A HERITABLE OR PRESUMED HERITABLE BASIS

Cataract occurring in young to middle-aged, pure breed dogs comprise the most common type of cataract seen clinically in veterinary medicine. Only in a minority of affected breeds have a heritable basis and mode of transmission been conclusively established (see Table 21.1 and Table 21.2). However, the frequent characteristic anatomic localization and appearance of the lens opacity in the initial stages, characteristic age of onset and course of progression, bilateral nature, and absence of other demonstrable ocular disorders that might cause cataract formation, suggest that in most of the other breeds, these cataracts likely also have a heritable basis (ACVO Genetics Committee, 2010; Gelatt & Mackay, 2005; Rubin, 1989). As of 2010, the Genetics Committee of the American College of Veterinary Ophthalmologists had documented 160 breeds of dogs (inclusive of those in Table 21.1) in which a heritable basis for cataract is suspected or proven (ACVO Genetics Committee, 2010). In a study of prevalence of breed-related cataract in North America, 59 breeds of dogs had prevalence greater than the control population (mixed-breed/hybrid dogs with a 1.61% prevalence). Smooth Fox Terrier, Havanese, Bichon Frise, Boston Terrier, Miniature Poodle, Silky Terrier, and Toy Poodle had the highest prevalence of 10%–12%, while the Boston Terrier, Miniature Poodle, American Cocker Spaniel, Standard Poodle, and Miniature Schnauzer had the highest numbers of cases with cataract (5%–12%) (Gelatt & Mackay, 2005). A similar breed predisposition has been noted in dogs presented for cataract evaluation at a U.S. teaching hospital with American Cocker Spaniel, Miniature Schnauzer, Toy Poodle, Boston Terrier, Miniature Poodle, and Bichon Frise being overrepresented breeds (Adkins & Hendrix, 2005). The Toy Poodle, American Cocker Spaniel, and Bichon Frise breeds were most commonly affected in a study of dogs presented for cataract evaluation in Brazil, (Baumworcel et al., 2009), and Miniature/Toy Poodle, Yorkshire Terrier, and Shih Tzu most frequently affected in a study in South Korea (Park et al., 2009).

The majority of proven, heritable cataracts in dogs are inherited as a simple autosomal recessive trait, with other modes of inheritance, such as incompletely dominant, being less common. The high prevalence of heritable cataracts in certain breeds has undoubtedly arisen from excessive line breeding or inbreeding to develop specific, desirable phenotypic features for a particular breed, which are in some fashion associated or linked to the genetic alteration causing a derangement in a lens metabolic pathway(s). The majority of inherited cataracts in humans are congenital (Hejmancick & Platigorsky, 2000; Merin, 1991), while they are more commonly juvenile or middle-age onset in dogs (Gelatt & Mackay, 2005). Heritable cataracts in dogs may additionally be classified according to whether they are heritable isolated (cataract alone), heritable with multiple ocular disorders (see multiple ocular defect section), or heritable associated (associated with another phenotypically apparent genetic disorder such as chondrodysplasia).

Very little is known about the pathogenesis of canine heritable cataracts (Barnett, 1982; Gelatt & Das, 1984), and information on cataractogenesis must be extrapolated from that available from human and laboratory animal cataract. Several laboratory mice strains with heritable cataract have been studied documenting derangements in specific crystallins or other lens proteins (Merin, 1991; Zigler, 1990). The Nakona mouse strain has autosomal recessive cataract with reduced synthesis of alpha and beta crystallin proteins, likely the consequence of a Na-K ATPase pump deficiency (Iwata & Kinoshita, 1971; Platigorsky et al., 1978). The deficiency may result from an excess polypeptide that inhibits the pump, as its activity can be abolished by peptidases (Fukui et al., 1978). Interestingly, like many canine cataracts, the Nakona mouse can have variable phenotypic expression of the disease and different morphologic and clinical features to the cataract (Lipman et al., 1981). The Frasier or shriveled mouse has an autosomal dominant cataract with reduced synthesis of alpha and beta crystallin proteins, likely the consequence of a Na-K ATPase pump deficiency (Carper et al., 1978). The eye lenses of the mouse have an autosomal dominant cataract associated with a preferential loss of gamma crystallins (Garber et al., 1985) and is caused by a specific transposon-induced splicing error on mouse chromosome 10 (Shiels & Bassnett, 1996). The Philp mouse has an autosomal dominant cataract associated with a failure of synthesis of a β crystallin polypeptide of 27kDa and the strain of mouse has a 12-base deletion of the functional messenger RNA responsible for this polypeptide (Carper et al., 1982; Chambers & Russell, 1991; Kador et al., 1980). The eye lens obsolescence (Elo) mouse cataract has a reduction in gamma-crystallin mRNA caused by a frame-shift mutation in the gammaE-crystallin gene on mouse chromosome 1 (Cartier et al., 1992; Quinlan et al., 1987). Distinct mutations in the murine major intrinsic protein (MIP) gene have been documented as the cause of autosomal dominant cataract in the mouse (Shiels & Bassnett, 1996). An autosomal dominant
Table 21.2  Breeds Predisposed to Cataracts: Inheritance Suspected*

<table>
<thead>
<tr>
<th>Breed</th>
<th>Basenji (a)</th>
<th>Bloodhound (a)</th>
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</thead>
<tbody>
<tr>
<td>Aflenpincher (a, b)</td>
<td>Basset Griffon Vendeen, Petite (a)</td>
<td>Border Collie (a)</td>
</tr>
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<td>Airedale Terrier (a)</td>
<td>Basset Hound (a, b)</td>
<td>Border Terrier (a)</td>
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<tr>
<td>Akita (a)</td>
<td>Beagle (a)</td>
<td>Borziol (a, b)</td>
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<td>Alaskan Malamute (a, b)</td>
<td>Bearded Collie (a)</td>
<td>Bouvier des Flandres (a)</td>
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<td>American Eskimo Dog (a)</td>
<td>Bedlington Terrier (a)</td>
<td>Boxer (a, b)</td>
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<tr>
<td>American Staffordshire Terrier (a, b)</td>
<td>Belgian Malinois (a)</td>
<td>Boykin Spaniel (a)</td>
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<tr>
<td>American Water Spaniel (a, b)</td>
<td>Belgian Picard (a)</td>
<td>Bracco Italiano (a)</td>
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<tr>
<td>Australian Cattle Dog (a)</td>
<td>Belgian Sheepdog (a)</td>
<td>Briard (a)</td>
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<td>Australian Kelp (a)</td>
<td>Belgian Tervuren (a, b)</td>
<td>Brittany Spaniel (a)</td>
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<td>Australian Shepherd (a)</td>
<td>Bernese Mountain Dog (a, b)</td>
<td>Brussels Griffon (a, b)</td>
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<tr>
<td>Australian Terrier (a)</td>
<td>Bichon Frise (a)</td>
<td>Bulldog (English) (a, b)</td>
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<td>Black and Tan Coonhound (a, b)</td>
<td>Pointer (a, b)</td>
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<td>Greater Swiss Mountain Dog (a)</td>
<td>Polski Owczarek Nizzinny (a)</td>
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<td>Cairn Terrier (a, b)</td>
<td>Greyhound (a)</td>
<td>Pomeranian (b)</td>
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<td>Canaan (a)</td>
<td>Harrier (a)</td>
<td>Poodle-Toy and Miniature (a)</td>
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<td>Havanes (a)</td>
<td>Portuguese Water Dog (a)</td>
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<td>Cavalier King Charles</td>
<td>Icelandic Sheepdog (a)</td>
<td>Pug (a)</td>
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<td>Spaniel (a)</td>
<td>Irish Setter (a, b)</td>
<td>Puli (a)</td>
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<td>Komodor (a, b)</td>
<td>Scottish Deerhound (b)</td>
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<td>Kuvasc (a, b)</td>
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<td>Dachshund (a, b)</td>
<td>Lakeland Terrier (b)</td>
<td>Sealyham Terrier (a, b)</td>
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<tr>
<td>Dalmatian (a)</td>
<td>Leonberger (a)</td>
<td>Shetland Sheepdog (a, b)</td>
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<tr>
<td>Doberman Pincher (a, b)</td>
<td>Lhasa Apso (a, b)</td>
<td>Shiba Inu (a)</td>
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<tr>
<td>Dogue De Bordeaux (a)</td>
<td>Lowchner (a)</td>
<td>Shih Tzu (a, b)</td>
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<td>English Cocker Spaniel (a, b)</td>
<td>Maltese (a)</td>
<td>Siberian Husky (a, b)</td>
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<td>English Setter (a)</td>
<td>Manchester Terrier (b)</td>
<td>Silky Terrier (a, b)</td>
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<td>Maremma Sheepdog (a)</td>
<td>Smooth Fox Terrier (a, b)</td>
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<td>Mastiff (a)</td>
<td>Soft-Coated Wheaten Terrier (a, b)</td>
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<td>Entlebucher (a)</td>
<td>Miki (a)</td>
<td>Spinone Italiano (a)</td>
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<td>Field Spaniel (a, b)</td>
<td>Miniature Australian Shepherd (a)</td>
<td>Standard Schnauzer (a, b)</td>
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<td>Miniature Bull Terrier (a)</td>
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<td>Giant Schnauzer (a, b)</td>
<td>Norwegian Elkhound (a, b)</td>
<td>Welsh Springer Spaniel (a)</td>
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<td>Glen of Imaal Terrier (a)</td>
<td>Norwich Terrier (a, b)</td>
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<td>Gordon Setter (a, b)</td>
<td>Nova Scotia Duck Tolling Retriever (a)</td>
<td>Whippet (a, b)</td>
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<td>Papillon (a, b)</td>
<td>Wire Fox Terrier (a, b)</td>
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<tr>
<td>Great Pyrenees (a)</td>
<td>Parson Russell Terrier (a)</td>
<td>Yorkshire Terrier (a, b)</td>
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Cataract has been described in guinea pigs resulting from an alteration in zeta-crystallin production (Amsbaugh & Stone, 1984; Huang et al., 1990). The biochemical basis for heritable cataract formation is unknown and only partly investigated in the congenital cataract in the Miniature Schnauzer (Gelatt et al., 1982). The biochemical and morphological changes documented are non-specific and are similar to those occurring in heritable and nonheritable cataracts found in many species. Studies in this breed have documented changes in the crystallin classes both with aging and with cataract formation, including an increase in alpha- and beta-L crystallins and a decrease in beta-H and gamma crystallins (Daniel et al., 1984). Morphologic changes in lens capsule, anterior lens epithelium, and lens fibers accompany biochemical alterations. Lens epithelium becomes taller and possesses basally located myelin-like bodies. Lens fibers become progressively swollen, resulting in plasma membrane rupture, cytoplasmic extrusion, and destruction of lens cells leading to granulation and liquefaction. The clinical appearance of these biochemical and ultrastructural changes by slit lamp biomicroscopy reveals vacuoles, water cleft formation, suture line changes, and opacification of lens fibers. The vacuoles represent focal lens cell death. Water clefts and pie-shaped cortical opacities correspond to hydration and lens fiber loss. The lens sutures, which consist of glycoconjugates and glycolipids, become opacified (Monaco et al., 1984).

Molecular, genetic studies in the Miniature Schnauzer, while not conclusive (as they do not eliminate the possibility of point mutations), have suggested that certain genes are not responsible for the development of congenital cataract. One study failed to document mutations, deletions, or rearrangements in the genes responsible for alpha, beta, or gamma lens crystallins, or M 26 (a lens cell protein) synthesis, and found normal structure in two genetic loci associated with heritable cataracts in humans (Zhang et al., 1991). A different study has also suggested no structural change in the homeobox containing gene, and the myotonic dystrophy gene (a gene associated with a multisystemic disorder and presenile cataract in humans) (Shastry & Reddy, 1994).

Studies have been conducted on a number of hereditary cataract in humans, identifying the specific chromosome and gene involved and suggesting “candidate genes” that might be causative (Hejmanick & Piatigorsky, 2000). Additionally, radiation hybrid mapping of 21 cataract associated genes and associated polygenic markers have been conducted in dogs and will facilitate identifying associated and linkage genes in canine cataract (Unter et al., 2006). These and other research efforts have led to molecular studies using candidate gene screening of a variety of breeds of dogs with inherited cataract and have identified or excluded an association of specific altered genes. For example, studies have identified a mutation in heat-shock transcription factor 4 (HSF4) as being associated with primary cataracts in Staffordshire Bull Terrier, early onset cataracts in Boston Terrier (Ellers et al., 2006, 2007), and Australian Shepherd (Ellers et al., 2009), and that different or multiple mutations of this same gene may be present in these three breeds (Ellers et al., 2006). Conversely, mutations in HSF4 have not been associated with cataract in English Cocker Spaniels, Wire-haired Kromfohrlanders (Engelhardt et al., 2007b), Siberian Huskies (Gentilini et al., 2008), Dachshund and Entlebucher Mountain Dogs (Muller et al., 2008), and Jack Russell Terriers (Oberbauer et al., 2008). A study of 31 candidate genes in the Entlebucher Mountain Dog has identified a putative chromosome region on Canine Chromosome One associated with cataract, although the specific responsible gene has not been identified (Muller & Distl, 2008a). A different study in this breed has excluded canine gamma crystallin C (CRYGC) as causative (Muller et al., 2006), and studies in the Wired- and Short-haired Dachshund have excluded three canine gamma crystallin (CRY GB, CRY GC, and CRY GS) (Muller et al., 2007) and the canine beta crystallin (Muller & Distl, 2008b) as causative. Mutations in canine galactokinase have also been excluded as associated in a group of Labrador Retrievers with cataracts (Sidjanin et al., 2005). Oculoskeletal dysplasia, seen as an autosomal recessive trait in the Labrador Retriever and Samoyed breeds and associated with cataract, has been associated with mutations in COL9A2 and COL9A3 genes (Goldstein et al., 2010).

Clinical and Morphologic Features of Heritable Cataracts

The clinical and morphologic features of heritable cataracts have been described for many breeds of dogs. It should be noted that the phenotypic expression of heritable cataract in dogs, most notably age of onset and progression, can vary within a breed, and the expression may be influenced by other modifying genes or environmental factors (as in the Nakona mouse). The following descriptions should therefore be interpreted only as general guidelines on expected features of cataracts in the specific breeds.

In the Miniature Schnauzer breed, two types of cataracts occur, both inherited as an autosomal recessive trait (Gelatt et al., 1983a, 1983b; Rubin et al., 1969). Congenital cataracts involve the nucleus and, to a lesser extent, the posterior cortex, and progression is variable. Microphthalmia and microphakia are associated, and lenticonus is present approximately 20% of the time. The second type of cataract is present in puppies at several weeks of age and primarily involves the posterior lens cortex.

The Boston Terrier and Staffordshire Terrier breeds have inherited cataracts that are present at birth and a few months of age, respectively. These cataracts affect primarily the nucleus and posterior cortices, generally progress to maturity, and are inherited as an autosomal recessive trait (Barnett, 1978, 1985). In the Boston Terrier, a second type of cataract, involving the equator and anterior cortex, is seen in 3- to 4-year-old dogs (Curtis, 1984). Progression of the cataract is often slow. In the Welsh Springer Spaniel, a bilateral, sym-
metrical, progressive cataract affecting the nucleus and posterior cortex can be observed by 8 weeks of age (Barnett, 1980). The cataract is inherited as an autosomal recessive trait and is often mature by 18–14 months of age. Bilateral nuclear and cortical cataracts have been reported in the Old English Sheepdog (Koch, 1972a, 1972b). Some of the cataracts were congenital. There was a high association with retinal detachment. The mode of inheritance was found to be autosomal recessive.

In the American Cocker Spaniel, cataracts are inherited as a simple autosomal recessive trait with polygenic inheritance (Yakely, 1978; Yakely et al., 1971). The cataracts affect the anterior and posterior cortex and may be apparent as early as 6 months of age. Progression is variable, but tends to be rapid in young dogs. In English Cocker Spaniels in Germany, both early onset (<3.5 years of age) and late onset (>3.5 years of age) have been noted, and these appear to be genetically distinct (Engelhardt et al., 2007a). Both color variants of this breed manifest different and quite varied forms of cataract with respect to location within the lens, even in closely related dogs, suggesting that the phenotype does not segregate according to familial lines (Engelhardt et al., 2008).

Anterior and posterior cortical cataract, with an age of onset of 2–8 years, have been reported in the Bichon Frise. Cataract formation appears to be inherited as an autosomal recessive trait, and retinal detachment is commonly associated (Gelatt et al., 2003; Wallace et al., 2005).

Posterior subcapsular cataracts occur in the Golden and Labrador Retriever breeds (Barnett, 1985; Curtis & Barnett, 1989; Gelatt, 1972; Rubin, 1974). The cataracts appear as triangular subcapsular opacities at the posterior pole at the confluence of suture lines and usually do not progress to blindness. A second form of cataract has been documented in both the Golden and Labrador Retriever and is a progressive cortical cataract (Curtis & Barnett, 1989; Krajner-Huver et al., 2008; Rubin, 1974). In the latter breed, dogs with posterior subcapsular cataract produced affected offspring with both focal and diffuse forms of the cataract, suggesting the two forms are genetically related (Krajner-Huver et al., 2008). It has been proposed that in both breeds, the cataract is transmitted as a dominant trait with incomplete penetrance (Curtis & Barnett, 1989; Rubin, 1974). Additionally, it has been suggested that those dogs with triangular cataract are heterozygotes, while those with more progressive cataract are homozygotes (Rubin, 1974). However, a study involving test breeding and pedigree analysis in the Golden and Labrador Retrievers has suggested an autosomal recessive mode of inheritance is more likely (Aguirre et al., 2004). Equatorial and posterior subcapsular cataracts occur in the Siberian Husky. Cataracts are present at 6–18 months of age and are typically slowly progressive. Ophthalmic examination of 122 German Pinchers in Finland found that 6.5% were affected with hereditary cataracts that were primarily posterior and subcapsular, and had a late onset, with a median age of 9 years at diagnosis. The mode of inheritance is suspected to be autosomal recessive, but incomplete dominant inheritance could not be completely ruled out (Leppanen et al., 2001). In this same study, PHTVL and changes in the “Y” sutures were found in 8.5% and 4.5% of German Pinchers examined, although the importance of the latter finding were not determined (Leppanen et al., 2001).

A study of 111 Rottweilers revealed a cataract of a presumed inherited nature in 37% of dogs (Bjerkas & Bergsjo, 1991). The cataracts were predominantly posterior polar and triangular shaped in half of the dogs, while the rest had more extensive lens changes, anterior polar cataract, or complete cataract. Dogs of varied ages were affected, with the youngest at 10 months of age. A pattern of inheritance could not be definitely determined.

Equatorial familial cataracts occur in the Afghan Hound (Roberts & Helper, 1972) and the Standard Poodle (Rubin & Flowers, 1972) and appear to be inherited as an autosomal recessive trait. In the Afghan Hound, initial changes occur as vacuoles in the lens equator at 4 months to 2 years of age. Progression is rapid with visual impairment often present by 2 years of age. In the Standard Poodle, equatorial cataracts are present early and tend to impair vision by 6–18 months of age.

Inherited cataracts have been described in 13 out of 27 related Chesapeake Bay Retrievers (Gelatt et al., 1979). The posterior pole (38%), Y-sutures (33%) and equatorial cortices (21%) were predominantly affected. The trait is believed to be dominant, with incomplete penetrance.

Two types of cataracts have been described in the West Highland White Terrier in Sweden, one which involves the primarily the tips of the posterior Y-sutures, and one a progressive, complete cataract (Narfstrom, 1981). Autosomal recessive inheritance is suspected. In the German Shepherd breed in England, cataract inherited as an autosomal recessive trait have been reported (Barnett, 1986). At 8 weeks of age, small dot opacities are seen at the posterior suture lines. Fine linear opacities radiate from the suture lines to the nucleus and subcapsular regions. With progression, by 1 year of age, nuclear and cortical cataracts with vision impairment are present. A different type of cataract in this breed, described in 1930, was congenital, nonprogressive, and inherited as an autosomal dominant trait (von Hippel, 1930).

An autosomal dominant cataract has been reported in Norwegian Buhunds. The cataracts appear as small dots in the fetal nucleus, and progress over 4–5 years to assume a purulent (“candy floss”) appearance (Bjerkas & Haaland, 1995). Entelbucher Moutain Dogs have been reported to develop a nonprogressive posterior polar cataract at 1–2 years of age, and less commonly a progressive cataract. The trait appears to be autosomal recessive, and progressive retinal atrophy (PRA) may be concurrently present (Heitmann et al., 2005; Kuster et al., 2011; Spiess, 1994). Nuclear, posterior nuclear, and posterior polar subcapsular cataract has been identified in closely related Leonberger in the United Kingdom (Heinrich et al., 2006).
CATARACTS ASSOCIATED WITH SYSTEMIC DISEASE

Diabetes Mellitus and Galactosemia

Diabetes mellitus is commonly associated with rapidly developing, bilaterally symmetric cataract formation in dogs from well-characterized alterations in lens metabolic pathways. With elevated blood glucose levels, lens levels of glucose increase, and anerobic metabolism of glucose by the hexokinase pathways becomes saturated, causing shunting toward an alternate energy pathway involving the enzyme aldose reductase (AR). AR activity in diabetic cataracts is increased due to increased amounts of AR rather than increased enzyme activation. By utilizing nicotinamide adenine dinucleotide phosphate (NADPH), AR reduces the aldehyde form of glucose to sorbitol, which is further oxidized to fructose by NAD-dependent sorbitol dehydrogenase. A cumulation of sorbitol (a polyol or sugar alcohol) results, which does not readily diffuse across the lens capsule. Water from the aqueous humor is imbibed into the lens due to osmotic forces, causing lens architectural changes, including fiber swelling and rupture, vacuole formation, and clinically evident cataract. Additionally, a series of biochemical changes occur, resulting in altered electrolyte concentrations, reduced levels of ATP, amino acids, glutathione, and myo-inositol, and reduced adenosine triphosphatase activity (Basher & Roberts, 1995; Sato et al., 1991; Wyman et al., 1988). The biochemical alterations provide some speculation that besides simple osmotic forces, other pathogenic mechanisms, such as a change in cell membrane permeability, oxidative forces, and nonenzymatic glycosylation of lens crystallins may also contribute to diabetic cataract formation (Basher & Roberts, 1995; Bron & Sparrow, 1993). Alternatively, these changes may be solely secondary to osmotic cataractogenesis.

The prevalence of diabetic cataract formation is related to the level of hyperglycemia, and lenticular AR activity and sorbitol concentration (Chylack & Khu, 2000; Kubo et al., 2001; Lee & Chung, 1999; Lee et al., 1995). The dog is highly susceptible to diabetic cataract, and it has been assumed this may relate to the difficulty in controlling diabetes in this species and resulting chronic hyperglycemia. However, one study in 23 diabetic dogs failed to identify a relationship between the development of cataract and the corresponding level of hyperglycemia (Salgado et al., 2000). Additionally, some diabetic dogs with a good therapeutic response to insulin and clinically acceptable blood glucose levels may still develop cataract (Richter et al., 2002). Species differences in susceptibility to diabetic cataract appear to more closely correlate with level of lenticular AR activity. AR activity in canine lens is similar to humans (0.39 nm/min/mg lens protein), 3× lower than rat lenses (a species highly susceptible to sugar cataract), and much higher than the mouse lens (a species highly resistant to sugar cataract) which has almost undetectable levels (Sato et al., 1991). In another study, AR activity was found to be significantly higher in dogs lens compared with lenses from cats >7 years of age (a species with a low incidence of diabetic cataract) (Richter et al., 2002).

The clinical appearance and progression of sugar cataracts has been most extensively studied in laboratory dogs with dietary induced galactosemia, used in the study of diabetic-associated ocular lesions. Compared with glucose to sorbitol conversion, galactose is metabolized by sorbitol to galactitol more readily, and is not further reduced by sorbitol dehydrogenase. Galactosemic dogs develop rapidly progressive cataracts, generally within 3 months of onset of galactose feeding, which are characterized initially by Y-suture accentuation, followed shortly by equatorial vacuole formation (Fig. 21.16), progressing to spoke-like cataracts in the anterior and posterior cortex and further accentuation of anterior and posterior Y-sutures. Punctate cortical cataract formation, progressing to complete cortical cataracts, follows. Interestingly, the cataract formation often decreases after 12 months of galactose feeding, causing new, superficial lens cortical fibers to appear clear. Light microscopic evaluation of canine lenses revealed the osmotic nature of sugar cataracts, with swollen, ruptured lens fibers, and vacuoles present near the lens bow (Sato et al., 1991; Wyman et al., 1988). The nature of galactosemic cataracts in dogs is also age dependent (owing to a decrease in AR activity with age), with young dogs more rapidly developing cataracts that also involve the lens nucleus, and in dogs older than 24 months, cataract development occurs less readily and is confined to the cortices (Lackner et al., 1995). Galactose-induced cataracts can be reduced in a dose-dependent manner when AR inhibitors are concurrently administered, but cannot be reversed past a critical point in cataract development (Sato et al., 1991, 1998).
Chapter 21: Diseases of the Lens and Cataract Formation

Hyperglycemic and galactosemic cataracts appear to have a similar pathogenesis, and similar morphologic changes to those described above have been noted with experimentally induced diabetes mellitus in dogs (Small et al., 1987). The punctate cortical changes and Y-suture changes described in galactosemic dogs are rarely noted in naturally occurring diabetes mellitus, probably owing to the rapid onset and progression of cataract. Cataracts are one of the most prevalent and important complications of canine diabetes mellitus, with one retrospective study (with relatively few animals) citing a 68% prevalence rate (Wilkinson, 1960). A study evaluating incidence and estimated median time to cataract formation in 200 dogs found that half of the population had developed cataracts by the 170th day after diagnosis of diabetes mellitus, while 75% and 80% of the population developed cataracts by 370 days and 470 days, respectively (Beam et al., 1999). The lifetime risk for the canine diabetic patient is probably even greater. While early equatorial vacuole changes may sometime dissipate following insulin therapy, substantial cataractous changes with canine diabetes are not reversible with control of hyperglycemia. Canine diabetic cataracts are often so rapidly progressive and osmotically active that intumescence of the lens and phacolytic uveitis commonly ensues. Spontaneous lens capsule rupture, usually equatorial, and subsequent varying degrees of phacolytic uveitis have also been identified in dogs with diabetic cataract (Wilkie et al., 2006).

Hypocalcemia

Hypocalcemia, most commonly caused by renal failure or primary or secondary hypoparathyroidism, may be associated with characteristic cataracts in dogs manifested by a multifocal, punctate opacities or coalescing lamellar cortical opacities that are bilaterally symmetric (Fig. 21.17) (Crawford & Dunstan, 1985; Bruyette & Feldman, 1988; Kornegay et al., 1980). The prevalence of hypocalcemic cataracts is estimated as high as 71% in humans (Delamere & Paterson, 1981; Pohjola, 1962). The opacities are thought to relate to hypocalcemic-associated defects in the active cation transport mechanism of the lens epithelium, causing an increase in sodium content and a loss of lens potassium. This derangement results in osmotic imbalance that leads to lens fiber swelling and rupture. In humans, hypocalcemic cataracts generally start in the posterior cortex, the site furthest from the ion regulatory pump mechanism in the anterior lens epithelium and therefore the area least able to compensate for alterations in the pump (Delamere & Paterson, 1981; Evans & Kern, 1931; Pohjola, 1962). Treatment of hypocalcemic disease state may be generally expected to stop progression, but not reverse existing lens opacities.

Hypercupremia

A characteristic, sunflower-shaped anterior subcapsular cataract is seen in 17% of humans suffering from Wilson’s disease, a genetic disorder of copper metabolism, as well as other disorders causing derangement of copper metabolism (Wiebers et al., 1977). A familial copper storage disorder similar to Wilson’s disease has been described in Bedlington and West Highland White Terriers (Fuentealba & Aburto, 2003; Twedt et al., 1979). Despite this, cataracts have not been described in these animals, probably because, unlike the disease in humans, serum copper levels are generally normal, or only transiently elevated during hemolytic crises, and also perhaps owing to the relatively short life span of severely affected dogs.

Inborn Errors of Metabolism

A single case report of cataracts (and concurrent keratitis) associated with congenital tyrosinemia in a German Shepherd has been reported (Kunkle et al., 1984). Cataracts are reported with inherited forms of tyrosinemia in humans who suffer skin and surface ocular disease, presumably from an inflammatory response to tyrosine crystal deposits in various tissues (Hunziker, 1980). The pathogenesis of the associated cataract is not known. Bilateral cataract and lens luxation, with the cataract likely occurring secondary to a lens luxation from zonular defects, was documented in a dog with Ehlers-Danlos syndrome, a hereditary connective tissue disease (Barrett & Cotrell, 1987). Capsular and subcapsular cataracts have been described in humans with Niemann-Pick disease (Eagle & Spencer, 1995) and while a description of similar cataracts was not found for dogs, it is likely that cataracts may occur in dogs with this disorder, as the enzyme deficiency (sphingomyelinase) is similar (Bandza et al., 1979).

Cataracts Associated with Medications or Other Toxic Substances

A number of environmental toxins and pharmacologic agents administered systemically have been reported to produce...
cataracts in dogs. As this species is commonly used in toxicologic screenings of new pharmacologic agents and chemicals, numerous cataractogenic agents have been noted in the laboratory dogs. Many of these agents have minor clinical significance, as they are typically produced during toxicologic studies, where the test compounds are administered chronically and in high dosages. Toxic cataracts may initially appear at a variety of locations within the lens, depending on the toxic principal, but often begin in either the anterior and posterior cortical region near the equator (in the area of lens fiber elongation), or the Y-suture regions, and are often associated with lens vacuole formation. Minute vacuole formation in the lens is reported to often be reversible, if the toxic insult is removed (Eagle & Spencer, 1995; Heywood, 1971a). Common feature of many types of toxic cataract are derangements in Na-K ATPase pumps, ion or osmotic balance, or cell membrane permeability.

In laboratory dogs, transient, reversible cataracts have been described with diazoxide (Schiavo, 1976; Schiavo et al., 1975), and progressive cataracts may follow subchronic administration of phenylpiperazine (Susick et al., 1991) (both antihypertensive agents). With the former, the opacities were thought to relate to hyperglycemia caused by the drug. The administration of high dosages of the commonly used cholesterol lowering drugs, hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors (“statin” drugs), produce anterior and posterior subcapsular cataracts, seen initially as accentuation of the suture lines (Gerson et al., 1990, 1991). This drug is thought to have a cataractogenic effect by inhibition of cholesterol synthesis in the outer cortical regions of the lens, where cholesterol synthesis in newly synthesized lens fiber cell membranes is critical. One of the widely used HMG-CoA reductase inhibitors, atorvastatin (Lipitor®), does not appear to have a cataractogenic effect in dogs, even at high doses (Robertson et al., 1997). Cholesterol-lowering drugs in the aminopyrimidine series, which inhibit oxidosuqualeine cyclase, also are associated with cataract in laboratory dogs (Funk & Landes, 2005; Pyrah et al., 2001). Administration of a sulphonylurea glimepiride (a hypoglycemic agent) (Schollmeier et al., 1993) and pefloxacin (a quinoline) (Chist et al., 1985) causes experimental cataracts in dogs when given chronically and in high doses. Dinitrophenol, a now archaic anthelmintic agent, when administered at 2–3× recommended dosages, produced variable cataracts in young puppies, but not adult animals. The cataracts were generally reversible, and administration at recommended dosages (10 mg/kg SC) produced minimal or no lens opacities (Martin, 1975; Martin et al., 1972). Experimental cataracts have also been produced in the dog following exposure to high dosages of 2,6-dichloro-4-nitroaniline (DNCA) (a fungicide) (Bernstein et al., 1970) and progesterone containing oral contraceptives (Orill et al., 1975). Chronic ketoconazole administration has been associated with bilateral, progressive cataract formation, mostly in young, large breed dogs, perhaps related to relatively higher dose (6.0–13.9 mg/kg/day) necessary in larger dogs. Cataracts were diagnosed 3.5–37 months following initiation of ketoconazole therapy for systemic mycoses (Da Costa et al., 1996). The pathogenesis of this imidazole-associated cataract is not known.

Chronic oral administration of dimethyl sulfoxide (DMSO) in dogs at a dosage of 2.5–40 g/kg was associated with unusual lens changes with an unexplained pathogenesis. The lens alteration was characterized by a reduction in the refractive index of newly synthesized lens fibers in the cortex causing them to appear optically clear instead of relucent. The lens nucleus remained unaffected and relucent causing a sharp optical demarcation and zone of discontinuity biomicroscopically. As the lens nucleus was unaffected, the refractive consequence was a myopic shift in the power of the central lens, as the lens nucleus was acting as an independent refractive surface (Rubin & Mattis, 1966). A another study described the same type of lenticular myopia with an increase in opalescence of the lens nucleus following repeated dermal DMSO application in dogs (Smith et al., 1969). Similar, naturally occurring lens changes following DM SO administration have not been described.

Other chemicals or drugs which classically induce cataracts in other laboratory animal besides dogs, and therefore would likely have potential to cause canine cataracts if administered in sufficiently high dosages, include naphthalene, ouabane, digitalis, heavy metals, chlorpromazine, diquat (Eagle & Spencer, 1995), and hygromycin B (Sanford & Dukes, 1981). Concurrent systemic signs of toxicity would generally be expected although the consequences of prolonged, low-dose exposure to these compounds is not determined. The subcapsular cataract associated with systemic and topical corticosteroid use (Urban & Cotlier, 1986), and topical organophosphate (miotics) use (Kaufman et al., 1977) in humans have not, to the authors’ knowledge, been noted in dogs.

The most clinically relevant type of cataract presumed to be toxic in nature is that associated with PRA or other types of retinal degeneration. Cataracts are commonly seen in dogs with moderate to advanced stages of PRA, often obscuring ophthalmoscopic detail of the fundus. For example, one report found a prevalence of PRA of approximately 50% in Miniature Poodles screened electrodiagnostically for cataract surgery (Gaiddon et al., 1995). A another report cited 66 of 244 dogs presented for evaluation of cataract did not subsequently have cataract surgery due to retinal degeneration (Adkins & Hendrix, 2005). The Labrador Retriever, Miniature, and Toy Poodle are the breeds in which cataractous lens changes have been suggested to most frequently accompany retinal degeneration (Gelatt, 1991), although many breeds are affected clinically. Cataract and retinal degeneration have also been reported in the Entlebucher Mountain Dog and Tibetan Terrier (Heitmann et al., 2005; Ketteritzsch et al., 2004). In earlier stages, these lens opacities are characterized by the formation of equatorial and posterior cortical vacuoles, Y-suture changes, and a diffuse increase in relucency to the posterior subcapsular region. The cataracts are often progressive, eventually involving the entire lens. As breeds of dogs at risk for PRA...
also have a high incidence of genetic cataracts, it is possible that in some dogs, the two disorders may not be interrelated, but rather reflect two heritable disease states. Degenerative rod outer segments may release water-soluble dialdehydes from peroxidation of photoreceptor lipid membranes that may diffuse through the vitreous and be toxic to lens cellular membranes (Zigler & Hess, 1985). An organ cultured lens system was used to demonstrate that toxic aldehyde products of lipid peroxidation can damage lens membranes and Na-K ATPase pumps (Zigler et al., 1983). The frequent, initial appearance of the cataracts in the posterior lens may be attributable to these dialdehydes affecting this portion of the lens first (from diffusing into the vitreous), or that posterior cortical cataracts, being the site most distant to the anterior lens epithelial and Na-K ATPase pump, are characteristic of subtotal injury to this ionic pump.

**DIETARY DEFICIENCIES**

A specific syndrome of neonatal cataracts is sporadically seen in puppies fed an oral milk replacement product. In mongrel pups experimentally fed milk replacements, the opacities began in the third week of life, and a biomicroscopically visible brown colored lamellar zone that separate the anterior and posterior nuclear/cortical junctions is seen. This zone progressed to a dense white perinuclear opacity. Other changes included a feathered appearance to the Y-sutures and a transient extra line of dysjunction in the anterior and posterior cortex (Martin & Chambreau, 1982). Similar lens changes, especially the nuclear-cortical junction ring and some vacuolization of the equatorial fibers and Y-sutures have been described in naturally occurring cases in puppies (Glaze & Blanchard, 1983) and timber wolves (Vanisi et al., 1981). The opacities are often mild and nonvision threatening, and often become less prominent or even resolve with age, although more advanced cataractous changes persist into adulthood and may necessitate surgical removal. Arginine deficiency at a critical stage in neonatal lens development has been proposed as a likely cause from observations made in arginine supplemented wolf pups (Vanisi et al., 1981), and kittens experimentally fed milk supplements (Remillard et al., 1993). Analysis of amino acid content of a commercial milk replacer showed an arginine content only half that found in milk of dams (Ranz et al., 2002). However, the pathogenesis of these opacities may be more complex than a single amino acid deficiency; other proposed mechanisms include other amino acid deficiencies (i.e., tryptophan, phenylalanine, histidine... deficiencies in all of which have been associated with cataracts in laboratory animals), amino acid imbalance, or a relative protein or glucose deficiency induced by the diet (Martin & Chambreau, 1982; Remillard et al., 1993; Vanisi et al., 1981). As the opacities appear to be most common and pronounced in pups totally deprived of dam's milk, or deprived during the first week of life, a suggested preventative effort, if practical, would be to attempt at least limited nursing of the pups during this time, supplemented with a high-quality milk replacement.

**INJURY TO THE LENS**

**Mild blunt injury to the globe rarely causes injury to the lens.** Moderate force blunt injury may result in posterior displacement of the iris, causing anterior capsular deposition of pigment from the posterior iris epithelium, sometimes in the shape of the pupillary aperture. Contusion to the lens from blunt injury may result in cataracts from resulting contrecoup or ocular compressive forces causing damage to the lens epithelia, and rupture and disruption of spacing of lens fiber membranes in the underlying cortex. Variable degrees of subcapsular cataract formation, generally adjacent to the site of injury in the anterior superficial cortex, may ensue. Traumatic cataracts may sometimes initially manifest along the anterior and posterior lens sutures, producing a stellate shape. The proposed pathogenesis of these Y-suture changes include distortion and irregular alignment of the intercellular spaces, cellular fragmentation, or a combination of these two effects. With increasing time from the injury, a focal traumatic cataract may be displaced to deeper layers of the lens, as new lens fibers are formed (Eagle & Spencer, 1995; Steeten, 2000). As, in general, fairly pronounced blunt trauma is necessary to induce cataracts, other signs of ocular injury are often concurrently present. Their location, unilateral nature, and other concurrent ocular findings suggestive of blunt trauma help distinguish them from heritable cataracts. Rupture of the lens capsule from blunt trauma, in the absence of profound globe injury or rupture of the entire globe, is rare in dogs but may occur (Gelatt, 1974).

Penetrating ocular injury that perforates the anterior lens capsule would be expected to invariably cause focal to diffuse cataract formation. Traumatic anterior lens capsule disruption is seen most commonly in young animals from cat claw wounds or dog bites, although a variety of other sources of penetrating injury are possible (Fig. 21.18). Small rents in the capsule...
lens capsule may spontaneously seal through fibrous metaplasia of lens epithelia assisted by exudate from the uveal tract, leaving only a focal residual cataract. Dogs and rabbits appear to more readily seal small rents in the lens capsule when compared with humans owing to a fibrinous anterior uveitis (Buschmann et al., 1987). The likelihood and degree of progression of capsular and subcapsular cataracts from a penetrating injury sometimes is difficult to predict both in humans (Buschmann et al., 1987) and dogs. Rents larger than 1.5 mm often cause progressive opacification of the lens, and in the dog are often associated with severe phacolenticular uveitis, which result in vision threatening sequel (Davidson et al., 1991b), but some larger rents seal spontaneously without clinically important consequences. Damage and expulsion of lens cortical material caused by the initial penetration, or intralenticular bacterial infection (Mariar & Dubielzig, 1995) may exacerbate the injury and increase the likelihood of progression and complicating uveitis. Critical evaluation with biomicroscopy following pharmacologic mydriasis is often necessary to detect disruption of the lens capsule, which should be suspected when evidence of penetrating corneal or scleral injury is present concurrent with a focal fibrinous exudate on the lens capsule, with or without visible cataract formation. Lens removal has been recommended with lens capsule rents >1.5 mm, and if substantial cortical cataract is present (Davidson et al., 1991b). In another study, young animals (6 months or less) with corneal laceration and lens rupture had higher success with corneal laceration repair and medical treatment than young patients treated with corneal laceration repair and lensectomy (100% vs. 25%, respectively) (Paulsen, 2005). Lens capsule tears with only minor underlying damage to the cortex may be carefully monitored for progression of cataract and phacolenticular uveitis.

Lens penetration with a metallic foreign body would be expected to result in at least a focal cataract, and more commonly, diffuse opacification from substantial disruption of fiber cells and lens metabolism. The effect of intraocular metallic foreign bodies not penetrating the lens but within the eye is dependent on inertness, position, and size of the foreign body (Eagle & Spencer, 1995). Most shot pellets are composed of lead, which are usually sterile due to high-velocity entry, and are surprisingly well tolerated by the globe, as they are usually covered with an insoluble carbonate which prevents diffusion of chemical reactivity (Schmidt et al., 1975). The authors have examined a dog with a lead pellet embedded in the lens that resulted in only a focal cataract and no progression for several years. Lead shot retained within the globe but which did not perforate the lens capsule might not be expected to de facto cause cataract. Gold, silver, glass, and rubber are also relatively inert within the eye. Conversely, copper, zinc, and brass foreign bodies have moderate oxidizing potential and often cause panophthalmitis, and iron and steel are most damaging, causing severe inflammatory reaction and secondary cataract (siderosis lentiis) (Carter & Blevins, 1970). Intralenticular iron foreign bodies cause siderotic deposition, resulting in slowly progressive, focal red-brown or rusty-appearing lens opacities. Iron deposited outside the lens but within the eye may result in siderosis bulbi, with secondary lens epithelial degeneration and necrosis, and lens cortical degeneration (Eagle & Spencer, 1995; Steeten, 2000).

Bilateral anterior subcapsular cataract formation has been reported in a three-year-old dog after biting an electric cord (Brightman et al., 1984), and the authors have examined a dog with progressive cataracts following lightning strike. Bilateral, subcapsular cataracts that are often progressive are a common sequela to lightning strike or other severe exposure to electric shock in humans (Fraunfelder & Hanna, 1972; Polellos et al., 1996). Histologic study in one human patient revealed anterior subcapsular epithelial proliferation, and posterior cortical cellular degeneration (Hanna & Fraunfelder, 1972).

Cataracts are a chronic complication of exposure of the eye to ionizing radiation of varying forms, most commonly seen clinically following radiotherapy of neoplasms in the head region, in which the eye is in the radiation field (Jamieson et al., 1991; Michaelson et al., 1971; Roberts et al., 1987; Theon, 1993). Cataract was a common late (>6 months) finding in dogs given 36–67.5 Gy in fractionated doses given over 4 weeks using a 6 MV linear accelerator (Ching et al., 1990). Cataracts were reported in 28% of the eyes with complications following megavoltage irradiations (Roberts et al., 1987) and 10.2% of the eyes following orthovoltage (cobalt source) (Jamieson et al., 1991) generally 6–12 months following therapy. The likelihood of development of cataracts following radiotherapy is related to degree of exposure of the eye to the radiation beam and the dose. The threshold dose for cataractogenesis in man is between 500–1000 rad (Eagle & Spencer, 1995). In mice and rats, cataracts develop within several months following total dosage greater than 30 Gy (Pelfer et al., 1981). The pathogenesis relates to the effect on mitosis and subsequent degenerative changes of the radiation on the equatorial lens epithelial and formation of newly synthesized lens fibers, resulting in an initial cataract that involves the equatorial and anterior and posterior subcapsular regions (Eagle & Spencer, 1995; Steeten, 2000). Attempts should be made to exclude the ocular tissues from the radiation field or shield the globe with lead shields or other devices during cancer radiotherapy. While there are some exceptions, in general, other collateral damage to the globe as a result of radiotherapy makes these dogs marginal candidates for cataract surgery.

**AGE-RELATED CATARACS**

Cataracts are commonly seen in the aged dog, and are often classified as “senile” or “age-related” if no other antecedent cause is apparent. The age of onset at which a cataract should be considered age-related is arbitrary and breed-related. For example, the authors generally use an age of 6 years for large breed dogs and 10 years for small breeds when applying this classification. While the clinical appearance and rate of progression of age-related cataracts can vary, they often are seen...
initially as an increase in relucency and punctate to linear opacification in the adult nucleus of the lens, generally occurring concurrent with and following dense nuclear sclerosis (Fig. 21.19). Cortical cataractous changes, often in a wedge or spoke pattern, may also occur to varying extents, either concurrent with or separate from nuclear cataracts. The rate of progression of these classic age-related cataracts is often slow, requiring many months to several years to result in demonstrable vision loss. Some degree of cataract formation is common in aged dogs, although the large majority do not substantially affect vision. A study of over 2000 dogs in the United Kingdom found the age at which prevalence of cataract was 50% (C50) was 9.4 ± 3.3 years, and that all dogs had some degree of lens opacity after 13.5 years of age (Williams et al., 2004). As discussed above, the C50 value varied according to expected longevity of some breeds, with the German Shepherd (median longevity of 10.3 years) having a value of 7.5 ± 3.1 years, and the West Highland White Terrier (median longevity of 12.8 years) having one of 11.2 ± 3.7 years. A study of retired racing Greyhounds found 17% of dogs had cataract, presumably age-related (Lynch, 2007).

Often, cataracts with varying biomicroscopic features and rate of progression are seen in 6- to 10-year-old dogs of breeds that are at risk for heritable cataracts. The designation of these cataracts as either age-related, and nonheritable (based on age of onset) or heritable (based on the risk of the breed for cataract development) is problematic. Owing to this breed predilection with these types of cataracts, it could be theorized that a genetic disorder of lens metabolism may be present and age-related changes in the lens, or other age-associated environmental factors, cause phenotypic expression or exacerbation of cataracts. Alternatively, some of these animals may simply suffer from heritable cataracts, with no environmental component that has an atypical or late phenotypic onset. The morphologic features of frequent initial and predominant nuclear involvement and slow progression may be useful features which distinguish age-related, nonheritable cataracts from heritable cataracts in some cases; however, insufficient information is currently available with regard to any distinguishing clinical features to make definitive statements.

The pathogenesis of age-related cataracts in dogs is unknown. Much of the speculation regarding the pathogenesis of senescent cataracts in humans focuses on the photooxidative injury to the lens, the consequence of decades of exposure to ambient solar radiation and ultraviolet wavelengths of light (Andley et al., 2000; Spector, 1995; Taylor et al., 1988). Evidence that oxidative damage occurs during cataractogenesis includes increased levels of mixed disulfides (Garner & Spector, 1980), cross-linked proteins (Buckingham, 1972), lipid peroxidation products (Bhuyan et al., 1981), and increased DNA strand breaks (Kleiman & Spector, 1993) any of which may culminate in lens fiber damage and irreversible opacification. Whether such photooxidative mechanisms are relevant in the dog lens, with an average life span only one-fifth that of humans, is speculative.

CATARACTS RESULTING FROM INFLAMMATIONS AND LENS-ASSOCIATED INFLAMMATION

The lens responds in a nonspecific fashion by development of a cataract to contiguous inflammation (uveitis) from any cause. Synechia formation to the anterior lens capsule, with or without proliferation of fibrovascular membranes onto the lens surface, may result. The location of inflammatory cataracts is most commonly anterior subcapsular or equatorial. Mediators of inflammation liberated during uveitis presumably diffuse across the lens capsule, causing a variety of alterations which may culminate in lens epithelial metaplasia, necrosis, or posterior migration and lens fiber degeneration, liquefication, or necrosis (Eagle & Spencer, 1995; Steeten, 2000). Cataract secondary to inflammation generally only occurs with moderate to severe or chronic uveitis; cataract attributable to chronic inflammation was found in 37% of 142 Golden Retrievers with chronic, idiopathic uveitis (Sapienza et al., 2000). The common occurrence of phacolytic (lens-induced) uveitis in dogs with hypermature cataracts sometimes presents a diagnostic challenge in distinguishing primary cataracts from those occurring secondary to inflammation. Clinical history, signalment, anatomic location, and the typical mild nature of phacolytic uveitis are useful distinguishing features.

A common form of lens-associated uveitis, occurring in conjunction with resorbing, typically hypermature cataracts, has been termed phacolytic uveitis (Fischer, 1972; Sapienza...
et al., 2000; Van Der Woerdt, 2000; van der Woerdt et al., 1992). The histologic features for a mild, lymphocytic-plasmocytic iridocyclitis is similar to many types of idiopathic uveitis seen in dogs (Wilcock & Peiffer, 1987). The prevalence of this usually mild uveitis has been reported to be as high as 71% in dogs screened for cataract surgery (Paulsen et al., 1986), although this study represented a population of dogs with long-standing cataracts in late stages of development. The prevalence of subclinical blood-ocular barrier disruption in dogs with hypermature cataracts may be even higher (Dziezyc et al., 1997; Krohne et al., 1995). Phacolytic uveitis may cause a reduction in electroretinogram parameters including a reduction in b-wave amplitudes and b/a wave ratio (Maehara et al., 2007). A more severe form of phacolytic uveitis, also termed granulomatous lens-induced uveitis, is sometimes encountered in dogs with hypermature cataracts (Fischer, 1972). In humans, phacolytic glaucoma occurs with hypermature cataracts, reportedly from soluble lens proteins being phagocytized by macrophages, resulting in obstruction of aqueous humor outflow (Kapinsky & Hutchinson, 2000). Although it is reasonable to speculate phacolytic glaucoma may occur in the dog, it has not been definitely documented.

Phacoclastic uveitis occurs in dogs with traumatic rupture of the lens capsule. Histologic study of advanced cases of lens capsule rupture has documented varying degrees and types of inflammation (suppurative to lymphocytic plasmocytic), intralenticular neutrophils, and prominent fibroplasia (presumably from the lens epithelia) (Van Der Woerdt, 2000; Wilcock & Peiffer, 1987). The prominent fibroplasia and lessened tendency for granulomatous, perilenticular inflammation are features suggested to be somewhat different from the human counterpart following lens capsule rupture, phacolytic endophthalmitis, although the histologic differences may reflect the time period following injury that the globes are studied microscopically. The condition usually responds poorly to anti-inflammatory therapy, and often culminates in the need for enucleation. Delayed onset, endophthalmitis and progressive cataract formation, the result of intralenticular bacterial infection, has been described in dogs following traumatic rupture of the lens capsule (Marlar & Dubielzig, 1995). Spontaneous lens capsule rupture, usually equatorial and with varying degrees of associated phacoclastic uveitis, have been identified in diabetic dogs with intumescent cataract (Wilkie et al., 2006), and the authors have documented cases of spontaneous posterior capsule rupture in non-diabetic cataract.

The pathogenesis of both phacolytic and phacoclastic uveitis currently remains speculative (see Chapter 20 on anterior uveitis). Because phacolytic (also called phacotoxic uveitis) in humans is rare, it has received virtually no investigation that might suggest a common pathogenesis with the disease in dogs. Lens-associated inflammation is proposed to occur following deviation of the normal low level of T-cell-mediated tolerance to lens proteins (crystallins) and other lens components (Simpson et al., 1989; Van Der Woerdt, 2000). With phacolytic uveitis, only recrystallized lens proteins are presented to the immune system, not membrane-associated antigens, while with lens capsule rupture, intact lens antigens, including membrane-associated antigens, are presented. A additionally, class II major histocompatibility encoded restricted T cells and macrophages are able to react with lens cell membrane proteins, soluble lens antigen, and other intracellular proteins (Marlar et al., 1978). The sustained release (with hypermature cataracts) or massive release (with lens capsule rupture) of altered lens proteins, presumably of varying protein structure, may supplant the normal anterior chamber-associated immune deviation (ACAI) phenomena and result in a cell-mediated or delayed type hypersensitivity reaction, normally suppressed from anterior chamber presented antigens. A CAID has been shown to be overwhelmed with excessive antigen load or sustained exposure or antigen (English, 1992). The T-cell response may lead to macrophage production of IL-1, and chemotaxis of neutrophils, causing release of other lymphokines. The local neutrophilia cause release of other proteolytic enzymes, a slow-reacting substance of anaphylaxis, and exudation from uveal vessels (Marak et al., 1978). Interestingly, a study of in dogs with and without cataract found a negative association between serum antilens crystallin serum antibody titer and presence and maturity of cataract (i.e., dogs with advancing stages of cataract had a lower prevalence of antilens crystallin antibody). The same study found a negative association between severity of uveitis and antilens crystallin antibody for immature and hypermature cataract. These authors speculated that changes in crystallin epitopes during cataract maturation, affinity maturation of anticrystallin antibodies, and the ACAID phenomena may explain this negative association (Denis et al., 2003). Regardless, these findings illustrate the complex and poorly understood nature of lens-induced uveitis.

NONSURGICAL CLINICAL CONSIDERATION FOR CANINE CATARACTS

Visual Consequences of Cataracts

Relatively little is known regarding the visual consequences of cataracts in dogs, and this is relevant when counseling an owner on surgical therapy for cataracts; that is, cataract removal is generally recommended when demonstrable visual deficits are apparent. Clinically evident visual deficits associated with canine cataracts vary greatly with the astuteness of the owner and with individual dogs and their level and type of activity, and acuity of other special senses, such as hearing and smell. Visual symptoms in humans with cataracts may be associated with the following aberrations: a myopic shift (from hardening of the lens nucleus), diplopia, lenticular astigmatism, a shift in contrast sensitivity (especially with low contrast objects), glare, a color shift with absorption of the blue end of the spectrum, reduced light transmission, field loss, and visual acuity reduction (Hurst, 1993). Some of these
Complications of Untreated Cataracts in Dogs

Should cataract surgery not be performed, many canine cataracts will progress, and may result in leakage of lens proteins and subsequent lens-induced uveitis requiring medical treatment. Spontaneous resorption of cataractous lens material occurs most frequently in dogs less than 6 years of age and may be more common in the Toy and Miniature Poodle, the Miniature Schnauzer, and the American Cocker Spaniel (Gelatt, 1975, 1991; Rubin & Gelatt, 1968; van der Woerdt et al., 1992). Leakage of lens material stimulates anterior uveitis. Young dogs are more likely to develop an inflammatory reaction that is difficult to control with medical treatment (van der Woerdt et al., 1992). The magnitude and duration of cataract resorption is highly variable in the dog. Seventy-two to seventy-five percent of cataracts causing lens-induced uveitis have visible evidence of resorption (Fischer, 1972; van der Woerdt et al., 1992). In some cases, particularly in very young dogs, significant lens resorption may lead to improved vision (Rubin & Gelatt, 1968), although the animal is rendered permanently hyperopic.

The most common complications of lens-induced uveitis include glaucoma and phthisis bulbi (Rubin & Gelatt, 1968; Paulsen et al., 1986; van der Woerdt et al., 1992). An increased frequency of vitreal degeneration and retinal detachment has also been observed in eyes with hypermature cataract (Davidson et al., 1991a; Peiffer et al., 1981; van der Woerdt et al., 1992). Long-standing, hypermature cataracts are also at risk for subluxation or luxation, which can also cause secondary complications. The lifelong complication rate of untreated cataracts in dogs has not been studied, and therefore definitive statements cannot be made; however, one study of 77 cataractous dog eyes compared surgical treatment with topical medical treatment and no treatment and success was greatest for eyes undergoing phacoemulsification with lens implant (IOL), and eyes receiving topical anti-inflammatory therapy had greater success than eyes with no treatment at all (Lim et al., 2011).

Clinical Management of the Blind Dog

Appropriate client education concerning management of the visually impaired or blind dog becomes an important role for the clinician. Although most blind dogs develop permanent behavioral changes and are limited functionally, blind dogs can cope within their environment and can function acceptably as pets. Common behavior changes noted in blind dogs include a tendency to stay closer to the owner and a more cautious approach to the environment. With these behavioral changes, a closer relationship between the dog and owner is often formed (Chester & Clark, 1988). In addition, many owners report that it is difficult to recognize their dog’s impairment when in a familiar environment due to compensatory development of other senses. Obvious safety precautions that should be taken by owners of a blind dog include adequate fencing or containment of the dog when outdoors, minimal movement of furniture within the home and limited access to stairs, decks, or pools. Educating owners to increase verbal and physical contact with their pet and to maintain a static, familiar environment are key factors in helping a dog to adjust to vision loss.

MEDICAL TREATMENT OF CATARACTS

A variety of therapeutic agents that claim to prevent, delay, or reverse cataracts are currently available and have been studied in both man and the dog (Babizhayev et al., 2004; Kador, 1983). None has been shown to be conclusively effective in man (Azad, 1989; Bron et al., 1987). Problems with clinical trials in man also exist as there is currently no accurate method to quantitate lens opacity, and the onset of cataract maturity is unpredictable (Azad, 1989; Bron et al., 1987). With one exception cited below, studies in dogs have not been controlled, are highly subjective, and do not account for lens
resorption (Babizhayev et al., 2004; Boldyrev et al., 1987; Brightman, 1986; Brooksby, 1979; Cobble & Lynd, 1977; Ivy et al., 1959; Lugaro et al., 1980; MacMillan et al., 1989; Paulos, 1966). In a nonplacebo, controlled, and unmasked study, administration of topical 2% N-acetyl carnosine 3 times a day for 8 weeks resulted in a marginal but statistically significant reduction in lens opacification (as assessed by retroillumination photography) in immature cataract and nuclear sclerosis (Williams & Munday, 2006). Further studies are clearly needed with this compound before a clinically relevant therapeutic effect can be documented.

Senile cataract therapy in humans has included inorganic salts, nutritional supplements, natural product extracts, sulfhydryl and sulfonic acid compounds, and nonsteroidal anti-inflammatory drug (NSAID) compounds (Babizhayev et al., 2004). Therapy with topical or systemic selenium-vitamin E (Brooksby, 1979; Paulos, 1966), superoxide dismutase (Cobble & Lynd, 1977), carnosine (a dipeptide antioxidant) (Boldyrev et al., 1987), N-acetylcarnosine (the prodrug of carnosine) (Babizhayev et al., 2004), and zinc citrate (Brightman, 1986; MacMillan et al., 1989) have been advocated for canine cataracts, although none have been proven efficacious in controlled studies. Radiation cataracts, including those that result from microwave, infrared, ultraviolet, X-rays, and gamma rays, have been treated with antioxidants and free radical scavengers, though none have been shown to be effective (Kador, 1983). Sugar cataracts have been treated with AR inhibitors, which provide the strongest evidence of potential efficacy as an anticataract agent (Kador, 1983; Lou et al., 1989; Sato et al., 1991).

Only the aldose reductase inhibitors (ARI) have undergone extensive animal studies, showing potential efficacy in the dog and in man (Kador et al., 2006; Lou et al., 1989; Sato et al., 1991; Takemoto et al., 2004). One study in galactosemic dogs treated with a proprietary ARI formulation documented an arrested development or progression of cataract compared with nontreated dogs (Kador et al., 2006). A randomized, prospective, double masked placebo study using the same ARI formulation in dogs with naturally occurring diabetes mellitus documented a beneficial effect in the onset and/or progression of cataracts in treated dogs compared with the placebo group (Kador et al., 2010).

Diets rich in vitamin E and low in vitamin A (sunflower seeds) delay the onset and reduce the incidence of secondary cataract in rats with inherited retinal degeneration (Hess et al., 1985). Cataractogenesis is associated with reactive oxygen species generation and stress-induced cell signaling markers and an in vitro study on LECs documented inhibition of these pathways with grape polyphenols, suggesting these compounds may warrant investigation for a therapeutic use for cataracts (Barden et al., 2008).

**DISLOCATION OF THE CRystALLIN LENS**

Dislocation of the lens from its normal position within the patellar fossa is referred to as subluxation (subtotal dislocation) or luxation (total dislocation), and is related to a pathologic alteration in the ciliary zonules from abnormal development, degeneration, rupture, tearing, or a combination of these factors. Associated clinical findings are varied according to the severity and cause. An increased mobility of the lens, manifesting as phacodenesis (tremor of the lens with globe movement) and iridodenedesis are early clinical manifestations. A change or asymmetry in the depth of the anterior chamber may be noted biomicroscopically. The lens equator and ciliary zonules of the normal canine crystalline lens is either not visible or only marginally so by biomicroscopy in the maximally dilated pupil. With lens dislocation, the margin of the lens may be visible and manifests as an aphakic crescent, an area of the widely dilated pupil devoid of lens coverage (Fig. 21.20).

Because most lens subluxations occur in a ventral direction due to gravity, the aphakic crescent is generally present dorsally. Degenerative vitreal strands, which appear by biomicroscopy as fine wispy fibers with increased relucency (Fig. 21.21), are often displaced or prolapsed into the anterior chamber and may be apparent with gonioscopy in the iridocorneal angle structures. A posterior lens luxation is associated with an obvious change in lens position, causing a forward displacement of the iris leaflets if the lens remains in the posterior chamber, or total luxation into the anterior chamber, both of which would cause an obvious reduction in anterior chamber depth. Posterior luxation occurs into the vitreous and follows syneresis and a disruption of the anterior hyaloid face, both of which are common with conditions causing total luxation, especially inflammatory or traumatic causes (Fig. 21.22). The posterior luxated lens sometimes gravitates to the ventral vitreous, lying adjacent to or on the ventral retina and/or pars plana. It is common for a luxated lens to freely move between...

![Figure 21.20. Anterior lens luxation in a 4-year-old, Jack Russell Terrier seen with direct focal illumination using a parallelepiped passed from left to right. Note asymmetry and decreased depth of the anterior chamber, and dorsal aphakic crescent.](image-url)
vitreal face may occlude the flow of aqueous humor from the posterior chamber through the pupil, causing diversion of aqueous posterior to the lens or into the vitreous (pupillary block glaucoma). Substantial amounts of prolapsed vitreous are often seen in the anterior chamber and iridocorneal angle, and this may theoretically cause mechanical obstruction to aqueous outflow. An anterior luxation into the anterior chamber may result in physical contact between the lens capsule and corneal endothelium, causing transient or permanent corneal edema. Secondary uveitis often accompanies lens dislocation, especially anterior luxation, presumably from abnormal physical contact of the lens or vitreous with anterior uveal structures, or other undefined changes in the milieu of the intraocular spaces.

Complete posterior luxation of the lens into the vitreous is more innocuous than anterior luxation, and the complications of glaucoma, uveitis, or corneal edema are less prevalent. Syneresis is necessary for the lens to fully luxate posteriorly, and therefore, mechanical obstruction glaucoma is uncommon. Tractional retinal detachment may occur from changes in the vitreous or direct contact of the lens capsule with the retinal surface. Additionally, because the fully luxated lens often freely moves between the posterior and anterior segments of the eye, surgical removal of the posteriorly luxated lens is often still indicated.

Similar to canine cataracts, lens dislocation has been classified according to different schemas, most commonly as congenital, primary, secondary, or traumatic (Curtis, 1990; Curtis & Barnett, 1980). Lens dislocations are generally classified as primary if occurring in the adult dog and if no other antecedent ocular disease is present. Primary lens luxation (PLL) has...
been identified in a variety of terrier breeds (most notably Sealyham, Jack Russell, Wire-haired Fox, and Miniature Bull Terrier), terrier crosses, the Tibetan Terrier (reportedly not a true terrier breed), and Shar Pei (Babizhayev et al., 2004; Chandler, 1970; Curtis, 1983a, 1983b, 1990; Curtis & Barnett, 1980; Ketternitzsch et al., 2004; Lazarus et al., 1998; Martin, 1978; Sargan et al., 2007; Oberbauer et al., 2008). Other breeds more sporadically reported include the Border Collie (Foster et al., 1986), German Shepherd, and certain spaniel breeds (Curtis, 1990; Sargan et al., 2007). A mutation in ADAMTS17 involving a nucleotide substitution and associated with PLL in Miniature Bull Terriers, Lancashire Heelers, and Jack Russell Terriers has been described (Farias et al., 2010). Subsequent to this report, this same mutation has been identified in 14 additional breeds mostly with terriers or breeds with terrier coancestry. The mutation appears to be present in high frequency within most breeds in which it segregates. Heterozygotes of this mutation also have an increased risk of developing PLL, estimated at 5%. Mutations in the ADAMTS17 in humans are associated with short stature and ocular anomalies, and the preponderance of PLL in terrier and other breeds with a miniature or short stature has led to speculation that selection for this body phenotype may have inadvertently led to selection of this mutation. This same study did not document this mutation in the Shar Pei and Brittany Spaniel with PLL, suggesting they may have a genetically distinct form of PLL (Gould et al., 2011).

PLL most commonly manifest bilaterally, although not necessarily with a symmetric clinical presentation. Lens displacement is documented most commonly in 3- to 6-year-old dogs, with the mean age reported to be 4.5 years in terriers and terrier-crosses (Curtis et al., 1983), and 4.9 years for the Shar Pei. However, some variation in this age of onset exists. In the Tibetan Terrier and Shar Pei breeds, pedigree and other genetic analyses strongly suggest primary luxation is inherited as a simple autosomal recessive trait (Curtis, 1983a, 1983b; Ketternitzsch et al., 2004; Lazarus et al., 1998; Willis et al., 1979).

There is evidence to suggest the pathogenesis of primary lens displacement relates to an inherited defect in the suspensory apparatus or ciliary zonules of the lens. Martin noted abnormal and haphazard lens equatorial attachment of zonules in two dogs with presumed primary displacement (Martin, 1978). One report documented inflammatory cells associated with zonular fibers in dogs with lens luxation cases and speculated that a primary inflammatory process involving the lens zonules was causative (Gwin et al., 1982); however, this contention has been questioned (Curtis, 1983b), and the inflammatory response noted was more likely secondary. The disease has been best characterized in the Tibetan Terrier (Curtis, 1983a), where a group of animals studied sequentially developed a disease course characterized by increased mobility of the lens, iridodonesis, zonular rupture initiating in the dorso-lateral quadrant, anterior displacement of vitreous, subluxation and variable progression to luxation of the lens. Increased intraocular pressure often developed subsequent to lens displacement. Prior to development of these clinical signs, the lens often assumed a globoid shape, allowing visualization of the lens equator, ciliary zonules, and anterior vitreous with maximal mydriasis, and suggesting a clinical feature which might be useful to predict which animals ultimately develop lens displacement. Ultrastructurally, an abnormal and haphazard arrangement of zonular material lying between the major processes of the ciliary body was found. These fibers insert on the posterior aspect of the lens equator. Importantly, no abnormalities were found in the lens zonules arising at the pars plana, zonular attachments to the lens, and the ultrastructural form, diameter, or periodicity of the individual zonules. Similar ultrastructural zonular abnormalities were noted in other terrier breeds. The authors suggested a pathogenesis relating to an abnormality in the fibroblast-like cell proposed to produce the zonular material. They further postulated that decreased laxity of the posterior equatorial lens zonules resulted in a globoid shape to the lens, and caused zonular rupture associated with globe or head movement and progression to displacement (Curtis, 1983a). Primary lens displacement seen in terrier breeds shares most of these clinical features and may share a similar pathogenesis to the one proposed for the Tibetan Terrier.

Lens displacement may be associated with glaucoma in a still incompletely defined fashion. Lens luxation often occurs secondary to chronic glaucoma and enlargement of the globe, and is presumably related to progressive stretching and rupture of zonules. However, the coexistence of increased intraocular pressure, subluxation of the lens, and an apparent normal globe size in some dogs on initial clinical presentation sometimes makes determination of the primary or antecedent disease difficult. This has led to speculation that, in some cases, ocular hypertension may precede and actually cause breakdown of the zonules in some cases through an undefined mechanism unrelated to a change in globe size (Gelatt, 1991). Subclinical changes in globe size with primary glaucoma may theoretically account for some of these cases. PLLs and primary glaucoma may coexist in some cases, as the terrier breed appears to be at risk for both. It is also possible that primary lens displacement alters the anatomic and physiologic factors related to aqueous humor outflow in a yet undefined fashion. In the Tibetan Terrier, subluxation precedes ocular hypertension, and one author has speculated that glaucoma is caused by mechanical obstruction of aqueous outflow by vitreal debris (Curtis, 1983a). Although further clinical study would be necessary to confirm these observations, this explanation seems most plausible and probably accounts for the majority of such cases.

Lens displacement in the absence of other ocular disease may also occur in older-aged dogs (>10 years of age), comprising various terrier and nonterrier breeds. Senescent lens displacement in terrier breeds may represent a late-onset presentation of primary lens displacement. Older-aged mixed breed and nonterrier breeds presumably develop lens displacement from undefined mechanisms that may reflect age-related degenerative process occurring in the zonules and/or anterior vitreous and vitreal base.
Zonulolysis and lens displacement can theoretically result from any contiguous inflammatory process, although uveitis appears to be a rare cause of lens luxation in dogs (Curtis et al., 1983). Lens subluxation is common in conjunction with hypermature cataracts. Zonular instability and/or an aphakic crescent are often present at the time of surgical removal of the hypermature cataract. Subluxation presumably results from a reduction in overall lens size with resorption, causing rupture of zonular rupture through a direct physical stretching. A zonulolytic effect from any associated lens-induced inflammation may also contribute.

Although lens luxation was historically suggested to commonly result from blunt trauma to the globe, this premise has not been substantiated with retrospective case studies (Curtis et al., 1983). Blunt trauma with force sufficient to cause lens displacement generally results in collateral and profound ocular injury. It has also been suggested that trauma may occasionally precipitate lens displacement in an animal predisposed to primary luxation (Curtis & Barnett, 1980; Formston, 1945).

Clinical evaluation of the patient with lens luxation should include critical ophthalmic examination for any primary cause. Because primary or inherited displacement is almost invariably a bilateral disorder, the contralateral eye should be evaluated biomicroscopically following mydriasis for evidence of lens instability, or signs compatible with subluxation. Gonioscopy should also routinely be performed, especially if ocular hypertension is documented, in both the affected (if possible) and unaffected eye, to attempt to determine any causal relationship. The most commonly recommended treatment for dislocated lenses is surgical removal through an intracapsular lens extraction, with or without sulcus IOL placement (see lens surgery in Chapter 22). If surgical treatment is not performed, subluxated and posteriorly luxated lenses may be managed conservatively with long-term topical miotic therapy (e.g., phospholine iodide, latanoprost, or demecarium bromide). The rationale for this approach is to maintain the lens in the posterior chamber, or vitreous, and prevent forward migration, where complications such as pupillary block glaucoma or corneal edema are more common. In one study of dogs with lens instability (subluxation or posterior luxation), conservative treatment with demecarium bromide maintained vision in 16 out of 20 dogs at 1 year and 11 out of 19 dogs at 2 years (Binder et al., 2007). Anteriorly luxated lenses may be managed conservatively with long-term topical miotic therapy (e.g., phospholine iodide, latanoprost, or demecarium bromide). The rationale for this approach is to maintain vision in 16 out of 20 dogs at 1 year and 11 out of 19 dogs at 2 years (Binder et al., 2007). Anteriorly luxated lenses may be managed conservatively with long-term topical miotic therapy (e.g., phospholine iodide, latanoprost, or demecarium bromide). The rationale for this approach is to maintain vision in 16 out of 20 dogs at 1 year and 11 out of 19 dogs at 2 years (Binder et al., 2007).

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CATARACT SURGERY

Cataract surgery has changed dramatically in recent years with regard to surgical technique, ocular pharmacology, and the availability of anti-inflammatory agents, viscoelastic agents, phacoemulsification, and the most recent advancement, intraocular lens (IOL) implantation for dogs. Despite these dramatic changes, cataract surgery remains a procedure whose successful outcome depends on meticulous attention to detail, surgeon skill and experience, and appropriate patient selection. As cataract surgeons, we tend to rely inappropriately on topical and systemic medications to achieve a successful outcome, blaming the dog and the medication for failure. The aim of the cataract surgeon should be to utilize a minimum of medications relying on delicate tissue handling, shortened surgical time, and smaller incisions to improve success.

Having said this, it is still essential to ensure that the eye and the patient are prepared appropriately for surgery to avoid unnecessary complications. Preoperative use of anti-inflammatory agents, preoperative and intraoperative mydriasis, proper patient positioning, appropriate use of magnification, and use of viscoelastics and nondepolarizing neuromuscular blockade are all steps that will minimize complications.

Preoperative complications include lens-induced uveitis (LIU), diabetes mellitus, vitreous presentation into the anterior chamber, lens subluxation, and posterior synechia, to name but a few. While there is no question that these changes will influence the approach to and success of a cataract surgery, they no longer need to eliminate the patient from surgery nor do they need to decrease success or ability to restore emmetropia in most instances (Fig. 22.1). LIU is best treated by lens extraction, posterior synechia can be broken down, vitreous in the anterior chamber can be tamponaded or removed, lens instability can be managed using a two-handed approach, and with new foldable IOLs and sulcus fixation, an IOL can still be placed. Diabetes mellitus-induced cataracts have a similar postsurgical outcome to nondiabetic cataracts (Bagley & Lavach, 1994), although it is the authors’ clinical impression that these eyes require longer postoperative topical anti-inflammatory therapy and are more likely to have inflammatory cell deposits on the IOL. Spontaneous lens capsule rupture is also a complication of diabetes mellitus and can necessitate emergency cataract surgery (Wilkie et al., 2006).

In addition to those complications noted above, we must be prepared to deal with unexpected and potentially devastating intraocular complications to ensure a successful outcome despite the obstacles encountered.

Patient Selection

Proper patient selection is essential to maximize a successful surgical outcome. First, a complete history and systemic examination are indicated to evaluate for systemic disease that may relate to the presence of the cataract (e.g., diabetes mellitus), may affect anesthesia (renal, hepatic, and cardiac disease), or may alter postoperative outcome (blepharitis, ocular hypertension) or life expectancy. Second, a complete vision history and ophthalmic examination are required. Vision history should ascertain when the cataract was first observed and when vision changes were noted. Special attention must be paid to vision loss prior to the onset of the cataract or a history suggestive of nystagia. Patient temperament is also important as administration of postoperative medications and exercise restriction are essential to a successful outcome. Fractious and aggressive patients can present problems for administration of postoperative medication.

Cataract surgery is an elective procedure as many animals will adapt well to vision loss. It must be remembered, however, that if the owner elects not to perform cataract surgery, the patient must be monitored long-term for lens-induced complications such as LIU, secondary glaucoma, retinal detachment, and lens luxation. Younger animals with cataracts that do not have surgery may go on to spontaneously resorb their cataract and regain aphakic vision. In addition, a case of spontaneous resorption of a diabetic cataract has been described (Gonzalez-Alonso-Alegre & Rodriguez-Alvaro, 2005). Owners must...
understand, however, that all decisions carry risks. In a study of 44 dogs with cataract comparing no treatment, topical medical management, and phacoemulsification, it was found that eyes receiving no treatment had failure rates 65 and 255 times greater than medically and surgically managed eyes, respectively (Lim et al., 2011). In addition, failure was four times greater in eyes treated medically as compared to those treated surgically (Lim et al., 2011). Failure included a painful globe, glaucoma, lens luxation, enucleation/evisceration, and in surgical eyes, loss of vision (Lim et al., 2011). Surgical outcome was better for immature cataracts as compared with mature and hypermature cataracts (Lim et al., 2011). The conclusion is that early surgical intervention is associated with the highest success rate and that animals that do not undergo phacoemulsification should be managed with a topical anti-inflammatory. (Lim et al., 2011) In addition, a retrospective study, involving 156 dogs, evaluated risk factors for canine secondary glaucoma. Nonsurgical uveitis accounted for 44.9% and cataracts accounted for 2.5% of cases of secondary glaucoma (Johnsen et al., 2006). While not specifically evaluated, it is assumed that a portion of these uveitis cases were secondary to LIU.

Cataract surgery is indicated in animals with a decrease in vision associated with the cataract or in animals with a progressive cataract for which vision loss is imminent. With the introduction of IOL implants, cataract surgery can also be offered in cases of unilateral cataract to restore binocular emmetropia. In general, axial lens opacities will result in a more significant visual disturbance, and anterior and equatorial cortical opacities are more likely to be progressive. Prior to surgery, a complete ophthalmic examination should be performed. This includes evaluation of the precorneal tear film, adnexal anatomy, and function, as well as the globe itself. Menace response, direct and consensual pupillary light reflexes, and intraocular pressure (IOP) should be evaluated (Leasure et al., 2001). Low IOP suggests LIU while a high normal to elevated IOP suggests early primary or secondary glaucoma. If IOP is normal, the pupil can be dilated with a

Figure 22.1.  A. Canine eye with a hypermature cataract and severe 360° posterior synechia. B. Same eye as in A intraoperatively as the synechia is broken using a cystotome. C. Postoperative view with an IOL in the lens capsule and the anterior capsulorhexis visible.
mydriatic and biomicroscopic, and indirect ophthalmoscopic examination can be performed. The cornea is examined for opacities that may interfere with visualization of the intraocular structures intraoperatively. In addition, corneal edema may indicate corneal endothelial dysfunction that may be exacerbated by surgery. The iris is evaluated for hyperpigmentation, synechia, or ectropion uvea suggestive of chronic LIU. The anterior chamber is examined for the presence of aqueous flare, keratic precipitates, or vitreous strands. The lens opacity is characterized with respect to stage and location of cataract, and the lens is examined for evidence of lens resorption, capsular fibrosis or plaques, capsular wrinkling, or lens instability. Hypermature cataracts, cataracts in older dogs, vitreous in the anterior chamber, phacodonesis, or an aphakic crescent are all suggestive of potential lens instability which must be noted and planned for prior to surgery. Anterior capsule wrinkles, fibrosis or plaques are suggestive that the same may be present on the posterior capsule and may necessitate a planned continuous tear posterior capsulorhexis (PCTPC). Anterior capsule wrinkles will also result in difficulty with the anterior capsulorhexis and may require capsulotomy scissors to manage. If possible, the fundus should be examined by indirect ophthalmoscopy. Retinal vasculature, tapetal reflectivity, and the optic nerve are assessed, if possible, and the retina is evaluated for possible tears or detachment. Gonioscopy is performed at the discretion of the surgeon. While there is no documented correlation between the presence of preoperative iridocorneal angle (ICA) abnormalities and immediate postoperative hypertension or long-term glaucoma, the knowledge of an abnormal angle may alter some surgeons’ approach or prognosis.

Additional diagnostic examination should include B-scan ultrasonography (Williams, 2004; Williams & Wilkie, 1996) and possibly high-resolution ultrasound (HRUS, 20 mHz) (Bentley et al., 2003), and ultrasound biomicroscopy (UBM, 50–100 mHz) (Rose et al., 2008). B-scan ultrasound using a 10-mHz probe is used to evaluate for vitreal degeneration/asteroid hyalosis, retinal detachment, posterior lenticonus, persistent hyperplastic tunica vasculosa lentis/persistent hyperplastic primary vitreous (PHTVL/PHPV), axial length of the lens and globe, and presence of spontaneous lens capsule rupture (Fig. 22.2 and Fig. 22.3) (Gemensky-Metzler & Wilkie, 2004; Ori et al., 2000; van der Woerd et al., 1993; Wilkie et al., 2002, 2006). It has been shown that the prevalence of vitreal degeneration and retinal detachment increase with progression of cataract (van der Woerd et al., 1993). Evaluation of the anterior segment, specifically the ICA and angle opening distance (AOD), can be performed using HRUS or UBM. It has been suggested that the ICA and AOD may correlate with the development of postoperative hypertension (Rose et al., 2008).

If the patient is still a surgical candidate based on the previous criteria, a quantitative electroretinogram (ERG) should be performed to determine retinal function and evaluate for the possibility of progressive retinal atrophy (PRA). Both photopic and scotopic values should be determined. Abnormally low values must be interpreted based on the age and breed of the dog. While a patient with PRA is not a good surgical candidate, an older dog with mild senile retinal atrophy may be acceptable provided the owner understands the expectations for postoperative visual outcome. In addition, some dogs with diabetes mellitus, LIU, and a mature cataract may have...
a reduced ERG preoperatively, but a normal fundic examination and vision testing postoperatively (Maehara et al., 2007).

Finally, the breed of dog must be considered. Postoperative complications such as retinal detachment and glaucoma vary by breed with certain breeds at increased risk (Lannek & Miller, 2001; Schmidt & Vainisi, 2004). The surgeon may, in selected breeds such as the Bichon Frise and Shih Tzu, choose to perform a prophylactic transscleral retinopexy (PTR) prior to cataract surgery to decrease the risk of postoperative retinal detachment (Schmidt & Vainisi, 2004). It has been shown in the Bichon Frise that the prevalence of retinal detachment following cataract surgery is 55% without diode laser PTR and is decreased to 12% with PTR (Schmidt & Vainisi, 2004).

The decisions of whether to perform cataract surgery and whether the procedure is to be performed on one or both eyes are matters of individual preference by the surgeon, and they reflect a balance between anticipated visual improvement versus the risk of substantial postoperative complications. Improvements in surgical techniques, IOL implantation and anticipated outcome, and that many primary canine cataracts ultimately (and predictably) progress to a complete state, have shifted the emphasis toward early, rather than late, removal of cataracts. Retrospective studies on outcomes after phacoemulsification have documented a statistically higher success rate with immature cataracts compared with those of mature and hypermature cataracts (Davidson et al., 1991b; Sigle & Nasisse, 2005). Long-standing cataracts are often associated with LIU, capsular plaques, and zonular instability, all of which increase intraoperative and postoperative complications and decrease visual outcome. Additionally, several reports have suggested an increased prevalence of both pre- and postoperative rhegmatogenous retinal detachments with hypermature cataracts (Davidson et al., 1991a; Dziezyc et al., 1986; Miller et al., 1987) and increased likelihood of postoperative glaucoma associated with hypermature cataracts (Sigle & Nasisse, 2005). When cataracts are present bilaterally, unilateral surgery is sometimes performed under the rationale of not subjecting both eyes to the same intraoperative risk factors (e.g., bacterial contamination, potential endophthalmitis). Unilateral surgery is also less expensive, and monocular sight generally leaves the dog functionally visual. The concern with unilateral surgery in a patient with bilateral cataracts is the unoperated eye remains at risk for chronic LIU, lens luxation, retinal detachment, and glaucoma, and these may require medical and/or surgical intervention negating any cost savings (Paulson et al., 1985; van der Woerdt et al., 1992). Conversely, bilateral surgery has the advantages of restoring sight to both eyes with a single anesthetic episode and convalescent period, lower overall costs when compared with those of two unilateral surgeries, and a higher percentage of patients who regain vision from one or both eyes (Davidson et al., 1990).

Preoperative Complications

Prior to cataract surgery, ocular changes may have occurred associated with the cataract that may result in a change in surgical technique or postoperative outcome. Such changes often occur as a result of stage and duration of the cataract, age of the patient, and LIU.

Spontaneous Lens Capsule Rupture

Spontaneous lens capsule rupture has been described in association with diabetes mellitus and rapidly progressive cataracts (Wilkie et al., 2002, 2006). Affected dogs had been diabetic for an average of 123 days and had cataracts for an average of 39 days. This compares to the general diabetic canine population in which 50% are described to have cataracts by 170 days post diagnosis of diabetes mellitus and 80% by 470 days (Beam et al., 1999). It would appear, therefore, that the more rapid onset and progression of cataracts in these dogs may be associated with spontaneous capsular rupture. Cataracts associated with diabetes mellitus have a significant osmotic component that results in rapid intumesence of the lens. On ultrasound, the axial length of the lens in dogs with spontaneous capsular rupture ranged from 8–11 mm with a mean of 9.3 mm. This rapid increase in lens size is associated with spontaneous lens capsule rupture and phacoanaphylaxis or phacoclastic uveitis. Clinically, most ruptures (>95%) occurred equatorially, but posterior capsule ruptures were also observed (Fig. 22.4 and Fig. 22.5). Often the anterior chamber appeared asymmetrically shallow and significant anterior uveitis was present. The diagnosis of spontaneous capsule rupture associated with cataract was made clinically in over 90% of the affected eyes with less than 10% being noted intraoperatively (Wilkie et al., 2006). Agressive anti-inflammatory therapy combined with rapid surgical intervention is indicated in affected dogs. Postoperatively, these eyes often have chronic uveitis and require long-term anti-inflammatory therapy, but long-term visual outcome is good (Wilkie et al., 2006).

![Figure 22.4. Spontaneous equatorial lens capsule rupture extending from 11 o’clock to 4 o’clock. The exposed lens cortex is visible with uveal pigment dispersed through the cortical lens fibers.](image)
Lens capsule rupture may also occur in association with penetrating trauma such as seen with a cat claw injury. Small capsule rents may spontaneously heal by lens epithelial cell (LEC) fibrous metaplasia and/or posterior synechia resulting in a focal cataract (Buschmann, 1987). Larger capsule tears can result in severe phacolytic uveitis, massive fibroplasia, and secondary glaucoma (Davidson et al., 1991c; Wilcock & Peiffer, 1987). In general, if the capsular tear exceeds 1.5 mm, removal of the lens is recommended. Smaller tears and focal cataracts can be monitored, but surgery is indicated if the cataract is progressive or inflammation ensues (Davidson et al., 1991c). Finally, a sealed capsular rent can open months to years following injury and is associated with progression of the cataract, swelling of lens fibers, and subsequent stretching of the capsule tear. A recent study of 77 patients (67 dogs, 10 cats) with traumatic lens capsule rupture has suggested that medical management may be effective for many cases of traumatic lens capsule rupture (Paulsen & Kass, 2012).

**Lens-Induced Uveitis**

Lens-induced or phacolytic uveitis is commonly seen in dogs with cataracts, with one study suggesting a prevalence as high as 71% (Paulson et al., 1985). All stages of cataract have LIU (Gelatt & Mackay, 2004). Indications of LIU include hypotony, aqueous flare, iris hyperpigmentation, ectropion uvea, keratic precipitates, delayed or incomplete pharmacologic mydriasis, and synechia. While early retrospective studies suggested that preexisting LIU significantly reduced long-term success with cataract surgery (Paulson et al., 1985), this does not appear to be as significant with current surgical techniques (Sigle & Nasisse, 2005). In general, pretreatment with topical and/or systemic anti-inflammatory therapy for a period of a few days followed by phacoemulsification is the most appropriate means to manage LIU and avoid long-term sequelae (Fisher, 1972; Paulson et al., 1985; van der Woerdt et al., 1992; Wilcock & Peiffer, 1987).

**Elevated IOP**

IOP is typically low to normal in most cataractous eyes (Leasure et al., 2001). A high normal to elevated IOP suggests impending or current glaucoma. The glaucoma may be primary or secondary in origin. In addition, a dog with a cataract and a history of primary glaucoma in the contralateral eye is at increased risk for the development of postoperative glaucoma following cataract surgery. While prognosis in these eyes is decreased, it may be possible to improve the outcome with concurrent diode endolaser cyclophotocoagulation, provided retinal function is acceptable based on ERG (Bras et al., 2005). Following standard phacoemulsification and IOL implantation, a 20-gauge endolaser probe is introduced through the limbal cataract surgery incision. Viscoelastic material is used to expand the area of the ciliary sulcus, and the ciliary processes can be visualized and treated using the endoscopic diode laser over a minimum of 180° of the ciliary body (Bras et al., 2005; I.D. Bras, personal communication).

**Other Complications**

Additional preoperative concerns may include congenital intraocular anomalies, lens subluxation/luxation, synchiae, corneal opacities, uncontrolled keratoconjunctivitis sicca, vitreous degeneration, partial retinal detachment, or other abnormalities that may interfere with surgical success intra- or postoperatively. Examples of congenital anomalies that may be associated with cataracts include persistent pupillary membranes, persistent hyaloid artery, PHTVL/PHPV, posterior lenticous, microphakia, lens coloboma, microphthalmos, and other such anomalies (Fig. 22.6). The presence of such abnor-
Surgical Equipment

Cataract surgery success depends on surgeon’s skill and appropriate pre- and postoperative therapy, but is also heavily dependent on the use of appropriate instrumentation. Microsurgical instrumentation, surgical microscopes, phacoemulsification machines, automated irrigation/aspiration (I/A) machines, and vitrectomy capabilities are considered standard of care. In addition, many surgeons choose to administer nondepolarizing neuromuscular blocking agents to paralyze the patient during surgery; this may require the use of ventilators and additional monitoring equipment. Failure to use this equipment and to understand the indications and techniques by which these instruments are used will result in a significant decrease in surgical success.

Preoperative Therapy

While all cataract surgeons agree on the goals of preoperative therapy, no surgeons agree completely on how best to achieve these goals, which drugs to use, and the route and frequency of preoperative therapy. The overall presurgical goals are to achieve mydriasis for surgical exposure, suppress ocular inflammation, and minimize ocular microbial flora (Wilkie & Gemensky-Metzler, 2004). Broad-spectrum bactericidal topical antibiotics are administered every 6 hours beginning 12–24 hours prior to surgery (Yu-Speight et al., 2005). In addition, many surgeons will administer an intravenous bolus of antibiotics at induction. Bacterial contamination of the anterior chamber has been shown to be a common occurrence in canine cataract surgery (Ledbetter et al., 2004). Topical corticosteroids are used every 6 hours starting at least 12–24 hours prior to surgery, and longer if LIU is present. The topical corticosteroid should be potent and have good corneal penetration, suggesting 1% prednisolone acetate as the corticosteroid of choice. Both the topical antibiotics and corticosteroids are continued every 6 hours in the postoperative period. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to suppress inflammation and to prevent miosis (Cillano et al., 1993; Holmes & Jay, 1991). Topical NSAIDs are administered every 30 minutes starting 1–2 hours preoperatively, and a systemic NSAID such as flunixin meglumine (0.5–1.0 mg/kg IV) or carprofen (2.2 mg/kg SQ) is administered at induction. Some surgeons will also administer a topical corticosteroid every 30 minutes along with the topical NSAID. Mydriasis is achieved using topical 1% atropine or tropicamide. While only a single dose is generally required 1–2 hours prior to surgery, some surgeons will choose to use it more frequently for a prolonged period of time. This is not necessary, nor advised. Protracted atropinization is not recommended because receptor hyperplasia can contribute to intraoperative miosis (Smith et al., 1984). In addition, some surgeons will administer 0.1–0.5 mL of intracameral 1:10,000 epinephrine in conjunction with preoperative mydriatics or as the sole dilating agent. In addition to mydriasis, epinephrine will facilitate vasoconstriction, control potential bleeding, and decrease postoperative aqueous flare and fibrin (Wilkie & Gemensky-Metzler, 2004).

Surgical Approach

Most cataract surgeons would choose a protocol of general anesthesia using standard premedication followed by inhalation anesthesia and often the use of nondepolarizing neuromuscular blocking agents. Recently, a paper evaluated the use of ketamine, xylazine, and diazepam along with a local retrobulbar nerve block for routine phacoemulsification in the dog (Hazra et al., 2008). Patient anesthesia, analgesia, globe position, and IOP were all felt to be acceptable using this protocol (Hazra et al., 2008).

The patient is positioned with the operated eye facing up and the eyelids parallel to the floor. The patient and head are immobilized, and a vacuum pillow around the head will help to stabilize and maintain head position. The table and surgical chair height and the microscope are positioned and adjusted for the primary and, if present, the assistant surgeon. The patient should be routinely clipped and prepared for surgery according to the surgeon’s preference.

A lateral canthotomy may be performed to increase exposure to the surgical field and reduce potential globe-deforming forces caused by the eyelids and eyelid speculum. A lateral canthotomy is unnecessary in most brachycephalic and in many types of mesocephalic breeds. It is advised when performing intracapsular lens extraction (ICLE) or suturing of an IOL. A stay suture or sutures are placed in the bulb conjunctiva and Tenon’s capsule using 4-0 to 6-0 suture material. In general, stay sutures are less essential if a neuromuscular blocking agent is to be administered, and often, a single stay suture at the ventral nasal limbus, beneath the nictitans, is sufficient. If neuromuscular blocking agents, such as atracurium, are to be used, they are administered at this time to facilitate globe position and decrease external forces on the globe caused by extraocular muscle contraction.

A clear corneal- or limbus-based incision is most common for the approach to the canine lens. In general, the more anterior surgical incisions are easier to create and provide better access to the anterior chamber. The more anterior the wound, however, the greater the degree of surgically induced astigmatism, and the greater the need for critical and accurate suture placement to provide watertight wound closure. Additionally, clear corneal incisions result in more wound fibrosis and visible scar. Conversely, posteriorly situated entry wounds are more difficult to construct but are associated with less astigmatism, less need for critical suture placement, and more
rapid wound healing. Scleral wounds, however, are associated with a greater tendency for iris prolapse and make access to the anterior chamber more difficult, particularly during the I/A of ventrally located cortical material. In addition, the highly vascular canine sclera often hemorrhages excessively during wound construction (Nelms et al., 1994). Therefore, the limbal wound may be viewed as a compromise between these two types of incisions and will subsequently be referred to as anterior-limbal (Fig. 22.7) (Nasisse & Davidson, 1999).

In general, most surgeons make a pseudo-limbal incision with one side of the incision cornea, the other sclera, but without an overlying conjunctival flap. With virtually all veterinary ophthalmic surgeons performing phacoemulsification, with an associated small incision, the use of conjunctival flaps to cover a limbal wound is no longer required. The length of the incision depends on the technique of choice to remove the lens and whether an IOL will be implanted, and if so, what type of IOL. Phacoemulsification is now the accepted standard of care in routine veterinary cataract surgery. This requires a 2.8–3.2 mm entry wound to accommodate a coaxial phacoemulsification tip and infusion sleeve. If a polymethylmethacrylate (PMMA) IOL is to be implanted, the wound will be inadequate to properly maintain the anterior chamber and prevent the tip from overheating (Nasisse & Davidson, 1999). If a two-handed approach is planned, the second incision should be made 70° away from the initial incision to the side of the surgeon’s nondominant hand. The size of this incision varies somewhat depending on the instrument to be inserted, but, in general, is a 1-mm full-thickness incision made using a keratome. This is made in a tunnel fashion and can be performed prior to entry through the primary incision or following insertion of the phaco tip with irrigation flow turned on. If the surgeon becomes comfortable with the second option, it will allow conversion to a two-handed approach at anytime during surgery rather than only at the onset of the procedure.

Use of Intraoperative Medications/Devices

Following entry into the anterior chamber, aqueous humor will leak out of the wound and the anterior chamber will collapse. Epinephrine, 1:10,000, can be placed intracamerally using a cannula to facilitate mydriasis and vasoconstriction of the anterior uveal vasculature. This is followed by injection of a viscoelastic material to reinflate and maintain the anterior chamber. The viscoelastic agent should be injected starting at the distal aspect of the anterior chamber, filling back toward the corneal incision and expelling all the aqueous humor.

Viscoelastic substances are used in ophthalmic surgery to protect tissue and cells from mechanical trauma, create and preserve space for surgical manipulation, lubricate, separate tissues, prevent adhesions, tamponade hemorrhage, and to move or relocate tissue. They are therefore, “tools for spacial tactics” (Eisner, 1990). In addition, during phacoemulsification, damage to corneal endothelial cells occurs from turbulence, cavitation, ultrasound, free radicals, and lens fragments. The use of viscoelastic substances has been demonstrated to minimize damage to and loss of corneal endothelial cells from all of these causes (Artola et al., 1993a, 1993b; Liesegang, 1990; Wilkie & Willis, 1999). Selection of a viscoelastic is dependant on the task required with no one viscoelastic fulfilling all needs, requiring the ophthalmic surgeon to be familiar with a variety of viscoelastic substances and their properties, and to select one most appropriate for the task performed. Viscoelastic substances must be sterile, nontoxic, nonpyrogenic, noninflammatory, and nonimmunogenic. In addition, they are balanced with respect to their electrolytes, osmolality, pH, and colloid osmotic pressure so that they are suitable for use in the anterior and posterior chambers and vitreous cavity. Injection of viscoelastic materials is critical, placing the viscoelastic precisely at the desired site and taking into consideration the volume shift that occurs with injection and the need to maintain pathways for these shifts to occur. Removal of exact length is critical. Excessively large incisions will result in fluid leakage and intraoperative variations in anterior chamber depth, and excessively small incisions will result in restriction of the irrigation fluid flow through the sleeve which will be inadequate to properly maintain the anterior chamber and prevent the tip from overheating.
of viscoelastic material can be done using automated irrigation-aspiration, manual irrigation, or the viscoelastic material can be left in the anterior chamber if its effects are still required postoperatively allowing removal by aqueous dilution and outflow. The decision to remove a viscoelastic material at the conclusion of surgery is based on preoperative gonioscopy, need for visco-occupation in the postoperative period, manipulation and trauma associated with removal, and ultimately, surgeon preference. Viscoelastics have properties of both fluids and solids and are described based on their rheologic properties of viscosity, pseudoplasticity, viscoelasticity, and surface tension (Liesegang, 1990; Wilkie & Willis, 1999). A variety of viscoelastic materials are available, containing hyaluronic acid, hydroxypropylmethylcellulose (HPMC), chondroitin sulfate, polyacrylamide, or some combination thereof. Viscoelastics have been discussed as being either cohesive (high viscosity/molecular weight) or dispersive (low viscosity/molecular weight) (Wilkie & Willis, 1999). With a cohesive viscoelastic, the molecules tend to aggregate and stay together while with a dispersive viscoelastic, the molecules tend to occupy available space and spread apart. Healon® (Abbott Medical Optics, Santa Ana, CA) is an example of a cohesive viscoelastic, while Viscoat® (Alcon Laboratories, Ft. Worth, TX) is a dispersive viscoelastic. Very high molecular weight viscoelastics have also been created, such as Healon GV® (Abbott Medical Optics, Santa Ana, CA), and are referred to as supercohesives. Cohesive viscoelastics tend to be better for creating space, dilating pupils, expanding capsular bags, and moving tissues while dispersives are better for coating instruments or corneal epithelial and endothelial cells, partitioning trouble zones, and tamponading posterior capsular tears. A cohesive viscoelastic tends to leave the eye rapidly when I/A begins or the incision is opened and pressure is applied. This not only facilitates removal at the completion of a procedure, but also results in a lack of viscoelastic material in the eye during surgery as it tends to be removed within seconds of initiation of phacoemulsification. Cohesive viscoelastics are also believed to be more likely to result in postsurgical intraocular hypertension and thus, easy removal is beneficial. This is especially true with supercohesive viscoelastics. Dispersive viscoelastics remain in the eye for a prolonged time, thereby offering better protection for the corneal endothelium during surgery. They require more effort and time to remove, but are also less associated with postoperative hypertension and can be left in the eye if needed, postoperatively. Since both properties are desirable for various aspects of cataract surgery, a new product, DuoVisc® (Alcon Laboratories, Ft. Worth, TX), containing both a cohesive and a dispersive viscoelastic, has been marketed. The dispersive viscoelastic is placed in the anterior chamber to protect and coat the corneal endothelium and the cohesive viscoelastic is then placed over the anterior lens capsule to create working space. A dispersive viscoelastic is especially valuable when performing cataract surgery on patients with dry eye, endothelial degeneration, or in managing posterior capsular tears. Dispersives protect the corneal endothelium from the trauma of cavitation bubbles, turbulence, lens fragments, and shearing forces. The disadvantage of a dispersive viscoelastic is its tendency to trap bubbles and lens fragments during surgery and thereby decrease visibility.

Viscoelastics are indicated during all cataract surgeries to maintain the anterior chamber, dilate the pupil, protect tissues, facilitate anterior and posterior capsulorhexis, dilate the lens capsule to facilitate lens implantation, cover posterior capsular tears, and tamponade the vitreous and hemorrhage. For most veterinary ophthalmologists, a cohesive viscoelastic is used with selection based on availability, cost, and volume supplied per syringe. Remember that cohesive viscoelastics are good for anterior chamber maintenance, facilitating capsulorhexis and IOL insertion, but are removed almost immediately by the high vacuum and fluid flow encountered during phacoemulsification, resulting in little endothelial and iris protection from turbulence, cavitation, ultrasound, free radicals, and lens fragments. The most common current viscoelastic used for veterinary cataract surgery is Hylartin V, an equine intra-articular form of sodium hyaluronate. While not specifically labeled for intraocular use, its availability in 2.0-mL quantities, cost, and lack of adverse sequelae make it a suitable viscoelastic for intraocular use. Cataract surgeons should be aware that not all equine intra-articular sodium hyaluronate is the same. Many of the less expensive products are of a lower molecular weight, are less cohesive and have a tendency to egress out the corneal incision rather than maintaining the anterior chamber space. Several companies are now supplying a sodium hyaluronate in 2.0-mL volume that is similar in cost, viscosity, and handling to the equine intra-articular product. In addition, a new synthetic sodium hyaluronate that does not require refrigeration is available for veterinary use. Perhaps the second most frequently used viscoelastic in veterinary ophthalmology is HPMC with its selection made primarily on cost. Of these two viscoelastics, sodium hyaluronate is a superior viscoelastic for cataract surgery. The cataract surgeon must remember, however, that a cohesive viscoelastic such as sodium hyaluronate does not provide significant endothelial protection once phacoemulsification begins and that it is more likely to be associated with a postoperative IOP rise. When comparing corneal endothelial protection of sodium hyaluronate viscoelastics to one containing chondroitin sulfate during phacoemulsification, one study demonstrated 32% endothelial cell damage without viscoelastic, 12%–15% damage when sodium hyaluronate was used, and only 2.5% damage when using 3% sodium hyaluronate: 4% chondroitin sulfate (Bresciani et al., 1996). Many surgeons will also seek cost savings by reusing canulas for placement of the viscoelastic substance or other intracameral substances. This practice is discouraged as it has been shown to result in the introduction of toxic residues into the anterior chamber (Glasser et al., 1992).

Much attention has been given to the postoperative IOP rise observed in the 2-48 hours following cataract surgery (Gerding et al., 1989; Harooni et al., 1998; Henry & Olander, 1996; Jurgens et al., 1997; Miller et al., 1997; Smith et al., 1996; Stuhr et al., 1998). The use of higher viscosity
viscoelastics and smaller incisions has been demonstrated to be associated with a higher prevalence of postoperative hypertension (Jurgens et al., 1997). Cohesive viscoelastics are more likely to be associated with postoperative hypertension and should be removed at the completion of surgery, if possible. Removal can be performed using an automated I/A system placing the I/A tip in the central anterior chamber. A cohesive viscoelastic is easily removed as it will tend to adhere to itself and be removed en masse. The I/A tip should be placed on the anterior surface of the IOL and the lens gently displaced posteriorly to express any viscoelastic that remains between the IOL and the posterior lens capsule. Removal of dispersive viscoelastics is more difficult, requiring manipulation of the I/A tip, and complete removal may not be possible without inducing trauma. One study suggested that Healon and Healon GV were completely aspirated within 20–25 seconds while removal of OcuCoat® (Bausch & Lomb, Rochester, NY) took 1–3 minutes, and Viscoat required 3.5 minutes of automated I/A to remove (Assia et al., 1992). It is important to remove viscoelastic material, especially the cohesive types, from the corneal incision prior to closure to avoid complications of poor wound apposition, wicking of aqueous humor outward or contaminants inward and epithelial downgrowth. Indications to leave the viscoelastic following surgery would include iris prolapse to the corneal incision, intraocular hemorrhage, vitreous presentation, or IOL instability. Evaluation of postoperative IOP should be performed at 1 and 3 hours following corneal closure and postoperative ocular hypertension (POH) managed according to surgeon’s preference (Smith et al., 1996). Some surgeons advocate the use of hyaluronidase (Harooni et al., 1998), topical beta blockers, (Anmarkrud et al., 1996), or intracameral miotics (Stuhr et al., 1998) at the completion of the surgery in an effort to avoid postoperative hypertension. Hyaluronidase has been shown to have efficacy with Healon, Healon GV, and Viscoat, but not with OcuCoat in avoiding the postoperative pressure rise seen following cataract surgery (Harooni et al., 1998). While there has been concern over the possibility of intracameral drug binding by the viscoelastic substance and subsequent alterations in efficacy or toxicity, this does not appear to be a significant concern (McDermott & Edelhauser, 1989).

In addition to facilitating routine, uncomplicated cataract surgeries, viscoelastics can also be essential in the management of intraoperative complications. The surgeon should not be afraid to use more viscoelastic if required and the extra cost incurred by the client is small when compared to the potential intra- and postoperative complications that can be managed or avoided through the use of viscoelastics. Examples of intraoperative complications where a viscoelastic agent is helpful include intraoperative miosis, iris prolapse, management of synechia and hemorrhage, posterior capsular tears, vitreous presentation, and posterior lens luxation.

Intraoperative miosis during cataract surgery is a rare occurrence with current methods of presurgical patient preparation and widespread use of intraoperative, intracameral 1:10,000 epinephrine. In a retrospective study in humans, a small pupil was encountered in 1.6% of cataract operations, and continuous tear anterior capsulorrhexis and in-the-bag phacoemulsification was the method of cataract extraction in these eyes (Gimbel, 1992). If intraoperative miosis occurs, a cohesive viscoelastic will facilitate manipulation of the iris when placed at the level of the pupil (see “Intraoperative Complications”).

Intraoperative iris prolapse occurs in association with vitreous expansion, incorrect placement of the limbal incision, presurgical iritis, intraoperative iris trauma, incorrect placement of viscoelastic material posterior to the iris and overinflation of the posterior chamber, and excessive irrigation fluid velocity. Placement of the incision slightly more anteriorly, decreasing infusion velocity, correct placement of viscoelastic agents, and gentle tissue handling will minimize the occurrence of iris prolapse. If iris prolapse occurs, a cohesive viscoelastic can be used to reposition the iris, facilitating closure and minimizing postoperative dyscoria (see “Intraoperative Complications”).

Intraoperative use of 1:10,000 epinephrine, gentle tissue handling, and use of viscoelastic agents has decreased the likelihood of intraoperative hemorrhage. If hemorrhage occurs, place a small amount of epinephrine at the site of the hemorrhage and tamponade it with a dispersive viscoelastic followed by a cohesive viscoelastic over this. Use of viscoelastics to provide anterior chamber tamponade has been shown to stop bleeding and to prevent vessel rupture during selected procedures (Rypniewska et al., 1993).

Posterior capsular tears are best avoided rather than managed. If they occur, it is essential to attempt to complete phacoemulsification away from the capsular tear to avoid enlarging it. A dispersive viscoelastic should be placed over the tear and then covered with a cohesive viscoelastic to tamponade the vitreous. The irrigation rate should be decreased and the irrigating fluid directed away from the posterior capsular tear. In many instances, it may be best to convert to a bimanual technique placing a separate infusion port into the anterior chamber, directing the infusion away from the capsular tear/vitreous face, thereby minimizing further progression of the tear. Finally, a small linear or triangular posterior capsular tear is best converted into a circular tear by means of a planned posterior circular capsulorrhexis (see “Intraoperative Complications”).

Expanding vitreous syndrome occurs in eyes with an intact or disrupted posterior lens capsule. It is seen most often in brachycephalic dogs. Clinically, the intact posterior lens capsule will be displaced anteriorly and in some instances will protrude through the anterior capsule opening into the anterior chamber. If the posterior capsule has been disrupted, the vitreous will expand through the posterior capsule tear, enlarging the tear and entwining itself with the lens material and phacoemulsification aspiration port. Expanding vitreous syndrome in the presence of an intact posterior capsule can be minimized by use of a nondepolarizing neuromuscular blocking agent, by use of a lateral canthotomy where indicated, and by ensuring external forces are not applied to the globe by the eyelid...
speculum, drapes, stay suture tension, or the surgeon once the anterior chamber has been entered. In addition, if the posterior lens capsule is observed to move anteriorly, a cohesive viscoelastic material should be introduced in an effort to maintain space and force the capsule posteriorly (see “Intraoperative Complications”).

Viscoelastic materials can be used to manage a posterior lens luxation or posterior displacement of a lens fragment through a posterior capsular tear. If the vitreous is degenerate and liquified, a viscoelastic may be carefully placed below a luxated lens or lens fragment and the lens floated into the anterior chamber where it can be more easily removed. If the vitreous is in a more normal state, a vitrectomy of the vitreous overlying the lens may be required prior to floating the lens with viscoelastic material.

In addition to above intraoperative medications and devices, systemic administration of lidocaine intraoperatively has been demonstrated, in a preliminary study, to provide analgesia similar to systemic morphine in dogs undergoing cataract surgery in one study (Park et al., 2010; Smith et al., 2004). Intracameral preservative free lidocaine has also been evaluated in the canine eye without adverse effects (Gerding et al., 2004; Park et al., 2009).

**Capsulorhexis/Capsulectomy**

Before 1985, most surgeons would remove the lens capsule with a cystotome or a bent hypodermic needle, in what is referred to as the “can-opener” capsulectomy. This method, however, makes it difficult to control the size of the capsulotomy, and it leaves many jagged capsular edges that predispose to radial tears. As the popularity of “in-the-bag” IOL implantation grew, so did the need for a capsulectomy of the appropriate size to prevent IOL luxation and with smooth margins to prevent radial tears. The capsulorhexis, or continuous tear curvilinear capsulorhexis (CTCC), was developed for these reasons (Arshinoff, 1992; Assia et al., 1991a, 1991b; Gimbel, 1990).

The CTCC is initiated using a needle, cystotome or Vannas scissors near the 12-o’clock position. If scissors are used, the incision is more controlled, and the capsulorhexis can be extended in both the left and right directions. Utrata capsulorhexis forceps are then used to complete the CTCC removing a circular portion of the axial anterior lens capsule. The size of the capsulorhexis should be approximately 1 mm smaller than the diameter of the IOL optic to be implanted. The advantage of a CTCC is that it can withstand tension without tearing, thereby minimizing the risk of a radial tear (Krag et al., 1994). A correctly made CTCC can withstand stretching by as much as 62% without tearing (Assia et al., 1991b). This increases safety during hydrodissection, fragmentation, I/A, and IOL implantation. To maintain control of the capsulectomy, it is necessary to grasp and regasp the capsule every 2- to 3-o’clock-hour positions during the tear. This is especially important in young dogs with thin, elastic capsules where the capsulorhexis can rapidly expand equato-

![Figure 22.8](image)

**Figure 22.8.** The anterior lens capsule is torn using Utrata forceps, folding it over and using shearing forces to create a continuous circular capsulorhexis.

rially making the capsulectomy too large. Alternatively, if the lens is to be removed by the endocapsular method, the capsulectomy may be completed after the lens has been fragmented. Completing the capsulectomy after phacoemulsification will increase the risk of radial capsular tears during phacoemulsification and prevent the use of a two-handed technique. In addition to its intraoperative advantages, a CTCC has the postoperative advantage of uniform distribution of forces within the capsule facilitating IOL centration (Zanini & Buratto, 2003a).

The most important concept to understand when performing a CTCC is how the direction of tension affects the direction of a tear. A tear will only proceed in the direction the capsule is pulled if the vector of tension produced by that pull is parallel to the initial incision. This results in shearing of the capsule and allows the direction of the tear to be easily controlled (Fig. 22.8). Shearing is only accomplished easily if the capsule is folded over or under and onto itself. If an attempt is made to enlarge the capsule incision by randomly pulling on the capsule, forces perpendicular to the tear are created, and the tear will generally go in a direction 90° to the vector of tension. In addition, tearing usually will not begin until the tension on the capsule is extreme, and the result will be a rapidly forming tear in an unpredictable direction (usually radially) with excessive tension on the lens zonules (Nasisse & Davidson, 1999; Zanini & Buratto, 2003a). When performing a capsulectomy, it is optimal to rely on shearing forces as much as possible to maximize control. A surgeon should be able to direct the tear in both a clockwise and counterclockwise direction. A capsulorhexis will often spiral inward as the circle is completed, resulting in a “Q,” that is, a radial tear off the circle (Fig. 22.9). If this is observed to be occurring, the surgeon must tear in the opposite direction using the larger diameter side of the capsulorhexis to turn the tear back into a complete circle. The initial CTCC may be made smaller than ultimately desired and then enlarged
following phacoemulsification. This ensures the lens can be emulsified in the bag without risk of herniation into the anterior chamber and allows better visualization for the final enlargement of the CTCC. To enlarge a capsulorhexis, a cut is made tangential and not perpendicular to the original capsulorhexis and then shearing forces are used to enlarge the rhexis (Zanini & Buratto, 2003a). In some hypermature cataracts, anterior capsular wrinkling will occur as a result of LEC pseudometaplasia. This may result in difficulty performing a CTCC, and the surgeon must be prepared to use long, curved Vannas scissors or other scissors to complete portions of the capsulorhexis. The use of stains, such as indocyanine green and trypan blue, have been advocated to stain the anterior lens capsule prior to performing CTCC to aid in visualization, especially in mature cataracts (Zanini & Buratto, 2003a).

Use of radiofrequency diathermy has also been described for performing the capsulorhexis (Luck et al., 1994; Morgan et al., 1996; Speiss et al., 1996). While this technique allows precise control of the capsulorhexis, it also results in significant loss of strength and stretching capability of the capsule margin (Luck et al., 1994; Morgan et al., 1996).

Phacoemulsification
Hydrodissection

Hydrodissection is advocated by many ophthalmologists to loosen the lens and allow manipulation required for the technique of two-handed phacoemulsification. Hydrodissection is designed to loosen the lens from the lens capsule, allowing the lens to be freely rotated within the capsular bag to facilitate its fragmentation. This technique is not advised for one-handed phacoemulsification as the lens will be too unstable to fragment efficiently without a lens-capsule adhesion.

Hydrodissection is performed immediately after the capsulectomy, using a balanced salt solution (BSS) injected through a 25- to 27-gauge blunt cannula attached to a 3.0-cc syringe. It is important that the cannula be inserted under and
immediately adjacent to the anterior capsule. Complete hydrodissection usually requires multiple injections in different quadrants of the lens. A fluid wave should be visualized as the injection occurs (Buratto et al., 2003a).

**Fluidics**

Fluidics describes the principles that govern the inflow and outflow of fluid to and from the eye. The fluid dynamics of phacoemulsification take place in a closed system consisting of the irrigation bottle and line, anterior and posterior chambers, aspiration line, and pump (Zanini & Buratto, 2003b). Fluidics affects the efficiency of the phacoemulsification handpiece and I/A procedure. The most important factor influencing fluidics is the type of pump used to generate the flow of fluid. In addition, the height of the infusion bottle will also affect fluidics. Ideally, the IOP should remain relatively constant throughout the surgical procedure although in reality, this does not always occur. To ensure and maintain appropriate IOP, the bottle height should be between 65 and 75 cm and the corneal entry wound 2.8–3.2 mm to correspond with the phacoemulsification needle selected.

In contemporary phacoemulsification machines, two pump types are used: flow pumps and vacuum pumps. The peristaltic and scroll pumps are flow pumps while the diaphragm and Venturi are vacuum pumps (Zanini & Buratto, 2003b). Peristaltic pumps have been used the longest and consist of a roller that compresses a plastic tubing against the circumference of a rigid cylinder. The rotation speed of the rollers will increase or decrease the aspiration flow rate. In diaphragm pumps, fluid flow is generated by a flexible diaphragm, which is made to move backward and forward by an electric motor. In Venturi pumps, vacuum results from a pressure differential (i.e., the Venturi effect) created when compressed gas (i.e., nitrogen) travels through a cylinder (Gilger, 1997; Zanini & Buratto, 2003b). Pumps are designed to create a vacuum to hold the lens fragments while they are emulsified and to remove the lens fragments and cortical material. The features of fluidics that are most affected by pump design are flow rate, vacuum, and vacuum rise time. Flow rate is the volume of fluid made to flow through the tubing per unit of time (mL/min), whereas vacuum is the actual suction force (millimeter of mercury [mmHg]) created within the tubing during periods of fluid flow. Vacuum rise time is the time the pump takes to reach the preset vacuum pressure in millimeter of mercury. With peristaltic pumps, to obtain substantial vacuum, the needle must be occluded; as occlusion occurs, vacuum slowly rises within the tubing until the occlusion stops, at which point vacuum abruptly drops. Peristaltic pumps have a longer vacuum rise time, allowing the surgeon greater reaction time, which many surgeons feel is safer, especially when a surgeon is learning (Zanini & Buratto, 2003b). Vacuum pressures achieved with diaphragm and Venturi pumps differ from peristaltic pumps mainly because of the high flow rates they can achieve; therefore, vacuum can be produced without tip occlusion. Because flow rates are higher, rise time is shorter. Venturi and diaphragm pumps are considered to be more “responsive” than peristaltic pumps because depressing the foot pedal causes a much more rapid change in flow rate (Nasisse & Davidson, 1999). Surgeons commonly generalize about which pump type is best, but in reality, each has its own inherent advantages and disadvantages. In general, most surgeons tend to prefer the pump type they are accustomed to using. In fact, each type behaves sufficiently differently that it is impossible to appreciate a pump’s inherent advantages without having used it consistently for a considerable period of time. Most agree that Venturi pumps are superior for retinal detachment surgery, however, because the fluidics are ideally suited for controlled vitrectomy (Nasisse & Davidson, 1999).

“Venting” is the process by which vacuum in the line is terminated when the foot pedal is withdrawn from the active-aspiration position. Venting is a crucial component to fluidics; without it, lens material would occlude the needle even after the pedal is released. Therefore, without venting, it would not be possible to easily release and regrasp lens fragments for efficient fragmentation. Depending on the machine, venting is accomplished by allowing either air or fluid into the system. Both systems function effectively, but venting with air increases the rise time because of its high compliance (Nasisse & Davidson, 1999).

“Reflux” is a feature that allows the surgeon to reverse flow in the irrigation line. Reflux creates positive pressure in the aspiration line. The primary purpose of reflux is to allow removal of tissue fragments occluding the needle tip. It also serves to release materials such as the posterior capsule or iris that have unintentionally occluded the aspiration tip. Reflux is controlled by an accessory switch located at the top or side of the foot pedal. Reflux may be either passive (i.e., gravity flow) or active (e.g., reverse revolution of the peristaltic pump) (Nasisse & Davidson, 1999; Zanini & Buratto, 2003b).

The final variable effecting fluidics is the phenomenon of “surge,” which is the sudden and rapid influx of fluid into the needle tip when a lens fragment held by high vacuum is suddenly broken and pulled into the needle. This can result in an excessive drop in IOP and collapse of the anterior chamber. In addition, it results in materials, such as the posterior lens capsule, rushing toward the phacoemulsification tip. Surge effects are exaggerated in systems with high compliance. Failure to anticipate surge is an important cause of posterior capsule rupture, and for this reason, lens fragmentation should be performed away from the posterior capsule. Though 45° phacoemulsification needles have more cutting capability than 15° or 30° needles, they can be safely used near the posterior capsule provided the bevel remains pointed upward (so that any surge effects are directed toward the pupil rather than the posterior capsule) (Nasisse & Davidson, 1999; Zanini & Buratto, 2003b).

**Handpiece**

The phacoemulsification handpiece is designed to convert electrical energy into mechanical energy and in doing so,
emulsify the lens. Most modern phacoemulsification handpieces are piezoelectric and do this using ceramic discs that vibrate at a specific frequency. Piezoelectric handpieces are lightweight and can be autoclaved. The frequency of the handpiece varies from 27,000–60,000 cycles per second (kHz). Lower frequencies are considered less efficient while higher frequencies generate excess heat. The optimal frequency is between 35,000–45,000 cycles/second. This vibration causes the tip to oscillate and the distance it oscillates is termed the stroke length. Therefore, the principal variables that work in concert to produce efficient phacoemulsification are frequency and stroke length. Most phaco tips have a stroked length of 2–4 thousands of an inch. The longer the stroke length, the greater the heat and cavitation generated and the greater the physical impact on the lens. Phacoemulsification takes place at the tip of the handpiece and is the result of the jackhammer effect of the tip as well as cavitation and formation and implosion of microbubbles. Tremendous heat and pressures are generated at the needle tip. It has been suggested at the moment of microimplosion of cavitation bubbles at the phacoemulsification tip, the bubbles create a temperature of 13,000°F and a shock wave of 75,000 pounds per square inch (PSI) (Fishkind, 2000). This compares to a temperature of 50°C that is generated at the corneal incision by the phacoemulsification needle.

There are a variety of needle tips to choose from with angulations of 0, 15, 30, and 45°. In addition, Kelman needles (tip bent at a 30° angle) and flared tips are also available. While a 0° tip generates greater cavitation, a 45° tip has a larger surface area for its opening and cuts better by the jackhammer effect. This greater surface area allows for more holding power for lens fragments. At a vacuum of 100 mmHg, a 0° tip has a holding strength of 0.0019lb, while a 45° tip has a holding strength of 0.0027lb. The advantage of the flared tip is the large distal lumen that provides good holding power, but the smaller proximal bore minimizes surge. Tips are made of titanium and designed in a fashion to minimize bubble formation. With coaxial phacoemulsification, the tip is covered by a silicone sleeve that protects the corneal-scleral tissue from thermal damage. The sleeve achieves this by having the irrigation fluid flow between the sleeve and the titanium tip, thereby cooling the tip. A wound that is too tight and restricts fluid flow will result in thermal damage seen as edema, swelling, and necrosis of the cornea adjacent to the entry wound.

The surgeon can adjust and customize the phacoemulsification machine to suit their technique, preferences, and particular lens to be emulsified. In general, most surgeons set the power to a preset maximum of 80%. This means at position 3 with the pedal fully depressed, the machine will deliver 80% of maximum power. The delivery of power is generally set to linear, increasing as the foot pedal is depressed. Increased power translates into a longer stroke length. Linear power, with a preset of 80%, allows the surgeon complete control to use higher power for sculpting and lower power as the bowl thins and the posterior capsule nears. If the dog is old or the lens is very hard, the preset can be increased to 100%, providing more effective emulsification, but also creates more cavitation bubbles. The vacuum setting for standard phacoemulsification is set at 70 mmHg, but is increased to 200-250 mmHg in the phacoemulsification pulse or burst modes. When sculpting, high vacuum is not required since the lens is stable in the capsule. The higher vacuum in the pulse setting is used to grasp loose fragments prior to emulsification and to tear down and collapse a sculpted bowl. The pulse mode will allow the tip time to grasp fragments prior to emulsification, thereby avoiding the baseball bat and ball effect of hitting fragments away before the aspiration can securely grasp them. In the pulse mode, short, fixed interval bursts of vibration are interspersed with short periods of ultrasound interruption. In burst mode, the surgeon can command the duration of the interruption in a linear fashion using the foot pedal. Use of pulse or burst modes will also decrease the total energy used to emulsify the lens. The vacuum can be increased in the I/A mode to 300 mmHg to facilitate removal of residual cortical material.

Newer technology, such as seen with the Alcon Series 20000 Legacy™ (Alcon Laboratories, Ft. Worth, TX), has added a 2° rotary motion to the phacoemulsification tip in addition to the standard forward and backward stroke traditionally used. This is termed Neosonix (Davison, 2005) and utilizes a slightly larger handpiece. Emulsification and cavitation efficiency are increased without increased heat. The oscillatory motion can be used alone for soft lenses or in combination with standard ultrasound for harder lenses. Emerging technology that may have application to veterinary ophthalmology includes erbium:YAG laser phacoemulsification (Bowman & Allen, 2003; Packer et al., 2003), aqualase cataract surgery (Hughes et al., 2005; Lehmann, 2003; Mackool & Brint, 2005), or a pulsed Q-switched neodymium:YAG (Nd:YAG) laser for cataract removal (Huetz & Eckhardt, 2001; Kanellopoulos, 2001). The erbium:YAG laser operates at a wavelength of 2940 nm, has a penetration of less than 1 μm and is well absorbed by tissues with a high water content (Packer et al., 2003). The absorption of the laser energy creates a cavitation bubble that emulsifies the lens (Packer et al., 2003). Aqulaize uses small energetic pulses (25–100 pulses/s) of warmed fluid which strain and dissolve the lens (Lehmann, 2003). The Aqulaize handpiece is lighter and smaller than a traditional ultrasound handpiece. Since Aqulaize produces no friction, there is no thermal effect created (Lehmann, 2003). In addition, Aqulaize may be more effective at removing LECs and decreasing posterior capsule opacification (PCO) (Lehmann, 2003). The Nd:YAG has been shown to be effective in removing cataracts in humans up to a hardness of 3.9 according to the Lens Opacities Classification System, version III (LOCS III) (Chylack et al., 1993) using 83% less energy than ultrasonic phacoemulsification (Huetz & Eckhardt, 2001). The goals of these new technologies are to remove the lens through ever smaller incisions using decreased amounts of energy. To see the benefits of smaller incisions, IOL designs and construction materials will
need to advance to a level that allows implantation or injection through a 1- to 2-mm incision.

In addition to the phacoemulsification handpiece, there are a variety of I/A handpieces and vitrectomy handpieces available for most machines. The I/A handpiece, when used in a coaxial method, has a 0.3- to 0.7-mm port and a silicone or metal infusion sleeve. The I/A tip can be straight, curved, or angled to allow for removal of the subincisinal cortex. Alternatively, when a two-handed approach is used, it is possible to perform I/A as a bimanual procedure with irrigation in one incision and aspiration in the other. This allows the surgeon to switch the aspiration handpiece to either entry port and makes removal of the subincisinal cortex easier. Vitrectomy handpieces may be either oscillating or guillotine and are discussed in Chapter 25.

**Techniques**

The surgeon must remember, duration of surgery, volume of irrigating fluid, amount and time of ultrasound energy used, turbulence, and chamber bounce or collapse of the anterior chamber are all traumatic to the eye and associated with intraoperative and postoperative complications. The surgeon must be efficient, removing the lens, implanting the IOL, and exiting the eye as quickly andatraumatically as possible. Newer phacoemulsification machines, sharp, unused cutting tips, Kelman or flared cutting tips, two-handed techniques and foldable IOLs will all contribute to this goal. The surgeon must be familiar with his/her equipment and know how and when to adjust the settings to maximize efficiency. In addition, a well-equipped microsurgical pack and operating microscope are essential to success. The surgeon must use these tools, increasing magnification for the CTCC, phacoemulsification, and capsule polishing. Microscopes have variable magnification for a reason, and the surgeon must utilize this to improve outcome.

**Basic Technique**

Phacoemulsification is the accepted method of choice for cataract surgery in veterinary ophthalmology (Gaiddon et al., 1987, 1988; Gilger, 1997; Glover & Constantinescu, 1997; Ozgencil, 2005; Sigle & Nasisse, 2005; Williams et al., 1996). For most cataract surgeons, the basic technique is one-handed, coaxial endocapsular phacoemulsification with automated I/A followed by implantation of a PMMA or foldable acrylic IOL. Variations on this include a two-handed technique where the second instrument is a chopper or manipulator or true bimanual phacoemulsification where the second instrument is also an irrigator and the phacoemulsification handpiece has only ultrasound and aspiration (Buratto et al., 2003b).

**One-Handed Phacoemulsification**

Most cataract surgeons first learn the technique of endocapsular phacoemulsification using a one-handed, coaxial technique. This allows the nondominant hand to grasp and manipulate the globe with forceps and the surgeon to devote all their attention to a single instrument within the eye. This procedure, unlike the two-handed procedures, does not involve hydrodissection or nucleofracture (Buratto et al., 2003b). Following CTCC, the phaco handpiece is introduced into the anterior chamber. Since there is only one instrument in the eye, hydrodissection is not performed, relying instead on the lens-capsule adhesion to stabilize the lens as the phacoemulsification needle engages the cortex and nucleus. There are three phases to the one-handed technique, central sculpting, nuclear rotation, and removal of residual central and deep nucleus (Buratto et al., 2003b). The foot pedal is engaged to position 2 activating I/A. With the bevel up, the ventral edge of the phacoemulsification needle engages the near cortex and nucleus at the proximal edge of the CTCC. Foot pedal position 3 is then engaged activating the ultrasound. The phacoemulsification needle is advanced across the lens sculpting a groove in the lens (Fig. 22.10). The speed of advancement is dictated by the percent ultrasound energy used and the hardness of the lens. The tip should be advanced at a rate such that the lens is cut and not pushed ahead of the needle to avoid excessive zonular tension. The surgeon controls the ultrasound power using the foot pedal with soft lenses in young dogs or diabetics perhaps only requiring 30%-40% power, while hard lenses in old dogs may require the pedal to be completely depressed using the maximum power that was preselected. Avoid embedding the phacoemulsification needle in the lens nucleus, the lollipop effect. Use long and deliberate strokes, decreasing the power as the far quadrant is reached. Once the needle is advanced as far as the surgeon feels comfortable, foot pedal position 3 is disengaged, but I/A is maintained. Do not waste
ultrasound energy “phacoing” the aqueous humor. The needle is retracted to the starting point, and the area immediately adjacent to the initial groove is engaged and the procedure is repeated (Fig. 22.11). This procedure is repeated, sculpting an ever larger, wider, and deeper bowl. In diabetic cataracts, the lens may already be split along the suture lines allowing removal of the lens in quadrants. Otherwise, it is necessary to sculpt the lens, rotating it in the bag in 90° increments to allow sculpting 360°. The nucleus is rotated with the foot pedal in position 1 or, if in position 2, to avoid tip occlusion as the vacuum will interfere with rotation (Buratto et al., 2003b). A posterior shell is left to protect the posterior lens capsule. Once formed, the bowl must be collapsed or flipped over to continue fragmentation safely. If suture lines are evident, these can be used to crack the bowl into sections which will collapse it inward. Alternatively, the surgeon can switch to pulse or burst mode which should also have a high vacuum preset (200–250 mmHg). This high vacuum is used to engage the far aspect of the bowl, and gentle traction is used to pull the wall of the bowl axially, collapsing and fragmenting the lens as this occurs. If these techniques do not work, the phacoemulsification needle can be used to flip the lens over within the lens capsule (Arnold, 1991). Once the lens is sculpted into a thin bowl, the phacoemulsification needle is used to engage the proximal aspect of the deep bowl, and gentle pressure is applied slightly downward and away. This will cause the lens to tumble within the capsule, bringing the posterior aspect of the lens forward where it can be safely fragmented away from the posterior capsule. Alternatively, the high vacuum setting can be used to grasp the far lip if the bowl and the lens can be pulled toward the surgeon, tumbling the lens in its capsule. Care must be taken as the lens tumblers to avoid lacerating the posterior lens capsule with the edge of the lens or the phacoemulsification needle.

The classic “divide-and-conquer” technique was intended as a two-handed procedure, but it can be modified for a one-handed technique in which pie-shaped lens sections are cut, the nucleus is rotated, and the cuts are repeated to allow the lens to be removed sections at a time (Pacifico, 1992). A technique termed V-style phacoemulsification has recently been described and does not require hydrodissection (Klemen, 1993). In this technique, two deep grooves are made from the 12-o’clock position to the 4- and the 8-o’clock positions, respectively, to isolate a central fragment, which can then be safely removed without placing excessive tension on the zonules.

**Two-Handed Phacoemulsification**

The standard concept of two-handed phacoemulsification uses a second instrument to manipulate, stabilize, divide, chop, or rotate the lens. The second instrument is inserted through a 1-mm incision 70° away from the initial incision to the side of the surgeon’s nondominant hand (Fig. 22.12). This second incision can be made at the start of the surgery or, if needed, a one-handed procedure can be converted to a two-handed approach at anytime during the fragmentation process. The advantage of the two-handed technique is that it allows the surgeon more options to crack and divide the lens. This relies on the technique of nucleofracture which subdivides the nucleus into smaller fragments that can be emulsified close to the center of the pupil and away from the posterior capsule. Depending on the technique used, nucleofracture can be mixed or pure (Buratto et al., 2003b). Mixed nucleofracture cuts deep grooves and uses the phacoemulsification tip and manipulator to crack the lens and repeats the procedure in each quadrant. Pure nucleofracture uses a chopper in the technique of Nagahara to mechanically fracture the nucleus at the start of the procedure (Buratto et al., 2003b; Warren, 2004). This is especially advantageous in hard cataracts, older dogs,
and unstable lenses. In addition, the second instrument can be used to stabilize the lens while the phacoemulsification needle fragments and to feed fragments into the phacoemulsification needle decreasing total phacoemulsification time and ultrasound energy. The disadvantage of the two-handed technique is the learning curve as the surgeon must now watch and account for two instruments within the eye. When not in use, the second instrument must be retracted into the anterior chamber to avoid inadvertently damaging the posterior lens capsule. The instrument used for lens manipulation will depend on surgeon preference and technique preferred. These instruments may be straight or curved and the tip varied from a simple rotator to a specially designed chopping device. There are a variety of techniques or maneuvers discussed in the following sections. Most are applicable to the dog and a surgeon should be familiar with a variety of techniques allowing them to respond to each cataract in the most efficient manner.

One of the most recent innovations in small-incision ocular surgery is the development of bimanual microincisional phacoemulsification (also commonly known as bimanual microphacoemulsification or Cold Phaco). With this technique, surgery is performed through two 1.0- to 1.5-mm incisions, and the infusion is removed from the phacoemulsification handpiece and attached to the second instrument such as a chopper. One major benefit of performing bimanual microincisional phacoemulsification with the Sovereign Whitestar Technology™ (Advanced Medical Optics, Inc., Santa Ana, CA) is the enhanced intraoperative control and stability the technique provides when operating in an almost completely closed anterior chamber. The ability to remove the infusion line from the phacoemulsification relies on Whitestar’s micropulse technology with high-frequency pulsing and microburst modes, which cool the phaco tip and allows surgeons to perform bimanual microincisional phacoemulsification without an irrigation sleeve. The absence of the irrigation sleeve allows the incision size to be decreased. The addition of the infusion to the second instrument allows the infusion to be directed where the surgeon chooses and improves movement of lens fragments to the aspiration port. Although micropulse phacoemulsification is also termed cold phacoemulsification, it is not cold. The decreased energy expenditure of the Whitestar technology, which results from rapid on/off cycles, further reduces the dispersive forces that drive nuclear fragments away from the phaco tip. Although ultrasound always pushes nuclear fragments away in other technologies, the Whitestar Technology’s ultrasound pulses are so short that the aspiration forces predominate (Donnenfeld & Olson, 2004; Donnenfeld et al., 2003; Soscia et al., 2002). To allow use of microincisional techniques, new instruments have been designed to allow work through a 1-mm incision (Microsurgical Technology, Redmond, WA).

**Divide and Conquer**

The “divide-and-conquer” method was initially popularized by Gimbel (1991). Initially, the lens is sculpted to form either a deep central crater (hard nuclei) or a deep trough (moderately hard nuclei). The trough should be cut to 70%-90% of the depth of the nucleus and the width should be twice as wide as the phacoemulsification tip (Buratto et al., 2003b). The nuclear rim is then fractured by inserting the phacoemulsification tip and lens manipulator deep into the groove. The instrument in the right hand engages the left side of the groove while the left instrument inserts against the right side. Gentle pressure is exerted to crack the lens moving the two instruments apart to separate the groove. If the instruments are not placed deep in the groove, this will result in a hinge rather than a crack. The nucleus is then rotated 90°, and a second groove is cut perpendicular to the first. The nucleus is again cracked to obtain a wedge of nuclear material that can be brought to the central pupil and emulsified. This procedure is repeated, rotating the lens, cracking it into four or more quadrants, and emulsifying each sector.

**Chip and Flip**

The original chip-and-flip method was described by Fine in 1991 (Fine, 1991). In this technique, both hydrodissection and hydrodelineation are performed so that the hard central nucleus and the epinucleus can be removed separately, the rationale being that the softer epinucleus will protect the posterior capsule during fragmentation of the hard nucleus. The procedure is initiated by sculpting a central bowl. The rim of the inner nuclear bowl is then removed at the 5- to 6-o’clock position. The bowl is rotated, and the procedure is repeated until the entire nuclear rim is removed. The second handpiece is then used to lift the inner nucleus to the superficial capsular bag, where it is removed. The soft outer nucleus is now removed by pulling the bowl toward the 12-o’clock position with the nucleus rotator, which allows the 5- to 6-o’clock rim to be safely fragmented. The 5- to 6-o’clock rim is then purchased with the phacoemulsification needle and pulled, whereas the nucleus rotator is used to depress the proximal extremity so that the outer nuclear bowl is flipped over, thereby allowing it to be easily fragmented. In a modification of this technique, which is called the "crack-and-flip" method, sectorial nuclear division is added to facilitate removal of the central hard nucleus (Buratto et al., 2003b; Fine et al., 1993; Nasisse & Davidson, 1999).

Hard canine lenses can be efficiently removed with another modification of the flip-and-chip technique that does not require hydrodissection and hydrodelineation. First, a large bowl is sculpted in the central nucleus and epinucleus, and a central groove is made. The nucleus is then fractured with the phacoemulsification needle and the nucleus rotator. The nuclear bowl is rotated and fractured again to isolate a pie-shaped fragment in the 5- to 6-o’clock position. After the nuclear rim is purchased with the phacoemulsification needle, the nucleus rotator is used to depress the apex of the segment so that it flips over and into the superficial capsular bag, where it can be easily fragmented. This is repeated as necessary with the remaining nucleus (Nasisse & Davidson, 1999).
Phaco Chop

The technique of phaco chop was first presented in 1993 by Dr. Kunihiro Nagahara. It has undergone several variations since then and has recently been modified for the dog (Warren, 2004). Instead of the typical nucleus rotator, the second instrument for this procedure is a chopper with a 90° angles 1- to 2-mm tip for humans (Buratto et al., 2003b) that is modified to 4 mm for use in the dog (Warren, 2004). The length of the chopper tip should be approximately 50% of the axial lens thickness (Warren, 2004). After the CTCC and complete hydrodissection, the phacoemulsification needle is introduced and the superior portion of the nucleus, immediately adjacent to the rhexis is engaged. A short burst of ultrasound with high vacuum is used to embed the phacoemulsification needle in the lens to hold the lens steady. This maneuver is easier if a tip of 30° or less is used as these are easier to occlude. Some surgeons will also choose to perform this maneuver with the bevel down to improve tip occlusion (Buratto et al., 2003b). The chopper is introduced under the anterior lens capsule and extended equatorially. The chopper is rotated 90° to engage the lens and gently pulled toward the phacoemulsification needle. When the chopper nears the phaco needle, it is moved slightly left while the phacoemulsification tip is moved right, splitting the nucleus into two parts (Buratto et al., 2003b; Warren, 2004). The nucleus is then rotated and a second chop performed, creating a pie-shaped wedge. Some surgeons will remove this wedge and continue to chop and fragment as they progress while others will rotate and chop the entire lens into small sections before removing any portion. If the first option is chosen, the vacuum should be high (150-250 mmHg) to engage the wedge and pull it toward the axial pupil for fragmentation. The advantage of the second technique is that the lens sections remain in place as the lens is rotated and chopped, thereby maintaining the capsular bag and protecting the posterior lens capsule.

A variation of this technique is Koch’s stop and chop which begins with two to three passes of the phacoemulsification tip to remove the axial superficial cortex and epinucleus and create a groove that will be fractured using the divide-and-conquer technique (Buratto et al., 2003b; Koch & Katzen, 1994). This is done to provide space into which the various lens fragments can be manipulated for emulsification since the Nagahara technique leaves fragments locked together in a puzzle fashion. The advantage of phaco chop as compared to a divided and conquer technique is a reduction in ultrasound emission and shortened surgical times (Buratto et al., 2003b).

Difficulties with the technique of phaco chop are generally related to a failure to perform a complete hydrodissection or a failure to embed the phacoemulsification needle or the chopper deep enough into the lens. In addition, the surgeon should become comfortable with entry-level two-handed procedures before performing phaco chop as this technique requires significant dexterity using the nondominant hand (Buratto et al., 2003b).

Irrigation/Aspiration

Following removal of the nucleus, all the residual cortical material must be aspirated. This is one of the most critical aspects of the surgery in ensuring a successful outcome. Residual cortical material may be free or more likely will be adhered to the equatorial lens capsule. Complete cortical removal lessens postoperative inflammation, after-cataract formation, IOL decentration, and capsular sac distortion and folding (Apple et al., 1992a, 2000b; Buratto et al., 2003b). The technique of cortical removal is best performed using an automated I/A handpiece. The I/A handpiece may be straight, bent, or curved to allow for removal of the subincisional cortex. The tip will be rounded and the aspiration port placed on the side rather than the end of the tip. The I/A handpiece, when used in a coaxial method, has a 0.3- to 0.7-mm port and a silicone or metal infusion sleeve. A larger aperture aspiration port (0.5-0.7 mm) works best for the canine cortex which tends to be thick, sticky, and more difficult to aspirate as compared to human cortex. A silicone sleeve will have less incisional leakage than a metal sleeve, but can be inadvertently occluded if the tip is manipulated far laterally. The infusion ports should be directed perpendicular to the aspiration port. The pumps discussed in the fluidics section are also used for I/A, and the same principles apply. Peristaltic pumps are slower to build vacuum and less responsive as compared to Venturi and diaphragm pumps, but are also more forgiving with respect to posterior capsular engagement and rupture. Again, vacuum will be linear with tip occlusion resulting in an increase in vacuum according to the preset and foot pedal position. The foot pedal in I/A mode has two positions as compared to the three positions in phacoemulsification mode.

The I/A tip is inserted through the incision and irrigation initiated to deepen the chamber and capsular bag. It is best to remove the subincisional cortex first as this is the most difficult to remove and easiest when adjacent cortex remains to help grasp and tease out the subincisional cortex. A bent or curved I/A tip, 45° or 90°, will facilitate access to this area of the capsular bag. The I/A port is placed adjacent to the cortex and away from the posterior capsule. Position 2 on the foot pedal is engaged with enough vacuum to grasp, but not aspirate the cortex. The tip is moved slowly toward the mid-pupil peeling the cortex off the equatorial lens capsule. The tip can also be rotated in an ice-cream scoop motion to aid in removal (Nasise & Davidson, 1999). The cortex is best removed in chunks to avoid leaving behind small fragments that are difficult to reach. In general, vacuum of 100-150 mmHg is used to grasp and peel the cortex with a preset maximum of 300-400 mmHg used to aspirate the cortex. Once the subincisional cortex is aspirated, the tip is moved around the circumference of the capsular bag to remove all cortical material. Care is taken to avoid inadvertent aspiration of the posterior capsule. If this occurs, the posterior capsule will wrinkle with numerous folds directed toward the I/A tip. If this occurs, tip movement should stop,
the foot pedal moved to the neutral position, and aspiration reflux used to disengage the capsule.

The I/A handpiece is also used for capsule polishing. Capsule polishing is performed at low vacuum (20–40 mmHg) that can be achieved by a low vacuum preset or gentle pressure in foot pedal position 2. Both the anterior and posterior capsules are polished to remove LEC, residual cortex and areas of capsular fibrosis. The removal is accomplished by a combination of vacuum and mechanical abrasion. The I/A port is directed toward the capsule and the capsule engaged using the low vacuum (Fig. 22.13). The I/A tip is moved gently back and forth with this procedure repeated in all sectors of both the anterior and posterior capsule. This is performed in an effort to decrease postoperative PCO. If a capsular tear is present and the surgeon still wishes to polish the capsule, all movements of the I/A tip must be directed toward the capsular tear once the capsule is engaged. There is some debate regarding the long-term benefit of the capsule vacuuming with respect to LECs (Davidson et al., 2000). While polishing the posterior capsule had no effect on the prevalence of PCO in one study (Khalifa, 1992), I/A of the anterior capsular epithelium lessened the prevalence in another study (Nishi et al., 1991).

**Intraocular Lens**

**IOL Design/Material**

The first modern IOL was implanted in humans by Dr. Harold Ridley in 1949. Since then, much has changed with respect to IOL design, construction material, and location of implantation. The most common biomaterials used in IOL construction are PMMA, acrylic (hydrophilic and hydrophobic), silicone, and hydrogels (Werner et al., 2003).

Several IOL designs constructed of a variety of biocompatible materials are now available for veterinary cataract surgeons. The current standard canine IOL is implanted in the capsular bag and made of either PMMA or acrylic materials. Implantation of silicone IOLs has also been described in the dog (Gaidon et al., 1997; Neumann, 1991). Dogs left aphakic after cataract surgery have been shown to be 14 D hyperopic (Davidson et al., 1993). The average canine lens diameter is approximately 12 mm, and a 15- to 17-mm haptic length is most commonly used for single piece PMMA canine IOLs and 12–14 mm for acrylic IOLs, with the actual length depending on individual surgeon preference, size of the eye implanted, and degree of memory of the haptics. Most canine IOL optics are 7 mm in diameter with a power of 41 D. With PMMA IOLs, the biconvex optic and forward haptic angulation designs encourage optic–posterior capsule contact and help to reduce the severity of LEC migration and posterior capsular opacification (Fig. 22.14) (Hansen et al., 1988). Acrylic IOLs are designed with single or multiple sharp or squared edges to the optic to inhibit LEC migration and PCO in the visual axis (Fig. 22.15) (Ursell et al., 1993; Werner et al., 2003). Dialing holes in the optic or haptics, which are designed to facilitate insertion and manipulation of the lens, or in certain instances to attach sutures for fixation, are available in some designs. In human ophthalmology, IOL design and manufacture is regulated by the FDA, and veterinary ophthalmologists should hold manufacturers of canine IOLs to the same standards to avoid problems associated with poor manufacturing, inadequate surface polishing, defects at the haptic–optic junction, improper sterilization, or presence of residual polishing compounds (Olivero et al., 1993). In addition, surgeons should record IOL manufacturer, lot number, and date of implantation to allow tracking if problems arise.

**Basic IOL Implantation**

Following I/A of residual cortical material and lens capsule polishing, the capsular bag and anterior chamber are distended...
using viscoelastic to provide space for implantation of the IOL. If a PMMA IOL is to be implanted, the 3.2-mm corneal incision will need to be enlarged to approximately 8 mm to facilitate implantation of a 7-mm optic. This is accomplished using corneal section scissors. The PMMA IOL is grasped using Shepherd IOL forceps or other similar type forceps. The haptics are oriented at 6 and 12 o'clock sweeping counterclockwise with the IOL forceps passing over the 12 o'clock haptic to grasp the optic. The ventral haptic and optic are advanced through the corneal incision and the anterior capsulorhexis into the lens capsular bag. The surgeon must visualize the ventral haptic and flatten the angle of insertion as it enters the capsular bag to avoid traumatizing the posterior lens capsule. The optic is advanced to the midpoint of the capsulorhexis. The implantation can be completed using an IOL manipulator to dial the lens in a clockwise direction which will bring the dorsal haptic into the lens capsular bag. The IOL is centered in the visual axis and the haptics should be placed at 3 and 9 o'clock. Alternately, tying forceps can be used to fold the dorsal haptic toward the optic, tucking it into the bag.

If a foldable acrylic IOL is to be implanted, this can be done using an injection cartridge or with IOL folding forceps (Fig. 22.16). A foldable IOL can be implanted through a smaller incision of approximately 3.5–4 mm, smaller if the injection cartridge is used. The IOL is grasped using tying forceps held in the nondominant hand. The IOL folding forceps are held in the dominant hand and used to grasp and fold the IOL for implantation. The IOL is turned 90° from its final orientation and inserted through the corneal wound. The forceps are then rotated back upright, the ventral haptic placed in the lens capsule with the optic oriented axially over the rhexis. The forceps are opened slowly and moved slightly toward the posterior lens capsule allowing the IOL to unfold and be directed posteriorly. This is done slowly to avoid a spring-like action as the IOL unfolds. The superior haptic can be positioned in the capsular bag using a lens manipulator. If an injection cartridge is used, the IOL is loaded according the manufacturer’s directions. A lower viscosity viscoelastic is used to fill the cartridge, the cartridge with the IOL are then placed into the injector. The tip of the cartridge is passed through the corneal incision, into the lens bag just past the anterior capsulorhexis and directed toward the ventral capsular equator. The IOL is injected in a slow, steady fashion with the surgeon visualizing the ventral haptic as it enters the bag and withdrawing the injector slightly as the optic emerges so as to avoid pressure on the equatorial capsule. Insertion is completed with a lens manipulator. The use of foldable IOLs has the advantage of a smaller incision, ability to implant an IOL in instances of capsular tears, expanding vitreous, and some instances of zonular instability. In addition, use of sharp edge acrylic IOL’s may result in decreased PCO.

While the techniques for lens implantation discussed above are appropriate for stable lens capsules implantation of an IOL
in instances of lens capsular instability, subluxation and complete luxation require a modification of the basic technique. In such cases, a lens may be sutured into the ciliary sulcus using an ab interno or modified ab externo procedure (Nasisse & Glover, 1997; Nasisse et al., 1995). This procedure is discussed in detail in the lens luxation section of this chapter.

Wound Closure

The goals of wound closure are to achieve a water-tight closure with minimal astigmatism and suture reaction using the smallest suture that is strong enough to ensure a successful closure. Most surgeons use 8-0 to 10-0 suture, with 9-0 most commonly used. Nonabsorbable polypropylene type suture or polygalactin 910 are most commonly chosen. Polygalactin 910 can be used as a monofilament at a 9-0 size and results in minimal tissue reaction, is easy to handle, and is of sufficient strength. A simple or double continuous pattern are most common, with the latter preferred for its increased wound strength and decreased astigmatism. If a two-handed approach was used, a single suture may be required if the tunnel entry is not self-sealing.

Outcome

With the use of phacoemulsification, smaller incisions, automated I/A, viscoelastic agents, improved anti-inflammatory agents, and IOL implants, both short-term and long-term outcomes for canine cataract surgery have significantly improved over recent decades (Davidson et al., 1991b; Klein et al., 2011; Magrane, 1961, 1969; Miller et al., 1987; Sigle & Nasisse, 2005). In addition, how we as surgeons measure success has changed with the expectation of emmetropia and a clear visual axis as our goals, compared to the intermittent menace response of past decades. While the outcomes for canine cataract surgery have improved (85%–95% or greater), depending on the stage of the cataract, diligent long-term monitoring of postoperative patients is essential (Davidson et al., 1991b; Klein et al., 2011; Miller et al., 1987; Nasisse & Davidson, 1999; Sigle & Nasisse, 2005). Retinal detachment, secondary glaucoma, PCO, uveitis, and other complications may occur months to years following cataract surgery (Sigle & Nasisse, 2005). There has been a report that Boston Terriers have an increased risk for blindness following phacoemulsification (Klein et al., 2011). The postoperative outcome appears to be similar in unilateral versus bilateral lensectomy by extracapsular cataract extraction (ECCE) in one study (Davidson et al., 1990) and in diabetic compared with nondiabetic dogs in another study (Bagley & Lavach, 1994).

Intraoperative Complications

Intraoperative complications are, of course, best avoided, but should they occur, the surgeon has a variety of tools and techniques at his/her disposal that will aid in the management of intraoperative complications (Packard & Buratto, 2003). Some intraoperative complications can be anticipated based on the preoperative examination. These would include anterior capsular fibrosis, vitreous in the anterior chamber, lens instability, synechia, PHPV/PHTVL, or other such preexisting conditions.

Certain intraoperative anesthetic complications may be increased in diabetic dogs undergoing cataract surgery. It has been shown that diabetic dogs were more likely to develop moderate and severe intraoperative hypotension as compared with nondiabetic dogs undergoing phacoemulsification (Oliver et al., 2010). In addition, 44% of diabetic dogs had at least one episode of severe hyperglycemia while anesthetized. It has been suggested that the increased incidence and severity of hypotension in diabetic dogs may be explained by hypovolemia secondary to hyperglycemia and resultant osmotic diuresis (Oliver et al., 2010).

Anterior Capsule Fibrosis

Anterior capsule fibrosis is most common in chronic and hypermature cataracts (Bernays & Peiffer, 2000; Colitz et al., 2000). The LECs undergo epithelial-mesenchymal transformation and proliferate creating a fibrous membrane underneath the anterior lens capsule (Chandler et al., 2005). This can result in capsular wrinkling and make completion of a CTCC difficult. It is always preferable to complete the CTCC prior to phacoemulsification if possible, and the use of long, curved Vannas capsulotomy scissors will facilitate the capsulotomy (Fig. 22.17A). A two-handed capsulorhexis using the Duet® microsurgical forceps and scissors (Microsurgical Technologies, Redmond, WA) will facilitate a capsulorhexis in cases of severe fibrosis or with lens instability (Fig. 22.17B). Alternatively, the capsulorhexis can be completed after phacoemulsification is performed through a small capsulotomy.

Intraoperative Miosis

Intraoperative miosis is a rare occurrence with current methods of presurgical patient preparation and cataract extraction. Clinically, it appears that less presurgical medication, especially mydriatics, is associated with a decrease in the prevalence of intraoperative miosis (Smith et al., 1984). In addition, with the use of 0.2 mL of intraoperative, intracameral 1:10,000 epinephrine, intracameral 1–2% lidocaine, viscoelastics, and phacoemulsification, many eyes with miosis can be persuaded to dilate once the anterior chamber is entered. In a retrospective study in humans, a small pupil was encountered in 1.6% of cataract operations and continuous tear anterior capsulorhexis, and in-the-bag phacoemulsification was the method of cataract extraction in these eyes (Gimbel, 1992).

Epinephrine is used by some surgeons to achieve and maintain mydriasis during surgery. It can be instilled directly into the anterior chamber at the onset of surgery, or if phacoemulsification is used, epinephrine can be placed in the irrigating solution in a lower concentration for continuous infusion. The 1:1000 intracameral epinephrine is used and is diluted to 1:10,000 with BSS for direct infusion, or 0.4 mL is placed in
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Intraoperative miotics can be administered, although they are of limited benefit, in the authors’ experience. The use of intraoperative miotics such as acetylcholine (Miochol®, Bausch & Lomb, Rochester, NY) or carbachol (Miostat®, Alcon Laborastories, Ft. Worth, TX) is advocated in human cataract surgery to protect the vitreous face, prevent iris incarceration into the limbal incision, to demonstrate proper position of an IOL implant, and to prevent POH (Solomon et al., 1998; Wedrich & Menapace, 1992). Both miotics are similar in their onset of action, but carbachol has a longer duration of action. In veterinary ophthalmology, carbachol has been advocated to decrease the incidence of immediate postoperative hypertension (Stuhr et al., 1998). Use of intraoperative miotics may be associated with increased postoperative flare, fibrin, miosis, and pain. The use of these agents may require postoperative mydriatics in the first 24 hours after surgery.

Intraoperative Hemorrhage

Intraoperative use of 1:10,000 epinephrine, gentle tissue handling, and use of viscoelastic agents has decreased the likelihood of hemorrhage. If hemorrhage occurs, place a small amount of epinephrine at the site of the hemorrhage and tamponade it with a cohesive viscoelastic. In addition, the I/A used with the technique of phacoemulsification will clear hemorrhage as it forms, making it less significant to intraoperative visibility. Postoperatively, use of tissue plasminogen activator (tPA) can be considered. The tPA can be placed intracameral if the surgeon is concerned about hemorrhage and/or fibrin in the anterior chamber (Gerding et al., 1992). The surgeon must consider the possibility of a re-bleed associated with the use of tPA and should consider a delay of 3–7 days prior to its administration.

Iris Prolapse

Intraoperative iris prolapse occurs in association with vitreous expansion, incorrect placement of the limbal incision, presurgical iritis, intraoperative iris trauma, excessive irrigation fluid velocity, and overfilling with viscoelastic agents placed posterior to the iris. Placement of the incision slightly more anteriorly, decreasing infusion velocity, use of correctly placed viscoelastic agents, and gentle tissue handling will minimize the occurrence of iris prolapse. If prolapse occurs, rapid wound closure and reforming of the anterior chamber will deal with this problem in most instances. Also, once the incision is closed, a 30-gauge cannula can be inserted through the incision and the iris gently irrigated and mechanically displaced from the corneal wound. Viscoelastic agents can be used for this purpose to reposition the iris. If all else fails, intraoperative miotics can be administered, although they are of limited benefit, in the authors’ experience.

Figure 22.17. A. Vannas scissors are used to perform an anterior capsulorhexis. B. Capsulorrhesis is performed using the Duet® scissors and forceps to incise and remove a capsule with significant fibrosis.

500 mL of irrigating fluid for continuous infusion (Packard & Buratto, 2003). Avoid using commercial 1:10,000 epinephrine for direct infusion as the concentration of the buffer is toxic to the corneal endothelium. In addition, sulfite-free epinephrine is available.

Use of epinephrine varies among intraocular surgeons from those who do not use it, those who use it for eyes with intraoperative miosis, to those who use it as the only means of achieving mydriasis, replacing parasympatholytic agents. Intracameral epinephrine helps to achieve maximal mydriasis, and the clinical impression is that there are less postoperative inflammatory products in the anterior chamber, as the result of vasoconstriction.

Intracameral 1% or 2% lidocaine has also been shown to result in significant mydriasis maintained for 74–142 minutes without significant adverse ocular or systemic side effects. The time to onset of mydriasis is related to both the concentration and volume of lidocaine administered (Park et al., 2009).

In addition to pharmacological mydriasis, mechanical mydriasis is achieved by use of viscoelastic agents and irrigation maintenance of the anterior chamber.

Lens Capsule: CTCC Too Small

Some surgeons prefer to make the initial CTCC small to prevent inadvertent displacement of the lens nucleus into
the anterior chamber during phacoemulsification. In some instances, the CTCC may be too small unintentionally. This is easily fixed and enlarged to the desired size before or following IOL implantation. Using Vannas capsulotomy scissors, a cut is made tangential to the edge of the rhexis to the diameter of the desired rhexis. A tangential cut is critical, and the cut should not be made parallel to the rhexis or the tear will extend radially as it is put under tension. Using Utrata capsule forceps, the edge of the anterior capsule is grasped at the cut margin and the tear extended circumferentially using shearing forces, grasping, and regrasping as it progresses (Packard & Buratto, 2003).

**Lens Capsule: Anterior Radial Tears**

Radial anterior capsular tears are best prevented, rather than managed. The CTCC is perhaps one of the most critical aspects of cataract surgery, especially if an IOL insertion is planned. Radial tears are associated with displacement of the IOL haptic out of the capsular bag and IOL decentration (Fig. 22.18) (Apple et al., 1992a; Assia et al., 1991a). The most common reason for IOL decentration is the presence of a radial tear (Assia et al., 1993; Hara & Hara, 1990). Factors that make capsulorhexis difficult include a lack of retroillumination associated with a mature cataract, inadequate magnification, capsular fibrosis/wrinkling, and failure to use a viscoelastic.

Capsulorhexis is best performed prior to phacoemulsification as this will decrease the chance of creating a radial tear (Arshinoff, 1992; Assia et al., 1991a, 1991b; Gimbel & Neuhman, 1990). In some instances, this is not possible, and partial or complete phacoemulsification must be performed prior to completion of the capsulorhexis. In such eyes, lateral movement of the phacoemulsification tip must be minimized to prevent radial tears. The surgeon must be able to tear the capsule in both a clockwise and counterclockwise direction. As the tear progresses, both ends of the tear are visualized to avoid inward spiraling and the resulting Q-shaped tear, as opposed to the desired O shape.

It has been demonstrated that the CTCC is the least likely to develop radial tears as compared with the can opener, linear capsulotomy, and capsulopuncture techniques (Assia et al., 1991a). Of those eyes in which the can opener technique was used, the incidence of radial tears ranged from 86% (Wasserman et al., 1991) to 100% (Assia et al., 1991a) in the operated eyes, many having more than a single radial tear. In addition, it has been demonstrated that the CTCC will stretch 62% over its original diameter to facilitate implantation of an IOL before a radial tear will occur (Assia et al., 1991b).

If a radial tear is discovered, it is best to attempt to bring this tear back into the central circular capsulorhexis, completing the circle and preventing extension of the tear equatorially and potentially involvement of the posterior lens capsule. This should be performed as soon as the tear is observed to avoid it extending radially. This is especially true if hydrodissection is to be performed as this will expand the capsule and extend the tear (Packard & Buratto, 2003).

If a radial tear is created, it is often still possible to successfully insert an IOL. In such eyes, the haptics should be directed as far from the radial tear as possible. An alternate approach is to implant an IOL with increased haptic-capsule contact resulting in increased IOL stability and a decreased likelihood of haptic displacement from the capsule into the sulcus. Alternately, an acrylic IOL that can be placed through a 3.2- to 3.6-mm incision will improve lens placement, and these lenses appear less likely to migrate and displace out a radial tear.

**Lens Capsule: Posterior Tears**

Even more than anterior radial tears, posterior capsular tears are best avoided rather than managed. If they occur, it is essential to attempt to complete phacoemulsification away from the capsular tear to avoid enlarging it. A cohesive viscoelastic should be placed over the tear to tamponade the vitreous (Packard & Buratto, 2003). Do not overinfl ate with viscoelastic as this will serve to expand the tear (Packard & Buratto, 2003). The irrigation rate should be decreased (by lowering the bottle) and the irrigating fluid directed away from the posterior capsular tear. The surgeon may wish to decrease the ultrasound power and increase vacuum (Packard & Buratto, 2003). In many instances, it may be best to convert to a bimanual technique placing a separate infusion port into the anterior chamber, directing the infusion away from the capsular tear/vitreous face thereby minimizing further progression of the tear. Finally, a small linear or triangular posterior capsular tear is best converted into a circular tear by means of a planned posterior circular capsulorhexis (Castaneda et al., 1992) using Utrata capsule forceps. It has been demonstrated that this will minimize progression of the capsular tear and facilitate IOL insertion. This is best performed under a cohesive viscoelastic and 12–20× magnification.

The most common time for posterior capsular tears to occur has been debated but includes during nucleus extraction (41%) (Mulhern et al., 1996; Osher & Cionni, 1990), during
posterior capsule polishing (28%) (Osher & Cionni, 1990), and during I/A (Gimbel & Neuhman, 1990). Posterior capsular rupture is also possible during hydrodissection if excessive pressure is used or by continued extension of an anterior capsular radial tear (Packard & Buratto, 2003). Deep sculpting and sharp nucleus edges are implicated in the generation of posterior capsule tears during nucleus fragmentation. In humans, the incidence of posterior capsular tears is approximately 5% for the inexperienced phacoemulsification surgeon, but decreases to ≤1% with experience (Mulhern et al., 1996; Osher & Cionni, 1990). In veterinary cataract surgery, the incidence of planned or accidental posterior capsular tears has been described to occur in 14%–16% of cases (Johnstone & Ward, 2005; Nasisse et al., 1991). (In humans with posterior capsular tears, anterior vitrectomy was required in 44% of the cases; Mulhern et al., 1996.) If an anterior vitrectomy is indicated, it is best performed using the techniques of dry vitrectomy, relying on viscoelastic agents to maintain the chamber, or using a low flow bimanual technique with the irrigating fluid directed into the anterior chamber. It is essential to minimize vitreous hydration and subsequent expansion. If the capsular tear occurs during capsule polishing, continued polishing may be ill advised. Remember, “the enemy of good is better” and a good surgeon will know when to stop. If the surgeon chooses to polish further, direct all movements toward the tear to avoid enlarging it.

The question of IOL placement must be addressed once all the lens material has been removed. If a small posterior capsule tear is present, but the remaining capsular bag is intact and stable, an endocapsular IOL is preferred. An acrylic IOL that can be placed through a 3.2- to 3.6-mm incision will improve lens placement and minimize vitreous presentation. The capsular bag should be distented to move the posterior capsule back and provide space for IOL insertion without further capsule damage. However, if the capsule disruption is severe, then a posterior chamber IOL can be sutured in the ciliary sulcus using an ab interno or modified ab externo approach (Nasisse & Davidson, 1999; Nasisse & Glover, 1997). One study reported IOL placement occurred in 76% of eyes without a posterior capsular tear, but in only 31% of eyes in which a posterior capsular tear occurred (Johnstone & Ward, 2005). When the posterior capsular tear was accidental, IOL placement occurred in only 15% of eyes (Johnstone & Ward, 2005). Associated with posterior capsular tears is vitreous prolapse, postoperative elevation in IOP, postoperative dyscoria, retained lens material in the vitreous, and retinal tears and detachments (Gimbel et al., 2001). When properly managed, a posterior capsular tear is still compatible with an excellent postoperative result.

**Lens Capsule: Polishing, Opacities**

Capsule polishing is an essential, but often ignored, procedure due to the concern for iatrogenic capsular tears. Capsule polishing should be performed on both the anterior and posterior lens capsule. It is easiest to use a 0.3-mm or 0.5-mm I/A cannula at a low vacuum setting for the posterior capsule (40–50 mmHg), with higher vacuum settings possible for the anterior capsule (50–100 mmHg). A spiration-reversal foot control is an essential feature of your equipment when performing this procedure. Capsule polishing should be performed using 12–14× magnification. The posterior capsule will be observed to wrinkle as it is aspirated into the I/A port.

Opacities of the anterior and posterior capsule are more common in eyes with hypermature cataracts, with or without LIU. If possible, these opacities should be removed by thorough capsule vacuuming and polishing. If they cannot be removed, but are not in the visual axis, or are insignificant in size, then they may be left. Larger opacities, especially those in the visual axis may require removal by a planned posterior capsule capsulorhexis using a cohesive viscoelastic, Vannas scissors, and Utrata forceps, or by use of a guillotine vitrector (Castaneda et al., 1992). Posterior capsulorhexis can be performed prior to or after IOL insertion using viscoelastic material to prevent vitreous presentation through the capsular opening. A planned CTCPC is also indicated for management of a persistent hyaloid associated with a cataract (Fig. 22.19) (Gemensky-Metzler & Wilkie, 2004). To perform a continuous tear curvilinear posterior capsulorhexis (CTCPC), deepen the anterior chamber and lens capsule using a cohesive viscoelastic. Increase the magnification on the operating microscope to 12–14×. Incise the axial posterior lens capsule using Vannas scissors, elevate the capsule from the vitreous face using viscoelastic. If a persistent hyaloid artery is present, evaluate the patency of the hyaloid. Most are nonpatent and can be cut without risk of hemorrhage. Using capsule scissors and/or Utrata capsule forceps, remove 2–4 mm of the axial posterior lens capsule to complete the CTCPC (Fig. 22.20). Use of 10–14 days of postoperative systemic antibiotics is indicated if the posterior lens capsule is opened and the vitreous face exposed (Beyer et al., 1985).

![Figure 22.19. Vannas scissors are used to perform a CTCPC in a dog with a PHPV/PHTVL.](image-url)
Cavitation/Bubbles

Cavitation is created by the process of phacoemulsification. This process results in the generation of bubbles which decrease visibility and interfere with probe-lens contact and reduce cutting power. In addition, cavitation bubbles store energy which when the bubble implodes is released as high pressure, high temperature “shock waves” and induce free radicals all of which can result in cell death (Svensson & Mellerio, 1994).

The threshold for bubble formation varies with the handpiece, and as the probe surface area increases, the power threshold for cavitation decreases (Svensson & Mellerio, 1994). Cavitation bubbles are formed at the probe tip (usually on the negative stoke) and at the shoulder of the probe where it joins the handpiece. These latter bubbles are brought into the eye by the infusion along the silicone sleeve. The threshold for bubbles at this location is considerably less than at the probe tip (Svensson & Mellerio, 1994). The streamlining of this shoulder in newer needles reduces the effect of cavitation.

Expanding Vitreous Syndrome/Vitreous Presentation

Expanding vitreous syndrome may occur in eyes with an intact or disrupted posterior lens capsule. It is seen most often in brachycephalic dogs. Clinically, the intact posterior lens capsule will be seen to be displaced anteriorly and in some instances will protrude through the anterior capsule opening and into the anterior chamber. If the posterior capsule has been disrupted, the vitreous will expand through the posterior capsule tear, enlarging the tear and entwining itself with the lens material and phacoemulsification needle aspiration port. Expanding vitreous syndrome, in the presence of an intact posterior capsule, can be minimized by use of a nondepolarizing neuromuscular blocking agent, such as atracurium, by use of a lateral canthotomy where indicated, and by ensuring external forces are not applied to the globe by the eyelid speculum, drapes, stay suture tension, or the surgeon once the anterior chamber has been entered. In addition, if the posterior lens capsule is observed to move anteriorly, a high viscosity viscoelastic material should be introduced in an effort to force the capsule posteriorly. Failure to prevent or control expansion of the vitreous may result in the inability to insert an IOL or in extrusion of the IOL following implantation if the anterior capsulorhexis is too large. While some surgeons choose to premedicate with carbonic anhydrase inhibitors or osmotic diuretics to prevent vitreous expansion, there is no evidence that this is efficacious.

Vitreous presentation will be encountered in eyes with posterior capsular tears and rupture of the anterior vitreous face, zonular dialysis (rupture) and lens subluxation, and in some eyes with vitreous degeneration. Although phacoemulsification has the advantage of maintaining the anterior chamber and anterior chamber pressure, and thereby, minimizing vitreous presentation, it also has the disadvantage of I/A which can incarcerate the vitreous. Vitreous may become overhydrated and incarcerated into the phacoemulsification tip resulting in further disruption and loss of vitreous and interfering with removal of lens material. If a posterior

Lens Capsule: Zonular Dehiscence

If capsular instability is severe, capsulorhexis and phacoemulsification will be compromised, and conversion to an open sky extracapsular or ICLE may be indicated. Phacoemulsification is, however, preferred if at all possible. Zonular dehiscence of 180° or less should be amenable to phacoemulsification (Por & Lavin, 2005), but some surgeons will perform phacoemulsification with even larger areas of dialysis (up to complete luxation) if the vitreous is stable. With zonular dehiscence, phacoemulsification should be performed with a minimum of lateral movement. Care is taken to avoid progression of the dehiscence. The capsulotomy is completed with scissors and not by tearing. Use of a two-handed technique is advised, with the second instrument used to stabilize the lens and aid in fragmentation.

Zonular dehiscence is less common than posterior capsular tears (Mulhern et al., 1996). If zonular dialysis is present and an endocapsular IOL is to be placed, the ideal lens is one with a large optic and increased haptic-capsular contact (C loop or 360° haptic). In addition, the IOL should be inserted by pressure on the superior haptic and not by dialing (Mulhern et al., 1996). A foldable acrylic IOL that can be placed through a 3.2- to 3.6-mm incision using an injector will improve lens placement. In addition, use of a capsular tension ring placed prior to or after phacoemulsification will facilitate lens capsule stability (Ahmed et al., 2005). Capsular tension rings are indicated with zonular dehiscence of less than 180° (Por & Lavin, 2005). Alternatively, a posterior chamber IOL can be placed in the ciliary sulcus and sutured. This can be done using an ab interno or modified ab externo approach. A modified ab externo approach works well if the lens has been removed through a 3.2-mm incision (see Surgery for Lens Instability).
capsular tear is observed, steps must first be taken to prevent enlargement of the tear and disruption of the vitreous face. In general, if vitreous is presented into the anterior chamber, a partial vitrectomy is indicated. Many of today’s phacoemulsification machines come with the ability to be expanded to include an oscillating and/or a guillotine vitrector. Vitrectomy can then easily be performed by exchanging handpieces while continuing to use the same tubing, infusion solution, and foot pedal. This allows for rapid conversion. In general, it is preferred to perform a dry- or slow flow bimanual vitrectomy using a separate infusion port rather than coaxial infusion. This will minimize further disruption of the posterior lens capsule and vitreous. The single port I/A sleeve provided with some vitrectors should not be used as this will direct infusion into the vitreous, exacerbating the problem (Gimbel, 1990).

Displaced/Dislocated Lens Fragments
The questions to be asked include whether the retained material is cortical or nuclear, what amount of lens material is in the vitreous, and what is the consistency of the vitreous. There is some debate, but a small amount of residual nuclear lens material can be left in the vitreous with minimal reaction (Mulhern et al., 1996). Retained cortical material is more reactive, however, and must be removed. In humans, it is suggested that long-term visual acuity is better in operated eyes as compared to conservatively managed eyes (Gilliland et al., 1992). The most appropriate method for removal of retained lens fragments is via a pars plana vitrectomy technique (Mulhern et al., 1996). Complications associated with retained lens material include elevation in IOP, corneal edema, inflammation, retinal tears, and detachments (Borne et al., 1996; Fastenberg et al., 1991; Mulhern et al., 1996). Postoperatively, systemic NSAIDs or corticosteroids and antibiotics may be indicated in these patients.

In veterinary medicine, surgeons do not have the luxury of closure and referral and would prefer to avoid a pars plana approach if they are already in the anterior chamber for the purpose of phacoemulsification. Removal of the lens fragments can be performed through the limbal incision provided care is taken to avoid further disruption of the vitreous, or if the vitreous must be disturbed, it should be done with appropriate instrumentation (not the phacoemulsification handpiece). Viscoselastic material can be used to tamponade the vitreous to help prevent further disruption. Alternatively, a Sheet’s glide can be inserted between the lens fragment and vitreous to enable continued phacoemulsification (Mulhern et al., 1996). As soon as a posterior capsular tear and displacement of a lens fragment is noted, infusion/aspiration should stop. A second entry wound is then made at the limbus for infusion, and the infusion is directed into the anterior chamber, parallel with the iris and away from the vitreous. If possible, the fragments are delivered into the anterior chamber at the level of the iris plane where they are fragmented. Viscoselastic material may be used to float the lens fragment into the lens capsule if the vitreous is liquefied, or in instances of more solid vitreous, after the overlying vitreous is removed using a vitrector. Alternately, a vitrectomy handpiece can be used to aspirate and cut smaller lens material in the vitreous body. This is especially effective for cortical material, and a guillotine vitrector works best. When performing a vitrectomy, a low-flow bimanual technique is used, or viscoelastic material is used to vault the chamber and a dry vitrectomy is performed (Borne et al., 1996; Fastenberg et al., 1991).

The question of IOL placement must be addressed once all the lens material has been removed. If a small posterior capsule tear is present, but the remaining capsular bag is intact and stable, an endocapsular IOL is preferred. However, if the capsule disruption is severe, then a posterior chamber IOL can be sutured in the ciliary sulcus as described by Nasisise (Nasisse & Glover, 1997).

Postoperative Complications of Phacoemulsification and IOL Implantation

Immediate Postoperative Complications

Wound Dehiscence Following Surgery
Most veterinary ophthalmologists perform bi-plane two-step groove incisions which serve to provide a watertight seal (Koch & Novak, 1995). For this reason, it is important to understand the normal healing of clear corneal incisions. A study using cats compared incisions in the clear cornea compared to those at the limbus. All limbal incisions were stable at 7 days postoperatively, whereas clear corneal incisions required 60 days to obtain similar incisional stability due to a delayed early fibroblastic response (Ernest et al., 1998). In a canine study, pericentral corneal wound healing was evaluated using 9-0 nylon or 9-0 polyglactin 910 (Vicryl™, Ethicon, Somerville, NJ) (van Ee et al., 1986). At days 8, 12, 16, and 21 postoperatively, both suture materials had similar inflammatory responses, that is, a granulomatous (foreign body) response. Both types of sutures also had similar wound strengths at 16 days postoperatively. This study suggested that canine corneas heal slightly faster than rabbits, cats, and humans (van Ee et al., 1986).

Wound dehiscence can occur due to many reasons including incisional weakness, improperly placed sutures, spike in IOP (Miller et al., 1997), or blunt- or self-trauma which compromise both the structural integrity of the globe and the optical quality of the eye (Koch & Novak, 1995). By addressing the problem promptly, short-term sequelae such as hypopyon, hyphema, and influx of microorganisms via the tears (K hurshid & Fahy, 2003) can be addressed or avoided as can long-term sequelae including endophthalmitis, excessive scarring, epithelial downgrowth, and fibrous ingrowth (Koch & Novak, 1995), or in severe cases, loss of the globe itself.

Wound dehiscence following phacoemulsification is uncommon and, though not documented, probably occurs in less than 1% of cases, depending on the suture pattern used to close the incision. A clear corneal or limbal incision is the most commonly used approach in veterinary ophthalmology...
because it is less time-consuming, results in minimal hemorrhage, and allows excellent visualization of the anterior chamber (Nelms et al., 1994). A small incision should provide adequate exposure for phacoemulsification and IOL implantation, minimize postoperative astigmatism, form a water-tight seal when closed, and have negligible scarring (Glover & Constantinescu, 1997). In addition, keeping the animal quiet following surgery and impeding the possibility of self-trauma will minimize this potential complication as well as further improve the success of the overall surgery. The new generation of foldable IOLs in veterinary ophthalmology has allowed for the use of a small incision approach (i.e., less than 4 mm) similar to ophthalmologists in human medicine. By decreasing the size of the incision, the incidence of wound dehiscence, as well as astigmatism (discussed below), is diminished in humans (Kumar et al., 2002); this has not yet been evaluated in dogs, but would be expected.

Most incisional complications are seen immediately postoperatively. A small amount of wound leakage that has plugged with fibrin, is maintaining the integrity of the anterior chamber and IOP, and has a negative Seidel test can be managed conservatively by keeping the animal quiet and confined to a small space with an Elizabethan collar. Actively leaking incisions or significant dehiscence of the incision should be addressed surgically to place additional sutures or replace broken or ineffective sutures, respectively. Systemic antibiotic therapy, if not already being administered, will decrease the risk of intraocular infection/endophthalmitis.

Epithelial downgrowth has not been documented in the veterinary literature but is a rare complication of human cataract surgery (Koch & Novak, 1995). It is further discussed in the section on long-term postoperative complications.

Surgery-Induced Corneal Astigmatism

Normal dogs have varying amounts of mild astigmatism. A study evaluating the corneal curvatures of normal dogs found that 33% of the eyes did not have astigmatism, 41% of eyes had with-the-rule astigmatism which had a mean difference of 1.6 ± 0.98 D while those with against-the-rule astigmatism had a mean difference of 1.05 ± 0.5 D (Gaiddon et al., 1991). Another study of 93 normal eyes found that 14% had more than 1 D of astigmatism (Pollet, 1984). For a variety of reasons, a clear corneal incision is presently the accepted approach to lens extractions, regardless of the surgery (i.e., phacoemulsification or intracapsular lens/cataract extraction). It is important to realize that some astigmatism remains long-term following surgery. A study by Nelms et al. evaluated the corneal curvatures of normal dogs prior to, immediately following, and 1 month following a 9-mm clear corneal or scleral incision. Prior to surgery, the average mean astigmatism was 0.82 D or 0.75 D in the corneal or scleral incision groups, respectively (p > 0.05). Significant astigmatism resulted immediately following the clear corneal approach (4.44 ± 3.4 D) when compared to the scleral approach (1.3 ± 1.56 D). However, astigmatism at 1 month postoperatively using the corneal approach was still present (2.35 ± 1.3 D) and greater than the scleral approach group (1.36 ± 1.3 D), but these differences were not significant (Nelms et al., 1994) and were similar to results in a human study (Beltrame et al., 2001). No studies, to date, have evaluated the astigmatism resulting from healing of smaller incisions (less than 4 mm) used when foldable IOLs are implanted in dogs. The larger incisions necessary for ECCE, and presumably for intracapsular cataract extraction (ICCE), cause more astigmatism than the small incision approach (George et al., 2005).

Corneal Ulceration

Corneal ulceration, although uncommon, may occur for a variety of reasons. These include decreased tear production or exposure secondary to anesthesia (Herring et al., 2000), undiagnosed or poorly controlled keratoconjunctivitis sicca, toxicity associated with the surgical betadine preparation solution, damage to the corneal sensory nerves from the incision resulting in focal neurotrophic keratitis, self trauma, or impeded healing which may be more likely in diabetic patients or in patients with prominent globes, that is, brachycephalic breeds, especially in the face of topical corticosteroid use (Fig. 22.21). Most of these ulcers are superficial and heal within 2 weeks. However, a balance must be achieved when managing postoperative uveitis with topical corticosteroids due to its inhibitory effect on corneal epithelialization. Oral corticosteroidal or nonsteroidal anti-inflammatory medications can be used to decrease the need for topical corticosteroids until the ulcer has healed. In addition, temporary use of topical corneal protectants such as viscous tear solution or gel will aid in corneal healing.

Corneal Edema and Endothelial Decompensation

Corneal edema can be a short-term and/or a long-term postoperative complication of cataract surgery. Corneal edema

Figure 22.21. The right eye of a patient that underwent intracapsular lens extraction and IOL implantation. The day following surgery, an axial superficial corneal ulcer is evident secondary to lagophthalmos in this brachycephalic dog.
that is evident immediately following cataract surgery can be due to excessive or improper irrigation fluid use resulting in damage to the endothelial cells, thermal effect of the phacoemulsification needle, or due to uveitis or increased IOP (Fig. 22.22). Longer irrigation times, higher flow rates (up to 50 cc/min), and larger volumes can be traumatic to the corneal endothelium (Hejny & Edelhauser, 2005). An ideal irrigating fluid for endothelial function should contain adequate bicarbonate as a buffer to maintain proper pH (between 6.7 and 8.1) and osmolality (between 270 and 350), and to maintain the endothelial transport system, a substrate such as calcium and glutathione to maintain junctional stability and the blood-aqueous barrier, and an energy source, that is, glucose (Edelhauser & Ubels, 2005).

Some loss of endothelial cells occurs even in the most routine of cataract surgeries. A study from 1983 in dogs found that there is an average endothelial cell loss of 22% centrally and a 13% loss peripherally following phacoemulsification (Gwin et al., 1983). Though significant, equipment technology and technique have vastly improved in the last three decades, but their overall conclusion is probably still valid; that is, endothelium of dogs responds to surgical trauma similarly to the endothelium of humans. Therefore, results from more recent human studies may be similar to what presently occurs in dogs. A study in humans compared endothelial cell loss following conventional ECCE, manual small-incision surgery, and phacoemulsification. ECCE resulted in a 4.72% loss, small-incision surgery resulted in a 4.21% loss, and phacoemulsification resulted in a 5.41% loss of endothelial cells (Gorge et al., 2005). Another study evaluated corneal changes following small-incision cataract surgery in diabetic and non-diabetic human patients. They found that there was more endothelial cell loss in diabetic patients than in nondiabetic patients (Morikubo et al., 2004). A study evaluating central corneal thickness in canine eyes following phacoemulsification found a significant transient increase in central corneal thickness (Lynch & Brinkis, 2006). This increase in corneal thickness was more significant in diabetic patients and took longer to return to normal in animals receiving a foldable acrylic IOL as compared to aphakic and PMMA pseudophakic eyes (Lynch & Brinkis, 2006). This would support the need for endothelial protection, particularly in diabetic patients. Interestingly, it does not support the value of small incision surgery with respect to endothelial protection.

Free radicals are generated by the high-intensity ultrasound energy associated with phacoemulsification (Holst et al., 1993; Takahashi, 2005; Topaz et al., 2005), leading to apoptosis of endothelial cells and potentially transient or permanent edema (Geffen et al., 2008). A scorbic acid added to the irrigation solution was shown to reduce endothelial cell loss by 70%, presumably by its free-radical scavenging properties (Rubowitz et al., 2003). A nother study comparing BSS, BSS Plus, as well as BSS with glutathione or with ascorbic acid found that corneal endothelial cells were significantly protected by inclusion of antioxidants (Nemet et al., 2007). A scorbic acid demonstrated the lowest endothelial cell loss (0.9%), and glutathione had a 5.2% loss, compared with BSS (19.3%) and BSS Plus (10.6%). A scorbic acid was measured in the aqueous humor of dogs following extracapsular lens extraction; ascorbic acid was reduced until day 15 following surgery (Barros et al., 2003). This suggests that use of antioxidants would protect endothelial cells during phacoemulsification.

One of the uses of viscoelastic substances is to physically protect the corneal endothelium. A study in dogs by Gerding et al. evaluated the corneal endothelium of dogs following intracameral injection of various viscoelastic substances. The viscoelastic substances included 1% sodium hyaluronate, 4% sodium chondroitin sulfate, 3% sodium hyaluronate, 2% hydroxypropyl methylcellulose, or BSS (control). They found that there were no changes in endothelial cell density or morphology in any treated group at either time point, that is, 72 hours and 168 hours postinjection. However, the mean corneal thickness of all treated eyes was increased 6% at 72 hours postinjection compared to nontreated eyes but by 168 hours postinjection had returned to baseline in all groups (Gerding et al., 1990). Other positive effects of viscoelastics, specifically hyaluronic acid, are that they avoid radical scavenging effects (Artola et al., 1993a, 1993b). The issue involves how long the hyaluronic acid is able to remain within the eye coating the endothelium. One percent hyaluronic acid (as Healon™) was shown to have a removal time of 20-25 seconds due to irrigation and aspiration, whereas the combination of 3% hyaluronic acid with 4% chondroitin sulfate (as Viscoat™) had a removal time of 3.5 minutes (Assia et al., 1992). In a study comparing various viscoelastic materials including Viscoat, Healon V™, Opegan™ (Seikagaku, Tokyo, Japan), and Healon, all inhibited free radicals; however, the ones with the highest retention rates were most effective when using a low flow rate for irrigation and aspiration (Takahashi, 2005).

Iatrogenic damage can include inadvertent contact of the endothelium with surgical instruments or the IOL, or by...
toucing the endothelium with lens fragments during surgery, resulting in focal edema (Steinert, 1995). Most of these cases will resolve as the endothelial cells expand and resume proper pump function. Chronically diseased corneal endothelial cells can increase the number of pump sites per cell as an adaptive mechanism and is probably the cause of restoration of corneal clarity in some severe cases (Steinert, 1995).

Corneal endothelial decompensation is a rare postoperative complication of cataract surgery occurring in less than 1% of human patients. This has not been objectively evaluated in canine cataract patients, though a recent study found that corneal edema was present in 3% of eyes in the 6- to 24-month postphacoemulsification (Sigle & Nasisse, 2005). Older dogs that already have fewer endothelial cells due to normal attrition (Gwin et al., 1982) or breeds such as the Boston Terrier may be at higher risk of corneal edema as are dogs that develop chronic uveitis or glaucoma (Sigle & Nasisse, 2005). Humans with diabetes mellitus can have endothelial abnormalities resulting in keratopathies (Schultz et al., 1984); this has not been described in dogs. Some damage to the endothelial cells may resolve with time, but if it does not, a penetrating keratoplasty may be necessary to restore vision.

Postoperative Ocular Hypertension

Postoperative ocular hypertension (POH) is a transient increase in IOP (>25 mmHg) that occurs within 72 hours following cataract surgery and occurs in 22.9%–50% of cases (Chahory et al., 2003; Crasta et al., 2010; Klein et al., 2011; Smith et al., 1996). POH can also uncommonly recur after discontinuation of antiglaucoma medications. This temporary elevation in IOP can overwhelm the corneal endothelial pump system resulting in corneal edema (Gelatt & Brooks, 1999; Steinert, 1995), and may be more detrimental to the optic nerve than slower elevations in IOP (Bito, 1992). POH is a multifactorial problem caused by a variety of factors including residual viscoelastic material, inflammation, RBCs in the ciliary cleft, and changes in the ICA. Other proposed causes have included trabecular meshwork swelling, residual lens particles, pigment, and viscous plasmoid aqueous (Miller et al., 1997).

A study by Smith et al. found that POH developed 3.9 hours following phacoemulsification in dogs (Smith et al., 1996). The development of POH was not correlated with gender, cataract stage, IOL placement, preoperative LIU, or posterior lens capsule tears and vitrectomy. POH was associated with longer phacoemulsification duration and was more likely in dogs that were older. A study by Miller et al. found that POH peaked by 3 hours but had decreased to normal by 24 hours postoperatively (Miller et al., 1997). Stuhr et al. found that POH was not significantly associated with phacoemulsification power or time or whether the dog received an IOL (Stuhr et al., 1998). In a recent study, the Labrador Retriever appears to have an increased incidence of POH as compared with non-Labrador Retrievers, 33% compared to 18%, respectively (Moeller et al., 2011). In addition, Labra-

dors were at increased risk for glaucoma and blindness as compared with non-Labradors (Moeller et al., 2011). It appears that increasing age and POH are risk factors in Labradors for the development of postoperative glaucoma (Moeller et al., 2011).

Residual viscoelastic material can result in or exacerbate a transient, and sometimes significant rise in IOP (Morgan & Skuta, 1994). Changes in IOP due to intracameral injection of various viscoelastic substances in dogs was evaluated by Gerdin et al. (Gerdin et al., 1989). A comparison of 1% sodium hyaluronate, 4% sodium chondroitin sulfate, and 3% sodium hyaluronate to BSS found that the three viscoelastic substances caused an increase in IOP at 2 hours postinjection. The IOP was lower than baseline from 12 to 72 hours postinjection and had approached baseline by 168 hours postinjection. A recent study in humans evaluated five different viscoelastic products (OcuCoat™ and Celoftal™ [2.0% hydroxypropyl methylcellulose] [Alcon Laboratories, Ft. Worth, TX], Viscoat [3.0% sodium hyaluronate, 4.0% chondroitin sulfate], Healon GV™ [1.4% sodium hyaluronate], and Healon5™ [2.3% sodium hyaluronate]) (Holzer et al., 2001). The Healon5 group had the highest mean IOP (24 mmHg). A study that also compared Healon5 and Viscoat found opposite results wherein the Viscoat group had significantly higher IOP (Schwenn et al., 2000). Though the results of these and other studies vary in which viscoelastic caused an increase in IOP, it is clear that any viscoelastic substance can potentially contribute to POH.

The study by Miller et al. disproved some of the previously proposed causes of POH (Miller et al., 1997). They found that evacuation of 2% hydroxypropyl methylcellulose from the anterior chamber prevented the previously reported mild IOP increase seen at 2 hours following intracameral injection. Other viscoelastic substances were not evaluated in this study, but the authors mentioned that other viscoelastic substances could still cause POH despite thorough evacuation from the anterior chamber. Histological evidence of residual lens fibers was not seen in the trabecular meshwork or anterior chamber and was not thought to contribute to POH following intercapsular phacoemulsification in this study. The authors hypothesized that release of tension on the lens zonules, along with cyclopentolate due to atropine, may result in peripheral movement of the ciliary body and compression of the trabecular meshwork. The residual increase in IOP would then further compress the ciliary body and exaggerate the ciliary cleft collapse. What is not understood is how the IOP returns to normal despite the fact that the aforementioned changes have not resolved by 24 hours postoperatively. It was suggested that the reduced aqueous humor production partially contributes to the normalization of IOP and that use of drugs that increase ciliary body tone could further control IOP.

A recent study using UBM evaluated the ICAs and AOD of dogs with cataracts prior to and following pharmacological mydriasis preoperatively, and also at 1 and 3 hours following phacoemulsification cataract extraction (Rose et al., 2008). It
was found that the preoperative ICA and AOD may correlate with the development of postoperative hypertension. They determined that postoperative narrowing and widening of the ICA did not correlate with POH. It was also determined that preoperative IOP did not significantly correlate with POH (Rose et al., 2008). A second study found the relationship between AOD as measured using UBM was weakly associated with IOP elevations at 1 day following phacoemulsification (Crumley et al., 2009).

The prevalence of POH may be reduced by complete removal of the viscoelastic material (Assia et al., 1992; Wilkie & Willis, 1999). Other methods to control POH include intracameral injection of carbachol or tPA or preoperative use of carbonic anhydrase inhibitors. A study in dogs evaluated the effect of intracameral carbachol on IOP at 3 and 6 hours and the morning following surgery (Stuhr et al., 1998). None of the dogs that received intracameral 0.01% carbachol developed POH whereas 75% of control dogs that did not receive carbachol did develop POH. The use of preoperative latanoprost in humans did not decrease the mean IOP at 3 hours or 24 hours after surgery (Lai et al., 2001). Regardless, the potent miosis seen in dogs following latanoprost use (Studer et al., 2000) would prohibit surgical removal of the cataract and may potentiate postoperative uveitis. A recent study comparing three treatment protocols on the prevalence of POH found that topical latanoprost or intracameral carbachol did not reduce POH or increase intraocular inflammation (Crasta et al., 2010). In fact, eyes treated with intracameral carbachol had a significantly higher IOP at 2 hours postoperatively as compared to the control group (Crasta et al., 2010). A nther study found that the use of intracameral carbachol is associated with a significantly increased risk of POH in the Labrador Retriever (Moeller et al., 2011). This same study found the use of intracameral carbachol in non-Labradors was associated with a decrease in the incidence of POH.

Postoperatively, IOP should be evaluated at several intervals during the first 4 hours following surgery. Surgeons who claim to not see POH do not evaluate IOP in the immediate postoperative period. If the IOP begins to rise following surgery, medical management should be initiated immediately. Management of POH varies greatly between surgeons. If the IOP is above 16 mmHg but below 40 mmHg, the authors will generally give a drop of topical carbonic anhydrase inhibitor with or without an oral carbonic anhydrase inhibitor, if the dog is awake enough to swallow. The IOP is then reevaluated 1 hour later to ensure that it is decreasing or at least not increasing. If the IOP was greater than 40 mmHg, then intravenous mannitol as well as the carbonic anhydrase inhibitors should be given to rapidly decrease the IOP. Some surgeons will also choose topical 2% pilocarpine or 0.005% latanoprost to manage POH. As long as the IOP remains below 15 mmHg until the animal is discharged to the owner, then no additional antiglaucoma medications are used. However, if the IOP increases to or remains above 15 mmHg, then topical and/or oral carbonic anhydrase inhibitors are used until the 1–2 week reevaluation.

Hyphema

Hyphema and/or vitreal hemorrhage occurring in the immediate postoperative period are relatively uncommon. Causes include hypotony or sudden changes in IOP, and unapparent or newly developed retinal detachment. Tension on the ciliary processes during surgery or due to an oversized IOL can also result in hemorrhage. The incision site is often cited as a location to observe for hemorrhage but clear corneal incisions make this less likely. Severe uveitis or iatrogenic trauma to the iris can result in hyphema. Preexisting bleeding tendencies can also precipitate hyphema or vitreal hemorrhage. Tension around the patient’s neck with a snug collar and/or pulling by the dog with such a collar during walking can cause immediate hyphema. Securing the leash around one forelimb or use of a body harness can diminish the potential for this complication. In addition, restricting the dog’s activity and minimizing barking can also help to avoid hyphema. In humans and presumably veterinary patients, vomiting can cause hyphema due to sudden rises in IOP (Slettedal & Bragadottir, 2005) and should be avoided in the immediate postoperative period. Unidentified intraocular masses can also be the origin of intraocular hemorrhage following cataract surgery. A less likely possibility that should still be considered is diabetic retinopathy or systemic hypertension (Kern & Engerman, 1995; Landry et al., 2004; Lane et al., 1993; Wyman et al., 1995). Small hemorrhages will resolve without further complications (Nasisse & Davidson, 1999; Yanoff & Fine, 2002b), but more substantial hemorrhages can result in numerous long-term complications. These can include secondary hemolytic glaucoma due to obstruction of the outflow tract with hemoglobin aggregates and/or hemolyzed red blood cells (ghost cells). Neither ghost cells nor fresh red blood cells can pass from the vitreous into the aqueous compartments; therefore, vitreal hemorrhage is unlikely to result in hemolytic glaucoma (Yanoff & Fine, 2002a).

Chronically, significant hyphema may result in fibropupillary membranes that can traverse the IOL impairing sight, causing dyscoria, or injuring the corneal endothelium (Nasisse & Davidson, 1999). In order to avoid these complications, intracameral tPA can be effective for clot resolution up to 2 weeks following hemorrhage once the fibrin clot has stabilized and further hemorrhage is not expected (Siatiri et al., 2005). There are cases in which tPA has resolved clots present for greater than 2 weeks. Intracameral tPA is used at a concentration of 25 μg/100 μL and 0.1–0.2 mL is injected (Wilkie & Gemensky-Metzler, 2004), and potential side effects of intracameral tPA may include corneal edema, increased IOP, and rebleeding. A study in dogs evaluated the corneal endothelium and IOP following intracameral injection of tPA (Gerdng et al., 1992). No changes in corneal thickness or IOP were found at 24, 48, or 168 hours postinjection. One prospective randomized multicenter human study found that tPA may also diminish PCO (Heiligenhaus et al., 1998). No further studies have shown this result.
but presents an interesting scenario. Resolution of the uveitis usually restores corneal clarity. A study in normal eyed mongrel dogs demonstrated a 72-fold increase in anterior chamber protein 24 hours postphacoemulsification (De Biaggi et al., 2006). This increase in aqueous protein remained significant at 15 days postoperatively. In addition, phacoemulsification decreased the total antioxidant capacity and the ascorbic acid concentration of the aqueous humor for 7–15 days following surgery (De Biaggi et al., 2006).

Some postoperative uveitis is expected and topical anti-inflammatory medications should be already in use. A recent retrospective study found a 16.2% incidence of uveitis following phacoemulsification (Klein et al., 2011). Oral steroidal or nonsteroidal anti-inflammatory medications may also be necessary to manage uveitis, depending on the severity of the uveitis. Uveitis should be managed aggressively immediately because chronic uveitis can result in pre-iridal fibrovascular membrane (PIFM) formation, PCO, permanent corneal edema, secondary glaucoma, and retinal detachment (Lannek & Miller, 2001; Moore et al., 2003).

Acute Endophthalmitis
Uncommonly, hypopyon may develop in the first 24–48 hours following surgery (Fig. 22.24). This may be due to improperly sterilized instruments, equipment or IOLs, unsterile fluids used for irrigation, or as a reaction to toxic substances on the IOL. A recall of BSS has occurred due to elevated levels of endotoxin causing toxic anterior segment syndrome (TASS). TASS is an acute, noninfectious anterior uveitis usually seen within 24 hours following surgery. It is felt that TASS does occur, but may be misdiagnosed following cataract surgery in our veterinary patients (Myrna et al., 2009). The onset of TASS is typically more acute than infectious endophthalmitis which may take several days to occur. These eyes must be managed with aggressive anti-inflammatory therapy, but in
the authors’ opinion, surgical management is also indicated as soon as the hypopyon is noticed. An antibiotic-spiked irrigating fluids should be used to copiously irrigate the anterior chamber and remove the hypopyon. If a contaminated IOL is suspected, an IOL from a different lot number may be used to replace the IOL of concern. The surgeon should always rinse the IOL prior to implantation with sterile BSS. A cytology slide should be examined and a culture and sensitivity should be performed on the anterior chamber contents in order to ensure that the antibiotics used are appropriate for any potential infection. If the anterior chamber contents are evidently sterile, aggressive antibiotic therapy should still be used in case the microorganism(s) are present but not able to be cultured. Oral corticosteroids should be avoided as the anti-inflammatory medication; NSAIDs are more appropriate. A polymerase chain reaction test can also be performed for bacterial and/or fungal DNA; however, this test is very sensitive and results should be interpreted in a case-specific manner.

Long-Term Postoperative Complications

Endophthalmitis

Infectious endophthalmitis is the most feared and certainly one of the most devastating complications that can occur postoperatively resulting in severe or complete loss of sight (Fig. 22.24). Blindness due to postoperative endophthalmitis is estimated to occur in up to 0.10% of human cataract patients (Olson, 2004). A recent study evaluating postoperative complications of cataract surgery in dogs found that 4 of 290 eyes (1.4%) developed endophthalmitis by 3 months postoperatively. However, no patients were identified with endophthalmitis in the later time points (from >3 months to >4 years) (Sigle & Nasisse, 2005). A further study that included eyes enucleated or eviscerated due to complications arising from cataract surgery has been recently published (Moore et al., 2003). Of 66 samples included in the study, 18 (27%) were diagnosed histologically with endophthalmitis and the average time until enucleation following cataract surgery was less than 1 month. These two canine studies vary widely in their incidence of endophthalmitis but both are higher than the incidence seen in humans. This may be due to a relatively small sample size in both studies compared with the large-scale studies carried out in humans and should be further evaluated to include eyes that were not enucleated or eviscerated for this complication.

Sources for this potential complication include the patient’s endogenous flora, contaminated irrigating fluids or equipment, bacterial adhesion to the IOL, airborne bacteria, hematicogenous bacteria, and the flora of the operating room personnel (Kodjikian et al., 2004; Ledbetter et al., 2004). It must be mentioned that some cases of endophthalmitis are sterile. Elderly human patients have pathogenic bacteria in their Meibomian glands, and this is thought to be another potential source for the development of endophthalmitis (Yoshitomi, 2005). The incidence of this, while unknown in dogs, is very possible in dogs with chronic eyelid disease.

Another review of the human literature included data published between 1963 through 2003 and evaluated cases with endophthalmitis; it included a total of 3,140,650 cataract extractions and determined that endophthalmitis occurred in 0.128% of cases (Taban et al., 2005). Interestingly, the rate of endophthalmitis increased in the 2000–2003 period and was attributed to incision type, specifically sutureless clear corneal incisions; scleral and limbal incisions had a lower risk of endophthalmitis (Olson, 2004; Taban et al., 2005). A study in dogs found that the aqueous humor from 12 of 50 eyes (24%) undergoing cataract surgery had positive bacterial cultures (Taylor et al., 1995). A more recent study in dogs evaluated 13 patients (22 eyes) for microbial contamination of the anterior chamber following cataract surgery; they found that 22.7% of eyes grew at least one bacterial or fungal organism which was consistent with the conjunctival flora cultured preoperatively (Ledbetter et al., 2004). The most common bacterial organisms grown from the conjunctiva and eyelid margins were Bacillus sp., Staphylococcus sp., and Clostridium sp. Of three eyes that grew organisms from the aqueous humor, one eye grew Bacillus sp., a second eye grew Staphylococcus sp., and the third grew Pantoaea sp. (Ledbetter et al., 2004). A prospective study of 230 human patients undergoing cataract surgery found that the most common organism (71%) cultured preoperatively from the periorcular areas was coagulase-negative Staphylococcus spp.; 27% of cultures grown from anterior chamber aspirates taken intraoperatively also grew coagulase-negative Staphylococcus spp. As might be expected, phacoemulsification cataract extraction has a significantly lower incidence of anterior chamber contamination than nonphacoemulsification cataract extraction in both humans and dogs (Egger et al., 1994; Taylor et al., 1995). Despite the relatively common occurrence of intraoperative contamination of the anterior chamber during cataract surgery, none of the patients in either the human or the dog studies developed infectious endophthalmitis (Egger et al., 1994; Ledbetter et al., 2004; Taylor et al., 1995). It has been shown in rabbits that the anterior chamber is able to clear live bacteria; in addition, inoculum size and organism virulence are important determinants of endophthalmitis development (Maylath & Leopold, 1955; Shockley et al., 1985).

Preoperative preparation of the periorcular area and the globe with povidone-iodine solution is the only prophylaxis that decreases postoperative endophthalmitis (Speaker & Menikoff, 1991). In addition, most veterinary ophthalmologists begin administering topical antibiotics 2–24 hours prior to surgery in addition to using perioperative antibiotics. Patients at higher risk for developing endophthalmitis should also receive postoperative oral antibiotics. Potential situations for this include patients that undergo longer phacoemulsification times, those that have an intentional or unintentional breech of the posterior lens capsule (Beyer et al., 1985), diabetics, and those with a history of skin allergies. Patients that have dermatitis, especially in the periorcular area including ear infections, should be treated with a course of antibiotics prior to and following cataract surgery. Eyes that develop
unexpected moderate to severe chronic uveitis should be treated with systemic antibiotics and nonsteroidal anti-inflammatory medications. If aqueoucentesis is performed, antibiotic therapy should be commensurate with culture and sensitivity testing. Should this complication become a more than unusual problem, intracameral cefazolin has been shown to significantly reduce the incidence of endophthalmitis (Garat et al., 2005).

Posterior Capsule Opacification
The most common long-term postoperative complication of phacoemulsification cataract surgery is PCO. PCO is a universal complication that occurs in 20%–60% of all human surgical patients within 5 years postoperatively, depending on age, geographic location, and IOL type (Apple et al., 2000b, 2001; Leysen et al., 2006; Mootha et al., 2004; Sundelin & Sjostrand, 1999). PCO occurs with a 100% incidence in dogs in one study (Bras et al., 2006) and 62% incidence in another recent study (Fig. 22.25) (Sigle & Nasisse, 2005). Both studies, though varied in PCO incidence, point out the importance of this postoperative complication. Clinically, PCO causes impaired visual acuity by directly blocking the visual axis. In addition, impairment of visual acuity can be further worsened by wrinkles and plaque formation on the posterior lens capsule (Apple et al., 1992b). Intraoperative factors that may influence PCO formation include the capsulorhexis, hydrodissection, composition of the irrigating solution, viscoelastic material used, capsule polishing, and configuration and material of the IOL (Apple et al., 1992b; Bras et al., 2006; Chandler et al., 2007; Haeussler et al., 2010; Pandey et al., 2002).

The primary response of the remaining LECs is to undergo epithelial-mesenchymal transition (EMT); that is, the LEC transform from sessile normal cuboidal epithelial cells into spindle-shaped myofibroblast-like cells that overexpress α-smooth muscle actin (Marcantonio & Vrensen, 1999). Additional morphological alterations include cell elongation, organelle loss, nucleolar chromatin condensation and abherent basement membrane synthesis (Chandler et al., 2007; Liu, 1994). This results in posterior migration and proliferation of the LEC. The hallmarks of EMT include the expression of cyclooxygenase-2 (COX-2) and alpha-smooth muscle actin

Figure 22.25. Appearance of posterior capsular opacification (PCO) in canine patients after phacoemulsification and intraocular lens implantation. Clinical examples of PCO grading scores (0−4+) in canine patients. (a) A faint haze or minimal opacity of the posterior lens capsule that permitted a thorough evaluation of the retina was graded as 1/2+ PCO. (b) A focal plaque, or a diffuse haze, or mild opacity on the posterior lens capsule that slightly impaired evaluation of the retina was graded as 1+ PCO. (c) More than one plaque, or dense haze, or moderate opacity of the posterior lens capsule that mildly impaired the fundic examination was graded as 2+ PCO. (d) Numerous dense posterior lens capsular plaques or severe opacification that moderately impaired the fundic examination was graded as 3+ PCO. (e) PCO that completely obstructed the view of the retina was graded as a 4+.
(Chandler et al., 2007). Evaluation of COX-2 expression in canine cataracts and an ex vivo PCO model show increased expression and compared to normal canine LEC (Chandler et al., 2007). Increased expression of alpha-smooth muscle actin results in LEC contraction with resultant capsule wrinkling, folds, and possible IOL decentration (Apple et al., 1992b). It has been shown that the anterior LECs in both rabbits and humans initially undergo hyperplasia and, by 4 days after surgery, transform to spindle-shaped myofibroblast cells (McDonnell et al., 1983, 1985) that, along with the LEC at the equatorial lens bow, migrate posteriorly and abnormally occupy the posterior capsule (Apple et al., 1992b; Kappelhof & Vrensen, 1992). This results in the clinically evident fibrous form of opacification around the anterior capsulotomy and along the posterior lens capsule. The germinative and equatorial LEC are mitotic and normally contribute to the terminally differentiated secondary lens fibers. Following cataract surgery, these equatorial LEC form large balloon-like bladder or Wedl cells, also known as Elschnig’s pearls (Fig. 22.26).

The average time to significant clinical PCO in humans is 26 months after surgery, with a range of 3 months to 4 years (Apple et al., 1992b). A similar amount of PCO develops in dogs by 12 months postoperatively (Braas et al., 2006). PCO causing decreased visual acuity has a varying incidence in humans ranging from 30.4% up to 50% with the use of PMMA IOLs (Apple et al., 1992b; McDonnell et al., 1983; Schmidbauer et al., 2001; Sinskey & Cain, 1978; Wilhelmus & Emery, 1980) with a higher risk in younger patients (Binkhorst & Gobin, 1964; Hiles & Wallar, 1980). The newer generation of foldable hydrophobic IOLs used in humans, not including the Alcon Acrysof IOL™ (Alcon Laboratories, Ft. Worth, TX), has decreased the incidence of Nd:YAG laser-treated PCO to 21.1% (Schmidbauer et al., 2001). The rate of Nd:YAG laser-treated PCO in cases with the Alcon Acrysof™ IOL was less than 2% up to 5 years postoperatively; however, in cases longer than 5 years, the rate of Nd:YAG laser-treated PCO was 29% (Apple et al., 2011). In addition, the total rate of peripherally or centrally located PCO on the optic was 66%. Therefore, the initially positive success of this IOL showed that it only prolonged the time of onset of PCO, not its occurrence.

AIcon Acrysof IOLs have been used following phacoemulsification cataract extraction in two captive lowland gorillas. The younger gorilla (17 months) developed PCO and required an Nd:YAG laser capsulotomy (de Faber et al., 2004). The acrylic IOLs available for use in dogs are hydrophilic, not hydrophobic, like the Alcon Acrysof IOL. Studies are currently underway evaluating the degree of PCO that develops over time with the use of these IOLs (I.D. Bras, personal communication). Based on the data showing that PCO occurrence is only prolonged, not reduced, in human eyes implanted with hydrophobic IOLs, it is likely that PCO behavior in dogs will not be reduced either.

Nd:YAG laser posterior capsulotomy is the most commonly used therapeutic modality for treatment of PCO in humans (Apple et al., 2000a). The procedure is not performed without its own potential complications including damage to the IOL, IOP elevation, cystoid macular edema, retinal detachment, IOL luxation, or endophthalmitis (Apple et al., 1992b, 2011; Lane, 2004). Not only does younger age predispose to increased severity of PCO in humans (and dogs), but in a 1989 study, it was determined that 70% of patients under 40 years of age require a second Nd:YAG laser capsulotomy, compared to 37% of patients greater than 60 years of age (Mosseiev et al., 1989). A study evaluated the effect of Nd:YAG laser energy on PMMA and acrylic IOLs in normal dog eyes (Beale et al., 2006). They determined that there was a therapeutic margin between capsulotomy threshold (2.6–2.7 mJ) and IOL damage threshold (4.9–5.7 mJ) that reliably achieved capsule severities with minimal IOL damage for both acrylic and PMMA IOLs (Beale et al., 2006). This may pose a problem in dogs with hypermature cataracts or in those that develop dense posterior capsular changes due to PCO wherein the capsule becomes excessively thickened and wrinkled. These changes may reduce the therapeutic effect of the laser procedure as the energy necessary to disrupt the posterior capsule would damage the IOL. The authors suggest that as foldable IOLs become more popular, the associated decrease in PCO frequency may allow for Nd:YAG laser capsulotomy to become more commonly used (Beale et al., 2006).

David Apple and his group have identified three surgery-related factors and three IOL-related factors that are important in the prevention of PCO in humans. These factors should translate laterally into our veterinary patients. The three surgery-related factors are small continuous curvilinear capsulorhexis with edge on IOL surface, hydrodissection, and in-the-bag fixation (Schmidbauer et al., 2001). Creating a capsulorhexis that is slightly smaller (0.5 mm) than the optic is the accepted standard in human cataract surgery (Zanini et al., 2005). By doing this, a tight fit of the anterior capsule is achieved and helps to sequester the optic in the capsular

Figure 22.26. Photograph of a patient that underwent phacoemulsification cataract extraction and PMMA IOL implantation. There is extensive cortical regrowth, that is, Elschnig’s pearls, around the entire IOL and extending under the IOL.
bag away from the surrounding aqueous humor and its macromolecules and inflammatory mediators (Schmidbauer et al., 2001). Hydrodissection is an important technique used in humans. A modification of traditional hydrodissection, cortical cleaving hydrodissection, permits the cleavage of the cortex from the posterior capsule which allows for thorough removal of most or all of the cortex and LEC during phacoemulsification (Buratto et al., 2005; Schmidbauer et al., 2001). A long-term advantage of meticulous hydrodissection is reduction in PCO (Peng et al., 2000a). The difficulty resulting from hydrodissection would be in using a one-handed approach to phacoemulsification as the lens material would be free to escape the lens capsule. The final surgery-related factor is in-the-bag fixation of the IOL. The primary function of this factor is enhancing the IOL-optic barrier effect which is maximal when the IOL directly contacts the posterior lens capsule (Peng et al., 2000b). The goal of IOL implantation is, obviously, to place the IOL in the lens capsule. In humans, the rate of in-the-bag fixation was only 60% prior to foldable IOLs. This rate has increased to 90% since the use of foldable IOLs became “mainstream.” The rate of in-the-bag fixation in veterinary medicine has not been evaluated, but at the authors’ institution, it is estimated to be greater than 98%.

IOL-related factors that decrease PCO include biocompatibility, maximal IOL optic-posterior capsule contact, and a mechanical barrier effect of the IOL optic. Lens material biocompatibility is often defined as the ability to inhibit postoperative stimulation of LEC proliferation (Apple et al., 2000a). This certainly takes into account other factors including surgical factors, duration of the IOL in the eye, and biomaterial factors. There are numerous reports in the human literature regarding biocompatibility of numerous IOLs but few in the veterinary literature. The second factor, maximal IOL optic-posterior capsule contact, uses the posterior angulation of the IOL haptic and posterior convexity of the optic to create a tight fit of the IOL optic with the posterior capsule. It has been suggested the optic biomaterial may also create an adhesion of the capsule to the IOL optic, termed bioadhesion (Apple et al., 2000a; Schmidbauer et al., 2001). Finally, the IOL optic barrier effect is the second line of defense against PCO. Nishi et al. first showed this effect in rabbits (Nishi & Nishi, 1998) followed by Apple et al. in humans (Apple et al., 1998). This concept puts the phrase “no space, no cells” into action by creating a physical barrier against LEC migration under the IOL and onto the posterior capsule. This is especially true with squared or sharp-edged optics. A study of canine IOL design and PCO suggests that squared-edge foldable acrylic IOL’s show a tendency toward less PCO than round-edged PMMA IOLs in the early postoperative period (Gift et al., 2009).

A number of pharmacologic agents have been tested to inhibit PCO formation. These agents may be delivered directly into the anterior chamber at the time of surgery, placed in the irrigating fluids used during surgery or delivered via impregnation of the IOL or capsule tension ring device. The difficulty with any drug delivery system is toxicity to other tissues, especially the corneal endothelium (Pandey et al., 2004). A variety of antimetabolites including methotrexate, mitomycin-C, daunomycin, 5-fluouracil, and colchicine have been shown to be effective in inhibiting PCO in vitro by lysing LEC (Biswas et al., 1999; Nishi, 1999). Unfortunately, in vivo concentrations high enough to inhibit LEC proliferation have resulted in toxic effects on corneal endothelial cells, the iris, ciliary body epithelial cells, and the retina (Nishi, 1999). Several proteins that are overexpressed in LEC that have undergone EMT, as in PCO, including COX-2, estrogen receptor alpha and telomerase (Colitz et al., 1999, 2004), aromatase (Colitz et al., 2005), as well as other proteins, and work is underway to manipulate them in an attempt to inhibit LEC proliferation, and therefore PCO. In addition, in an ex vivo canine LEC model COX-2 inhibition prevented EMT, and as a result, may decrease PCO (Chandler et al., 2007). This may be clinically applicable as COX-2 inhibitors could be administered intra- or postoperatively. This is supported by a decrease in PCO in human patients administered topical diclofenac three times daily for a year, postoperatively (Seki et al., 1992).

**IOL Decentration/Luxation out of Bag**

The traditional PMMA IOLs can occasionally decenter due to various reasons including an excessively large lens capsule as in intumescent diabetic cases, or if an IOL is implanted that was too small in diameter for the lens capsule (Fig. 22.27). PMMA IOLs can luxate out of the lens capsule if the anterior capsulotomy is too large which allows aqueous humor to continually flow through the capsule and under IOL, if there is an extensive large radial tear, and after a longer time period due to PCO causing contraction that forces the IOL out of the lens capsule (Fig. 22.28). The newer acrylic foldable IOLs, in the authors’ opinion, do not decenter or dislocate as often as the PMMA IOLs.

**Figure 22.27.** Photograph of the left eye of a dog that underwent phacoemulsification and PMMA IOL implantation. The IOL is ventrally decentered, and the dorsal haptic is seen through the mydriatic pupil. Mild PCO is also evident.
Capsule contraction syndrome is uncommon but still should be mentioned as a complication of continuous curvilinear capsulorhexis (Davison, 1993; Tadros et al., 2005). Capsule contraction syndrome is an exaggerated reduction in anterior capsulotomy and capsular bag diameter after extracapsular cataract surgery. In humans, it is seen in patients with pseudoexfoliation, which is not seen in veterinary patients, and also in patients with moderate to severe uveitis, which is seen in veterinary medicine. This syndrome not only reduces and malpositions the capsulotomy opening, but it can cause IOL decentration, tilting, or displacement (Fig. 22.29 and Fig. 22.30) (Tadros et al., 2005). Severe cases will cause zonular traction leading to IOL dislocation and predispose to retinal detachment (Davison, 1990). Capsule contraction syndrome is caused by the anterior LEC undergoing EMT, which causes expression of \( \alpha \)-smooth muscle actin and contraction and wrinkling of the anterior capsule (Tanaka et al., 2004). Removal of anterior subcapsular LECs by aspiration has been shown to significantly prevent capsule contraction syndrome (Tadros et al., 2005).

**Figure 22.28.** A. (a and b) The eyes of a patient that underwent bilateral phacoemulsification and PMMA IOL implantation. The IOLs luxated out of the lens capsules, and the ventral haptic and adjacent optic (arrows) are protruding through the pupil and onto the anterior aspect of the iris. There is diffuse corneal edema consistent with uveitis and secondary glaucoma. B. A PMMA IOL with partial IOL dislocation out of the capsular bag, temporal iris entrapment posterior to the IOL optic and PCO.

**Figure 22.29.** Photograph of a dog’s eye after phacoemulsification cataract surgery and PMMA IOL implantation. There is anterior capsular opacification around the anterior capsulotomy as well as posterior capsule opacification around the posterior capsulotomy. In addition, the PCO has caused contraction of the lens capsule and the lateral haptic can be seen curving toward the optic.
Woundotomy is decentered as well.

to bend around the optic more than they should and the anterior capsu-

lens capsule has contracted severely due to PCO, and the haptics are seen to bend around the optic more than they should and the anterior capsulotomy is decentered as well.

Figure 22.30. A lens capsule with a PMMA IOL implanted within it. The lens capsule has contracted severely due to PCO, and the haptics are seen to bend around the optic more than they should and the anterior capsulotomy is decentered as well.

What are the options for these patients? In humans, the IOLs are usually left dislocated as they do not cause significant clinical complications, though problems with refractive error would be expected. In dogs, however, any irritation to the iris or ciliary processes results in low-grade uveitis and possibly fibrin formation that requires constant medical management and increases the risk of permanent corneal edema, PIFM formation, secondary glaucoma, and retinal detachment (Lannek & Miller, 2001; Moore et al., 2003; Sigle & Nasisse, 2005; Zarfoss et al., 2010). Should this occur, removal of the IOL is indicated. If a more suitable IOL can be reinserted, such as one with a better fit, a foldable IOL, or a sutured IOL, then this can be attempted. Control of anterior uveitis prior to this surgery is imperative due to dogs’ amplified uveal inflammatory response, compared to that in humans (Bito, 1984).

**Glaucoma**

A large retrospective study spanning a 39-year time span evaluated the prevalence of secondary glaucoma in dogs (Gelatt & MacKay, 2004). For the total 39-year period, 19.3% of those dogs had cataract formation with secondary glaucoma; when the total group was evaluated by 10 year periods, this percentage remained constant. They estimated that 5.1% of dogs developed secondary glaucoma as a sequela to cataract surgery. Dogs with unoperated cataracts have an approximately 20% risk of developing secondary glaucoma in at least one eye, and dogs that undergo cataract surgery have a 5.1% risk of developing secondary glaucoma (Gelatt & MacKay, 2004). Two recent retrospective studies have evaluated the risk factors that predispose dogs to secondary glaucoma following cataract surgery. The first study included 220 cases (346 eyes) and found that 16.8% of eyes developed postoperative glaucoma. This study had a relatively short median follow-up period of 5.8 months. They also found that eyes with hypermature cataracts had an increased risk of developing glaucoma while eyes that had IOLs placed had a significantly lower risk of developing glaucoma (Biros et al., 2000). Mixed breed dogs were significantly less likely to develop glaucoma, compared with other breeds. A second study evaluated 154 dogs with one or both eyes undergoing phacoemulsification; after excluding 95 dogs that did not fit into the stringent inclusion criteria, they followed 59 eyes of 43 dogs in which 29 eyes from 22 dogs developed glaucoma (Lannek & Miller, 2001). Based on number of dogs that developed glaucoma, the incidence was 18.8% (29 out of 154), which is similar to the study by Gelatt and MacKay. The mean duration of follow-up for dogs that developed glaucoma was 31.7 months and was 41.7 months for dogs that did not develop glaucoma. An increased risk of developing glaucoma was observed in dogs with preexisting uveal or retinal abnormalities, with intraoperative hemorrhage, and in Boston Terriers. This study did not find that the presence of LIU, placement of an IOL, or POH were risk factors for developing glaucoma. A retrospective study evaluating 179 eyes following phacoemulsification found a glaucoma prevalence of 6.7% (Klein et al., 2011). In this study, the likelihood of glaucoma increased 1.88 times for each year of increasing patient age (Klein et al., 2011). A retrospective study of secondary glaucoma evaluating risk factors found that anterior uveitis secondary to phacoemulsification accounted for 15.8% of secondary glaucoma cases of the 156 dogs evaluated (Johnsen et al., 2006). In a recent study, the Labrador Retriever was at increased risk for glaucoma and blindness as compared with non-Labradors (Moeller et al., 2011). It appears that increasing age and POH are risk factors in Labradors for the development of postoperative glaucoma (Moeller et al., 2011).

The development of glaucoma following cataract surgery is an important reason for periodic reevaluations. Medical management of secondary glaucoma should be aggressive and early. Oral and/or topical carbonic anhydrase inhibitors are the first medications to include in glaucoma management. If these fail or if another mechanism of action is necessary, then topical prostaglandin analogs can be used, though their proinflammatory effects should be monitored (Fechtner et al., 1998). Endoscopic laser cyclophotocoagulation performed immediately following phacoemulsification and IOL implantation is a new approach being evaluated in order to determine whether this will delay or indefinitely postpone the onset of secondary glaucoma. Details are in the lens instability section of this chapter. Given the chosen criteria for long-term success including management of IOP, diminished number of antiglaucoma medications, sight, and requirement for a second laser procedure, traditional transscleral diode cycloablation technique (Cook et al., 1997) is moderately successful, and until recently, one of the few methods available of surgically addressing this complication. Other approaches include placement of drainage valves such as the Ahmed valve (Garcia-Sanchez et al., 2005) with or without transscleral cyclophotoablation.
Retinal Detachment

A recent retrospective study of 172 cases by Sigle and Nasisse, found that retinal detachment is an infrequent complication following phacoemulsification, with a prevalence of 1%-2% in all time periods evaluated (up to greater than 4 years) (Sigle & Nasisse, 2005). In this study, all cases of retinal detachment occurred prior to 3 years postoperatively. This prevalence is lower than the 4.7% (Davidson et al., 1991b), 4.8% (Miller et al., 1987), or 8.4% (Klein et al., 2011) previously or recently reported. The authors speculated that patient selection or few intraoperative variables may have contributed to this lower prevalence. It is also possible that ultrasound technology has advanced sufficiently in the past 15 years to allow diagnosis of smaller retinal detachments or that fewer hypermature cataracts overall are undergoing surgery. Phacoemulsification cataract surgery in humans has a similar rate of retinal detachment as the Sigle study with a range between 0.75% and 1.65% (Ramos et al., 2002).

Though no Bichon Frises in the retrospective study by Sigle and Nasisse developed retinal detachments, the Bichon Frise has been reported to be at increased risk of retinal detachment, and it has been suggested that prophylactic retinopexy should be performed to prevent this complication (Schmidt & Vainisi, 2004; Vainisi & Wolfer, 2004). In a retrospective study that evaluated 58 eyes from nondiabetic Bichon Frise dogs with breed-related cataracts, cases were divided into four groups (Schmidt & Vainisi, 2004). In group 1, dogs that did not undergo prophylactic random transscleral retinopexy nor phacoemulsification had a 60% incidence (12 of 20 eyes) of rhegmatogenous retinal detachment. In group 2, dogs that did not undergo prophylactic random transscleral retinopexy but had phacoemulsification had a 55.5% incidence (10 of 18 eyes) of rhegmatogenous retinal detachment. In group 3, dogs that underwent prophylactic random transscleral retinopexy but no phacoemulsification had a 10.5% incidence of rhegmatogenous retinal detachment. In group 4, dogs that underwent prophylactic random transscleral retinopexy and had phacoemulsification had a 5.1% incidence of rhegmatogenous retinal detachment. This study showed that prophylactic retinopexy significantly diminished the risk of retinal detachment in this breed. A nother study suggested that the Bichon did not appear to be at increased risk for retinal detachment (Klein et al., 2011). Further, this study suggested that prophylactic transscleral diode retinopexy did not prevent and may in fact increase the risk for postoperative retinal detachment (Klein et al., 2011). A recent retrospective evaluation of preoperative findings and outcomes in 40 eyes did not find an associated risk of retinal detachment in the Bichon Frise breed from the United Kingdom (Braus et al., 2011). Risk factors that have been identified for retinal detachments include hypermature cataracts and vitreal degeneration.

Dogs that develop retinal detachments may be amenable to laser retinopexy (Vainisi & Wolfer, 2004) depending on the health status of the retina and the globe. A small rhegmatogenous retinal detachment can be addressed using transpupil-
series of case studies had positive cultures, one grew Streptococcus pneumoniae while the other grew Staphylococcus aureus. All incisions were secure without leakage, but they hypothesized that the sutures were a nidus of infection and the suture tract provided an entry for bacteria from the tears and periocular sites (Khurshid & Fahy, 2003).

Diabetic neuropathy and/or epitheliopathy, commonly seen in humans, may be manifesting as corneal stromal abscesses, keratoconjunctivitis sicca, or other keratoconjunctival abnormalities in our veterinary patients. A study by Good, et al. assessed corneal sensitivity in diabetic and nondiabetic dogs (Good et al., 2003). They found that diabetic dogs have significantly reduced corneal sensitivity in all corneal regions evaluated. However, they did not find that glycemic control nor estimated duration of diabetes was correlated with corneal hyposensitivity (Good et al., 2003). This is also true in humans wherein there is no relationship between corneal sensitivity and duration of diabetes, but there is a decrease in corneal sensitivity as both diabetic and nondiabetic humans age (Murphy et al., 2004). A study of dogs with endocrinopathies found a decrease in corneal sensitivity and Schirmer’s tear test (STT) in dogs with diabetes mellitus (Williams et al., 2007). A larger study by Cullen et al. evaluated tear production and quality, corneal sensitivity, tear glucose concentrations relative to ocular microflora, and conjunctival changes in diabetic and nondiabetic canine patients with or without cataracts (Cullen et al., 2005). Tear production was lower, and tear film breakup times were shorter in diabetic cataractous dogs. Four of seven dogs had histological evidence of reduced goblet cell density. Consistent with the aforementioned study, this group found that diabetic cataractous dogs had corneal hyposensitivity. Diabetic cataractous dogs also had higher tear glucose concentrations, but their conjunctival microflora was not different from the other groups (Cullen et al., 2005). Extensive work carried out in diabetic humans has identified clinically observed disorders including tear and epithelial barrier dysfunction, recurrent epithelial defects and erosions, delayed epithelial wound healing, corneal edema, superficial punctate keratitis, endothelial dysfunction, and corneal nerve tortuosity and decreased nerve density (Saghizadeh et al., 2005). Some of these disorders may be a result of increased activity of specific proteinases working to degrade the epithelial cell basement membrane altering cell-basement membrane adhesion and migration (Saghizadeh et al., 2005). The percentage of diabetic human patients with corneal disease is increased in patients with diabetic retinopathy (Saito et al., 2003). The possibility of a similar correlation has not been evaluated in diabetic dogs. A study in humans that evaluated corneal sensitivity and tear physiology following phacoemulsification found that corneal sensitivity does not return to presurgical levels until 3 months postoperatively and tear function recovers by 30 days postoperatively (Khanal et al., 2008). The authors advocate the use of topical tear replacers in the postoperative period.

Epithelial Inclusion Cysts

Epithelial downgrowth has not been documented in the veterinary literature but is a rare complication of human cataract surgery (Koch & Novak, 1995). In humans, epithelial downgrowth can manifest as corneal decompensation, glaucoma, chronic anterior uveitis, and a retrocorneal membrane with a demarcated leading edge (Koch & Novak, 1995).

Surgery for Lens Instability

Lens instability can occur as a primary abnormality or occur secondary to abnormalities such as hypermature cataract, chronic LIU, trauma, or glaucoma. Primary lens luxation (PLL) is breed associated and has been reported in at least 45 canine breeds in the literature (Curtis, 1990; Curtis & Barnett, 1980). Primary lens instability is considered common in as many as 8–10 terrier breeds, the Australian Cattle Dog, Border Collie, and Shar-Pei (Curtis, 1983; Curtis & Barnett, 1980; Curtis et al., 1983a, 1983b; Morris & Dubielzig, 2005; Sargan et al., 2007; Willis et al., 1979). Primary lens instability is considered common in as many as 8–10 terrier breeds, the Australian Cattle Dog, Border Collie, and Shar-Pei (Curtis, 1983; Curtis & Barnett, 1980; Curtis et al., 1983a, 1983b; Morris & Dubielzig, 2005; Sargan et al., 2007; Willis et al., 1979). Primary lens instability typically appears between ages 2 and 6 years, and while often asymmetrical at presentation, is typically a bilateral disease. The mode of inheritance is autosomal recessive (Farias et al., 2010; Sargan et al., 2007; Willis et al., 1979) with the mutation being a single nucleotide substitution in the ADAMTS17 gene (Farias et al., 2010). The ADAMTS17 mutation would appear to be widespread among several breeds of dogs (Gould et al., 2011). While affected dogs are typically homozygous for the PLL mutation, a small minority of affected dogs are
heterozygous for the mutation, suggesting that carriers may be at increased risk (Gould et al., 2011). There is now a genetic test commercially available for the PLL mutation. DNA results suggest that some breeds, such as the Miniature Bull Terrier in the United Kingdom, may have as many as 40% of the breed as carriers. As clinicians, we are now faced with the dilemma of what to do with dogs homozygous for the PLL mutation. Knowing that these dogs will experience lens instability between the ages of 2 and 6 years and knowing the dismal outcome of medical therapy or surgical therapy following lens luxation, should these affected dogs undergo lensectomy early in life prior to lens luxation?

There is considerable diversity of opinion among veterinary ophthalmologists regarding when unstable lenses should be removed, and some individuals avoid surgical intervention for as long as possible. Recent studies, however, have revealed that the prognosis for vision after ICLE is poor if glaucoma is present at surgery (Glover et al., 1995). The mechanisms by which unstable lenses cause glaucoma have not been identified, but some believe this begins early in the course of lens instability and then rapidly become irreversible. As a result, it has been advocated that unstable lenses should be removed as soon as the instability is detected (Nasisse & Davidson, 1999). In addition, it has been shown that medical management of unstable lenses offers a similar outcome to ICLE, neither of which is very satisfactory (Binder et al., 2007). As a result, DNA testing for PLL combined with early surgical intervention for unstable lenses using phacoemulsification with or without IOL implantation and use of capsule tension rings should be considered in an effort to improve long-term outcomes.

**Medical Management of Posterior Lens or Cataract Luxations**

Surgical removal of a posteriorly luxated lens is a more difficult endeavor than anteriorly luxated lenses due to the requirement for floating the lens anteriorly for its extraction. Many veterinary ophthalmologists use topical prostaglandin analogs (latanoprost, travoprost, bimatoprost) or other miotics as a therapeutic approach in managing posterior luxations without surgery. The prostaglandin analogs, especially 0.005% latanoprost (Xalatan), cause potent miosis in dogs along with excellent antiglaucoma effects (Gelatt & MacKay, 2001; Studer et al., 2000). In addition, if at the time of surgery the anteriorly luxated lens has dropped into the vitreous chamber, some surgeons will abort surgery and give a miotic and then maintain the patient on topical miotics twice daily indefinitely. Evaluation of medical management for lens instability using demecarium bromide indicated that the only significant effect of miotic treatment was to delay anterior lens luxation in eyes with lens instability (Binder et al., 2007). Miotic treatment did not significantly affect the time from anterior lens luxation in one eye to anterior luxation in the other eye, time to onset of glaucoma, or time to loss of vision in eyes with an unstable lens (Binder et al., 2007). Of the 34 dogs with lens instability managed medically, vision was maintained in 80% at 1 year and 57% at 2 years (Binder et al., 2007). The most common cause of vision loss was secondary glaucoma. In a separate retrospective study of secondary glaucoma evaluating risk factors, it was found that lens dislocation accounted for 15.2% of secondary glaucoma cases while glaucoma secondary to ICLE only accounted for 3.8% of the 156 dogs evaluated (Johnson et al., 2006). Another retrospective evaluation of secondary glaucoma in 217 dogs found that lens luxation was the cause in 22.6% of dogs (Strom et al., 2011).

Surgical management of a posteriorly luxated lens is difficult and may be controversial. The surgeon must be prepared to perform a vitrectomy to remove the vitreous overlaying the lens to allow room for the lens to be elevated. This is required when the vitreous is semisolid or in strands but may not be needed if the vitreous is completely liquefied. The lens can then be elevated into the anterior chamber by using a cohesive, high-viscosity viscoelastic to float the lens by filling from underneath the lens. Once the lens is in the anterior chamber, it can be removed in an intracapsular fashion according to the surgeon’s preferred method. These patients are at high risk for retinal detachment and postoperative glaucoma.

**Surgical Management of Lens Luxations**

The technique for removal of an unstable lens will depend on the degree of instability, equipment availability, health of the vitreous, and surgeon preference. In general, if the lens is stable enough to allow phacoemulsification, this should be the preferred method of extraction. This allows for use of small incision techniques and has been shown to have significantly improved outcome as compared with ICLE (S. Manning, personal communication). With improvements in viscoelastics, use of two-handed techniques, and CTRs, many unstable lenses can now be safely removed by phacoemulsification (Wilkie et al., 2008).

**Preoperative Medications**

A similar preoperative medical plan to that of phacoemulsification is used by most veterinary ophthalmologists, with the exception of the mydriatic, and is extensively described earlier in this chapter. A strong mydriatic such as atropine may cause the lens to drop into the vitreous chamber, especially if the vitreous is somewhat degenerated, and should be avoided. A weaker mydriatic, tropicamide or intracameral 1:10,000 epinephrine, may be used instead. Use of $\alpha$-chymotrypsin to induce zonulolysis has been recently evaluated in normal dogs (Maggs et al., 2010). The investigators administered 75U of $\alpha$-chymotrypsin (diluted to 1:5000 with NaCl) placing it in the posterior chamber and allowing it remain for 7 minutes prior to ICLE (Maggs et al., 2010). When administered in this manner, $\alpha$-chymotrypsin facilitated ICLE without adverse effects (Maggs et al., 2010).
In humans, two-handed phacoemulsification is performed with the aid of a capsular tension ring (Por & Lavin, 2005).

If the lens has up to a 180° (6 clock hours) instability, the capsular tension ring can be left in place to prevent decentration of the IOL. They also advocate using viscoelastic material placed often in the area of the subluxated quadrant(s) (Coret & Elies, 2005).

The authors have routinely performed two-handed phacoemulsification in cases of severe to total lens instability to minimize trauma to the globe from the traditional 160° incision necessary for ICLE. Depending on the degree of lens instability, an IOL may be placed with or without a CTR or the lens capsule can then be removed via the small incision, again leaving the vitreous face intact, if possible. If an IOL cannot be placed in the capsular bag, a sutured IOL can be considered. It has been advised that if the zonal instability is less than 180° in the dogs, a CTR can be implanted and a foldable acrylic IOL may be placed in the bag (Wilkie et al., 2008). It is best if the CTR can be placed prior to phacoemulsification to provide increased stability during two-handed phacoemulsification. If the instability exceeds 180°, then the entire lens capsule should be removed. Vitrectomy is performed only in cases where the vitreous is disrupted and has potential for complications. If an IOL is not going to be sutured into the sulcus, then the small incision is closed and medical management is continued as usual.

**Sulcus IOL Fixation**

The standard ab interno and ab externo approaches to suturing an IOL into the ciliary sulcus have not changed substantially (Nasisse & Davidson, 1999). The location where the suture will exit or enter the sclera is marked, depending on whether an ab interno or ab externo approach is used, respectively. Small conjunctival flaps should be made 1.5 mm posterior to the limbus in these marked locations prior to making the clear corneal incision to facilitate entry or exit of the needle and to allow suturing to the sclera at the end of the procedure. To avoid the nictitating membrane, approximate landmarks are 2 o’clock and 8 o’clock for the right eye and 10 o’clock and 4 o’clock for the left eye. Until now, only nonfoldable PMMA IOLs that have an eyelet in the haptic for attaching the suture have been used for this purpose. These lenses are specific for the technique of sutured IOLs and differ in size and design from the standard endocapsular IOL. The most commonly used suture type is 10-0 polypropylene; however, the author and others have used 9-0 nylon successfully. The needle type is also the surgeon’s preference, and choices include a straight needle on the 10-0 polypropylene or a curved spatula needle on the 9-0 nylon. It is imperative that the suture placement is accurate to minimize refractive error and tilt of the IOL. While most surgeons use two-point fixation to fix the lens, this does not prevent lens rotation around these two points, and for this reason, a three-point fixation should be considered.

Once the conjunctival windows are made and the sclera is marked, the corneal incision can be made. The traditional approach is an approximately 160–170° incision that avoids the long posterior ciliary vessels and the nictitating mem-
branes. Following lensectomy, discussed earlier, viscoelastic is again injected intracameraly to vault the anterior chamber and displace the vitreous posteriorly. Sutures must not be passed through the vitreous as this will interfere with correct lens placement in the ciliary sulcus.

The ab interno method is accomplished by first attaching the chosen suture to the haptics prior to making the corneal incision. Once the lens is extracted, the first needle is passed into the anterior chamber, behind the iris, and through the ciliary sulcus in the ventrolateral position exiting through the sclera where the conjunctival window was made (Fig. 22.33 and Fig. 22.34). If the straight needle is used, it is usually bent to 110°; if a curved spatula needle is used, its proximal half is straightened leaving the distal curve. This distal curve makes driving it through the sclera easier. The second needle is then passed at the same level through the sclera where the conjunctival window was made 180° across from the first suture. The IOL is rinsed with BSS and can be coated with viscoelastic material to protect the corneal endothelium while it is inserted. The haptics are gently guided under the iris and into the ciliary sulcus while placing tension on the sutures until the IOL is centered. If vitreous is incarcerating the IOL, a vitrectomy should be performed carefully to avoid tilt or decentration of the IOL. After the corneal incision has been closed and the globe reinflated, the lens-anchoring sutures are gently pulled taut to position the lens in the axial pupil opening and tied to the sclera. The conjunctival window is then closed using 8-0 Vicryl. The drawback of this technique is that the lens-anchoring sutures are placed into the ciliary sulcus blindly. The use of endoscopy would greatly enhance this technique by making suture placement more accurate. A retrospective study of ICLE by cryoextraction followed by a placement of a sutured IOL using the ab interno technique found preservation of vision in 70% of eyes with a mean time to vision loss of 41 months (Stuhr et al., 2009). The most common reason for vision loss was glaucoma and/or retinal detachment.

The ab externo method places the lens-anchoring suture prior to entering the eye, which achieves more accurate suture placement (Nasisse & Davidson, 1999; Nasisse & Glover, 1997; Wilkie et al., 2008). This technique can only be performed if the lens is posteriorly luxated or if the lens has been extracted at a prior time; therefore, it is uncommonly performed (Fig. 22.35, Fig. 22.36, Fig. 22.37, and Fig. 22.38). After the conjunctival windows are made over the sites of needle placement 1.5 mm posterior to the limbus, a partial thickness score incision is made at the site of each proposed

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**Figure 22.33.** In the ab interno method of sulcus IOL fixation, the suture is passed beneath the iris to exit the sclera 2 mm posterior to the limbus.

**Figure 22.34.** In the ab interno method, the IOL haptic is then pulled into the ciliary sulcus as tension is placed on the suture.

**Figure 22.35.** In the ab externo method, the suture is first preplaced by threading the suture needle through the ciliary sulcus and into the lumen of a hypodermic needle.
the anterior chamber is reinflated, and the sutures are secured to the sclera.

The ab externo technique has been modified to allow the surgeon to combine small incision phacoemulsification and placement of a sutured IOL (Wilkie et al., 2008). The conjunctival flaps and sclera are prepared as previously described. Prior to entry into the eye, the PMMA IOL is prepared by attaching 9-0 nylon suture to the haptic eyelets for either two- or three-point fixation. The needles are then removed from the suture. The unstable lens is removed using two-handed phacoemulsification. If the lens capsule is completely unstable, the entire capsule is then removed through the 3.2-mm incision. If the posterior lens capsule is stable enough to be preserved, as occurs in some diabetic patients with severe lens capsule ruptures, it can be left to keep the vitreous face intact and the entire anterior capsule removed. The anterior chamber is reformed using viscoelastic. A 30-gauge needle is passed from outside of the globe, at the site of the ventral suture placement. This needle enters the sclera 1.5 mm posterior to the limbus, passes into the eye at the level of the ciliary sulcus, and is directed toward and out the 3.2-mm corneal incision (Fig. 22.39A, B). The 9-0 nylon suture is passed into the lumen of the needle and the needle withdrawn so that the suture exits the sclera. Next, a 30-gauge needle is passed through the dorsal sclera in a similar fashion and the second suture passed into the lumen and the needle withdrawn (Fig. 22.40A, B). If three-point fixation is planned, the third suture is now positioned in the same fashion as the first two. The corneal incision is opened to a distance of 8 mm using corneal section scissors and the IOL positioned in the ciliary sulcus. The corneal incision is closed, the anterior chamber is re-formed, and the IOL sutures fixed to the sclera as previously described (Fig. 22.41). The advantage of this technique is that it allows removal of the lens and placement of the suture through a
Prophylactic Endoscopic Cyclophotocoagulation to Prevent Secondary Glaucoma

Diode endoscopic cyclophotocoagulation glaucoma surgery is the newest approach being used to manage or prevent secondary glaucoma in dogs and cats (Bras et al., 2005). The procedure can be performed alone or just after lensectomy or phacoemulsification, extending the surgery time by an average of 10 minutes. Average settings used by Bras et al. were 0.4 mW (0.25–0.5 mW) with continuous duration. Though the average treated area was 160° (90°–180°), the author commented that a minimum of 180° of the ciliary processes should be lasered for maximal effect. Thirteen of 14 patients in this study, thus far, have had well-controlled IOP, have required

Figure 22.39. A. Drawing. B. Intraoperative photograph. The lens and lens capsule have been removed through a 3.2-mm incision. A 30-gauge needle is passed 1.5 mm posterior to the limbus, anterior to the vitreous, and emerges from the corneal incision. A 9-0 nylon suture, attached to the IOL haptic is passed into the lumen of the needle.

Figure 22.40. A. Drawing. B. Intraoperative photograph. The second suture is passed into the anterior chamber and into the lumen of the 30-gauge needle. Duet® microsurgical tying forceps are used to pass the suture while in the anterior chamber.
fewer antiglaucoma medications than prior to surgery, and 81% were sighted as of the last reevaluation. In addition, compared to transscleral cyclophotoablation, there was less inflammation, and only one patient has experienced an IOP spike within 4 hours of surgery. The same group is presently evaluating the success of using endolaser immediately following ICLE compared with ICLE alone, then followed by endolaser. Eight patients have undergone ICLE immediately followed by endolaser, and 87% have had controlled IOPs, maintained sight, and are on fewer antiglaucoma medications than prior to surgery, as of the last reevaluation (range is from 2 weeks to 1 year). Certainly, a more extensive, critically evaluated prospective study comparing its results to those of the transscleral approach (Cook et al., 1997; O’Reilly et al., 2003) is necessary to deem endolaser cycloablation superior to transscleral cyclophotoablation.

Postoperative Complications

Long-term postoperative complications of surgery for lens instability are not vastly different from those following phacoemulsification; however, the larger incision, longer surgical duration, and increased incidence of uveitis may predispose these patients to an increased risk of complications. Only a few of the complications will be discussed as they have unique differences from those occurring following phacoemulsification. These include refractive errors, incision dehiscence, secondary glaucoma, and retinal detachment.

Refractive Error

Perfect placement of a sulcus IOL is nearly impossible; therefore, some refractive error is to be expected. A 0.5-mm increase in anterior chamber depth will result in 4–6 D of hyperopia (Nasisse & Glover, 1997). IOL tilt results in oblique astigmatism and IOL tilt of greater than 5° will induce refractive error (Por & Lavin, 2005). Significant lens tilt of greater than 10° occurs in 11.4%–16.7% of human patients with sutured sulcus IOLs (Hayashi et al., 1999). Dogs will adapt to most errors, though if the IOL is tilted or is improperly positioned, they may have subtle signs of visual impairment.

Incision Dehiscence

Intracapsular lens extraction requires a larger incision (160°) which increases the risk of dehiscence with less trauma than the smaller incision used for phacoemulsification. In a retro-
incidence of this complication.

forming ICLE soon after the luxation occurs may decrease the\
scopic attachment (Sullivan, 1997; Sullivan et al., 1997). Per-
position to retinal detachments. Diode laser retinopexy can
(Schmidt & Vainisi, 2004) can be used in cases with a predis-
mologists. Prophylactic random transscleral retinopexy
mated to occur in 0.4%–3.6% of cases (Ramos et al., 2002).

Retinal detachment following ICLE is the second most
common postoperative complication after secondary glau-
coma (Nasisse & Davidson, 1999). This is thought to be due to
preexisting retinal tears that enlarge following surgery
(Nasisse & Davidson, 1999), and disruption of the anterior
hyaloid face may predispose eyes to this complication (Por &
Lavin, 2005). There are no studies in dogs evaluating the
incidence of this specific problem, but in humans, it is esti-
mated to occur in 0.4%–3.6% of cases (Ramos et al., 2002).
Retinal detachments can be amenable to laser retinopexy, a
procedure that has gained favor by many veterinary ophthalm-
ologists. Prophylactic random transscleral retinopexy
(Schmidt & Vainisi, 2004) can be used in cases with a predis-
position to retinal detachments. Diode laser retinopexy can
also be performed using an endprobe for intracocular delivery
or using a transpupillary probe with an indirect ophthalmol-
oscopic attachment (Sullivan, 1997; Sullivan et al., 1997). Per-
forming ICLE soon after the luxation occurs may decrease the
incidence of this complication.

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The vitreous, also called the vitreous body or corpus vitreum, is a transparent, elastic hydrogel accounting for approximately 80% of the volume of the canine globe (Evans, 1993). The volume of the canine vitreous humor has been quantified to an average of 1.7 mL (±0.86) (Gilger et al., 2005). Posteriorly, the vitreous is bordered by the retina, for which it provides support, and the optic disc, and, at the anterior side, by the posterior lens capsule and the Zinn zonules (i.e., fossa pateellaris). It is composed of water (about 99%), collagen fibrils, hyalocytes, hyaluronic acid, and other glycosaminoglycans.

DEVELOPMENT AND ANATOMY

To understand vitreous pathology, some basic knowledge of vitreal ontogenesis is important. In the dog, the lens vesicle becomes separated from the surface ectoderm from which it originates by day 16–24 of gestation (Aguirre et al., 1972; Boevé et al., 1988a). During the same period, ectodermal and mesodermal fibrillar material extends into the space between the lens vesicle and presumptive retina, thus forming the primitive vitreous. Later, the primitive vitreous is concentrated centrally, in the optic cup, while the definitive or secondary vitreous develops around it (Aguirre et al., 1972; Balazs, 1975; Boevé et al., 1988a; Gloor, 1973b; Mann, 1964).

After formation of the lens vesicle, the hyaloid artery, which is of mesodermal origin, penetrates into the primary vitreous through the optic fissure and grows toward the posterior pole of the lens. Just retrolentally, the hyaloid artery branches, generally into three main trunks, which subsequently develop into a vascular network around the primitive lens, thus forming the tunica vasculosa lentis. More proximally in the vitreous space, the hyaloid artery branches into the vasa hyaloidea propriae. On the anterior side of the lens, the primitive vascular system anastomoses with the annular vessel at the rim of the optic cup, which is the location where the iridal base will later be formed.

In the dog, the hyaloid system is at its maximal development by day 45. At this stage, the hyaloid system has developed into an elaborate vascular network. After approximately day 45, however, the hyaloid system starts to regress, and between the second and the fourth week after birth, the entire vitreal vascular system has degenerated (Gloor, 1970). Eventually, only a small, short, usually corkscrew-shaped, rudimentary string of the hyaloid artery remains, which is attached retrolentally to the posterior lens capsule just ventral to the posterior pole between the two ventral suture lines. By a slit lamp biomicroscope, this rudiment can be observed in most normal canine eyes; the site of attachment to the posterior lens capsule is named Mittendorf’s dot. Remains of the primitive vitreous concentrate around the hyaloid artery. After regression of the latter, a channel-like structure (i.e., Cloquet’s channel) remains, but this structure is only barely observable in normal adult canine eyes.

Some authors regard the hyaloid system as part of the primitive vitreous, while others do not. This partly accounts for the existence of two names, persistent hyperplastic primary vitreous (PHPV) and persistent hyperplastic tunica vasculosa lentis (PHTVL), for the same disease.

The vitreous forms one of the refractive media of the eye, and it provides the necessary pressure to hold the neuroretina properly positioned against the pigment epithelium. The two main solid components of the vitreous are hyaluronic acid and collagen. Approximately 1% of the vitreous consists of a network of polygonal, hydrated fibrils of hyaluronic acid (type II, with a helical structure of $\alpha_1(II)_3$). (McLaughlin & McLaughlin, 1986; Snowden & Swann, 1980). These polymers are electronegative, thus causing expansion of the gel. Introducing electropositive ions into the vitreous may cause the gel to collapse (Osterlin & Jacobson, 1968). Such collapse has been described for ferrous ions in the rabbit (Hui et al., 1988). As cellular component, few hyalocytes, which originated from blood macrophages, are mainly located peripherally, near the ciliary body (Gloor 1973a). The hyalocytes are believed to be responsible for the production of...
glycosaminoglycans, especially hyaluronic acid (Sebag, 1993). The remaining 98%–99% of the vitreous consists of water (Balazs, 1961).

The outer limits of the vitreous do not consist of membranes; rather, they consist of condensations of fibrils that are firmly attached to the ora ciliaris retinae and the pars plana ciliaris (Tolentino et al., 1976).

The anterior portion of the vitreous is strongly attached to the posterior lens capsule, which has given rise to the confusing term hyaloidocapsular ligament (i.e., Weiger’s ligament, Egger’s line). The vitreous is also attached to the region of the ora ciliaris retinae and to the prepapillary area (Evans, 1993). The vitreoretinal interface consists of outer part of the vitreous, anchoring fibrils of the vitreous body and the inner limiting membrane of the neuroretina (Fine & Tousimis, 1961; Gärtner, 1964; Heegaard, 1997). Vitreous detachment is a condition whereby the vitreous shrinks and pulls away from the retina, impairing the vitreous attachment. This condition is common in humans but has not been described in the dog. In humans, vitreous detachment rarely leads to serious problems, although it can cause retinal tears or holes that may be vision-threatening.

**PHYSIOLOGY**

The most essential (patho)physiological relationships and functional aspects of the vitreous can be summarized as follows (Lund-Andersen & Sander, 2003):

- support function for the retina and filling-up function of the vitreous body cavity (prevention of retinal detachment, absorption of external forces, reduction of mechanical deformation of the globe)
- diffusion barrier between the anterior and the posterior segment of the eye (the gel structure contains a barrier function for bulk movement of substances)
- metabolic buffer function (dilution of substances produced in the retina, and supplementation of the retinal metabolism, especially during anoxic conditions)
- establishment of an unhindered path of light (specific structural aspects, low concentration of macromolecules).

**AGING**

Both the fibrillar condensations and the colloidal state of the vitreous provide for maintenance of the water contents, and both seek to prevent penetration by “strange” cells (e.g., inflammatory cells) or bacteria. In addition, the gel structure acts as a barrier against movement of solutes. Some increase in vitreal density occurs with age, and the stability of the colloidal decreases with age as well, thus leading to liquefaction of the hydrosol (Eisner & Bachmann, 1974). As a consequence, fine, white, fibrous structures may become visible in the vitreous of older dogs during slit lamp biomicroscopic examination.

During life, the vitreous goes through considerable physiological changes that are significant for its function (Lund-Andersen & Sander, 2003). The most fundamental aging-determined change consists of a disintegration of the gel structure (liquefaction; syneresis), which is especially notable in the center of the vitreous, where the collagen concentration is lowest (Swann, 1980; Swann & Constable, 1972). Common aging processes, such as the cumulative effect of light exposure, possibly photooxidative stress, and nonenzymatic glycosylation are considered to be important factors in the mechanism behind liquefaction (Kasai et al. 1983 & Stitt, 2001). Concerning signs of aging, see also section on “Degenerative Vitreal Disorders and Reactions.”

**DIAGNOSTIC PROCEDURES**

To facilitate clinical observation and evaluation of the vitreous, the pupil should be dilated using a short-acting mydriatic agent, such as tropicamide. In puppies, however, tropicamide may not cause adequate pupil dilation in all cases; use of atropine may be indicated. The part of the ophthalmic examination dealing with the posterior segment of the globe should be performed in twilight conditions.

**Focal Light**

The eye is both illuminated and inspected from a distance (≈40–60 cm). The light source should be powerful and focal, such as a penlight of good quality, a direct ophthalmoscope, or an otoscope, to allow any vitreal opacities or condensations to be visualized by indirect illumination (i.e., by light reflected from the tapetal fundus [tapetum lucidum]). Because opacities will either partly or completely block the reflected light, they will be seen as dark structures against a bright tapetal reflectivity. Movement of vitreal structures following motions of the globe or lagging behind ocular motions may be determined more easily in this way.

**Slit Lamp Biomicroscopy**

A slit lamp biomicroscope is a highly useful and necessary tool for examination of the vitreous, even though such inspection using a slit lamp biomicroscope will be limited to the anterior part. A slit lamp biomicroscope is therefore especially useful to evaluate disorders at the lens/vitreous interface, such as persistence of parts of the tunica vasculosa lentis posterior, persistent hyaloid artery (PHA), PHTVL/PHPV, as well as posterior lental pathology.

**Ophthalmoscopy**

A direct ophthalmoscope may be used as previously described. By decreasing the distance between the light source and the eye, direct illumination of vitreal structures will increase, enabling better visualization of their morphology. Vitreous liquefaction and floaters may also be visualized with an indirect ophthalmoscope, and use of a fundus contact lens to eliminate the refractive power of the ocular lens enables...
cytologic examination or microbiologic culture (Gelatt et al., 2011). Hyalocentesis is performed after instillation of a short-acting mydriatic agent, preferably under general anesthesia, and after antiseptic pretreatment of the conjunctival sac (e.g., with a 0.5% aqueous povidone-iodine ophthalmic solution). A 22- to 26-gauge (0.70–0.45 mm) needle is used to penetrate the sclera, and the exact location of needle penetration is of great importance (Fig. 23.2). The eye should be penetrated via the anterior or medial region of the pars plana ciliaris (Smith et al., 1997). The corresponding external sites in medium-sized mesocephalic dogs are 7 mm (i.e., superotemporal quadrant), 6 mm (i.e., inferotemporal quadrant), 5 mm (i.e., inferonasal quadrant), and 4–5 mm (i.e., superonasal quadrant) posterior to the limbus (Smith et al., 1997). There are indications that these sites will be more posterior in larger dogs with larger eyes (Smith et al., 1997). Needle penetration through the pars plicata ciliaris will result in considerable intraocular hemorrhage, whereas penetration posterior to the pars plana ciliaris will cause punctures of the retina. For these reasons, hyalocentesis should be performed only when essential.

The needle should be directed toward the posterior pole of the globe. Great care should be taken to avoid touching the lens in the process. Under observation via an indirect ophthalmoscope through the dilated pupil, the needle can be directed to the opacities under investigation. If the vitreous at the needle tip is gelatinous instead of liquefied, it may obstruct the needle. In that case, the needle should be gently flushed to remove the obstruction and repositioned for another

Figure 23.1. Ultrasonography of the eye of a Doberman Pinscher with PHTVL/PHPV. The posterior portion of the lens has a flattened appearance and shows increased density because of cataract. A persisting hyaloid artery is visible in the vitreous, running from the optic disc to the posterior pole of the lens. (Courtesy of Dr. S. Boroffka.)

Figure 23.2. Hyalocentesis. The point of insertion of a 22- to 26-gauge needle (0.70–0.45 mm), 5–7 mm posterior to the limbus, depending on the ocular quadrant and globe size as determined by calipers or ultrasonography, is of utmost importance.
attempt. An amount of balanced salt solution (BSS) or other vitreal substitute equal to the volume of aspirated vitreous should be injected at the same site to restore the vitreous volume and intraocular pressure. Conversely, if drugs are injected, the same volume of vitreous should be aspirated. In endophthalmitis, diagnostic hyalocentesis is believed to have a higher sensitivity than aqueous paracentesis (Brightman et al., 1986).

**THERAPEUTIC PROCEDURES**

**Medical Treatment**

Because the vitreous is avascular in adult dogs, penetration of systemically administered drugs is poor. When the blood-aqueous barrier is compromised, such as occurs in uveitis, accessibility of the vitreous for drugs increases. Hence, systemic administration of drugs, even though relatively safe, is of limited use in reaching the vitreous medically. The most direct way to achieve high drug concentrations in the vitreous is by intraocular injection. The globe only tolerates rather low doses and volumes, however, and large doses may produce severe ocular damage (Gelatt, 1978). This latter phenomenon is used by injecting gentamicin into the vitreous as a treatment in globes with absolute glaucoma and in which enucleation is contraindicated. For therapeutic intravitreal injections, hyalocentesis is performed. Topical or subconjunctival administration of drugs is indicated only in ciliary body-dependent vitreal pathology; such administration is of limited value in treatment of other posterior segment disease (Gelatt, 1978).

**Surgical Treatment**

Surgical treatment is necessary when the vitreous is displaced within the pupil during anterior segment surgeries and in the treatment of retinal detachments. Additional details on vitreous surgery are provided in Chapter 25.

**Vitrectomy**

Vitrectomy is generally indicated when vitreous presentation or protrusion occurs during anterior segment surgery. A further indication for vitrectomy is during vitreoretinal surgery for the treatment of retinal detachments and vitreal traction bands.

**Anterior Vitrectomy**

An anterior vitrectomy is indicated when formed vitreous protrudes into the pupil or the anterior chamber during anterior segment surgery. During intracapsular lens removal, presentation of vitreous may be prevented by trying to carefully separate the posterior lens capsule from the anterior surface of the vitreous. In humans, this is thought to be practically successful only in patients older than 50 years (McLeod, 1987). In most cases involving dogs, protrusion occurs during or directly after intracapsular lens removal. If the posterior lens capsule is perforated during cataract surgery, the vitreous may protrude into the capsular bag, pupil, anterior chamber, or even into the corneal incision. Protrusion of vitreous in the pupil or the anterior chamber may physically impair or obstruct the flow or drainage of aqueous, resulting in an increased intraocular pressure. In addition, vitreous touching the corneal endothelium may cause persistent corneal edema. If left untreated, vitreous protrusions may cause the development of traction bands, with the risk of subsequent retinal detachment.

**Pars Plana Posterior Vitrectomy**

In pars plana posterior vitrectomy, part of the vitreous is removed using an automated vitrectome. Successful use of this method requires considerable experience. The surgical entrance is where the dorsolateral sclera is positioned over the pars plana ciliaris. This procedure is commonly included in surgical treatment of complicated retinal detachment and vitreal traction bands. For a description of vitreoretinal surgery, see Chapter 25. Other indications for this procedure includeophthalmo(myiasis interna posterior (Ollivier et al., 2006) and uveitis (mainly used in horses with equine recurrent uveitis).

For surgical procedures concerning the vitreous, the same pre- and postoperative measures and anesthesiologic considerations that are valid for other intraocular surgeries are applicable.
VITREAL DISEASES

Developmental Disorders

Developmental disorders form a group of relatively rare opthalmic anomalies. Usually, these anomalies are part of syndromes associated with persisting intraocular vasculature or with other ocular developmental disorders, such as microphthalmia, Collie eye anomaly (CEA) (Roberts et al., 1966; Roberts, 1969), and retinal dysplasia (Rubin, 1974; Saunders & Rubin, 1975). Their causes are not well understood, but these anomalies may result from a chance error during embryogenesis or have a hereditary cause, as has been determined for several canine breeds.

Persistent Hyaloid Artery (PHA)

The anomaly PHA results from failure of part or all of the hyaloid artery to regress (Fig. 23.3). The artery may have persisted as a string (in some cases containing blood) situated in the vitreous space, between the optic disc and the lens (Duddy et al., 1983). In PHA, only a small, dense, white, connective-tissue string usually remains adhered to the posterior lens capsule. The optic disc may have a conical shape (i.e., Bergmeister’s papilla), and during ocular movements, PHA structures lag slightly behind and thus may show a “waving” motion. In addition, there may be scar-like lesions in or against the posterior lens capsule where the PHA is in contact with or attached to the capsule and in the immediately surrounding area. In some cases, such “scars” may lead to cataract formation in the adjacent lens fibers. PHA has been suggested to be hereditary in the Sussex Spaniel (Stades & Boevé, 1989) and the Doberman (Stades, 1980).

PHA alone rarely requires surgical treatment. If the associated cataract formation leads to visual impairment, however, surgery may be indicated. In these cases, the risk of complications is slightly higher than that in cases of cataract alone, because in PHA-related cataracts, central fenestration of the posterior lens capsule and anterior vitrectomy are indicated. This may be especially hazardous when the hyaloid artery is still patent. In such cases, the hyaloid artery must be closed before transection, preferably by wet-field coagulation.

Persistent Tunica Vasculosa Lentis

In persistent tunica vasculosa lentis, there are fine, white, strand-like deformities (i.e., “spiderweb”), or parts of vascular structures, attached to the posterior lens capsule (i.e., persistent tunica vasculosa lentis posterior). These structures are the remainder of the tunica vasculosa lentis (posterior), retrolentally connected to, or “printed” on, the posterior lens capsule. Fine strands may also extend from the equator through the pupil to the “collarette” on the anterior surface of the iris (persistent tunica vasculosa lentis anterior). These structures generally have no clinical significance, and they may be observed incidentally during routine ophthalmic examinations. Slit lamp biomicroscopy, using a very narrow light beam, will reveal their presence as well as their typical retrolental–capsular location. The lens contents should be free of any opacity.

PHTVL/PHPV

In this group of apparently rare and generally unilateral disorders (Barnett & Grimes, 1973; Gelatt, 1973; Grimes & Mullaney, 1969; Kern, 1981; Rebhun, 1976; Rubin, 1974; Peiffer et al., 1977) parts of the hyaloid system and primitive vitreous have become hyperplastic during early fetal development, combined with a subsequently incomplete regression. This anomaly has been described in several species. In the dog, PHTVL/PHPV has been described in the Bloodhound, Bouvier des Flandres, Samoyed, Siberian Husky, and Spanish Pacho (Bayón et al., 2001; Gemensky-Metzler & Wilkie, 2004; Rensburg et al., 1992; Ori et al., 1998; Venter et al., 1996). In 1980, bilateral PHTVL/PHPV has been studied extensively and was recognized as a hereditary eye disease in the Doberman (Stades, 1980, 1983a, 1983b; Van der Linde-Sipman et al., 1983) and later also recognized hereditary in the Staffordshire Bull Terrier (Curtis et al., 1984; Boevé et al., 1988b). The early morphogenesis of the canine lens, hyaloid system and the vitreous body, and later the fetal development of PHTVL/PHPV in the Doberman, have been studied extensively (Boevé et al., 1988b 1990, 1992; Boevé & Van Zoelen, 1989).

In Doberman fetuses with PHTVL/PHPV, the hyaloid system and tunica vasculosa lentis posterior have been
described to be hyperplastic as early as day 30 of gestation, compared to the development in normal Beagle fetuses as controls.

The clinical relevance of this condition is its association with cataract formation and hence visual impairment (Stades, 1980). In both the Doberman and the Staffordshire Bull Terrier, PHTVL/PHPV generally occurs bilaterally, is inherited (probably because of an incomplete dominant gene in the Doberman), and hence has a higher prevalence in these breeds compared with that in others (Boevé et al., 1992; Curtis et al., 1984; Stades, 1980, 1983b).

The pathophysiology of this anomaly has not been determined. Mice lacking arf and p53 tumor suppressor genes as well as Norrie disease pseudoglioma and ARPS, or Norrie disease and FZD4 genes suggest that at least these genes are needed for hyaloid vasculature regression (Shastry, 2009).

Signs range from very small, retrolentally positioned fibrovascular dots that represent minor remnants of the tunica vasculosa lentis vasculature (i.e., grade 1) (Fig. 23.4, Fig. 23.5, Fig. 23.6, and Fig. 23.7). The pathologic findings in the different grades of PHTVL/PHPV are depicted in Table 23.1.

The retrolental dots alone (grade 1) to lens deformation and complete opacification cause no further ocular changes during life, and they do not impair vision. These dots are generally visible with the aid of a slit lamp microscope. The severe grades, as in the hereditary forms of PHTVL/PHPV, occur bilaterally and usually lead to visual impairment. In grade 2, a retrolental plaque of white fibrovascular tissue, which is sometimes combined with glial tissue components, is centrally located against the posterior capsule and is accompanied by grade 1 dots peripherally. In the more severe grades (i.e., grades 3–6), there may be larger parts of the hyaloid system (grade 3), which are sometimes accompanied by glial tissue, lenticonus (grade 4), or some combination (grade 5). Grade 6 comprises the most severe ocular malformations resulting

Figure 23.4. Slit lamp micrograph of the posterior lens capsule of a Doberman with grade 1 PHTVL/PHPV. Yellow-brown pigment dots are visible on the posterior capsule.

Figure 23.5. Scanning electron micrograph of the posterior lens capsule, as observed from posterior, of a Doberman with grade 1 PHTVL/PHPV. Two retrolental dots are visible on the posterior lens capsule. (Original magnification, 1600×.) (Courtesy of Professor G.F.J.M. Vrensen.)

Figure 23.6. Postnatal persistence of vasculature belonging to the hyaloid system, including the hyaloid artery, the vasa hyaloidea, and the TVL, as seen in the right eye of a Doberman puppy with grade 3 PHTVL/PHPV.
Table 23.1 Classification of the Lentinal and Retrolental Anomalies in Doberman with PHTVL/PHPV

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical Findings</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Limited posterior capsular cataract with capsular/retrolental pigment dots, about 0.5mm in diameter.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>More extensive central posterior capsular cataract with yellow-brown capsular/retrolental fibrous tissue. Multiple pigment dots in the central part as well as in the periphery of the posterior capsule. In cross section, the appearance of persistent pupillary membrane occurred frequently in Dobermans with PHTVL/PHPV.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Persistent tunica vasculosa lentis-hyaloid system vessels appearing as a meshwork combined with grade 2 abnormalities.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Lenticonus of varying extent combined with more or less extensive elevation and grade 2 abnormalities.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Combination of grade 3 and grade 4 abnormalities.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Combinations of the first five grades, such as lens coloboma, microphakia, larger (retro)lental clots of pigment, or red material like free blood.</td>
<td></td>
</tr>
</tbody>
</table>

*Cataract formation is depicted in the frontal and sagittal views. Cataract progression may occur in grades 2 through 6 based on the extent of the retrolental anomalies, and mature cataracts may develop in grades 2 and higher.*
The differential diagnosis of PHTVL/PHPV includes cataracts resulting from other causes, microphthalmia alone, and other solitary dysplastic disorders of the lens. In severely affected blind eyes (i.e., grades 2–6), cataract surgery with fenestration of the posterior capsule and transection of the hyaloid artery, if applicable, combined with anterior vitrectomy may be indicated. The prognosis for surgery in severely affected cases of PHTVL/PHPV is less favorable than that in routine cataract surgery because of the higher complication risks (Stades, 1983a). Especially in cases with a patent PHA or when extensive vitrectomy is indicated, the prognosis is less favorable because of the possibility of intra- or postoperative vitreal hemorrhage, formation of traction bands, and retinal detachment. The owner should be well informed about these risks.

Preventive examinations for PHTVL/PHPV can be performed in puppies. Preferably, the puppies should be older than 6 weeks and be positively identifiable by tattoo or microchip. Because the globes are still small at this age, fine dots (grade 1) may easily be overlooked. Hence, the result of a litter examination should always be regarded as preliminary. On the other hand, early examination prevents new owners from receiving severely affected puppies.

Dogs with severe PHTVL/PHPV (grades 2–6) should be excluded from breeding. The prevalence of Dobermans with severe forms of PHTVL/PHPV in the Netherlands decreased significantly after implementation of an adequate breeding program (Stades et al., 1991).

Other Anomalies
The vitreous may be involved in diseases of its bordering structures as well. In CEA, a partial failure of vitreal development, which is only recognizable with use of a slit lamp microscope, has been described (Tolentino et al., 1965). Vitreal syneresis, vascular anomalies, hemorrhages, and retinal detachment may also be found in CEA. These anomalies may include preretinal vascular loops penetrating into the vitreous, and such vessels may easily give rise to vitreal hemorrhage. In case of retinal detachment, the neuroretina is partially or totally detached into the vitreous.

In the focal and geographic forms of retinal dysplasia, the retina folds slightly into the vitreous. In severe forms of retinal dysplasia, as has been described for the Bedlington Terrier (Rubin, 1968), Yorkshire Terrier (Stades, 1979), and in the Labrador Retriever (in combination with skeletal abnormalities) (Barnett et al., 1970; Blair et al., 1985; Carrig et al., 1977), the retina is partly or totally detached and dislocated into the vitreous space. Syneresis may be present in retinal dysplasia as well.

Acquired Disorders
Trauma
Penetrating trauma, such as caused by air-rifle or shotgun pellets, easily causes floaters of blood in the vitreous. The penetration tunnel is usually marked by prolapsed lens material, blood residues, traction bands, and other scars, and the foreign body itself may still be present in the vitreous. Less often, blunt trauma causes vitreal hemorrhage. Dogs that show ophthalmic problems of sudden onset that include signs of trauma such as corneal edema, hyphema, uveitis, and vitreal hemorrhage should additionally be examined with diagnostic imaging techniques, especially ultrasonography, for the presence of foreign bodies, vitreal changes, and retinal detachment. Survey radiography alone will be sufficient for demonstrating metallic foreign bodies.

Depending on the severity of the concurrent uveitis, therapy in such patients consists of topical antimicrobial treatment/prophylaxis, mydriatics/cycloplegics (e.g., 1% atropine), and dexamethasone (four to six times daily), as well as systemic prophylactic antimicrobial and extensive antiinflammatory treatment (e.g., corticosteroids or nonsteroidal anti-inflammatory drugs). In case of ocular hypertension, the intraocular pressure should be reduced as well, in which case the use of parasympatholytic mydriatics, and especially atropine, would be contraindicated.

Degenerative Vitreal Disorders and Reactions
The term vitreous degeneration is clinically used to indicate vitreous changes that are consistent with breakdown of the vitreous hydrogel. Signs may comprise liquefaction (syneresis) and opacities (floaters, asteroid hyalosis, and synchysis scintillans). However, in "normal" dogs, a wide variety of vitreous gel consistencies can clinically be noticed.

Over the last years, an entity called primary vitreous degeneration has become an issue in a number of breeds, such as Brussels Griffon, Chihuahua, Chinese Crested, Havanese,
Chapter 23: Diseases and Surgery of the Canine Vitreous

The etiology and pathophysiology of vitreous degeneration is diverse. Other than possible breed predispositions as mentioned before, a hereditary etiology has not been determined in the dog. In humans, mutations in the collagen COL2A1 and COL11A1 genes have been reported to cause vitreous degeneration. Vitreous degeneration has been described to be related to the rate of oxygen consumption and ascorbate concentration in (human) samples obtained by vitrectomy (Shui et al., 2009).

**Syneresis**

Syneresis is a degenerative breakdown of the vitreous gel that separates its liquid from its solid components, resulting in liquefaction and development of fluid-filled cavities within the vitreous. This breakdown may occur with age, but it can also be the result of inflammatory reactions or unknown causes (Okun et al., 1961). For human and bovine vitreous fibrils, it has been described that the shielding of type II collagen from exposure on the fibril surface by type IX collagen decreases with age. This predisposes the vitreous collagen fibrils to fusion, which may lead to liquefaction (Bishop et al., 2004). Another pathophysiological momentum of age-related vitreous liquefaction might be the increase in potential degradative activity in (human) vitreous (Voughan-Thomas et al., 2000).

Syneresis predisposes to posterior vitreous detachment. Foss & Wheeler (1982) reported a strong correlation between vitreous liquefaction and posterior vitreous detachment in man. Posterior vitreous detachment rapidly progresses into total vitreous detachment, separating the posterior vitreous cortex from the neuroretina by traction, thus potentially leading to a retinal tear and to rhegmatogenous retinal detachment. For the dog, this was recently suggested in a publication of Itoh et al. (2010). In this publication, the development of rhegmatogenous retinal detachment in the Shih Tzu was suggested to occur through primary retinal degeneration and secondary vitreous degeneration (syneresis).

In humans, loss of vitreous gel has been described to increase the risk of age-related nuclear cataracts (Harocopos et al., 2004). The process of syneresis usually starts retroentially. It can be recognized by the presence of fine, cloudy structures whose slow movements follow the movement of the eye.

**Vitreous Floaters**

Vitreous floaters, muscae volitantes, or “flying flies” are larger flakes or streaks in the vitreous that may lag behind ocular movements. If these structures are very movable, especially against bright light, they can give the impression that something resembling a fly is passing by. In the past, this was thought to cause the so-called fly-biting syndrome, but today, this behavior is suspected to result mainly from nonophthalmic causes, such as temporal or occipital lobe dysfunction (Chrisman, 1991). Vitreous floaters are uncommon and rarely require surgical treatment.
Asteroid Hyalosis

Asteroid hyalosis (Fig. 23.11) is characterized by many small and possibly slightly pigmented particles (i.e., “asteroid bodies” from 0.03 to 0.10 mm in diameter) in the vitreous of one or both eyes (Miller et al., 1983; Rubin, 1963; Schaeffer, 1985).

These particles move both during and following movements of the globe, but they also return to their initial position. They generally have no distinct influence on vision by their presence alone; however, asteroid hyalosis may be associated with posterior uveal changes or (progressive) retinal atrophy.

Asteroid hyalosis has been described to occur in experimentally galactose-fed beagles that develop the advanced stages of diabetes-like retinopathy (Wang et al., 2006). Comparisons of vitreous humor containing asteroid bodies collected from these beagles and vitreous samples from age-matched normal beagles have indicated that asteroid bodies contain calcium and phosphorus (Kador & Wyman, 2008). Further analyses resulted in the identification of the quasimolecular ion of 1,2-dipalmitoyl-glycero-3-phosphoethanolamine (DPPE) as the main component of asteroid bodies (Kador & Wyman, 2008). In the same publication, it was suggested that these lipid components diffuse into the vitreous originating from a degenerating retina.

A steroid hyalosis and synchysis scintillans may be difficult to differentiate clinically.

Synchysis Scintillans

Synchysis scintillans is characterized by numerous cholesterol particles in a more or less liquefied vitreous. Especially after eye movements, they can resemble a snow flurry behind the lens, and against bright light, they may cause dazzling. The abnormality is rare and seldom causes recognizable problems in dogs. It may be associated with retinal atrophy (Barnett, 1966a, 1966b; Leon, 1988) or with posterior uveitis (Hogan & Zimmerman, 1962). Synchysis scintillans and asteroid hyalosis may be difficult to differentiate clinically.

Intravitreal membranes

Intravitreal membranes are associated with intraviteal hemorrhage. In one study, intravitreal membranes were determined to be of glial origin predominantly (Zeiss & Dubielzig, 2004). Additional common findings in that study included epiretinal membranes, retinal neovascularization, preiridal fibrovascular membranes, and glaucoma.

Vitreal Inflammations

Because the adult vitreous has no intrinsic vasculature nor nerve supply, the possibilities of reaction to noxae are limited. Hence, inflammation of the vitreous itself (i.e., hyalitis, vitritis) will almost always be secondary to inflammatory reactions of adjacent structures. Floaters of hemorrhagic or other exudate in the vitreous, especially if diffuse or bilateral, often result from exudative uveitis, chorioretinitis, retinitis, or optic neuritis. Vitreal exudates may also be secondary to perforating, iatrogenic, or blunt trauma, to retinal detachment, or to intraocular neoplastic or paraneoplastic diseases (e.g., lymphosarcoma, malignant histiocytosis). Therefore, the history as well as further examinations in such cases should be directed at revealing both the direct and any possible underlying causes.

Free blood in the vitreous is relatively uncommon (Fig. 23.12). Hemorrhage may result from congenital anomalies, such as the persistence of fetal vasculature (e.g., PHA, PHTVL/PHPV), CEA, trauma, infection, or systemic diseases (e.g., coagulopathies, vasculitis, systemic hypertension, neoplasms). Blood in the vitreous has been described to have a destructive effect on the gel structure: vitreous adjacent to a...
Depending on the geographic location of the patient, various infectious agents are known to induce vitreal exudates. Infections reported to cause vitreal exudates include blastomycosis, cryptococcosis, histoplasmosis, brucellosis, and other diseases (Gwin et al., 1980; Legendre et al., 1981; Moore et al., 1985).

In these cases therapy should be directed primarily at the underlying cause. If signs of infection are present, high doses of antimicrobial agents with high intraocular penetration are indicated. In such severe cases, vitreous culturing and biopsy may be indicated, followed by intravitreal administration of antimicrobials. At present, the types of vitreal surgery advocated in such cases among humans, including extensive vitrectomy, have found only limited application in veterinary ophthalmology.

The prognosis of vitritis strongly depends on the underlying cause. Small amounts of blood or exudate may be resorbed, but larger amounts usually cause visual disturbances, even if the inflammatory reaction can be controlled. Vitreal membranes and traction bands may develop. In turn, vitreal displacement, prolapse, herniation, and traction caused by traction bands or membranes may cause secondary retinal detachments even months after the primary disorder has resolved.

Cysts

Cysts, most likely originating from the pigmented epithelial layer of the iris or the ciliary body, may extend into the vitreous (Leon, 1988). These cysts are much less common than anterior chamber uveal cysts. In humans, use of miotic agents has been described to cause cysts of uveal origin (Shields...
SECTION III: Canine Ophthalmology

Canine Ophthalmology

Primary neoplasms of the retina, choroid, and optic nerve are extremely rare in the dog, and neoplasms originating from the anterior uvea are relatively uncommon in this species. Uveal neoplasms mainly comprise malignant melanomas, but other neoplasms have been reported (Barrie & Gelatt, 1981; Langloss et al., 1976; Meyerholz & Haynes, 2004; Saunders & Barron, 1958).

Retinoblastoma, which is a well-known tumor with vitreal extension in humans, is virtually nonexistent in the dog (Hogan & Albert, 1991), and has only once been positively identified according to the criteria used in humans (Syed et al., 1997). The prognosis for an eye affected by a neoplasm extending into the vitreous depends on both the type of neoplasm and its extension, but such a neoplasm generally should be considered an indication for enucleation.

Tumors located in the vitreal space generally appear as a retrolental mass of grayish, red, or darkly pigmented tissue, often containing wildly arranged vasculature. Patients suspected of having intravitreal neoplasms should be examined clinically by diagnostic hyalocentesis and diagnostic imaging techniques (i.e., ultrasonography, CT, MRI), and they should be referred for oncologic evaluation. Treatment and prognosis depend on the underlying cause, the range and locations of the affected areas, and the existence of related neoplasms in other parts of the body.

THE VITREOUS IN RELATION TO OTHER OPHTHALMIC DISORDERS

Lens Luxation

The lens may dislocate when its suspension system is compromised by degeneration or rupture of the Zinn zonular fibers. The zonular fibers may have developed abnormally or have degenerated; in exceptional situations, they can rupture from external trauma (Curtis, 1990; Martin, 1978).

If several zonular fibers have ruptured, vitreous may leak into the anterior chamber along the lens equator and through the pupil. If the fibers have ruptured over a greater area, subluxation of the lens will occur. If the lens becomes completely unattached, it may remain more or less in its normal position, be displaced toward anterior or posterior, or topple. Because of its volume and the strong attachment of the posterior lens capsule to the vitreous, a dislocated lens will dislocate part of the vitreous as well. Subsequently, vitreous may prolapse or herniate in the pupil, thus impairing, or even blocking, drainage of aqueous between the posterior surface of the lens and the anterior surface of the iris (if the lens has become dislocated into the anterior chamber) or, at the level of the drainage angle, causing secondary glaucoma in all cases.

The earliest recognizable sign of a lens luxation is the presence of slight vitreous protrusions, which are recognizable on slit lamp biomicroscopy as thin, white clouds along the pupil margin. These protrusions are visualized best when illumi-
Mountain Dog suffering from systemic hypertension.

Figure 23.15. Bullous retinal detachment in the left eye of a Bernese Mountain Dog suffering from systemic hypertension.

Retinal Detachment

A retinal detachment may occupy part, or almost all, of the vitreous space (Fig. 23.15). A small retinal detachment is observed as an indistinctly bordered, grayish blue “cyst” or fold of the retina. Large detachments look more like grayish blue to red, parachute-shaped, vascularized bullae positioned either directly behind the posterior lens capsule or deeper in the vitreous. Depending on the type of detachment, the optic disk may be obscured. Also, dark sheets of blood, pigment, or other inflammatory signs may be found. The combination of intraocular (intravitreal) hemorrhage and retinal detachment may be indicative of systemic hypertension. Diagnostics should therefore include an internistic workup including blood pressure measurement.

In retinal detachments, the outer layer of the neuroretina (i.e., photoreceptors) and the pigment epithelium have separated. Only the aspects directly related to the vitreous have been discussed in this chapter; Chapter 24 addresses retinal detachment and its implications in detail. Retinal detachments of vitreous origin may develop because of vitreous traction bands (e.g., after perforating trauma or lens luxation), by dissolution of the vitreous (i.e., syneresis), or as a complication following vitreous surgery or hyalocentesis. Vitreous prolapse, or traction caused by secondary strings or membranes in the vitreous, resulting from posttraumatic uveitis, including postoperative uveitis after intracapsular lens extraction, may cause secondary retinal detachment even months after surgery. Surgical techniques to reattach the retina are described in Chapter 25.

REFERENCES


Chapter 24

Diseases of the Canine Ocular Fundus

Kristina Narfström and Simon M. Petersen-Jones

METHODS OF EXAMINATION

The ocular fundus is examined with various direct and indirect diagnostic methods. Several methods are routinely used clinically, while others are more investigative.

Behavioral Testing

Careful questioning of the owner is usually an important source of information about a dog’s visual performance; however, this information may be incomplete or invalid. Furthermore, the ability of a visually impaired or blind dog to adapt to familiar surroundings by relying on other senses and a memorized image of the environment can mask the signs of impaired vision. Therefore, observing the dog’s behavior in an unfamiliar environment is a valuable and necessary complement to the history.

A simple maze, in which several buckets can be used as obstacles, can be set up in a room unfamiliar to the dog. The dog’s ability to negotiate the obstacle course will add information on the dog’s visual capacity. The dog’s performance should be tested in both daylight conditions and dim light to assess photopic and scotopic vision. The lighting level for the dim light assessment should be low: below the human threshold for color vision. Furthermore, the dog should be tested with both eyes uncovered, but also with each eye covered in turn to enhance detection of unilateral visual impairment. A dog usually learns the path through the maze after a few attempts, so the obstacles must be rearranged frequently for the test to provide objective results. A more standardized obstacle course testing method has been recently described (Garcia et al., 2010). A novel method for standardized and objective vision testing has been developed for dogs (Gearhart et al., 2008).

It should be noted that in certain disease conditions, such as in day blindness, vision testing in normal room light may not be sufficient to diagnose a cone disorder (Ropstad et al., 2007a). Outside, in bright daylight, however, the clinical changes in regard to the cone system are more obvious, such as difficulties in negotiating the maze and, in some cases of day blindness, marked miosis (Hurn et al., 2003).

Vision may also be assessed from the dog’s response to falling objects (visual tracking) that do not create a noise or current of air (e.g., small cotton balls). The balls can be dropped both in front of the dog and to the sides to get an impression of central and peripheral vision. The results should be interpreted with some caution, however, because of patient indifference.

Some diseases that affect the retina also affect the central pathways, including the visual cortex. For example, the neuronal ceroid lipofuscinoses (NCLs) involve vision loss that may be attributed to progressive retinal degeneration, involvement of central neuronal structures, or both. The disease complex is characterized by progressive cognitive decline and associated behavioral changes. For these disorders, objective tests have been developed and are also becoming widely used in the pharmaceutical industry to assess the effects of drug formulations on vision, cognitive function, and behavior (Milgram et al., 1994). In the NCL group of diseases, the pupillary light reflexes (PLRs) are also important to evaluate.

Testing Reflexes and Responses

The PLR requires a functional retina but also depends on postretinal transmission of signals. Loss of the PLRs is not a definite sign of retinal dysfunction or even of loss of vision. They can also be partially inhibited in an apprehensive patient because of an increased sympathetic tone. Furthermore, residual PLRs are often present in dogs even with advanced retinal degeneration, such as in progressive retinal atrophy (PRA), especially if the inner retina is preserved. The reason for this phenomenon is that the PLRs are driven by the photoreceptors at low light levels and have been shown in various species to be driven by the melanopsin-containing ganglion cells at high light-intensity stimulation (Guler et al., 2008; Kardon et al., 2008).
The presence of the PLRs is therefore not a guarantee of a healthy retina in dogs with opaque media (e.g., preoperatively in those with dense, extensive cataracts) that prevents ophthalmoscopic examination. A totally unresponsive pupil might suggest any kind of generalized retinopathy, glaucoma, or lesion involving the reflex pathway including the pupillary sphincter muscle. The direct and indirect PLRs are routinely tested in mesopic conditions using a strong focal light. For investigational and research purposes, the PLRs are often tested both in scotopic and photopic conditions, using either a custom-made or a commercially available pupillometer (Thompson et al., 2010). The menace response (i.e., the reaction to a sudden, threatening object coming into the near field of view) may also be used to assess vision. This cortical response requires both a functional sensory pathway from the photoreceptors to the visual cortex and an intact motor pathway, including the facial nerve. Blinking and, possibly, withdrawal of the head is the normal response. Objects the dog can smell or that cause air currents will incorrectly stimulate senses other than vision. It is noteworthy that absence of a menace reaction may be caused by pathologic conditions other than severe visual impairment, and also normal dogs may react differently. It should be remembered that this is a learned response and not present in young puppies.

**Structural Visualization of the Fundus**

Direct and indirect ophthalmoscopy are both used in veterinary ophthalmology to visualize the fundus. The ophthalmoscopic examination is performed in a darkened room using short-acting mydriatics, such as 0.5%–1.0% tropicamide (Mydriacyl; Alcon Laboratories, Fort Worth, TX). Direct ophthalmoscopy in general provides the observer with a smaller field of view that is of greater magnification and detail than that with indirect ophthalmoscopy. Direct ophthalmoscopy is mainly used to examine the central parts of the fundus, especially the region of the optic nerve head (ONH), but it is considered inadequate to examine the peripheral fundus of domestic animals. Indirect ophthalmoscopy allows a more complete examination of the fundus in a shorter time. Moreover, it allows stereopsis, which is useful in appreciating the topographic features of the retinal surface such as when appraising retinal detachments, colobomas, and papillary edema. Different indirect lenses can be selected to allow for a more highly magnified view when required. Also, indirect ophthalmoscopy simplifies examination when the fundus is partly obscured by opacities of the ocular media (e.g., cataracts). Both techniques, however, have advantages that complement each other when used together.

In both direct and indirect ophthalmoscopy, lateral magnification varies inversely with the focal length of the eye and axial magnification with the inverse square of focal length, but linear field size varies directly with the focal length of the eye. These variations result in large, species-dependent differences in axial magnification that must be considered when interpreting ophthalmoscopic findings in different animals (Murphy & Howland, 1987). For example, a mild elevation of the disc margin in a horse should be given much more significance as a clinical finding than a disc of similar ophthalmoscopic appearance in a dog because the axial magnification of the ophthalmic image of a horse eye is proportionally much less than that of a dog eye, and the topography of the image is correspondingly flattened. When working in the field of comparative ophthalmology, it is important to keep these aspects in mind.

**Scanning Laser Ophthalmoscopy (SLO)**

Scanning laser ophthalmoscopy (SLO) is a diagnostic imaging technique developed for very precise and detailed fundus visualization. Lasers of different wavelengths allow the examiner to obtain information about specific tissues and layers on the basis of their reflection and transmission characteristics (Cideciyan et al., 2005b; Rosolen et al., 2001; Seeliger et al., 2000, 2005). The laser beam is used to scan the fundus, thereby allowing examinations with low levels of light, high resolution, and high contrast of retinal details as well as simultaneous video display of the fundus. The SLO can also be utilized in an angiography mode in order to correlate functional with morphological aspects in disease processes affecting the retina and/or the choroidal vasculature (Fig. 24.1).

**Optical Coherence Tomography (OCT)**

During the past decade, an imaging technique called optical coherence tomography (OCT) has been developed and used both in research and for clinical purposes to evaluate in vivo retinal structure (Cideciyan et al., 2005a; Drexler & Fujimoto, 2008; Jacobson et al., 2004; Panzan et al., 2004). High-resolution, cross-sectional images of optical reflectivity are obtained. The technique is based on the principle of low-coherence interferometry in which distance information concerning various ocular structures is extracted from time delays of reflected signals. This in vivo microscopy technique gives information about retinal organization and structural integrity. For example, photoreceptor-layer thickness can be quantified using OCT. The technique is mainly used for evaluation of retinal layers in disease processes and can also be used in the determination of therapeutic progress (Jacobson et al., 2005). Instrumentation has also been developed that utilizes both OCT and SLO techniques simultaneously.

**Adaptive Optics**

Newer noninvasive imaging techniques are under development. Some use adaptive optics to adjust for the aberrations of the optical media allowing for highly magnified examination of the retina in vivo. Individual photoreceptors can be imaged using the adaptive optic techniques (Williams, 2011).
SECTION III

Angiography

All phases in angiography—the choroidal, retinal arterial, arteriovenous, venous, and late phases—are visualized, with all but the last phase occurring within the first 15 seconds.

Angiography can also be performed with SLO equipment (Seeliger et al., 2005). The HRA I SLO, produced by Heidelberg Engineering (Dossenheim, Germany), has been modified for use in animals (Seeliger et al., 2000). It provides two argon laser wavelengths (488 and 514 nm, respectively) in the short wavelength range and two infrared diode lasers (795 and 830 nm) in the long wavelength range. The 488 and 795 nm lasers are used not only for FL angiography, but also for indocyanine green (ICG) (ICG-Pulsion, Pulsion Medical Systems AG, Munich, Germany) angiography. Appropriate barrier filters of 500 and 800 nm, respectively, remove the reflected light with unchanged wavelength and allow the light emitted by the dye upon stimulation to pass through. ICG angiography is used to visualize the choroidal structures simultaneously with the retinal vessels (Seeliger et al., 2005). In pigmented animals, the short wavelength lasers provide the highest quality images of the retina but do not penetrate the retinal pigment epithelium (RPE) and choroid well. In contrast, infrared lasers show less retinal detail but also reveal choroidal structures clearly, down to the sclera. FL provides the most detailed images of retinal capillaries, whereas ICG adds information about choroidal vessels but shows less detail of the retinal vasculature (Fig. 24.1). The two dyes behave differently because of the difference in their affinity to large plasma proteins: ICG is bound more than 98% to such proteins, while FL tends to leak rapidly.

Ultrasonography

Ultrasonography is a valuable aid in detecting and monitoring pathologic conditions in the canine posterior segment (Dziezyc et al., 1987; van der Woerdt et al., 1993). In patients with opaque media (e.g., dense cataracts, intraocular hemorrhage), ultrasonography can be used to detect, for example, a detached retina or posterior segment neoplasm. Furthermore, ultrasonography can be used to study space-occupying conditions that are difficult to examine because of their location (e.g., neoplasms in the choroid close to the ciliary body). B-mode is generally preferred to A-mode ultrasonography because of its versatility and more easily interpreted images.

Angiography

Angiography is a helpful adjunct in the diagnosis of retinal diseases. It is mainly used to evaluate disease processes in which the vasculature of the eye is involved, such as vascular anomalies, posterior segment neoplasms, hypertension, retinal detachment, inflammatory processes, diabetic retinopathy, and degenerative processes. The procedure is performed either in sedated, anesthetized, or conscious dogs, depending on the preference and need of the examiner. Fluorescein sodium solution (FL) (Fluoresceine 10%; Faure, France) is given as an intravenous bolus into the cephalic vein. Fundus photography is then performed using a fundus camera connected to a power-back unit to allow for quick recycling of the black-and-white or color film. Excitation and barrier filters are used in the camera. Transmission of the excitation filter is recommended to be a maximum at 492 nm, and that of the barrier filter 575 nm, for good visualization in the dog (de Schaepdrijver et al., 1996). Digital fundus cameras are currently more frequently used, simplifying the procedures in angiography significantly. All phases in angiography—the choroidal, retinal arterial, arteriovenous, venous, and late phases—are visualized, with all but the last phase occurring within the first 15 seconds.

Angiography can also be performed with SLO equipment (Seeliger et al., 2005). The HRA I SLO, produced by Heidelberg Engineering (Dossenheim, Germany), has been modified for use in animals (Seeliger et al., 2000). It provides two argon laser wavelengths (488 and 514 nm, respectively) in the short wavelength range and two infrared diode lasers (795 and 830 nm) in the long wavelength range. The 488 and 795 nm lasers are used not only for FL angiography, but also for indocyanine green (ICG) (ICG-Pulsion, Pulsion Medical Systems AG, Munich, Germany) angiography. Appropriate barrier filters of 500 and 800 nm, respectively, remove the reflected light with unchanged wavelength and allow the light emitted by the dye upon stimulation to pass through. ICG angiography is used to visualize the choroidal structures simultaneously with the retinal vessels (Seeliger et al., 2005). In pigmented animals, the short wavelength lasers provide the highest quality images of the retina but do not penetrate the retinal pigment epithelium (RPE) and choroid well. In contrast, infrared lasers show less retinal detail but also reveal choroidal structures clearly, down to the sclera. FL provides the most detailed images of retinal capillaries, whereas ICG adds information about choroidal vessels but shows less detail of the retinal vasculature (Fig. 24.1). The two dyes behave differently because of the difference in their affinity to large plasma proteins: ICG is bound more than 98% to such proteins, while FL is bound to only about 70% (Destro & Puliafito, 1989). Consequently, ICG diffuses very slowly out of the vascular lumen, while FL tends to leak rapidly.
Functional Testing of the Retina
Electroretinography

When the retina is stimulated by light, a diffuse electrical response is generated by neuronal and nonneuronal cells that can be recorded as the electroretinogram (ERG) (Gouras, 1970). This response is a summation of electrical potentials that result from light-induced changes in the movement of ions, mainly sodium and potassium, within the extracellular space. Thus, the ERG is an objective, functional test of the retina and is critically dependent on the function of the photoreceptors (i.e., the rods and cones). It has a characteristic waveform that varies depending on several factors, but mostly on the type of stimuli used. The intensity, duration, frequency, and wavelength of the light stimulus as well as the interval between stimuli, size of the retinal area illuminated, pupil size, and (very important) stage of retinal adaptation are variables that account for alterations in the ERG response. Other variables affecting the ERG are depth of anesthesia or other drugs in use, type of recording electrodes, age and breed of the dog, stage of retinal development, and clarity of the ocular media.

The ERG is recorded by using an active contact lens electrode, and a reference and a ground electrode, and the results are displayed on an oscilloscope, ink-writer, or computer screen. Except for the overall appearance of the ERG waveform, the a-, b-, and in some types of recordings, c-waves, are evaluated regarding the implicit times and amplitudes of their peaks. Because the ERG is a complex response of the summed action potential of different retinal cell classes, the waveform obtained can be further analyzed to obtain other specific cell responses by varying one or more of the previously mentioned parameters, adjusting the equipment, or both (Fig. 24.2).

In clinical veterinary ophthalmology, the flash ERG is used in two broad applications (Acland, 1988; Aguirre, 1975; Narfström, 2006; Narfström et al., 1995). The first is to test whether a standard stimulus elicits an ERG response. This is useful in assessing retinal activity when the fundus is obscured (e.g., before cataract surgery) and in the differential diagnosis of retinal disease when ophthalmoscopic lesions are absent. The second is to specifically test rod and cone function in conjunction with research into retinal disease processes and in the early diagnosis of hereditary retinal degenerations and dystrophies. This second application requires knowledge of retinal physiology and basic electrophysiology, more complicated equipment than that for the first application, and standardized procedures. Procedures for standardization of ERG procedures have been adopted in human ophthalmology (Marmor et al., 2004). Guidelines have also been developed for performing dog ERGs (Narfström et al., 2002).

Pattern ERG (PERG)

The pattern ERG (PERG) measures a retinal response to a phase-reversing pattern stimulus which is focused onto the retina and maintains a constant overall mean luminance. The response is an electrical potential thought to derive from the retinal ganglion cells and the neighboring inner retinal structures (Arden et al., 1982).

The main characteristics of a pattern stimulus include overall screen brightness (i.e., mean luminance), brightness contrast of neighboring bars or checks (i.e., percent contrast), rate of pattern reversal (i.e., temporal frequency), and bar or check size (i.e., spatial frequency). In a description of PERG measurements, it is necessary to monitor one or more of these
visually evoked cortical potential, or visually evoked potentials (VEP). Visually Evoked Potentials (VEP) are recorded as a gross electrical signal generated at the occipital cortex in response to visual stimulation. These responses are used for clinical testing and are measured in microvolts. They are often also used for specific evaluation, such as detecting early glaucoma in humans (Bach et al., 1992). Further investigations have been performed also in dogs with suspected and early glaucoma (Bach et al., 1992; Graham et al., 1996; Hamor et al., 2000; Ofri et al., 1993).

In addition, PERG amplitudes correlate with visual field indices. Canine visual acuity was studied using evoked retinal and cortical field potentials by pattern stimulation, and canine acuity was 0.2 to 0.4 times that reported for primates (Odom et al., 1983). Differences in retinal anatomy, such as maximum density of ganglion cells, total number of ganglion cells, and total number of optic nerve fibers, may account for this variation between species. Another study using PERG estimated the mean acuity of the central 15 degrees of the canine retina to be 6.9 minutes of arc per phase and the mean acuity of the toroidal 15 degrees of retina around this central area to be 11.8 minutes of arc per phase (Ofri et al., 1993). Other methods to estimate canine visual acuity include behavioral testing, assessment of the optokinetic response, and measurement of visually evoked cortical potentials (Miller & Murphy, 1995).

**Visually Evoked Potentials (VEP)**

The visually evoked cortical potential, or visually evoked response, is a gross electrical signal generated at the occipital cortex in response to visual stimulation. These responses are of small amplitude (1–40 μV) and are extremely sensitive to stimulus changes. Therefore, computer averaging is necessary for their recording, and correct placement of electrodes is a necessary factor in achieving correct and reproducible results. The VEP reflects the electrical activity of the central part of the fundus because this area has a much larger cortical representation than the peripheral regions. Thus, in veterinary ophthalmology, the VEP is a test not only of the central visual function but also of the optic nerve and the higher visual tracts and visual cortex. It is useful in patients with normal ophthalmic examination results and a normal ERG.

The VEP is typically recorded in response to flash or pattern stimuli. In flash VEP, which is used most often clinically in the dog (Sims et al., 1989), luminance, stimulus rate, and color of the flash can be varied. In pattern VEP, the field size, pattern size, contrast, retinal location, and rate of pattern presentation can be varied. The latter type of stimuli is either phase-reversed or flashed on and off. Important factors affecting the VEP are pupil diameter, age, and refractive error.

Latency is the most useful clinical parameter to be evaluated in VEP, but waveform morphology and amplitude of the responses are often also used for specific evaluation. The VEP latency provides a sensitive means of detecting subclinical lesions in the canine visual pathways and of monitoring developmental changes in both neonatal and young animals (Ofri, 1993; Sjöström, 1985).

The SLO uses an incident laser beam of variable intensity to project any type of fixed or mobile stimulus onto a precise area of the retina (Cohen et al., 1994). Therefore, focal VEPs using the SLO can be obtained and recorded, thereby allowing direct functional tests under visualization of specific retinal areas. The fundus and the stimulation area are then observed simultaneously by the examiner on a monitor, and videoclips are captured.

**Multifocal ERGs and VEPs**

Regional functional testing procedures have been developed for both ERG and VEP recordings in order to obtain precise topographical mapping of disease (Hood & Zhang, 2000; Seeliger et al., 2000; Sutter & Tran, 1992). Both techniques allow for simultaneous measurements of ERG or VEP activity from many different retinal locations. The former technique utilizes SLOs for laser stimulation and direct visualization of the procedure with an additional stimulus in the optical pathway of the SLO by means of a wavelength-sensitive mirror. Multifocal ERGs can also be used to evaluate progress in the treatment of generalized retinal disease, such as has been performed after gene transfer in RPE65-null mutation dogs (Le Meur et al., 2007; Mayser et al., 2003) (Fig. 24.45).

**DNA-Based Tests for Retinal Dystrophies**

A discussion of DNA-based tests for hereditary retinal diseases is included in Chapter 9. Table 9.1 lists the tests available at the time of writing. However, this is a rapidly progressing field, and the reader is advised to review the current literature and websites of the laboratories offering genetic tests for up-to-date information.

**THE NORMAL OCULAR FUNDUS**

The canine ocular fundus is a challenge for the examiner because of its enormous variation in normal ophthalmoscopic appearance (Fig. 24.3). The great range of normal variation in fundic appearance could, perhaps, be expected when the diversity in the gross appearance of different canine breeds is considered; few would anticipate the ophthalmoscopic appearance of the fundus in a Chihuahua and an Irish Wolfhound to be similar. Certain features of the fundus relate to macroscopic properties (e.g., iris color, coat color). Similar to the situation in the cat, the appearance of the normal canine fundus also varies according to age, with obvious color changes usually occurring during the first 3–4 months of life. The eyes of one individual are often mirror images of another, though marked differences may be seen in some dogs (e.g., one eye may have a subalbinotic fundus and one fundus with a brightly colored tapetum and pigmented nontapetal area in a Collie or Siberian Husky).
It is essential that the extent of variation in the normal fundus be recognized and understood before making the diagnosis of any pathologic condition of this structure. This is particularly important for the progress of programs to eradicate hereditary eye disease, when the veterinary ophthalmologist is asked to examine and certify that a dog, usually without any history or evidence of visual impairment, does not exhibit any sign of hereditary retinal dystrophy.

In most dogs, as in most domestic mammals, the fundus can be subdivided into a tapetal and a nontapetal zone. The tapetal fundus may occasionally be absent in the dog.

**Tapetal Fundus**

The combination of the tapetum lucidum and an absence of pigment in the overlying RPE is the anatomic basis for the tapetal fundus. The tapetal fundus forms an almost triangular area, with a horizontal base, in the dorsal half of the fundus. The area is usually brightly and beautifully colored and reflective. The size of the tapetal fundus varies extensively. Usually, it is large, and it may sometimes surround the ONH in gaze hounds (i.e., dogs that hunt by sight [e.g., Greyhounds]) and large breeds. It is often poorly developed, however, in toy dogs.
breeds (e.g., Papillons). In the latter case, the tapetum often only occupies a small area, usually temporal and dorsal to the ONH. The retinal blood vessels transverse the tapetum, and the vessels are more easily viewed in the tapetal zone than in the nontapetal area when ophthalmoscopy is performed. The nontapetal fundus surrounds the entire tapetal area and is typically darkly pigmented.

In dogs with a merle coat color (e.g., blue merle Collies, Shetland Sheepdogs, and related breeds), the tapetal fundus may be absent. Occasionally, the tapetal fundus may also be missing in other dogs, and in this case, the entire fundus resembles the nontapetal zone (i.e., dark, dull, and nonreflective). A combination of an absent tapetum lucidum and lack of pigment in the pigment epithelium will cause the fundus to have a reddish brown appearance because of the partial exposure of underlying choroidal vessels, a variant that has been observed in Beagles with a pale lemon iris.

The palette of the tapetal fundus includes hues of yellow, orange, green, and blue. Often, more than one color is present. A common combination (e.g., in Retrievers and Spaniels) is a mainly yellow tapetal fundus, with a transition to green and finally to blue at the junction with the nontapetal fundus. A greenish tapetal fundus bordered with blue is often seen in Doberman Pinschers and Miniature Schnauzers, but there is no general association between tapetal color and breed. Also, it should be remembered that different individuals in the same breed may exhibit different tapetal colors. Furthermore, there is no firm relationship between coat color and tapetal color.

One intriguing normal variation is a brightly colored center of the tapetal area with a distinct, grayish border zone. This variation, which is nonprogressive, may resemble changes seen in, for example, early cases of PRA, and sometimes it is seen in Cocker Spaniels and occasionally in other breeds. The tapetal fundus is usually described to be bright and reflective in the normal dog, but it should not have an intense, metallic glare.

In certain dogs, the area just above the ONH appears dull and pale reddish brown, and it lacks the foci of bright, reflective color. In other dogs, the area corresponding to the tapetal fundus is sparsely or densely scattered with minute, colored foci of tapetal cells, which are surrounded by the reddish brown background. Some dogs, again, may have a distinct tapetal fundus with a bright, homogenous color, at least in the center, whereas other dogs may exhibit a distinctly bordered but coarse and granular tapetal area. These variations are different degrees of the same phenomenon and occur in related dogs of the same breed.

Among breeds in which pale blue or heterochromic irides may appear (e.g., merle-coated Collies, Shetland Sheepdogs, and related breeds, harlequin-coated Great Danes, and Cardigan Welsh Corgis, which also carry merle genes, and some arctic breeds such as Siberian Huskies), a subalbinotic fundus may be found. The appearance of the fundus ranges from a small segment of albinism or subalbinism situated randomly in the tapetal or nontapetal fundus to almost complete absence of pigmentation in the fundus. The subalbinotic areas are identified by the readily visible, reddish, brick-colored choroidal vessels against the white scleral background. In dogs with a complete subalbinotic fundus, the tapetum is invariably absent.

Pathologic conditions that lead to a decrease in retinal thickness (e.g., PRA) will reduce the number of cell layers overlying the tapetal fundus. In these cases, the tapetal reflectivity will be increased (i.e., tapetal hyperreflectivity), and in late stages of the retinal atrophy, the tapetal fundus will have a metallic glare. In contrast, if the tissue overlying the tapetal fundus absorbs more light than normal, the tapetal area will have a gray or brown coloration and appear hyporeflective (i.e., less light than normal will be reflected). Dogs that do not have a tapetal fundus or that have a poorly developed tapetal zone, causes difficulties in the process of obtaining a diagnosis of the pathologic conditions affecting retinal thickness and retinal vasculature. The tapetal fundus has a light or dark blue color in young pups up to the age of 5–7 weeks. After this age, the adult coloration starts to develop.

**Nontapetal Fundus**

The nontapetal fundus comprises the largest area of the ocular fundus in the dog. The junction between the tapetal and nontapetal fundus exhibits a continuous variation, from a distinct line of demarcation to a gradual transition with scattered foci of tapetal cells, which become more and more sparse with increasing distance from the center of the tapetal fundus. Isolated islets of tapetal fundus are commonly seen in the nontapetal region. In contrast, nontapetal patches of varying size may be seen within the tapetal fundus in the normal dog. The border between the patches and the adjacent tapetal fundus can be clearly demarcated, or they can merge gradually, as described earlier.

The nontapetal fundus has a nonreflective, usually dark or grayish brown to black color. Sometimes, the nontapetal fundus adjacent to the tapetal fundus may appear paler and more brown compared with the darker, ventral region. In the dog (regardless of the breed) with a brown, chocolate, or liver coat color associated with a paler brown iris, the nontapetal fundus is less heavily pigmented and will appear paler brown or reddish brown. Sometimes, the choroidal vessels will cause a striped or tigroid appearance when viewed through the ophthalmoscope.

In the dog with a subalbinotic fundus, parts of the nontapetal fundus will be unpigmented, thus showing the choroidal vessels overlying the white sclera. Absence of pigment in the entire nontapetal region is common (e.g., in blue merle Collies).

**Optic Nerve Head (ONH)**

The canine ONH, or the optic disc or papilla, also exhibits a wide range of normal variations in ophthalmoscopic appearance. It is located in the center of the fundus, sometimes in
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The course of these vessels is a useful aid in determining the topography of the ONH.

The fundus surrounding the ONH may present as a partial or complete, pigmented ring, with focal absence of tapetal tissue. In contrast, the ONH may be encircled by a bright reflective zone, less than one optic-nerve-head diameter in width, in which the retinal layers over the tapetal tissue are thinned (this is known as conus) (Fig. 24.5).

Retinal Vasculature

The vascular architecture of the canine fundus is classified as holangiotic. The vasculature consists of arterioles and venules located at the surface of the retina. The diameter of the vessels decreases with increasing distance from the ONH, but otherwise, no differences should be observed with location.

The arterioles (usually 15 to 20 in number) radiate away from their origin close to the periphery of the ONH. They appear slightly lighter in color compared with the vessels transporting venous blood, and they may be more tortuous than the venules. The main veins (usually three or four in number) are obviously larger and darker red in color than the arterioles. They end in the usually incomplete venous circle on the top of the ONH but may, in part, be covered by the ONH tissue. Several smaller venules coalesce with the major veins, thereby building a branching tree of vessels over the optic fundus. The area centralis is an indistinctly bordered area slightly superior and about two optic-nerve-head diam-
etters temporal to the ONH, which is devoid of blood vessels but encircled by fine branches (Mowat et al., 2008).

In the dog with a poorly pigmented or subalbinotic fundus, the choroidal blood vessels are readily visible. They are reddish, brick-colored, and radiate out from the ONH in a regular pattern, resembling rays of the rising sun. Wider sinusoidal veins separated by narrower arterioles can be seen. The edges of the choroidal vessels usually appear less distinct than the retinal vessels. Blurred edges and a chaotic pattern should not be found in the normal fundus.

Development of the Canine Fundus

The difference between the immature ocular fundus of a young pup and the fully developed, functional fundus of an adult dog is striking. The process of development includes both a successive series of morphologic events and a functional maturation of the retina.

Ophthalmoscopy

It is normally impossible to examine the ocular fundus in pups younger than 2 weeks, because the eyelids remain closed and the ocular media, especially the cornea, are not sufficiently clear. When the eyelids open and ophthalmoscopic examination can be performed, there is no discernible difference between the tapetal and nontapetal fundus. At this stage of development, the entire ocular fundus has a dull, dark gray color, the ONH is small and flat due to immature myelination. The retinal blood vessels, however, are easily identifiable and appear relatively large in size. The developing tapetal fundus appears paler, and the nontapetal region is relatively darker, after 3–4 weeks of age. The tapetal fundus then takes on a lilac to blue coloration, which becomes more intense with increasing age. After approximately 7–8 weeks, the tapetal fundus becomes more granular in appearance. The bluish immature tapetal fundus then becomes more brightly colored over time, until a tapetal fundus of adult structure and coloration is developed at approximately 3–4 months of age (Fig. 24.6).

The timing of the ophthalmoscopic development of the fundus is variable, and different stages of maturation should be expected when a litter is examined. The developmental state of the fundus usually relates to the general development of the pup; in other words, the best-developed puppies in a litter usually have a more mature ocular fundus compared with the less-developed littermates.

Functional and Morphological Development of the Retina

Retinal differentiation and maturation (mainly of the photoreceptors) in dogs is complete by 7–8 weeks of age. At the end of this period, the retina, as monitored by ERG and both light and electron microscopy, is adultlike (Acland & Aguirre, 1987; Aguirre et al., 1972; Gum et al., 1984; Parry, 1953a).

DEVELOPMENTAL ANOMALIES

Congenital abnormalities of the eye can either be hereditary or nonhereditary.

Collie Eye Anomaly (CEA)

Collie eye anomaly is a congenital ocular syndrome involving defects of the posterior vascular and fibrous tunics of the eye. The pathogenesis of the defect is considered to be an abnormal mesodermal differentiation, which results in defects, mainly of the sclera, choroid, optic disc, retina, and retinal vasculature. The severity of the disease varies from no apparent visual deficit to total blindness. CEA is bilateral and has no sex predisposition. There is no difference in frequency related to coat color, type of coat, or presence of the merling gene (Rubin, 1989). The cardinal sign is a geographically defined region of choroidal hypoplasia lateral to the optic disc, which may or may not be accompanied by obvious retinal or scleral defects or by colobomas. Other anomalies are retinal detachment and intraocular hemorrhage. CEA affects primarily the Collie types of dog and also some other breeds (OptiGen, 2012): Rough and Smooth Collie, Shetland Sheepdog, Australian Shepherd, Border Collie, Nova Scotia Duck Tolling

The disease was described in the United States in 1953 by Magrane (1953). The ophthalmoscopic and histopathologic findings in CEA were reported in 1960 by Roberts (1960). Some years later, the hereditary trait for the disorder was established, and a simple autosomal recessive inheritance was postulated by Yakely et al. (1968) through a test breeding scheme. This mode of inheritance was further supported by the results of pedigree analysis and test matings conducted by Bedford in 1982 (Bedford, 1982a). Some investigators have suggested the choroidal hypoplasia results from a simple, autosomal recessive trait, whereas the coloboma/staphyloma results from a simple dominance, and the vascular abnormalities are inherited as a separate factor (Donovan et al., 1969). So far, genetic studies have not been published to support this hypothesis. There is, however, strong evidence for segregation distortion in the transmission of CEA. This has caused some investigators to propose a polygenic inheritance for the defect (Wallin-Hakanson et al., 2000a, 2000b). Recently, further genetic studies were reported that established the primary CEA phenotype, choroidal hypoplasia, to segregate as an autosomal recessive trait with nearly 100% penetrance. Some heterozygotes for the mutant allele showed mild choroidal hypoplasia (Lowe et al., 2003). The CEA locus was mapped to a 3.9-cM region of canine chromosome 37. An intronic deletion in the NEHJ1 gene was identified. Part of the deleted region, although not a coding region, is very well conserved across species and probably plays an important regulatory role, perhaps in NEHJ1 expression (Parker et al., 2007). Interestingly, the Soft-Coated Wheaten Terrier with a similar phenotype to CEA does not share this mutation, suggesting that other gene defects can cause a similar condition.

The prevalence of CEA has been high in Rough and Smooth Collies and Shetland Sheepdogs throughout the world. In 1969, the incidence of CEA in the collie was between 75% and 97% in the United States (Donovan et al., 1969; Roberts, 1969). Because of selected breeding, this prevalence decreased within a few years to 59% (Yakely, 1972). Later studies have shown a frequency of 64% among Collies in England (Bedford, 1982a), greater than 50% in Sweden (Wikström, 1986), and 41% in Norway (Bjerkaas, 1991). In Shetland Sheepdogs, the prevalence is also high (Bedford, 1982a), but the incidence appears to vary in different countries. The incidence of CEA in Border Collies is low, and only sporadic cases are diagnosed, while in the Lancashire Heeler, a somewhat high incidence was reported (13.7%) (Bedford, 1998).

**Clinical Findings**

Clinical findings in CEA include a high degree of pleomorphism. In a single litter, there is often great variation in the severity of the changes, and there may be variation between the eyes of an affected individual. Choroidal hypoplasia is considered the diagnostic lesion for CEA and is always bilateral, though the extent of the lesion may vary between eyes.

The four main defects included in the CEA syndrome are:

1. choroidal hypoplasia
2. posterior polar colobomas
3. partial or complete retinal detachments and
4. intraocular hyphema.

The latter two (items 3 and 4) are often regarded as complications of large colobomas. Other changes also included in this syndrome by some authors are excessive tortuosity of the retinal vasculature and retinal folds in young pups (Barrie et al., 1981). The CEA syndrome is most accurately diagnosed in pups at 6–7 weeks of age.

**Choroidal Hypoplasia**

Choroidal hypoplasia is a bilateral, but often asymmetrical, defect. The area involved is usually temporal or superotemporal to the optic disc, generally at the junction of the tapetal and nontapetal fundi, and can be from one to several disc diameters in size. Within this area, the choroidal tissue can be visualized because there is an associated lack of pigment in the overlying RPE in the nontapetal fundus and a focal absence of tapetal tissue in the tapetal fundus. The white scleral tissue is visualized behind the abnormal choroid, which gives the defect a whitish appearance. The diagnosis of choroidal hypoplasia can be difficult in eyes with albinotic or...
subalbinotic fundi in dogs with merle coats, especially if there is a patchy absence of pigment that coincides with the specific area where choroidal hypoplasia occurs. In such cases, specific assessment of the choroidal vasculature in the temporal region of the optic disc must be performed. This is, however, often a difficult and highly subjective evaluation.

Mild defects with choroidal hypoplasia observed at 5–7 weeks of age can become masked by the development of more pigment in the RPE as the dog grows older. Such cases are often referred to as “go-normals,” and they may present up to 7 months of age. In a study by Bjerkås (1991), this phenomenon was specifically examined and found to be surprisingly frequent. Of 22 pups given the diagnosis of minor changes before 3 months of age, 15 had ophtalmoscopically normal fundi at reexamination several months later, whereas only seven were unchanged compared with the first examination. Another study (Buening & Erhardt, 2002), showed that the frequency of CEA was dependant on age, believed to be due to a go-normal rate of 53% in Shelties and 63% in Collies. Through the frequency studies and linkage mapping performed by Lowe et al. (2003), it was established that the go-normal problem was the primary cause for the segregation distortion transmission of CEA described above.

Posterior Polar Colobomas
Colobomatous defects involving the optic disc (i.e., papillary colobomas) or the adjacent area (i.e., peripapillary colobomas) are common in dogs with CEA (Fig. 24.8). They are most often situated inferior to or toward the medial or lateral borders of the optic disc and are caused by ectasia of the cribiform plate or the peripapillary sclera. The papillary lesions are often seen as a gray or pink indentation, and they vary in size, from shallow depressions to more extensive excavations or “holes” up to 30 D in depth (Fig. 24.9) (Bedford, 1982a). Large colobomas may distort the area of the disc severely (Fig. 24.10). Colobomas are easily identified by the color of the lesion and the way the retinal vasculature changes course or disappears at the rim of the defect. Small colobomas, however, especially if they are shallow and located centrally in the optic disc, may be confused with the normal physiologic cup.

In a large survey by Bedford in 1982, 34% of 2000 Rough Collies with choroidal hypoplasia had posterior polar colobomas that were mostly unilateral and sometimes bilateral (Bedford, 1982a). Another 24 dogs had unilateral or bilateral colobomas in the absence of choroidal hypoplasia, in which the diagnosis of CEA could not be confirmed. Several, or even most, of these dogs could be go-normals, but some could also be affected by primary colobomatous defects not associated with CEA.

Retinal Detachment
Partial or total retinal detachments may be seen in as many as 10% of CEA-affected Collies (Fig. 24.11). They are most often unilateral, but bilateral cases occur sporadically. Detachments are most often diagnosed in the young pup but also...
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Figure 24.11. Retinal detachment is part of the CEA complex. A. Partial retinal detachments near the disc as well as vascular abnormalities in a young Collie. B. Complete retinal detachment in a 3-year-old blue merle Collie.

Intraocular Hemorrhage

Hemorrhage in the posterior segment of the eye is seen in a small percentage of CEA-affected animals. Colobomatous defects and retinal detachments are thought to be predisposing factors. In some cases, preretinal looping of major vessels may be seen, particularly in association with large colobomatous defects (Bedford, 1982a). There may also be neovascularization of the retina extending into the vitreous. The fragility of the capillaries may result in sudden leakage of blood, which
passes through the vitreous and into the aqueous fluid, thereby causing hyphema (Barrie et al., 1981). The vascular leakage may continue in affected dogs, with the risk for development of glaucoma.

Other Signs

Excessive tortuosity of retinal vessels is almost always present in eyes affected by CEA. Blood vessel tortuosity can also be found, however, in genetically clear Collies and dogs of other breeds and usually, therefore, is not regarded as being diagnostic for CEA. Even so, tortuosity of both arterioles and venules should raise the examiner’s index of suspicion for CEA.

Vermiform streaks or rosettes are folds in the neurosensory retina of the neonate, which arise because of the unequal growth of the sclera, the choroid, and the retinal layers. They are seen as linear or circular, grayish (in the tapetal area) or white (in the nontapetal area) configurations, usually in the central fundus and most prevalent near the optic disc (Fig. 24.12). These neuroretinal folds are seen in both normal and affected dogs and therefore are not diagnostic for CEA. Their frequency, however, appears to be greater in dogs affected with other congenital defects, such as CEA.

Microphthalmia has sometimes been claimed, though not proved, to be part of the CEA syndrome. It appears there has been a selective breeding of Collies with small eyes. This selection pressure might favor a high incidence of CEA in Collies compared with Border Collies, in which the frequency of CEA is low and the eyes are comparably larger (Barrie et al., 1981).

It is not unusual to find a central corneal horizontal or ovoid streak-like opacity in young affected and nonaffected Collies and Shetland Sheepdogs. The corneal opacity usually clears within a few weeks, however, and is not considered to be diagnostic for CEA.

Histopathologic Findings

In dogs with choroidal hypoplasia, there is a marked thinning of the choroid in the area, with a decrease in melanocytes and hypoplasia or an absence of tapetal cells. In mild lesions, the RPE may show only a focal absence of pigment. It is only in severe cases of choroidal hypoplasia that the neural retina is also affected. The RPE then is often hypertrophied and hyperplastic, and the neural retina is thin, with cyst formation in inner layers and vacuolization of the ganglion cells. In some eyes, the outer nuclear layer is reduced in thickness, thus indicating a reduced number of photoreceptor cells in the area (Roberts et al., 1966a, 1966b).

Colobomas may originate embryologically from deformities in the primitive epithelial papilla or from defects in the fetal fissure. If localized in the optic disc, they represent a focal absence of tissue in the ONH. The retina overlying peripapillary colobomas is attenuated, and the outer nuclear layer may be absent. In extremely large colobomas, the RPE and choroid may be lacking, and the sclera is thin. Posterior ectatic areas may originate from orbital cysts, which result from a primary defect in the neuroectoderm when the optic fissure is closing. There is protrusion of the inner retinal layers, because they develop more rapidly than the outer layers, through the fissure. The fissure cannot close in a normal way, and a cyst lined with retinal tissue develops. Retinal duplication in the region of the embryonic fissure may result from eversion of the inner retinal layer of the optic cup or from abnormal differentiation of the RPE. The most common defect, which has been observed after 28 days of gestation (Latshaw et al., 1969), is rosette-like structures near the optic disc in the region of the optic fissure. Such rosettes may result from abnormal differentiation of the RPE. Epithelial layers of cells and rosettes that prevent normal interaction of the inner and outer retinal layers and interfere with proper development and differentiation may cause the defect in the optic vesicle.

Problems in Diagnosis, Interpretation, and Control

Now that the causal gene mutation has been identified and a commercial mutation detection test has been developed, breeders will be able to eventually eliminate the condition. The high incidence of CEA in some breeds dictates that breeders should only attempt to reduce the mutation incidence within the breed over several generations. Restricting breeding to homozygous normal dogs could limit the gene pool and could lead to loss of desirable features from the breed and possibly the emergence of a new hereditary disease that was present at low frequency within the breed. To avoid the
production of CEA-affected puppies, breeders just need to ensure that one of the breeding pair is homozygous normal.

Prior to the development of the DNA-based test for CEA, the incidence in certain Collie breeds has remained high throughout the world. There are several reasons for this, including both problems with diagnosis as well as unwillingness from some owners and breeders to adhering to strict recommendations that might eliminate a large part of their breeding potential.

Difficulties in trying to eliminate the condition by ophthalmoscopic screening have been partly due to certain difficulties in diagnosis. The go-normal phenomenon was a major issue with genetically affected animals being indistinguishable from unaffected animals by ophthalmoscopic examination as described previously. Another problem of diagnosis is the differentiation between a small, centrally located coloboma in the optic disc and a normal physiologic pit. These two entities are sometimes very difficult to differentiate ophthalmoscopically. Another variation in the dog occurs in the degree of myelination among fibers of the optic disc. Cessation of myelin growth at the level of the scleral lamina cribrosa may give the impression of a uniformly recessed optic disc, which may be classified as a broad, shallow coloboma.

The location of colobomas at the optic disc has been another problem because of differences in opinion between examiners. In CEA, colobomas are frequently seen at the nasal or temporal border of the optic disc (i.e., "atypical" colobomas). The existence of a "typical" coloboma in the six-o’clock position as the only finding in a Collie raises the question whether it is a go-normal dog with a typical coloboma and therefore should be considered as CEA-affected or whether the coloboma is a concurrent problem unrelated to CEA.

Color-dilute animals can also cause problems in making an ophthalmoscopic diagnosis of CEA when only mild choroidal hypoplasia is present. In merles, it is important to closely evaluate the area temporal to the optic disc for changes due to choroidal hypoplasia. Inexperienced examiners may fail to recognize slight vascular changes lateral to the optic disc and thus may incorrectly consider the animal to be normal. Others may erroneously classify a color-dilute animal as abnormal because there is a lack of pigment nasally to the optic disc. A lack of pigment temporally to the optic disc may, however, indicate choroidal hypoplasia.

**Merle Ocular Dysgenesis (MOD)**

The Australian Shepherd dog is affected by multiple ocular anomalies (Gelatt & McGill, 1973; Gelatt & Veith, 1970). Affected dogs may show microphthalmia to varying extent and varying size of the globes. The defect is associated with microcornea of an irregular shape and, infrequently, with mineralization of the anterior corneal stroma. Affected dogs also exhibit heterochromia irides with dyscoria and corectopia with an oval pupil in which the long axis is vertical. The hypoplastic irides permit transillumination and respond poorly to mydriatics. False polycoria occurs in 5%–10% of affected dogs. Often, the defect extends into the iridocorneal angle and posteriorly into the ciliary body. Cataracts occur in 60% of affected dogs with microphthalmia and colobomas.

In 54% of affected Australian Shepherds, large equatorial staphylomas occur. The staphylomas are either a single depression or several small excavations grouped together. The choroidal vasculature is greatly reduced or absent in the staphylomas, and the sclera is irregular and thin. Large staphylomas may extend from the ora serrata to the optic disc. Retinal vasculature in the staphylomas may be markedly reduced or even absent. In 50% of cases, complete retinal detachment occurs, and approximately 30% of the detachments have intraocular hemorrhage. Microphthalmia with colobomas in Australian Shepherds is inherited as an autosomal recessive trait with incomplete penetrance. Affected dogs are homozygous merles and have excessively white hair coats. A similar syndrome has been observed in merled Collies, Shetland Sheepdogs, Harlequin Great Danes, and other merle breeds.

Histopathologic changes in the Australian Shepherd syndrome are confined to the posterior segment. It has been shown that the defect is the result of a primary dysplasia of the outer layer of the optic cup, the future RPE (Cook et al., 1991). Failure of normal RPE development leads to failure of differentiation of the adjacent retina and pericocular mesenchyme to form choroid and sclera. The neurosensory retina is usually normal, but the tapetum is either absent or only a few cells thick. The RPE contains few melanin granules as well, but the defect is not related to failure of melanization. In the staphylomas, the retina is reduced to thin glial membranes, and the sclera and choroid are markedly thin. The vitreous is often liquefied in affected dogs, and development of the secondary vitreous is usually absent.

**Retinal Dysplasia**

Retinal dysplasia has been defined as an anomalous differentiation of the retina accompanied by a proliferation of one or more of its constituent elements (Duke-Elder, 1963). It is characterized histopathologically by linear folding of the sensory retina and formation of rosettes composed of variable numbers of neuronal retinal layers (Lahav et al., 1973) around a central lumen. The defect is associated with several spontaneously occurring and experimentally induced disorders of the developing eye in both humans and animals. Dysplastic retinal lesions may be associated with systemic abnormalities, or they can be a primary ocular defect, either as a single defect or together with other lesions such as microphthalmos or colobomatous defects. Retinal dysplasia involves multiple retinal layers and, occasionally, the vitreous (depending on its severity), is mainly nonprogressive, and may or may not interfere with vision. Known causes of retinal dysplasia include viral infections, vitamin A deficiency, X-ray irradiation, certain drugs, and intrauterine trauma. Many forms in dogs have a hereditary basis.
Spontaneous Retinal Dysplasia

The pathogenesis for spontaneous retinal dysplasia may vary. Silverstein et al. (1971) proposed four different mechanisms:

1. hyperplastic extension of the neural retina into abnormal sites away from the RPE
2. dysplastic processes within the neural retina that is detached from the RPE
3. occurring in neuroretinal areas devoid of RPE (i.e., colobomas) and
4. dysplastic processes in most or all of the neural retina, or only focal areas, without evidence of separation from the pigment epithelium; the latter (4) could possibly involve defects in the pigment epithelium itself, because this structure has been shown to be important during retinal development (Silverstein et al., 1971; Vollmer & Layer, 1986).

Clinical Signs

Clinically, the lesions of retinal dysplasia are unilateral or bilateral and may be grossly divided into three different types or forms:

1. **Focal or multifocal retinal dysplasia.** In focal or multifocal retinal dysplasia, the retinal folds and rosettes are seen as areas of reduced tapetal reflectivity, appearing as gray or green dots or linear streaks (or V- or Y-shaped streaks). They may occur anywhere in the tapetal region but most often are prevalent in the central region of the fundus, around the dorsal retinal vessels, and, usually, dorsal to the optic disc (Fig. 24.13). Sometimes, the folds may appear elevated and distort the course of the overlying vessels. Retinal folds in the nontapetal fundus appear as gray or white linear or irregular streaks.

2. **Geographic retinal dysplasia.** In geographic retinal dysplasia (Fig. 24.14), an irregular or horseshoe-shaped area, most often in the central tapetal fundus, is affected. This area includes parts with retinal thinning and parts with retinal elevation. Usually, a demarcation is seen that is gray or black and encircles the area. Frequently, there are hyperreflective parts, often in streaks, indicative of focal neuroretinal degeneration. With time, the focal or streak-like areas with pigmentation may increase, which indicates RPE hypertrophy or hyperplasia in the dysplastic area. The central part of the geographic dysplasia may stay slightly elevated (i.e., the neuroretina is partially detached).

3. **Complete retinal dysplasia with detachment.** In complete retinal dysplasia with detachment, a completely detached neural retina is seen floating in the vitreous, usually only attached around the ONH. Vitreous dysplasia may also be prevalent in such eyes. There sometimes is leukocoria and a rotary-searching nystagmus in conjunction with complete retinal dysplasia in neonates.

Usually, multifocal retinal dysplasia does not affect vision, whereas the second type can cause marked visual impairment and the third form blindness.
Clinical, most lesions in retinal dysplasia do not appear to change with time. The least severe type (i.e., focal or multifocal retinal dysplasia) usually remains unaltered. In a few cases, however, the lesions become less obvious, and some folds may disappear. At the same time, the area around others, especially if the lesions are numerous, may become more demarcated, with hyperpigmented spots and streaks as well as hyperreflective areas in the vicinity of the dysplastic lesions (Fig. 24.15). In the geographic type, the lesions never disappear but instead become focally more demarcated with time. The most severe form, with complete retinal detachment, remains unaltered in most cases, but complications including vitreal hemorrhage, cataracts, and secondary glaucoma may arise.

Since retinal dysplasia is a defect of retinal differentiation, lesions are mainly congenital in nature. Therefore, early screening of dogs at 6–8 weeks has been encouraged for breeds in which the defect is prevalent. A study performed using dogs within The Seeing Eye, Incorporated program, which included five different breeds in which geographic retinal dysplasia had been recorded, showed that the lesions were not always congenital (Holle et al., 1999). It was found that the geographic form of retinal dysplasia was rarely diagnosed in dogs before 9 weeks of age (1 affected early out of 23). These findings led to the conclusion that in dogs, an initial examination at 5–9 weeks can only determine the presence or severity of ocular abnormalities that manifest in the congenital or perinatal period. A second examination was recommended to be performed between 6 months and 1 year of age in breeds affected with the geographic form of retinal dysplasia.

**Histopathology**

Histopathologically, multifocal retinal dysplasia has been classified, according to the layers involved, into four types of rosettes (Lahav et al., 1973): primitive unilayered rosettes, and one-, two-, and three-layered rosettes. The first type consists of primitive, undifferentiated cells surrounding a lumen, and the last type consists of a mature and otherwise normal retina that is thrown into folds. Also, there may be neural retinal degeneration in the vicinity of the rosettes. In the complete type of retinal dysplasia, the neural retina may be thrown into folds and rosettes with severe degenerative changes and atrophy of the neural retina. The pigment epithelium may show hypertrophy or hyperplasia of pigment epithelial cells.

The external limiting membrane of dysplastic English Springer Spaniel fetal eyes were studied with transmission electron microscopy and freeze-fracture techniques (Whiteley & Young, 1986). It was found that at day 46 of gestation, there was already a marked decrease in the size and area occupied by gap junctions within the external limiting membrane compared with those in the retinas of aged-matched, mongrel control fetuses. This apparent loss of gap junctions coincident with the onset of histopathologically detectable dysplastic changes in the neural retina may contribute to the morphogen-
Breed Incidence and Inheritance

Spontaneous retinal dysplasia occurs in several breeds, and hereditary factors have been shown or suspected to be the cause in many, such as the Bedlington Terrier (Rubin, 1968), Sealyham Terrier (Ashton et al., 1968), Yorkshire Terrier (Stades, 1978), Rottweiler (Bedford, 1982b), English Springer Spaniel (Schmidt et al., 1979), American Cocker Spaniel (MacMillan & Lipton, 1978), Labrador Retriever (Barnett et al., 1970; Carrig et al., 1988; Nelson & MacMillan, 1983), and Golden Retriever (Long & Crispin, 1999). Cases of primary retinal dysplasia have also been observed in the Beagle (Heywood & Wells, 1970).

It is not uncommon to find retinal dysplasia in conjunction with other severe ocular defects, as described in the Doberman Pinscher (Bergsjö et al., 1984; Lewis et al., 1986; Peiffer & Fischer, 1983), Akita (Laratta et al., 1985), Chow Chow (Collins et al., 1992), and Australian Shepherd dog (Gelatt & McGill, 1973; Gelatt & Veith, 1970). In some breeds, such as in the Samoyed (Meyers et al., 1983) and the Labrador Retriever (Carrig et al., 1977), retinal dysplasia has been described in combination with other nonocular defects. The syndrome in the two latter breeds has been termed canine oculo-skeletal dysplasia (Du et al., 2000) and is further discussed later in this chapter.

In the Bedlington and Sealyham Terriers, the presenting signs may be esotropia, leukocoria, and blindness. There are variable induced pupillary light responses. Most affected dogs have infundibular (i.e., complete) retinal detachments. Parts of the retina may be attached to the posterior lens capsule, and there may be intraocular hemorrhage. In the Bedlington Terriers, the secondary vitreous is absent; therefore, the disease has been referred to as vitreoretinal dysplasia in this breed. Microphthalmia is not uncommon in conjunction with retinal dysplasia in Sealyham Terriers. In both breeds, an autosomal recessive trait for the defect has been postulated.

In the American Cocker Spaniel, English Springer Spaniel, Beagle, Rottweiler, Labrador Retriever, and Golden Retriever, multifocal retinal dysplasia has been reported. The dysplasia is unilateral or bilateral, and it appears as multiple round, oval, linear, or vermiform areas with decreased tapetal fundus reflectivity, usually in the posterior pole superior to the optic disc (Fig. 24.16). The size of the lesions varies between the size of a retinal venule and twice this size. Y- and V-shaped lesions appear to result from the joining of two or three of the linear or vermiform shapes. The multifocal dysplasia lesions are often seen near the major retinal vessels. The nontapetal foci appear as hypopigmented linear streaks and occur less frequently than in the central tapetal lesions. Multifocal retinal dysplasia in American Cocker and English Springer Spaniels is postulated to be caused by an autosomal simple recessive
gene, whereas in the Labrador Retriever, a dominant inheritance with incomplete penetrance is postulated.

The histopathologic appearance is either an invaginated retinal fold involving the outer retinal layers or two- or three-layered rosettes, with the latter rosettes consisting of poorly differentiated photoreceptors and both outer and inner segments within a central lumen lined by external limiting membrane. Rosette photoreceptor cell nuclei usually are variably preserved and, in general, are reduced in number. The RPE is often unaltered beneath the dysplastic areas. In some folds, however, there may be a decrease in pigment granules, hyperplasia, or hypertrophy, with clumping of the RPE cells.

Geographic retinal dysplasia has been described as an irregular, large, but focal area of dysplastic retina. In English Springer Spaniels with retinal dysplasia, focal bullous retinal detachments and complete retinal detachments were observed to occur within the first 6 months of life (O'Toole et al., 1983). Geographic retinal dysplasia has also been observed in Cavalier King Charles Spaniels and Golden Retrievers (Narfström, unpublished observations 2000). In both breeds, large and often circular or irregular focal areas of the central tapetal fundus with dysplastic retina occur. The focal retinal defects, which do not detach completely, most often do not progress in size with age, though some alterations in the area, such as increased pigmentation and focal areas of hyperreflectivity, are seen after 6 months to several years.

In the Labrador Retriever, all three types of retinal dysplasia occur (i.e., multifocal, geographic, and complete). Multifocal retinal dysplasia has specifically been described in the field-trial Labrador Retriever (Nelson & MacMillan, 1983). The complete type, however, was the first to be described in the breed (Barnett et al., 1970), whereas the geographic type has been observed in the breed more recently.

Retinal dysplasia is usually diagnosed in Labrador Retrievers at 6–8 weeks of age or younger. The animal may exhibit nystagmus, cataracts, and blindness if there is complete detachment. The pathogenesis of the detachment may be an imbalance in the growth of the choroid, sclera, and neural retina (Koch, 1974).

Canine Oculo-Skeletal Dysplasia: Dwarfism with Retinal Dysplasia

Labrador Retrievers and Samoyed dogs are affected by another inherited syndrome, canine oculo-skeletal dysplasia, in which there are both ocular lesions and skeletal abnormalities (Fig. 24.17). Cataracts and complete retinal detachment are seen together with retarded growth of the radius, ulna, and tibia; separated hypoplastic anconeal and coronoid processes; hip dysplasia; and delayed development of the epiphysis (Carrig et al., 1977; Meyers et al., 1983). Investigations into the inheritance of the disorder in Labradors have shown it is caused by one abnormal gene, which has recessive effects on the skeleton as well as effects on the eye. Obligate heterozygous animals may exhibit mild ocular clinical signs, such as vitreal strands and/or localized retinal dysplasia characterized by focal or multifocal retinal folds, but have a normal appendicular skeleton (Carrig et al., 1988). In the two breeds, the disease loci are nonallelic. They have been termed dwarfism with retinal dysplasia type 1 (drd1) for the Labrador type and dwarfism with retinal dysplasia type 2 (drd2) for the Samoyed. Dwarfism with retinal dysplasia results from mutations in the collagen 9 genes COL9A2 and COL9A3. Drd1 in the Labrador results from an insertional mutation in COL9A3 whereas drd2 in the Samoyed results from a deletion in COL9A2. Affected dogs have reduced retina mRNA levels for the respective collagen 9A transcripts. Identification of the mutations has allowed the development of DNA-based genotyping tests. It has also allowed the incidence of multifocal retinal folds in heterozygote animals to be investigated. Of 34 animals heterozygous for the drd1 mutation, 14 had retinal folds. The incidence of retinal folds in drd2 heterozygotes was reportedly higher (Du et al., 2000; Goldstein et al., 2010a; Pellegrini et al., 2002).

Inherited Retinal Dysplasia and Persistent Hyperplastic Primary Vitreous (PHPV)

A clinical syndrome of congenital retinal dysplasia and persistent primary vitreous has been described in the Miniature Schnauzer dog (Grahn et al., 2004). Through analysis of an extended pedigree and by test breeding, a simple autosomal inheritance for the disorder has been postulated. In affected dogs, the retinal dysplasia is usually generalized, involves the temporal and nasal retina most severely, and is most extensive dorsal to the optic disc (Fig. 24.18). The retina is noticeably...
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they involved both tapetal and nontapetal fundus. Morphologic studies showed lesions indicative of aberrant development after radiation-induced damage. The pathogenesis of the induced retinal dysplasia appeared to include necrosis of the neuroblastic or nuclear layers, disruption of the outer limiting membrane, ectopic mitosis and migration of photoreceptor cells to the subretinal space, and development of rosettes and tubules.

Problems in Diagnosis, Interpretation, and Control

Retinal dysplasia includes a diverse group of entities with variable clinical and histopathologic appearances, variable pathogeneses, and variable etiologies. Retinal dysplasia is an abnormality that can occur in conjunction with many other eye anomalies, with or without systemic anomalies, either unilaterally or bilaterally. Primary insults (e.g., viral, toxic) may directly affect dividing retinal cells and pigment epithelium with secondary dysgenesis of the retina. The defect has been classified histopathologically as to type of rosettes (Lahav et al., 1973) into three-layer rosettes suggestive of mature retina that has undergone detachment and been thrown into folds, two-layer rosettes, and one-layer rosettes that arise from either the outer or inner retinal layers and appear to represent true dysgenesis (Fig. 24.19).

Induced Retinal Dysplasia

Infection with canine adenovirus has been shown to cause retinal dysplasia (Appel et al., 1973). Another infectious agent causing retinal dysplasia is canine herpesvirus. Experimental studies have demonstrated that severe ocular inflammation with subsequent retinal dysplasia and associated ocular anomalies can be induced in neonatal pups (Albert et al., 1976). Oral, nasal, and intraperitoneal inoculation at 1–4 days postnatal caused panuveitis and systemic signs of infection. Histopathologically, folds and rosettes were found in the retina, and there was a retardation of retinal cell maturation and retinal reorganization.

The immature mammalian retina is susceptible to radiation, which has been demonstrated in the dog. Irradiated newborn puppies exhibited retinal rosette formation (Shively et al., 1972). The rosettes were either few or numerous, and they involved both tapetal and nontapetal fundus. Morphologic studies showed lesions indicative of aberrant development after radiation-induced damage. The pathogenesis of the induced retinal dysplasia appeared to include necrosis of the neuroblastic or nuclear layers, disruption of the outer limiting membrane, ectopic mitosis and migration of photoreceptor cells to the subretinal space, and development of rosettes and tubules.

Problems in Diagnosis, Interpretation, and Control

Retinal dysplasia includes a diverse group of entities with variable clinical and histopathologic appearances, variable pathogeneses, and variable etiologies. Retinal dysplasia is an abnormality that can occur in conjunction with many other eye anomalies, with or without systemic anomalies, either unilaterally or bilaterally. Primary insults (e.g., viral, toxic) may directly affect dividing retinal cells and pigment epithelium with secondary dysgenesis of the retina. The defect has been classified histopathologically as to type of rosettes (Lahav et al., 1973) into three-layer rosettes suggestive of mature retina that has undergone detachment and been thrown into folds, two-layer rosettes, and one-layer rosettes that arise from either the outer or inner retinal layers and appear to represent true dysgenesis (Fig. 24.19).

The clinical appearance of retinal dysplasia is often similar regardless of the cause. Among the breeds in which the defect has been recognized to be inherited, certain characteristic features, such as the central, mainly tapetal location of the folds and rosettes, are evident, which simplifies diagnosis. Lesions associated with external insults, such as intrauterine infection or irradiation, may cause problems in clinical diagnostics. Histopathologically, however, the lesions show evidence of inflammatory changes, with retinal necrosis as well as dysplasia throughout the affected areas. The lesions in such cases may be prevalent in any part of the fundus, not just...
Canine Ophthalmology

Section III

Canine Multifocal Retinopathy (cmr)

A unique inherited multifocal serous and bullous retinopathy was first described in the Great Pyrenees dog (Grahn & Cullen, 2001; Grahn et al., 1998). Similar changes were then observed in the Coton de Tulear, English and French Mastiff and Bull mastiff dog breeds, and the Lapponian Herder. Pedigree analysis and prospective matings in the Great Pyrenees dog indicate an autosomal recessive inheritance for the disorder (Grahn & Sandmeyer, 2006; Grahn et al., 2006, 2008).

Ophthalmoscopical lesions have been described as multifocal, gray to tan fundic patches that vary in size from barely visible to some lesions that are larger than the optic disc. Lesions start to develop at approximately 11 weeks of age; usually they are sparse, but they develop bilaterally in the peripheral tapetal fundus, around the optic discs, and occasionally under the major veins inferior to the optic disc (Fig. 24.20). The peripapillary lesions, observed as serous retinal detachments, develop within a few hours but remain the same size for years, while the peripheral lesions develop gradually over years and appear to increase slowly in size and number until the age of 20 weeks. Fluorescein angiography is considered normal at 7 weeks, but later, at the time of visible serous detachments, there is blocked choroidal fluorescence and sub-RPE pooling of fluorescein. ERG and serial fundus photography have shown a lack of progression of the retinal degeneration.

Morphologically, there were areas of multifocal serous retinal detachments in which photoreceptor outer segments degenerate (Grahn & Cullen, 2001). Marked changes were also found in RPE cells in the detachment areas: RPE cells were hyperplastic, hypertrophied, and showed increased pigmentation. Some of the cells in these lesions contained several small and large, clear vacuoles, generally located in the basal part of the affected cells. Bruch’s membrane, under the basal part of the affected RPE cells, demonstrated areas with oval-shaped holes.

The lesions do not appear to be congenital but are detected suddenly in young puppies. The retinal degeneration and RPE changes are focal and related only to the serous retinal and RPE detachments. A defect in the RPE blood-ocular barrier has not been shown. The sudden development of the serous lesions and focal detachments support the theory that lesions are multifocal, and the pigment changes are secondary to the serous detachments.

Other breeds may also be affected by retinal folds and rosettes. The folds often resolve with growth and maturation of the eye and are, as described, believed to result from the disparity of the growth rates between the outer and inner retinal layers. In contrast, retinal dysplasia represents abnormal differentiation of the retina and therefore would be expected to be permanent. Thus, a follow-up of these funduscopic alterations could indicate whether the lesions should be designated as retinal folds or retinal dysplasia.

There appear to be problems in controlling inherited retinal dysplasia among several breeds. Specifically, among breeds in which all types of retinal dysplasia occur, such as the Springer Spaniel, mild forms of the disease are often neglected by breeders. The reason that the dysplasia is ignored is that in most instances, there are not any noticeable visual problems. This is also the case for the American Cocker Spaniel and Cavalier King Charles Spaniel. These two breeds are mainly affected by the milder forms of retinal dysplasia, and it is difficult to convince owners and breeders to withhold from breeding an affected dog with minor, nonprogressive abnormalities and (apparently) more or less normal vision. It is still not clear, though it is certainly suspected by some investigators, that there is a genetic relationship between the different forms of primary hereditary retinal dysplasia in the various breeds.

**Figure 24.19.** A retinal fold was observed upon routine ophthalmoscopy in the central fundus of a 7-week-old Cavalier King Charles Spaniel with no visual problems. Histology showed a one-layered rosette (i.e., a true retinal dysplasia).
develop secondarily to focal secretion of defective RPE cells, indicating that this retinopathy may be due to a focal dysplasia of specific RPE cells. An investigation of potential candidate genes revealed that affected dogs had a mutation in the canine BEST1 gene (cBEST1) (Guziewicz et al., 2007). In humans, mutations of this gene cause vitelliform macular dystrophy type 2, or Best macular dystrophy. The cBEST1 gene is predominantly expressed in RPE/choroid and encodes bestrophin, a 580-amino acid protein of 66 kDa. Immunohistochemistry of normal canine retina shows specific localization of the protein to the RPE basolateral plasma membranes. Two disease-specific mutations were identified in the cBEST1 gene of affected dogs, cmr1 mutation in mastiff-related and the Great Pyrene dog breeds, and cmr2 in the Coton de Tulear dog breed. The cmr1 mutation results in a lack of protein while the cmr2 missense mutation means that the bestrophin protein is mislocalized. Recently, a third form of cmr disease was identified in the Lapponian Herder breed (Zangerl et al., 2010), although this also resulted from a mutation in cBEST1. It manifested as a somewhat later onset of the multifocal lesions, at approximately 1 year of age. While exhibiting a phenotype most often comparable to cmr1 and cmr2, the novel cmr3 mutation appears to be based on a distinctly different molecular mechanism. The cmr3 mutation introduces a premature stop codon that is predicted to shorten the cBEST1 gene product. It was suggested that the mutation might not alter the protein production or localization but may alter its function. Zangerl et al. (2010) suggested that the cmr3 mutation might also be involved in other retinal phenotypes seen in the Lapponian Herder; namely a multifocal retinal dysplasia and a generalized retinal degeneration. They also pointed out the potential for confusion between cmr lesions and multifocal retinal dysplasia. Further studies are required to elucidate the phenotypes that can result from the cmr3 mutation (Guziewicz et al., 2011).

### INHERITED RETINAL DEGENERATIONS/DYSTROPHIES

All cellular layers of the retina are potentially susceptible to hereditary abnormalities. Most of these, however, relate to the parts that are physiologically the most complex: the layers of the photoreceptors and the RPE. In the dog, there is a broad range and diversity of inherited retinal diseases that affect these structures. An important reason for this diversity is certainly the establishment of different breeds and the custom to inbreed dogs, which has favored the emergence and expression of recessive genes causing a wide spectrum of retinal disorders.

Similar diseases also affect humans, and the canine diseases therefore seem to offer a convenient basis for comparison. The paucity of knowledge concerning the underlying biochemical, physiological, and morphological disease mechanisms of humans renders dogs with similar naturally occurring diseases especially important as animal models. Thus, the rat, mouse, chicken, cat, and also the dog are frequently used for comparative studies of human retinal dystrophies (Baehr & Frederick, 2009).
Classification of Canine Hereditary Retinal Degenerations

Canine retinal degenerations primarily affect the photoreceptors, RPE, or both. Since the first well-documented report of an inherited retinal degeneration in a Gordon Setter from Sweden by Magnusson (1911), many breeds have been found to be affected by hereditary retinal degenerations. To these conditions, the general term progressive retinal atrophy, or PRA, has been applied. Throughout the years, clinicians have divided PRA into two types depending on the ophthalmoscopic appearance of the fundus lesions: generalized PRA and central PRA (CPRA). In generalized PRA, there is generalized hyperreflectivity of the retina at the end stage of the disease, indicating a generalized atrophy of the neural retinal structures and clinical blindness. In CPRA, there are multifocal accumulations of pigment within the retina, and encircling these changes are areas of hyperreflectivity at the end stage. The latter disorder is the result of a primary defect in the RPE and does not always lead to blindness. Thus, the two disease entities represent completely different disorders. During the last few decades, PRA has been subdivided further into more specific diseases at the cellular level and also at the molecular level, and gene symbols are used to differentiate these disorders (Table 24.1). The term CPRA has been replaced by the term retinal pigment epithelial dystrophy (RPED), which more specifically relates to the disease entity.

The classification of hereditary retinal degenerations is an issue of differing opinions and discussion. Because the diseases are so diverse regarding involved structures and pathogenesis, a strict classification is not feasible and, perhaps, not scientifically correct. It is, however, possible to subdivide

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Breed(s)</th>
<th>Mode of Inheritance</th>
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<tbody>
<tr>
<td>Rod Dysplasia (rd)</td>
<td>b</td>
<td></td>
<td></td>
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<tr>
<td>Early retinal degeneration (erd)</td>
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<tr>
<td>Rod cone dysplasia type 1 (rcd1)</td>
<td>STK3BL</td>
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<td>PDE6B</td>
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<td>Rod cone dysplasia type 2 (rcd2)</td>
<td>c1orf36</td>
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<tr>
<td>Rod cone dysplasia type 3 (rcd3)</td>
<td>PDE6A</td>
<td></td>
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<tr>
<td>Progressive rod cone degeneration (prcd)</td>
<td>PRCD</td>
<td>Approx 30 breeds. See Table 9.1 for more details</td>
<td></td>
</tr>
<tr>
<td>Cone rod dystrophy 1 (CORD1)</td>
<td>RPGRIP1</td>
<td>Miniature Long-Haired Dachshund</td>
<td>AR</td>
</tr>
<tr>
<td>Cone rod dystrophy</td>
<td>NPHP4</td>
<td>Standard and Miniature Wire-Haired Dachshund</td>
<td>AR</td>
</tr>
<tr>
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<td>b</td>
<td>American Staffordshire Bull Terrier</td>
<td>AR</td>
</tr>
<tr>
<td>Cone-rod dystrophy 2 (crd2)</td>
<td></td>
<td>American Pit Bull Terrier</td>
<td>AR</td>
</tr>
<tr>
<td>Cone-rod dystrophy 3 (crd3)</td>
<td>ADAM9</td>
<td>Glen of Amaal Terrier</td>
<td>AR</td>
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<tr>
<td>Photoreceptor dysplasia (pd) PRA type A</td>
<td>Phosducin</td>
<td>Miniature Schnauzer</td>
<td>Dominant incomplete penetrance</td>
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<td>Rhodopsin</td>
<td>Old English Mastiff; Bull Mastiff</td>
<td>AD</td>
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<tr>
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<td>RPGR</td>
<td>Siberian Husky; Samoyed</td>
<td>XL</td>
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<tr>
<td>X-linked PRA2</td>
<td>RPGR</td>
<td>Crossbred</td>
<td>XL</td>
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<tr>
<td>PRA</td>
<td>CCDC66</td>
<td>Schapendoes</td>
<td>AR</td>
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<tr>
<td>PRA type 1</td>
<td>a</td>
<td>Papillon (a second form exists in the breed)</td>
<td>AR</td>
</tr>
<tr>
<td>PRA gr-PRA type 1</td>
<td>SLC4A3</td>
<td>Golden Retriever (PRCD and a third unidentified form of PRA occurs in the breed)</td>
<td>AR</td>
</tr>
<tr>
<td>Late onset PRA—rod cone dystrophy 4 (rcd4)</td>
<td>a</td>
<td>Gordon Setter; Irish Setter</td>
<td>AR</td>
</tr>
<tr>
<td>Achromatopsia</td>
<td>CNGB3</td>
<td>Alaskan Malamute</td>
<td>AR</td>
</tr>
<tr>
<td>Achromatopsia</td>
<td>CNGB3</td>
<td>German Short-Haired Pointer</td>
<td>AR</td>
</tr>
</tbody>
</table>

NB: This is not a complete list of hereditary photoreceptor disorders.

aGene mutation identified but not published.
bGene mutation not identified.
AR, autosomal recessive; AD, autosomal dominant; XL, X-linked.
PRA grossly into developmental and degenerative diseases. The developmental class represents a large aggregate of genetically distinct disorders expressed cytologically during the postnatal period, when the visual cells are beginning to differentiate. These developmental disorders usually represent a dysplasia of the rod or cone photoreceptors (or both), and each has its own unique disease course and phenotype as assessed by functional and morphologic criteria (Acland et al., 1989; Parshall et al., 1991). Typical for the dysplasias is that before the retina is adultlike (approximately 8 weeks of age in the dog) (Gum et al., 1984), they show rather severe structural alterations of the rod or cone photoreceptor cells, and the rate of progression and loss of photoreceptors in the disease process is most often rapid. In contrast, the degenerative diseases represent defects in which photoreceptor cells degenerate after having differentiated mainly in a normal way. In the latter group, disease occurs more slowly and is modified by temporal and topographic factors. One form of primary photoreceptor degeneration (progressive rod-cone degeneration, prcd) is known to be allelic in many breeds of dog, and the underlying gene mutation has been identified (discussed later).

Within the photoreceptor dysplasia and degeneration groups, the diseases are subdivided still further according to the type of cell primarily affected (e.g., rod-cone dysplasia [rcd] of Irish Setters, cone degeneration of Alaskan Malamutes). For several diseases, however, insufficient data on morphology or electrophysiology are available, and the term PRA is then still appropriate for the lay public. The generic term retinal dystrophy implies heredity, and it may also be applied to the hereditary retinal diseases. It is particularly useful for describing new disease conditions until a specific name is substantiated by further research.

**Clinical Signs of Hereditary Retinal Degeneration/Progressive Retinal Atrophy (PRA)**

Clinical manifestations of PRA are often remarkably similar, no matter the type of disorder present at the cellular level. Nonspecific features associated with primary photoreceptor degenerations leading to retinal atrophy are described briefly here; particular features associated with specific genetic disorders are described later in the text.

PRA is always bilateral and almost always leads to blindness. It should be emphasized that familiarity with the environment can greatly conceal severe visual deficits (Rubin, 1989). In fact, it is not unusual to obtain animals for diagnosis late in the disease process, when owners have noticed visual problems only after having moved or refurnished their homes.

The most common clinical sign of early disease is impaired vision in dim light and darkness (i.e., night blindness), since it is most often the rods that are affected first in PRA. The reduced visual capacity in darkness may often be observed by visual testing, which is performed by testing the menace reaction, using falling cotton balls in front of the dog in a dimly lit room, or by using a specially designed forced-choice vision testing device (Gearhart et al., 2008). In some instances, impaired day vision (day blindness) may be observed by the owner or the examiner as an initial clinical sign if the cone system is involved primarily in the disease process.

Ophthalmoscopically, some change in tapetal reflectivity or hyporeflectivity is often seen, such as a grayish discoloration mainly in the peripheral tapetal fundus. A slight vascular attenuation and beading of retinal vessels in the midperipheral and peripheral parts of the tapetal fundus may be observed at this early stage as well. With progression of the disease, the color changes in the tapetal fundus become more marked and generalized, as does the vascular attenuation. In moderately advanced and advanced stages, there is increased reflectivity, or hyperreflectivity, of the tapetal fundus, which is usually most marked in the midperipheral tapetal fundus (Fig. 24.21). The hyperreflectivity progresses to involve all parts of the tapetal fundus (Fig. 24.22). Some depigmentation and mottling of the nontapetal fundus may be seen at moderately advanced and advanced stages. Vascular attenuation becomes marked and, especially at the advanced stage, only the contours of vessels (i.e., ghost vessels) are observed, mainly centrally in the fundus. The area that often appears most spared late in the disease is the superior central part, which is sometimes observed as a discolored streak somewhat dorsal to and on both sides of the optic disc.

As pointed out previously, changes in the nontapetal fundus are usually not seen until the more advanced stages of disease because of the dark coloration of this part of the fundus, making it more difficult to appreciate retinal thinning in the nontapetal fundus than in the tapetum fundus. When changes appear, they are observed as a patchy or uneven distribution of pigment in the nontapetal fundus, with depigmented areas in between. These changes are often described as mottling or “pavementing” of the nontapetal fundus (Fig. 24.22B).

The optic disc often becomes pallid with progression of disease, and indistinct borders are often observed. This is because of the loss of retinal circulation that occurs in the retinal degenerative process and because of the specific degeneration of neural tissue at the level of the disc and resulting demyelination.

The PLRs become progressively more sluggish as the disease progresses, and the resting pupil is more mydriatic than expected for the lighting conditions. In some cases, the PLRs are not lost entirely.

Secondary cataract often develops in the more advanced stages of disease (Fig. 24.23). The initial changes tend to occur in the posterior cortex and include vacuolation and opacification. Often, irregular radiations are seen emanating from the posterior pole of the lens and extending to involve the equatorial cortex and, later, the entire lens. Mature cataracts, especially in certain breeds, make the evaluation of retinal function using ERG of utmost importance before cataract surgery is performed in order to rule out retinal degeneration.
Figure 24.21. Moderately advanced cases of bilateral retinal degeneration (PRA) in two different canine breeds. Note the generalized change in reflectivity or hyperreflectivity and vascular attenuation in both cases. A. A 3-year-old Irish Wolfhound. B. A 4-year-old Dachshund.

Figure 24.22. An advanced case of retinal degeneration (PRA) in a 5-year-old Tibetan Terrier. A. The tapetal fundus is hyperreflective, and only ghost vessels are visible. B. The nontapetal fundus is decolored and hyperpigmented in striae and patches.
Section III

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EARLY-ONSET PHOTORECEPTOR DEGENERATIONS

Photoreceptor Dysplasias

Rod-Cone Dysplasia Type 1 (rcd1)

Rod-cone dysplasia type 1 (rcd1), initially described in the Irish Setter but also found in the Irish Red and White Setter, is an early-onset, recessively inherited disease (Aguirre et al., 1978, 1982b). It is characterized by arrested differentiation of visual cells resulting from a nonsense mutation in the β-subunit of cyclic guanosine-monophosphate (cGMP) metabolism. By 10 days of age, deficient cGMP-phosphodiesterase (cGMP-PDE) activity causes the retinal levels of cGMP to rise sharply, to concentrations as much as 10-fold higher than normal. These biochemical abnormalities are present before degenerative changes are observed in photoreceptor cells. The defect in Irish Setters is similar to that in the retinal degeneration, rd1 mouse (Farber & Lolley, 1974), in which the beta-subunit of cGMP-PDE (PDE6B) was identified by Bowes et al. (1990) as being defective. The PDE6B gene was subsequently considered to be a candidate gene for the rcd1 defect. A marked reduction in levels of messenger RNA for PDE6B early during development in Irish Setter rcd was shown (Farber et al., 1990, 1992). Two independent groups then identified a mutation in codon 807 of the PDE6B gene (Clements et al., 1993; Suber et al., 1993) that causes rcd1. Studies have shown the codon 807 mutation to be the only defect present in rcd1-affected dogs (Ray et al., 1994). Furthermore, the defect has been excluded from various forms of PRA present in other breeds (Ray et al., 1994). The lack of functional PDE6B results in a failure of the rod phototransduction explaining the accumulation of the phosphodiesterase substrate cGMP.

The disease was the first form of PRA to be described clinically in great detail, first in England and then in the United States (Aguirre & Rubin, 1975b; Hodgman et al., 1949; Parry, 1953b). Night blindness is an early behavioral sign, detectable from 6–8 weeks of age. Day vision is usually lost during the first year, but there is considerable variation in this respect. The first ophthalmoscopic signs are usually visible by 3–4 months of age, and the end stage, with generalized atrophic changes, is reached at approximately 1 year. However, some families with a slower rate of degeneration have been reported (Hodgman et al., 1949). The ERG is abnormal before the time of retinal maturation in the dog. By this time, the rod-mediated responses are absent, and the residual ERG represents abnormal cone responses with reduced amplitudes and delayed implicit times. The ERG is nonrecordable at approximately 18 weeks of age. The distinctive ERG findings in this disease are useful in making an early diagnosis.

Although PDE6B is only expressed in rod photoreceptors resulting in a rapid death of rods, the genetically normal cones also degenerate. This is because a surviving population of rods is required for maintenance of the cone photoreceptors, which secondarily die. Morphologic studies have shown that the retina develops normally until 13 days of age, after which photoreceptor differentiation is arrested (Aguirre et al., 1982b; Buyukmihci et al., 1980). Rods are particularly affected. Their inner segments remain diminutive, and the shortened outer segments contain disorganized lamellar material. Cones are less obviously affected, but outer segment disorganization does occur. The central retina appears to be affected more severely than, and earlier than, the peripheral retina. After 25 days of age, photoreceptors begin to degenerate, and by 2–3 months of age, the photoreceptor layer is severely reduced. At this age, usually only four to five rows of photoreceptor nuclei remain.

The important interactions between photoreceptors and the RPE occur through the interphotoreceptor matrix, which is a complex and highly ordered structure consisting of both soluble and insoluble constituents (Hageman & Johnson, 1991). The matrix conforms to the shape of the individual rods and cones that it surrounds, and structural changes associated with normal photoreceptor development also occur in the matrix (Mieziewska et al., 1993a). It has been discovered that there is no change in matrix structure during the period of developmental arrest (13–24 days postnatal) or after the onset of photoreceptor degeneration (Schmidt & Aguirre, 1985). Survival of cones late in the disease is a feature of rcd1, and peanut agglutinin-labeled cone domains remain intact even when the cones are severely degenerated (Mieziewska et al., 1993a).

A different mutation in PDE6B has been identified as a cause of PRA in Sloughi dogs (Dekomien et al., 2000). The disease in Sloughi dogs has similar clinical and morphologic characteristics as in the early-onset disease of Irish Setter dogs, and it has been suggested that it be given the gene symbol rcd1a. Mutation-based tests are available for rcd1 for Irish Setter and for rcd1a for Sloughi dogs (Clements et al., 1993; Petersen-Jones et al., 1995) (Table 9.1 and www.optigen.com).
Rod-Cone Dysplasia Type 2 (rcd2)

Rod-cone dysplasia type 2 (rcd2) has been described in the Collie and is another recessively inherited, early-onset retinal degeneration. Based on clinical, electrophysiologic, morphologic, and biochemical criteria, rcd1 and rcd2 are very similar diseases. There is an equally early and rapid increase in retinal cGMP levels in the postnatal period, and the magnitude of this increase as well as the time course are similar. There is deficient cGMP-PDE activity in both diseases, though in rcd2, the activity is calmodulin-independent (Chader et al., 1981).

The two dysplasias of Irish Setter and Collies represent mutations of different genes. With the advantage of having an early molecular diagnosis in rcd1, it was established that the rcd1 mutation was not present in rcd2 (Ray et al., 1994). Furthermore, previous work using test matings between dogs affected with rcd1 and rcd2 produced normal progeny as indicated by ERG, morphologic, and biochemical methods of analysis (Acland et al., 1989; Chader, 1991). These results indicate that rcd1 and rcd2 represent nonallelic diseases with similar effects on retinal cGMP metabolism. Recently, the rcd2 mutation was discovered (Kukekova et al., 2009) in the C1orf36 gene (now named RD3). Mutations in the homologous gene are responsible for a comparable disease of humans and murines (retinal degeneration 3, rd3).

Clinically, night blindness is the earliest sign, detectable by 6 weeks of age (Santos-Anderson et al., 1980; Wolf et al., 1978). Visual capacity is gradually reduced over time, just as in affected Irish Setters, and affected dogs become blind, usually before 1 year of age (Fig. 24.24). Ophthalmoscopically, at 3.5–4 months of age, a granularity is observed, primarily in the central tapetal fundus, that spreads out into the peripheral parts. Within another 4 months, a generalized hyperreflective tapetal fundus is seen, as well as other signs of classic PRA. The ERG is abnormal from day 16 and shows an absence of rod responses and an abnormal cone function. The condition is not influenced by coat color, merling, CEA, or other forms of eye disease, but at times, it may appear simultaneously and coincidentally with them (Fig. 24.25).

Rod-Cone Dysplasia Type 3 (rcd3)

PRA in the Cardigan Welsh Corgi was initially described in 1972 (Keep, 1972). Just as in Irish Setters, Sloughis, and Collies with the rcd1 and rcd2, respectively, the disorder in the Cardigan Welsh Corgi is of early onset, leading to blindness in young adult dogs (Fig. 24.26 and Fig. 24.27). The causal mutation is a one base-pair deletion in codon 616 of the alpha subunit of rod cyclic GMP phosphodiesterase (PDE6A) (Petersen-Jones et al., 1999). The mutation shortens the translated protein by 218 amino acids, and the resultant protein misses part of the catalytic domain and the c-terminal cysteine responsible for membrane binding. Immunohistochemical studies and Western blotting have shown a complete lack of PDE6A protein in affected retinae. Interestingly, the lack of PDE6A appears to interfere with the expression of the other two PDE6 subunits (PDE6B and PDE6G). This is in contrast to the rcd1 dogs where the PDE6 alpha and gamma subunits are present prior to rod death. There is a mutation detection test available for the disorder (Clements et al., 1993; Petersen-Jones & Entz, 2002; Petersen-Jones & Zhu, 2000). The affected dogs never develop normal rod function as assessed by ERG and have very reduced dark-adapted ERG responses with elevated response thresholds. Cone ERG abnormalities are also present at an early age (Fig. 24.26).
Figure 24.26. Representative dark-adapted (A–D) and light-adapted (to a background light of 30 cd/m²) (E–H) ERG intensity series responses from a normal control dog (indicated by the symbol +/+) (A, C, E, and G) compared to a PDE6A mutant/rcd3 dog (indicated by the symbol −/−) at 3 weeks (A, B and E, F) and 7 weeks (C, D and G, H) of age. Arrowheads indicate the onset of flash. The flash intensity is indicated in log candelas seconds/m². Note the difference in scales between the tracings. The vertical scale bar indicates amplitude in microvolts and the horizontal bars time in milliseconds. The rcd3 puppies do not develop normal rod-mediated responses, and there is a rapid loss of the small amplitude response that is recordable. Much of this response is likely to represent cone responses. The light-adapted (cone) responses are also reduced from an early age. The cone a-wave is reduced at 3 weeks, and both a- and b-waves at 7 weeks. (Adapted with permission from Petersen-Jones, S.M., Tuntivanich, N., Montiani-Ferreira, F., Wali Khan, N. ERGs of dog and chicken. In: Heckenlively, J.R., Arden, G.B., eds, Principles and Practices of Clinical Electrophysiology of Vision, MIT Press.)

Figure 24.27. Light microscopy of the central retina from a normal 7-week-old dog (A) and an rcd3 mutant dog at the same age (B). Note the ordered arrangement of photoreceptor inner and outer segments in the normal dog. The rcd3 dog has a reduction in numbers of outer and inner segments with the remaining outer segments being shortened and distorted. The loss of rod inner and outer segments makes the residual cones inner and outer segments appear more prominent. The cone inner segments also appear swollen. There is also a loss of photoreceptor nuclei in the outer nuclear layer with a reduction in the number of rows of nuclei as well as a reduction in the number of nuclei per unit area.
photoreceptor development with a rapid loss of rod photoreceptors by apoptosis. Cone photoreceptors are lost at a much slower rate than rods (Tuntivanich et al., 2009). Ophthalmoscopic changes are present by 12 weeks of age.

**Rod Dysplasia**

A recessively inherited form of retinal dysplasia was described in the Norwegian Elkhound many years ago (Aguirre & Rubin, 1971a, 1971c). Subsequently, the mutant strain was lost (Acland & Aguirre, 1987; Aguirre, 1978). The disease was first described as “photoreceptor abiotrophy” because it was first believed that normal photoreceptor development preceded photoreceptor degeneration (Cogan & Kuwabara, 1965). Later studies, however, showed developmental abnormalities, specifically of rods.

Clinically affected dogs became night blind at 6 months of age, and visual problems progressed to total blindness at 3–5 years. Ophthalmoscopically, there was a brownish granular appearance of the central tapetal fundus. More severe ophthalmoscopic changes (i.e., vascular attenuation and hyperreflectivity of the tapetal fundus) were not observed until approximately 2 years of age. At this time, there was also loss of pigment in the nontapetal fundus, which resulted in pale areas interspersed with patches of dark brown changes.

The ERG showed major alterations by 6 weeks of age. Rod responses were absent, whereas cone responses were initially normal but subsequently became abnormal. The photopic b-wave was nonrecordable at approximately 3 years of age (Aguirre & Rubin, 1971b). Morphologically, changes in the rod photoreceptors were observed at 12 weeks of age. The rod inner segments were short and the outer segments disorganized. At 1 year of age, the rod inner segments were also disorganized, and pyknotic photoreceptor cell nuclei were seen. These changes were followed by degeneration of the cones. The retina was completely atrophic at approximately 6 years of age (Aguirre, 1978).

In rod dysplasia of Norwegian Elkhounds, there were no abnormalities in the cyclic nucleotide metabolism, thus distinguishing the disorder from rcd1 in Irish Setters (Acland et al., 1980). Also, matings between the two breeds failed to produce affected progeny, showing that the two conditions were nonallelic.

**Early Retinal Degeneration (erd)**

Early retinal degeneration is a recessively inherited condition in the Norwegian Elkhound (Acland & Aguirre, 1987). Abnormalities in retinal cyclic nucleotide metabolism as well as mutations in the *PDE6B* gene were excluded for erd by breeding and molecular studies (Acland et al., 1989; Ray et al., 1994). The gene defect was mapped to a region of the canine genome that was subsequently found to be canine chromosome 27 (Acland et al., 1999). Recently, a mutation was found in the *STK38L* gene, affecting a pathway important for neural and photoreceptor cell function (Goldstein et al., 2010b).

Clinically affected dogs are night blind by 6 weeks of age and blind by 12–18 months. Early ophthalmoscopic alterations are present by 6 months and progress to atrophic changes, which are observed at approximately 1 year. ERGs from affected puppies are abnormal in both waveform and amplitudes. Typical for the disorder is an a-wave-dominated ERG in which amplitude of the b-wave is never greater than the corresponding amplitude of the a-wave. This waveform suggests that there is interference with the normal transmission from photoreceptors to second-order neurons. There is a successive deterioration of both a- and b-wave amplitudes with age. Both rod and cone flicker responses are abnormal as well, with a switch from positive (i.e., b-wave dominated) to negative (i.e., a-wave dominated) as age increases. Rod function is lost before cone function, with the latter not being lost until approximately 1 year of age.

Morphologically, the disease is already expressed at the earliest age studied (Acland & Aguirre, 1987). Rod inner and outer segments are irregular in both their length and proportions compared with those of similar, age-matched control animals as seen at ultrastructural analysis. In the interphotoreceptor space, discrete, isolated sectional profiles are seen and, in many areas, are in continuity with the rod and cone inner segments. With progression of the disease, there is a marked reduction of both size and number of rod and cone inner and outer segments. Regarding severity, these changes vary in different regions of the fundus. By 20 weeks of age, the visual cell layer (outer nuclear layer) is severely diminished, and by 4 years, the degeneration has progressed to affect the inner retinal layers as well. At this age, a few neuronal cells retain the morphology reminiscent of photoreceptors; otherwise, both rods and cones are lacking. An interesting finding in the disease is that both rod and cone synaptic terminals have an abnormal development. The rod spherules are few and appear immature. Cone synaptic terminals appear normal at first but then fail to develop properly with age. At 20 weeks, pedicles have degenerated, with vacuolated cytoplasm (Acland & Aguirre, 1987). Recent studies have shown that in addition to photoreceptor death, proliferation occurs, producing hybrid photoreceptors expressing both rod and cone proteins. These subsequently degenerate (Berta et al., 2011).

**Photoreceptor Dysplasia**

Photoreceptor dysplasia of Miniature Schnauzers is an unusual disease of the photoreceptors that, through pedigree analysis and test mating, has been shown to be inherited as an autosomal recessive trait. The disease is unusual in that it has a slow clinical progression when assessed with behavioral testing and ophthalmoscopy. When judged with histopathology and ERG, however, it is an early-onset disorder (Parshall et al., 1991).

Clinically affected dogs show initial night blindness, followed by progressive loss of day vision. This finding was most easily discovered when lowering the light level from...
increased with age, and advanced rod degeneration was seen at 7.5 months. At 3 years of age, the outer nuclear layer showed only a double row of surviving rod nuclei. Later, at 5 years, only a single row of photoreceptor nuclei was present in the posterior pole, whereas advanced gliosis and disruption of all retinal layers were observed in the peripheral fundus. Thus, the changes represent not only a developmental retardation but also an aberrant differentiation process.

The mutation responsible for PRA in the Miniature Schnauzer is designated as type A-PRA (www.optigen.com). There is a mutation-based test available for the disorder (Zhang et al., 1998, 1999). Further studies have shown that other genetic defects appear to also be involved in cases of PRA in the Miniature Schnauzer breed (Jeong et al., 2008).

Cone-Rod Dystrophy (crd)

The crd’s are a heterogeneous group of inherited retinal degenerative disorders naturally occurring in humans and in dogs. The diseases are characterized by simultaneous involvement of cone and rod photoreceptors, the former being more severely affected than the latter, initially. So far, the disorder has been described in comparatively few canine breeds. Cone-rod dystrophy was discovered in the Pit Bull Terriers and was further studied through clinical and molecular genetic investigations (Kijas et al., 2004). After weaning, affected dogs already show distinct pupillary dilatation, severe visual difficulties under well-lit conditions, and intermittent nystagmus. ERGs demonstrate severe dysfunction of both cones and rods, with cone function consistently more severely impaired than that of rods. In some cases, cone function is nonrecordable. Ophthalmoscopic signs of disease become apparent in affected animals between 3 and 6 months of age. By 12 months, affected dogs show fixed dilated pupils and advanced generalized retinal degeneration on funduscopic examination, and their ERGs are nonrecordable. Morphologic examinations have confirmed the diagnosis; a diffuse, severe retinal degeneration was observed. Two founder Pit Bull Terriers were used for the studies; descendents from each dog had similar recessively inherited retinal diseases, although cross breeding showed that they were nonallelic. These two forms of crd were named crd1 and crd2. Crd1 is reported in the American Staffordshire Bull Terrier and crd2 in the American Pit Bull Terrier. The crd2 mutation has been identified and a DNA-based test offered, although the mutation was not published at the time of writing (www.optigen.com).

Recently, crd was identified in the Glen of Imaal Terrier and designated as crd3. Thorough clinical and laboratory studies of the Glen of Imaal Terrier (Goldstein et al., 2010c) have shown early fundus changes at the age of 3 years. Two distinct phenotypes have been described: either there are generalized subtle alterations in the fundus as typically seen in PRA, or an area of change confined to the area centralis, as a discrete, distinctly hyperreflective lesion. The latter area stays unchanged for at least 12 months but eventually progresses to generalized retinal involvement. ERG shows normal retinal
SECTION III: Canine Ophthalmology

function in young crd3-affected dogs, but by 15 months, cone function is reduced and with time, responses from both the rod and cone systems are nonrecordable. Morphology at 4.7 weeks shows subtle changes which progress slowly with age. At 5 years of age, rod and cone nuclei are severely reduced in numbers and mainly rod-like nuclei are observed in the outer nuclear layer. Ultrastructural changes in the RPE have shown interesting changes in the apical microvilli: instead of encircling the photoreceptor outer segment tips, they form a flattened, entangled mat between the RPE cells and the distal outer segment tips. Molecular genetic studies by two groups identified a deletion with the ADAM9 gene in crd3-affected dogs, which establishes the disease orthologous to CORD9 in humans (Goldstein et al., 2010c; Kropatsch et al., 2010). A DNA-based test is offered for crd3.

In the Short-Haired Dachshund, an early onset, recessively inherited crd has been described including clinical and electrophysiological findings (Ropstad et al., 2007a, 2007b). In young affected dogs, approximately 60% showed severe miosis in light-adapted conditions. Already at the age of 5 weeks, the cone system is affected with severely reduced or nonrecordable cone-derived ERG responses (Ropstad et al., 2007b), while rod responses are either normal or only slightly reduced at this early age. Funduscopic changes are, in most cases, not observed until the age of 3 years, however. Then signs of a generalized retinal degeneration appear, with marked changes in the nontapetal fundus, with severe mottling (Fig. 24.29) and, within another year, pigmented ridges and spots. An unusual pigment migration into the neural retina has been described in a comparably early stage of the disease by light and electron microscopy (Ropstad et al., 2008). A novel gene for this early-onset crd has been described: a deletion in the nephronophthisis 4 (NPHP4) gene, also known as nephroretinin, causing simultaneous eye and kidney disease in humans, and naturally occurring crd without additional kidney disease in the canine (Wiik et al., 2008).

In the Long-Haired Dachshund, the clinical and morphological characteristics of a rod-cone dystrophy were described (Curtis & Barnett, 1993). This was later given the gene symbol cord1. Ophthalmoscopic changes were observed at the age of 6 months and included changes in the granular appearance of the fundus followed by tapetal hyperreflectivity and retinal vascular attenuation. There was irregular loss of pigment in the nontapetal fundus and optic atrophy. A marked variation in age of onset and progression of the disease was observed, even within a single litter. Significant histological changes were found in the outer retina at both light and electron microscopic levels at the age of 10.5 weeks. There was a reduction in numbers of nuclei in the outer nuclear layer. More recent electrophysiological studies have shown that the hereditary disorder is a crd. Already at the age of 6 weeks, cone-specific ERG responses were found to be significantly reduced in amplitude, while rod responses were normal (Busse et al., 2011; Turney et al., 2007). In the Miniature Long-Haired Dachshund, crd has been reported to be due to a mutation in the RPGRIP1 (retinitis pigmentosa GTPase regulator-interacting protein 1) gene (Mellersh et al., 2006). These studies were based on an inbred colony of dogs. More recent electrophysiological studies have shown that the hereditary disorder is a crd. Already at the age of 6 weeks, cone-specific ERG responses were found to be significantly reduced in amplitude, while rod responses were normal (Busse et al., 2011; Turney et al., 2007). In the Miniature Long-Haired Dachshund, crd has been reported to be due to a mutation in the RPGRIP1 (retinitis pigmentosa GTPase regulator-interacting protein 1) gene (Mellersh et al., 2006). These studies were based on an inbred colony of dogs. Recent studies have suggested the situation may be more complex. Some dogs homozygous for the RPGRIP1 mutation do not appear to develop the retinal disease. The possibility of interaction with a second genetic locus is being investigated (Miyadera et al., 2009, 2011).

Figure 24.29. Early cone-rod dystrophy seen in a 1-year-old Wire-Haired Dachshund. A. In the tapetal fundus, hyperreflectivity is seen and vessels are moderately attenuated. B. In the nontapetal fundus, marked mottling is visualized. (Courtesy of Ernst-Otto Ropstad.)
LATE-ONSET PHOTORECEPTOR DEGENERATIONS

Progressive Rod-Cone Degeneration (prcd)

The “classical type of PRA” that is termed prcd has an autosomal recessive inheritance. The defect has been known for some time to be an allelic condition in many dog breeds with late-onset type of PRA (www.optigen.com) (Aguirre & Acland, 1988). A mutation in a previously unidentified gene, PRCD has been identified and expression studies showed that this gene is predominantly expressed in the retina, with equal expression in the RPE, photoreceptor, and in the ganglion cell layers (Zangerl et al., 2006). Interestingly, a human retinitis pigmentosa (RP) patient was identified with an identical mutation in the human PRCD gene.

prcd in the Miniature and Toy Poodle

In the Toy and Miniature Poodles, structural and functional abnormalities in prcd do not become evident until after the visual cells have developed normally. The frequency of prcd in Poodles has been high over the years (Priester, 1974). Night blindness is the first behavioral sign, being observed in affected dogs usually at 3–5 years of age, but there is considerable variation in onset. Impaired vision usually does not become obvious to the owner earlier unless the dog is placed in an unfamiliar environment or furniture or other obstacles in the home are rearranged. Affected dogs may be apprehensive of the dark and experience particular difficulty in negotiating stairs. Night blindness is followed by reduced vision in daylight and, finally, by complete blindness, which occurs at a variable age, usually between 5 and 7 years. The rate of progression is believed to be faster in dogs that become affected at a young age than in those that develop the disease later in life. Development of a secondary cataract may exacerbate vision loss and therefore influence the age at which the condition first becomes apparent to the owner. It is not unusual for owners to have only noticed the marbled, white, or more diffusely clouded lenses and to want a cataract extraction be performed. Then ERG plays an important part in ruling out retinal degeneration before even considering surgery.

Ophthalmoscopic fundus changes are usually advanced by the time owners have noticed vision problems. Often, affected dogs are found during routine ophthalmoscopic examination. A change in tapetal coloration into grayish discolorations is usually seen, which are most prevalent in the midperipheral and peripheral tapetal fundus, near the border of the nontapetal fundus. The discoloration is followed by progressive attenuation of the retinal vessels, commencing with the small arterioles. Loss of pigment is usually not seen until the disease has progressed to a more advanced stage. A change in tapetal reflectivity and hyperreflectivity are then observed, mainly in the midperipheral and peripheral tapetal fundus. At the advanced stage, radial striae, due to indentation of the underlying choroidal vasculature, are seen in many cases in the midperipheral and peripheral fundus, underneath the atrophic neural retina. The retinal vasculature is severely attenuated at this advanced stage. Eventually, the retinal vessels virtually disappear, and the ONH atrophies, becoming pallid and irregular in outline and, later, appear reduced in size (Fig. 24.30).

In affected Poodles, ERG studies have shown a normal maturation of retinal function. At 28 weeks of age, however, affected dogs have ERG responses that fail to increase in amplitude with dark adaptation, and the dark-adapted responses are lower than normal in amplitude (Aguirre et al., 1982a). With progression of disease, the response amplitudes decrease. By 18 months, only small b-wave amplitudes are recorded in response to red and white stimuli. A number of researchers have failed to detect abnormalities of rod and cone responses until 10 months of age (Sandberg et al., 1986). This variation in results could be caused by differences in ERG procedures or in the phenotype of the dogs being studied. There is usually a rather great variation regarding disease debut and progression. In practical terms, however, ERGs from dogs younger than 10 months are unlikely to be meaningful in the early detection of PRA in this breed.

At light microscopy, the photoreceptors of affected dogs develop normally, but at 14.5 weeks of age, there is disorganization of some outer segment lamellae observed at ultrastructural analysis, as well as vesicular profiles in the scleral half of the outer segment layer (Aguirre et al., 1982a). Cone photoreceptors are morphologically normal at this early age. At 30 weeks, there are distinct abnormalities in rod outer segments, which are also evident at light microscopy. In young prcd-affected dogs, there is a central-to-peripheral gradation of disease severity.

There is a highly characteristic sequence of disease in prcd, which has been characterized on the basis of structure into three major phases (Aguirre & Acland, 1988; Long & Aguirre, 1991):

1. early disease (stages 0–1)
2. degeneration (stages 2–4)
3. atrophy (stages 5–8).

Beginning at 12–14 weeks of age, all photoreceptor cells start developing the stage-specific pathology characteristic of the disease, but the rate of progression depends on topographic factors (Aguirre et al., 1982a). Pathology is always more severe in the inferior quadrants, whereas the visual cells in the superior and temporal retinal quadrants are spared until later in the disease process. So far, no specific properties have been identified in the inferior retina that selectively predispose this area to earlier and more severe disease. Moreover, the rate of progression is not influenced by the presence or density of pigmentation in the RPE. Throughout these three phases, the pigment epithelium remains normal in affected animals. It is only in very advanced disease that the pigment epithelium shows nonspecific, atrophic changes and, sometimes, migratory responses.

Using the techniques of lectin cytochemistry, the molecular components of the insoluble interphotoreceptor matrix have been studied to determine if abnormalities are present in
prcd-affected retinas (Mieziewska et al., 1993b). Except for the late atrophic stages of the disease, the lectin specificity remains normal, thus indicating the photoreceptor-specific, insoluble interphotoreceptor matrix constituents are not primarily involved in prcd.

Autoradiographic studies of affected retinas after intravitreal injection of tritiated leucine or tritiated fucose have shown a reduced rate of rod outer segment renewal, which is a finding also shown to precede the appearance of structural changes (Aguirre & O’Brien, 1986; Aguirre et al., 1982a). This hallmark abnormality identified in prcd rods is a uniform decrease in renewal, initially of 30%-35%, that is associated with stage 1 of the disease. Thereafter, renewal decreases further, and both rod disease and degeneration progress. The transition

Figure 24.30. Advanced progressive rod-cone degeneration (prcd) observed in a 7-year-old Miniature Poodle. A. Central part of fundus, with severe vascular attenuation and a grayish tapetal discoloration. B. Midperipheral fundus, with hyperreflectivity and discoloration in the peripheral part. C. Periphery of the tapetal fundus, with a marked striation. The contours of the choroidal vascular pattern are observed underlying the atrophic neural retina.
from stage 1 to stage 2 marks the end of renewal by membrane addition, and only low levels of diffuse label are present in the rod outer segments at stage 2 and later. Cone pathology is not obvious until later, after rods have begun to degenerate (e.g., stage 2 and later). Because of structural differences between the disc membranes of rod and cone outer segments, renewal by membrane addition cannot be followed in the cones. The label in this type of photoreceptor diffuses laterally and longitudinal throughout the entire cone disc membrane domain. Therefore, early phases of renewal in prcd using retinal explants were performed to evaluate the transfer of newly synthesized protein label from the photoreceptor inner to outer segments (Fahlman, 1990). In this in vitro study, the renewal defect was observed, as previously, in rods but not in cones. Thus, the disease in cones certainly appears to be secondary to a primary defect in the rod photoreceptors.

associated with the transitions from stage 1 to stage 2 is a decrease in the expression of opsin mRNA transcripts and immunoreactivity (Huang et al., 1994). It is interesting that all rods demonstrate the same changes in opsin mRNA and immunoreactivity as well as in renewal deficits, regardless of their topographic position.

Several other photoreceptor-specific proteins have been studied in prcd using immunocytochemistry. The change in immunoreactivity for each is unique. The most stably expressed protein appears to be an interphotoreceptor retinoid-binding protein, which has demonstrated sustained labeling of the interphotoreceptor matrix even after most photoreceptors have been lost (Wiggert et al., 1993).

In the search for systemic markers in human RP and for animal models of the disease, several groups have investigated the level of plasma lipids in affected individuals (Converse et al., 1983; Gong et al., 1992). In Miniature Poodles, significantly lower levels of plasma docosahexaenoic acid (22:6n-3) have been found when affected dogs were compared with normal dogs (Anderson et al., 1991). The effects of 22:6n-3 supplementation on polyunsaturated fatty acid metabolism were also determined in both normal and affected dogs (Anderson et al., 1994). The results showed a defect in 22:6n-3 metabolism among prcd-affected animals. It is not yet clear, however, if there is any correlation between the reduced renewal rate of photoreceptor outer segments, the lower 22:6n-3 levels, and retinal degeneration in prcd-affected dogs.

prcd in Some Other Common Breeds

There is a variation in age of onset, rate of progression, and topographic changes in the retina between (and within) breeds that suffer from prcd. This variation is likely to eventually prove to be due, at least in part, to background genetics (presence of modifying loci).

In pure-bred English Cocker Spaniels, prcd differs phenotypically from that in Poodles both in rate of progression and in topographic distribution of the disease in the retina. Cross-breeding experiments with prcd-affected Miniature Poodles and retinal-degenerate English and American Cocker Spaniels have, however, shown that the gene mutation in each is at the same (prcd) locus (Aguirre & Acland, 1988).

clinically, prcd in English Cocker Spaniels is phenotypically expressed late in life, with funduscopic alterations indicative of retinal degeneration usually not prevalent until between the ages of 4-8 years. Moreover, appearance of the fundus in affected dogs may be quite variable. In some cases, there are changes such as those described earlier for the disease; in others, the severity of retinal alterations varies greatly in different areas of the fundus (Fig. 24.31). Thus, hyporeflective changes along the visual streak can be seen (centrally on either side of the optic disc), whereas other areas are brownish gray and still others quite normal in appearance. Secondary cataracts are usually found early in the disease process.

Diagnosis by ERG is also not possible until comparably late, at 1 year of age in some cases but not until after 2 years in others. A few cases may have ERG responses indistinguishable from those of normal dogs at age 2.5 years.

Early ERG changes consist of mild decreases in b-wave amplitude to scotopically balanced red and blue light stimuli and white light stimuli, with b-wave implicit times remaining normal (Aguirre & Acland, 1988). Flickering light stimuli at different frequencies readily differentiate rod and cone responses and show unequal functional deficits. Rod components are affected earlier, and become nonrecordable earlier, than cone components. Isolated rod signals cannot be elicited...
at a time when cone signals are still distinct. It was shown that Miniature Poodles affected with prcd lost b-wave function at approximately twice the rate of affected English Cocker Spaniels (G. Aguirre and G. Acland, personal communication).

Morphologic findings corroborated clinical findings, especially in dogs with advanced disease (Aguirre & Acland, 1988). In dogs with early disease, changes were limited to rod outer segments and were mainly seen as disorganization of the outer segment lamellae. Later, degenerative changes were seen in the outer and inner segments as well as in the photoreceptor nuclei of rods; phagocytic cells were often present in the subretinal space at this degenerative stage. In late atrophy, the inner retinal layers were affected as well. At light microscopy, the changes appeared similar to those described for prcd in Miniature Poodles. At the ultrastructural level, however, the histopathology was somewhat different, and importantly, the temporal and spatial distribution of visual cell lesions varied between the two breeds. In English Cocker Spaniels, vesicular profiles were absent or present only in small numbers during early stage of disease. Also, there was a varying distribution of disease, which was readily observed on the spatial maps constructed. Disease was more severe in the inferior than in the superior, temporal, or nasal meridians, but there was a great variation regarding the severity of degenerative changes within meridians. Moreover, not all locations degenerated at the same rate. Older animals showed a “mosaic” of different disease stages across a meridian. The most significant difference in prcd among English Cocker Spaniels compared with that in Miniature Poodles was in the rate of degenerative changes, and this confirmed the results of the ERG observations.

In American Cocker Spaniels, affected dogs become night blind at 3–5 years of age (LaVail, 1981). There is a successive reduction of visual capacity in daylight as well, and within 1–2 years, the dogs are blind. Secondary cataracts are prevalent, often from the moderately advanced stage. Ophthalmoscopically, early changes may be seen from the age of 2.5–3.0 years or older (Fig. 24.32). Most often, there is a generalized change in tapetal reflectivity, with a slight vascular attenuation. Over time, the tapetal fundus becomes hyperreflective, first in the midperipheral and peripheral tapetal area. The central parts of the fundus are usually spared late in the disease process, as observed at ophthalmoscopy.

There are some difficulties in making the diagnosis of fundus changes in American Cocker Spaniels that should be discussed. It is not unusual that individual animals have a thin and uneven peripheral tapetal border, and in this area, there is often a gray to brownish sheen, which may look like an early stage of prcd (Fig. 24.33). Also, some dogs may have focal and circular, but most often curvilinear, folds in the peripheral tapetal fundus. Over time, these lesions may become pigmented and may even have hyperreflective parts, which is indicative of scar formation. Because of these aberrations, ERG is often performed to exclude prcd in American Cocker Spaniels. As in Miniature Poodles, an early diagnosis of prcd using ERG may be possible in the American Cocker Spaniels at 9–10 months of age. In addition, morphologic studies have shown alterations comparable to those of Miniature Poodle prcd.

Prcd has been a significant worldwide problem among Labrador Retrievers and especially from the Nordic countries for more than 25 years (Aguirre & Acland, 1991; Garmer, 1986; Kommonen & Karhunen, 1990). Clinically affected animals become night blind rather late, usually between 4 and 6 years of age. There is a slow progression of the visual problems, and affected dogs have severe visual impairment at 6–8 years. There is, however, considerable variation in this finding. In solitary cases, visual impairment has been observed as early as 2.5 years, and blindness has prevailed only 2 years later. Ophthalmoscopically, changes are usually seen in the midperipheral and peripheral fundus (as a change in tapetal reflectivity) (Fig. 24.34). Often, a horizontal streak on both sides of the optic disc in the tapetal area is seen, with a marked grayish brown discoloration that, depending on the incident light, may appear hyperreflective (Fig. 24.35). The changes in the midperipheral area progress to complete hyperreflectivity of the tapetal fundus, and severe vascular attenuation is observed at the end stage. In many cases, the central fundus is somewhat spared late in the disease, sometimes with a dark, grayish streak observed still on either side of the optic disc.

Results of ERG studies have shown a successive reduction of scotopic b-wave amplitudes (Kommonen & Raitta, 1987). Rod function is severely reduced, whereas cone function is
Figure 24.33. A 7-year-old American Cocker Spaniel not affected by prcd. The fundus vasculature is normal in both the central (A) and peripheral (B) parts. In the peripheral tapetal fundus, there is a bilateral, slightly grayish discoloration, probably resulting from a thin tapetal area in this region. These ophthalmoscopic signs can, however, be confused with those found in early prcd. Often, an ERG must be performed to differentiate the conditions.

Figure 24.34. A generalized change in tapetal reflectivity, though the retinal vasculature still appears normal, in a 4-year-old Labrador Retriever with early prcd. The dog had visual problems at night and a nonrecordable scotopic ERG.

spared until late in the disease. Definite diagnosis on the basis of ERG results is possible by 15 months of age using ERG under stable recording conditions. Studies by Kommonen et al. (1997), however, showed that by using a sensitive DC-ERG system, significant differences were found between affected and normal dogs as well as between dogs heterozygous for the defect and normal dogs at 3–4 months of age.

Analysis of retinal morphology in the disease has shown changes at a comparably early age (Fig. 24.36). By 1 month, distinct alterations have already been found in the rod outer segments of the central tapetal fundus, whereas the midperipheral and peripheral areas have been normal until at least 5 months. It has been speculated that photoreceptors in the central fundus never completely reach normal development, whereas other parts of the fundus do (Kommonen et al., 1994). At light and electron microscopy, degenerative changes in photoreceptors have been observed at 5 months in affected dogs. After this age, there is a slow progression of disease, as described for prcd in Miniature Poodles.

For a comprehensive list of other canine breeds affected by the prcd mutation, see www.optigen.com.

Autosomal Recessive PRA (Non-prcd) in Other Breeds

In the Tibetan Terrier dog, PRA was first described in Sweden and later in England (Barnett & Curtis, 1978; Garmer et al., 1974). An autosomal recessive inheritance for the defect was
established through a test-breeding scheme, and the disease was investigated further using both electrophysiologic and morphologic techniques (Millichamp et al., 1988). Molecular genetic studies (examining the opsin gene for polymorphism) were performed in Tibetan Terriers as well as in Miniature Schnauzers, Irish Setters, Miniature Poodles, Labrador Retrievers, and English Cocker Spaniels (Gould et al., 1995). Two polymorphisms were found. One, segregating within the Tibetan Terrier population but not in the other breeds, was a synonymous transition at nucleotide position 780 in exon 3. Inheritance of this polymorphism suggests that opsin is unlikely to contain mutations causing PRA in this breed.

Clinical signs of disease in affected Tibetan Terriers manifest rather early compared with those of the pccd-affected dogs. Night blindness is often found well before 1 year of age. The disease has a fast progression, and blindness before 2 years is not unusual. At this early age, the PLRs are slow and incomplete. Bilateral cortical (and then complete) cataracts often develop after 4 years. Typical funduscopic signs of disease are grayish tapetal discolorations in the midperipheral and peripheral fundus and, very soon, a slight vascular attenuation. The discoloration changes toward hyperreflectivity as the degenerative disease progresses, especially in the peripheral tapetal fundus. These alterations spread centrally to involve all tapetal areas and are especially prominent around the optic disc, which becomes pale and devoid of its normal vascularity. The end stage is a generalized atrophy that is also observed in the nontapetal fundus, where depigmented areas surround hyperpigmented spots.

ERG findings include a reduced scotopic b-wave at approximately 10 months of age, but with normal timing characteristics at this age and normal sensitivity of the b-wave responses. After 30 months, the ERG is nonrecordable (Millichamp et al., 1988). Light microscopy in one study revealed no major aberrations at 10 weeks in affected dogs (Millichamp et al., 1988). At 8 months, however, the neural retina had thinned.
considerably, and at 24 months, there was a generalized atrophy of the retina and the outer nuclear layer was reduced to only three or four rows of photoreceptor nuclei. At ultrastructural analysis, distinct alterations were observed in rod and cone outer segments in 10-week-old affected dogs. Interspersed between normal rod and cone outer segments were other (both rod and cone) outer segments that were severely disorganized and disoriented. Numerous vesicular profiles were seen in the interphotoreceptor space at this early age as well. The changes were seen in all sections from different areas of the retina; no region was less or more affected.

Biochemical studies of retinal cGMP and plasma taurine have been performed in groups of normal and affected Tibetan Terriers (Hussain et al., 1988). No evidence for abnormalities in cGMP or taurine homeostasis, however, was found.

In the Tibetan Spaniel, cases of PRA have been found in several countries, including England, Sweden, Norway, and the United States, and the clinical findings were described (Bjerkås & Narfström, 1994). Ophthalmoscopic signs have been recorded from the age of 3–5 years. Thereafter, affected dogs lose vision rather quickly, and they are severely visually impaired after another year. Funduscopic changes are the classic findings for late-onset PRA, including hyperreflectivity of the peripheral tapetal fundus and severe attenuation of retinal vessels (Fig. 24.37). The retinal atrophic changes spread inward, toward the optic disc. Secondary cataract is seen in older affected dogs but does not seem to be an early finding. Because of the variation in tapetal distribution and size, the fundus of Tibetan Spaniels is highly variable, thereby causing difficulties in making an early diagnosis on the basis of ophthalmoscopic findings. ERG is an invaluable aid under these circumstances. Electrophysiologic and histopathologic data are not yet available.

In Akitas, PRA has been described as a variable disease regarding first appearance and type of initial clinical symptoms (O’Toole & Roberts, 1984; Paulsen et al., 1988). In this recessively inherited disease, night blindness occurs between 1 and 3 years of age, with complete blindness developing between 3 and 5 years of age. Ophthalmoscopically, two patterns of initial funduscopic changes have been described: The most common involves a hyperreflective horizontal band in the central tapetal fundus, which is first seen in the area centrales region and then extending horizontally on either side of the optic disc. The other pattern is characterized by retinal alterations, which are indicative of retinal thinning, in the peripheral tapetal fundus. With progression of both patterns, there is a generalized hyperreflectivity of the entire tapetal fundus, vascular attenuation, and atrophy of the ONH.

Early ERG findings include significant reductions in scotopic b-wave amplitudes among dogs younger than 1 year. Dark adaptation curves are abnormal, but there appears to be both rod and cone dysfunction. Because there appears to be great variation regarding electrophysiologic changes in the disease, a definite diagnosis on the basis of ERG cannot be made until 1.5–2.0 years of age.

Progressive retinal atrophy has also been described in the Papillon breed of dog. In a study of 707 dogs, 5% were affected with a generalized retinal degenerative disease (Håkanson & Narfström, 1995). The disease appears to be inherited by an autosomal recessive gene, has a late onset, and undergoes a slow progression of clinical signs. Clinically affected dogs seldom show evidence of severe visual impairment, even at a late stage of disease. Night blindness is, however, an early clinical sign, which may be found in some middle-aged dogs at visual testing in dim light and in darkness. Visual impairment or blindness is usually not prevalent until the age of 7–8 years. Ophthalmoscopic findings as well as disease progression are similar to those described for prcd in Miniature Poodles. Thus far, secondary cataract has not been a concurrent finding in most of the affected dogs examined so far, as found in other breeds affected with PRA (Håkanson & Narfström, 1995; Narfström & Ekesten, 1998).

There is great variability in the extent and coloration of the visible tapetum in Papillons. Some dogs lack visible tapetal cells, and some have subalbinotic eyes. These variables often render making the diagnosis difficult. ERG is therefore extremely useful for making an early diagnosis of disease in these dogs.

Groups of Papillons have been evaluated using ERG (Narfström & Ekesten, 1998). Full-field/Ganzfeld ERG was used to test outer retinal function in 45 young normal and affected Papillons. Eleven specific responses were recorded, plotted onto graphs, and evaluated using age-matched groups of dogs. A severely decreased retinal function in eight Papillons, with

Figure 24.37. An advanced case of PRA in a 7-year-old Tibetan Spaniel. Note the generalized hyperreflectivity and ghost vessels in the fundus.
the youngest being 1.2 years of age, was found. Response amplitudes mainly originating from the rod system were severely reduced when the cone responses were only slightly reduced or even normal (Fig. 24.38). The results showed that early diagnosis using ERG may be confidently performed by 1.5 years of age in the Papillon breed using techniques previously described (Narfström et al., 1995).

Results of morphologic studies corroborate these ERG findings. In a 7-year-old affected dog, there was primarily a generalized retinal degeneration of rods, with less obvious degenerative changes in cones. There also was a regional variation of disease severity, in that the inferior nontapetal retina was more severely affected than the superior tapetal area (Narfström & Wrigstad, 1999).

More recent studies have shown that there are at least two forms of PRA in the Papillon. One form is characterized by an early reduction and then loss of rod function that is accompanied by a progressive thinning of the outer nuclear layer. Early fundus changes are of an initial tapetal hyporeflectivity which is accompanied by early retinal vascular attenuation.

Figure 24.38. Representative ERGs in a 1.4-year-old Papillon with PRA and in an age-matched, normal Papillon using blue, red, and white light stimuli in the scotopic (dark-adapted) state. A. After 20 minutes using blue light stimuli, there is a marked reduction of b-wave amplitude in the affected compared with the normal dog. Calibration depicts 20 µV vertically and 15 ms horizontally. B. Using red light stimuli, a biphasic curve is obtained, showing the responses of the cones and rods, respectively. Note in the affected dog that both responses are reduced, though somewhat more so for the rod than for the cone system. Calibration depicts 2 µV vertically and 15 ms horizontally. C. Using white light stimuli, there is a distinct a- and b-wave in the normal dog, but only a severely reduced b-wave in the affected dog. Calibration depicts 20 µV vertically and 15 ms horizontally. D. Flicker recordings (30 Hz) show somewhat reduced amplitudes and timing characteristics for the affected compared with the normal dog. Calibration depicts 5 µV vertically and 15 ms horizontally.
and progresses to tapetal hyperreflectivity (Petersen-Jones et al., 2011) (Fig. 24.39). The gene mutation for the first form of PRA in the Papillon has been identified (Petersen-Jones, unpublished results). Electroretinographic studies revealed a second retinopathy characterized by abnormal cone-derived ERG responses suggestive of an abnormality of cone ON-bipolar cells (Petersen-Jones et al., 2011).

In the English Springer Spaniel, recessively inherited progressive retinal degeneration has been described also, although the disease appears clinically somewhat different from classical PRA (Hyman et al., 2001; Koch et al., 1997; Wheeler, 1998). The disease is of late onset and is slowly progressive. Visual impairment is usually not noticed by the examiner in affected dogs until they are 3 years old or older. There appears to be a marked variation in time of appearance of clinical signs, however (2–9 years were described). Ophthalmoscopically, changes are first observed in the periphery of the fundus, at the tapetal–nontapetal junction as a slight color change and a mottling. The degeneration is seen to advance more centrally with time and has a scalloped appearance with hyperreflectivity that starts to become more apparent. The retinal vasculature in the altered area remains normal at this stage. The zone of retinal degeneration is characteristically horizontal, with a clear demarcation of normal fundus to the abnormal fundus. There is also a slight vascular attenuation at this time. With progression, clinical signs of classical PRA become more apparent but without the “spoking” or “furrowing” that is commonly seen in other breeds. Secondary cataract is prevalent at this stage and progress to maturity in some cases. Recently, functional studies using ERG have shown that the disease appears to be a form of crd, in that cone function is more affected than rod function early in the disease process. Morphologic studies have corroborated these findings with early changes in cone photoreceptors observed when rods appear normal.

Former breeding practices allowed for both English Cocker Spaniel and Springer Spaniels to be in the same litter, the only distinction being made for size. It would be logical to assume that the prcd seen in the American and English Cocker Spaniels would be the same as in the English Springer Spaniel dog breed. This gene does not seem to be affected, however, in cases of PRA in the English Springer Spaniel (T. Bergström, personal communication). Instead, a high frequency of dogs are either homo- or heterozygous for the RPGRIP1 mutation, disease designated as cord1 (G. Johnson, personal communication). English Springer Spaniel dogs affected by the CORD1 mutation was also described in conjunction with documented studies of cord1 disease in regard to the Long-Haired Dachshund (Miyadera et al., 2009).

In order to study the genotype-phenotype correlation with the RPGRIP1 mutation a masked study was undertaken in which the examiner (KN) did not know the genotype of the dogs: four of six dogs, age between 8 and 14 years, homozygous for the RPGRIP1 mutation, showed clinical signs of retinal degeneration. Two of the homozygous dogs were functionally and ophthalmoscopically completely normal. It was concluded that there are strong indications that the RPGRIP1 mutation is involved in the cone rod dystrophy described in the English Springer Spaniel, but that the genotype-phenotype discordance found shows that the genetic background for development the retinal disease is more complex than previously thought. There are indications that other mutations or modulating genes are involved in development of cone rod dystrophy and and that there may be other forms of PRA-like disease in the breed (Narfström et al., 2012).

The Schapendoes breed of dog has recently been shown to have autosomal recessive PRA caused by a mutation in a newly identified gene; coiled-coil domain containing 66 (CCDC66). The one-basepair insertion leads to a premature stop codon and a lack of CCDC66 protein in the retinal of affected dogs (Dekomien et al., 2010). Immunohistochemical studies showed that the CCDC66 gene is detected in the inner segments of the photoreceptors of mouse, dog, and man and that the protein was missing in affected Schapendoes dogs (Gerding et al., 2011).

The Golden Retriever is also affected by the prcd mutation. A recent study indicated a second disease-causing gene for...
PRA in Golden Retriever: GR_PRA1, in which there is a frameshift mutation in the SLC4A3 gene (Downs et al., 2011). A large proportion of the PRA-cases still remain unexplained (44%), however, which indicate that PRA in the breed is genetically heterogenous and that there are at least three different forms in the breed (mutations in prcd, SLC4A3 and an as yet unidentified mutation) (Downs et al., 2011).

X-Linked Progressive Retinal Atrophy (X-Linked PRA)

Hereditary retinal degeneration in Siberian Huskies has been described (Rubin, 1989). There seemed to be an excess of affected male dogs with the disorder, and further studies, including test-breeding schemes, showed there was an X-linked transmission for the disease (Acland et al., 1994). Clinical signs of X-linked retinal degeneration include initial night blindness and early ophthalmoscopic signs of the retinal degeneration, usually observed at 2–4 years of age. ERG recordings in affected dogs showed diminished rod-mediated function, as described for prcd of other breeds. Morphologic evidence for hereditary retinal degeneration is also comparable to that in the affected breeds previously described, although there is significant variation in disease despite the presence of the same disease allele in the affected dogs of one study. Further, it was found that carrier females displayed generalised reduction in photoreceptor cells density as well as multifocal areas of complete cell loss, consistent with random X-chromosome inactivation (Zeiss et al., 1999) (i.e., the portions of the retina expressing the mutant allele degenerated while those expressing the normal allele did not). The same form of PRA was described in the Samoyed and has been shown to be due to a mutation in the open reading frame (ORF) 15 of the RP GTPase regulator (RPGR) gene. The X-linked PRA described in both the Siberian Husky and in the Samoyed is termed X-linked PRA type 1 (XL PRA1). A mutation-based DNA test is available for the disease.

A second form (XL PRA2) was identified in a line of crossbred dogs (Zhang et al., 2002). Interestingly, the mutation for XL PRA2 was also in ORF 15 of RPGR, although it was a different mutation. XL PRA2 is a more severe disease than XL PRA1. With XL PRA1, electroretinographic abnormalities are present from 6 months of age, and there is a rod-led retinal degeneration (i.e., the rods die before the cones) leading to an “end-stage” retina, one with advanced tapetal hyperreflectivity and severe blood vessel attenuation, by 4 years of age. XL PRA2-affected dogs have abnormal photoreceptor development with ERG abnormalities from 6 weeks of age. A progressive retinal degeneration follows, resulting in an end-stage retina by approximately 2 years of age. XL PRA2 female carriers develop a retinal degeneration of the entire retina, not just those regions in which the mutant X chromosome is expressed (in contrast to XL PRA1 carrier females) (Zhang et al., 2002). The process by which photoreceptors of XL PRA2 carrier females that are expressing the normal X-chromosome are damaged is called an “innocent bystander effect.”

Retinal histopathology in female carriers of X-linked PRA was specifically studied, showing that the time of onset and the progression of the disease differed between the two types. In the more severe XL PRA2 type, morphologic appearance of the retinal mosaic changed as a function of age, showing that a structural plasticity persists in the early postnatal retina as mutant photoreceptors degenerate. This caused remodeling events in the retina, which could be clinically challenging to diagnose. In the late-onset form, XL PRA1, patches of disease persist until later ages, and there were no major changes in the nonplastic adult retina (Beltran et al., 2006, 2009).

Dominant Progressive Retinal Atrophy (PRA)

In the Old English Mastiff and in Bull Mastiff dogs, a specific retinal disease unlike those previously described was discovered (Cideciyan et al., 1998, 2005a; Kijas et al., 2002). The disease displayed an ambiguous mode of inheritance, and therefore, outcross matings were performed in order to elucidate the specific mode of inheritance for the disorder, which was shown to follow a dominant pattern. The defect found is the first opsin mutation described for dogs. The gene defect is a T4R mutation (a point mutation that changes the coding at codon 4 from threonine to arginine), indicating a different cause of PRA than previously described in other breeds of dog (Kijas et al., 2002).

Clinical examination in early disease by ophthalmoscopy and OCT showed a variably sized and located area of retinal thinning in the central fundus, clearly demarcated from surrounding clinically normal retina around the age of 6 months. Through clinical ERGs, the disease was defined as a progressive retinal degeneration. ERG rod- and cone-mediated responses were not significantly different between 2-month-old normal and affected dogs. By 12–18 months of age, however, affected dogs had severely reduced b-wave amplitudes. Defective dark adaptation was also found in affected dogs. The nonuniform degeneration of photoreceptors detected was verified morphologically. The photoreceptors developed normally and were indistinguishable from normal at 9 weeks of age. In affected, young adult dogs, the regional distribution of disease was striking: normal appearing photoreceptors could be seen to show different gradations of disease. In general, more severe disease was observed surrounding the ONH but centered in the temporal tapetal region of the fundus. Beyond this, there was an abrupt transition zone beyond which photoreceptors were structurally and quantitatively normal. Advanced retinal degeneration was observed at the age of 4.5–11 years.

The disease is distinctly different from other canine retinal degenerations, and the differences are exactly the similarities it shares with certain human rhodopsin mutations. The defect in dark adaptation and the focal initiation of photoreceptor degeneration characterize both this canine disease and human patients with RP, due to class B1 rhodopsin mutations (Cideciyan et al., 1998).
An intriguing finding is that environmental light appears to contribute to the regional variation of early disease. It was further found that modest light levels, such as used in routine clinical practice when performing retinal photography, dramatically accelerated the retinal degeneration (Cideciyan et al., 2005a). These findings do not immediately lead to modifications in clinical examination procedures. However, retinal photography should not be standard in human patients with rhodopsin mutations; retinal examinations should be of short duration; and light exposure during intraocular surgery should be reduced (Cideciyan et al., 2005a). Similar recommendations certainly appear valid for dog patients with the rhodopsin mutation.

**PRA in Other Breeds Not Yet Characterized**

Progressive retinal atrophy has been described in more than 100 different canine breeds. The disease in all of these breeds has not been reported in detail in the scientific literature. Rubin (1989) provided a valuable summary on retinal degeneration/PRA in various breeds. Specific information about retinal diseases in the various breeds can also be obtained from the American College of Veterinary Ophthalmologists (ACVO) Genetic Committee (see latest edition of Hereditary Ocular Disease of Purebred Dogs) and from the European College of Veterinary Ophthalmologists (ECVO) Hereditary Eye Disease Committee (HED).

**OTHER GENERALIZED RETINOPATHIES/RETINAL DYSTROPHIES**

**Early Retinopathy**

In the Bernese Mountain dog, an early-onset retinal degeneration has been described (Krahenmann, 1974). The disease can be detected by ophthalmoscopy and behavioral studies at approximately 1 year of age. Then, a juxtapapillary tapetal, hyperreflective, horizontal zone parallel to the junction between tapetal and nontapetal regions develops. There is a concomitant decrease in ERG b-wave amplitudes in affected dogs compared to normals. The progression of clinical changes is slow. Histology of affected retina corroborated that the most serious early abnormalities were found in the peripapillary and juxtapapillary regions (Chaudieu & Molon-Noblot, 2004). The hereditary characteristics of the retinopathy of Bernese Mountain dogs have not been elucidated.

**Cone Degeneration (cd)**

A recessively inherited disease has been described in Alaskan Malamutes that specifically affects the cones and causes congenital day blindness (originally described as hemeralopia) (Aguirre & Rubin, 1974, 1975a; Long & Aguirre, 1991). In humans, the comparable disease is termed achromatopsia, characterized by specific functional and structural abnormalities limited to cone photoreceptors. After the initial studies of hemeralopia in Alaskan Malamutes, the colony of dogs with this retinal disorder was nearly lost. The cone degeneration (cd) mutation, however, was rescued by breeding heterozygous animals and using frozen semen from the dogs originally affected.

Clinically, behavioral signs in affected dogs are usually apparent at 8–10 weeks of age. The affected dog shows severe loss of vision in daylight and in high levels of artificial illumination, but it becomes less insecure when taken into dim lighting conditions. Recovery of vision takes several minutes, though loss of vision on returning to bright light is immediate. The behavioral signs remain unaltered throughout life, and night vision is never abnormal. No funduscopic changes are observed at any stage of disease, and the PLRs are normal in both dim and bright light.

The ERG of an affected dog reveals normal rod function but an absence of cone responses. In the day blind dog, the cone contribution to the ERG, including the response to rapidly flickering lights, is lost. Flicker fusion studies are particularly valuable in diagnosing day blindness: the cone branch of the bipartite flicker fusion response curve (20–70 Hz) is usually absent, whereas the rod branch (less than 20 Hz) resembles a normal response (Aguirre & Rubin, 1975a).

Histopathologically, the cones develop normally but subsequently degenerate. There is an early reduction of cone nuclei in affected dogs. Ultrastructural studies performed at 7 weeks of age have shown that only some cones are affected; others appear normal. There is lamellar disorganization in the outer segments of specific cones, and the inner segments and perinuclear cytoplasm develop bundles of filaments that increase in number and extent with age. By 6 months, all cones are affected, and there is successive degeneration with loss of cone nuclei and synaptic terminals. The end stage is a pure rod retina at approximately 4 years of age.

Studies have been performed in cd dogs to identify proteins or genes associated with the disease through immunocytochemistry and in situ hybridization. The expression and localization of cone- or rod-specific proteins (or both) in normal and affected retinas have been examined (Gropp et al., 1996). The results demonstrate that cone outer segments in cd retina show a selective absence of b-3-transducin expression early in the disease and before the cells degenerate. In conjunction with these studies, it was also demonstrated that the cone nuclei ectopically located in the interphotoreceptor space are viable as judged by the expression of cone-specific transcripts and proteins; these nuclei are not dying cells as was previously suspected. Recently, the mutation responsible for the canine cd, as described for the Alaskan M alamute, was identified. Data indicate that the entire CNGB3 gene is deleted in affected dogs (Sidjanin et al., 2002).

Cone dystrophy has also been reported in the German Short-Haired Pointer (Sidjanin et al., 2002). Breeding studies showed that the disease in the German Short-Haired Pointer is allelic with the Alaskan M alamute cd (Sidjanin et al., 2002). A point-mutation in CNGB3 was identified in German
Short-Haired Pointers (Sidjanin et al., 2002). Gene therapy using an adeno-associated viral vector to introduce a normal copy of the CNGB3 gene to affected Alaskan Malamutes and German Short-Haired Pointers restored cone function.

The clinical condition has also been described in the Miniature Poodle (Millichamp, 1990) and three single cases: in a Rhodesian Ridgeback cross, an Australian Cattledog, and a Chihuahua (Hurn et al., 2003). The three latter dogs all had the typical signs of day blindness, or canine achromatopsia: complete blindness or clumsiness in outdoor bright lighting conditions, with a subsequent slow recovery of vision when moving back into a dim environment, normal fundus appearances, and low amplitude or absent ERG cone flicker responses. A n interesting finding was the pinpoint-sized pupils found in bright daylight in the first of the latter three cases.

**Photoreceptor Dysplasia**

A condition was described in Belgian Shepherds as a form of photoreceptor dysplasia (Millichamp, 1990; Wolf & Samuelson, 1981) in which complete blindness was observed at 8 weeks in the absence of ophthalmoscopic changes. By 11 weeks, a multifocal pattern of retinal folding or thickening was seen. The foci degenerated, and subsequently, there were hyperreflective lesions with a marked central pigmentation. The ERG was nonrecordable from at least 4 weeks of age. Histopathologically, a disorganization of photoreceptor outer segments was observed, and there were elevated parts of the outer retina at age 7 weeks. Little progression of the disease was shown, however, after the age of 6 months.

**RPE Autofluorescent Inclusion Epitheliopathy/RPED**

The term central progressive retinal atrophy, or CPRA, has been used for a group of conditions with ophthalmoscopic changes that can be characterized by an accumulation of irregular foci or light-brown pigment spots in the central tapetal fundus (Aguirre & Laties, 1976; Parry, 1954b). Over time, these foci increase in size and become distributed throughout the tapetal zone. At this stage, there are also atrophic changes, such as hyperreflectivity around the pigment foci that indicate atrophy of the overlying neural retina. The nontapetal fundus shows similar foci, with hyperpigmentation and depigmented areas in between.

Originally, CPRA was used to differentiate the condition from generalized PRA. For many years, it has been clear that CPRA affects the RPE primarily, with secondary effects on the neural retina, and that the condition is quite different from PRA, which primarily affects the photoreceptor layer. It is the general opinion among veterinary ophthalmologists today that at least among those breeds in which the defect has been established microscopically, the term retinal pigment epithelial dystrophy, or RPED, is preferred (Bedford, 1984). CPRA or RPED has been recognized in many breeds all over the world but appeared for many years most prevalently in England. In particular, cases were recorded in Labrador and Golden Retrievers, Border Collies, Rough and Smooth Collies, Shetland Sheepdogs, English Cocker Spaniels, English Springer Spaniels, Chesapeake Bay Retrievers, and others (Barnett, 1965, 1969, 1979). In Briards, an unusually high frequency of the disorder was reported: between 30% and 40% (Bedford, 1984; Lightfoot et al., 1996). In recent years, however, the condition is more rarely observed in the various breeds.

It has been suggested that CPRA/RPED in Labrador Retrievers is inherited as a dominant trait with variable penetrance (Barnett, 1969). The reduction in incidence, which has been accomplished in Border Collies, through selective breeding, is perhaps consistent with this view. A recessive mode of inheritance was thought to be likely in the Briard, but this has not been proved. Further studies are needed to elucidate whether or not there is a simple Mendelian inheritance for the defect. It is possible that a genetic predisposition in an individual breed can be modified by environmental factors. Important in this context is that lesions similar to CPRA/RPED have been produced in dogs fed diets deficient in vitamin E, an antioxidant that retards the intracellular accumulation of lipofuscin pigment (Riis et al., 1981; Robison et al., 1979). Naturally acquired retinopathy resulting from vitamin E deficiency has also been described in the dog (Hayes et al., 1970). The similarities between CPRA/RPED and vitamin E deficiency may explain its unique geographic distribution. (For further discussion on this issue, see the section on nutritional retinopathies.)

The ophthalmoscopic changes described earlier are often found before any signs of visual impairment in the dog are noted. With progression of the disease, pigmented lesions coalesce into widely spaced, irregular patches, interspersed with hyperreflective areas in the tapetal fundus (Fig. 24.40). End-stage atrophy includes a more generalized hyperreflectivity, with sparse amounts of pigmented foci or striae (or both), with the latter findings not always being obvious to the examiner. With these severely advanced changes, making the ophthalmoscopic diagnosis is not always easy, and similarities to generalized PRA may be found. Retinal changes are always bilateral in CPRA/RPED, as in PRA, and more or less symmetrical. ERG is not diagnostic for CPRA, but there is a reduction in ERG amplitudes with disease progression.

The behavioral signs of CPRA/RPED are typical. Visual impairment usually is not found until a moderately advanced stage. Then, because of the relative sparing of the peripheral as opposed to the central retina, peripheral vision is retained until late in the disease. Vision tends to improve at low light levels. AIso, vision may appear normal for moving and distant objects but impaired for stationary and nearby objects. Not all affected dogs become blind. Secondary cataracts are often seen at the advanced stage.

In Briards, an extremely high frequency of the disease was found in a 5-year survey (Bedford, 1984). Almost one-third of dogs examined, older than 18 months, were clinically affected. In this breed, the typical pigmented changes were first seen toward the periphery of the tapetal fundus, temporal
to the optic disc, before spreading to involve the entire tapetal zone. There are, however, significant differences among funduscopic alterations in the various breeds, which probably indicate a spectrum of disease entities at the level of the RPE.

In affected Briards, biochemical and morphologic studies of retinal tissue and blood was performed (Bedford, 1984; Lightfoot, 1988). Results of these studies showed that rod outer segment renewal is normal, as is acid phosphatase activity in the RPE. Also, some affected dogs were described as being hypercholesterolemic and systemically deficient in vitamin E and taurine.

Further investigations into the blood biochemistry of both normal and affected Briards in the United Kingdom have shown a hyperlipidemia characterized by increased plasma cholesterol but normal triglyceride concentrations (Watson et al., 1993). No significant difference in plasma cholesterol concentrations between affected and ophthalmoscopically normal dogs were found. The absence of obvious metabolic derangements associated with hypercholesterolemia appeared to indicate that Briards in the United Kingdom had a primary abnormality in cholesterol metabolism.

Morphologic studies showed that the earliest recognizable lesions in RPED occur in the RPE (Fig. 24.41). The cells become hypertrophied and accumulate a light-brown granular material in the cytoplasm. Opposite the hypertrophied cells, the photoreceptor outer segments are shortened. With progression of disease, more cells become hypertrophied, and at the end stage, hypertrophic pigment epithelial cells form multilayer nests. Focal degeneration of photoreceptors overlying the hypertrophied cells is then seen, and this is followed by complete retinal degeneration, with intraretinal migration of nonmelanin-containing cells. Diseased pigment epithelial cells contain autofluorescent lipopigment similar to ceroid or lipofuscin (Aguirre & Laties, 1976). Biochemical studies of affected retinas showed that the pigment accumulating in the disease varied with the breed and appeared to result from peroxidation of the rod outer segment lipids (Watson & Bedford, 1992).

**Hereditary Retinal Dystrophy/Lipid Retinopathy/RPE65 Null Mutation/Canine Leber’s Congenital Amaurosis (LCA)**

In the Briard dog, an interesting retinal dystrophy (with many names) has been described. The hereditary, clinical, and morphological characteristics of the disease were elucidated in groups of inbred and outcrossed dogs in Sweden (Narfström et al., 1989, 1994; Nilsson et al., 1992; Wrigstad et al., 1994). Initially, the disease was described as congenital stationary night blindness, since it affected Briards from birth; affected dogs had nonrecordable rod ERGs, and no funduscopic changes were observed until the dogs were 2-3 years old. Further clinical and morphologic studies showed that there was a progressive component in the disorder. The neural retina and the RPE were both affected by a retinal degenerative disease with unusually slow progression.

![Figure 24.40](image)
The hereditary and clinical characteristics were elucidated initially through test breeding and the study of seven generations of dogs. In- and outbreedings as well as backcrossing showed an autosomal recessive pattern of inheritance, but there was a variable expression for the defect (Narfström et al., 1994). Some of the dogs homozygous for the hereditary disorder were more severely affected than others. There were even variations as to severity of disease among affected dogs in the same litter.

Clinically affected dogs were congenitally night blind, whereas daylight vision could vary from near normal to more or less severely impaired. A rapid, horizontal nystagmus was seen in most (but not all) affected pups, and it was obvious in some of the animals that they were congenitally day and night blind. The resting pupillary diameter was approximately twice as wide both in bright and in dim lighting conditions among affected dogs compared with the diameter in normal dogs. Ophthalmoscopically, the fundus appearance in dogs up to approximately 3 years of age was normal. There were no alterations in fluorescein angiograms among young affected animals.

With progression, a subtle alteration in tapetal sheen was seen in affected dogs, and in certain individuals, whitish gray spots were observed in the central and midperipheral nontapetal fundus, spreading peripherally with increasing age (Fig. 24.42). A generalized, slight attenuation of the retinal vascu-
lature was prevalent in older affected dogs. There was no clinically observable increase in visual impairment with time among affected dogs, however. Dogs that were mainly night blind at birth, were still visual in daylight up to age 6–7 years.

The ERGs of young affected dogs differed markedly from those of normal age-matched dogs (Narfström et al., 1994; Nilsson et al., 1992). At 5 weeks of age, there was a severe reduction of dark-adapted b-wave amplitude responses compared to normal dogs, whereas ERGs of other affected puppies were nonrecordable. Responses to 30 Hz flicker recordings were also markedly reduced so as to be barely recordable in affected animals, while ERGs of others were nonrecordable. Use of DC-recording techniques in blind affected dogs showed the c-wave response to be replaced by a slow, negative response, with a very long latency and peak time. The rod system appeared more severely affected than the cone system. Furthermore, it was postulated that the lack of a c-wave indicated an impaired activity of the RPE.

Morphologically, the RPE showed large inclusion bodies in the central and midperipheral tapetal regions of the fundus as early as 3.5 months of age (Fig. 24.43). These inclusions increased in number and spread peripherally with increasing age (Wrigstad et al., 1994). There was also a concurrent abnormality in photoreceptors, with disorientation of rod outer segment discs already at age 5 weeks. At 7 months, degenerative changes of rod photoreceptors were seen, most prominently in the peripheral parts of the retina. In older affected dogs (5–7 years), there was a reduction of the photoreceptor layer of the central retina and almost complete photoreceptor atrophy in the peripheral parts. The photoreceptor degenerative changes did not correlate spatially to the changes in the RPE cells.

Cases with similar clinical and morphologic characteristics were described in the United States (Riis & Siakotos, 1989) and in France (M. Roze, personal communication), and were termed lipid retinopathy in the United States. Levels of plasma arachidonic acid were found to be elevated twofold in affected American Briards. In Swedish Briards, plasma lipids as well as pigment epithelial and neuroretinal lipids were analyzed (Anderson et al., 1997), but no difference between lipids in plasma and the RPE were found between affected and normal Briards. For the neural retina, affected dogs had relatively more phosphatidylethanolamine and phosphatidylinositol, and less phosphatidylcholine, than normal dogs. The studies showed that the Briard retinal dystrophy appeared to include a defect in retinal polyunsaturated fatty acid metabolism.

Through candidate gene analysis, the defect in Swedish Briards was discovered to be a four base-pair deletion in the RPE65 gene (Veske et al., 1999). This gene defect resulted in a frameshift and a premature stop codon, which truncated the protein and resulted in no RPE65 formation in the RPE. Clinical signs of the defect in affected Briard dogs had close similarities to the human counterpart, LCA type II (Wrigstad, 1994). Studies in RPE65 knockout mice with clinical signs similar to those of affected dogs showed that the lipid inclusions consisted of all-trans-retinyl esters (Redmond et al., 1998). Previous studies had shown that RPE65 was necessary for the synthesis of the 11-cis chromophore of photoreceptor visual pigment. Lack of RPE65 in the RPE thus results in severely reduced vision, an early-onset depression of the normal ERG responses, and a slow but progressive retinal degeneration (Hamel et al., 1993; Seeberger et al., 2001). Recently, RPE65 was identified as the isomerohydrolase, an enzyme converting all-trans-retinyl ester to 11-cis retinol in the visual cycle (Moiseyev et al., 2005). In another study, it was shown that retinyl esters are the substrate for isomerohydrolase (Moiseyev et al., 2003).

Gene therapy is a promising treatment modality, feasible when the specific mutation is known. Diseases of the eye are prime candidates for this form of therapy (Dejneka & Bennett, 2001). A proof-of-concept study was performed by Acland and collaborators, 2001, treating three dogs affected with the retinal dystrophy with a corrective gene construct (Acland et al., 2001). Subretinal injections were performed using a recombinant adeno-associated virus (AAV) carrying normal dog RPE65. Vision was improved in eyes treated subretinally demonstrated by ERG recordings, and transmission of the retinal activity was shown by pupillometry. An independent research group performed similar experiments in 12 affected dogs and demonstrated not only that vision and ERG amplitudes were improved in all treated dogs, by 4–6 weeks after the subretinal injections (Fig. 24.44 and Fig. 24.45), but

Figure 24.43. Ultrastructure of hereditary retinal dystrophy in a 4-month-old Briard dog. In the RPE, electron-lucent inclusions are seen (arrows). Early changes in the photoreceptors’ outer segments are seen as a slight disorganization of some outer segment lamellar discs. (Original magnification, 4200×.) (Courtesy of Anders Wrigstad.)
also that there were morphological improvements after treatment: the lipid inclusions were abolished or reduced in the area of the subretinal injection (Ford et al., 2003; Narfström et al., 2003a). Further studies have shown long-term visual improvement (Acland et al., 2005; Narfström et al., 2003b, 2005). A recent study showed that the AAV gene therapy could also successfully be performed on the second eye of affected dogs without interference from immune responses that developed following treatment of the first eye (Annear et al., 2011). Intravitreal administration of artificial retinoid (9-cis-retinal) is also capable of restoring some visual function to affected dogs. The 9-cis-retinal is capable of substituting for 11-cis-retinal in visual pigment formation, thus overcoming the effects of lack of 11-cis-retinal supply to the photoreceptors from the RPE (Gearhart et al., 2010).

**Figure 24.44.** Simultaneous bilateral ERGs after gene transfer in an RPE65 null mutation dog. The dog was treated with replacement gene therapy subretinally in the right eye. ERGs 4 weeks after treatment show significantly increased a- and b-wave amplitudes and a normalized ERG wave-form in the treated eye. ERGs in the left, untreated eye were nonrecordable (for parameters recorded in an age-matched normal dog of the same strain see Fig. 21.2).

**Pigmentary Chorioretinopathy**

A novel disease has recently been described to cause retinal impairment and blindness in the Chinese Crested Dog (CCD) (Narfström et al., 2011). The disease is bilaterally symmetrical and has been observed in CCDs from northern Europe and the United States. Affected animals have been negative for the prcd mutation, which previously has been described (www.optigen.com) to be prevalent in the breed. Ophthalmoscopically, in 3- to 4-year-old affected dogs, darkly pigmented lesions, with a light center (doughnut-like lesions), are seen in the peripheral fundus, most easily observed in the tapetal fundus, but prevalent also in the nontapetal area. Lesions multiply and appear also centrally with increasing age. ERG recordings in normal and affected dogs at age 3–4 years, show similar response amplitudes; however, with progression, a- and b-wave amplitudes become reduced in the affected animal. Morphological studies have shown that the RPE cells are affected early in the disease with multiple RPE cell layering, hypertrophy and bulging into the subretinal space, apparently causing secondary atrophy of the photoreceptors. Dystrophic changes in the choriocapillaris are also observed in conjunction with the RPE lesions. In older affected dogs (6- to 8-year-old), areas with geographic atrophy are found mainly in the midperiphereal and peripheral fundus. The mode of inheritance for the defect is not yet established.

**Neuronal Ceroid Lipofuscinosis (NCL)**

The NCLs are a group of recessively inherited progressive neurodegenerative diseases that are characterized by brain and retinal atrophy and associated with selective necrosis of neurons (Jolly, 1995). The term ceroid lipofuscinosis is derived from the histochemical and fluorescent properties of accumulated pigment, which resembles those of the lipopigments ceroid and lipofuscin common to these diseases. They are also linked to brain atrophy, a defect not found to the same degree in other lysosomal storage diseases.

These diseases affect both humans and several other animal species, such as bovine, ovine, caprine, feline, and canine (Goebel, 1992a). In humans, the disorder is often termed Batten’s disease and is clinically characterized by blindness, dementia, and seizures, inevitably resulting in death (Boustany & Kolodny, 1989). There are four classical variants of NCL in humans: the infantile type, the late infantile type, the juvenile type, and the adult type, the latter also called Kuf’s disease.

A spectrum of biochemical defects have been implicated in these disorders. Most forms reflect an accumulation of subunit c of mitochondrial ATP synthase, while in other forms there is sphingolipid activator proteins (SAPs) storage in granular osmiophilic deposits, mainly in neuronal cells (Palmer et al., 1997). The central nervous system (CNS) appears to be the main focus of the pathogenetic defect (Rider et al., 1992). The causal association between lipopigment storage, cell dysfunction, and cell death has so far not been elucidated. A spectrum of biochemical defects have been implicated in these disorders. Most forms reflect an accumulation of subunit c of mitochondrial ATP synthase, while in other forms there is sphingolipid activator proteins (SAPs) storage in granular osmiophilic deposits, mainly in neuronal cells (Palmer et al., 1997). The central nervous system (CNS) appears to be the main focus of the pathogenetic defect (Rider et al., 1992). The causal association between lipopigment storage, cell dysfunction, and cell death has so far not been elucidated. As in other generalized hereditary retinal diseases, the latter occurs through apoptosis (Lane et al., 1996).

NCLs have been described in several dog breeds, including the English Setter, Dalmatian, Border Collie, Tibetan Terrier, American Bulldog, Miniature Schnauzer, Polish Owczarek Nizinny (PON), Long-Haired Dachshund, and others (Armstrong et al., 1982; Goebel & Dahme, 1986; Katz et al., 2005a, 2005b, 2008; Koppang, 1992; Narfström et al., 2007; Palmer et al., 1997; Riis et al., 1992; Taylor & Farrow, 1988, 1992; for reviews on the disease in various breeds, see www.caninegeneticdiseases.net). A common clinical manifestation in both humans and dogs is blindness, which occurs with a broad spectrum of neurologic abnormalities caused by the
accumulation of autofluorescent lipopigments in neurons and in some other cells. With some exceptions, the blindness is usually cortical in origin, because photoreceptor function and structure are generally preserved (Goebel, 1992b; Jolly et al., 1994; Taylor & Farrow, 1992). There are some exceptions, however. In the Tibetan Terrier, night blindness may occur in middle-aged animals, while the more severe neurologic abnormalities are not observed until later in life (Riis et al., 1992). In the PON, visual dysfunction and funduscopic alterations occur early in life (Fig. 24.46), often between 1 and 2 years of age, while neurological changes become apparent in middle-aged dogs (Wrigstad et al., 1995). In the Miniature Schnauzer (Smith et al., 1996), blindness was described to develop quickly, over a 3-month period, between the age of 3 and 4 years, accompanied by neurologic signs. In affected English Setter dogs, retinal function is normal at a time when neurologic abnormalities are present. In this breed, clinical signs usually develop at approximately 1 year of age and
include progressive cortical blindness, ataxia, muscle weakness, and dementia. The disease is ultimately fatal in 2- to 3-year-old dogs.

Specific functional and morphologic characteristics have been described for some affected breeds. In the English Setter, ERG responses are normal in young dogs but become grossly abnormal with time (Aguirre et al., 1986; Berson & Watson, 1980). In advanced cases, the c-wave of the ERG becomes nonrecordable, and the standing potential of the eye is reduced (Nilsson et al., 1983). In the PON dog, the scotopic ERG responses were absent, and the cone flicker responses were reduced but recordable in a 2-year-old affected dog (Wrigstad et al., 1995). The c-wave was replaced by a slow negative potential, thus indicating a dysfunction of the RPE. For the Tibetan Terrier, recent ERG studies in a group of 7- to 10-year-old affected dogs revealed moderately or severely depressed rod responses, while there was only slight impairment of cone function (Katz et al., 2005b).

Morphologically, retinal changes vary within affected breeds. Ganglion cells and RPE cells are most often affected by the disease process. An accumulation of PAS-positive material may be seen in the RPE and in neuronal cells of the inner retina (Fig. 24.47). Ultrastructurally, intracellular inclusions with a granular appearance, known as granular osmeophilic dense deposits (GRODs), may be seen in neuronal cells of brain and retina. These cells may also contain membranous fingerprint-like material or curvilinear profiles (resembling ceroid) enclosed by a membrane, especially in RPE and ganglion cells. In the brain, the size and the morphological appearances of the storage bodies differ among brain regions but are comparable to those found in the retina.

So far, eight genes have been revealed as responsible for different variants of the human disorder: PPT1, CLN2, CLN3, CLN5, CLN6, CTSD, MFSD8, and CLN8. In animals, CLN2, CLN5, CLN6, CTSD, MFSD8, and CLN8 have been implicated in NCL. The mutation for NCL in the English Setter dog was elucidated: a mutation in the CLN8 gene was found to be responsible for the disorder (Katz et al., 2005a). A group of American Bulldogs were revealed to have NCL and a defect in the gene for cathepsin D (CTSD) was elucidated (Awano et al., 2006). Soon thereafter, the genetic defect for NCL in Border Collie dogs was elucidated: a mutation in the CLN5 gene (Menville et al., 2005) (see Table 9.1). Recently, mutations in the CLN2 gene in the Long-Haired Dachshund (Katz et al., 2008) and a mutation in CLN6 in the Australian Shepherd have been identified as causes of NCL (Katz et al., 2011). A young Miniature Dachshund with neurological signs in keeping with NCL was found to have a mutation in the PPT1 gene (Sanders et al., 2010).

**Mucopolysaccharide Storage Diseases (MPS)**

In both humans and animals, mucopolysaccharide storage diseases (MPS) are caused by the inherited deficiency of lysosomal enzymes, and they represent generalized, multisystemic abnormalities, of which ocular lesions are but one component. The lysosomal enzymes participate in degradation of glycosaminoglycans. Morphologic studies have shown accumulation of intracellular inclusions in secondary lysosomes in the enzyme-deficient RPE. In the dog, MPS VI and VII have been described (Haskins et al., 1991; Ponder et al., 2002; Stramm et al., 1990). In MPS VII, single cytoplasmic inclusions are initially present in the RPE during the early postnatal period.
Their number and size increase during the period of photoreceptor differentiation. The pigment epithelial cells enlarge, and the whole monolayer becomes hypertrophied. Despite the pigment epithelial histopathology, the neuroretinal structures and functions are preserved, and there is no photoreceptor degeneration in the disorder (Aguirre et al., 1986). MPS VI dogs are homozygous for an arginine to histidine substitution at amino acid 166 in the canine GUSB protein (Ray et al., 1998).

Hereditary Tapetal Degeneration

An autosomal, recessively inherited tapetal abnormality of laboratory beagles has been described (Bellhorn et al., 1975; Burns et al., 1988). Affected dogs have a light, uniform choroidal pigmentation, which precludes visualization of the choroidal vessels.

Morphologically, there are normal numbers of tapetal cells at birth. With time, however, there is progressive degeneration of the tapetal cell layer. Even so, the retinal structure and function remain normal.

INFLAMMATION AND INFECTIONS AFFECTING THE OCULAR FUNDUS

Inflammatory lesions of the ocular fundus are not uncommon in the dog. Retinal involvement, however, is usually secondary to disease processes extending from the choroid or sometimes the vitreous, whereas primary retinal inflammation (i.e., retinitis) is uncommon. The terms chorioretinitis (i.e., starting in the choroid) and retinochoroiditis (i.e., initially involving the retina) indicate the primary site and direction of spread when both the choroid and retina are involved. There may also be concurrent involvement of the anterior uvea (see Chapter 20) as in panuveitis (inflammation of the entire uveal tract), endophthalmitis (inflammation of the internal structures of the eye), and panophthalmitis (inflammation of the entire eyeball). The inflammatory process may accompany a systemic disease; a full physical examination is an essential part of the work-up, and further investigations such as chest radiographs and abdominal ultrasound should be considered.

In addition to routine laboratory investigations such as a complete blood count, serum chemistry, and urinalysis, serology for antibody titers to specific infectious agents may be indicated. Sensitive polymerase chain reaction (PCR) diagnostic tests for the presence of the DNA of pathogens in samples have been, and are being developed. In certain instances, aspirates (e.g., from lymph nodes, aqueous humor, vitreous, subretinal fluid) may be obtained and subjected to a variety of tests including cytology, culture, and PCR amplification. Diagnostic testing should be fully utilized in an attempt to identify the etiology of the inflammation, particularly as the use of nonspecific anti-inflammatory medications (such as systemic corticosteroids), although desired in idiopathic or immune-mediated inflammation, may be contraindicated in certain infectious diseases.

Chorioretinitis

Chorioretinitis may have various causes, including several infectious diseases, neoplasia, foreign bodies, and trauma. Infectious agents may be restricted to the eye, but signs in the ocular fundus may also be part of, or secondary to, a systemic infection. In many instances, the exact cause of the inflammatory process cannot be identified. The appearance of the lesions in the fundus may give some guidance as to the etiology, but this is seldom specific. Sampling from the choroid and retina presents certain difficulties and can be associated with undesired complications. Vitreous paracentesis to obtain material for cytology and culture can be informative, but is usually reserved for patients presenting with severe posterior-segment inflammatory disease.

An active inflammation in the retina, with or without involvement of the choroid, results in a number of ophthalmoscopic signs, which may vary according to both the severity and the stage of the disease process (Albert, 1970; Rubin, 1974). Inflammatory lesions may be unilateral or bilateral, and they are usually irregular in shape. In contrast to the appearance of inherited retinal dystrophies, inflammatory lesions of the fundus are rarely bilaterally symmetrical, and lesions at different stages may be observed both within one eye and between the eyes of an individual dog. Certain noninflammatory conditions, however, such as geographic retinal dysplasia, may give rise to lesions resembling chorioretinitis.

The lesions caused by acute stages of inflammation can be subtler in appearance than chronic stage lesions. In acute inflammation there may be perivascular cuffing, which appears as gray-white, perivascular opacities due to inflammatory cells accumulating around the blood vessels. There may be retinal edema or cellular infiltration that, in the tapetal area, appears as grayish hyporeflective lesions (see Fig. 24.53A) and in the nontapetal area may appear grayish to white in color (see Fig. 24.53B). Hemorrhage may accompany more severe inflammatory processes. The ophthalmoscopic appearance of the hemorrhages depends on their location. Discrete, round hemorrhages are seen if the blood is enclosed within the retinal layers. Bleeding within the nerve fiber layer results in a flame-shaped appearance, whereas a subretinal hemorrhage causes an indistinctly bordered, diffuse, dull-red area. Bleeding from the superficial retinal vessels can cause a separation of the vitreous from the retina, which in turn causes the hemorrhage to assume a keelboat shape, thus reflecting the force of gravity. Hemorrhages may be a common feature of certain infectious chorioretinitis cases, such as those caused by rickettsial infections.

A accumulation of exudate between the photoreceptors and pigment epithelium causes a detachment of the neurosensory retina. The detached area of retina is elevated compared with the surrounding retina and appears grayish, with a distinct border, in contrast to areas infiltrated only by inflammatory cells. The cellularity of the subretinal fluid influences the appearance of the detached area. If the fluid has a low cellularity, the color of the tapetum will be seen through the detached
retina in the tapetal area (see Fig. 24.64A), but a high cellular-
ity, or the presence of red blood cells will make the detached
area appear dull or red respectively.

Granulomatous lesions may be seen in some forms of cho-
rioretinitis, particularly those caused by fungal infections.
Inflammatory changes affecting the RPE can cause release of
pigment. A cute alterations of the RPE are often obscured by
other inflammatory changes. Inflammations involving the
retina may also cause secondary inflammatory changes in the
vitreous, which manifest as haze, nodules of inflammatory
cells, and syneresis. In some instances, the ONH may also be
involved in the inflammatory process, showing swelling and
possibly hemorrhages in the acute stages and atrophy in the
chronic stages.

Debris from degenerating neuroretina as well as pigment
from a disrupted RPE are removed by macrophages. Prolifera-
tion of connective tissue elements occurs in the damaged
areas, and organization of the scar tissue may cause retinal
folding. Fusion of the outer limiting membrane of the retina
to the choroid is common in scarring due to chorioretinitis.
The RPE contributes significantly to the progress of healing;
it can become hypertrophic or hyperplastic or even migrate
into the lesions. The RPE cells overlying the tapetum are
normally nonpigmented but may produce pigment as a result
of inflammation.

Ophthalmoscopic signs of an inactive, chronic inflamma-
tory process are quite different from those of an acute inflam-
mation. A trophy of the neural retina in the tapetal fundus is
seen as irregular, hyperreflective areas with a distinct border
(Fig. 24.48 and Fig. 24.49). A well-demarcated zone in the
center of the lesions may be heavily pigmented if the RPE is
affected. The color of the tapetum may be altered in the
affected area or even destroyed, exposing choroidal vessels
and sclera. Chronic inflammatory lesions in the nontapetal
fundus appear as distinctly bordered, depigmented areas with
exposure of choroidal vessels and sclera. Sometimes, areas of
pigment clumping will also be apparent (Fig. 24.50). The
retinal vasculature may also be altered during the chronic
stages of inflammation. Vessels crossing the inflammatory
lesions may be attenuated or sometimes tortuous. Pigment
may also outline the vessels within affected areas. When
visible, choroidal vessels may also appear atrophied or even
destroyed (Fig. 24.51).

Choroiditis

Choroiditis (or posterior uveitis), which is an inflammation
strictly confined to the choroid, without involvement of the
anterior uvea or retina, appears to be an uncommon condition.
Ophthalmoscopically, nongranulomatous choroiditis in the
tapetal fundus can cause loss of tapetal reflectivity or changes
in tapetal color. In the nontapetal fundus, areas of increased
redness can be observed. Subretinal accumulation of fluid can
cause elevation of the overlying retina. Retinal blood vessels
should not show signs of active inflammation (e.g., perivas-
cular infiltrates) when only the choroid is inflamed.
Figure 24.50. Inactive chorioretinitis lesions in the nontapetal fundus. A. There are irregular patches of loss of retinal pigment epithelial pigment revealing choroidal vasculature. Some white-colored retinal surface deposits are also present. B. This dog had multiple small areas of depigmentation and choroidal damage revealing the white of the underlying sclera.

Figure 24.51. Right (A) and left (B) eyes of an 8-year-old Bulldog with a chronic, presumed immune-mediated chorioretinitis. There are extensive changes with tapetal destruction, extensive depigmentation, and the right eye has attenuation of the retinal vasculature and evidence of optic nerve head atrophy. Azathioprine was needed to control the inflammation. An extensive laboratory workup had failed to ascertain the etiology. (Illustration supplied by Michigan State University Comparative Ophthalmology Service.)

Complete destruction of the tapetum lucidum, thereby allowing the choroidal vessels to be readily viewed in the affected area, can occur during the chronic stages of severe choroiditis. In less severe cases, increased pigmentation can obscure the tapetum if the RPE is involved in the transition from active to inactive inflammation. Reddish foci, however, can often be detected in the tapetal area, which enables the examiner to distinguish between a postchoroiditis status and a congenital absence of tapetal tissue.

Viral Diseases

Viral diseases can sometimes cause detectable signs in the ocular fundus. Several systemic viral diseases can affect the
tissues of the eye, and the fundus is considered to be most susceptible to viruses preferentially affecting the CNS.

**Canine Distemper**

Canine distemper virus, a morbillivirus, is the most frequent viral cause of posterior segment disease in the dog. Multifocal, irregular areas of retinochoroiditis, with or without inflammation of the optic nerve, are typical findings, but there are no ophthalmoscopic findings pathognomonic for canine distemper. The signs of posterior segment disease do not necessarily correlate with the usually more obvious, external ocular signs (e.g., mucopurulent conjunctivitis). Retinal lesions caused by canine distemper virus infection cannot be treated.

During the acute stages, the ophthalmoscopic picture is characterized by active retinochoroiditis, and the appearance of multifocal inflammatory lesions corresponds with the previous, general description of active inflammation in the retina and choroid. The appearance of the lesions changes during the transition from acute to chronic retinochoroiditis (as discussed in the section on chorioretinitis). Visual impairment usually is not detectable in patients with retinochoroiditis unless there is involvement of the optic nerve. In severely affected eyes, however, the inflamed areas can coalesce and produce complete destruction of the retina, thereby causing blindness.

Optic neuritis may accompany the retinochoroiditis. Signs of active inflammation of the ONH may be visible ophthalmoscopically, and a hyperreflective, peripapillary crescent or, in more severe cases, optic atrophy can be found in dogs with chronic distemper. Optic neuritis is likely to cause an obvious impairment of vision.

The histopathologic changes, which reflect primary localization of the virus in the retina, have been described (Jubb et al., 1957; Parry, 1954a). Parry subdivided the primary retinochoroidal lesions into four types:

1. peracute generalized retinopathy
2. chronic generalized retinopathy
3. dystrophy of the RPE, with or without damage to the retina and optic atrophy, and sclerosis.

The nontapetal fundus has been considered to be more involved during the acute phase, and eosinophilic inclusion bodies in glial cells may be found during these stages (Jubb et al., 1957). Ganglion cells exhibit the most severe degeneration, but photoreceptors also degenerate. Depending on severity of the disease, disorganization of the retinal layers may occur. Hypertrophy and proliferation of the RPE are common in dogs with distemper retinochoroiditis.

The presence of virus in the retina may result from primary localization concurrent with the infection of other organs or from secondary extension from the brain (Jubb et al., 1957). Active retinitis without detectable involvement of the brain or optic nerve is seen when the canine distemper virus is primarily located to the retina. Ganglion cell degeneration in dogs with optic neuritis but without other inflammatory changes in the retina is suggestive of a retrograde degenerative process.

**Canine Herpesvirus**

Retinal involvement, including focal edema, neuronal degeneration, gliosis and infiltration of the ganglion cell layer, and choroiditis, may be seen histopathologically in canine herpesvirus infection (Rubin, 1974). Chronic signs of inflammatory disease may be present at ophthalmoscopy in dogs surviving this infection, but the most characteristic feature is probably retinal dysplasia.

**Mokola Virus**

Focal, inflammatory, nonspecific lesions were observed in the retina of a dog experimentally infected with Mokola virus, which is a rabies serogroup virus (Percy et al., 1973). Histopathologically, focal degeneration of ganglion cells and perivascular cuffing were observed.

**Infectious Rhinotonsillitis**

A contagious viral infection, infectious rhinotonsillitis, in which the ophthalmoscopic and systemic findings cannot be distinguished from those of canine distemper, has been described (Darraspen & Lescure, 1962; Fontaine, 1962). The signs of posterior segment disease include nonpathognomonic focal chorioretinitis and optic neuritis. Corneal ulceration has also been associated with this condition.

**Tick-Borne Diseases**

Tick-borne infections may affect the posterior segment of the eye as part of the systemic disease. The posterior segment lesions are not pathognomonic, but hemorrhage is a common feature. The frequency of posterior segment involvement varies.

**Canine Ehrlichiosis**

Ehrlichiosis is a tick-borne rickettsial infection reported in several parts of the New and Old World. Ehrlichia canis, Ehrlichia chaffeensis, Ehrlichia risticii, Ehrlichia ewingii, Ehrlichia equi, Ehrlichia phagocytophilia, and Ehrlichia platys (now reclassified as Anaplasma platys) are canine pathogens (see Stiles, 2000 for a review) transmitted by ticks such as Rhipicephalus sanguineus, but Ixodes spp. can also act as a vector for Ehrlichia spp. (Neer et al., 2002). E. canis is the main species associated with uveitis, although there is a case report of uveitis associated with E. platys infection (Glaze & Gaunt, 1986). In a study of experimental infections with E. canis, E. ewingii, E. chaffeensis, or human granulocytic ehrlichia (HGE), only dogs infected with E. canis developed uveitis (Panciera et al., 2001). Species-specific PCR testing has shown that individual dogs may be infected with more than one Ehrlichia species at one time (Breitschwerdt et al., 1998). Furthermore, ehrlichiosis may be
complicated by other diseases transmitted through the same vector, for example, with Bartonella spp. (Breitschwerdt et al., 1998), Rocky Mountain Spotted Fever (see next section), or babesiosis. Canine ehrlichiosis is an acute, febrile disease with an associated pancytopenia, especially thrombocytopenia, which can lead to serosal and mucosal hemorrhages. Severe hemorrhage or secondary bacterial infections may lead to death. Ophthalmoscopically, signs of retinal inflammation, retinal hemorrhage, and hyphema can be observed (Ellett et al., 1974; Swan & Dubielzig, 1986). Authors of one study reported retinal vasculature engorgement and tortuosity in 15.6% of 64 dogs, retinal hemorrhages in 7.8%, and findings corresponding to chronic chorioretinitis in 12.5% (Thirunavukkarasu et al., 1994). The experimental study reported by Panciera et al. showed that in experimental E. canis infection, ocular inflammation was most common and most intense in the ciliary body, becoming less intense in the choroid, iris, and retina, respectively (Panciera et al., 2001). In a retrospective study of 46 dogs in Spain with ocular signs and a positive antibody titer to E. canis, exudative retinal detachment was the commonest ocular change. Other ocular changes seen were exudative anterior uveitis, optic neuritis, and intraocular hemorrhage (Leiva et al., 2005).

Granulocytic ehrlichial species (E. equi, E. phagocytophilia, and HGE) replicate and spread in neutrophils and eosinophils. E. equi is spread by Ixodes pacificus and is commonest along the West Coast of the United States. It is reported to have been associated with chorioretinitis and retinal detachment (Stiles, 2000).

The causative agent can be demonstrated on Giemsa-stained smears, where it appears as blue cytoplasmic inclusions, mainly in monocytes and lymphocytes. Diagnostic tests (e.g., serology: indirect-fluorescent antibody test showing a rising titer in the active phase of the infection, possibly in combination with PCR or Western blot) are used to confirm infection and to detect chronically infected carriers, in which the ehrlichia organism rarely can be demonstrated in blood cells. Note that in chronic infections, the organism may be sequestered in reticulendothelial cells, and therefore a PCR performed on a blood sample may be negative. PCR should therefore not be used in isolation but should be combined with serology (Neer et al., 2002). Systemic tetracyclines, such as doxycycline, have been recommended as the treatment of choice (Cohn, 2003; Neer et al., 2002). These drugs may be combined with systemic steroids (Cohn, 2003) to control the ocular inflammation and immune-mediated inflammation resulting from ehrlichial infection.

Rocky Mountain Spotted Fever (RMSF)

Rocky Mountain Spotted Fever (RMSF) is an acute infectious disease caused by Rickettsia rickettsii, which is transmitted by ticks of the genus Dermacentor. Widespread vasculitis accompanied by hemorrhage results from damage to the vascular endothelium. The ocular lesions resemble those in canine ehrlichiosis, although hyphema has been considered to be less common. Anterior uveitis, chorioretinitis, and retinal hemorrhage, however, have been described in dogs infected with R. rickettsii (Davidson et al., 1990; Rutgers et al., 1985).

Davidson et al. (1990) observed multifocal retinal vasculitis, which corresponded to areas of altered vascular permeability, within 1–2 days after the onset of fever and rickettsemia. Furthermore, the retinal vascular permeability was demonstrated to be abnormal by fluorescein angiography, even during the third week after onset, which was past the period of clinical and clinopathologic recovery. Development of retinal vasculitis was associated with thrombocytopenia, increased circulating fibrinogen level, and prolonged activated partial thromboplastin time.

The diagnosis may be confirmed serologically with the indirect fluorescent-antibody or ELISA methods. A PCR-based assay is also available (Breitschwerdt et al., 1999). Systemic treatment with doxycycline is the treatment of choice, although enrofloxacin or trovafloxacin is also efficacious (Breitschwerdt et al., 1991, 1999). A study of experimentally induced RMSF concluded that concurrent use of prednisolone at anti-inflammatory or immunosuppressive doses with doxycycline did not have any clinically relevant detrimental effects, with the caveat that the experimental infection resulted in a mild to moderate disease. Therefore, extrapolation to severe, naturally occurring disease could not be made (Breitschwerdt et al., 1997).

Bartonella

Bartonella species are small, gram-negative bacteria, which have been identified in a wide range of mammalian species. Infections in dogs are associated with endocarditis, myocarditis, and granulomatous disease (Breitschwerdt et al., 2004). There is a single case report of a dog seropositive for Bartonella vinsonii (berkhoffii) that presented with fever, anterior uveitis, and chorioretinitis lesions, although the authors could not conclusively prove that the ocular lesions were caused by the B. vinsonii (berkhoffii) infection (Michau et al., 2003). Serology, culture, and PCR-based diagnostic tests are available. There is limited information regarding treatment. However, prolonged medication is recommended, and azithromycin, doxycycline, and enrofloxacin have been used (Guptill, 2003).

Bacterial Chorioretinitis

In addition to the bacterial organisms transmitted by ticks, other organisms, such as Leptospira spp. and Brucella spp., have been suggested as a cause of uveitis in dogs. A recently reviewed by Dziezyc (2000), there is little evidence that leptospirosis is a significant cause of uveitis in dogs. Brucellosis is similarly not a commonly cited cause of uveitis in dogs, although it has been demonstrated in experimental studies and case reports (Gordon et al., 1985; Gwin et al., 1980a; Saegusa et al., 1977).
Mycotic Diseases

Posterior segment disease may be seen in a number of systemic mycoses in the dog (see Krohne, 2000 for a review). The frequency of ocular involvement, however, varies considerably. The infection may spread hematogenously, directly from the anterior parts of the eye, or by infiltration along the optic nerve and meninges.

Acromoniasis

Systemic disease accompanied with anterior uveitis, focal chorioretinitis, and secondary retinal detachment has been described in a case of infection with Acromion sp., which is a saprophytic fungus found in soil (Simpson et al., 1993). The dog exhibited ataxia, progressive head tilt, anorexia, lethargy, and weight loss. The patient was treated with antibiotics and antifungal drugs (initially ketoconazole and later itraconazole) but was finally euthanized because of poor general condition. Histopathologic examination revealed chronic pyogranulomatous, necrotizing inflammation, and granulomatous inflammation affecting several vital organs, including the retina. The clinical and histopathologic findings closely relate to those seen in disseminated aspergillosis, which is a fungus belonging to the same group (i.e., nonnematode hyphomycetes) as Acromion sp.

Aspergillosis

A multifocal infection with Aspergillus fumigatus, which is a fungus mainly composed of septate hyphae measuring 4 mm in diameter, was diagnosed in a dog presenting with severe neurologic and ophtalmic signs (Gelatt et al., 1991). The causative organism was demonstrated by cytology and culture from vitreous paracentesis. PAS-positive, slender septate hyphae were observed on the lens capsules, vitreous body, in the ganglion and nerve fiber layers of the retina, and in the choroid and optic nerve. Identification from smears only, however, may be difficult, because conidial heads may be absent and other fungi also show septate hyphae when invading tissue. The infection had caused an inflammatory reaction resulting in panuveitis and inflammation of the iridocorneal angles and ciliary clefts; partial syneresis; infiltration of the vitreous body with inflammatory cells, blood, and debris; and partial retinal detachment and optic neuritis.

Blastomycosis

Blastomycosis appears to be the most frequently reported ocular disease of mycotic origin (Bloom et al., 1996; Brooks et al., 1991; Buyukmihci & Moore, 1987; Simon & Helper, 1970; Trevino, 1966). Blastomycosis is commonest in the regions of the Mississippi, Wisconsin, and Ohio River systems and the Great Lake region in North America; however, it is not a clinical problem in other parts of the world (e.g., Northern Europe).

Blastomyces dermatitidis is a dimorphic soil fungus, and infection occurs when its conidia are inhaled and incubated in the lungs. The fungus then assumes the yeast phase and may spread hematogenously or lymphogenously to, for example, the eyes and the CNS. Ocular disease, including anterior uveitis, hyalitis, retinitis and chorioretinitis, optic neuritis, and their sequelae (e.g., secondary glaucoma, retinal detachment), is seen in approximately 30%-40% of dogs with systemic blastomycosis (Fig. 24.52) (Brooks et al., 1991; Legendre et al., 1981). Furthermore, extraocular blastomycosis can cause exophthalmus and strabismus.

Figure 24.52. Blastomycosis in a 2-year-old West Highland White Terrier. The dog initially developed respiratory signs and then presented with sudden vision loss. A. At initial presentation, there was retinal detachment and the appearance or subretinal granulomas. B. After 3 months of itraconazole treatment, the retina has reattached but shows evidence of the previous inflammation with depigmentation in the nontapetal fundus. (Illustration supplied by Michigan State University Comparative Ophthalmology Service.)
Confirmation of diagnosis can be difficult without an aspirate for cytology. Some animals may present with discharging skin tracts that offer an opportunity to easily obtain material for cytology. In others, lymph node aspirates may provide the diagnosis. When severe ocular changes are present, vitreous paracentesis can often provide material for culture and cytology, whereas it is less common for anterior chamber paracentesis to be diagnostic. In smears and histopathologic sections, B. dermatitidis can be identified as a PAS-positive, round, single, budding yeast cell with thick walls. Thoracic radiographs in patients without respiratory signs showing multiple noncalcified nodules in the lungs and hilar lymphadenopathy may be suggestive of blastomycosis. These changes are not pathognomonic. Serological testing is available but may not be reliable (see Kerl, 2003 for a review). An enzyme immunoassay urine test for B. dermatitidis antigen is available and has been shown to be more sensitive than antibody testing (Spector et al., 2008).

Histopathologic examination reveals widespread granulomatous inflammation and destruction of ocular tissue. Small granulomas are often present in the retina, and the fungus usually may be identified in subretinal exudates.

Systemic antifungal therapy with amphotericin B, ketoconazole, a combination of these drugs, or itraconazole has been used (Bloom et al., 1996; Brooks et al., 1991). The dose of potentially nephrotoxic amphotericin B can be lowered without compromising efficacy when used concomitantly with oral ketoconazole; improvement was seen in 40% of eyes after a combined amphotericin B and ketoconazole therapy (Bloom et al., 1996). Vision was retained in two dogs with optic neuritis during this therapeutic regime, whereas eyes with severe endophthalmitis did not respond to the combination of antifungics. Current treatment is typically with itraconazole and ketoconazole or itraconazole. Orally administered itraconazole, usually may be identified in subretinal exudates.

Cytology of rectal mucosal scrapings in dogs with GI involvement may be diagnostic. A spirillum of lymph node, dermal nodules, bone marrow, liver, spleen, and endotracheal washes may be useful in obtaining material for cytological diagnosis (Kerl, 2003). Serology is unreliable, and although a PCR test has been developed, publications studying its reliability are not available.

Literature on the treatment of histoplasmosis is sparse. Long-term success was not achieved in one dog by systemic treatment with ketoconazole and amphotericin B (Huss et al., 1994). Currently, itraconazole appears to be the drug of choice (Kerl, 2003).

Cryptococcosis

Cryptococcus neoformans is a saprophytic organism that only exists in a yeast form, not in a mycelial form, unlike other fungi causing mycotic diseases. C. neoformans may cause focal or disseminated infections in the dog. Infection usually manifests clinically with signs caused by involvement of the CNS (e.g., ataxia, circling, head tilt). So far, ocular cryptococcosis has only been reported in cases of disseminated infection, and the organism may spread by direct extension from granulomatous meningitis and optic neuritis or hematogenously from more remote locations (Bistner et al., 1971; Carlton et al., 1976; Gelatt et al., 1973; Jergens et al., 1986; Kutz & Finch, 1970; Lipton, 1973; Walde & Burtscher, 1980). Ocular signs without systematic signs are rare in canine cryptococcosis but have been reported (Wolfer et al., 1996).

The ocular findings (Fig. 24.53) relate to subretinal granulomas, usually grayish white and translucent to opaque, that initiate an exudative inflammation. Ophthalmoscopically, the tapetal fundus appears discolored in areas of retinal elevation after the accumulation of exudate in the subretinal space, whereas corresponding findings in the nontapetal fundus are gray to tan areas. Inflammatory changes may be observed in the ONH. In chronic cases, several small, pigmented nodules (i.e., cryptococcal granulomas) can be scattered throughout the tapetal fundus. Intravitreal hemorrhage and exudates may obscure the ophthalmoscopic view of the fundus in dogs with severe cases. Complete retinal detachment causing blindness has been described as well.

Histoplasmosis

Infection with Histoplasma capsulatum, which is a dimorphic fungus, occurs mainly by inhaling spores of the mycelial form (Turner et al., 1972), but there are also indications that the gastrointestinal (GI) tract may serve as a secondary entrance. The subsequent course of infection usually is subclinical in nature, which is suggestive that animals may be resistant or, mainly, develop latent infections. Dysfunction of the immune system has been proposed to be important for generalization of the disease (Berry, 1969).

Ocular involvement in histoplasmosis infections has been reported infrequently (Gwin et al., 1980b; Huss et al., 1994). Multifocal inflammatory lesions, retinitis, chorioretinitis, and retinal detachment have been reported. Granulomatous uveitis in 50% of experimentally infected dogs has been reported as well (Salfelder et al., 1963), with H. capsulatum demonstrated in the uvea, sclera, orbital tissues, muscles, and lacrimal gland. Diagnosis is typically by cytology or histopathology. Cytology of rectal mucosal scrapings in dogs with GI involvement may be diagnostic. A spirillum of lymph node, dermal nodules, bone marrow, liver, spleen, and endotracheal washes may be useful in obtaining material for cytological diagnosis (Kerl, 2003). Serology is unreliable, and although a PCR test has been developed, publications studying its reliability are not available.
Vitreous paracentesis for cytology and culture can be diagnostic in ocular cryptococcosis. New methylene blue, PAS, and hematoxylin and eosin stains can be used to identify the fungus. C. neoformans appears as a round to ovoid organism approximately 20 µm in diameter. The cryptococcal elements are surrounded by a thick, polysaccharide capsule that distinguishes them from Blastomyces. Serological testing is available (latex agglutination assay), which identifies the capsular antigen of the organism rather than an antibody response from the infected dog. For this reason, it may be more useful than the available serology tests for other fungal organisms (Kerl, 2003). It may also be useful for CSF samples. A PCR-based assay has been used in people (Rappelli et al., 1998), but its use is not reported in dogs.

Histopathologic changes are usually confined to the posterior segment. In the choroid and retina, large, multifocal accumulations of macrophages and plasma cells, and also of neutrophils and lymphocytes and abundant cryptococci, are usually seen. Both the size and location of the inflammatory lesions vary considerably. Small granulomas containing fungal elements may involve the choroid at several locations. Other inflammatory foci may involve extensive areas of all retinal layers, whereas small inflammatory lesions may be distributed within just one or two layers. Cryptococci may be present in the choroid as well as in the proteinaceous subretinal exudates in cases of retinal detachment.

Cryptococcosis is ultimately fatal if not treated. Ketoconazole has been used both alone and in combination with amphotericin B and 5-fluorocytosine (Mason et al., 1989; Noxon et al., 1986). Combination chemotherapy with amphotericin B and either fluconazole or flucytosine (or both) has also been successful in the dog (Malik et al., 1996). There is one report of successful fluconazole treatment in a dog with cryptococcosis (Faggi et al., 1993). Symptomatic therapy with glucocorticoids can favor dissemination of the infection (Walde & Burtscher, 1980).

**Coccidioidomycosis (Coccidioidomycosis)**

Valley fever, or coccidioidomycosis, is caused by a dimorphic, saprophytic soil fungus Coccidioides immitis. The disease is endemic in the semiarid, low-altitude areas of the southwestern United States (i.e., lower Sonoran life zone), but it may occur elsewhere through the mobility of the canine population.
Coccidioidomycosis is mainly caused by the inhalation of spores, whereas transmission from animal to animal is rare (apparently because the endospores are too fragile). Thus, C. immitis mainly causes respiratory disease characterized by granuloma formation in the pulmonary and thoracic lymph nodes. It is usually an insidious and chronic disease. Disseminated coccidioidomycosis is most likely to occur in dogs with a reduced capacity to resist infections or to develop immunity.

Signs of ocular disease may be the only apparent clinical manifestation in some patients (Angell et al., 1987; Armstrong & Di Bartola, 1983; Cello, 1980; Shively & Whitman, 1970). Ocular coccidioidomycosis can affect one or both eyes. Angell et al. (1987) reported that no evidence of systemic disease was present in 15 of 35 patients (∼43%) and that anterior segment changes such as iritis and granulomatous uveitis were the most frequent presenting signs, although on histopathological investigation, these appeared to have arisen from extension of posterior segment changes such as chorioretinitis and retinal detachment. Systemic signs included weight loss, lethargy, lameness, and respiratory disease.

Histopathologically, the disease is essentially a granulomatous panuveitis, with granulomas appearing most frequently in the ciliary cleft, iris root, ciliary body, choroid, and retina. Various stages of retinal degeneration and exudative retinal detachment may be present. Presence of respiratory disease and exposure to the endemic areas should alert the examiner. The diagnosis should, however, be confirmed by culture or serology. Aqueous or vitreous paracentesis may yield mononuclear inflammatory cells and fungal elements. C. immitis is a spherical organism (diameter, 20–100 µm) containing endospores (diameter, 2–5 µm). Serological diagnosis can be useful in the diagnosis of coccidioidomycosis (see Kerl, 2003 for a review) but is of limited sensitivity (Shubitz & Dial, 2005). A PCR assay for the presence of coccidoidal DNA has been developed. Both experimentally in mice and in natural infections in humans, it was shown that there is a transient presence of PCR-amplifiable coccidoidal DNA in serum before the development of antibodies. However, because the presence of detectable coccidoidal DNA is transient, the use of PCR from serum samples is limited as a diagnostic aid (Johnson et al., 2004).

Long-term treatment with ketoconazole is the therapy of choice for disseminated coccidioidomycosis (Angell et al., 1987). Such therapy should be evaluated with caution, however, because a recently published study indicates that long-term ketoconazole treatment in the dog can cause bilateral, rapidly progressive cataracts (da Costa et al., 1996). Itraconazole may be an alternative to ketoconazole. Relapses may occur if the treatment is discontinued too early. Enucleation may be indicated if the eye appears to be the only site of active infection; otherwise, the ocular lesions are treated symptomatically. The chitin synthase inhibitor Iufenuron has been used in clinical trial to treat coccidioidomycosis in dogs with some apparent success (Bartsch & Greene, 1997). However, an experimental study failed to show that the drug had any action on in vitro fungal growth and did not increase the survival time of experimentally infected mice (Johnson et al., 1999).

**Geotrichosis**

Geotrichum candidum is a fungus that can cause disseminated infections in the dog (Rhyan et al., 1990). Uveitis with choroidal granulomas and subsequent exudative retinal detachment has been reported in geotrichosis with ocular involvement (Lincoln & Adcock, 1968).

**Pseudallescheriasis**

Severe bilateral exudative chorioretinitis and retinal detachment in combination with systemic signs, including intermittent fever, lethargy, and lameness, have been described in a dog with disseminated pseudallescheriasis (Bazler et al., 1988). Histopathology revealed granulomatous to pyogranulomatous inflammation in all affected organs, and hyphae invading blood vessels and thrombosis were frequently observed. Irregularly branched septate hyphae, often with thick-walled terminal or intercalated vesicles, were demonstrated. The immunofluorescence test was positive for Pseudallescheria boydii.

**Candidiasis**

Candida albicans has been reported as a cause of unilateral endophthalmitis in a dog that had a history of bloody diarrhea and a positive titer to Candida (Linek, 2004). A retinal detachment was identified on ocular ultrasound; the eye developed secondary glaucoma and was removed. The causal agent was identified on histopathology.

**Algal Disease**

Plant material is rarely associated with posterior segment disease. The most frequent lesions caused by plant material are seen in the external ocular structures or in the anterior segment after corneal penetration. One alga, Prototheca, which indeed is a primitive plant, has been reported to cause posterior segment disease.

**Protothecosis**

The chlorophyllifer alga Prototheca is a saprophyte widely spread in the environment. Two species, Prototheca wickerhamii and Prototheca zopfii, are reportedly capable of causing systemic disease in the dog (see Hollingsworth, 2000 for a thorough review). It is thought that the organisms are ingested and localized to the colon, and then are spread further both hematogenously and lymphogenously. The alga usually causes a slowly disseminating disease affecting the brain, eyes, heart, intestines, kidney, and liver. An acute dissemination has been reported in dogs with colitis.

Prototheca occasionally reaches the eye hematogenously, and ocular disease (e.g., blindness) may be the presenting sign
in some patients (Blogg & Sykes, 1995; Buyukmihci et al., 1975; Carlton & Austin, 1973; Hosaka & Hosaka, 2004; Merideth et al., 1984). The alga causes anterior uveitis, chorioretinitis, or panuveitis, which may progress to chronic endophthalmitis (Buyukmihci et al., 1975; Carlton & Austin, 1973; Font & Hook, 1984). The retina is often detached secondary to the posterior segment inflammation, and blindness is reported in approximately 50% of the cases (Migaki et al., 1982).

Vitreous paracentesis or tissue sampling can be used to obtain material so the organism can be demonstrated and identified by culture. Histopathologically, prototheca organisms, which resemble the fungi organisms, Cryptococcus, Blastomyces, Candida, and Pneumocystis, are usually found bilaterally in the choroid and subretinal exudates. It is a unicellular, ovoid organism with a refractile cellulose wall surrounding a nucleus and granular cytoplasm. So far, treatment of disseminated protothecosis in the dog has been unsuccessful (Cook et al., 1984; Moore et al., 1985). A recent study reported that Prototheca sp. organisms could be identified in urine sediment (4 out of 8 cases) and on urine culture (5 out of 7 dogs), suggesting that urine cytology and culture may aid in the diagnosis of protothecosis in dogs (Pressler et al., 2005).

Protozoal Diseases

Posterior segment diseases caused by protozoans are infrequently reported in the dog. Ocular involvement in toxoplasmosis and leishmaniasis has been known for decades, whereas Neospora caninum has been identified as a potential ocular pathogen only recently.

Toxoplasmosis

Infections with the protozoan Toxoplasma gondii have been observed in several avian and mammalian species and in most areas of the world. The protozoan has an enteropneumonic cycle occurring only in domestic cats and some other members of the family Felidae, however, resulting in the production of oocysts. T. gondii also has an extraintestinal cycle that occurs in several mammals and birds. In the acute disease, the GI tract is involved, which leads to hematogenous and lymphogenous dissemination to other organs. The lungs and liver are frequently involved, but other organs, such as the lymph nodes and muscles, may show disease as well. Subacute or chronic infections may affect the brain, and common signs of toxoplasmosis in the dog include pneumonia, hepatitis, and encephalitis (Frenkel et al., 1970; Jones, 1973; Turner, 1978). Concurrent, active infections with canine distemper virus and toxoplasmosis have, for uncertain reasons, been frequently recorded.

In addition, T. gondii is recognized as a cause of ocular disease in several species. The most common findings are iridocyclitis and retinochoroiditis, but lesions may occur in most ocular structures. Histopathologically, there is perivascular accumulations of cells, hyalinization of vessel walls, and infiltration of cells into the retina. Retinal detachment may be seen in severely affected dogs. Retinal elevations without detachment can result from the accumulation of exudate within the choroid. Piper et al. (1970) reported that in 37 dogs with toxoplasmosis, 30 had ciliary body involvement, 27 had retinal lesions, 18 had choroidal lesions, and 15 exhibited involvement of the iris.

The diagnosis is usually confirmed by high or rising titers of toxoplasma antibodies in sera (Jones, 1973). It has been stated that toxoplasma retinochoroiditis is usually associated with a stable antibody titer. A PCR test for T. gondii DNA is also available.

Toxoplasmosis is typically treated with clindamycin or trimethoprim/sulfa combinations. The ocular disease may demand additional treatment (e.g., anti-inflammatory therapy in dogs with extensive retinochoroiditis). Glucocorticoid therapy, however, has been associated with increased spread of the organism (Bussanich & Rootman, 1985).

Neosporosis

N. caninum is a cyst-forming coccidium. It is intracellular in neural and other cells of the body, and its tissue cysts are found in neural tissue (Dubey et al., 1988). Thus, signs of neuromuscular dysfunction appear to be common. Repeated transplacental transmission of the organism has been described in a kennel (Dubey et al., 1990), and ocular involvement caused local retinitis (primarily of the inner retinal layers), retinochoroiditis (in severe cases), choroiditis, and mild anterior uveitis. N. caninum tissue cysts and tachyzoites (i.e., proliferative organisms) were associated with the retinal lesions in some dogs. The mortality was remarkably high among the pups and young dogs (29 of 39 dogs) included in the study. Serological and PCR testing is available. Treatment is as for toxoplasmosis.

Leishmaniasis

Leishmania donovani is a flagellate protozoan naturally transmitted by sand flies. It is mainly found in the Mediterranean countries of southern Europe, but increasing mobility of the canine population has produced cases elsewhere (McConnell et al., 1970; Roze, 1986; Thorson et al., 1955). One case has been reported in a dog native to the United States (Swenson et al., 1988).

Ocular involvement seems to be common in the dog, with keratoconjunctivitis being the most common sign. Other signs of ocular leishmaniasis are blepharitis and anterior uveitis. The uveal inflammation progresses to endophthalmitis, and the posterior segment appears to be involved by extension from the anterior parts of the eye.

Histopathologically, the lesions are characterized by massive infiltration of histiocytes, lymphocytes, and plasma cells in the affected parts of the eye. The organism may be present in the cytoplasm of histiocytes. Detection of the organism, serologic testing, and PCR detection of the presence of the organism’s DNA can be used to establish the diagnosis.
Parasitic Diseases

A hematogenous invasion of the eye by a migrating nematode larva, or ocular larva migrans, is a rare condition in the dog. Even so, the host may be invaded by several nematode species. Ocular larva migrans, however, is an important zoonotic disease, and posterior segment disease caused by migrating Toxocara canis has been confused with retinoblastoma, a highly malignant condition, in children.

Toxocara Chorioretinitis

T. canis, which is an ascarid nematode, is a common and important intestinal parasite in the dog, but cases of intraocular larva migrans are infrequently reported in this species (Johnson et al., 1989; Rubin & Saunders, 1965). Nevertheless, multifocal fundus lesions, some of which were histologically proven to be associated with Toxocara invasion were present in 39% of working sheepdogs in New Zealand (Hughes et al., 1987).

The parasitic granulomas appear as small, raised, translucent nodules in the tapetal retina, whereas the corresponding lesions in the nontapetal fundus have a grayish color. Multifocal, well-delineated areas of subacute to chronic inflammatory lesions in the fundus, which are characterized by tapetal hyperreflectivity, depigmented areas in the nontapetal fundus, and vessel attenuation, may also be observed ophthalmoscopically (Hughes et al., 1987; Johnson et al., 1989). End-stage chorioretinopathy appears similar to generalized retinal atrophy and is difficult to differentiate from PRA. Vision is then severely impaired, or affected animals become nonvisual unilaterally or bilaterally. These findings are similar to those of diffuse subacute neuroretinitis in humans (which may be unilateral or bilateral), which is a condition attributed to damage secondary to nematode migration in the subretinal space (Audo et al., 2006). A direct toxic effect of worm by-products on the retina was proposed as well as secondary inflammatory and autoimmune processes.

Well-organized granulomas extending from the choroid to the subretinal space, and eventually with a focally detached retina, are typical histopathologic findings. Granulomas may also be found in the optic nerve. Parts of the larvae may be seen within the granuloma, and eosinophils may be present around its periphery. Because of the focal nature of the granulomas, they can be easily missed at routine sectioning.

Treatment against the parasite in the retina normally is not indicated, because vivid larvae are unlikely to be present within ophthalmoscopically detectable granulomas. The public health and hygiene aspects of migrating T. canis larvae, however, should be considered.

Angiostrongylosis

Angiostrongylus vasorum is endzoonotic in parts of Europe and Africa, but it may appear elsewhere (e.g., in imported dogs). It is a nematode usually found in the pulmonary arteries and right side of the heart in both dogs and wild carnivores. The parasite can occasionally, however, affect the eyes, and in some spectacular cases, the nematode has even been free-floating in the anterior chamber (i.e., ocular larva migrans) (King et al., 1994; Rosenlund et al., 1991). Aangiostrongylus is also capable of causing posterior segment disease, with subsequent impairment of vision (Perry et al., 1991). Wild foxes act as a reservoir for domestic dogs. Canids are infected by ingestion of gastropod intermediate hosts (snails and slugs).

Ocular signs include granulomatous uveitis or panuveitis, subretinal hemorrhage, and chorioretinitis. Patent angiostrongylosis can be diagnosed on the basis of larvae in the feces or tracheal mucus. The pulmonary nodules associated with the disease may be seen on thoracic radiographs. Authors of one study reported successful treatment consisting of surgical removal of the organism from the anterior chamber combined with systemic therapy using levamisole (Rosenlund et al., 1991).

Ophthalmomyiasis

In humans, migration of fly larvae from the order Diptera beneath the retina (i.e., ophthalmomyiasis interna posterior) results in subretinal tracks, retinal hemorrhage, pigmentary disturbances, and other signs. A similar condition has been reported in a dog with a 48-hour history of unilateral blepharospasm and miosis, in which migration of a larva within the tissues of the posterior segment was monitored (Gwin et al., 1984). The larva could not be identified but resembled those of Diptera.

Diseases of Unknown Cause

Inclusion Retinitis

Perry et al. (1991) described a 6-year-old Bassett Hound with a history of night blindness and ophthalmoscopic findings similar to those of end-stage hereditary PRA. Histopathologic examination revealed an uneven distribution of the degeneration and cells in the inner nuclear layer containing eosinophilic inclusion-like bodies.

Breed-Related Multifocal Chorioretinitis

A breed-related chorioretinitis has been reported in different breeds of dog including Beagles (Weisse et al., 1981), Borzois (Acland et al., 2004; Scagliotti & MacMillan, 1977; Storey et al., 2005), and Border Collies. Ophthalmoscopic examination of 2887 research-quality Beagles revealed chorioretinitis without clinically apparent signs in 2.3% of the dogs (Weisse et al., 1981). Multifocal serous retinal detachments, mainly in the lower quadrants of the fundus and not associated with the retinal vessels, were observed during the acute phase. After 8 days, multifocal depigmented areas could be seen ophthalmoscopically in the nontapetal fundus, whereas small detachments healed without visible lesions. Histopathologically, focal accumulation of serous fluid between the RPE and
photoreceptors, without other inflammatory changes in the retina and choroid, were observed. In large areas of detachment, however, total loss of the outer nuclear layer and focal rarefaction of the tapetal lucidum were present. Tests for canine distemper virus were negative, and the lesions either healed or became inactive within 4-8 days without treatment.

In another study of this condition in Beagles, fluorescein angiograms showed leakage of fluorescein into the subretinal space on the first day, whereas no leakage could be seen at day 7 (von Landenberg et al., 1990). The retinal vessels appeared to be patent during the entire course of the disease. Results of virologic examination were negative, but a filiform, microaerobically growing bacteria was isolated from the ocular specimens. The bacteria, however, was not identified.

In one study a multifocal chorioretinitis in 25 (20 males and 5 females) of 180 Borzois examined was detected (Saglotti & MCMillan, 1977); in a second survey, similar lesions were detected in 12 (7 males and 5 females) of 103 Borzois examined (Storey et al., 2005). The lesions were often detected at the inferior-temporal tapetal border and initially appeared as multiple focal areas of retinal edema with loss of choriocapillaris and tapetum (Fig. 24.54). They occurred unilaterally or bilaterally. Within days, the tapetal defect was obscured by pigment proliferation. The chronic lesions appeared as well-circumscribed hyperreflective lesions with pigment proliferation and clumping within the borders of the lesions. Fluorescein angiography revealed the presence of lesions in the nontapetal fundus (Chaudieu, 1995; Storey et al., 2005) that ophthalmoscopically appeared as mild pigmentary changes (Storey et al., 2005). The lesions could be up to two times the diameter of the optic disc (Storey et al., 2005). Although one group suggested the condition might be a manifestation of PRA (Saglotti & MCMillan, 1977), others found that this was most probably unlikely. Pedigree analysis and a test mating failed to prove the condition to be inherited (Storey et al., 2005).

A another group also described the condition in Borzois and an apparently similar disease entity in Border Collies (Acland et al., 2004). They found that the initiating lesion was hemorrhage from the subretinal vasculature. A higher incidence in males was also noted in this study, as was the progressive nature of the condition in some individual dogs. They also noted that left eyes were affected more frequently than right eyes and found no evidence of heritability. A another group published a report on further studies in the Border Collie, in which unilateral or bilateral chronic chorioretinitis-like lesions were found to develop initially, at the age between 6 months and 9 years, that progressed into generalized retinal degeneration in most cases (Vilboux et al., 2008). ERG showed normal responses if lesions were unilateral and focal or more diffusely spread. Segregation analysis suggested an X-linked mode of transmission for the defect; however, XLPRA1 and XLPRA2 were excluded through genetic testing.

Specific Retinopathies

Uveodermatologic/Vogt-Koyanagi-Harada Syndrome

The uveodermatologic or Vogt-Koyanagi-Harada (VKH) syndrome of humans encompasses a variety of clinical signs, including uveitis, chorioretinitis, skin depigmentation (i.e., vitiligo), loss of hair pigment (i.e., poliosis), and various neurologic signs. The disease has been reported in the dog as an immune-mediated syndrome resembling VKH in humans. Several cases have been reported in Akitas, though numerous other breeds have been affected as well (Asakura, 1977; Furlong et al., 1989; Kern et al., 1985; Murphy et al., 1991; Romatowski, 1985). In the dog, cases may present with a history of sudden blindness or with chronic uveitis leading to secondary glaucoma. Dermatologic changes include vitiligo and poliosis affecting the periorcular skin, lips, and muzzle most frequently. Ocular examination may reveal anterior or posterior uveitis (or both) and serous retinal detachment. The uveitis is usually granulomatous, with cellular infiltrates of lymphocytes, plasma cells, epitheloid cells, and macrophages containing ingested melanocytes. A preliminary immunologic study in two cases revealed that the ocular lesions were consistent with a B cell and macrophage response (Th2 immunity), while the skin lesions were mediated by T cells and macrophages (Th1 immunity) (Carter et al., 2005). The precise cause of the disease is unknown. The histopathology is consistent with antimalanocyte autoimmunity, however, and the breed incidence, such as in Akitas, suggests the involvement

![Figure 24.54.](image-url) Left fundus of a 13-month-old male Borzoi dog with Borzoi chorioretinopathy. Note the circular area of pigmentation and the perivascular foci of chorioretinal degeneration. (Courtesy of Bruce Grahn.)
of genetic factors. A similar disease was induced experimentally in two Akitas by immunizing them to tyrosine-related protein 1 (Yamaki et al., 2005). Unfortunately, similar studies in other breeds of dog have not been reported. A relationship between circulating antiretinal antibodies and clinical signs has been found, which could be indicative of a breakdown in the blood-retina barrier and exposure to retina-specific antigens and a secondary production of the antiretinal antibodies (Murphy et al., 1991). A study of canine leukocyte antigen (DLA) complex class II alleles in Akitas with and without uveodermatologic syndrome showed that DLA-DQA1*00201 was associated with a significantly higher relative risk for uveodermatologic syndrome than other DLA class II antigens (Angles et al., 2005). Unfortunately, presence of DLA-DQA1*00201 is not a useful predictor for the condition, because in the study, 19 of 26 affected Akitas did not carry the allele.

**Sudden Acquired Retinal Degeneration Syndrome (SARDS)**

Sudden acquired retinal degeneration syndrome (SARDS) is a retinal disorder of unknown cause that results in a sudden and permanent blindness in affected adult dogs (Acland et al., 1984; Curtis, 1988; Matson et al., 1992; Miller et al., 1998; Riis, 1990; Van der Woerdt et al., 1991). There is currently no treatment that has been proven to be effective for this disorder. Clinical signs are characterized by a sudden loss of vision, usually within days or 1–2 weeks. Most affected dogs show pupillary dilatation and unresponsive pupils, although some may retain a PLR. Typically, there is an absence of ophthalmoscopic fundus abnormalities at the early stage (Fig. 24.55), although occasionally areas of mild retinal edema may be noted. The main diagnostic technique to distinguish between SARDS and central causes of sudden-onset vision loss is electroretinography. In SARDS, the ERG is nonrecordable, while with central causes of blindness, the ERG is relatively normal. It appears that all breeds, including crossbreeds, may be affected, often in middle age. After several weeks to months, slowly progressive ophthalmoscopic changes may be observed that are indicative of a generalized retinal degenerative process.

Morphologically, abnormalities initially involve the photoreceptor cell layer (Riis, 1990; O’Toole et al., 1992). There is a rapid loss of photoreceptor outer segments (both rod and cone) (Fig. 24.56). Photoreceptor cells die by apoptosis (Miller et al., 1998), which is followed by a slow degeneration of the other retinal layers leading eventually to the appearance of an end-stage retinal degeneration. Different regions of the retina are equally affected, in contrast to many of the hereditary retinal degenerative diseases described earlier. However, ophthalmoscopically, the end-stage retinal degeneration looks similar to generalized retinal degenerations of other etiologies (such as PRA).

Affected dogs are usually healthy, but many have a history of weight gain, polyuria, polydipsia, and polyphagia. There are often clinical signs and initial laboratory blood work such as elevated serum alkaline phosphatase, serum amino transferase, serum cholesterol, or serum bilirubin levels suggestive of hyperadrenocorticism. Van der Woerdt et al. found that 17 of 25 cases tested had abnormal serum biochemistry (Van der Woerdt et al., 1991). Some cases will be confirmed as having
Cushing’s disease (e.g., 6 out of 10 dogs tested in the series) (Van der Woerd et al., 1991). However, further investigations often do not support the initial suggestion of hyperadrenocorticism (Matson et al., 1992). A study of 16 dogs diagnosed with SARDS failed to find evidence of pulmonary, adrenal, or pituitary neoplasia (Bellhorn et al., 1988). Carter et al. measured serum cortisol and sex-hormone levels before and after ACTH stimulation in 13 dogs diagnosed with SARDS. They found elevations of one or more sex hormones in 11 of the 13 dogs and cortisol elevations in 9 of the 13 dogs (Carter et al., 2009). Studies looking at the presence of circulating antiretinal antibodies in dogs with SARDS have been contradictory. One study showed the presence of such antibodies (Bellhorn et al., 1988), while other studies showed that affected dogs had no higher incidence of antiretinal antibodies than normal dogs (Gilmour et al., 2004; Keller et al., 2006). In one study, 25% of SARDS dogs had antibodies to neuron-specific enolase (Braus et al., 2008).

Dogs with and without SARDS have been used as tools for studying PLR activity and the physiological properties regulating these reflexes (Grozdanic et al., 2007).

RETNAL TOXICITIES

Systemic Toxicities
A toxic chorioretinitis caused by ingestion of unknown toxins has been observed in dogs (Fig. 24.57A, B).

Drug-Induced Retinotoxicity
Some compounds can directly cause retinal damage by damaging neuroretinal or RPE cells or indirectly cause such damage by inflammatory reactions that lead to focal or more generalized cell death. Assessment of retinal integrity is an essential component in ocular safety evaluations. Usually, ophthalmoscopy and biomicroscopy of treated animals and histopathology of retinal tissues are used in routine toxicologic studies. These methods are adequate to detect gross retinal degenerative changes; however, they fail to detect minor pathology of the retina, such changes involving subtle though generalized structural alterations without degeneration (Aguirre, 1990). Minor morphologic changes may be elucidated using improved methods of tissue fixation and both light and electron microscopy. Functional evaluation can be accomplished using electrophysiologic testing, such as ERG or VEP (or both). To determine target-tissue specificity and examine mechanisms of compound-associated retinal damage, in vitro methods (e.g., tissue culture) can be used. Preliminary extended protocols for ocular toxicity testing have already been proposed in some areas of toxicology (Hamernik, 1994; Rosolen et al., 2005).

Drug-induced retinopathies are usually characterized by bilateral symmetry. There is usually a relationship between the duration of the administration of a toxic compound, the dosage, and the onset of clinical signs. Some well-known and representative drug-related retinotoxic compounds are discussed here. For examples see Figure 24.57A and 24.57B.

Vasodilating Drugs
Some experimental vasodilating drugs have been reported to cause a tapetal color change in the region overlying the long posterior ciliary arteries, thought to be due to a slight distortion of the choroid overlying the vessels altering the direction of light reflected off the tapetum (Fig. 24.57C) (Rubin, 1974).

Ethambutol
Ethambutol is an antitubercular drug that produces discoloration of the tapetal fundus (Fig. 24.57D, E, F); this discoloration is reversible (Kaiser, 1963; Vogel & Kaiser, 1963). There is no effect on vision, and the ERG and VEP remain normal (Sato, 1985). Morphologically, affected tapetal cells have swollen and disoriented, intracellular rodlike bodies, which appear to interfere with the diffraction and reflection of light. In humans, ethambutol produces a decrease in visual acuity and loss of ability to perceive the color green (Rubin, 1974).

Diphenylthiocarbazone
Diphenylthiocarbazone (Dithizone) toxicity produces funduscopic alterations within 24 hours of intravenous injection (Fig. 24.57G, H). This metal-chelating agent causes funduscopic changes that include a dark-red color and diffuse retinal edema. Pigmentary aberrations follow, thus giving the fundus a mottled appearance. Minimum doses may cause reversible changes but also bullous retinal detachment, thereby causing blindness. High doses cause irreversible damage with retinal degeneration (Rubin, 1974).

Hydroxyppyridinethione
Hydroxyppyridinethione is a zinc-chelating drug that can cause blindness in dogs as a sequel to tapetal necrosis, edema, and retinal detachment (DeLahunet al., 1962).

Quinine
Quinine and some of the cinchona derivatives produce a rapid vasoconstriction of retinal arterioles and pallor of the optic disc within a few hours of administration in the dog. Later, a partial or complete destruction of ganglion cells with subsequent optic atrophy is found (Rubin, 1974).

Rafoxanide
Rafoxanide toxicity causes a rapidly progressing optic nerve edema that can result in blindness (Brown et al., 1971). Histopathologically, there is vacuolation and edema of the optic nerve, chiasm, and white matter of the brain and spinal cord.
Figure 24.57. Drug-induced retinal effects and toxicities have been described for the dog fundus. A and B. Toxic neuroretinitis is shown in a 6-month-old dog with initial intestinal problems, then clinically blind, 3 days after rummaging in a trash heap. The tapetal fundus (A) shows comma-shaped pigmentary changes. In the nontapetal fundus (B), there are multiple areas with retinal edema. C. Some experimental vasodilating agents produce transient color changes in the dog retina, generally in the zone corresponding to the distribution of the long posterior ciliary arteries. The color changes observed are related to localized distortion of the retinal and choroidal curvature by the widely dilated larger vessels. D, E, and F. Fundus of a 1-year-old Beagle treated with ethambutol. The tapetal junctional area is shown prior to treatment (D). There is progressive decoloration of the tapetal retina after oral administration of ethambutol, 800 mg/kg body weight, after 9 and 23 days (E and F), respectively. G and H. Diphenylthiocarbazone (Dithizone) toxicity is shown in a German Shepherd. The normal fundus of the dog is shown prior to treatment (G), and the same area after IV administration of 20 mg/kg body weight of Dithizone (H). Note that after only 24 hours after treatment, the retina is detached in some areas and thrown into multiple folds in others. I. Chloroquine toxicity is shown in a dog, most easily observed in the nontapetal fundus as scattered gray-white specks. Histologically, these lesions correspond to membranous cytoplasmic bodies mainly in ganglion cells. (The original figures have been reprinted with permission from Lionel F. Rubin from Atlas of Veterinary Ophthalmoscopy, Lea & Febiger, Philadelphia, 1974. Copyright Lionel F. Rubin.)
**Chloroquine**

Chloroquine is an antimalaria drug with an affinity for melanin and ocular tissues containing melanin. In the dog, the earliest changes may be seen in the nontapetal fundus as scattered, gray-white specks (Fig. 24.57I). Histopathologically, membranous cytoplasmic bodies are seen in ganglion cells at ultrastructural analysis (Rubin, 1974).

**Azalide**

Azalide is an antibiotic drug that can cause tapetal color changes if administered in high doses (e.g., 100-fold the recommended clinical dose) (Fortner et al., 1993). Ophthalmoscopically, there is a dull white appearance of the tapetal fundus. Microscopic examination of ocular tissue shows tapetal cells that are swollen and vacuolated as well as retinal cells (primarily ganglion cells) that contain lysosomal lamellar bodies. No other effects have been found, either in the eye or systemically.

**Closantel**

Intoxication with closantel, which is an anthelmintic used in domestic ruminants, has been described in a dog (Entee et al., 1995). Eye examination revealed bilateral mydriasis with absent pupillary reflexes. Funduscopically, the optic discs were swollen, and several small papillary and peripapillary hemorrhages were seen. The tapetal fundus was diffusely hyperreflective. Retinal vasculature appeared to be normal. Over time, there was progression of the lesions, which resulted in generalized retinal and optic disc atrophy. Blindness was irreversible.

**Thiram**

Thiram (tetramethylthiuram disulfide) is a general-purpose pesticide. Toxicity studies in dogs showed that thiram caused ocular lesions including fundus changes as well as more generalized changes such as liver failure and kidney damage (Maita et al., 1991).

**Retinopathy Induced by Light and Oxygen**

There is a well-established association between high light intensity and retinotoxicity. Phototoxicity in the rat model has been extensively studied (Penn et al., 1992). Illumination of the canine fundus with light from an indirect ophthalmoscope for 20 minutes may be sufficient to cause ophthalmoscopically visible changes. Prolonged exposure results in areas of increased granularity in the tapetal fundus, which is followed by retinal pigmentation and increased tapetal reflectivity. The nontapetal fundus, however, is virtually unaffected, thereby showing the protective effect of pigmentation. Histopathologic changes in minor retinopathies include vesiculation and shortening of photoreceptor outer segments, but also vesiculation of the pigment epithelial cells. More advanced cases show photoreceptor degeneration and atrophy of the RPE (Buyukmihci, 1981). The risk of phototoxic retinopathy should be considered during intracocular surgery because it is possible for light from the operating microscope to cause a focal area of retinal damage.

Exposure to high oxygen tensions produces selective damage to the visual cells in the dog (Rubin, 1974). Oxygen administration has been strongly linked with human retinopathy of prematurity, and there is evidence that light exposure may play a role in its pathogenesis (Glass, 1990). Oxidative processes and generation of free radicals have also been suggested to be important in development of the disease (Penn et al., 1992). The dog has been established as an experimental model for human retinopathy of prematurity (Micleod et al., 1996, 1998). Neonatal dogs exposed to 95% to 100% oxygen for 4 days develop a peak of revascularization of the posterior segment between 3 and 10 days following return to room air (Micleod et al., 1996). Lesions include dilated and tortuous retinal vessels, pigmentary changes, incomplete vascularization of peripheral retina, vitreal hemorrhage, and persistence of intravitreal neovascularization with retinal folds due to traction bands (Micleod et al., 1998).

The combination of light and oxygen can interact to produce oxygen-free radicals in a process known as photosensitization (Satta et al., 1994). Experimental studies in newborn Beagles showed both clinical and histopathologic abnormalities in eyes exposed to light in the presence of rose bengal, which is a photosensitizing agent. A spectrum of retinal lesions were obtained, including vitreous hemorrhage, fibrovascular and fibrocellular proliferation with traction on the retina, complete and partial retinal detachment, and retinal dysplasia. This study showed that photosensitization can produce a spectrum of retinal pathology in the dog that resembles human retinopathy of prematurity.

**Retinopathy Induced by Radiation**

Radiation-induced ocular injury secondary to treatment of nasal cancer occurs in both humans and animals. In a clinical and histopathologic study (Ching et al., 1990), immediate changes such as blepharitis and keratoconjunctivitis were found. At 3–6 months posttreatment (i.e., 36.0–67.5 Gy in fractionated doses given over 4 weeks using a 6-mV linear accelerator), however, a degenerative angiopathy of retinal vessels appeared, with multifocal retinal hemorrhage and mild, diffuse retinal degeneration, first affecting the outer retinal layers but then progressing inward. At 1–2 years posttreatment, there was a moderate retinal degeneration, with swelling and loss of ganglion cells and, subsequently, optic nerve axonal degeneration. Even tapetal and choroidal atrophy was observed. Thus, structures of the canine eye are sufficiently sensitive that even relatively low total doses of radiation cause significant long-term injury.

A study of the ocular effects of intravenous radium in Beagles showed that the radium was retained within the tapetum and induced varying degrees of tapetal degeneration. However, the major changes involved the anterior uvea and
consisted of the development of melanotic plaques and melanomas (Taylor et al., 2000). Experimental in utero exposure to radiation resulted in bilateral focal retinal dysplasia and, in some instances, a slowly progressive retinal degeneration with the portion of the retina most severely affected being that which was differentiating at the time of radiation exposure (Schweitzer et al., 1987).

RETINOPATHIES OF NUTRITIONAL CAUSES

Vitamin A Deficiency
Systemic vitamin A deficiency is characterized by night blindness in several species (Dowling & Wald, 1958; Hayes, 1974). Specific objective studies using psychophysical testing and fundus reflectometry in humans with vitamin A deficiency, both before and after supplementation, showed that subjects initially had no measurable rod function and delayed cone adaptation. A fer oral supplementation with vitamin A, visual function was restored to normal (Kemp et al., 1988). In the dog, systemic diseases causing impaired fat absorption could result in vitamin A deficiency, but this clinical situation is extremely rare.

Vitamin E Deficiency
Vitamin E is an antioxidant with an important function in maintaining cell membrane stability by preventing lipid peroxidation. A deficiency in vitamin E may result in pathologic changes in the muscle, CNS, reproductive tract, and retina (Hayes et al., 1970) (Fig. 24.58). Experimental studies that produced vitamin E deficiency have been performed in the dog by Riis et al. (1981). After weaning, dogs were fed a diet deficient in vitamin E. Ophthalmoscopic signs of disease developed early and were described as a mottled tapetal fundus appearance, particularly centrally, with numerous, discrete yellow-brown foci. Over time, the central fundus became hyperreflective, and there was an attenuation of the retinal vessels. The ERG was nonrecordable at 4 months of age.

Histopathologically, an accumulation of autofluorescent pigment within the RPE cells was observed and, at later stages, within migrating cells in all retinal layers. Photoreceptor damage occurred in areas overlying affected regions of the pigment epithelium. After 6 months of age, there was complete atrophy of the photoreceptor layer. The obvious similarities between vitamin E deficiency and hereditary CPRA/RPED suggest some common etiologic factor, and recent reports have substantiated this suggestion. Davidson et al. (1998) described retinopathy from vitamin E deficiency in a group of 16 Walker Hounds and in two Beagles. These dogs were kept in a common pen and fed a diet consisting of meat scraps, poultry carcasses, and offals. A spectrum of funduscopic changes, which varied in severity with increasing age, was found. Results of clinical as well as laboratory investigations showed the retinopathy resembled CPRA/RPED. McLellan et al. measured $\alpha$-tocopherol levels (the predominant vitamin E homologue in the retina and RPE) in 15 dogs (including 11 English Cocker Spaniels) with clinical signs of CPRA/RPED and 28 clinically normal dogs. All 11 CPRA/RPED-affected English Cocker Spaniels had very low plasma $\alpha$-tocopherol levels and very low ratios of plasma $\alpha$-tocopherol to cholesterol and triglycerides compared to normal controls (McLellan et al., 2002). The results from the four CPRA/RPED-affected dogs of other breeds were not conclusive. This suggests that in the English Cocker Spaniel at least, CPRA/RPED may be due to a familial primary vitamin E deficiency not related to dietary insufficiency or evidence of any GI malabsorption syndrome (McLellan et al., 2002, 2003). Apha-tocopherol-deficient English Cocker Spaniels showed neurological dysfunction in additional to fundus changes. The neurological signs included ataxia, proprioceptive deficits, abnormal spinal reflexes, and muscle weakness. Although the dogs had not been fed a diet low in vitamin E, dietary supplementation with vitamin E was reported to halt the progression of neurological changes and resulted in an improvement of the neurological signs and in exercise tolerance. It did not, however, appear to alter the ocular changes that had already developed (McLellan et al., 2003). Histopathological examination revealed central neuronal fiber degeneration and prominent neuroaxonal dystrophy of affected English Cocker Spaniels.
NUTRITIONAL SUPPLEMENTATION

Results of several studies show that dietary supplementation in dogs with omega-3 fatty acids, from a natural source, such as salmon oil, with a high level of docosahexanoic acid (DHA), increases plasma and red blood cell levels of fatty acids. Also, the ratio of omega-6 to omega-3 is improved, which has been shown to positively benefit cognitive development and visual acuity (for a review, see Filburn & Griffin, 2005). It has also been shown that DHA deficiency can cause decreases in ERG amplitudes and thus affects phototransduction parameters. DHA plays a demonstrable role in the development of vision in infants (D. Birch, personal communication). The possible role of DHA levels in patients with severe forms of hereditary retinal degeneration was studied clinically by ophthalmoscopy and ERGs. The DHA group of patients showed less change in funduscopy progression of disease during a 4-year period, although ERG cone function tested in supplemented and in placebo groups showed no statistical significant benefit between groups (Hoffman et al., 2004).

Supplementation with vitamins A and E have also been further studied in groups of human patients with RP, a disease complex comparable to PRA (Berson et al., 1993). The results support a beneficial effect of 15,000 IU/day of vitamin A and suggest an adverse effect of 400 IU/day of vitamin E on the disease course of RP. Approximately 10 years after this initial study in humans, another clinical trial was performed investigating the effects of combining DHA with vitamin A (Berson et al., 2004). In patients assigned to receive 15,000 IU/day of vitamin A, the randomized trial showed that 1200 mg/day of DHA over a 4-year period did not slow the course of disease in RP patients. Lutein and zeaxanthin, more commonly referred to as macular pigments in humans, have also been implicated with the health of ocular tissues through their antioxidative effects (Stringham & Hammond, 2005). A recent trial showed that the addition of lutein to vitamin A supplementation had a beneficial effect in human RP patients slowing midperipheral visual field loss (Berson et al., 2010). It is worth noting that in some retinopathies, vitamin A supplementation is to be avoided. For example, in Stargardt’s disease which is characterized by lipofuscin accumulation, studies in experimental animals suggest that a reduction in vitamin A levels may slow down lipofuscin accumulation (Radu et al., 2005).

Another element that influences cell metabolism and appears to play an integral role in maintaining ocular function is zinc (Grahn et al., 2001). Zinc supplementation trials and epidemiological studies in humans have, however, produced conflicting results, and additional well-controlled investigations are indicated to further clarify the possible beneficial role of zinc for ocular morphology and function.

VASCULAR DISEASE PROCESSES

The retinal vasculature is well-suited to direct, noninvasive examination. Systemic disease as well as local ocular pathology can produce observable changes in both retinal and choroidal vessels (Lane et al., 1993). Except for blood constituent analysis, blood flow and blood pressure measurements, and coagulation studies, specific methods of examination include ophthalmoscopy and fluorescein angiography. Furthermore, in the research environment, specific histopathologic studies may be performed, as well as studies of the ocular circulation and the sequelae of vascular disease processes by using radioactively marked microspheres (Alm & Bill, 1972; Hillerdal et al., 1987). A short description of funduscopy lesions associated with systemic hypertension, hyperviscosity, and hyperlipidemia is given here; for a more comprehensive discussion on these disorders, see Chapter 35.1.

Systemic Hypertension

Dogs with experimentally induced hypertension exhibit retinal hemorrhage, retinal detachment, and arteriolar changes (Preswerk & Breitenfeld, 1984). In cases of spontaneous systemic hypertension, visual disturbance is often the initial presentation. The most common ocular findings in clinical cases are posterior segment hemorrhage (retinal, preretinal, and vitreal), retinal detachment, and in some cases hyphema (Booee et al., 1989; Gwin et al., 1978; Litman et al., 1988; Paulsen et al., 1989; Sansom & Bodey, 1997).

Hyperviscosity Syndromes

In dogs with hyperviscosity syndromes, for example, with multiple myelomas or polycythemia, distended and tortuous retinal blood vessels are seen in conjunction with sacculation of venules, retinal hemorrhage and, in severe cases, retinal edema, retinal detachment, and papilledema (Fig. 24.59) (Brightman et al., 1980; Gray et al., 2003; Hendrix et al., 1998; Lane et al., 1993; McEwen et al., 1977; Martin, 1982). In a single case report of a dog with polychromatemia vera, the ocular presentation was of unilateral anterior uveitis and active chorioretinitis (Gray et al., 2003).

Hyperlipidemia

Hyperlipidemia may impart a milky pink coloration to retinal vessels, which is most easily observed in the nontapetal fundus (Brightman et al., 1980; Martin, 1982).

Diabetic Retinopathy

Though diabetic retinopathy occurs in the dog, the extent and severity of the retinal lesions are milder compared with those that can develop in diabetic humans. In the dog, the ocular lesions include anomalies of the retinal vasculature and cataract formation, as they do in humans. Whereas the vascular changes in humans are of major importance in the disease and contribute to blindness, they are much less severe and are of minor clinical importance in the dog with spontaneously occurring diabetes (Fig. 24.60). Cataract formation, on the other hand, is an early finding in the dog, and it is often the
reason for a patient with diabetes to be presented for the first time.

In humans, the initial retinal vascular change is the formation of microaneurysms, which result from sacculation of a small area of the capillary wall. Rupture of these aneurysms results in ophthalmoscopically visible focal hemorrhages, and there may be accompanying exudation as well. The vasculature may also form coils and loops. These are the so-called background changes in diabetic retinopathy. Proliferative changes, including preretinal and vitreal neovascularization, often with connective tissue formation in the vitreous, may also develop. The accompanying severe vitreal hemorrhage and nonrhegmatogenous retinal detachments that may follow will often cause blindness. In the dog with diabetes, background retinopathy occurs, but not the proliferative changes that develop in humans. A retrospective study of 52 diabetic dogs and 174 nondiabetic dogs that had undergone cataract surgery found retinal hemorrhages or microaneurysms in 21% of the diabetic dogs and in only 1 (0.6%) of the 174 nondiabetics. The mean time from the onset of diabetes to the diagnosis of diabetic retinopathy was 1.4 years (range 0.5–3.2 years) (Landry et al., 2004).

Recently, induced canine diabetic retinopathy has provided a useful model for the study of the condition in humans. There are several means to induce diabetes in the dog, but administration of alloxan and experimental galactosemia are currently used (Engerman & Kern, 1987; Frank, 1995; Kador et al., 1995; Kern & Engerman, 1995; Takahashi et al., 1992).

Morphologic changes in both spontaneous and induced diabetic retinopathy of the dog include thickening of the
vascular basement membrane, pericyte loss, microaneurysm formation, and capillary closure. There is also a loss of smooth muscle cells in the retinal arterioles (most obvious in the central retina) that accompanies the loss of pericytes (Gardiner et al., 1994). Regional differences in the distribution of vascular lesions within the same retina also are evident (Kern & Engerman, 1995). Thus, microaneurysms and acellular capillaries are more prevalent in the superior temporal retina than in the inferior nasal quadrant, whereas the distribution of pericyte ghosts (i.e., a pocket in the basement membrane at the site from which a pericyte has disappeared) in the same eye was not significantly different between quadrants. These findings show that local factors within the eye are important in the response of the retinal microvasculature to the disease process.

RETINOPATHIES WITH IMMUNOLOGIC DISEASES

Immune-Mediated Thrombocytopenia

Immune-mediated thrombocytopenia is a clinical disease characterized by anemia, hemorrhage, and low platelet counts. The presenting sign is often petechiation and ecchymosis of the gingiva or conjunctiva, and both hyphema and retinal hemorrhage are common findings. Treatment consists of controlling the hemorrhage; blood transfusion may be necessary in severe cases. Systemic corticosteroid treatment, 1–2 mg/kg per day, is used for several weeks and then tapered to a low-maintenance dose.

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia is an autoimmune disease of both humans and the dog. Presenting clinical signs are acute to chronic anemia, and ophthalmoscopically, the retinal vessels are light red and difficult to follow because of the blood disorder (Curtis et al., 1991). Treatment is systemic corticosteroids, 2–4 mg/kg for 2 weeks and then decreasing to maintenance levels. Supportive therapy is often indicated for the anemia.

Systemic Lupus Erythematosus

Systemic lupus erythematosus is a multisystem disorder with immunologic abnormalities related to autoantibodies in both the blood and the lesions of the body. There is a genetic predisposition for the disease, and genetic processes may initiate the systemic problem. Ocular lesions include hemorrhages and serous retinal detachments. Recommended treatment is the same as that for autoimmune hemolytic anemia.

Cancer-Associated Retinopathy (CAR)

Cancer-associated retinopathy (CAR) is a form of autoimmune retinopathy in which cancer patients develop antibodies that cross-react with retinal antigens; the resulting immuno-

logical attack on the retina causes retinal cell death and vision loss (for a review, see Shildkrot et al., 2011). Several tumor types may lead to this condition, but melanomas appear to do so in particular. The vision loss may be apparent before the tumor is detected. There is little information on the occurrence of CAR in dogs.

SECONDARY RETINAL DEGENERATIONS

Glaucoma

Glaucoma can lead to retinal degeneration, particularly as a result of the high IOPs that are common in many primary canine glaucomas. In acute stages, the retina may appear normal ophthalmoscopically or show areas of edema. When there is severe retinal damage, retinal degeneration becomes apparent surprisingly rapidly; sometimes, this may appear as more severe zones of retinal thinning radiating out from the ONH. Cupping and atrophy of the ONH also develops (Fig. 24.61). Histopathological studies of eyes removed because of primary narrow-angle glaucoma show that essentially all retinal layers are affected and that the progression of retinal changes occurs rapidly. Within 1 day of the onset of glaucoma, necrosis of retinal ganglion cells has developed and is followed by the induction of apoptosis of cells in the ganglion cell layer as well as the inner and outer nuclear layers (White- man et al., 2002). There is release of taurine and glutamate...
Chapter 24: Diseases of the Canine Ocular Fundus

SECTION III

Ophthalmoscopy reveals an anterior displacement of the retinal surface and the retinal blood vessels (see Fig. 24.64). Large volumes of subretinal fluid can cause segments of the retina to balloon anteriorly, even extending to the posterior surface of the lens in extreme cases. When there is anterior displacement of the detached retina, it can often be readily viewed directly through the pupil with a focal light source. If there is a total detachment with dialysis, the retina will hang in folds from the ONH, where it remains attached due to the ganglion cell axons converging from the retina to form the optic nerve. The retina resembles a grayish-colored curtain hanging in the vitreous. The exposed tapetum will appear hyperreflective because there is no overlying retina. In other instances of retinal detachment, holes or tears in the retina may be seen and the exposed choroid and RPE can appear very clear through the retinal defect, particularly if there is not a great deal of cellular infiltration. The presence of retinal tears or holes is important in making decisions about management (see Chapter 25), so the detached retina should be examined carefully for the presence of tears or holes. Scleral depression may be required to view the complete periphery to the ora ciliaris retinae. Extensive detachments may induce iridal neovascularization in the long term. Cataract and other pathological changes can also develop in severely affected eyes. It is noteworthy that in the acute phase of detachments, some residual PLR may still be present.

Retinal Detachments

Various pathologic conditions of the eye can cause focal, multifocal, or total retinal detachment. The neuroretina is usually separated from the underlying RPE, which implies a disruption of the intimate and essential (but structurally weak) association between the outer segments of the photoreceptors and the RPE. This loss of structural integrity is associated with a loss of function and secondary retinal degeneration in the affected area. Thus, a focal retinal detachment affecting a minor area will usually not result in clinically detectable impairment of vision, whereas detachment of the entire retina is a blinding condition. Detachments involving large areas of the retina may result in tearing of the peripheral retina as the multilayered neurosensory retina becomes thinner at the periphery to continue as the nonpigmented ciliary body epithelium at the ora ciliaris retinae. The complete tearing of the peripheral retina is often termed disinsertion or dialysis (Fig. 24.62).

Figure 24.62. Retinal detachment with disinsertion (dialysis). The retina has torn at its periphery (ora ciliaris retinae) and now hangs ventrally in the vitreous, still attached at the optic nerve head. The gray membrane (neuroretina) hanging from the optic nerve head obscures direct visualization of the optic nerve head.

From photoreceptors, possibly secondary to ischemic damage (Madl et al., 2005). Glutamate release may induce excitotoxicity, thus inducing apoptosis in additional retinal neurons. Glutamate accumulates in Müller cells in glaucoma-affected dogs (Madl et al., 2005), and an increased level of glutamate in the vitreous has also been reported (Brooks et al., 1997). Interestingly, there is a notable sparing effect over the tapetal area, with the retina in this area being less severely affected than in the nontapetal areas (Brooks et al., 1997; Madl et al., 2005; Smedes & Dubielzig, 1994; Whiteman et al., 2002). The reason for the tapetal sparing effect is not known. Other changes include partial or panretinal necrosis, hypertrophy of the RPE, disorganization of retinal layers, and severe retinal atrophy. Changes in the retina of dogs with glaucoma-associated retinopathy that have less severe IOP increases than typically seen in narrow-angle glaucoma and are likely to be more slowly progressive.

The effects of raised intraocular pressure (IOP) on retinal function can be detected by electroretinography. A study of the flash ERG with raised IOP showed a decay of b-wave amplitude, whereas the a-wave amplitude was less affected (Howard & Sawyer, 1975). This indicates a more pronounced effect of glaucoma on the bipolar cells, which are the origin of Granit’s PII, an ERG component corresponding to the b-wave, as compared to the photoreceptors, the major generators of PIII, which cause the increasing negativity of the a-wave. The PERG would be expected to be a more sensitive indicator of early retinal damage due to glaucoma because the response originates predominantly from the inner retina (Sievig & Steinberg, 1987), which is more severely affected in glaucoma. In a study of short-term-induced IOP rise in dogs, Hamor et al. found that the PERG was more sensitive to IOP rises than the flash ERG (Hamor et al., 2000). Grozdanic et al. recently reported the sensitivity of PERG over flash ERG in dogs with angle closure glaucoma (Grozdanic et al., 2010).

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SECTION III: Canine Ophthalmology

Retinal traction band. An inflammatory chorioretinitis lesion is associated with a band running anteriorly in the vitreous. The band appears as a gray-colored structure; the arrow shows its attachment to the retina. The chorioretinitis lesion associated with the traction band can be seen as an area of depigmentation in the nontapetal fundus. There is slightly raised, gray subretinal granuloma shown by the arrowhead. An inactive chorioretinitis lesion is present in the tapetal fundus. (Illustration supplied by Michigan State University Comparative Ophthalmology Service.)

Figure 24.63.

Retinal detachments associated with retinal dysplasia are a congenital condition caused by impaired retinal structure, dysfunction of the RPE, or retinal nonattachment (see previous discussion of retinal dysplasia). Retinal detachments, which are not solely associated with the aforementioned developmental defects in the neuroretina and RPE, can be subdivided according to the causative mechanism into rhegmatogenous, traction, and exudative detachments. A rhegmatogenous detachment is one associated with a tear or hole in the neuroretina; the retinal defect allows vitreous and fluid to dissect the neuroretina from the RPE, thus exacerbating the lesion. A force from the vitreous body pulling the neuroretina anteriorly (e.g., from an organizing hemorrhage in the vitreous body) can result in traction detachment (Fig. 24.63). Fluid and cell deposition (e.g., in chorioretinitis or hypertension) in the subretinal space elevates the retina and causes an exudative detachment.

Rhegmatogenous retinal detachments may be the most common form in the dog. This is because most detachments are associated with ocular diseases known to induce retinal tears, such as CEA, lenticular disease, retinal dysplasia, and glaucoma (Hendrix et al., 1993).

Hendrix et al. (1993) reported that in 23 of 46 dogs (62 eyes) with retinal detachment, the detachments were associated with lenticular disease. In 23% of the eyes, the detachment occurred after extracapsular cataract extraction. Retinal detachments secondary to cataract surgery are generally believed to be rhegmatogenous, though the cause of these neuroretinal tears is difficult to determine. Other causes of retinal detachment identified in the Hendrix study included panuveitis, infectious disease (including bacterial, rickettsial, and mycotic infections), systemic hypertension, trauma, and congenital ocular disease. Retinal tears were seen in 26% of the eyes and traction bands in 5%.

Rhegmatogenous detachments in Labrador Retrievers with oculoskeletal dysplasia (see previous discussion) have been investigated as a model for rhegmatogenous retinal detachments in humans (Blair et al., 1985a, 1985b). The cause of retinal tears leading to detachment in this animal model appears to be traction on the retina from the vitreous. Formation of fibrocellular membranes on the surface of the totally detached retina, to which the RPE, nonpigmented ciliary epithelium, macrophages, and glial cells contribute, occurs later in the disease. A proliferative vitreoretinopathy of this type is an important cause of failed retinal detachment surgery in humans.

Exudative retinal detachment for which an etiology is not established despite laboratory workup has been well recognized for many years (Gwin et al., 1980c). Recently, it has been termed steroid-responsive retinal detachment (Andrew et al., 1997); the affected dogs typically present with a history of an acute-onset loss of vision. The detachments are bilateral nonrhegmatogenous, and in some cases, vitreal hemorrhage may develop (Fig. 24.64). Andrew et al. recorded a series of 22 cases in which German Shepherd crosses (6 out of 22), German Shepherds (3 out of 22), and Labrador crosses (2 out of 22) were overpresented. Vitreal hemorrhage was shown to be associated with an increased time to reattachment; the mean time to reattachment was 18.2 days (range 4–51) for the eyes with no hemorrhage and 63.5 days (range 14–144) for eyes with vitreal hemorrhage (Andrew et al., 1997).

Treatment of the retinal detachments depends on the presence of a detectable underlying disease and both the cause and the extent of the detached area. Even extensive detachments may be reattached with return of vision provided that treatment is commenced early (Fig. 24.65). When a steroid-responsive exudative detachment is suspected, systemic steroids should be started as soon as possible after ruling out potential infectious and systemic causes for which systemic corticosteroids might be contraindicated. Failure to reattach leads to retinal degeneration and loss of visual capacity in the affected area. Further treatment options are discussed in Chapter 25.

PERIPHERAL CYSTOID RETINAL DEGENERATION

This is a common incidental finding in older dogs. The peripheral retina adjacent to the ora ciliaris retinae undergoes a cystic change leading to the appearance of multiple cystic structures that protrude into the vitreous (Fig. 24.66) (Bellhorn & Haring, 1974). These protrusions can be quite large in some dogs. Their peripheral nature means that they are unlikely to have any effect on vision.
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Figure 24.64. Steroid-responsive retinal detachment. In both cases, the condition was bilateral, and the dogs presented with a sudden-onset vision loss. Physical examination, blood work, and serology failed to find an underlying etiology. Both dogs were treated with systemic steroids and regained vision. A. On ophthalmoscopic examination, the retina can be seen ballooning forward in the vitreous as a semilucent gray membrane with superficial vessels. It remains attached at the optic nerve head and is thrown into a fold ventral to the optic nerve head. The tapetum is seen through the detached retina in the dorsal fundus. B. Complete bullous retinal detachment. The retina can be viewed directly through the pupil as a gray membrane with superficial vessels that are thrown into folds and is adjacent to the posterior surface of the lens. Preretinal hemorrhages are present. (Illustration supplied by Michigan State University Comparative Ophthalmology Service.)

Figure 24.65. This eye had previously had a complete bullous retinal detachment. It had been steroid responsive and reattached. There are pigmentary changes that have resulted from the chorioretinitis that induced the detachment. There is a resolving hemorrhage on the optic nerve head.

Figure 24.66. Peripheral cystoid retinal degeneration in a dog. The peripheral retina has a number of cystic protrusions into the vitreous running circumferentially at the peripheral edge of the neurosensory retina.

RETINOSCHISIS

Retinoschisis is a splitting of retinal layers that occurs in humans as either an inherited disorder or an acquired condition. The splitting of retinal layers can progress to retinal detachment, and the inherited form can impair vision. A histological diagnosis of secondary retinoschisis was reported in an 8-month-old English Springer Spaniel with retinal detachment and glaucoma (Schuh, 1995).

NEOPLASTIC AND PROLIFERATIVE CONDITIONS

Granulomatous Meningoencephalitis (GME) (Reticulosis)

Granulomatous meningoencephalitis (GME) is an idiopathic, nonsuppurative, inflammatory disease of the CNS that can affect the eye. The disseminated form of GME has been previously described as inflammatory or granulomatous reticulosis, whereas the focal form was previously described as neoplastic reticulosis. GME is characterized by the proliferation of
Primary Tumors

Primary tumors of the retina, choroid, and optic disc are very rare in the dog.

Astrocytoma

Tumors of astrocytic origin are rarely reported in the dog (Caswell et al., 1999; Dubielzig, 1993; M. eyerholz & Haynes, 2004; Naranjo et al., 2008). Immunohistochemistry aids in the possible identification of astrocytomas because of their positive staining for glial fibrillary acidic protein.

Medulloepithelioma

Primary intraocular neuroepithelial tumors are divided into two groups: neoplasms derived from mature neuroepithelium and neoplasms derived from primitive medullary epithelium. Neoplasms from mature neuroepithelium include adenomas and adenocarcinomas, which develop from the ciliary epithelium. Tumors derived from primitive medullary epithelium are thought to originate from embryonic neuroepithelium of the posterior segment of the eye and the anterior uvea. Sporadic cases of canine ocular involvement have been reported from different parts of the world (Fischer & Lice, 1971; Garmer et al., 1981; Rubin, 1974; Smith, 1995).

Perivascular infiltration of mainly histiocytes and mononuclear white blood cells forming cuffs around blood vessels in the CNS, posterior segments of the eyes, and uveal tract have been described histopathologically. Silver-stained sections have shown a whorled pattern of reticulin fibrils around the vessels (Garmer et al., 1981; Smith, 1995).

Ocular signs may develop before CNS abnormalities. The disease is usually bilateral, but the extent of involvement varies. Papillitis and peripapillary edema have been reported to be the single ophthalmoscopic sign in blind patients. Various secondary ocular disease processes may be found depending on localization of the inflammatory lesions. Infiltration of the uveal tract has been reported to cause uveitis, and retinal detachment may be found secondary to choroidal involvement. Secondary glaucoma caused by obstructed flow of aqueous humor through the pupil by posterior synechiae or exudates has been reported as has glaucoma secondary to obliteration of the aqueous outflow pathways.

Vision may be improved temporarily in dogs presenting with papillitis through treatment with corticosteroids (Garmer et al., 1981; Smith, 1995). The prognosis for vision, however, and even for long-term survival, is considered to be very poor.

Choroidal Melanomas

In the dog, intraocular primary melanomas typically arise in the anterior uvea, and the choroid is usually involved through extension from the anterior uvea. Melanomas with their origin in the choroid are less frequently detected (Aguirre et al., 1981; Collinson & Peiffer, 1993; Dubielzig et al., 1985; Morgan & Patton, 1993; Ryan & Diter, 1984; Schoster et al., 1993; Weiss et al., 1985). Choroidal melanomas are generally described as darkly pigmented masses arising from the choroid underlying the tapetum lucidum, most typically adjacent to or near the optic disc (Fig. 24.67 and Fig. 24.68). The tapetellar cells may be absent in the area of tumor development. To date, most reported primary melanomas of the choroid have tended to be clearly demarcated, raised, subretinal masses, with some showing similarities to a uveal nevus in humans.

Histopathologically, large, round, plump cells predominate. Plump or thin spindle cells may also be found, as well as small epithelioid-type cells. The tumors are generally considered to be benign because of the lack of mitotic figures.
vascular invasion, and nuclear anaplasia. Extension of the tumor into the optic nerve and retrobulbar tissue, however, has been reported (Collinson & Peiffer, 1993; Schoster et al., 1993).

Obvious clinical signs are reported to be rare, but infiltration beneath the retina can lead to retinal detachment and hemorrhage. Secondary glaucoma may result from obstruction or closure of the iridocorneal angle by pre-iridal fibrovascular membranes.

**Ocular Melanosis**

Ocular melanosis in Cairn Terriers manifests as a proliferation of melanocytes predominantly involving the anterior uvea and sclera, which leads to a secondary glaucoma. However, the characteristic plump pigment-laden cells are present histologically within the retina and choroid of dogs with advanced disease. Close monitoring of affected dogs reveals that there is a slowly progressive posterior segment pigmentation that leads to a reduction in tapetal area due to the pigmented cells encroaching over the tapetal area (Fig. 24.69) (Petersen-Jones et al., 2007).

**Secondary Tumors**

Tumors may involve the posterior segment by extension from a primary focus in the anterior segment, optic nerve, or extraocular tissues, or by metastasis from a more remote site. Clinical signs usually develop late in the disease, thus delaying both detection and diagnosis. Signs may include intraocular hemorrhage, uveitis, glaucoma, and blindness. With metastatic tumors, systemic signs may be present and the ocular findings incidental.

Tumors located outside the eye may cause signs suggestive of posterior segment disease, such as retinal detachment and blindness. Cases have been reported in which tumors affected the optic nerve, optic tract, or visual cortex, thereby causing visual impairment, or in which serum hyperviscosity secondary to plasma cell myelomas is followed by retinal detachment (Davidson et al., 1991; Hare, 1993; Sansom & Dunn, 1993).

**Metastatic Tumors**

Metastatic neoplasms in the choroid and retina are often incidental findings, and their ophthalmoscopic appearance and clinical course vary. Several tumors and sites of origin have been reported, including mammary gland adenocarcinomas, thyroid adenocarcinoma, renal adenocarcinoma, malignant melanoma, hemangiosarcoma, rhabdomyosarcoma, neurogenic sarcoma, and pheochromocytomas (Barron et al., 1963; Bellhorn, 1972; Cello & Hutcherson, 1962; Crow et al., 1995; Fidler & Brodey, 1967; K rhone et al., 1994; Ladds et al., 1970; Nyska et al., 1992; Szymanski, 1972). Tumors that metastasize to the anterior uvea may also extend to involve the retina and choroid.
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SECTION III

Lymphomas

Malignant lymphoma, usually affecting both eyes, seems to be the most common secondary intraocular tumor. Ocular involvement has been reported to be the second-most consistent presenting sign (after lymphadenopathy) in dogs affected with multicentric lymphoma (Krohne et al., 1994). Involvement of the choroid and the retina is noticed infrequently, but signs from the posterior segment may sometimes be masked by the more frequently observed changes in the anterior segment (Cello & Hutcherson, 1962; Peiffer et al., 1976; Saunders & Barron, 1964; Whitford, 1965).

Ophthalmic signs depend on whether the anterior or posterior segment (or both) are involved. Krohne et al. (1994) detected posterior uveitis in 3% of dogs with multicentric lymphomas, panuveitis in 5%, and retinal hemorrhages in 9% (Fig. 24.70). Flame-shaped retinal hemorrhages are considered to be the earliest ophthalmoscopic sign. In more advanced stages, alterations in tapetal color occur, and papilledema may be present. Generally, systemic involvement precedes or accompanies intraocular disease, although dogs with intravascular lymphoma may present initially with only ocular changes (Cullen et al., 2000; Kilrain et al., 1994).

Microscopic changes vary with the tissue affected. Tumor cells in the choroid, especially in the tapetal fundus, contribute to the color changes. There can be extensive invasion of tumor cells in the retina and the optic disc as well.

Malignant angioendotheliomatosis (i.e., malignant intra-vascular lymphoma) is a proliferation of neoplastic lymphocytes from the vascular bed. Dogs with this condition may present with only ocular changes, and the systemic nature of the condition may only become apparent later. Affected dogs may present with ocular changes including bilateral subretinal hemorrhages and retinal detachments (Cullen et al., 2000; Saunders & Barron, 1964) and only show systemic signs later in the disease. Histopathologic examination reveals multifocal, intravascular proliferation of large, pleomorphic mononuclear cells within the lumen of blood vessels of affected organs.

REFERENCES


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During the past 15 years, an increasing number of veterinary ophthalmologists entered an area of ophthalmology that for many years eluded them: posterior segment surgery. Previously, posterior segment surgery was performed mainly for procedures such as vitreocentesis for diagnostic procedures, vitreous injections for endophthalmitis therapy, anterior vitrectomy associated with persistent hyperplastic primary vitreous (PHPV), or retrieval of intravitreal lens fragments. Surgery for rhegmatogenous retinal detachments (RRDs) was attempted by relatively few veterinary ophthalmologists, who were no longer content with restoring vision solely through anterior segment surgery. They wanted to join those "peculiar" individuals in human medicine who were willing to spend long hours on seemingly hopeless cases. Instead of dealing with predictable procedures that restore sight, they became eager for the challenge to prevent blindness. As Gini (2004) so aptly said it, "The vitreoretinal [surgeons like] the challenge of this type of surgery. They are conscious that there is an enormous difference between restoring sight and having no sight at all."

The level of animal care has risen to new heights. Animal owners are no longer willing to accept that their pets lose vision when the retina detaches after a cataract surgery or lens luxation or because of inherited conditions such as vitreous degeneration, retinal dysplasia, or Collie eye anomaly (CEA). The use of a retinal prosthesis in humans is gaining momentum and at some point will cross over to the canine species, necessitating posterior segment surgeons in the veterinary community to employ this new technology (Chow et al., 2004; Hetling & Baig Silva, 2004; Liu et al., 2003). In addition, the development of gene therapy has made great advances in the treatment of inherited retinopathies. Success has already been achieved in some animals (Acland et al., 2001; Ali, 1996; Bainbridge et al., 2003). The vitreoretinal surgeon will play an important role in future research and development of this exciting therapy.

ANATOMIC CONSIDERATIONS

Knowledge of the anatomy of the posterior segment is crucial to understanding proper surgical technique. Thus, the specific segments involved with vitreoretinal surgery are briefly discussed.

Vitreous

The vitreous body is the most important intraocular tissue in the pathogenesis of retinal detachment (RD). It is the gel that fills the vitreous cavity and is in contact with the retina, ciliary body, lens zonules, and posterior surface of the lens. Physically, it is composed of salts, proteins, and hyaluronic acid contained in a network of insoluble protein fibrils (Balaza, 1994; Eisner, 1995). These collagen fibrils are arranged randomly within the gel. They are most dense along the posterior lens capsule (hyaloideocapsular ligament), a circumferential area attached to the pars plana and peripheral retina (vitreous base), and along the vitreoretinal interface, especially around the margins of the optic nerve. The vitreous is attached to the retina via collagen fibrillar insertions into the internal limiting membrane, which is formed by the fused terminations of Müller cells (Balaza, 1994; Eisner, 1995). The fibrillar network of the vitreous is attached or anchored in a basal lamina (basement membrane), which is tightly attached to the cell membrane of Müller fibers (Balaza, 1973). In the canine, the vitreous has been described as being of the "nuclear type," in which the central vitreous is dense and the peripheral cortex is semifluid (Eisner & Bachmann, 1974; Tolentino et al., 1965). This is just the opposite of that in humans, in which the center is more fluid and the cortex is denser.

The vitreoretinal interface formed by the outer surface of the vitreous cortex and the internal limiting membrane of the retina contribute to the pathogenesis of RRD. Normal vitreous exerts traction where it adheres to the retina; whenever
It appears to be associated with the lens-induced uveitis (LIU) that accompanies the hypermature cataract. This type of uveitis can result in vitreous retraction. These vitreous changes along with the inflammatory changes in the retina, such as obliteration of peripheral retinal vessels, thinning of the retina, formation of retinal cysts, pigment proliferation in the choroid, and retinal and choroidal atrophy, create circumstances that predispose to RRD (Banker & Freeman, 2001).

Proliferative vitreoretinopathy (PVR) is an important pathologic change seen with RRD and is probably the largest single factor resulting in the failure of human retinal reattachment surgery (Retina Society Terminology Committee, 1983). The basic pathologic process in eyes with PVR is the growth and contraction of cellular membranes on the posterior vitreous surface, and within the vitreous base, both in contact with the retinal surface (Lagua & Machemer, 1975; Machemer & Lagua, 1975; Rice & Wilkinson, 1997a). A full-thickness retinal break and release of retinal pigment cells into the vitreous base are probably necessary for the development of clinically significant PVR. Laboratory animal experiments and clinicopathologic correlations have shown pigment epithelial cells, glial cells, macrophages, and fibroblasts in these epiretinal and subretinal membranes (Lagua & Machemer, 1975; Machemer & Lagua, 1975; Rice & Wilkinson, 1997a). A full-thickness retinal break and release of retinal pigment cells into the vitreous base are probably necessary for the development of clinically significant PVR. Laboratory animal experiments and clinicopathologic correlations have shown pigment epithelial cells, glial cells, macrophages, and fibroblasts in these epiretinal and subretinal membranes (Lagua & Machemer, 1975; Machemer & Lagua, 1975; Rice & Wilkinson, 1997a). A full-thickness retinal break and release of retinal pigment cells into the vitreous base are probably necessary for the development of clinically significant PVR. Laboratory animal experiments and clinicopathologic correlations have shown pigment epithelial cells, glial cells, macrophages, and fibroblasts in these epiretinal and subretinal membranes (Lagua & Machemer, 1975; Machemer & Lagua, 1975; Rice & Wilkinson, 1997a).
PVR occasionally occurs in the dog. It is rarely seen with spontaneous RRD. It has been reported in the Labrador Retriever with RRD associated with oculoskeletal dysplasia (Blair et al., 1985a). We have also seen canine PVR associated with lens surgery and, most notably, trauma. PVR can be seen in dogs with RD secondary to full-thickness retinal holes after transscleral laser retinopexy (Fig. 25.4).

**Intrascleral Plexus**

The vascular intrascleral plexus (circle of Hovius) is a network of veins that receives aqueous drainage (Fig. 25.5). This venous network, which is 4–5 mm wide, is situated 3–4 mm from the limbus, precisely in the area where surgical sclerotomies are placed. Judicious cautery is needed to avoid serious bleeding before penetrating the eye. It is not uncommon to induce additional bleeding during insertion of instruments through sclerotomies or during closure, necessitating additional cautery.

**TYPES OF RETINAL DETACHMENTS**

Retinal detachment is the separation of the neurosensory retina from the underlying retinal pigment epithelium (RPE). A RD can be either rhegmatogenous or nonrhegmatogenous (non-RRD). In an RRD, fluid from the vitreous cavity enters the subretinal space through a break in the retina. A non RRD
can be either primary or secondary. Primary RRDs are spontaneous and are not the result of trauma, inflammation, surgery, or other specific ocular disorder. Primary RRDs are preceded by alteration or degeneration of the vitreous, which predisposes the retina to detachment. The most common type of primary RRD is retinal dialysis or giant retinal tear, seen frequently in the Shih Tzu. In this breed, the retinal dialysis or giant retinal tear is thought to occur after vigorous head shaking and is predisposed to by vitreal syneresis or liquefaction. A retinal dialysis is distinguished from a giant retinal tear. When a retinal dialysis occurs, the neurosensory retina tears away from the pigmented ciliary epithelium at the ora ciliaris retinae. A giant retinal tear involves 90 degrees or more of the retinal circumference, with attached vitreous gel to an anterior flap of retina. These tears usually progress from a dorsal RD and then to a complete RD, resulting in a retina that hangs in a veil-like configuration attached at the optic nerve (see Fig. 25.2). A nether form of primary RRD occurs in instances of optic nerve coloboma where there is a separation of the retinal layers at the junction of coloboma and normal retina, which allows fluid from the vitreous space to enter the subretinal space. This phenomenon has been documented in the CEA (Vainisi et al., 1989). Other types of primary RRDs include atrophic retinal holes or tears. Secondary RRDs are the result of trauma, glaucoma, lens surgery, aggressive laser retinopexy, or surgery involving the ciliary body or ora ciliaris retinae, the most prominent of these being cataract surgery (Hendrix et al., 1993).

Non-RRDs are classified as serous or tractional. A serous non-RRD occurs without a break in the retinal tissue and results from fluid accumulation in the subretinal space between the photoreceptors and the RPE. Serous non-RRDs are further specified as either inflammatory or exudative, although this distinction is now clouded by the fact that permeability factors that lead to exudation below the retina may possess proinflammatory influences heretofore unknown (Adamis & Shima, 2005). Tractional non-RRD occurs when there is a pulling force (band or membrane) in the vitreous that forces the retina to separate from the RPE.

FACTORS RESPONSIBLE FOR RETINAL DETACHMENT

Although the exact mechanism of RD in the dog is unknown, it is assumed that, as in humans, canine RD can be ultimately attributed to retinal tear formation, exudation, or traction (Green, 1985; Kanski & Gregor, 1994).

Postoperative Phacoemulsification

Cataract surgery is one of the most common causes of RD in the dog (Gelatt et al., 2003; Hendrix et al., 1993; Schmidt & Vainisi, 2004; Vainisi & Wolfer, 2004). The exact incidence of RD after cataract surgery is unknown. However, in one study, the second most common histopathologic finding in eyes enucleated or eviscerated because of complications following cataract surgery was RD, present in 64% of the eyes studied (M oore et al., 2003a). In this study, 24% of all eyes had a retinal tear. The underlying cause of the RD was generally not histopathologically evident in most cases (Moore et al., 2003a). Interestingly, the incidence of the RD being noted on the clinical examination before enucleation was very low compared with the incidence of RD in these eyes in general, suggesting that RD after cataract surgery may be higher than is generally thought. Another retrospective clinical study found an incidence of RD after phacoemulsification of 4.7% in the first 23 weeks after surgery (Davidson et al., 1991a).

Patients that experience an alteration of the vitreous during cataract surgery (e.g., posterior capsular tear or vitreal hemorrhage) are at even greater risk of RD. Eyes that have previously had LIU are at greater risk of postoperative RD than eyes that have not. This finding is likely related to liquefaction or alteration of the vitreous base and/or cystoid change in the peripheral retina resulting from the iridocyclitis. Microcystoid or cystoid peripheral retina degeneration may cause weakening of the attachment of the retina at the ora ciliaris retinae. This, combined with dynamic contraction of the vitreous base, could predispose to a retinal tear with potential for complete detachment. This phenomenon most often results in a dorso-temporal giant retinal tear or dialysis (Fig. 25.6). In humans with retinal tears related to posterior vitreous detachment, the break is most often superior (Peyman & Schulman, 1994a). Breeds with rapidly progressive cataract formation, such as the Bichon Frise, Maltese, and American Cocker Spaniel, are more prone to LIU as immune tolerance to lens proteins is overcome. These breeds may be the most susceptible to RD due to LIU. Lens surgery in humans is generally recognized as increasing the risk of RD. Thus, in dogs that undergo any
Retinal Abnormalities

Retinal factors that predispose to detachment include genetic vitreoretinal dysplasias (Labrador Retriever and English Springer Spaniel), peripheral retinal thinning and microcystoid degeneration, atrophic retinal holes, and PVR. Vitreoretinal dysplasia results in areas of abnormally thin retina and holes which, combined with liquefaction of the vitreous, can lead to RD (Blair et al., 1985a, 1985b). Also, many dogs will concomitantly have abnormally developed vitreous with firmer retinal attachments.

Peripheral retinal thinning with microcystoid degeneration or retinoschisis, or both, allows for a potential weakening of the retina and/or the ora ciliaris, potentially resulting in a retinal tear and subsequent detachment. Retinoschisis has been observed by one of the authors (A.R.H.) in geriatric Italian Greyhounds. Atrophic retinal holes can occur spontaneously or because of trauma or other inflammation. Liquefaction of vitreous or vitreal traction on the edge of the hole can elevate the retina from the RPE and lead to detachment. PVR results when a full-thickness hole in the retina allows RPE cells to migrate into the vitreous space and form sheets or bands on the surface of the inner limiting membrane of the retina (see Fig. 25.4). Metaplasia of the RPE cells allows fibrous contraction to occur, lifting the retina into a detached state, and is characterized by retinal folding and rigidity (Kanski & Gregor, 1994, pp. 49–64). Treatment of RD with PVR has a lower success rate because of reformation of PVR bands. The authors of the chapter have used intravitreal vascular endothelial growth factor (VEGF) inhibitors preoperatively to address contractile membranes and to improve surgical outcome (Chen & Park, 2006).

Vitreous

As previously mentioned, the vitreous plays a major role in retinal attachment, and thus any changes in the status of the vitreous can lead to RD. Posterior vitreous detachment is a well-recognized predisposing factor for RD in humans (Sebag, 1989). Vitreous diseases are poorly understood in the dog; however, it is well recognized that vitreous liquefaction predisposes to RD, especially in certain breeds, such as the Shih Tzu. Vitreous degeneration is listed as a heritable disease in 11 breeds of dogs by the Canine Eye Registration Foundation and reported in 85 other breeds (Genetics Committee of the American College of Veterinary Ophthalmologists, 1999).

Trauma

Trauma is a common cause of RD in the dog. Penetrating trauma, including bite wounds, can result in infection, phacoemulsiﬁcation or intracapsular lensectomy for lens luxation, the potential is present for vitreoretinal disease. Risk factors for pseudophakic RD in humans include age, presence of RD in the fellow eye, increased axial length (myopia), lattice retinal degeneration, vitreous loss, and capsular integrity (Grand, 2003; Lois & Wong, 2003; Ramos et al., 2002; Ripandelli et al., 2003). Although it is readily accepted that cataract surgery and LIU contribute to the incidence of RD in dogs, no deﬁnitive study has been performed to elucidate the exact cause of the retinal tears in these cases.
in RD. Blunt trauma can result in a retinal tear, retinal dialysis, or both, with subsequent RD (Peyman & Schulman, 1994b). In cases of trauma with vitreal hemorrhage, the hemorrhage may be removed, either by treatment with intravitreal tissue plasminogen activator (tPA) or by vitrectomy, to prevent tractional RD. Early surgical intervention is important in cases of trauma prior to the onset of endophthalmitis, scleral or retinal necrosis, or PVR in dogs.

**Iatrogenic Causes**

Several forms of iatrogenic RD exist, usually related to either laser or cryoablation of the ciliary body for the treatment of glaucoma. It is also possible, if the surgeon is too aggressive, to cause RD during prophylactic laser or cryoablation of the peripheral retina before cataract surgery. These can be effusive in nature or, in the worst instances, can be related to full-thickness retinal holes and PVR. Inaccurate placement of needles for intravitreal injections or during retrobulbar injections can result in RD as well. In these examples, the retina can be pierced or the drug may be injected subretinally.

**Tractional Retinal Detachment**

Tractional RDs occur most commonly after membrane formation subsequent to a bleed into the vitreous cavity, or after the development of PVR secondary to a full-thickness retinal hole. Tractional detachments occasionally are seen with anomalous development of retinal vasculature associated with persistent hyaloid remnants. In canine cataract surgery, collectively we have noted complications that led to RD in the dog. Most common are posterior lens capsular rents with vitreous presentation, residual lens fibers leading to cortical regrowth, dropped nuclear lens fragments, or displaced IOLs. For those cases with cortical regrowth and RD, the patient history is often consistent. Patients have an uneventful recovery from cataract surgery and then present with severe LIU obscuring binocular indirect ophthalmoscopy. Aggressive therapy with anti-inflammatory medications is initiated, and when the inflammation is finally controlled, a RD is then viewed by the ophthalmologist. Because of this, it is recommended to perform ultrasound on patients that have significant postoperative inflammation that hinders the view of the retina. The cortical regrowth in these cases leads to tractional membranes and RD. Thorough removal of traction bands and lens material at the time of vitrectomy prevents recurrence of the RD and will allow for visualization during vitrectomy. The most common cause of tractional RDs in humans is diabetic retinopathy, and this type of RD is a result of preretinal fibrovascular proliferation (Regillo & Benson, 1999).

**Effusion**

Effusive RD occurs when fluid accumulates in the potential subretinal space elevating the retina away from the RPE. Effusive RD can be caused by immune-mediated, neoplastic, or infectious diseases. In all instances, the effusion results from a breakdown in the blood-ocular barrier, at the level of either the RPE or the retinal vasculature. Infectious causes include bacterial, fungal, viral, or rickettsial disease (Vainisi & Wolfer, 2004). Systemic hypertension in cats can also cause effusive RD because RPE necrosis occurs, breaking down the blood-ocular barrier. This breakdown leads to leakage of fluid, proteins, and fibrin from the choroid through the RPE and into the subretinal space (Crispin & Mould, 2001).

**Persistent Hyperplastic Primary Vitreous**

Persistent hyperplastic primary vitreous has been reported sporadically in a variety of breeds of dogs and as an inherited condition in the Doberman Pinscher (Stades, 1983) and the Staffordshire Bull Terrier (Leon et al., 1986). It is a complicated disease of the lens-vitreous-hyaloid system that results in a wide spectrum of disease, which can include RD (Boeve & Stades, 1999). If severe, PHPV can result in RD or retinal nonattachment. Not uncommonly, PHPV is a cause of leukokoria, often with cataract development. Surgery to restore vision can result in hemorrhage from the patent hyaloid vasculature, which in time can result in vitreous traction and RD (Bayón et al., 2001; Gemensky-Metzler & Wilkie, 2004). In humans, PHPV is often associated with severe optic nerve and retinal malformations (Goldberg & Mafee, 1983). The diagnosis and treatment of PHPV is discussed in Chapter 23.

**Endophthalmitis**

Endophthalmitis is an inflammatory response to ocular infection—bacterial, viral, fungal, or parasitic. The most common cause of endophthalmitis in the veterinary population is cataract surgery. Bacterial and fungal contamination of the anterior chamber is common during cataract surgery (Ledbetter et al., 2004); nevertheless, endophthalmitis is rare. Any form of intraocular surgery, such as lens luxation surgery, glaucoma filtering procedures, intravitreal injection, or vitrectomy can result in endophthalmitis. Trauma, especially cat scratch wounds or foreign body penetrations, can result in endophthalmitis. Endophthalmitis, if untreated, results in massive neutrophil migration and cellular proliferation with destruction of intraocular tissues. RD is a common complication of endophthalmitis. Treatment consists of appropriate topical, systemic, and intravitreal antibiotic and anti-inflammatory therapy. If the endophthalmitis is severe, complete vitrectomy may be a more appropriate therapy than antibiotics alone (Endophthalmitis Vitrectomy Study Group, 1995). One author (A.R.H.) has used the 27-gauge diagnostic vitrectomy system (Dutch Ophthalmic USA, Exeter, NH) for the treatment of endophthalmitis in dogs.

**Collie Eye Anomaly**

The CEA syndrome encompasses several manifestations, including chorioretinal hypoplasia, optic nerve colobomas,
RD, intraocular hemorrhage, and scleral staphyloma (Barnett, 1979; Roberts et al., 1966). This ocular anomaly occurs in the Rough and Smooth Collie (Sargan, 2001), Shetland Sheepdog (Barnett & Stades, 1979), Australian Shepherd (Rubin et al., 1991), and Border Collie (Bedford, 1982). Choroidal hypoplasia, the primary CEA phenotype, is inherited as an autosomal recessive trait with almost 100% penetrance (Lowe et al., 2003). As it relates to RD, the phenotype of interest in dogs with CEA is optic nerve coloboma. A defect has been shown to exist in the optic nerve coloboma or pit that directly communicates with the subretinal space and can allow fluid from liquefied vitreous to create an RD (Brown et al., 1979). The first successful treatment of serous RD in Collies involved transscleral diathermy of the affected area. Subretinal fluid was drained via the first or second diathermy puncture (Rubin, 1974). Serous RD due to optic nerve coloboma in the CEA syndrome is presently successfully treated, if detected before total RD, with transpupillary laser retinopexy (Fig. 25.7) (Vainisi et al., 1989). Xenon arc, argon, neodymium (Nd):YAG, or diode lasers may be used, although the diode laser will be less effective in poorly pigmented fundi. Intraocular hemorrhage seen with CEA usually is due to tearing of retinal vessels associated with RRD. The CEA may also cause RD due to vitreous hemorrhage from abnormal vessels in the coloboma or from PHPV (Tolentino et al., 1965). Unfortunately, Collies seen at very young ages that have complete RDs associated with colobomas or scleral ectasia have not been acceptable candidates for reattachment surgery.

**Lens Luxation**

Lens luxation predisposes the eye to RD. Lens instability causes a disruption in the anterior hyaloid face, causing disturbance of the vitreous and enabling the process of RD. Traction on the peripheral retina as the lens and vitreous move during luxation can cause tearing of weak areas of retina that can lead to detachment. The incidence of RD in humans ranges between 0.75% and 1.65% after phacoemulsification, 0.55%–1.65% after extracapsular cataract extraction (ECCE), and 0.4%–3.6% after intracapsular cataract extraction (Ramos et al., 2002). This implies that removal of the entire lens with subsequent disruption of the anterior hyaloid face, as in the case of lens luxation, increases the risk of RD. In a study by Hendrix et al. (1993), 15% of 46 dogs studied with RD presented with lens luxation or had been treated surgically for anterior lens luxation. Nasisse & Davidson (1999) reported that RD occurred less frequently if lens removal was accomplished early in the course of the disease. Adjunctive transpupillary retinopexy is believed to decrease the incidence of RD following lensectomy procedures.
Dropped Nuclear Fragments

In humans, three-port pars plana vitrectomy (PPV) is indicated if large (>25% of the nucleus) lens fragments are dropped through the posterior lens capsule during ECCE procedures; otherwise, serious sequelae, primarily intractable uveitis with retinal damage and/RD, are likely to occur. Retained lens fragments after cataract surgery cause secondary complications directly related to the volume of the retained intraocular material and the degree of manipulation used in attempting to remove the fragments (Wood, 1994). Efforts to manually retrieve or to flush such fragments forward with fluid from anterior segment incisions likely will create inflammation that leads to vitreoretinal traction or tears, both of which can result in RRD.

If lens fragments fall posteriorly into the vitreous, the surgeon should remove any lens material that can be easily obtained from the anterior segment and perform an anterior vitrectomy. Manipulation of lens material in the vitreous should be avoided or minimized because this will increase the inflammation and significantly increase the occurrence of RD (Wood, 1994). If the lens nucleus is rock hard (i.e., would not fragment with low power during PPV), retrieval can be performed using techniques to bring the lens forward, such as impaling with a needle or grasping with forceps, but again, these techniques carry a greater risk of creating retinal tears. A higher-concentration viscoelastic substance placed posteriorly may levitate a single lens fragment, but visibility can be challenging and may risk posterior segment trauma. Perfluorocarbon liquids (PFCLs) may facilitate the return of dropped lens fragments to the anterior chamber, but once injected, all fluorocarbon must be removed because of the potential retinotoxicity. Such removal is difficult to perform from the anterior segment.

A small fragment of lens material may be managed by close observation, with frequent topical and sub-Tenon’s injections of steroids, cycloplegic agents, and systemic anti-inflammatory medications. If inflammation or intraocular pressure (IOP) is not easily controlled in such cases, vitrectomy is indicated. If dropped fragments are greater than 25% of the nucleus, it is best to perform posterior vitrectomy in the same operation, after closure of the anterior incisions. Surgery is performed via a three-port pars plana procedure (discussed later), and the posterior vitrectomy is followed by fragmentation. During removal of lens fragments from the vitreous, it is best to remove as much vitreous as possible before attempting to draw up (aspirate), as inadvertent traction on the retina can result in RD (Eller & Berger, 2001). Low power (5%-10%) should be used to prevent the lens fragments from being blown onto the retina, and a second instrument can facilitate the direction of fragments to the phacofragmentopump (Wood, 1994). Whether lens fragments are retrieved immediately after their posterior displacement or in a separate vitreoretinal procedure, scleral depression at the conclusion of the procedure should be performed while still in the operating room. Thus, if retinal tears are identified, immediate intervention (e.g., laser or cryoretinopexy, or gas tamponade) can be performed. If no tears are identified, close postoperative evaluation of the peripheral retina should always be part of any follow-up examination, again to detect retinal tears or RDs at an early stage.

In humans, RD is a common complication in eyes that require PPV for retained lens fragments (Moor et al., 2003b), and visual acuity can also be affected by cystoid macular edema (Scott et al., 2003; Yang et al., 2002). Rapidity of intervention may enhance long-term results, indicating the need for immediate removal of the fragments or timely referral for PPV (Lai et al., 2000).

Posterior luxation of IOLs, either intraoperatively or as a postoperative complication, should be treated using PPV procedures. IOLs may be tolerated for long time periods in the vitreous without removal, but if inflammation, vitreal hemorrhage, retinal edema, or RD develops, surgical intervention is indicated. During retrieval, perfluorocarbons may be used to float the IOL anteriorly for haptic fixation (Liu et al., 1991) or removal. The human literature should be consulted for details on treating these complications; to our knowledge, no reports are found in the canine literature (Liu et al., 1991; Wood, 1994).

PROPHYLACTIC RETINOPEXY

Although there has been an increasing awareness that prophylactic treatment of normal fellow eyes in cases of spontaneous RD may be beneficial (Wolfensberger, 2000), it remains a controversial issue. In humans, the natural history of fellow eyes on nontraumatic giant retinal tears is characterized by a high combined incidence of retinal breaks and RDs in up to 60% of cases (Freeman, 2001). The results of a large human study on high-risk eyes have shown the benefit of prophylactic treatment. Retinal breaks developed in 27% of untreated eyes compared with 4% of treated fellow eyes (Freeman & Castilijos, 1981). In a study of 302 eyes with RRD, 205 fellow eyes were treated with argon laser (360 degrees, four radial rows) and followed up for 46 months. The incidence of bilateral RD was 2.4% in treated eyes compared with 11% in untreated eyes (Madelain & Turut, 1990).

In another study of 760 eyes with RRD, 350 fellow eyes had predisposing lesions and were given prophylactic treatment; RRD developed in 1.2% of treated eyes compared with 13.4% in the untreated group (Avitable et al., 2004). Despite numerous studies supporting prophylactic treatment for predisposed fellow eyes, the American Academy of Ophthalmology Preferred Practice Pattern does not strongly suggest prophylactic treatment of fellow eyes other than for symptomatic flap tears (Wilkinson, 2000). Although there may still be controversy in humans regarding prophylactic treatment, very few studies have been performed in the veterinary field. One such study compared treatment versus no treatment in the Bichon Frise with cataracts associated with LIU (Schmidt & Vainisi, 2004). Although the study consisted of only 57 dogs, it was statistically significant that prophylactic treatment is...
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beneficial. Of the 39 dogs that received prior laser photocoagulation retinopexy before surgery, RRD developed in 5 dogs (12%). In 18 dogs that did not receive treatment, 10 dogs (55%) experienced RRD.

Several studies reveal the risk factors as well as the breeds associated with RRD (Boydell, 1991; Curtis et al., 1991; Gelatt et al., 2003; Hendrix et al., 1991, 1993). Risk factors include cataract surgery, spontaneous cataract resorption, LIU associated with the previous two, lens luxation, vitreous degeneration, retinal dysplasia, and the CEA. Because of the frequency of RD after cataract surgery when LIU previously has occurred, either laser or cryopexy is recommended. A study of 46 eyes with RDs attributed 50% of the cases to lenticular disease or cataract extraction (Gelatt et al., 2003). More than 75% of the cataracts were hypermature and presumably had LIU. It is important to obtain ultrasonograms in eyes before performing retinopexy to be sure the retina has not already detached (Fig. 25.8). Because RDs occur frequently with luxated lenses or luxated lens surgery, we recommend retinopexy before surgery if possible or shortly afterward. In dogs with vitreous degeneration, especially certain breeds (Shih Tzu, Boston Terrier, Jack Russell Terrier, Italian Greyhound, Yorkshire Terrier, Maltese, and Poodle), there is a risk of developing giant retinal tears at the peripheral aspect of the retina, especially if the dog violently shakes its head while playing with toys. For some animals with geographic areas of retinal dysplasia, where the retina is extremely thin and there is associated vitreous degeneration, prophylactic retinopexy in the form of a contiguous barrier is advised. Labrador Retrievers affected with the oculoskeletal syndrome usually have larger globes, retinal dysplasia, cataracts, and vitreous degeneration and frequently experience RRD at an early age. We find it beneficial to perform retinopexy in these eyes as soon as possible, before the cataract worsens or the retina detaches. The reader should remember that perhaps the most important recommendation for prophylactic retinopexy should be the condition of the vitreous. One can consider the vitreous body as the silent protagonist in the drama of RD.

Procedure for Retinopexy

Retinopexy can be performed with either cryosurgery or laser. Cryosurgery is performed either transsclerally alone or combined with the indirect ophthalmoscope. Laser surgery is best performed in a transpupillary fashion with the indirect ophthalmoscope when possible or transsclerally when observation of the retina is not possible (Mehta et al., 2000). It is important not to give excessive treatment (photocoagulation or cryosurgery) because it can result in vitreous contraction or retinal holes and induce a giant retinal tear (Mehta et al., 2000).

When using the cryoprobe, the surgeon should treat the peripheral portion of the retina and not the ciliary body. In most dogs, this area is approximately 9 mm posterior to the limbus, except inferiorly and nasally, where it is 2 mm and 4 mm closer, respectively (Sullivan et al., 1997). We recommend 10 to 12 contiguous sites around the globe (Fig. 25.9). Care must be taken not to overfreeze because it may result in excessive retinal damage or even RD. Cryotherapy causes breakdown of the blood-retinal barrier with leakage of serum protein into the intraocular fluids; thus, excessive freezing can result in membrane formation (Jaccoma et al., 1985). It is


Figure 25.9. Cryopexy applications to the canine eye. (Copyright 2005, University of Illinois Board of Trustees. Used with permission.)
most cases. A gain, power and time setting will vary depending on the type of laser used, clarity of ocular media, degree of tissue pigmentation, and angle of incidence of the laser beam. Thinning of the peripheral retina can predispose to formation of a retinal hole during laser retinopexy.

The diode laser is preferable in eyes with media opacities because infrared light has the advantage of both transmission through lens opacities and vitreous hemorrhage (Isola et al., 2001). As diode laser energy can produce variable tissue effects, there may be some difficulty in obtaining reproducible burns because of change in melanin density of the retinal pigment epithelium and choroid. This is especially true in animals with a tapetum lucidum; therefore, laser settings must be adjusted to effect. This 250-mW setting is higher than that recommended by others (Pizzirani et al., 2003).

When using the transscleral probe before cataract surgery (in cases of LIU), one of the authors (S.J.V.) prefers to start at the 12-o’clock position approximately 9 mm from the limbus and give four to five burns directed toward the posterior pole (Fig. 25.11). This procedure is done clockwise around the globe, giving 75 to 85 burns depending on the size of the globe. As mentioned earlier, when retinopexy is performed inferiorly and nasally, treatment can begin closer to the limbus. Care should be taken temporally to avoid the area centralis. The transscleral probe is used on the conjunctival surface. The amount of energy and duration to produce a lesion may vary between probes; therefore, the surgeon should determine the wattage and time necessary to produce a lesion. If the conjunctiva is reflected, exposing the sclera, then less
The breaks are closed by bringing the edge of the tear in contact with the underlying pigment epithelium and choroid. This is accomplished by indenting the sclera, thus moving the choroid and pigment epithelium in contact with the torn or detached retina. The retinal break is then sealed by creating a chorioretinal scar. Vitreous traction is also relieved by indentation of the sclera. If one is unable to reduce the vitreous traction, other forms of vitreous surgery may be required. It is not uncommon to perform scleral buckles in combination with vitreous surgery.

Scleral buckling surgery for treatment of RRD in humans has for years been the gold standard and is still performed for most cases (Rice & Wilkinson, 1997b). However, in recent years there has been a trend to treat smaller tears first with intraocular gases and then proceed to scleral buckles if the former fails. Also, with the advent of newer, more efficient surgical equipment, many surgeons have switched to vitreoretinal surgery for repair of larger RRDs.

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Pneumatic Retinopexy

Pneumatic retinopexy (PR) was first described in human patients in the mid-1980s (Dominguez, 1985; Hilton & Grizzard, 1986); however, the technique using air for somewhat similar surgery had been described a half century earlier (Rosengren, 1938). PR involves the transscleral injection of gas into the vitreous cavity, combined with cryosurgery or laser retinopexy followed by positioning of the gas tamponade.
over the retinal break until a chorioretinal adhesion occurs. The technique was introduced as an alternative surgery to scleral buckling for retinal tears no larger than one clock hour located in the superior half of the peripheral retina. A more expertise was acquired, reports of PR for treatment of retinal tears in more than one quadrant, inferior tears, and giant retinal tears have been published (Chang et al., 2003; Irvine & Lokey, 1994; MacAllister et al., 1987; McElgen & Michels, 1994; Parver & Lincoff, 1978; Smith et al., 1997a; Tornambe, 1988, 1992; Tornambe et al., 1988).

The surgery is relatively easy and can be done as a single- or two-step procedure. It is usually an outpatient surgery; however, close observation is required for changes in IOP and retinal perfusion. Cryosurgery usually is performed around the area of the retinal tear before the infusion of gas, but freezing or photoagulation can be done as a second procedure after the gas bubble has reattached the retina. The patient must keep his or her head in the desired position for 10–15 hours a day for several days until the chorioretinal scar forms.

The most common gases used for PR are sulfur hexafluoride (SF6) or octafluoropropane (C3F8). The gases are nontoxic to the retina and have different expansile properties as well as length of duration in the eye. Furthermore, SF6 will double in volume within 36 hours and remain in the eye 10–14 days, and C3F8 will quadruple its volume within 72 hours and can persist 4–6 weeks. The expansion of the gases is not due to expansion per se but due to invasion of gases, notably nitrogen and oxygen from surrounding tissues. The time of most rapid expansion is during the first 6 hours after injection. If either gas is diluted with air (20% with SF6, 16% with C3F8), it will not expand but will probably persist in the eye longer than the pure concentration. In humans, usually 0.3–0.4 mL of SF6 or C3F8 is injected. A nonexpendable mixture is to be used. It is important to inject the gas shortly after positioning the dog. The gas (SF6 or C3F8) is injected. An injection of 0.3 mL of SF6 or C3F8 in people will expand to 1.2 mL and cover approximately four clock hours (Tornambe, 1988). We have injected both SF6 and C3F8 in dogs—usually 0.5 mL unless it is diluted; then 2–3 mL is used. Reports of PR surgery in the dog are scant. One case report in which PR was performed was a postcataract RRD with associated glaucoma. The retina detached again 6 days postoperatively (Smith et al., 1997a).

**Patient Selection**

Unless the surgeon is exceptionally skilled with PR surgery, it is best to confine cases to the classic-type RRD, that is, small retinal tears located in the superior eight clock hours (clock hours 8–4). Whereas small tears are immediately diagnosed in people, they are rarely diagnosed in dogs. By the time most RRDs are diagnosed in dogs, they have progressed to giant tears (over three clock hours). Patients who undergo PR need to be able to endure positioning of their head for many hours daily for several days. Although this is possible for most humans, it is impossible for dogs. One of the authors (S.J.V.) keeps dogs on heavy sedation for 2–3 hours after PR in order to keep the head properly positioned. Afterward, the dog receives sedatives or tranquilizers for several days in an attempt to limit activity. PR should be avoided in patients with elevated IOP, cloudy media, inferior or multiple retinal breaks, giant tears, or PVR. Phakes and pseudophakes, while acceptable patients, tend to have a poorer success rate in humans (Parver & Lincoff, 1978). This may be because of difficulty in viewing smaller tears located at the distal periphery, especially in pseudophakes that have some capsular opacities. In aphakic dogs, one of the authors (S.J.V.) has had difficulty maintaining the gas bubble in the vitreous cavity unless the pupil is made extremely miotic at the time of injection and maintained for 7–10 days after injection.

**Procedure**

Preoperatively, the pupil should be maximally dilated. Carbonic anhydrase inhibitors should be given to lower IOP. The anesthetized dog is placed in dorsal recumbency. If the eye is not soft, then globe massage should be performed. The eyelids and conjunctival fornices are antiseptically treated with povidone isopropyl (1%) solution. One surgeon has had endophthalmitis develop and recommends the 10% concentration (Tornambe, 1992). The dog’s head is then positioned so that the superior tear will be ventral to the injection site. Using the indirect ophthalmoscope, the surgeon treats the area around the retinal tear with contiguous applications of cryosurgery (Fig. 25.13A). It is important to indent the globe as much as possible in order to apply cryosurgery to the retina. If the eye is not soft enough to allow sufficient indentation, then it may be necessary to perform paracentesis. In aphakic dogs, one of us (S.J.V) will inject carbachol after applying cryosurgery, to induce miosis and help prevent gas from entering the anterior chamber. The disadvantage of this is the inability to examine the gas bubble before positioning the dog. The gas (SF6 or C3F8) is drawn from the gas cylinder into a tuberculin syringe attached to a Millipore filter. It is recommended that a pressure-reducing system be attached to the gas cylinder to allow the gas to be drawn at low pressure. High pressure from the cylinder can blow out the Millipore filter and render it useless in sterilizing the gas. A condom catheter can be attached to the cylinder or a step-down valve system can be used. We use rubber tubing directly attached to the cylinder and then attached to a double Millipore filter and syringe. It is important to flush out any air in catheters or tubing before accepting gas into the syringe. If a nonexpendable mixture is to be used, the proper amount of air should be added to the gas to achieve a 20% mixture. It is important to inject the gas shortly after preparation so it does not become further diluted with air. The injection should be made through either the inferonasal or inferotemporal pars plana depending on the location of the tear. The injection site should be farthest away from the tear. Inferonasally, this is approximately 3–4 mm from the limbus, while inferotemporally it is 5–6 mm. In dogs, the needle will pass through the intrascleral venous plexus (circle of Hovius) and even though the needle is extremely small, the surgeon should attempt to avoid large veins. The 0.5-inch (1.27-cm) 30-gauge needle is then placed perpendicular to the eye,
because they can migrate under retinal breaks and prevent reattachment (Fig. 25.14B). As the syringe is removed, quickly cover the injection site with a cotton-tipped applicator for several minutes to prevent escape of gas subconjunctivally. It is also helpful to slightly rotate the globe to move the bubble away from the injection site. Subconjunctival gas is not harmful unless a large quantity escapes. If fish eggs are present, tapping the globe with your finger or flicking the globe with a cotton-tipped applicator is usually helpful in coalescing the small bubbles. The animal can now be carefully rolled over and placed in sternal recumbency (see Fig. 25.13C). It is important to keep the head properly positioned as long as possible. The IOP should be monitored closely for several hours.

Two physical properties of gas, surface tension and buoyancy, are responsible for PR benefiting anterior retinal breaks. The surface tension of any gas is higher than any other substance in the eye and allows the gas to occlude the retinal break. Buoyancy provides the force that pushes the upper retina against the wall of the eye (DeJarn et al., 1985). Any subretinal fluid can then be resorbed via the pigment epithelium pumping action and the osmotic gradient of the choroid. Because gases expand at low atmospheric pressure, air travel

Figure 25.13. Pneumatic retinopexy in the dog. A. Contiguous applications of cryosurgery around the retinal tear. B. Injection of gas bubble in the eye. C. Gas bubble positioning against the retinal tear when the animal is in sternal recumbency. (Copyright 2005, University of Illinois Board of Trustees, used with permission.)

Figure 25.14. A. Improper gas injection resulting in “fish eggs.” B. Fish eggs migrating under retinal break. (Copyright 2005, University of Illinois Board of Trustees. Used with permission.)
is not advised until most of the gas has resorbed. Because of this restriction, SF₆ is more commonly used in humans. Although postoperative complications from PR are not common, a number have been reported in humans (Chen et al., 1988; Hilton et al., 1990; Kim & D’Amico, 2000). These include glaucoma, subretinal gas, vitreous hemorrhage, failed reattachment, new retinal tears, cataract, PVR, gas in the anterior chamber, and gas in the anterior hyaloid (canal of Petit). Similar complications could also happen in dogs. If bubbles end up in wrong places such as subretinally or in the canal of Petit, attempts should be made to remove them. If the bubble lies in the canal of Petit, it will appear sausage-shaped and immobile. It can be removed with a 30-gauge needle, without an attached syringe, placed within the bubble. If gas is subretinal (usually fish eggs), place the animal in dorsal recumbency and massage the globe where the break is with a cotton-tipped applicator in an attempt to release bubbles into the vitreous cavity. Complications encountered in the dog by one of the authors (S.J.V.) include glaucoma, subretinal gas, gas in the anterior chamber, subconjunctival gas, and failed RD.

In humans, the success rate ranges from 60% to 80%; however, with a second operation, a 99% rate can be achieved. A 2-year multicenter, randomized, controlled clinical trial comparing PR with scleral buckling had an overall reattachment rate of 99% for PR and 98% for scleral buckling (Tornambe et al., 1991). The study included second surgeries when needed. Another study of 302 consecutive cases by one surgeon reports a single-operation success rate of 68%, with 95% ultimately attached with additional surgery (Tornambe, 1997). As with any other surgery, PR has a learning curve, and results improve with experience, case selection, and improved surgical techniques. The single-operation success rate for Tornambe (1997) was 54% for the first 100 cases, 72% for the second 100 cases, and 78% for the last 102 eyes. He also reported that a 97% single-surgery success rate was achieved on selected cases if a 360-degree laser retinopexy was done before the PR. Although PR appears to be a simple surgery, the surgeon must be able to determine which cases are the best candidates and must be skilled in handling any complications that can arise. Cases that are not typically of the classic type of RRD are generally not recommended for PR. PR can repair more complex detachments, but the single-operation success rate will be lower (Tornambe et al., 1988). In 75 dogs treated with PR, one of us (S.J.V) had an approximately 60% success rate for short-term follow-up (6 months).

Pneumatic retinopexy has become widely accepted in North America as the treatment of choice for selected RRD: 87% of vitreoretinal surgeons perform the procedure (Ai & Gardner, 1993). Because most RRDs seen in dogs are giant tears and because most pet owners have to travel long distances to reach a veterinary vitreoretinal specialist, the tendency has been to do the surgery that offers the best chance of success. Thus, PR has never been given the clinical trial it should have. Hopefully, this will improve in the near future.

Demarcation and Barrier Retinopexy

Demarcation retinopexy is an attempt to halt a RD in progress. In humans, it has been helpful in stopping temporal rhegmatogenous detachments before the RD extends to the macula (Vrabec & Baumal, 2000). This “salvage retinopexy” in the dog can be used for vertical dialysis, either nasal or temporal, moving toward the optic disc (Vainisi, 2002). If one or two rows of laser burns are made along the leading edge of the RD (Fig. 25.15A, B), it is sometimes possible to stop the detachment. Surgeons should avoid aggressive laser treatment at the leading edge of the tear, and avoid a coalescing burn effect. Inadvertent laser treatment of an area of low-height retinal separation will incite thermal damage and accelerate the detachment. Barrier retinopexy has often been helpful on inferior and horizontal RDs, but not superior detachments, because gravitational forces usually overcome the adhesions. It is effective in treating serous RDs resulting from optic nerve pits or colobomas in the Collie breed (see Fig. 25.7A). In one study, a row of xenon photocoagulation burns adjacent to the optic disc (see Fig. 25.7B), when choroidal pigment was present, or around the serous detachment resulted in reattachment in all of 23 dogs (Vainisi et al., 1989).

Barrier retinopexy is generally indicated for small tears, retinal holes (Fig. 25.16A), or thin areas of retina associated with geographic retinal dysplasia (Fig. 25.17). A noncontiguous row of cryotherapy or photocoagulation treatments is placed around the affected areas (Fig. 25.16B).

Demarcation retinopexy has also been performed using diode endolaser in a series of 14 cases of partial RD detected on ultrasound prior to cataract surgery (Webb et al., 2008). After phacoemulsification, a posterior capsulotomy was performed to gain access to the retina. Other approaches included limbal with peripheral capsulotomy and pars plana sclerotomy. A curved or straight endolaser probe was used to create a double row of retinal burns, with an average energy of 0.3 W (Webb et al., 2008).

Vitrectomy for Giant Retinal Tears

As mentioned earlier, most RRDs seen in the canine are giant retinal tears or giant dialyses. These are circumferential breaks of 90 degrees (three clock hours) or more. In a series of more than 500 surgical cases with giant retinal tears, the tears were 270 or more degrees in approximately 75% of cases (Vainisi & Wolfer, 2004). These RDs are too far advanced to benefit from demarcation or PR and thus require vitrectomy.

Criteria for Vitrectomy

The duration of the RD is important in predicting any anticipated return of vision. In humans, determining the duration of the detachment is not a problem, but in animals, the timeline of events is often unknown. A stote owners will notice acute vision loss in their pet. In most spontaneous RDs in dogs, one retina has been detached long term, and only when the fellow retina detaches is the owner aware of a visual problem. The
fellow retina might also be partly detached for weeks or even months before completely detaching and producing obvious vision problems.

In humans, if a return of 20/20 visual acuity is to be achieved, the retina must be reattached within 7–9 days. Studies on nonhuman primates have shown considerable retinal degeneration after 1 week of RRD. Surgical reattachment, however, results in prompt reversal of the disorganized retina (Kroll & Machemer, 1969a, 1969b).

In the dog, in a previously published series on giant retinal tear repair (Vainisi & Packo, 1995) and in our series of surgeries for treatment of giant tears (Vainisi & Wolfer, 2004), it

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was observed that if the retina is reattached within 4 weeks, there is a reasonable chance of return of some functional vision. Giant RDs that have remained partly detached for months appear to recover quite useful vision after being reattached. Obviously, the sooner the repair, the better the odds of good vision. Dogs whose retina has been detached for less than 1 week are more likely to have vision within days of surgery, compared with those dogs with a more chronic detachment, which may take 3 weeks or more for sight to be restored. Histopathologic findings of an eye with a 360-degree RRD of approximately 2 weeks’ duration in a dog that died shortly after reattachment surgery showed loss of photoreceptors on the superior retina, with preservation of the inferior photoreceptors (Fig. 25.18). This is typical of most spontaneous RRDs in the dog: the superior retina detaches first, then the inferior retina. These surgical cases generally require 2–3 weeks before owners report a return of vision. A positive pupillary light response is a good sign; however, it can be misleading because it is not uncommon in certain cases to see a good pupillary light response in retinas that have been detached for several months. Electroretinograms (ERGs) have not been reliable indicators in determining cases suitable for surgery. We have operated on numerous cases in which the ERG has almost been extinguished and the patient still recovered useful vision. Studies on nonhuman primates with RRD revealed an abolished ERG within 1 week. After reattachment of the retina, the ERG gradually returned within 1 week and continued to improve (Hamasaki et al., 1969).

Fortunately, PVR is not commonly seen in most cases of canine RRD. It has been reported in the Labrador Retriever breed with oculoskeletal dysplasia (Blair et al., 1985a). We have encountered it in some breeds, namely the Italian Greyhound, in long-standing detachments. If PVR is present, the prognosis for surgical success is reduced. Reproliferation of contractile membranes is common in dogs and humans and may ultimately lead to redetachment of the retina. Any signs of inflammation or elevated IOP must be treated. Operating on an inflamed globe is almost certain to result in failure or serious complications. Although gonioscopy is controversial for predicting glaucoma, we suggest it be performed, as it may be helpful in planning postoperative care. Dogs that undergo vitreoretinal surgery are at greater risk of glaucoma and must be monitored postoperatively. Corneal scars, synechiae, and capsular opacities can all interfere with proper visualization. Postcataract surgeries, especially in pseudophakic eyes with
capsular opacities, are more difficult and generally require removal of these opacities. Aphakic eyes in which silicone oil is used occasionally have a problem maintaining the silicone oil in the vitreous cavity. In cases in which vitreous opacities prevent full view of the retina, it is important to examine the vitreous-retina interface using B-scan ultrasonography to avoid potential damage to the retina. Also important is the health of the patient that will be subjected to a 2-hour surgery.

**Surgical Equipment**

An operating microscope with coaxial illumination and X-Y functions is needed. A beam splitter will give the assistant a coaxial view. Several different lens viewing systems work satisfactorily in the dog. The Machemer irrigating lens (Fig. 25.19A) as well as sew-on ring sets (Fig. 25.19B) can be used on the dog; however, these lenses are made for the human cornea, which is considerably smaller than the canine cornea. These lenses generally have only approximately a 30-degree field of view; thus, prism lenses need to be used to view the peripheral retina. Self-retaining silicone lenses, both wide-angle and prism-type, work well in the dog (Fig. 25.19C). We have successfully used all three types of lenses on dogs (Fig. 25.20A, B).

Wide-angle systems, either contact or noncontact, work very well on dogs but are more expensive. The wide-angle lenses give a panoramic view, between 90 and 130 degrees. These systems are based on principles of binocular indirect ophthalmoscopy and thus require an inverter to be mounted on the microscope. The SDI-BIOM (Insight Instruments, Sanford, FL) is an excellent wide-angle, noncontact system (Fig. 25.21A). An alternative to the SDI-BIOM system is the...
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are available to meet the budget of the veterinary ophthalmologist. Illuminating sources, electrocautery, air infusion units, ultrasonic fragmentation, and silicone oil pumps are built into these units (Fig. 25.22A). Most present-day vitrectomy probes (20, 23, and 25 gauge) are small, pneumatic, and disposable; however, some are electric with only the tip disposable. New vitrectomy probes have a guillotine-type cutter on the side of a blunt tube. Most cutters operate at 1500–2500 cuts per minute, but some currently attain speeds of 5000 cuts per minute. With the faster cutters and using less vacuum pressure, there is a lower risk of drawing the retina into the tip, causing iatrogenic tears. The newest technology includes integrated lasers, intraocular tonography at the infusion port, ability to titrate the duty cycle, and halogen.

Figure 25.21. Wide-angle viewing systems. A. SDI-BIOM (Insight Instruments, Sanford, FL). B. Eibos (Möller-Wedel GmbH, Wedel, Germany). C. Volk ROLS (Reinverter Operating Lens System) with Volk Mini Quad contact lens at right (Volk Optical, Mentor, OH). D. Volk Merlin noncontact system and associated lenses (inset).

Eibos (Möller-Wedel GmbH, Wedel, Germany). The Eibos is a noncontact, wide-angle viewing system, similar to the SDI-BIOM, which uses mirrors to invert the indirect image and therefore does not require a microscope-mounted inverter (Fig. 25.21B). This system is less expensive than the SDI-BIOM. The Volk wide-angle system (Volk Optical, Mentor, OH), which requires an inverter, is inexpensive and works well on animals. It is a contact system with a large lens, thus requiring an assistant to help secure the lens in position (Fig. 25.21C). Volk also has a noncontact system (Optiflex/Merlin) with detachable condensing lenses to switch between 80- and 120-degree viewing (Fig. 25.21D).

There are numerous vitrectomy machines available, and with the constant updating of these units, many older units
and mercury light sources (Fig. 25.23A, B). This new technology offers 20-, 23-, or 25-gauge probes (Fig. 25.24A, B). These units are very expensive but will become more affordable as demonstrator models become available. Although 20-gauge vitrectors have been the mainstay for veterinary surgeons, 23-gauge and 25-gauge vitrectors are now available and will be discussed later in this chapter. Diagnostic vitreous sampling can be performed with a 27-gauge vitrectomy system, which has recently become available (Dutch Ophthalmic USA, Exeter, NH).

### Light Sources

Halogen and metal halide light sources have been used extensively for vitreoretinal work. More recently, xenon illumination has been introduced as a brighter and more powerful source to improve visualization, particularly for smaller-gauge vitrectomy (23 and 25 gauge). The newer vitrectomy units (see Fig. 25.23A, B) have a built-in xenon or mercury vapor light source. Xenon is a “whiter” light source. Mercury vapor light decreases the risk of phototoxicity for prolonged procedures. Additionally, optional integrated color filters can be employed. Some surgeons are better able to visualize the vitreous using a yellow filter, and traction bands using a green filter.

### Laser Technology

Newer vitrectomy systems are equipped with integrated laser systems. Veterinary vitreoretinal surgeons can also have a separate diode or argon laser console. One surgeon (ARH) employs the argon laser for vitreoretinal work in breeds with less retinal pigment or with subalbinism. Several options are available when choosing laser probes. These include a tapered probe for ease of entry, an adjustable curvature to the probe tip manually operated at the handpiece, combined laser and aspiration probe, and white light illumination surrounding the laser spot for better visualization. Micropulse technology (Iridex IQ810, Iridex Corporation, Mountain View, CA) is recently available to replace continuous-wave energy. This minimizes thermal damage to the adjacent retina, while still creating chorioretinal adhesion.

Other equipment and accessories necessary for vitreoretinal surgery include microvitreoretinal (MVR) blades (20 gauge), high-viscosity infusion tubing (4 or 6 mm cannula), scleral plugs and plug holder, electrocautery sets, endocautery, vitreous scissors and forceps, silicone soft-tipped 20-gauge cannula, Charles flute needle and handle, PFCLs, and silicone oil (1000–5000 centistokes). If not integrated in the vitrectomy machine, then adjustable illumination, air, and cautery systems will be needed.
There is a wide variety of vitreoretinal surgery accessories depending on the surgeon’s preferences and best surgical approach for the case. Options include an illuminated infusion cannula, adjustable curvature to the light pipe, illuminated vitrector, and an irrigating light pipe.

Most canine vitreoretinal surgeons now place valved (Fig. 25.25A, B) or nonvalved cannulas (Fig. 25.25C, D) for ease of entry and exit, and to minimize surgical trauma. Valved cannulas control for hypotony, which can lead to choroidal hemorrhage, particularly in the dog.

It is best to place all instrument consoles (vitrectomy machine, laser, etc.) on an instrument table at the foot of the patient (Fig. 25.26A) so that all lines can be draped in a sterile fashion over the patient and be easily accessible to the surgeon (Fig. 25.26B). Another instrument table with surgical instruments and supplies is located alongside the surgeon and assistant. Surgical preparedness is essential to time efficiency and success of the surgery.

**Vitreous Substitutes**

Canine postoperative mobility (i.e., head shaking and inability to keep the eye in a fixed orientation) increases the need for a long-term vitreous substitute that can, either alone or in
Figure 25.25. A. 20-gauge valved cannula system (Dutch Ophthalmic USA, Exeter NH). B. 20-gauge valved cannulas placed in the canine eye (Dutch Ophthalmic USA, Exeter NH). C. Trocar placement of 23-gauge cannulas (Alcon Laboratories Inc, Fort Worth, TX). D. Canine eye prepared for vitrectomy with 23-gauge cannulas and closure valves (Alcon Laboratories Inc, Fort Worth, TX) and a self-retaining silicone lens (Dutch Ophthalmic USA, Exeter NH).

Figure 25.26. A. Instrument table setup for canine vitreoretinal surgery allows easy access to instruments for surgeon. B. All lines are placed over the patient.
combination, close both superior and inferior retinal breaks. In addition, because of the complicated and large nature of RRD in the dog, both intraoperative and postoperative use of vitreous substitutes is highly beneficial for successful vitreoretinal surgery in this species.

**Perfluorocarbons**

Previous experience with PFCLs as artificial blood replacements suggests these compounds are biologically inert (Koester & Lutz, 1980; Meyer et al., 1992). These properties have led to investigations of their use as vitreal substitutes. PFCLs have unique physical properties that facilitate complex vitreoretinal surgery, including low viscosity, transparency, immiscibility with water, biologic inertness (and thus nontoxicity), and a specific gravity (1.73–2.03 g/cm³) higher than that of saline (Doi & Refojo, 1994; Millsap et al., 1992). Because PFCLs are clear, with refractive indices similar to that of water, minimal optical aberrations occur when working through the liquid, and conventional vitrectomy contact lenses may be used. An interface can be visualized between the PFCL and saline, and visualization of this interface facilitates complete removal of the PFCL from the eye, thus reducing the incidence of residual droplets. The PFCLs currently in use are perfluoro-octane (PFO), perfluorotributylamine, perfluorodecalin, and perfluorohydrophenanthrene.

The characteristics of PFCLs make them a useful surgical tool for intraoperative or short-term retinal tamponade. They can flatten a detached retina intraoperatively as well as float posteriorly displaced lens fragments or IOL implants. Use of PFCLs to help flatten and unroll complicated RRD with a giant retinal tear is well established (Augustin et al., 1995; Bryan et al., 1994; Eller & Berger, 2001; Han et al., 1994; Millsap et al., 1992). Because PFCLs are clear, with refractive indices similar to that of water, minimal optical aberrations occur when working through the liquid, and conventional vitrectomy contact lenses may be used. An interface can be visualized between the PFCL and saline, and visualization of this interface facilitates complete removal of the PFCL from the eye, thus reducing the incidence of residual droplets. The PFCLs currently in use are perfluoro-octane (PFO), perfluorotributylamine, perfluorodecalin, and perfluorohydrophenanthrene.

The specific gravity of PFCLs is almost twice that of water, thereby providing a tamponade force far greater than that of silicone oil. This characteristic makes it possible for PFCLs to flatten the retina intraoperatively, by displacing subretinal fluid anteriorly through the peripheral breaks and into the vitreous cavity. The interfacial tension of PFCLs tends to remain as one cohesive bubble. The low viscosity of PFCLs (0.8–8.0 centistokes at 25°C versus 1000–5000 centistokes at 25°C for silicone oil) allows for easy introduction and removal with small-gauge instruments.

**Silicone Oil**

Silicone oil is a polymer of several different molecular-weight polydimethylsiloxane chains. Its viscosity is related to the length of the polymer chain or chains, and thus its molecular weight (Hutton & Fuller, 1994). Silicone oil is available in different viscosities, of 1000, 1300, or 5000 centistokes. The 5000-centistoke silicone oil has been used in all reported canine cases except the cases that were performed with the 25-gauge vitrectomy system, in which 1000 or 1300-centistoke silicone oil was used. Intraocular silicone oil is used to provide long-term tamponade of the retina. Silicone oil has a specific gravity of 0.971 (less than that of water) and forms a buoyant sphere within the vitreous cavity, exerting a tamponade effect. The interfacial tension of silicone oil with water helps maintain an oil sphere. These properties result in a silicone oil bubble that floats toward the superior vitreous cavity. Failure to completely fill the vitreous cavity prevents proper tamponade of the inferior retinal surface, possibly leading to RD and/or retinal slippage.

The major indication for silicone oil in domestic species is giant retinal tears and RRD associated with PVR. In humans, conventional surgery is performed before considering silicone oil tamponade. This usually entails vitrectomy, membrane peeling, C3F8 gas tamponade, scleral buckling, or some combination (Cox et al., 1986; Hutton & Fuller, 1994; McCuen et al., 1985). Silicone oil usually is necessary in the dog, however, because this species represents a similar situation to uncooperative human patients. In the dog, use of silicone oil is a first choice, both because of the complexity and large nature of RRDs and because of the dog’s inability to stay immobile and maintain a designated head position for 18 hours a day. When silicone oil is used, it is important that all retinal traction be released and the retina be completely reattached before injection.

In humans, when silicone oil is used in aphakic and pseudophakic eyes, inferior peripheral iridectomy is required to help prevent glaucoma; alternatively, an inferior sector iridectomy or sphincterotomy extending the inferior aspect of the pupil margin may be used. Without iridectomy or creation of a flow route under the oil bubble, the silicone oil may block the pupil, thus resulting in aqueous misdirection or malignant glaucoma. This aqueous misdirection also leads to forward migration of the silicone oil and secondary keratopathy, which is seen clinically as corneal edema. Inferior peripheral iridectomy allows the aqueous to flow into the anterior chamber, avoiding this complication (The Silicone Study Group, 1992a). In the dog, pupillary block in pseudophakes and aphakes from silicone oil has not been a problem. However, if necessary, an inferior sphincterotomy would be a safer procedure than an inferior iridectomy. This can be done with the vitrector probe at the time of surgery.

Several complications have been documented with the use of silicone oil as a permanent tamponade in humans (Nakamura et al., 1990), rabbits (Chan & Okun, 1986), nonhuman primates (Lin et al., 2005), and dogs (Vainisi & Packo, 1995; Vainisi & Wolfer, 2004). These complications include silicone oil emulsification (Nakamura et al., 1990; Valone & McCarthy, 1994), anterior chamber migration (Vainisi & Packo, 1995; Vainisi & Wolfer, 2004), keratopathy (Choi et al., 1993;
limbus above the oil bubble (Fig. 25.28A) and continue injecting the viscoelastic until the oil bubble has been removed (Fig. 25.28B). Do not allow the eye to become hypotonic because hyphema may occur. One suture should adequately close the incision. Antiglaucoma therapy should be given for 24–48 hours.

In humans, silicone oil is generally removed 2–6 months postoperatively. Removal of silicone oil in humans helps avoid cataract formation, PVR, and to correct anisometropia. The rate of retinal slippage or redetachment after complete oil removal varies from 3% to 33% (The Silicone Study Group, 1992a, 1992b). There is, however, a gradual increase of RD over time in eyes with silicone oil retention compared with those in which the oil is removed (Hutton & Fuller, 1994). A follow-up study on silicone oil in humans revealed a significant likelihood of improved visual acuity in eyes in which the oil was removed, along with a slight increase in recurrent RRD (Hutton et al., 1994). The visual acuity retained in human eyes that receive vitrectomy and oil, with or without removal, is often no better than 5/200 (Hutton et al., 1994; McCuen et al., 1985; The Silicone Study Group, 1992a). This probably relates to the severe retinal disease and history of repeated operations rather than to a direct relationship to the use of silicone oil. We do not routinely remove silicone oil except in cases in which it continually escapes into the anterior chamber.

If necessary to remove silicone oil from the anterior chamber, it is best to wait at least 3 weeks to allow chorioretinal scars to form. The pupil should be made miotic before surgery. The dog is placed in ventral recumbency so the eye is vertical. The silicone oil bubble will float superiorly (Fig. 25.27A). If there is already considerable corneal edema or scarring superiority, place the dog in dorsal recumbency so silicone bubbles will float away from the scarred area (Fig. 25.27B). Using a 27-gauge needle, inject a viscoelastic into the inferior anterior chamber, slightly elevating the IOP. At the same time, make a 2- to 3-mm stab incision at the dorsal limbus above the oil bubble (Fig. 25.28A) and continue injecting the viscoelastic until the oil bubble has been removed (Fig. 25.28B). Do not allow the eye to become hypotonic because hyphema may occur. One suture should adequately close the incision. Antiglaucoma therapy should be given for 24–48 hours.

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Figure 25.27. Silicone oil in canine anterior chamber. A. Sternal recumbency. B. Dorsal recumbency when superior cornea is edematous or fibrotic.
act as a vitreous substitute. Thus, until studies become available to show the benefit of silicone oil removal in dogs, we believe it should be left in place.

The refractive index of silicone oil and vitreous differs (1.405 D and 1.336 D, respectively) and leads to refractive changes postoperatively. Hoffman et al. (2012) compared refractive errors with lens status (phakic, pseudophakic, or aphakic) and to the type of silicone oil viscosity in 63 eyes. Hyperopia was observed in all dogs that received silicone oil as a vitreous substitute. Thus, until studies become available to show the benefit of silicone oil removal in dogs, we believe it should be left in place.

The conjunctiva is incised 6 mm posterior to the limbus, reflected anteriorly, to expose the sclera, intrascleral venous plexus, and the anterior ciliary vein. One author (J.C.W.) performs a 180-degree peritomy right at the limbus and reflects the conjunctiva posteriorly. Relaxing incisions may be necessary at the three- and nine-o’clock positions. Closure of the peritomy is accomplished with two simple, interrupted sutures at the three- and nine-o’clock positions.

With the conjunctiva reflected, a 4-0 silk suture is placed around the horizontal rectus muscles. These sutures help control the eye and are important for repeated proptosis of the globe in case it should fall back into the orbit. A suture placed at the three-o’clock position is critical. Most ports are 5–6 mm from the limbus; however, in most cases, a temporal canthotomy is necessary. At the canthotomy 4-0 silk sutures are placed, to be tied after the proptosis to secure the globe in position. The surgeon grasps the globe with a fixation forceps while the assistant, using two muscle hooks, presses against the lids, gently proptosing the globe. Care must be taken that the canthal sutures are not too tight as to cause venous stasis but tight enough that the globe does not fall back into the orbit. If there is considerable venous congestion after proptosis, it is best to abort the proptosis. A rubber dental dam can be fitted over the prolapsed globe to ensure sterility. A transparent incise drape can also be used over the patient and table for better anesthetic monitoring. In cases in which the globe cannot be proptosed, a liberal canthotomy should be performed along with placement of a large speculum. It is helpful in these cases to place 4-0 silk sutures around the horizontal rectus muscles and attach them to adjacent tissue to partially elevate the globe. If a sew-on contact lens is to be used, the lens holder is sutured in place on the temporal and nasal sclera just posterior to the limbus.

A three-port vitrectomy is the routine approach to the vitreous cavity. The ports will penetrate the pars plana and thus will be placed 5–7 mm from the limbus. All ports may be placed superiorly (see Fig. 25.20A, B); however, one breed exception is the Siberian Husky. In this breed, the nasal pars plana is frequently very narrow (1 mm); thus, the ports may need to be placed temporally. To avoid the larger draining veins and allow for more room between working ports, the infusion cannula can be placed inferotemporally and is preferred by two authors (J.C.W. and A.R.H.).

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After adequate cautery of the venous plexus, a horizontal mattress suture of polyester fiber (5-0 Mersilene or 6-0 polyglactin) is preplaced for the infusion port. A 20-gauge MVR blade is passed between the sutures, and directed toward the center of the vitreous cavity, avoiding the crystalline lens. The flow is turned on for the infusion tubing to release any air, then shut off, and the tip secured in the port. A horizontal mattress suture of polyester fiber (5-0 Mersilene or 6-0 polyglactin) is preplaced for the infusion port. A 20-gauge MVR blade is passed between the sutures, and directed toward the center of the vitreous cavity, avoiding the crystalline lens. The flow is turned on for the infusion tubing to release any air, then shut off, and the tip secured in the port. A

Vitrectomy Surgical (20-Gauge) Technique

The patient is prepared as for cataract surgery, in dorsal recumbency with the head deviated medially. Sufficient globe exposure for a three-port vitrectomy can be difficult in many canine patients; therefore, an attempt should be made to propouse the globe. In the brachiocephalic breeds and in most mesocephalic breeds, the globe can be proptosed quite easily. Some brachiocephalic breeds are so exophthalmic that minimal eyelid pressure on the side of the globe will easily proptose it; however, in most cases, a temporal canthotomy is necessary. At the canthotomy 4-0 silk sutures are placed, to be tied after the proptosis to secure the globe in position. The surgeon grasps the globe with a fixation forceps while the assistant, using two muscle hooks, presses against the lids, gently proptosing the globe. Care must be taken that the canthal sutures are not too tight as to cause venous stasis but tight enough that the globe does not fall back into the orbit. If there is considerable venous congestion after proptosis, it is best to abort the proptosis. A rubber dental dam can be fitted over the prolapsed globe to ensure sterility. A transparent incise drape can also be used over the patient and table for better anesthetic monitoring. In cases in which the globe cannot be proptosed, a liberal canthotomy should be performed along with placement of a large speculum. It is helpful in these cases to place 4-0 silk sutures around the horizontal rectus muscles and attach them to adjacent tissue to partially elevate the globe. If a sew-on contact lens is to be used, the lens holder is sutured in place on the temporal and nasal sclera just posterior to the limbus.

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Figure 25.28. Removal of silicone oil from the anterior chamber. A. Injection of a viscoelastic agent inferiorly while a stab incision is made at the dorsal cornea. B. Continued injection of viscoelastic until silicone is completely removed. (Copyright 2005, University of Illinois Board of Trustees. Used with permission.)
the horizontal mattress suture is a figure-of-8 pattern tied with a slip knot. This allows rapid closure of the infusion port at the end of the surgery. It is important that the tip (cannula) is inserted through the pars plana in cases where the retina is not detached, before the infusion of balanced salt solution (BSS) is turned on to ensure it is not under the choroid or retina. If the globe is indented with the cannula, the tip should be visualized by the surgeon. The two other ports are made nasal and temporal to the infusion port approximately 160 degrees from each other. Narrower working distances decrease surgeon comfort and instrument range. The ports are closed with plugs until the surgeon is ready to insert the light pipe and the vitrectomy probe (see Fig. 25.20A), except where valved cannulas are used and fluid loss is less a concern. Using the nondominant hand, the surgeon inserts the light pipe into the globe. Instruments should always be directed posteriorly to avoid touching the lens. If a wide-angle viewing system (contact or noncontact) is used, inversion and focusing are now performed. The vitrectomy probe can now be inserted and vitrectomy started.

If a cataract is present, it is necessary to have it removed prior to reattachment surgery by the referring veterinarian, or it can be removed by the retinal surgeon as a dual procedure. For simultaneous cataract removal and PPV, routine phaco-emulsification can be performed before the eye is proptosed or via the pars plana approach with the phacofragmentome. The lens equator can be penetrated with the tip of the fragmatome needle, which is then placed in the center of the lens nucleus. With the use of high vacuum and low phacofragmentation power, first the nucleus is removed, then the cortex. If during phacofragmentation of the nucleus “lens milk” appears, especially in hard lenses, the phacofragmentation needle is probably plugged and must be removed from the eye and backflushed to clean the needle. If lens fragments accidentally fall posteriorly, they can be removed after the vitrectomy. The fragments can be attached to the phacofragmentation tip using only vacuum suction and then emulsified away from the retina. As mentioned previously, fragmentation should be done with low power (5%–10%) to prevent blowing fragments into the retina. Fluorocarbon liquids are also helpful in floating lens fragments for easier removal. Most canine vitreoretinal surgeons routinely perform cataract surgery with an anterior approach and IOL placement, and then proceed with three-port PPV.

RDs present commonly in canine patients that have undergone prior cataract surgery. When cortical regrowth or lens capsular opacities are present that prevent proper viewing, they must be removed. Soft cortical regrowth can be removed with the vitreotor but will be more difficult with small-gauge instrumentation. Dense capsular opacification often requires removal with end-gripping forceps (Fig. 25.29A) and scissors (Fig. 25.29B) designed to fit through variable-sized cannulas such as those made by Alcon/Grieshaber AG (Schaffhausen, Switzerland). Care must be taken not to disrupt the capsular integrity to the extent of causing IOL instability.

The eye can be easily manipulated with the two instruments. It is best to keep the light pipe just inside the globe at the edge of the pupil and directed posteriorly to optimally illuminate the vitreous cavity. Removal of the vitreous occurs in small pieces (Fig. 25.30A). It is desirable to keep the vacuum pressure low (below 150 mmHg), and when closer to the retinal surface, the vacuum pressure should be lowered further (to 80 mmHg). By increasing the cut rate and decreasing the vacuum pressure, there is less tendency to draw the retina into the tip. The cutting port on the vitrectomy probe should always face away from the retina. Vitrectomy probes have recently been engineered with the port opening 0.15 mm closer to the tip, enabling the surgeon to work closer to the retina. The duty cycle (time when the port is open) should be adjusted depending on whether the surgeon is performing the core vitrectomy or shaving the vitreous base or close to the retina. When cutting close to the retina, it may be necessary to keep the tip of the light pipe close to the vitrectomy probe to help prevent aspirating the retina into the cutter.

Approximating the vitrectomy probe and light pipe may help outline very clear, indiscernible vitreous. If it is difficult to identify clear vitreous, an injection of triamcinolone (0.1 mL plus 0.3 mL BSS) into the vitreous cavity will become suspended within the vitreous matrix, making identification easier. In most cases of giant retinal tears in dogs, there will

Figure 25.29. A. 25-gauge end-gripping forceps (Alcon Laboratories Inc, Fort Worth, TX). B. Tip design of vertical scissors (Alcon Laboratories Inc, Fort Worth, TX). C. 23-gauge intraocular scissors (Alcon Laboratories Inc, Fort Worth, TX).
be numerous blood clots mixed with the vitreous. It is more difficult to remove the peripheral vitreous (base) than the posterior vitreous, especially in the phakic animal. In these animals, it is best to cut the vitreous base and any torn retina on the same side as the port for the vitrectomy probe. This area can be illuminated indirectly in order to avoid touching the lens (Fig. 25.31); then the procedure is reversed for the opposite side. On a protruded globe, the surgeon can indent the sclera opposite the cutting port with his or her finger to bring the vitreous base in view. However, with this maneuver, care must be taken not to touch the large canine lens. A wide-angle viewing system is very helpful in removing the vitreous base; however, scleral depression may still be required. For more chronic RDs, the peripheral retina may be fibrotic and scroll inward. It is necessary to perform a peripheral retinectomy of the devitalized, fibrotic retina as it will not be amenable to flattening with PFCLs (Fig. 25.32).

Once the vitreous has been removed, the retina can be gently manipulated using the tip of the light pipe and the vitrectomy probe. Occasionally, a 360-degree RD will be rotated at the optic disc and require gentle rotation before attempting to flatten with PFCLs. As the retina is manipulated, one often will uncover retinal holes or radial tears (those that extend from the optic nerve and tear peripherally). For small tears or dialyses (less than 90 degrees), the retinal configuration will be released as long as a complete vitrectomy has been performed. As previously mentioned, more than 75% of canine retinal surgeries involve tears over 270 degrees; therefore, a PFCL will be needed to flatten and hold the retina in position.

The PFCL is injected slowly via a soft-tipped silicone needle over the optic nerve in the surgeon’s dominant hand (Fig. 25.30B, C). It is important to maintain the PFCL in a large bubble, especially if retinal holes or radial tears are present, in order to prevent subretinal migration. It also is important to inject the PFCL under any retinal flap in contact with internal limiting membrane. It may also be necessary to rotate the eye so the PFCL stays under the flap. This same rotational procedure is also needed when large retinal holes are present, to keep PFCL from entering the holes. If PFCL
migrates under the retina (sometimes occurring in multiple bubbles), it must be removed via a flute needle.

After PFCL injection, the retina should slowly begin to unravel and flatten against the eye wall. If there is resistance to the injection of PFCL, it is probably because of an incomplete vitrectomy procedure. At this stage, the vitrectomy probe is reinserted, and residual vitreous is removed. As the retina flattens, it is not uncommon to have folds still present. These can be gently flattened using the soft silicone-tipped needle (Fig. 25.33). If, during the PFCL infusion, membranes are


Figure 25.33. Flattening a retinal fold under PFCL, with a soft-tipped silicone sleeve, during canine retinal surgery.
noted that prevent the retina from flattening, PFCL infusion is stopped and the membranes are removed. Occasionally, a relaxing retinotomy is necessary to flatten the retina (see Fig. 25.32). This can be done with the vitrectomy probe, and endodacryotomy should be performed to avoid bleeding, but usually, this area of retina has poor viability. Endodacryotomy can be performed with unipolar diathermy along the path of the intended retinotomy. PFCL is often useful in this manner of membrane removal when it is difficult to stabilize the retina. As the retina is flattened, any fluid under the retina will be forced out anteriorly.

The eye is now ready for endolaser photoocoagulation. Either diode or argon lasers work well for laser retinopexy. Power and time settings should be set at the lowest settings needed to produce a burn. Settings will vary depending on the amount of pigment present, the angle of incidence required, and the precision of the focused laser light. Two rows of noncontiguous burns near the ora ciliaris retinae for 360 degrees are applied (Fig. 25.30D). Laser should be applied around all holes and tears as well as minimal scatter in all four quadrants. In subalbinotic animals, it may be necessary to apply cryosurgery transsclerally or to use an argon laser. The final step is to replace the PFCL with silicone oil (Fig. 25.30E) or with air. PFCLs are very toxic to the retina and therefore must be removed. For smaller tears, a PFCL–air exchange followed by an air–gas exchange can be done. A nonexpandable gas—either C3F8 or SF6 at nonexpandable concentrations (16% or 20%, respectively)—can be used.

For larger tears, silicone oil has been more helpful in preventing retinal slippage than has air. When the PFCL is exchanged with air, the edge of a giant tear can slip (slide posteriorly), creating a retinal fold. This slippage is produced by fluid collection behind the anterior retina that may not be fully attached by the PFCL. As more air goes in the eye, it forces the fluid more posteriorly, causing more slippage and folds (Abrams & Werner, 2001). In a reported series of retinal surgeries in the canine for giant retinal tears, stainless steel tacks were placed throughout the retina, choroid, and sclera near the peripheral retina in an attempt to prevent retinal slippage (Vainisi & Packo, 1995). Tacks have been used historically in human vitreoretinal surgery. In most cases, some or all of the tacks dislodged into the anterior chamber and had to be surgically removed by one of the authors (S.J.V.). We prefer a PFCL–silicone oil exchange for all large tears. Silicone oil (5000 centistokes) is injected through the infusion cannula using either a three-ring glass syringe or via an automated infusion pump. This PFCL–silicone oil exchange is a critical maneuver in the dog because any hypotony during this transfer can result in expulsive choroidal or retinal hemorrhages. The infusion tube is temporarily clamped, and the intravenous line of BSS is exchanged for the silicone oil syringe. The infusion line is opened, and the silicone oil injection is started (Fig. 25.30E). The Charles flute needle and handle are placed just above the optic disc and will passively evacuate the PFCL. A gain, in the dog, it is important to avoid hypotony during this exchange. The PFCL removal should be a passive process while the silicone oil is actively filling at a steady rate. The interface between the silicone oil and PFCL will become obvious as the PFCL becomes a smaller sphere over the posterior pole. After the silicone oil fills, it is important to examine the eye carefully to be sure all drops of PFCL have been removed (Fig. 25.30F). We prefer to use indirect ophthalmoscopy at this time to examine the entire fundus.

The nasal and temporal ports are closed first with 7-0 polyglactin sutures using a three-throw pattern; then the infusion port is closed with either a similar pattern or the figure-of-8 pattern previously discussed. The conjunctiva is closed with 7-0 polyglactin sutures, and the globe repositioned. After the canthotomy is closed, a subconjunctival antibiotic is given and a temporary tarsorrhaphy is placed. The tarsorrhaphy can be removed 1 week postoperatively. Corneal coverage is particularly necessary in brachiocephalic breeds with shallow orbits, as corneal erosions secondary to exposure are not uncommon.

Transconjunctival Sutureless Vitrectomy

Pars plana vitrectomy using sutureless incisions has been reported in the literature over the past 15 years (Chen, 1996; Fujii et al., 2002a, 2002b; Hilton et al., 2002; Jackson, 2000; Josephberg, 2003; Kwok et al., 1999; Milibak & Suveges, 1998; Rahman et al., 2000). Fujii et al. (2002a, 2002b) reported the use of a 25-gauge transconjunctival sutureless vitrectomy (TSV) system. Purported advantages of the sutureless, narrow-gauge system include less trauma to the eye, reduced postoperative inflammation, less astigmatism, greater patient comfort, and possibly a faster recovery (Ibarra et al., 2005). Sutureless vitrectomy may, however, present theoretical risks of postoperative vitreous incarceration, hypotony, endophthalmitis, or retinal traction (Lam et al., 2003; Meyer et al., 2003).

Newer techniques such as beveled incisions with linear trocars result in smaller incisions and have helped reduce the chances of wound leakage and bacterial entry. If it is obvious that a wound is leaking or may leak, then a partial-thickness suture should be placed through the conjunctiva and sclera.

The 23-Gauge Transconjunctival Sutureless Vitrectomy

One author (J.C.W.) uses this technique almost exclusively and employs the Eckardt 23-gauge TSV system (Eckardt, 2005). It is important to note that the infusion line and cannula will support infusion of 1300-centistoke oil. Other systems may not, and individual surgeons will need to bear this in mind when choosing a sutureless system. The steps for preparing the globe up to the point of entry into the eye are similar to the technique for standard 20-gauge vitrectomy. Once the eye has been proptosed, three 23-gauge working ports are placed 5-7 mm posterior to the limbus at approximately the 10-, 12-, and 2-o’clock positions. The first port at 12 o’clock is placed by slightly distracting the conjunctiva and entering the pars plana with the working port and trocar at an oblique
angle. Once the tip of the trocar has penetrated the sclera, the trocar is then moved perpendicular to the scleral surface and advanced into the vitreous cavity. This procedure creates a self-sealing wound. The trocar is removed from the working port, and the infusion cannula is placed into the working port. Scleral indentation is used to ensure that the cannula is not in the subretinal space, and the infusion line is opened. The 10- and 2-o’clock ports are then placed in an identical fashion. Use of self-sealing valves on the working ports ensures that hypotony does not occur during entry and exit from the eye. A 23-gauge light pipe is inserted through one working port and a 23-gauge vitrector through the other. Core and peripheral vitrectomy are performed in a standard fashion as described earlier in this chapter for the 20-gauge technique. Improved fluidics and vitreous cutting are inherent advantages of the 23-gauge system (according to J.C.W.) and diminish the chances of incarceration of retinal tissue into the vitrectomy cutter.

Once the vitrectomy has been performed, the vitrector is removed from the eye, leaving the light pipe in place. PFO (or other PFCL) is then injected through a 23-gauge infusion cannula placed through the working port vacated by the vitrector. Use of an infusion cannula with a soft silicone flange, will allow gentle manipulation of the retina as the PFO is infused. After the retina has been flattened in place, the infusion cannula is removed and a 23-gauge endolaser probe is inserted and a 360-degree, double-row laser retinopexy is performed. All retinal tears and holes are also sealed with the laser. The surgeon may have to move the laser from the 10-o’clock port to the 2-o’clock port to complete the entire laser procedure. Next, the infusion line is clamped, and the silicone syringe, attached to a viscous fluid pump, is attached to the infusion line. A 23-gauge Charles flute needle is then inserted through the trocar and the tip placed just above the optic nerve. Silicone oil is then infused, and PFO is passively vented through the flute needle. As in the 20-gauge technique, the PFO meniscus will become apparent and allow good visualization so that all PFO can be removed.

Once a complete vitreous fill is achieved, the working ports may be removed, starting with the 10- and 2-o’clock ports. A small amount of silicone may leak from the scleral wounds, and very light pressure with a sterile cotton-tipped applicator may be used to complete the seal. Applying too much pressure with the cotton-tipped applicator will actually damage the wound architecture and cause more silicone leakage. Next, IOP can be approximated with a sterile Barraquer tonometer with Terry calibration (Ocular Instruments, Bellvue, WA), and silicone oil added or removed by the viscous fluid system until IOP is between 15 and 20 mmHg. The infusion port is then removed.

In a variant of this technique, the right-hand working port is actually made as a standard 20-gauge sclerotomy, after a small conjunctival peritomy. This is done to allow the use of an electric high-speed vitrectomy handpiece, in the event that a high-speed pneumatic 23-gauge vitrector is not available. In this instance, it is important to place a scleral plug in the 20-gauge port before beginning the conversion from PFO to silicone oil. It is very important at this stage to prevent hypotony, so a slightly different maneuver is employed to seal the entire system before entering the eye with the flute needle. The viewing system is moved out of the way, so that the eye can be visualized directly on low power through the operating microscope. At this point, the entire system is sealed by the clamp on the working port and scleral plug. The clamp is then removed, and silicone is slowly infused into the eye. PFO and remaining BSS will passively be expelled through the valve on the 2-o’clock working port. Enough silicone should be infused to completely cover the back of the lens. At this point, the system is completely sealed by the silicone oil, and the 10-o’clock working port can be used without fear of hypotony. PFO–silicone oil conversion can now proceed as previously described. Closure then proceeds according to the discussion on 20-gauge vitrectomy. The 23-gauge technique provides excellent instrument handling within the eye and allows minimal disruption to the conjunctival tissues, which speeds healing and enhances patient comfort. In the opinion of two of the authors’ (J.C.W. and A.R.H.), 23-gauge vitrectomy is far more versatile and robust, compared with 25-gauge vitrectomy.

The 25-Gauge Transconjunctival Sutureless Vitrectomy

The 25-gauge TSV system employs working ports that are placed through the sclera and conjunctiva in a similar manner as that described for 23-gauge surgery. One of the authors (J.C.W.) has successfully used the 25-gauge TSV system to treat a giant retinal tear in a dog (Fig. 25.34). This system has some drawbacks—namely, expense and the more delicate nature of the instruments. However, in recent years, 25-gauge systems have become much firmer. Vitrectomy, PFO placement, and endolaser treatment is performed as previously
described. The authors have found use of chandelier-type lights (25-gauge Tornambe torpedo light; Insight Instruments, Sanford, FL) helpful in more fully illuminating the posterior segment. The PFO–silicone oil exchange method described earlier in this chapter does require some modifications for 25-gauge surgery. Lower-viscosity silicone oil (1000–1300 centistokes) must be used, as the 5000- to 5700-centistoke silicone oil is too viscous to be pumped through the narrow-gauge ports. Also, the oil must be pumped through one of the working ports because the 25-gauge infusion line cannot handle silicone oil, which necessitates using both working ports in the exchange process: one for silicone oil infusion and one for PFO venting. The chandelier-type light previously mentioned is especially helpful during this exchange.

The 25-gauge TSV system has replaced the 20-gauge TSV surgery for all but the most complicated retinal surgeries for many MD vitreoretinal surgeons. In dogs, the 25-gauge TSV system lends itself well to the treatment of vitreous diseases such as nonclearing vitreous hemorrhage, vitreal degeneration, and chronic endophthalmitis.

Endoscopic Pars Plana Vitrectomy with Perfluorocarbon Liquid (PFCL)/Silicone Oil Exchange

Endoscopic surgery is finding new purpose in the hands of the canine vitreoretinal surgeon. The endoscopic visualization lends a view of the posterior segment not possible with standard vitrectomy. The view can be described as “inside-out” as opposed to “outside-in.” We have likened standard vitrectomy to snorkeling with a face mask, and endoscopic vitrectomy to scuba diving.

Endoscopic vitrectomy can be used in the setting of anterior segment–based media opacities, which would diminish the surgeon’s view and restrict the ability to reattach the retina. Conditions that lend themselves to the endoscopic approach, because of a diminished view, are significant anterior or posterior synchiae, a pupil that will not dilate with mydriatics, endophthalmitis, corectopia, corneal melanosis, postoperative corneal grafts, or corneal mineralization.

The sclerotomy for the endoscope port requires a 19-gauge MVR stab incision. The probe moves three-dimensionally inside the eye and replaces the nondominant hand where the light pipe is typically held for standard vitrectomy. The straight endoscopic probe is recommended for vitrectomy work, as it is more intuitive to use. When using the endoscope, lighting levels are adjusted depending on the work performed. Higher illumination is needed when the endoscope is retracted. Low illumination eliminates whiteout on the video monitor and is ideal for closer work. Other variables beyond the X-Y-Z position to using a camera in the eye that contribute to the learning curve are the presence of torsion and vector distance. Once mastered, the surgeon can proceed with vitreous removal, PFCL injection, endolaser, and silicone oil fill with excellent viewing potential (Fig. 25.35). One author (A.R.H.) prefers 20-, 23-, or 25-gauge endolaser in the dominant hand for the retinopexy stage of surgery, as the laser from the endoscope creates excessive chorioretinal damage from the larger spot size.

SUCCESS OF RETINAL DETACHMENT REPAIR

Experimental Rhegmatogenous Retinal Detachment (RRD)

Experiments on RDs in the rabbit, nonhuman primates, and the cat provide some information on the retina’s ability to recover from detachment, which influences the functional success of vitreoretinal surgery. Studies in the rabbit showed that retinal degeneration occurs more rapidly if the retina is more elevated (i.e., bullous detachments) and when subretinal fluid is hemorrhagic or exudative (inflammatory) compared with serous (Erickson et al., 1983; Glatt & Machemer, 1982). Presumably, this relates to the limits of the diffusion of oxygen and nutrients from the RPE and lamina choriocapillaris through a subretinal space that is wider or is filled with exudates or red blood cells. Possibly most important to visual recovery is the duration of detachment (Erickson et al., 1983) and recovery of acuity (Guerin et al., 1989), with longer durations producing a progressive decline in final acuity. Results of experimental studies in animals support this latter finding.

In most species studied, the primary changes occurring in the first week after RD are marked outer segment degeneration, cystoid edema in the inner retinal layers, RPE dedifferentiation (i.e., truncation or loss of microvilli and disappearance of melanin), and hypertrophy of RPE cells (Anderson et al., 1983; Erickson et al., 1983; Guerin et al., 1989; Kroll & Machemer, 1969a, 1969b; Machemer & Norton, 1968). The owl monkey is a rod-dominant species with an area centralis but no fovea, which is somewhat similar to the situation in the dog and cat. After RRD in the owl monkey, most photoreceptor outer segments appear disorganized and degenerate within 1 week. Phagocytic cells move into the subretinal space to phagocytize the material, and by 4 weeks, cystic spaces are seen in the inner and middle retinal layers (Kroll et al., 1968).

Subsequent investigators using this monkey model studied the retina’s ability to recover after being detached for 4 weeks; they found that after surgical reattachment, prompt and progressive reversal of the atrophic and disorganized outer segments occurred, and that cystoid retinal spaces disappeared (Kroll & Machemer, 1969a). Marked loss of photoreceptor nuclei in the outer nuclear layer was not reported. In a Rhesus monkey model (a foveate species), similar changes were observed (Kroll & Machemer, 1969b). After 1 day of reattachment, outer segment material was regenerating, and by 1 month after RRD, the outer segment–RPE interface was often indistinguishable from control retinas. In other studies on macular detachment in Rhesus monkeys, good recovery followed RD that was relatively shallow and of short duration (1 week) (Guerin et al., 1989).
In the cat, retinas were surgically detached for 30 minutes to 14 months (Erickson et al., 1983). Results indicate the longer the duration and the greater the height of RDs, the greater the occurrence of cell death. By 1 hour after detachment, outer segment disorganization and early hypertrophic changes in the RPE were evident. By 2 weeks, most synaptic terminals were necrotic or in the process of retracting. After 4 weeks, the photoreceptor nuclei had decreased to approximately 40% that of control areas. At 50 days, synaptic contact between the photoreceptors and second-order neurons was essentially absent. Müller cells proliferated and hypertrophied to fill the spaces left after loss of nuclei in the outer nuclear layer. Müller cells also protruded into the subretinal space,

Studies in owl monkeys with RRD revealed that the ERG amplitude was abolished by 1 week after total RRD, but with partial RRD, some response could be elicited (Kroll & Machemer, 1969a). Retinas reattached after 4 weeks had a small ERG, which appeared as early as 17 hours but more typically approximately 1 week after reattachment. The b-wave amplitude and threshold progressively improved over the subsequent 12-week follow-up. The authors did not comment on whether values returned to normal, but examination of their data suggests that good recovery of b-wave amplitude occurred. All these findings in the owl monkey suggest that a fair prognosis may be given in the dog for a successfully reattached retina with an RD duration of 4 weeks or less.

In the cat, retinas were surgically detached for 30 minutes to 14 months (Erickson et al., 1983). Results indicate the longer the duration and the greater the height of RDs, the greater the occurrence of cell death. By 1 hour after detachment, outer segment disorganization and early hypertrophic changes in the RPE were evident. By 2 weeks, most synaptic terminals were necrotic or in the process of retracting. After 4 weeks, the photoreceptor nuclei had decreased to approximately 40% that of control areas. At 50 days, synaptic contact between the photoreceptors and second-order neurons was essentially absent. Müller cells proliferated and hypertrophied to fill the spaces left after loss of nuclei in the outer nuclear layer. Müller cells also protruded into the subretinal space,
achieving 20/50 visual acuity (Ferrone et al., 1994; Fiderman & Schubert, 1988; Lichter, 1988). On the other hand, our canine cases are usually first-time retinal surgeries. In those animals with RRDs secondary to vitreous degeneration (50% of cases), if operated on early (within 4 weeks), the surgeries are anatomically successful 90%–95% of the time, with a visual success rate of 85% (Fig. 25.36). For more complicated cases, such as those secondary to vitreoretinal dysplasia, occasionally seen with PVR or those secondary to cataract surgery or trauma, the anatomic success rate is closer to 80%, with a 70% visual success rate. The extent of globe trauma from bite wounds or blunt force varies considerably in dogs. It is not uncommon for us to see choroidal detachments with RD following trauma. For those cases, anatomic success is 50%, with a visual success rate less than that. In some cases, choroidal drainage may be necessary, which is approached via a scleral microincisional cut-down. In a reported series of more than 500 cases of canine RRD, a reattachment rate of 90% was achieved, with vision in 76% of animals (Vainisi & Wolfer, 2004). In two other large series of retinal reattachment surgery, reattachment rates of 95% and 99% were achieved, and vision returned in 73% and 90% of cases, respectively (Nadelstein, 2010; Steele et al., 2012). Onset of vision can occur as early as 24 hours or as long as several weeks after surgery. Most cases regain vision within 10–14 days. A gain, the sooner the reattachment is done, the better the chance of good vision. Because animals can adapt to their environment, we can only speculate that the range of visual success is anywhere from 20/100 to light perception. It has been reported that normal vision in the dog is approximately 20/65 (Miller & Murphy, 1997). Although some dogs appear to see normally postsurgically and both their fundus findings and ERG studies appear normal, it would be presumptuous forming layers of cell bodies between the RPE and retina. By 14 months, the retina appeared as an astroglial scar (composed of Müller cells), with no identifiable retinal cells being evident (Erickson et al., 1983).

Clinical Rhegmatogenous Retinal Detachment (RRD)

Successful reattachment of the retina does not necessarily imply visual success. In the earlier section “Criteria for Vitrectomy,” we mention that many of our patients, if their retinas are reattached within 4 weeks, have a reasonable chance of achieving some functional vision. We are referring to blind animals with giant tears, which are often 360 degrees. Four weeks is the time used arbitrarily, as we have no way of definitely knowing how long a dog’s retina has been detaching. Dogs can navigate well with limited vision. It is not uncommon for a veterinary ophthalmologist to encounter an owner who is unaware that his or her pet is blind since the dog can adjust to its environment. Many of our retinal cases have likely been detaching for weeks or months before the retina finally breaks loose and the animal experiences a sudden loss of vision.

Obviously, those animals whose retinas completely detach earlier than later should recover better vision after reattachment surgery. Human patients who receive the same type of vitreoretinal surgery we perform in dogs are usually complicated cases. They are frequently second or third surgeries with PVR, proliferative diabetic retinopathy, giant tears, or trauma. The vision before surgery is usually very poor, often hand motion or worse. Although the anatomic success is good in humans—well over 90% reattachment—the visual success is considerably lower, with only a very small percentage

for us to claim 20/65 visual acuity. The goal is for dogs to have functional vision, characterized by the ability to return to normal activity and have an improved quality of life. If they have their former personality restored and are able to recognize their owners, then we should be able to call the procedure a success.

**RETNAL PROSTHESIS**

Retinitis pigmentosa, and its variants, is one of the most common and, as yet, untreated forms of blindness. The canine and feline species also are commonly afflicted with heritable degenerations of the retina. Many gene defects have been discovered in the inherited retinal degenerations and are a common and devastating condition in both humans and canines that result in premature degeneration of the retina and loss of photoreceptors. In dogs, treatment of individual cases is not yet possible, and most of the effort to reduce the effect of these diseases has centered on genetic eye testing programs and selective breeding. Recently, gene therapy has been successful in reversing retinal degeneration in one form of heritable retinal degeneration in the dog (Aguirre, 2004; Ford et al., 2003; Narfstrom et al., 2003). Nevertheless, retinal degeneration remains a devastating disease that can have a huge emotional impact on humans and their pets alike.

Recent technological advances have made the concept of a retinal prosthesis possible. The first indication that the inner retina possibly could be stimulated even if the photoreceptors were damaged came about with the discovery of the electrical-evoked response (Potts et al., 1968). Stimulation of the retina with electric current produced the sensation of light (phosphenes) and elicited perception of light in patients with retinitis pigmentosa. Work was then done to document cortical visual activation by microelectrical stimulation of the retina (Humayun et al., 1995). This research has ushered in vast amounts of research into determining the best materials and the best anatomic placement of an artificial photoreceptor array. Much of this initial work has been animal based, using rats (Eckhorn et al., 2001), rabbits (Humayun et al., 1994; Nadig, 1999; Walter & Heimann, 2000), sheep (Kerdraon et al., 2002), dogs (Majji et al., 1999), cats (Hesse et al., 2000; Schanzle et al., 2002), and miniature pigs (Laube et al., 2003). It would be only fair, then, that this technology should someday benefit pets with retinal degeneration. In this spirit, we give a short overview of the fascinating advances that have been made in restoring vision to those with retinal degeneration.

The first report of the retinal prosthesis concept was by Humayun et al. (1994). They concluded that multifocal electrical stimulation of the retina might be possible to provide some vision to those with outer retinal degeneration. As well as the basic research done in animals to look at various anatomic and physiologic questions surrounding the use of a retinal prosthesis, early research was done in human volunteers that determined that light sensation could be achieved with electrical stimulation of the retina (Humayun et al., 1996). This technique has been improved, and testing has been done with permanently implanted microelectrode arrays (Humayun et al., 2003). At this time, there are basically two designs being studied: subretinal and epiretinal prosthetics (Margalit et al., 2002). With the epiretinal prosthesis, images are taken with a camera and then transmitted to an encoder, and the retina is then electrically stimulated by the epiretinal prosthesis. The epiretinal implant varies with the type of camera components and their location, either intraocular or extraocular (Loewenstein et al., 2004). With the subretinal implant, the microphotodiode array, driven by incident light, directly stimulates the outer retinal surface (Chow et al., 2004). When light is absorbed by the microphotodiode, it is converted to electricity. Each photodiode acts like an artificial photoreceptor receiving ambient light and converting it to an electrical response (Chow & Chow, 1997; Zrenner et al., 1997). The electrical response may then act to stimulate adjacent nerve cells, such as bipolar cells, and the impulse is forwarded via the optic nerve to the brain. Animal experiments with both types of implants have shown that local activation of the visual cortex can be achieved with stimulation currents and charge transfers that are in a biocompatible range. Initial trials in human subjects have shown that visual precepts can be achieved. It is hoped with this clinical approach that ambulatory vision can be restored to otherwise nontreatable degenerative diseases of the retina (Walter, 2004).

Despite intense competition and research, a working, long-lasting retinal implant does not seem to be on the immediate horizon. However, much of the recent research highlights how close this technology is to becoming reality. Because of its simplicity, if a functional subretinal implant ever becomes a reality, it would be the most practical prosthetic device for canine application. Our better understanding of how phosphene production in the retina by electrical stimulation translates into cortical activity is certainly encouraging (Eger et al., 2005; Schanzle et al., 2003). Ongoing research will evaluate safety and biocompatibility issues with retinal implants (Volker et al., 2004). Various other approaches are being examined and include a visual cortex prosthesis, suprachoroidal prosthesis, and direct optic nerve stimulation (Chowdhury, 2004; Fujikado, 2004; Xiaoyun et al., 2005).

**GENE THERAPY**

There is significant interest in the development of gene therapy to treat inherited retinal disease in humans, and some of the most significant research has been in the canine species (Bainbridge et al., 2003). It is conceivable that in the next decade, we will treat dogs affected with inherited retinal disorders via gene therapy. Already we have seen the successful treatment of a canine model of a human blindness, Leber congenital amaurosis (Acland et al., 2001). Recombinant adeno-associated virus vectors (rAAV) mediate sustained gene expression in both photoreceptors and RPE cells (Ali, 1996).
The technique for vector inoculation consists of a simple procedure involving a scleral incision, through which a 33-g needle is inserted into a subretinal position and the rAAV solution is injected into the subretinal space (Shen et al., 2003). It appears, however, that different rAAV serotypes have different specificities and that proper targeting of affected cell types in the different forms of retinal degeneration will require the use of specific serovars (Weber et al., 2003). Species differences also exist, and it was found that rAAV-mediated gene expression in the photoreceptor and RPE cells does not extend beyond the area of treatment (Bainbridge et al., 2003); however, gene transduction occurred in both rods and cones, and this finding extended to the feline species as well. It was also found in RPE65 mutation dogs that vision improvement after rAAV-RPE65 functioned in a volume-dependent manner (Ford et al., 2003). Postoperative inflammation has been seen in some animals, possibly related to an immune response to expressed green fluorescent protein (Bainbridge et al., 2003). Inflammation was found in a significant number of dogs in another study and was thought to be caused by the rAAV-RPE65 construct itself (Narfstrom et al., 2003). These findings have implications for the further study of gene-mediated treatment of both human and canine inherited retinal degenerations.

Interestingly, research has found a neuroprotective-rescue effect from erythropoietin (Epo) gene transfer in the rds/peripherin and light damage models of retinal degeneration. Most surprisingly, this effect was found after systemic but not after intraocular Epo gene transfer (Rex et al., 2004). The rescue effect was not found in the rd10 model of retinal degeneration, suggesting that the apoptotic mechanisms in various models are different. This finding may have implications in the future for the treatment of sudden acquired retinal degeneration in dogs.

The field of medical genetics holds great promise for the future treatment of inherited retinopathies, but many obstacles remain. Important considerations that must be addressed include evaluation of different rAAV serovars, testing of serovars to ensure that they are safe and long-lasting, regulation of gene expression, evaluation of vectors, appropriate case selection, and production of medical-grade vectors (Rolling, 2004).

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The optic nerve is not truly a cranial nerve but a white matter tract of the diencephalon composed principally of the axons of retinal ganglion cells (RGCs) (Brooks et al., 1999a). RGC axons project without synapses from the retinal nerve fiber layer (RNFL) through the optic chiasm and the optic tracts to either the lateral geniculate nucleus (LGN), the superior colliculus, the hypothalamus, or to the pretectal nucleus and other midbrain centers (Fig. 26.1) (Evans, 1993). RGCs and their optic nerve axons provide the sole connecting link between photoreceptors of the retina and the more central components of the visual system. The concentration of RGC axons into a single optic “nerve” results in the optic nerve being an extremely vulnerable segment of the visual pathway as, compared to other types of neurons in the visual system, there is little functional redundancy in the dog optic nerve due to the comparatively small total population of canine RGC (Enroth-Cugell & Robson, 1984). The ratio of RGC to optic nerve axons in the dog is one to one (Arey & Gore, 1942).

The optic nerve consists of four different regions (Jonas & Naumann, 1993). The intraocular optic nerve includes the RGC layer, the nerve fiber layer (NFL), the optic nerve head (ONH) or optic disc, and the intralaminar optic nerve region within the sclera. Posterior to the globe, the optic nerve consists of the intraorbital optic nerve, the intracanalicular optic nerve (within the optic canal), and the small in length intracranial optic nerve that merges into the optic chiasm (Jonas & Naumann, 1993). The optic nerves form the optic tracts between the optic chiasm and the LGN, and the optic radiations between the LGN and visual cortex (VC).

**INTRAOCULAR OPTIC NERVE**

**Retinal Ganglion Cells**

The RGC somata (Fig. 26.2) are found in the RGC layer located between the inner plexiform layer and the NFL. A macrione, interplexiform cells, and bipolar cells of the inner nuclear layer provide input to RGC. The RGC layer in the high acuity, cone rich, central retinal area of dogs is up to 3 ganglion cell layers thick, and is single layered in the thinner retinal periphery (Peichl, 1992a).

Retinal ganglion cells and Müller cells are the first cells to differentiate in the fetal retina (Jonas & Naumann, 1993; Mao et al., 2008). RGCs near the ONH differentiate earlier than peripheral RGCs. In cats, axons of the RGC begin to grow through the optic stalk on embryonic day 19 (E19) (Williams et al., 1986). The first RGC that makes a synaptic connection with the brain carry the neurotrophin brain-derived neurotrophic factor (BDNF) back to the RGC by retrograde axoplasmic flow (Nickells, 2007). Embryonic and fetal RGC do not initially require BDNF for survival, but all RGCs become dependent on BDNF once the first synaptic connections are made. Those RGCs that fail to synapse with appropriate targets in the brain subsequently die by apoptosis from neurotrophin deprivation (Nickells, 2007). Canine RGCs also contain ciliary neurotrophic factor receptor alpha (Beltran et al., 2005).

RGCs and their optic nerve axons are added at a rate of 50,000 per day until embryonic day 39 (E39) in cats at which a peak of 600,000–700,000 axons is reached. Four hundred thousand feline optic nerve axons are then lost between E-39 and E-53 (Williams et al., 1986). The final number of axons in the cat optic nerve is greater than 150,000 at 6 weeks postpartum (Williams et al., 1986).

The region of highest RGC density, smallest RGC dendritic fields, and greatest visual acuity in afoveate animals is in the central retinal area (Hebel, 1976; Krinke et al., 1981; Peichl, 1992a, 1992b; Rowe & Dreher, 1982). This RGC-rich region termed the visual streak in dogs is a horizontally oriented band of densely packed RGC located in the central retina immediately dorsal and temporal to the optic disc (Gonzalez-Soriano et al., 1995; Krinke et al., 1981; Peichl, 1992a, 1992b). The lowest concentration of RGC in humans and dogs is found in the peripheral retina (Table 26.1). (Anderson, 2005; Curcio &
Figure 26.1A. Generalized diagram of a mammalian optic nerve head and intralaminar optic nerve. Müller cell processes forming the retinal inner limiting membrane (1a) are in continuity with astrocyte processes that form the internal limiting membrane of Elschnig (1b) on the surface of the optic disc. Elschnig’s membrane becomes thickened in the center of the disc in some species to form the central meniscus of Kuhnt (2). The scleral border tissue of Elschnig (3) lies between the choroidal stroma and a collection of astrocytes surrounding the optic nerve bundles known as the border tissue of Jacoby (4). The border tissue of Jacoby is continuous anteriorly with astrocytes of the intermediate tissue of Kuhnt (5) at the termination of the retina. Axons are segregated by astrocytes anterior to the lamina into bundles (6) prior to reaching the lamina cribrosa (7). The optic cup, neuroretinal rim (NRR), nerve fiber layer (NFL), retinal ganglion cell (RGC) layer, choroid, sclera, and short posterior ciliary arteries (SPCA) are illustrated. Retinal ganglion cells with cell bodies located near the optic disc (A), midperipheral retina (B), and peripheral retina (C) send their axons (RED) to the central, middle, and peripheral regions of the optic disc and nerve, respectively. (Modified from Brooks D.E., Komaromy A.M. & Kallberg M.B. (1999) Comparative RGC and optic nerve morphology, *Veterinary Ophthalmology*, 2(1), 3–12.)

Figure 26.1B. Van Gieson stained image of the dog optic nerve head illustrates the prelaminar (PL) tissue thickness (black arrow), total lamina cribrosa (LC) thickness (blue arrow), optic nerve diameter at internal neural canal (green arrow), and optic nerve diameter 1 mm behind the posterior boundary of the lamina cribrosa (red arrow). Scale bar equals 400 mm. Courtesy and modified from Balaratnasingam et al. 2009.

Figure 26.1C. Van Gieson stained image of the human optic nerve head illustrates the large central retinal artery (star), prelaminar (PL) thickness (black arrow), total lamina cribrosa (LC) thickness (blue arrow), optic nerve diameter at internal neural canal (green arrow), and optic nerve diameter 1 mm behind the posterior boundary of the lamina cribrosa (red arrow). Scale bar equals 400 mm. (Courtesy of and modified from Balaratnasingam, C., Morgan, W.H., Johnstone, V., et al. (2009) Histomorphometric measurements in human and dog optic nerve and an estimation of optic nerve pressure gradients in human. *Experimental Eye Research*, 89(5), 618–628.)
central region in these breeds as compared to the wolf (McGreevy et al., 2004). Alpha RGCs have large somata (21–23 to 33–44 µm in central to peripheral retinal regions, respectively in dogs) (Peichl, 1992b), large dendritic fields (160–200 to 1100 µm in diameter in the central to peripheral retina, respectively in dogs) (Peichl, 1992b), large diameter axons, and are found in greatest density in the peripheral retina (Jonas & Naumann, 1993; Peichl, 1992b; Williams & Chalupa, 1983). Alpha-type RGC corresponds to the physiological or functional category of RGC, the “phasic” Y cells, the primate magnocellular or M cells, and to the primate parasol RGC (Rodieck, 1998). M-type RGCs have large retinal receptive fields, high conduction velocities (21 m/s), possess high temporal but low spatial resolution, are color insensitive, and predominate at scotopic light levels. (Jonas & Naumann, 1993; Shapley, 1993) M cells (luminance pathway) generally give the same type of response to all wavelengths of light (Shapley, 1993). Alpha RGCs generally represent a small population of the total number of RGCs being 3%–14% in dogs (Peichl, 1992b). There is a notable absence of alpha RGC in the temporal peripheral retina of dogs and wolves (Coli & Marroni, 1996; Peichl, 1992a). Large diameter neurons are extremely sensitive to metabolic alterations in their microenvironments that cause hypoxia and ischemia, tend to have poor regenerative capability in the peripheral nervous system, and are more sensitive to the effects of anesthetic drugs (Allcutt et al., 1984; Dawson et al., 1989) and to the effects of glaucoma (Glovinsky et al., 1991).

Beta RGCs have smaller diameter somata (14 to 21–30 µm in dogs from the central to peripheral retina, respectively) (Peichl, 1992b), smaller dendritic fields (25–360 µm in diameter in central to peripheral retina, respectively in dogs) (Peichl, 1992b), small diameter axons, and predominate in the central retina (Bunt & Horder, 1983; Minckler, 1980; Peichl, 1992a).

![Figure 26.2. Several normal beta-type canine RGCs are fluorescing with the lipophilic dye 4-di-10 ASP. (Original magnification, 200×.)](image)

Table 26.1 Retinal Ganglion Cells

<table>
<thead>
<tr>
<th>Species</th>
<th>RGC Density in Area Centralis (cells/mm²)</th>
<th>RGC Density in Peripheral Retina (cells/mm²)</th>
<th>Total RGC Count</th>
<th>Percent Alpha RGC</th>
<th>Percent Beta RGC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>5,300–14,400 (Gonzalez-Soriano et al., 1995; Krinke et al., 1981; Peichl, 1992a, 1992b)</td>
<td>1,000 (Gonzalez-Soriano et al., 1995)</td>
<td>115,000–167,308 (May, 2008; Peichl, 1992a)</td>
<td>4.1% in peripheral retina (Peichl, 1992b)</td>
<td>99% in area centralis (Gonzalez-Soriano et al., 1995)</td>
</tr>
<tr>
<td>Primate</td>
<td>32,000–38,000 near fovea (Cucio &amp; Allen, 1990)</td>
<td>350 at ora serrata (Cucio &amp; Allen, 1990)</td>
<td>1,070,000 (Cucio &amp; Allen, 1990; May, 2008)</td>
<td>10% (Shapley, 1993)</td>
<td>90% (Shapley, 1993)</td>
</tr>
<tr>
<td>Cat</td>
<td>8,900 (Stone et al., 1982)</td>
<td></td>
<td>193,000 (May, 2008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td></td>
<td></td>
<td>32,000–87,000 (May, 2008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td></td>
<td></td>
<td>72,371–113,000 (May, 2008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pig</td>
<td>4,285 ± 139 (Ruiz-Ederra et al., 2005)</td>
<td>239 ± 28 (Ruiz-Ederra et al., 2005)</td>
<td>442,629 (May, 2008)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1992b; Williams & Chalupa, 1983). They correspond to the physiological or functional category of RGC, the “tonic” X cells, the primate parvocellular or P cells, and the primate midget RGC (Rodieck, 1998). P-type RGCs in primates have small retinal receptive fields, high spatial frequency but low temporal resolution, slower conduction velocities (13 m/s), and conduct visual information concerning color, acuity, and spatial contrast sensitivity (Jonas & Naumann, 1993; Shapley, 1993). P cells (color pathway) respond depending on the wavelength of the stimulating light (Shapley, 1993). Beta RGCs are more common than alphas and represent the majority of canine RGCs (Peichl, 1992a). Dog alpha and beta RGCs are nearly identical morphologically (Peichl, 1992a).

Gamma RGCs are a heterogenous class of cells with several subtypes (Peichl, 1992b). They have small diameter axons (1 µm in cats (Williams & Chalupa, 1983), and rather slow axon conduction velocity (2–18 m/s (Williams & Chalupa, 1983). Gamma RGCs correspond to the physiological or functional category of RGC, the W cells. The gamma RGC group also exists in the dog, but limited information is available for this RGC type in dogs (Peichl, 1992b).

The spatial distribution and organization of RGC axons extends retinotopically through the NFL, optic nerve, optic chiasm, optic tract, LGN, and VC (Bunt & Horder, 1983; Jonas & Naumann, 1993). Visual fields are represented on the retina in a direct point-to-point relationship with the superior visual field projected onto inferior retina and the nasal field onto temporal retina. In general, this inverted relationship holds true throughout the anterior visual pathways of the optic nerve, optic tract, LGN, and VC (Bunt & Horder, 1983; Jonas & Naumann, 1993).

The axons of the RGC extend from their soma, perpendicular to the NFL, toward the vitreous, passing between the axons in theNFL, and then bend to enter theNFL to project toward the optic disc (Brooks et al., 1986). A xons from RGC near the ONH must project through the nerve fibers coming from peripheral RGCs to take a position in the more superficial peripapillary retinalNFL as the axons of RGC lying in the retinal periphery are deep in theNFL near the ONH (Jonas & Naumann, 1993; M inckler, 1980). A xons arising from RGC near the fovea and RGC central area are situated more centrally in the optic disc and nerve, while axons arising from RGC in the peripheral retina lie in the periphery of the optic disc and nerve (M inckler, 1980). Optic nerve axons from ganglion cells in the superior retina of avovete animals are found in the superior half of the optic disc, and axons from the inferior retina lie in the inferior half of the disc, with a similar pattern noted for axons in the nasal and temporal quadrants (Jonas & Naumann, 1993).

The nasal and temporal halves of the retina of carnivores are divided by an imaginary line called the vertical meridian that passes vertically through the cone-rich area centralis or fovea (Cooper & Pettigrew, 1979; Jones, 1985). RGC axons nasal to the vertical meridian cross at the optic chiasm to the contralateral LGN and VC, while axons from the temporal retina do not cross and project to the ipsilateral LGN and VC.

Retinal Nerve Fiber Layer

The NFL is composed of astrocytes, retinal blood vessels, Müller cell processes, and RGC axons (Jonas & Naumann, 1993). Retinal NFL thickness correlates with the distribution of RGCs and increases from the periphery toward the optic disc with theNFL thickest at the superior and inferior rims of the primate optic disc, and thinnest at the nasal and temporal rims. The mean ± SD of the dogretinalNFL thickness using scanning laser polarimetry was 141.69 ± 18 µm for normal dogs. The average retinal NFL thickness in the superior and inferior retinal quadrants was 148.03 ± 8.5 and 141.06 ± 8.73 µm, respectively, for normal dogs. The superior to nasal retinal NFL thickness ratio was 1.45 µm for normal dogs (Iwabe et al., 2007). The entire retinal thickness and NFL thickness measured by optical coherence tomography (OCT) were greater in the superior than in the inferior retina (198.7 ± 9.6 µm vs. 164.4 ± 6.4 µm, P < 0.0001; and 26.4 ± 1.6 µm, vs. 25.0 ± 1.9 µm, P = 0.0236, respectively) (Hernandez- Merino et al., 2011).

The Optic Nerve Head

The prelamellar optic nerve is known as the optic disc, ONH, or optic papilla, and is surrounded by the white, peripapillary scleral ring of Elschnig (Fig. 26.1) (Jonas & Naumann, 1993). Pigmentation and/or myelin obscure the view of the ring of Elschnig in most dogs. Optic disc shape varies according to species, the degree of myelination, and the number of axons. Myelin extends anterior to the canine lamina cribrosa to cover the surface of the optic disc and continues into the NFL beyond the edge of the scleral canal such that the shape of the dog optic disc may be circular, triangular, or irregular. The canine ONH is white to pink in color with a dark central spot being the physiological pit, a remnant of the hyaloid artery. In general, larger optic discs contain more nerve fibers than smaller discs (Are y et al., 1942; D. Brooks et al., 1995; Jonas & Naumann, 1993).

The predominant cell type in the ONH is the astrocyte as no RGC somata or Müller cells are present (M inckler, 1993; Netland et al., 1995; Veral & Hernandez, 1997). Astrocytes in the ONH function similarly to retinal Müller cells as they provide physical support, absorb excess extracellular potassium released by depolarizing axons, and store glycogen. The astrocyte cell processes isolate individual axons and axon bundles from the neural, vascular, and connective tissue elements of the ONH.

Pax2 is a paired box transcription factor known to play important roles in the development of neural tube, inner ear, eyes, and kidneys. It is also found in the canine peripheral retina in older dogs, and in the glial cells of the ONH and optic nerve (Stanke et al., 2010).

The Optic Cup

The intrapapillary region of the ONH is the area inside Bruch’s membrane at the scleral canal, and consists of the neuroretinal
“cupping” is associated with advanced glaucoma in humans (Jonas & Naumann, 1993) and dogs (Brooks et al., 1986). Optic nerve “cupping” occurs due to axonal loss, laminar plate compression, rotation of the scleral insertion zone posteriorly, outward bowing of the lamina cribrosa, and a widening of the scleral canal behind Bruch’s membrane. The associated enlargement of the ONH cup with these laminar and axonal changes is unique to glaucoma, and not found in other optic neuropathies (Anderson, 1995a; Quigley, 1995a). The viscoelastic connective tissue and myelin in the NFL anterior to the canine lamina cribrosa appears to inhibit and obscure the detection of early increases in optic cup size in dogs with early glaucoma (EG) that are found in humans with glaucoma.

The Neuroretinal Rim

The neuroretinal rim is the intrapapillary equivalent to the NFL (Jonas & Naumann, 1993). The neuroretinal rim is larger in large-sized primate ONH (Jonas & Naumann, 1993). Nerve fibers in the rim are retinotopically organized (Arey et al., 1942; Hebel, 1976). The neuroretinal rim becomes narrowed as RGC and axons are lost in glaucoma (Jonas & Naumann, 1993; Shields & Spaeth, 2011; Spaeth, 1993a).

The Cup to Disc Area Ratio

The ratio of the cup to disc diameter or area is used to evaluate progression of glaucomatous optic nerve damage in humans. Enlargement of the cup to disc ratio indicates optic nerve axonal loss and is associated with deterioration in visual fields (Quigley et al., 1982). The normal cup to disc ratio for humans, and normal Beagle dogs, and normal Whippet dogs is 0.32 (Jonas et al., 1994), 0.31 (Brooks, unpublished data), and 0.29 (Brooks, 2012, unpublished data), respectively. Cup depth increases and NFL thickness decreases, but the optic disc size increases due to compression and flattening of the viscoelastic myelinated optic nerve axons on the surface of the ONH in early canine glaucoma such that the cup to disc ratio is actually reduced in early stages of glaucoma in the dog. The cup to disc ratio becomes increased in size as the demyelination of optic nerve axons occurs with RGC death in advanced glaucoma in the dog.

The Optic Nerve as a Biomechanical Structure

The ONH is a high stress environment that requires strong connective tissue to withstand the considerable stresses produced by normal to high levels of IOP (Fig. 26.5, Fig. 26.6, Fig. 26.7, and Fig. 26.8) (Burgoyne et al., 2004, 2005; Downs et al., 2005; Spoerl et al., 2005). A progressive posterior displacement of the surface of the ONH and progressive excavation of the prelaminar tissues beneath the anteriormost aspect of the scleral canal are clinical hallmarks of glaucomatos optic neuropathy (Burgoyne et al., 2005). Vascular insufficiency to the ONH and IOP-induced mechanical deformation of the scleral lamina cribrosa are two theories proposed to
explain the optic nerve axonal flow obstruction and RCG death in glaucoma. A new hypothesis incorporates the previous theories into the concept that the ONH is a biomechanical structure susceptible to IOP-related stress (force/cross-sectional area) and strain (local tissue deformation under those stresses) (Burgoyne et al., 2005). IOP-related strain influences the ONH load bearing connective tissues, optic nerve axons, and ONH astrocytes and glial cells. ONH capillary patency is also reduced by these IOP-related stresses (Burgoyne et al., 2005).

Stress and strain at a given level of IOP are physiologic or pathologic depending on the responsiveness of the ONH...
tissues. IOP-related stress and strain are substantial in the load-bearing connective tissue of the ONH even at normal levels of IOP. IOP-generated stress is 30 times IOP within the peripapillary sclera, 30–100 times IOP within the scleral canal wall, and 50–180 times IOP within the laminar beams. Elevated IOP accentuates the levels of laminar connective tissue strain (Burgoyne et al., 2005).

**ADDENDUM**

These formulas are useful in understanding the effects of elevated IOP on optic nerve axons:

1. *LaPlace’s equation for a spherical shell (globe)* relates pressure and radius of the sphere (globe) to sphere wall stress.

\[ S = \frac{(p_i - p_o)R}{2h} \]

where \( S \) = radial wall stress forces; \((p_i - p_o)\) = transmural pressure gradient (or the difference between internal (IOP or \(p_i\)) and external pressures (retrolaminar tissue pressure [RLTP] or \(p_o\)); \( R \) = sphere or globe radius; and \( h \) = thickness of the sphere or globe wall.

Once load-bearing laminar connective tissues are damaged with sustained levels of IOP, further damage to the ONH neural and connective tissues can occur at substantially lower IOP (Burgoyne et al., 2005). Collagen disruption precedes elastin changes in the lamina. Ischemic damage to the axons can occur from IOP-related strain within the ONH load-bearing tissues. Occlusion of laminar capillaries and reduced diffusion of nutrients to ONH capillaries adversely affect axon function. Individual connective tissue trabeculae of the anterior lamina cribrosa fail mechanically and transfer the force they were resisting to the immediately adjacent laminar trabeculae. The increased load on the remaining normal connective tissue at the same level of IOP reduces their ability to respond to further IOP-related increases. The more trabeculae that fail, the higher the stress of the remaining trabeculae at the same level of overall IOP-induced load and distribution of IOP-related stress and strain (Burgoyne et al., 2005).

The canine ONH deforms rapidly in response to increases in IOP. The lamina cribrosa and scleral canal wall act like an expandable trampoline at low IOP with the canal expanding and the lamina thinning and more stretched at increased IOP (0–10 mmHg). Higher IOP (10–30 mmHg) causes laminar bowing posteriorly and permanent deformation of the lamina with time. The viscoelastic properties of the posterior sclera are altered early in glaucoma (Burgoyne et al., 2005).

Cupping precedes visual field loss in humans but is hard to see in dogs with EG due to optic disc myelin (Spoerl et al., 2005). The tissues of the ONH reacts differently to equal IOP levels in different subgroups of human glaucoma patients. These differences may be caused by differences in the biomechanical properties of the of the lamina cribrosa and peripapillary sclera (Sigal, 2009). Differences in the elastin, collagen, and proteoglycans of the extracellular matrix (ECM) induce differences in elasticity of the ONH. Variation in collagen and elastin cross-linking could make the ONH stiffer, and collagenolytic activity of activated astrocytes could induce a reduction in ONH stiffness and support. The stiffening increases the risk of axonal damage and the collagenolytic activity induces the excavation or cupping noted in the ONH (Downs et al., 2005; Spoerl et al., 2005).

It is possible that as yet uninvestigated differences in laminar ECM and/or ONH astrocyte activity could explain clinical differences in canine breed ONH susceptibility to glaucoma (Palko et al., 2012; Spoerl et al., 2005).

Permanent posterior deformation of the central lamina cribrosa, as well as expansion of the scleral canal, as occurs in glaucoma, are present at the onset of detectable ONH surface change. Regardless of the mechanism of insult or the level of IOP at it occurs, IOP-related connective tissue stress and strain underlies the onset and progression of glaucomatous optic nerve axonal insult. For cupping to occur, the ONH tissues must become damaged and undergo mechanical failure in a process that is governed by the distribution of IOP-related stress and strain, regardless of the level of IOP at which it occurs. Posterior deformation indicates mechanical failure (Burgoyne et al., 2005).

**RETROBULBAR OPTIC NERVE**

The retrobulbar or intraorbital optic nerve begins posterior to the lamina cribrosa and consists of optic nerve axons, oligodendrocytes, and astrocytes. Optic nerve septae derived from the meninges contain blood vessels and subdivide the axons into bundles. Meningeal sheaths of pia mater, arachnoid, and outer dura mater surround the retrobulbar optic nerve (Jonas & Naumann, 1993). Arteriolar and capillary blood vessels pierce the dura mater, cross the trabeculae of the arachnoid, and branch to enter the pia mater. The dural sheath of the intraorbital optic nerve merges with the sclera anteriorly, and is continuous posteriorly at the orbital apex with the periesteum of the optic canal (Jonas & Naumann, 1993). At the orbital apex, the nerve enters the bony optic canal, surrounded by the origins of the superior, medial, and inferior recti muscles. The dura of the optic nerve and the periosteum of the bone are fused in the optic canal, but the subarachnoid space of the intraorbital optic nerve contains cerebrospinal fluid (CSF) and communicates with the intracranial subarachnoid. The orbital optic nerve is longer than the direct distance between the globe and optic canal such that it has an S-shaped curve in it to allow for globe movement (Evans, 1993).

The normal dog has fewer total numbers of myelinated optic nerve axons than humans (Jonas et al., 1990, 1992) and nonhuman primates (Sanchez et al., 1986), but has a larger mean optic nerve fiber diameter (Table 26.2) (Brooks et al., 1995; Jonas et al., 1990, 1992; Sanchez et al., 1986). The optic nerve of the human is larger in diameter at 2590 ± 80.6 µm than the dog at 1825.8 ± 59.7 µm (Balaraatnasingam et al., 2009). The canine retrobulbar optic nerve increases in diameter by 1.4 times the diameter of the nerve diameter at the sclera canal due to myelination compared to the diameter.
neral nervous system have an outer membrane known as the neurilemma which is essential for nerve regeneration following injury. The absence of the neurilemma membrane in cells of the central nervous system is thought to partially account for the failure of optic nerve axons to regenerate. The myelin sheath of optic nerve axons is interrupted to form nodes of Ranvier at the termination of the boundary of one oligodendrocyte and the beginning of another. Nodes of Ranvier are important in the saltatory conduction of optic nerve impulses (Jonas & Naumann, 1993). Myelin is an insulating material, and is associated with reduced neural metabolism with blood flow greater in unmyelinated optic nerve regions (Bill, 1993). Myelination of the optic nerve begins near the optic chiasm and progresses toward the lamina cribrosa (Jonas & Naumann, 1993). The myelination of the canine anterior ONH becomes more prominent after birth. Axons in the NFL are unmyelinated in order to keep the retina sufficiently transparent for light to reach the photoreceptors. Myelination of the ONH varies according to species, but all axons are myelinated posterior to the lamina cribrosa in mammals in order to conserve energy and speed neural conduction (Bill, 1993). The primate optic nerve nearly doubles in diameter posterior to the lamina cribrosa due to the axonal myelination (Jonas & Naumann, 1993).

### Optic Chiasm, Optic Tracts, and Lateral Geniculate Nucleus

The optic chiasm in the dog is located at the rostroventral surface of the brain stem, demarcates the rostral level of the diencephalon, and is closely associated with the 3rd ventricle, hypothalamus and, to some extent, the pituitary gland (Evans, 1993). The occurrence of decussation of optic nerve axons within the optic chiasm was first discussed by Isaac Newton in 1704 (Senelick, 1997). Nasal RGC axons cross the midline at the optic chiasm to reach the contralateral side of the brain.

### Table 26.2  Optic Nerve Axon Data for Several Species

<table>
<thead>
<tr>
<th>Species</th>
<th>Diameter of the Optic Nerve at the Level of the Sclera/Lamina Cribrosa (µm)</th>
<th>Total Axon Count</th>
<th>Percent Myelinated</th>
<th>Mean Individual Axon Diameter (µm)</th>
<th>Axon Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>1.01–1.02 million (Jonas et al., 1992, 1994)</td>
<td>100 (Jonas et al., 1992, 1994)</td>
<td>1.00 (Jonas et al., 1992, 1994)</td>
<td>150,000 (Jonas et al., 1992, 1994)</td>
<td></td>
</tr>
<tr>
<td>Monkey</td>
<td>1,717 ± 21(May, 2008)</td>
<td>100 (Sanchez et al., 1986)</td>
<td>1.00 (Sanchez et al., 1986)</td>
<td>150,000 (Sanchez et al., 1986)</td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>1,592 (May, 2008)</td>
<td>145,000–165,000 (Brooks et al., 1995, 1999a)</td>
<td>1.5 (Brooks et al., 1995, 1999a)</td>
<td>−50,000 (Brooks et al., 1995, 1999a)</td>
<td></td>
</tr>
<tr>
<td>Cat</td>
<td>1,187 (May, 2008)</td>
<td>193 ± 8 (May, 2008)</td>
<td>−8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>1,624 ± 15 (May, 2008)</td>
<td>145,000–165,000 (Brooks et al., 1995, 1999a)</td>
<td>1.5 (Brooks et al., 1995, 1999a)</td>
<td>−50,000 (Brooks et al., 1995, 1999a)</td>
<td></td>
</tr>
<tr>
<td>Pig</td>
<td>1,187 (May, 2008)</td>
<td>193 ± 8 (May, 2008)</td>
<td>−8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 26.3  The Percent of Optic Nerve Axons of Large Diameter (>2µm)

<table>
<thead>
<tr>
<th>Species</th>
<th>Percent Axons &gt;2µm in Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog (Brooks et al., 1995)</td>
<td>12.7</td>
</tr>
<tr>
<td>Human (Jonas et al., 1992, 1994)</td>
<td>−8</td>
</tr>
<tr>
<td>Monkey (Sanchez et al., 1986)</td>
<td>2.7</td>
</tr>
</tbody>
</table>
while temporal RGC axons remain ipsilateral. The percentage of axons crossing the midline at the optic chiasm varies widely with 100% decussation in most birds and fish, 65% in the cat, 75% in the dog, 80%–90% in large animals, and 50% in primates (Prince et al., 1960).

Molecular biology studies have revealed that numerous guidance molecules control the development of the visual pathway in each critical step during optic axon guidance (Inatani, 2005). Axonal projections to the optic disc are thought to depend on adhesion molecules and inhibitory extraCELLular matrices such as chondroitin sulfate and heparin sulfate (Ogata-Iwao et al., 2011). The formation of the head of the optic nerve and the optic chiasm require ligand–receptor interactions between netrin-1 and the deleted in colorectal cancer (DCC) receptor, and Slit proteins and Robo receptors, respectively. The gradient distributions of ephrin ligands and Eph receptors are essential for correct ipsilateral projections at the optic chiasm and the topographic mapping of axons in the superior colliculus/optic tectum. The precise gradient is regulated by transcription factors determining the retinal dorso-ventral and nasal–temporal polarities. Moreover, the axon guidance activities by Slit and semaphorin 5A require the existence of heparin sulfate, which binds to numerous guidance molecules (Inatani, 2005).

During the early stages of chiasm formation, pioneering axons from the left eye arrive earlier than their counterparts from the right eye although there is no known functional significance to this (Thanos et al., 2004). A xonal pathfinding for axonal decussation is under balanced expression and control of the transcription factor Pax2 (Thanos et al., 2004).

Pax genes play a pivotal role in development of the vertebrate visual system. Pax6 is the master control gene for eye development. Pax6 is involved in formation of the RGCs, as well as cells of the lens, iris, and cornea (Ziman et al., 2001). Pax2 regulates differentiation of the optic disk through which RGC axons exit the eye. Furthermore, Pax2 plays a critical role in development of the optic chiasm and in the guidance of axons along the contralateral or ipsilateral tracts of the optic nerve to visual targets in the brain. During development, Pax7 is expressed in neuronal cells of one of the major visual targets in the brain, the optic tectum/superior colliculus. Neurons expressing Pax7 migrate toward the pia and concentrate in the stratum griseum superficiale (SGFSs), the target site for retinal axons. Together, expression of Pax2, 6, and 7 may guide axons during formation of functional retinotectal/collicular projections. Highly regulated Pax gene expression is also observed in mature animals. Moreover, evidence suggests that Pax genes are important for optic nerve regeneration (Ziman et al., 2001).

The optic tracts arise at the optic chiasm, and in dogs are located on the lateral surface of the internal capsule of the diencephalon (Evans, 1993). The optic tracts connect to the hypothalamus, dorsal LGN, pretectal nuclei and rostral colliculus via the brachium of the rostral colliculus, and to the accessory nucleus of the optic tract (Evans, 1993). Most (77%) optic tract fibers in the cat terminate in the LGN (Iilling & Wassle, 1981).

The dorsal LGN possesses retinotopic organization and functions as a complex relay to the conscious vision pathway. The dorsal nucleus is more complex in species with binocular vision and is the only part of the LGN that projects via the optic radiations to the ipsilateral VC (Evans, 1993; Jones, 1985).

The dorsal LGN of carnivores has a sigmoid curved, layered laminar structure (Howard & Breazile, 1973; Jones, 1985; Morimoto et al., 1984) while the dorsal LGN of primates is usually in the shape of an inverted “U” (Jones, 1985). The number of LGN cell layers varies according to species with three laminae and three sublaminae in carnivores such as the cat and dog, and six layers in primates (Howard & Breazile, 1973; Jones, 1985; Morimoto et al., 1984). The LGN lamina are usually referred to as A, A1, C, and C1-3 in carnivores, (Howard & Breazile, 1973; Jones, 1985; Morimoto et al., 1984) and 1-6 in primates (layer 1 and C are the deepest) (Jones, 1985). The carnivore A, C, and C2 layers, and primate layers 1, 4, and 6 receive crossed contralateral optic tract fibers from the nasal retina, whereas the A1 and C1 layers, and layers 2, 3, and 5 receive uncrossed ipsilateral fibers from the temporal retina (Howard & Breazile, 1973; Jones, 1985; Morimoto et al., 1984). M-type RGC axons pass to the two magnocellular layers, 1 and 2, of the primate LGN, while P-type RGC axons pass to the four parvocellular layers, 3–6, of the primate LGN (Jones, 1985). X- and Y-type RGC axons of cats produce the greatest portion of their synapses in lamina A (if from the contralateral retina) or A1 (if from the ipsilateral retina) (Sur et al., 1987).

**Centrifugal Axons**

Centrifugal, antidromic, or efferent axons are also found in the optic nerve of several species and may represent a method by which the brain can influence retinal activity (Senelick, 1997). These axons included myelinated axons that can be traced back to the LGN, axons that supply the blood vessels of the optic nerve and retina, and unmyelinated fibers that enter the optic chiasm from the hypothalamus and pituitary (Senelick, 1997; Wolter, 1965). Centrifugal fibers to amacrine cells of the IPL are present in cats (Wakakura & Ishikawa, 1982) and dogs (Terubayashi et al., 1983). Ten percent of the optic nerve fibers in humans may be efferent (Wolter, 1965). The bird retina receives a substantial centrifugal input from the brain. Approximately 10,000 fibers originating in a small midbrain nucleus, the isthmo-optic nucleus (ION), terminate in each retina. The input to the ION is chiefly from the optic tectum which, in the bird, is the primary recipient of retinal input. These neural elements constitute a closed loop, the centrifugal visual system (CVS), beginning and ending in the retina, that delivers positive feedback to active ganglion cells (Wilson & Lindstrom, 2011). All fibers from the avian ION terminate in a ventral retina and an unusual axon-bearing amacrine cell, the target cell. While the rest of the CVS is orderly and retinotopic, target cell axons project seemingly at random, mostly to distant parts of the retina. It may be that...
OPTIC NERVE PHYSIOLOGY

Axoplasmic Flow

Optic nerve axons consist of an outer sheath of myelin, a hollow thin, collapsible, bilayered lipid cell wall, and a gel-like viscoelastic axoplasm containing transmitter molecules, proteins, microtubules, and organelles such as mitochondria. The axoplasm moves in the axons along an intra-axonal pressure gradient (Brooks et al., 1999b; Yablonski & Asamoto, 1993). Axoplasmic movement is orthograde from the RGC somata toward the synapse, and retrograde from the synapse toward the RGC somata. The orthograde and retrograde intra-axonal flow of the RGC somata to the synapses in the LGN indicates the tendency for collapse. Critical collapsing pressure (CCP) is the transmural pressure at which the axon collapses and axoplasmic flow ceases. CCP is inversely related to the cube of the axon radius such that the CCP = 3IE/R^3, where I = viscosity of the axoplasm, E = elasticity of the axon wall, and R = axon radius (Brooks et al., 1999b). Note that the CCP is inversely related to the cube of the axon radius such that large diameter axons, found in great number in the dog optic nerve, are most susceptible to changes in IOP.

Axons are also subjected to a rapid change in tissue pressure as they exit the globe. LaPlace’s equation for a spherical shell (globe) relates pressure and radius of the sphere (globe) to sphere wall stress. S = (p_i – p_e)R/2h, where: S = radial wall stress forces; (p_i–p_e) = transmural pressure gradient (or the difference between internal (IOP or p_i) and external pressures (RLTP or p_e); R = sphere or globe radius; and h = thickness of the sphere or globe wall (Brooks et al., 1999b). Thus, large diameter axons are most vulnerable to collapse during periods of both normotension and periods of IOP elevation (Yablonski & Asamoto, 1993). Astrocytic cell support tethers the axon bundles to prevent axon collapse at the lamina cribrosa (Yablonski & Asamoto, 1993). ONH autoradiography in normal dogs at IOP of 25 mmHg revealed 10% of the optic nerve axons to have mild obstruction of axoplasmic flow (Williams et al., 1983). This increased to near 100% obstruction at IOP of 50 mmHg in normal dogs. Beagles with primary glaucoma had 87% of the optic nerve axons displaying mild to moderate obstruction of axoplasmic flow by ONH autoradiography at IOP of 30–35 mmHg (Samuelson et al., 1983). This suggests that the axoplasmic flow of dogs with primary glaucoma is more susceptible to elevations in IOP than that of normal dogs, and that the therapeutic target IOP to maintain vision in dogs with primary glaucoma must be as low as 12–15 mmHg in order to minimize axoplasmic flow obstruction and maintain canine RGC health (Brooks et al., 1999b).

THE LAMINA CRIBROSA

To paraphrase the noted glaucomatologist, Harry A Quigley, “How do you get the axons of the 150,000 canine RGCs out of the inside of the eye without causing a leak that results in globe collapse and hypotony? And, with those nerve fibers not being kinked, hurt or destroyed in some way such that through 15 years or so of life that they do not just drop dead?” (Brooks et al., 1999b; Quigley, 1995a). This feat of biological engineering is accomplished at the sclera lamina cribrosa (Quigley, 1995b). The scleral lamina cribrosa is not just a porous region of the sclera through which the optic nerve axons pass, but a complex and specialized tissue that differs from the contiguous sclera in its elasticity and biochemical composition (Anderson, 1995a; Anderson & Cynader, 1997; Burgoyne et al., 2005). It is a dynamic and compliant structure whose movement during normal and abnormal fluctuations in IOP can affect optic nerve axoplasmic flow (see Fig. 26.8) (Burgoyne et al., 2005; Sigal, 2009; Yablonski & Asamoto, 1993).

The lamina cribrosa consists of multiple adjacent plates or layers of an ECM, astrocytes, and capillaries (Fig. 26.9, Fig. 26.10, Fig. 26.11, and Fig. 26.12) (Anderson, 1969; Brooks et al., 1986; Emery et al., 1974; >; Fukuchi et al., 1987; Furuta et al., 1993; Hernandez & Pena, 1997; Johansson, 1983, 1987; May, 2008; Radius, 1981a, 1981b; Radius & Bade, 1982; Tansley, 1956). It is divided into retinal or optic disc, choroidal, and scleral regions, and provides nutrition and mechanical support to the RGC axons as they turn from the retinal NFL into the scleral canal to form the optic nerve (Anderson, 1995a; Brooks et al., 1986; Emery et al., 1974; Fukuchi et al., 1987; Furuta et al., 1993; Johansson, 1983, 1987; Radius, 1981a, 1981b; Radius & Bade, 1982; Tansley, 1956). Axons of the retinal NFL become arranged into fiber bundles by astrocytes in the anterior or choroidal lamina cribrosa, and are insulated by tubes of astrocytes from the surrounding capillaries and ECM through the entire length of the lamina. Individual laminar plates contain astrocyte-lined pores through which optic nerve fiber bundles pass (Anderson, 1969; Brooks et al., 1999b).
Nerve fiber bundles generally follow a direct channel through aligned sets of laminar pores in adjacent laminar plates, although not all laminar pores are perfectly aligned between the laminar sheets (Fig. 26.13). The lamina has a natural backward curve in it like a hammock across a hole, with some laminar pores appearing to branch and coalesce (Burgoyne et al., 2005; Quigley, 1995a).

The canine lamina cribrosa consists of 10–15 layers, and 250 pores of 12–50 µ diameter. There are no regional differences in pore size of the dog lamina (Brooks et al., 1986;
The laminar insertion zone functions to attach the lamina cribrosa to the surrounding sclera (Fig. 26.14). It is a specialized region of the laminar and prelaminar ONH that contains concentric, circumferential, tightly organized bundles of the choriocapillaris from the ONH such that a potential defect exists in the blood-ocular barrier at the level of the ONH. Substances may thus enter the ECM of the optic nerve and lamina cribrosa from the choroid, but are prevented from entering the subretinal space by the tight cell junctions adjoining glial cells in the intermediate tissue of Kuhnt (Jonas & Naumann, 1993).

The lamina cribrosa represents a specialized ECM of the central nervous system (Hernandez et al., 1987; Rehnberg et al., 1986). Laminar plates or beams in humans are composed of elastin, capillaries, proteoglycans, collagen types I, III, IV, V, VI, laminin and fibronectin, and are lined by astrocytes with the collagen type IV in the BM of the astrocytes separating the laminar plate core from the surrounding astrocytes (Hernandez et al., 1987; Rehnberg et al., 1986). Laminar collagen in young dogs is primarily types I, III, and VI. (Brooks, unpublished data). Laminar collagen is twice the thickness (47 nm) of corneal collagen (Quigley et al., 1991). The ECM of the lamina differs from that of sclera which contains primarily fibrillar collagen type I (Hernandez et al., 1987; Rehnberg et al., 1986). A ging results in a loss of laminar resiliency, compliance, and elasticity in the human lamina cribrosa due to increases in the fibrillar collagen types I and III (Downs et al., 2005; Hernandez et al., 1989). Genetic changes in the canine trabecular meshwork resulting in altered biochemical properties could be an inciting cause for canine glaucoma, as the ECM of the lamina cribrosa closely resembles that of the anterior segment trabecular meshwork and is altered in some dog breeds with genetic glaucoma (Clark et al., 1995; Palko et al 2012).

The elastin fibers and collagen in the lamina cribrosa act as parallel mechanical elements to applied stress or strain (Hernandez et al., 1987). Proteoglycans also have hydrodynamic properties, and can compress under load and expand when the load is released (Hernandez & Pena, 1997; Hernandez et al., 1987). Elastin functions as biological rubber that absorbs mechanical stress linearly. Collagen behaves like a viscoelastic material as it is prone to creep, relaxation, and conditioning (Downs et al., 2005; Spoerl et al., 2005; Zeimer, 1995). The laminar tissue consists of straight elastin fibers, and wavy collagen fibers. When stressed, the straight elastic fibers first carry the load and an elastic response is observed. As the stress increases, the collagen fibers straighten and exhibit a viscoelastic behavior. Continued stress causes elastin fibers to disinsert, and the collagen to creep and relax such that the scleral canal widens due to a reduction in the inward pulling forces in the scleral canal. The relaxation of the collagen fibers in the lamina transfers the tension back to the remaining elastin fibers. Such loading of the elastin fibers that are already at the limits of their range of elasticity makes the lamina stiffer, and predisposes to further disinsertion (Burgoyne et al., 2005; Zeimer, 1995).

The laminar insertion zone functions to attach the lamina cribrosa to the surrounding sclera (Fig. 26.14). It is a specialized region of the laminar and prelaminar ONH that contains concentric, circumferential, tightly organized bundles of

Fukuchi et al., 1987). The central laminar thickens is 508.9 ± 17.2 µm in the dog and 539.0 ± 26.5 µm in humans (Balaratnasingam et al., 2009).

During embryonic development of the eye, the RGC axons and the hyaloid vessels appear in the scleral canal prior to formation of the lamina cribrosa (Jonas & Naumann, 1993). Glial cells of the optic stalk then invade the laminar region of the scleral canal to form a sieve-like scaffolding around the preexisting RGC axons. This is followed by an ingrowth of sclera-derived cells which form the vascularized connective tissue of the lamina (Jonas & Naumann, 1993). The optic nerve axons in the lamina cribrosa and scleral canal are separated from the choroid and sclera by a continuous sheet of astrocytes, the border tissue of Jacoby (Jonas & Naumann, 1993). Anteriorly, the intermediate tissue of Jacoby is continuous with the border tissue of Kuhnt and separates the axons from contact with the retina. The border tissue of Elschnig is the scleral layer surrounding the border tissue of Jacoby. Bergmeister’s papilla is formed by glial cells covering the hyaloid artery. The retinal inner limiting membrane covers the anterior surface of the optic disc as the inner limiting membrane of Elschnig, or the thicker central meniscus of Kuhnt (Jonas & Naumann, 1993). Capillaries with a continuous basement membrane (BM) are surrounded by astrocytes in the laminar tissue, but there is no cell layer with tight junctions separating the choriocapillaris from the ONH such that a potential defect exists in the blood-ocular barrier at the level of the ONH. Substances may thus enter the ECM of the optic nerve and lamina cribrosa from the choroid, but are prevented from entering the subretinal space by the tight cell junctions adjoining glial cells in the intermediate tissue of Kuhnt (Jonas & Naumann, 1993).

The laminar insertion zone functions to attach the lamina cribrosa to the surrounding sclera (Fig. 26.14). It is a specialized region of the laminar and prelaminar ONH that contains concentric, circumferential, tightly organized bundles of

Figure 26.13. Scanning electron micrograph, longitudinal section, of a trypsin digest of a normal canine optic nerve demonstrates axon bundles passing through the laminar plates. The laminar insertion zone is prominent in this image. (Original magnification, 250×.)
Dogs with elevated IOP initially demonstrated anterior movement of the lamina (Brooks, unpublished data), perhaps due to posterior laminar pressure on the prominent canine orbital blood supply causing a vascular rebounding effect to force the lamina forward (Brooks et al., 1999b; Dawson et al., 1996).

The scleral lamina cribrosa is a transition zone of high to low hydrostatic tissue pressure due to the prominent pressure gradient formed by the IOP and intraorbital pressure (Balaratnasingam et al., 2009; Burgoyne et al., 2005; Fechtner & Weinreb, 1994; Krinke et al., 1981; Morgan et al., 1995; Nickells, 1996). A translaminar, axial force vector pushing posteriorly through the scleral canal induces compression of the laminar plates, while a second force vector pulls radially on the laminar scleral insertion zone and contributes to stress within the scleral wall (Fechtner & Weinreb, 1994).

Mathematical equations predict that, for a given transmural pressure gradient, the larger the radius of the globe (i.e., the greater the axial length), the greater the scleral wall stress, and hence, the greater the potential distorting forces on the scleral lamina cribrosa and optic nerve axons. An elevated transmural pressure gradient caused by increased IOP would also increase radial stress forces acting on the laminar insertion zone at the scleral lamina cribrosa. Differences in the rigidity or compliance of the laminar tissue may account in part for individual, breed, and species differences in susceptibility of the optic nerve to IOP-induced damage (Krinke et al., 1981; Nickells, 1996; Spoerl et al., 2005).

In a study comparing dogs and humans, it was found that there is no significant difference in lamina cribrosa thickness between dogs and humans; the shortest distance between the intraocular space and subarachnoid space is greater in dogs than in humans; the diameter of the human optic nerve 1 mm behind the lamina cribrosa is greater than dogs; the pia mater thickness is greatest at the termination of the optic nerve subarachnoid space in humans and dogs and gradually declines in thickness along the proximal 500 µm of the optic nerve in humans and proximal 1000 µm of the optic nerve in dogs; and in the more distal optic nerve, the pia mater thickness is stable with human pia mater (approximately 60 µm) being twice as thick as that of dogs (approximately 30 µm) (Balaratnasingam et al., 2009).

The optic nerve blood vessels and the axoplasmic flow in the optic nerve axons of the dog are subjected to this severe drop in tissue pressure over the inner 400–600 µm of the scleral lamina cribrosa as they pass from inside the eye to outside the globe (Fig. 26.15) (Morgan et al., 1995). This translaminar tissue pressure gradient (TLTG), calculated by subtracting the RLTP in the optic nerve meninges from the IOP, predisposes the optic nerve axons and blood vessels to collapse at the lamina cribrosa during episodes of ocular hypertension (OHT) or glaucoma. The translaminar pressure gradient in the dog is 3.1 ± 0.3 mmHg/100 µm tissue (Morgan et al., 1995). This is predicted to be 3.3 ± 1.4 mmHg/100 µm tissue in the human (Balaratnasingam et al., 2009). The RLTP averaged 8.6 ± 3.5 mmHg higher than the cerebrospinal fluid pressure (CSFp)
in the dog (Morgan et al., 1995) and averaged $3.7 \pm 0.2 \text{ mmHg}$ when the CSFp was 0 mmHg (Morgan et al., 1998). There is direct hydrostatic continuity between the optic nerve subarachnoid space and the intracranial lateral ventricle in the dog. The RLTP is independent of IOP in the dog and largely determined by CSFp such that increased CSFp could cause a reduction in slow axoplasmic flow to result in papilledema in dogs as it does in humans (Morgan et al., 1995, 1998). Why this is so infrequently noticed clinically in dogs with increased CSFp is not known.

**THE LAMINA CRIBROSA AND GLAUCOMA**

IOP-induced conformational distortion within the scleral lamina cribrosa results in rotation, compression, misalignment, and collapse of the laminar pores and laminar channels such that optic nerve axoplasmic flow is reduced and eventually blocked to cause RGC death (Brooks et al., 1986; Fechtner & Weinreb, 1994; Minckler & Spaeth, 1981; Quigley & Addicks, 1981; Quigley et al., 1980, 1983; Yablonski & Asamoto, 1993). This RGC death and axon loss is observed ophthalmoscopically and histologically in humans and dogs with glaucoma as an increase in ONH cup size and a decrease in neuroretinal rim area (Fig. 26.16, Fig. 26.17, Fig. 26.18, Fig. 26.19, Fig. 26.20, Fig. 26.21, Fig. 26.22, Fig. 26.23, Fig. 26.24, and Fig. 26.25) (Brooks, 1997; Brooks et al., 1986; D. Brooks et al., 1995a, 1995b; Quigley et al., 1983, 1991). While IOP-induced forces are uniformly distributed across the optic nerve, regional differences in the structure of the lamina cribrosa may make specific segments of the optic nerve more susceptible to damage (Quigley & Addicks, 1981; Quigley et al., 1980; Radius, 1981b). In humans, most early glaucomatous optic nerve damage occurs in the superior and inferior quadrants of the optic nerve where the pores of the scleral

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**Figure 26.15.** Pressures of various regions of the carnivore posterior segment are illustrated. (Courtesy of K.N. Gelatt.)

**Figure 26.16.** Scanning electron micrograph, longitudinal section, of a trypsin digest of the ONH of a glaucomatous Beagle dog demonstrates ONH cupping, laminar rotation, and laminar compression. (Original magnification, 110×.)
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Figure 26.17. Scanning electron micrograph, longitudinal section, of a trypsin digest of the ONH of a glaucomatous Beagle dog demonstrates ONH cupping, laminar rotation, and laminar compression. (Original magnification, 50×.)

Figure 26.18. Scanning electron micrograph, longitudinal section, of a trypsin digest of a glaucomatous Beagle (late-stage disease) demonstrates ONH cupping and severe laminar plate compression. Axon bundles would be mechanically compressed by the laminar plate distortion. (Original magnification, 86×.)

Figure 26.19. Early optic disc cupping in a dog with glaucoma.

Figure 26.20. More advanced cupping of the optic disc and nerve fiber layer hemorrhages in a dog with glaucoma.

Lamina cribrosa are large and the supportive interpore trabecular connective tissue is thin (Fechtner & Weinreb, 1994; Quigley & Addicks, 1981; Quigley et al., 1981; Yablonski & Asamoto, 1993). Regional differences in laminar pore size, similar to humans, are also known to exist in nonhuman primates (Radius, 1981a). Large pores of the scleral lamina cribrosa may provide less structural support for maintaining the integrity of the laminar channels under conditions of increased IOP due to their thinner interpore connective tissue septae (M inckler & Spaeth, 1981; Quigley & Addicks, 1981; Yablonski & Asamoto, 1993). If the scleral lamina cribrosa was rigid, large pores would provide less resistance to axoplasmic flow in the optic nerve axons (Yablonski & Asamoto, 1993), but since the lamina is an elastic, compliant tissue, the lack of support provided by large pores may make the axons in them more susceptible to collapse and cause a reduction or obstruction to optic nerve axoplasmic flow. Thicker interpore laminar trabecular septae found with smaller laminar pores may provide more resistance to early mechanical deformation.
of the laminar channels, sparing the optic nerve fibers from injury until late in the disease (Quigley & Addicks, 1981).

The laminar plates display evidence of breakdown and rehealing with progression of glaucoma which may cause them to become stiff or less compliant with time (Quigley, 1995a). Astrocyte responses in glaucoma may induce or exacerbate the changes found in the ECM in glaucoma (Nickells, 1996; Veral & Hernandez, 1997). Reactive laminar type 1B astrocytes in human chronic glaucoma show increased immunoreactivity to glial fibrillary acidic protein (GFAP) and neural cell adhesion molecule (NCAM), while type 1A astrocytes that normally express only GFAP are absent in the glaucomatous laminas (Hernandez & Pena, 1997).

The ADAMTS10 mutation in beagles with glaucoma is associated with altered biochemical properties of the extracellular matrix of the posterior sclera (Palko et al., 2012). Angiopoietin-like 7 (ANGPTL7) protein is a candidate glau-
VASCULAR SUPPLY OF THE OPTIC NERVE

The rich optic nerve vasculature is associated with a high rate of blood flow. The primary blood supply to the eye of dogs, the large external ophthalmic artery (EOA), arises from the maxillary artery and is thus extracranial. The internal ophthalmic artery (IOA) in dogs is a small artery that arises from the anterior cerebral artery at the level of the optic chiasm (Evans, 1993). It passes through the optic canal on the dorsal surface of the optic nerve in dogs and cats, and runs rostral on the nerve to anastomose with the EOA about midway between the optic canal and the posterior pole of the globe. Neural innervation to the IOA may play some role in the regulation of blood flow to the optic nerve (Chou et al., 1996). Two long posterior ciliary arteries (LPCA), one medial and one lateral, and several short posterior ciliary arteries (SPCA) arise from the anastomoses of the external and internal ophthalmic arteries in dogs. Six to ten SPCA surround the scleral canal of the canine optic nerve and supply the canine lamina cribrosa, choroid, retina, and ONH circulations (Fig. 26.26 and Fig. 26.27) (D.E. Brooks et al., 1989). The retrolaminar optic nerve receives a centripetal vascular supply from the pial vessels (Hayreh, 1995). The extensive, nonfenestrated capillary beds of the surface, prelaminar, laminar, and retrolaminar optic nerve regions are confluent (Cioffi & Van Buskirk, 1996; Hayreh, 1995).

Figure 26.25. Scanning laser ophthalmoscopic images of the optic disc of a Beagle dog with primary open-angle glaucoma illustrates the changes in cup depth and NRR width as the disease progresses. Red is posterior movement of the lamina cribrosa.
optic nerve receives a centripetal vascular supply from pial vessels (Hayreh, 1995). The extensive, nonfenestrated capillary beds of the surface, prelaminar, laminar, and retrolaminar optic nerve regions are confluent (Cioffi & Van Buskirk, 1996; Hayreh, 1995). The vessels in the superficial and laminar layers of the optic nerve are under the influence of IOP, whereas vessels in the retrolaminar region are not. Vasopactive nerves influence ocular blood flow with a rich innervation to the SPCAs (Cioffi & Van Buskirk, 1996; Funk et al., 1997; Morrison et al., 1997).

In primates, blood moves from the periphery of the retina and ONH to the single central retinal vein in the center of the optic disc (Cioffi & Van Buskirk, 1996). Venous drainage of the retina and optic disc in dogs and cats, in contrast, is via multiple, adjacent, short posterior ciliary collecting veins located at the disc margin, as these animals lack a central retinal vein. This creates a multidirectional circulatory flow pattern within the dog anterior optic nerve that is not found in primate species, and that provides the dog retina and optic nerve with a more abundant and varied system of venous drainage (Brooks et al., 1989; Cioffi & Van Buskirk, 1996; de Schaepdrijver et al., 1996; Hayreh, 1995). This centripetal vascular supply pattern to the primate optic nerve may predispose the primate retina and optic nerve to ischemic disorders if obstruction of venous drainage occurs (Cioffi & Van Buskirk, 1996). The peripapillary choroid derives its blood supply from the SPCA at the ONH margin, although the choroidal and ONH circulations are not continuous (Cioffi & Van Buskirk, 1996; Hayreh, 1995). Peripapillary choroidal arterial and venous blood flow is directed anteriorly away from the optic disc, as the venous drainage of the peripapillary choroid is to the vortex veins (Cioffi & Van Buskirk, 1996; Hayreh, 1995).

The SPCA function as end arteries in the eye, with each individual SPCA supplying specific and independent choroidal and retinal regions (Cioffi & Van Buskirk, 1996; Hayreh, 1995). The regions of the choroid and retina supplied by adjacent short posterior ciliary arteries are “watershed zones” (Hayreh, 1995). A watershed zone is a border between two regions supplied by end-arteries than can result, under conditions of increased IOP or vessel occlusion, in an area of hypoperfusion. A potential watershed zone thus intervenes immediately adjacent to the optic nerve due to the isolation of the ONH and choroidal circulations, and also between choroidal and retinal regions supplied by a single SPCA (Cioffi & Van Buskirk, 1996; Hayreh, 1995).

**AUTOREGULATION OF THE OPTIC NERVE VASCULATURE**

Maintenance of adequate perfusion is a basic requirement of all tissue beds (Orgül et al., 1995). Perfusion pressure to a tissue can be defined as the local arterial blood pressure (PA) minus the local venous pressure (PV). In the eye, PA is related to the ophthalmic artery blood pressure, and is PV related to IOP, such that the ocular perfusion pressure (OPP) is often
denoted as OPP = P_A – P_IOP (Alm, 1983). The OPP is the driving force for blood entering the ocular circulation. Retinal arterial pressure (P_R) is related to IOP and systemic blood pressure while retinal vein pressure (P_V) is related to IOP only (Attariwala et al., 1994). Retinal P_V in cats is known; however, to be higher than the IOP, such that using the IOP to calculate OPP results in an overestimation of OPP (Attariwala et al., 1994). The OPPs in humans (Alm, 1983), cats (Attariwala et al., 1994), and dogs (Morgan et al., 1997) are approximately 50, 38, and 70 mm Hg, respectively. Increasing the IOP decreases the OPP, as does lowering the blood pressure. Increased IOP results in increased venous intravascular pressure, restricts capillary flow, reduces the arteriovenous pressure gradient, and increases the arteriolar transmural pressure (Orgül, 1997). In normal eyes, moderate increases in IOP have only minor effects on retinal and optic nerve blood flow due to a vascular flow control process called autoregulation. A utoregulation means that, within a range of OPP, moderate reductions in OPP caused by increased IOP induce a dilatation of the ocular vessels and maintain a constant level of blood flow (Orgül, 1997). When autoregulation is not present in a tissue, each reduction in perfusion pressure is followed by a linear reduction in blood flow (Orgül, 1997). Blood flow in the retina and prelaminar ONH circulations is autoregulated and able to respond to IOP-induced OPP changes, whereas blood flow in the choroid is sensitive to changes in IOP in most species with the exception of the rabbit (Orgül et al., 1995). Disturbance of autoregulation and optic nerve blood flow in glaucoma may be associated with the development of glaucomatous optic neuropathy in dogs (Brooks et al., 1989) and humans (Emery et al., 1974; Shields, 1994; Van Buskirk & Cioffi, 1992; Wilson, 1994; Yablonski & Asamoto, 1993).

A utoregulation is accomplished through the ability of the microvasculature to adjust the resistance of arterioles and capillaries by altering their luminal diameters (Bill, 1993; Orgül, 1997; Orgül et al., 1995). A utoregulation may be initiated from stretching forces acting on vascular smooth muscle, viscous shearing effects from blood flow on endothelial cells, and the metabolic state of the cells (Anderson, 1995b). Metabolic and myogenic autoregulatory mechanisms are proposed (Bill, 1993; Orgül et al., 1995). Vascular muscle tone may be influenced by changes in pO₂ or pCO₂. Increased production of vasodilator substances is found with hypoxia and is considered an important mechanism for metabolic autoregulation. Prostaglandins mediate increased blood flow in the anterior optic nerve and retina if high levels of CO₂ are present (Orgül et al., 1995). Flickering light increases the metabolic needs of the retina and results in increased ONH blood flow (Riva et al., 1991).

Vascular endothelium is an active participant in the maintenance of vascular tone and regulation of blood flow through myogenic pathways (Orgül et al., 1995). Endothelial cells detect changes in their microenvironment, and respond with the synthesis of various vasoactive factors in order to maintain a delicate balance between vasoconstriction and vasodilation. Endothelial-derived relaxing factors include prostanoids such as prostacyclin (PGI₂) and nitric oxide (NO), and the endothelial-derived constricting factor, endothelin. PGI₂ causes increased intracellular cAMP in vascular smooth muscle cells which reduces intracellular calcium and induces myorelaxation (Orgül et al., 1995). NO is synthesized in endothelial cells from L-arginine by nitric oxide synthase (NOS) (Neufeld et al., 1997; Orgül et al., 1995). It diffuses into the vascular smooth muscle cell layer, activates guanylyl cyclase, decreases intracellular calcium, and induces smooth muscle relaxation. NO may also affect the pericytes to induce vasodilation of capillaries. It maintains a constant state of vasodilatation in the ocular circulation (Orgül et al., 1995; Zeiher, 1995). Endothelin-1 (ET-1) generation results in increased release of intracellular calcium, opening of membrane calcium channels, and vascular constriction. ET-1 decreases ONH blood flow at high concentrations (Orgül, 1997). ET-1and NO are increased in aqueous humor and vitreous of dogs with spontaneous glaucoma (Källberg et al., 2007). Bunazosin hydrochloride, a potent and highly selective α₁-adrenergic antagonist, has been shown to increase the capillary blood flow in the ONH of rabbits and to antagonize the ET-1-induced reduction in ONH blood flow (Goto et al., 2005).

**CLINICAL EXAMINATION OF THE OPTIC NERVE**

**Direct Ophthalmoscopy**

The invention of the ophthalmoscope by Hermann von Helmholtz in 1850 revolutionized examination of the retina and optic nerve (Colenbrander, 1997; Helmholtz, 1951). Use of the ophthalmoscope did, however, require some time to adapt to its relative depth of focus and was subject to both optical and perceptual variation in interpretation (Schwartz, 1993). The glaucomatous optic disc was initially observed to be swollen and prominent (Ajraksinen et al., 1996; Albert, 1972; Kronfeld, 2005; Schwartz, 1993). Different examiners could not agree from ophthalmoscopic examinations whether the colobomatous-like physiologic cup of the rabbit ONH was elevated or depressed. The correct ophthalmoscopic interpretation of a depression of the rabbit optic disc was promptly confirmed, however, by pathologic findings (Kronfeld, 2005; Müller, 1858).

An appropriate direct ophthalmoscope for examination of the ONH requires a full range of clean, properly aligned lenses and a source of bright light providing a beam with a width less than the ONH diameter (Spaeth, 1993b). ONH examination is best accomplished with the pupil dilated. The ophthalmologist must decide whether the benefits of mydriasis for examination outweigh the risk of inducing angle-closure glaucoma (Spaeth, 1993b). The smallest width illumination beam, which is preferably one-third to one-half the diameter of the optic disc, should be used. The beam is swept back and forth, vertically and horizontally, across the surface of the optic disc. This sweeping motion results in shadows, which enhances the
fluorescein angiography allows simultaneous, sequential visualization of blood flow through the retina, ONH, and choroid (Maguire & Federman, 2005). Because it is a small molecule, sodium fluorescein (NaF) dye does not cross the normal blood-ocular barriers, but remains in the vessels. Choroidal capillaries leak NaF, but the retinal pigment epithelium (RPE) obscures this effect. Photographs are obtained before NaF injection to detect autofluorescence. Choroidal filling is first indicated by the choroidal flush, which is a lobular, central-to-peripheral brightening of the RPE background. Cilioretinal arteries fill, and the optic disc begins to fluoresce as the choroid fills. The retinal arteries then fill, and the retinal capillaries near the disc fill and empty. The retinal venous phase is characterized by a laminar flow pattern of the marginal areas, in which small veins close to the ONH fill with dye before larger veins. Optic discs develop a persistent hyperfluorescence through leakage of dye into the ONH from the choroid. Because the ONH does not bind fluorescein, the ONH is autofluorescent and displays a background level of fluorescence. Fluorescein angiography can show areas of slow filling, nonperfusion, and hemorrhage in diseased segments of the optic disc (Fishbein & Schwartz, 1977; Schwartz et al., 1977; Spaeth, 1975; Talusan & Schwartz, 1977). Shifts in the course of ONH arterioles occur as the optic cup deepens and widens with advancing glaucoma. Sodium fluorescein is insensitive to the early phases of tissue loss in the optic disc rim.

Digitized NaF sequential images can be evaluated for intensity buildup curves of fluorescence, analyzed per pixel for changes in pixel gray scale caused by fluorescein passage, with great precision (Van-Stokkum et al., 1995).

Fundus Photography

Both standard photography and stereophotography allow objective, sequential documentation of ONH changes. Optic cup enlargement and disc hemorrhages can be seen; however, fundus photographs are often inadequate at analyzing and documenting subtle changes (Van-Stokkum et al., 1995).

Imaging the Optic Nerve

Optic nerve head analyzers were introduced to quantitate changes in optic disc cupping, neuroretinal rim changes, and other optic disc parameters. They provide a detailed topographic map of the ONH. Digital stereofunduscopic images, as well as both red-free and standard stereoscopic videocameras, have also been developed that analyze spaced lines projected on the ONH (Schuman, 1997). These units cannot differentiate normal from early glaucomatous human or canine optic discs, however, and they are limited in their ability to document subtle glaucomatous optic disc changes (Schuman, 1997).
Confocal laser scanning methods have recently been applied to the human and canine ocular fundi. Confocal optics assures that only a thin “slice” of tissue is in focus on the image plane; therefore, high-resolution tomographic images are obtained. A series of images are obtained at sequential tissue depths, and the 3-D structure of the ONH is then constructed (Dreher et al., 1991; Schuman, 1997; Weinreb et al., 1993).

The Heidelberg retinal tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany) is a confocal scanning laser ophthalmoscope, which has been shown to be an accurate and reliable method of assessing the 3-D optic disc topography (Schuman, 1997). The HRT uses a diode laser beam (670 nm) projected onto the retina with a confocal system. The confocal principle ensures that only light reflected from a defined focal plane is detected by the photomultiplier, thus rendering a high-resolution, small depth-of-focus image. The instrument automatically performs 32 consecutive, two-dimensional (2-D), tomographic scans perpendicular to the optic axis in 1.6 seconds, covering a section of ONH varying from 0.5- to 4.0-mm deep. The integrated computer then constructs a single mean topographic image in three dimensions from the 32 section image (see Fig. 26.10, Fig. 26.11, Fig. 26.12, and Fig. 26.25).

Scanning laser polarimetry is a method that provides in vivo quantitative assessment of the peripapillary RNFL in healthy and glaucomatous individuals. The instrument is a scanning laser ophthalmoscope with a polarization modulator, a cornea polarization compensator, and a polarization detection unit. The light source consists of a near-infrared diode laser (wavelength: 780 nm) in which the state of polarization is modulated. It is based on the assumption that the RNFL is birefringent because of the radial arrangement of the microtubules contained in the optic nerve fibers. The birefringence causes a change in the state of polarization of the illuminating laser beam. When the polarized, modulated light beam is focused onto a point of the retina, it penetrates the birefringent NFL, double-passes through the microtubules in the RNFL, and is partially reflected from deeper layers of the retina; the birefringent property of the axons then causes the polarized light to undergo a phase-shift between extraordinary and ordinary beams. The degree of phase-shift or state of polarization is called retardation and is linearly correlated with the thickness of the RNFL. The retardation data are then transformed into a thickness measure (micrometers), whereby one degree of retardation is equivalent to an RNFL thickness of approximately 7.4 µm when birefringence was measured in terms of degrees or 16.2 µm when it was evaluated in pitch length (Iwabe et al., 2007). The mean ± SD of the dog peripapillary RNFL thickness using scanning laser polarimetry was 141.69 ± 18 µm for normal dogs and 105.08 ± 23.86 µm for visual glaucomatous dogs. The average RNFL thickness near the optic disc in the superior and inferior retinal quadrants was 148.03 ± 8.5 and 141.06 ± 8.73 µm, respectively, for normal dogs, and 106.61 ± 25.77 and 107.08 ± 24.99 µm respectively for glaucomatous dogs. The peripapillary superi-

Optical coherence tomography is a new technology that can perform micron-resolution, cross-sectional, or tomographic imaging in the eye (Fig. 26.28, Fig. 26.29, and Fig. 26.30) (Dawson et al., 1996; Schuman, 1997). This technology is analogous to B-mode ultrasonography, except that light is used rather than acoustic waves. Optical axial ranging and imaging function by measuring the time delay of light reflected from various intraocular structures. Optical techniques have higher spatial resolution than ultrasonography, which allows imaging of fine microstructures in the eye. Tomographic or cross-sectional imaging of the ocular tissue is achieved by performing approximately 100 rapid, successive, axial, or longitudinal scans of the eye. This provides a cross-sectional map of the reflection and backscatter of the ocular tissue. Most tissue layers of the canine retina and optic nerve, including the NFL, inner nuclear layer, photoreceptor layer, RPE, optic cup, and choriocapillaris, can be imaged with this technology (Dawson et al., 1996). The entire retinal thickness and NFL thickness measured near the area centralis by OCT in normal dogs were greater in the superior than in the inferior retina (198.7 ± 9.6 µm vs. 164.4 ± 6.4 µm, P < 0.001; and 26.4 ± 1.6 µm vs. 25.0 ± 1.9 µm, P = 0.0236, respectively) (Hernandez-Merino et al., 2011). The average of
all retinal quadrants of the peripapillary NFL measured by OCT was 75.7 µm (Hernandez-Merino et al., 2011).

**Magnetic Resonance Imaging and Computed Tomography**

Thin-section, contrast-enhanced computed tomography (CT) (Leib, 1994; Peyster et al., 1983) is a medical imaging method that produces a 3-D image from a series of X-ray scans taken around a single axis of rotation. The CT can demonstrate details of the optic nerve anatomy on both axial and coronal views such that abnormalities, distortion, or increases of the optic nerve shape, and diameter can be detected (Fig. 26.31, Fig. 26.32, and Fig. 26.33). Orbital CT scans with axial and coronal views also allow the integrity of the optic nerve and the presence of an optic nerve sheath hematoma, orbital hemorrhage, or orbital fracture to be assessed. CT provides a high-contrast view of the optic nerve relative to the orbital fat and bony orbit (Leib, 1994). It also provides detail superior to that of plain-film radiography of orbital bone, soft tissue, and foreign bodies. CT is used to analyze orbital trauma, optic neuritis, orbital cellulitis, and optic nerve, and orbital neoplasia (Leib, 1994). CT of optic nerve tumors may cause the optic nerve to appear to be diffusely enlarged, irregularly thickened, or fusiform. Calcification of optic nerve tumors may be noted (Samuelson et al., 1983). Congenital optic disc colobomas can be identified in the presence of cataracts with CT (Mafee et al., 1983).

Magnetic resonance imaging (MRI) with gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA), contrast enhancement, and fat-suppression techniques analyzes atomic nuclear rotation in response to rotating magnetic and radio-frequency fields to produce highly detailed 3-D spatial infor-

**Figure 26.30.** Spectral-domain optical coherence tomographic (SD-OCT) imaging of the peripapillary retinal nerve fiber layer (RNFL) in a glaucomatous Basset Hound prior to and 12 hours after IOP spike (50 mmHg). IOP was reduced to 9 mmHg with the aggressive medical therapy. Image shows significant edema of the RNFL (delineated red areas marked with open arrows) and increase in retinal vein diameter (marked with closed arrows). S, superior; T, temporal; N, nasal; I, inferior. (Courtesy of Sinisa Grozdanic, Iowa City Veterans Administration Center for Prevention and Treatment of Visual Loss.)

**Figure 26.31.** SD-OCT imaging of the optic nerve head cup development in a glaucomatous Basset Hound. **A.** Initial imaging; IOP, 14 mmHg. **B.** Same patient 24 months later (IOP, 55 mmHg). (Courtesy of Sinisa Grozdanic, Iowa City Veterans Administration Center for Prevention and Treatment of Visual Loss.)
Ultrasonography

Real-time, B-scan ultrasonography units emit focused sound waves to produce a 2-D cross section of tissue, and they are most useful in evaluating intraocular and orbital disease (Hager et al., 1987; Paulsen et al., 1989). Ultrasonic scan heads of 7.5- or 10.0-MHz provide the best resolution of ocular tissues. This technique allows visualization of the optic nerve; differentiation of solid, soft-tissue masses versus cystic orbital masses; determination of the size of various globe or orbital components; and localization of foreign bodies. Color-flow Doppler imaging combines conventional B-mode ultrasonography with Doppler flow analysis to evaluate the orbital vascular structures, and it may prove to be useful for analysis of optic nerve lesions in the dog (Gelatt-Nicholson et al., 1999; Schmid & Murisier, 1996).

Pattern ERG

In the pattern electroretinogram (PERG), the retina is stimulated by a checkboard pattern which reverses its local luminance while keeping average luminance constant (Bach & Hoffmann, 2008). This technique is in contrast to the Flash ERG (FERG) which is the retinal response to changes in luminance (Ekesten, 2007). PERG is considered to be generated at the level of RGC and/or optic nerve (Rosolen et al., 2008), and is used to evaluate RGC function in humans and animals (Ekesten, 2007).

Since the PERG is a direct indicator of ganglion cell function, this technique is a promising candidate to indicate EG damage (Bach & Hoffmann, 2008). Also, PERG stimulus can be precisely located on the retina, thereby allowing quantitative structure-function correlation for specific retinal regions (Porciatti et al., 2007). In humans, the PERG has been shown to be of use in early diagnosis of glaucoma, and with appropriate recording techniques and paradigms can identify eyes at risk of visual deterioration. A reduction of the PERG amplitude is observed in glaucomatous patients without major effects on PERG latency. This amplitude reduction correlates to the visual field loss observed in the same patients (Bach & Hoffmann, 2008).

In experimental primate models of optic nerve transection and glaucoma, the amount of PERG amplitude reduction is consistent with the degree of damage apparent by counting either RGCs or optic nerve fibers. In the same experimental animals, the a- and b-waves of the conventional bright flash-ERG are only slightly or not affected (Porciatti et al., 2007). The PERG was found dramatically reduced in the glaucomatous (DBA/2J mouse model of glaucoma, and was used to monitor progression of functional changes of the inner retina in those animals. PERG and FERG were compared in prehypertensive DBA/2J mice to evaluate the capability of the techniques to detect early glaucomatous changes. Smaller amplitudes were obtained with the PERG while FERG exhibited higher values. PERG also detected longer latency than the cone-driven FERG (Porciatti et al., 2007).
Functional deficits may also precede significant elevation of IOP in canine glaucoma. Analysis of the RGC function evaluated by PERG in Basset Hounds with primary angle-closure glaucoma revealed that dogs with glaucoma develop significant and progressive functional deficits as early as 18 months of age before marked increases in IOP (IOP at 18 months of age, $17.5 \pm 1.2$ mmHg; glaucomatous $3.5 \pm 0.42 \mu V$; control $6.2 \pm 0.35 \mu V$). PERG amplitudes continued to decline and remained significantly lower in glaucomatous dogs compared with healthy control eyes at 20 months of age (glaucomatous $3.3 \pm 0.17 \mu V$; control $6.3 \pm 0.35 \mu V$) and 30 months of age (glaucomatous $1.84 \pm 1 \mu V$; control $6.2 \pm 0.35 \mu V$). A significant correlation between PERG amplitudes and IOP levels was observed. Scopotic ERG analysis of the same dogs did not reveal any deficits (Grozdanic et al., 2010).

The correlation of PERG amplitude and RNFL thickness (measured by OCT) was examined in patients with OHT and EG in humans. Mean PERG amplitude was decreased in both OHT and EG patients compared to controls while mean RNFL thicknesses were reduced only in EG patients. In OHT patients, PERG amplitude did not correlate significantly with RNFL thickness while in EG patients, PERG amplitude was positively correlated with RNFL thickness. These results reveal a lack of structure–function relationship in OHT, suggesting that, at this disease stage, PERG losses appear to affect primarily retinal/ONH function. In EG they reflect both dysfunction and RNFL loss (Falsini et al., 2008).

It should be recognized that PERG recording is one of the more demanding electrophysiological techniques, and that experience and care is required to achieve reliable and reproducible results (Bach & Hoffmann, 2008).

**Visual-Evoked Potential**

The visual-evoked potential (VEP) is an electrical signal generated by the occipital cortex in response to visual stimuli, and it is used to evaluate optic nerve function (Odom et al., 2005; Ofri et al., 1993a; Sims et al., 1989). Stroboscopic photo-stimulators and other light sources can be used to generate the flash VEP in the dog (Sims et al., 1989). The components of the canine flash VEP are three positive (P1, P2, and P3) and two negative (N1 and N2) peaks occurring 150 $\mu$s after the flash (Kimotsuki et al., 2006). Flash VEP recordings in dogs stimulated with a low-intensity, red-diode matrix light source have produced mean latencies to the three positive peaks (i.e., P1, P2, and P3) that comprise the canine VEP (Cz-Ch electrode pairs) of $22.6 \pm 3.0$, $46.9 \pm 3.4$, and $66.6 \pm 5.0$ ms, respectively (Sims et al., 1989). In addition, repetitive checkerboard or bar-grating patterns can be used as the visual stimulus for the pattern VEP in the dog (Ofri et al., 1993a); this approach takes advantage of the functional organization of the canine VC, which responds best to pattern stimuli of small spatial frequencies (Ofri et al., 1993a). The VEP can be used to distinguish vision loss from retinal or optic nerve dysfunction. The latency of P2, N2, and P3 is delayed by aging. The amplitudes of the P2-N2 and N2-P3 also were reduced by aging in dogs (Kimotsuki et al., 2006). Diseases that involve the optic nerve or preferentially cause demyelination are associated with a delayed latency, and consistently prolonged latencies are present in dogs with optic neuritis. Canine glaucoma reduces the amplitudes and increases the latencies of the flash and the pattern VEP (Ofri et al., 1993b). Optic nerve transaction results in absence of the flash VEP, but not of the flash electroretinogram (Sims et al., 1989).

**CONGENITAL OPTIC NEUROPATHIES**

**Optic Nerve Hypoplasia/Optic Nerve Aplasia/ Micropapilla**

There is a range in the number of RGCs and thus, in the number of optic nerve axons present between individual dogs. Optic nerve hypoplasia can be numerically described in relation to the mean optic nerve diameter. Optic nerves that are less than two SDs from the mean diameter are considered statistically abnormal (Jonas & Naumann, 1993). This would be less than or equal to 1706 $\mu$m in the dog (Balataratnasingam et al., 2008). Two mechanisms for optic nerve hypoplasia are proposed. A failure of RGC development and/or premature RGC death could produce the small number of optic nerve axons. The optic nerve hypoplasia phenotype may also be due to the failure of RGC axons to exit the optic disc and project to other visual regions. (Inatani, 2005; Ogata-Iwao et al., 2011). This is illustrated by the optic nerve hypoplasia observed in DCC- and netrin-1-deficient mouse embryos despite intact RGC pathfinding to the disc (Inatani, 2005).

Small optic nerves are associated with smaller numbers of RGCs and small optic discs. If the number of axons is so low that visual and pupillary light reflex (PLR) deficits are present, the condition is termed optic nerve hypoplasia (Fig. 26.34, Fig. 26.35, and Fig. 26.36). Hypoplasia of the optic nerve may be unilateral or bilateral, marked or minimal, and associated with either near normal or reduced visual function. In the dog, this condition may occur alone, or it may accompany other ocular malformations (Kern & Riis, 1981; Rubin, 1989; Wheeler, 1999). It is reported in several breeds including the Beagle and Shi Tzu (Negishi et al., 2008; Silva et al., 2008). The optic disc of the hypoplastic canine optic nerve is small and gray with no myelinated fibers on the disc surface. The appearance of the retina and retinal blood vessels is normal, but they also appear large in relation to the small optic disc size. The afferent portion of this PLR is abnormal, and the efferent component of the PLR normal is dogs with unilateral optic nerve hypoplasia. The pupil is generally partially dilated in dogs with optic nerve hypoplasia. Electoretinography shows no abnormal findings in the affected globe. Histopathologically, the hypoplastic optic nerve is markedly hypoplastic and composed of sparse neural elements and a moderate amount of connective and glial tissues. The retinal nerve fiber layer and the ganglion cell layer will be reduced in thickness, although a small

The heritability of optic nerve hypoplasia is reported to be recessive (Kern & Riis, 1981), dominant (Curtis et al., 1991), and undefined (Rubin, 1989; Wheeler, 1999) in Miniature and Toy Poodles. Complete absence of RGCs and the optic nerve is termed optic nerve aplasia. No retinal vessels will be present with optic nerve aplasia. I have observed bilateral optic nerve aplasia in a Beagle and mixed breed dog, and it is reported in the Irish Wolfhound (Fig. 26.37 and Fig. 26.38) (Curtis et al., 2008).
Micropapilla, or a slightly small optic disc, has a normal PLR and vision, yet probably is a form of optic nerve hypoplasia (Rubin, 1989). Micropapilla is found in Belgian Shepherds, Belgian Tervuren, Dachshunds, Irish Wolfhounds, Tibetan Spaniels, Miniature Schnauzers, Norfolk Terriers, Old English Shepherds, Shih Tzus, Gordon Setters, Great Pyrenees, Irish Setters, Labrador Retrievers, Pulis, Shelties, Beagles, Collies, Flat-Coated Retrievers, German Shepherds, Miniature Poodles, and Soft-Coated Wheaten Terriers (Rubin, 1989; Wheeler, 1999). The PLR and pupil size are normal in dogs with micropapilla.

Optic Nerve Colobomas

Optic nerve colobomas are congenital malformations of the ONH and peripapillary retina that enlarge or distort the ONH circumference (Curtis et al., 1991; Rubin, 1989). They may appear as enlarged discs with a deep excavation, or as slightly enlarged, irregular discs containing deep pits within the borders of the nerve head. Slightly enlarged physiologic pits in collies with choroidal hypoplasia may actually be shallow optic nerve colobomas.

Colobomas of the optic nerve in Collies are caused by faulty closure or fusion (or both) of the embryonic ventral (i.e., fetal) fissure of the optic stalk and cup; peripapillary colobomas originate from orbital cysts (Fig. 26.39, Fig. 26.40, Fig. 26.41, Fig. 26.42, and Fig. 26.43) (Curtis et al., 1991). Optic disc colobomas in Collies may be small and hard to differentiate from a deep, physiologic cup, or they may be very large in diameter and up to 30 D in depth. They may be “typical” at the 6-o’clock position or “atypical” at the nasal or temporal disc margin. Colobomas of the optic disc in Collies result from ectasia of the lamina cribrosa, whereas colobomas of the peripapillary retina are best characterized as foci of ectatic sclera lined by attenuated retinal and choroidal tissues (Curtis et al., 1991). Disc colobomas communicate
with the vitreous and subretinal space in the dog, and optic nerve colobomas of Collies are always associated with varying degrees of choroidal hypoplasia. Colobomas are also found in mixed breed dogs (Rampazzo et al., 2005) and Australian Shepherds, Shelties, Basenjis, American as well as English Cocker Spaniels, Norfolk Terriers, Huskies, Tibetan Spaniels, Irish Setters, Labrador as well as Golden Retrievers, Whippets, Samoyeds, Malamutes, Beagles, Bernese Mountain Dogs, Flat-Coated Retrievers and German Shepherds (Rampazzo et al., 2005; Rubin, 1989; Wheeler, 1999).

### Pseudopapilledema

Anomalous elevation of the ONH may resemble optic disc swelling caused by brain tumors, optic neuritis or elevated intracranial pressure (i.e., noninflammatory papilledema), and may be a cause for alarm and misdirected diagnostic procedures in humans (Glaser, 2005). In humans, pseudopapilledema is also referred to as optic disc drusen which are remnants of degenerate RGC axons (Friedman et al., 1975). In the dog, pseudopapilledema is not associated with pathology and most commonly results from excessive myelination of optic nerve axons beyond the anterior lamina cribrosa (Fig. 26.44 and Fig. 26.45). This may occur in isolated regions of the disc, along the retinal blood vessels, or involve most of the ONH. Because the fundusoscopic appearance suggests papilledema or optic neuritis, some patients may receive diagnostic workups or therapy (or both) for intracranial disease. Pseudopapilledema is reported in Curly-Coated Retrievers, Miniature Poodles, English Springer Spaniels, Labrador Retrievers, English Toy Spaniels, German Shepherds, and Golden Retrievers (Rubin, 1989).

### ACQUIRED OPTIC NERVE DISEASES

Disorders of the prechiasmal visual pathways are a diagnostic challenge. Optic nerve disorders may be caused by inflamma-
Differential Diagnosis of the “Swollen Disc”

Active or passive edematous swelling of the optic disc provides nonspecific evidence for distal optic nerve dysfunction (Glaser, 2005). Papilledema, or disc swelling because of increased intracranial pressure, must be differentiated from the apparently “swollen disc” of pseudopapilledema, and optic neuritis. The distinction of congenitally elevated discs (i.e., pseudopapilledema) from papilledema must be made. In its early stage, true papilledema does not affect vision (Glaser, 2005; Paulsen et al., 1989), but optic neuritis is associated with acute loss of vision and diminished PLR. Disc edema can accompany glaucoma, uveitis, or postoperative hypotony. Primary and metastatic ONH tumors (e.g., meningioma, glioma) may cause a “swollen disc,” and disc tumors may have hemorrhagic elevation of the disc and peripapillary retina as well as drastic reduction of vision. Orbital mass lesions characteristically produce proptosis, but they may also present as very chronic, unilateral disc edema, with insidiously advancing field loss (Glaser, 2005). Axonal swelling caused by the accumulation of mitochondria and other axoplasmic structures at the lamina cribrosa is primarily responsible for papilledema from elevated intracranial pressure as well as disc swelling from orbital tumors, ocular hypotony, and acute glaucoma (Tso & Hayreh, 1977a, 1977b). Disturbance of both fast and slow axoplasmic transport results in axonal swelling (Tso & Hayreh, 1977b).

Neuroimaging techniques such as MRI can aid differentiation of the causes of “swollen disc” (Glaser, 2005). Relatively thin-section techniques (e.g., 3 mm) are required especially for adequate visualization of the optic canal and prechiasmatic portions of optic nerves, with and without gadolinium enhancement. Ideally, high-resolution (1–1.5 tesla unit magnet systems) T1- and T2-weighted views should include axial, coronal, and sagittal sections; oblique views aligned with the long axis of the optic nerve (oblique sagittal) are of dubious value. The fat tissue of the orbit permits excellent contrast because fat appears bright (hyperintense) on T1-weighted images, whereas muscles, vessels, and nerves are darker (hypointense). Moreover, the optic nerve shares MRI characteristics with myelinated white matter of the brain. Blood vessels appear dark because of proton “flow voids.” Protocols that delineate optic nerves from orbital fat and minimize eye movement artifacts, such as fat-suppression fast spin-echo, are more effective than conventional T1- or T2-weighted images (Glaser, 2005).

Papilledema of Raised Intracranial Pressure

The term papilledema is reserved for passive, noninflammatory disc swelling associated with increased intracranial pressure. Papilledema is almost always bilateral and is not associated with visual deficits, at least in those developmental stages that precede atrophy (Glaser, 2005; Palmer et al., 1974). In the dog, brain tumors are associated with papilledema (Palmer et al., 1974). The pathogenesis involves a stasis of cellular infiltration, ischemia, infection, and mechanical compression. In the dog, abrupt onset of vision loss with a normal-appearing ONH is highly suggestive of sudden acquired retinal degeneration syndrome or of retrobulbar optic neuritis. Slowly progressive loss of vision is typical of neoplastic compression or infiltration of the prechiasmal optic nerve (Glaser, 2005).
both fast and slow axoplasmic flow at the lamina cribrosa of the ONH (Tso & Hayreh, 1977b). Optic nerve fibers are compressed in the subarachnoid space of the intraorbital portion of the optic nerve because of an elevation of CSFp. The subsequent obstruction of intra-axonal fluid mechanics results in leakage of water, protein, and other axoplasmic contents into the extracellular space of the prelaminar region of the optic disc (Glaser, 2005). This protein-rich fluid adds to the osmotic pressure of the extracellular space of the disc substance. The subsequent reduction in axoplasmic flow results in swelling of the axons in the prelaminar region of the optic disc (Glaser, 2005; Tso & Hayreh, 1977b). Venous obstruction and dilation and nerve fiber hypoxia are secondary events (Glaser, 2005). Therefore, it is likely that papilledema is primarily a mechanical rather than a vascular phenomenon (Glaser, 2005).

Papilledema in humans may develop within hours from subarachnoid or intracerebral hemorrhage (Glaser, 2005). Once the intracranial space is decompressed, venous congestion of the disc will diminish rapidly, but disc swelling, hemorrhages, and exudates will resolve slowly after lowering of the intracranial pressure (Glaser, 2005). Early and even well-developed papilledema may not be symptomatic. When papilledema has existed for many weeks or months, nerve fiber attrition results in progressive loss of vision and optic nerve atrophy.

In one veterinary report, papilledema was associated with brain tumors in 10 of 21 dogs, 15 of which had no vision or had PLR deficits (Palmer et al., 1974). Spindle cell sarcoma, microglioma, oligodendroglioma, astrocytoma, ependymoma, and meningiomas were also reported, possibly associated with increased intracranial pressure, in dogs with papilledema. Most dogs in this series were bilaterally affected. Dogs are thought to develop papilledema with increased CSFp only rarely, because this species does not have a central retinal artery and vein whose flow could be affected by elevated CSFp (Curtis et al., 1991). We do not believe this theory is necessarily valid, however, because papilledema from increased CSFp does not occur from vascular compromise (Glaser, 2005). CSFp in the dog is transmitted directly to the retrolaminar tissue space (Morgan et al., 1995, 1998), and a rise in CSFp could affect the ONH. If true papilledema has no associated PLR or vision deficits during its early stages, we simply may not be aware of the true incidence of papilledema in dogs with increased CSFp. Myelin anterior to the lamina cribrosa in the canine ONH also could provide stability to the axoplasmic flow under conditions of increased intracranial pressure and thus minimize the occurrence of true papilledema in the dog.

**Inflammatory Optic Neuropathies**

Optic neuritis is more of a clinical syndrome than a single disease (Glaser, 2005). It includes

- inflammatory diseases that contiguously involve the optic nerves of the adjacent paranasal sinuses, retina, brain and meninges, and orbit
- granulomatous and neoplastic infiltration syndromes such as reticulosis (Cuddon & Smith-Maxie, 1984; Glaser, 2005; Nafe & Carter, 1981; Palmer et al., 1974; Paulsen et al., 1989; Ryan et al., 2001; Stadtbäumer et al., 2004).

The term papillitis refers to the intraocular form of optic neuritis, in which optic disc swelling of varying degrees is observed. Optic neuritis must be distinguished from papilledema and pseudopapilledema. Optic neuritis is generally idiopathic in the dog (Nafe & Carter, 1981; Stadtbäumer et al., 2004).

**Optic Neuritis**

Inflammation of the canine optic nerve may be either unilateral or bilateral (Curtis et al., 1991; Nafe & Carter, 1981; Nell, 2008). The optic papilla and retrobulbar optic nerve may be affected. Clinical signs of blindness appear suddenly, and the pupils are fixed and dilated. The optic disc appears to be swollen and edematous, with blurring of the disc margins (Fig. 26.46 and Fig. 26.47). The physiologic cup may be lost as well (Nafe & Carter, 1981). The blood vessels on the disc surface are raised, and hemorrhages may be present. Papillitis is frequently associated with cells in the vitreous. Peripapillary retinal edema and neuroretinitis are commonly seen with optic neuritis in the dog (Nafe & Carter, 1981; Nell, 2008); no ophthalmoscopic signs of disc inflammation may be seen.

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- idiopathic, neoplastic, immune-mediated, and infective causes of optic neuritis
- inflammatory diseases that contiguously involve the optic nerves of the adjacent paranasal sinuses, retina, brain and meninges, and orbit
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**Optic Neuritis**

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reactive astrocytes expressing GFAP. Astroglia-like cells expressing vimentin, which is characteristic of immature astrocytes, were also found within the malacic lesions (Spitzbarth et al., 2010).

**Reticulosus and Granulomatous Meningoencephalitis**

The term reticulosus is confusing but generally refers to a group of neoplastic and idiopathic inflammatory diseases of the CNS including granulomatous meningoencephalitis (GME). It actually more specifically refers to neoplastic CNS disease processes with a pronounced inflammatory cell component. Chronic severe CNS inflammation in comparison can also develop histologic characteristics of neoplasia. Both the inflammatory and neoplastic forms of reticulosus include a continuous spectrum of cellular responses (Cuddon & Smith-Maxie, 1984; Curtis et al., 1991; Nuhsbaum et al., 2002; Ryan et al., 2001). A variety of mononuclear cells, lymphocytes, plasma cells, monocytes, and macrophages proliferate and accumulate in perivascular aggregates in the central nervous system to cause reticulosus (Cuddon & Smith-Maxie, 1984; Nuhsbaum et al., 2002; Ryan et al., 2001). A net of reticulin fibers also forms (Cuddon & Smith-Maxie, 1984). Proliferation of the reticulohistiocytic elements of the central nervous system can cause papillitis, optic neuritis, retino-choroiditis, choroiditis, iridocyclitis, and retinal detachments. Sudden blindness in both eyes with fixed, dilated pupils is a common presentation. Other neurologic signs may be present as well. The ONH can be hyperemic and swollen, though retrobulbar forms of reticulosus have been noted in the dog (Fig. 26.48, Fig. 26.49, Fig. 26.50, Fig. 26.51, and Fig. 26.52) (Cuddon &

**Canine necrotizing meningoencephalitis (NME), an inflammatory disease of unknown etiology, has been described in Pug dogs, Maltese Terriers, and Pekingese dogs, French Bulldogs, and Chihuahuas, and may lead to optic neuritis.** This idiopathic disorder affects both grey and white matter of the cerebral hemispheres and is accompanied by meningitis. Affected dogs can present with blindness, staggering, and ataxia. A nonsuppurative leukoencephalitis with extensive malacia within the forebrain has been found on histological examination. Necrotizing optic neuritis and focal retinitis can also be detected. Immunohistochemistry has revealed a CD3+ T-cell dominated inflammatory response with intralesional

![](image1)

**Figure 26.47.** Early venous phase of a fluorescein angiogram in the dog from Figure 26.46 with optic neuritis and a swollen, hyperfluorescent optic nerve head. A dorsal optic disc hemorrhage obstructs fluorescence. Note the autofluorescence of the dorsal tapetal fundus.

![](image2)

**Figure 26.48.** Optic neuritis caused by reticulosus appears as a swollen, hyperemic disc with indistinct margins. There is no apparent physiologic cup.
Smith-Maxie, 1984; Nell, 2008). The CSF will have increased protein levels and pleocytosis. The specific causes of these conditions are not known, but reticulosis may be a form of primary brain lymphoma. GME is a more disseminated form of inflammatory nonneoplastic reticulosis and may be an immuned-mediated disease caused by T-cell mediated delayed type hypersensitivity reaction to CNS antigens (Cuddon & Smith-Maxie, 1984; Nell, 2008; Nuhsbaum et al., 2002; Ryan et al., 2001).

Systemically administered corticosteroids remain the standard of therapy and are generally effective in the early stages of GME and reticulosis (Cuddon & Smith-Maxie, 1984; Nell, 2008; Nell, 2008; Ryan et al., 2001).
Vision is at least temporarily restored in many cases. Cytosine arabinoside and procarbazine have also been utilized for therapy (Cuddon & Smith-Maxie, 1984; Curtis et al., 1991; Nuhsbaum et al., 2002; Ryan et al., 2001). Discontinuation of therapy is rarely achieved.

Contiguous Inflammations

The optic nerve may be secondarily affected by various inflammatory or neoplastic lesions of adjacent tissues, including the uvea, retina, sclera, orbit, paranasal sinuses, and meninges. Vision defects may be caused by development of a true optic neuritis or by pressure on the optic nerve from cellular infiltration or mass compression (Glaser, 2005).

Immune-Mediated Optic Neuritis

Experimental allergic optic neuritis can be produced by immunizing guinea pigs with an isogenic spinal-cord emulsion in complete Freund’s adjuvant (Rao, 1981). The animals develop retrobulbar optic neuritis with infiltration of the optic nerve, chiasm, or brain by mononuclear cells. Focal demyelination of the nerve and neuroretinitis may also occur.

Traumatic Optic Neuropathies

All portions of the optic nerve (i.e., intraocular, intraorbital, intracanalicular, intracranial) are susceptible to injury, and traumatic proptosis and orbital fractures are common problems in the dog. Rapid deceleration of the anterior portion of the optic nerve relative to the fixed posterior portion of the canine optic nerve in traumatic globe proptosis can cause ONH avulsion, globe rupture, optic nerve laceration and atrophy, and vascular compromise to the ONH (Fritsche et al., 1996; Gilger et al., 1995; Glaser, 2005). In avulsion injuries, vision is lost immediately, and an afferent pupillary defect is evident. Vitreous and retinal hemorrhages may also be found. There is a massive proliferation of glial connective tissue around the ONH after optic nerve avulsion in dogs (Fig. 26.53).

Hemorrhage after trauma may disrupt the optic nerve parenchyma or accumulate within the nerve sheaths. Hemorrhage into the optic nerve or interference with its blood supply as the result of trauma can result in optic neuropathy (Iwamoto & Iliff, 2005; Wylie et al., 1972).

The optic disc may initially appear to be normal with damage to the nerve posterior to the entrance of the retinal vessels (Iwamoto & Iliff, 2005). Intracanalicular optic nerve trauma can result from direct damage by penetrating foreign bodies, compression, and fractures, or it can result from indirect damage, such as a blow to the frontal region (Iwamoto & Iliff, 2005; Kennerdell et al., 1976). Force applied to the anterior orbit can be transmitted to the optic foramen, with subsequent traction, contusion, and shearing forces applied to the optic nerve and small nutrient vessels (Anderson et al., 1982). In addition, traumatic optic neuropathy may result from vascular compromise or as a consequence of short PCA vessel shearing, vascular spasm, thrombosis, or subsequent ischemia or contusion necrosis (Frenkel & Spoor, 1987; Iwamoto & Iliff, 2005).

A number of treatment options for traumatic optic neuropathy in humans have been advocated, including osmotic agents (Matsuzuki et al., 1982), systemic corticosteroids, and surgical decompression of the optic nerve sheath or canal (Iwamoto & Iliff, 2005). Spontaneous visual recovery has been reported in humans (Hughes, 1962; Wolin & Lavin, 1990) and has been noted in some traumatic neuropathies in dogs, but aggressive medical treatment is advocated in the absence of optic nerve avulsion. When clinical findings include disc swelling, which suggests a compressive effect, and CT and MRI scans show an enlarged optic nerve, immediate decompression of an enlarging optic nerve sheath hematoma can salvage vision (Guy et al., 1989; Iwamoto & Iliff, 2005). Surgery has been advocated on the rationale that decompression may reduce the compressive effect of hemorrhage. The rationale for high-dose steroid use arises from the ability of steroids to reduce trauma-induced edema, microvascular spasm, and nerve cell necrosis (Gross et al., 1981).

Optic Nerve Tumors

Optic nerve tumors in the dog may present with exophthalmos alone or with exophthalmos and a unilateral or bilateral papilledema and subsequent optic neuritis (Mauldin et al., 2000). Impingement and infiltration of the tumor to the optic nerve can reduce the axoplasmic flow (Nafe & Carter, 1981).
Primary optic nerve tumors reported in the dog include teratoid medulloepithelioma, ganglioglioma, and meningioma (Fig. 26.54). Squamous cell carcinomas, nasal tumors, and orbital tumors may affect the optic nerve (Curtis et al., 1991; Mauldin et al., 2000; Nafe & Carter, 1981; Paulsen et al., 1989).

Retinal and optic nerve gliomas such as astrocytomas, oligodendrogliomas, mixed tumors (oligoastrocytomas), and ependymomas may be considered as differential diagnoses of intraocular and orbital masses. The metastatic potential appears to be low, but ascending invasion into the ventral aspect of the brain is possible. Glaucoma, pre-iridal fibrovascular membrane, and hyphema are associated with these tumors (Naranjo et al., 2008).

Canine optic nerve meningiomas were demonstrated to stain positive with vimentin, and concentric whirls of cells showed more intense labeling than did bundles of fibroblastic cells. S100 and NSE (neuron-specific enolase) labeling were detected in all tumors. They were negative to cytokeratin (CK) and GFAP (Montoliu et al., 2006).

THE GLAUCOMAS AND RGC AND THE OPTIC NERVE

Glaucoma is the final common pathway of a group of diseases with decreased RGC sensitivity and function, RGC death and ONH cup enlargement, an incremental reduction in visual fields, and blindness. Glaucomas are neurodegenerative diseases as they result in the death of a neural cell, the RGC. Most of these diseases result in or are associated with increased IOP (Fechtner & Weinreb, 1994; Shields, 1994; Van Buskirk & Cioffi, 1992; Wilson, 1994; Yablonski & Asamoto, 1993). The glaucomas consist of five stages:

- an initial pathologic event or series of events that leads to aqueous humor outflow system obstruction
- an increased level of IOP too high for optic nerve axoplasmic flow
- RGC dysfunction with resulting optic nerve degeneration and atrophy, and subsequently
- visual fields loss and blindness (Shields, 1994).

Elevated IOP is a risk factor for optic nerve damage. Elevated levels of excitotoxic amino acids, perfusion deficits in the ONH microcirculation, failure of autoregulation, neurotrophin deprivation, and laminar ECM abnormalities are other risk factors that may also contribute to the optic nerve damage in glaucoma (Bill, 1993; Fechtner & Weinreb, 1994; Hager et al., 1987; Hernandez & Pena, 1997; Mafee et al., 1983; Palko et al., 2012; Shields, 1994; Van Buskirk & Cioffi, 1992; Wilson, 1994; Yablonski & Asamoto, 1993). Nevertheless, it has been reported that the canine retina has the capacity to recover at least some visual function even at 14 days after acute elevation of the IOP (Grozdanic et al., 2007; Zeimer, 1995).

Retinal Ganglion Cell Degeneration in Glaucoma

High IOP, a compromised vascular supply to the ONH, amino acid excitotoxicity, a less compliant or stiff lamina cribrosa, and neurotrophin deprivation all play a role in glaucomatous optic nerve damage (Brooks et al., 1999b; Burgoyne et al., 2005; Nickells, 1996). At every level of IOP there is a risk of glaucomatous damage, although the risk increases with increasing IOP. Damage can occur with extreme rapidity as in angle closure glaucoma, or may progress slowly in the chronic types of glaucoma (Spaeth, 1993a). Sensitivity of the optic nerve to a particular level of IOP may change with time with progressive damage occurring at an IOP previously believed to be a safe IOP (Burgoyne et al., 2005; Spaeth, 1993a). IOP measurement cannot be used by itself as a determinant of whether glaucoma is or is not present, or whether optic nerve damage will occur or progress in humans (Spaeth, 1993a) or dogs. This variation in ONH susceptibility has been suggested to result from varying capacity for autoregulation to prevent IOP-induced ischemia, and particular sensitivity of large RGC to retinal excitotoxic amino acids (Fechtner & Weinreb, 1994; Spaeth, 1993a). Glaucomatous optic nerve damage at relatively low IOP may be more associated with mechanically induced optic nerve stresses, while optic nerve damage due to high IOP results more from a failure of autoregulation (Caprioli, 1995).

In the early stages of neural tissue pressure rise, there are both astrocyte and axonal injury (Balaratnasingam et al., 2008). Extensive gliosis of retinal astrocytes in the glaucomatous dog retina is manifested by GFAP accumulation (Bill,
Large diameter optic nerve axons appear particularly sensitive to the elevated IOP and other inciting factors found in human, monkey, dog, and equine glaucomas (Brooks et al., 1995a, 1995b; Quigley et al., 1987, 1988). Although axons of all sizes are subjected at the lamina cribrosa to severe shearing forces from the abrupt reduction in transpulmonary hydrostatic pressure (Fechtner & Weinreb, 1994; Yablonski & Asamoto, 1993), large diameter axons appear most susceptible to this sudden pressure transition as the CCP of axons is inversely proportional to the cube of the axon’s radius (Yablonski & Asamoto, 1993). Even small elevations in IOP may cause a reduction of axoplasmic flow in large diameter axons, with subsequent axon collapse and axonal degeneration and atrophy (Hollander et al., 1995; Williams et al., 1983). Weakness or disruption in the supportive ECM tissue of the lamina cribrosa, as is found in glaucomatous human eyes and may exist in other species with glaucoma (Burgoyne et al., 2005; Hernandez & Pena, 1997; Quigley et al., 1991), may also exacerbate this tendency for collapse of these large diameter axons.

Structural changes induced by glaucoma precede the ability to detect functional changes in the retina and optic nerve of human eyes with glaucoma (Burgoyne et al., 2005; Caprioli, 1995; Spoerl et al., 2005). Psychophysical function testing of the IOP sensitive, large diameter M, and the large diameter, short wavelength P or “blue”-type RGCs may be better indicators of glaucoma progression than tests of other types of RGC despite the known progressive damage to all sized diameter RGC and optic nerve axons (Johnson, 1994; Sample et al., 1994; Steward & Chauhan, 1995). The small total numbers of these types of large RGC are associated with reduced functional redundancy, with the loss of even a few of these RGC being more easily demonstrated than that of functional loss in more common RGC (Johnson, 1994; Sample et al., 1994; Steward & Chauhan, 1995).

In glaucoma of the Basset Hound dog, scotopic and photopic ERGs do not show much evidence of reduced function in the early stages of the disease but PERG analysis shows reduced amplitudes prior to major elevations in IOP. Functional vision deficits may precede IOP elevation in dogs with primary glaucoma (Grozdanic et al., 2010).

### Mechanisms of Glaucomatous Optic Neuropathy

Glutamate is the primary retinal neurotransmitter in vertebrates, and RGC and bipolar cells have extensive glutaminergic input (Choi, 1995; Kapin, 1995). Several subtypes of glutamate ionotropic and metabotropic receptors regulate metabolic events in the postsynaptic neurons by increasing the free intraneuronal calcium concentrations. Normal glutaminergic synaptic activity results in intermittent intraneuronal calcium signaling. In diseases, such as glaucoma that are associated with ONH ischemia and increased retinal glutamate content (Brooks et al., 1997; Schwartz et al., 1996), this intermittent calcium signaling transforms to continuous calcium stimulation at RGC ionotropic glutamate receptors. Excess extracellular glutamate thus causes RGC and neuronal cell death by overstimulating the glutamate receptors. This type of overactivation is termed excitotoxicity (Choi, 1995).

Excitotoxicity to RGC from excess glutamate can occur from ischemia, hypoglycemia, or direct mechanical neuronal trauma (Costa, 1995). N-methyl-D-aspartate (NMDA) glutamate receptors cause an increase in intraneuronal calcium which activates NOS and other enzymes. NOS may mediate glutamate excitotoxicity as it catalyzes arginine to form NO which acts as an oxygen free radical (OFR) by generating peroxynitrite (ONOO⁻) (Costa, 1995; Sawada et al., 1998). Simultaneous glutamate activation of NMDA and amino-3-hydroxy-5-methyl-isoxazol-4-propionic acid (AMPA)/kainate receptors causes RGC membrane depolarization which moves the magnesium ion blocking the NMDA receptor ion channel away from the ion channel, and allows calcium to enter the RGC. Voltage-dependent calcium channels (VDCC) are also triggered to open to allow more calcium entry (Choi, 1995; Dreyer, 1998). Intracellular calcium is also released from damaged mitochondria. Calcium leads to neuronal cell death by activating lipolytic enzymes, altering protein phosphorylation, decreasing mitochondrial function, forming OFR, and causing microtubule breakdown (Siejsjö, 1995).

RGC injured in glaucoma from mechanical and/or ischemic insults release their intracellular glutamate into the retina and affect neighboring healthy noninjured RGC by changing the local retinal microenvironment from a “good to a bad neighborhood” (Choi, 1995). Glutamate receptors on the healthy RGC are overstimulated, their intraneuronal calcium homeostasis disturbed, and the healthy RGC then becomes diseased and die (Dreyer, 1998; Schwartz et al., 1996). Astrocytes also have glutamate receptors and may become influenced by the excess glutamate to have an adverse effect directly on the optic nerve axons, although the axons themselves do not have glutamate receptors (Choi, 1995). Glutamate is also directly toxic to oligodendrocytes causing demyelination, although this toxicity is not due to NMDA receptors (Costa, 1995). Nonastrocytic inner retinal glia-like (NIRG) cells are found in canine astrocytes and NIRG-like cells scattered across inner layers of the retina and within the optic nerve. These cells are stimulated by insulin-like growth factor 1 (IGF-1) to proliferate, migrate distally into the retina, and upregulate the nestin-related intermediate filament transint. These changes in glial activity correspond with increased susceptibility of neurons to excitotoxic damage (Fischer et al., 2010).

Optic nerve head hypoperfusion, independent of elevated IOP, causing ischemia to the RGC and optic nerve axons may also be important in the pathogenesis of some types or stages of glaucomatous optic neuropathy (Brooks et al., 1997; Fechtner & Weinreb, 1994; Shields, 1994; Van Buskirk & Cioffi, 1992; Wilson, 1994). Significant RGC damage may occur at normal IOP in some types of glaucoma in humans (Spaeth, 1993a) and functional alterations of large diameter...
RGC occur at normal IOP prior to increases in IOP in canine primary glaucoma (Ofri et al., 1993b), although most glaucomas in all species are associated with increased IOP (Brooks et al., 1989, 1995a, 1995b; Shields, 1994). Reduced perfusion to the SPCA and EOA prior to elevation of IOP is associated with the hereditary glaucoma of Beagle dogs (Gelatt-Nicholson et al., 1999). Elevated IOP could exacerbate any preexisting ONH circulatory problems to cause ONH ischemia (Fig. 26.55 and Fig. 26.56).

In dogs, elevations in IOP result in complete or intermittent reductions in axoplasmic flow in morphologically or physiologically predisposed canine optic nerve axons, probable neurotrophin deprivation to the RGC soma of these axons with resultant RGC, and possibly Müller cell dysfunction, elevated retinal glutamate levels potentially toxic to canine RGC (Brooks et al., 1997), increased retinal and ONH NOS-1 (Franco-Bourland et al., 1998), GFAP (Komáromy et al., 1998), and tumor suppressor gene p53 levels (Whiteman et al., 2002). Neuroinflammation may also play a role in canine glaucoma as indicated by increased NFLs of TNF alpha (Jiang et al., 2010), RGC and photoreceptor apoptosis (Whiteman et al., 2002), and subsequent optic nerve axonal degeneration and atrophy (Brooks et al., 1995). Secondary degeneration of undamaged, healthy RGC axons that escaped the initial insult of sustained or intermittent elevation of IOP occurs due to release of toxic levels of retinal glutamate from the cell bodies of the directly damaged RGC into the local retinal microenvironment (Schwartz et al., 1996). The secondary axonal degenerative effects occur and continue independent of the normalization of IOP. The induced or secondary damage is more extensive than that of the initial injury. Excitotoxic amino acids, intra-axonal calcium ion influx, OFR and NO production, neurotrophin deprivation, and apoptosis induction may be involved in the pathogenesis of the optic neuropathy of canine glaucoma (Brooks et al., 1997; Schwartz et al., 1996). The increased level of intravitreal glutamate provides evidence for an ischemic mechanism for RGC death and optic nerve atrophy in canine glaucoma (Brooks et al., 1997; Nickells, 1996; Schwartz et al., 1996).

Brain derived neurotrophic factor (BDNF) retrograde axonal transport is substantially inhibited by intraocular pressure elevation in American Cocker Spaniel dogs. Tyrosine kinase receptors type B (TrkB) accumulation at the ONH in glaucoma suggests a role for neurotrophin deprivation in the pathogenesis of RGC death in canine glaucoma, as well as a possible paracrine and/or autocrine signaling within the lamina cribrosa. Neurotrophin signaling may regulate more than neuronal development, survival, and differentiation. BDNF neurotrophin and its TrkB receptor expression by lamina cribrosa cells and ONH astrocytes in glaucomatous eyes may help to determine the role of these cells as a paracrine source in terms of RGC survival, during episodes of elevated intraocular pressure (Iwabe et al., 2007).

**Optic Nerve Neuroprotection and Optic Nerve Rescue in Glaucoma**

Optic nerve neuroprotection is the guarding of intact healthy RGC and their axons that escaped damage during the initial glaucoma-induced trauma from secondary excitotoxic-induced degeneration. Optic nerve rescue involves the preservation, survival, and healing of healthy RGC bodies that have injured axons (Schwartz et al., 1996). Excitatory amino acid antagonists, agents that improve mitochondrial function, glutamate NMDA receptor antagonists which block NMDA receptors but do not affect non-NMDA receptors, NOS inhibitors, OFR scavengers, neurotrophic factors such as BDNF, apoptosis inhibitors, and calcium channel blockers may
provide RGC and their axons protection against the glutamate-mediated toxicity found under the ischemic conditions in the retina and ONH of dogs with glaucoma (Brooks et al., 1997; Nickells, 1996; Wilson, 1994). Neuroprotective treatment for the optic neuropathy of glaucoma will include IOP reduction therapy, as well as compounds to neutralize mediators of glutamate damage, and compounds that upregulate cell-survival regulatory genes such as bcl-2, or downregulate genes that promoted apoptosis such as bax (Schwartz et al., 1996).

**Neuroregeneration**

Neuroregeneration is the regrowth and elongation of injured optic nerve axons of RGC with healthy cell bodies, and the acquisition and reconnection to the neural target. Spontaneous regeneration of CNS neurons does not occur in mammals, although it does in fish and amphibians. The prevailing hypothesis is that the central neurons of adult mammals do have the capacity to regenerate, but that the cellular and molecular environment that surrounds neurons in the adult mammalian CNS inhibits regrowth of neural fibers (Costa, 1995; García-Valenzuela & Sharma, 1996; Sivron et al., 1991). Macrophages and/or activated astrocytes in fish optic nerves possess soluble regenerative factors which are responsible for the ability of fish optic nerve axons to regenerate (Sivron et al., 1991).

Axons grow first by elongation, followed by growth in radial diameter. Tubulin microtubules are essential in axon elongation for stabilizing cytoplasmic processes arising from growth cones at the tips of elongating axons. Neurofilaments (NFs) are important in radial growth of myelinated axons. NF movement in RGC axons move primarily NF which is not conducive for elongation. Neurotrophic factors such as BDNF may promote tubulin movement in RGC axons. Schwann cells of peripheral nerves promote regeneration, while oligodendroglial cells produce proteins which inhibit regeneration (Hoffman, 1995). Myelinated-associated inhibitory molecules in the myelinated optic nerve, and the presence of astrocytes in the nonmyelinated ONH may prevent regeneration by blocking axonal growth (Bray, 1995; Schwartz, 2005).

**REFERENCES**


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Section IV

SPECIAL OPHTHALMOLOGY
Cats are very popular companion animals. In a 2010 survey in the United States, the total number of pet cats kept was greater than the number of pet dogs. Clients increasingly seek specialized veterinary care for their companion animals, emphasizing the need for ophthalmologists to be well versed in the feline eye and its diseases. Well cared for cats may live into their mid- or late teens, and thus health problems of the geriatric patient, including ocular problems such as hypertensive retinopathy, are more common today than ever before.

A number of ocular diseases occur uniquely in cats, such as corneal sequestra, eosinophilic proliferative keratitis, and herpetic keratoconjunctivitis. Common problems seen in dogs such as adnexal disorders, dry eye, and cataract are encountered much less frequently in feline patients. Infectious agents that may affect the eye such as feline herpesvirus and Chlamydia felis are commonly encountered in young patients, particularly those from shelter or cattery environments.

This chapter presents a broad scope of ophthalmic conditions in the domestic cat, including important differences in anatomy, physiology, and disease conditions in the cat compared with the dog.

**DISEASES OF THE EYELIDS**

**Congenital and Developmental Eyelid Disorders**

Eyelid colobomas (eyelid agenesis) are usually bilateral and occur primarily along the lateral portion of the upper lids (Fig. 27.1). The cause is unknown. While possible in any breed, eyelid agenesis has been reported in the domestic shorthair (Dziezyc & Millichamp, 1989; Martin et al., 1997), Persian (Bellhorn et al., 1971), and Burmese (Koch, 1979). Eyelid agenesis in combination with other ocular abnormalities has been reported in the snow leopard (Barnett, 1981; Barnett & Lewis, 2002) and Texas cougar (Felis concolor) (Cutler, 2002). Eyelid colobomas are generally accompanied by trichiasis, exposure keratitis, corneal vascularization, epithelial hyperplasia, and occasional ulceration attributable to inadequate eyelid function. All cats with eyelid colobomas should be carefully examined by slit lamp biomicroscopy and ophthalmoscopy, because intracocular anomalies are often concurrent (Martin et al., 1997). The most common intracocular anomaly is a persistent pupillary membrane, although occasionally, choroidal and optic nerve colobomas and retinal dysplasia are observed. If the eyelid defect is small and the cornea is healthy, no treatment may be necessary. For larger eyelid defects, surgical reconstruction of the upper eyelid and lid margin is indicated for ocular health and the comfort of the cat.

Several surgical procedures have been described to correct eyelid agenesis. The size of the defect is an important consideration when selecting a method for reconstruction. Blogg (1985) described a technique in which a small defect is repaired by undermining the skin dorsal to the defect and directly suturing the lid margin at the medial and lateral aspects of the coloboma. The upper eyelid is then lengthened by a lateral canthotomy, which is unevenly closed so that extra skin is left at the dorsal aspect. The classical technique is the Roberts & Bistner (1968) procedure in which a pedicle of skin, orbicularis oculi muscle, and the tarsus are rotated from the lower eyelid to the upper eyelid defect. The pedicle is sutured into place and the lower eyelid defect closed. Superior palpebral conjunctiva is advanced and sutured to the ventral margin of the graft. Dziezyc & Millichamp (1989) modified this technique by creating a conjunctival pedicle from the anterior surface of the nictitating membrane to the upper eyelid to ensure adequate conjunctival lining of the posterior surface of the graft.

A recently described technique involves a lip commissure to eyelid transposition (Whittaker et al., 2010). Although the commissure of the mouth is shortened, the technique allows for the rotation of skin already lined by a mucous membrane, and with hair growing in an appropriate direction away from the eye. Additionally, the commissure of the mouth becomes the new lateral canthus with a good approximation of normal eyelid anatomy (Fig. 27.2a, b).
Figure 27.1. Extensive eyelid agenesis involving the lateral two-thirds of the upper eyelid as well as the lateral canthus in an adult domestic shorthair cat. Corneal vascularization and fibrosis are the result of the marked trichiasis and corneal exposure.

Correction can also be achieved by performing sliding skin grafts; Z-plasty skin flaps; semicircular skin grafts; the Cutler-Bead or bucket-handle technique; a modification of the Mustardé cross-lid technique using the full-thickness lower eyelid to reconstruct the upper eyelid and then repairing the lower lid defect with an upper lid graft (Esson, 2001); or injection of subdermal collagen to replace the eyelid stroma combined with a modified Stades technique to remove misdirected hairs (Wolfer, 2002). The overall objective of these surgical techniques is to provide a cosmetic upper eyelid, a functional dorsolateral lid, and corneal protection (Gelatt & Gelatt, 1994).

The main disadvantage of the lower lid rotational flap is that trichiasis may occur, because hair from the new upper lid tends to project toward the cornea. Trichiasis can be treated by cryoepilation, redirecting the cilia by repeated applications of petrolatum, or evertong the new lid margin through a modified Hotz–Celsius procedure very close to the lid margin. The main disadvantage of direct apposition is that large defects are difficult to close.

Structural defects of the feline adnexa occur uncommonly. Cats are occasionally presented with traumatic eyelid lacerations usually attributable to fighting. Cilia disorders are rare in cats, though an ectopic cillum has been described in a Siamese cat (Hacker, 1989), and multiple distichia described in a domestic shorthair cat (Reinstein et al., 2011). Unless cicatricial in origin, ectropion appears to be nearly non-existent; entropion (usually of the lower lid) is probably the most commonly acquired structural defect of the feline adnexa. Although much less common than in the dog, primary entropion does occur (Fig. 27.3), and a predilection for Persian and other brachycephalic breeds, as well as the Maine Coon cat, has been suggested (Roberts & Lipton, 1975; Williams & Kim, 2009). Older cats may develop entropion in association with enophthalmos due to atrophy of orbital fat and muscle. Kittens born with microphthalmia may have entropion due to lack of globe support for the eyelids (Fig. 27.4). Cicatricial entropion has been suggested to be the most common cause of feline entropion (Roberts & Lipton, 1975; Weiss, 1980), although in a case series of 50 cats, no cases of cicatricial entropion were found (Williams & Kim, 2009). Entropion may also occur secondary to painful ocular diseases that induce chronic blepharospasm. Initially, the entropion might be described as spastic, but the eyelid inversion tends to become permanent with chronicity, thereby suggesting that cicatrices eventually develop. The modified Hotz-Celsius technique (see Chapter 14) is the procedure of choice for correcting all forms of feline entropion, and it can readily be modified for each patient’s abnormality (Glaze, 2005). If excess eyelid length is a contributing factor, shortening of the eyelid by a wedge resection in conjunction with the modified Hotz-Celsius procedure is indicated (Read & Broun, 2007).

Focal and Diffuse Blepharitis

While uncommon, localized demodecosis, a parasitic skin disease in the cat, may occur around the eyes and on the face and neck (Medleau & Hnilica, 2001) (Fig. 27.5). The causative agents are Demodex cati, Demodex gatoi, and a third unnamed Demodex mite (Desh & Stewart, 1999; Kano et al., 2012). The condition is characterized by periocular alopecia, erythema, scaling, crusts, and usually pruritus if caused by D. gatoi (Craig, 2003). The diagnosis is made on the basis of identifying the mites in scrapings from the affected skin. Plucking periocular hair with hemostats is gentler and safer than scraping, although samples may be nondiagnostic for the deep mite. D. cati. Localized lesions may resolve spontaneously without treatment. Topical therapy with rotenone ointment or 0.025% amitraz solution (do not use in diabetic cats) is reportedly effective. The treatment of choice for D. gatoi is 2% lime sulfur dips once a week for at least four treatments or past negative skin scrapings. Alternative therapies include ivermectin 0.2 mg/kg orally or subcutaneously twice, 2 weeks apart (Medleau & Hnilica, 2001), or doramectin 0.2 mg/kg subcutaneously once.

Feline dermatophytosis is caused by Microsporum canis and, to a lesser extent, by Microsporum gypseum and Trichophyton mentagrophytes, and may involve the eyelids (Sparkes, 2004). Lesions are circular, oval, or irregularly shaped areas of alopecia, typically accompanied by folliculitis. The diagnosis is made on the basis of fungal culture and microscopic evaluation. Treatment of localized dermatophytosis is with topical application of an azole antifungal agent, such as 1%–2% miconazole, 1% clotrimazole, 2% ketoconazole, or 4% thiabendazole. In the generalized form, systemic therapy with griseofulvin (Sparkes, 2004) oritraconazole (Colombo
Figure 27.2.  

- **a.** Preoperative appearance of a Persian cat with a large upper eyelid defect and trichiasis.  
- **b.** Immediate postoperative appearance following surgical correction of the eyelid agenesis using the lip commissure to eyelid transposition technique. Note the reformation of the lateral canthus from the lip commissure.  
- **c.** Three months postoperatively, the upper eyelid has an excellent cosmetic appearance and good function. (Courtesy of Dr. Sari Jalomäki.)

Figure 27.3.  
Primary lower eyelid entropion in a domestic shorthair cat. The lower eyelid is excessively long resulting in entropion.

Figure 27.4.  
Entropion in a kitten secondary to microphthalmia.
Section IV: Special Ophthalmology

Special Ophthalmology

Inflammation and Infections

Cystitis. Drainage and appropriate systemic antimicrobial agents are indicated.

Cystic Lesions

Single to multiple soft, smooth, round, fluid-filled, nonpainful cysts, 2–10 mm in diameter and located in the skin of the eyelids, particularly the medial canthus, have been reported in six Persians and one Himalayan cat (Cantaloube et al., 2004; Chaitman et al., 1999; Yang et al., 2007). The cyst fluid ranges from translucent to brown in color. The lesions have been termed apocrine hidrocystomas or cystic adenomas of the apocrine sweat glands because of their histopathologic similarity to the apocrine hidrocystomas observed in human eyelids. A histopathologic and immunohistochemical study suggested that the cysts were proliferative lesions rather than neoplastic or retention cysts (Giudice et al., 2009). Therapeutic options include observation, drainage, or surgical excision of the cysts. In the reported cases, within 8–12 months of surgical excision, several of the cats had developed new cystic lesions. One case report describes the successful treatment of hidrocystomas by debridement and topical treatment with 20% trichloroacetic acid (Yang et al., 2007).

Nodular Lesions

Although leishmaniasis is rare in cats, the cutaneous form with nodular or ulcerative dermatitis has been reported in Texas, Mediterranean countries, Asia, and South America.
Section IV

Pavletic, 1982). Excision of extensive lesions may require procedures such as a caudal–auricular–axial pattern flap to close the surgical defect (Stiles et al., 2003). The primary limitation of surgical therapy for SCC is the difficulty in visually identifying the exact margins of the tumor. SCCs are often radiosensitive, so either teletherapy or brachytherapy may be used (Hardman & Stanley, 2001). Cryosurgery is an effective and inexpensive option as well, and hyperthermia is effective for superficial lesions. Photodynamic therapy has been reported as well, but in one study, 64% (7/11) of cases had recurrence (Stell et al., 2001). Orbital exenteration with wide skin margins and a grafting procedure should be considered in cats with extensive periocular SCC.

Basal cell carcinoma (i.e., basal cell epithelioma) is a common dermal neoplasm in cats, and though it has no particular site predilection, it can affect the eyelids (Diters & Walsh, 1984). These carcinomas are usually round and well circumscribed, but their tendency to become ulcerated allows their appearance to be confused with that of SCC. Unlike SCC, however, basal cell tumors are generally benign. Surgical excision and cryotherapy are effective means of treatment.

Mast cell tumors are also common dermal neoplasms in cats. Though demonstrating no site predilection, they do occasionally affect the eyelids and periocular region (Buerger & Scott, 1987; Garner & Lingeman, 1970). The tumors appear as single or multiple dermal masses. Their appearance is variable, however. They may be raised, ulcerated, well or poorly circumscribed, and may be dermal, epidermal, or subcutaneous in location (Fig. 27.8). Two studies indicated that most cutaneous mastocytomas are benign (Buerger & Scott, 1987;...
generally focal, nodular neoplasms that are dermal and subcutaneously situated, often with an alopecic and ulcerated surface. They are characterized histopathologically by immature fibroblasts interspersed among bundles of collagen fibers. Recommended therapy is wide surgical excision, and the prognosis correlates with the mitotic index (Bostock & Dye, 1979). In younger cats, multicentric fibrosarcomas are caused by the feline sarcoma virus (FeSV), which is a mutant of the feline leukemia virus (FeLV) (Hardy, 1971). Cats with FeSV-induced fibrosarcomas are leukemia virus positive, thus indicating a poor prognosis regardless of therapy.

Peripheral nerve sheath tumors (aka schwannoma, neurilemmoma, neurogenic sarcoma, neurofibroma, or neurofibrosarcoma) are infrequently seen in the periocular region (Hoffman et al., 2005) (Fig. 27.10). Local aggressive recurrence is common, and wide surgical excision combined with enucleation, or exenteration may be indicated.

Cutaneous papillomas are rare feline tumors that appear clinically as well-circumscribed, pedunculated, alopecic masses. Sebaceous gland tumors (i.e., sebaceous adenoma, adenocarcinoma, epithelioma) rarely occur in cats.

DISEASES OF THE NASOLACRIMAL AND TEAR SYSTEMS

Nasolacrimal (NL) and tear film disorders occur infrequently in domestic cats. The normal NL drainage system in the cat has recently been described using computed tomography (CT) and three-dimensional reconstruction (Noller et al., 2006). Epiphora is the most common NL abnormality in cats, most often as a conformational condition in brachycephalic breeds. In a study of brachycephalic cat skulls utilizing CT, it was determined that the greater the degree of brachycephalia, the more the facial bones and upper canine teeth are displaced dorsally (Schlueter et al., 2009). This facial deformity leads to the NL drainage system being forced to pass under the canine tooth and then being steeply oriented upward in a V
fashion. This leads to failure of tears to adequately pass through the NL system. Symblepharon formation from prior conjunctivitis may result in punctal occlusion and epiphora in any cat. While primarily a cosmetic problem, dermatitis may occur because of chronic facial wetting. Surgical conjunctivohiostomy can be utilized to divert tears into the nasal cavity and relieve epiphora, although the success of this surgery is variable (Covitz et al., 1977). Congenitally imperforate lacrimal puncta are uncommon in cats and can be surgically opened as described for other animals (see Chapter 15). Dacryocystitis is likewise rare in cats, presumably because the relatively short NL duct provides less opportunity for obstruction. A case report describes NL duct obstruction by compression from an adjacent canine tooth root abscess in a cat (Anthony et al., 2010).

Though uncommon, keratoconjunctivitis sicca (KCS) is the most important lacrimal disease in cats. The actual causes, however, have been poorly defined. In contrast to KCS in dogs, a hereditary or immune-mediated component to feline KCS has not been identified. Decreased tear production secondary to administration of sulfonamide drugs has not been described in cats. As would be expected, atropinization and ketamine hydrochloride anesthesia transiently decrease tear production (Amett et al., 1984). Neurogenic KCS may occur secondary to diseases disrupting parasympathetic innervation of the lacrimal glands such as dysautonomia (Kidder et al., 2008). Most cases of feline KCS occur secondary to chronic blepharocconjunctivitis, at least some of which appears in turn to be secondary to recurrent or chronic feline herpesvirus type 1 (FHV-1) infection. Experimentally, transient KCS has been seen in cats with chronic FHV-1 infection (Nasissie et al., 1989a). Whether the decreased Schirmer tear test (STT) values were attributable to glandular or ductule damage, however, is not known.

The diagnosis of feline KCS is made on the basis of compatible clinical signs in conjunction with decreased STT values. A less than 5 mm of wetting is considered to be diagnostic (mean normal feline wetting, 17 mm), though many cats will have no clinical signs associated with such low values (Veith et al., 1970; Waters, 1994). Use of the phenol-red-thread tear test has also been reported in cats, with normal values being 21–25 mm wetting in 15 seconds (Brown et al., 1997).

Feline KCS is characterized by conjunctival hyperemia, mild and diffuse corneal opacification resulting from epithelial hyperplasia, and rarely, corneal vascularization and pigmentation as well as conjunctival discharge. In some cases, epithelial ulceration may also be present.

Treatment of feline KCS differs little from that of canine KCS. The foremost consideration is to correct, if possible, any underlying cause. Palliative relief is achieved by application of artificial tear products as needed (four times a day to hourly) and topical antibiotics to prevent bacterial infection. Pilocarpine may be used (one or two drops of 0.25%–0.50% solution mixed in the food), but the patient should be monitored for any adverse systemic effects such as vomiting, diarrhea, and salivation. Topical cyclosporine or tacrolimus are the current therapies of choice for the treatment of canine KCS. While the efficacy in feline KCS has not been established, ocular complications are uncommon except for demonstrated conjunctival hypersensitivities (Algoewer et al., 2001; Grahn & Storey, 2004). Cats tolerate the ointment formulation of cyclosporine better than the oil formulation. Parotid duct transposition has been described in cats and is reserved for those cases in which medical therapy is either impractical or unsuccessful (Gelatt & Gelatt, 1994; Gwin et al., 1977a).

Cullen et al. (1999) reported an association between ulcerative keratitis and qualitative tear film abnormalities in some cats. The cats presented with indolent corneal ulcers or corneal sequestra and demonstrated normal aqueous tear production with a lower tear breakup time or TBUT (2.5 seconds). The normal TBUT in young healthy cats is 12–21 seconds (Cullen et al., 2005a). In a study that evaluated tear film osmolarity as well as TBUT in normal cats and cats with conjunctivitis, there was no difference in osmolarity between the groups (Davis & Townsend, 2011). However, cats with conjunctivitis had significantly lower TBUT (mean of 7.8 seconds). Tear film osmolarity of normal cats was 325 mOsm/L.

**DISEASES OF THE THIRD EYELID**

The third eyelid, or nictitating membrane, moves passively in cats due to lack of any striated musculature (Nuyttens & Simoens, 1995). The third eyelid is typically visible only with changes in the position of the globe (enophthalmos or exophthalmos) or the loss of sympathetic tone, any of which may lead to elevation or protrusion. The third eyelid may also be visible if grossly thickened or swollen, as in neoplastic or inflammatory conditions affecting the third eyelid.

**Horner’s Syndrome**

Horner’s syndrome occurs when the sympathetic innervation to the eye is disrupted. Features of feline Horner’s syndrome include elevation of the third eyelid, miosis, ptosis, and enophthalmos (Fig. 27.11). Third eyelid elevation and miosis are the most consistent features of Horner’s syndrome in cats. Reported causes of Horner’s syndrome in cats include nasopharyngeal polyps (Kudnig, 2002); surgical treatment of nasopharyngeal polyps (Muilenburg & Fry, 2002); ear canal ablation (Bacon et al., 2003; Williams & White, 1992); bulla osteotomy (Trevor & Martin, 1993); percutaneous radiofrequency heat or chemical ablation of the thyroid tissue (Allergy et al., 2003; Wells et al., 2001); SCC (Manning, 1998); acute intervertebral disk extrusion (Lu et al., 2002); trauma to the head, neck, or chest wall (Frye, 1973); mediatinal or spinal neoplasia (Fox & Gutnick, 1972); otitis media (Cook, 2004); cleaning of the external ear canal, neck surgery, and skull fractures (Baines & Langley-Hobbs, 2001); brachial plexus root avulsion or catheterization of the common carotid artery.
SECTION IV: Special Ophthalmology

**Bilateral Third Eyelid Protrusion**

Bilateral third eyelid protrusion without other ocular abnormalities is fairly common in cats (Fig. 27.12). The condition may be associated with systemic illness or dehydration, or in older cats with loss of orbital fat and muscle mass. It may also occur in cats that have or recently have had diarrhea. In a study of 50 cats with diarrhea and bilateral third eyelid protrusion, a number of cats had a positive fecal isolation of an agent that resembled toravirus (Muir et al., 1990). An infectious disease was further suggested for this syndrome by the fact that in 87% of affected cats that were from multicat households, more than one cat was affected. In cats with idiopathic bilateral third eyelid protrusion and no other clinical signs, treatment is not indicated. The condition generally resolves, although it may take several weeks.

**Neoplasia**

Neoplasia of the third eyelid appears to be uncommon in cats. Reported neoplasms affecting the third eyelid include mast cell tumor (Crafts & Pulley, 1975; Larocca, 2000), hemangiosarcoma (Muitari et al., 2002), fibrosarcoma (Buyukmihci, 1975), adenocarcinoma (Komaromy et al., 1997; Pelffer & Simons, 2002; Williams et al., 1981), and melanoma (Schobert et al., 2010). Lymphoma arising from the third eyelid has also been seen (Fig. 27.13). SCC of the third eyelid appears to be most often associated with extension from the eyelids. Any mass of the third eyelid warrants a biopsy. Depending on the nature and extent of the neoplasia, excision of the mass alone or excision of the entire third eyelid should be performed. In the reported cases of a mast cell tumor (Larocca,
determine in many cats, particularly in the chronic state. Following are some of the most common and well-documented causes of conjunctivitis in cats.

**Herpesvirus**

FHV-1 is a major cause of conjunctivitis in both kittens and adult cats. Infection with FHV-1 is common, and the virus is widespread among cat populations (Crandell, 1971; Ellis, 1981; Studdert & Martin, 1970; Wardley et al., 1976). Primary (first exposure) FHV-1 disease is characterized by malaise, fever, sneezing or coughing, rhinitis and nasal discharge, as well as conjunctivitis with ocular discharge. The virus is spread from cat to cat either by direct contact or by aerosolization of virus. The virus infects the epithelial surfaces of the respiratory tract and conjunctiva and, to a lesser degree, the corneal epithelium. The cytopathic virus causes lysis of these tissues as the virus replicates and invades adjacent cells (Hoover et al., 1970; Nasisse et al., 1989a). Neutrophilic inflammation is marked and results in purulent ocular and nasal discharge, even if secondary bacterial infection is not present. Conjunctivitis is characterized by hyperemia, blepharospasm, chemosis, and ocular discharge (Fig. 27.15). In some cats, conjunctivitis is severe and includes large areas of ulceration of the conjunctival surface. Fibrinous and cellular exudates may be marked on the conjunctival surface. Ulcerated areas will form adhesions to one another and to ulcerated corneal lesions very quickly. These areas will become permanent adhesions (symblepharon) if not broken down quickly and repeatedly. Symblepharon most commonly occurs during a severe primary infection and is less likely to occur in older cats with recurrent herpesvirus conjunctivitis. In some cases, symblepharon may involve the entire ocular surface, resulting in blindness (Fig. 27.16). Severe symblepharon is very difficult to resolve surgically; therefore, every effort should be made to prevent symblepharon from occurring.
Neonatal ophthalmia may be caused by FHV-1, either from maternal transmission to the kitten or infection shortly after birth (Bistner et al., 1971; Nasisse, 1982). Primary exposure to FHV-1 typically occurs in kittens, especially during the age range of 8–12 weeks when maternal antibodies are waning. Older cats that were not exposed as kittens may become ill with a primary exposure. Immunity from vaccination against FHV-1 is incomplete and temporary, whether parenteral or intranasal vaccination is administered (Greene, 2006). Although intranasal (and conjunctival sac) vaccination has been recommended for cats that suffer from chronic persistent infection, there are no data to document any beneficial effect. Intranasal vaccination, although attenuated compared with the parenteral modified live vaccine, predictably causes upper respiratory disease, frequently with conjunctivitis as well. The parenteral vaccine, if it contacts oronasal or conjunctival mucosal surfaces, will incite disease as well.

Once cats are infected with FHV-1, they become latent carriers. Though cats can be reinfected with FHV-1 despite previous infection or vaccination, recurrent conjunctivitis is most likely to be associated with recrudescence of latent virus (Bistner et al., 1971; Bodle, 1976; Nasisse, 1982). The virus has been documented to establish latency in the trigeminal ganglia (Gaskell et al., 1985; Nasisse et al., 1992; Ohmura et al., 1993; Reubel et al., 1993; Townsend et al., 2004; Weigler et al., 1997) and travel back to the eye via anterograde axonal transport. Other tissues, such as the cornea, may also harbor the virus in either a truly latent state or a state of very low-level replicative activity (Stiles & Pogranichniy, 2008; Townsend et al., 2004). Recurrent conjunctivitis varies in severity among cats and may be bilateral or unilateral. It is not uncommon for an individual cat to have repeated episodes of conjunctivitis in the same eye, while the fellow eye remains clinically normal. Clinical signs may range from transient episodes of mild conjunctival hyperemia with no discomfort to severe discomfort, hyperemia, chemosis, and serous to purulent ocular discharge. Concurrent sneezing or other mild signs of respiratory tract infection may or may not be present. KCS has been reported in cats with FHV-1-related conjunctivitis as well (Peiffer, 1981; Stiles, 1995), although it does not appear to be common. In some cats, stressful events (other illness, surgery, environmental changes, pregnancy and lactation, vaccination, administration of systemic or ocular corticosteroids) may precede an outbreak; however, in other cats, no apparent stressor can be identified as a trigger. Occasionally, cats have ulcerative and pruritic skin disease associated with cutaneous herpesvirus infection. This condition has also been reported in a cheetah (Junge et al., 1991).

Establishing an accurate diagnosis of FHV-1 as a cause of conjunctivitis in adult cats has been problematic. Diagnostic tests such as virus isolation (VI) and FA, both of which are widely available, are relatively insensitive in cats with chronic or recurrent conjunctivitis (Nasisse et al., 1993; Stiles et al., 1997a). Serum antibody titers are only potentially useful in unvaccinated cats, and even then, such titers may not rise in a predictable manner (Nasisse, 1990). In one study of clinically normal cats, cats with chronic conjunctivitis, and cats with acute upper respiratory disease, serum neutralizing antibody and enzyme-linked immunosorbent assay (ELISA) tests were not helpful in diagnosing FHV-1 in individual cats (Maggs et al., 1999). PCR assay is the most sensitive test for detecting viral DNA. Several studies have demonstrated the sensitivity of PCR and the relative insensitivity of VI and FA staining (Nasisse et al., 1993; Stiles et al., 1997a, 1997b). However, studies have also found that samples from the conjunctiva of clinically normal cats may be positive for FHV-1 DNA when evaluated by PCR (Burgesser et al., 1999; Kang & Park, 2008; Low et al., 2007; Rampazzo et al., 2003; Stiles et al., 1997b). This is likely because cats may harbor the virus in a quiescent state in both the cornea and conjunctiva, and viral DNA will be detected by the sensitive PCR test. One study found that 11% of clinically normal cats were positive for FHV-1 by VI and FA (Burgesser et al., 1999). However, another study found that no clinically normal cats were positive by VI or FA (Stiles et al., 1997a).

In any cat with conjunctivitis, conjunctival scraping or brushing (Willis et al., 1997) and cytology are warranted. In conjunctivitis caused by FHV-1, the typical cytologic findings are epithelial cells and neutrophils (Fig. 27.17). Careful examination of the preparation to detect C. felis inclusion bodies is an important step in making a differential diagnosis, although the lack of inclusions does not rule out chlamydiosis.

Because of the difficulty in establishing a definitive diagnosis of FHV-1 as the cause of conjunctivitis in many cats, presumption of cause may be based on clinical signs (particularly recurrent episodes of conjunctivitis, or the presence of respiratory signs), cytologic findings, and response to treat-
ment. Therapy for herpesvirus ocular disease is discussed in the section on cornea.

**Chlamyphila**

C. felis, which is an obligate intracellular bacterium, is a common pathogen of cats, primarily causing conjunctivitis (Cello, 1967, 1971; Hoover et al., 1978; Johnson, 1984; Shewen et al., 1978; Studdert et al., 1981; Wills et al., 1984). The organism can also infect the gastrointestinal tract (Gaillard et al., 1984; Hargis et al., 1983; O’Dair et al., 1994) and respiratory system, but clinical signs associated with these systems are often mild or absent. Airborne transmission, direct cat-to-cat contact, and fomites may all spread chlamydial infections (Storz & Kaltenboeck, 1993; Sykes, 2005). The incubation period is approximately 3–5 days. Chlamydial elementary bodies survive in the environment for a few days at room temperature but are easily inactivated by lipid solvents and detergents. Serological studies suggest that multiple strains of C. felis exist and may differ in virulence (Kuroda-Kitogawa et al., 1993; Yerasimides, 1960). At least two strains that infect the cat have been documented on the basis of DNA fingerprinting (Pudjatmoko et al., 1997). Young cats are most likely to be infected, as a natural immunity tends to develop with increasing age. Cats greater than 5 years of age are very unlikely to be infected (Sykes & Greene, 2012). In a recent study, Chlamyphila pneumoniae, a human pathogen, was detected by PCR in five cats with conjunctivitis (Sibitz et al., 2011).

The acute phase of C. felis infection results in conjunctival hyperemia, chemosis, serous ocular discharge, and blepharo-spasms (Fig. 27.18a, b). Mild nasal discharge and sneezing may also occur. Conjunctivitis is often unilateral initially, then progresses to involve the second eye during the next few days. In some cases, the conjunctivitis remains unilateral. Ocular disease is produced by lytic cellular damage during the release of C. felis elementary bodies (Wyrick & Richmond, 1989). If untreated, infection with C. felis can produce chronic conjunctivitis (O’Dair et al., 1994). Asymptomatic carrier states can exist, which may be significant in spreading the organism.
within the cat population (Storz & Kaltenboeck, 1993). Persistence of the organism in the genital and gastrointestinal systems may also contribute to the spread of chlamydiosis (Wills et al., 1987).

Experimentally, coinfection with the feline immunodeficiency virus (FIV) led to a prolonged duration of clinical signs and the development of chronic conjunctivitis (O’Dair et al., 1994). In this study, clinical signs of conjunctivitis in control cats were resolved by day 109 after infection with C. felis, whereas FIV-infected cats still had conjunctivitis up to day 200. C. felis organisms were excreted from the conjunctival sac for up to 270 days in FIV-infected cats but for only 70 days in control cats. Both FIV-infected and control cats excreted C. felis from the gastrointestinal tract for 35 days.

C. felis is considered to be a zoonotic agent. Transmission from cats to humans has been reported (Hartley et al., 2001; Ostler et al., 1969; Schmeer et al., 1987; Shewen et al., 1978), as has transmission from a macaw to a cat (Lipman et al., 1994). The rate of transmission from cats to humans is probably low, but washing hands after handling an affected cat is prudent.

The diagnosis can be established on the basis of finding the characteristic inclusion body within the conjunctival epithelial cell cytoplasm (Fig. 27.19) or a positive FA test from a conjunctival scraping. Inclusion bodies are present in conjunctival cells from the third day after inoculation and then decrease in numbers over the next 2 weeks, making this an unreliable method of diagnosis (Storz & Kaltenboeck, 1993). Chlamydophila inclusion bodies should not be confused with “blue bodies,” which are epithelial cell cytoplasmic inclusions associated with the use of topical medications, particularly neomycin (Streeten & Streeten, 1985) (Fig. 27.20). Blue bodies are phagolysosomal vacuoles containing complex lipids, indicating injury to epithelial cells. They typically stain blue with routine cytologic preparations, thus the name.

Serum antibody titers using indirect immunofluorescence correlate well with recent infection (Sykes, 2005). Most cats (>95%) infected with C. felis have titers higher than 32, compared with less than 10% of uninfected cats.

C. felis can also be cultured in many types of mammalian and avian cells (O’Dair et al., 1994; Storz & Kaltenboeck, 1993). More recently, PCR tests have been developed to identify chlamydial DNA (Cai et al., 2002; Sykes et al., 1997, 1999a, 1999b; Von Bomhard et al., 2003). In a study that compared PCR and culture for detection of C. felis in untreated and doxycycline-treated experimentally infected cats, PCR was found to be more sensitive in untreated cats and in chronically infected cats (Sykes et al., 1999b). Most cats had positive culture results beginning on day 3 following infection. If untreated, cultures remained positive until day 25 postinfection. If treated, culture results remained positive for 1 day following commencement of oral doxycycline.

Through the use of a top-down PCR strategy, a new chlamydial agent was detected in 39% of 226 conjunctival samples from cats in Switzerland with conjunctivitis or keratitis, and 23% of 30 samples from healthy cats (Von Bomhard et al., 2003). The organism had a genetic sequence that was very close to that of Neochlamydia hartmannellae, an endosymbi-
ont of the amoeba Hartmannella vermiformis. It was theorized that N. hartmannellae could be transmitted via amoebae-contaminated water. In all cases in this study in which eosinophilic inflammation was present, N. hartmannellae DNA was identified by PCR. This information may prove important if further studies verify a relationship to eosinophilic conjunctivitis or keratitis in cats. In this same study, 47% of 189 cats had positive PCR results for feline herpesvirus, with a fairly high number having positive PCR results for herpesvirus and C. felis or N. hamannellae, thus making the determination of which agents might be responsible for the observed ocular disease unclear. In this study, the majority of cats that had C. felis infections were under 5 years old, while the majority positive for N. hartmannellae were older than 10 years.

Chlamydial organisms are sensitive to tetracyclines, erythromycin, rifampin, fluoroquinolones, and azithromycin (Johnson et al., 1983; Stamm, 1998). Topical administration of tetracycline four times daily to both eyes for 1–2 weeks after resolution of conjunctivitis is sufficient in many cats; however, this treatment will not clear the gastrointestinal tract of infection and, in some cats, does not clear the conjunctiva (Donati et al., 2005; O’Dair et al., 1994). In one study, oxytetracycline, 50 mg twice daily for 60 days, cleared FIV-infected cats of both conjunctival and gastric mucosal infection (O’Dair et al., 1994). In another study in which experimentally infected cats were treated with 5 mg/kg of oral doxycycline twice daily for 3 weeks, clinical signs improved within 3 days of commencing therapy (Sykes et al., 1999a). In these cats, there was no recurrence of clinical signs, and the organism could not be detected by culture or PCR 2 weeks after cessation of therapy. Azithromycin, even when administered daily, was ineffective in clearing cats of C. felis (Owen et al., 2003). In feline research colonies, chlamydiosis was effectively cleared using systemic doxycycline alone for 3 weeks at a dose of 5 mg/kg q 12 hours (Sykes et al., 1999b). In another study, doxycycline at 10 mg/kg once daily for 7, 14, or, in some cases, even 21 days, did not ensure elimination of the organism (Dean et al., 2005). At least 28 days of doxycycline at 10 mg/kg/day was needed to clear all cats. To minimize the potential for doxycycline-induced esophagitis and stricture, a suspension should be administered, or a water bolus delivered via syringe should be given following administration of unbroken tablets (Sykes, 2005).

Vaccination with a live chlamydial vaccine provides the best clinical protection against infection (Kolar & Rude, 1977; Mitzel & Strating, 1977; Shewen et al., 1980a; Wills et al., 1987). When challenged by the conjunctival and nasal routes, vaccinated cats developed milder ocular and upper respiratory tract signs than did unvaccinated cats. Some vaccinated cats did shed organisms from the eye and respiratory tract, but for a shorter duration than unvaccinated cats. In a small percentage of vaccinated cats, atypical reactions have occurred, including fever, lethargy, anorexia, and lameness for 7–21 days after vaccination (Sykes, 2005). Vaccines may be of some benefit as part of a control program in catteries with a high prevalence of chlamydiosis.
Bordetellosis

The bacterium Bordetella bronchiseptica has been documented as a respiratory tract pathogen of cats (Binns et al., 1999; Coutts et al., 1996). Although clinical disease is more common in dogs, cats in shelters, catteries, and research facilities were more likely to be affected than cats in pet homes in one study. In both naturally occurring disease and experimental infection, B. bronchiseptica caused sneezing, coughing, nasal discharge, and conjunctivitis with ocular discharge. In one study of 740 cats sampled (both healthy and ill) in England, 82 (11%) had positive cultures from the oropharynx or nose (Binns et al., 1999). In this same study, FHV-1 was isolated from 30 of 622 cats (5%) and FCV was isolated from 126 of 622 cats (26%). Of the reported clinical signs, only sneezing was significantly associated with the isolation of B. bronchiseptica. There was no association between the isolation of the bacterium and of respiratory viruses, leading the authors to conclude that in some cases, feline bordetellosis alone can cause the clinical signs reported. In specific pathogen-free cats experimentally infected, mild upper respiratory tract disease and serous ocular discharge was seen following nasal inoculation (Coutts et al., 1996).

Neonatal Conjunctivitis

Neonatal conjunctivitis is a syndrome of acute conjunctival inflammation in neonatal kittens. Copious ocular discharge, which is usually purulent, is the consistent finding (Fig. 27.23). If infection develops before the resolution of physiologic ankyloblepharon at 10–14 days of age, the eyelids take on a characteristic distended appearance. The causes of neonatal conjunctivitis include most of the agents discussed earlier as well as bacterial pathogens. The problem usually resolves promptly after topical therapy with broad-spectrum antibiotics. If the eyelid margins are adhered, the palpebral fissure should be opened by inserting the blade of a small round-tipped scissors into the medial canthus and then sliding the blade laterally. Sometimes, the eyelids can be manually pulled apart. If the kitten is younger than 10–14 days, tear production and the blink reflex may be inadequate when the eyelids are opened. In these patients, topical antibiotics, artificial tears, and even temporary, incomplete closure of the eyelids may be indicated. In severe cases, symblepharon and corneal scarring may be sequelae of neonatal conjunctivitis.

Figure 27.22. Cytologic preparation from a conjunctival cytobrush sample in a cat with mycoplasmosis. Note the numerous small dark staining Mycoplasma sp. organisms within the cytoplasm of epithelial cells (Wright's stain). (Courtesy of Craig Thompson.)
Eosinophilic Conjunctivitis

Eosinophilic conjunctivitis occurs in cats with or without keratitis. The underlying cause of this disease remains undetermined. In a report of five cats with eosinophilic conjunctivitis, eosinophils and mast cells were present on cytologic examination of conjunctival scrapings (Pentlarge, 1991). Three cats had unilateral involvement; two had bilateral disease. In a study of 12 cats with eosinophilic conjunctivitis, seven cats were unilaterally affected, while five had bilateral disease (Allgoewer et al., 2001). Histologically, the conjunctiva was infiltrated with eosinophils, lymphocytes, plasma cells, mast cells, and macrophages. Viral particles were not detected on electron microscopy. Similar to eosinophilic keratitis, this condition usually responds favorably to topical corticosteroid therapy. The administration of oral megesterol acetate is highly effective for eosinophilic conjunctivitis and is discussed further under eosinophilic proliferative keratitis. The concurrent topical use of a nonsteroidal anti-inflammatory agent and cyclosporine is effective in some cats with eosinophilic conjunctivitis.

Parasitic Conjunctivitis

Feline conjunctivitis has been associated with the nematode Thelazia californiensis, particularly in the western United States, and Thelazia callipaeda in Europe (Dorchies et al., 2007; Kapp et al., 1961; Otranto et al., 2003). The vector for T. californiensis is the Fannia sp. fly (Bowman et al., 2002), whereas the vector for T. callipaeda is under investigation, but may be Phortica variegata, a type of fruit fly. Clinical signs are conjunctival hyperemia and serous ocular discharge; the parasite is easily removed from the conjunctival fornix.
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Lymphoma

Conjunctival lymphoma in cats has rarely been reported. A case report describes bilateral palpebral conjunctival masses in a 13-year-old cat without other signs of disease (Zaher et al., 2004). The masses were excised, and based on immunohistochemistry, B-cell lymphoma was diagnosed. No other clinical information was provided in this report. Another case report describes a 7-year-old cat with a unilateral palpebral conjunctival mass as well as peripheral lymphadenopathy (Holt et al., 2006). The histopathologic features of the conjunctival mass suggested a Hodgkin’s-like lymphoma. Chemotherapy did not result in improvement; however, the cat had full remission of disease with radiation therapy with no recurrence for a 3-year follow-up period.

Squamous Cell Carcinoma

SCC has not been reported as a primary conjunctival tumor in cats, with the exception of a single case report in which SCC and hemangioma were present on the cornea and conjunctiva of a cat without apparent eyelid involvement (Perlmann et al., 2010). This tumor frequently affects the eyelid margins of cats and invades the palpebral conjunctiva and third eyelid as it progresses. This tumor is discussed further in the eyelid section.

DISEASES OF THE CORNEA

The Normal Cornea

The feline cornea matures over the first 1–2 years of life, changing in curvature and thickness (Moodie et al., 2001). The central corneal thickness of 9-week-old kittens was 0.38 mm, that of 16-week-old kittens was 0.55 mm, and that of cats 67 weeks of age was 0.57 mm. Corneal sensitivity has been reported for domestic shorthair cats and brachycephalic cats (Blocker & Van der Woerdt, 2001a; Wagner et al., 2003). In one study (Blocker & Van der Woerdt, 2001a), the mean corneal touch threshold (g/mm²) for the central cornea of domestic shorthaired cats was approximately 1.7, while the peripheral cornea was 5. Values for brachycephalic cats were 4 and 6.2, respectively, indicating a diminished corneal sensitivity in the brachycephalic cat relative to the shorthair cat. In the second study (Wagner et al., 2003), the central corneal sensitivity in domestic shorthair cats was 3.58 cm (length of aesthesiometer filament), whereas that of Persian cats was 2.97 cm. Cats with centrally located corneal sequestra had a mean sensitivity of 2.0 cm in this region. The distribution and density of corneal nerves as evaluated by confocal microscopy has been studied in both mesocephalic and brachycephalic cats (Kafarnik et al., 2008). Nerve fiber density was found to be higher in domestic shorthair cats compared with dogs, and higher in domestic shorthair cats compared with Persian cats.

The feline cornea has been shown to potentially harbor pathogenic viruses even when it is clinically normal in appearance. In 17 cats that were positive for FeLV, 11 had FeLV with forceps, although continued exposure to the vector will result in reinfection. The larvae of Cuterebra sp. may be deposited within the conjunctival tissue, leading to severe inflammation (Fig. 27.25). Treatment is manual removal of the larva, followed by the use of a topical antibiotic and an anti-inflammatory drug until the conjunctivitis has resolved.

Neoplasia

Melanoma

Conjunctival melanoma has been reported in cats, though it does not appear to be common (Cook et al., 1985; Patnaik & Mooney, 1988). In the four cats of these two reports, the tumors involved bulbar and palpebral conjunctiva. In three cats in which surgical resection was performed (Patnaik & Mooney, 1988), enucleation was subsequently required because of tumor recurrence. Despite enucleation, all three cats developed widespread metastases, surviving from 3 months to 3 years following diagnosis. In the other report of one cat (Cook et al., 1985), surgical resection of the tumor was performed, and recurrence was not noted during an 11-month follow-up period, but no information was provided beyond that time frame. A more recent report describes 21 cases of feline conjunctival melanoma (Schobert et al., 2010). Of the 21 cases, 13 tumors occurred on the bulbar conjunctiva and extended deep into the orbit, 4 arose on the third eyelid, 3 on the palpebral conjunctiva, and 1 in which it was impossible to determine the origin. Sixteen tumors were pigmented, and five were amelanotic. Thirteen cases had adequate follow-up. Of these 13 cats, 4 had documented local recurrence and 3 had metastasis—2 to submandibular lymph nodes and 1 to the abdomen. Eight cats died with a survival time of 0.5–36 months. In another case report, a cat with a bulbar conjunctival melanoma had no recurrence for 34 months following surgical excision (Payen et al., 2008).
present within the cornea when evaluated by PCR (Herring et al., 2001). Immunohistochemical staining of the corneas documented the presence of FeLV gp70 in nine of the FeLV-positive cats. Two separate studies have found that approximately half of clinically normal-appearing corneas of cats are positive for FHV-1 DNA when evaluated by PCR (Stiles et al., 1997b; Townsend et al., 2004), and another study documented virulent FHV-1 in the corneas of clinically normal cats (Stiles & Pogranichny, 2008). These findings suggest that it would be risky to use corneal donor tissue from one cat to another. The presence of the FIV has not been evaluated in the cornea, although it has been documented in the aqueous humor of infected cats (Ryan et al., 2003) and also could be a corneal pathogen.

The prevalence of conjunctival and corneal surface bacterial flora is lower in cats than in other domestic species (Campbell et al., 1973b; Espinola & Lilenbaum, 1996; Shewen et al., 1980b). Organisms isolated commonly from normal cats include Staphylococcus epidermidis and Mycoplasma spp. Cytologic examination of the normal feline conjunctiva reveals predominantly epithelial cells, which sometimes contain melanin granules. Lymphocytes, plasma cells, and neutrophils are seen uncommonly, and eosinophils and basophils are never seen (Lavach et al., 1977). Goblet cells are found only in scrapings taken from the fornix. The prevalence of fungal flora in cats also appears to be low (Samuelson et al., 1984).

**Herpesvirus Keratitis**

Corneal ulceration is the second most common ocular manifestation of FHV-1 infection, following conjunctivitis. In most cases, with corneal involvement, conjunctivitis is also present. Ulceration occurs with the spread of FHV-1 to the corneal epithelium, with ulcers typically confined to the epithelial layer unless secondary bacterial infection causes progression into the stroma. While early corneal ulcers may have the classic dendritic or branching form (Fig. 27.26), they quickly develop into larger areas of epithelial loss, making superficial geographic ulcers the most common clinically evident sign. Kittens affected with primary FHV-1 infections may have corneal ulcers as well as conjunctivitis, increasing the chances of severe symblepharon that may lead to blindness later on.

Corneal ulcers secondary to FHV-1, which are typically very painful, may heal spontaneously or may become chronic indolent ulcers even with antiviral therapy. Chronic ulcers usually incite a corneal vascular response, typically a superficial yet dense ingrowth of vessels from the limbus to the ulcer. Stromal keratitis is a secondary immune-mediated inflammatory reaction to the presence of virus within the epithelium or within the stroma itself. It is evidenced by inflammatory cell infiltrates and haziness within the corneal stroma, usually accompanied by deep stromal vascularization (Fig. 27.27) (Nasisse et al., 1995). Stromal keratitis is more likely to develop if cats receive topical or subconjunctival corticosteroids.

Cats treated with topical corticosteroids for nonherpetic disease may be at risk of developing corneal ulcers from activation of latent herpesvirus. Up to 50% of clinically normal cats have FHV-1 DNA in the cornea (Stiles et al., 1997b; Townsend et al., 2004). Virulent FHV-1, documented through VI, has been demonstrated in the corneas of clinically normal cats as well (Stiles & Pogranichny, 2008). In the latter study, the use of dexamethasone in the cell culture media enhanced viral replication.

Corneal sequestra represent areas of corneal stromal necrosis and may develop secondary to chronic corneal ulceration from FHV-1. Although the exact mechanism of sequestra formation is unknown, cats with ulcers that fail to heal for several weeks are at high risk for the development of sequestra within the exposed corneal stroma. Likewise, cats receiving topical or subconjunctival corticosteroids are more likely to develop...
SECTION IV: Special Ophthalmology

Figure 27.28. A chronic, superficial corneal ulcer in an adult domestic shorthair cat with herpesvirus keratitis. Note the dense infiltration of deep and superficial blood vessels, as well as the change in color of the exposed corneal stroma, representing an early corneal sequestrum. (Reprinted with permission from Stiles, J. (2003) Feline herpesvirus. Clinical Techniques in Small Animal Practice, 18, 178–185.)

corneal sequestra, possibly through activation of FHV-1 (Nasisse et al., 1989a). The first evidence of sequestra development may be a faint amber or brown color to the exposed stroma. As the affected cornea undergoes a necrotic process, it takes on a darker brown to black color (Fig. 27.28).

Once a significant sequestrum develops within an ulcer bed, healing of the epithelium is unlikely. The vascular response to a sequestrum is often more dramatic than the response incited by an ulcer alone. Typically, cats remain in as much pain with the onset of sequestration as they were with a corneal ulcer.

Occasionally, entropion develops secondary to ocular pain associated with corneal ulcers or conjunctivitis. Entropion will exacerbate the pain response as hair contacts the cornea and may cause or hasten the development of corneal sequestra. Entropion may also develop in older cats that have entrophtalmos secondary to loss of muscle and fat mass within the orbit. These cats may develop corneal ulceration and even sequestra secondary to the entropion.

**Therapy for Herpesvirus Ocular Disease**

Treatment of recurrent FHV-1 ocular disease may or may not be required. Many cats with transient conjunctivitis recover spontaneously and need no therapy. Cats with ocular pain associated with FHV-1, moderate to severe conjunctivitis, or corneal ulcers should be treated specifically with antiviral agents. Kittens with primary disease and moderate to severe conjunctivitis and those with corneal ulcers should be treated with specific antiviral therapy. Additionally, early symblepharon adhesions should be broken down to prevent the condition from becoming permanent. This can be accomplished with topical anesthesia and the use of cotton-tipped swabs or small forceps. In severe cases, the procedure may need to be repeated frequently as new adhesions form.

One in vitro study (Nasisse et al., 1989b) has shown FHV-1 to be susceptible to the following antiviral agents, which are listed in order of decreasing effect: trifluridine, idoxuridine, vidarabine, bromovinyldeoxyuridine, and acyclovir. Another study found the following decreasing susceptibilities: idoxuridine, ganciclovir, cidofovir, penciclovir, and acyclovir. Foscarnet was considered completely ineffective (Maggs & Clarke, 2004).

Currently, only trifluridine is available as a commercial ophthalmic preparation, but other agents such as idoxuridine and cidofovir can be compounded into ophthalmic preparations. Traditionally, topical antiviral drugs have been used four to eight times daily, as they are all virostatic agents. It is interesting to note that in one study of herpetic keratitis in a rabbit model, trifluridine given twice daily was as effective as when it was given seven times daily (Kaufman et al., 1998). The use of topical cidofovir is especially attractive as a therapeutic agent in cats as it has been shown to be highly effective at reducing FHV-1 replication, and the long half-life of its metabolites allows less frequent application than other antiviral agents (Sandmeyer et al., 2005a). Cidofovir at concentrations as low as 0.02 mg/mL (0.002%) completely inhibited cytopathic effect of FHV-1 on feline corneal epithelial cells when added after virus adsorption. Two studies evaluated the effectiveness of cidofovir compared with trifluridine in a rabbit model of herpes simplex keratitis. In the first study (Kaufman et al., 1998), 0.2% cidofovir given topically twice daily was equally as effective as 1% trifluridine given two, four, or seven times daily. In the second study (Romanowski et al., 1999), 1% cidofovir and 0.5% cidofovir were given twice daily and compared with 1% trifluridine given nine times daily for 3 days and then four times daily for 4 days. Cidofovir at both concentrations was judged to be superior in effect to trifluridine. In an in vivo experimental study in cats, the use of 0.5% cidofovir twice daily resulted in lower clinical scores and viral shedding in treated compared with control cats (Fontenelle et al., 2008a).

Treatment of cats with FHV-1 corneal ulcers should include debridement to remove loose epithelium and reduce the number of viral particles. Grid keratotomies should not be performed in cats because of the increased likelihood of sequestra formation (La Croix et al., 2001). Topical antiviral treatment of FHV-1 ocular disease should continue for at least 1 week, if not longer, beyond the resolution of clinical signs. Some cats may be irritated by topical antiviral agents, particularly trifluridine. Idoxuridine appears less irritating than trifluridine in most cats, whereas cidofovir appears to be well tolerated by cats.

The decision whether to use an anti-inflammatory agent in cats with herpesvirus ocular disease remains a difficult one in many cases. Particularly in adult cats with chronic conjunctivitis, antiviral agents alone usually do not bring about resolu-
tion of clinical disease. The authors’ choice is to use antiviral therapy initially, without anti-inflammatory agents, and assess the response after 1–2 weeks. At that time, if the inflammatory component of the disease is still marked, a nonsteroidal anti-inflammatory agent such as 0.1% diclofenac or 0.2% cyclosporine may be added while maintaining the antiviral therapy. Topical diclofenac is less irritating than flurbiprofen in most cats. Concomitant topical use of cyclosporine and ganciclovir, as well as the use of topical cyclosporine and trifluridine, decreased the severity of herpetic stromal keratitis in rabbit models (Boisjoly et al., 1984; Naito et al., 1991). In humans with herpes simplex virus, keratitis was successfully treated with a combination of cyclosporine and acyclovir, both applied topically (Heiligenhaus & Steuhl, 1999). Flurbiprofen has been evaluated in rabbit and mouse models of herpetic keratitis, although not in conjunction with an antiviral drug. In one study, topical 0.03% flurbiprofen used in reduced keratitis in some mice and no improvement in others, although worsening of disease was not documented (Hendricks et al., 1990). In this same study, topical dexamethasone resulted in severe exacerbation of disease in some animals. In another study, 0.1% flurbiprofen was found to be comparable with 0.1% dexamethasone in exacerbating disease in rabbits (Trousdale et al., 1980). Ketorolac 0.5% was evaluated in rabbits and was found to not exacerbate herpetic keratitis as did dexamethasone, but it did not lessen disease either (Fraser-Smith & Matthews, 1988). There is ample evidence that corticosteroids exacerbate ocular herpesvirus disease in many species and should be avoided, even in conjunction with an antiviral agent (Hæsaert, 1986).

Recombinant interferon has been used in cats with FHV-1-related ocular disease, though studies to document its effectiveness have been limited. In one report, natural human interferon given orally at a dose of 5 and 25 IU reduced the severity of clinical signs in experimentally infected cats when given on days 1 and 2 of infection (Nasisse et al., 1996). In addition, synergistic antiviral activity of recombinant and natural human interferon and acyclovir on FHV-1 replication has been shown in vitro (Weiss, 1989), though the effectiveness of this combination used clinically has not been reported in cats. Topical administration of interferon has been used for herpetic keratitis in humans (McLeish et al., 1990; Sundmacher et al., 1978, 1987). Good results were achieved when topical trifluridine was combined with high-titer (30 million IU/mL) alpha- or lambda-interferon given once daily or with moderate-titer (2 × 0.3 million IU/mL) mixtures of the two interferons (Sundmacher et al., 1987). Patients were treated for only 3–4 days with interferon. Interferon has no effect on infected cells, but it may prevent healthy cells from becoming infected, thus shortening the course of disease (Missonetten, 1994). An in vitro study of the effects of recombinant human alpha-interferon on feline corneal epithelial cells and FHV-1 replication found that at a concentration of 10^3 IU/mL, there was a significant reduction in the cytopathic effect of the virus on cells (Sandelmeyer et al., 2005b). In one study of experimentally infected cats, pretreatment topically and orally with 20,000 U of feline omega-interferon had no beneficial effect on the clinical course of disease, although cats were not treated during the active disease stage (Haid et al., 2007).

The use of oral famciclovir, the prodrug of penciclovir, has been evaluated in experimentally infected cats (Thomasy et al., 2011). Cats treated with 90 mg/kg TID of famciclovir had lower clinical scores and shed less virus throughout the 21-day study period than control cats. No hematologic or biochemical abnormalities were found during the study. Even at the dose of 90 mg/kg TID, the peak plasma concentrations of penciclovir in the treated cats were approximately 2.0 µg/mL, which still fell short of the target concentration of 3.5 µg/mL. Nonetheless, a wide variety of dosages and treatment frequencies of penciclovir have been used in cats. It appears that the cat may absorb and/or metabolize famciclovir, or eliminate penciclovir, in a nonlinear fashion resulting in complex pharmacokinetics in this species (Thomasy et al., 2011).

Treatment with 500 mg twice daily of oral L-lysine has been shown to lessen the severity of herpesvirus conjunctivitis in an experimental model in adult cats, although the overall duration of disease did not differ from untreated cats (Stiles et al., 2002). Plasma lysine concentrations were significantly elevated in treated cats, but arginine levels were not affected. In a study of recrudescent FHV-1, 400 mg of lysine once daily reduced viral shedding in cats during environmental stress (but not corticosteroid administration), but did not result in elevated plasma lysine levels for more than 3 hours, suggesting that twice-daily administration is needed (Maggs et al., 2003). An additional study also found no adverse effect on plasma arginine levels in cats given excess dietary lysine (Fascetti et al., 2004). In a study of 261 shelter cats fed a normal diet or one supplemented with lysine for 4 weeks, upper respiratory disease assessed as mild did not differ between groups. Disease assessed as severe occurred in more treated cats than control cats during week 4 (Drazenovich et al., 2009). The mechanism of action of lysine is thought to be competitive inhibition of arginine (an essential amino acid for herpesviruses) uptake by the virus and subsequent reduction in the formation of viral proteins. Lysine may be most beneficial in some cats when combined with other more targeted antitherapeutic therapies, rather than used as a sole agent. Lysine should be administered with food to prevent gastric upset. The recommended dosage for kittens is 250 mg twice daily.

Sequestra

Corneal sequestration is a common disorder in cats, particularly in the Persian and Himalayan breeds. Sequestra may occur after chronic corneal ulcers or keratitis caused by infection with FHV-1 or by corneal irritation from entropion or trichiasis (Featherstone & Sansom, 2004; Morgan, 1994; Startup, 1988). It may also appear as a primary stromal disease in Persians and Himalayans (Fig. 27.29). The author has seen many cats with intact corneal epithelium, no history or signs
of herpetic disease, and early areas of corneal necrosis in the anterior stroma. The condition is characterized by an area of corneal degeneration with an amber (early) or brown-to-black discoloration, which was suggested in one study to be from melanin particles based on absorbance spectra and optical microscopy (Featherstone et al., 2004). In another study, high-resolution light and transmission electron microscopy were used to study corneal sequestra from keratectomy specimens (Cullen et al., 2005b). In this study, no structures resembling melanin granules were seen. Necrotic keratocytes, disarranged collagen, and perilesional inflammatory cells were present in all samples. Electron-dense deposits seen were interpreted as being degraded epithelial basement membrane and in one sample mineralization. A poptotic keratocytes were noted and apoptosis theorized to play a role in the pathogenesis of corneal sequestra. In another study, keratectomy samples from cats with sequestra were evaluated with spectrofluorometry, and it was determined that porphyrins were not present (Newkirk & Hendrix, 2011). The cause of the corneal discoloration remains undefined.

Sequestra vary in size from 1 to 2 mm in diameter to those occupying more than half the cornea, and the depth from the superficial stroma to lesions that extend to Descemet’s membrane. Vascularization may be intense or absent, and ocular pain ranges from none to marked. Sequestra may have been noted to develop after topical corticosteroid use in cats experimentally infected with FHV-1 (Nasisse et al., 1989a) as well as in naturally infected cats. Sequestra may occur in some cats with superficial corneal ulcers following grid keratotomy (La Croix et al., 2001). In a study that analyzed 28 keratectomy specimens from Persian and Himalayan cats with corneal sequestra by PCR for the presence of FHV-1 DNA, only 18% were positive, while in the clinically normal control group, 46% of corneal samples were positive (Stiles et al., 1997b). This finding suggests that FHV-1 is not the inciting factor in many Persian and Himalayan cats with sequestra. Supporting this finding, another study found that domestic shorthair cats with sequestra had a significantly higher level of FHV-1 DNA detection by PCR than Persian or Himalayan cats (Nasisse et al., 1998). A recent study found no difference in TBUT or conjunctival goblet cell densities in eyes with sequestra compared with unaffected control eyes from the same cat or from normal age-matched control cats (Grahn et al., 2005).

The necrotic cornea can be surgically removed by keratectomy. If superficial, no graft may be required, although covering the defect with a soft contact lens and/or tarsorrhaphy during healing is recommended to reduce chances of recurrence. If the keratectomy is deep, a graft will be necessary. Conjunctival grafts may help to prevent recurrence (Fig. 27.30) (Blogg et al., 1989; Morgan, 1994). Alternatively, a corneoconjunctival transposition can be performed following the keratectomy (Fig. 27.31a, b). This procedure provides for better corneal clarity, and in one study of 15 cats, results were considered good in all cases (Andrew et al., 2001). Recurrences of sequestra were not noted in these cats during follow-up times that ranged from 30 days to 7 years. Porcine small intestinal submucosa graft material and amniotic membrane transplantation have also been used in feline corneas following keratectomy for sequestra, with good cosmetic results reported (Barachetti et al., 2010; Featherstone et al., 2001). Penetrating keratoplasty with use of a heterologous graft in a cat has also been reported (Townsend et al., 2008).

**Eosinophilic–Proliferative Keratitis**

Domestic cats experience a form of proliferative keratitis, marked by eosinophilic inflammation, that appears to be
may become affected (Fig. 27.33). The condition is more often unilateral, but bilateral involvement may occur. Signs of ocular discomfort are inconsistent. Early lesions tend to be painless, but blepharospasm and ocular discharge become more pronounced as lesions progress. Dermatologic lesions typical of the eosinophilic complex are absent.

The clinical presentation varies somewhat, but the typical lesion is a proliferative, white to pink, irregular, and vascularized ingrowth of tissue that most commonly originates from the nasal or temporal limbus, peripheral cornea, and adjacent bulbar conjunctiva (Fig. 27.32). The nictitating membrane may be affected as well, and with chronicity, the entire cornea may become affected (Fig. 27.33). The condition is more often unilateral, but bilateral involvement may occur. Signs of ocular discomfort are inconsistent. Early lesions tend to be painless, but blepharospasm and ocular discharge become more pronounced as lesions progress. Dermatologic lesions typical of the eosinophilic complex are absent.

Histopathologically, proliferative keratitis is a disease characterized by an inflammatory cell infiltrate of neutrophils, plasma cells, lymphocytes, eosinophils, mast cells, and occasionally histiocytes (Prasse & Winston, 1996). In cytologic preparations collected by corneal scraping, eosinophils and neutrophils are usually the most conspicuous cell type (Fig. 27.34). Mast cells are usually present but may be disrupted.
such that the cytoplasmic granules are scattered on the slide. Hematologic evaluation may reveal eosinophilia, although in most cases this does not occur.

Feline proliferative keratoconjunctivitis usually responds dramatically to topical therapy with 0.1% dexamethasone or 1% prednisolone acetate. Treatment should be initiated at a frequency of three to four times daily, depending on severity. As the lesion improves, therapy is reduced gradually to find the maintenance dose required to control disease. Some cats may be well maintained on a topical corticosteroid administered only once or twice a week. The use of topical cyclosporine has also been reported to be effective in controlling eosinophilic proliferative keratitis in some cats (Spiess et al., 2009). In the author’s experience, the concurrent topical use of a nonsteroidal anti-inflammatory agent such as diclofenac and cyclosporine is effective in some cats with eosinophilic keratitis, although the lesions tend to regress more slowly than with a topical corticosteroid agent.

Megestrol acetate is highly effective for treating eosinophilic keratitis at an oral dose of 5 mg daily for 5 days, then 5 mg every other day for 7 days, followed by 5 mg weekly for maintenance. The use of megestrol acetate has the potential for serious systemic side effects including diabetes mellitus, adrenocortical suppression, behavior changes, and mammary hyperplasia and neoplasia (Plumb, 2005). A baseline serum glucose should be determined prior to starting megestrol acetate and reevaluated at each visit. If the glucose is noted to rise significantly, the drug should be discontinued immediately.

The role of FHV-1 and antiviral therapy in eosinophilic proliferative keratitis remains obscure. In one report, 45 (76%) of 59 biopsy specimens from cats with proliferative keratoconjunctivitis were positive for FHV-1 by PCR analysis (Nasisse et al., 1998). This finding, however, may represent FHV-1 DNA, which is present in the cornea without initiating the disease. In light of the recent discovery of a new chlamydial agent, N. hartmannellae, in cats with conjunctivitis and keratitis accompanied by an eosinophilic inflammatory cell infiltrate (Von Bomhard et al., 2003) (see discussion under “Diseases of the Conjunctiva”), evaluation of the benefit of topical or systemic therapy with tetracycline or doxycycline may be warranted.

Long-term maintenance of therapy is usually required to control proliferative keratitis. The use of chronic topical corticosteroids in the cat always carries the risk of allowing a latent FHV-1 infection to recrudesce.

**Corneal Dystrophies and Degenerations**

Corneal dystrophy is defined as a primary, inherited corneal disease. It typically arises early in life, is bilateral, and preferentially affects the central cornea. Feline corneal diseases that conform to this definition are rare, but a syndrome of progressive stromal edema without endothelial disease has been described in the Manx cat and may affect other breeds as well (Bistner et al., 1976). Edema of the anterior stroma, which is evident as early as 4 months of age, is associated with swelling and disintegration of collagen fibers. Eventually, fluid vesicles and bullae form within the stroma. The course is progressive, and the entire cornea will become affected. Epithelial changes, including intracellular edema and separation of the basal cells from their basement membrane, are considered to be secondary. The pathogenesis of the edema has not been determined. In the original report in Manx cats, ultrastructural evidence showed that a normal endothelium was present (Bistner et al., 1976). In one case report, a description of the corneal endothelium was lacking (Olin & TenBroeck, 1973). In another description of the condition, the earliest histopathologic abnormality was cytoplasmic vacuolation of the endothelial cells (Crispin, 1982; Godfrey & Nasisse, 1985). The success rate of feline corneal transplantation in an experimental model was comparable with that of humans (Bahn et al., 1982).

Corneal degenerations involve the extracellular deposition of lipid and, less commonly, calcium in the corneal stroma secondary to some other disease. Corneal degenerations are uncommon in the cat, but two cases of lipid keratopathy have been described (Carrington, 1983; Kipnis, 1975). Lipid degeneration was a sequel to corneal ulceration in one domestic shorthair cat. Lipid was identified by special stains in frozen corneal sections; extracellular lipid was confined to the superficial stroma and associated with a secondary inflammatory response. In the second case, a Siamese cat had probable lipid degeneration presumed to be secondary to chemical irritation. Corneal stromal calcification (i.e., band keratopathy) may follow chronic, experimental, stromal FHV-1 infection in the cat, but under natural conditions, band keratopathy in the cat is rare (Nasisse et al., 1989a).
Corneal cloudiness is a prominent feature in cats with mucopolysaccharidosis types I and VI. The cloudiness appears to be a result of altered stromal structure, including abnormal spacing, size, and arrangement of collagen fibrils (Alroy et al., 1999).

**Acute Bullous Keratopathy**

Acute bullous keratopathy in cats is characterized clinically by rapid formation of corneal edema, large bullous lesions in the cornea, corneal melting, and sometimes corneal perforation. The entire process can occur in as little as 24 hours (Fig. 27.35a–c). This condition, although uncommon, probably occurs more frequently than the one case series (Glover et al., 1994) and one single case report (Pattullo, 2008) in the literature suggest. In the case series, four young (age range, 1.5–3.0 years) cats were presented with acute bullous keratopathy of unknown cause. There was no history of systemic disease or trauma, but two cats had anterior uveitis. In addition, all corneas were variably edematous, with either focal edema or involvement of the entire cornea with perforation and iris prolapse. Treatment consisted of conjunctival grafts or enucleation. In the single case report, a 14-year-old cat with bullous keratopathy in one eye and corneal perforation in the fellow eye was presented. The cat was successfully treated with bilateral conjunctival grafts. The cause of this condition remains unknown, but it appears to be a possible stromal defect rather than a focal-to-diffuse corneal endothelial dysfunction. The author has had success in some cats with third eyelid flaps to provide tamponade of a cornea with bullae and edema but no perforation (see Fig. 27.35c).

**Florida Keratopathy (Florida Spots)**

An asymptomatic corneal disease referred to as “Florida spots” is recognized in the dog and cat in the southeastern United States (Peiffer & Jackson, 1979) and the Caribbean, but it also occurs among horses and birds. The condition

![Figure 27.35](image)

**Figure 27.35.** Acute bullous keratopathy in cats. **a.** The entire cornea is edematous in this domestic shorthair cat, with a large central bulla where the cornea is very thin and close to perforating. **b.** Ventromedial bulla in a domestic shorthair cat. A conjunctival graft was placed but failed as the bulla enlarged around the graft. **c.** A third eyelid flap was placed and left up for 10 days, leading to resolution of the corneal edema and bulla.
Bacterial Keratitis

In all species of animals, bacterial keratitis is initiated by a traumatic disruption of the corneal epithelium, which allows bacteria to gain access to the underlying stroma. Epithelial ulcers caused by FHV-1, a common occurrence in cats, may become infected with bacteria and progress to stromal ulcers or perforations. Traumatic injuries may also inoculate bacteria into the cornea or allow endogenous ocular flora to become opportunistic pathogens. The use of topical corticosteroids in cats with apparently normal corneas may lead to activation of local FHV-1, with resulting corneal ulceration. The clinical signs, diagnostic approach, and treatment of feline bacterial keratitis are similar to those in dogs (see Chapter 18).

Fungal Keratitis

Fungal keratitis is uncommon in cats. Individual case reports of feline keratomycosis include cats with infections caused by Cladosporium, Candida sp., Aspergillus fumigatus, Aspergillus flavus, and Acremonium sp. (Binder et al., 2011; Labelle et al., 2009; Miller et al., 1983; Schmidt, 1974). In the two most recent cases, one with infection caused by A. flavus and one with Acremonium, topical 1% voriconazole solution was used successfully to resolve the keratomycosis (Binder et al., 2011; Labelle et al., 2009).

Chlamydiales Keratitis

PCR assays for Chlamydiales order organisms have identified Parachlamydia acanthamoebae, C. felis, and Chlamydiales unable to be speciated, within the corneas of both cats with keratitis and other corneal disease and normal-appearing corneas (Richter et al., 2010). The clinical significance and pathogenesis of these organisms remains unknown.

Acid-Fast Bacilli Keratopathy

One report described keratopathy in two cats in the northwestern United States that was characterized histopathologically by acid-fast bacilli (Dice, 1977). In this report, however, the corneal lesions were progressive and described as “fleshy” in appearance. Histopathologically, the lesions contained neutrophils, mononuclear inflammatory cells, and organisms within histiocytes. The histopathologic appearance was considered to be similar to that seen in the skin of cats with feline leprosy (Brown et al., 1962; Lawrence & Wickham, 1963; Schiefer et al., 1974). The contrasting features between this syndrome and Florida keratopathy suggest they are different diseases. A case report from Italy describes a cat with a conjunctivo-corneal and scleral mass with acid-fast bacilli within histiocytes (Lamagna et al., 2009). Tissue from the mass was positive by PCR for Mycobacterium sp.

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N. hartmannellae, an endosymbiont of the amoeba H. vermiformis, has been identified in the conjunctiva of cats with keratitis and/or conjunctivitis (Von Bomhard et al., 2003). This organism is discussed further under “Diseases of the Conjunctiva.”

Corneal Dermoids and Neoplasia

Ocular dermoids occur infrequently in cats (Fig. 27.37) (Carter & Himes, 1971; Labue et al., 1985). Corneal dermoids have been described in the domestic shorthair, Burmese, and Birman breeds (Hendy-Ibbs, 1985). Lateral limbal dermoids, with prolapse of the nictitans gland, occur in Burmese cats (Koch, 1979). Complete excision of corneal dermoids by lamellar keratectomy is the treatment of choice. A nevoid dermoids are readily corrected by conjunctivectomy or various blepharoplastical procedures.

A proliferative stromal lesion diagnosed as fibrous histiocytoma has been described in a domestic shorthair cat (Smith et al., 1976). Like its counterpart in the dog, the lesion began at the temporal limbus and was characterized histopathologically by the presence of lymphocytes, plasma cells, and his-
stereopsis compared with normal cats. The visual pathways of the Siamese have been extensively studied to determine the neuroanatomic abnormalities producing these conditions (Chino et al., 1977; Elekessy et al., 1973; Johnson, 1991; Kalil et al., 1971; Moore et al., 1966; Sherman, 1972). The changes include a decrease in the number of uncrossed retinogeniculate projections, an increase in the number of crossed retinogeniculate projections, and a disruption in the normal pattern of geniculate lamination (Cucchiaro, 1985). All of the neurons that project abnormally exist in an area of the retina 20–25° in width immediately temporal to the area centralis (Guillery & Kaas, 1971). The primary difference seen in Siamese cats, with the degree of involvement varying between individuals, is an increase in the number of ganglion cells that project contralaterally (Kaas & Guillery, 1973; Kliot & Shatz, 1985).

While the abnormal projections route to the correct position in the lateral geniculate nuclei, they go by way of the wrong side (Guillery, 1974). Therefore, the cat's brain sometimes receives contradictory information because it has come from the wrong eye (Johnson, 1991). The resulting disruption of the visual field causes a portion of the visual field to be inverted (Guillery et al., 1974). The cats compensate by either suppressing a portion of the temporal visual field input to the visual cortex (termed the Midwest cat) (Kaas & Guillery, 1973) or by rewiring the projections from the lateral geniculate nuclei to the visual cortex to recreate an orderly representation of the perceived world (termed the Boston cat) (Guillery et al., 1974; Shatz, 1977). Using either approach, the ipsilateral cortex only receives monocular input (Johnson, 1991). Therefore, all Siamese cats lack binocular vision (Kaas & Guillery, 1973).

The abnormal visual perception and an effort by the brain to create stereopsis compared with normal cats. The visual pathways of the Siamese have been extensively studied to determine the neuroanatomic abnormalities producing these conditions (Chino et al., 1977; Elekessy et al., 1973; Johnson, 1991; Kalil et al., 1971; Moore et al., 1966; Sherman, 1972). The changes include a decrease in the number of uncrossed retinogeniculate projections, an increase in the number of crossed retinogeniculate projections, and a disruption in the normal pattern of geniculate lamination (Cucchiaro, 1985). All of the neurons that project abnormally exist in an area of the retina 20–25° in width immediately temporal to the area centralis (Guillery & Kaas, 1971). The primary difference seen in Siamese cats, with the degree of involvement varying between individuals, is an increase in the number of ganglion cells that project contralaterally (Kaas & Guillery, 1973; Kliot & Shatz, 1985). While the abnormal projections route to the correct position in the lateral geniculate nuclei, they go by way of the wrong side (Guillery, 1974). Therefore, the cat's brain sometimes receives contradictory information because it has come from the wrong eye (Johnson, 1991). The resulting disruption of the visual field causes a portion of the visual field to be inverted (Guillery et al., 1974).

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Esotropia (convergent strabismus) may result from the abnormal visual perception and an effort by the brain to create...
a complete visual field (Johnson, 1991). The esotropia develops during the third month of age. Surgical correction of the strabismus does not correct the problem because the cat depends on the abnormal eye position to maximize visual acuity. A nystagmus is often present as well and probably results from the contradictory information perceived at the mesencephalon (rostral colliculus and rostral tectum). By studying the extracellular action potentials from optic tract fibers, Siamese cats have also been demonstrated to have a lower percentage of W- and X-type ganglion cells (8%) than normal cats (32%) (Chino et al., 1977). This explains the decreased spatial contrast sensitivity of Siamese cats. Misrouted projections of the central visual pathways are also present in cats with the Chédiak–Higashi syndrome (Creel et al., 1982).

Blue Irides and Other Diseases

Blue irides, deafness, and white coat color occur as a dominantly inherited condition in domestic cats with complete penetrance in the production of white fur, incomplete penetrance of deafness, and incomplete dominance in the production of blue irides (Bergsma & Brown, 1971). The condition is similar, but not analogous, to Waardenburg’s syndrome in humans; features absent or not recognizable in the feline condition are dystopia canthorum (wide skin folds between the nose and eyes with wide-set lacrimal puncta), a prominent nasal root, and hyperplastic medial eyebrows. The hearing deficit is linked to bony alterations in the modiolus and membranous changes in the labyrinth.

Chédiak–Higashi syndrome is an autosomal recessive disease in Persian cats characterized by partial oculocutaneous albinism, a bleeding tendency, and increased susceptibility to infection due to neutropenia (Collier et al., 1979, 1984, 1985a, 1985b). Affected cats have lightly colored irides (pale yellow green), reduced pigmentation of the nontapetal fundi, and often, congenital cataracts. The characteristic histopathologic feature is giant cytoplasmic granules within neutrophils, lysosomes, and melanosomes. The hypopigmentation is theorized to result from fusion of the lysosomes with premelanosomes, with resultant destruction of the premelanosomes. Postnatal tapetal degeneration is also a feature of the disease. Affected cats have misrouting of retinal ganglion cells and retinogeniculate projections, similar to the disruptions reported for the Siamese cat (Creel et al., 1982). The diagnosis is made on the basis of identifying compatible clinical signs and demonstrating enlarged melanin granules in hair shafts examined with light microscopy.

Congenital Iris Abnormalities

Congenital iris and ciliary body cysts are occasionally seen in cats, and they are identified by their spherical shape, tendency to be attached at the pupillary margin, and translucency when illuminated with a focal light source (Peiffer, 1977). Iris cysts in cats, as in other species, rarely pose a threat to vision; however, their surgical removal has been described (Belkin, 1983).

Iridal colobomas result if a portion of the uvea fails to develop normally (Barnett and Crispin, 1998). Iridal colobomas are rare in cats. Iridal colobomas may occur as part of the colobomatous syndrome in cats with eyelid agenesis (Cutler, 2002). If extensive, these colobomas may permit direct inspection of the exposed ciliary body and peripheral lens. They also produce an obvious, irregularly shaped pupil with a less-than-complete response to mydriatics. In themselves, iridal colobomas do not produce visual impairment, but when coupled with other ocular anomalies, they may be associated with blindness.

Persistent pupillary membranes (PPMs) are rare in cats, appear not to be inherited, and may occur in eyes that are otherwise normal or that have multiple ocular anomalies (Martin et al., 1997). The PPMs consist of thin, translucent to heavily pigmented tissue strands extending from the iridal collarette to other areas of the iris, posterior cornea, or anterior lens capsule (Fig. 27.39). Most PPMs require no treatment, but medical therapy with long-term mydriatics or surgical or laser transection may be used.

Partial anterior segment cleavage syndrome occurs in cats as well as in dogs. It appears as a broad adherence of the iris to the posterior cornea, with loss of the anterior chamber, focal corneal edema, and a distorted pupil (Williams, 1993). The globe is often microphthalmic, but other anomalies are usually absent. The condition is nonprogressive, and treatment is not indicated. The cause of the condition is unknown, but in utero influences late in development of the globe appear to be likely. This condition must be distinguished from previous penetrating corneal injuries and the resultant anterior synechia and leukoma.

Figure 27.39. Multiple iris-to-cornea persistent pupillary membranes with a resultant leukoma in a 6-month-old Maine Coon cat.
Acquired Iris Abnormalities

Atrophy

Iris atrophy occurs in cats less frequently than in dogs and appears to be more common in blue-eyed cats. In older cats, the iridal stroma may thin and permit partial transillumination with an intense light source. Iris atrophy may be focal, and some color changes may be evident (Fig. 27.40). A trophy may also affect the iris at the pupillary margin, resulting in varying degrees of mydriasis with an irregular pupil and sluggish or absent pupillary light reflex.

Acquired Cysts

Acquired iris and ciliary body cysts in cats are more common than those that occur congenitally. They are generally attached to the posterior aspect of the pupillary margin or the posterior iris (Fig. 27.41). Iridal cysts may be confused with early melanomas. The cysts are sometimes heavily pigmented and thick walled and thus not readily transilluminated (Gelatt & Gelatt, 2011; Nasisse, 1991). Treatment is not usually necessary. However, if the cysts are large or numerous enough to impair vision, obstruct aqueous flow such that intraocular pressure (IOP) is elevated, or mechanically damage the corneal endothelium, treatment may be required. The least invasive method of treatment is deflation with a semiconductor diode laser under an operating microscope. A 0.3- or 0.8-mm spot size is recommended, and the energy and duration of laser application are altered to achieve rupture and coagulation of the cysts (Gemensky-Metzler et al., 2004). Caution is recommended as laser energy hitting the retina will cause damage to this tissue.

Anterior Uveitis

Anterior uveitis, with or without chorioretinitis, is one of the most frequent and significant ophthalmic disorders in domestic cats. Both the direct and secondary effects of anterior uveitis may be destructive to the eye and maintenance of vision. Cats with serious, and often fatal, systemic diseases may first be presented to the veterinarian for the ophthalmic signs of anterior uveitis. During clinical evaluation of all feline uveitis patients, a complete history and vaccination status should be obtained, and a thorough physical examination, complete blood count, serum biochemistry, and urinalysis should be performed. Other diagnostic tests are discussed under the specific causes of feline uveitis. For additional information, the reader is referred to the sections on clinical microbiology (see Chapter 6), ophthalmic pathology (see Chapter 8), and systemic diseases with ophthalmic manifestations (see Chapter 35).

Epidemiology and Clinical Signs of Anterior Uveitis

In one study of cases of uveitis associated with systemic diseases, the cats typically had bilateral ocular involvement, approximately 80% were males, 22% were purebred, and the mean age of affected cats was 7.6 years (age range, 6 months to 15 years) (Gemensky et al., 1996). In cases of idiopathic uveitis with histopathologic evidence of lymphoplasmacytic inflammation, bilateral involvement was present in 48% of the cats, 72% of cats were males or neutered males, 8% were purebred, and the mean age of affected cats was 9.6 years (age range, 3–15 years). In addition, 76% of cats were older than 5 years.
The clinical signs of feline anterior uveitis are numerous. Possible clinical signs include decreased vision, blepharospasm, conjunctival hyperemia, ciliary flush, nictitating membrane protrusion, corneal edema, circumlimbal corneal vascularization, aqueous flare or fibrin, hyphopyon, hypHEMA, keratic precipitates, iridal hyperemia, iridal nodules, iris color change, miosis, decreased IOP, cellular infiltrates in the anterior vitreous, and variable posterior segment involvement (Fig. 27.42, Fig. 27.43, and Fig. 27.44). In chronic cases, posterior synechia, cataract, lens subluxation/luxation, secondary glaucoma, and ruberosis iridis may also be noted. None of the clinical signs are pathognomonic for specific causes of feline anterior uveitis. However, some clinical signs occur more frequently with certain etiologies and are noted in the following discussion.

Causes of Anterior Uveitis

Potential causes of anterior and posterior uveitis in cats are summarized in Table 27.1. In some reports, approximately 38%–70% of affected cats have had concurrent systemic diseases (Chavkin et al., 1992; Gemensky et al., 1996; Glaze & Gelatt, 1999). In a histopathologic study of 158 uveitic globes from 139 cats, the causes of uveitis in decreasing order of frequency were lymphoplasmacytic, Feline Infectious Peritonitis (FIP), FeLV-associated lymphosarcoma, trauma, and lens induced (Peiffer & Wilcock, 1991). It should be noted that chronic lymphoplasmacytic uveitis is a condition seen in cats in which the cause is unknown and should not be considered a specific diagnosis.

Feline Immunodeficiency Virus

Infection with FIV causes chronic immunosuppression in cats and in some cats a mild to moderately severe, chronic uveitis (Connaughton, 1989; Hardy, 1988; Ishida et al., 1989; Pedersen et al., 1987; Yamamoto et al., 1989). The ocular inflammation may be caused by direct viral damage or by allowing opportunistic infections of the eye (English et al., 1990). In an immunohistochemical and histopathologic study of the eyes of 15 cats with chronic FIV infections, anterior uveitis was present in 13 cats (Loesenbeck et al., 1996). Retinal lesions were not found, nor were opportunistic pathogens. Immune complexes were identified and suggested to play a role in the uveitis. Coinfection with Toxoplasma gondii increases the possibility of ocular disease (Davidson et al., 1993a). Keratic precipitates tend to be uncommon and few in number when present (English et al., 1990). A aqueous cytology...
FIP, which is caused by a coronavirus, produces a chronic and progressive anorexia, depression, weight loss, fluctuating fever, and variable peritoneal and thoracic effusions. Anterior uveitis and/or chorioretinitis may develop with or without concurrent systemic signs (Fig. 27.46) (Campbell & Reed, 2000). Table 27.1 Potential Causes of Uveitis in Cats

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>Blunt trauma, Penetrating wound</td>
</tr>
<tr>
<td>Infectious</td>
<td>Feline immunodeficiency virus (FIV), Feline infectious peritonitis (FIP), Feline leukemia virus (FeLV), Toxoplasma gondii, Cryptococcus neoformans, Histoplasma capsulatum, Coccioidiodes immitis, Blastomyces dermatitidis, Bartonella spp. (role in uveitis uncertain), Leishmania infantum</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Diffuse iridal melanoma, Primary ocular sarcoma, Primary ciliary body adenoma and adenocarcinoma, Lymphosarcoma (with or without associated FeLV or FIV), Metastatic uveal neoplasms</td>
</tr>
<tr>
<td>Lens</td>
<td>Cataract induced, Lens luxation, Septic lens implantation syndrome</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Periarteritis, Ophthalmomyiasis, Idiopathic (chronic lymphoplasmacytic)</td>
</tr>
</tbody>
</table>

reveals variable amounts of plasmacytes and lymphocytes. While cellular infiltrates in the anterior vitreous (i.e., pars planitis) occur often with FIV, other evidence of posterior segment disease is infrequent (Willis, 2000). With chronic FIV infection, formation of posterior synechiae, cortical cataracts, and secondary glaucoma are likely. Ocular lymphosarcoma may also be associated with FIV infection and is a poor prognostic indicator for survival (Fischer et al., 1999) (Fig. 27.45). The mainstay for clinical diagnosis has been ELISA detection of circulating antibodies against FIV (Willis, 2000). However, vaccination of cats against FIV results in the production of antibodies indistinguishable from those used for the diagnosis of FIV infection (Levy et al., 2004). Therefore, one cannot reliably determine the FIV infection status using ELISA, Western blot, or immunofluorescent antibody tests. While PCR assays are commercially available, their performance varies significantly in diagnostic accuracy (Crawford et al., 2005). Unfortunately, vaccination of cats against FIV has caused a diagnostic dilemma.

**Feline Infectious Peritonitis**

FIP, which is caused by a coronavirus, produces a chronic and progressive anorexia, depression, weight loss, fluctuating fever, and variable peritoneal and thoracic effusions. Anterior uveitis and/or chorioretinitis may develop with or without concurrent systemic signs (Fig. 27.46) (Campbell & Reed, 2000).
However, a recent study found concordance of histopathology with a final diagnosis of FIP to be poor (Giori et al., 2011). In this study, the highest concordance was found for serum concentration of alpha-1-acid glycoprotein (AGP) combined with immunohistochemistry. Affected cats are generally 6 months to 3 years of age, come from shelters or cat-teries, and show signs of cyclical antibiotic-resistant fevers. Pleural or peritoneal effusions (or both) are typically straw-colored and high in proteins, particularly globulins. A complete blood count often reveals a neutrophilia with a left shift, nonregenerative anemia, hyperproteinemia, and a low albumin-to-globulin ratio (Andrew, 2000; Barr, 1998). Hyperproteinemia resulting from polyclonal gammopathy occurs in approximately 50% of cats with effusive FIP and 70% of cats with noneffusive FIP (Barr, 1998). Aqueous cytology reveals variable amounts of fibrin, red blood cells, mononuclear cells, and neutrophils. Immunosuppressive and anti-inflammatory agents provide palliative therapy (Evermann et al., 1995).

Feline Leukemia Virus

The FeLV complex may cause both direct and indirect (i.e., lymphosarcoma related) uveitis in cats. Ocular involvement from FeLV can range from orbital masses, eyelid masses, conjunctival and nictitating membrane masses, anterior uveal tumors, iridocyclitis with or without hypopyon, secondary glaucoma, chorioretinitis, chorioretinal masses, retinal hemorrhage, retinal detachments, and optic neuritis (Brightman et al., 1991; Carlton, 1976; Corcoran et al., 1995; Dubielzig, 1990; Meincke, 1966; Miller & Dubielzig, 2007; Slatter et al., 1974). The FeLV-induced anterior uveitis may progress to either diffuse inflammation of all intraocular tissues or frank tumor formation (Fig. 27.48). If a serum ELISA antigen test is positive, an immunofluorescent antibody test can be performed to confirm infection (not 100% reliable), or the ELISA...
can be repeated in 3–4 months (Willis, 2000). Other diagnostic options include FA, ELISA, or PCR on bone marrow aspirates, lymph node biopsies, and direct biopsies of intraocular masses (Hartmann, 2006). Aqueous humor cytology usually reveals variable numbers of lymphocytes and occasional plasmacytes and neutrophils. The presence of abnormal lymphocytes may help confirm ocular lymphosarcoma (Clerc & Lafortune, 1995).

**Toxoplasma gondii**

Ocular lesions are common in animals with toxoplasmosis because the eye is a target organ (Davidson, 2000). In cats, T. gondii more commonly causes anterior uveitis (Chavkin et al., 1994; Lappin et al., 1992) but also produces posterior segment disease such as granulomatous chorioretinitis and retinal vasculitis (Burr ridge, 1980; Campbell, 1974; Campbell & Schiessl, 1978; Dubey & Carpenter, 1993; Dubey & Johnstone, 1982; Lappin et al., 1989a, 1989b, 1989c; Piper et al., 1970; Vainisi & Campbell, 1969; Witt et al., 1989). The diagnosis of toxoplasmosis is made either on the basis of demonstrating organisms in the uveal tissues or measurement of immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies (Davidson et al., 1991; Hill et al., 1995; Lappin & Black, 1999; Lappin et al., 1995). An ELISA test for IgM antibodies with a single titer greater than 1:256 is suggestive of infection. A high or rising IgG titer is also consistent with active toxoplasmosis (Dubey & Carpenter, 1993; Lappin et al., 1989a). The IgG class of antibody can stay elevated for years, however, and thus is not necessarily an indicator of active disease. In cats with anterior uveitis and a positive serum titer, it may be helpful to measure antibodies in the aqueous humor and serum concurrently so that the relative level of antibodies in the eye can be determined through calculation of the Goldmann-Witmer coefficient (C value) (Davidson, 2000). C values of 3 or greater are suggestive of local antibody production. PCR tests for T. gondii have been evaluated in both serum and aqueous humor samples (Burney et al., 1998, 1999; Lappin et al., 1996). However, in an experimental study, PCR on whole blood samples was not an effective diagnostic test (Burney et al., 1999). The most commonly used therapy for toxoplasmosis is clindamycin hydrochloride at a dose of 12.5 mg/kg orally twice daily for 14–21 days. The anterior uveitis should also be treated with anti-inflammatory therapy.

**Bartonellosis**

Bartonella henselae is the causative agent of cat scratch disease in humans and ocular manifestations such as neuroretinitis are well documented. B. henselae infection is common in cats, particularly in warm climates where flea populations are high, as this is the mode of transmission (Guptill, 2010; Guptill et al., 2004). Four other species of Bartonella (Bartonella clarridgeiae, Bartonella koehlerae, Bartonella quintana, and Bartonella bovis) may also infect cats naturally, although infection with species other than B. henselae and B. clarridgeiae is rare. Cats are considered the adapted reservoir species for B. henselae, which makes ascribing disease states caused by the organism difficult as most carrier cats are clinically healthy. Infected cats may develop recurrent bouts of bacteremia that may last for years or perhaps indefinitely (Kordick et al., 1995). It has been suggested that cats might be more likely to develop clinical disease when infected with a non-reservoir-adapted species of Bartonella such as Bartonella vinsonii subspp. berkhoffii, which commonly infects dogs (Breitschwerdt et al., 2010).

In both naturally and experimentally infected cats, Bartonella has been detected in aqueous humor (Lappin & Black, 1999; Lappin et al., 2000), although its role as a cause of uveitis in cats remains speculative (Stiles, 2011). A study that compared serum antibody titers in 113 cats with uveitis and 156 clinically ill cats without uveitis found that the highest titers were in the healthy cats (Fontenelle et al., 2008b). Likewise, a study of 104 cats with uveitis and 19 healthy shelter cats found that no cat with uveitis had Bartonella DNA amplified from the aqueous humor by PCR, whereas 1 healthy shelter cat was positive. The healthy shelter cats had a higher percentage of positive serum antibody titers, likely reflecting their flea exposure (Powell et al., 2010).

The prevalence of seropositive cats tested has ranged from 5% to 93% (Guptill et al., 2004; Marston et al., 1999; Maruyama et al., 2000; Nutter et al., 2004). This high prevalence within cat populations makes it impossible to correlate clinical disease with serum antibody titers, whether utilizing the ELISA test or the Western immunoblot. Serum antibody titers are useful for identifying the sero-negative cat. The current recommendation from the American Association of Feline Practitioners for diagnostic testing in a sick cat includes serum antibody titer coupled with blood culture or PCR on whole blood. Aqueous humor can be submitted for both PCR and detection of Bartonella sp. specific antibody and calculation of the C value (Goldmann-Witmer coefficient). C values of greater than 3 are suggestive of local antibody production (Stiles, 2011).

No definitive treatment protocol has been identified that will clear a cat of Bartonella infection. The current recommendation for treating an ill cat (not healthy) with suspected bartonellosis is doxycycline at a dose of 10–22 mg/kg every 12 hours for 2–6 weeks, with the dose rounded up or down to give a whole pill to avoid esophageal irritation (Breitschwerdt et al., 2010; Guptill, 2010; Kordick et al., 1997). Doxycycline suspensions can also be prepared by a compounding pharmacist for use in the cat.

**Systemic Fungal Infection**

Granulomatous anterior uveitis, usually with concurrent chorioretinitis, may be associated with cryptococcosis (Bliouin & Cello, 1980; Fischer, 1971; Rosenthal et al., 1981; Schulman, 1985; Trivedi et al., 2011; Wilkinson, 1979, 1984), histoplasmosis (Breitschwerdt et al., 1977; Clinkenbeard et al., 1987; Gwin et al., 1980; Noxon et al., 1982; Percy, 1981; Wolf &
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Belden, 1984), blastomycosis (Alden & Mohan, 1974; Hatkin et al., 1979; Jasmin et al., 1969; Nasisse et al., 1985; Sheldon, 1966), and coccidioidomycosis (Angell et al., 1985; Tofflemire & Betbeze, 2010). The presence of ocular fungal agents is usually from hematogenous spread to the eye, except in cryptococcosis, in which extension from the central nervous system and optic nerve is also possible. The diagnosis of mycotic uveitis may not always be easy to verify. Complete physical examination, thoracic radiography, hematology, serum chemistries, and specific serological tests for fungal agents or antibody levels may allow for the diagnosis. Aqueous and vitreous centesis to identify fungal organisms may be used depending on the principal area of involvement. Lymph node and bone marrow aspirates may also be indicated for histoplasmosis, and cerebrospinal fluid collection may be indicated for the diagnosis of cryptococcosis. The preferred treatment for ocular fungal infections is oral fluconazole because it penetrates the eye and brain well (Gionfriddo, 2000). However, with the blood-ocular barriers disrupted by inflammation, itraconazole will also achieve therapeutic levels within the eye and has been documented to be safe and effective in cats (Boothe et al., 1997). The use of systemic voriconazole in cats has resulted in serious side effects (Quimby et al., 2010; Smith & Hoffman, 2010). With severe posterior segment inflammation, oral corticosteroids at anti-inflammatory doses are indicated along with antifungal therapy.

Experimental Sarcoma Virus Uveitis

An oncogenic RNA virus, FeSV is thought to have evolved by mutation from FeLV. The virus is responsible for causing spontaneous tumor formation in naturally infected cats. Experimental subcutaneous injection, however, induces anterior uveitis (Lubin et al., 1983). The first clinical signs are conjunctival hyperemia and ciliary flush, which become apparent 37 days after inoculation. Iritis, posterior synechiae, pigment deposits on the lens capsule, and cataracts subsequently develop. Histopathologic studies reveal that inflammation is confined to the iris and ciliary body, where a cellular infiltrate of lymphocytes and plasma cells is found. In addition, bizarre transformed cells and large multinucleate cells, resembling those with sarcomatous changes, are seen. The presence of high quantities of virus in the aqueous humor suggests that local virus replication occurs, but inflammatory changes have been attributed to virus-antibody interaction or a cell-mediated immune response. A role for FeSV in naturally occurring feline uveitis has not been demonstrated.

Periarteritis and Uveitis

Periarteritis is a rare disease of cats in which medium and small arteries undergo fibrinoid necrosis. Histopathologically, a zone of lymphocytes and plasma cells surrounds a neutrophilic infiltrate, primarily in the tunica media. Subsequent formation of granulation tissue results in vascular occlusion. The cause of the disease is unknown, but a hypersensitivity response to collagen is suspected. Ocular manifestations of periarteritis nodosa have been seen in several cats; in one report, a description of the ocular disease was provided (Campbell et al., 1972). The anterior chambers contained large amounts of proteinaceous exudate. The ciliary bodies were infiltrated with lymphocytes and plasma cells, and foci of necrosis were seen as well. Other changes included presence of a cyclitic membrane, choroidal thickening by cellular infiltrates, and exudative retinal detachment. Lesions were also seen in the kidneys, lungs, and spleen. The diagnosis of periarteritis nodosa is usually made at necropsy.

Ophthalmomyiasis

Ophthalmomyiasis is uncommon in cats. The condition most commonly manifests as the migration of parasites both in and under the sensory retina, and most affected cats are asymptomatic (Fig. 27.49). Intraocular Cuterebra larvae have caused uveitis in cats (Fig. 27.50) (Gwin et al., 1984; Harris et al., 2000; Johnson et al., 1988; Stiles & Rankin, 2006; Wyman et al., 2005). Clinical signs include ocular pain, aqueous flare and fibrin, and corneal edema. In one case (Johnson et al., 1988), the globe was salvaged through surgical extraction of the parasite, but corneal edema was permanent. The parasite’s mode of entry to the eye was not determined. In a second case, despite successful removal of the larva, the cat developed retinal degeneration and lost vision in the affected eye several weeks following surgery (Harris et al., 2000). In another case in which the larva was surgically removed from the anterior chamber, the uveitis resolved and the cat remained visual with normal retinal function (Stiles & Rankin, 2006). In another reported case (Wyman et al., 2005), a cat was euthanized because of worsening systemic and neurologic signs. The larva, as well as coagulation necrosis and hemorrhage of the retina, choroid, and optic nerve were demonstrated upon histopathologic examination.

Invasion of the globe by a nematode of the family Metastrongylidae has also been described in a cat (Bussanich &

Figure 27.49. Ophthalmomyiasis tracks in the tapetal fundus of a cat. (Courtesy of Michigan State University College of Veterinary Medicine Ophthalmology Department.)
Rootman, 1983). Clinical signs were blepharospasm as well as inflammatory cells, fibrin, and blood in the anterior chamber. The eye eventually required enucleation. One case of ophthalmomyiasis interna had, as a component to the retinal lesions, a large fibrinohemorrhagic clot in the anterior chamber, presumably induced by anterior uveal migration of the parasite (Gwin et al., 1984).

**Leishmaniasis**

Leishmaniasis caused by *L. infantum* does occur in cats, although it has been less reported than in dogs. Dogs have been considered the primary reservoir hosts, although cats may serve as an alternate reservoir species (Navarro et al., 2010). Although lesions in cats have most often been reported as skin nodules (see “Diseases of the Eyelids”), conjunctivitis, keratitis, and panuveitis have also been reported in three reports of cats from Spain (Hervas et al., 2001; Leiva et al., 2005; Navarro et al., 2010). Diffuse granulomatous inflammation with amastigotes present in the cytoplasm of macrophages characterized the histopathologic appearance of ocular lesions. Immunohistochemical staining of tissues, or electron microscopy, confirmed the diagnosis of leishmaniasis in all cases. Treatment in one cat with allopurinol resulted in clinical improvement, although both eyes were enucleated for corneal perforations and panuveitis (Leiva et al., 2005).

**Traumatic Anterior Uveitis**

Anterior uveitis may follow both blunt and penetrating ocular trauma. Clinical signs include those of acute anterior uveitis plus hyphema, with the hyphema having variable amounts of fibrin (Fig. 27.51a, b). With a more intense anterior uveitis and additional fibrin, exit of the erythrocytes may be prolonged. With limited blunt injury, the hyphema usually clears within a few days. With significant blunt trauma, damage to the uveal tissues and lens may occur, as well as retinal detachment.

Penetrating ocular injuries may affect the cornea, lens, and posterior segment. When the lens and posterior segment cannot be visualized at slit lamp biomicroscopy and ophthalmoscopy, ultrasonography is indicated. Skull radiographs can illustrate metallic projectiles within the orbit. Intraocular infection may result from bacterial or fungal contamination associated with globe penetration. In the early stage following ocular injury, it may not be apparent that infection is present. Thus, all penetrating wounds to the globe should be

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**Figure 27.50.** Ophthalmomyiasis interna in a cat. Arrow denotes a fibrin-covered dipteran larva in the anterior chamber. Following surgical removal, the larva was identified as a first instar *Cuterebra* spp. (Reprinted with permission from Stiles, J. & Rankin, A. (2006) Ophthalmomyiasis interna anterior in a cat: surgical resolution. *Veterinary Ophthalmology*, 9, 165–168.)

**Figure 27.51.** a. Hyphema and fibrin fill the anterior chamber of a 1-year-old domestic shorthair cat after blunt ocular trauma. b. The same eye after an intracameral injection of 25µg of tissue plasminogen activator cleared the fibrin.
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Use of tropicamide to move the pupil may help prevent synchiae. If intravitreal hemorrhage occurs, however, exit of blood from the vitreous may require several months. If the lens capsule is penetrated, lens removal should be performed (if possible) soon after the injury to prevent ongoing lens-induced uveitis. Septic lens implantation syndrome occurs when a penetrating wound inoculates bacteria within the lens (Dalesandro et al., 2011; Dubielzig & Pirie, 2005; Mairar & Dubielzig, 1995). Clinical signs of anterior uveitis and glaucoma may progress slowly, and it may not be readily apparent that a bacterial infection within the lens is present. The diagnosis is usually made upon histopathologic examination of an enucleated globe. Gram-positive cocci have been the most common bacteria seen.

Lens-Induced Anterior Uveitis

Lens-induced anterior uveitis in cats may be associated with cataract formation, hypermature cataracts, perforation of the lens capsule, and lens luxation. Perforation of the lens capsule in cats usually follows lacerations by cat claws or foreign bodies. As in the dog, large or nonsealing anterior capsule lacerations result in exposure of the anterior uvea to progressively increasing amounts of lens material. Extracapsular lensectomy or phacoemulsification is recommended before the anterior uveitis becomes medically uncontrollable and threatens vision. Septic lens implantation syndrome is discussed under “Traumatic Anterior Uveitis.”

Lens-induced uveitis related to cataract formation in cats is usually less intense than its counterpart in dogs. Feline cataract surgery has received limited attention in the veterinary literature, but the large cornea, prominent eye, and less-intense postoperative anterior uveitis in cats result in success rates equal to, and even exceeding, those achieved in dogs.

Idiopathic Uveitis

Many cats are presented for chronic uveitis that remains idiopathic despite evaluations for infectious or neoplastic diseases. These cats tend to be middle aged to older and may have one or both eyes affected. Common clinical findings are iris nodules, which are foci of lymphocytes and plasma cells, iris neovascularization, keratic precipitates, inflammatory debris (melanin pigment, fibrin, cells) on the lens capsule, cataract, anterior vitreal inflammatory debris, and glaucoma (see Fig. 27.42) (Peiffer & Wilcock, 1991). These cats generally do not exhibit overt pain, and the condition may be advanced before the animals are presented. Typically, the uveitis must be managed long term and enucleation for glaucoma is not an uncommon eventuality.

Therapy for Uveitis

The nonspecific therapy for feline anterior uveitis includes mydriatics, topical (and occasionally systemic) corticosteroids, and topical and/or systemic nonsteroidal anti-inflammatory drugs. Systemic corticosteroids and nonsteroidal
agents should never be used together. The mydriatic of choice is 1% atropine ointment, which causes less salivation than atropine solution in cats. The iridocycloplegia causes pupilary dilation, relieves the ciliary pain, and decreases the possibility of posterior synechia. If a risk of secondary glaucoma exists, tropicamide is an alternative cycloplegic medication. A short-acting parasympatholytic agent, the effects of tropicamide typically last only 4–6 hours and can easily be discontinued if the IOP becomes elevated. Topical corticosteroids usually include 1% prednisolone acetate or 0.1% dexamethasone. Monitoring of aqueous flare and IOP can be used to determine both the frequency and duration of the corticosteroid and mydriatic therapy. If the posterior segment is involved, systemic anti-inflammatory therapy is required. If fibrin is present in the anterior chamber and does not resolve on its own within a few days of formation, tissue plasminogen activator at a dose of 25µg in a volume of 0.10 mL can be injected into the anterior chamber. The fibrin usually resolves within 1–2 hours if it has not been present for more than 7–10 days (see Fig. 27.51). Treatment of chronic idiopathic anterior uveitis in cats needs to be continuous. The use of topical corticosteroids will cause recrudescent herpesvirus disease in some cats; thus, with long-term therapy, nonsteroidal agents should be considered.

Ophthalmic Complications of Uveitis

Several complications from anterior and posterior uveitis may develop in cats. These complications usually relate directly to the duration and cause of the uveal inflammation. Glaucoma may result from peripheral anterior synechiae, iridocorneal angle and ciliary cleft closure, complete posterior synechiae with iris bombe, and development of preiridal fibrovascular membranes, which may cover the iris and aqueous humor outflow pathways as well as the pupil. In one study, secondary glaucoma developed in 50% of eyes with uveitis and systemic diseases and in 28% of eyes with uveitis without systemic diseases (Gemensky et al., 1996). Cataracts, often associated with posterior synechiae, occurred in approximately 36% of cats with idiopathic lymphoplasmacytic uveitis but in only 22% of cats with anterior uveitis and concurrent systemic diseases. In cases with T. gondii infection, 70% of eyes developed secondary glaucoma. The end-stage sequelae may be an enlarged, absolute glaucomatous globe (Fig. 27.53) or, less commonly, a phthisical globe.

In one report (Gemensky et al., 1996), blindness or visual impairment occurred in 72% of cats with uveitis and systemic disease, and uveitis responded to therapy in only 33% of cats. Idiopathic uveitis and uveitis secondary to FIV infection were more responsive (56%) to therapy than those uveitides associated with other systemic diseases (33%).

Anterior Uveal Neoplasia

Both primary and secondary uveal neoplasms occur in cats. Early diagnosis in cats is vital, because primary malignant neoplasms are locally invasive and have a high metastatic potential. Feline intraocular neoplasms tend to involve the anterior uvea, whereas posterior uveal involvement is less common. Anterior uveal tumors generally affect cats older than 10 years. No breed or sex predisposition has been reported (Day & Lucke, 1995; Dubielzig, 1990; Miller & Dubielzig, 2007).

Diffuse Iridal Melanoma

The diffuse iridal melanoma of the cat appears as progressive pigmentation of the iris, which occurs over months to several years (Fig. 27.54a–c) (Acland, 1979; Acland et al., 1980; Bellhorn & Henkind, 1970; Betroy et al., 1988; Blodi & Ramsey, 1967; Cardy, 1977; Morgan, 1969; Peiffer et al., 1977). The pigmentation may develop simultaneously in several areas on the anterior iridal surface. Generally, both the extent and amount of pigmentation increase with time. Changes in pupil shape and mobility may result as the iris becomes thicker. Glaucoma secondary to tumor infiltration of the iridocorneal angle indicates the condition is advanced. These tumors have also presented clinically as amelanotic melanomas (Bjerkas et al., 1997). Metastasis may be noted as late as 1–3 years after enucleation and usually involves the liver and lungs. One report describes a cat with widespread metastasis, including to the long bones, of a uveal melanoma (Planellas et al., 2010). The metastatic rate may be as high as 63%, but metastasis is not always noted until death occurs. One study suggested an association between anterior uveal melanoma and FeLV/FeSV infection (Stiles et al., 1999);
however, a subsequent study failed to confirm that association (Cullen et al., 2002).

Several investigators have attempted to develop clinical and histopathologic parameters to assist clinicians in treatment of these patients. A grave prognosis in one report was based on histopathologic findings including a high mitotic index, full-thickness iris involvement, and the presence of tumor cells in the scleral venous plexus (Duncan & Peiffer, 1991). Another report correlated histopathologic findings with survival times in affected cats (Kalishman et al., 1998). Cats with the tumor confined to the iris and cats with moderate spread, which included diffuse iridal involvement (spread into the iridocorneal angle, with and without glaucoma), had survival times similar to those in the control group. Cats with advanced melanoma consisting of aggressive infiltration of the iris, its posterior epithelium, and the ciliary body, however, had shortened survival times, and the cause of death almost always suggested metastatic disease.

A dilemma for veterinarians is deciding when removal of the eye will benefit the patient. Pigmentary changes may progress over several months to a few years. The benign, small, angular pigmented cell proliferation on the iridal surface may eventually transform into larger rounded cells, which are typical of a malignant diffuse iridal melanoma, then infiltrate the iridal stroma and ultimately obstruct aqueous outflow pathways (Fig. 27.55) (Dubielzig & Lindley, 1993). Once tumor cells are within the filtration angle and scleral venous plexus, metastasis to distant organs (e.g., liver, lungs) is highly likely.

Enucleation may be justified on the basis of increases in the amount and size of pigmented areas, any pigmented mass within the iridocorneal angle and sclerociliary cleft on gonioscopy, changes in the pupillary shape and mobility, and elevation in IOP.

The use of diode laser energy to photoablate small iridal pigmented lesions in the cat is an option. However, the use of this therapy and its ability to prevent progression of iris melanoma development has not been reported. Since the tumor is multifocal in nature, new lesions can be expected to form.

**Feline Ocular Sarcomas**

Feline ocular sarcomas are the second most common primary intraocular tumor, after diffuse iridal melanomas, and are
Primary Ciliary Body Neoplasms

Primary ciliary body adenomas and adenocarcinomas are uncommon in cats (Fig. 27.57) (Cotchin, 1957; Peiffer, 1988; Woog et al., 1983). Ocular trauma seems to be the inciting event. Affected cats have ranged in age from 7 to 15 years; time from trauma to detection of tumor averaged 5 years. Risk factors include trauma to the lens, chronic uveitis, possibly intraocular surgery, and gentamicin injections to destroy the ciliary body for advanced glaucoma.

Presenting clinical signs include chronic uveitis, glaucoma, intraocular hemorrhage, and possible single or multiple, white-to-pink masses. Often, intraocular evaluations are impossible because of corneal edema and the anterior chamber mass. Because cartilage and bone formation may occur within this tumor, ultrasonography and radiography may be helpful. Early enucleation, with exenteration of the orbit, is recommended because involvement of the optic nerve and regional lymph nodes, and distant metastasis occurs (Dubielzig, 2002). After the diagnosis and surgical removal of affected globes, most cats will unfortunately die from neoplasm-related causes within several months.

Histopathologic findings range from granulation tissue, fibrosarcoma, and osteosarcoma to an anaplastic spindle cell sarcoma. These tumors infiltrate the choroid circumferentially, and they quickly extend into the retina and optic nerve (Fig. 27.56). The variety of neoplastic types suggests that the oncogenesis may involve undifferentiated stem cells with pluripotential tendencies. The tumor has been postulated to arise from a malignant transformation of lens epithelium (Zeiss et al., 2003). Clinical assessment of these patients provides a convincing argument for early removal of nonvisual globes with severe trauma, absolute glaucoma, chronic uveitis, and phthisis bulbi. Blind eyes in cats with chronic uveitis should not be neglected clinically; they should be examined periodically for tumor formation.

A case of an anterior uveal spindle cell tumor in a cat has been reported (Evans et al., 2010). The tumor originated in the iris as a peripheral nerve sheath tumor and resembled the spindle cell tumor of blue-eyed dogs.

Primary Ciliary Body Neoplasms

Primary ciliary body adenomas and adenocarcinomas are uncommon in cats (Fig. 27.57) (Cotchin, 1957; Peiffer,
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1983a). They appear as nonpigmented masses within the pupil or at the iris root that originate from the ciliary pars plicata, and they often produce secondary glaucoma. They are usually slow growing and seldom penetrate the sclera. Once the diagnosis is established, enucleation is recommended. In a histopathologic study of 17 eyes from cats with ciliary body neoplasia, only 2 showed scleral invasion, which was considered indicative of an adenocarcinoma rather than adenoma (Dubielzig et al., 1998). Although one tumor recurred following attempted local excision, enucleation appeared to be adequate for removing all neoplastic tissue in the cats.

Metastatic Uveal Neoplasms

Lymphosarcoma is the most frequent metastatic intraocular tumor in cats. The anterior uveal involvement occurs in nearly all globes as an anterior uveitis, an intraocular mass, or a combination of both (Fig. 27.58 and Fig. 27.59) (Corcoran et al., 1995). Typically, there is a pink-to-white mass in the anterior chamber or within the anterior uvea. Signs of inflammation include miosis, reduced IOP, aqueous flare, keratic precipitates, and hypopyon. Secondary glaucoma may result from neoplastic obstruction of the aqueous humor outflow pathways. Lymphosarcoma in cats may be associated with FeLV or FIV; however, the disease also occurs in uninfected cats.

The diagnosis of ocular lymphosarcoma is based on the examination of cells. Intraocular biopsy of the anterior uvea is not usually indicated, but aqueous humor cytology is frequently diagnostic. Histopathologic examination of affected eyes reveals considerable tumor involvement of the entire uveal tract. Neoplastic cells may also occur in the retina, vitreous, anterior chamber, and occasionally, in the cornea and sclera. Tumor cells appear as pleomorphic, round-to-oval cells with vesicular nuclei.

Lymphosarcoma affecting ophthalmic tissues is considered to be a manifestation of multicentric disease. Therefore, systemic chemotherapy is recommended. Topical corticosteroids may reduce the size of an intraocular mass and improve signs of uveitis. Treatment of secondary glaucoma is usually with topical carbonic anhydrase inhibitors, and topical beta-agonists.

Other metastatic neoplasms in cats may involve the uveal tract. Adenocarcinomas with a mammary and uterine origin, as well as a metastatic hemangiosarcoma, have been reported (Bellhorn, 1972; Kirschner et al., 1986; Murphy et al., 1989; O’Rourke & Geib, 1970; West et al., 1979). Four intraocular SCCs from various sites have also been reported (Cook et al., 1984; Hamilton et al., 1984; Hayden, 1976). An anterior uveal involvement usually presents as masses of the ciliary body. Choroidal masses produce retinal hemorrhages and detachments.

GLAUCOMA

Causes

Glaucoma in cats is less common than in dogs, and most cases of feline glaucoma appear to be secondary. There are surprisingly few clinical and histopathologic reports in the literature regarding feline glaucoma (Brown et al., 1994; Coop & Thomas, 1958; Gelatt & Ladds, 1971; Hampson et al., 2002; Jacobi & Dubielzig, 2008; McCalla et al., 1988; McLaughlin et al., 1987; McLellan et al., 2004; Ridgeway & Brightman, 1989; Trost et al., 2007; Wilcock et al., 1990), although a published review of feline glaucoma provides an excellent summary of the subject (McLellan & Miller, 2011). As with dogs, most cats with glaucoma are presented late in the

Figure 27.58. Ocular lymphosarcoma in an adult domestic shorthair cat. The lateral iris is thickened with a cellular infiltrate, and a fibrin clot obscures the iris medially.

Figure 27.59. Ocular lymphosarcoma in a 15-year-old domestic long-haired cat. Note the deposition of tumor cells across the endothelium and the corneal vascularization.
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In another study of 82 cats (93 eyes), glaucoma appeared to be primary in only five eyes based on clinical examination (Blocker & Van der Woerdt, 2001b). Breed predispositions for glaucoma have been described in the Siamese (Brown et al., 1994; McLellan et al., 2004; Peiffer, 1982), Persian and European shorthair (Trost et al., 2007; Walde & Rapp, 1992), and Burmese breeds (Hampson et al., 2002). In most cats with primary glaucoma, the iridocorneal angle is open (Wilcock et al., 1990). However, a recent case report describes a group of closely related Siamese with congenital glaucoma resulting from pectinate ligament dysplasia (McLellan et al., 2004). In an additional report, Burmese cats were reported to have narrow- or closed-angle glaucoma (Hampson et al., 2002). Open-angle glaucoma was described in a histopathology report of eight cats, six of which were domestic short- or longhair, and two of which were Burmese (Jacobi & Dubielzig, 2008).

The gonioscopic appearance of the normal feline iridocorneal angle and ciliary cleft reveals a long, slender, and slightly branching pectinate ligament that is usually the same color as the iris and a pigmented trabecular meshwork (Fig. 27.61 and Fig. 27.62). Visualization of the iridocorneal angle and pectinate ligament is often possible without a goniolens.

### Congenital glaucoma
- Secondary to structural outflow anomalies

### Primary glaucoma
- Open/normal angle, with and without collapsed ciliary cleft
- Narrow/closed angle (Burmese)
- Pectinate ligament dysplasia (Siamese)

### Secondary glaucoma
- Anterior uveitis (chronic)
- Lens luxations (trauma/primary/cataract)
- Phacolytic/phacoclastic uveitis (lens perforation)
- Hyphema (systemic hypertension, bleeding disorders, trauma)
- Intraocular neoplasia (primary/secondary neoplasms)
- Aqueous misdirection (shallow anterior chamber and anteriorly displaced lens)

### Table 27.2 Types and Causes of Glaucoma in Cats

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tr>
<td>Congenital glaucoma</td>
<td>Secondary to structural outflow anomalies</td>
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<tr>
<td>Primary glaucoma</td>
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<td></td>
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<td></td>
<td>Aqueous misdirection (shallow anterior chamber and anteriorly displaced lens)</td>
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</table>

An attempt to classify the different types of feline glaucoma from the available literature is summarized in Table 27.2. Congenital glaucomas may be either unilateral or bilateral and occur because of developmental abnormalities of the aqueous humor outflow pathways (Fig. 27.60). Primary glaucoma has been reported but appears to be much less common than secondary glaucoma in cats. In a histopathologic study of 131 enucleated glaucomatous feline eyes, a primary cause was suspected in only three cases in which the associated inflammatory changes were considered to be either absent or mild and because iridocorneal angle closure or obstruction was not a prominent histopathologic feature of the disease (Wilcock et al., 1990). In another study of 82 cats (93 eyes), glaucoma appeared to be primary in only five eyes based on clinical examination (Blocker & Van der Woerdt, 2001b). Breed predispositions for glaucoma have been described in the Siamese (Brown et al., 1994; McLellan et al., 2004; Peiffer, 1982), Persian and European shorthair (Trost et al., 2007; Walde & Rapp, 1992), and Burmese breeds (Hampson et al., 2002). In most cats with primary glaucoma, the iridocorneal angle is open (Wilcock et al., 1990). However, a recent case report describes a group of closely related Siamese with congenital glaucoma resulting from pectinate ligament dysplasia (McLellan et al., 2004). In an additional report, Burmese cats were reported to have narrow- or closed-angle glaucoma (Hampson et al., 2002). Open-angle glaucoma was described in a histopathology report of eight cats, six of which were domestic short- or longhair, and two of which were Burmese (Jacobi & Dubielzig, 2008). The gonioscopic appearance of the normal feline iridocorneal angle and ciliary cleft reveals a long, slender, and slightly branching pectinate ligament that is usually the same color as the iris and a pigmented trabecular meshwork (Fig. 27.61 and Fig. 27.62). Visualization of the iridocorneal angle and pectinate ligament is often possible without a goniolens.

Most cases of feline glaucoma are secondary to either anterior uveitis or intraocular neoplasia (Blocker & Van der Woerdt, 2001b; Wilcock et al., 1990). In two separate histopathologic studies, the majority of glaucoma cases occurred secondary to chronic, idiopathic, lymphocytic-plasmacytic uveitis (Gelatt & Ladds, 1971; Peiffer & Wilcock, 1991). However, other causes were FIP, iridal melanoma, FeLV-associated lymphosarcoma, trauma, and lens-induced uveitis.
of angle recession and globe enlargement. However, the ciliary cleft is collapsed, and peripheral anterior synechiae may be scattered among the pectinate ligaments.

Intraocular neoplasia is the other predominant cause of feline secondary glaucoma. While any intraocular neoplasm may cause secondary glaucoma, diffuse iridal melanoma presents the highest risk. The second most common neoplasm to cause glaucoma is lymphosarcoma (Peiffer & Wilcock, 1991; Wilcock et al., 1990). Intraocular neoplasia can cause impaired aqueous humor outflow via several mechanisms, including infiltration of the trabecular meshwork and ciliary cleft by neoplastic cells, direct damage to the trabecular cells, formation of peripheral anterior synechiae, formation of preiridal fibrovascular membranes, and secondary inflammation from neoplastic factors and necrosis.

Other, less common causes of feline secondary glaucoma include corneal perforation with anterior synechia (and subsequent angle and cleft closure) and traumatic lenticular rupture (Mccalla et al., 1988). The severe inflammation after corneal and lens perforations may induce pupillary seclusion due to annular posterior synechiae. The cat’s vertical, slit-shaped pupil appears to be more difficult to occlude except in cases of severe inflammation.

Anterior lens luxation may cause feline secondary glaucoma by obstructing aqueous outflow (Olivero et al., 1991). Because the feline anterior chamber depth is greater than the canine, glaucoma secondary to anterior lens luxation is less common in cats than in dogs (Sapienza, 2005). Lens subluxations or luxations may occur in cats with chronic glaucoma and buphthalmic globes. Buphthalmos may contribute to zonular disinsertion and lens instability resulting in an anterior lens luxation. Therefore, determining whether the lens displacement or the glaucoma was the primary event is critical for treatment and prognosis.

Glaucoma due to aqueous humor misdirection, sometimes termed malignant glaucoma, has been described in cats (Cze-derpiltz et al., 2005; La Croix et al., 2003; Miller et al., 1999). The pathogenesis appears to be misdirection of the aqueous humor posteriorly into the vitreous humor through small breaks in the hyaloid near the vitreous base. The resultant increased vitreal pressure causes anterior displacement of the lens and marked shallowing of the anterior chamber. Typical clinical signs include mydriasis, a shallow anterior chamber visible on slit lamp biomicroscopy, and IOP elevations that range from mild to marked. In a study of 32 cats (La Croix et al., 2003), the mean age at presentation was 12 years, with female cats significantly more affected than males. The IOP ranged from 12 to 58 mmHg at presentation, with an IOP of 20 mmHg or higher in 32 of 40 affected eyes. Ultrasonography and histopathologic examinations have revealed a thickened anterior vitreal face interposed between the lens and ciliary body, partial ciliary cleft collapse, and cavitated vitreal regions corresponding to fluid pockets. Medical therapy to reduce aqueous humor production or improve aqueous outflow has variable results in these cases. In many cats, the progression of disease is relatively slow, and topical medications such as

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**Figure 27.62.** Photomicrograph of a normal feline iridocorneal angle and ciliary cleft (hematoxylin and eosin).

**Figure 27.63.** Photomicrograph from a feline globe with glaucoma secondary to chronic uveitis. A lymphoplasmacytic infiltrate is present in the iris and sclera. The iridocorneal angle and ciliary cleft are obstructed by the inflammatory infiltrate (hematoxylin and eosin). (Courtesy of Evelyn Kazakos.)
timolol maleate and dorzolamide maintain relatively normal IOPs for prolonged periods. Surgical pars plana vitrectomy (Miller et al., 1999) or lensectomy and anterior vitrectomy (Czederpiltz et al., 2005; Miller et al., 1999; Sapienza, 2005) in some cats has been successful in controlling IOP.

Clinical Signs and IOP Measurement

Making the diagnosis of feline glaucoma is the same as in other animal species, but the clinical signs may be more subtle and therefore easily overlooked. Often, the clinical signs have been present for extended periods of time and the eyes are already permanently blind (Blocker & Van der Woerd, 2001b; Dietrich, 2005). In one study, the most common complaints and clinical signs were cataract, corneal edema, mydriasis, buphthalmos, “cloudy eye,” and blindness (Blocker & Van der Woerd, 2001b). Conjunctival or episcleral hyperemia was often absent. Cats often do not develop the conspicuous corneal edema that occurs in dogs, which may indicate the ability of the feline corneal endothelium to pump against significant hydrostatic pressure or signal lower elevations of IOP. In acute glaucoma, pupillary dilation is the most common finding and may be the only symptom observed (Brooks, 1990). Buphthalmia, exposure keratitis with vascularization, and lens luxation (usually subluxation and anterior luxation) are common sequelae to chronic intraocular hypertension (Fig. 27.64). Buphthalmia, however, is easily overlooked, because the orbit and eyelids effectively camouflage the enlarged globe. Retinal degeneration is recognized ophthalmoscopically by vascular attenuation and tapetal hyperreflectivity. Because the small optic papilla of the cat normally lacks myelin, optic nerve cupping is often difficult to visualize. Even so, the atrophic optic nerve head is darker in color.

The circadian rhythm of IOP in normal cats has been evaluated (Del Sole et al., 2007). The peak IOP occurred between 9 p.m. and 12 a.m. while the lowest values occurred between 9 a.m. and 6 p.m. Mean IOP as measured with application tonometry in this study was 18 mmHg over the 24-hour period. A study evaluating IOP in normal cats by use of application tonometry reported values of 9–31 mmHg (Miller et al., 1991). An experimental study determined that application tonometry in the cat underestimates IOP, such that the TonoPen XL® reading should be multiplied by 1.6 to approximate the actual IOP (Passaglia et al., 2004). In a study to establish reference values of IOP in normal cats by use of a rebound tonometer (Tonovet®), the mean value was 21 mmHg (Rusanen et al., 2010). The rebound tonometer was found to correlate well with direct manometry in the clinically important pressure range.

Treatment

Therapy for feline glaucoma generally follows the same guidelines used in other species. The foremost considerations are to correct, when possible, the underlying cause and to reduce IOP. Glaucoma secondary to idiopathic uveitis is sometimes effectively treated using aggressive anti-inflammatory therapy with topical and subconjunctival corticosteroids (described earlier). These corticosteroids offer both benefits and limitations, however. Long-term topical dexamethasone can elevate IOP in normal cats (Zhan et al., 1992), and the ongoing use of topical steroids in cats can cause recrudescence of latent herpesvirus infections. If lens luxation or rupture is the cause, lens extraction is beneficial. In the study by Blocker & Van der Woerd (2001b), 58% of the eyes maintained an IOP within the normal range and appeared comfortable with medical therapy alone.

In acute cases of glaucoma, when the IOP is greater than 50 mmHg and accompanied by mydriasis, a hyperosmotic agent is generally indicated to lower the IOP and to preserve optic nerve and retinal functions. Because the efficacy of osmotic agents relies on an established blood-aqueous and blood-vitreous barrier, their effect is diminished in the face of intraocular inflammation (Willis, 2004). Withholding water from the patient for up to 4 hours is required to produce the desired hypotensive effect (Dugan et al., 1989). The most commonly used osmotic agents are intravenous mannitol and oral glycerin.

Other medical therapeutic options include systemic and topical carbonic anhydrase inhibitors, topical beta-blockers, topical alpha-2 agonists, parasympathomimetics, and prostaglandin analogs. Systemic carbonic anhydrase inhibitors are not recommended in cats due to side effects, which include decreased appetite, vomiting, and lethargy (Blocker & Van der Woerd, 2001b). Options for topical carbonic anhydrase inhibitors are dorzolamide and brinzolamide. A application of 2% dorzolamide resulted in a significant decrease in IOP in...
SECTION IV

DISEASES OF THE LENS AND CATARACT FORMATION

Congenital Cataracts and Lens Anomalies

Multiple ocular defects rarely occur in cats, but the few reported cases have all included some form of lenticonal abnormality. Microphakia with elongated ciliary processes and subsequent anterior lens luxation has been described in three unrelated Siamese cats and a domestic shorthair cat (Aguirre & Bistner, 1973; Molleda et al., 1995). In one case, cataracts were present (Aguirre & Bistner, 1973). Bilateral aphakia associated with retinal detachment has been reported in a domestic shorthair; however, the retinal detachment was considered to be secondary (Peiffer, 1982). A condition characterized by sagittal lenticonal elongation and contact of the abnormal lens with ectatic axial cornea has been described in a 4-month-old Persian kitten (Peiffer, 1983b). The defect was termed keratolenticular dysgenesis and was presumed to represent anomalous formation of the lens vesicle from the surface ectoderm.

Congenital cataracts occasionally occur in domestic cats (Fig. 27.65) (Peiffer & Gelatt, 1974, 1975; Rubin, 1986;
Schwink, 1986). Incomplete posterior nuclear cataracts, which were presumed to be congenital, have been described in several Birman kittens (Schwink, 1986). The cataracts involved primarily the area of the Y sutures, in the form of either linear or triangular opacification. In a third report, both complete and incomplete triangular cortical cataracts were described in several Himalayan kittens (Fig. 27.66a, b) (Rubin, 1986). These were also located in the posterior cortex, and because one parent had posterior triangular lenticular opacities, a recessive mode of inheritance was suspected. Congenital cataracts have been described as a frequent manifestation of the Chédiak–Higashi syndrome in cats (Collier et al., 1979). The cataracts vary in size but typically involve the posterior nucleus, sutures, cortex, and capsule.

Bilateral macrophakia has been reported in three cats (Benz et al., 2011a). All cats had visual deficits and the vitreous was completely replaced by the lens. Retinal degeneration was also present in all cats.

**Primary and Secondary Cataract Formation**

In contrast to dogs, primary and inherited cataracts are rare in cats. To date, all reported feline cataracts presumed to be hereditary have been present congenitally. Most cataracts in cats are secondary and are classified according to association with trauma, anterior uveitis, glaucoma, or lens luxation.

Traumatic cataracts are relatively common in cats and are often sequelae to perforating ocular injury, particularly from cat claws. Traumatic cataracts tend to be focal, occurring primarily in the region of the insult, and are often associated with focal posterior synechia. Traumatic cataracts generally are slowly progressive or nonprogressive. When the lens capsule rupture is sufficiently large, lens protein may escape, thereby causing severe uveitis.

The most common cause of secondary feline cataracts is chronic anterior uveitis. Cataracts due to uveitis are typically slow to progress, begin in the cortex, and may be associated with posterior synechiae, rubeosis iridis, and preiridal and pupillary inflammatory membranes. Lens luxation is a common sequelae (Fig. 27.67).

Several types of metabolic/toxic cataracts have been reported in cats. Kittens fed a commercially available kitten milk replacer developed cataracts consisting of diffuse anterior and posterior lens opacification and vacuolation of the posterior Y sutures (Remillard et al., 1993). These lens
opacities were resolved in older kittens, becoming residual perinuclear halos and a few incipient cortical opacities. Investigators concluded that their diet contained inadequate levels of arginine.

Infectious causes of cataract in cats appear to be uncommon. A study from Austria demonstrated the presence of Encephalitozoon cuniculi within the cataractous lenses of 19 eyes from 11 cats (Benz et al., 2011b). The organism was confirmed by PCR and sequencing in 18 of 19 lenses and 10 of 19 aqueous humor samples. All cats had positive serum antibody titers. All cats underwent phacoemulsification and subsequently had clinical improvement in the anterior uveitis that was present preoperatively. Bacteria may be inoculated into the lens with a penetrating wound, leading to septic lens implantation syndrome (Dalesandro et al., 2011; Dubielzig & Pirie, 2005; M arlar & Dubielzig, 1995).

Theoretically, the feline lens should respond to elevated blood glucose levels by cataract formation, but diabetic cataracts are uncommon (Salgado et al., 2000). When they do occur, feline diabetic cataracts have been described as progressing more slowly than canine diabetic cataracts (Peiffer & Gelatt, 1974). Because the onset of diabetes mellitus usually occurs in cats older than 7 years, low activity of aldose reductase in lenses of older cats may explain why diabetic cataracts are a rare occurrence in this species (Richter et al., 2002). Diabetes mellitus and bilateral cataracts have been reported in an 18-week-old domestic longhair kitten (Thoresen et al., 2002).

A kitten with cataracts and nutritional secondary hyperparathyroidism and hypocalcemia has been documented (Stiles, 1991). The immature cataracts appeared as axial posterior subcapsular opacities. Bassett (1998) described a kitten with cataracts and hypocalcemia and hyperphosphatemia due to primary hypoparathyroidism. The cataracts were bilateral, incipient to immature, anterior and posterior subcapsular opacities typical of the lenticular changes noted in cats with hypocalcemia (Peterson et al., 1991). Normal cats, in a long-term investigation using topical 0.1% dexamethasone to elevate IOP, developed cataracts (Zhan et al., 1992). The lens changes in these cats consisted of subcapsular opacities.

In a study that examined the lenses of 2000 normal cats, 50 cats with diabetes mellitus and 100 cats following a dehydration crisis, all cats over 17 years of age had some lens opacity although the opacities were typically small and not of clinical significance (Williams & Heath, 2006). The ages at which the prevalence of cataract was 50% was 12.7 years for normal cats and 5.6 years for diabetic cats. Cats with a history of severe dehydration had no greater prevalence of cataract than normal cats.

Figure 27.67. Hypermature cataract and anterior lens luxation in a cat with chronic anterior uveitis. Note the pigment deposition on the lens capsule from the posterior synechia.

Lens Luxation

Feline lens luxations are most commonly associated with chronic uveitis and glaucoma (see Fig. 27.67). In a retrospective study (Olivero et al., 1991), the most common age at presentation was 7–9 years. Siamese cats were overrepresented, as were male cats. An apparently primary zonular degeneration occurred in aged felines, but was infrequent (2.4% of cases). In a report of 10 related domestic shorthair cats spanning three generations, nine cats had primary lens instability (Payen et al., 2011). A zonular defect caused by a possible dominantly inherited genetic disorder was suggested. As in other species, complications of lens luxation in cats are direct corneal endothelial cell damage, secondary glaucoma, persistent uveal inflammation, and vision loss. Because the feline anterior chamber depth is greater than that of dogs, glaucoma due to anterior lens luxation is less common in cats than in dogs (Sapienza, 2005). Specific treatment is by intra-capsular lens extraction, and the prognosis depends on the duration and the underlying cause. In one study, 89.5% of the cats undergoing lensectomy benefited from the procedure (Olivero et al., 1991). Primary lens luxations generally have an excellent prognosis after surgery. The prognosis in other types is less favorable, but lens luxation secondary to idiopathic uveitis can be successfully treated surgically if attentive therapy for the underlying uveitis is concurrently provided.

Cataract Surgery and Lensectomy

Feline cataract surgery is performed in a fashion identical to that of canine cataract surgery, but reports of clinical operative series are not available in the literature. Phacoemulsification is an effective procedure in cats (see Chapter 22). The success rate for cataract surgery in cats appears better than it is in dogs. Clinical impressions suggest this is, in part, because the feline uvea responds less intensively to surgical trauma and because postoperative inflammation can be controlled more easily. Cats with preexisting chronic uveitis and secondary cataract have a less favorable prognosis following phacoemulsification in the author’s experience. Opacification of the posterior lens capsule has been investigated in normal cats after extracapsular lensectomy (Cobo et al., 1984). The postopera-
tive changes appear to result from the transformation of the residual lens epithelial cells into fibroblasts containing contractile elements, proliferation of a pigment-contacting membrane from the iris and ciliary body, and migration of pigment cells from the iris or ciliary body (or both). Using keratometry and A-mode ultrasonography in normal cats, the dioptic power of a prototype posterior chamber intraocular lens was determined to be 53–55 D, which is substantially higher than that required in dogs (Gilger et al., 1998a). However, experimental implantation of posterior chamber prototype intraocular lenses revealed that a 52- to 53-D intraocular lens is required to achieve emmetropia (Gilger et al., 1998b).

VITREOUS

Congenital and Developmental Disorders

Persistent hyaloid arteries appear to be rare in cats. Ketring & Glaze (1994) have documented a 2-year-old domestic short-hair with a persistent hyaloid artery and anterior lens luxation. Barnett & Crispin (1998) have documented a 7-month-old Ragdoll kitten with a unilateral persistent hyaloid artery. Persistent hyperplastic tunica vasculosa lentis and persistent primary vitreous has been reported in two cats (Allgoewer & Pfefferkorn, 2001).

Acquired Disorders

Vitreal infiltrates of inflammatory and red blood cells may occur. Inflammatory cell infiltrates typically occur in cases of chronic anterior uveitis or posterior uveitis, particularly pars planitis. Accumulation of inflammatory cells on the posterior lens capsule and within the anterior vitreous, often termed

Figure 27.68. The typical appearance of a normal feline fundus includes a yellow-green tapetum dorsally and melanin pigment within the retinal pigment epithelial layer in the ventral fundus.

Figure 27.69. The normal feline fundus appearance in a color dilute cat. There is a lack of pigment within the retinal pigment epithelial layer and a lack of tapetum. The choroidal vasculature is visible.
elements to form rosettes, folds, and gliosis (Fig. 27.73). The causes of retinal dysplasia are numerous, but in cats, the condition has most often been associated with intrauterine or early neonatal viral infections. Retinal dysplasia has also been reported in feline colobomatous syndrome (see previous

Figure 27.70. Although the optic disk is typically unmyelinated in the cat, occasionally cats have myelin that extends along the nerve fiber layer for varying distances from the optic disk. This is a variation of normal.

Figure 27.71. Fundus photograph of a kitten with colobomatous syndrome. There is a large coloboma involving the optic nerve and adjacent choroid. (Reprinted with permission from Martin, C.L., Stiles, J. & Willis, A.M. (1997) Feline colobomatous syndrome. Veterinary and Comparative Ophthalmology, 7, 39–43.)

Figure 27.72. Fundus photograph of a kitten with retinal dysplasia associated with colobomatous syndrome. (Reprinted with permission from Martin, C.L., Stiles, J. & Willis, A.M. (1997) Feline colobomatous syndrome. Veterinary and Comparative Ophthalmology, 7, 39–43.)

RETINA AND CHOROID

Congenital, Developmental, and Acquired Disorders

Focal retinal, choroidal, and optic disk colobomas are rare in cats. These defects usually occur in association with the colobomatous syndrome in cats with eyelid agenesis. In some eyes, focal retinal dysplasia is also present, and vision may or may not be impaired. In one report, four kittens from a litter of five were examined and found to have lesions that included eyelid agenesis, microphthalmia, choroidal colobomas, focal retinal dysplasia, and optic disk coloboma (Fig. 27.71 and Fig. 27.72) (Martin et al., 1997).

Retinal Dysplasia

Retinal dysplasia is loosely defined as anomalous retinal development with resultant aberrant organization of retinal

snowbanking or snowballing, is frequently noted with pars planitis.

Vitreal hemorrhage is the condition most likely to be encountered clinically. Hemorrhage may be caused by inflammation, trauma, neoplasia, clotting disorders, systemic hypertension, and severe anemia.

Asteroid hyalosis occurs less frequently in cats than in dogs but is occasionally seen in middle-aged to older cats. It may be unilateral or bilateral. A case of ophthalmomyiasis interna, with the larva in the vitreous humor, has been reported (Brooks et al., 1984).
Bilateral optic nerve aplasia has been described in a domestic longhair kitten (Barnett & Grimes, 1974). The absence of optic nerves and tracts was confirmed histopathologically, and associated ocular defects included absence of the ganglion cell layer and presence of rosettes in the peripheral retina. That the dam and littermates were normal argues against a genetic basis for this condition. Optic nerve hyperplasia has also been recognized in conjunction with retinal lesions in a cat after fetal infection with panleukopenia virus (Greene et al., 1982).

**Taurine Deficiency Retinopathy**

Taurine is a sulfur-containing amino acid essential to cats because they have limited ability to synthesize it from cysteine, which is a precursor amino acid for most animal species. Taurine is stored in the liver, but the highest tissue concentrations are found in the heart muscle and retina, where especially high concentrations are found in the photoreceptor cells (Sturman et al., 1978). A dietary taurine level of 500–750 ppm has been suggested as being necessary to prevent retinal disease. The function of taurine is not fully understood, but it has been speculated to act as a neurotransmitter and to have a protective influence on cell membranes.

The retinopathies known as nutritional retinal degeneration and feline central retinal degeneration (FCRD) appear to be identical and associated with inadequate levels of dietary taurine. The first report of feline retinal disease that, in retrospect, probably related to the amino acid taurine was described by Bruckner (1949). In 1964 a report described a nutrition-linked retinal degeneration in cats fed a semipurified diet containing casein (Scott et al., 1964); because the abnormalities included conjunctivitis, keratitis, and squamous metaplasia of the oral cavity, vitamin A deficiency was suspected as the cause. A subsequent study by Morris (1965), who described the ophthalmoscopic changes, demonstrated the photoreceptor degeneration. At approximately the same time, a unique feline retinopathy was characterized by bilateral degeneration of the central sensory retina, termed FCRD (Bellhorn & Fischer, 1970). This condition occurred infrequently among cats fed seemingly appropriate diets but in unrelated animals. In studies of the photoreceptor function in cats with nutritional retinal degeneration, Rabin et al. (1973) documented that the photoreceptor degeneration in the area centralis preceded the advanced retinal degeneration, and they concluded that FCRD was, in fact, the initial stage of the nutritional degeneration. A guirre (1978) documented that the various stages of central retinal degeneration were associated with feeding dog food to cats. The deficient dietary element was identified as taurine, an amino acid that was eventually shown to be essential to cats and to be critical for retinal and cardiac function (Anderson et al., 1979; Barnett & Burger, 1980; Bedford, 1983; Bellhorn et al., 1974; Berson et al., 1976, 1981; Blake & Bellhorn, 1978; Hayes, 1982; Hayes et al., 1975a, 1975b; Knopf et al., 1978; O’Donnell et al., 1981; Orr et al., 1976; Pasantes-Moraes et al., 1986; Pickett et al., 1990; Pion et al., 1987; Ricketts, 1983; Schmidt et al., 1976a, 1976b, 1977; Wen et al., 1983; Wilce et al., 1981).

**Figure 27.73.** Retinal dysplasia with multiple retinal folds in a kitten. Cataracts were also present. (Courtesy of Kerry Ketting.)
outside the area of the lesion. Electrophysiologic studies have revealed decreased amplitudes and increased implicit times of cone responses but normal rod function. Angiographic abnormalities are absent. Through behavioral studies, visual acuity has been shown to be decreased, but most deficits are only detectable clinically during the advanced stages.

Dietary deficiency of taurine results in selective depletion of plasma and retinal amino acid levels within 5 weeks. Electrophysiologic studies have revealed an increase in cone implicit times, thus indicating that cone photoreceptors are initially affected. After 10 weeks of dietary deficiency, the amplitudes of both rod and cone electroretinograms are decreased (Schmidt et al., 1976a). Functional abnormalities are estimated to occur at least 10 weeks before photoreceptor cell death. Ophthalmoscopic signs of retinal disease become apparent between 3 and 7 months, with complete retinal degeneration becoming apparent by 9 months (Rabin et al., 1973). The histopathologic appearance is one of progressive photoreceptor degeneration, which is first recognized by vesiculation and disorientation of cone outer segment disks (Hayes et al., 1975b). Ultrastructural studies have also demonstrated that tapetal rods lose their normal lattice structure in the absence of taurine (Hayes et al., 1975a). The retinal effects of taurine deficiency are only partially reversible. The electroretinographic changes, and particularly those of the rods, are readily reversed after dietary correction, but the ophthalmoscopic lesions are permanent (Berson et al., 1981).

Because taurine deficiency has been linked to feline cardiomyopathy, cardiac function should be evaluated in all cats.
affected with these ophthalmoscopic abnormalities (Pion et al., 1987).

Although taurine deficiency retinopathy occurs much less frequently today than it did before the dietary requirements for taurine in cats were understood, affected cats may still be seen. Cats that eat diets deficient in taurine are at risk, and some cats eating an adequate diet may not absorb the amino acid normally. Any cat with suspected taurine deficiency should have plasma taurine levels evaluated. Normal values for cats fed dry food are 80–120 nmol/mL (University of California, Davis Amino Acid Laboratory). Values less than 40 nmol/mL are considered deficient.

Inherited Rod–Cone Dysplasia, Dystrophy, and Degenerations

With the exception of those disorders having a nutritional basis, retinal degenerations are relatively rare in cats, as evidenced by the infrequent reports in the literature (Barnett, 1965; Bedford, 1989; Carille, 1981; Kelly & Lewis, 1985; Rubin, 1963; Rubin & Lipton, 1973; Souri, 1972; West-Hyde & Buyukmihci, 1982). The first report describing an apparently primary retinal degeneration in three cats appeared in 1963 (Rubin, 1963). The lack of historical evidence for nutritional deficiency, the ophthalmoscopic appearance of diffuse vascular attenuation, and histopathologically selective photoreceptor degeneration suggested a genetic basis. Photoreceptor degeneration, which is characterized ophthalmoscopically by tapetal hyperreflectivity and vascular attenuation, was described in several related Persian cats, with a suspected autosomal recessive mode of inheritance (Rubin & Lipton, 1973). A breeding colony of Persian cats was established, and an early-onset, autosomal recessive, progressive retinal atrophy was confirmed (Rah et al., 2005). The earliest clinical sign was reduced pupillary light reflex, which could be noted at age 2–3 weeks. By 16 weeks, retinal degeneration was complete. Histologically, the lesions were primarily located in the photoreceptors, the outer nuclear layer, and the RPE. The specific genetic defect has yet to be identified. The retinal degeneration was found not to be associated with coat color or polycystic kidney disease, an inherited disease of Persian cats (Rah et al., 2006).

Electrophysiologic and histopathologic findings reported in a family of domestic cats with signs of retinal degeneration suggested a genetic basis, with a dominant mode of inheritance suspected (West-Hyde & Buyukmihci, 1982). The early onset described in this report, however, is most compatible with rod–cone dysplasia. Findings in one clinical report of feline retinal degeneration with a possible genetic origin suggest that the Siamese breed, at least in Great Britain, is at risk (Barnett, 1965). A more recent report of 26 cats in the United States with diffuse retinal degeneration also found the Siamese cat to be overrepresented (Giuliano & Van der Woerd, 1999). It was also found in this study that a variety of medications had been administered to the cats in the 12 months preceding examination, with enrofloxacin being the most common (see “Drug-Associated Retinal Toxicity”). Other than enrofloxacin toxicity (which was not recognized at the time of this publication), a cause for retinal degeneration could not be determined in this group of cats.

Rod–Cone Dysplasia in the Abyssinian

An autosomal dominant rod–cone dysplasia has been described in the Abyssinian breed (Curtis et al., 1987). Affected kittens as young as 4 weeks may show mydriasis and nystagmus, which is variable, intermittent, and often rapid. The first ophthalmoscopically visible lesions consist of tapetal dullness and loss of detail, present by 8–12 weeks of age. Progression of the disease is fairly rapid and is evidenced by tapetal hyperreflectivity, loss of pigmentation in the nontapetal fundus, and retinal vascular attenuation. The disease is very advanced by 1 year of age. Secondary cataracts have not been observed. The rods and cones are both affected, and disorganized outer segments as well as diminutive inner segments can be detected as early as 14 days of age (Leon & Curtis, 1990). The photoreceptor inner segments remain rudimentary, and the outer segments fail to elongate. Outer segment material is sparse and consists mostly of whorls of disorganized and disoriented disk lamellae. Degeneration begins in the central retina and advances toward the periphery, with progressive loss of the photoreceptor cell layers. At 30 weeks of age, only two to five rows of nuclei in the outer nuclear layer remain in affected cats. This condition has more recently been termed a cone–rod dysplasia as the cones have been documented to degenerate prior to the rods (Narfström et al., 2011). Affected cats have abnormal and retarded photoreceptor development, caused by a single base deletion in the CRX gene, which is critical for photoreceptor development and maintenance.

Rod–Cone Degeneration in the Abyssinian

A recessively inherited rod–cone degeneration in Abyssinian and Somali cats is termed rdAc (retinal degeneration in Abyssinian cats) (Anderson et al., 1991; Carille et al., 1984; Ehinger et al., 1991; Gorin et al., 1995; Jacobson et al., 1989; Narfström, 1985; Narfström & Nilsson, 1986, 1989; Narfström et al., 1985, 2009; Wiggert et al., 1994). A single base-pair change in the intron 50 of the centrosomal protein 290 (CPE290) gene results in alternative splicing of the transcript with subsequent introduction of a stop codon and truncation of the mature protein (Menotti-Raymond et al., 2007). The disease typically begins at 1.5–2.0 years of age, then progresses to complete retinal degeneration over the next 2–4 years. However, in a recent study, the progression of disease was found to be quite variable (Narfström et al., 2009). Four distinct ophthalmoscopic categories have been described (Narfström, 1985). In the stage of suspected disease (S1), a subtle, gray discoloration of the peripapillary area on one or both sides of the optic disk is seen. The early stage (S2) (Fig. 27.76a) is characterized by a more diffuse, gray tapetal discoloration, usually associated with mild vascular attenuation. In the moderately advanced stage (S3), hyperreflective areas
ally reduced, starting in cats at 8–12 weeks of age, and are commensurate with the stage of disease. Loss of the b-wave amplitude correlates with loss of rhodopsin (Narfström et al., 1985). One study found that Abyssinian cats heterozygous for the disease can be identified by their abnormal, dark-adapted electroretinograms, even though their fundi appear normal ophthalmoscopically (Ekesten & Narfström, 2004).

Another study found that heterozygous carrier cats could be differentiated from homozygous affected cats prior to clinically evident retinal degeneration by comparing the electroretinographic b-wave to a-wave ratio (Hyman et al., 2005).

become visible in a diffusely discolored tapetal fundus, and vascular attenuation is prominent. In the advanced stage (S4) (Fig. 27.76b), generalized tapetal hyperreflectivity is accompanied by severely attenuated or absent retinal vessels. The appearance varies somewhat with the age of the animal, however, and younger cats demonstrate more prominent areas of hyperreflectivity in the midperipheral and peripheral fundus. Focal pale areas as well as heavily pigmented lesions occur in the nontapetal fundus of severely affected animals. Significant fluorescein angiographic changes are limited to vascular constriction.Electroretinographic amplitudes are proportionally reduced, starting in cats at 8–12 weeks of age, and are commensurate with the stage of disease. Loss of the b-wave amplitude correlates with loss of rhodopsin (Narfström et al., 1985). One study found that Abyssinian cats heterozygous for the disease can be identified by their abnormal, dark-adapted electroretinograms, even though their fundi appear normal ophthalmoscopically (Ekesten & Narfström, 2004).

A another study found that heterozygous carrier cats could be differentiated from homozygous affected cats prior to clinically evident retinal degeneration by comparing the electroretinographic b-wave to a-wave ratio (Hyman et al., 2005).

**Figure 27.76.** Fundus photographs of Abyssinian cats homozygous for inherited rod–cone degeneration. a. Early changes in a 2-year-old cat. There is a gray discoloration in the peripheral tapetal fundus, but retinal vasculature is still normal. b. Late changes in a 6-year-old cat. There is marked hyperreflectivity and grayish discoloration to the tapetal fundus, and retinal vasculature is attenuated. (Courtesy of Kristina Narfström.)

**Figure 27.77.** Inherited rod–cone degeneration in the Abyssinian cat. a. Light micrograph of a 2.5-year-old cat in a moderately advanced stage of rod–cone degeneration. The inferior nontapetal fundus is shown. Note the reduced numbers of photoreceptor nuclei in the outer nuclear layer, the short and degenerating rod, and cone outer and inner segments. There is hypertrophy of some retinal pigment epithelial cells and a few displaced photoreceptor cell nuclei are observed in the subretinal space. The inner retina is normal appearing (hematoxylin and eosin). b. Ultrastructure from the same region of the outer retina. Note the severe degenerative changes in the photoreceptor outer and inner segments and in the outer nuclear layer. (Courtesy of Kristina Narfström.)
The initial histopathologic changes are disorganization of the photoreceptors, beginning in the midperipheral portions of the fundus, with reduced numbers of photoreceptor nuclei (Fig. 27.77a, b) (Narfström & Nilsson, 1989). In the moderately advanced stage, the photoreceptor outer segments disappear, and the inner segments become extremely shortened in the peripheral and midperipheral retina. In the advanced stage, the outer segments are absent, the inner segments are reduced in number, and thinning of other retinal layers becomes apparent. As in the other stages, the central retina is less severely affected in the advanced stage.

In affected kittens, a high number of immature-appearing rod outer segment disks are present at 35 days postnatally, but the cones appear to be normal at this stage. In cats 5 months of age, affected rod outer segments demonstrate disintegration, as evidenced by vacuolization and clumping of the disk material and by formation of debris. In a study that utilized immunolabeling for green-sensitive and blue-sensitive cones, it was determined that by age 12 months, cones are affected (Narfström et al., 2001). The inner retina is largely preserved throughout the disease.

Rhodopsin levels are reduced in affected cats as early as 6 months of age (20% reduction; by 2.5 years of age, 60% reduction; in a 7-year-old cat, not measurable) (Jacobson et al., 1989). Gamma-aminobutyric acid (GABA) and its synthesizing enzyme, glutamate decarboxylase (GAD), gradually decrease in both the inner and outer layers of the retina in affected cats (Ehinger et al., 1991). Loss of the photoreceptors was a prerequisite for loss of GABA immunoreactivity. Loss of GABA was not likely the result of neuron loss, but it was related to the persistence of GAD-immunoreactive neurons. Measurements of the interphotoreceptor retinoid-binding (IRB) protein and message in affected cats indicate that levels of both are significantly reduced in kittens as young as 4 weeks old and at the earliest stage of retinal disorientation (Wiggert et al., 1994). Opsin messenger RNA was more abundant in affected cats at least 1 year before the onset of clinical visual impairment. The reduction in IRB protein gene expression below normal levels and before the onset of retinal degeneration suggests this may represent either a primary defect or an early disorder that itself could cause adverse effects. Subsequent sequence analysis has excluded phosducin as the gene for this recessive retinal degeneration in the Abyssinian breed (Gorin et al., 1995). Plasma lipid abnormalities have been recently reported in Abyssinian cats with hereditary rod-cone degeneration, and affected cats had lower levels of ω3 polyunsaturated fatty acids, thereby suggesting a deficiency of the Δ-4 desaturase (Anderson et al., 1991).

Recent studies of the rdAc mutation document that the defective allele is present in moderate abundance in the Abyssinian breed in Europe and Australia (Narfström et al., 2009). The mutation is also present in a large number of cat breeds in addition to the Abyssinian and Somali in North America and Europe (Menotti-Raymond et al., 2010). The mutation was found in 14/41 breeds (34%) sampled, and was particularly high in Siamese and Siamese-related breeds. The mutation in the Siamese was only found in wedge-faced cats and was absent in the apple-head cats, suggesting a divergence of the gene pool in these two phenotypes of Siamese cats.

Other Retinal Degenerations

An isolated case of feline retinal degeneration has been described that has similarities to the rare human condition of gyrate atrophy (Valle et al., 1981). Common abnormalities include severe photoreceptor degeneration, decreased numbers of choriocapillaries and smaller choroidal vessels, increased plasma ornithine and glutathione levels, and undetectable ornithine aminotransferase activity. Cataracts, however, which are consistently found in the human condition, were absent. This appears to be an extremely rare condition in cats.

A single case report describes a 4-year-old domestic short-haired cat with a 2.5-year history of progressive ataxia and a 1-year history of progressive vision loss (Barone et al., 2002). On necropsy, the cat was found to have adult onset cerebellar atrophy and retinal degeneration. Although the two conditions could not be definitively linked, the authors speculated that an essential protein or process involved in neuronal pathways of the cerebellar Purkinje cells is also critical in retinal pathways.

Drug-Associated Retinal Toxicity

The most significant ocular drug toxicity to be identified in cats is enrofloxacin-associated retinal degeneration (Ford et al., 2007; Gelatt et al., 2001; Wiebe & Hamilton, 2002). Beginning in 1997, the enrofloxacin label dosing was changed from the previous recommendation of 2.5 mg/kg every 12 hours to a flexible dose ranging from 5 to 20 mg/kg as a split or single dose. Very soon afterward, cases of acute and severe retinal degeneration and blindness began to be seen in cats receiving enrofloxacin. In an experimental study in which young healthy cats were given 50 mg/kg q 24 hours enrofloxacin, vascular attenuation and tapetal hyperreflectivity were noted on funduscopic examination beginning on day 2. By day 3, decreased b-wave amplitudes on electroretinography and generalized retinal degeneration on histopathology were present, worsening by day 7 (Fig. 27.78a–c) (Ford et al., 2007). Behavioral, neurologic, and musculoskeletal abnormalities also occurred.

In most cases seen to date, the blindness has been permanent, although a few cats have retained some vision. One of the remarkable findings of this toxicity is the rapidity with which the retina degenerates (Fig. 27.79a, b). Tapetal hyperreflectivity and vessel attenuation are dramatic even in cats that have received enrofloxacin as a single dose. Electroretinographic responses are typically extinguished, even in cats that appear to retain some vision.

Although enrofloxacin has been the compound most identified with feline retinal degeneration, all of the fluoroquinolones must be considered potentially retinotoxic (Wiebe & Hamilton, 2002). The newer fluoroquinolone pradofloxacin...
was demonstrated to have no retinal toxicity in young healthy cats at 6–10 times the recommended dose, based on electroretinography, optical coherence tomography and histopathology (Messias et al., 2008). Older cats and those with impaired renal or hepatic function may have reduced clearance and increased plasma levels of fluoroquinolones compared with young, healthy cats. There is limited information about the metabolism of enrofloxacin in cats, but approximately 40% of the drug is metabolized to ciprofloxacin in dogs, and this compound is further transformed to metabolites that are excreted in the urine. Decreased glomerular filtration rate in dogs increases the plasma levels of the primary metabolite of marbofloxacin (Lefebvre et al., 1998).

A molecular genetic basis for fluoroquinolone-induced retinal degeneration in cats has been documented (Ramirez et al., 2011). Distribution of fluoroquinolones to the retina is normally restricted by the transport protein ABCG2 at the blood-retinal barrier. In the cat, specific amino acid changes in this transport protein cause a functional defect that allows photoreactive fluoroquinolones to accumulate in the feline retina, leading to the formation of reactive oxygen species and retinal damage.

Figure 27.78.  a. Histopathologic appearance of a normal feline retina.  b. Degenerative changes are apparent in all layers of the retina by day 3 in a cat receiving 50 mg/kg enrofloxacin.  c. Severe degeneration of the retina by day 7 in a cat receiving 50 mg/kg enrofloxacin (toluidine blue). (Courtesy of Richard Dubielzig.)
to inflammations that originate in the retina and eventually involve the choroid, though the former is more common. Active chorioretinal inflammations are characterized ophthalmoscopically by edema, hemorrhages, inflammatory or neoplastic cell infiltration, mycotic and parasitic granulomas, and exudates or transudates. Chorioretinitis that has abated leaves scars, which appear ophthalmoscopically as areas of hyperreflectivity, with or without pigment deposition in the tapetal fundus, and areas of depigmentation or pigment clumping in the nontapetal fundus.

Viral chorioretinitis in cats has been associated with FIP virus (see Fig. 27.47) (Campbell & Schiessl, 1978), FIV (Hopper et al., 1989), and FeLV (Brightman et al., 1991; Corcoran et al., 1995).

Fungal chorioretinitis has been associated with cryptococcosis (Fig. 27.80) (Davies & Troy, 1996; Dye & Campbell, 1988; Fischer, 1971; Gionfriddo, 2000; Gwin et al., 1977b; Jacobs et al., 1997; Reed et al., 1963; Rosenthal et al., 1981; Wilkinson, 1979), histoplasmosis (Davies & Troy, 1996; Jasmin et al., 1969; Peiffer & Belkin, 1979; Wolf & Belden, 1984), blastomycosis (Alden & Mohan, 1974; Breider et al., 1988; Davies & Troy, 1996; Hatkin et al., 1979; Jasmin et al., 1969; Miller et al., 1990; Nasisse et al., 1985; Neunzig, 1983; Sheldon, 1966), and coccidioidomycosis (Angell et al., 1985; Greene & Troy, 1995; Reed et al., 1963; Tofflemire & Betbeze, 2010).

The protozoal agent T. gondii is a documented cause of chorioretinitis in cats (Campbell, 1974; Davidson et al., 1993a, 1993b, 1996; Dubey, 1986, 1988; Dubey & Carpenter, 1993; Heeley, 1975; Hirth & Nielsen, 1969; Lappin et al., 1989a; Risk factors for fluoroquinolone retinal toxicity in cats include old age, renal or hepatic impairment, dose and duration of drug administration, as well as route of administration. Intravenous administration was found to be a contributing factor to retinal toxicity in a study of 17 cats (Gelatt et al., 2001). The fluoroquinolones as a drug class, and particularly enrofloxacin with its widespread use, should be viewed as potentially dangerous to cats and used only when no alternative exists. Even then, the dose should be kept as low as possible, should never exceed the current manufacturer’s recommended dose of 2.5 mg/kg every 12 hours, and should be administered for the minimum possible time length.

Concurrent administration of methylnitrosourea (a carcinogen) and ketamine hydrochloride caused severe retinal degeneration in cats (Schaller et al., 1981), while administration of methylnitrosourea alone did not damage the retina. The toxicity is characterized by photoreceptor and outer nuclear layer degeneration, which is evident by 5 days of exposure. The pathophysiologic mechanisms involved were not identified.

Griseofulvin toxicity led to bone marrow suppression and death in one cat (Rottman et al., 1991). The cat also presented with mydriasis and vision impairment. On histologic examination of the retinas, the photoreceptors were found to have generalized loss of distinction, but definitive degeneration was not documented.

**Inflammation**

Chorioretinitis refers to inflammatory conditions that arise in the choroid and extend into the retina. Retinochoroiditis refers to inflammations that originate in the retina and eventually involve the choroid, though the former is more common. Active chorioretinal inflammations are characterized ophthalmoscopically by edema, hemorrhages, inflammatory or neoplastic cell infiltration, mycotic and parasitic granulomas, and exudates or transudates. Chorioretinitis that has abated leaves scars, which appear ophthalmoscopically as areas of hyperreflectivity, with or without pigment deposition in the tapetal fundus, and areas of depigmentation or pigment clumping in the nontapetal fundus.

Viral chorioretinitis in cats has been associated with FIP virus (see Fig. 27.47) (Campbell & Schiessl, 1978), FIV (Hopper et al., 1989), and FeLV (Brightman et al., 1991; Corcoran et al., 1995).

Fungal chorioretinitis has been associated with cryptococcosis (Fig. 27.80) (Davies & Troy, 1996; Dye & Campbell, 1988; Fischer, 1971; Gionfriddo, 2000; Gwin et al., 1977b; Jacobs et al., 1997; Reed et al., 1963; Rosenthal et al., 1981; Wilkinson, 1979), histoplasmosis (Davies & Troy, 1996; Jasmin et al., 1969; Peiffer & Belkin, 1979; Wolf & Belden, 1984), blastomycosis (Alden & Mohan, 1974; Breider et al., 1988; Davies & Troy, 1996; Hatkin et al., 1979; Jasmin et al., 1969; Miller et al., 1990; Nasisse et al., 1985; Neunzig, 1983; Sheldon, 1966), and coccidioidomycosis (Angell et al., 1985; Greene & Troy, 1995; Reed et al., 1963; Tofflemire & Betbeze, 2010).

The protozoal agent T. gondii is a documented cause of chorioretinitis in cats (Campbell, 1974; Davidson et al., 1993a, 1993b, 1996; Dubey, 1986, 1988; Dubey & Carpenter, 1993; Heeley, 1975; Hirth & Nielsen, 1969; Lappin et al., 1989a;
In cats with renal dysfunction, the presence or magnitude of hypertension is unrelated to azotemia. Persistent lack of urine concentrating ability may be the only indication of chronic renal disease. The mechanism of systemic hypertension in cats with renal disease remains unclear. Renal disease leads to increased sodium chloride retention, which leads to increased intracellular calcium. This in turn increases arteriolar tone and sensitivity to vasopressors such as angiotensin II and catecholamines. Renal disease also causes activation of the renin–angiotensin–aldosterone system, which raises blood pressure by increasing stroke volume and total peripheral resistance. Angiotensin II is a potent vasoconstrictor, while aldosterone causes renal sodium chloride retention (Dukes, 1992). In one study of normotensive and hypertensive cats, hypertensive cats were found to have variable levels of renin–angiotensin–aldosterone activation (Jensen et al., 1997). Another experimental study had results that did support the renin–angiotensin–aldosterone system in sustaining hypertension in cats (Mathur et al., 2004).

Hyperthyroidism may contribute to systemic hypertension through its effects on the heart. Hyperthyroidism increases stroke volume and cardiac output, leading to systolic hypertension. In chronic hypertension, small muscular arteries become fibrotic and sclerotic, leading to systolic and diastolic hypertension. Chronic hypertension causes left ventricular hypertrophy, which is often misdiagnosed as hypertrophic cardiomyopathy.

The eye, because of its small caliber vessels, is a target organ for hypertensive damage (Henik et al., 1997; Stiles et al., 1994). Prolonged systemic hypertension leads to sustained vasoconstriction of retinal arterioles via autoregulation. Beyond certain critical pressures, autoregulation breaks down and vascular integrity is compromised. Occlusion of precapillary arterioles can lead to ischemia and retinal degeneration. Leakage of plasma and red blood cells occurs when endothelial cells and vascular smooth muscle become damaged (fibrosis and sclerosis). Leakage of plasma within the retina leads to retinal edema and foci of fluid accumulation within the neurosensory layer (Fig. 27.81). Retinal detachment is thought to be associated primarily with plasma effusion from diseased choroidal vasculature. Additionally, the RPE undergoes ischemic damage, contributing to retinal detachment (Crispin & Mould, 2001). Cotton-wool spots, or swollen axons, are a hallmark of hypertensive retinopathy in primates and may be seen early in the course of disease. This finding has not been reported in feline hypertensive retinopathy.

Clinically, the ocular manifestations of systemic hypertension can be severe and include retinal arterial tortuosity, intraretinal hemorrhage, preretinal hemorrhage, subretinal hemorrhage, retinal edema and focal bullae, retinal detachment, retinal degeneration, hyphema, and secondary glaucoma (Fig. 27.82a, b and Fig. 27.83) (Elliott et al., 2001; Stiles et al., 1994). The iris and ciliary body vessels may be compromised, leading to bleeding within the vitreous cavity and posterior or anterior chambers. More commonly, hyphema is associated with massive posterior segment (retinal or cho-
Figure 27.81. Photomicrograph of the retina from a 14-year-old domestic shorthair cat with hypertensive retinopathy. The retina is detached with a subretinal transudate present. Note the cystic spaces within the retina from the leakage of plasma (hematoxylin and eosin).

Figure 27.82. Fundus photographs of cats with hypertensive retinopathy. a. Multiple well-defined foci of tapetal hyporeflectivity representing sites of retinal edema and intraretinal fluid accumulation in a 13-year-old domestic shorthair cat. b. A large retinal detachment and retinal hemorrhage in a 16-year-old Siamese cat. (Part (b) is reprinted with permission from Ketrin, K.L. & Glaze, M.B. (1994) Atlas of Feline Ophthalmology. Trenton, NJ: Veterinary Learning Systems.)

Figure 27.83. Retinal edema has the appearance of retinal folds in this 9-year-old domestic shorthair cat. There are multiple small retinal hemorrhages and a focal area of retinal detachment. (Reprinted with permission from Ketrin, K.L. & Glaze, M.B. (1994) Atlas of Feline Ophthalmology. Trenton, NJ: Veterinary Learning Systems.)

Recognition of animals at risk for systemic hypertension is an important factor in preventing blindness. Any cat over 10 years of age should have a fundic examination performed as well as blood pressure measurement at least once per year. Cats with renal disease or hyperthyroidism should have these examinations more frequently.
tests performed at diagnosis and subsequently as the disease is managed.

Measurement of blood pressure in cats is most easily accomplished in a clinical setting by use of indirect measurement with a Doppler ultrasonic detection device. The oscillometric devices are unreliable in cats. Accurate readings can be difficult to obtain because a stressed cat can have significant elevation of blood pressure (Blew et al., 1999). Repeated measurements in a calm environment may be needed to detect trends in blood pressure. Normal blood pressure for cats is usually defined as 120/80 mmHg. The Doppler is unreliable in obtaining a diastolic value, so the systolic value is typically used to assess blood pressure. One study of 181 cats found that an age-related increase in blood pressure occurred in healthy cats as it does in humans and dogs (Sansom et al., 2004). In this study, hypertensive retinopathy was reported to be common in cats 10 years of age or older; however, details of ophthalmic examinations were not provided. Systolic blood pressure values were found to be a better predictor of hypertensive retinopathy than diastolic or mean values.

Placement and size of the cuff are important in obtaining accurate blood pressure measurement. The cuff width should be 30%–40% of the circumference of the limb. The median artery of the forelimb has been shown to give the most accurate readings in cats (Blew et al., 1999). The cuff is placed over the median artery, and the transducer is placed between the carpal and metacarpal pad. The hair should be clipped and a coupling gel applied prior to placing the transducer. Cuffs that are too large will give falsely low readings, whereas cuffs that are too small will give falsely elevated readings. If a proper cuff size falls between two available cuffs, the larger should be used. When making a judgment as to whether a cat is hypertensive, fear and excitement must be taken into account. Typically, systolic values greater than 160 mmHg are considered hypertensive. Cats with hypertensive retinopathy often have systolic blood pressure values that approach or exceed 200 mmHg. The same size cuff, the same limb, and preferably the same Doppler unit should be used each time when rechecking blood pressure in a patient (Haberman et al., 2004).

Treatment of hypertensive retinopathy includes controlling the underlying disease processes and treating the systemic hypertension. There is the potential in some animals for blindness to be reversible if systemic hypertension can be quickly controlled. Bullous retinal detachments can resolve if the underlying effusion is controlled. Depending on the length of time the retina has been detached, vision may be regained. There is some evidence that the feline retina begins to degenerate within the first week of detachment. Return of vision in all cases is dependent on the degree of damage the retina has undergone. Ideally, hypertension should be recognized and treated before severe ocular disease occurs. Even if vision is not restored, treating hypertension is important to prevent other serious effects such as neurologic disease.

The calcium channel blocker amlodipine has been used very successfully in cats at a dose of 0.625 mg to 1.25 mg orally once daily and has become the drug of choice for hypertensive cats (Cooke & Snyder, 1998; Elliott et al., 2001; Henik et al., 1997; Snyder, 1998). Enalapril and propranolol were ineffective at controlling blood pressure in cats in one study (Jensen et al., 1997), whereas the use of benazepril was associated with small but significant reduction in blood pressure in cats with renal compromise (Brown et al., 2001). Most cats of average weight will require 1.25 mg of amlodipine daily, while a few cats require 1.25 mg twice daily. In an experimental study of hypertensive cats treated with 0.25 mg/kg/day amlodipine, significant reductions in blood pressure were documented (Mathur et al., 2002). Cats should be reevaluated in approximately 7 days after starting amlodipine. Adverse effects seem to be few in cats receiving amlodipine. Reported side effects include azotemia, lethargy, hypokalemia, reflex tachycardia, and weight loss. Once cats are normotensive and are being maintained on amlodipine, they should be reevaluated at least every 6 months. All hypertensive cats should also have a cardiac evaluation.

Sodium-restricted diets are not recommended for hypertensive cats. In one study, low sodium chloride intake was associated with inappropriate kaliuresis, reduced glomerular filtration rate, and activation of the renin-angiotensin-aldosterone axis without evidence of a beneficial effect on arterial blood pressure (BuranaKar et al., 2004).

Lipemia Retinalis

The term lipemia retinalis describes the ophthalmoscopic visibility of lipids and/or lipoproteins in retinal blood vessels. The condition is of diagnostic significance only, because an elevated blood lipid level has not been demonstrated to adversely affect retinal tissue. Theoretically, any condition predisposing a patient to elevated plasma lipoprotein levels could cause lipemia retinalis. Examples of diseases characterized by defective lipid synthesis or degradation are diabetes mellitus and hypothyroidism.

Lipemia retinalis occurs infrequently in cats (Crispin, 1993; Ginzing et al., 1996; Gunn-Moore et al., 1997; Jones et al., 1983; Wyman & MCKissick, 1973). The condition has been experimentally induced in neonatal kittens by parenteral administration of large doses of methylprednisolone. Lipemia retinalis also occurs in cats secondary to primary, familial hypercholesterolemia (Ginzing et al., 1996; Jones et al., 1983). In addition to lipemic retinal vessels, clinical manifestations include subcutaneous nodules over bony protuberances, particularly in the hock region of the rear legs. Histopathologically, these subcutaneous xanthomas resemble lipid granulomas. The cause is suspected to be a lipoprotein lipase deficiency. The result is fasting hyperlipoproteinemia because of elevations in the levels of plasma cholesterol and triglycerides. In normal cats, most triglycerides are contained in very low-density lipoproteins; in affected cats, most triglycerides and cholesterol are contained in chylomicrons. Both the
ocular and dermatologic abnormalities resolve after feeding the cat a low-fat diet.

**Anemic Retinopathy**

Retinal hemorrhages were documented in 20 of 26 anemic cats, some of which were also thrombocytopenic (Fischer, 1970). Hemorrhages occurred at all depths in the retina and with equal frequency in both the tapetal and nontapetal fundus. The mechanism of retinal hemorrhage formation is thought to be anemia-induced hypoxia of retinal vessels, followed by compensatory venule dilation to maintain retinal perfusion and a subsequent increase in capillary fragility, which ultimately leads to hemorrhage. Anemic retinopathy occurs in a high percentage of cats with hemoglobin levels of less than 5 g/dL, and the condition is aggravated by concurrent thrombocytopenia.

**Diabetic Retinopathy**

A case of presumed diabetic retinopathy has been described in a 10-year-old cat (Herrtage et al., 1985). Retinal and vitreal hemorrhages as well as retinal detachments were the prominent ophthalmoscopic changes, and microaneurysms were present as well. With insulin therapy, the retinas partially reattached, with some return of vision. The cause of the diabetes in this case was prolonged administration of megestrol acetate. The severe ocular abnormalities in this cat were consistent with those of hypertension, which is a disease that was not excluded in this case by blood pressure measurement.

In an experimental study, intraretinal oxygen levels were measured in diabetic cats (Linsenmeier et al., 1998). Oxygen levels were abnormally low in the inner half of the retina of diabetic cats, with some regional variation. Histologic changes included microaneurysms, leukocyte and platelet plugging of aneuryms and venules, and degenerating endothelial cells in capillary walls. In a recent study of 52 diabetic dogs, 11 (21%) developed retinal hemorrhages or microaneurysms, although in all dogs, the lesions were small and did not interfere with vision (Landry et al., 2004).

**Hyperviscosity Retinopathy**

The retina of the domestic cat is sensitive to the effects of increased plasma viscosity. Ocular lesions in a cat with serum hyperviscosity syndrome caused by an IgG-secreting myeloma were retinal hemorrhages, optic disk swelling, and partial retinal detachment (Hribernik et al., 1982). Two cats with IgG monoclonal gammopathy were reported to have retinal hemorrhages and tortuous retinal vessels (Forrester et al., 1992). A another case with hyperviscosity syndrome and an orbital plasmacytoma had dilated and tortuous retinal vessels (Ward et al., 1997).

Common systemic clinical manifestations of hyperviscosity syndrome in cats include listlessness, weight loss, neurologic signs, and heart murmur. The ophthalmologic manifestations of serum hyperviscosity are ascribed to a decrease in retinal blood flow, thus causing secondary hypoxic damage to the retinal capillaries.

**Ophthalmomyiasis Interna Posterior**

In ophthalmomyiasis interna, there is intraocular migration of parasites, with the suffix posterior added to indicate posterior segment involvement. Five such cases, all with strikingly similar clinical findings, have been described in asymptomatic domestic cats (Brooks et al., 1984; Gwin et al., 1984; Kaswan & Martin, 1984). Ophthalmoscopic examination reveals multiple, crisscrossing, curvilinear tracks in the sensory retina (see Fig. 27.49). The tracks are of uniform width, have distinct margins, and occur in both the tapetal and nontapetal fundus. Tapetal hyperreflectivity with foci of pigment deposition typify the tapetal lesions, whereas those in the nontapetal fundus demonstrate pigment loss and clumping. Retinal hemorrhage and edema were interpreted as indicating recent migration. In one case, in which histopathologic results were available, degeneration of the outer retinal layers was present, thereby indicating parasite migration probably occurred in the subretinal space. The actual parasite may or may not be seen at ophthalmoscopy.

One case has been reported in which a cat presented for anorexia and lethargy and the parasite was visualized in the fundus (Wyman et al., 2005). The cat was euthanized for the deteriorating condition and a Culicoides sp. larva was identified. Coagulation necrosis and hemorrhage of the optic nerve, retina, and choroid as well as anterior uveitis were present on histopathology. No significant cerebrum or brainstem lesions were found.

**Retinal Folds and Detachments**

Retinal folds may occur as congenital lesions but are also recognized in cats as a secondary response to other ocular diseases (MacMillan, 1976). Five such cases have been described, with the histopathologic changes in six eyes having been studied. Ophthalmoscopically, acquired retinal folds may be focal or diffuse, and they occupy either the tapetal or nontapetal fundus. Their appearance is characteristic. Folds are recognized as irregular, vermiform lesions that are hyporeflective in the tapetal fundus and appear white to gray in the nontapetal fundus. Histopathologically, the photoreceptor, outer nuclear, and outer plexiform layers are elevated from the RPE. The inner retinal layers, however, remain normal.

The causes of retinal folding are variable. Folds may occur secondary to retinal detachment or as a sequela to intraocular inflammation. Retinal detachment or separation of the sensory and epithelial retina in cats has been described in association with a wide variety of ophthalmic and systemic abnormalities, including systemic hypertension, hyperviscosity syndromes, periarthritis nodosa, toxoplasmosis, trauma, cryptococcosis, blastomycosis, histoplasmosis, coccidiomycosis, FIP, ethylene glycol toxicosis, polycythemia, and primary as well as
secondary intraocular neoplasms (Barclay & Riis, 1979; Lombard & Twitchell, 1978; Roberts, 1959). The specific pathologic mechanisms of detachment appear to be similar to those in other animal species. The specific responses of the feline retina to detachment, however, have some unique features (Anderson et al., 1986; Erickson et al., 1981). Degenerative changes rapidly occur at the epithelial cell—photoreceptor interface, and histopathologic changes are evident within 1 hour. By the third day of detachment, both rod and cone outer segments become degenerated and are replaced by membrane-bound sacs. A assembly of new outer segment material in the form of disorganized disks and membranous whorls continues for as long as 2 months. A significant decrease in the outer nuclear layer by the first month of detachment is attributable to necrosis and migration of photoreceptor cell nuclei into the subretinal space. Photoreceptor synaptic contact with second-order neurons is diminished by day 30 and absent by day 50. These findings appear to contrast with those in dogs, in which the outer nuclear layer survives for 6 months. Interestingly, cone inner segments, cell bodies, and synaptic terminals remain relatively well preserved at a time when rods are necrotic. The severity of changes correlates with the duration and height of the detachment. Early retinal pigment cell abnormalities are mounding of the apical cell surface, increased DNA synthesis, and eventually, RPE proliferation. In chronic detachment, Müller cell proliferation and hypertrophy contribute to scar formation.

### Posterior Segment Neoplasia

Primary neoplasms of the posterior segment appear to be quite rare in cats. An astrocytoma of retinal origin has been described in one cat (Gross & Dubielzig, 1984). The presenting signs were leukocoria with a vascularized mass visible within the pupil. Histopathologically, the tumor infiltrated the optic nerve head, choroid, and vitreous humor. A choroidal melanocytoma has been reported in a cat (Semin et al., 2011). The cat later died from lymphoma, and at necropsy, no evidence of metastatic melanoma was detected.

### Lysosomal Storage Diseases

Storage disorders are a group of progressive, inherited diseases caused by the deficiency of a specific lysosomal enzyme (Aguirre et al., 1983; Alroy et al., 1999; Blakemore, 1972, 1986; Breton et al., 1983; Burditt et al., 1980; Cork et al., 1978; Cowell et al., 1976; Cummings et al., 1988; Haskins et al., 1979, 1980; Hubier et al., 1996; Jezyk et al., 1977, 1986; Langweiler et al., 1978; Mazier et al., 2003; Murray et al., 1977; Neuwelt et al., 1985; Stramm et al., 1985, 1986; Vandevelde et al., 1982; Wenger et al., 1980). Disease ultimately results from abnormal accumulation of the deficient enzyme’s substrate within lysosomes of affected cells. Lysosomal storage diseases reported to have ophthalmic manifestations are mucopolysaccharidosis I and IV, GM1- and GM2-gangliosidosis, mannosidosis, and mucolipidosis II. Table 27.3 lists the distinguishing features of each disease.

### DISEASES OF THE OPTIC NERVE AND CENTRAL NERVOUS SYSTEM

#### Congenital and Developmental Disorders

Colobomas of the optic disk and peripapillary region are rare in cats (Fig. 27.84) (Bellhorn et al., 1971). Optic disk colobomas may occur in association with eyelid agenesis as well as with other developmental anomalies (Martin et al., 1997). Optic disk aplasia has been reported in a cat in which the retinal vasculature, nerve fiber layer, ganglion cell layer, optic nerves, and optic tract also failed to develop (Barnett & Grimes, 1974). Additional abnormalities include cyclopia, anophthalmia, rudimentary optic tracts, and numerous central nervous system and skeletal abnormalities.

Optic disk hypoplasia may also occur, though uncommonly. The visual deficits depend upon the extent of the defect (Barnett & Crispin, 1998). Histologically, fewer retinal nerve fibers and ganglion cells are present.

### Acquired Disorders

#### Optic Neuritis

Optic neuritis appears to be less common in cats than in dogs. Inflammation of the optic nerve may have a variety of causes in cats. Viral, parasitic, and fungal infections can all cause...
<table>
<thead>
<tr>
<th>Disease</th>
<th>Breeds Affected</th>
<th>Deficient Enzyme</th>
<th>Affected Tissues</th>
<th>Clinical Signs</th>
<th>Ocular Pathology</th>
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</thead>
<tbody>
<tr>
<td>GM1- gangliosidosis</td>
<td>Domestic shorthair, Siamese, Korat</td>
<td>β-Galactosidase</td>
<td>Liver (hepatocytes)</td>
<td>Ataxia, muscular tremor, hypermetria, weakness</td>
<td>Membrane-bound inclusions in keratocytes, especially adjacent to epithelium and endothelium; vacuolated endothelial cells and lens epithelium, membrane-bound inclusions in ganglion cell and inner nuclear layers</td>
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<td>CNS (neurons)</td>
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<td>GM2- gangliosidosis</td>
<td>Domestic shorthair, Korat</td>
<td>β-D-N acetylhexosaminidase</td>
<td>Liver (hepatocytes)</td>
<td>Ataxia, hypermetria, head tremors, paralysis</td>
<td>Corneal cloudiness</td>
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<td>Ataxia, hypermetria, head tremors,</td>
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<td>head tremors, paralysis</td>
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<td>α-Mannosidosis</td>
<td>Persian Domestic shorthair</td>
<td>α-Mannosidase</td>
<td>Liver</td>
<td>Stillbirth, neonatal death, tremor, ataxia,</td>
<td>Vacuoles in ganglion cells</td>
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<td>CNS</td>
<td>hypermetria, calvarial abnormalities</td>
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<td>Peripheral nerves</td>
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<td>Salivary glands</td>
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<td>Choroid</td>
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<td>Mucopolysaccharidosis I</td>
<td>Domestic shorthair</td>
<td>α-L-iduronidase</td>
<td>Skull (chondrocytes)</td>
<td>Short maxilla, frontal bossing, depressed nasal</td>
<td>Corneal cloudiness, ground glass appearance</td>
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<td>CNS (neurons)</td>
<td>bridge, abnormal postural reactions, gait</td>
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<td>Heart (fibroblasts)</td>
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<td>Cornea</td>
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<td>Mucopolysaccharidosis VI</td>
<td>Siamese</td>
<td>Arylsulfatase B</td>
<td>Blood (leukocytes)</td>
<td>Facial dysmorphia, diffuse corneal cloudiness,</td>
<td>Vacuolated inclusions in connective tissue of cornea, conjunctiva, sclera, choroid, and iris and ciliary body, keratocyte vacuolation in posterior cornea early; eventually entire cornea affected, vacuolated inclusions in ciliary epithelium and RPE, RPE hypertrophy</td>
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<td>Liver (hepatocytes)</td>
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<td>Skin (fibroblasts)</td>
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<td>RPE</td>
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<td>Mucolipidosis II</td>
<td>Domestic shorthair</td>
<td>Failure of trafficking of several</td>
<td>CNS Bones</td>
<td>Failure to thrive as kittens, facial dysmorphia,</td>
<td>Photoreceptor degeneration</td>
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<td>lysosomal enzymes</td>
<td>Heart</td>
<td>long bone lesions, cardiac failure, respiratory</td>
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<td>Retina</td>
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optic neuritis. Of the viral diseases, FIP is most likely to affect the central nervous system and the optic nerve (Andrew, 2000). Associated ocular signs may include anterior uveitis, chorioretinitis, perivascular cuffing, and retinal detachment. The typical histopathologic findings consist of pyogranulomatous inflammation of the meninges (Foley & Leutenegger, 2001).

Toxoplasmosis may cause optic neuritis as well (Dubey & Carpenter, 1993). Upon histopathologic examination, tachyzoites have been noted within the optic nerve (Vainisi & Campbell, 1969). Of the systemic fungal infections, Cryptococcus neoformans is the most frequently recognized systemic fungal infection in cats (Pentlarge & Martin, 1986; Wilkinson, 1979). Optic neuritis is the second most commonly reported ocular lesion in cases of feline cryptococcosis (Davies & Troy, 1996).

**Optic Nerve Atrophy**

Arophy of the optic nerve is the sequelae to any process that damages the retinal ganglion cells or their axons. Examples of such causes include injury to the optic nerve during traumatic ocular proptosis, traction-related damage to the optic nerve at the level of the optic chiasm during enucleation of the contralateral eye (Stiles et al., 1993), and previous episodes of optic neuritis. Chronic glaucoma and retinal degeneration will also result in optic nerve atrophy.

**Optic Nerve Neoplasia**

Primary neoplasia of the feline optic nerve is uncommon (Buyukmihci et al., 2002). While no report defines the most common primary neoplasm of the feline optic nerve, meningioma is the most common primary neoplasm of the canine optic nerve (Andrews, 1973) and the most common feline intracranial neoplasm (Troxel et al., 2003). A stromyomas or gliomas may also occur. Secondary neoplasia of the optic nerve is possible as well. Lymphoma is the most common secondary feline intracranial neoplasm and has been detected within cranial nerves (Andrews, 1973). Traumatic ocular sarcoma has a propensity for growth into and along the optic nerve, often into the brain, resulting in death (Dubielzig, 2002; Dubielzig et al., 1990). A n intraocular myxoid leiomyosarcoma in a cat was reported to partially fill the globe and extend into the optic nerve (Labelle & Holmberg, 2010).

**Central Nervous System Blindness**

Inflammations, infections, neoplasia, encephalopathies, head trauma, nutritional deficiencies, toxicities, and cerebrovascular accidents may all lead to blindness. Pupillary light and dazzle reflexes may remain intact or be absent depending on the areas of the central nervous system that are affected. Specific central nervous system disorders that have been reported to cause blindness include Cuterebra larvae migration (Glass et al., 1998; Williams et al., 1998), hypovitaminosis A (Bartsch et al., 1975), hepatic encephalopathy from portosystemic shunt and shunt ligations (Kyles et al., 2002), and from hepatic lipidosis (Burrows et al., 1981), central nervous system blastomycosis (Miller et al., 1990), permethrin toxicity (Boland & Angles, 2010), and methylmercury toxicity (Gruber et al., 1978).

In a retrospective study of post-anesthetic cortical blindness in 20 cats, central blindness was present in all cats and 17 of 20 cats had other neurologic abnormalities as well (Stiles et al., 2012). Spring-loaded mouth gags were identified as a risk factor for cerebral ischemia and blindness due to presumptive interference with blood flow through the maxillary artery. Blood supply to the feline brain is primarily via the maxillary artery, a branch off the external carotid artery. Any interference with this artery in the cat can lead to significant cortical ischemia compared with other species such as the dog in which more than one arterial vessel supplies the cerebral cortex. In this study, 70% of cats had documented recovery of at least some vision, whereas 59% recovered from the other neurologic deficits. In a study that included three cats with postretinal blindness that were evaluated by magnetic resonance imaging (MRI), one cat had a nasal carcinoma with intracranial extension, one cat had a nasal osteosarcoma with intracranial extension, and one cat had a pituitary carcinoma (Seruca et al., 2010). All cats had sudden and permanent vision loss as the presenting clinical sign. In a study of nine cats with intracranial meningioma, preoperative signs were resolved after surgery, except for central blindness which persisted (Forterre et al., 2000).

**Diseases of the Orbit**

**Congenital and Developmental Disorders**

Multiple abnormalities or colobomas of the eye and associated ophthalmic structures occur in the domestic cat. In one report, the breeds represented included the domestic shorthair and Persian (Bellhorn et al., 1971). The condition is characterized by congenital colobomatous defects in single or multiple ocular tissues, which may include the eyelid, iris, optic nerve, and sclera. Similar ocular anomalies have been reported in the snow leopard (Barnett & Lewis, 2002; Gripenberg et al., 1985). Another report described a litter of domestic shorthair kittens with the multiple ocular anomalies (sufficient to produce blindness) that included microphthalmia, choroidal and optic disk colobomas, retinal dysplasia, and tapetal aplasia (Martin et al., 1997). The most consistent anomalies in these kittens were focal dorsolateral eyelid agenesis and trichiasis. Both heredity and in utero viral causes have been proposed for this syndrome, but no supporting evidence is currently available.

**Griseofulvin Teratogenesis**

The cat is particularly sensitive to the teratogenic effects of griseofulvin (Scott et al., 1975). When given to cats at a weekly dose of 500–1000 mg during the first half of gestation, griseofulvin produces ocular defects consisting of cyclopia, anophthalmia, and optic nerve aplasia. Extraocular defects
include numerous central nervous system and skeletal abnormalities.

**Acquired Disorders**

**Traumatic Proptosis**

Proptosis of the globe is a serious disease in cats, because to occur, it requires considerable trauma to the orbit and head and is associated with concurrent facial fractures and optic nerve damage. In one series of traumatic proptosis among 18 cats, no eyes regained vision (Gilger et al., 1995). Sexually intact males were more frequently affected, and being hit by a car was the most frequently established source of trauma. In 16 of the 18 affected cats, facial bone fractures, hyphema, corneal perforation, and ocular desiccation were common. In only 2 of the 18 cats was replacement of the globe and temporary tarsorrhaphy even attempted.

**Orbital Inflammations and Infections**

The feline orbit has relatively limited space compared with that of the dog. Hence, space-occupying orbital inflammations and neoplasms will produce exophthalmos, deviation of the globe and protrusion of the nictitating membrane early in the disease process. Orbital surgeries are also more difficult to perform because of the limited peribulbar space.

Orbital cellulitis and abscessation caused by bacteria occur infrequently in cats (Fig. 27.85) but are usually amenable to traditional therapy of drainage and antibiotic administration (Ramsey et al., 1996). In a study of orbital bacterial infections, five of seven cats had positive bacterial isolation, with Pasteurella and Bacteroides as the most common genera (Wang et al., 2009). Onchocerca lupi was the causative agent of orbital cellulitis in two cats (Labelle et al., 2011). The organism was identified on histopathology and confirmed by molecular diagnostic techniques.

Orbital infections caused by fungal agents are occasionally reported. Bilateral orbital cellulitis and exophthalmos caused by Penicillium sp. has been described in a domestic cat (Peiffer et al., 1980), as well as a retrobulbar mass caused by Pythium insidiosum (Bissonnette et al., 1991). Aspergillus spp. have been documented to cause orbital infections in several cats (Barachetti et al., 2009; Hamilton et al., 2000; Kano et al., 2008; McLellan et al., 2006; Smith & Hoffman, 2010; Wilkinson et al., 1982). Clinical signs in these animals may include exophthalmos, corneal drying with possible ulceration secondary to lagophthalmos, ocular discharge, oral cavity ulceration, pain upon opening of the mouth, and nasal discharge if the infection involves the nasal cavity or sinuses.

In most reports of feline orbital aspergillosis, the cats have been Persians. Surgical therapy alone, including orbital exenteration, has not typically been successful. In one report, a cat was successfully treated with posaconazole after surgery, and treatment with itraconazole and amphotericin B failed (McLellan et al., 2006). In a report of three domestic shorthair cats with orbital aspergillosis, therapy with oral voriconazole was utilized in two of the cats (Smith & Hoffman, 2010). The drug resulted in serious systemic side effects that necessitated discontinuation of therapy.

Orbital foreign bodies have occasionally been reported in cats (Kim et al., 2011; Lybaert et al., 2009; Tovar et al., 2005). CT successfully identified a linear metallic foreign body in one cat (Kim et al., 2011) and a linear wood foreign body in another cat (Lybaert et al., 2009), both of which were removed surgically with good results. Ocular and orbital ultrasound identified a retrobulbar abscess in one cat, but failed to demonstrate a plant foreign body (Tovar et al., 2005). The plant material penetrated the globe and was identified at enucleation.

A 13-year-old cat with a 1-week history of periorbital swelling and exophthalmos had a predominantly eosinophilic inflammatory cell infiltrate in the orbital tissue that was biopsied (Dziezyc & Barton, 1992). The cat was treated with oral prednisolone in a tapering dose over 4 weeks and had no recurrence in a 2-year follow-up time. Orbital emphysema associated with frontal sinus penetration has also been reported in a cat (Wolfer & Grahn, 1995).

An idiopathic sclerosing orbital disease has been described in seven cats (six domestic shorthair cats and one Persian) in one case series (Billson et al., 2006) and in one domestic shorthair cat in a single case report (Miller et al., 2000). The features of the condition are similar to those of sclerosing orbital pseudotumor in humans. In affected cats, the onset of the disease is insidious with progression over weeks to months. Orbital tissues and eyelids become fixed in place by fibrous tissue. In all of the described cats, the condition became bilateral. Exposure keratitis, corneal ulceration, and corneal perforation were prominent features of the disease due to inability...
response to treatment was poor. Six of the eight cats were euthanized; one cat later died from chronic renal failure, and one cat had bilateral exenteration performed.

In a report of the histopathologic features of tissues from affected cats, infiltration of neoplastic spindle cells were found in the orbit, eyelids, and periocular skin with collagen deposition and a few inflammatory cells (Bell et al., 2011). The spindle cells spread along fascial planes but did not form a discrete mass. The authors suggested the term feline restrictive orbital myofibroblastic sarcoma as a more appropriate name for this disease in cats.

Orbital Neoplasia

Orbital neoplasia is fairly common in cats. In one series, approximately two-thirds of the neoplasms were epithelial in origin, with SCCs being the most frequent type (Fig. 27.87) (Gilger et al., 1992). Approximately 15 different types of orbital tumors have been reported in cats, including osteoma of the zygomatic arch, parosteal osteoma, and fibrosarcoma (Cottrill et al., 1987; Knecht & Greene, 1977; Peiffer et al., 1978; Pentlarge et al., 1989). Orbital lymphosarcoma may occur either unilaterally or bilaterally in cats. A well-differentiated teratoma causing exophthalmos in a 3-year-old cat has been reported (Wray et al., 2008).

In one cat with an orbital osteosarcoma, the imaging techniques of ultrasound, radiography, CT, and MRI were all performed and compared with the postmortem examination results (Ramsey et al., 1994). Only the use of MRI delineated the exact borders of the neoplasm. In a case series using CT for evaluating orbital disease in 13 cats, bony lysis was the feature that was most consistently associated with neoplasia, which was ultimately diagnosed in 11 of the cats (Calia et al., 1994). Indentation of the globe was most often seen with lymphoma. In a study of 13 cats using MRI to evaluate orbital disease, lymphoma, sarcoma, and carcinoma were the most
commonly diagnosed neoplasms in the 11 cats that had tumors (Armour et al., 2011).

Depending on the tissue of origin and the invasiveness of an orbital tumor, therapeutic options may include surgery (orbiotomy with tumor resection or exenteration), radiation therapy, and chemotherapy.

Enucleation

Enucleation or exenteration in cats must be approached with more caution than the same surgical procedure in dogs because of the higher risk for damage to the optic chiasm (Stiles et al., 1993). The feline optic nerve is short and lacks the same degree of S-curve present in dogs. Traction placed on the globe during enucleation may lead to optic chiasm damage and blindness in the fellow eye (Fig. 27.88). There is little free space in the feline orbit, so the use of large instruments or inappropriate technique may place undue traction on the optic nerve. This is especially true in cats with glaucoma and buphthalmic globes, a common reason for enucleation. It is recommended that the subconjunctival approach to enucleation be used in cats so that tissues can be identified and transected carefully, and that only a small hemostat be used to clamp the optic nerve, vessels, and retractor bulbi muscle behind and close to the globe. The hemostat should be removed prior to the use of a small scissor to cut these tissues so that two instruments are not being introduced behind the globe.

In cases of enucleation or exenteration in which there is insufficient skin to close the orbital defect, a caudal–auricular–axial pattern flap may be useful (Smith et al., 1993; Spodnick et al., 1996; Stiles et al., 2003; Trevor et al., 1992). A skin graft from the neck and scapular region that includes the caudal–auricular artery is harvested and rotated into the orbital defect. The most common complication of this procedure is distal flap necrosis from loss of blood supply. An axial pattern flap based on the superficial temporal artery can also be used and may have less tendency for distal flap necrosis (Fahie & Smith, 1997).

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Figure 27.88. Damage to the optic chiasm during enucleation of the right eye has caused blindness in the left eye. Note the mydriasis.


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Chapter 28

Equine Ophthalmology

Brian C. Gilger

INTRODUCTION

Knowledge and experience in equine ophthalmology has expanded greatly in the past 10 years. There has been a heightened awareness of the need for specialized equine ocular diagnostic, therapeutic, and surgical methods among veterinarians, veterinary ophthalmologists, and horse owners. The American Association for Equine Practitioners (AAEP) held 2-day “Focus on Ophthalmology” continuing education symposiums for general practitioners in 2009 and 2012, and in 2010, the AAEP awarded noted equine ophthalmologist, Dr. Dennis Brooks, with the Milne Lecture, one of the AAEP’s highest honors. Furthermore, an international society has been formed devoted to the advancement of equine ophthalmology, the International Equine Ophthalmology Consortium (IEOC) (www.equineophtho.org). The IEOC has to date organized two U.S. and two international symposia over the past 4 years dedicated to equine ophthalmology. The Dorothy Havemeyer Foundation (www.havemeyerfoundation.org) for the first time in their history has provided financial support for two of these scientific meetings on equine ophthalmology.

We have finally realized that the equine eye is not simply a large canine or human eye, but has its own distinct disease states, responds to medication in many cases differently, and surgery (and its aftercare) differs from small animal surgery. The clinician must always keep this in mind and not expect the same response to treatment in the horse compared to other animals. For example, although cataract surgery is successful in horses, the surgical procedure differs greatly, requires specialized equine equipment, and requires much more postsurgical care than most dogs. Equine cataract surgery differs as much from canine cataract surgery as does canine cataract surgery differs from human surgery. Fortunately, equine-specific diagnostic and surgical equipment (e.g., equine phacoemulsification units, intraocular lenses [IOLs], equine contact lenses) have been marketed in the past several years to support this growing need in equine ophthalmology (e.g., Acrivet [www.acrivet.eu], other distributors).

There has been several comprehensive textbooks published recently dedicated entirely to equine ophthalmology (Barnett et al., 2004; Brooks, 2010; Gilger, 2011a). Therefore, the goal of this chapter is not to rewrite or replace these textbooks, but instead the goal is to review the most common ocular diseases in horses and to provide an update. I encourage the reader who is looking for in-depth information and complete reference lists regarding a specific subject to also read one of the aforementioned comprehensive equine textbooks (Barnett et al., 2004; Brooks, 2010; Gilger, 2011a). Also, anatomy, physiology, ocular examination, and ocular manifestations of systemic disease of the horse are reviewed elsewhere in this textbook and will not be extensively repeated in this chapter.

Equine ophthalmology is in an exciting period of increasing knowledge and growth. However, we must keep in mind the economic struggles of many horse owners and the high cost of maintaining a horse. We must also keep in mind when recommending treatment that horses are not as easy to medicate as small animals and can become dangerous to their owners. Therefore, practical, cost-effective, and reasonable therapies should be considered. At the same time, one must remember that early surgical intervention may in some cases lead more rapidly to recovery, thereby shortening treatment time, and easing the financial, time, and emotional burden of the horse owner. Careful discussions with the horse owners to help them make informed decisions should be a main goal.

VISION IN HORSES

Vision testing in horses is subjective, and there are no objective methods of testing vision in horses. Environmental observation (i.e., observing the horse in the stall, pasture, or while being worked by the owner or trainer), menace response, dazzle reflex, and maze testing (with or without unilaterally blindfolding the horse) together may provide some informa-
tion regarding the presence or absence of vision. Determining total blindness is possible with these tests, but determining whether a horse has decreased vision is not easily done. Advanced diagnostic testing such as electoretinography (ERG) (see Chapter 10.4) may help determine if there are abnormalities in retinal electrical function, but an ERG does not test vision. To understand the response to the aforementioned vision function tests, the clinician needs to understand the equine vision capabilities (Miller & Murphy, 2011).

The horse has several aspects of its vision that are important clinically and behaviorally. Functional vision for any species depends on (1) light entering into the eye, (2) the eye efficiently transmitting and properly focusing the images of these objects on the retina, (3) the transmission of this information to the brain, and (4) the brain processing and interpreting this information (Miller & Murphy, 2011). Therefore, a complete and thorough ophthalmic examination is needed to rule out ocular disease as the source of vision loss. However, effective vision depends not only on normal health and function of the eye, but also on the cognitive processes in the brain. How and what a horse processes in its brain are nearly completely unknown (Miller & Murphy, 2011).

To improve vision in both dim and bright light, the horse eye has evolved to have several ocular adaptations. Among the terrestrial vertebrates, horses have one of the largest eyes that allows more light to enter the eye, which improves vision in dim light (Miller & Murphy, 2011). The horse’s vision in dim light is also improved by a superiorly located, roughly triangular, reflective tapetum lucidum consisting of collagen fibrils and functions to reflect light back through the retina to interact with photoreceptors a second time (Miller & Murphy, 2011). In bright light, the large upper central corpora nigra may reduce glare by blocking direct sunlight exposure of the inferior retina and by augmenting pupillary constriction. The smaller inferior corpora nigra may also reduce glare by inhibiting light reflected off the ground from entering the eye (Miller & Murphy, 2011). The lateral position of the eyes in the skull affords the horse a wide, panoramic view (Fig. 28.1). The horse has a monocular visual field in the horizontal meridian of approximately 190–195° and up to 178° in the vertical meridian. When the visual fields of the two eyes are combined, the total horizontal visual field is up to 350°. Accommodation is limited (less than 2 diopters [D]), but only small changes by the lens are needed to maintain a focused image on the retina (Miller & Murphy, 2011). The average resting refraction as measured most commonly by streak retinoscopy is near emmetropia, and astigmatism is uncommon (McMullen, 2011). Horses have dichromatic color vision with two cone types: a short-wavelength-sensitive (blue) cone with a peak sensitivity of approximately 428 nm, and a second cone with a peak sensitivity around 540 nm (Fig. 28.2) which is between the human red and green cones. Therefore, horses likely have difficulties in differentiating orange and blue (Miller & Murphy, 2011). For detailed information regarding equine vision, please see the excellent chapter by Miller & Murphy (2011).

Figure 28.1. The view from the front of the horse allows the examiner to compare the symmetry between the eyes. This horse has ventral strabismus in the right eye.

**OCULAR EXAMINATION OF HORSES**

Details and techniques of the ocular examination are described in Chapter 10. Examination of the equine eye includes obtaining a thorough history, evaluating the patient in a well-lit environment, and finally examining the ocular structures in a darkened environment. In most horses, the examination is facilitated with proper restraint, sedation, and local nerve blocks. Indications and technique for advanced diagnostics, such as ultrasound, ERG, computed tomography (CT), and magnetic resonance imaging (MRI), are discussed in Chapters 10.2–10.4.

Examination of the equine eye should be done in a systematic manner. Following assessment of vision, and prior to instillation of any medication in or around the eye, the examiner should examine initially the horse in a lit environment. The examiner should first evaluate for symmetry of the head, bony orbits, eyelids, globes, and pupils, and this is best accomplished with the examiner positioned in front of the horse (see Fig. 28.1). Ocular comfort may be assessed by evaluation of palpebral fissure size, position of the eyelashes, ocular discharge, and blink rate (Gilger & Stoppini, 2011). The upper eyelashes of the healthy horse are nearly perpendicular to the cornea (Fig. 28.3), while a ventral or downward direction of the eyelashes may indicate blepharospasm, enophthalmos, or ptosis (Fig. 28.4) (Gilger & Stoppini, 2011).
A cranial nerve (CN) evaluation (i.e., CNs II, III, IV, V, VI, VII) is performed prior to sedation by assessing the menace response, pupillary light and dazzle reflexes, globe and eyelid position and mobility, and sensation of ocular and adnexal structures (see Chapter 34, “Comparative Neuro-Ophthalmology”).

Following the initial examination and assessment of vision, most horses require sedation to allow a complete ophthalmic examination. An effective tranquilizer for equine ophthalmic examinations is detomidine hydrochloride (HCl) (0.02–0.04 mg/kg IV; Pfizer Animal Health, Madison, NJ) because it induces the horse to lower the head and remain still. Other common equine tranquilizers, such as xylazine and butorphanol, are effective but may induce head tremors or exaggerated response to stimuli (such as sound), which can be frustrating when performing a detailed ocular examination. Pretreatment with IV acepromazine (0.02–0.04 mg/kg IV; 20 mg IV in a 500-kg horse) followed 10–15 minutes later with xylazine or detomidine may also reduce head tremors in horses.

Two ophthalmic periocular nerves are commonly denervated (“blocked”) to facilitate the equine ocular examination: the palpebral branch of the facial nerve (CN VII) and the frontal (supraorbital) branch of the trigeminal nerve (CN V). When these nerves are blocked, akinesia and anesthesia, respectively, of the upper eyelid occurs. The palpebral branch of the auriculopalpebral nerve is most easily and precisely blocked as it courses over the zygomatic arch caudal to the bony process of the frontal bone (Fig. 28.5). One to two milliliters of 2% lidocaine HCl (or 2% mepivacaine; Carbocaine, Pharmacia & Upjohn Company, Division of Pfizer Inc., New York, NY) is injected subcutaneously using a 25-gauge, 5/8-inch needle adjacent to the nerve, and the injection site is massaged to facilitate anesthetic diffusion. Onset of action is approximately 4–6 minutes, and the block has a duration of 60–120 minutes, depending on the type of anesthetic used.
The frontal (supraorbital) nerve is blocked as it emerges from the supraorbital foramen within the frontal bone (Fig. 28.6). This foramen can be palpated if the examiner places his or her thumb below the dorsal orbital rim and the middle finger in the supraorbital fossa. The examiner then places the index finger straight down midway between the thumb and middle finger to locate the supraorbital foramen (Fig. 28.7). A 25-gauge, 5/8-inch needle is then inserted subcutaneously over the foramen, and 1–2 mL of anesthetic is injected. Passing the needle into the foramen is not recommended or necessary.

**Figure 28.5.** Palpation of the location of the palpebral branch of the auriculopalpebral nerve as it courses over the zygomatic arch caudal to the bony process of the frontal bone.

**Figure 28.6.** The frontal (supraorbital) nerve is a branch of the trigeminal nerve, is blocked as it emerges from the supraorbital foramen within the frontal bone. (With permission from Giuliano, E. (2011) Equine ocular adnexal and nasolacrimal disease. In: Equine Ophthalmology (ed. Gilger, B.C.), 2nd ed. Philadelphia: Elsevier.)

**Figure 28.7.** To locate the supraorbital foramen, the examiner places his/her thumb under the orbital rim, the middle finger in the supraorbital fossa, then places the index finger straight down midway between the thumb and middle finger to locate the supraorbital foramen.
because this may damage the supraorbital artery and vein, which also exit the skull through the supraorbital foramen.

With the horse in a well-lit environment, the periorcular tissues, orbit, eyelids, conjunctiva, and ocular surface should be examined. If a lesion is present on the cornea or conjunctiva, a bacterial ± fungal culture and sensitivity may be indicated and should be collected followed by performing a Schirmer tear test (type 1). Both tests need to be performed prior to administration of topical medications.

In a darkened environment, the cornea should be examined for abnormalities (e.g., opacities, ulceration, blood vessels, edema) by using transillumination with magnification (e.g., loupes) and/or slit lamp biomicroscopy. When indicated, cytology is collected next, usually after application of 0.5% proparacaine HCl topical anesthetic (Alcaine 0.5%, Alcon Laboratories, Fort Worth, TX). Fluorescein and/or rose bengal staining of the cornea are then performed. Examination of the nasolacrimal system, third eyelid, and conjunctiva is performed using magnification (e.g., loupes) and/or slit lamp biomicroscopy. The anterior surface of the third eyelid can be examined by gently retropulsing the globe to produce passive prolapse of the nictitans. For evaluation of the posterior surface, the third eyelid can be gently grasped and retracted using Graefe fixation forceps. Evaluation of resting pupil size, shape, and mobility and appearance of the anterior chamber structures should follow, including the assessment for aqueous flare. The attachment of the iridocorneal angle pectinate ligaments to Descemet's membrane (i.e., gray line) can be observed medially and laterally in the adult horse and allows for direct visualization of the horse's iridocorneal angle (Fig. 28.8). Induction of topical anesthesia with proparacaine is performed, if not already applied, and tonometry using a TonoPenVet (Reichert Ophthalmic Instruments, Depew, NY) or TonoVet (Icare, Finland) tonometer is then performed (Fig. 28.9).

Mydriasis is required for complete examination of the lens and ocular posterior segment. The most common mydriatic used is tropicamide (Mydriacyl 1%, Alcon Laboratories, Fort Worth, TX), which takes effect in approximately 10–20 minutes and lasts 4–6 hours in the horse (Gelatt et al., 1995; Gilger & Stoppani, 2011). If the horse has intraocular inflammation or uveitis secondary to corneal disease or trauma, a single application of tropicamide may not be sufficient to dilate the pupil. Topical phenylephrine (2.5% or 10%) does not cause mydriasis in normal horses, nor does it enhance the mydriatic effect of tropicamide (Hacker et al., 1987). The use of atropine for routine examination is not recommended because of its longer duration of action and potential adverse effects in the horse (Davis et al., 2003). After mydriasis has been achieved, the clarity, position, and size of the lens, vitreous body, optic nerve, retinal blood vessels, and the tapetal and nontapetal fundus are evaluated (Fig. 28.10).

Examination of the ocular fundus can be performed with a direct, indirect, or panoptic ophthalmoscope, depending on

Figure 28.8. The attachment of the iridocorneal angle pectinate ligaments to Descemet’s membrane (i.e., gray line) can be observed medially and laterally in the adult horse and allows for direct visualization of the horse’s iridocorneal angle.

Figure 28.9. A. Measurement of intraocular pressure using a TonoPenVet (Reichert Ophthalmic Instruments, Depew, NY) tonometer. B. Measurement of intraocular pressure using a TonoVet tonometer (Icare, Finland). (Photograph courtesy of Dr. David Wilkie.)
most commonly 12–36 hours after birth (Dwyer, 2011). The neonatal iris may be slightly gray in color, the pupil round to oval, and the pupillary light reflex (PLR) sluggish (Barnett, 1975; Dwyer, 2011; Latimer & Wyman, 1985). Menace response is commonly diminished until the foal is several weeks old (Latimer & Wyman, 1985).

Common ophthalmic findings in neonatal foals include episcleral or retinal hemorrhage, and corneal ulceration, both likely from birthing trauma. Furthermore, a persistent remnant of the hyaloid artery is common and appears as a white or blood-filled line running through the central vitreous (Latimer & Wyman, 1985). Entropion of one or both lids is likely the most common ocular problem in neonatal foals, and it is usually associated with neonatal maladjustment. Temporary tacking sutures can be used to roll out the eyelid to prevent or treat corneal ulceration; however, the underlying maladjustment needs to be resolved to prevent recurrence of the entropion. If any congenital anomalies have been observed in the foal, the mare should get a thorough eye examination to determine if she has similar conditions and to assess potential heritable disease (Dwyer, 2011; Turner, 2004).

Yearlings

Because of exuberant behavior of young adult horses, herd and pasture injuries are common in yearling horses. Also, because training commonly starts in older yearlings, accidents can occur. Eyelid lacerations, corneal ulcerations, blunt trauma uveitis, and even retinal detachments can occur due to trauma (Dwyer, 2011). Nasolacrimal duct (NLD) atresia, which is usually manifested by an imperforate nasal punctum, appears clinically as mild to moderate, unilateral or bilateral epiphora at 4–6 months of age and, if not managed appropriately, will develop into severe mucopurulent discharge by 10–12 months of age due to the development of secondary bacterial dacryocystitis. To treat definitively, a 5 French male silastic or plastic urinary catheter is placed normograde from the proximal nasolacrimal puncta. The end of the catheter is palpated at the site of the distal imperforate puncta and an incision, generally using electrocautery, is made over the catheter through the nasal mucosa, and the catheter is pulled through the nares. Topical and systemic antibiotics are given for 2–4 weeks, and the silastic tubing is removed typically 30 days after surgery (Giuliano, 2011).

Adult

The most common diseases in young adult horses, depending on the breed and environment, include recurrent or insidious uveitis (either genetically predisposed or associated with acquired leptospiral infections), fungal keratitis, corneal ulceration, squamous cell carcinoma (SCC), and ocular trauma. Horses living in warm and humid climates like the southeastern United States are prone to fungal keratitis. Mature horses living in sunny climates or high altitudes are at risk for development of actinic blepharitis or SCC of the adnexa or globe, particularly draft horses, Appaloosas, and...
color dilute breeds like Paints (Dwyer, 2011). Mature horses frequently develop nuclear sclerosis as they age. This can give the lens a faint blue appearance that may be opaque on transillumination.

**Geriatric**

Geriatric horses often present with degenerative or age-related conditions of the eyes (Cutler, 2002; Dwyer, 2011). In one study of 83 horses over the age of 15 years, 49% had retinal lesions (e.g., senile retinopathy, retinal degeneration, peripapillary chorioretinopathy, optic nerve atrophy, or proliferative optic neuropathy), 46% had vitreal degeneration, and 19% had cataracts. However, only 7 (8%) had vision loss (Chandler et al., 2003). Horses over the age of 15 years are also at increased risk for many kinds of neoplasia, including intraocular neoplasia (such as melanoma in aged gray horses) and adnexal SCC. Geriatric horses commonly develop chronic conditions that may have ocular manifestations including dental disease, sinus infections, and Cushing’s syndrome (Dwyer, 2011). See Chapter 35 for more details regarding these systemic diseases.

**Ophthalmic Disease and Activity of the Horse**

**Western Performance and Rodeo**

Western performance and rodeo horses are at an increased risk of ocular trauma because they are commonly housed in group pens and are trailered for long distances (Dwyer, 2011). Corneal ulcers are the most common ocular problem seen in western performance horses and may develop from rope abrasions during roping activities (Dwyer, 2011). Unilaterally blind or enucleated horses are allowed to compete in western performance events. For detailed information regarding competition rules, medication, and ocular disease, please see Dr. Ann Dwyer’s recent chapter (Dwyer, 2011) or the organization websites.

**English/Hunter-Jumper**

Show, hunter-jumper, eventing, and dressage horses are frequently transported long distances and housed in show grounds that may be dusty, insect infested, windy, or humid. As a result, they have a high incidence of general irritation of the conjunctiva and cornea, and often suffer chemosis, blepharitis, epiphora, and mild corneal edema (Dwyer, 2011). This ocular irritation and pruritus may predispose to rubbing on buckets and stall walls, leading to secondary eyelid lacerations and corneal ulcers. To minimize ocular trauma, competitors and grooms should carefully inspect the show ground stalls for nails, hooks, splinters, and so on that may cause damage. Twenty-four-hour use of a quality fly mask may help prevent ocular trauma. Unilaterally blind horses are permitted to compete as jumpers but may be excluded from competition as hunters in rated shows judged under the rules of the United States Equestrian Federation (USEF) (Dwyer, 2011). Unilaterally blind horses are permitted to compete in both dressage and eventing (Dwyer, 2011). Any event that is an officially sanctioned competition (e.g., USEF or Fédération Equestre Internationale [FEI]) will require that treatment for any acute injury or inflammation be reported. The veterinarian must be thoroughly familiar with the prevailing rules if the horse is to be allowed to continue to compete (Dwyer, 2011).

**Endurance**

Like show horses, endurance horses competing in long-distance rides usually are trailered to the ride site, and on arrival are often confined in small pens. These horses are at increased risk of debris-associated conjunctivitis and corneal ulcers as well as blunt trauma and eyelid lacerations (Dwyer, 2011). Endurance is essentially a drug-free sport, and the American Endurance Ride Conference (www.aerc.org/) has an extensive list of substances prohibited during rides. Unilaterally blind horses and horses that have been enucleated on one side are permitted to compete in endurance events (Dwyer, 2011).

**Racehorses**

Many racehorses are young, have high energy, are transported frequently (sometimes for long distances), and are nearly exclusively housed in stalls when in training or racing. Trauma-related injuries, therefore, are very common, including eyelid laceration and corneal ulceration. The veterinarian must clearly understand the medication rules in racing; for example, injectable anesthetics, such as lidocaine, are banned in horses that are entered in races (Dwyer, 2011). Thoroughbred horses are at increased risk for blunt trauma to the orbit and periorbit from starting gate accidents. Thoroughbred and Standardbred horses not in the lead during races or training are subject to debris kicked up by horses and are at high risk for corneal injuries caused by particulate matter from the racetrack surface (Dwyer, 2011; Hurn & Turner, 2006). Blinkers or eyecups may provide a partial physical barrier, but considerable grit (sand, clay, small stones, or synthetic material) still pelts the facial area. Enucleated horses are permitted to race at all levels in most states; however, the unilateral blind condition should be declared to the betting public (Dwyer, 2011).

**Polo Horses/Ponies**

Travel injuries are particularly a problem in polo ponies because typically, they are transported in large trailers that hold the large group of horses required for each match. Polo ponies are at increased risk for blunt trauma to the globe and periorbital region from swinging mallets, airborne balls, and collisions with other ponies. Such trauma may be severe as the mallets and balls are propelled at high speed (Dwyer, 2011). There are currently no medication rules governing the sport of polo, so horses requiring therapy for ocular problems may be treated at the veterinarian’s discretion. The
U.S. Polo Association (www.us-polo.org) requires that polo ponies be visual in both eyes (Dwyer, 2011). For detailed information regarding competition rules, medication, and ocular disease, please see Dr. Ann Dwyer’s recent chapter (Dwyer, 2011) or the organization websites.

EQUINE OCULAR DISEASE BY ANATOMIC LOCATION

Diseases of the Equine Orbit

Anatomy and physiology of the equine orbit is reviewed in Chapters 2 and 3. For more information on diseases of the equine orbit, such as in-depth details of management of orbital disease, please see a recent book chapter in the book, Equine Ophthalmology (Gilger, 2011b). The predominant ocular clinical sign of diseases of the equine orbit is abnormal position of the eye, either anteriorly displaced (exophthalmos), posteriorly displaced (enophthalmos), or when the eyes are not aligned (strabismus) (Fig. 28.12). Unlike the dog, the horse has a nearly complete bony orbit (see Chapter 2, “Ophthalmic Anatomy”). This complete bony orbital rim anteriorly and bony orbital walls posteriorly is a factor in the horse sustaining comparatively more orbital fractures than in other domestic animals. Because of this bony protection and strong extraocular muscles, horses rarely develop other orbital trauma other than penetrating injury. However, the adjacent large paranasal sinuses are a common location for infection, neoplasia, and other clinical abnormalities that result in swelling of tissues that frequently impinge on the orbital structures.

Imaging of the equine orbit and skull is very important for the diagnosis of orbital disease. Commonly used diagnostic imaging tools include orbital ultrasound and skull radiographs. Although commonly used, the extent and severity of injury are not well characterized by these modalities. When possible, CT is the imaging modality of choice in equine orbital disease (Fig. 28.13). For more information on these imaging modalities, please see Chapter 10.2.

Paranasal Sinuses

Periorbital sinuses, the frontal (conchofrontal), maxillary (caudal and rostral), and sphenopalatine, are in close anatomic proximity to the orbit (Fig. 28.14). Primary sinus diseases may secondarily affect one or both orbits. Sinusitis or empyema (i.e., purulent material within the sinus) is one of the most common nonneoplastic diseases of the equine head. Clinical signs of sinus disease include possible exophthalmos, from pressure or swelling that extends to the orbital contents, unilateral nasal discharge, facial swelling, and decreased nasal airflow (Nickels, 2006). Deformation or protrusion of maxillary bone may also be present. Orbital disease is usually associated with chronic sinus disease and can result in unilateral or bilateral blindness from compression of adjacent optic nerve(s) and optic chiasm (Barnett et al., 2008). Diagnosis is based on typical clinical signs of sinusitis and on skull radiographs or, preferably, CT. In primary infectious maxillary sinusitis, the fluid should be drained, the sinus lavaged, and appropriate systemic antimicrobial agents given. In secondary infectious sinusitis, the primary underlying disease, such as dental disease, facial fractures, granulomatous disease, or neoplasia, should be corrected if possible (Nickels, 2006).

Other diseases of the periorbital sinuses that can affect orbital contents include maxillary sinus cysts that are slow growing, expandable masses that must be differentiated from neoplasia. Dentigerous cysts, or cysts from the dental arcade,
SECTION IV: Special Ophthalmology

occur uncommonly in the horse but may result in exophthalmos or deformation of the orbit. Exophthalmos occurs in approximately 20% of cases of sinus neoplasia (Dixon & Head, 1999; Head & Dixon, 1999). Unilateral nasal discharge, facial swelling, and epistaxis are also common clinical signs in cases of neoplasms of the sinonasal structures (Dixon & Head, 1999; Head & Dixon, 1999). The most common neoplasms of the periorbital sinuses that cause exophthalmos are, in order of frequency, adenocarcinoma, adenoma, osteoma, SCC, fibrosarcoma, undifferentiated sarcoma, lymphosarcoma (LSA), and esthesioneuroblastoma. Diagnosis is based on clinical signs, radiology, and/or CT.

Orbital Fractures

Fractures of the dorsal orbital rim are most common (Fig. 28.15), likely because the dorsal orbital rim protrudes externally and laterally and is thus highly vulnerable to trauma. These fractures may result in displacement, impingement, functional restriction, or laceration of the globe. In most cases, the injury causing the fracture is not observed. Instead, the horse is found with a swollen peri orbital area. Fractures from vehicular accidents or from falling over backward and hitting the poll of the head may entail fractures to the basioccipital bone and consequently basisphenoid bone in the inner orbit. This can result in blindness if it involves the sphenoid foramina.

Diagnosis and assessment of orbital rim fractures should be accomplished by a thorough ophthalmic examination and digital palpation. The horse should be adequately tranquilized.
and restrained, and after use of topical anesthetic, a lubricated gloved finger should carefully palpate the orbital rim and wall. Pressure on the globe or orbital rim should be avoided. Imaging by radiography, and preferably CT, should be performed prior to considering surgical intervention. Skyline views are helpful for the orbital rim, but they can be difficult to interpret. A CT scan is nearly always recommended when orbital fractures are present. The extent of the fractures and damage are readily visualized (Fig. 28.16).

Any section of bone that is impinging on the globe or orbital contents needs to be reduced or removed. When the ultimate cosmetic outcome is desired, closed fracture reduction is highly desirable. With the horse placed under general anesthesia, zygomatic process fractures may be reduced closed by manipulation of the bone piece into position using a bone hook (Caron et al., 1986; Gilger, 2011b). More complex fractures of the dorsal orbital rim may be reduced with a malleable plate or bone plate (Koch et al., 1980). Repair of fractures should be done within 7 days after injury prior to development of a callus. Closed nondisplaced fractures and some closed displaced fractures that are not impinging on orbital structures are frequently permitted to heal by second intention. Open fractures typically are managed by debridement and cleaning of the wound, reduction of displaced by viable bone fragments, and removal of small, grossly contaminated fragments. Depending on the extent of contamination, some or all of the wound is left open for adequate drainage, or drains are placed to facilitate healing.

Fractures that expose the periorbital sinuses may result in emphysema and epistaxis. Sinus fractures are considered open wounds and should be treated aggressively. A drain may be placed if there is any evidence of infection (purulent exudate, cytologic evidence of bacteria or fungus), and creation of drainage should be considered (externally or into the nasal cavity) if there is inadequate drainage (Gilger, 2011b).

**Orbital Cellulitis**

Perforation by a foreign body, direct trauma, and seeding by septic emboli are among the more common causes of orbital cellulitis. Extension of inflammatory and infectious conditions from adjacent sinuses and cavities also occurs commonly. If septic endophthalmitis is untreated or is poorly responsive to therapy, it may progress to panuveitis and orbital cellulitis. Enucleation to prevent microbial colonization of deeper tissues may be necessary. In contrast, orbital cellulitis does not readily induce uveitis within the globe. Granulomas resulting from Actinomyces spp., the nematode Habronema, and phycomycosis may occur. Clinical signs include exophthalmos, blepharoadema/blepharitis, serous to mucoid discharge, anterior displaced nictitans engorged conjunctiva, and possible lagophthalmos. Fever, elevated white blood count, and general malaise may also be present with orbital cellulitis. Orbital ultrasonography, CT, and fine needle aspiration may also be helpful in the diagnosis (Van Den Top et al., 2007). Agressive use of nonsteroidal anti-inflammatory drug (NSAID) and antibiotics should be considered. Rarely is there a discrete fluid pocket in the abscess, so drainage per se is not usually therapeutic (Gilger, 2011b). However, debridement of any visible necrotic tissue is recommended. If there is no

![Figure 28.16.](image-url) Three-dimensional reconstruction of a CT scan of a horse with a right-sided dorsal orbital fracture. Arrows demonstrate fractures and depression of the zygomatic process of the frontal bone and the frontal process of the zygomatic in a lateral (A) and dorsal view (B).
very common problem in horses, especially eyelid lacerations and neoplasia. Appropriate initial management of these conditions is very important because dehiscence of wounds or recurrence of neoplasia result in conditions that are much more difficult to manage and at best result in decreased cosmesis and at worst can threaten the integrity of the eye. For more information on diseases of the equine ocular adnexa, such as uncommon conditions such as blepharitis and including in-depth details of management of adnexal neoplasia, please see an excellent recent book chapter by Elizabeth Giuliano (Giuliano, 2011).

**Congenital Adnexa Diseases**

The most common congenital or neonatal eyelid abnormality is entropion, which is most commonly seen in foals that are sick or have neonatal maladjustment syndrome (see earlier discussion in diseases of the neonate). Other congenital diseases of the eyelids and adnexa are uncommon but may include ankyloblepharon, coloboma, or dermoids (Barnett, 1975; Latimer & Wyman, 1985; Munroe & Barnett, 1984; Turner, 2004).

**Eyelid Lacerations**

Eyelid trauma and lacerations are very common in horses. Modern equine management, in many cases, involves keeping horses in confined spaces, such as box stalls, and often horses are subjected to frequent transport. This close confinement, the prominent lateral positioning of eyes, and the horses’ characteristic acute “flight response” in which horses react to stimuli by exaggerated movements of their heads contribute to the horses’ propensity for eyelid trauma (Giuliano, 2011). In most instances, the laceration is recognized early by the owners and therefore evaluated by the veterinarian when the condition is still acute. The severity of the initial appearance of the lesion does not correlate with overall prognosis (Giuliano, 2011). Due to the excellent blood supply to the eyelids, most lacerations can be repaired to achieve a relatively well-functioning and cosmetic eyelid; therefore, every attempt should be made to surgically repair all eyelid lacerations, taking care to avoid cutting any hanging eyelid pedicles (Fig. 28.18). Lacerations can develop from blunt trauma from a crushing injury against the orbital rim, direct contact with sharp objects (e.g., nail, metal edge), and ripping of the eyelid which usually results when the eyelid margin is caught on a hook with subsequent rapid head movement by the horse (Giuliano, 2011). A complete ocular examination is very important to ensure that other associated ocular problems are present, such as corneal ulceration, uveitis, hyphema, or retinal detachment.

Prompt surgical repair is recommended for eyelid lacerations to reduce scarring and secondary damage to the eye, primarily corneal damage. Very minimal debridement is required of the wound because the eyelids are very vascular and even dangling pieces of eyelid in most cases are still viable (Giuliano, 2011). A two-layer closure with an initial...
deep, subconjunctival layer of a continuous absorbable suture, such as 6-0 polyglactin 910 (Vicryl, Ethicon, Somerville, NJ), is used to ensure that the conjunctival aspect of the eyelid does not gape during healing and induce scar formation. Inadequate closure of the conjunctiva resulting from scar formation or poorly placed sutures (e.g. full-thickness conjunctival sutures) resulting in corneal trauma are the most common causes for dehiscence and complications, respectively. The eyelid margin must be meticulously re-apposed by first suturing the margin with preferably a figure-of-eight suture pattern of nonabsorbable 4-0 to 6-0 suture (Fig. 28.19) (Rebhun, 1980). Additional simple interrupted skin sutures are placed as needed to close the remainder of the eyelid defect. Incorrect closure of the eyelid margin or failure to use a two-layer closure may lead to chronic corneal irritation (Fig. 28.20). Skin sutures may be removed in 10–14 days.

Figure 28.18. A. Lower eyelid laceration of 1-day duration. B. Because of the excellent blood supply typically in eyelids, minimal debridement and a two-layer closure generally provides a good cosmetic and functional results.

Figure 28.19. Meticulous apposition of the eyelid margin, as seen in this immediate postoperative image, is needed to prevent scarring and ocular irritation.

Figure 28.20. Corneal irritation from irritation secondary to a malaligned eyelid laceration repair. Failure to use a two-layer closure and meticulous re-apposition of the eyelid margin can lead to dehiscence and secondary chronic corneal irritation.

Neoplasia

Neoplasia of the equine eyelids is very common and can be one of the most challenging ocular diseases to manage. Certainly, sarcoids SCC are the most common neoplasms, but melanoma, lymphoma, and angiosarcoma (among others) are not infrequent. Clinically, cutaneous or subcutaneous masses, proliferative conjunctiva, nonhealing eyelid ulcerations, or an elevated third eyelid are typical of adnexal neoplasia. In some cases, the only observed clinical sign is mucopurulent ocular discharge. Periocular neoplasia, in general, should always be confirmed by biopsy (and histopathology), and treated early and aggressively. Recurrent disease is always more resistant.
to treatment, is more likely to result in poor cosmesis, and can lead to loss of the globe. In some cases, especially in untreated chronic SCC, local and distant metastasis can occur, resulting in death of the horse.

Periocular Sarcomas

Sarcomas are cutaneous tumors of fibroblastic origin and have proliferative and hyperplastic epithelial components, and while metastasis is rare, recurrence is common, especially with the more invasive lesions. Periocular/eyelid sarcomas are common and may result in significant pathology to the eye either by disrupting normal eyelid function or by directly rubbing on the eye. Sarcomas usually develop in young horses between 3 and 6 years of age. Nearly all breeds have been reported to develop sarcomas, but Quarter horses, Appaloosas, and Arabians may be at increased risk, while Standardbreds may be at decreased risk (Angelos et al., 1988; Mohammed et al., 1992). An association between sarcoma susceptibility and the major histocompatibility complex (MHC)-encoded class II allele ELA W13 has been found in several breeds (Gerber et al., 1998). The clinical appearance of sarcomas varies, and they are most commonly classified into five broad categories: occult, verrucose, nodular (A and B), fibroblastic (A and B), and mixed equine sarcomas (Knottenbelt & Kelly, 2000; Martens et al., 2000). Periocular sarcomas are most commonly nodular, fibroblastic, or mixed (Fig. 28.21) (Knottenbelt & Kelly, 2000).

A surgical biopsy is always required for definitive diagnosis, but treatment needs to be done concurrently or soon after the biopsy since the mass usually is stimulated to proliferate after the surgical trauma of the biopsy. Due to the close proximity of periocular structures to the globe, some treatments reported for use on sarcomas elsewhere on the body cannot be used on eyelids without risking significant damage to the globe (Knottenbelt & Kelly, 2000). Various treatments have been reported for the treatment of equine periocular sarcomas (Table 28.1)

Table 28.1 Treatment for Periocular Sarcomas

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Treatment</th>
<th>Therapy</th>
<th>Reported % Nonrecurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical therapy</td>
<td>5% 5-fluorouracil</td>
<td>Bid x 5 days, then qd for 5 days, the QOD for 5 application</td>
<td>67%</td>
</tr>
<tr>
<td>Intralesional immunotherapy</td>
<td>BCG</td>
<td>1 mL per cm² of tumor surface</td>
<td>0%–100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repeat every 2–4 weeks</td>
<td></td>
</tr>
<tr>
<td>Intralesional chemotherapy</td>
<td>Cisplatin</td>
<td>1 mg/cm³ every 2 weeks for 4 treatments</td>
<td>33%–95%</td>
</tr>
<tr>
<td>Surgical excision</td>
<td>Excision</td>
<td>Once</td>
<td>50%</td>
</tr>
<tr>
<td>Excision and cryotherapy</td>
<td>Cryotherapy</td>
<td>Double or triple freeze—thaw</td>
<td>8%–18%</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>Hyperthermia</td>
<td>Tissue temperatures between 41°C and 45°C</td>
<td>0%</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>Radon, gold, iridium</td>
<td>6000–9000 cGy</td>
<td>87%–100%</td>
</tr>
</tbody>
</table>

Modified from Giuliano (2011).

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the most common neoplasm of the equine eye and ocular adnexa (Giuliano, 2011; Lavach & Severin, 1977). Horses with a lack of periocular pigmentation are at increased risk for development of SCC (Dugan et al., 1991a; Schwink, 1987). An increased prevalence of ocular SCC may occur with age, and a breed predilection for draft breeds and Appaloosas has been reported (Dugan et al., 1991a; Schwink, 1987). Development of SCC is associated with various environmental factors including geographic influences of increased longitude, decreased latitude, increased altitude, and increased mean annual solar radiation exposure (Dugan et al., 1991a; Giuliano, 2011).

The most common ocular locations for SCC are the nictitating membrane or medial canthus (approximately 28%) (Fig. 28.22), limbus (approximately 28%), and lower eyelid (approximately 23%) (Fig. 28.23). Other locations such as the cornea, conjunctiva, and orbit represent approximately 21%
adjunctive therapies, and the frequent recurrence of SCC contributes to clinical frustration in the treatment of SCC. In general, the ocular or periocular location of the SCC directs to the type of treatment that is indicated (Table 28.2). For example, corneal-scleral SCC generally responds to excision and adjunctive therapy of beta-irradiation, topical chemotherapeutics (e.g., mitomycin C), or possibly cryotherapy. Eyelid SCC is treated with excision and adjunctive therapy using cryotherapy, intralesional chemotherapy (i.e., cisplatin), immunotherapy, brachytherapy, or photodynamic

(Lavach & Severin, 1977; Schwink, 1987). Actinic solar keratitis may transform to carcinoma in situ SCC that often appears as hyperemic eyelid erosive plaques with dark-staining crusts, to eventually become papillomatous SCC or, alternatively, SCC may appear as a raised mass with a pink, cobblestone appearance (Fig. 28.24), to ultimately develop into large, fleshy masses with variable degrees of ulceration, necrosis, and inflammation (Fig. 28.25) (Giuliano, 2011; Lavach & Severin, 1977; Schwink, 1987).

Treatment for SCC is variable, and commonly reported therapies are summarized in Table 28.2. In one large retrospective study of equine ocular SCC, a main key to long-term success of management was found to be the owner’s willingness to return horses for reexamination (Dugan et al., 1991b). The need for adjunctive therapy, which may need to be repeated and is expensive, the adverse effects from these

Figure 28.22. Squamous cell carcinoma on the leading edge of the third eyelid. This is one of the most common locations for squamous cell carcinoma in the horse.

Figure 28.23. Squamous cell carcinoma involving the lateral lower eyelid in a paint horse.

Figure 28.24. Squamous cell carcinoma may appear as a raised mass with a pink, cobblestone appearance, as seen in this horse with an eyelid squamous cell carcinoma.

Figure 28.25. Squamous cell carcinoma may appear as large, fleshy masses with variable degrees of ulceration, necrosis, and inflammation.
therapy (PDT) (among others). Third eyelid/medial canthal SCC generally is treated with excision of the third eyelid with adjunctive treatment such as cryotherapy, brachytherapy, and possibly (depending on the extent of the lesion) intralesional chemotherapy, PDT, or immunotherapy (Table 28.2) (Giuliano, 2011). Recurrence rates of periocular SCC when treated with both surgical excision and an adjunctive therapy range from 25% to 67% (Giuliano, 2011). Rechecks for recurrence should continue for 3–5 years after treatment. Recurrence may develop distal to the primary location, such as the NLD (Elce et al., 2011).

Appropriate treatment of equine ocular SCC usually involves surgical excision combined with adjunctive therapy selected as appropriate for the anatomic site of the lesion. The horse owner should be carefully educated to understand that for best long-term results of the treatment of periocular SCC, they must be diligent in observing signs of recurrence or metastasis and be willing to have the horse examined as soon as adverse signs are observed (Dugan et al., 1991b).

### Table 28.2 Treatment for Periocular Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Treatment</th>
<th>Therapy</th>
<th>Reported % Nonrecurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intralesional immunotherapy</td>
<td>BCG</td>
<td>1 mL per cm² of tumor surface</td>
<td>100% (1 of 1 case)</td>
</tr>
<tr>
<td>Intralesional chemotherapy</td>
<td>Cisplatin</td>
<td>1 mg/cm³ every 2 weeks for 4 treatments</td>
<td>71%</td>
</tr>
<tr>
<td>Surgical excision</td>
<td>Excision</td>
<td>Once</td>
<td>56%</td>
</tr>
<tr>
<td>Excision and cryotherapy</td>
<td>Cryotherapy</td>
<td>Double or triple freeze—thaw</td>
<td>33%–100%</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>Hyperthermia</td>
<td>Tissue temperatures between 41°C and 45°C</td>
<td>75%–100%</td>
</tr>
<tr>
<td>CO₂ laser</td>
<td>Laser ablation</td>
<td>Ablate tissues</td>
<td>100%</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>Radon, cobalt, gold, iridium, stronquium</td>
<td>5000–25,000 cGy</td>
<td>74%–100%</td>
</tr>
</tbody>
</table>

Modified from Giuliano (2011).

**Melanoma**

Melanoma is a relatively uncommon tumor of the horse and usually is observed in horses with gray or white hair (Giuliano, 2011). A slowly progressive, cutaneous, partially alopecic, pigmented mass of the eyelids is the typical clinical appearance of most equine adnexal melanoma (Fig. 28.26). The size and location of the mass will dictate the clinical signs, varying from no ocular irritation to blepharospasm and corneal irritation. Older horses are predisposed to the development of melanoma, possibly because proliferation of melanocytes is a manifestation of aging (Fleury et al., 2000). Oral cimetidine (dose 2.5 mg/kg of body weight orally every 8 hours) has been used to shrink nonocular melanomas in horses, but no studies have been published on this treatment modality for adnexal melanomas (Giuliano, 2011). Surgical excision, CO₂ laser ablation, cryotherapy, and local PDT have been recommended. Excision of an eyelid melanoma is usually curative because most of the masses are benign.

**Lymphosarcoma**

Lymphosarcoma (LSA) is a relatively uncommon neoplasm in the horse. Infiltration of the eyelids and conjunctiva are the most common ocular manifestation of LSA, but orbital and/or third eyelid involvement can also occur (Fig. 28.27) (Rebhun & Del Piero, 1997). Adnexal LSA must be differentiated from other causes of eyelid tumors or swelling such as sarcoid, habronemiasis, SCC, papilloma, melanoma, conjunctival pseudotumors or nodular lymphocytic conjunctivitis (NLC), and orbital fat prolapse. Biopsy and histopathology are required for definitive diagnosis. LSA should be differentiated from conjunctival pseudotumors or NLC, which can be unilateral or bilateral, nodular or smooth, pink, nonulcerated conjunctival masses (Stoppini et al., 2005). Surgical debulking and local administration of anti-inflammatory agents (i.e., intralesional corticosteroid ± topical corticosteroids) are recommended.
Initially, NLD obstructions can be treated with antibiotic solutions (ideally selected based on culture sensitivity results—but commonly triple antibiotic is used) that contain a topical corticosteroid, which may be beneficial to decrease swelling in the NLD, provided there are no ocular surface contraindications (e.g., a corneal ulcer). If the NLD obstruction is chronic, recurrent, or does not respond to treatment after 2 weeks, DCR or other imaging modalities as mentioned earlier should be done. A 5 French male silastic or plastic canine urinary catheter can be threaded either normograde (from proximal to distal) or retrograde with an attempt to pass through or break up the obstructions. It helps to gently irrigate with eyewash or saline through the catheter as it is passed to help remove debris and to expand the NLD. The catheter should not be forced if resistance is encountered, because severe hemorrhage may develop (Latimer & Wyman, 1984). Once passed, the silastic tubing is sutured in place for 4–6 weeks (Fig. 28.29). Use of oral anti-inflammatory and oral antibiotic medication may be considered in these cases. Correction of primary sinus or dental disease should be done to minimize pressure on the NLD. Creating a new pathway from the canaliculi to the nasal cavity (canaliculorhinostomy) or from the ventral medial conjunctival surface to the maxillary sinus (conjunctivosinostomy) can be done as a last resort but have not been extensively studied in the horse (Giuliano, 2011).

Nasolacrimal Duct Obstruction

Congenital nasolacrimal atresia is one of the most common congenital ocular diseases in horses and is described earlier in this chapter under diseases of yearlings. Acquired nasolacrimal disorders include obstructions from inflammation (dacryocystitis), strictures, foreign bodies, diseases of the paranasal sinuses, diseases of the upper dental arcade, and external trauma (Cassotis & Schiffman, 2006).

Obstruction of the NLD occurs most commonly from accumulation of foreign material followed by bacterial growth and inflammation (i.e., dacryocystitis) in the NLD. Obstructions can occur from environmental debris accumulating in the NLD most commonly at a location immediately prior to the NLD exit from the lacrimal canal of the maxilla bone (Latimer et al., 1984). Clinical signs of NLD obstruction include epiphora, conjunctivitis, and usually mucopurulent discharge. Initial diagnosis is made following a complete normal ophthalmic examination (no cause of ocular discomfort found) and the inability of topical fluorescein dye to exit the ventral nasolacrimal puncta (a negative Jones test).

If mucopurulent discharge is present, bacterial culture and sensitivity, and cytology of the discharge should be performed prior to administering additional medications. Following these tests, retrograde and normograde nasolacrimal irrigation should be attempted with the horse tranquilized. If irrigation is successful at clearing an obstruction, copious irrigation of the NLD should then be performed to ensure all debris has been cleared. Excessive force when irrigating the NLD should be avoided so as to prevent damage to the NLD. Unsuccessful NLD irrigation attempts with the horse under standing sedation warrant additional diagnostic testing such as dacryocystorhinography (DCR) via radiology or CT (Fig. 28.28) to locate site of obstruction and assess the surrounding structures. Having the horse anesthetized may assist in removing an obstruction via irrigation, likely from relaxation of facial muscles.

Initially, NLD obstructions can be treated with antibiotic solutions (ideally selected based on culture sensitivity results—but commonly triple antibiotic is used) that contain a topical corticosteroid, which may be beneficial to decrease swelling in the NLD, provided there are no ocular surface contraindications (e.g., a corneal ulcer). If the NLD obstruction is chronic, recurrent, or does not respond to treatment after 2 weeks, DCR or other imaging modalities as mentioned earlier should be done. A 5 French male silastic or plastic canine urinary catheter can be threaded either normograde (from proximal to distal) or retrograde with an attempt to pass through or break up the obstructions. It helps to gently irrigate with eyewash or saline through the catheter as it is passed to help remove debris and to expand the NLD. The catheter should not be forced if resistance is encountered, because severe hemorrhage may develop (Latimer & Wyman, 1984). Once passed, the silastic tubing is sutured in place for 4–6 weeks (Fig. 28.29). Use of oral anti-inflammatory and oral antibiotic medication may be considered in these cases. Correction of primary sinus or dental disease should be done to minimize pressure on the NLD. Creating a new pathway from the canaliculi to the nasal cavity (canaliculorhinostomy) (McIlney et al., 2001) or from the ventral medial conjunctival surface to the maxillary sinus (conjunctivosinostomy) can be done as a last resort but have not been extensively studied in the horse (Giuliano, 2011).
Ulcerative Corneal Disease

A corneal ulcer is present when there is a break in the corneal epithelium, most commonly caused by trauma. The clinical appearance of a corneal ulcer, to the owner, is lacrimation, blepharospasm, photophobia, conjunctival hyperemia, and ocular cloudiness, likely from development of corneal edema, aqueous flare, and possibly hypopyon.

Diagnosis

When evaluating a horse with a possible corneal ulcer, it is important to look carefully for any abnormality that may prevent the ulcer from healing and to eliminate this abnormality. Prior to instilling any medication, the palpebral conjunctiva and bulbar surface of the third eyelid are examined for the presence of a foreign body, the palpebral reflex and corneal reflex are evaluated, and the tear film is examined. A corneal ulcer should be characterized with regard to size, depth, and the presence or absence of cellular infiltration (white or yellow stromal infiltrate). If the ulcer is chronic (e.g., greater than 5–7 days in duration) or if there is cellular infiltrate present, then culture (bacterial and fungal culture and sensitivities; possibly viral culture) should be collected, followed by a Schirmer tear test, then application of fluorescein dye. Cytology of the corneal lesion is particularly helpful in the initial treatment of the ulcer. Following scraping of the equine cornea, cells are transferred to a glass slide and stained (Gram, Giemsa, and Diff-quik stains) to examine for bacteria, fungal hyphae, and predominant cell type that is present (Dwyer, 2011). The presence of gram-negative rods may indicate an infection with Pseudomonas sp. The presence of fungal hyphae is pathognomonic for mycotic keratitis, with Aspergillus sp. and Fusarium sp. being the most frequent corneal pathogens. Mixed bacterial and fungal infections are not uncommon. Common specific types of corneal ulcers seen in the horse include superficial uncomplicated corneal ulcers, indolent ulcers, collagenase and mycotic ulcers, and possibly viral ulcerative keratitis.

Superficial, Uncomplicated Corneal Ulcers

Simple, uncomplicated corneal ulcers have the characteristics of having corneal epithelial cell loss with exposed corneal stroma, are acute in onset, do not have characteristics typical of infection (stromal malacia, cellular infiltrate, stromal defects—see later discussion), and a foreign body is not present. Diagnosis of a superficial, uncomplicated corneal ulcer is based on the history of an acute-onset painful eye and findings on a complete ophthalmic examination of possible focal corneal edema and fluorescein dye retention. Usually, the fluorescein dye retention is intense and uniform across the ulcerated area (Fig. 28.30). It is always recommended to collect bacterial and fungal cultures and examine corneal cytology, even in these suspected uncomplicated ulcers. A superficial uncomplicated corneal ulcer should have no micro-
organisms (on culture or cytology), no cellular infiltrate, no foreign body, and no secondary uveitis. Treatment for an uncomplicated superficial ulcer should consist of a topical broad-spectrum antibiotic every 6 hours (e.g., neomycin, bacitracin, gramicidin, ofloxacin); topical 1% atropine once daily; and treatment of any secondary uveitis, if present (e.g., systemic NSAIDs). Topical corticosteroids are contraindicated in equine ulcerative keratitis, and topical NSAIDs may delay re-epithelialization of the cornea and therefore also are contraindicated.

Complicated Corneal Ulcers
Complicated corneal ulcers are those that do not heal within 72 hours, have a collagenase component (i.e., melting corneal ulcers), have a mechanical obstruction to healing (i.e., foreign body, indolent), are infected (either with bacteria or fungus), and/or are in danger of perforation.

Indolent Corneal Ulcers
Indolent corneal ulcers in horses are similar to small animal indolent ulcers. They are chronic, superficial corneal ulcers where the corneal epithelium will not adhere to the underlying corneal stroma. The characteristic appearance is a superficial ulcer with a redundant epithelial border (Fig. 28.31). Other signs include minimal corneal neovascularization, focal edema, and moderate discomfort. Treatment of indolent ulcers includes searching for the cause (foreign bodies, ectopic cilia, eyelid abnormality, repeated trauma). Indolent ulcer treatment is similar to that for small animals except that grid keratotomy was demonstrated, in one study, not to speed healing of these ulcers in horses (Michau et al., 2003). It is therefore recommended that treatment consist of debridement and use of topical oxy-

tetracycline antibiotic with or without a soft contact lens. If indolent ulcers persist, or develop a plaque-like area in the superficial stroma (Fig. 28.32), then a superficial keratectomy must be performed.

**Fungal/Mycotic Keratitis**
Fungal or mycotic keratitis is particularly common in horses, especially in the southeastern United States or in other areas in which the climate is warm and humid. Infections most commonly involve Aspergillus spp. or Fusarium spp. of fungi, but other fungal organisms have been reported. Most commonly, fungal keratitis appears clinically as a worsening, subacute keratitis that generally appears very painful, with severe secondary uveitis. A typical history includes the use of previous topical corticosteroids and/or an ulcer present for 7–14 days. There are four common clinical presentations of fungal keratitis: superficial ulcerative, stromal ulcerative, stromal nonulcerative, and deep stromal-endothelial nonulcerative (Fig. 28.33A–D) (Gaarder et al., 1998). Diagnosis of fungal keratitis is made by history, clinical appearance, and demonstration of the organisms on cytology or culture (Fig. 28.34).

In general, the diagnosis of fungal keratitis carries a poor prognosis and requires long-term aggressive therapy. Treatment must be directed at killing the fungus, killing secondary bacteria, and controlling secondary uveitis. Because most fungal ulcers also have a bacterial component, treatment is initially similar to severe midstromal ulcers (frequent topical antibiotics, atropine). A antifungal therapy needs to be started early, be aggressive, and involve both topical and systemic therapy. A combination of 1% voriconazole (VFend®, Pfizer, New York, NY) topically every 1–4 hours and oral fluconazole (14 mg/kg starting dose on day 1, followed by 5 mg/kg/day each subsequent day) is the treatment protocol used at North Carolina State University. Natamycin (Pimaricin®, Alcon Laboratories, Ft Worth, TX) is the only commercially
available ophthalmic antifungal agent and can be added to the voriconazole treatment. In resistant cases, subconjunctival injections of amphotericin B (0.2 mL of a 5-mg/mL solution administered subconjunctivally every 48 hours, generally for 3 doses) has also been used, but it can be irritating and the effectiveness is unknown. Client education is also very important because most cases of fungal keratitis will take 4–8 weeks to heal and will heal by corneal vascularization with a scar formation.

Surgical treatment of fungal keratitis is generally indicated in most cases, but especially when there is no response to medical management, if a corneal furrow develops, or if the lesion is very deep in the cornea. The development of a corneal furrow surrounding the area of keratitis (Fig. 28.35) in a superficial or stromal type of fungal keratitis generally indicates a particularly poor prognosis and suggests that rapid necrosis of the cornea is developing. When a furrow is observed, then emergency surgery is needed to remove the infected cornea and place a corneal or conjunctival graft or both (Fig. 28.36). Deep fungal keratitis lesions are best managed by a penetrating keratoplasty, lamellar keratoplasty, or a deep lamellar endothelial keratoplasty. See Chapter 18 on corneal surgical procedures or a recent comprehensive description of equine corneal surgery by Dr. Alison Clode (Clode, 2011).

**Bacterial Keratitis** Bacterial keratitis commonly induces blepharospasm, epiphora, ocular discharge, photophobia, and corneal opacification. However, unlike uncomplicated corneal ulcers, bacterial ulcers generally have stromal involvement that produces marked edema, cellular infiltration, and deepening of the ulcer bed, potentially accompanied by keratomalacia, or “melting” (Fig. 28.37). Anterior uveitis may be severe, manifesting as miosis, flare, hypopyon, and hypotony. Treatment should be aggressive with frequent use of broad-spectrum topical antibiotics (e.g., moxifloxacin [Vigamox, Alcon, Fort Worth, TX] every 1–2 hours), topical atropine (q8–12 hours), systemic NSAIDs, and an anticollagenase medication to counteract the keratomalacia. Commonly used anticollagenase medications include autogenous serum (q1–2 hours),...
There are four common clinical presentations of fungal keratitis: A. superficial ulcerative (fluorescein dye has been applied); B. stromal ulcerative; C. stromal nonulcerative; and D. deep stromal-endothelial nonulcerative.

Septated hyphae of aspergillus are visible on this cytology of a horse with fungal keratitis. PAS stain, 100× magnification.

A corneal furrow, or “moat,” indicating a deepening of the ulceration and sloughing of central necrotic corneal tissue, is suggestive of rapid progression of the disease, and surgery is indicated to prevent perforation.
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Superficial Punctate Keratitis

Superficial punctate keratitis is characterized by multifocal, lace-like epithelial to subepithelial corneal opacities some of which may be fluorescein positive with mild corneal edema (Fig. 28.39). Blepharospasm may be noted, but many horses are asymptomatic. The cause is unknown, but viral agents, specifically equine herpesvirus (EHV) type 2 and 5, and immune-mediated causes have been proposed (Borchers et al., 2006; Clode, 2011). Treatment recommendations vary and include topical antibiotic-corticosteroid, topical cyclosporine (CsA), and/or topical antiviral therapy. Although the condition responds well to topical corticosteroids, recurrence is common.
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Corneal Perforation/Laceration

Once the cornea perforates, either as a result of a progressive corneal ulcer or penetrating trauma, the prognosis for vision and saving the globe in general is poor. The prognosis is worse if the corneal laceration involves the limbus; significant hyphema is present; the lens is perforated; if a large uveal prolapse through the incision is present; or if a dazzle and consensual PLRs are absent. Examination of perforated eyes should include complete ophthalmic examination (including evaluation of dazzle and consensual PLRs) with the horse adequately tranquilized and eyelid nerve blocks performed to ensure that no further damage is done as a result of the examination. If the posterior segment (vitreous and retina) of the eye cannot be visualized on the ophthalmic examination, then an ultrasound should be done. If the vitreous is hyperechoic (i.e., blood or cellular infiltrate) or a retinal detachment is observed on the ultrasound (Fig. 28.40), then the prognosis for return to vision is very poor. Repair of the laceration or correction of the perforation is recommended if the lens and posterior segment are normal. Enucleation should be done if there is no consensual PLR, a large uveal prolapse is present, or if ultrasound shows significant blood in the vitreous or retinal detachment.

Figure 28.38. An amnion membrane graft has been used to treat a progressive, "melting" ulcer. A. Keratomalacia associated with a bacterial infection in a horse. B. Application of a double layer of amnion membrane after keratectomy of the keratomalacia. C. Clinical appearance approximately 4 months after surgery.

Figure 28.39. Superficial punctate keratitis characterized by multifocal, lacelike epithelial to subepithelial corneal opacities.
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Nonulcerative Equine Corneal Diseases

There are four general categories of nonulcerative corneal diseases in the horse: corneal edema, pigmentation, scarring, and cellular and noncellular infiltrate. These lesions are similar to small animal corneal disease except for specific conditions.

Corneal Stromal Abscesses

This lesion is most commonly seen in the horse and is the most common disease in the cellular infiltrate category of nonulcerative corneal diseases. A penetrating corneal injury causes an inoculation of microorganisms or foreign material into the corneal stroma. The overlying corneal epithelium heals. One to three weeks later, an abscess forms in the stroma. Clinical appearance of stromal abscess varies greatly depending on severity; however, all have a creamy-yellow cellular corneal infiltrate (Fig. 28.41). Most, if chronic enough, have deep corneal vascularization. Characteristically, most horses have severe blepharospasm and usually severe secondary uveitis. Surrounding most abscesses is a variable amount of corneal edema. Diagnosis of corneal stromal abscess is usually by clinical appearance and history. A culture and cytology would be helpful, but unfortunately, this frequently requires surgery to get below the intact corneal epithelium. In our practice, these stromal abscesses are due to fungal infections. Treatment depends on the level of vascularization. If the lesion is completely vascularized, then surgery (e.g., keratectomy and conjunctival graft) is usually indicated to debride and obtain a culture. Deep endothelial plaques that are usually fungal in origin do best with penetrating keratoplasty.

Immune-Mediated Keratitis

Primary nonulcerative corneal inflammatory diseases where the etiopathogenesis is thought to be immune-mediated have
been described as IMMK (Gilger et al., 2005; Matthews, 2000a; Matthews & Gilger, 2009, 2010). A diagnosis of IMMK is made if there is a progressive or chronic (>3 months in duration) nonulcerative or recurring corneal opacity with mild to moderate signs of cellular infiltrate, corneal vascularization, and corneal edema (Gilger et al., 2005; Matthews, 2000a). IMMK is characterized by having only mild signs of ocular discomfort (i.e., only mild epiphora and/or slight blepharospasm). Other characteristic features include absence of secondary uveitis, absence of microorganisms on culture, cytology, or histopathology, and clinical improvement with anti-inflammatory medications (Gilger et al., 2005; Matthews, 2000a). In most instances where IMMK is suspected, ocular cytology and culture collection should be attempted to rule out an infectious cause of the lesions. If the diagnosis is still in doubt, a superficial keratectomy/biopsy should be considered for routine histopathology, special organism staining, and if possible, immunostaining and polymerase chain reaction (PCR) testing for presence of microbial or viral DNA.

The most common clinical presentation of IMMK is superficial stromal disease (45% of cases), with midstromal (27% of cases) and endothelial disease being less common (23% of cases), and epithelial disease being much less common. Unilateral presentation of IMMK is most common although bilateral cases do occur. There is no breed or gender predilection, and the average age of diagnosis of all clinical manifestations in the United States was approximately 12 years (Gilger et al., 2005).

**Epithelial IMMK** Epithelial IMMK is characterized by multifocal punctate areas in the ventral and ventral-paracentral corneal epithelium (Fig. 28.42). These lesions are not ulcerated but may have very faint surrounding cellular infiltrate. Most commonly, there is no corneal vascularization, and the horse has no signs of discomfort. A viral etiology needs to be ruled out, in particular EHV 2 or 5.

**Superficial IMMK** Horses with superficial stromal IMMK are characterized by a nonpainful, waxing, and waning chronic corneal opacity. The opacity consists of a subepithelial, superficial, white to yellow stromal cellular infiltrate that is surrounded by superficial, branching corneal vascularization (Fig. 28.43). Superficial IMMK is most commonly located in the ventral paracentral cornea, followed by ventral perilimbal corneal location, then a central location. Superficial IMMK can usually be controlled with topical corticosteroids and CsA. Typically, the steroids are tapered after clinical resolution of the corneal cloudiness with continuing the topical CsA at once a day to help prevent recurrence (Gilger et al., 2005). Superficial keratectomy, however, may prevent recurrence, as seen in 13 eyes of 12 patients in a recent study (Pate et al., 2011).

**Midstromal IMMK** Midstromal IMMK is clinically similar to superficial IMMK except that the location of the vascularization and cellular infiltrate is in the central layers of the corneal stroma. Also, the cellular infiltrate is denser, resulting in a more opaque cornea than superficial IMMK (Fig. 28.44). Because of the deeper corneal location, vascularization is typically less branching and more straight than that observed in superficial IMMK. Most commonly, midstromal IMMK is located in the lateral paracentral, ventral, or central cornea. Treatment is similar to superficial IMMK but it is generally less responsive to therapy. For midstromal IMMK in horses, a superficial keratectomy may be beneficial for the long-term control of the disease. It is possible that this therapy is beneficial because of the surgical removal of the autoantigen(s) in the cornea, and thus eliminating the source of inflammation (Gilger et al., 2005; Pate et al., 2011).
Endothelial Immune-Mediated Keratitis

Endothelial IMMK, or endotheliitis, is characterized by a chronic, slowly progressive, nonpainful, diffuse ventrolateral or ventral full-thickness area of corneal edema (Fig. 28.45). When examined with a slit lamp biomicroscope, dark cellular infiltrate can usually be observed at the edge of the corneal edema at the level of the endothelial cells. Occasionally, with chronic disease, bullous keratopathy may develop, resulting in focal or multifocal superficial corneal ulcers. Horses with endothelial IMMK have normal intraocular pressure and no aqueous flare or miosis, so glaucoma and uveitis are not likely primary causes. Deep corneal abscesses may appear similar, but these horses are generally painful and have secondary uveitis. Endothelial IMMK in horses is slowly progressive and, in general, is poorly responsive to medications (Gilger et al., 2005). Topical steroids and CsA therapy are not generally effective; however, recently, there have been anecdotal reports of response of endothelial IMMK to potent topical nonsteroidal anti-inflammatory medication (e.g., bromfenac) (Clode, 2011).

**Eosinophilic Keratitis**

Eosinophilic keratitis (EK) is a condition that is being seen more frequently in the past 20 years (Brooks, 2004; Ramsey et al., 1994; Yamagata et al., 1996). Horses with EK have chronic corneal pathology (± corneal ulcers) with moderate discomfort. The clinical appearance of this condition is either a unilateral or bilateral white plaque on the surface of the cornea with surrounding corneal edema (Fig. 28.46) or a superficial stromal, perilimbal yellow infiltrate. The most common location is the cornea located under the third eyelid, followed by the ventral-medial and ventral-lateral cornea. The white plaques are almost 100% eosinophils when examined cytologically (Dwyer, 2011). Eosinophilic keratitis seems to occur most commonly in the early or late summer months and develops in well-managed horses given appropriate vaccinations and deworming protocols. Several animals in a barn may be affected, some with only conjunctivitis characterized by a white, cheesy exudate. Eosinophilic keratitis is generally self-limiting and will resolve over 8–12 weeks. However, several treatments have been suggested to enhance or speed healing, including topical corticosteroids, topical nonsteroidal anti-inflammatory medications, topical mast cell stabilizers, and superficial keratectomy.

**Histopathology**

Histopathology of non-eosinophilic, superficial, or midstromal IMMK revealed stromal fibrosis, vascu-
Corneal Neoplasia

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the most common tumor of the equine cornea and is most commonly, but not exclusively, observed in horses with minimal ocular and periorcular pigmentation such as Appaloosas, Quarter Horses, Paints, Haflingers, and draft horses (Belgians, Shires, Clydesdales). The disease most commonly develops between 9 and 13 years, has no gender predilection, and can be bilateral. Other factors associated with increased prevalence include heredity, high levels of solar radiation and UV light exposure, increasing longitude and altitude, and decreasing latitude (Dugan et al., 1991a).

Corneal SCC originates from the cornea, conjunctiva, or limbus, with the lateral limbus the most common location. Corneal SCC most commonly appears nodular, elevated, white-pink, and fleshy (Fig. 28.47). Affected horses generally demonstrate minimal discomfort (i.e., blepharospasm, epiphora), no uveitis, but commonly high amounts of mucopurulent ocular discharge.

Treatment involves surgical excision of the mass (e.g., superficial keratectomy) followed by an appropriate corneal adjunctive therapy. The most commonly used corneal adjunctive therapies include strontium-90 beta irradiation, carbon dioxide laser, cryotherapy, and topical chemotherapy (5-fluorouracil or mitomycin-C). See the recent chapter by Clode et al. (2011) for a complete description of these adjunctive therapy techniques and associated nonrecurrence rates.

Other neoplasms involving the cornea are rare but include mast cell tumors, melanoma, LSA, and vascular neoplasms, such as hemangioma, hemangiosarcoma, lymphangioma, and lymphangiosarcoma (Bolton et al., 1990; Clode, 2011; Rebhun & Del Piero, 1997).

Diseases of the Equine Uvea

Diseases of the equine uvea are among the most common ocular problems in horses—mainly equine recurrent uveitis (ERU). Congenital uveal defects, primary uveitis, uveal cysts, and neoplasia are also common in the horse eye. Some, but not all, of these defects may result in vision or globe loss. A natomy and physiology of the equine uveal tract is reviewed in Chapters 2 and 3. For more information on diseases of the equine uvea, uveitis, and ERU, including in-depth details of medical and surgical management of these diseases, please see these recent reviews (Gilger & Deeg, 2011; Hollingsworth, 2011).

Congenital Defects of the Equine Uvea

Congenital defects of the equine uvea are relatively uncommon and have included aniridia, which is the lack of or only partial iridal tissue present, and anterior segment dysgenesis. Aniridia, which is characterized clinically by the visualization of ciliary body processes and edge of the lens has been reported to be inherited as an autosomal dominant trait and observed in the Belgian Draft horse, the Quarter horse, a Thoroughbred, and a Thoroughbred/Welsh cross (Eriksson, 1955; Joyce, 1990). Anterior segment dysgenesis is characterized variably by observation of persistent pupillary membranes and may be a component of the MCOA syndrome of Rocky Mountain Horses (Andersson et al., 2008; Ramsey et al., 1999a, 1999b). Iris colobomas, both typical and atypical, may occur uncommonly in horses but should be differentiated from iris hypoplasia, which is an iris defect commonly observed in lightly pigmented irises (Fig. 28.48).

Uveal Cysts

The corpora nigra, or granula iridica, which are vacuolated extensions of the posterior iris epithelium, normally extend from the dorsal and ventral pupillary margin into the anterior chamber. When the corpora nigra becomes cystic, its normally roughened appearance becomes smooth and spherical (Fig. 28.49). Most cysts are small and do not cause significant interference with vision. However, some cysts, depending on their location, may inhibit the visual field, especially when the horse is in bright light and the pupil is miotic. Differential diagnoses include inflammatory or neoplastic changes to the iris. Although ultrasonography could be used to differentiate cystic corpora nigra from inflammatory or neoplastic...
Iridal and ciliary body cysts are believed to originate from failure of the two layers of the neuroectoderm to fuse in the area of the iris and ciliary body, respectively. These translucent cysts may enlarge but rarely obstruct vision and can be associated with the MCOA syndrome of Rocky Mountain Horses (Ramsey et al., 1999b). They do need to be differentiated from inflammatory or neoplastic masses and usually can be differentiated from these more solid masses by ophthalmoscopy or ultrasonography.

**Primary Uveitis**

Primary, acute uveitis (inflammation of the uveal tract) must be distinguished from the chronic, recurrent form (ERU). It is very important that the clinician not assume that every case of uveitis in a horse is ERU. As the name suggests, ERU is characterized by multiple, recurrent episodes of uveitis, whereas acute uveitis is limited to a single event. There is no age, breed, or sex predisposition for acute anterior uveitis. Typical clinical signs associated with acute anterior uveitis are all due to damage of the anterior uvea and subsequent compromise of the blood-aqueous barrier and include photophobia, blepharospasm, corneal edema, aqueous flare, hypopyon, miosis, vitreous haze, and chorioretinitis (Fig. 28.50) (Hollingsworth, 2011).

The initial diagnosis of anterior uveitis is based on clinical signs. There is a large list of potential causes of anterior uveitis in horses, including corneal disease and trauma. Several organisms have been associated with the initiation of equine uveitis. In some instances, but not all, the uveitis associated with these systemic infections may develop into immune-medicated uveitis or ERU. One of the most commonly associated systemic diseases associated with uveitis is leptospirosis (Dwyer et al., 1995; Faber et al., 2000; Sillerud et al., 1987). Roberts demonstrated that ERU could develop after primary infection (and acute uveitis) of leptospirosis; however, ERU typically did not develop until 1 year after the systemic infection (Roberts, 1963; Roberts et al., 1952). Onchocerciasis is another systemic disease associated with equine uveitis. This disease is much less common now with

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**Figure 28.48.** A. Typical iris coloboma, ventral notch-like defect, in a horse. (Photograph courtesy of Dr. Riccardo Stoppini.) B. Iris hypoplasia, an iris defect commonly observed in lightly pigmented irises.

**Figure 28.49.** Multiple cystic corpora nigra of the upper and lower iris. Cystic corpora nigra have a smooth and spherical appearance.
Section IV

2011). Fortunately, recent advances in the treatment of horses with ERU have led to the successful management of this disease.

ERU is characterized by episodes of intraocular inflammation that develop weeks to months after an initial uveitis episode subsides; however, not every case of primary equine uveitis will develop into ERU. Horses can develop ERU at any age, but the peak time of the initial uveitis episode is 4–6 years, a time when most horses are at or nearing their prime performance years.

Clinical Signs of ERU

Three main clinical syndromes are observed in ERU: the “classic,” “insidious,” and “posterior” type of ERU. Classic ERU is most common and is characterized by active inflammatory episodes in the eye followed by periods of minimal ocular inflammation. The acute, active phase of ERU predominantly involves inflammation of the iris, ciliary body, and choroid, with concurrent involvement of the cornea, anterior chamber, lens, retina, and vitreous (Fig. 28.51). After several weeks, typical (shorter with appropriate therapy) signs of active, acute uveitis can recede, and the disease enters a quiescent or chronic phase. After variable periods of time, the quiescent phase is generally followed by further and increasingly severe episodes of uveitis. It is the recurrent, progressive nature of the disease that is responsible for the development of cataract, intraocular adhesions, and phthisis bulbi (Fig. 28.52). In the insidious type of ERU, however, the inflammation never completely resolves, and a low-grade inflammatory response continues that leads to progression to chronic clinical signs of ERU (Fig. 28.53). Frequently, these horses do not demonstrate overt ocular discomfort, and owners of these horses may not be aware of the disease until it is advanced.

Equine Recurrent Uveitis

Equine recurrent uveitis (ERU) (also known as moon blindness, iridocyclitis, and periodic ophthalmitis) is a major ophthalmic disease of the horse and is the most common cause of blindness in this species (Gilger & Deeg, 2011). This immune-mediated, panuveitis has approximately a 2%–10% prevalence rate in horses in the United States (Gilger & Deeg, 2011). The inciting cause for the uveitis is the inflammatory reaction associated with dead and dying onchocerca larvae in the cornea after treatment with an anthelmintic. Other systemic infectious causes of uveitis include Streptococcus equi, brucellosis, toxoplasmosis, EHV-1, EHV-2, equine viral arteritis, para-influenza type 3, and generalized septicemia, endotoxemia, neoplasia, tooth root abscess, or trauma.

Diagnostic testing for primary equine uveitis may help determine the underlying cause of a specific episode of acute anterior uveitis. These would include complete blood count, serum chemistry profiles, serologic tests for specific infectious causes such as leptospirosis, and conjunctival biopsies for detection of Onchocerca microfilaria. For leptospirosis, concurrent aqueous humor and serum serology is recommended to determine if there is intraocular production of anti-leptospiral antibodies (Gilger et al., 2008). Analysis of intraocular organism DNA, by PCR, should also be done when available. A positive C value (intraocular titer greater than serum titer) and detection of organism DNA is strongly suggestive that the organism is playing a causative role in the uveitis (Gilger et al., 2008).

Treatment of primary uveitis is a combination of specific treatment of the underlying cause of the inflammation and nonspecific treatment of the uveitis. See treatment of ERU in a later discussion for nonspecific treatment of uveitis.

Figure 28.50. Horse with acute anterior uveitis with clinical signs of photophobia, blepharospasm, corneal edema, aqueous flare, hypopyon, and miosis.

Figure 28.51. Acute, active uveitis episode of equine recurrent uveitis. There is miosis, aqueous flare, fibrin in the anterior chamber, and mild corneal edema present.
horses may not recognize the presence of disease until a cataract forms or the eye becomes blind. This type of uveitis is most commonly seen in Appaloosa and draft breed horses. The posterior type of ERU has clinical signs existing entirely in the vitreous and retina, with little or no anterior signs of uveitis. In this syndrome, there are vitreal opacities, retinal inflammation (± detachment), and degeneration (Fig. 28.54). This is the least common type of uveitis in the United States (Gilger & Deeg, 2011).

Typical clinical signs of active ERU are similar to signs of acute primary uveitis including photophobia, blepharospasm, corneal edema, aqueous flare, hypopyon, miosis, vitreous haze, and chorioretinitis (see Fig. 28.53). Clinical signs of chronic ERU include corneal edema, iris fibrosis and hyperpigmentation, posterior synechia, corpora nigra degeneration (smooth edges), miosis, cataract formation, vitreous degeneration and discoloration, and peripapillary retinal degeneration (Fig. 28.55). Either type of ERU (classic or insidious) can have either predominantly anterior (cornea, iris, lens, and ciliary body inflammation) or posterior (ciliary body, vitreous, and chorioretinal inflammation) segment involvement. Ultimately, even with aggressive treatment, many horses develop a chronically painful eye and blindness as a result of secondary cataract, synechia (intraocular adhesions), scarring, glaucoma, and development of phthisis bulbi (see Fig. 28.55).

**Pathogenesis of Recurrent Episodes of Uveitis**

ERU is a nonspecific immune-mediated disease that results in recurrent or persistent inflammatory episodes in the eye. To diagnose the syndrome of ERU, the clinician must differentiate it from non-ERU primary uveitis. As mentioned above, there is a long list of infectious and noninfectious agents responsible for causing primary uveitis in the horse. Although
any of these causes of uveitis may allow horses to develop ERU, not all of these acute uveitis cases will develop into ERU.

Current concepts to explain the origin and perpetuation of autoimmune diseases include molecular mimicry, bystander activation, and epitope spreading (Deeg et al., 2006a, 2006b; Gilger & Deeg, 2011). These mechanisms do not exclude each other but could appear together and even interact. Epitope spreading is defined as the diversification of epitope specificity from the initial focused, dominant, epitope-specific immune response, directed against a self or foreign protein to cryptic epitopes on that protein (intramolecular spreading) or other proteins (intermolecular spreading) (Deeg et al., 2006a; Gilger & Deeg, 2011). In most autoimmune diseases, several autoantigens participate in the pathogenesis (Deeg et al., 2006b), and epitope spreading is accountable for disease induction, progression, and inflammatory relapses (Deeg et al., 2006a). The shifts in immunoreactivity could account for the remitting/remitting character of ERU. Genetic background and antigens encountered influence the direction and extent of epitope reactivity and probably play an important role in the heterogeneous clinical manifestations of ERU (Gilger & Deeg, 2011).

Epitope spreading in autoimmune diseases results in the detection of an increasing array of autoantibodies against various target antigens. Initial studies have confirmed epitope spreading in a high percentage of cases of ERU (Deeg et al., 2006a). A reactive immune response to cellular retinaldehyde-binding protein (CRALBP) (Deeg et al., 2006b) was detectable in a large percentage of ERU cases. CRALBP was detected as a novel uveitis autoantigen. CRALBP and interphotoreceptor binding protein (IRBP) demonstrated 100% uveitogenicity in the horse, and both autoantigens were capable of causing recurrent uveitis in the horse (Deeg et al., 2006b), closely resembling the clinical course of spontaneous ERU.

Histologic Features of ERU

In chronic ERU, infiltration of the uveal tract with lymphocytes and macrophages was most evident in the ciliary body and base of the iris. Lymphoid follicles are occasionally present in the base of the iris. Loss of tissue structure/destruction was evident in the ciliary processes. Dubielzig (Dubielzig et al., 1997) noted several histologic distinguishing features of ERU globes: a nonecellular hyaline membrane adhered to the inner surface of the nonpigmented ciliary epithelium, linear intracytoplasmic inclusions in the nonpigmented ciliary epithelium (Cooley et al., 1990), and an influx of lymphocytes and plasma cells into the ciliary body. The choroid also revealed infiltration of mononuclear cells, with overlying retinal degeneration. Previous study of ERU eyes in our laboratory revealed infiltration of the uveal tract with lymphocytes, plasma cells, and macrophages are most evident in the ciliary body and base of the iris. Loss of tissue structure (destruction) is most evident in the ciliary processes. Infiltrating lymphocytes were predominantly CD4+ T cells (e.g., 48% CD4+ and 18% CD8+ in the ciliary body stroma), as determined by immunohistochemistry, and few inflammatory cells were observed in the normal eyes (Gilger et al., 1999).

Clinical Diagnosis of ERU

The clinical diagnosis of ERU is based on the presence of characteristic clinical signs (corneal edema, aqueous flare, posterior synechiae, corpora nigrina atrophy, cataract formation, vitreous degeneration, retinal edema or degeneration with or without signs of associated ocular discomfort such as episclera, periorcular swelling, and blepharospasm) and history of documented recurrent or persistent episodes of uveitis. Both features are required to make this clinical diagnosis, especially to differentiate from non-ERU uveitis and other causes of recurrent or persistent ocular inflammation, such as herpesvirus keratitis or IMMK.

Treatment of Equine Recurrent Uveitis

The main goals of therapy for ERU are to preserve vision and reduce and control ocular inflammation in an attempt to limit permanent damage to the eye. In horses where a definite inciting cause has been identified, treatment is directed at eliminating the primary problem, and initial tests to isolate an inciting agent are performed. These tests may consist of a complete blood count, biochemistry profile, conjunctival biopsy, and serology for bacterial and viral agents. Due to the likely immune-mediated underlying pathogenesis, however, an inciting cause cannot be identified in most cases; therefore, therapy is directed at the alleviating of symptoms and reducing ocular inflammation.

Medical Therapy for ERU

Because vision loss is a common long-term manifestation of ERU, initial therapy must be aggressive. In acute cases, treatment in the form of systemic and local therapy consisting of antibiotics, corticosteroids, and anti-inflammatory drugs is used. Initial therapy is instituted for at least 2 weeks, and should be tapered off over an additional 2 weeks after the resolution of clinical signs. In severe cases, local subconjunctival or intravitreal injections of corticosteroids may be indicated as an adjunct to therapy (Yi et al., 2008). If used, these injections must be used with the understanding that they will predispose the horse to infectious keratitis, especially fungal keratitis. In most instances, a subpalpebral lavage catheter is placed to facilitate delivery of topical medications. Most horses respond well to intermittent topical and/or systemic therapy of their active episodes of ERU and in many cases, observant owners can minimize an active episode by initiating therapy at the onset of clinical signs. Some horses, however, do not respond to traditional therapy and may experience frequent recurrences of uveitis.

Topical corticosteroids are most commonly used to decrease inflammation. Prednisolone acetate 1% and dexamethasone HCl 0.1% are the most commonly used topical corticosteroids. Both medications have excellent ocular penetration. Frequency of therapy varies according to the severity of the disease and ranges from hourly topical application to
once-daily application. Dexamethasone is used most often in clinical situations because it is available in an ointment form and is inexpensive. Topical corticosteroids have side effects, including the ability to potentiate infections and collagenase enzymes (melting of the cornea), delaying epithelialization of corneal ulcers and possibly the potentiation of calcific band keratopathy.

Topical NSAIDs (e.g., 0.03% flurbiprofen, 0.09% bromfenac sodium, or 0.1% diclofenac sodium) can also be used. Their main advantages are that they can be administered without concern for potentiating infections, but they do delay epithelialization of corneal ulcers. Although bromfenac is a very potent NSAID compared to the others, in general, the anti-inflammatory effect of topical NSAIDs is much less than topical dexamethasone and prednisolone.

Systemic therapy is the most potent therapy for management of ERU. Oral, intramuscular, or IV flunixin meglumine is one of the most potent anti-inflammatory medications for the eye. Phenylbutazone and aspirin are much less effective. Systemic dexamethasone or prednisolone are also effective but generally are only recommended in severe cases that will not respond to other anti-inflammatory medication (Gilger & Michau, 2004).

Traditional treatments used for ERU (i.e., corticosteroids and non-steroidal anti-inflammatory medications) are aimed at reducing inflammation and minimizing permanent ocular damage at each active episode. They are not effective in preventing recurrence of disease. Other medications used to prevent or decrease severity of recurrent episodes, such as aspirin, phenylbutazone, and various herbal treatments have limited efficacy and potential detrimental effects on the gastrointestinal and hematologic systems when used chronically in the horse.

**Immunosuppressive Drugs**

Cyclosporine Cyclosporine (CsA) is a 1.2-kD cyclic peptide that blocks the transcription of interleukin-2 production through the inhibition of calcineurin, a protein of the transcription factor NFATc (Nuclear Factor of Activated T cell, cytoplasmic). CsA may be the ideal drug to prevent the activation of T lymphocytes and recurrence of uveitis. However, CsA is hydrophobic and does not penetrate into the eye when applied topically, and the pharmacokinetics, toxicology, and cost of preventative systemic treatment in horses has not been evaluated.

Ocular sustained-release medication devices or implants have many advantages over more traditional methods of drug administration to the eye because they can deliver constant therapeutic levels of drug directly to the site of action, bypassing some of the blood–ocular barriers, and they can eliminate the need to rely on owners to treat their horse. Release rates are typically well below toxic levels of the drug; therefore, higher concentrations of the drug are achieved in the eye without any systemic side effects. Devices also have the benefit of being more convenient for the patient and reducing the risk involved with frequent intravitreal injections (Davis et al., 2004).

CsA-releasing devices, placed in or near the suprachoroidal space, have been used in horses with chronic ERU for nearly 10 years (Fig. 28.56) (Gilger et al., 2000a, 2000b, 2001, 2006). Recently, data from 186 eyes of 156 horses that had CsA devices implanted for ERU were reviewed (Gilger et al., 2010b). Horses with ERU from six centers in the United States and two in Europe had the CsA device implanted. Mean follow-up was 29 months (1–7 years). Horses with implants had significantly fewer flares after surgery (mean 0.05 flares/month) than prior to implantation. Overall, 79.9% were visual at the last follow-up time. Only three eyes required a repeat implant, all 4 years or longer after the first implant. These results suggested that the suprachoroidal placement of the CsA device resulted in excellent long-term control of ERU (Gilger et al., 2010b). Because recurrences of inflammation did not increase after the theoretical depletion of the CsA (approximately 3 years), it is possible that autoreactive T cells may undergo anergy after a period of time in the presence of CsA, after which recurrence of disease will not occur.

Rapamycin Rapamycin (RAPA) is a carbocyclic lactone-lactam microlide antibiotic immunosuppressive drug that is similar in structure to CsA but is not a calcineurin inhibitor. RAPA causes the suppression of T-lymphocyte activation and proliferation by preventing the cell cycle from progressing from G1 to the S phase (Sehgal, 1998). Intravitreal injection of RAPA in normal horses was well tolerated without signs of toxicity (Douglas et al., 2008). The lack of ocular toxicity, potency, and positive effect on experimental and clinical uveitis suggests that RAPA may be an excellent candidate for local treatment of ERU. In a preliminary study, 10mg of RAPA in PEG-400 was injected intravitreally into advanced...
stage, chronic ERU eyes. With a mean follow-up of over 14 months, it was found that 10 of 13 (77%) RAPA-injected eyes were comfortable and only 3 eyes had frequent or persistent uveitis flares (Gilger et al., 2010a). Further study is needed to determine the effectiveness of intravitreal RAPA for long-term treatment of ERU.

Vitrectomy  Pars plana vitrectomy (PPV) has been used in the management of chronic endogenous uveitis in humans and horses (Fruhauf et al., 1998; Gilger & Spiess, 2006), with the goal to improve vision by clearing the media or removing membranes and decreasing recurrent episodes of inflammation. PPV for ERU is used commonly in central Europe, but rarely in the United States. PPV may have a beneficial effect on the clinical course of chronic endogenous posterior uveitis by physically removing any resident inflammatory cells with the vitreous (Fruhauf et al., 1998; Gilger & Spiess, 2006). Success has been reported in leptospiral-induced ERU although complications (i.e., vitreal hemorrhage, cataract formation, retinal detachment) can occur following PPV.

Uveal Neoplasia

Melanoma

Although melanoma is relatively rare in horses, it usually occurs in gray or partially gray horses between 5 and 10 years of age. The most common site of origin is the iris, but melanomas arising from the ciliary body have been reported. Common clinical signs include appearance of a dark mass extending from the iris into the anterior chamber (Fig. 28.57), or if advanced, a dark mass filling the anterior chamber with focal corneal edema associated with contact with the posterior surface of the cornea. Masses may also appear pink and fleshy in horses with lightly colored irises. Early in the course of the disease, there are no signs of discomfort; however, as the neoplasm gets larger, common clinical signs include blindness, blepharospasm, epiphora, diffuse corneal edema, and buphthalmos (Hollingsworth, 2011).

Treatment options are limited, and the prognosis for saving the eye is generally poor, but better if the lesion is small. Treatments include a sector iridectomy, diode or surgical Nd:YAG laser therapy, or use of cimetidine. Oral cimetidine (dose 2.5 mg/kg body weight, administered orally [PO] every 8 hours) has been used to shrink nonocular melanomas in horses, but no studies have been done to determine the effect of cimetidine on uveal masses (Goetz et al., 1990). Corneal edema and secondary uveitis are common adverse effects of laser therapy. Generally, intraocular melanoma in horses has been treated by enucleation or exenteration.

Lymphoma

Lymphoma commonly involves the eye and adnexa, and in one study, 27% of horses with confirmed systemic lymphoma had ocular disease. In these horses, eyelid swelling and inflammation were the most common ocular signs followed by involvement of the anterior uvea (Rebhun & Del Piero, 1997). Signs associated with anterior uveal manifestation of systemic lymphoma are nonspecific uveal inflammation and include blepharospasm, episcleral injection, corneal edema and vascularization, aqueous flare, hypopyon, hyphema, iridal congestion, and swelling (Fig. 28.58). Frequently, these nonspecific signs are accompanied by a history of chronicity, poor response to anti-inflammatory medication, and nonspecific signs of...
systemic disease such as fever, respiratory disorders, weight loss, peripheral lymphadenopathy, and anemia (Germann et al., 2008b; Rebhun & Bertone, 1984). Intraocular lymphoma cannot usually be differentiated from other causes of primary uveitis based on ocular signs. The diagnosis of systemic lymphoma should be considered in any horse with anterior uveitis, especially when it is accompanied by systemic signs of illness such as fever, weight loss, lethargy, and swollen lymph nodes (Hollingsworth, 2011). The diagnosis of lymphoma can be confirmed by identification of neoplastic lymphocytes from samples (i.e., aspirates/biopsy) of lymph nodes or skin nodules; however, definitive diagnosis can be challenging, and prognosis is poor (Hollingsworth, 2011).

**Clinical Features of Equine Glaucoma**

**Primary Glaucoma**

Horses with primary glaucoma most commonly present with partial or diffuse corneal edema (Fig. 28.59). These eyes may or may not be painful. Early in the disease process, vision and the pupil size may be normal. Intraocular pressure can range from 35–80 mmHg. With chronic primary glaucoma, vision decreases, the cornea becomes diffusely edematous, and other signs of chronic intraocular inflammation may become evident (e.g., diffuse corneal edema, corneal striae, retinal and optic nerve degeneration) (Fig. 28.60). In general, however, the horse tends to lose vision much later in the disease process compared to dogs and humans (Utter & Brooks, 2011; Wilkie, 2010; Wilkie & Gilger, 2004). An increased size of the eye (greater than 40–45 mm anterior to posterior) and lens subluxation can also occur late in the disease.

**Secondary Glaucoma**

The most common cause of glaucoma in horses is chronic or recurrent uveitis (a type of secondary glaucoma) (Gilger & Deeg, 2011; Utter & Brooks, 2011). Historically, these horses have multiple episodes of intraocular inflammation followed by a severe unrelenting bout of ocular cloudiness and discomfort (as a result of the development of glaucoma) that does not respond to traditional uveitis therapy. These eyes have high intraocular pressures (40–80 mmHg), diffusely edematous corneas, and signs of chronic intraocular inflammation, such as posterior synechia (adhesions), a miotic pupil, and...


cataract formation. These eyes may appear enlarged or normal sized.

**Diagnosis of Equine Glaucoma**

A tonometer is essential for the diagnosis of equine glaucoma. Indentation tonometers, such as the Schiotz tonometer cannot be used in horses because of the horse’s thick cornea and because the horse’s cornea cannot be positioned horizontally. Therefore, applanation tonometers must be used. The most practical and portable applanation tonometers for use in horses are the Tonopen (Tonopen Tonometer, Medtronic, Jacksonville, FL) or TonoVet (iCare, Espoo, Finland) tonometers (K Nollinger et al., 2005; Komaromy et al., 2006; Miller et al., 1990; Van Der Woerdt et al., 1995). For accurate tonometry, auriculopalpebral nerve blocks should be performed because tension on the eyelids may artificially elevate the intraocular pressure (Van Der Woerdt et al., 1995). In addition, tranquilization may artificially lower the intraocular pressure (Van Der Woerdt et al., 1995). The pressure measurement should be taken from the most normal, least edematous location of the cornea if possible, and the head should be held in a consistent head position above the level of the heart (Komaromy et al., 2006).

A thorough and complete ophthalmic examination should also be done to help differentiate the cause of the glaucoma and to rule out other causes of corneal edema, such as keratitis. With glaucoma, the cornea is edematous, but rarely is there yellow or creamy cellular infiltrate, epithelial loss (i.e., corneal ulceration), or diffuse vascularization. These findings are more common with primary corneal disease. The complete ophthalmic examination will also determine if the glaucoma is primary or secondary. Glaucoma secondary to intraocular disease other than uveitis is rare, but is possible with intraocular tumors and luxation of the lens. Finally, glaucoma also needs to be differentiated from endothelial IM MK, which also commonly presents with the primary clinical sign of diffuse corneal edema. However, endothelial IM MK commonly has endothelial precipitates and a normal intraocular pressure.

**Treatment of Equine Glaucoma**

Ideally, glaucoma should be treated by using methods to increase the outflow of the fluid from the eye. This theoretically can be accomplished by medical or surgical methods. Usually, treatment options for equine glaucoma have centered around two main categories: treatment of the underlying inflammation and decreasing the production of aqueous humor. Because the outflow pathways of aqueous humor from the equine eye is primarily through the uveoscleral pathway, traditional medications to increase outflow through the iridocorneal angle, such as miotic medications, are not useful in horses (Van Der Woerdt et al., 1998). Because the uveo-scleral outflow pathway is not well characterized and treatment modalities have not been developed specifically for horses, medications designed to increase the uveo-scleral outflow in humans and dogs (i.e., prostaglandin analogs) have not proven beneficial in horses and may be associated with inflammatory side effects (Davidson et al., 2002; Willis et al., 2001).

Topical carbonic anhydrase inhibitors, such as brinzolamide, appear to be most beneficial in the medical treatment of equine glaucoma (Germann et al., 2008a; Wilkie, 2010).

Surgical methods to increase outflow (i.e., glaucoma shunts or valves, drainage surgeries such as sclerostomies or iridocyclotomies) are usually not successful because of the horse’s high inflammatory response to intraocular surgery; however, glaucoma shunts may be attempted in cases unresponsive to other therapies. If there continues to be poor intraocular pressure control with medication and there is potential for vision, then laser cycloablation (laser destruction of the ciliary body) is indicated (Wilkie, 2010).

**Diode Laser Cycloablation**

If there is poor or no response to medical therapy, the laser cycloablation may be considered. Prior to laser therapy, existing uveitis must be controlled to minimize complications. Ideally, other ocular disease, such as corneal ulceration, should be resolved, and diseases such as intraocular neoplasia should be ruled out. Laser surgery is most indicated if there are signs that the eye has vision—for example, a consensual pupillary light response or dazzle reflex. Blind, painful globes should be removed. Laser can be done to help control the pressures in these chronic eyes but with poorer response than less chronic cases.

General anesthesia or standing sedation with a retrobulbar block is required. Topical proparacaine is given immediately prior to laser application and diode laser settings are 1200–1500 mW power; 5000 ms Duration; Repeat interval 0 (visual eye—40 laser sites; blind eye 40–50 laser spots). The laser energy is delivered through the sclera by placing the laser probe at 5–7 o’clock (ventrally) 4 mm posterior to the limbus and 10–1 o’clock (dorsally) 4–6 mm posterior to the limbus.

**Figure 28.60.** Horse with corneal edema and striae associated with chronic glaucoma.
Aqueocentesis is usually performed, either before or after laser applications, and 0.25–0.5 mL of aqueous humor is removed through the limbus with a 25 to 27-gauge needle. Insufficient laser application may not be effective in controlling the glaucoma. Too high of energy use or too many treatment spots may result in ocular hemorrhage or subsequent hypotony resulting in decreased vision in the eye. Therefore, the amount of laser therapy applied should be adjusted for each case. The intraocular pressure should be checked approximately 2, 4, 6, 8, and 24 hours after surgery. The pressure should be measured again 1 week later, then monthly if pressures are low. Anti-glaucoma medications are generally required after surgery (usually indefinitely). Systemic anti-inflammatory medications should be continued for 7–10 days after laser therapy. A recent review of efficacy of trans-scleral diode laser therapy in horses revealed at a mean follow-up of 49 months that 59% of the eyes treated with laser remained sighted, but 64% required continued topical antiglaucoma medication (Annear et al., 2010).

Endoscopic cyclophotocoagulation (ECP), a procedure utilizing a small endoscope to visualize and deliver the laser energy directly to the ciliary body, has been investigated in normal horses and parameters developed (Harrington et al., 2011b). However, no studies of the use of this modality has been reported in horses, and the high risks of development of cataracts and inflammation in phakic horses likely makes this modality unsuitable currently for treatment of equine glaucoma. More study is needed before routine use of ECP is recommended for client horses.

Diseases of the Equine Lens

Cataracts, or opacities of the lens of the eye, are the most common abnormality of the equine lens, and cataracts are a leading cause of blindness in horses. Luxation or subluxation of the lens is much less common and is usually associated with advanced ocular disease. Unfortunately, the most common cause of cataracts and lens luxation in horses is chronic uveitis, or ERU. This disease not only causes lens abnormalities, but also causes blindness from corneal, iridal, vitreal, and retinal degeneration. Cataracts also may occur in horses from inherited causes (these can be congenital or juvenile) or occur spontaneously following trauma to the eye. For more information on diseases of the equine lens, including in-depth details of medical and surgical management of these diseases, please see an excellent recent book chapter by Carmen Colitz and Richard MCMullen (Colitz & McMullen, 2011).

Congenital Diseases of the Lens

Congenital defects may be due to genetic causes (inherited), toxins, nutritional imbalance, ionizing radiation, or other idiopathic causes, although these causes have not been well characterized in horses. However, cataracts are the most common congenital abnormality in foals, representing approximately 35% of all congenital ocular defects (Latimer & Wyman, 1985; Latimer et al., 1983; Munroe & Barnett, 1984; Turner, 2004). Other lens anomalies that have been described in horses include spheroophakia, lenticousus, and coloboma (Fig. 28.61). Inherited congenital cataracts have been documented in Thoroughbreds, Quarter Horses, and Morgans (Beech et al., 1984; Beech & Irby, 1985; Colitz & MCMullen, 2011). Rocky Mountain horses can also develop congenital nuclear cataracts but have concurrent multiple anterior segment anomalies (Ramsey et al., 1999b).

Lens Luxation/Subluxation

Lens luxation or subluxation may be caused by congenital anomalies of the zonules, chronic uveitis, chronic glaucoma, or trauma (Colitz & MCMullen, 2011). A luxated lens, a lens that has either moved into the anterior or posterior chamber, will usually become cataractous appearing immediately or weeks following the inciting incident (Fig. 28.62). Intracapsular lens extraction has been recommended in cases of lens luxation; however, a recent retrospective long-term evaluation in such cases has revealed that surgical intervention is coupled with a poor prognosis for both retention of vision and the globe (Brooks et al., 2009). This is likely due to the fact that lens luxation in horses is accompanied by advanced disease processes, such as ERU, glaucoma, severe trauma, that by themselves carry a poor long-term prognosis. Usually, medical management of the underlying cause of the lens luxation or treatment to minimize associated inflammation is preferable for globe retention rather than surgery removal of the lens. Enucleation of blind and painful eyes is usually recommended.

Cataract

Cataract is the opacity of the lens. Classification of cataracts in the horse is similar to the description in other species and...
Whether or not a small cataract (Fig. 28.64), which may not affect vision, will progress to a larger, visually inhibiting cataract is often a concern in horses, especially on pre-purchase examinations. Certainly, in juvenile horses, the presence of any cataract, especially those that are bilateral, suggests that the defect may be hereditary, especially in Thoroughbreds, Quarter Horses, and Morgan horses (Beech & Irby, 1985; Beech et al., 1984; Eriksson, 1955; Joyce, 1990; Munroe & Barnett, 1984). Because ERU is the most common cause of cataracts in adult horses, the presence of any cataract, especially those that are bilateral, suggests that the defect may be hereditary, especially in Thoroughbreds, Quarter Horses, and Morgan horses (Beech & Irby, 1985; Beech et al., 1984; Eriksson, 1955; Joyce, 1990; Munroe & Barnett, 1984). Because ERU is the most common cause of cataracts in adult horses, the presence of other signs typical of ERU (e.g., corpora nigra atrophy, iris hyperpigmentation, posterior synechia, vitreal degeneration) suggests that the cataracts will progress as the ERU recurs. A cataract's location and cause may help give some clue to the rate of progression (see Table 28.3) (Matthews, 2000b). Other cataractous changes observed in horses include anterior lens capsule/anterior cortex cystic lesions (Fig. 28.65) likely associated with anterior uveitis and age-related nuclear sclerosis, which is a relatively common finding among aged horses (Colitz & McMullen, 2011).
Preoperative Preparation

Because of the concern for the development of bacterial contamination and endophthalmitis after cataract surgery in horses, routine use of systemic and topical antibiotics is recommended prior to surgery. Also, in most cases, because of the risk for endophthalmitis and the high amount aftercare, if both eyes are candidates for cataract surgery, then only one eye should have surgery performed at a time. Topical fourth-generation fluoroquinolones (Moxifloxacin, Vigamox®, Alcon, Fort Worth, TX), which have been demonstrated to penetrate the intact cornea well and have a broad spectrum activity, are used for at least 24 hours prior to surgery and 3 days after surgery. A topical antibiotic is generally recommended for the length of time that the eye requires topical corticosteroid treatment. Intravenous antibiotics are generally also recommended for the 24-hour perisurgical time period followed by 10–14 days of oral antibiotics. Topical atropine is used starting

Table 28.3  Clinical Classification of Cataracts (Matthews, 2000b)

<table>
<thead>
<tr>
<th>Acquired (secondary cataracts)</th>
<th>Intraocular disease</th>
<th>Uveitis</th>
<th>Anterior</th>
<th>Progressive</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Posterior</td>
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<td>Panuveitis</td>
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<td></td>
<td></td>
<td>Recurrent</td>
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<td>Trauma/injury</td>
<td>Glaucoma</td>
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<td>Systemic toxic or metabolic</td>
<td>Retinal detachment</td>
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<tr>
<td>Age-related senile</td>
<td>Neoplasia</td>
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<tr>
<td>Extralenticular</td>
<td>Retro lenticular fibroplasia</td>
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<td></td>
<td>Mittendorf's dot</td>
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<tr>
<td></td>
<td>Persistent pupillary membranes</td>
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<tr>
<td>Capsulolenticular</td>
<td>Pigmentation</td>
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<td></td>
<td>Anterior capsular</td>
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<td></td>
<td>Posterior capsular</td>
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<td></td>
<td>Anterior polar</td>
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<td></td>
<td>Posterior polar</td>
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<tr>
<td>Lenticular</td>
<td>Zonal cataracts</td>
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<td>Embryonic nuclear</td>
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<td>Fetal nuclear</td>
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<td></td>
<td>Perinuclear (lamellar)</td>
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<td>± progressive</td>
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<td></td>
<td>Equatorial</td>
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<tr>
<td>Sutural cataracts</td>
<td>Posterior suture cataract</td>
<td></td>
<td>Progressive (slow)</td>
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<tr>
<td></td>
<td>Anterior suture cataract</td>
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<td>?</td>
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<tr>
<td>Axial cataracts</td>
<td>Floriform cataract</td>
<td></td>
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<td>Nonprogressive</td>
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<td></td>
<td>Elliptical cataract</td>
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<td></td>
<td>Nonprogressive</td>
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<tr>
<td>Complete cataract</td>
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<td>NA</td>
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Treatment: Cataract Surgery

Surgical Assessment

Similar to other animals, workup for a horse that is a candidate for cataract surgery should include a complete ocular and physical examination (including a rectal exam to assess predisposition for colic), routine blood work (CBC), serum chemistry profile, urinalysis), an electroretinogram, and ocular ultrasound (Colitz & McMullen, 2011). Historically, horses with cataracts associated with ERU were not considered appropriate candidates for cataract surgery. However, horses with well-controlled uveitis should be considered reasonable candidates for cataract surgery assuming they have retinal function and otherwise minimal ocular damage. Careful consideration should also be made of the horses’ temperament to determine if it will be able tolerate the long-term treatment and care that will be required after surgery (Colitz & McMullen, 2011).
12–18 hours prior to surgery. Systemic NSAIDs, preferably flunixin meglumine, is given starting at least 1 hour prior to surgery and continued in a decreasing dosage for up to 3 weeks after surgery. Gastric protectants, such as ranitidine and/or omeprazole (Gastrogard®, Merial, Duluth, GA) are routinely used to help prevent gastrointestinal side effects (Colitz & McMullen, 2011).

Patient Positioning
Correct positioning of the horse is critical for success for any type of intraocular surgery. For cataract surgery, the horse is placed in lateral recumbency. The down eye is protected from pressure or exposure trauma, either by pillows or an inflatable ring. Lubricating the down eye and performing a temporary tarsorrhaphy is recommended to ensure the down eye remains uninjured. The horse’s nose is elevated using foam pillows so that the cornea of the eye to be operated on is parallel to the floor (Fig. 28.66). The head and pillows must be taped into place with strong elastic tape, such as elasticon, to secure it firmly. To prevent facial nerve paralysis after surgery, one must be careful that there is no pressure on the facial nerve, pillows, or tape and that the halter is removed during surgery. The surgeon is generally positioned at the 12 o’clock position of the eye; therefore, the head should be positioned so the head is at the outside of the surgery table so the surgeon does not have to reach across the table or lean over to reach the operating microscope (Fig. 28.67). If surgery is going to be performed on both eyes, the horse is placed in dorsal recumbency and the head turned right or left to position the surgical eye so that the cornea is parallel to the floor (Fig. 28.68).

An operating microscope with coaxial illumination is essential to perform cataract surgery in the horse. Adequate visualization and lighting cannot be accomplished with any other system. The microscope base is placed opposite the surgeon, with the microscope arm extending over the horse’s body to position above the eye. The foot pedal is placed under the operating table so that the surgeon can reach it comfortably (See Fig. 28.67). Whenever possible, the light from the operating microscope should be turned off or blocked so that thermal or photic injury to the cornea or retina is avoided. Newer microscope models have effective “pupil guard” light...
filters that can be used during surgery when performing surgery in the axial light area (e.g., when suturing the corneal wound).

Surgical Preparation
After the horse is in a stable plane of general anesthesia, it should either be paralyzed or have a retrobulbar block (Gilger & Stoppini, 2011a) performed to prevent ocular movement and pressure on the eyes from tension of the extraocular muscles. At NCSU, we generally perform a retrobulbar block with lidocaine instead of using a neuromuscular blockade to allow the animal to be in a slightly lighter plane of anesthesia and provide some ocular analgesia postoperatively. Intraoperative complications from retrobulbar injections have not been observed during equine intraocular surgery.

Surgical Approach
A three-step, hinged clear corneal incision is essential for successful equine cataract surgery (Fig. 28.69), especially when an IOL will be used (Colitz & McMullen, 2011; McMullen & Utter, 2010). Using a #64 microsurgical blade, the right-handed surgeon makes a 75%–90% 5-mm long groove in either the dorsolateral (right eye) or dorso temporal cornea (left eye), 1–2 mm from the limbus. The left-handed surgeon would use an opposite approach. The goal is to avoid the corpora nigra (Fig. 28.70).

During surgical entry into the equine eye, the iris is rarely completely dilated and the anterior chamber is relatively shallow. Therefore, inadvertent iris trauma is common and should be avoided as much as possible. Angling the blade parallel to iris will help prevent iris trauma and allow complete entry with the blade. When removing the blade, this should be done slowly to again avoid iris trauma and to allow slow leakage of aqueous humor. Rapid release of aqueous humor, and its resultant rapid pressure drop, may cause the iris or ciliary body to hemorrhage. If hemorrhage occurs, either during iris trauma or rapid pressure drop, or if the pupil becomes miotic, use of approximately 0.5 mL of 1:10,000 epinephrine (diluted in balanced salt solution [BSS]) injected intracamerally generally assists in minimizing the hemorrhage. If the iris appears to be in the path of the triangular blade during ocular entry, place a small bleb of viscoelastic (VE) to deepen the anterior chamber near the incision. Use of higher concentration 2.0% hyaluronic acid VE (BioVisc®, AcriVet, Berlin) is particularly effective for this maneuver.

Capsulorhexis
With the routine use of equine IOLs, the perfect anterior capsulotomy is required. To perform a continuous curvilinear capsulotomy (CCC), the anterior chamber is vaulted with VE and an incision is made in the peripheral lens capsule. How this incision is made is personal preference. Some people like to make a radial incision using a 25-g needle or cystotome; others prefer to make a horizontal incision using a needle or blade. The CCC can be started from this incision, or the incision can first be initiated, generally clockwise, using capsulorhexis scissors. Due to the large equine eye, shallow anterior chamber, and relatively small corneal incision, standard or

Figure 28.69. Three-step, hinged clear corneal incision is essential for successful equine cataract surgery, especially when an intraocular lens (IOL) will be used. An initial deep corneal groove is made (1). At approximately half-thickness, a tunnel is made into the cornea (2). After several millimeters, an incision into the anterior chamber is made (3). This technique prevents excessive loss of viscoelastic substances and resulting iris prolapse when placing the intraocular lens. (With permission from Colitz, C. & McMullen, R. (2011) Diseases and surgery of the lens. In: Equine Ophthalmology (ed. Gilger, B.C.), 2nd ed. Philadelphia: Elsevier.)

Figure 28.70. Two-handed surgical technique for phacofragmentation of an equine cataract. The right-handed surgeon generally approaches the eye from the approximately 4 o’clock position to avoid the corpora nigra.
bubbles that are commonly produced may be damaging to the eye.

Use of one- or two-handed PA technique can be done depending on the density of the lens. If the horse is older than 8–10 years of age, it is recommended to perform the two-handed PA technique (Fig. 28.72). The posterior capsule in the horse is especially fragile, even in older horses; so much care is needed to prevent posterior capsular rupture. The "conquer and divide" PA method works well in horses and entails splitting the lens with a central groove, then splitting the halves and removing lens quadrants. Because of the large and deep equine lens, the surgeon should keep one foot on focus of the operating microscope, which generally needs frequent adjustments.

**Hydrodissection**

Hydrodissection is a method to separate the lens cortex from the lens capsule using BSS. This is usually done following the CCC, but can precede it, depending on surgeon preference. The hydrodissection should always be done with a 27 to 30-g cannula and BSS. Use of VE for hydrodissection is not recommended because the fragile equine posterior lens capsule may rupture with VE use.

**Phacoemulsification and Aspiration (PA)**

Although PA can be accomplished successfully with a standard human or canine cataract system, use of a dedicated equine-specific PA system (e.g., ALEXOS, AcriVet, Berlin, Germany) is highly recommended. The long needle, power, and irrigation and aspiration system designed for the horse eliminates the need to make multiple ocular incisions and allows the surgeon to be able to “reach across” the eye (Fig. 28.72). Placement of long needles on standard PA hand pieces is also not recommended because microscopic cavitation

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**Figure 28.71.** Anterior capsulotomy using a radiofrequency unit. This instrument nearly always makes a perfect, central capsulotomy.

**Figure 28.72.** Two-handed surgical technique for phacofragmentation of an equine cataract. The right white probe is contains the ultrasonic fragmenting and aspirating needle. The white sleeve is the irrigation sleeve. The other probe (left) is a lens nucleus manipulator that is inserted into the anterior chamber through a small limbal incision at approximately 7 o’clock. Also see Figure 28.70.
IOL Placement
Although the appropriate equine IOL power has yet to be determined, studies indicate that the correct IOL power will ultimately be approximately 14-18 D. Use of the commercially available 18D equine IOL (AcriVet, Berlin, Germany) is recommended in adult horses and the 14D equine IOL in horses less than 6 months. Although these lenses may not have the correct power, horses that have received it have done well and have had excellent visual outcomes—far superior to eyes left aphakic. Studies are ongoing evaluating the long-term outcome in refraction in horses receiving the 14- and 18-D equine IOL (MCMullen & Gilger, 2006; MCMullen et al., 2010; Townsend et al., 2011).

To place the equine IOL, the lens capsular bag and anterior chamber are filled with VE. The cornea is opened along the original groove to a width of 5 mm using standard size right and left corneal section scissors. The IOL is folded in half with custom lens folding forceps and coated with VE. The leading haptic of the IOL is placed into the distal lens capsular bag, and the IOL forceps are removed leaving the IOL partially in the anterior chamber. The second IOL haptic is manipulated using a buttonhook lens manipulator so that the haptics are in the ventral capsule. A diagonal or horizontal placement of the haptics is ideal with a 24-mm diameter IOL (Fig. 28.73).

Surgical Closure
The cornea is closed with simple interrupted, simple continuous, or a shoelace continuous pattern of 7-0 to 8-0 absorbable suture, such as polyglactin 910 (Vicryl, Ethicon). The advantages of the shoelace continuous pattern include a lack of lateral wound shifting, a tight nonleaking incision, and a low incidence of dehiscence; therefore, it is recommended over the other patterns. Removal of the VE by irrigation and aspiration is recommended prior to final tightening of the incision. Because of the high chance of inflammation, low incidence of postoperative pressure spikes, and lack of safety data, use of an intraocular miotic is not recommended in horses.

If concerned about the integrity of the corneal incision, a fornix-based micro-hood conjunctival graft over the incision to further safeguard the eye for any type of dehiscence can be performed (Fig. 28.74). The equine cornea commonly has mild to moderate corneal edema surrounding the incision, so the conjunctival graft makes me feel more confident of the incision. An incision through the conjunctiva is made at the limbus adjacent to the corneal wound. The conjunctiva is undermined and advanced over the incision. Generally three to four simple interrupted sutures of 7-0 to 8-0 polyglactin 910 are used to tack the conjunctiva in place.

To minimize ocular trauma on recovery, a lateral temporary tarsorrhaphy is performed. The suture is removed after the horse has recovered and is standing. Head protectants (hoods) and eyecups are not recommended because they may cause further trauma on recovery and should not be used after surgery in a horse not trained to wearing them. Frequent postoperative lubrication with a hyaluronic-based artificial tear (Blink®, CibaVision, Duluth, GA) is also done to minimize drying trauma.

Postoperative Considerations
Complications after equine cataract surgery seem to be higher than in canine surgery (Brooks, 2008; Colitz & McMullen,
Congenital Diseases of the Equine Posterior Segment

Congenital abnormalities of the equine posterior segment are uncommon and rarely have clinical significance, such as focal coloboma (Fig. 28.76). Other defects, such as congenital retinal detachment, retinal dysplasia, congenital stationary night blindness, and the MCOA syndrome (i.e., the Rocky Mountain horse syndrome) may be associated with vision loss (Ramsey et al., 1999b; Wilkie, 2011).

Congenital Stationary Night Blindness

Congenital stationary night blindness (CSNB) has been reported in the Appaloosa, Quarter Horse, Thoroughbred, Paso Fino, and Standardbred (Nunnery et al., 2005; Sandmeyer et al., 2007; Witzel, 1978). CSNB may have an incidence of up to 33% of the Appaloosa horses studied, and a significant association has been demonstrated between CSNB and homozygosity of the leopard complex gene (Lp) (Bellone et al., 2008). Affected horses may demonstrate abnormal behavior or vision loss in low-light conditions (nyctalopia), and some may also have decreased vision in normal light (Sandmeyer et al., 2007; Witzel, 1978). Ophthalmic examination is normal, although some horses may also have microphthalmia, dorsomedial strabismus, nystagmus, and an unusual dorsal ocular deviation and head elevation, which have been termed star gazing (Wilkie, 2011). Diagnosis of CSNB can be confirmed by ERG that has a normal a-wave but a decreased
photopic and absent scotopic b-wave (Nunnery et al., 2005; Sandmeyer et al., 2007; Witzel, 1978). There is no treatment for CSNB.

Vitreal Changes

Vitreal alterations are commonly of developmental, degenerative, age-related, traumatic, or inflammatory origin; however, only hyalitis (inflammation) and degeneration are common in horses, and only hyalitis has clinical significance (Nell & Walde, 2010; Wilkie, 2011). Hyalitis or inflammation of the vitreous is most commonly observed in horses with posterior ERU and appears as yellow strands in the vitreous with vitreal cellular infiltrate (Fig. 28.77). Vitreal degeneration, or syneresis, which is a common finding in older horses, is cobweb-like white strands in the vitreous (Fig. 28.78). Vitreal degeneration is rarely associated with other ocular pathology in horses.

Chorioretinitis

Chorioretinitis, inflammation of the choroid and retina, may be the result of ERU or may be a manifestation of systemic disease. Active lesions are characterized by edema, cellular infiltrate, and hemorrhage or retinal detachment and they often appear gray, white, or hazy (Fig. 28.79). The retina may be elevated by subretinal fluid and inflammatory cells. Inactive lesions, or chorioretinal scars, appear as hyperreflective or hyperpigmented in the tapetal fundus and may appear to be depigmented or to have pigment clumping in the nontapetal fundus (Fig. 28.80). If the retina was elevated during the active phase of the disease, it may reattach in a wrinkled or folded fashion, appearing as gray linear folds. These folds are most commonly seen radiating from the optic nerve. Chorioretinitis lesions can be focal or diffuse and unilateral or bilateral, and are most commonly seen in the peripapillary region.
Focal chorioretinopathy, termed bullet-hole chorioretinitis, are multifocal, depigmented lesions that appear most commonly ventral to the optic disc in the nontapetal fundus (Fig. 28.82). On histologic examination, a loss of normal retinal architecture with retinal pigment epithelium (RPE) hyperplasia and migration of RPE cells into the retina can be observed. It has been suggested that these lesions may be the result of previous chorioretinitis, but these lesions are often seen, as incidental findings, in many horses (Wilkie, 2011).

Retinal Detachment
A retinal detachment is the separation of the neurosensory retina from the outer retinal pigmented epithelium. The retina can detach as a result of fluid accumulation, a retinal tear, blunt force trauma, or traction toward the vitreous secondary to resolution of vitreal hemorrhage (Fig. 28.83). A focal

Figure 28.80. Nontapetal chorioretinal scar demonstrating sector retinal pigmented epithelial loss, pigment clumping, and exposure of choroidal blood vessels and sclera.

Figure 28.81. Peripapillary depigmentation, termed the butterfly lesion, in a horse after blunt trauma. These lesions are also associated in horses with chronic equine recurrent uveitis.

Figure 28.82. Focal chorioretinopathy, or bullet-hole chorioretinitis, are multifocal, depigmented lesions that appear most commonly ventral to the optic disc in the nontapetal fundus.

Figure 28.83. Diffuse retinal detachment in the nontapetal ocular fundus in a horse.
bullous detachment appears as an elevated, hazy area of retina with subretinal fluid. This bullous detachment may reattach with folds or wrinkles, most commonly radiating outward from the optic nerve. With a complete detachment, the retina appears as a gray, floating veil of tissue extending into the vitreous toward the lens. Complete detachments with tears or disinsertions, will not resolve with therapy resulting in blindness (Wilkie, 2011). In a retrospective study of 40 horses (46 eyes) with retinal detachment, the etiology was diagnosed to be ERU in 27 horses (33 eyes) (67.5%) and trauma in 10 horses (10 eyes) (25%) (Strobel et al., 2007). The prognosis for a retinal detachment depends on the severity, underlying cause, and chronicity of the lesions, but in general, it is poor for return of vision (Strobel et al., 2007).

Retinal Degeneration
Primary retinal degeneration or progressive retinal atrophy is uncommon in horses, but when present will be bilateral and progressive, and Thoroughbreds may be predisposed (Matthews et al., 1990; Nell & Walde, 2010; Wilkie, 2011). Affected horses show progressive vision loss. Retinal degeneration appears as hyperreflective changes in the tapetal retina and as multifocal depigmentation and hyperpigmentation in the nontapetal retina. The optic nerve becomes pale, and the peripapillary retinal vessels are attenuated. Vision loss may begin with nyctalopia (night blindness) and progress to day vision loss (Matthews et al., 1990; Nell & Walde, 2010; Wilkie, 2011). Unilateral retinal degeneration can be associated with glaucoma, trauma, or vascular ischemia (Wilkie, 2011).

Equine Motor Neuron Disease
Equine motor neuron disease (EMND) is a neurodegenerative disease that occurs as a result of a chronic dietary deficiency of the antioxidant, vitamin E (Davis, 2011). Ceroid-lipofuscin subsequently accumulates in the RPE in the tapetal and nontapetal fundus. EMND appears as an irregular, reticulated, or honeycomb pattern of accumulations of yellow-brown to black pigment in the tapetal and nontapetal retina (Fig. 28.84). Clinically, horses affected with EMND may exhibit weight loss, weakness, muscle atrophy, trembling, low head carriage, and an abnormal stance (Davis, 2011).

DISEASES OF THE OPTIC NERVE
Pathologic changes to the optic nerve are commonly observed, especially in older horses, but rarely are these changes associated with vision loss. The most common abnormality is a condition called proliferative optic neuropathy, which appears as a focal growth on typically one edge of the optic nerve (Fig. 28.85). These are seen commonly in elderly horses, are rarely associated with vision deficits, and may be benign neoplasms (e.g., glioma) (Cutler, 2002; Wilkie, 2011). Proliferative optic neuropathy must be differentiated from exudative or ischemic optic neuropathy, which are acute lesions associated
with complete vision loss in the affected eye (Hardy et al., 1990; Wilkie, 2011). Ipsilateral ischemic optic neuropathy has been reported after treatment of guttural pouch disease via arterial occlusion (Hardy et al., 1990).

Optic neuritis may occur along with posterior uveitis or in cases of chorioretinitis from systemic disease, but this disease entity is uncommon. Optic nerve degeneration appears as a pale optic nerve head with absent or decreased vascularity (Fig. 28.86). Degeneration most commonly occurs after head trauma and if severe can result in complete and permanent blindness (Wilkie, 2011).

For more information on diseases of the equine ocular posterior segment, including in-depth details of medical and surgical management of these diseases, please see an excellent recent chapter by David Wilkie (Wilkie, 2011).

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Chapter 29

Food Animal Ophthalmology
Jacqueline W. Pearce and Cecil P. Moore

Food producing animals include cattle, sheep, goats, and pigs. Most information in this chapter reflects older sources as there is a relative paucity of new material since the last edition of this text. Therefore, practitioners are encouraged to contribute to this portion of the literature in future editions. This chapter covers the available literature by species. For each species, the congenital and acquired abnormalities of each ocular region are discussed.

BOVINE

The Orbit and Globe

Congenital Globe Abnormalities and Blindness

True anophthalmos is rare. Most animals with suspected anophthalmos actually have microphthalmia because vestigial remnants of ocular tissue remain (Fig. 29.1). Microphthalmia is usually combined with other ocular defects, including corneal opacities, cataracts, aniridia, corectopia, persistent pupillary membranes, thickening or ossification of the choroid, and various retinal abnormalities, such as gliosis, folds, and rosette formation, as well as retinal nonattachment and detachment (Fig. 29.2).

Congenital globe abnormalities are often linked genetically with abnormalities in other body systems (Leipold, 1984). Congenital anophthalmia/microphthalmia syndrome with malformations of the posterior vertebral column was reported in 26 dairy and beef cattle (Leipold & Huston, 1968). The exact etiology was not known, but some cases were speculated to have a hereditary basis. Congenital anophthalmia with caudal vertebral anomalies, such as wedge vertebra, hemivertebra, and sagittal cleft vertebra, has been reported in 10 Japanese Brown cattle (Moritomo et al., 1995). Vestiges of ocular remnants were reported, albeit dysplastic or hypoplastic (or both), thus implying these cattle actually had microphthalmia rather than true anophthalmia. It was speculated that these calves were exposed to some unknown teratogen at the critical time of optic organogenesis and notochordal formation. Congenital blindness with multiple ocular anomalies, including dysplasia of the lens, retinal detachment, persistence of the hyaloid artery, retinal dysplasia, and microphthalmia, has also been reported in cattle for many years, with recessive (Saunders & Fincher, 1951) and dominant (Kaswan et al., 1987) inheritance being postulated in the past. The locus responsible for this syndrome has been mapped to the proximal region of bovine chromosome 18. Comparison of nucleotide sequence of genes in this region revealed a one-nucleotide insertion in the WFDC1 gene. This results in a frame shift mutation and premature termination codon in the middle of the protein WFDC1, which has been demonstrated to play an essential role in mammalian eye development (Abbasi et al., 2009). Several infectious agents have been associated with congenital ophthalmic anomalies in food animals. The most common maternal infection causing multiple ophthalmic defects in cattle is bovine viral diarrhea (BVD). Ocular lesions associated with BVD include cataract, persistent pupillary membranes, retinal degeneration, retinal dysplasia, optic neuritis, and microphthalmia (see Chapter 35). Bluetongue virus has also been associated with blindness and so-called “dummy” calves, which are affected with hydranencephaly and are blind with normal pupillary light responses (Vercauteren et al., 2008). Profound corneal edema has also been reported in some calves infected in utero with bluetongue virus (Holzhauer & Vos, 2009).

Abnormalities of Globe Position and Movement

Abnormalities in globe position in cattle are usually bilateral and convergent (i.e., esotropia) (Distl et al., 1991; Gelatt, 1976), but they can also be unilateral or bilateral and divergent (i.e., exotropia) (Distl & Scheider, 1994; Julian, 1975). Two castrated male full siblings were reported to have divergent unilateral strabismus, and other anatomic abnormalities were also seen in the affected animals. The reason for the eye defect was a displacement of the lateral rectus muscle by 40 degrees ventrally (Distl & Scheider, 1994). Conclusions regarding inheritance of the condition could not be drawn. Divergent bilateral strabismus in association with hydrocephalus has
explained the relationship of 107 affected animals with BCSE within six pedigrees (Distl et al., 1991). In two other studies of German Brown Swiss cattle, a dominant autosomal gene model with incomplete penetrance of 70% gave the best fit (Distl, 1993; Distl & Gerst, 2000). A whole-genome scan for BCSE loci revealed one locus mapped to the centromeric region on bovine chromosome 5 (BTA5) and another locus mapped to the telomeric region of chromosome 18 (BTA18) (Momke et al., 2008). These data suggest that two genes may be responsible for the disease or that one gene causes the disease and the other could affect progression or severity. Environmental effects may also be important (Distl et al., 1991). On the basis of histopathologic results, a defect in the motor nucleus of the abducent nerve might be responsible for the symptoms of BCSE (Schutz-Hanke et al., 1979). Esotropia also occurs in Holstein and Ayrshire cattle (Rebhun, 1979). Exophthalmia and esotropia progress until the animal reaches maturity. Nystagmus may be present, and vision is compromised. A neurologic component to the disease may be present as well.

In some cases, the strabismus may be associated with a generalized systemic infection (Rebhun, 1984). Bilateral dorsomedial strabismus is suggestive of polioencephalomalacia (PEM). Affected calves are usually blind and exhibit opisthotonus. Ipsilateral neurologic signs in association with a medial strabismus are suggestive of listeriosis (Fig. 29.4) (Rebhun, 1984). The inflammation of the brainstem impinges on the abducens nucleus, resulting in medial strabismus through loss of function of the lateral rectus muscle.

Retrobulbar Space-Occupying Lesions

Unilateral strabismus or exophthalmia (or both) usually results from space-occupying orbital lesions due to inflammation or neoplasia (Fig. 29.5). However, other anatomic defects have been implicated (Distl & Scheider, 1994; Lamb & Naylor,
Figure 29.4. Drooping of the left upper lip and ear in a Jersey cow with systemic listeriosis. (Courtesy of L. Horstman.)

Figure 29.5. Unilateral exophthalmos and strabismus of unknown cause in a Holstein cow. (Courtesy of C. Rohde.)

Figure 29.6. Marked bilateral exophthalmos due to retrobulbar fat deposition in a 1-month-old Holstein bull calf treated with dexamethasone as part of a metabolic study. (Courtesy of W. Townsend.)

sinusitis) is usually more amenable to treatment (Ward & Rebhun, 1992). Fine-needle aspirates of the orbital tissue, particularly guided by B-mode ultrasonography, may be helpful. A 3-in, 18-gauge needle can be used for this procedure, which is similar to that described for the Peterson nerve block (Whitley & Moore, 1984).

Orbital Neoplasia

Lymphosarcoma in cattle affects the retrobulbar tissues and is the most frequent cause of exophthalmos with and without strabismus (Fig. 29.7) (Rebhun, 1979). The complete physical examination may reveal lymphadenopathy, cardiac arrhythmia, and melena, as well as uterine and renal masses. Cases of primary ocular lymphoma have been reported without retrobulbar extension (Ruggles et al., 1992). Bovine leukemia virus is the cause of lymphoma in cattle (Miller, 1980). Serologic tests and PCR are available to determine presence of bovine leukemia virus, serology is usually more economically viable, and animals remain seropositive throughout life. A positive test will not confirm the diagnosis of lymphoma, but a negative test for bovine leukemia virus rules out the possibility of lymphoma. The only definitive diagnostic for bovine lymphoma is a biopsy. Treatment is usually palliative, because most cattle with orbital lymphosarcoma die within 6 months. The only indication for orbital exenteration is to relieve the pain associated with exposure and subsequent panophthalmitis in a valuable pregnant cow until she delivers her calf (Rebhun, 1979).
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SECTION IV

area, drainage and lavage of any nidi of infection, possibly topical and systemic antibiotics, and if panophthalmitis is present, enucleation (Rebhun, 1979).

Exophthalmos and orbital inflammation may be sequelae to chronic frontal sinusitis in cattle. In one study of 12 cattle (Ward & Rebhun, 1992), the sinusitis in 67% of animals resulted from dehorning, whereas the sinusitis in 25% was associated with respiratory tract disease. In the former group, the most common organism isolated was Actinomyces pyogenes; in the latter, it was Pasteurella multocida. Clinical signs included anorexia, pyrexia, frontal bone distortion, exophthalmos, nasal discharge, and neurologic abnormalities. Treatment consisted of trephination, drainage, and lavage of the sinus cavity. Eight of the 12 cattle responded well to this treatment, whereas the other four animals with central nervous system (CNS) signs died or were euthanized.

Figure 29.7. Exophthalmos with marked hyperemia and thickening of both the palpebral and bulbar conjunctiva in a cow with systemic lymphosarcoma involving the orbit. (Courtesy of L. Horstman.)

Other reported retrobulbar orbital neoplasms include metastatic squamous cell carcinoma and adenocarcinoma (Guard et al., 1984). These tumors appeared to originate from the nasopharynx and extended into the nasal cavity. In both cases, Horner’s syndrome was present. While these tumors typically carry an extremely guarded prognosis (Rebhun, 1979), the geriatric cattle in the case report lived for months to years (Guard et al., 1984).

A Holstein cow with a nonpainful swelling of the forehead and exophthalmos of the right eye was diagnosed with an extracranial meningioma after histopathologic examination of a biopsy specimen (Yamada et al., 2005). The animal was subsequently euthanized. A retrobulbar meningioma has also been reported in a Simmental cow (Reis et al., 2007).

Ocular lymphangiosarcoma has been reported in an 8-year-old multiparous Holstein cow (Ruggles et al., 1992). The light tan mass was attached to the perilimbal sclera, and both cytologic and histopathologic examinations confirmed lymphangiosarcoma. Orbital recurrence was not seen for 2 years after exenteration.

Orbital Inflammation

Inflammatory orbital disease is common in cattle and involves orbital and periocular tissue. Trauma, puncture wounds of the eyelids or conjunctiva, foreign-body migration from the mouth to the retrobulbar space, actinobacillosis, and panophthalmitis are potential causes. Associated systemic signs may include pyrexia, anorexia, temporomandibular pain, exophthalmos and associated sequelae, and leukocytosis. Treatment involves identifying the underlying cause, hot packing the area, drainage and lavage of any nidi of infection, possibly topical and systemic antibiotics, and if panophthalmitis is present, enucleation (Rebhun, 1979).

Exophthalmos and orbital inflammation may be sequelae to chronic frontal sinusitis in cattle. In one study of 12 cattle (Ward & Rebhun, 1992), the sinusitis in 67% of animals resulted from dehorning, whereas the sinusitis in 25% was associated with respiratory tract disease. In the former group, the most common organism isolated was Actinomyces pyogenes; in the latter, it was Pasteurella multocida. Clinical signs included anorexia, pyrexia, frontal bone distortion, exophthalmos, nasal discharge, and neurologic abnormalities. Treatment consisted of trephination, drainage, and lavage of the sinus cavity. Eight of the 12 cattle responded well to this treatment, whereas the other four animals with central nervous system (CNS) signs died or were euthanized.

Nystagmus

In cattle, nystagmus may be either congenital or acquired. A congenital rapid pendular nystagmus, which is usually horizontal, is observed in Holstein-Friesians especially and in other breeds as well (McConnon et al., 1983). Clinical vision is not significantly affected, and the animals are affected for life. A possible genetic relationship may exist. Other causes include brain tumors and abscesses; intoxication by chemicals, plants, and heavy metals; cerebral anemia and vascular disease; and congenital or early postnatal blindness.

Other Orbital Diseases

Bilateral episcleral prolapse of orbital fat has been reported in a 10-month-old Santa Gertrudis bull (Gilger et al., 1992). The masses were located in the dorsomedial episcleral space, were slightly lobulated in appearance, and were freely movable under the bulbar conjunctiva. No treatment was performed. The inheritance pattern of this condition in cattle is not known.

Bilateral exophthalmos, epiphora, third eyelid prolapse, and bulbar subconjunctival emphysema developed after tracheostomy in a 3-month-old Simmental bull calf (Fig. 29.8) (Grahn & Wolfer, 1995). Crepitation was detected during palpation of the eyelids and retropulsion of the globes. Treatment was symptomatic, and the calf recovered completely. It was postulated that the orbital and subcutaneous emphysema were complications of the tracheostomy.

The Eyelids

Entropion and Lid Defects

Entropion is relatively rare in cattle, but it has been reported in the Simmental breed (Leipold et al., 1972; Thier & Bay, 1965). Spastic and cicatricial entropion are more common than congenital entropion. Surgical intervention in an affected Gelbvieh bull using a modified Hotz-Celsus procedure was successful after a second surgery (Brown et al., 1995). No offspring from this bull were affected.
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agent more commonly associated with infectious bovine keratoconjunctivitis (IBK) was isolated. Isolation of this organism came from a cow that also had concurrent corneal ulceration so true etiologic relationship cannot be confirmed (Galvao & Angelos, 2010). Nonetheless, it is appropriate to consider culture and evaluation in cases of cattle with ulcerative blepharitis and concurrent ulcerative conjunctivitis and/or keratitis.

Mycotic

Trichophyton spp. can affect all food-producing animals (Radostits et al., 2007). Despite the self-limiting nature of dermatophytosis, treatment is recommended to limit any further infection of unaffected animals and humans (Kielstein, 1990). Topical and systemic fungicidal agents, iodine shampoos, improved nutrition, and dry environs all may assist in eliminating the disease. Vaccination of newly infected herds shows potential as a prophylactic measure as well (Radostits et al., 2007).

Ectoparasites

Sarcoptic mange is caused by Sarcoptes scabiei, with a subspecies specific for each host species. This host specificity is not complete, however, and transference from one host species to another can occur (Radostits et al., 2007). The disease is characterized by intense pruritus, papules, and general erythema. The first clinical signs may include facial dermatitis, with thick, crusty, wrinkled, and denuded areas around the face and eyelids. The lesions become widespread. The disease is uncommon in the United States. At the time of publication, it is not considered to be a reportable disease. However, sarcoptic mange in cattle has been cited as a reportable disease in the past; readers are referred to online documentation for current status of this disease (U.S.D.A., 2011). Treatment of all affected and contact animals is indicated. For many years, the most common way to treat infected animals was using dip vats, but the efficacy of new compounds that may be applied topically as sprays, drenches, and pour-ons has reduced the cost and time needed to treat this disease (Cortinas & Jones, 2006).

Demodex spp. are host specific (Demodex bovis affects cattle). The adult mites invade hair follicles and sebaceous glands of the face, limbs, and back, which then become distended with mites and inflammatory material. Secondary bacterial invasion of these lesions will result in formation of pustules and abscesses. Pustules may be seen around the eyes, and pruritus may be present. The disease tends to be generalized in cattle (Radostits et al., 2007). Chronic granulomatous eosinophilic blepharitis has been reported in a cow (Gearhart et al., 1981). A caracidal treatments may be used; however, self-resolution has been reported.

Photosensitization

Direct solar irritation (i.e., sunburn) may occur in food animals with little periocular pigmentation, but acute periocular
dermatitis is more likely the result of photosensitization. If photosensitizing substances are present in sufficient concentration in the skin, dermatitis occurs when that skin is exposed to light. The causative photodynamic agents may be ingested preformed (i.e., primary photosensitization), be products of abnormal metabolism, or be normal metabolic products that accumulate in tissues because of faulty excretion through the liver (Radostits et al., 2007). Photodynamic agents include hypericin in Hypericum perforatum (St. John's wort), fagopyrin in Polygonum fagopyrum (buckwheat), and perloline from Lolium perenne (perennial ryegrass); miscellaneous agents include phenothiazine sulfoxide from phenothiazine, rose Bengal, and acridine dyes (Kako et al., 1993; Radostits et al., 2007). In all cases of secondary photosensitization, phylloerythrin, which is a normal end product of chlorophyll metabolism, is the photodynamic agent. When biliary secretion is obstructed by hepatitis or biliary duct obstruction, phylloerythrin accumulates in the body. The progressive clinical manifestations of both primary and secondary photosensitization consists of lacrimation, photophobia, erythema, cutaneous edema, fissuring of the epithelium, exudation and crusting of serum and necrosis, and sloughing of nonpigmented exposed skin (Casteel et al., 1986). Corneal edema is also evident in many cases (Casteel et al., 1991). Treatment involves removing the affected animal from sunlight, preventing ingestion of toxic material, and administering laxatives. In secondary photosensitization, treatment of the underlying disease is recommended, but death of the animal may still result (Radostits et al., 2007).

Neoplasia

Ocular squamous cell carcinoma (OSCC) is the most common tumor of the eye and eyelids in cattle and will be dealt with in the conjunctiva and cornea section. Meibomian carcinoma of the eyelid has been reported in a Simmental cow in Turkey (Gokhan et al., 2010). Infection with bovine papillomavirus may cause neoplastic lesions to form on the periorcular skin and eyelids. Manifestations include acanthosis (epidermal hyperplasia), papillomas (Fig. 29.9) and keratinized elongated proliferative lesions (Fig. 29.10) (keratoacanthoma, cutaneous horn). In most cases, the disease is self-limiting, and the lesions will resolve over time, but potential for malignant transformation into squamous cell carcinoma exists (Ford et al., 1982). Surgical excision has been shown to be successful if lesions are small and limited in number (Welker et al., 1991).

THE NASOLACRIMAL SYSTEM

The tear-producing glands in food animals rarely have any primary abnormality. Epiphora is the most common abnormality. The epiphora is usually secondary to irritative ocular disease causing increased tear production rather than to defects in tear outflow.
SECTION IV: Special Ophthalmology

THE CONJUNCTIVA AND CORNEA

The conjunctiva and cornea are major sites for ophthalmic diseases in food-producing animals, with profound economic effects. In cattle, IBK and OSCC are the predominant conditions affecting the conjunctiva and cornea.

Congenital Anomalies

Dermoid

Dermoids occur principally in cattle, but they can occur in other food animal species as well (Fig. 29.13) (Brightman...
Fig. 29.14. A large dermoid involving the cornea, bulbar conjunctiva, and bulbar aspect of the nictitating membrane in a 4-month-old Angus cross calf. (Courtesy of W. Townsend.)

Fig. 29.15. Subconjunctival hemorrhage in a calf. (Courtesy of C. Moore.)

et al., 1985). Of 229 ocular defects in cattle reported in one study, dermoids accounted for four (Barkyoubm & Leipold, 1984). The defect in Herefords is genetically transferred, with characteristics of autosomal recessive and polygenic inheritance (Barkyoubm & Leipold, 1984). In cattle, the site predilection of ocular dermoids is, in decreasing order, the limbus, third eyelid, canthi, eyelid, and conjunctiva. There is one case report of a dermoid cyst arising from the bony part of the nasolacrimal duct in a Scottish highland cattle heifer (Steinmetz et al., 2009). Dermoids rarely appear bilaterally except in certain lines of Hereford cattle (Barkyoubm & Leipold, 1984; Croshaw, 1959). The clinical manifestation varies from an unsightly blemish to various degrees of visual impairment, keratoconjunctivitis with epiphora, blepharo-spasm, and corneal ulceration (Fig. 29.14). In some cases, other congenital defects may exist concurrently. One report of bilateral corneoconjunctival dermoids, nasal choristomas, and ectopic glandular tissue in an Angus × Hereford calf exists (Brudenall et al., 2008). Surgical removal is recommended if vision is impaired or the eye is painful (Brudenall et al., 2008).

Birth Trauma

Subconjunctival hemorrhage subsequent to birth trauma has been documented in a Shorthorn calf (Vestre et al., 1978). Resorption of the blood usually occurs without complications (Fig. 29.15).

Congenital Porphyria and Protoporphyria

Inherited defects of porphyrin metabolism in cattle and swine are characterized by excessive deposition of porphyrin isomers in the tissues (Wass & Hoyt, 1965). Congenital porphyria is similar to Gunther’s porphyria in humans and is inherited as an autosomal recessive trait (Jorgensen & With, 1963). The incidence is higher in females than in males, but the disease is rare. Even so, it has been recorded in Shorthorn, Holstein, Black and White Danish, Jamaica Red and Black cattle, and Ayrshires (Jorgensen, 1961). Congenital erythropoietic porphyria in cattle is caused by an inherited deficiency of the enzyme uroporphyrinogen III synthase (Agerholm et al., 2011; Levin, 1968). Insufficient activity of this enzyme leads to the formation of the metabolites uroporphyrinogen I and coproporphyrinogen I. These porphyrinogenes are oxidized to their end products uroporphyrin I and coproporphyrin I, which accumulate in the body. These high levels of porphyrins sensitize the skin and eyes to light (Jorgensen & With, 1963).

Protoporphyria is a less common, milder disease than porphyria and is thought to be inherited in cattle. In this disease, there is deficient activity of the enzyme ferrochelase, resulting in excessive synthesis of protoporphyrin (Radostits et al., 2007). Ocular clinical signs related to abnormal porphyrin metabolism result from photosensitization. These signs include photophobia, edema, inflammation, and necrosis of the eyelids and the periorcular skin. Treatment consists of maintaining the affected animals indoors. Genetic selection against lines of cattle with these inherited defects is recommended.

Inherited Corneal Disease

Most cases of corneal edema seen in food animals are secondary either to intraocular disease that affects endothelial cell function or extraocular disease that causes a defect in the overlying corneal epithelium. Primary endothelial disease is extremely rare in food animals, but an autosomal recessive corneal disease of Holstein and other cattle has been reported (Deas, 1959). Affected animals show bilateral corneal edema either at or soon after birth. The condition is not amenable to
Phenothiazine-Induced Corneal Disease
Phenothiazine is used as a prophylactic in the control of manure-breeding insects and as an anthelmintic in livestock (Radostits et al., 2007). Corneal edema and keratitis have been associated with phenothiazine toxicity, but this is a condition seen mainly in calves and, to a lesser extent, in pigs and goats (Bistner et al., 1981; Enzie & Whitmore, 1953; Vestre, 1984). Most ophthalmic cases result from a high dose of phenothiazine, but low daily doses may produce ophthalmic disease as well (Radostits et al., 2007).

The metabolism of orally administered phenothiazine varies by species. In calves and sheep, phenothiazine is absorbed from the rumen as the sulfoxide and conjugated in the liver to form leucophenothiazine ethereal sulphate, which is then excreted into the urine and bile. Cattle are unable to detoxify all the phenothiazine sulfoxide, however, and a proportion enters the systemic circulation and aqueous humor of the eye, thereby causing photosensitization (Whitten et al., 1946).

Beginning with lacrimation, clinical signs of phenothiazine toxicity may occur unilaterally or bilaterally within 12–36 hours after treatment (Bistner et al., 1981). This is followed by edema in the parts of the cornea exposed to light (Bistner et al., 1981; Radostits et al., 2007). Photophobia, blepharo-spasm, and keratitis may subsequently occur, and eyelid edema has also been reported.

Treatment for the condition is symptomatic, but affected animals may show no clinical signs or may even recover spontaneously if access to sunlight is restricted, especially for 12–36 hours after treatment (Whitten et al., 1946). Affected animals may recover within 5–7 days, but recovery may also be prolonged (60–90 days) (Bistner et al., 1981).

Parasitic Keratoconjunctivitis
Thelazia Species
The pathogenic significance of Thelazia spp. is not known, but some thelazial conjunctivitis may be mistakenly attributed to bacterial infection (Prange et al., 1968). In North America and Europe, Thelazia spp. are regarded as being nonpathogenic to mildly pathogenic (Arbuckle, 1977; Kennedy, 1993; Patton & Marbury, 1978). In contrast, more severe disease, and even blindness, has been reported in other countries (Patton & Marbury, 1978; Vohradsky, 1970). The variability in pathogenicity may result from host, parasite, livestock management, and climatic factors (Geden & Stoffolano, 1980).

Thelazia spp. nematodes are small, slender, white worms. The males are 7–13 mm in length and the females are 12 to 18 mm. Female worms are more often recovered from cattle than male worms (ratio, 2:1) (Kennedy et al., 1990). They occur in the conjunctival sac and nasolacrimal ducts, and they move rapidly in the preocular tear film. Thelazia rhodesi, Thelazia gulosa, Thelazia skrjabini, and Thelazia lacrymalis affect cattle (Kennedy & Moraito, 1987; Kennedy et al., 1990; Overend, 1983). Mixed infections of two or more genera of parasites have also been reported (Kennedy, 1993). Significant numbers of normal cattle may be infected (Kennedy, 1993; Overend, 1983). The prevalence of the parasite may be in excess of 20%, and seasonal variations occur. The worms are more abundant in beef than in dairy breeds. In a study of 1322 slaughtered cattle throughout Alberta, Canada, 700 eye worms from 121 eyes were recovered (Kennedy & MacKinnon, 1994). The distribution of T. skrjabini across nine different sites differed significantly from that of T. gulosa, and suggests that T. skrjabini and T. gulosa are more site specific than previously believed. A study in 2005 showed marked reduction in the prevalence of Thelazia spp. recovered from the eyes of cattle in England compared with a similar population evaluated in 1978. The prevalence of Thelazia spp. was 41% in 1978 and 1.5% in 2005 (Tweedle et al., 2005). A possible factor explaining the reduced incidence is the widespread use of endectocides in the cattle industry since the late 1970s.

In North America, unilateral chronic follicular or mucoid conjunctivitis is most common, with irregularities in the lining of the nictitans gland ducts (Patton & Marbury, 1978). Other clinical signs include profuse epiphora, photophobia, and ulcerative keratitis (Radostits et al., 2007). A subconjunctival cyst has been reported in a Simmental calf caused by T. gulosa (Muller & Campbell, 1992). Face flies, especially Musca autumnalis, act as biologic vectors (Oostenbeek & Surgeoner, 1980) and transfer the larvae to the eyes while feeding. Hence, cases are more prevalent in the summer and fall months. The prevalence is lower among cattle grazing short and mid-size grass pastures than among those grazing transitional or aspen parkland pastures, rough fescue, or woodland-type pastures (Kennedy, 1993).

The diagnosis is usually made postmortem on the basis of identifying the parasite in the conjunctival sac or nasolacrimal duct. Antemortem diagnosis can be made by careful gross examination of the whole lacrimal apparatus or by demonstration of fully embryonated eggs, larvae, or immature worms using specialized techniques. Often, the clinical diagnosis is made when the eye is being manipulated for unrelated diagnostic or surgical procedures (Miller & Campbell, 1992). Treatment modalities include simple lavage; mechanical removal after topical anesthesia; administration of levamisole (5 mg/kg orally or 1% solution topically) or fenbendazole; and topical administration of ivermectin or echetriophate iodide (Kennedy, 1992; Kennedy, 1994). Subcutaneous ivermectin (0.2 mg/kg) is 100% effective against T. skrjabini and more than 99% effective against T. rhodesii (Kennedy, 1992; Soll et al., 1992). A pour-on preparation of ivermectin (0.5 mg/kg) reduces the burden of T. gulosa by 100% and decreases the burden of T. skrjabini by 97%. Doramectin given subcutaneously was found to be 100% effective against Thelazia spp. in both experimental and naturally infected animals (Kennedy...
& Phillips, 1993). The incidence of disease can be reduced by adequate fly control.

**Infectious Keratoconjunctivitides**

Infectious keratoconjunctivitis in food animals represents an important group of diseases, not only from an economic standpoint but also for the well-being of the affected animals.

**Keratomycosis**

Fungal infection of the bovine cornea is quite uncommon. A confirmed case of Aspergillus and Fusarium keratitis was reported in a 5-year-old Holstein cow. Clinical signs included ocular discharge, periorbital swelling, an area of full-thickness corneal cellular infiltrate, fibrin, hypopyon, diffuse corneal edema, and miosis. The patient was diagnosed with a corneal stromal abscess and secondary anterior uveitis. Histopathology, mycotic culture, and PCR confirmed the presence of fungal infection with *Aspergillus* and *Fusarium* spp. Response to standard topical therapy was good; follow-up with the patient 1 year after diagnosis revealed a focal area of corneal fibrosis with maintenance of vision (Elligott et al., 2006).

**Infectious Bovine Rhinotracheitis**

Infectious bovine rhinotracheitis (IBR) may cause nonulcerative keratoconjunctivitis. Conjunctivitis is the most common manifestation of IBR and is characterized by raised, white plaques on the bulbar and palpebral conjunctival surfaces (Fig. 29.16). Chemosis is also often present. Variable degrees of nonulcerative keratitis can also develop with peripheral edema and vascularization initially. In severe cases, the corneal edema and cellular infiltrate can be quite extensive, resulting in blindness (Fig. 29.17) (Rebhun et al., 1978). Please see Chapter 35 for additional information.

**Listerial Keratoconjunctivitis**

This condition is also known as silage eye and ophthalmitis. The etiologic agent is *Listeria monocytogenes*. Lesions are located unilaterally or bilaterally, but unilateral presentation is most common. Ocular surface signs include conjunctivitis with excessive lacrimation, and photophobia. Keratitis is manifested by punctate abscesses, peripheral clouding (corneal edema), ulceration and corneal vascularization (Fig. 29.18). Uveitis is also a classic manifestation of this condition with the presence of infiltrative uveal disease, hypopyon, and miosis (Erdogan, 2010). Further discussion of this condition can be found in Chapter 35.
Chlamydial Keratoconjunctivitis

Chlamydiae have been isolated from cattle with conjunctivitis (Storz, 1988). Two case reports describe incidents of recurrent bilateral keratoconjunctivitis in three different cattle herds (Otter et al., 2003; Twomey et al., 2003). The cases were quite persistent and responded poorly to antibiotic treatment. Chlamydia phila spp. DNA was detected in conjunctival swabs by polymerase chain reaction (PCR). No other pathogens were detected. Two herdsman also developed concurrent eye disease, suggesting a possible zoonotic risk. A similar association has been recognized between the development of human conjunctivitis and contact with Chlamydia phila felis-infected cats (Twomey et al., 2003).

Other Systemic Infections

Malignant catarrhal fever and other systemic infections may cause nonulcerative keratoconjunctivitis. Please see Chapter 35 for additional information.

Infectious Bovine Keratoconjunctivitis

History

IBK, also known as pink eye, contagious ophthalmia, and New Forest disease, has received considerable attention because of its worldwide distribution and economic impact. The first possible report of IBK appeared in 1888 (Billings, 1889). Cattle with keratitis were shown to have bacilli on histopathologic sections of the cornea, yet at that time, experimental transmission of the disease was unsuccessful. In 1897, the term “contagious ophthalmia” was used subsequent to the successful transmission of keratitis from two affected to two noninfected cattle via conjunctival inoculation (Penberthy, 1897). In 1936, the primary pathologic nature of the causative organism was proposed, and in 1952, Barner concluded that the keratitis was caused by Moraxella bovis (Barner, 1952; Magens, 1936).

Economic Impact

Both regional and national surveys have documented the economic impact of IBK (Killinger et al., 1977; Simms et al., 1993; Slatter et al., 1982a). Financial losses resulting from decreased weight gain, decreased milk production, and treatment costs have been estimated to be $150 million in the United States in 1993 (Simms et al., 1993). The decreases in weight gain can range from 8 to 18 kg (Snowder et al., 2005; Troutt, 1985). Less tangible economic losses can also occur, such as a loss of value in show or breeding stock, weight loss and injury from handling animals for treatment, condemnation at slaughter due to ocular lesion detection, and lost productivity during time devoted to treatment.

Incidence

IBK occurs worldwide. In a 1997 report of the U.S. National Animal Health Monitoring System, IBK (1.1% infection rate) was the second-most prevalent condition affecting unweaned beef calves over 3 weeks of age (U.S.D.A., 1997). In the same report, IBK (1.3% infection rate) was the most prevalent condition affecting all beef heifers and cows. In studies at the University of California–Davis field station in Browns Valley, the yearly prevalence of IBK in yearling calves ranges from 57% to 98% (Allen et al., 1995; Eastman et al., 1998; George et al., 1988).

IBK occurs primarily during the summer months, though winter outbreaks occur (Hughes & Pugh, 1970; Pugh & Hughes, 1972; Webber & Selby, 1981). This seasonal fluctuation may result from the increased presence of hemolytic M. bovis, the fly population, and solar radiation during the summer months (Pugh & Hughes, 1975). The decline through the fall season may result from the lack of susceptible calves, fewer vectors, and decreased intensity of enhancing factors.

Etiology

While M. bovis, a gram-negative bacillus (Fig. 29.19), is considered to be the sole cause of IBK, other microbial agents have also been implicated (Angelos, 2010; Gourlay et al., 1974; Hughes et al., 1964; Pugh & Hughes, 1971, 1972; Pugh et al., 1976; Webber & Selby, 1981). However, M. bovis is the only organism for which Koch’s postulates have been satisfied (Angelos et al., 2011). Keratitis in gnotobiotic calves may be induced by inoculation of M. bovis into the conjunctival cul-de-sac (Rogers et al., 1987). Other infective agents that may play a role in development of IBK include Moraxella ovis (formerly Neisseria/Branhamella ovis), Moraxella bovoculi, IBR virus, Mycoplasma spp., Thelazia spp., and Listeria monocytogenes (Angelos, 2010; Pugh & Hughes, 1971; Rosenbusch, 1983; Rosenbusch & Ostle, 1986). Concurrent infection with IBR causes more severe clinical signs than with IBK alone (Pugh & Hughes, 1971). Herds vaccinated with modified live IBR virus have an increased incidence of IBK (Webber & Selby, 1981), more severe clinical signs (Pugh &
Hughes, 1971), and increased numbers of M. bovis isolates in the tear film (Pugh et al., 1984). Mycoplasma spp. have also been speculated to play an ancillary role in IBK (Pugh et al., 1976). In the summer of 2002, IBK-affected eyes of dairy and beef calves were cultured and in most calves hemolytic gram-negative cocci (but not M. bovis) was isolated (Angelos et al., 2007c). These hemolytic gram-negative cocci were characterized. Biochemical and molecular data indicated that these isolates were distinct from M. ovis and M. bovis and warranted their classification as a novel species called Moraxella bovoculi (Angelos et al., 2007c). The new bacteria, M. bovoculi, can be differentiated from M. bovis and M. ovis using polymerase chain reaction and via a positive phenylalanine deaminase (PD) test, which is positive in M. bovoculi and negative in both M. bovis and M. ovis. Although PD-negative M. bovoculi has been identified, these can be differentiated from M. ovis and M. bovis using previously cited PCR methods (Angelos, 2010; Angelos & Ball, 2007a). In the succeeding period since M. bovoculi was identified and characterized, it has become clear that the vast majority of M. ovis recovered from bovine eyes would now be reclassified as M. bovoculi. However, the causal role of M. bovoculi and M. ovis in naturally occurring IBK is unclear. A recent study showed that M. bovoculi and M. bovis are both more frequently recovered from eyes with IBK lesions than unaffected eyes, which provides weak evidence for a causal role for M. bovoculi in IBK (O’Connor et al., 2011).

**Morphology of Moraxella bovis**

The morphology of M. bovis colonies is either rough or smooth. Clinical cases of IBK are associated with the rough type, which have cell-surface pili, autoagglutinate in distilled water, stain with crystal violet, and hemagglutinate (Brown et al., 1998; Sandhu et al., 1974; Simpson et al., 1976). M. bovis colonies are easy to identify, do not require complex growth media, and may be identified by characteristic growth patterns (McMichael, 1992; Pugh et al., 1966; Riley, 1984). However, a semiselective media of brain–heart infusion agar with 5% bovine or ovine red blood cells and 2.5 mcg/mL of cloxacillin will reduce overgrowth by other organisms and increase the yield of M. bovis isolates (Webber et al., 1982b). The beta-hemolytic variants are usually associated with clinical disease (Brown et al., 1998).

Electron microscopy has revealed that bacteria from rough colonies of M. bovis are piliated and able to cause disease, whereas those from smooth colonies are nonpiliated and non-pathogenic (Fig. 29.20 and Fig. 29.21) (Sandhu et al., 1974; Simpson et al., 1976). Spontaneous transformation of rough to smooth colony type also occurs (Sandhu et al., 1974). Therefore, different strains of M. bovis, as well as different isolates of the same strain, may vary in virulence (Lepper & Power, 1988; Pugh & Hughes, 1971). The capsular pili promote cellular adhesion and enhance the ability to overcome host defenses and maintain an established infection.

**Figure 29.20.** Cross-section of a Moraxella bovis bacterium harvested from rough colony showing peritrichous distribution of pili (P) on the cell surface. Insert is a higher magnification of these pili. (Original magnification, ×47,570.) (With permission and modified from Simpson, C.F., White, F.H., & Sandhu, T.S. [1976] The structure of pili (fimbriae) of Moraxella bovis. Canadian Journal Comparative Medicine 40, 1–4.)
Without flies, transmission of IBK throughout a herd may be slow. Spread of the disease over long distances is probably associated with the movement of carrier cattle (Alexander, 2010).

Predisposing Factors

The sex of an animal is not a significant factor in development of the disease (Powe et al., 1992). All breeds may be affected, but breed-related differences in susceptibility occur. Bos indicus breeds are more resistant than Bos taurus breeds and Herefords as well as Hereford crossbreeds appear to have a much higher susceptibility, as do Murray Greys (Slatter et al., 1982b; Snowder et al., 2005). Because of the predilection for IBK in Herefords, the role of periocular pigmentation has been investigated. Some investigators have concluded that increased pigmentation has a protective effect, but others have not found a significant difference (Caspari et al., 1980; Clegg et al., 1982). One investigator noted that scleral color appeared to have a greater bearing on the incidence of infection than did periocular hair color (darker sclera appeared protective) (Wettemann et al., 2002). Other genetic variables may also be a factor, because significant familial differences in susceptibility have been reported in Herefords (Pugh et al., 1986a). A specific single nucleotide polymorphism (A/G in -26 Ex2 position of Intron 1 of Toll-like receptor 4) was found to be associated with significantly increased infection rates in American Angus cattle (Kizilkaya et al., 2011).

The age of cattle affects the persistence and severity of infection with M. bovis. Younger cattle, less than 2 years, consistently have an increased risk and severity of clinical
The mechanism of increased resistance among older cattle is unknown. Previous contact with *M. bovis* and subsequent development of antibodies may be responsible (Hughes & Pugh, 1970; Pugh & McDonald, 1986; Wilcox, 1970). Studies have shown that calves with increased antibody titers to *M. bovis* have significantly lower rates of infection and disease. However, increased serum antibody levels do not necessarily protect cattle from reinfection with *M. bovis* (Hughes et al., 1976). This apparent contradiction may be explained by the presence of varying strains of *M. bovis* (Pugh et al., 1978). Cattle usually possess greater resistance to reinfection by homologous rather than heterologous strains (George, 1984).

On the basis of long-term field studies, a good correlation exists between the annual peak incidence of IBK and annual peak levels of UV radiation. Nuclear fragmentation and loosening of bovine corneal epithelial cells occur with increased UV radiation, thereby increasing sites for bacterial adherence. UV radiation also causes degeneration of corneal epithelium (Vogelweid et al., 1986) and enhances *M. bovis*-induced keratitis in mice (Gerber & Frank, 1983). Increased UV radiation also assists in the transformation of *M. bovis* from nonhemolytic to hemolytic strains (Agora et al., 1976a). However, in one study of calves naturally infected with a nonhemolytic, nonpiliated strain of *M. bovis*, exposure to UV radiation and topically applied betamethasone failed to induce clinical signs of IBK. Ocular contact with ragweed pollen, both alone and in addition to UV light, enhances keratitis (Gerber & Frank, 1983).

The number of face flies present correlates well with the infection rate and the number of new isolates (Gerhardt et al., 1982). Once the number of flies exceeds 10 per animal, IBK spreads from one herd to another. Cattle housed indoors have a higher infection rate of longer duration, but milder clinical disease compared with those housed outdoors (Kopecky et al., 1981). Other environmental factors, such as mechanical irritants to the conjunctiva and cornea and ingestion of aflatoxin, have also been suggested as enhancing factors (Pugh et al., 1984).

**Pathogenesis**

In clinical outbreaks of IBK, *M. bovis* can be isolated from most affected cattle (Bryan et al., 1973; Gil-Turnes & Albuquerque, 1984). The initial corneal lesions probably result from bacterial cytotoxicity, whereas advanced lesions may be associated with bacterial/host inflammatory interaction. While *M. bovis* does not produce collagenase, the pathophysiology of IBK is likely associated with collagenase release from damaged epithelial cells, fibroblasts, and neutrophils (Frank & Gerber, 1981). In addition gelatinase and DNAase have been detected in whole cultures, while dermonecrototins and cytotoxins for BHK 21 cell line monolayers (Franco & Turnes, 1994) and soluble factors that cause reversible detachment of cultured corneal epithelial cells have been detected in *M. bovis* culture filtrates (Marrion & Riley, 2000).

Numerous neutrophils surround the corneal lesions and may contain phagocytosed organisms (Chandler et al., 1981). *M. bovis* has a marked cytotoxicity for bovine neutrophils and corneal epithelial cells (Kagonyera et al., 1989). A leukocidin has been identified that can damage neutrophils in a dose-dependent manner (Hoien-Dalen et al., 1990). Both hemolytic and cytotoxic activities are important in the pathogenesis of IBK and may be linked to a specific toxic protein of 110 kDa (Gray et al., 1995). Cytotoxic factors are calcium dependent and found only in whole cells and filtrates of hemolytic strains (Kagonyera et al., 1989). A positive correlation exists between the percentage of hemolytic strains isolated and the incidence of clinical disease (Brown et al., 1998). A hemolytic fraction of *M. bovis* is cytotoxic to calf corneal epithelial cells (Beard & Moore, 1994). Lipopolysaccharide of both rough and smooth *M. bovis* colonies induces production of tumor necrosis factor, which also may be important in the pathogenesis of IBK (Johansen et al., 1990).

Some studies have characterized the *M. bovis*-host relationship by using tear film analysis. Bovine lacrimal secretions contain secretory immunoglobulin (Ig) A, IgGa, IgGb, and IgM (Arora et al., 1976b). Bovine tears do not contain lysozyme, which may reduce their ability to control infection (Brightman et al., 1991; Gionfriddo et al., 2000). Lactoferrin, however, has been identified in bovine tears (Brown et al., 1996). In the absence of lysozyme, lactoferrin and secretory IgA are important to the defense of the host. Lactoferrin exerts a bacteriostatic effect by chelating iron, an essential growth element. Lactoferrin may also be a potential source of iron for pathogenic bacteria (Brown et al., 1998). *M. bovis* possesses receptors and siderophores (iron acquisition systems) that can compete with host lactoferrin for iron (Fenwick et al., 1996). It is currently unknown whether iron acquisition by *M. bovis* from lactoferrin in bovine tears enhances infection, but if so, immunologic recognition of iron-acquisition systems may provide an effective means of preventing IBK (Brown et al., 1998). Phospholipase B enzyme production is another potential virulence factor of *M. bovis* (Farn et al., 2001).

Pathogenic factors of *M. bovis* include pilin and cytotoxin (hemolysin, cytolsin) (Postma et al., 2008). Pilin facilitates attachment to the corneal surface. Cytotoxin lyses bovine neutrophils, erythrocytes, lymphocytes, and corneal epithelial cells (Angelos et al., 2007b). The cytotoxin is known to be an RTX (repeats in the structural ToXin) toxin (Angelos et al., 2001). The *M. bovis* cytotoxin is maintained within an operon composed of four genes (mbxCA BD) that encode proteins for cytotoxin activation (mbxC gene product), cytotoxin (mbxA gene product), and secretion (mbxB and mbxD gene products). A closely linked gene involved in secretion (tolC) flanks the mbxA gene. When *M. bovis* was examined for the presence of similar RTX genes, a complete RTX operon (designated the mbvCA BD operon) was identified. A high degree
of nucleotide and deduced amino acid sequence similarity exists between the *M. bovoculi* and *M. bovis* RTX operon genes. These results suggest a possible role for *M. bovoculi* in the pathogenesis of IBK (Angelos et al., 2007a). The *M. bovis* cytotoxin (mbxA) appears to be conserved among geographically diverse isolates of *M. bovis* from the United States and appears to be a candidate target for vaccine (Angelos & Ball, 2007b).

**Clinical Signs**

The earliest clinical signs are varying degrees of epiphora, blepharospasm, and photophobia; conjunctival hyperemia and chemosis also occur. Often, this stage may be missed clinically because of an inability to carefully observe affected animals. Within 24–48 hours after the onset of clinical signs, the axial cornea may develop small epithelial defects. Small corneal vesicles may precede ulceration. A small, pale, yellow to white raised abscess may appear near the center of the cornea, and over the following 24–48 hours, the corneal opacity may increase in size or slough, leaving a shallow, round to oval, superficial ulcer with perilimbal edema (Fig. 29.22 and Fig. 29.23). During the next few days, the corneal ulcer may expand and deepen (Fig. 29.24).

There is marked circumlimbal conjunctival vascular hyperemia and initiation of superficial corneal vascularization. Blepharospasm, mild to moderate aqueous flare, and iridocyclitis are present. The conjunctival exudate becomes mucopurulent, with matting of the eyelashes. Vascularization of the cornea proceeds rapidly toward the primary central lesion. By 7–9 days postinfection, an area of inflammation and corneal vascularization surrounds the well-delineated corneal ulcer (Fig. 29.25). As the vascularization reaches the ulceration, the corneal opacity clears from the periphery toward the center. The ulcer epithelializes and the facet gradually reduces by stromal regeneration, leaving a slightly raised, dense scar (Fig. 29.26). Corneal healing is well-advanced in 2–3 weeks and in 1–2 months only a faint localized central corneal opacity may remain.

The keratoconjunctivitis may result in secondary iridocyclitis, hypopyon, synechiae, and even panophthalmitis. Occasionally, perforation of the corneal ulcer results in iris prolapse (Fig. 29.27), in which case blindness may result. The eye may...

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**Figure 29.22.** Early, faint fluorescein retention by a central cornea affected with infectious bovine keratoconjunctivitis (IBK). (Courtesy of K.N. Gelatt.)

**Figure 29.23.** Mid-stromal corneal ulcer surrounded by corneal edema and early limbal corneal vascularization associated with infectious bovine keratoconjunctivitis (IBK). (Courtesy of J. Pearce.)

**Figure 29.24.** Large, deep-stromal corneal ulcer surrounded by cellular infiltrate, corneal edema, and ciliary flush associated with infectious bovine keratoconjunctivitis (IBK). (Courtesy of J. Pearce.)
also become hypotensive and phthisical or buphthalmic from secondary glaucoma (Fig. 29.28).

In 75% of cases, ocular involvement is unilateral (Slatter et al., 1982a) but subsequent bilateral involvement is frequent. Affected animals are reluctant to compete for food, milk production is reduced, and weight gain is suppressed, usually in direct relation to the severity of the lesion. In young cattle, the disease process is usually more severe than in older animals.

**Medical Treatment**

A recent review of randomized clinical trials reporting antibiotic treatment of infectious bovine keratoconjunctivitis in cattle was performed. The objective of the study was to evaluate treatments for IBK, based on a systematic review of the published literature, which yielded 196 manuscripts. Overall, the study suggested that antibiotic treatment is successful in reducing healing times of IBK-associated corneal lesions. The review identified very few manuscripts that reported a direct comparison of different antibiotic classes, so it was not possible to evaluate comparative antibiotic efficacy. There is clearly a need for further randomized controlled trials that evaluate the efficacy of antibiotic treatment for IBK, including direct comparisons of two or more antibiotics (O’Connor et al., 2006).

Currently, oxytetracycline formulations such as Liquamycin/LA-200 (Pfizer Animal Health, New York, NY) and Bovimycin 200 (Boehringer Ingelheim Vetmedica Inc., St. Joseph, MO) and the tulathromycin formulation Draxxin (Pfizer Animal Health) are the only parenteral antibiotics labeled for IBK in cattle. Topical medications approved for IBK at the time of publication include the oxytetracycline formulation Terramycin (Pfizer Animal Health) and Vetericyn Pink Eye Spray (Innovacyn Inc., Rialto, CA). Veterinarians are encouraged to consult current online publications for up to date information on IBK labeled drugs. Other treatment options require extralabel drug use in food animals, which is very
carefully regulated by the U.S. Food and Drug Administration and by the American Veterinary Medical Association via the Animal Medicinal Drug Use Clarification Act. Therefore, other treatment options should only be used if currently labeled drug have been shown ineffective and as long as the drugs are not prohibited for extralabel use in food animals (AVMA, 2007).

Therapy for IBK is recommended to relieve pain and maintain productivity. Combined parenteral (20 mg/kg) and oral (alfalfa pellets containing 1 g/0.45 kg of pellet administered daily for 10 days at a dosage of 2 g/calf/day) administration of oxytetracycline appears to be an effective method of reducing the severity of herd outbreaks of IBK (Eastman et al., 1998). Oxytetracycline therapy appears to be superior to treatment of affected animals with procaine penicillin G. Calves treated with oxytetracycline had fewer recurrences and less shedding of M. bovis compared with those treated with penicillin G (Eastman et al., 1998; George, 1990). Parenteral oxytetracycline is effective even with relatively low tear drug concentrations, because the concentrations are maintained above the MIC for a prolonged period of time (George & Smith, 1985; Smith & George, 1985). Oxytetracycline is selectively distributed to the conjunctiva and lacrimal gland (George et al., 1985). This treatment option is particularly appealing because long-acting oxytetracycline formulations (LA -200 and Bio-Mycin 200) are currently approved for treatment of IBK in the United States. While parenteral long-acting oxytetracycline formulations can be used in lactating dairy cattle, alfalfa pellets containing oxytetracycline cannot. The duration of the carrier stage (i.e., a normal eye with hemolytic M. bovis) is reduced by two injections of long-acting oxytetracycline at 20 mg/kg each. In addition to shortening the carrier stage, treatment reduces the progression of lesions and shortens healing times in affected animals (Brown et al., 1998).

Antibiotics demonstrating efficacy against M. bovis include tilmicosin (one dose of 5–10 mg/kg subcutaneously) (Zielinski et al., 2002), long-acting ceftiofur crystalline-free acid (one dose of 6.6 mg of ceftiofur equivalents/kg subcutaneously into the posterior aspect of the pinna) (Dueger et al., 2004), florfenicol (two injections of 20 mg/kg intramuscularly q 48 hours or a single dose of 40 mg/kg subcutaneously) (Angelos et al., 2000), tulathromycin (2.5 mg/kg, subcutaneously) (Lane et al., 2006), and clindamycin (150 mg subconjunctivally q 24 hours for 3 days) (Senturk et al., 2007). Other drugs recommended by various authors include penicillin, ampicillin, ormetoprim-sulfadimethoxine (prohibited for extralabel use in lactating dairy cattle in the United States), furazolidone (prohibited for use in food animals in the United States), gentamicin, and neomycin (Edmondson et al., 1989; George, 1990; George & Smith, 1985; George et al., 1984; Wilson et al., 1987).

M. bovis is usually resistant to tylosin, lincomycin, and erythromycin, and has variable susceptibility to cloxacillin (George, 1990; George et al., 1989; Webber et al., 1982a). Given intravenously (prohibited in lactating dairy cattle in the United States), sulfadimethoxine establishes effective levels in the tear film and eliminates both ocular and nasal infections with artificially induced IBK (Angelos et al., 2011; Wilson et al., 1987). Some M. bovis strains, however, may be sulfa-resistant. While M. bovis is sensitive to many antibiotics, regional and strain differences may necessitate culture and sensitivity tests to select a specific antibiotic, especially during a severe outbreak (George, 1990; Webber et al., 1982a). The treatment selected is influenced by the management practice of the affected animals. Dairy operations usually have daily access to the animals, but milk withdrawal times become important issues. Dairy operations therefore may choose procaine penicillin because of the short milk-withdrawal times (Miller & Fales, 1984). Because beef cattle are infrequently handled, beef practitioners may opt for long-lasting parenteral medications such as oxytetracycline (Brown et al., 1998). As antibiotic drug residues vary according to the drug formulation, dose, frequency, route of administration, and weight of the animal, the Food Animal Residue Avoidance Database should be contacted to determine withdrawal times and legality of use of a particular drug in an extralabel fashion.

A study of minimum inhibitory concentrations of several antimicrobial agents has been published for M. bovoculi since it was identified. The low MIC (90) of M. bovoculi isolates suggests that commonly used antibiotics for treatment of IBK associated with M. bovis should also be effective against M. bovoculi (Angelos et al., 2011).

Other medical treatments for IBK include topical atropine and non-steroidal anti-inflammatory drugs. These medications assist in relief of intraocular pain and decrease the incidence of inflammatory-induced ocular lesions such as synchiae, secondary glaucoma, and cataracts. Some reports detail use of local corticosteroids in IBK-affected eyes without any detrimental effect (Allen et al., 1995). The lack of evidence-based medicine indicating corticosteroids are beneficial in IBK cases, and the possibility of potentiating collagenases and prolonging healing times must be considered. Therefore, corticosteroids are best avoided in IBK.

Regardless of the therapy chosen, additional treatment steps should be taken to control the herd infection and minimize the economic effects. Critical measures include use of insecticides to control face flies, segregation of affected animals, personal disinfection between treatments of affected and noninfected animals, and frequent mowing of pastures.

**Surgical Treatment**

Nictitating membrane flaps and complete temporary tarsorrhaphies have been used in treatment of deep and perforated corneal ulcers in IBK (Anderson et al., 1976). There are, however, no published, controlled studies assessing the benefits of third eyelid flaps. These methods have been modified from the surgical procedures used in small animals (see Chapter 14). Often, 0- or 1-chromic gut sutures are used in beef animals so that suture removal is avoided.
Vaccination

Several vaccines for *M. bovis*, including live or formalin-killed cells, ribosomes, pili, and cytolysin, have been tested. Early vaccines provided only limited protection, and unfortunately the recent vaccines appear to be only slightly more efficacious (Angelos, 2010; Angelos et al., 2007b; M Connel & House, 2005; Pugh et al., 1982). Passive immunity from vaccinated animals may occur. Calves of vaccinated cows or calves fed colostrum from vaccinated animals show reduced incidence of IBK, reduced severity of clinical signs, and delay in onset of clinical signs (Pugh et al., 1980, 1982, 1986b).

Vaccination with homologous strains reduces the incidence and severity of disease, whereas heterologous strain vaccines against IBK have limited success (Hughes & Pugh, 1975; Hughes et al., 1968; Pugh & Hughes, 1976; Pugh et al., 1977). Because endemics of IBK have been associated with *M. bovis* isolates possessing novel pili types (Vandergaast & Rosenbusch, 1989), multivalent vaccines should include pili from one representative strain of each serogroup to be effective (Lepper et al., 1992, 1995). Pili-antigen vaccines have demonstrated reduction of incidence and severity of IBK (Lepper, 1988); ribosomal vaccines are not effective (Pugh et al., 1981). Recombinant DNA technology has also been used to develop low-dose pili vaccines (Lepper et al., 1993). A recent cytolysin-enriched vaccine provided partial protection from IBK (George et al., 2005). A recombinant *M. bovis* cytotoxin–ISCOM matrix adjuvanted vaccine was slightly more effective than currently available vaccines in reducing IBK within vaccinated calves (Angelos et al., 2004). Angelos also recently tested a recombinant *M. bovis* pilin–*M. bovis* cytotoxin subunit vaccine that delivered a conserved pilin domain with a previously tested recombinant carboxy terminus of mbxA (Angelos et al., 2007b). He found a reduced cumulative proportion of IBK in the pilin-cytotoxin vaccinated calves compared with those given the cytotoxin vaccine alone. Concerns have arisen that the efficacy of *M. bovis* vaccines may be reduced in herds where IBK has been associated with *M. bovoculi*. Another study evaluated a recombinant *M. bovoculi* cytotoxin–ISCOM matrix adjuvanted vaccine potential to prevent naturally occurring IBK in California. In this study, the use of *M. bovoculi* antigens alone in vaccines to prevent IBK did not appear to be beneficial, perhaps because IBK in the tested herds was associated with both *M. bovoculi* and *M. bovis* (Angelos et al., 2010).

After vaccination, natural challenge, or experimental exposure, levels of lacrimal and serum antibodies to *M. bovis* vary. There is evidence for general immunity after exposure to *M. bovis* (Kopecky et al., 1983). The immunoglobulin content of the lacrimal secretion has been variably reported as IgG or IgA (Bishop et al., 1982; Hughes et al., 1977; Yancey, 1993). Initial immunity to infection with *M. bovis* is thought to be mediated by humoral IgG, with assistance 2 weeks later from secretory IgA (Miller & Fales, 1984). Protection against a second episode of IBK appears to relate more to lacrimal IgA, however, than to serum IgG (Rosenbusch, 1987). Vaccination causes a rise in anti-*M. bovis* IgG titers in the serum (Bishop et al., 1982; Miller & Fales, 1984). Unfortunately, the presence of anti-*M. bovis* IgM, IgG, and IgA does not preclude development of disease (Powe et al., 1992).

The protection provided by vaccination is also a function of the route of administration. The highest level of protection is provided when tear film antibodies (i.e., IgA) are induced by mucosal vaccination (Nayar & Saunders, 1975). However, subcutaneous bacterins afford protection as good as, or better than, that afforded by bacterins given subconjunctivally (Pugh et al., 1985). A study also evaluated the local ocular mucosal IgA response against *M. bovis*-purified pili, produced after intranasal inoculation of experimental vaccines by an indirect enzyme-linked immunosorbent assay (ELISA). Significantly higher anti-pili IgA response was detected in calves vaccinated intranasally with pili compared with control calves, although this specific immune response did not seem to be related to protection against *M. bovis* infection or typical IBK lesion development (Zbrun et al., 2011).

After outbreaks of IBK, antihemolysin antibodies can be found in all cattle, even those without a history of clinical IBK (Ostle & Rosenbusch, 1985). These antihemolysin antibodies will react with all strains of *M. bovis*. Several outer membrane protein antigens common to all strains have also been identified (Ostle & Rosenbusch, 1986). The possibility of a common antigen among all *M. bovis* serovars suggests that a reliable vaccine may be possible.

In herds severely affected by IBK, vaccination may be worthwhile. Current recommendations are to vaccinate 6 weeks before onset of the expected disease season (Miller & Fales, 1984). Calves should be vaccinated at 21–30 days of age, with a second vaccination occurring 21 days later. Vaccine administration should be at least 21 days before the fly season. It is not known whether colostral antibodies will interfere with the vaccines. A dual cattle should receive two initial vaccinations, followed by yearly boosters near the beginning of the vector season. Vaccination programs work best if calving is performed at a time with decreased flies and UV-B radiation.

Neoplasia of the Conjunctiva and Cornea

Of the food animal species, cattle are most affected by ocular and periorcular neoplasia. The most common neoplasia is OSCC. In one study of 95 ocular tumor types in cattle, 91 cases were either OSCC (84 cases) or papillomas (7 cases). The other conjunctival tumors were eyelid lymphomas (3 cases) and adenocarcinoma (1 case) (Blodi & Ramsey, 1967).

Ocular Squamous Cell Carcinoma

Ocular squamous cell carcinoma has considerable economic impact, particularly from the loss of older breeding animals and due to partial carcass condemnation at slaughter. In a study performed in 2009, OSCC/epithelioma was the fourth leading cause (9.15%) of carcass condemnation at postmortem...
examinations of animals sent to harvest for beef in the United States from 2003 through 2007 (White & Moore, 2009). Cattle with OSCC are condemned if the eye has been destroyed, if there is extensive infection, if the animal is in poor condition, or if there is evidence of spread to other parts of the body, including structures around the eye. Cattle with small, localized lesions may pass inspection after condemnation of affected parts such as the head. The presence of OSCC in slaughter animals is estimated to cause annual losses of $20 million in the United States alone. The National Cattlemen’s Association has focused on ocular neoplasia as part of their Beef Quality Assurance program because a negative public perception results when cows with prominent, unsightly external lesions are seen at a livestock market or slaughterhouse (McKinnon, 1997; Roeber, 2003).

Incidence
A ctual incidence in the general cattle population of the United States is often difficult to assess. In herds of live cattle, the incidence of OSCC has shown to vary from 4.4% to 5.6%. However, many of these studies considered herds of Hereford or Hereford cross cattle only and hence it is difficult to extrapolate from them (Heeney & Valli, 1985). In the Netherlands, the incidence is 0.04%, as determined from unpublished data from examinations of 35,000 animals (Kein et al., 1984). In some breeds, the incidence may be much higher.

Geographic Distribution
Bovine OSCC occurs worldwide, but there is an association between the occurrence of OSCC and an increased level of solar radiation (Anderson & Badzioch, 1991). Using disposal data for 4960 female Herefords born between 1926 and 1954 in nine herds, Anderson and Skinner showed that after adjusting for age, the incidence of OSCC increased significantly with decreases in latitude, and increases in altitude and mean annual hours of sunlight (Anderson & Skinner, 1961).

Signalment
The onset of OSCC is age related, with older cattle having a significantly greater risk (Anderson & Skinner, 1961). The tumors are uncommon in cattle younger than 5 years, and they are rare in cattle younger than 3 years (Russell & Loquvam, 1951). The average age of cattle with OSCC is 8.1 years (Anderson & Badzioch, 1991).

In an experimental herd of 276 female cattle examined sequentially between 1979 and 1988, OSCC was first observed at 4.5 years of age (Bailey et al., 1990). In a herd of pedigreed Simmental cattle 12% had OSCC at 3 years of age, and this percentage increased to 50% at 7 years (Anderson & Badzioch, 1991). In another study involving five breeding herds of Simmental cattle OSCC prevalence increased with age such that from 36% to 53% of cattle older than 7 years had one or more tumors (Russell & Loquvam, 1951). The odds ratios for age in a study of 595 affected animals indicated a 2% increase in the risk of affliction for each additional month of age (Anderson & Badzioch, 1991). It has been suggested that in a herd of Simmental cattle, virtually all cattle without periorbital pigmentation will acquire OSCC (Anderson & Skinner, 1961).

The incidence of OSCC is significantly higher in Bos taurus than in Bos indicus breeds (Bailey et al., 1990). Though other cattle breeds are affected, the Hereford is overrepresented. This may result, in part, from the popularity of this breed in the United States; Herefords outnumber all other breeds of range cattle combined (Russell & Loquvam, 1951). This association is also partially related to the typical periorcular depigmentation. Examinations of 2775 female Herefords from 34 herds located in the United States and Canada found that 595 (21%) had OSCC (Anderson & Badzioch, 1991). Logistic regression analysis indicated that age and lack of corneoconjunctival pigmentation were significant risk factors. In another study, significantly more Hereford × Shorthorn cattle than Bos indicus-based breeds were culled because of OSCC (Bailey et al., 1990). Finally, a reduced incidence of all types of OSCC was observed in F1 Brahman-cross dams versus F1 Red Poll × Herefords, F1 Hereford × Red Polls, or F1 Angus × Herefords. Ayrshires are the most susceptible dairy breed and have a corresponding predilection for SCC of the vulva (Radostits et al., 2007).

The sites of OSCC may be single or multiple, unilateral or bilateral (Anderson & Skinner, 1961). Of 93 tumors recorded in the eyes of 46 adult Simmental cattle, 22 cattle had a single tumor, 15 had two tumors, 4 had three tumors, 4 had four tumors, and 1 had nine tumors. Both eyes were affected in 35% of cattle. This contrasts with a herd of 523 Friesians in which 1.4% were affected with OSCC and only single tumors were present.

There is no true sex difference in the incidence of OSCC. The higher incidence observed in females results from the males having been marketed before the age of peak incidence (Heeney & Valli, 1985).

Genetic Predisposition
There is considerable evidence suggestive of a genetic basis for OSCC, such as variable morbidity rates among various breeds of cattle, lines of sires, and increased rates in the progeny of affected compared with that of unaffected parents (Anderson, 1963; Cleaver et al., 1972; Dennis et al., 1984, 1985). Lesion development is not heritable directly, but the genetic effect on periorcular pigmentation determines to a large extent the degree to which the eye is susceptible (Anderson & Badzioch, 1991). In Zimbabwe, OSCC has not been observed in breeds with fully pigmented heads, such as the Jersey, Brahman, and Mashona (Anderson & Skinner, 1961). When cattle were older than 7 years, 60% of eyes without periorbital pigmentation had OSCC, whereas only 24% of eyes with periorbital pigmentation had tumors.

clearly has an inhibitory effect on eyelid lesions, but seems to have little effect on development of the much more frequent, conjunctival OSCC.

Corneoscleral (i.e., limbal) and bulbar conjunctival pigmentation have a local inhibitory effect on the development of OSCC. eyelid and corneoscleral pigmentation are related both phenotypically and genetically (Anderson, 1991). Corneonconjunctival pigment has a heritability of 0.53 (Anderson, 1991). Some animals have OSCC in pigmented areas of the limbus, which would argue against the protective effect of pigment (Anderson, 1991). However, serial photographs and observations of 120 animals over 15 years indicate that pigment can develop in previously unpigmented areas in response to OSCC (Russell & Loquvam, 1951). Subsequent observations then reveal OSCC in a pigmented area. While ocular pigmentation may not be discernible in Herefords younger than 1 year or be fully expressed until 5 years, the inhibitory effect on lesion frequency is significant when adjusted for age and compared with animals having little or no corneonconjunctival pigmentation. Hence, breed susceptibilities are predominantly a function of periocular pigmentation (Anderson et al., 1957).

Etiology of OSCC
A specific carcinogen has not been identified. A number of factors, including age, gender, breed, periorcular and corneoscleral pigmentation, exposure to sunlight, viral infection, and nutrition, likely contribute to development of OSCC (Anderson, 1991; Anderson & Badzioch, 1991; Chapman et al., 1995; Den Otter et al., 1995a; Heeney & Valli, 1985; Kuchroo & Spradbrown, 1985; Rutten et al., 1992; Taylor & Hanks, 1969).

Exposure to sunlight plays a significant causal role in the development of OSCC (Den Otter et al., 1995a). In cattle, all measures of solar radiation indicate a significant association between increasing risks of OSCC and increasing levels of radiation (Anderson & Badzioch, 1991). Associations are evident whether affliction is defined as the occurrence of any type of tumor (i.e., plaque, papilloma, and carcinoma) or as the occurrence of only papilloma or carcinoma. Average ages of affected cattle are lower at high levels than at low levels of radiation. The total UV solar irradiance varies markedly with latitude and season (Chapman et al., 1995). UV-B affects all living organisms, and it damages DNA (Mayer, 1992).

Humans with xeroderma pigmentosum suffer an enzyme deficiency that prevents the repair of DNA defects (Cleaver et al., 1972) and exhibit a very high frequency of OSCC. They are the best example of a direct link between unrepaired DNA lesions and cancer induction (Arnault et al., 2004). A similar enzymatic defect has not been found in cattle with OSCC (Cleaver et al., 1972). Enzymatic assays for superoxide dismutase and catalase have shown no correlation with OSCC (Hamlet & Lavin, 1987). While most solar-induced DNA lesions are repaired very efficiently in normal cells (Ley, 1984; Ley et al., 1988), UV radiation causes mutations in oncogenes and tumor-suppressor genes, and specific p53 mutations have been detected in UV light-induced cutaneous SCC of humans, cats, dogs, horses, and cattle (Coulter et al., 1995; Oram et al., 1994; Telfke & Lohr, 1996).

Viral cofactors have been suggested in the etiology of OSCC, but there is no definite evidence. IBR virus has been isolated from ocular carcinoma and one of its precursor lesions, and “IBR-type” inclusion bodies have been consistently observed in all types of OSCC lesions (Sykes et al., 1959; Taylor & Hanks, 1969). It is not known whether IBR virus has a predilection for the epithelial tissue in ocular tumors. In addition, because IBR virus can be frequently isolated from early plaque lesions, it apparently exists early in the course of the disease among many animals. Whether IBR has a part in initiating tumor growth is only speculative (Taylor & Hanks, 1969). Bovine herpesvirus-5 antigens have been detected in OSCC cell cultures (Anson et al., 1982).

The role of bovine papilloma virus (BPV) in OSCC has also been examined. Neither the use of papilloma virus-specific antibodies nor DNA hybridization assays for all six known types of BPV could demonstrate a directed association with OSCC (Rutten et al., 1992; Sundberg et al., 1984). While not needed for tumor maintenance, BPV may play a role initially in tumor formation (Rutten et al., 1992).

Nutritional status affects the development of OSCC from 6 to 9 years of age (Russell & Loquvam, 1951). Cattle with high nutritional levels have an occurrence of OSCC of 14%, whereas cattle on lower feed intakes have an occurrence of 1.5% (Radostits et al., 2007). Animals on a high nutritional plane also have increased severity and number of tumors and reduced 5-year survival rates compared with that in animals at a low level of nutrition. Similar results have been demonstrated in laboratory animals (Anderson, 1970).

Clinical Signs
Approximately 75% of OSCC and precursor lesions affect the bulbar conjunctiva and cornea, and of these, 90% involve the limbus and 10% the cornea. The remaining 25% of OSCC lesions are distributed in the palpebral conjunctiva, nictitating membrane, and eyelids (Russell et al., 1956). Limbal lesions occur more frequently in the horizontal than in the vertical meridian, which could result from greater exposure to irritation by foreign matter and sunlight. Bovine OSCC has a characteristic progression through a series of benign stages and then, possibly, to a malignant stage (Russell et al., 1956). On the globe and third eyelid, the initial lesion is a plaque. Plaques may progress to a papilloma, then to a noninvasive carcinoma (i.e., carcinoma in situ), and finally to an invasive carcinoma. In the eyelids, however, extensive keratosis (i.e., keratoma) may occur, particularly near the mucocutaneous junction. This keratosis may appear as a cutaneous horn and be the precursor to carcinoma formation (Moulton, 1961). The keratotic lesions are moistened by tears, collect debris, and become brown. They can be easily removed, leaving a bleeding surface.

A plaque is a small area of hyperplastic epithelium (Anderson et al., 1957). Plaques may be single or multiple, raised,
of various shapes, and found in the conjunctiva following the curvature of the limbus. Their surfaces are smooth or irregular, and their consistency may be firm (because of keratinization). Plaques are opaque and grayish white (Fig. 29.29) (Taylor & Hanks, 1972). Papillomas are distributed similarly to plaques, and they may be thrown up into fronds. They have a connective tissue core with multiple hard, spinelike projections of variable size, and they may be sessile or pedunculated (Fig. 29.30) (Anderson et al., 1957). Papillomas often merge with underlying plaques.

Carcinoma in situ arises directly from plaques and is characterized microscopically as the stage before the neoplastic cells have penetrated the subepithelial lamina propria. Grossly, they resemble papillomas and exhibit no invasive tendencies (Fig. 29.31) (Anderson et al., 1957). Invasive carcinomas are generally large and protrude through the lamina propria (Fig. 29.32 and Fig. 29.33). They can invade the anterior chamber and eventually infiltrate the entire globe (Fig. 29.34). Carcinomas arising from the nictitating membrane are locally invasive, seldom invade the cartilage, but may infiltrate the medial orbit (Fig. 29.35). Secondary changes, such as necrosis, ulceration, hemorrhage, and inflammatory cell infiltration, appear in more than 40% of the invasive carcinomas (Anderson et al., 1957).

Metastatic Potential
Systemic metastases occur late in OSCC; however, local invasion may be particularly aggressive (French, 1959). As the carcinomas penetrate the lamina propria, they extend “fingers” of neoplastic cells into the surrounding tissues. To some extent, the consistency and nature of that tissue will determine

Figure 29.29. Limbal gray-white plaque in a Hereford cow. (Courtesy of C. Moore.)

Figure 29.30. Limbal papilloma in a Hereford cow. (Courtesy of C. Moore.)

Figure 29.31. Limbal carcinoma in situ. (Courtesy of C. Moore.)

Figure 29.32. Extensive invasive limbal squamous cell carcinoma involving more than two thirds of the cornea and protruding through the palpebral aperture. (Courtesy of L. Horstman.)
the progression of the tumor. Limbal OSCC shows less inward invasion, resulting from resistance of the stroma, Descemet's membrane, and the sclera. However, the anterior chamber of the eye may still be involved, and in one series, intraocular extension was reported in 67 (14%) of 471 carcinomas (Anderson et al., 1957). The posterior segment is rarely affected (Fig. 26.27–26.29).

A greater percentage of systemic metastases occur from tumors of the lid and nictitating membrane (Tsujita & Plummer, 2010). Metastases often involve the regional lymph nodes and orbital bones (McKinnon, 1997). Intracranial metastasis, probably by extension through the foramen orbitotundum, has been reported (Zeman & Cho, 1986), and intracranial invasion via the cranial nerves (i.e., optic nerve and ophthalmic branch of trigeminal) has been documented (Samuel et al., 1987). Systemic metastasis usually occurs via the parotid lymph node to the regional lymph nodes, including the atlantal, retropharyngeal, submaxillary, mandibular, and cervical nodes. Once the metastatic cells gain access to the thoracic duct, they spread hematogenously via the venous circulation. Metastases can affect the lungs, heart, pleura, liver, kidney, and bronchial as well as mediastinal lymph nodes (Moulton, 1961).

Diagnosis: Cytologic Examination
Cytology should not be used as an alternative to histopathology, although a strong correlation exists between cytologic and histopathologic diagnoses. High rates of agreement (86.5%) between the two diagnostic modalities have been reported (Hoffmann et al., 1978). Any time an equivocal cytologic decision occurs, a histopathologic specimen should be examined (Garma-Avina, 1994). With very anaplastic tumors, it may be impossible to decide if it is epithelial or mesenchymal in nature on the basis of cytology or histopathologic sections (Kadota et al., 1985). Immunohistochemical evaluation may assist in diagnosing these borderline cases (Garma-Avina, 1994).

In a series of 40 OSCCs, the cytologic changes were compared with the histopathologic results (Garma-Avina, 1994). In this study, the well-differentiated OSCCs showed a marked predominance of large, markedly angular, nucleated squamous cells with nuclear features of malignancy, such as hyperchromatic chromatin and large multiple nucleoli of various shapes. The predominance of medium-sized, round to oval cells with a high nucleus-cytoplasm ratio, malignant-looking nuclei, and clear-cut cytoplasmic evidence of squamous origin suggested a moderately differentiated OSCC. The predominance of small, round cells with a high nucleus-cytoplasm...
the underlying connective tissue proliferates into the over­
lying epithelium. At this stage, the plaque becomes a
papilloma.

When fully developed, the papilloma consists of multiple
papillary projections (i.e., fronds), which are covered by pro­
liferative epithelium and supported by vascular connective
tissue stalks. The overlying epithelium exhibits varying
extents of hyperkeratosis.

Carcinoma in situ exhibits malignant transformation of the
epithelial cells in the basilar layer or, less commonly, in the
stratum spinosum. These cells display hyperchromatic nuclei,
increased numbers of mitotic figures, pleomorphism, and loss
of polarity. The neoplasm may show signs of early invasive­
ness, and infiltration of mononuclear cells is common at these
sites.

Invasive carcinomas have been graded on the basis of the
World Health Organization classification of tumors. The his­
topathologic gradations are well-differentiated, moderately
differentiated, and poorly differentiated OSCC.

Treatment

Before therapeutic intervention, the extent of the lesion should
be evaluated. Topical anesthesia and a lubricated, gloved hand
are usually sufficient to palpate the orbital rim. OSCC extends
firm tendrils, which can be followed to their most invasive
extent. A thorough physical examination concentrating on
possible sites of metastasis is essential. Extensive systemic
invasion may preclude further treatment because of financial
and prognostic reasons. Examination at slaughter revealed
that 5% of animals had metastatic lesions (Anderson et al.,
1957). Animals with invasive OSCC have an even higher
level of metastasis (11%) (Hamir & Parry, 1980). If indicated
and finances allow, complete blood counts and serum bio­
chemistry profiles are also suggested. Orbital radiography
may be useful in determining bony involvement; dorsal
oblique radiography provides the most useful information.
Bony involvement carries a very guarded prognosis.

When deciding on treatment strategies, it is important to
realize that not all precancerous lesions progress. In one herd
study, 52% exhibited precursor lesions (e.g., plaque, papil­
loma, keratosis) of OSCC. Of these lesions, approximately
one-third regressed spontaneously and disappeared (Taylor &
Hanks, 1972). Other reports suggest spontaneous regression
rates as high as 50% (French, 1959). Whether such lesions
recur over a long period of time is not known.

If treatment is undertaken, the options include surgical
excision with or without adjunctive therapy, cryotherapy,
hyperthermia, immunotherapy, radiation therapy, and possibly
chemotherapy. The most common method of treatment is
surgery, and when combined with other treatment modalities,
the success rates are quite good (Tsujita & Plummer, 2010).

Surgery

Salvage Procedures Salvage procedures used together
may either cure or prolong an animal’s life, which may be

Figure 29.36. Hematoxylin and eosin stained photomicrograph dem­
onstrating typical histological appearance of bovine squamous cell carci­
noma with desmoplasia. The neoplastic cells have moderate amounts to
abundant cytoplasm, distinct cell borders, and round to oval nuclei with a
prominent nucleolus. Individual cell keratinization and a keratin pearl are
seen in the center of the neoplasm. (Courtesy of K. Kuroki.)
desirable for pregnant cows or for bulls to allow semen collection. Enucleation may be performed via subconjunctival or transpalpebral approaches. The latter procedure is frequently used in cattle with extensive neoplasia of the globe, eyelids, nictitating membrane, or conjunctiva. Exenteration should be considered if any orbital involvement by the tumor is detected or suspected.

In animals with evidence of local lymph node metastasis only, which may be up to 33% of cases, block resection offers cure rates as high as 90%. Transpalpebral enucleation alone may show a recurrence rate of 37% (Klein et al., 1984). Block resection involves removal of the retropharyngeal lymph node, mandibular salivary gland, and parotid salivary gland/submandibular lymph node as well as a transpalpebral enucleation (Bier et al., 1979). Care must be taken not to damage the vagosympathetic trunk (Klein et al., 1984). This procedure is suggested for animals that are valuable and have local lymph node enlargement but no radiographic evidence of spread to the lungs.

Eyelid and orbital surgery are performed most frequently in standing cattle, and regional anesthesia for most ocular surgeries in food animals may be achieved with either a Peterson nerve block (Peterson, 1951) or a four-point block of the orbit. In a comparison of the retrobulbar and Peterson nerve block techniques in bovine cadavers (Pearce et al., 2003), the retrobulbar technique was characterized by widespread distribution of contrast medium around the periorbital structures, along the optic nerve, and in the ethmoid turbinates and nasopharynx. The Peterson technique was characterized by contrast medium repeatedly located in the pterygopalatine fossa with minimal distribution to the surrounding structures. However, though rare, it is important to inform clients that apnea and occasionally death may occur 8–9 minutes after performing a Peterson nerve block (Ramakrishna, 1995). This may result from injection of the anesthetic agent directly into a blood vessel, which can be avoided by aspirating first, or injection into the dural sheath.

The Peterson nerve block is a retrobulbar injection that blocks the optic, oculomotor, trochlear, abducens, and ophthalmic as well as maxillary branches of the trigeminal nerve (Fig. 29.37). Lack of pupillary constriction indicates successful application of this block, in which a slightly curved, 10-cm, 18-gauge needle is inserted at the caudal angle between the supraorbital process and the zygomatic arch. The concavity of the curvature is directed posteriorly to allow passage of the needle anterior to the anterior border of the coronoid process of the mandible. The needle may not need to be walked off the coronoid process anteriorly. The needle is advanced in a slightly ventral direction to the pterygopalatine fossa and the foramen orbitalis; complications may be avoided if the needle is not advanced to the bony floor of the pterygopalatine fossa. Aspiration is then performed, and approximately 15–20 mL of lidocaine (2%) is injected. Alternatively, a four-point block (Fig. 29.38) may achieve sufficient anesthesia. In this block, a 6-cm needle is inserted transconjunctivally adjacent to the globe at the twelve-, three-, six-, and nine-o’clock positions, and 5–10 mL of lidocaine are injected at each site. A variation of this technique is to direct the needles through the eyelids rather than the conjunctiva. Possible complications of retrobulbar nerve block in cattle include orbital hemorrhage, penetration of the globe, damage to the optic nerve, and injection of local anesthetic into the optic nerve meninges (Edge & Nicoll, 1993; Rubin, 1995; Skarda, 1996).

A kinesia of the eyelids is obtained by an auriculopalpebral nerve block. Local anesthetic is injected subcutaneously 5–7 cm caudal to the supraorbital process, where the nerve crosses the zygomatic arch. Eyelid anesthesia is achieved with local anesthetic infiltration.

After enucleation, most animals do not require systemic postoperative antibiotic treatment; however, an injection of...
Surgery: Eyelid Neoplasia If any doubt exists regarding the extent of an eyelid OSCC, then exenteration, with or without radical surgery, is advised. If, however, there is no evidence of lymph node metastasis, some form of blepharoplasty procedure by itself may cure the animal. Use of an H-plasty in cattle with OSCC affecting the lower lid provides excellent results (Welker et al., 1991). Tumors larger than 50 mm in diameter or with ill-defined margins are suitable candidates. In 14 animals treated in one study, 12 did not have recurrence at the 6-month follow-up (Welker et al., 1991). All wounds were cosmetically acceptable, and all wounds healed by primary intention. In addition, all but two animals had normal eyelid function postoperatively. These high success rates resulted from the large excisions that can be performed with this technique.

Surgery: Nictitating Membrane Neoplasia Small OSCCs may be removed, leaving an intact nictitating membrane, but larger ones usually require total excision of the structure. OSCC in this area may frequently recur after surgical removal, and it may invade the orbit either hematogenously or by direct infiltration due to the difficulty in completely removing the glands surrounding the base of the cartilage.

Surgery: Conjunctival Neoplasia Neoplasms may affect the fornix, palpebral, and bulbar conjunctiva. In the early stages, these tumors may be amenable to local excision with a scalpel, electrocautery, or carbon dioxide laser. Though not reported in cattle, the CO₂ laser has been used in other animals (English et al., 1990).

Surgery: Limbal and Corneal Neoplasia Keratectomies may be used to remove corneal and limbal neoplasms limited to the outer layers of these tissues. Postoperative corneal scarring is not a significant problem in cattle. Limbal lesions affecting the cornea and adjacent bulbar conjunctiva are similarly removed. A conjunctival grafting procedure may be performed using 7-0 absorbable suture.

Cryotherapy Cryotherapy is a popular treatment of OSCC (Farris & Fraunfelder, 1976), and high success rates have been achieved. In one study using a double freeze–thaw technique, 97% of OSCC regressed, including 73% of those larger than 20 mm in diameter (Farris, 1980). The data must be interpreted carefully, however, because 76% of the samples were smaller than 10 mm, and it is not known what percentage would have spontaneously regressed. Joyce (Joyce, 1976) has reported an 86.6% success rate in treating limbal and corneal SCCs.

All suspected premalignant lesions (e.g., focal ulceration or keratosis on eyelids, with or without epidermal plaques) and OSCCs smaller than 50 mm in diameter may be treated. Advantages of cryosurgery are its ease and rapidity, low cost, prolonged analgesia because of sensory nerve injury, minimal requirement for pre- and postoperative medications, minimal side effects, ability to be repeated, and excellent success for suspect premalignant lesions. Disadvantages of cryotherapy include local hair depigmentation, lid necrosis, loss of function of normal structures, and cicatrix formation, which can cause entropion or ectropion. Lesions that are not successfully treated with cryotherapy are those that have metastasized, those larger than 50 mm in diameter and with poorly defined margins, and those with invasion of adjacent bones (Farris & Fraunfelder, 1976). Large OSCCs should be debulked surgically prior to performing cryotherapy.

Nitrous oxide and liquid nitrogen are most commonly used, and several cryosurgical units are available. Cryosurgical units designed to deliver liquid nitrogen are more effective than units designed to deliver nitrogen vapor (Farris, 1980). A closed-tip probe or spray gun is available as well. The former offers a more controlled freeze, whereas the latter is much quicker. With the spray gun there is the potential for damage due to “runoff” onto adjacent structures (Schoster, 1992).

The most important factor in the success or failure of cryosurgery is the extent of freezing. Surgical debulking of large tumors prior to cryotherapy is ideal, and a uniform freeze of −25°C should be sought to address the wound bed following debulking of the tumor. Polystyrene, surgical lubricant, or petrolatum-impregnated gauze may be used to protect surrounding normal tissue (Farris, 1980; Farris & Fraunfelder, 1976).

Hyperthermia/Electrothermal Therapy Hyperthermia has been successful in treatment of bovine OSCC (Grier et al., 1980; Overgaard & Bichel, 1977). Often, hyperthermia is combined with some other treatment modality, such as surgical debulking or immunotherapy (Grier et al., 1980; Witt, 1984). In one study of 45 tumors, 80% regressed completely and 16% partially after a single treatment (Farris, 1980). Fifty percent of these tumors had been previously treated by some other modality. In another study with 3- to 12-month follow-ups and an average of 1.5 treatments, 96% of tumors either disappeared (53%) or were represented by suspicious scar tissue (43%), which was retreated (Grier et al., 1980). No permanent, functional eye impairment resulted from hyperthermia, but treated portions of the cornea were edematous for several weeks after therapy.

Neoplastic cells are selectively destroyed with hyperthermia (Cavaliere et al., 1967). Increased acidity, poor cell nutrition, and increased cell density all contribute to selective destruction of neoplastic cells. Of these, the pH may be the determining factor of lethality (Doss, 1977; Overgaard & Bichel, 1977).
Electrothermal treatment involves the passage of radiofrequency (i.e., 2 MHz) electric current between two electrodes. A small, handheld radiofrequency device (Western Instrument Company, Denver, CO) has been developed for the treatment of OSCC (Doss, 1977). Electrodes are placed directly on the tumor. Resistance of the tissue to the flow of electric current causes heat to be generated in that tissue. High-frequency current produces no sensation of electrical shock. The temperature of the tumor tissue is raised to approximately 50°C. Temperature control is monitored with a temperature-sensitive device (i.e., a thermistor) that is built into one electrode. Thirty seconds are allowed to elapse after the tissue temperature reaches 50°C (i.e., 122°F).

Hyperthermia is not recommended for tumors that extend deeper than 3 mm or are larger than 4 cm in diameter (Grier et al., 1980). Surgical debulking may reduce the size of the tumor sufficiently to allow adequate results from treatment with hyperthermia. Follow-up evaluation at 30 days is generally recommended, with possible further treatment if needed.

Immunotherapy

In bovine OSCC, antibodies to tumor cells have been demonstrated in sera (Atluru et al., 1982; Chung et al., 1977). Common antigens exist among cattle with OSCC. Sera from animals with plaque, papilloma, or carcinoma react best to cultured autologous tumor cells and, to a variable degree, to cultured allogenic cells (Atluru et al., 1982). IgG-containing cells accumulate in precancerous and neoplastic tissues (Hamir et al., 1980). The regional lymph nodes on the affected side have larger and more active follicles. This may account for the finding that as many as 30% of OSCC lesions regress spontaneously (Taylor & Hanks, 1972).

Successful use of immunotherapy has been reported in treatment of bovine OSCC (Den Otter et al., 1995b; Heck & England, 1977; Klein et al., 1982, 1986; Witt, 1984). Between 78% and 94% of cows with OSCC showed arrest and resolution of the tumor within 8 weeks after a single, intramuscular injection of a concentrated saline-phenol extract of fresh tumor tissue, which consisted primarily of tumor nucleoproteins (Hoffmann et al., 1981; Van Kampen et al., 1973). Subconjunctival inoculation of tumor cells has also been shown to cause regression of the primary tumor (Dennis et al., 1984). Use of peritumoral interleukin-2 (injected as close to the base of the tumor as possible) has also demonstrated promise. Complete regression of OSCC was observed at 20 months in 67% of cases treated with 10 injections of 200,000 U of interleukin-2; lower doses were associated with higher rates of relapse (Den Otter et al., 1995b). Low peritumoral doses of interleukin-2 appeared to be as effective as high doses. Third eyelid tumors seem to be more sensitive to interleukin-2 therapy than tumors found in other periocular areas (Tsujita & Plummer, 2010).

Nonspecific immunotherapy includes use of bacillus Calmette–Guerin (BCG) inoculations (Klein et al., 1982; Ribi et al., 1986). Ribi and colleagues gave two to four injections of BCG vaccine at 3-week intervals in cattle with OSCC (Ribi et al., 1986). Using a dose of 5 mL of vaccine per 2.5 cm of tumor diameter, regression occurred in 88% of tumors smaller than 2.5 cm and in 74% smaller than 7 cm. The recurrence rate was 5%. A single injection of BCG vaccine in 30 cases resulted in permanent regression of the neoplasm in 11 and temporary regression in eight (Klein et al., 1982, 1986).

Radiation

Ionizing radiation has been used to treat OSCC in food animals. The expense and legal requirements to possess such radioactive materials, however, results in low usage of radiation as a treatment modality. Disadvantages of brachytherapy include temporary corneal opacity, local necrosis, hair loss, damage to normal structures, and local depigmentation. Three types of radiation are used: beta emitters, gamma emitters, and roentgen rays. Beta radiation, such as Strontium-90, may be used after superficial keratectomy (i.e., to minimize the possibility of tumor recurrence), or it may be applied directly (i.e., for corneal and limbal neoplasms) (Banks & England, 1973; Weh et al., 1954). Use of beta radiation is often combined with surgical debulking, because 75% of the beta rays are absorbed within the first 2 mm and much of the rest in the next 1 mm. Therefore, a lesion should be less than 2-mm thick before beta radiation therapy is attempted. Furthermore, a 2-mm margin around the lesion should be treated as well, because the lesion often is surrounded by a precancerous plaque or is incompletely excised (Elkon & Constable, 1979).

Complications following beta radiation therapy are rare but have been reported in the veterinary literature (Moore et al., 1983). In humans, keratopathies resulting from radiation therapy include nonresponsive punctate ulcerations, corneal edema with bullous keratopathy, and neovascularization.

Interstitial brachytherapy has been used in various species, and implants have included radon, gold, iridium, cobalt, and cesium (Banks & England, 1973; Theon & Pascoe, 1995). These gamma emitters, as well as roentgen rays, are especially useful for eyelid masses. However, use of brachytherapy in cattle is often not feasible because of financial constraints. Even so, gamma emitters offer several advantages, including a high dose of radiation to the tumor and not to the surrounding tissue, placement of the needles under heavy sedation, possible increased effectiveness due to continuous low-dose irradiation (Bloedorn et al., 1977), a short therapy interval (7–10 days), and a good cosmetic result. Among the disadvantages, however, is that neoplastic cells may be forced into vascular and lymphatic channels during implantation. In addition, the implantation procedure may be harmful to those performing the procedure itself; however, this risk can be minimized with an afterloading technique (Gavin, 1997).

Radioactive gold seeds have been used successfully in treatment of OSCC (Banks & England, 1973). Because of their short half-life and lack of a foreign-body reaction, gold seeds do not need to be removed. Seeds are considered to be nonhazardous after 10 half-lives, after 27 days the
radioactivity in the seeds is reduced to a noninjurious level (Lavach, 1987). The desired tumor dose is 5000 rads (Shalek et al., 1957). Accurate dosage requires that radioactive seeds be properly calibrated, and that measurement of the ocular mass is accurate to facilitate plotting dose curves and dosimetry calculations.

Prevention and Control
Past studies indicate that selective breeding can be employed toward control of OSCC (Anderson, 1991). Animals should be selected with increased amounts of lid and corneoconjunctival pigment, but the latter pigmentation is not fully expressed until 5 years of age (French, 1959). Selection on the basis of eyelid margin pigmentation alone leads to only a slight reduction in the incidence of OSCC because the eyelids are sites only for approximately 10% of these tumors (Russell et al., 1956; Vogt & Anderson, 1964).

In purebred herds, offspring of affected animals should be culled (Moulton, 1961). Bulls with a history of OSCC should not be used as herd sires (Woodward & Knapp, 1950). Introduction of animals into purebred herds should include consideration of phenotypes together with information on the resistance of parents, siblings, or progeny.

GLAUCOMA
Glaucoma is an optic neuropathy usually associated with elevated intraocular pressure (IOP). The incidence of glaucoma in cattle is less than 1% (Mertel et al., 1996; Sarma et al., 1990). In India, three cows (0.23%) in a herd of 1302 animals had glaucoma, and in Italy, one case was found among 500 Friesian dairy cows examined (Sarma et al., 1990). Congenital (Greene & Leipold, 1974; Rebhun, 1979; Schuh, 1989), hereditary (Carter, 1960; Gregory et al., 1943), and secondary glaucomas (from inflammatory or neoplastic processes) (Meeke et al., 1987; Mertel et al., 1996; Miller & Fales, 1984) have been reported. Steroid-induced ocular hypertension has been consistently produced within 30 days by application of prednisolone acetate three times daily to the eyes of normal cows and sheep (Gerometta et al., 2004, 2009). Endogenous inflammatory episodes, such as those seen with neoplastic or granulomatous processes, may cause both peripheral anterior and posterior synchiae, which in turn may impede aqueous outflow sufficiently to elevate IOP. Perforated corneal ulcers, especially from IBK, may result in globe rupture, iris prolapse, and synchiae, which may also result in glaucoma.

Clinical signs in cattle with glaucoma depend on the cause of the condition. Cattle with primary glaucoma show nonpainful and enlarged globes, little or no episcleral injection, mild corneal edema, corneal vascularization and striae, a pupil poorly responsive to light stimulation, lens subluxation, and fundus abnormalities (Fig. 29.39 and Fig. 29.40) (Mertel et al., 1996).

In one well-documented patient with glaucoma, lens-induced uveitis arising from the leakage of lens proteins through an intact lens capsule was the most likely cause (Mertel et al., 1996). Ophthalmic findings included retinal vascular attenuation, generalized tapetal hyperreflectivity, and optic disc atrophy. IOPs were greater than 39 mmHg for longer than 1 year. Electroretinography (ERG) confirmed the outer retinal damage suspected on ophthalmoscopy, as the b-wave amplitude recorded in the glaucomatous eye was less than half that in the normal eye.
On subsequent histopathologic and gross examinations, the globe in the affected left eye had an axial length of 4.5 cm compared with the normal right eye at 3.7 cm. Optic nerve histomorphometry demonstrated severe reduction (98%) in the total number of optic nerve axons in the glaucomatous compared with the nonglaucomatous eye. The lamina cribrosa was also depressed (Fig. 29.41). The remaining axons were of small diameter and located in the central part of the optic nerve (Mertel et al., 1996). Successful treatment of glaucoma in cattle has not been reported.

UVEAL TRACT

Cattle possess a small corpora nigra (granula iridica) compared with camels and horses, and an oval pupil on the horizontal axis (Fig. 29.42).

Congenital Disorders of the Anterior Uvea

Congenital disorders of the anterior uvea in food animals are not, with a few notable exceptions, clinically significant. Such anomalies include persistent pupillary membranes (Fig. 29.43), heterochromia, aniridia and iris hypoplasia, polycoria, cysts, pigment nevi, and colobomas.

Heterochromia Iridis

In cattle, heterochromia iridis is represented almost 10% of ocular defects in one study (Barkyoumb & Leipold, 1984). Heterochromia iridis may be unilateral or bilateral, complete or partial. Iridal pigmentation may vary between white, light pink, blue, gray, and brown (Fig. 29.44). Heterochromia iridis may be associated with other ocular anomalies (e.g., tapetal hypoplasia and colobomas of the fundus) (Gelatt et al., 1969). Dominant and recessive forms of inheritance have been reported (Leipold & Huston, 1966; Ojo, 1982).

Among cattle, heterochromia iridis has been reported in various breeds, including Ayrshires, Holsteins, Angus, Brown Swiss, and Guernseys (Barkyoub & Leipold, 1984; Huston et al., 1968; Leipold & Huston, 1966; Leipold et al., 1968). In most cases, vision is unaffected; however, photophobia and nystagmus have been reported (Gelatt et al., 1969; Leipold et al., 1968). Among eight cattle examined in one study, fundi coloration varied from red to yellow-red in seven and from...
Iris Abnormalities

An autosomal recessive, hereditary iridal defect has been observed in Jersey calves as part of multiple eye defects (Saunders & Fincher, 1951). Affected animals may show bilateral aniridia or iridal hypoplasia in association with microphakia, cataracts, and ectopia lentis. The calves exhibit visual impairment and even blindness.

Inflammation of the Uvea

Uveitis does not suggest a causative diagnosis in and of itself but represents nonspecific ocular pathologic processes derived from inflammatory mediators. The associations of uveitides with systemic diseases are numerous (see Chapter 35). Specific etiologies of uveitis include neonatal infections; bacterial septicemia associated with severe mastitis, metritis, or traumatic reticuloperitonitis; malignant catarhal fever; tuberculosis; IBK; thromboembolic meningoencephalitis; leptospirosis; toxoplasmosis; listeriosis; parasitic migration (Setaria digitata); toxins such as lead; poisonous plants such as Dryopteris filix-mas; and lymphoma (Bardsley, 1989; Hindson, 1989; Lavach, 1990; Mee & Rea, 1989; Rebhun, 1984; Rubin, 1974; Watson, 1989). In one outbreak of idiopathic uveitis in a herd of 44 milking Holsteins, 18% were affected with lesions that included aqueous flare, hyphema, iritis, anterior capsular cataracts, retinal hemorrhages, chorioretinitis, and optic nerve granulomas, and phthisis bulbi. An extensive diagnostic workup failed to identify a causative agent.

Uveal Tumors

Primary tumors of the anterior and posterior uvea in food animals are rare. Sarcomas and ciliary body epitheliomas do occur in cattle (Saunders & Barron, 1958). A congenital intraocular melanoma has been reported in a Charolais cross-calf as well (Schuh, 1989). The tumor was well-differentiated, with rare mitotic figures and no evidence of extrascleral or vascular invasion.

Secondary intraocular tumors of the uveal tract can occur by extension from the orbit, conjunctiva, and cornea. The sclera is resistant to external invasion, but it may be breached by squamous cell carcinomas. One study reported penetration of the globe in 67 (14%) of 471 cases of OSCC in cattle.

yellow-green to red-yellow in one (Gelatt et al., 1969). All cattle had typical optic nerve colobomas that were always bilateral but not always symmetrical.

In 23 cases of heterochromia iridis reported in another study, Herefords and Ayrshires were overrepresented, but this may reflect the popularity of the breeds at the time (Barky-umb & Leipold, 1984). In Guernseys, there is a suggestion that the condition is inherited recessively (Huston et al., 1968; Leipold et al., 1968). Heterochromia iridis with incomplete albinism are inherited as an autosomal dominant trait with variable expressivity in Herefords (Fig. 29.45) (Gelatt et al., 1969; Leipold & Huston, 1966). The cattle are usually totally white, though some have patches of pigmentation on the shoulder and hip. Most irides have a white periphery and a medium-blue center, but a few exhibit distinct zones of blue, white, and tan. Ocular fundus anomalies, including typical optic disc colobomas, are also present.
Cataracts in food animals are rarely reported. However, the actual incidence may be much higher because careful inspection of the lens is not routinely performed unless the animal has visual impairment. Small, focal lens opacities do not usually result in visual impairment and are usually missed unless mydriasis is induced before the ophthalmic examination. Among food animals, cataracts have been classified on the basis of etiopathogenesis (Gelatt, 1971). Congenital cataracts (with or without associated ocular anomalies), secondary cataracts, and cataracts of unknown origin have been described (Lavach, 1990).

Congenital Cataracts

Congenital cataracts have been reported in cattle (Fig. 29.46) (Gelatt, 1971). Though not specifically designated as such in one study, cataracts, which were presumed to be congenital, were present in 31% of 72 calves as old as 22 weeks and in 18% of adults (Odorfer, 1995). The cataract was nuclear in 28% of calves and in 18% of adults. Congenital bilateral cataracts are autosomal recessively inherited in several breeds of cattle, including the Jersey, Hereford, and Holstein-Friesian (Gelatt, 1971; Gregory et al., 1943). The cataracts are usually mature when the calves are 4–11 months of age. Congenital, nuclear, nonprogressive cataracts have also been reported in cattle (Ashton et al., 1977; France & Shaw, 1990). In the cases described by Ashton (Ashton et al., 1977), the nuclear opacity ranged from abnormal refractivity to a dense, white opacity. The incidence of cataracts was 31% in one herd and 34% in another, and no sex predilection was noted. Similar cataracts were seen among 3.73% of 830 calves examined in England and Wales (Clay, 1977). Environmental causes were suspected with cataracts that were more common in calves born during late summer months and were rarely seen in calves born to heifers (France & Shaw, 1990). Gelatt has also reported congenital cataracts, documenting a Hereford cow and its bull calf with complete, mature, cortical cataracts (Gelatt, 1971).

Other ocular abnormalities in association with cataracts have been described in the Hereford, Holstein-Friesian, Jersey, and Shorthorn breeds. Multiple ocular anomalies including cataracts have been attributed to a dominant inherited trait in a herd of cows bred with a Hereford bull (Kaswan et al., 1987). The ocular defects in Holstein-Friesian cattle are lens luxation, buphthalmia, retinal detachment, and occasional lens rupture (Carter, 1960). Aniridia, microphakia, lens luxation, and cataracts occurred in Jersey calves as an autosomal recessive trait in one study (Saunders & Fincher, 1951) and as a dominant gene in another (Carter, 1960). Hydrocephalus in association with ocular defects, including cataracts, occurred in Shorthorn calves with a suspected dominant inheritance (Greene & Leipold, 1974; Leipold et al., 1971). Microphthalmia and cataracts with retinal lesions may occur in calves exposed to bovine viral diarrhea in utero at days 76–150 of gestation (Bistner et al., 1970) (see Chapter 35).

Acquired and Secondary Cataracts

Secondary cataracts occur as sequelae to an inflammatory episode. Examination typically reveals ocular changes compatible with previous inflammation, such as posterior synechiae and pigment deposition on the lens (Fig. 29.47). Most infectious systemic diseases have the potential to affect the lens (Tsujita & Plummer, 2010). Secondary intraocular tumors are also possible by hematogenous metastasis from other sites. Intraocular lymphosarcoma is rare but has been reported (Peiffer & Simons, 2002).

**Figure 29.46.** Complete congenital cataract of unknown cause in a calf. (Courtesy of C. Moore.)

**Figure 29.47.** Anterior segment of a cow with cataract secondary to chronic uveitis. Posterior synechia, capsular pigment deposits and cortical cataract are present. (Courtesy of University of Madison-Wisconsin Comparative Ophthalmology Service.)
ueval tract and cause secondary cataracts. Various infectious causes of bovine uveitis are listed above in the “Inflammation of the Uvea” section. A hematogenously disseminated infection with Rhizopus spp. that resulted in endophthalmitis and cataracts has been reported (Vasconcelos & Grahn, 1995). Microscopic ocular lesions in this case included vasculitis, supplicative keratitis, anterior uveitis, chorioretinitis, and extensive subcapsular cataracts.

Cataracts, goiter, and infertility have been reported as a result of an exclusive diet of Leucaena leucocephala (Holmes et al., 1981). The toxic component was suspected to be mimose, which may lead to formation of insoluble protein aggregates within the lens. Radiation-induced cataracts have been seen in some cattle (Brown et al., 1972). The cataracts typically begin at the posterior pole and may subsequently involve the entire lens. Hereford cows were exposed to between 200 and 600 rads of cobalt-60 gamma radiation at 15–20 months of age, and 6.7% developed cataracts.

In some cataract cases, the cause remains unknown. Among five calves in one report, the idiopathic cataracts were bilateral and involved the axial anterior lens capsules and anterior cortices. In one older Hereford bull, punctate bilateral lens opacities were observed throughout the anterior and posterior lens cortex. The lens nucleus and capsules were normal, but the cortices were translucent. All other ocular structures were normal, and the cataracts were nonprogressive (Fig. 29.48) (Gelatt, 1971).

**Treatment of Cataracts**

Cataract surgery has been successfully performed in food animals (Gelatt, 1971). The decision to perform surgery is governed by economic factors, general health of the animal, presence of coexisting ocular disease, technical expertise of the individual, and intended use of the animal. Ethical questions also arise. The suggested inherited nature of cataracts implies that breeding animals should not be operated on, or that if they are, they should not be bred subsequently. Previous reports are favorable regarding the success of cataract extraction in cattle (Gelatt, 1971).

**THE OCULAR FUNDI**

**Ophthalmoscopic Examination**

Fundic examination is facilitated by administration of 0.5%–1.0% tropicamide topically, though incomplete mydriasis occurs in cattle (Gelatt et al., 1995). Maximum mydriasis within 1 hour resulted with 1% and 3% atropine and with 0.25% scopolamine. Phenylephrine (10%) caused either no or limited mydriasis. With adequate restraint of the animal’s head and mydriasis, both direct and indirect ophthalmoscopy are easily performed in food animals, because eye movements are limited.

The clearest focus of the bovine fundus is obtained by setting the dioptr reading on the direct ophthalmoscope in the range from 21 to 25 D; most are in focus at 23 or 24 D. The bovine retina is typical of mammalian retinas (Fig. 29.49) (Mason et al., 1973). Like most domestic ruminants, the retina of the cow is holangiastic. Three, and occasionally four, major

![Figure 29.48](image1.png)  Punctate cortical cataract of undetermined cause in a Hereford bull. (Reprinted with permission from Gelatt, K.N. [1971] Cataracts in cattle. *Journal of the American Veterinary Medical Association*, **159**, 195–200).

![Figure 29.49](image2.png)  Normal bovine ocular fundus. The optic disc is predominantly in the nontapetal fundus. The large, primary blood vessels emerge from the surface of the optic disc. (Courtesy of Wendy Townsend.)
venules drain the retina, and these are accompanied by paral­
leling arterioles. The superior arteriole and venule may twist
about each other. Additional arterioles radiate from the optic
disc; from the major vessels, secondary and tertiary branches
may arise. The vessels also project far more vitread than in
most other domestic species. Increased tortuosity of many,
or all, retinal vessels may occur, and the tortuosity may be
bilateral (McCormack, 1974). Inflammatory signs are usually
absent.

The tapetal fundus varies from yellow to bluish purple, and
it is uniformly stippled by end-on capillaries (i.e., stars of
Winslow). The reflective material of the bovine tapetum is a
large array of extracellular collagen fibrils arranged in lamel­
lae of varying thickness (Ollivier et al., 2004). Pigment occurs
commonly in the tapetal fundus, especially in the dorsomedial
quadrant. The average size of the bovine tapetal fundus is 55.8
by 32.2 by 39.6 mm (McCormack, 1974). It follows the
general shape of a right triangle with a horizontal base that
traverses just superior to the optic disc.

The nontapetal fundus is generally a uniform shade of
brown, and there is little variation with the coat color or breed.
The optic disc is always located at the junctional area of the
nontapetal and the tapetal fundi, usually within the nontapetal
fundus just below the junction.

The optic disc is in the shape of a horizontally flattened
oval. In most, the temporal portion is located nearer to the
tapetal fundus than is the nasal portion. Myelination of the
optic nerve fibers normally stops at the lamina cribrosa.
Myelin may occasionally continue onto the retina for a short
distance and appear as white fiber bundles with featherlike
margins protruding from the optic disc. These medullated
fibers are not usually present at birth, but they may develop
within the first months of life. A physiologic cup is present in
older animals but not usually in the young. The average size
of the optic disc in cattle is 4.2 mm horizontally and 2.9 mm
vertically. The size of the disc, however, is directly propon­
tional to the animal’s size. The largest disc occurs in adult
bulls and the smallest disc in newborn calves. The mature bull
has a disc more circular in shape, with margins more indistinct
than those in the cows.

The optic disc varies in color. In general, the young animal
(<6 months) has a white to salmon-pink disc with distinct
margins. Older animals may have discs of orange, gray, tan,
or various combinations. The most common disc coloration
in adult animals is an orange center with a grayish brown
periphery. The orange central zone contains the vessels, and
the darker, grayish outer zone is the sheath of the optic nerve.
Hyaloid remnants (specifically, Bergmeister’s papilla) fre­
quently protrude from the center of the optic disc into the
vitreous body, appearing as gray, translucent protuberances
(Fig. 29.50) (McCormack, 1974).

In addition to the primary pairs of vessels that emerge from
the disc, 15–20 other vessels cross the margins of the disc.
These small arterioles and venules emerge from the disc in a
radiating fashion and disappear from view approximately 0.5-
to 1.0-disc diameters from the optic disc. An “area striata,”

the bovine equivalent of the area centralis, consists of a band­
shaped area running horizontally above the disc in the lower
part of the tapetal fundus.

**Congenital Disorders**

Congenital fundus abnormalities are unusual, but they may
mimic acquired lesions. The prognostic implications of an
acquired versus a congenital lesion may be profound. A curred
lesions may affect the entire herd if due to infectious diseases.
Therefore, careful ophthalmic and systemic evaluations of
affected animals should be performed.

**Ocular Albinism**

Complete albinism is rare, but it has been documented in
cattle (Leipold & Huston, 1966; Leipold et al., 1968). More
commonly, a partial albinism (i.e., subalbinism) is described
(Gelatt et al., 1969; Ojo, 1982). In one study of congenital
ocular defects in calves, complete albinism accounted for 5%
of defects and incomplete albinism for 38% (Barkyomb &
Leipold, 1984). Albinism is an inherited disorder of melanin
metabolism in which the ocular, cutaneous, or oculocutaneous
melanocytes do not possess the normal amount of melanin.
Albinism may relate to faulty tyrosine metabolism.

In cattle, complete albinism is characterized by pink skin
and a lack of pigment in the muzzle, eyelids, iris, and choroid
(Greene et al., 1973). Affected animals have clinically normal
vision. However, they may have variable amounts of photo­
phobia, and nystagmus may be present as well. Ophthalmic­
scopic examination reveals a normal, beige (albinotic) or
yellow (subalbinotic) tapetal fundus, but no pigment in the
nontapetal fundus. Retinal blood vessels are superimposed
on the underlying choroidal blood vessels (Fig. 29.51).

![Figure 29.50. Bovine ocular fundus showing the presence of a hyaloid remnant (Bergmeister’s papilla) protruding from the center of the optic disc. Also note intertwined dorsal retinal arteriole and venule characteristic of typical bovine fundus. (Courtesy of G. Klauss.)](image)
Histopathologic examination reveals pigment only in the posterior layer of the iris and the ciliary body; the retinal pigment epithelium contains few melanin granules.

**Colobomatous Malformations**

Colobomas of the choroid are relatively common among cattle. Various estimates indicate a prevalence rate of 1%-2%. Typical colobomas of the optic disc occur in the dominant form of incomplete albinism among Hereford cattle (Fig. 29.52 and Fig. 29.53) (Gelatt et al., 1969). In this syndrome, the colobomas are always bilateral, but they are not necessarily symmetrical. Both the clinical and histopathologic features of ocular anomalies, including colobomas, in such animals have been documented (Fig. 29.54) (Ojo, 1982). The colobomas vary markedly in size and depth (i.e., from one-quarter to five-disc diameters wide and 1–6 D deep). Vision in cattle affected with colobomas may vary depending on the extent of the colobomatous change (Barnett & Ogien, 1972).

Histopathologically, smaller colobomas show retinal thinning (primarily from photoreceptor loss and loss of the outer nuclear layer), choroidal hypoplasia, and normal sclera (Ojo, 1982). Occasional retinal rosettes occur as well. In larger colobomas, changes of the optic nerve head (ONH), retina, choroid, and sclera are pronounced. Retina within these large colobomas either is thickened and disorganized or is a thin glial membrane. The retinal pigment epithelium is incomplete, the choroid absent, and the sclera thinner than normal.

Typical colobomas of the optic disc occur in Charolais cattle; they are bilateral and often small, though not symmetrical, and are generally restricted to the posterior segment (Barnett & Ogien, 1972). Larger colobomas involve the entire optic disc and occasionally extend into the choroid and sclera in other areas of the ocular fundus. The effect of the ocular defect on vision ranges from slight to severe. In some extreme cases, calves have been born blind with grossly affected eyes.
The pattern of inheritance for typical colobomas in Charolais cattle is suggestive of a dominant mode, but test breedings are indicative of a polygenic inheritance (Barnett & Ogien, 1972).

**Congenital Vascular Anomalies**

Remnants of the hyaloid vessel appear as a white, irregular tube extending from the optic disc to the posterior pole of the lens. If the vitreous body is fluid, small movements of these structures can occur. Normally, only a small, translucent structure (Bergmeister’s papilla) projects from the optic disc into the posterior vitreous. Sometimes, these hyaloid remnants may terminate in a fine fiber. Histopathologically, the persistent hyaloid artery is surrounded by glial cells. The fine thread is made of those arterial remnants not surrounded by glial cells (Schebitz & Reike, 1953).

A persistent hyaloid artery has been found in 54% of calves aged 6 weeks or less (Odorfer, 1995). Some hyaloid vestige can nearly always be found. In older cattle, 80% of animals may still have some remnant of the hyaloid.

**Retinal Dysplasia**

Inherited forms of dysplasia must be differentiated from those resulting from intrauterine infection with infectious agents, such as bovine virus diarrhea (BVD). On histopathologic sections, the retinal rosette is diagnostic of retinal dysplasia (Fig. 29.55). Multiple inherited ocular anomalies, including retinal dysplasia and internal hydrocephalus, have been reported in Shorthorn cattle (Fig. 29.56) (Greene & Leipold, 1974; Leipold et al., 1971). Data collected were consistent with either recessive or incomplete penetrant dominant mode of inheritance. The retinas were not only dysplastic but were often detached. These detachments were believed to result from differences in the growth rate of the inner and outer layers of the embryonic eye.

**Osteopetrosis-Induced Ocular Fundus Disease**

Osteopetrosis in cattle is a generalized skeletal disease characterized by the absence of bone cavities because of defective bone remodeling (Greene et al., 1974). The disease is expressed as an autosomal recessive trait (Huston & Leipold, 1971). Clinical signs resulting from this condition include fragile bones, brachygnathia, hypoplastic foraminae, and various neurologic defects (e.g., blindness). Most animals are premature at birth and are stillborn. The disease has been described only among North American Black Angus cattle (Greene et al., 1974).

The ocular complications of osteopetrosis include defects in the retina and optic nerve. The optic nerves have prominent, thick interfascicular connective tissue septa and round to irregular basophilic bodies in surrounding areas of spongy...
nervous tissue. Retinal lesions are characterized by numerous vacuoles that result from necrotic ganglion layer cells (Greene et al., 1974).

**Inflammations of the Ocular Fundus**

Various infectious agents have been implicated as causing posterior segment inflammatory changes in food animals. Cattle have been reported to be affected by neonatal septicemic infections (Escherichia and Pasteurella spp.), thromboembolic meningoencephalitis (Histophilus somni, formerly Hemophilus somnus), rabies and other viral causes, toxoplasmosis, tuberculosis, and listeriosis (Bardsley, 1989; Crispin, 1989; Hindson, 1989; Mee & Rea, 1989; Rubin, 1974; Watson, 1989). See Chapter 35 for detailed descriptions.

**Degeneration of the Ocular Fundus**

Most documented retinal degenerations in food animals are acquired and arise from ingestion of forage material. Ocular defects usually are only one of several systemic signs in such cases. Chronic inflammatory diseases may also result in degenerative retinal disease. Possible genetically based retinal degenerations have also been reported in cattle (Bradley et al., 1982; Stehman & Rebhun, 1987).

Abnormalities in outer retinal or visual cortex function may be assessed, when feasible, by electrodiagnostic means. Normal values for the ERG and visual-evoked potentials have been reported for cattle (Kotani et al., 1993; Strain et al., 1990). In Holstein-Friesian cattle, a significant difference in ERG amplitude and latencies was found between adults and calves, and the a- and b-wave ERG latencies in Japanese Black calves were significantly different from those in adult Japanese Black cattle (Kotani et al., 1993). Electrodiagnostic visual testing has been used in ruminants with thiamine responsive PEM or suspected listeriosis (Strain et al., 1990).

**Possible Hereditary Retinal Degeneration**

A condition similar to canine progressive retinal atrophy occurs in cattle (Rubin, 1974). A familial occurrence, implying a possible genetic link, has been suggested but not proven (Bradley et al., 1982; Stehman & Rebhun, 1987). Clinical signs initially include pupils that are poorly responsive to light stimulation and nyctalopia with subsequent blindness. Fundus examination is typical of retinal degeneration. Tapetal hyperreflectivity, small vessel attenuation (but preservation of the larger vessels until late in disease), and minimal optic nerve abnormalities characterize the disease initially. The end stage shows diffuse pigmentation of the tapetal fundus. There may be little difference in color between the tapetal and nontapetal fundi. The optic disc appears a brownish gray (Fig. 29.57) (Bradley et al., 1982; Kotani et al., 1993).

**Vitamin A Deficiency**

Vitamin A is essential for rhodopsin regeneration, normal bone maturation and remodeling, and normal epithelial function. Vitamin A deficiency may cause blindness, abnormal bone growth, abnormal epithelial function, and embryologic maldevelopment. This topic is covered in detail in Chapter 36.
Retrobulbar Neuropathy and Retinal Degeneration

Ingestion of Dryopteris filix-mas (i.e., male fern) is associated with vision loss due to retrobulbar optic nerve disease (Mitchell & Wain, 1983; Rosen et al., 1970). Bilateral blindness is the main presenting sign, but weakness, malaise, and constipation can also occur. In severely affected animals, optic nerve atrophy occurs with subsequent retinal degeneration. Fundoscopy reveals hemorrhage on or about the optic disc and various amounts of papilledema (Fig. 29.59). Chronically affected animals exhibit blindness, optic nerve atrophy, attenuated retinal vasculature, and tapetal degeneration.

Histopathologic findings reveal both death of retinal ganglion cells and loss of optic nerve fibers. Within the optic nerve, myelin and axons are widely destroyed, but axons persist in areas where myelin is absent. These findings suggest that the primary toxic action is on the medullary sheaths and their associated oligodendrocytes, which may be more vulnerable because of their lipoid nature.

Hypothiaminosis

PEM, or cerebrocortical necrosis, is most often caused by thiamine deficiency (Edwin et al., 1968; Markson et al., 1972). The disease of PEM is most commonly seen in young feedlot cattle on low-fiber, high-concentrate rations. Under these dietary conditions, ruminal concentrations of thiamine are decreased (Smith, 2009). Ingestion of thiaminase-containing plants, such as bracken fern (Pteris aquilina), can cause secondary thiamine deficiencies. PEM has also been caused by water deprivation and intake of high levels of sulfur, either through ad libitum ingestion of concentrates, mineral premixes, plants in the family Brassicaceae, or high sulfur content in the water (Gooneratne et al., 1989; Hamlen et al., 1993; Low et al., 1996; McKenzie et al., 2009; Padovan, 1980). Treatment with copper, as well as vitamin B₁, appears to be beneficial for the sulfur-induced cases (Hamlen et al., 1993).

The basic lesion of PEM is necrosis of the cerebrocortical neurons, with associated perineuronal and pericapillary edema (Markson et al., 1972). Neurologic signs are associated with increased cerebrospinal fluid pressure and neuronal necrosis; impaired vision may be an early sign. The blindness is cortical, but ocular signs of papilledema and decreased pupillary light reflexes may occur. ERGs remain normal, but visual-evoked potentials are abnormal (Strain et al., 1990). Bilateral dorsomedial strabismus may be present as well (Rebhun, 1984).

Treatment consists of thiamine hydrochloride (6–10 mg/kg) either intramuscularly or intravenously every 8 hours (Daly, 1968). Corticosteroids may benefit cases early in the course of disease. Recovery may be slow and decreased vision or blindness may persist.

Locoweed Poisoning

Poisoning with locoweed (Astragalus and Oxytropus spp.) causes retinal degeneration in cattle, sheep, and other species (Smith, 2009; Van Kampen & James, 1970). Bipolar, ganglion, and ciliary body epithelial cells show vacuolation of the cytoplasm. Similar changes occur in brain neurons (Van Kampen & James, 1970, 1971). The lacrimal gland has marked cytoplasmic vacuolation of the secretory cells, and poisoned animals show vision disturbances and dry, lusterless eyes.

Other Toxic Plants

Several other plant species may also cause neurologic disease with visual impairment, and in some cases, blindness precedes death. Water hemlock (Cicuta spp.) causes an acute syndrome associated with sudden death (Radostits et al., 2007). A new, fatal mycotoxicosis of cattle has been recognized in Australia, and feeding trials have demonstrated a previously unknown mycotoxic species of Corallocytostroma that grows on Mitchell grass (Astrebla spp.) (Jubb et al., 1996). The disease is colloquially called “black soil blindness.” The onset of blindness and rapid progression to death are the main clinical features of this disease.

Kochia scoparia (Mexican fireweed, summer cypress, or burning bush) can produce blindness and nystagmus (Dickie & Berryman, 1979). Darling pea (Swainsona galegifolia) causes signs similar to those of locoweed in cattle and sheep (Hartley & Gibson, 1971).

Inherited Lysosomal Storage Diseases

A variety of inherited lysosomal storage diseases with ophthalmic implications have been reported, including...
GM1-gangliosidosis (i.e., leukodystrophy in Holstein cattle), GM2-gangliosidosis (i.e., lipodystrophy in Angus and Beefmaster cattle), and mannosidosis (Smith, 2009). The inherited lysosomal storage diseases are covered in Chapter 35.

**OPTIC NERVE DISEASES**

A primary demyelinating disorder of young Limousin cross-calves has been described (Palmer et al., 1991). Approximately 1 month after birth, affected animals showed signs of blindness, nystagmus, rotation of the eyes, opisthotonus, hyperprotraction of the forelegs, and in one case, seizures. Histopathologically, there was necrosis of the optic chiasm and focal areas of myelin sheath vacuolation or demyelin-ation, particularly in the cerebellar peduncles. In one case that lived for 7 months, there was remyelination by Schwann cells of some axons, but there was no evidence of oligodendrocyte remyelination. A genetic association was considered to be likely.

Papilledema is a descriptive term for noninflammatory swelling of the optic disc caused by various conditions. It may signal increased intracranial pressure. In cattle and sheep, papilledema is commonly encountered. Causes may be vitamin A deficiency (Fig. 29.60) (Divers et al., 1986), acquired and congenital hydrocephalus (Leipold et al., 1971), space-occupying brain lesions (McCormack, 1973), meningitis, encephalitis, and hexachlorophene toxicity (Udall, 1972).

Papilledema is usually bilateral. The optic disc margins appear to be hazy, and the physiologic depression is lost. The disc becomes thickened and swollen and appears to be grayish white with striations. The retinal veins and arteries show a distinct bend as they pass down over the edge of the disc and onto the retina. The retinal venules may be dilated and engorged peripherally and hidden centrally within the swollen disc. Many more fine veins are visible. The arterioles are a brighter red and more threadlike than the congested venules. If the cerebrospinal fluid pressure remains elevated, the optic nerve and disc will atrophy.

**SHEEP AND GOATS**

**The Orbit and Globe**

**Congenital Globe Abnormalities and Blindness**

In a study of congenital malformations in the eyes of sheep, microphthalmia with multiple cysts was observed (Rosenfield & Beath, 1947). In histopathologic studies of the malformed eyes, both cellular and structural misplacement occurred during early embryonic development. The purported cause of these malformations was selenium toxicity, but this suggestion has been disputed (O’Toole et al., 1996). Through collaborative research in Switzerland, Germany, and Australia, microphthalmos in Texel sheep has been linked to a region on chromosome 23 (Tetens et al., 2007). The condition is an autosomal recessive trait and results from a missense mutation in the homeobox gene PITX3 (Becker et al., 2010). The most common maternal infection causing multiple ophthal-mic defects in offspring is bluetongue disease in sheep (see Chapter 35).

**Teratogenic Agents**

*Veratrum californicum*

Among domestic animals, the best-documented teratogenic ocular defects have been those associated with ingestion of *Veratrum californicum* in sheep. Various globe abnormalities, such as anophthalmia, cyclopia, and synophthalmia, may be induced in lambs by the maternal ingestion of *V. californicum* (Fig. 29.61) (Binns et al., 1962, 1963). The common names of *V. californicum* include skunk cabbage, western helibore, false helibore, and wild corn. The plant varies widely in toxicity and teratogenic agent between the different range areas. A mong affected flocks, the incidence of malformations may be 25%. Such malformations have been reproduced under controlled, experimental conditions by feeding sheep both fresh and dried *V. californicum*. The agents responsible are a group of alkaloids (e.g., jervine, pseudojervine, isorubijervine, and veratrosine) that occur throughout the plant but are concentrated in the roots (Keeler & Binns, 1966).

Sheep embryos are highly susceptible to the teratogenic agent cyclopamine, a steroidal alkaloid, from the plant *V. californicum* when the plant is eaten by the ewe on gestational day 14 (Binns et al., 1965). In cases of cyclopia, this timing corresponds to the period of gastrulation and formation of the neural plate, before separation of the optic fields. Ewes fed plants on gestational days 11, 12, 13, 15, and 16 had normally
developed fetuses or normally developed embryos that died between the eighteenth and twenty-third days of embryonic development. All embryonic deaths occurred in ewes with severe clinical signs of poisoning. The dose of *V. californicum* that had a teratogenic effect was less than that necessary to cause clinical signs of poisoning in the ewes. The elimination half-life of cyclopamine in ewes has been determined and is 1.1 ± 0.1 hours. The rapid clearance of cyclopamine confirms that ingestion of *V. californicum* must occur during a very narrow window for synophthalmia formation to occur (Welch et al., 2009).

Other teratogenic effects arising from ingestion of *V. californicum* include distortion of the facial bones, fusion of the cerebral hemispheres, absence of the pituitary gland, hydrocephalus, cyclopia, and anophthalmia. Occasionally, the anomaly involves full-term twin lambs, one of which is malformed and the other normal. This discrepancy could result from a difference in the developmental rates of the respective embryos. Teratogenic effects of *V. californicum* have also been reported in cattle and goats (Binns et al., 1972).

**Apholate**

Congenital orbital anomalies in sheep have been associated with a polyfunctional alkylating agent, apholate, which is used as an insect chemosterilant (Younger, 1965). The congenital anomalies consisted of anophthalmia, absence of orbital cavities, and defective formation of cranial and facial bones. The liver was ectopic, and the spleen was malpositioned.

**Selenium**

Selenium has been credited historically with causing “blind staggers” in livestock and being a teratogenic agent (Rosenfield & Beath, 1947, 1964). Reported necropsy findings attributed to ewes grazing on seleniferous pastures include microphthalmia with multiple cysts; corneal, lens, and iris defects; and colobomas of various structures. However, examination of the original data (Draize & Beath, 1935; Rosenfield & Beath, 1946) reveals many inconsistencies and false conclusions (O’Toole et al., 1996). Furthermore, some of the reported selenium values are not consistent with current guidelines for acute toxicity (O’Toole et al., 1996). Thus, it has now been speculated that many field cases of blind staggers were in fact sulfur-related PEM. Plants that bioaccumulate selenium are often associated with waters high in sulfate, and high sulfate levels have been linked with PEM (Gooneratne et al., 1989; Hamlen et al., 1993; Jeffrey et al., 1994). A review of 40 years of data from the laboratory that proposed the original association revealed no substantiated cases of naturally occurring selenosis (Raisbeck et al., 1993).

Other possible causes of blind staggers include malignant catarrhal fever, the polyhydroxyindolizidine alkaloid swainsonine, chronic laminitis, parasitism, thromboembolic meningoencephalitis, lead poisoning, and starvation (O’Toole et al., 1996). The cause of the congenital ocular defects may actually have been maternal ingestion of *V. californicum* or some other teratogen.
Blepharitis

Bacterial

Pyogranulomatous cutaneous nodules with associated draining tracts may occur on the face of sheep and goats following cutaneous punctures and secondary infection with Actinobacillus lignieresii (Moore & Whitley, 1984). Eyelid edema and facial swelling are observed with “bighead” disease in sheep, in which blepharoeedema may develop secondary to anaerobic infection with C. novyi (Wyman, 1983). Secondary keratitis and conjunctivitis may develop because of a resulting lagophthalmos. Dermatophilosis (rain scald or lumpy wool) occurs as in cattle. See the bovine section for more details.

Mycotic

Trichophyton spp. (usually verrucosum) can affect all food-producing animals (Smith, 2009). Sheep and goats may also be affected by Microsporum spp. (Radostits et al., 2007; Smith, 1983). Dermatomycoses occur most commonly in goats and may result in crusty areas of periocular and facial alopecia (Moore & W hitley, 1984). Owners should be informed of the zoonotic potential. The disease may resolve spontaneously within 4–5 weeks in an individual animal, but it may persist in a flock for some months. Despite the self-limiting nature of the disease, treatment is recommended to limit any further infection of unaffected animals and humans (Radostits et al., 2007). Topical and systemic fungicidal agents, iodine shampoos, improved nutrition, and dry environs all may assist in eliminating the disease. Vaccination of newly infected herds shows potential as a prophylactic measure (Smith, 2009).

Viral

Viral diseases implicated in eyelid disease include pox viruses, orbivirus, and papilloma virus (Moore & Whitley, 1984). The pox viruses are species specific under natural conditions;
however, multiple antigens are shared by members of the same subgroup. Sheep and goat pox (Capripoxviruses) may have morbidity rates of up to 70%, and the mortality rate may reach 50% (Wyman, 1983). The first ocular signs are circular, hyperemic maculae of the eyelids, which then progress to firm papules elevated above the surrounding tissue. Serum exudate and blepharospasm may occur as well. Contagious viral pustular dermatitis (contagious ecthyma, sore mouth, and orf) is a Parapoxvirus causing a sequence of papules, vesicles, pustules, and scabs on the eyelids, lips, muzzles, and nostrils of sheep and goats, but it does not usually cause systemic illness. Ovine ulcerative dermatosis virus (lip and leg ulcer) is an unclassified pox virus similar to contagious ecthyma, but the former causes lesions that are ulcerative and destructive rather than proliferative, as with contagious ecthyma (Smith, 1983). Specific treatment is neither necessary nor effective in uncomplicated cases, but symptomatic treatment is advised. The potential for zoonotic infection does exist. Vaccinations are available for contagious ecthyma, sheep pox, and goat pox.

Bluetongue virus is an acute, noncontagious orbivirus spread by Culicoides variipennis midges. The virus may cause blepharitis and conjunctivitis in sheep, and it occasionally affects cattle. Hyperemia and eczema of the periorcular skin may occur. The most notable change, however, is retinal dysplasia in lambs born to infected ewes (Moore & Whitley, 1984).

Papillomatosis is caused by a DNA virus that may affect the eyelids of sheep with a predilection for young animals up to 5 years of age (Wyman, 1983). Papillomas are usually benign, self-limiting, and may have an associated blepharitis. Surgical removal of the papillomas may potentiate the immune system to the virus (Moore & Whitley, 1984).

Ectoparasites

Sarcoptic mange is caused by Sarcoptes scabiei, with a subspecies specific for each host species (Smith, 2009). The lesions become widespread except in sheep, in which they are restricted to the haired skin of the face and eyelids (see bovine section) (Moore & Whitley, 1984). Treatment with moxidectin at a dose of 0.2 mg/kg given twice at 10-day intervals or ivermectin injected subcutaneously at a dose of 0.2 mg/kg both provide satisfactory results (Gnad & Mock, 2001).

Demodex caprae is a mite that can inhabit hair follicles in goats (Gnad & Mock, 2001). Pustules form around the mites, causing skin lumps on the head, neck, and shoulders. The diagnosis is made by microscopically identifying the cigar-shaped mite. Demodectic mange is generally not harmful, and treatment is usually not necessary (Loomis, 1986). Psoroptes, Pseudogamas, and Choriotopes spp. are cutaneous mites that may cause intense pruritus but infrequently involve the facial area (Lofstedt, 1983; Radostits et al., 2007).

Keds (Melophagus ovinus), lice (Bovicola and Linognathus spp.), and ticks may cause pruritus and self-trauma. Periorcular involvement is secondary to self-trauma and results in mild conjunctivitis and blepharitis (Moore & Whitley, 1984). Drugs such as coumaphos, diazinon (do not use on goats), fenvalerate, malathion, methoxychlor, and permethrin may be used to control infestations (Gnad & Mock, 2001).

Endoparasites

Elaeophorosis (sore head) is a disease of sheep caused by Elaeophora schneideri, an intraarterial parasite of deer, elk, and domestic sheep (Abdelbaki & Davis, 1972; Smith, 2009). The horseflies Hybomitra and Tabanus spp. are the intermediate hosts (Pence & Gray, 1981; Wyman, 1983). Local inflammation due to migration of Elaeophora microfilaria may cause severe facial dermatitis, keratoconjunctivitis, uveitis, chorioretinitis, optic neuritis, and CNS disease. The skin lesions involve the face and are pruritic, alopecic, ulcerated, and encrusted. Adult animals are more often affected in the winter months. The demonstration of microfilariae in biopsy specimens is diagnostic (Moore & Whitley, 1984), and treatment is symptomatic for the secondary ocular lesions (Wyman, 1983). Treatment of the parasite may cause death by occlusion of the carotid arteries in heavily parasitized animals (Smith, 2009). Treatment options include piperazine, diethylcarbamazine, and stibophen.

Photosensitization

Direct solar irritation (i.e., sunburn) may occur in food animals with little periocular pigmentation, but acute periorcular dermatitis is more likely the result of photosensitization (see bovine section).

The Conjunctiva and Cornea

Infectious Keratoconjunctivitides

Decreased twinning rates in ewes, increased cases of pregnancy toxemia, starvation, weight loss, blind ewes trampling offspring, and decreased economic return have all been attributed to infectious keratoconjunctivitis (Egwu, 1991). Numerous infectious agents have been implicated, and the terms pink eye, heather blindness, or blight are therefore used somewhat broadly. The causative agents producing the clinical sign of keratoconjunctivitis in small ruminants are probably varied, with no one organism consistently being responsible.

Chlamydial Keratoconjunctivitis

Chlamyophila pecorum (formerly a serotype of Chlamydia psittaci) is an important cause of keratoconjunctivitis in sheep and goats and polyarthritis in sheep (Nietfeld, 2001). C. pecorum is introduced into a flock by affected animals often with mild infection (Hosie, 2000; Matthews, 1999). Transmission can occur between sheep and goats. Direct contact is the most important method of transmission. Chlamydiae are obligate, intracellular bacteria (Everett, 2000). They have a unique development cycle involving two morphologic forms: the elementary body and the reticulate
body. The elementary bodies are specialized for extracellular survival, insensitive to antibiotics, and infectious. The reticulate bodies are sensitive to antibiotics and are obligate, intracellular organisms engaged in active multiplication within eukaryotic host cells (Bogaard, 1984). They are found in cytoplasmic vesicles termed cytoplasmic inclusion bodies.

C. pecorum is associated with an infectious keratoconjunctivitis in sheep that occurs worldwide (Andrews et al., 1987; Surman, 1979). Outbreaks usually occur during the lambing season, when ewes and lambs are confined with maximal contact and stress. Carrier animals may be reservoirs for the disease. The pathogenesis is probably multifactorial, with the immune status of the animal, secondary infection, and other factors all playing a role (Bogaard, 1984). Experimental transmission has been successfully performed to naive animals through inoculation of infective lacrimal fluids into the lacrimal sac (Wilsmore et al., 1990). In the clinical setting, immunity appears to be of short duration because animals may be infected repeatedly. However, in experimental disease, not all lambs could subsequently be reinjured (Wilsmore et al., 1990). Those animals from which Chlamydophila were recovered had less severe conjunctivitis, thereby implying at least a limited immunity to subsequent challenge.

In experimental conditions, clinical signs begin within 4 days of infection and initially include epiphora, chemosis, and conjunctival hyperemia. By 11 days postinfection, the serous conjunctival exudates become more purulent with associated blepharospasm. Lymphoid follicles begin to develop by 23 days postinfection (Wilsmore et al., 1990), but they can also develop as early as 6 days after inoculation with C. pecorum and Branhamella ovis (Dagnall, 1994b). The follicular reaction is not unique to this disease; many causes of conjunctivitis may result in follicular hyperplasia (Dagnall, 1994b). Approximately 10% of patients develop interstitial keratitis 1 week after the initial signs develop with deep vascularization and edema of the cornea (Cello, 1967). Because corneal ulceration is uncommon, permanent scarring of the cornea is infrequent (Egwu, 1991; Hosie, 2000).

A diagnosis is most easily obtained from scrapings of infected conjunctival epithelial cells early in the course of the disease (Bogaard, 1984; Wilsmore et al., 1990). New methylene blue, Wright’s, or Giemsa stains show the typical cytoplasmic inclusions in infected cells. However, fluorescent antibody staining is preferable because Chlamydiae can be confused with melanin granules (Hosie, 2000). Failure to culture Chlamydiae in the latter stage of the disease process does not necessarily preclude Chlamydia in the initial causative agent. Culture in the latter stages of chlamydophila-induced ocular disease may show a variety of commensals, such as B. ovis (Wilsmore et al., 1990). Fourteen days after experimental inoculation, Chlamydiae could be isolated from 80% of lambs, but by 18 days postinfection, Chlamydiae usually could not be isolated. However, immunofluorescent antibody tests were able to detect chlamydial antigens 5 weeks postinfection. Therefore, fluorescent antibody tests may be more sensitive than culture in detecting Chlamydiae.

The currently available ELISA kits are manufactured for identification of C. trachomatis and have not been evaluated for diagnosis of C. pecorum (Nietfeld, 2001). While identification with PCR is possible, false-negative results due to inhibitors in the samples could be a problem (Rodolakis et al., 1998).

In most clinical settings, testing is not economically viable and treatment is instituted empirically. The most effective treatment is a single intramuscular injection of long-lasting oxytetracycline (20 mg/kg) (Hosie, 2000). Daily feeding of 150–200 mg of tetracycline per head to lambs and kids reduces the incidence and severity of disease. Intramuscular injection of tylosin or topical application of tetracycline ophthalmic ointment provides satisfactory results (Hosie, 2000; Matthews, 1999; Smith & Sherman, 1994).

**Mycoplasmal Keratoconjunctivitis**

Although typically thought to be more common in goats, Mycoplasma spp. have been associated with conjunctivitis in sheep and goats both clinically (Egwu et al., 1989; McCauley et al., 1971; ter Laak et al., 1988b; Van Halderen et al., 1994) and experimentally (Egwu & Faul, 1991; ter Laak et al., 1988a). Subclinical carrier states of Mycoplasma spp. exist as well (Dagnall, 1994c). In some animals, the presence of Mycoplasma conjunctivae is not associated with clinical disease (Dagnall, 1994a). The lack of association may result from differences in the pathogenicity between individual strains, or the samples may have been taken just before development of clinical signs. The respective conjunctival isolates for sheep and goats were M. conjunctivae var ovis and M. mycoides var capri. Concurrent presence of B. ovis, Escherichia coli and Staphylococcus aureus may enhance the severity of keratoconjunctivitis (Dagnall, 1994a; Egwu et al., 1989).

There may be a slight variation in clinical signs between sheep and goats (Dagnall, 1993a; Egwu, 1991; Konig, 1983; ter Laak et al., 1988a, 1988b). There is an initial hyperemia of the palpebral and conjunctival vessels, serous lacrimation, and blepharospasm (Fig. 29.64). Keratitis with superficial and deep vascularization may also develop (Egwu, 1991). In more advanced cases in sheep, a mucopurulent conjunctivitis, occasional follicular conjunctivitis, iritis with hypopyon, and corneal ulceration occur (Fig. 29.65). Phthisis bulbi rarely results, and the disease usually lasts between 1 and 4 weeks. Older sheep are generally more affected (Egwu, 1991; Van Halderen et al., 1994). Goats do not usually develop corneal ulcers or hypopyon, but permanent corneal opacity and blindness may result (Fig. 29.66 and Fig. 29.67).

The diagnosis of infection with Mycoplasma spp. is made on the basis of clinical signs and results of conjunctival cytology, culture, and serology (Dagnall, 1994c; Levisohn et al., 1991; Wyman, 1983). Cytologic preparations can be stained with Giemsa stain, carbol basic fuchsin stain of Gimenez, or Gram’s stain. Cytologic specimens from healthy ovine eyes show predominantly epithelial cells, with occasional lympho-
cytes; neutrophils are rarely present (Dagnall, 1994c). In acute mycoplasmal keratoconjunctivitis, large numbers of neutrophils, but no plasma cells, are seen. Intracytoplasmic coccobacillary and ring-shaped bodies may be observed in epithelial cells with *Mycoplasma* spp. infection (Dagnall, 1994c).

Bright-field as well as dark-ground examination of Giemsa-stained smears demonstrate *Mycoplasma* spp. in scrapes from the conjunctivae of affected and even healthy sheep. In some cases, the conjunctival epithelial cells contain phagocytosed neutrophils but no bacteria (Fig. 29.68). The role of phagocytic conjunctival epithelial cells in the development of latent infections is uncertain.

The organism can also be cultured, provided that special nutrient requirements and incubation methods are used (Marmion, 1967; Van Halderen et al., 1994). Previous use of antibiotics can interfere with the growth of the organism in culture. Serology, including complement fixation, indirect
### Diseases concurrent with mycoplasma conjunctivitis

Diseases concurrent with mycoplasma conjunctivitis include mastitis, pleuropneumonia, and arthritis in sheep and goats (Smith & Sherman, 1994). *M. agalactiae* has been associated with mastitis, arthritis, and conjunctivitis, with pregnant animals being more severely affected than nonpregnant animals (Hasso & Al-Aubaidi, 1993). A case of uveitis, pneumonia, and arthritis caused by infection with *Mycoplasma* spp. in the absence of keratoconjunctivitis has also been reported (Whitley & Albert, 1984). *Acholeplasma oculi* has been implicated as a cause of keratoconjunctivitis in sheep (Arbuckle & Bonson, 1980), with approximately 25% exhibiting blepharospasm, conjunctivitis, keratitis, and pannus. Subsequently, approximately half the flock was affected. Treatment with subconjunctival oxytetracycline was successful. *A. oculi* was also isolated from a group of goats with conjunctivitis and pneumonitis (al-Aubaidi et al., 1973).

### Branhamella Keratoconjunctivitis

Cases of keratoconjunctivitis in sheep and goats have been attributed to *Branhamella ovis* (formerly known as *Neisseria ovis*), either alone or in combination with other microorganisms (Bankemper et al., 1990; Dagnall, 1994a, 1994b, 1994c; Fatimah et al., 1994). The role of *Branhamella* spp. as a primary pathogen is questioned by some authors, however, because it may be normal conjunctival flora (Bogaard, 1984; Fatimah et al., 1994). *B. ovis* occurs in conjunctival scrapings from affected as well as healthy sheep (Fig. 29.69) (Dagnall, 1994c). In one study of an infectious keratoconjunctivitis outbreak, *Branhamella* spp. were isolated in 40% of affected eyes, compared with 30% of unaffected eyes, but this difference was not statistically significant (Fatimah et al., 1994).
Phenothiazine-Associated Corneal Disease

Corneal edema and keratitis have been associated with phenothiazine toxicity, but this condition is seen mainly in calves and, to a lesser extent, in pigs and goats (see bovine section) (Bistner et al., 1981; Enzie & Whitmore, 1953; Whitten et al., 1946).

Ocular Squamous Cell Carcinoma

While uncommon, OSCC has been reported in sheep (Wilcock, 1993). In 2005, spontaneous OSCC in twin goats was reported (Mara et al., 2005). In both goats, Papillomavirus-like sequences were detected with PCR analysis, suggesting that, as in cattle, Papillomavirus may have played a role in the pathogenesis of the OSCC.

Glaucoma

Steroid-induced ocular hypertension is reported in sheep to increase after 1 week of prednisolone acetate topical treatment administered three times daily. After discontinuation of the corticosteroid instillation, IOP declined to baseline values over 1–3 weeks (Gerometta et al., 2009). A single dose of a gene therapy vector carrying an inducible metalloproteinase human gene is protective against the IOP increase produced by corticosteroid instillation in the sheep model and quickly reverses the IOP increase elicited by the corticosteroid (Gerometta et al., 2010).

The Uveal Tract

Iris Abnormalities

Defects in iris anatomy, termed “essential iris atrophy”, have been described among purebred Shropshire sheep in Pennsylvania (Aguirre et al., 1981). Affected animals are normal at birth, but by 1.0–1.5 years of age may be affected with full-thickness holes in the iris stroma. The corpora nigra is rudimentary or absent, and animals are affected bilaterally but not symmetrically. Reported lesions have not been associated with any previous inflammatory episodes.

Inflammation of the Uvea

In sheep and goats, neonatal pyosepticemia, listeriosis, mycoplasma, toxoplasmosis, eaeophorosis, thiamine deficiency, trypanosomiasis, blunt trauma, retroviral, and toxic causes have been reported for uveitis (Moore & Whitley, 1984; Radostits et al., 2007; Raoofi et al., 2004; Smith, 2009; Smith & Sherman, 1994) (see Chapter 35).

Uveal Tumors

While primary tumors of the anterior and posterior uvea are rare, a malignant melanoma has been reported in a sheep (Saunders & Barron, 1958). An iridociliary adenoma in a sheep has also been reported (Raoofi et al., 2004). One month

Parasitic Keratoconjunctivitis

Oestrus Ovis

Oestrus ovis may cause conjunctivitis if larvae invade the ocular mucous membranes (Moore & Whitley, 1984). The adult flies deposit eggs around the mucous membranes of the face. When the eggs hatch, the larvae migrate to the nasal cavity, turbinates, and the maxillary and frontal sinuses. Larvae may progress to the nasolacrimal duct and eye. The larvae are large (2.5 cm), spiny, and cause irritation. Secondary infection, epithora, and conjunctivitis may result. The larvae mature within several weeks to months and then return to the nostril, where they drop or are sneezed onto the ground to pupate.

Treatment usually involves physical removal of larvae and systemic organophosphates. The only drug labeled for control of sheep nasal bots in the United States is Ivermectin Sheep Drench (0.08% ivermectin), which may be administered only to sheep at 0.2 mg/kg (Gnad & Mock, 2001). Treatment is best performed in the fall months, when the larvae are small (Moore & Whitley, 1984).

Thelazia Species

Thelazia californiensis occurs in sheep, deer, and other species (see bovine section).

Other Parasites

Trypanosoma spp. are reported to cause blepharitis, conjunctivitis and keratitis in sheep and goats (Moore & Whitley, 1984). Conjunctival cysts may be seen in the bulbar conjunctiva of sheep and goats infected with Besnoitia spp. Besnoitiosis, which is associated with alopecia, infertility, and abortion, is widespread in Africa and the Middle East (Bwangamoi et al., 1989).

Miscellaneous Conjunctival Abnormalities

Locoweed poisoning may cause keratoconjunctivitis sicca in sheep (Van Kampen & James, 1971). Drying of the eyes may result from chronic degenerative neurotoxicosis, causing failed neurogenic stimulation of tear secretion and an inadequate blink response.

Both smooth and rough types of B. ovis have experimentally induced conjunctivitis, either alone or together with M. conjunctivae and C. pecorum (Dagnall, 1993b, 1994b). An isolate of B. ovis with smooth-colony morphology from a field case of follicular conjunctivitis could produce lesions similar to the field case when inoculated into the conjunctival sac of lambs. In association with M. conjunctivae, B. ovis contributes to the severity of the keratoconjunctivitis (Dagnall, 1994b).

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after the affected globe had been enucleated, the ewe was doing well.

The Lens

Congenital Cataracts

Congenital cataracts have been reported in sheep, but they are rare in goats (Brooks et al., 1982a, 1982b; Smith & Sherman, 1994). Congenital nuclear cataracts have been observed in sheep and goats (Lavach, 1990). The cataracts did not progress to involve the cortex.

Acquired Cataracts

Inflammatory cataracts result from lenticular trauma or from severe uveitis. The nematode *Elaeophora schneideri* has induced cataracts among domestic sheep in the western United States (Abdelbaki & Davis, 1972). Diabetes mellitus has been implicated as the cause of cataracts in ram lambs (Mattheeuws et al., 1982).

The Ocular Fundi

Ophthalmoscopic Examination

The ocular fundi of cattle and sheep are quite similar ophthalmoscopically. The retina of the sheep is holangiatic (Fig. 29.70). Three, and occasionally four, major venules drain the retina, and these are accompanied by paralleling arterioles. Occasionally, in sheep, the superior arteriole and venule may twist about each other.

The tapetal fundus reflects a greenish blue color and is a horizontal strip in shape with its lower edge just touching the point of entry of the optic nerve (Ollivier et al., 2004). The upper edge is not clearly defined. The optic disc is always located at the junctional area of the nontapetal and tapetal fundus, usually within the nontapetal fundus just below the junction.

In sheep, the optic disc has a kidney shape. Myelinization of the optic nerve fibers normally stops at the lamina cribrosa. Small ruminants have stereoscopic vision, at least in medium- and long-distance vision but not in near vision (Moore & Whitley, 1984). Histopathologically, a high density of ganglion cell nuclei occurs in the retina (Nilsson et al., 1973). A study recently looked at the topography of ganglion cells and photoreceptors in the sheep retina. Retinal ganglion cells were distributed densely in the area centralis, horizontal visual streak, and anakatabatic (dorsotemporal) area. The highest density in the area centralis was approximately 18,000 RGCs/mm². Cones showed high density in the horizontal area crossing the optic disc and dorso-temporal area, whereas rods showed high density in the horizontal area, which was greater in height than the horizontal area of high cone density. The rod/cone ratios were high horizontally in the retina dorsal to the optic disc, with a mean value of 11:1. This suggests that sheep have better visual acuity in horizontal and anteroinferior visual fields, which may be of ecologic benefit to them (Shinozaki et al., 2010).

The ocular fundus of the goat is somewhat different from that of cattle and sheep. The retinal blood vessels are more numerous, and five to eight primary venules often occur. The optic disc is rounder than in sheep and cattle, and it frequently is situated totally within the tapetal fundus. A pigment ring often surrounds the optic disc as well (Fig. 29.71) (Galan et al., 2006).

Fluorescein angiography without sedative or anesthetic agents has been evaluated in normal goats and sheep. All of the angiographic phases were observed using 20 mg/kg fluorescein IV in both species. Fundus fluorescein angiography

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**Figure 29.70.** Normal ovine ocular fundus. The kidney-shaped optic disc is at the junction of the tapetal and nontapetal fundi. (Courtesy of the University of California-Davis Comparative Ophthalmology Service.)

**Figure 29.71.** Normal caprine ocular fundus. The round optic disc is at the junction of the tapetal and non-tapetal fundus. (Courtesy of G. Klauss.)
results revealed wide stars of Winslow in the tapetal fundus, central or marginal flow during the first part of the arterial phase, delayed filling of the focal areas in the choroid near the optic disc that often coincided with others in the disc, and lack of evidence of the “striate area” in the tapetal fundi. In goats, the angiographic times were $6.54 \pm 1.25$ seconds for the arterial phase, $7.80 \pm 1.37$ seconds for the arteriovenous phase, and $14.13 \pm 2.01$ seconds for the venous phase. In sheep, times were $9.54 \pm 2.18$ seconds, $11.73 \pm 2.10$ seconds, and $20.86 \pm 2.74$ seconds (Galan et al., 2006).

Ocular Albinism
Complete albinism is rare, but it has been documented in sheep (Adalsteinsson, 1977). In Icelandic sheep, albino animals have occurred among both white and nonwhite strains. A affected animals have visual deficits in bright light, and albino lambs with a normal twin are often deserted by the dam in open country. The albino condition in sheep totally inhibits the formation of both eumelanin and phaeomelanin. The condition is autosomal recessive and is assumed to be a mutation at the C locus (Adalsteinsson, 1977). In Suffolk sheep, albinism is an autosomal recessive trait: the cmr (albino marrabel) gene on the C locus encodes a defective tyrosinase (Rowett & Fleet, 1993). This condition appears homologous to albinism in rodents (Adalsteinsson, 1977).

Retinal Dysplasia
Inherited retinal dysplasia must be differentiated from dysplastic changes resulting from intruterine infection. Infectious agents, particularly bluetongue in sheep, have been implicated as causing retinal dysplasia (see Chapter 35).

Inflammation of the Ocular Fundus
Various infectious agents have been implicated as causing posterior segment inflammatory changes in food animals. Small domestic ruminants have been reported to have posterior segment changes related to bacterial and parasitic causes (mycoplasmosis, listeriosis, elaeophorosis, trypanosomiasis, and toxoplasmosis) and viral causes (bluetongue and scrapie) (Barnett & Palmer, 1971; Moore & Whitley, 1984; Piper et al., 1970; Strain et al., 1990) (see Chapter 35).

Degeneration of the Retina and Optic Nerve
Abnormalities in outer retinal or visual cortex function may be assessed, when feasible, by electrodiagnostic means. Normal values for the ERG and visual-evoked potentials have been reported for sheep (Strain et al., 1991).

Retinal Degeneration in Toggenburg Goats
Retinal degeneration has been reported in Toggenburg goats (Buyukmihci, 1980; Wolfer & Grahn, 1991). In the cases reported by Wolfer and Grahn, two kid goats born of half-sisters bred by the same buck were born blind. Clinically posterior segment abnormalities were the only significant lesions, and these consisted of generalized tapetal hyperreflectivity and retinal vascular attenuation (Fig. 29.72). Both kids had a searching nystagmus. Histopathology showed diffuse photoreceptor loss and the loss of virtually all the outer nuclear and outer plexiform layers. The inner nuclear layer was in an early stage of degeneration, but the ganglion cell layer and optic nerve were histopathologically normal (Fig. 29.73).

Stypandra glauca Intoxication
In sheep and goats, a syndrome of retrobulbar optic neuropathy and retinal degeneration occurs after ingestion of...
Stypandra glauca (i.e., blind grass) (Main et al., 1981; Whittington et al., 1988). Field evidence suggests that S. glauca is toxic in the flowering stage. Affected animals may die after an acute illness with signs of neurologic disturbances, or they may survive but remain permanently blind. Funduscopy shows multifocal tapetal and peripapillary hyperpigmented foci interspersed with other areas of tapetal hyperreflectivity. Optic nerve atrophy may be present as well.

An ERG reveals a decreased b-wave amplitude (Whittington et al., 1988). Fluorescein angiography shows no leakage. Histopathology shows multifocal photoreceptor degeneration with accompanying hypertrophy of the retinal pigment epithelium. Optic nerve lesions are most evident in the intracanicular and intracranial regions, with the orbital portion being relatively unaffected. Stypandrol, a binaphthalene tetrol, is most likely the toxic principle. The pathogenesis of the optic neuropathy may relate to acute swelling of the optic nerve because of myelin edema, thereby resulting in compression and irreversible injury to the optic nerve within the bony optic canal. Stypandrol may also be directly retinotoxic.

Hypothiaminosis

PEM, or cerebrocortical necrosis, may be caused by thiamine deficiency (Edwin et al., 1982; Markson et al., 1972). The disease is especially common in goats fed a sudden excess of carbohydrates (Smith, 2009). Affected animals display blindness, ataxia, depression, opisthotonus, nystagmus, convulsions, coma, and can die of respiratory failure (see bovine section in this chapter) (Loew, 1975).

Pteris aquilinum-Induced Retinal Degeneration

Pteris aquilinum (i.e., bracken fern, brake fern, hog brake) has been associated with a progressive retinal degeneration (PRD) of the outer layers in sheep (Barnett & Watson, 1970; Watson et al., 1965, 1972a; Watson & Barnett, 1970). Affected animals have variously been called “bright blind,” “moonlight blind,” “clear blind,” or simply “glass eyed”; this terminology has arisen on the basis of the abnormal shine of the affected eyes in semidarkness (Barnett & Watson, 1970). The disease has been seen clinically in sheep grazing bracken (P. aquilinum), and it has been reproduced experimentally by feeding a concentrate ration containing 50% dried bracken at 1 kg/day for up to 63 weeks (Watson & Barnett, 1970; Watson et al., 1972b). Ptaquiloside, which is a norsesquiterpene glucoside of the illudane type, is a bracken carcinogen and the principal causative agent of PRD (Hirono et al., 1993).

The disease is limited to certain areas, including northern England, Scotland, and possibly Wales. In flocks grazing bracken-laden fields, up to 25.6% of sheep may have PRD (Watson et al., 1972b). In any one flock, 37% of sheep may be affected. The incidence is highest among 3- to 4-year-old sheep. It is seldom seen in sheep younger than 2 years, but a 9-month-old ewe lamb has been affected. In field conditions, rams have never been affected (Watson et al., 1972a).

Clinically, the sheep are permanently blind. Affected animals have dilated pupils and sluggish pupillary responses. The earliest ophthalmoscopic sign is an increased tapetal reflection. The optic disc is normal. There is attenuation of the retinal blood vessels (Fig. 29.74). In advanced cases, the non-tapetal area is affected (Watson et al., 1965).

Biochemical and hematologic abnormalities also exist in PRD. Retinal lactate dehydrogenase isoenzyme activity decreases, and the ratio of H- to M-type monomers increases. Platelet and leukocyte counts are lowered as well. Histopathologic changes are confined to the retina. Initially, there is degeneration of the rod and cone outer segments, which fragment and break into fine, granular forms. As the disease progresses, there is loss of the rod, cone, and outer nuclear layers, as well as parts of the inner nuclear layer. As a result, the retinal pigment epithelium appears to abut directly onto the remains of the inner nuclear layer (Watson et al., 1965).

Locoweed Poisoning

As in cattle, poisoning with locoweed (Astragalus and Oxytropus spp.) causes retinal degeneration in sheep (see bovine section in this chapter) (James, 1972).

Other Toxic Plants

Sarcostemma spp. cause neurologic disease among sheep in Africa, and they may also be associated with visual impairment (Terblanche & VanStraten, 1966). Darling pea (Swainsonia galegifolia) causes signs similar to those of locoweed in cattle and sheep (Watson et al., 1972a).
Other Ocular Toxins
Toxins other than those involving plants may cause retinal and optic nerve disease as well. Antiparasitic drugs, such as hexachlorophene and rafloxanide, may cause optic nerve pathology (M oore & Whitley, 1984). The toxic effects include degeneration and gliosis of the CNS, retina, and optic nerve, resulting in blindness and even death. In one flock of 168 sheep, 83 animals were affected, of which 25 (30%) died within 1 week of treatment (Prozesky & Pienaar, 1977). Histopathology of the optic nerves showed demyelination with Schwann cell proliferation, edema, and congestion. No structural abnormalities were seen in the retina.

Inherited Lysosomal Storage Diseases
Lysosomal storage diseases with ophthalmic implications include GM1 gangliosidosis (i.e., leukodystrophy in Suffolk sheep), GM2 gangliosidosis (i.e., lipodystrophy in sheep), mannosidosis in Anglo-Nubian goats, and ceroid lipofuscinosis in South Hampshire sheep in New Zealand (Smith, 2009). The inherited lysosomal storage diseases are covered in Chapter 35.

Scrapie
Transmissible spongiform encephalopathies are fatal neurodegenerative diseases in which an abnormal isoform of the cellular prion protein accumulates in tissues of the central nervous system. In sheep affected with scrapie, prion protein also accumulate in the inner and outer plexiform layers of the retina. Electrotoretinograms on scrapie-affected sheep show reduced b-waves in one study (Smith et al., 2009), and reduced a-waves and b-waves in another study (Regnier et al., 2011). Histopathology of affected retinas is variable. Reports of very few morphologic lesions exist, as do reports showing marked lengthening and disorganization of photoreceptor segments and substantial reduction in cellularity/thickness of the inner nuclear layer (Regnier et al., 2011; Smith et al., 2009).

Central Blindness
Diseases that may cause central blindness include pregnancy toxemia, CNS abscesses, Taenia multiceps (Coenurus cerebralis)-cysts (Vicary, 1979), PEM, listeriosis, and lead poisoning (Hindson & Winter, 2002). Additional information can be found in Chapter 35.

PIGS
The Orbit and Globe
Pigs possess an open orbit which is continuous with the temporal fossa. The field of vision is probably 260–275° with an estimated binocular field of 30–50° (Middleton, 2010). An orbital venous sinus in pigs has been described as a site for blood collection. The pig is placed in dorsal recumbency, and the fibrous conjunctival tissue is punctured using a glass pipette to rupture the venous sinus and the medial canthus just inside the nictitating membrane (Muirhead, 1981). This technique is not recommended and there are other preferred methods of blood collection in pigs. The corneal epithelium of pigs contains angiostatin, an inhibitor of angiogenesis, which may have a regulatory role in the maintenance of corneal clarity (Pearce et al., 2007). IOP in pigs has been measured and found to be 15.2 mmHg using the Tono-Pen XL in adult pigs under general anesthesia with ketamine and xylazine (Ruiz-Ederra et al., 2005). Another study showed average IOPs of 27.3 mmHg in the right eyes and 26.3 mmHg in the left eyes of awake Gottingen minipigs using the Tono-Pen XL (Middleton, 2010).

Congenital Globe Abnormalities and Blindness
In a study of 319 congenitally malformed pigs, 653 distinct malformations occurred (Selby et al., 1971). Among these pigs, 16 had cyclopia, 13 anophthalmia, and 7 microphthalmia. Genetic studies were not reported, but 92% of the anophthalmic defects were associated with other malformations. Holoprosencephaly with varying degrees of optic hypotelorism, including cyclopia, has also been reported in the pig (Fisher et al., 1989).

Maternal vitamin A deficiency has been linked with anophthalmia, microphthalmia, macrophthalmia, retinal dysplasia and other ocular abnormalities in piglets (Goodwin & Jennings, 1958; Huston, 1978; Palludan, 1976; Watt & Barlow, 1956). The severity varies between litters, between littermates, and even between eyes in the same animal (Palludan, 1976). Microphthalmia is the most common abnormality (Huston, 1978). Congenital microphthalmos is seen in Yorkshire pigs and is thought to be inherited as an autosomal recessive trait (Howard & Smith, 1999).

The Eyelids
Entropion
The popularity of the pot-bellied pig has resulted in an increased number of entropion cases being seen by veterinary ophthalmologists. The large amount of subcutaneous fat in the forehead and periorbital region of this breed, as well as the enophthalmos, contributes to the development of entropion (Fig. 29.75). Surgical intervention is usually required, and successful use of a modified Hotz-Celsius procedure has been reported (Linton & Collins, 1993). A modified brow sling (Elder, 1993; Kirschner, 1994), using either mesiline mesh or polyester suture coated with polybutylate, is effective in some cases. The large suture or mesh acts as a scaffold for the attachment of fibroblasts. A novel method for removal of redundant fat and skin can be used to alleviate clinical signs of entropion and vision loss secondary to periorbital fat pad hypertrophy of pot-bellied pigs (Allbaugh & Davidson, 2009; Andrea & George, 1999). A small percentage of Vietnamese pot-bellied pigs are prone to abnormal fat accumulations in the facial region, particularly the periorbital region, that...
forms characteristic of chlamydial development. It was concluded that both chlamydiae and mycoplasma play a role in the pathogenesis of some cases of conjunctivitis and keratoconjunctivitis in swine (Rogers et al., 1993). It has been demonstrated in swine with an outbreak of mucopurulent conjunctivitis that organisms identical to *Mycoplasma* spp. could remain intact within conjunctival epithelial cells (Fig. 29.76) (Rogers et al., 1991).

**Acquired Corneal Diseases**

**Phenothiazine**

Phenothiazine has caused corneal edema and keratitis in pigs (see bovine section) (Mathalone, 1968; McClanahan et al., 1966; Radostits et al., 2007; Wheeler et al., 1969).

**Congenital Porphyria and Protoporphyria**

Inherited defects of porphyrin metabolism have been reported in swine (Jorgensen & With, 1963). In pigs, the inheritance is uncertain, but it may result from one or more dominant genes (see bovine section in this chapter).

**Neoplasia of the Conjunctiva and Cornea**

Primary tumors of any site, including the eye, are rare in swine (incidence, 0.64%) (Priester & Mantel, 1971).

**The Uveal Tract**

**Congenital Disorders of the Anterior Uvea**

Congenital disorders include PPMs, heterochromia, aniridia and iris hypoplasia, polycoria, cysts, pigment nevi, and...
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SECTION IV

Glasser disease, and erysipelas have been reported (Vestre, 1984).

The Lens

Congenital Cataracts

Congenital cataracts have been reported (Saint-Macary & Berthoux, 1994). In Yucatan micropigs, posterior cortical pinpoint opacities were seen in 20.5% of 7- to 12-month-old animals. Posterior capsular pinpoint opacities, nuclear opacities, and suture line abnormalities were seen.

Acquired and Secondary Cataracts

Bilateral cortical opacities have been described in mature sows fed hygromycin B (Cargill et al., 1983). Formation of cataracts due to hygromycin B appears to be dose-dependent and potentially cumulative. Amount of cataract formation with hygromycin B varied from small posterior polar opacities to mature cataracts and may be asymmetric between eyes (Sanford & Dukes, 1978). Development of cataracts may have depended on the age of the pigs at the onset of supplementation. Approximately 30% of sows older than 2.5 years were affected. Sows treated with alloxan gave birth to piglets with nuclear cataracts (Cargill et al., 1983). The cataracts were most prominent at the nuclear cortical junction and did not progress or significantly affect vision.

Radiation-induced cataracts have also been seen in swine (see the bovine section) (Brown et al., 1972). Starvation and riboflavin deficiencies have been described as causing incomplete cataracts (Howard & Smith, 1999). Vietnamese pot-bellied pigs have juvenile cataracts that are thought to be inherited.

The Ocular Fundi

Ophthalmoscopic Examination

The pig ocular fundus lacks a tapetum. The disc is horizontal and sharply defined, with 8–10 arterioles, 3–4 of which are more prominent. The vascular pattern is holangiotic and vessels branch dichotomously, a single artery and vein accompany each other. Vessels may bulge internally into the vitreous body. In white pigs, the fundus is pink; in heavily pigmented animals, the background is gray to brown (Fig. 29.78). More commonly, partial albinism (i.e., subalbinism) is described (Gelatt, 1973; Saint-Macary & Berthoux, 1994).

The photoreceptor mosaic of pigs and humans are similar and supports the use of the pig retina as a model for human/animal research (Samuelson et al., 1993; Severin et al., 1976). The pig retina is well-endowed with cones, an extensive vascular tree, and an area sufficiently free of blood vessels to suggest an area centralis close to the posterior pole (Chandler et al., 1999).

Colobomatous Malformations

In swine, there are few reports of colobomas. In one report of 112 Yucatan micropigs from 7 to 12 months of age, an optic disc...
abnormality suggestive of a coloboma was found in one female (Saint-Macary & Berthoux, 1994). In miniature swine, large colobomas of the optic nerve and choroid have been observed (Rubin, 1974). Optic nerve hypoplasia has been observed in piglets raised for research purposes (Rubin, 1974). The condition was bilateral, and direct pupillary responses to light were absent in both eyes. Families of swine have also been reported to have optic atrophy with multiple ocular anomalies, including scleral staphylomas, hydrophthalmos, retinal and choroidal atrophy, retinal calcification, and microphthalmia, all of which are possibly hereditary anomalies.

**Congenital Vascular Anomalies**

In Yucatan minipigs, hyaloid remnants (82.1%) and pupillary membrane remnants (66.1%) were the most frequently reported ophthalmic findings. Persistence of the hyaloid remnants even occurs in some micropigs older than 33 months (Saint-Macary & Berthoux, 1994).

**Inflammation of the Ocular Fundus**

Most fundus abnormalities induced by systemic diseases are discussed in Chapter 35. Chorioretinal lesions may result from pseudorabies, hog cholera, listeriosis, toxoplasmosis, Glasser disease, ocular cysticercosis, Teschen encephalitis, and swine erysipelas (Busch et al., 1971; Cardenas-Ramirez et al., 1984; Gordon & Luke, 1952; Howarth & De Paoli, 1968; Saunders et al., 1958; Schneider & Harvarth, 1973).

**Degeneration of the Ocular Fundus**

Amaranthus retroflexus (redroot pigweed) and Chenopodium album (lamb’s-quarters) cause neurologic signs and decreased vision in pigs (Buck et al., 1966; Osweiler et al., 1969). A rsanilic acid toxicity may result in blindness among pigs (Menges et al., 1970; Vorhies et al., 1969; Witzel et al., 1976). A rsanilic acid is used therapeutically for swine dysentery and as a growth stimulant. Clinical signs appear when arsanilic acid is given in excess, for a prolonged period of time, or during times of restricted water intake (Menges et al., 1970; Vorhies et al., 1969). A ffected swine show blindness, weakness, torticollis, and incoordination. The pupillary light reflexes are absent, and ophthalmoscopic examination reveals bilateral optic disc atrophy, which is characterized by pallor, well-defined margins and narrowed retinal arterioles. The ERG is normal in blind pigs, but visual-evoked potentials are not recordable or are abnormal compared with those in normal animals. The essential histopathologic lesion of arsanilic acid toxicity is a parenchymatous neuropathy, with demyelination and axonal destruction of the optic nerves and tracts (Witzel et al., 1976). Lesions have not been detected in the outer layers of the retina (Vorhies et al., 1969). The optic nerve lesions are detected 4 or more days after the onset of blindness, and these lesions continue to develop even after the arsanilic acid has been withdrawn.

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INTRODUCTION

Camelids are thought to have evolved in North America 40-50 million years ago with a subsequent outward dispersion. Although the exact evolutionary sequence that led to the animals of today has not been completely elucidated, it is thought that three camelid tribes arose in North America: the Camelopini, the Camelini, and the Lamini. During the height of the Pleistocene epoch, these animals flourished with some migrating back and forth across the Bering Strait (Webb, 1974). The camel lines eventually settled within Asia, Europe, the Middle East, and North Africa, and the lamoids moved into South America 3 million years ago via the Isthmus of Panama. All wild camelids had become extinct in North America by 3000 BC, but they flourished in South America where some of the species became domesticated.

Today the camelids are divided into two categories, Old World camelids, which contains the dromedary camel (Camelus dromedaries) and the Bactrian camel (Camelus bactrianus), and New World camelids, which contains llamas (Lama glama), alpacas (Lama pacos), guanacos (Lama guanicoe), and vicunas (Vicugna vicugna), of which there are two subspecies (Fowler, 1998). The domestication of llamas and alpacas in the Andes was started around 4000–5000 BC. The other two New World camelids remain wild in South America (Nowak, 1991). In the past 20–30 years, many domesticated South American camelids have been imported to and bred in North America (Fowler, 1998). The popularity of llamas in the United States and Canada reached its height in the 1990s with a subsequent decline. Currently, there are thought to be 158,000 llamas in these countries. The popularity of alpacas, however, continues to rise slowly with an estimated 155,000 alpacas in Canada and the United States in 2011 (www.scla.us/llamafacts.html; www.genesialpacas.com). As such, veterinary care is important for these animals, including the need to understand the anatomy, physiology, and diseases of the camelid eye.

In order to better understand camelid ocular problems, several surveys investigating their ocular health and disease have been published. In a 1997 retrospective study using the Veterinary Medical Database (VMDB), we documented the ocular diseases for which llamas were presented to veterinary hospitals in North America over a 13-year period (Gionfriddo et al., 1997). Not surprisingly, traumatic ocular disease was the most common presenting complaint, although other diseases were also seen, both congenital and acquired. Around this same time, Gelatt et al. published the results of ophthalmic examinations of 29 apparently healthy alpacas in South America (Gelatt et al., 1995). Although these animals had no reported clinical signs, 38% had at least one ocular abnormality, including conjunctivitis, corneal scars, posterior synechiae, cataracts, a subluxated lens, vitreous opacities, and/or an optic disk coloboma. Many lesions were thought to be secondary to trauma, but some may have been hereditary (Gelatt et al., 1995).

More recently in 2006 and 2010, Webb et al. published reports of ophthalmic findings and auditory abilities in a group of llamas and alpacas living in eastern Canada (Webb & Cullen, 2010; Webb et al., 2006). These studies investigated the idea that the possible increased incidence of genetic problems in Canadian camelids was associated with the closure of the Canadian registry of llamas and alpacas to newly imported animals from South America. This may have led to increased inbreeding with subsequent expression of undesired phenotypic traits. Interestingly, they found that many of the 17 llamas and 23 alpacas with ophthalmic examinations had potentially hereditary ocular abnormalities including persistent pupillary membranes (PPMs) (14/17 llamas and 5/23 alpacas), cataracts (9/17 llamas and 5/23 alpacas), and corneal dystrophy (0/17 llamas and 2/23 alpacas). In the same study, 25 llamas and 38 alpacas were tested for deafness by brainstem auditory evoked response (BAER). The results of the BAER tests were compared with coat and iris colors. Seven of 10 pure white haired, blue eyed animals were bilaterally deaf and 1 was unilaterally deaf. The authors concluded that there was an association between skin, iris hypopigmentation, and congenital sensorineural deafness in llamas and alpacas (Webb & Cullen, 2010; Webb et al., 2006).
The database of the Cooperative Ophthalmic Pathology Laboratory of Wisconsin (COPLOW), housed at the University of Wisconsin, Madison, has information on the histopathologic evaluations of 35 enucleated camelid eyes presented to the Laboratory from 1990 to December 2009 (R. Dubielzig, 2009, unpublished data). Twenty-two of these eyes were from llamas, 12 were from alpacas, and 1 was from a guanaco. Five eyes were from crias less than 2 months of age and had various congenital disorders, while the rest of the disorders were either infectious, traumatic, or age-related problems. These diagnoses and those from the above studies will be discussed further in the following pages.

**VISION**

What little is known about vision in South American camelids is extracted from anecdotal reports (Beacham, 2003) or extrapolated from studies of camel retinas (Harman et al., 2001). Only a few reports exist concerning physiologic or anatomic vision studies.

The position of the eyes on the sides of the llama and alpaca head suggests that they principally have monocular vision (Beacham, 2003), and their ecological role as prey animals tends to support this. However, a study of the retinal cells in dromedary camels, which are closely related to South American camelids, found that they have neither an area centralis (prominent in primates) nor a visual streak (which is prominent in horses, pigs, and cows) (Harman et al., 2001). Instead, they have areas of high ganglion cell densities in the nasal retina and in the temporal retina with low densities of ganglion cells between the two regions. Since regions of high ganglion cell densities are those with corresponding high visual acuities, the authors speculate that dromedary camels have some degree of binocular vision due to their high densities of ganglion cells in the temporal retina. The purpose of high ganglion cell density in the nasal retina is not clear. The authors suggest that the mobile, flexible necks in camels allow the animals to cover the visual field more fully than other species, and thus they need to have another area of acute vision outside the binocular field (Harman et al., 2001). Since South American camelids are closely related to camels, and they also have very flexible necks, it is possible that they have two areas of visual acuity as well. Interestingly, some of the dromedary camels that were examined had vertical retinal streaks which were highly dense with retinal cells, possibly amacrine cells (Fig. 30.1) (Harman et al., 2001). The function of this streak is unknown and it is not known if South American camelids also have this streak. On the basis of ganglion cell densities in the retinas, the authors estimated that the peak acuity of the camelid eye is 9.5–10 cycles per degree in the high ganglion cell density retinal regions and 2–3 cycles per degree in the central portion of the retina. This is comparable to the visual acuity of a domestic cat (6–9 cycles per degree in the visual axis) (Bloom & Berkeley, 1977; Jacobson et al., 1976) but poorer than the horse (18–20 cycles per degree) (Harman et al., 1999). On the basis of behavioral testing, the estimate of visual acuity in the dromedary camel was 10 cycles per degree (Harman et al., 2001).

In 1901, Johnson published a treatise describing the comparative ophthalmoscopy of many species including the llama. He suspected llamas to be slightly myopic (Johnson, 1901), and this was confirmed in 2000 using refractometry (Willis et al., 2000). They estimated the mean refractive error of llamas to be −0.6 diopters horizontally and −1.11 diopters vertically. Females were slightly more myopic than intact or castrated males. In contrast, alpacas were almost emmetropic measuring −0.12 diopters horizontally and −0.7 diopters vertically (Willis et al., 2000).

**EXAMINATION TECHNIQUES**

Ocular examination is optimally undertaken with the llama or alpaca restrained in stocks although some can be examined in a stall or in a “cushed” position (Fig. 30.2). Most domestic camelids are amenable to examination; however, chemical sedation (butorphanol, 0.02–0.04 mg/kg) may be necessary to control head movement (Gionfriddo, 1994; Gionfriddo & Friedman, 1993). A transilluminator or halogen pen light is recommended as regular penlights are not bright enough to elicit pupillary light reflexes (PLRs) in camelids. Their menace reflex, however, is particularly pronounced, and they will often jump or throw their heads in response. It is very easy to trigger a false response by touching the very long vibrissae that are present above and below the eye. Direct and indirect PLRs of camelids are slow, and movement of the iris will be discussed further in the following pages.
In a recent study, the mean Schirmer tear test I (STT I) of llamas was found to be 17.3 (range of 15–19 mm/min) while the mean STT II of 14 eyes of 7 llamas was 15.4 mm/min (range 12.5–17.5 mm/min) (Trbolova et al., 2012). Tear production is somewhat slow in a stressed animal, and to obtain an accurate measurement, it often requires having the tear test strip in place for the entire minute.

Applanation tonometry with either a TonoPen® (Mentor Ophthalmics, Inc., Norwell, MA) or TonoVet® (Icare, Finland) is the easiest and most accurate method of measuring intraocular pressures (IOPs) in camelids. In one study, IOPs taken with a TonoPen showed that there were no differences between llamas and alpacas, and that the mean IOP was 16.5 mmHg with a range of 14.89–18.21 mmHg (Nuhsbaum et al., 2000). However, in a 2006 survey of camelids in Canada, significant differences were found in IOP between the two species. In that study, llamas had significantly lower IOPs than alpacas (mean IOP in 33 llama eyes was 19 mmHg; mean IOP in 46 alpaca eyes was 16 mm Hg) (Webb et al., 2006). This difference between the species was thought to be due to the fact that the llamas in the study were older than the alpacas, and IOPs decrease as llamas and alpacas age (Webb et al., 2006). This difference, although significant statistically, is probably clinically irrelevant.

Imaging techniques, such as plain film radiographs, contrast radiographs, magnetic resonance imaging (MRI), computed tomography (CT), and ocular ultrasound, have been used to diagnose both ocular and periocular diseases in camelids. Dacryocystorhinography has been a particularly useful tool to diagnose the site of obstruction in alpacas with nasolacrimal disease (Fig. 30.3). For this procedure, about 5 mL of a mixture of sodium and meglumine diatrizoate is injected into the dorsal lacrimal punctum, and lateral and dorsoventral radiographs are then taken (Mangan et al., 2008; Sapienza et al., 1992). Alternatively, the dye can be tracked with fluoroscopy as it moves through the nasolacrimal drainage pathway (Mangan et al., 2008; Sapienza et al., 1992). If a camelid with congenital or juvenile-onset cataracts is going to undergo cataract surgery, ocular ultrasonography should be
used prior to the procedure. This technique was essential for detecting the presence of a patent hyaloid artery in a young llama with bilateral cataracts (Gionfriddo & Blair, 2002). Orbital ultrasound, MRI, and CT have also proved useful to detect and characterize intraocular and retrobulbar masses in camelids (Hamor et al., 1999; Hendrix et al., 2000).

**Ocular Medications**

Topical ocular medications that are used in other species are generally safe for camelids. The exception is topical corticosteroids in pregnant animals. In a study on llamas in the late stages of pregnancy, giving one drop three times daily of topical dexamethasone-containing ophthalmic preparation for 8 days caused them to abort their near-term fetuses (B. Grahn, 2004, unpublished data).

Delivery of topical ocular medicines in camelids can be facilitated by a nasolacrimal lavage system (NLLS) or subpalpebral lavage system (SPLS). Since the nasal punctum of camelids is relatively easy to locate, a NLLS is not difficult to place but may require that the animal be under sedation or general anesthesia. The procedure is accomplished by threading soft tubing (such as 22-guage polyethylene) into the nasal opening and up the nasolacrimal duct until it stops at the level of the nasolacrimal sac. The nasal end of the tubing can then exit the nostril, or may be threaded through a large-diameter needle puncture that is made in the alar fold of the nose, and fastened via tape-tabs to the face. Medication can be injected through an injection port which has been placed into the end of the tubing. Although this method is effective, the tubing that exits the nose is vulnerable to damage and traction forces caused by the animal.

It was originally thought that the SPLS might cause corneal trauma in camelids because of the tight fit of the eyelids around the globe. However, an adaption of a commercially available equine SPLS with a soft low-profile footplate was recently reported to deliver constant topical therapy to the eyes of two llamas with severe corneal ulcers (Borkowski et al., 2007). Initially, the medication was manually injected to the llamas’ eyes through the tubing, but when the ulcers failed to heal readily, the device was modified to connect with a balloon infusion system. This involved placing commercial balloon infusor and flow control to the tubing which delivered medication at a constant rate of 1 mL/h. No corneal complications were associated with the devices in the two animals, but mild swelling and irritation of one eyelid at the site of SPLS tubing penetration was reported (Borkowski et al., 2007).

**General Features of the Eye and Orbit**

Anatomically, the eyes of South American camelids are very similar to those of other ruminants (pseudoruminants) with some notable exceptions. The camelid eye is well adapted for the high altitude regions of South America, where there is increased UV light and little shade. Structures important to preventing UV light damage are their long eyelashes, the “pupillary ruff,” (Fig. 30.4), and the darkly pigmented scleral band around the limbus.

One interesting adaptation to high altitude living in camelids may be extrapolated from the retinal vascular pattern of the dromedary camel (Harman et al., 2001). In that species, even though there are specific high-density areas of ganglion cells within the retina, the major blood vessels do not avoid these regions as they do in other species. This could be a mechanism to improve oxygenation to these important retinal areas at high altitudes where partial pressure of oxygen is low (Harman et al., 2001).

The camelid globe is large in proportion to the head size and is only slightly smaller than the globe of cattle. The appearance of large eyes in these animals is accentuated by their prominent placement laterally in the skull and by the long upper and lower eyelashes present in most animals.

The bony orbit of camelids is complete. It is made up of portions of the frontal, lacrimal, zygomatic, maxillary, palatine, temporal, and sphenoid bones. There is a large palpable dorsal notch in the frontal bone. Rostral to the medial aspect of the orbit is a 2-cm-diameter opening into the nasal cavity which is probably associated with a scent gland.

**Eyelids and Nasolacrimal System**

Camelid eyelids fit tightly to the globe, and conformational eyelid defects are rare. The eyelids cover much of the sclera so almost no “white” is showing which makes their corneas appear very large. The sclera and exposed conjunctiva may be largely pigmented or nonpigmented, but there seems to always be a darkly pigmented, 2- to 3-mm band at the limbus. This may protect their eyes from solar radiation damage.
No cases of entropion have yet been reported in South American camelids; however, one case of very severe bilateral upper eyelid entropion has been described in a female one-humped camel (Yeruham et al., 2002). The entropion was diagnosed when she was 18 years old but had been noted at 4 months of age. Clinical signs were severe blepharospasm, epiphora, conjunctival edema and mucopurulent ocular discharge, and almost 360° rolling-in of the eyelid. Secondary corneal ulcers were present as was extensive corneal neovascularization. This camel had given birth to two offspring who were similarly affected and so the owner was advised not to breed the camel again (Yeruham et al., 2002).

Periocular neoplasms are also rare in camelids. This is an interesting finding as members of this family have evolved in areas of increased UV light exposure and little shade, which happen to be predisposing factors for periocular neoplasia in horses and cows. A report on the prevalence of neoplasms in llamas and alpacas in Oregon from 2001 to 2006 documented the presence of squamous cell carcinomas on the nictitating membranes of one llama and one alpaca (Valentine & Martin, 2007). In a case report of a 4.5-year-old llama, a firm mass near the medial canthus of the left eye was diagnosed as an ossifying fibroma which had originated in the area of the second premolar (McCaulery et al., 2000). Nasal endoscopy revealed a mucosa-covered mass that was originating by the tooth and extending to the soft palate. Although this mass was close to the nasolacrimal system, no epiphora was seen (McCaulery et al., 2000).

Congenital nasolacrimal duct disorders that have been reported in camelids include nasolacrimal duct atresia, conjunctival punctal atresia, nasal punctal atresia, or combinations of these (Boer & Schoon, 1984; Gionfriddo & Friedman, 1993; Mangan et al., 2008; Sapienza et al., 1992). Alpacas seem to be more commonly affected than llamas. Affected animals usually present with a “wet face” due to the tears spilling out of the eye and mucopurulent ocular discharge due to a secondary dacryocystitis. Most often, these animals are young when they presented for treatment, but older animals may also present because of secondary periocular dermatitis and/or fly strike.

In the 1997 VMDB database study, we reported that only two crias had been presented for nasolacrimal defects in a 10-year period, but the incidence (or reports of the condition) appears to be increasing. In the early 1990s, four llamas had congenital conjunctival eyelid punctal atresia (G. Severin, personal communication). More recently, five alpaca crias were presented to Colorado State University (CSU) for bilateral nasolacrimal duct obstructions (Juliet R. Gionfriddo, DVM, Fort Collins, CO, unpublished data, 2010). The abnormal puncta were surgically opened and catheterized using a procedure similar to that in horses (Lavach, 1990). Three of these crias were distantly related. Failure of nasal punctal formation was the cause of the obstruction in four of the five crias, and in the remaining cria, the duct was not patent but blind ended in the bony canal as it traversed the nasal cavity.

Diseases

Blepharitis is the most common eyelid problem in camelids. This is often present in conjunction with generalized dermatitis. Bacterial infections can lead to blepharitis and concurrent bacterial conjunctivitis (Gionfriddo et al., 1997). Reports of eyelid lacerations in camelids are rare, and in the VMDB study they were reported in only two llamas (Gionfriddo et al., 1997). Because the camelid eyelid fits so closely to the globe, there is a high potential for corneal injury with full-thickness eyelid lacerations due to concurrent trauma and subsequent increased exposure.
A case of severe epiphora due to bilateral atresia of the nasolacrimal ducts at the level of the nasal puncta was reported in a llama cria (Sapienza et al., 1992). Surgical opening of the ducts was successful. In a 2002 report, Arnold et al. described three cases of nasal punctal atresia in alpaca crias that were apparently unrelated (Arnold et al., 2002). In each of these animals, the presenting complaints were chemosis, lacrimation, and mucopurulent ocular discharge that were not responsive to topical antibiotic therapy. In one of these crias, the problem was unilateral, and it was bilateral in the other two. In all of these cases, the atresia was close to the site of the nasal puncta, and all animals responded well to surgical opening similar to the method described below.

Dacryocystitis is relatively common in camelids, perhaps because their large conjunctival puncta are vulnerable to invasion by foreign bodies such as grass awns. Animals with this disorder are typically adults with a history of chronic mucopurulent ocular discharge, which can be profuse (Fig. 30.6). There can also be a history of blepharospasm and conjunctival hyperemia.

Treatment

Because of the potential for secondary corneal injury or exposure keratitis, all full-thickness eyelid lacerations should be sutured in a two-layer closure, with the first layer in the muscle and the second in the skin. Since the camelid eyelids are so closely fit on the cornea, great care must be taken to avoid exposure of the suture or knots to the corneal surface.

Initial treatment of camelids with clinical signs of nasolacrimal obstruction involves identifying and attempting to cannulate both the upper and lower nasolacrimal puncta. Imperforate puncta are relatively common, especially in alpaca crias. Correction of an imperforate punctum involves incising the mucous membrane covering the opening. If the puncta are present and patent, the nasolacrimal duct should be flushed through one of the conjunctival puncta. This can be performed with local anesthetic alone in some animals, but some individuals are head-shy and must be sedated or anesthetized for the procedure. If the fluid fails to pass through the ducts and into the nasal cavity, the animal should be placed under general anesthesia, and catheterization of the nasolacrimal ducts through the conjunctival puncta should be attempted. Catheterization is performed with large suture material or with polyethylene tubing. If the material will not pass, then imaging procedures such as dacryocystorhinography are indicated in order to locate the site of the blockage.

The above procedures were performed on four of five alpacas that were presented to CSU and subsequently diagnosed with nasolacrimal atresia. In the four crias, the puncta were present and patent but attempted flushing of the ducts was unsuccessful. Next, a piece of polyethylene tubing was threaded down the nasolacrimal duct until it stopped at the point where the duct prematurely terminated. In three of the animals, the tip of the tubing could be palpated through the nasal mucosa on each side at the point where the nasal punctal opening should have been. An incision through the mucosa over the tubing was made and the tubing was passed into the nasal cavity at which point it was anchored to the surrounding nasal mucosa with a Chinese finger trap suture technique. It was then threaded through a large needle, which was used to pierce the skin of the nares, and attached to the skin with tape-tabs. The tubing was left in place for 6 weeks to prevent closure of the punctum. This corrected the problem in each case. In the fifth cria, the tubing could not be palpated through the nasal mucosa. A dacryocystorhinogram showed that the blockage was at the level of the maxillary bones. This indicated that the obstructions were due to failure of formation of the distal one-third of the nasolacrimal duct (Mangan et al., 2008). A bilateral conjunctivosinostomy (creation of a new opening from the conjunctiva into the sinus) was performed to allow for lacrimal drainage. This technique is relatively complicated (Mangan et al., 2008).

Treatment of dacryocystitis is aimed at clearing the nasolacrimal system of foreign material and clearing up the associated secondary bacterial infection. Topical antibiotics can be attempted initially but frequently do not lead to resolution. Flushing of the nasolacrimal duct through the upper or lower punctum will often remove foreign material, pus, and infectious agents. This can sometimes be performed on an awake animal after instillation of topical anesthetic drops. If the system does not flush easily, general anesthesia is required to allow for more aggressive flushing.

CONJUNCTIVA

Diseases

Congenital

Dermoids and cysts are congenital conjunctival abnormalities that have been reported in camelids (Fowler, 1989; Gionfriddo...
et al., 1997; Moore et al. 1999; Schuh et al., 1991). Large cysts have been reported infrequently in the conjunctiva of neonatal crias (Schuh et al., 1991). Schuh et al. reported on a case of a cria with a cyst-like structure on the bulbar conjunctiva. A spiration of this structure yielded a clear fluid. Because the same eye had other defects, the cyst was thought to be part of a general ocular maldevelopment (Schuh et al., 1991). A very large conjunctival cyst was seen in a cria who had no other ocular abnormalities (L. Johnson, personal communication). After drainage of the cyst, it refilled with clear fluid but surgical excision proved curative.

**Acquired**

Conjunctivitis is common in camelids. The clinical signs are similar to those seen in other ruminants and typically include mild blepharospasm, conjunctival hyperemia, epiphora, and occasionally, chemosis. Irritation from dust or foreign bodies is a common cause for self-limiting mild conjunctivitis. Fisher and Hendrix reported on 16 alpacas from the same herd who concurrently were afflicted with conjunctivitis and ulcerative keratitis. Because of the multiple animals involved, an infectious cause was suspected but upon thorough examination, plant foreign bodies were found in the temporal conjunctival fornix in 9 eyes of 6 animals, and the other 10 animals had corneal ulcers or conjunctivitis indicative of prior foreign bodies (Fisher & Hendrix, 2010).

Since foreign bodies are common, careful inspection of the conjunctival sacs is important. In the VMDB study, however, 19 (10%) of the llamas with conjunctival disease had no definitive cause identified (Gionfriddo et al., 1997). Several cases of bacterial conjunctivitis were also documented in that study (Gionfriddo et al., 1997). In those cases, the clinical signs were more severe and included marked hyperemia, mucopurulent ocular discharge, and blepharospasm. In an unpublished study of five llamas with severe conjunctivitis, pathogenic bacterial species were isolated from the lower conjunctival fornix of each animal and were suspected to be the primary cause of the disease (J. Gionfriddo, 1990, unpublished data). In a case of keratoconjunctivitis in a llama, Brightman et al. reported that Staphylococcus aureus was isolated from the conjunctival sac while M. oraxella liquifaciens was isolated from the cornea (Brightman et al., 1981). Chlamydiae have also been isolated from camels with conjunctivitis (G. Severin, personal communication). No herd outbreaks of M. oraxella bovis keratoconjunctivitis (like in “pink eye” in cattle) have been reported in the literature in New World camelids although a single case of ulcerative keratitis from which M. liquifaciens was cultured has been reported (Brightman et al., 1981). There is one report of two outbreaks of keratoconjunctivitis in a dromedary cattle herd in Spain that was caused by M. oraxella canis, but this has not been reported in llamas or alpacas (Tejedor-Junco et al., 2010). In general, cytologic evaluation of a conjunctival scraping and microbiologic culture (both bacterial and fungal) and sensitivity testing are recommended in cases of conjunctivitis and keratoconjunctivitis.

In addition to bacterial conjunctivitis, parasites have been reported to lead to moderately severe conjunctivitis in camelids. The larvae of the nematode parasite, Thelazia californiensis, can be present in the conjunctival sacs of many species, including llamas and alpacas. This disease seems to be particularly prevalent in the western United States (Fowler, 1989). Clinical signs of Thelazia infection range from mild epiphora and hyperemia to severe epiphora and blepharospasm (Fowler, 1989). This larval nematode is transmitted between animals by face flies. It is small and may be seen moving across the surface of the eye or hiding beneath the third eyelid. Occasionally, its presence can cause enough irritation that the animal will self-traumatize and which can lead to a secondary corneal ulcer.

Toxoplasmosis was the suspected cause of a case of uveokeratoconjunctivitis in a 15-year-old male llama (D. Tinsley, DVM, Diplomate ACVO, Gloucester ON, Canada, 2011, unpublished data). This animal had neurologic signs plus marked blepharospasm, lacrimation, and mucopurulent periocular discharge. There was severe conjunctival hyperemia and chemosis and signs of uveitis consisting of iridal swelling, posterior synechiae, and debris on the anterior lens epithelium. Based on ruling out other causes of these symptoms and the presence of a rising vitreal IgG titer to Toxoplasma gondii, a presumptive diagnosis of ocular toxoplasmosis was made.

**Treatment**

Infectious and irritative conjunctivitis should be treated according to the cause. A culture and sensitivity should be done on all cases of suspected bacterial conjunctivitis. Prior to receiving the results of culture, a broad spectrum antibiotic, such as a triple antibiotic, should be applied three to six times daily. If a Thelazia larva is seen, mechanical removal of the worm under topical anesthetic is curative. Alternatively, topical diethylcarbamazine or a drop of injectable ivermectin instilled into the conjunctival sac will kill the parasite, and it will either be flushed out with the tears or may be removed manually (Fowler, 1989). Many types of flies feed on llama lacrimal secretions and can cause conjunctival irritation. Consequently, fly control is important for minimizing this form of conjunctivitis.

Large conjunctival wounds should be sutured with small-gauge (e.g., 6-0), absorbable suture material. Small wounds usually heal with medical therapy alone.

**CORNEA**

**Anatomy**

The corneas of llamas and alpacas are large and semi-oval-shaped (see Fig. 30.4). Although the head size of alpaca is smaller than that of the llama, the corneal diameters of the two species are very similar. In one study, the mean horizontal corneal diameter of llamas was 28.2 mm while that of alpacas...
was 30.2 mm (Andrews et al., 2002). The mean vertical diameters were 24.2 mm in llamas and 22.2 mm in alpacas. The mean corneal thicknesses were also very similar. When measured by ultrasonographic pachymetry, they were 608 µm in llamas and 595 µm in alpacas. Both the thickness and diameter of their corneas increased significantly with the increasing ages of the animals (juvenile vs. adult animals) (Andrews et al., 2002).

Because of the propensity of camelids to develop marked corneal edema secondary to intraocular surgeries, trauma, and uveitis, it was thought that these animals might have low numbers of corneal endothelial cells (which are principally responsible for fluid removal from the cornea) compared to species who do not have problems with excessive edema formation (Gionfriddo et al., 1997). A recent study, however, showed that the densities of endothelial cells in camelids (2673 cells/mm² in llamas, and 2275 cells/mm² in alpacas) are only slightly lower than those of other species that have been studied (Andrews et al., 2002). In that study, the investigators observed frequent polymegathism (variability in cell size) and pleomorphism (variability in shape) of the endothelial cells of normal camelids. This is a common finding in other species having pathologically decreased endothelial cell density which suggests that clinically normal alpacas and llamas have potential corneal endothelial instability and increased vulnerability to the development of corneal edema (Andrews et al., 2002).

An esthesiometric study of alpaca corneas was recently reported in order to determine the relative sensitivities of the different regions of the alpaca cornea (Welihozkiy et al., 2011). As in other species, the center of the cornea was more sensitive than the peripheral areas. The next most sensitive area was the ventral region followed in order by the medial, dorsal, and lateral regions.

**Diseases**

**Corneal trauma** is probably the most common ocular disease in New World camelids. In studies of apparently healthy camelids having no history of pain or squinting, many animals had corneal scars suggestive of prior trauma (Gelatt et al., 1995; Webb et al., 2006). Of llamas that were presented to veterinary teaching hospitals for all eye diseases, 41% had corneal disease and more than half of these had an active corneal ulcer (Gionfriddo et al., 1997). Most of these ulcers were of unknown cause but likely traumatic in origin.

The prominence and vulnerability of the corneal cornea predispose to injury. Trauma may be caused by fighting, penetration, or scratching of the cornea by foreign bodies or from prolonged recumbency due to tick paralysis, meningeal worms, prolonged anesthesia, or lack of passive transfer in crias (Gionfriddo et al., 1997). Other trauma-associated corneal diseases reported in the 1997 study included lacerations, foreign bodies, and stromal abscesses (Gionfriddo et al., 1997). Of the two enucleated eyes of alpacas having corneal perforations and secondary panophthalmitis sent to the COPLOW database (Rubelitzig, 2009, unpublished data), one of the eyes also had an expulsive choroidal hemorrhage which was presumed to be secondary to the perforation. Another enucleated llama eye also sent to COPLOW had an extensive corneal abscess initiated by trauma (Rubelitzig, 2009, unpublished data). A case of one llama with a corneal ulcer that was infected with M. liquificaciens was reported, but no herd outbreaks of a “pink eye”-like disease have, to my knowledge, been seen (Brightman et al., 1981).

**Abscesses** frequently develop in camelid corneas due to trauma that perforates the epithelium and enters the stroma (J. Gionfriddo, 2010, unpublished data; Rubelitzig, 2009, unpublished data). These appear as yellowish-white collections of purulent material at various depths in the corneal stroma; they are often very deep. These abscesses are generally infected by bacteria, but unlike in horses, if treated aggressively medically, they will often resolve quickly. Some of these may be fungal in origin, and mycotic keratitis has been seen in several camelids (J. Gionfriddo, 2010, unpublished data). A case of a 7-year-old llama with unilateral corneal abscesses, uveitis, and weight loss was described (Coster et al., 2010). The corneal lesions were multifocal and cream-colored. In addition, there was corneal edema and neovascularization but no ulceration. Neither cytologic evaluations of deep scrapings nor cultures of an abscessed area revealed any organisms. Histopathologic evaluation of the globe after enucleation showed multiple granulomas containing spherules of Coccidiodes posadasii throughout the cornea, iris, and ciliary body. Ten months after enucleation, the llama was euthanized, and necropsy revealed disseminated coccidiomycosis (Coster et al., 2010). Although camelids are susceptible to this disease, this was the first reported case of the organism causing ocular disease.

**Spontaneous corneal epithelial defects** (also called indolent or undermined ulcers) have been diagnosed in camelids (Jones et al., 2007). The cause for these is unknown but could be the same as for dogs. They generally heal well with proper therapy (see later discussion).

A limbal-based corneal epithelial inclusion cyst was reported by Pirie et al. in 2008. This lesion in a 13-year-old female llama may have been secondary to trauma or a previous corneal biopsy that had been done to aid in the diagnosis of a spontaneous chronic corneal epithelial defect. Mass excision followed by a conjunctival advancement flap graft was curative (Pirie et al., 2008).

Recently, cases of superficial, dendritic ulcers in camelids have been documented (U. Dietrich, personal communication; M. Blair, personal communication; J. Gionfriddo, 2009, unpublished data). These ulcers appear to be very similar to herpesvirus-induced ulcers in cats but as of yet, the causative organism has not been positively identified. The fact that these corneal ulcers generally heal well if the animal is placed on eye drops containing cidofovir suggests that they may be indeed viral in origin.

Nonulcerative corneal degeneration is rarely reported in camelids; however, dystrophies and degenerations have been
seen in clinical practice (G. Severin, personal communication) and have been reported in surveys of ocular diseases of camelids (Webb et al., 2006). Recently, a survey was conducted to examine the possible increased incidence of genetic problems in Canadian camelids (Webb et al., 2006). Potentially hereditary ocular defects were present in 23 of the 40 animals, with anterior stromal corneal dystrophy present in 2 of the 23 alpacas.

While many of the corneal degenerations/dystrophies seen in camelids may be hereditary, acquired corneal degeneration has also been reported. A lipid keratopathy was described in a case report about an 8-year-old castrated male alpaca (Richter et al., 2008). The alpaca had a history of cloudy corneas and fluorescein-positive erosions. The erosions were surrounded by areas of neovascularization and dense-white crystalline deposits. A diagnosis of bilateral lipid keratopathy was made based on the results of a histopathologic examination of keratectomy samples. The source of the lipid was most likely due to the very high serum cholesterol concentrations of unknown origin that led to corneal lipid deposition as well as atherosclerosis in this animal (Richter et al., 2008).

Other corneal diseases reported in camelids include dermoids, a mass and spontaneous edema (Barrie et al., 1978; Gionfriddo et al., 1997; Kilic et al., 2010; G. Severin, personal communication). Bilateral, spontaneous, corneal edema was reported in a captive guanaco and her offspring (Barrie et al., 1978). The cause was not found, but corneal endothelial dystrophy was suspected. An interesting case of a corneal papilloma in a dromedary camel was recently published (Kilic et al., 2010). The camel had clinical signs of severe keratoconjunctivitis which resolved after surgical resection of the mass.

**Treatment**

Aggressive, prompt treatment of corneal ulcers, lacerations, and abscesses in camelids is important in order to provide the best chance of a good outcome (Gionfriddo, 1994). Numerous opportunistic bacterial pathogens such as Pseudomonas spp. grow in the conjunctival sacs of normal camelids, and therefore, topical broad-spectrum ophthalmic antibiotics should be used in all cases in which the corneal epithelium has been compromised (Gionfriddo, 1994). If an infection is present, then antibiotic and anaerobic (if stromal abscesses are present) bacterial culture and sensitivity testing should be performed (J. Gionfriddo, 2009, unpublished data). Topical antibiotics and antifungal drugs that can be used in horses can be used in camelids. Ofloxacin appears to be a good antibiotic choice for treatment of infected ulcers in camelids (J. Gionfriddo, 2009, unpublished data). Topical silver sulfadiazine and miconazole have been successfully used to treat mycotic keratitis in camelids (J. Gionfriddo, 2011, unpublished data).

The optimal treatment of corneal lacerations, perforations, and ulcers depends on the initial depth of the lesion, the desires of the owner, the duration of the problem, and whether or not the lesion is infected. Greater-than-half-depth lacerations, which have little to no corneal tissue missing, may be sutured directly with small-gauge (6-0 to 8-0), absorbable, suture material such as Prolene® (Ethicon, Somerville, NJ). Deep ulcers and ulcers with perforations may be successfully repaired using a conjunctival pedicle graft or corneal conjunctival transposition. An adult alpaca in the Zoo-Aquarium in Madrid was reported with a corneal perforation and a secondary prolapsed iris (Rodriguez-Alvaro et al., 2005). This was repaired with a pedicle graft harvested from the bulbar conjunctiva. After amputation of the protruding iris, the graft was sutured to the cornea with 6-0 Vicryl® (Ethicon, Somerville, NJ) in a simple interrupted pattern. Rotation of the globe was minimized by paralyzing the animal with atracurium, and the anterior chamber was maintained with viscoelastic material (Rodriguez-Alvaro et al., 2005). This procedure allowed the eye to remain visual as all that remained long-term was a corneal scar and dyscoria.

Debridement of spontaneous chronic corneal epithelial defects may be done with a cotton-tipped applicator and grid keratotomy or a diamond burr. The grid keratotomy was reported to treat an “indolent ulcer” in a 13-year-old llama (Jones et al., 2007). The ulcer had been present for 12 days and was unresponsive to medical therapy. After debridement and a grid keratotomy (using a 64 Beaver blade), the cornea healed slowly and was fluorescein-negative at 38 days post-debridement. Diamond burr removal of the loose epithelium and “polishing” of the basement membrane has been described in dogs (Garcia da Silva et al., 2011; Sila et al., 2009) and has been successfully used to promote rapid healing in camelids (E. Garcia da Silva, 2010, unpublished data).

**ANTERIOR SEGMENT**

**Anatomy**

The iris of the camelid is similar to that of the cow except for the “pupillary ruff” in camelids which is a modification of the corpora nigra (granula iridica) seen in horses and cows (see Fig. 30.4). This structure is an unusual and interesting adaptation to life in areas of excessive UV radiation. It is present on the dorsal and ventral papillary margins but is more prominent dorsally as it acts to shade the pupil. Anatomically, the pupillary ruff is a modified portion of the posterior pigment epithelium of the iris which is very large, protrudes into the pupil, and is folded vertically.

The iris pigmentation is usually moderate to dark brown but not uniform in color. There are usually various shades of brown scattered through an individual iris, and heterochromia iridis is common in color dilute camelids. Clear blue or grey irides are also normal in camelids having low amounts of pigment. As in many other species (e.g., cats), coat and iris color may be associated with hearing loss. A recent study examined the correlation between deafness and iris pigmentation in llamas and alpacas (Gauly et al., 2005). None of the animals that had pigment in their coats or irides were hearing impaired while 7 out of 10 of the pure-white animals were bilaterally deaf, one was unilaterally deaf, and 2 had normal...
hearing ability. Blue-eyed animals having pigment in their coats, all white animals with iris pigmentation, and one animal having one iris pigmented and one nonpigmented had normal auditory function. This study, along with numerous anecdotal observations, clearly suggests that there is a strong association between iridal hypopigmentation and congenital deafness in llamas and alpacas (Gauly et al., 2005). It has long been rumored among breeders that blue-eyed llamas are blind, but there is no evidence to support this.

The ciliary body of the camelid is anatomically very similar to that of other species. It is usually heavily pigmented even in color-dilute animals.

Diseases

Many diseases affect both the anterior and posterior uvea leading to panuveitis. Those that affect mainly the anterior uvea are discussed later while those that affect both are discussed under “Posterior Segment.”

Congenital

Persistent pupillary membranes (PPMs) have been reported as congenital, and possibly hereditary, ocular defects in crias. A high incidence of PPMs was reported in the 40 llamas that were examined but without the exact number (Webb et al., 2006). In all of the affected animals, the PPMs were iris-to-iris and hence were not causing any visual deficits.

Acquired

Anterior uveitis is a common sequela of traumatic ocular injury and systemic disease in camelids. Clinical signs of anterior uveitis can range from mild squinting and epiphora to severe pain signs, episcleral injection, synchiae, and corneal edema. Gelatt et al. found that several alpacas examined in South America had evidence of previous uveitis. This consisted of cataracts and anterior and posterior synchiae (Gelatt et al., 1995). In our VMDB study, 18% of the llamas with eye disease had active anterior uveitis (Gionfriddo et al., 1997).

Infectious diseases causing anterior uveitis include bacterial septicemia in neonates and crias with juvenile llama immunodeficiency syndrome, equine herpesvirus type 1 (EHV-1) (Paulsen et al., 1989; Rebhun et al., 1988), toxoplasmosis, and other systemic infections (Gionfriddo et al., 1997). Uveitis may also be secondary to deep corneal ulcers and cataracts (lens-induced uveitis) (R. Dubielzig, 2009, unpublished data). Many of these problems cause both anterior and posterior uveitis (panuveitis).

POSTERIOR SEGMENT

Anatomy

The appearance of the camelid fundus is highly variable among individuals and often between eyes of the same individual. This variability is attributable to the amount of pigment in the choroid which in turn depends on the coat color of the animal. When observed ophthalmoscopically, it may appear dark brown, red-brown, or nonpigmented. A single fundus can contain streaks of dark pigment in some areas while other areas are nonpigmented. The prominent choroidal vessels provide a red coloration of the fundus that is seen in many camelids (Fig. 30.7). The colors of the iris and fundus are directly related to the coat and skin color of the camelid (Webb & Cullen, 2010). Hypopigmented animals with light coat colors generally have various combinations of gray, blue, and brown irides and reduced pigmentation of the fundus. Those with dark coat colors generally have brown irides and pigmented fundi (Webb & Cullen, 2010). The retinal vasculature and optic disc of the camelid are similar to those of the bovine. A prominent holangiotic vascular pattern is easily visible, and there are often anastomoses on the optic disc surface. Three to five pairs of prominent retinal vessels emerge from the optic disc periphery; one pair of vessels emerges dorsally and extends peripherally with the artery and vein spiraling around each other. Two pairs of vessels leave the optic disc horizontally and are usually accompanied by myelin, which extends several disc diameters peripherally into the fundus. A large Bergmeister papilla (hyaloid remnant) may protrude from the disc into the vitreous.

Disease

Diseases of the posterior segment are relatively common in camelids. Congenital abnormalities, inflammatory diseases,
parasitic diseases, toxic retinopathy, and retinal and optic nerve degenerations have been noted. In the VMDB study, 12 of 65 animals were reported to have posterior segment problems. These were either confined to a single structure such as the retina, choroid, or optic nerve or, more often, involved multiple structures and even the entire globe (Gionfriddo et al., 1997).

**Congenital**

Congenital defects of the posterior segment have been observed antemortem in camelid crias; however, most of the reported defects were identified from histopathologic evaluation of the eyes postmortem (Gelatt et al., 1995; Gionfriddo et al., 1997; Schuh et al., 1991; R. Dubielzig, 2009, unpublished data). In the COLOW database, there were histopathologic reports of the eyes of 7 camelid crias under 8 weeks of age (R. Dubielzig, 2009, unpublished data) which had multiple ocular defects. Six of these eyes had peripapillary colobomas which suggested that the ocular fetal fissures failed to close. Of the seven eyes, two were microphthalmic; one of these also had a lens rupture, and the other had a coloboma and retinal dysplasia (R. Dubielzig, 2009, unpublished data). Other congenital posterior segment findings in the cria eyes included a retinal detachment in an eye that also had vitreous fibrosis and ossification, optic nerve hypoplasia, tunica vasculosa lentis, and suspected retinal aplasia (R. Dubielzig, 2009, unpublished data). Hostnick et al. described a 5-day-old alpaca cria with multiple neurologic abnormalities. Following euthanasia, the brain and eyes were examined on necropsy. The brain lacked olfactory bulbs and tracts, and there were “smaller-than-normal” optic tracts. The eyes had bilateral detached, dysplastic retinas and persistent hyperplastic primary vitreous (Hostnik et al., 2011, unpublished data).

Only a few congenital posterior segment defects have been reported in living animals. Schuh et al. described an adult llama with a large coloboma near the optic disk in one eye (Schuh et al., 1991). In the 1997 VMDB study, congenital optic nerve disease was reported to have been seen in two llamas: one had optic nerve hypoplasia and the other had a coloboma (Gionfriddo et al., 1997). These reports, along with anecdotal reports of finding colobomas in allegedly normal adult camelids, suggest that they may be relatively common defects but go undiagnosed due to an absence of obvious visual defects. Although there are no studies documenting the potential heritability of colobomas in camelids, they are hereditary in some breeds of cattle (Lavach, 1990) and dogs (Roberts, 1960). Therefore, animals with this defect should either not be bred or should be outcrossed.

**Acquired**

Causes of acquired uveitis include systemic infections, ocular parasites, and toxicities. Several systemic infectious diseases have been reported to cause posterior segment inflammatory disease in camelids; the most notorious is EHV-1, which is discussed later. Other infectious diseases reported to cause posterior uveitis in llamas include aspergillosis, toxoplasmosis, and septicemia (Adams & Garry, 1992; Pickett et al., 1985; D. Tinsley, 2011, unpublished data).

In a 1992 report about six camelid crias (five llamas and one alpaca) with gram-negative septicemias attributed to perinatal factors and poor transfer of maternal antibodies, only two crias survived (Adams & Garry, 1992). After initiation of treatments for the infections, one cria developed secondary, bilateral retinal detachments and chorioretinitis. Other clinical signs of septicemia included obtundation, convulsions, diarrhea, and respiratory distress.

Aspergillosis was implicated as a cause of neurologic disease and chorioretinitis in a wild-caught, zoo-housed alpaca (Pickett et al., 1985). During postmortem examination, Aspergillus was identified in the lung and eye. The fungus was thought to have spread from the lungs to the eye hematogenously (Pickett et al., 1985).

The most well-known viral cause of both anterior and posterior uveitis, as well as neurologic disease, in camelids is EHV-1 (Rebhun et al., 1988). Camelids acquire EHV-1 by contact with members of the family Equidae, such as horses and zebras. The incidence of this disorder appears to be decreasing since it was first described in 1988 in a mixed herd of camelids. Many members of that herd became blind after close contact with infected zebras (Rebhun et al., 1988). The neurologic signs which developed included head tilt, nystagmus, and paralysis. Signs of panuveitis developed in two alpacas as evidenced by hypopyon, iritis, vitritis, retinitis, and optic neuritis. All attempted treatments failed to restore vision to any animal (Rebhun et al., 1988). Rising serum antibody titers to EHV-1, along with the histologic finding of eosinophilic inclusions in the brain, and isolation of the virus from tissues of affected animals confirmed this virus as the cause (Rebhun et al., 1988).

A similar outbreak occurred in a herd of llamas in Illinois in 1989 (D. Friedman, 1989, unpublished data). Twenty-eight llamas were exposed to zebras with rhinitis. Ten to 17 days after exposure, most of the llamas developed blindness, deafness, head tilt, and circling. Ophthalmic examination showed severe anterior uveitis and chorioretinitis. EHV-1 was confirmed as the cause of this outbreak based on serology and histopathologic evidence (D. Friedman, 1989, unpublished data).

To further document EHV-1 as a severe neurologic pathogen, House et al. experimentally infected three llamas with EHV-1. Two of the three developed clinical signs that were similar to those that were naturally infected (House et al., 1991). These consisted of blindness, staggering, head tremors, and obtundation. Histopathologic evaluation of the brain and optic nerve revealed severe neuronal changes; however, isolation of EHV-1 was successful in only one (the most clinically ill) of the three animals. This suggested that it may be difficult to isolate the virus from infected animals (House et al., 1991).

A case report described a llama that had severe clinical ocular and cerebral signs which consisted of chorioretinitis,
optic neuritis, and encephalitis (Paulsen et al., 1989). Serologic tests failed to implicate EHV-1, and no intranuclear inclusion bodies were seen on histopathologic evaluation of any tissues. The similarity of the clinical signs of this animal to those of the alpacas described by Rebhun et al. suggests that it may have been a case of chronic EHV-1 in which the virus was not identified. To the author’s knowledge, no outbreaks of this disease have been reported in camelids since the 1990s. The reason for this is unknown but could possibly be that there is greater awareness of the disease and therefore better separation of mixed herds or quarantine of sick equids.

Toxoplasmosis, a known cause of chorioretinitis in dogs and cats, may also cause chorioretinitis and blindness in camels (L. Johnson, 1993, unpublished data; D. Tinsley, 2011, unpublished data). During an investigation of causes of late-term abortions in llamas, a serologic survey showed an extremely high antibody titer for Toxoplasma gondii in a blind llama who did not abort (L. Johnson, 1993, unpublished data). The llama had lesions consistent with chronic panophthalmitis. Tinsley described a 15-year-old llama with signs of bilateral chorioretinitis secondary to suspected toxoplasmosis. Vitreous humor was collected from one eye at hospital admission and 1 month later. Vitreous convalescent Toxoplasma antibody titers showed a marked rise, although serum antibody titers were negative. These results suggested that an ocular T. gondii infection may have caused the posterior uveitis (D. Tinsley, 2011, unpublished data).

Harrison et al. reported on a possible enrofloxacin-induced toxic retinopathy in a male guanaco in a zoo (Harrison et al., 2006). The animal underwent surgery to repair an abdominal laceration and had been treated with penicillin G procaine and benzathine and enrofloxacin (2.4 mg/kg IM q24h for 10 days) postoperatively. Later, trimethoprim-sulfadiazine was added. Twenty-six days after surgery, the guanaco was blind with optic nerve pallor on fundoscopic examination. Histopathologic examination of the eyes following euthanasia revealed diffuse outer-layer atrophy which was more pronounced in the central retina. The brain had scattered areas of neuronal necrosis, microglialosis, and cerebral edema. The authors concluded that this was a case of enrofloxacin toxicity because of its similarity to the toxicity found in cats; however, this could not be proven (Harrison et al., 2006).

A case of ophthalmomyiasis interna has been described in a 12-year-old female llama that had an acute onset of recumbency and blindness (Dunkel et al., 2011). Upon ophthalmoscopic examination, a 2-cm long mobile helminth larva was observed in the posterior vitreous near the retina of the right eye. Despite anthelmintic and anti-inflammatory therapy, the neurologic condition worsened and the llama was euthanized. No progression in ocular clinical signs was seen during therapy. Necropsy results were unremarkable aside from the central nervous system and right eye. In the vitreous of the right eye, there was a live 2.5 cm parasite. Based on the necropsy results, parasitic migration into the eye was most likely through the spinal cord, along the brainstem, through the optic nerve, and into the eye. A diagnosis of ocular nematodiasis by the nematode, Parelaphostrongylus tenuis, was made. The blindness in this case was thought to be to the central nervous system pathology caused by the parasite rather than by ocular invasion (Dunkel et al., 2011).

To the author’s knowledge, no hereditary retinal atrophic diseases such as progressive retinal atrophy have been reported in camelid species. In adult camelid eyes in the COPLOW database, retinal atrophy was reported in one 10-year-old alpaca whose eye had been enucleated due to chronic glaucoma. Retinal detachments were reported in two glaucomatous eyes in older llamas (R. Dubielzig, 2009, unpublished data).

**Treatment**

In not all cases of uveitis can a cause be found. A case of idiopathic uveitis in a 9-year-old female llama was published in 2001. The llama had a “several-month” history of red eye followed by the development of photophobia and ocular discharge just prior to presentation (Grahn & Cullen, 2001). Ophthalmic examination showed bilateral focal corneal degeneration, multiple areas of anterior and posterior synchiae (with iris bombé in the right eye), and aqueous and vitreous flare. Basic blood work values were within the reference ranges, and further diagnostics were declined by the owner. A diagnosis of bilateral idiopathic uveitis was made, and intense anti-inflammatory therapy was instituted, which consisted of frequent topical applications of atropine, flurbiprofen and prednisolone acetate and oral flunixin meglumine (1mg/kg Q 24h for 7 days). The llama was rechecked at 4 days and again at 1 month, and by the 1-month recheck, the right eye had lost vision and had developed glaucoma. A poor prognosis for vision was given due to the glaucoma (Grahn & Cullen, 2001).

Camelids with uveitis, which is not attributable to an obvious cause, should be examined carefully for signs of systemic disease. A thorough history and physical and ophthalmic examinations should be performed. Routine blood work is indicated in these cases as well as serology that is appropriate for the geographic area and physical examination findings. Titers should be performed for infectious diseases including toxoplasmosis, leptospirosis, brucellosis, and systemic fungal infections including blastomycosis, coccidioidomycosis, and aspergillosis (rare) (Pickett et al., 1985). Even though, to my knowledge, several of these diseases have not specifically been demonstrated to cause uveitis in camelids, the fact that they have been in other species is reason enough to look for them in camelids with uveitis.

If a cause for the uveitis is found, then specific therapy should be instituted along with anti-inflammatory therapy. If not, then one must diagnose it as idiopathic uveitis, and the animal should be given intensive anti-inflammatory therapy. This generally includes topical nonsteroidal anti-inflammatory drugs (NSAIDs) or topical steroid drugs. Topical atropine is also indicated to prevent synchiae and alleviate pain. Systemic NSAIDs may also be instituted and are relatively safe.
in camelids. Intravenous, intramuscular, or subcutaneous flu-nixin meglumine can be administered at a dose of 1 mg/kg once daily or 5 mg/kg of oral etodolac (Etogesic, Boehringer) can be given once daily. Systemic steroids should be avoided in camelids as they can lead to abortions (B. Grahn, 2004, unpublished data) and hepatic lipidosis.

LENS
Anatomy
The lens of the camelid is large and spherical in shape (Johnson, 1901). Its structure and function is very similar to that of cattle, sheep, and goats.

Disease
As in other mammalian species, cataracts are the most common abnormalities of the camelid lens. Cataracts have been reported in survey studies of apparently normal camelids as well as in individual case reports. They were seen in 10% of the animals in the 1997 VMDB study (Gionfriddo et al., 1997). In a South American herd of 29 alpacas, Gelatt et al. found 1 apparently visual animal with nuclear cataracts (Gelatt et al., 1995). In a survey of camelids in Canada, Webb et al. found incipient anterior cortical cataracts in two llamas and three alpacas, incipient posterior cortical cataracts in five llamas and one alpaca, immature posterior capsular and cortical cataracts in three llamas (Webb & Cullen, 2010).

Mature, hypermature, and immature cataracts, as well as both congenital and acquired opacities, have been reported (Barrie et al., 1978; Donaldson et al., 1992; Gelatt et al., 1995; Gionfriddo, 1993, unpublished data; Gionfriddo & Blair, 2002; Gionfriddo & Friedman, 1993; Gionfriddo et al., 1997; Ingram & Sigler, 1993; Middleton et al., 2005; Powell et al., 2002). The significance of small, immature cataracts in camelids is unknown. Some have been thought to progress to maturity while others have not. It also has not been determined whether or not they are genetically transmitted. Many of these immature cataracts are located at the posterior “Y” sutures of the lens similar to the inherited, but usually non-progressive, cataracts in Golden Retrievers (Barrie et al., 1978; Fowler, 1989; Gelatt, 1972; Ingram & Sigler, 1993).

Congenital cataracts can be solitary findings or may be found in conjunction with other ocular abnormalities. In a case report documenting cataract surgery in a 9-month-old female llama, a persistent hyperplastic primary vitreous, persistent tunicas vasculosa lentis, and persistent hyaloid artery (filled with blood) were present in the right eye and were thought to be the cause of the cataracts (Gionfriddo & Blair, 2002). These abnormalities, however, were not discovered until the lens was being removed. Thus, color Doppler ultrasound was performed prior to surgery in the contralateral eye on which a patent hyaloid artery and tunicas vasculosa lentis could be seen. Surgery thus involved an anterior vitrectomy with vessel cautery, and vision was restored in both eyes of the llama (Gionfriddo & Blair, 2002). Because of the possibility of retrolental abnormalities in camelids with cataracts, ocular ultrasonography is recommended prior to cataract surgery in these species.

While type 1 diabetes mellitus occurs in camelids, the incidence of diabetic cataracts is not known. In a 2005 case report of a diabetic alpaca, the authors reported that the animal had bilateral opacities that covered over 50% of the posterior lens capsule (Middleton et al., 2005). It is unknown if these were secondary to the systemic disease, but their appearance was dissimilar to diabetic cataracts in dogs which develop rapidly and progress to maturity (Middleton et al., 2005).

Surgical removal of cataracts in camelids has proven successful in restoring vision (Donaldson et al., 1992; Gionfriddo & Blair, 2002; Powell et al., 2002). With recent developments and improvements in the procedure (Gionfriddo & Blair, 2002; Powell et al., 2002), the severe post-operative complications reported by Ingram and Sigler can be avoided. In that case report of cataract surgery in a llama, manual lens extraction was followed by severe corneal edema, ulcerative keratitis, and eventually, phthisis bulbi (Ingram & Sigler, 1993).

The changes which have radically improved the success rate of lens removal surgery include use of phacoemulsification technique during which endothelial-sparing methods are employed. Irrigation with balanced salt solution (BSS)-plus (a BSS containing glutathione) rather than normal saline, intensive application of pre- and postoperative anti-inflammatory drugs, and the use of copious amounts of viscoelastic during surgery all aid in protecting the corneal endothelium. To the author’s knowledge, intraocular lens placement has not been attempted in camelids.

Senile cataracts were reported in a 14-year-old llama (Powell et al., 2002). The cataracts were not associated with any other ocular defects. Surgery was done with routine phacoemulsification techniques. Although the surgery was uncomplicated, the llama developed severely elevated IOPs postoperatively with protrusion of the vitreous face into the anterior chamber to the point of nearly touching the cornea. At a second surgery, the posterior capsule was surgically perforated, and the IOPs returned to normal. This suggested that the elevated IOPs were due to blockage of the pupil and drainage angle by the vitreous which had imbibed fluid and moved anteriorly (aqueous misdirection) (Powell et al., 2002).

Luxated lenses, traumatic lens ruptures, and lens colobomas are rare. A lens coloboma was seen in the temporal quadrant of the left lens of a female guanaco. This abnormality was observed in conjunction with nuclear and perilimbal cataracts and corneal edema, and a hereditary cause was suspected for the defects (Barrie et al., 1978). In an eye of a 1-year-old llama that was recorded in the COPLOW database, a lens rupture was noted. Other concurrent abnormalities, such as microphthalmia and an “ocular coloboma,” occurred (R. Dubielzig, Diplomate ACVPMadison WI, unpublished data, 2009). Lens ruptures can also occur secondary to severe ocular trauma.
GLAUCOMA

Glaucoma is uncommon in llamas and alpacas, and there are no known cases of primary, potentially inherited, glaucoma in these species. Therefore, glaucoma is considered to be either congenital or secondary to intraocular inflammation. A few reports of congenitally abnormal drainage angles appear in the literature. Barrie et al. used gonioscopy to examine the drainage angle of a guanaco with corneal edema. They found that the animal had “closed” drainage angles due to goniodysgenesis; however, it had normal IOPs (Barrie et al., 1978). A case of a 6-month-old female llama was diagnosed with congenital glaucoma (Cullen & Grahn, 1997). Since birth, the owners noticed that she had prominent eyes, epiphora, and corneal cloudiness but was not blind. Ocular examination showed numerous anomalies including PPMs, corneal edema and striae, buphthalmos, and vitreous prolapse. Histopathologic examination of the globes after euthanasia revealed iris hypoplasia and poorly developed iridocorneal angles. Since the dam and sire had been bred several times prior to the birth of this cria and had produced only normal animals, the etiology was thought to be a congenital anomaly rather than a hereditary condition (Cullen & Grahn, 1997).

In the VMDB study in 1997, only two llamas were reported to have glaucoma, but no cause was given (Gionfriddo et al., 1997). Three cases of secondary glaucoma were described in the COПLOW database; one had a lens rupture, one was due to suppurative endophthalmitis, and one was “due to unknown inflammation” (R. Dubielzig, 2009, unpublished data). Despite these case reports, the incidence of goniodysgenesis and subsequent glaucoma in camelids is apparently low. Routine tonometry and gonioscopy on diseased and healthy eyes, however, may reveal a higher incidence of glaucoma or goniodysgenesis than has been previously reported.

AMAUROSIS

Visual deficits of unknown origin have been reported. Eleven blind neonatal crias with apparently normal fundi were seen at the Colorado State University Veterinary Teaching Hospital over a 20-year period (G. Severin, personal communication). Vision gradually returned to all crias; however, no cause was found. Congenital nystagmus and amblyopia have also been diagnosed in crias. There are also anecdotal reports of blindness with no apparent ocular defects or disease in adult llamas (L. Johnson, personal communication). These cases may be undiagnosed optic nerve or brain disorder.

An electroretinogram (ERG) may be performed in blind camelids to distinguish between a retinal disorder and an optic nerve or cerebral cortical lesions (Fig. 30.8). The ERG amplitude of a normal camelid is much higher than that of most normal dogs and cats (J. Gionfriddo, 2011, unpublished data). A recent study of ERGs in alpacas used a portable, handheld ERG system (Handheld MultiSpecies Electroretinograph®, Oculoscience, Kansas City, MO) to document the magnitude of the ERG responses of 12 normal animals. The active corneal electrode used was a DTL™ microfiber electrode, and single white flashes of light intensities of 10, 3000, and 10,000 mcd.s/m² were administered. The mean amplitudes and implicit times of the a and b waves were recorded at each time period. At both 3000 and 10,000 mcd.s/m² intensities, the alpacas had very high mean a wave amplitudes (162 and 200 µv) and b wave amplitudes (441 and 446 µv) (Reinstein et al., 2011). Visual evoked potentials can also be generated in camelids to test the visual pathways and explore the cause of the blindness (Reinstein et al., 2011).

OCULAR NEOPLASIA

Ocular and periocular neoplasia appear to be more common in domestic camelids than previously thought. In the VMDB study published in 1997, only two cases of neoplasia, an intraocular medulloepithelioma, and an unspecified corneal tumor, were reported in llamas (Gionfriddo et al., 1997). Recently, five case reports of intraocular tumors in llamas have appeared in the literature (Fugaro et al., 2005; Hendrix et al., 2000, 2006; Schoeniger et al., 2000). Interestingly, three of these were primitive round cell tumors derived from the inner layer of the optic cup prior to differentiation and considered to be congenital tumors. Also in 2000, Hendrix et al. reported about a malignant, intraocular, teratoid medulloepithelioma in the eye of a 1-year-old llama (Hendrix et al., 2000). Presenting signs in this patient included anterior uveitis, blindness, and retinal detachment. Because these findings were suggestive of infectious uveitis, blood work and serology for Toxoplasma, Blastomyces, and Histoplasma were performed. The Toxoplasma IgM titer was positive so the llama was placed on sulfadimethoxine. When the symptoms worsened, the eye was removed, and the tumor was diagnosed upon histopathologic examination of the globe (Hendrix et al., 2000). In 2000, a case of a malignant nonteratoid medulloepithelioma was published (Schoeniger et al., 2000). This patient was a 6-year-old female llama who had epiphora, buphthal-
mos, and a visible intraocular mass. The eye was removed, but a mass appeared in the orbit 1 month later. While radiation therapy initially shrunk the mass, it returned along with lymphadenopathy and masses in the mandible. Euthanasia was performed, and metastatic disease was seen in the orbit, mandible, mandibular lymph nodes, lungs, liver, and mesenteric and sublumbar lymph nodes. Histopathologic evaluation of all of the masses was similar with a diagnosis of primary intraocular medulloepithelioma with systemic metastases (Schoeninger et al., 2000). A nother case of malignant non-keratoid medulloepithelioma in a llama was reported by Hendrix et al. in 2006. This intraocular tumor was also highly metastatic and on necropsy of the animal was found to have spread to the orbit, mandible, lymph nodes, and liver (Hendrix et al., 2006).

A retinoblastoma, another type of primitive intraocular neoplasia, was found in the left eye of a pregnant, 6-year-old llama that was enucleated after the clinical signs of chronic epiphora, buphthalmos, and vision loss failed to respond to therapy (Fugaro et al., 2005). Histopathologic results and results of immunohistochemical analysis showed that the tumor was a retinoblastoma (Fugaro et al., 2005). In humans, retinoblastomas occur in children, are often hereditary (Ellias et al., 2001), and malignant. No metastases were reported in this llama, and she was still alive 4 years after the eye was removed (Fugaro et al., 2005).

Two cases of intraocular melanomas in alpacas have been reported. One case was a 2-year-old alpaca with an intraocular melanoma presented for a corneal opacity (Hamor et al., 1999). The opacity was corneal edema secondary to two large pigmented iridal masses in contact with the corneal endothelium. Histopathologic examination showed that these masses originated from a single melanoma. A 10-year-old pregnant female alpaca was presented to a veterinary clinic in New Zealand for evaluation of a “discolored” and enlarged right eye. The enucleated globe was very firm, and histopathologic examination revealed a soft tissue mass surrounding a 25 × 6 mm piece of bone. Immunohistochemistry confirmed that the mass was a melanoma. The tumor cells were thought to have induced metaplastic neoplasia in the surrounding tissue (Hill & Hughes, 2009).

CONCLUSIONS

Fortunately, information regarding the South American camelid eye continues to expand and has progressed beyond anecdotal reports to publications of disease surveys, case reports, and studies on llamas and alpacas. Investigations into the genetics of potentially heritable eye diseases and infectious eye conditions (e.g., herpesvirus keratitis) are ongoing. Hopefully, in the next 10 years, our knowledge base will have increased to the point where we can advise owners and breeders on the inheritance of diseases such as congenital nasolacrimal disorders, cataracts, and colobomas, and on the susceptibilities, treatments, and prognosis of ocular diseases in camelids.

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Laboratory animal ophthalmology is an important subject both for veterinary ophthalmologists and laboratory animal veterinarians, for the individual animal presented with an ocular problem, for the colony of animals involved, and for the scientific research program in which the animals are used (Harkness & Wagner, 1989). For veterinary ophthalmologists, ocular examination in many laboratory animal species presents challenges, both because of the small size of the eye and because of the differences in ocular and periocular anatomy from that of canine or feline eyes. Rodents, lagomorphs, and primates have somewhat different ocular anatomy and pathology from those mammals with which veterinarians may be more familiar. Even so, several of these species are regularly presented as pets outside the laboratory arena. For laboratory animal veterinarians and researchers using these species, three key issues necessitate a full understanding of ocular disease. First, ocular health is an important issue for the individual animal because ocular pain and blindness often compromise laboratory animal welfare. Second, for the whole laboratory animal colony, several eye diseases are important signs of systemic diseases that have implications for the health of individual animals as well as of entire laboratory animal colonies. Third, and especially important for research scientists using laboratory animals in experimental studies, ocular disease may complicate research endeavors, especially those investigating the toxicologic effects of agents. Thus, understanding ocular disease is important for the welfare of the laboratory animals themselves, for more general laboratory animal colony management, and for the scientists who use laboratory animals in their research.

This chapter seeks to cover laboratory animal ophthalmology in a comprehensive manner although there is so much information in the literature that it cannot hope to be exhaustive. It aims to concentrate on conditions with implications regarding welfare or with relevance to systemic disease and colony management because these conditions are most important to laboratory animal veterinarians. In the third and fourth editions of this book, the chapters compared ocular disease between all laboratory animal species, while in this edition, the rabbit is covered in Chapter 32. This allows some more space for discussion of the visual capabilities of the species discussed here and a somewhat deeper appreciation of the ocular diseases covered. Relevant anatomic features are included for each species, as abnormalities can only be understood fully when placed in the context of normal ocular anatomy and physiology. Ophthalmic examination techniques and certain conditions are similar across species and will be detailed before discussion of each species separately. The dog and cat are not considered in this chapter. They are important laboratory animals and were included in this discussion in previous editions (Bellhorn, 1991). Similarly, while other species such as reptiles, birds, and particularly, amphibians, are kept as laboratory species, these are amply covered in their own exotic species chapter. To allow the majority of this chapter to focus on species not considered elsewhere, we confine the discussion to rodents, ferrets, and primates with a new section on the laboratory pig provided by Dr. Glenwood Gum.

**EXAMINATION TECHNIQUES**

The small size of laboratory rodent eyes renders ophthalmoscopic examination more difficult in these species than in dogs or cats. Slit lamp biomicroscopy of the adnexa, cornea, and anterior segment is relatively straightforward, whereas fundoscopy can be difficult, especially in pigmented strains, among which mydriasis may be exceptionally difficult to achieve. Indirect ophthalmoscopy is readily performed in lagomorphs and primates (Bellhorn, 1973; Saunders, 1967) and can, with practice, be mastered in rodents. Some examiners prefer a 90-D lens used in conjunction with a table-mounted slit lamp; others use a 28-D lens and an indirect headpiece for preference. Still others find a 2.2 panretinal lens to be useful in the latter context. Photography is essential in the documentation of ocular changes during experimental studies, and although the Kowa laboratory animal retinal camera is useful (Schiavo, 1990), some have reported use of a Topcon® fundus camera (Topcon Medical Systems, Oakland,
appears to be too small to allow noninvasive applanation
attached to a pressure transducer, because the mouse cornea
measurement of IOP with a water-filled glass microneedle
significant differences in IOP between different strains of
other strains of rat, however, because a recent study found
report using the TonoPen found the mean IOP in Lewis rats
also been favorably evaluated in the small eyes of both ferrets
the simplest system to use in such animals. The TonoPen has
found between each instrument, but the TonoPen is generally
with the Schiotz and a human calibration table (Suzuki et al.,
minder the mean IOP in more than 50 cynomolgus monkeys
(cblood volume 1.5
mL) than in adult humans (blood volume 5000 mL) when both are administered a drug drop volume of 30 µL.
The small size of the globe in many species also complicates methods for measuring intraocular pressure (IOP). The Drager applanation tonometer has been used in monkeys (Schiavo, 1973). More recently, comparison of the Schiotz, Perkins, Topcon, and TonoPen applanation tonometers determined the mean IOP in more than 50 cynomologus monkeys to be 15.2 ± 4.3 mmHg with the TonoPen and 16.4 ± 3.1 mmHg with the Schiotz and a human calibration table (Suzuki et al., 1993). In that report, statistically significant correlations were found between each instrument, but the TonoPen is generally the simplest system to use in such animals. The TonoPen has also been favorably evaluated in the small eyes of both ferrets (Sapienza et al., 1991) and rats (M ore et al., 1993). A further report using the TonoPen found the mean IOP in Lewis rats to be 13.9 ± 4.2 mmHg. This figure may not be accurate for other strains of rat, however, because a recent study found significant differences in IOP between different strains of mice (John et al., 1997). That study used a direct manometric measurement of IOP with a water-filled glass microneedle attached to a pressure transducer, because the mouse cornea appears to be too small to allow noninvasive applanation	onometry. IOP measured directly in that study was 13.7 ± 0.8 mmHg in the C3H strain, compared with values of 12.3 ± 0.5 mmHg in the B6, 9.4 ± 0.5 mmHg in the A/J, and 7.7 ± 0.5 mmHg in the BALBc. As noted earlier, the mouse cornea is too small to accommodate the foot plate of even the TonoPen applanation tonometer, but a more recently developed rebound tonometer, which measures the speed of rebound of a small plastic probe fired at the ocular surface, is small enough to provide accurate measurements of IOP in even the smallest eyes. The instrument was first used in the rat eye (Goldblum et al., 2002; Kontiola et al., 2001) and subsequently in the mouse eye (Dancias et al., 2003) with accuracy and repeatability (Wang et al., 2005); correlation between tonometrically measured and directly measured IOP in the mouse was extremely high (r² = 0.99).

Angiography is readily achieved with either 10% fluorescein solution (Kanemaki & Oiwa, 1993) or indocyanine green (M asaoka et al., 2000; Satoh & Y amaguchi, 2000). Understanding the differences in ocular anatomy between species and the range of normal variants are essential when interpreting ophthalmic findings (Rubin, 1974).

More generally speaking, when interpreting ocular findings in experimental animals, one must consider the prevalence of inherited disease as a background against which other ocular disease is noted. This is particularly important among inbred strains, in which recessive traits may occur in a given strain not being used to study that specific trait. Also to be noted are changes in the prevalence of spontaneous abnormalities among laboratory animals at different ages, from congenital lesions in young animals through senile changes in older individuals (Taradach & Greaves, 1984).

GENERAL FEATURES OF THE RODENT EYE

Retrobulbar Venous Sinus Anatomy and Orbital Bleeding

Blood collection from the retrobulbar venous sinuses of rodents relates both to laboratory animal welfare and to comparative orbital anatomy in rodents (Timm, 1989). For many years, one of the optimum sites for collecting small venous blood samples in several rodent species has been the orbital venous sinus (Fig. 31.1). For animals such as the hamster without tail veins or the gerbil with pigmented tail skin, the venous sinus behind the eye is an acceptable site for sampling under anesthesia in experienced hands. A 23-gauge needle or capillary tube can be inserted under the upper eyelid at the lateral canthus and directed medially while compressing the jugular vein. Reportedly, this procedure can be performed many times without apparent detriment (Pansky et al., 1961).

Others, however, have suggested that postbleeding exophthalmos is seen (Beynen et al., 1988), that hemorrhages and subsequent inflammatory foci are found in the puncture track (van Herck et al., 1992), and that dark focal areas in the nasal fundus subsequent to orbital bleeding in the rat may be.
SECTION IV: Special Ophthalmology

To date, such evaluation appears not to have been attempted on animals bled while conscious, which is a technique now practiced in fewer centers than previously. A recent paper comparing collection techniques in hemophiliac mice in which excess hemorrhage would seem to be a prime concern showed that retrobulbar blood collection caused less unintended hemorrhage than did submandibular venipuncture in which 60% of animals had to be euthanized for postcollection hemorrhage (Holmberg et al., 2011). It may be that technical skill and practice in collection techniques explain the marked differences between success rates in different reports.

Lacrimal Gland Biology and Chromodacryorrhea

The glands contributing to the precorneal tear film differ significantly among experimental species (Djeridane, 1996; Sakai, 1981). In rodents, tears are formed by several glands, which are different in each species. The rat and mouse have an intraorbital tear gland, an extraorbital tear gland, and a hardierian gland; the latter is associated with the nictitating membrane but is clearly not the nictitans gland of the dog. The guinea pig has a large intraorbital gland occupying the lateral and anteroventral aspects of the orbit. The extensive zygomatic salivary gland is posteromedial and superior in the orbit. The rabbit has three glands: the lacrimal, nictitans, and hardierian, covered in detail in Chapter 32. The Mongolian gerbil has both a nictitans and a hardierian gland.

Many laboratory rodents, but particularly rats, exhibit red crusting around their eyes in cases of ocular irritation, upper respiratory tract infection, and general stress (Fig. 31.2) (Bauck, 1989). Porphyrin pigmented and lipid-laden tears are produced in normal amounts by the hardierian glands in several rodent species (Paule & Hayes, 1958). In the laboratory rat, however, excess tear production is common, with character-
istic red deposits on the peri orbital fur, nose, and paws after wiping the eyes (Eida & Kitutani, 1969; Venable & Grafflin, 1923). Several causes for parasympathetic stimulation of the harderian glands resulting in this secretion are known, and the condition can be blocked by parasympatholytics such as atropine (Harkness & Ridgway, 1980). Infections such as mycoplasmosis and SDA, nutritional deficiencies, and other physiologic stresses like restraint and transport may cause chromodacryorrhea.

Harderian gland secretions in the gerbil, unlike other rodents, are released at the external nares, having passed down the nasolacrimal duct. This secretion is mixed with saliva, and it is spread widely over the pelage during a thermoregulatory salivary groom. Overproduction of such secretion, possibly caused by harderian gland hypertrophy, causes profound periocular and facial dermatitis. Such lesions are reported to be unresponsive to all medications, and the only remedy has been harderian gland removal with provision of a sand substrate as a less effective but minimally invasive environmental substitute (Thiessen & Pendergrass, 1982).

Harderian gland pathology with swelling (Johnson et al., 1979) and necrosis (O’Steen et al., 1978) occur after protracted exposure to light. Clinical signs of exophthalmos may be noted in affected animals (Johnson et al., 1979, Rothwell & Everitt, 1986), and decreased porphyrin content was noted in affected harderian glands in one study (Kurisu et al., 1996; Shirama et al., 1987). Photic injury is considered to be caused by the photodynamic action of harderian gland porphyrins (Shirama et al., 1987; Strum & Shear, 1982) and has complex interactions with systemic hormone release (Buzzell et al., 1992; Ebling et al., 1975).

**Orbital Space-Occupying Lesions**

Retrobulbar space-occupying lesions cause exophthalmos in any species. Exophthalmos has been reported in species as diverse as a ground squirrel with a harderian gland adenocarcinoma (Morrow & Day-Lollini, 1990), laboratory rats with optic nerve schwannomas (Yoshitomi & Boorman, 1991), and ferrets with conditions ranging from zygomatic gland mucoceles (Miller & Pickett, 1989) to orbital involvement of multifocal lymphoma (McCalla et al., 1997). As noted above, harderian gland pathology can result in exophthalmos in laboratory rodents (Johnson et al., 1979; Rothwell & Everitt, 1986). A commonly occurring pathological condition is orbital cellulitis with retrobulbar abscessation most commonly associated with Pasteurella multocida in the rabbit (Chapter 32), but similar conditions can occur in chinchillas and other rodents with continually growing molar and incisor teeth. Even with radical orbital exenteration and meticulous antibiotic coverage, these infections often recur, with euthanasia then being the only option.

It is important to differentiate an orbital mass producing exophthalmos from dacryoadenitis due to a swollen lacrimal or harderian gland that can result in similar periocular swelling with exophthalmos (Hunt, 1963).

**Ocular Surface Disease**

Certain rodent strains are used as models for keratoconjunctivitis sicca and Sjögren’s syndrome, but occurrence of keratoconjunctivitis associated with spontaneous tear-film abnormalities in laboratory rodents and lagomorphs is rarely, if ever, documented. Indeed, Schirmer tear test (STT) values are not widely reported in the literature. Evaluation of the tear film in smaller rodents is difficult, if not impossible, with the STT strip. Instead, the phenol red thread test may be useful. Few studies have used this test in the mouse, generally seeking to measure tear volume rather than production, though these two values are clearly linked (Lin et al., 2011; Stewart et al., 2005; Xiao et al., 2009).

**Conjunctivitis and Systemic Disease in Rodents**

Inflammation of the conjunctiva can occur as one of the signs of more severe disease affecting the whole eye, may relate to upper respiratory tract infections, or be a sole clinical symptom. In both rats and mice, the most common cause of conjunctivitis unrelated to intraocular disease is mycoplasmal respiratory infection, but other agents can also be involved (Hill, 1974; Needham & Cooper, 1975; Nelson, 1950; Wagner et al., 1969). Numerous infectious agents may be isolated from the conjunctival sac of affected animals. Interpreting these bacteriologic findings is difficult because there is little evidence to show that any of these organisms is causing the conjunctival inflammation (Young & Hill, 1974). One report strongly suggested that Corynebacterium sp. were an important causative factor in keratoconjunctivitis of varying severity within a large group of aging C57BL mice, but not in young animals in the same colony (McWilliams et al., 1993). In rodents, significant differences in the prevalence of disease are seen among animals of different ages (Timm, 1989).

During some outbreaks of conjunctivitis, as many as 50% of stock may be affected soon after weaning in conditions of poor ventilation or other stressors. Discharge and reddening of the conjunctiva can be readily noted in many animals although some may have subtle lesions (McGarry et al., 1976). Some cases of more overt purulent conjunctivitis have been reported to be associated with opportunistic Pasteurella sp. infections in rats already exhibiting signs of chronic respiratory disease (Roberts & Gregory, 1980); other infectious agents are likely to be causal factors in other cases. Such conditions respond to topical antibiotic therapy, but it is important to investigate these cases thoroughly so as not to miss any possible systemic diseases underlying the condition.

It is possible that environmental and not infectious factors may be important in conjunctival inflammatory disease. One report noted the influence of ventilation currents in rodent cages, which caused airborne suspension of fine bedding matter that subsequently caused a severe keratoconjunctivitis in athymic (nu/nu) mice (Griffin et al., 1995). In this case, it...
was the lack of eyelashes and forearm hair in these nude mice that prevented the animals from removing particulate matter and fibers from their ocular surfaces (McGarry et al., 1976). It is not only such external irritative foci which may cause conjunctival inflammation; on occasion, adnexal abnormalities such as entropion occur (discussed later). Investigation of conjunctivitis in a group of experimental animals includes a full and thorough history and clinical examination of individual animals as well as of the group as a whole.

**Retinal Vasculature in Experimental Species**

The rat and mouse both have holangiotic retinas with vessels radiating from the disc (Fig. 31.3a–c). The rabbit has a merangiotic retina (see Chapter 32) with vessels and myelinated nerve fibers emanating from the disc in a horizontal band. The guinea pig has an anangiotic fundus. The ferret fundus is holangiotic and has a tapetum of variable size. Nonprosimian primates have a holangiotic fundi lacking a tapetum with a macula almost indistinguishable from the human fundus. Lemurs and lorises possess a tapetum but not a macula.

**THE RAT**

Much has been written on the ocular diseases of rats, and I have sought to summarize this both in the previous editions of this text and in a review paper (Williams, 2002). But first, perhaps, we should ask “what do rats see?” How important is vision to these animals? These predominantly nocturnal or crepuscular animals do not appear unduly perturbed by blindness. They have rod-dominated retinas but with cones containing visual pigments absorbing light at wavelengths of
510 nm, a mid-green cone, and the exceptionally low wavelength of 359 nm, a blue-UV cone (Jacobs et al., 2001). Around 88% of the rat’s cones are of the mid-green type, and only 12% respond to UV light. As crepuscular animals, the relative importance of UV vision is understandable since at dawn and dusk, there is a higher proportion of light in the UV wavelength. But rats’ visual acuity, as might be expected for a rod-dominated retina, is relatively poor, at 1 cycle per degree (cpd) for pigmented rats and 0.5 cpd for albino animals (Prusky et al., 2002) or even as low as 0.35 cpd in another earlier report (Birch & Jacobs, 1979). This equates to a Snellen acuity of 20/600 for pigmented rats and 20/1200 for albinos. The lateral placement of the rat eyes allows a wide visual field but poor binocular vision. Rats use motion parallax to judge distances as shown in an experiment which required rats to jump between two platforms. They showed a greater number and more pronounced head bobs before jumping as the gap between platforms increased (Legg & Lambert, 1990).

What then of ocular disease in these animals? Perhaps the most devastating adnexal disease in rats in both its acute and chronic form is SDA virus infection. First described in 1961 (Innes & Stanton, 1961), coronavirus infection in rats causes ocular irritation with conjunctivitis and periorbital swelling followed by sneezing, edematous cervical swelling, and enlarged lymph nodes and salivary glands. This is a highly contagious but self-limiting disease in rat colonies. The classic epizootic disease has a high morbidity but a low mortality rate. The acute form is rarely seen and the subacute or chronic disease is much more common (Eisenbrandt et al., 1982). Ocular signs may be primary or occur secondary to reduced tear production (Weisbroth & Peress, 1977). Primary signs include blepharospasm and photophobia as well as eye rubbing (Lai et al., 1976). Lacrimal gland involvement leads to reduced tear production and hence keratitis, conjunctivitis, periorbital swelling aggravated by self-mutilation, and chromodacryorrhea. Occasionally, more severe signs of anterior uveitis and glaucoma can also occur, but the prevalence of these intracocular complications is low. The disease itself is usually self-limiting within 1 week, whereas resolution of the secondary signs may take as long as 1 month. The characteristic signs of the disease are linked to the interaction of the virus and the host immune system. Expression of the disease varies between different strains (Percy et al., 1984) and in different laboratory environments (Bhatt & Jacoby, 1985). In a study examining the disease among immunosuppressed and normal rats, cyclophosphamide-treated animals had delayed onset of signs, a lower degree of gland damage, but also a longer period to resolution of signs and persistent viral shedding (Hanna et al., 1984). These findings have important clinical implications because introduction of a naive group of rats into a subclinically affected animal house, with the attendant immunosuppression linked to the moving and rehousing of animals, may provoke clinical onset of disease with prolonged viral shedding. Normal repair of infected glands involves considerable ductal squamous metaplasia with potential subsequent lacrimal inadequacy (Jacoby et al., 1975). The diagnosis of SDA infection can be made on the basis of observing the classic pathognomonic signs, but detection of coronavirus antigen or serologic testing of animals are also possible (Carthew & Slinger, 1981). Such serologic testing has previously shown the agent to be present in 45% of colonies within the United Kingdom, although the incidence of overt disease is lower (Gannon & Carthew, 1980).

Another common condition is microphthalmos. Several experimental microphthalmic rodent models exist, but microphthalmos also occurs sporadically as an incidental finding in several standard rat and mouse lines (Fig. 31.4). Microphthalmos in the Fischer-344 (F344) rat was found predominantly in females more commonly in the left eye than the right (Lee, 1989). Not all cases of microphthalmos have a genetic basis, however. Microphthalmos or anophthalmos is a congenital defect, but this does not necessarily imply inheritance. Although colobomatous microphthalmos has been identified as a dominantly inherited trait in rabbits, rats, and mice, it may also be associated with several nutritional deficiencies, including vitamin A (Lamming et al., 1954), vitamin E (Nielsen & Carlton, 1995), pantothenic acid (Nelson et al., 1957), niacin (Chamberlain & Nelson, 1963), and zinc (Hurley et al., 1971). In another study, nutritional deficiency was not shown to be responsible for ocular defects (Tyan, 1992), but this does not preclude nutritional influences from being an important factor in microphthalmos in other situations. Anophthalmos is a condition similarly related both to genetic and environmental factors. In many cases, clinical anophthalmos is merely an extreme form of microphthalmos, and serial histopathologic sections of the orbital contents should be examined to ensure that globe remnants are not present, confirming a diagnosis of microphthalmos and not anophthalmos. A nophthalmos has
been reported in laboratory mice (Chase, 1942), rats (Rao & Sesikeran, 1992), guinea pigs (Kornich, 1971), and hamsters (Knopp & Polivanov, 1958).

Corneal opacification is relatively common in rodents, perhaps more so in mice than rats. Sprague-Dawley and F344 rats have been reported to have subepithelial mineralization in 5%–15% of males and 6%–10% of females between 7 and 26 weeks of age. This mineralization was reported in some rats to manifest as fine basophilic granules at the epithelial-stromal interface, whereas in others, a coarser deposit was noted in either the subepithelial stroma or the epithelium itself (Losco & Troup, 1992; Yoshitomi & Boorman, 1990). In Wistar rats, similar lesions were noted (Bellhorn et al., 1988). A report comparing corneal degeneration in different rat strains demonstrated calcium deposition in the subepithelial stroma of the interpalpebral cornea among Wistar and Sprague-Dawley but not Lewis and Long-Evans strains (Bellhorn et al., 1988). This interstrain variation is suggestive that genetic factors and not merely environmental influences are responsible for this corneal lesion. Epithelial inclusion cysts have been reported rarely in the rat cornea because of trauma or as congenital lesions consisting of a keratinized stratified squamous epithelial cell-lined cyst (Mittl et al., 1975).

It is surprising, given the large number of rats and mice examined, that dermoids in these species have only been reported once: as a haired, limbal plaque in one rat (Nichols & Yanoff, 1969). Squamous cell papillomas and more invasive carcinomata with dyskeratosis and keratin pearl formation noted at histopathology have also been reported in the rat (Mittl et al., 1975).

Several causes of corneal inflammation exist in this species; therefore, recognition of the lesion is important. Opacities in the nasal part of the cornea are common, and while they may relate to anterior segment inflammation, they can also relate to orbital gland inflammation. More severe keratitis can also occur with and is probably caused by reduced tear secretion, although as noted earlier, evaluation of tear production is rarely undertaken in these rodents. The dystrophic changes in rodents begin as purely mineral subepithelial deposits, but stromal inflammation supervenes in many cases producing a secondary keratitis. Thus, keratitis may occur without any obvious infective or environmental factors. The agents causing conjunctivitis often cause a keratoconjunctivitis when the disease is severe. Anything from SDA virus to excessive hay dust can cause keratitis, and investigation of corneal inflammation must take this into account. One additional factor that may produce corneal changes is nutrition. Keratitis from diets deficient in constituents such as vitamin A may be severe, but the high quality of current laboratory animal diets makes these changes exceptionally rare. Exposure keratopathy in rodents can appear as interpalpebral corneal ulceration after prolonged anesthesia, especially with xylazine and ketamine, during which the lids are held open (unless taped closed) (Fig. 31.5). Alternatively, an ocular surface protective lubricant such as the lanolin-based, tear-replacement ointment Lacrilube or the carbomer-based Viscoatears can be used to prevent ulceration.

A study of this phenomenon showed the problem to be more associated with xylazine and ketamine than with other anesthetic regimens and seen less frequently in the Sprague-Dawley and Lewis rat strains than in the Wistar, Long-Evans, and Fischer 344 strains, suggesting that these latter strains may be more predisposed to the condition (Turner & Albassam, 2005). The use of topical medications including the preservative benzalkonium chloride can cause dry eye problems in rodents; this has been developed an experimental model of keratoconjunctivitis sicca in rats (Paques et al., 2007).

Glaucoma and buphthalmos have also been noted in rats and mice (Fig. 31.6) (Addison & How, 1926; Young et al., 1974). The failure of aqueous drainage is not necessarily because of an abnormality of the iridocorneal angle as in many inherited glaucomas in the dog or in the bu/bu rabbit (see Chapter 32). In many cases in the rat, it results from persistent pupillary membranes causing pupil-block glaucoma or from peripheral anterior synechiae causing angle-closure glaucoma.

Lesions of the anterior uvea in rodents can, for the most part, be divided into congenital anomalies and those secondary with inflammation. The former include keratolenticular adhesions (discussed earlier) and the persistence of the pupillary vasculature. Some laboratory animal ophthalmologists find a high incidence of inflammatory lesions in the anterior segment of rats and even suggest that it is the most common ophthalmic condition. Synechiae from iritis may cause opacities in either or both lens and cornea. Keratoconjunctivitis may result in corneal perforations if severe. Some perforations are associated with bacterial infections with Staphylococcus...
These reports concerned the Sprague-Dawley rat, but other rat strains (e.g., the albino Sherman strain) (Balazs et al., 1970) and the F344 strain are also affected (Yoshitomi & Boorman, 1990). Although occurring at a low incidence, these spontaneous lesions complicate experimental work on cataract induction and toxicologic studies. It is important to differentiate lenticular changes caused by aging from those caused by toxicity in drug trials or other interventions. In rats with retinal dystrophy or degeneration, cataracts occur secondarily, probably because of the release of various posterior segment metabolic by-products (Zigler & Hess, 1985).

Abnormalities of the fundus may be divided into congenital lesions, inherited retinal dystrophies, chorioretinal inflammatory lesions, acquired retinal degenerations, and retinal detachments (Matsui & Kuno, 1987). Some of these are defined lesions on which experimental models of retinal disease are based but several others are spontaneous conditions that may interfere with experimental work or may have implications for animal welfare through their blinding results. Most congenital lesions of the rodent fundus are either abnormalities of the retinal and hyaloid vasculature or colobomatous defects of the retina or optic disc. A small number of other anomalies also occur. In rats 5–6 weeks of age, persistence of the hyaloid vasculature is common (Fig. 31.8). This may consist of a single vessel or more commonly three to four branches of the hyaloid artery traversing the vitreous posteriorly from the posterior lens capsule. These vessels regress over the next few months but during this period, considerable vitreal hemorrhage may occur. Unless extensive, these hemorrhages resolve, leaving little in the way of a
remnant. Yellow to brown pigment may, however, be visible as the hemorrhage, hemosiderin, or both are removed by vitreal macrophages. Other posterior segment vascular anomalies include preretinal loops; in one study, 12% of rats had such an anomaly (Hubert et al., 1994).

The rat has comparatively fewer examples of hereditary retinal dystrophy or degeneration than does the mouse. The Royal College of Surgeons (RCS) rat with its retinal epithelial dystrophy is one such example (Herron et al., 1969), as is the Osborne-Mendel rat with its retinal degeneration (Von Sallmann & Grimes, 1972).

Some retinal lesions in young laboratory rodents might be considered to be congenital, but careful examination shows their incidence to increase from 0.3% in weanling rats to 3% at 14 weeks of age. Thus, they are considered to be early acquired lesions. They have been described as sharply demarcated pale linear lesions characterized histopathologically by focal outer retinal thinning (Hubert et al., 1994) rather than by the generalized photoreceptor loss found in the dystrophic animals noted earlier (Herron et al., 1969). Other workers have described these lesions as retinal dystrophy (Schordein et al., 1975) or degeneration (Fig. 31.9) (Lin & Essner, 1987). One study is even suggestive that the focal atrophy represents retinal detachment and reattachment (Heywood, 1976).

Laboratory rodents are used as models for several retinal degenerations, some of which have been beautifully photographed by Hawes et al. (1999). Figure 31.10 shows the example of a mouse with the rd1 degeneration, followed over time. These images show the depigmentation of the retinal pigment epithelium as a classic change in many rodent retinal degenerations and reduction in the caliber of retinal vessels is also seen in progressive retinal atrophy in the dog or cat. Rodents are also very sensitive to the toxic effects of light on the retina. The lesions caused by light-induced retinal degeneration can be severe and obscure other lesions, and they can also cause blindness. First described in rats housed under constant illumination (Noell et al., 1966), the degeneration has now been studied extensively in rats and, more recently, mice of different strains (LaVail et al., 1987). This condition can occur in albino rats exposed to as little as 2–3 weeks of constant illumination with fluorescent or incandescent lights, but environmental and body temperatures are also important. Even in standard lighting, more than 11% of 2-year-old rats had lesions, but the relationship between light-induced and age-related retinal degenerations is not entirely clear. Fundus changes involving alterations in vessel caliber, fundus reflectivity, and optic disc pallor could be observed ophthalmoscopically after 7 days of continuous light but electroretinography demonstrated changes after only 1 day (Kobayashi et al., 1993). Measurement of pupil diameter also showed alterations earlier than funduscopy and with electroretinography. The diagnosis of this phototoxic change can be substantiated by noting simple correlates of the disease, such as increased degeneration among animals in top cages or in clear-plastic as opposed to metal-topped cages. Now that the condition is well-known, the most common causes are malfunctions in light-timing switches caused by mechanical faults or human error. Even given our understanding of the pathogenesis of this condition, it still can all too easily complicate and confuse other retinal research. Retinal changes in the WAG/Rij rat were first thought to be an inherited degeneration (Lai & Jones, 1977) but later were discounted as probable light-induced retinal changes (LaVail, 1987). Interestingly, even among strains with a defined inherited trait, light has a significant effect. The RCS rat was first described as a model for retinal research (Bourne et al., 1938), and its degeneration was shown conclusively to be a recessive trait by those same workers a year later (Bourne & Gruneberg, 1939); however, it was not defined as a retinal pigment epithelial dystrophy until later (Herron et al., 1969). In such a strain with a defined genetic defect, environmental light levels may have a profound effect. Rats kept in the dark have a significantly slower rate of degenerative change than do those kept in the light (Dowling & Sidman, 1962). There are other retinal mutants in the mouse and rat. Other defects not primarily affecting the retina (e.g., achondroplasia) do cause some abnormalities in the retina, usually primary vessel dilation (Fig. 31.11). Other mutations lead to optic nerve colobomas.

An infectious retinopathy is seen among neonatal rats infected with lymphocytic choriomeningitis (LCM) virus (Monjan et al., 1972). In mice, the virus produces a fatal choriomeningitis after intracerebral infection, but neonatal infection or transmission from an infected dam in utero produces an asymptomatic life-long infection (Lehmann-Grube, 1971). Intracerebral inoculation of LCM virus in neonatal rats produces aggressive retinitis which affects the outer nuclear layer without viral antigen being detected there. In contrary fashion, LCM virus has been isolated from retinas in infected mice without any pathologic change (Brown, 1968; Mims, 1966). Whether a naturally occurring infection or vertical

Figure 31.9. Retinal degeneration in a young rat.
transmission of the virus in rats produces a similar pathology is not clear.

Other retinal lesions include focal retinal atrophy, which manifests as a well-demarcated area of highly reflective retina at an early age but which also appears to be nonprogressive. This atrophy possibly occurs secondary to an inflammatory lesion in the choroid extending from periorbital gland inflammation (van Herck et al., 1992). Cotton-wool spots have also been noted in some rats (Fig. 31.12), but whether these are retinal swelling secondary to ischemia, as in humans, is unclear.

Saccular aneurysms of the retinal vessels have been reported as a common finding in older laboratory rodents (Fig. 31.13) (Bellhorn, 1973; Lee, 1989). Retinal vessel tortuosity and preretal arteriolar loops have also been noted as common retinal abnormalities among CD and Sprague-Dawley rats sometimes associated with preretal hemorrhages (Matsui & Kuno, 1987). Senile degenerations of the retina such as microcystoid degeneration or accumulation of lipofuscin pigment are seen on histopathology examination but rarely on fundoscopy.

Colobomas of the optic nerve head are regularly reported among laboratory rodents either as a sporadic finding or as an inherited trait. Typical colobomas, with or without involvement of the peripapillary choroid, were found in 0.5% of Sprague-Dawley rats in one study (Hubert et al., 1994), and others have found the lesion in 0.2% (Matsui & Kuno, 1987) and 1.0% (Taradach et al., 1981) of the same strain. Occasionally, these optic disc colobomas are associated with iridal colobomas (Kuno et al., 1991; Rubin, 1974). They also may occur with colobomatous microphthalmos (Wyse & Hollenberg, 1977), which has also been reported as an inherited trait in mice (Müller, 1950). Optic nerve hypoplasia is less common but has been reported among many strains of laboratory rats and mice (Shibuya et al., 1989).

Unilateral degeneration of the optic nerve was reported in a group of Slc: Wistar rats (Shibuya et al., 1989, 1993a, 1993b). These authors suggested that the clinical and histopathologic findings of retrograde and anterograde transneuronal degeneration indicated this change occurred secondary to a local circulatory disturbance. Unilateral degeneration of the optic nerve and retina has also been reported in F344

Figure 31.10. Retinal degeneration in rd1 mice followed over time (from Hawes et al., 1999).
Figure 31.11. Other mutations giving retinal degeneration in mice. (Reprinted from Hawes et al., 1999.)

Figure 31.12. Cotton wool spots showing retinal edema in a rat.

Figure 31.13. Retinal vessel aneurysm in an aging rat.
ranging from 0.5 cycles per degree in young Dj A2J mice, which reduced to 0.4 cpd as these animals, a classic experimental model of glaucoma, developed an increased IOP (Burroughs et al., 2011). Even in healthy normal laboratory mice, visual acuity and rod function deteriorates with age; age-matched control animals in toxicity testing or other research where visual dysfunction may be an important factor should be considered (Kolesnikov et al., 2010).

**Microphthalmos**

As in the rat, abnormalities in globe development are relatively frequently seen, and many are associated with a specific defect either in lens development or in pigmentation. A valuable overview of microphthalmos and associated ocular defects among inbred black mice was previously published (Smith et al., 1994). Interestingly in rats, the left eye was most commonly microphthalmic (Lee, 1989). In mice, the right eye was more commonly affected than the left (Smith et al., 1994). They also confirmed that females were more commonly affected than males (6.2 times). A further large survey reported the incidence of this condition to be between 1% and 10% among nine different congenic strains of C57BL mice (Shibuya et al., 1993a, 1993b). Several reports have also documented microphthalmos with associated keratolenticular adhesion similar to that seen with Peters’ anomaly in humans and in fetal alcohol syndrome (Cook et al., 1987; Pierro, 1966; Pierro & Spiggle, 1967). Associated clinical findings include central corneal opacities, corneolenticular and iridocorneal adhesions, cataracts, extravasation of lens cortical material with dispersion throughout the eye, vitreal dysgenesis, and retinal folding. Clinical features of mild microphthalmos are microcornea, engorged episcleral vessels, and abnormal vasculature in the iris and posterior segment (Lee, 1989). The important features from a laboratory management perspective are the potential for spontaneous inherited microphthalmos to complicate teratology research programs and the propensity of microphthalmic animals to develop defective tear drainage and microbial contamination of the unusually large and deep conjunctival sac (Sundberg et al., 1991).

**Corneal Dystrophies**

Corneal opacification has been more frequently reported in mice than rats. One study documented spontaneously occurring corneal lesions among nine strains of mice, including BDF1, B6C3F1, and C57BL/6 (Shibuya et al., 1993a, 1993b). Corneal dystrophies in the C3H/He and DBA/2 mice were characterized by a deposition of basophilic material in the subepithelial stroma with subsequent vascularization and
leukocyte infiltration. ICR-n/n mice showed neutrophil and lymphocyte infiltration as well as vascularization in the stroma without basophilic deposition, whereas ICR and ICR-n/l mice showed no such lesions. CD-1 and CF-1 mouse strains exhibit a dystrophy seen as a characteristic elliptical corneal opacity (Fig. 31.14). Histopathologically, subepithelial mineralization leads to epithelial separation from the underlying stroma (Rubin, 1986). Corneal calcification has been reported in KK mice that have concurrent but not necessarily associated spontaneous diabetes mellitus (Mittl et al., 1975). Calcium carbonate and phosphate deposits appear at the level of the epithelial basement membrane as early as 3 weeks of age in these mice. Serum calcium and phosphorus levels were equivalent to those in control nondiabetic mice, though serum alkaline phosphatase levels were elevated. A similar subepithelial calcification has been reported in severe combined immunodeficient (SCID) mice with concurrent cardiac mineralization (Meador et al., 1992). These lesions were histopathologically similar to those reported in other rodents. A nether group compared similar dystrophic corneal mineralization among different strains of mice, finding that 26% of DBA, 16% of C3H, and 10% of Balb/c mice had mineralized opacities (Van Winkle & Balk, 1986). These authors suggested the lesions were sequelae to processes initiated by excess ammonia in the cage bedding.

These findings of superior stromal calcium deposition in otherwise normal rodent eyes must be considered when evaluating pathologic change in research models. One such case was the finding of calcium deposition in MRL lpr/lpr mice. Calcium deposition in this model of systemic autoimmune disease was suggested to be analogous to band keratopathy occurring in humans affected by iritis associated with juvenile arthritis. The corneal pathology, however, was seen in control (MRL/n) as well as in MRL lpr/lpr (MRL/l) mice, so it was deemed to be a spontaneous lesion in several strains and not associated with ocular inflammatory disease (Hoffman et al., 1983). In these mice, atomic absorption spectrophotometry revealed significant hypercalcemia in MRL strains with calcium deposition but not in control mice without corneal pathology. Renal insufficiency was not present in these animals and the authors concluded from the results of further unreported studies that primary hyperparathyroidism was likely to be the root cause of the circulating and corneal calcium changes in these mice.

Identifying pathologic change in rodent corneas may also be complicated by corneal vascularization as a normal finding in at least two mouse strains. This aberrant vascularization occurs in the athymic nude mouse. It is not related to the immunologic abnormalities in this strain, however, because it also occurs in the euthymic hairless mouse (Nelderkorn et al., 1990).

Dyscoria and other abnormalities in pupil shape among young rodents and especially in mice (Fig. 31.15a, b) are considered by some to be colobomatous lesions, but one reliable report suggests that ventrally displaced, eccentric pupils are associated with inflammatory iridal changes (Rubin & Daly, 1982). In that latter report, lesions were acquired rather than congenital and thus were not colobomatous in nature.

**Cataracts**

In mice, acquired cataracts may develop from infection with a helical spiroplasma termed the suckling mouse cataract agent (Tully et al., 1976). Inherited cataracts have also been documented in mice, such as those occurring in the Scat and Lop-10 strains, which have autosomal dominant cataracts. In these mutant strains, heterozygotes have an incomplete suture line or nuclear opacities, whereas homozygotic affected animals have microphthalmos and more severe cataracts (Graw et al., 1989). The age at incidence of age-related cataract in different strains of laboratory mouse has been studied; mutant strains such as glutathione peroxidase knock-out mice and growth hormone receptor knock-out mice had earlier onset cataracts (Wolf et al., 2005) while the same group showed that caloric restriction (Wolf et al., 2000) extended the lifespan not only of the mice themselves but of lens clarity. Producing overexpression of the enzyme catalase in mitochondria had the same effect of lengthening lifespan and extending the duration of lens transparency (Schriner et al., 2005).

Inherited retinal dystrophies and degenerations are not seen only among experimental animals bred specifically for the study of their particular retinal disease. The widespread nature of these dystrophic genes throughout rat and, particularly, mouse strains, means that blindness caused by inherited retinal dystrophy or degeneration may occur in a supposedly normal group of rodents (Schmidt, 1983). The rd gene, for instance, is seen in C57BL/6J, CBA, C3H, and various outbred albino mouse strains (Caley et al., 1972; LaVail & Sidman, 1974). Within a few months after birth, the outer retinal layers degenerate, leaving the retinal pigment epithelium adjacent to
the inner nuclear layer. In several strains, a similar if not identical condition is known as the “rodless retina” (Keeler, 1970). The rds allele seems to be less prevalent among the general laboratory population, though it is an important model for human retinitis pigmentosa.

**THE GUINEA PIG**

There is very little work published on ocular disease in this species, even though it is a commonly kept animal in laboratories and as a pet, and has a high prevalence of ocular disease. In our recently published survey of ocular disease in 1000 apparently normal cavies, 45% had some ocular disorder, ranging from cataracts to heterotopic bone formation (Williams & Sullivan, 2010).

A number of these conditions will render the animal blind, yet with little apparent change in their behavior. This is somewhat perplexing, since guinea pigs, unlike the rat and mouse above, are highly visual animals, using their sight from the moment they are born fully furred and alert. Their visual acuity has been assessed as 2.7 cycles per degree, an equivalent of a Snellen acuity of 6/70, although this estimate was made by counting retinal ganglion cells and not by behavioral visual evaluation (Buttery et al., 1991). Most guinea pigs appear to be somewhat hypermetropic on refraction (Lu et al., 2009), while one report shows albino guinea pigs to be spontaneously myopic to varying degrees (Wang et al., 2007).

Congenital defects ranging from those as severe as clinical anophthalmos (Fig. 31.16) to posterior polar subcapsular cataracts (Fig. 31.17) are seen in a significant proportion of guinea pigs, particularly those of roan × roan matings. Congenital cataracts have been reported in a litter of guinea pigs also affected with urogenital abnormalities after treatment of pregnant sows with the antibiotic Tylan. This oculourogenital association is interesting, reminiscent of the human conditions Alport’s and Potter’s syndrome (Swann & Patel, 2005). For laboratory animal veterinarians, it shows how important it is to be aware of potential teratogenic consequences from medicating gestating females (Wilson et al., 1978).
SECTION IV: Special Ophthalmology

Ocular surface defects in young animals may be caused by trichiasis in Texel cavies where the coat is composed of short bristly hairs which can easily abrade the eye in the first few days of life. Breeders use petrolatum ointment to encourage periocular hairs to be directed away from the ocular surface but even so corneal ulceration and edema can still occur (Fig. 31.18). Dermoids have been reported several times in guinea pigs, both typical (Alessandarini, 1907; Chan, 1932; Gupta, 1972) and hairless (Fig. 31.19) (Otto et al., 1991).

Conjunctivitis among guinea pigs has been regularly associated with chlamydial organisms (Murray, 1964). Some animals have only slight reddening of the eyelid margins whereas others have thick purulent exudate. Infection in young animals is characterized by inclusion bodies in conjunctival epithelial cells with leukocytic infiltrates, but in many cases it resolves spontaneously in 1 month. The disease is now recognized to be associated with Chlamydophila psittaci. Guinea pigs also develop a particularly severe keratoconjunctivitis when infected with Listeria monocytogenes, an organism that causes only mild disease in other rodents, rabbits, and nonhuman primates. This is of interest from the perspective of the guinea pig as a useful model for the disease, but it is also important to remember when confronted with a guinea pig having severe conjunctivitis (Stams, 1967). Other infectious causes of conjunctivitis in guinea pigs include salmonellosis (Voino-Iasenetskii et al., 1997). Infectious agents are not the only cause of conjunctival lesions in this species. Because they are incapable of forming their own vitamin C, guinea pigs are at considerable risk of scurvy, one of the early signs of which is conjunctival disease. Individual cases of entropion and posttraumatic eyelid defects have been reported in guinea pigs. Foreign bodies may be the cause of chronic and/or proliferative conjunctivitis (Fig. 31.20).

Guinea pigs may be presented with ocular irritation secondary to keratoconjunctivitis sicca (Fig. 31.21). The average STT in 1 minute has been reported as 3 mm with a range form 0 to 12 mm/min in one study (Coster et al., 2008) while...
another specifically addressing tear production in Duncan Hartley cavies gave the average STT value as 0.4 mm/min (Trost et al., 2007). This profound difference shows the importance of taking a set of normal readings from cage mates of the same breed, age, and gender.

So-called “fatty eye” involves excess lipid deposition in the inferior conjunctiva and is particularly seen in animals being fed to put on weight prior to showing (Fig. 31.22a, b). Note that this latter animal also has diabetes with an associated cataract (see below). “Flesh eye” on the other hand involves a smaller pink-colored mass in the medial canthus (Fig. 31.23) and is probably analogous to prolapsed nictitating membrane in the dog or rabbit, although histopathological confirmation of this has yet to be reported. Neither of these

Figure 31.20. Proliferative conjunctivitis associated with a hay awn in a guinea pig.

Figure 31.21. Keratoconjunctivitis sicca in a guinea pig.

Figure 31.22. a. “Fatty eye” in a guinea pig. b. “Fatty eye” commonly seen in obese guinea pigs prior to showing, here with a diabetic cataract also.
two conditions showed a high prevalence in our study of a thousand animals, but “fatty eye” is particularly seen in some what obese animals being prepared for cavy shows.

Bony spicules surrounded by a fibrous envelope have been reported in the ciliary body of guinea pigs (Fig. 31.24a, b). Some investigators have likened these lesions to osseous choristomas in the choroid of humans (Griffith et al., 1988), but others have more cautiously termed them heterotopic bone formations (Brooks et al., 1991). Whereas calcification of diseased tissue is termed dystrophic calcification, heterotopic bony metaplasia and calcification occurs in healthy tissue and is regularly seen among guinea pigs in various nonocular sites. In one report, a link was suggested between secondary glaucoma with buphthalmos and heterotopic bone formation (Schäffer & Pfleghaar, 1995). It is difficult to substantiate a causal relationship was occurring given the relatively high prevalence of this heterotopic bone formation in the normal guinea pig eye; with the proximity of the abnormality to the iridocorneal angle, it is easy to envisage a pathogenetic link between the two conditions. In our study, animals with this condition did not have raised IOP, but animals in which the entire circumference of the iridocorneal angle, or indeed the entire globe is filled with calcium might be expected to have increased IOP (Williams & Sullivan, 2010) (Fig. 31.24c). Regarding the cause of this bone formation, the role of the guinea pig ciliary body in concentrating plasma ascorbic acid into the aqueous humor may be important. Ascorbic acid is known to promote bone formation in the presence of a rich blood supply.

Cataracts are commonly seen in guinea pigs—18% of outbred animals in our study were affected, and inherited cataracts have been reported in the N13 strain of guinea pigs (Bettelheim et al., 1997; Williams & Sullivan, 2010). Lens opacities in these latter animals are caused by a single splice-site mutation in the zeta-crystallin gene. Quite apart from these rare inherited cataracts, the frequent occurrence of lens opacities in outbred guinea pigs in our study differs markedly from the rabbit; in a comparative study of 1000 outbred rabbits, the prevalence of lens opacities is significantly lower (unpublished data). The reason for the difference in two species otherwise similar in habits and diet is unclear. It may well be associated with the inability of the guinea pig to synthesize ascorbic acid; lenticular ascorbate is essential in the guinea pig and rabbit as a lenticular UV filter and antioxidant so reduced levels in poorly supplemented cavies may be a causative factor in cataractogenesis (Matsukura et al., 2001). High levels of dietary ascorbate protect guinea pig lenses from UV irradiation damage (Blondin et al., 1986), but whether this is relevant to normal dietary intake and daylight-associated damage is uncertain. Nuclear sclerosis as an early lens change prior to overt opacification is seen in the guinea pig as in other species (Fig. 31.25). Diabetic animals are often noted to have mature cataracts, but whether these occur in the majority of diabetic guinea pigs is unclear (see Fig. 31.22).

The guinea pig has an anangiotic retina (Fig. 31.26), but no reports of fundus abnormalities have been reported in the literature. A recent report documents a spontaneous disorder of rod function determined by electroretinography in a group of animals as a result of consanguineous mating (Racine et al., 2003).

THE CHINCHILLA

The scientific literature yields little regarding diseases of the chinchilla eye and nothing on their visual capabilities or refraction. They are nocturnal and crepuscular animals with a vertical pupil that can close to a narrow slit, protecting their scotopically adjusted retina from bright light, which can render fundoscopy somewhat difficult without mydriasis. Examination results of 14 aged chinchillas revealed a shallow orbit, a rudimentary nictitating membrane, a large cornea, a densely pigmented iris in pigmented individuals with a vertically positioned pupil, and an anangiotic fundus with variable vascularization of the optic disc (Peiffer & Johnson, 1980). Pupil constriction and dilation are less complete in light and dark conditions in lightly pigmented individuals than in ones with a darkly pigmented iris. Mean IOP in that study was 18.5 ± 5.8 mmHg. Bilateral posterior cortical cataracts and asteroid hyalosis were observed in two animals. Reference values for diagnostic tests in 61 healthy normal chinchillas have been reported (Müller et al., 2010). STTs were low and inconsistent while phenol red thread test values gave an average thread wetting length of 14 mm in 15 seconds. Average IOP measured with a TonoVet rebound tonometer was 2.9 ± 1.8 mmHg. Another study published simultaneously gave Schirmer readings of 0.1 ± 0.5 mm/min and IOP measured with the TonoVet, of 17.7 ± 4.2 mmHg (Lima et al.,

Figure 31.23. “Flesh eye” in a guinea pig, analogous to prolapsed nictitans gland in the dog.
Figure 31.24. Heterotropic bone formation in a guinea pig as a focal lesion (a) or larger area (b). Heterotropic bone formation filling a globe in the guinea pig (c).

2010). The tonometric differences between these two reports are difficult to explain. Orbital sinus bleeding has been adapted for use under anesthetic in the chinchilla (Brookhyser et al., 1977). While monitoring of food intake and body weight showed no deleterious effects of orbital bleeding on general health, some hemorrhage and occasional corneal opacity were seen when samples were taken twice weekly over a 2-month period.

A significant problem in this species when kept in captivity is dental disease (Crossley, 2001). Like rabbits, chinchillas are hypsodont with continually growing teeth. Without adequate wear from a rough coarse dietary intake, the molar teeth lengthen with resulting root extension into the orbit and subsequent epiphora (Crossley & Miguélez, 2001). The use of imaging techniques such as computerized tomography to detect such changes at a subclinical level has been shown to be valuable (Crossley et al., 1998).

THE FERRET

Ocular disease in pet ferrets has been well reviewed (Good, 2002; Williams, 2012). The ferret eye is adapted for dim light
conditions; predation by ferrets occurs between dawn and dusk but even in daytime within the scotopic conditions of rabbit warrens and prairie dog burrows. Thus, the ferret retina is predominantly rod-based although like in the cat, there is a cone-rich strip, the area centralis, allowing a higher acuity to be achieved. Ferrets’ visual resolution reaches a photopic Snellen acuity of 20/170 and a scotopic acuity of 20/350. Thus, ferret vision is markedly inferior to that of the cat (around 20/100), but its visual sensitivity, the lower limit of light needed for vision, appears much better—the threshold of light needed for vision in the ferret is estimated to be five to seven times lower than in man. Ferrets seem particularly attuned to moving objects.

Reference values for IOP (14.5 ± 3.2 mmHg) and STT (5.3 ± 1.3 mm/min) have been reported (Montani-Ferreira et al., 2006). Ocular biometry measured globe size to be 7.0 ± 0.2 mm and lens thickness to be 3.4 mm (Hernández-Guerra et al., 2007).

Congenital ocular disease in ferrets is relatively rare, although persistent hyaloid artery, tunica vasculosa lentis, and hyperplastic primary vitreous have been reported (Lipsitz et al., 2001). The eyelids of ferret kits do not separate until about 20 days postpartum; this late opening may account for the relatively high prevalence of ophthalmia neonatorum in this species. For treatment of this condition, careful eyelid separation should be combined with topical and systemic broad-spectrum antibiotic therapy. Note carefully whether nursing mothers have mastitis as this can lead to conjunctivitis or more severe adenoidal infection (Miller, 1997). A large poorly encapsulated zygomatic salivary gland is located posteroinferior in the orbit in the ferret, and head trauma may result in a salivary mucocele with associated exophthalmos (Miller & Pickett, 1989). Conjunctivitis in ferrets has been caused by human influenza virus, canine distemper virus, systemic mycobacteriosis (Lucas et al., 2000), and salmonellosis. Canine distemper in this species may cause photophobia and serous oculonasal discharge which becomes mucopurulent with associated chemosis and corneal ulceration. Brown crusts form around the mouth and eyes, often causing symblepharon. The diagnostic signs are a skin rash, occurring days later, and hyperkeratosis of the foot pads (Besch-Williford, 1987). Canine distemper infection in ferrets is usually fatal, but with influenza, the almost identical early signs often resolve. With distemper conjunctival scrapings may show eosinophilic intracytoplasmic epithelial inclusions or indirect immunofluorescence testing of conjunctival scrapings may confirm the diagnosis (Fox et al., 1988). Viral isolation from blood and serologic evaluation are diagnostic in the case of influenza. Salmonellosis is characterized by hemorrhagic diarrhea and fever in addition to conjunctivitis. Conjunctivitis may be a constant sign in systemic mycoplasmosis (Miller & Dubielzig, 1995).

The ferret has a large retrobulbar venous sinus that has been suggested as a potential site for blood collection (Fox et al., 1984). Given the ease of blood collection from the ventral tail vein or jugular in this species, however, orbital blood collection cannot be recommended. The importance of recognizing the venous sinus in ferrets comes during enucleation, in which hemorrhage from this plexus should be controlled by direct pressure, packing with gelatin sponge, or applying bovine thrombin at a concentration of 1000 IU/mL (Miller, 1997).

The depth of the orbit in a ferret renders detection of an orbital space-occupying lesion difficult until it has reached a considerable size (He & Killiaridis, 2004; Poddar & Jacob, 1977).
Cataracts have been reported several times in ferrets (Fig. 31.27). Two groups were documented in one ferret colony (Miller et al., 1993). One group manifested a continuum of lens changes from fine, multifocal punctate lens opacities through cortical change to complete, mature cataracts. The second group showed cataracts associated with microphthalmos and in some cases unusual periodic acid-Schiff (PAS)-positive material in the lens capsule. Lens luxations have been reported in ferrets as primary lens dislocations and as secondary to chronic cataract. Removal is difficult because of the small size of the globe, but since glaucoma can supervene, it is considered necessary. The small size of the globe also renders phacoemulsification for cataract difficult but irrigation-aspiration techniques can be used with a smaller diameter handpiece.

Ferrets have a holangiotic retina with a reflective tapetum in pigmented animals which may also be present in albino individuals (Wen et al., 1985). A necotally, retinal degeneration is believed to be common in the ferret, with inherited atrophy and degeneration associated with taurine deficiency in this obligate carnivore suggested in review but not reported in the primary literature.

**NONHUMAN PRIMATES**

Several elements of ocular anatomy in man are only mirrored perfectly in the eye of the nonhuman primate whether this is the anatomy of the structures associated with aqueous drainage, or the anatomy and pathology of the fundus and specifically the macula. Thus, from a research perspective, the primate eye is highly important. But in addition the three perspectives outlined at the beginning of the chapter—ocular conditions as important presenting features of systemic disease, spontaneously occurring ocular disease which may have welfare implications, and ophthalmic abnormalities which may complicate or mask experimentally induced disease—are as important in the primate as in any laboratory species.

Visual acuity in nonhuman primates such as the rhesus macaque (Macaca mulatta) appears similar to that in man (Yarczower et al., 1966) while squirrel monkeys have a lower acuity (Rolls & Cowey, 1970). Color vision gives trichromacy in these animals like in man (Regan et al., 2001) since these animals evolved to visualize colored fruit in green tree canopies as did we (Lucas et al., 2003). The Old World catarrhine monkeys and apes that have a uniform trichromacy with photopigments have sensitivities of 424–434, 531–539, and 562–568 nm (Bowmaker et al., 1991), but the New World platyrrhine monkeys have a polymorphic color vision with males being dichromatic while two-thirds of females are trichromats (Mollon et al., 1984). The explanation for this is that a single X chromosome locus has three or more opsin alleles depending on species, and the third autosomal locus gives trichromacy in females and dichromatic vision in males. Quite what implications this has for primate behavior in these New World monkeys is uncertain, but clearly, their vision is highly important to them. Ophthalmic examination of the Western lowland gorilla (Gorilla gorilla gorilla) has been reported with a mean IOP of 12.0 ± 4.3 by Schiotz tonometry; retinoscopy showed mild hyperopia of +1.2 ± 0.6 D (Liang et al., 2005). Tonometry in the capuchin monkey (Cebus apella) yielded IOP values of 18.4 ± 3.8 mmHg and STT values of 14.9 ± 5.1 mm/min (Montiani-Ferreira et al., 2008).

Outbreaks of infective conjunctivitis occur in nonhuman primates with viral diseases such as SV-15 (Landen & Bennett, 1969) and SV-17 (Tyrrell et al., 1960). Outbreaks of sterile conjunctivitis have been noted in macaques (Schmidt, 1971a, 1971b), and another individual nonhuman primate has been reported with allergic conjunctivitis (Hoopes et al., 1977). A macaque recently attended by the author had conjunctivitis, blepharitis, and orbital cellulitis unresponsive to antibiotics and corticosteroids which was related to a foreign body from wood shavings presumed to have lodged in the conjunctival fornix but which resolved in time (Fig. 31.28).

Keratitis associated with entropion and palpebral folds were seen in one crab-eating macaque and were treated using excisional techniques similar to those employed in canine lid surgery (Peiffer et al., 1980). The adnexal lesions of Molluscum contagiosum have been noted in several chimpanzees, with warty dermal swellings characterized histopathologically by classic Molluscum bodies similar to those seen in humans (Douglas et al., 1967). In a survey of ocular disease among marmosets and tamarins, meibomian gland obstructions were seen in almost 10% of cotton-top marmosets (Saguinus oedipus), with inspissated yellow-white material at the meibomian orifice opening and eyelid swelling in some cases (Buyukmihci & Richter, 1979).

There is considerable interest in evaluating glaucoma in primates given the similarity in their iridocorneal angle anatomy with that of humans. One report of glaucoma in...
SECTION IV: Special Ophthalmology

From a relatively benign retinal elevation (Fig. 31.29) to aggressive necrotic panretinitis (West et al., 1981). Cataracts have been documented in captive nonhuman primates (Fig. 31.30), with resorption noted in one spider monkey (Peiffer & Jacobson, 1981) and phacoemulsification performed in another (Whitley et al., 1980). More recent papers report cataract surgery in great apes including orangutan (Montiani-Ferreira et al., 2010) and gorillas (De Faber et al., 2004) both in captivity and both with successful outcomes.

Amelioration of visual deprivation from cataract formation is important in nonhuman primates, given the importance of vision in their behavior. A study of the behavioral development of an infant cynomolgus with congenital cataracts,

vervet monkeys (Cercopithecus aethiops) evaluated the iridocorneal angle of three individuals with elevated IOP (Barany & Rohen, 1963). In one animal, a thickened trabecular meshwork was noted, with PAS-positive hyaline material in the trabecular meshwork. The second animal also had a trabecular covering of hyaline material but also a clearly excavated optic disc. The third animal showed little pathology except for hemorrhage and protein in Schlemm’s canal of both eyes. The authors considered the glaucoma to be secondary in the first two cases and only primary in the third. The coexistence of resorbing cataract in the first two eyes together with evidence of lens-induced uveitis suggested that in these cases, the glaucoma was secondary. Extrapolating from these studies on small groups of primates to the wider primate population (including man) is difficult but a large closed colony of several hundred rhesus macaques raised on a small island off the coast of Puerto Rico which has remained without further genetic input since 1930 has yielded some valuable research. Glaucoma was discovered in several colony animals (Dawson et al., 1993, 1998; Komaromy et al., 1998). The colony remains a valuable research tool in the study of human primary open-angle glaucoma although more recently, rhesus macaques with increased IOP experimentally generated by trabecular meshwork laser photocoagulation have been studied as a more malleable tool in the evaluation of pathological changes in glaucoma (Bellezza et al., 2003; Burgoyne et al., 2004, Downs et al., 2007; Yang et al., 2011).

The anatomy of the prosimian iridocorneal angle has undergone limited investigation (Wolin, 1974). Glaucoma has been reported in red-fronted lemurs (Eulemur fulvus rufus) (Shields & Ritch, 1991) and other wild lemurs (I. Porteous, personal communication).

Nonhuman primates are particularly susceptible to tuberculosis which may cause uveitis. In the anterior segment, signs range from a caseous anterior chamber exudate to hyphema and iridal granulomas. Tuberculous inflammatory disease in the posterior segment may produce signs ranging

Figure 31.28. Blepharitis in a macaque associated with a conjunctival foreign body.

Figure 31.29. Tuberculous choroiditis in a rhesus macaque.

Figure 31.30. Mature cataract in a rhesus macaque.
however, showed few abnormalities, at least in the development of mother-infant interactions (Minami, 1986). Two colonies of grey mouse lemurs were noted to have a surprisingly high incidence of lens opacification with 21% and 40% of animals being affected and more than 50% having cataract by the age of 7 years (Beltran et al., 2007). Cataracts have also been reported in wild-caught and colony-bred African green monkeys, with the cataract determined to be inherited in two reports involving this species (Souri, 1973; Suzuki et al., 1988).

The nonprosimian primate fundus is similar to that of humans and normal variations have been well-documented in several reports (Fukui, 1983; Suzuki et al., 1983). It is important to be aware of these differences in fundus anatomy because knowledge of the normal fundus allows detection of an abnormal fundus during ophthalmic examinations of clinical patients or during toxicologic screening. Fundus lesions have been observed in several wild-caught cynomolgus monkeys and reported also in a study more than 2000 animals in which cohort there was a 7.9% incidence of ocular lesions and a 6.6% incidence of fundus lesions (Kuhlman et al., 1992b). These fundus lesions were predominantly chorioretinal scars, both peripheral (Fig. 31.31) and macular (Fig. 31.32), but they also include retinal hemorrhages and, in my experience, retinal vasculitis and cotton-wool spots in some cases. Differences in fundus pigmentation were described in different groups of rhesus monkeys with a geographic variation in fundus pigmentation associated with coat color (Dawson et al., 2004).

The similarity of nonhuman primate eyes to those of humans is particularly relevant when considering diseases of the macula and the posterior segment vasculature, both of which differ considerably from those of nonprimate eyes. Cynomolgus monkeys with macular degeneration have been studied and their visual capability estimated by recording their visual attention to observers both with or without a neutral-density face mask (Suzuki et al., 1989a, 1989b). Macular lesions consisted of hypopigmented spots. Visual dysfunction determined by this crude assessment appeared to correlate with the degree of macular abnormality. The closed colony of rhesus macaques with glaucoma noted above have also proved a valuable resource with which to study age-related macular degeneration (AMD) (Dawson et al., 1989; Hope et al., 1992). Macular drusen are twice as common in older females than in males similar to the condition in humans. Specific findings of interest include the high variability in prevalence between differing social groups in the colony and the paucity of neovascular macular lesions in these eyes (“wet” macular degeneration), a finding which differs significantly from the situation in man. Electoretinographic abnormalities in animals from this colony were reported earlier (Mofty, 1980), and the pigment variants seen in those animals were also noted in a group of cynomolgus monkeys that showed some histological photoreceptor degeneration (Feeney-Burns et al., 1981). All rhesus macaques in the colony were genotyped and association of the genes HTRA1 and ARMS2 with drusen formation at the macula was noted although the macular degeneration could be attributed to promoter polymorphism of the HTRA1 gene, coding for a serine protease central to macular angiogenesis (Zhang et al., 2011) seen in humans and macaques (Francis et al., 2008). The retinal pigment epithelial changes also seen in these studies and characterized by excess lipid.

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Figure 31.31. Chorioretinal scars in a rhesus macaque.

Figure 31.32. Macular scars in a rhesus macaque.
incorporation were also found in a single rhesus monkey in another report (Fine & Kwapien, 1978). The histologic retinal lesions in this monkey correlated with the fundus changes of white-yellow hypopigmented spots, but there were no degenerative changes found at either histopathology or electrophysiology. Vascular anomalies reported in primates have included a racemose posterior segment angiomaticus anomaly in a rhesus monkey (Bellhorn et al., 1972) and two arteriovenous malformations in the retinas of rhesus monkeys (Bellhorn et al., 1975; Horiuchi et al., 1976). These individual cases are of interest, but they probably tell us little regarding ocular disease among the general primate population. Vascular occlusive disease of the retina has been reported (Friedman et al., 1975) and has greater potential for interest given the propensity for this same disease among humans. Similarly, central retinal artery occlusion, which is a common and severe problem in humans, has also been suggested in one primate (Bellhorn, 1991). Lipemia retinalis has been documented in cynomolgus monkeys kept in a standard laboratory facility (Suzuki et al., 1989a, 1989b), and choroidal colobomatous lesions have been reported several times with or without associated optic nerve colobomas (Kuhlman et al., 1992a; Schmidt, 1971a, 1971b; Suzuki & Cho, 1986). Retinal and optic nerve degeneration has been documented in a cynomolgus monkey that was normal at 8 years of age but that by 15 years had a unilateral pallid disc, an abnormal b-wave amplitude in the affected eye, and a marked delay of the retinal arterial phase at fluorescein angiography (Suzuki et al., 1992). The value of such single case reports is unclear. A larger study in a group of 38 rhesus monkeys showed 9 animals to have bilateral optic atrophy, but none of these animals showed substantial alterations in retinal electrophysiological parameters nor in circulating blood levels of vitamins B12, E, folate, or lead (Fortune et al., 2005). Such reports show the importance of assessing the ophthalmic parameters of all animals used in research as models of human eye disease.

MINIATURE SWINE/MINIPIGS

Contribution by Glenwood G. Gum

Domestic pigs developed by agriculture during the last century have resulted in fast growing and high-quality animals, but their massive adult size limited use for biomedical research, aging, pharmacologic, and toxicologic investigations (Svendsen, 2006). A piglet a few weeks old at 1–2kg within a year or so may weigh 100–200kg, which limits greatly their use for chronic duration studies. These adult pigs required very large holding pens and their size presented possible injury of their handlers, and specialized facilities.

As a result, the search for smaller pigs (miniature swine; mini-pigs-Sus scrofa) started in Europe in the 1960s, and resulted in animals with adult weights of about 20–60kg and litter sizes of 3–6 offspring. These pigs are about 25% of the size of domestic pigs. Hence, the minipigs have become popular for worldwide biomedical research and as pet animals. Review of miniature pig reports in the biomedical literature revealed in excess of 2000 refereed articles in the past two decades. Some breeds of miniature swine, minipigs, and micropigs include Yucatan (Saint-Macary & Berthoux, 1994), Göttingen, Hanford, Sinclair breeds, and others. Other miniature swine include the Ossabaw (or Ossabaw Island Hog), the Vietnamese pot-bellied pig, and the Chinese Bama minipig. Other minipig breeds are still emerging! The Vietnamese pot-bellied minipig is a popular pet in America, and not infrequently is presented to veterinary ophthalmologists for bilateral entropion and marked obesity.

In some biomedical investigations, the miniature swine breeds display greater pharmacological similarity to humans than rodents, and represent a “large animal” laboratory animal that is replacing the more expensive and less available nonhuman primates (Liu et al., 2008; van der Staay et al., 2009). Hence, the miniature swine breeds are useful models to bridge the gap between preclinical testing in rodents and clinical testing in humans. In these biomedical, pharmacological, and toxicological investigations, as well as the development of specific eye disease animal models, veterinary ophthalmologists can be presented these animals. The eye of the pig has many similarities to the human eye, and has an atapetal ocular fundus (see Chapter 2, “Ophthalmic Anatomy” and Middleton, 2010). Surgical manipulations of the porcine globe are more similar to humans than the dog or cat. As all swine, the miniature pigs are also susceptible to all of the different diseases affecting this species (see Chapters 29, “Food Animal Ophthalmology” and 35.4, “Ocular Manifestations of Systemic Disease: Food Animals”).

Ophthalmic Diagnostics

Like all animal species, the miniature pig can be examined by all of the different noninvasive ophthalmic diagnostics, including ophthalmoscopy (direct and indirect), tonometry (applanation tonometry using topical anesthesia and the TonoPen tonometer or rebound tonometry using the TonoVet tonometer); slit lamp biomicroscopy; all types of ultrasonography; fundus photography (Fig. 31.33a–c); fluorescein angiography of the ocular fundus (De Schaepdryver et al., 1992; Gathuys et al., 1990); optical coherence tomography (OCT; Fig. 31.34), confocal scanning laser ophthalmoscopy (CSLO; Fig. 31.35); and other procedures. IOP has been reported as 15.2mmHg (±1.8) in pigs (breed not stated; Ruiz-Eserra et al., 2005) and 14.1mmHg (±2.2) by anterior chamber manometry (Castejon et al., 2010).

Like all animal species, close human contact, proper animal housing, and adequate socialization are very important in minipigs for eye research (Ellegaard et al., 2010; Nicholls et al., 2011). Repeat diagnostics such as tonometry require animals well accustomed to human contact to yield representative and consistent IOP measurements. A distinct advantage of both canine and swine models of glaucoma is tonometry does not require general anesthesia, and multiple daily measurements of IOP can be obtained with only topical
Figure 31.33.  

a. Fundus photography in a sedated minipig (Göttingen) using the portable Kowa Fundus camera. (Courtesy of Serge Rosolens, Asnières, France.)  
b. Fundus photograph with the optic nerve head of a minipig.  
c. Fundus photograph of a minipig showing the peripheral fundus (Courtesy of Glenwood Gum).

Figure 31.34. Optical coherence tomography (OCT) in an anesthetized minipig. The monitor of the OCT instrument has displayed the human eye recordings.

Figure 31.35. Fundus photograph using the Confocal Scanning Laser Ophthalmoscope (CSLO) in the minipig. The optic disc, lamina cribrosa (from 10 to 12 o’clock), arteries, veins, and the venous circle on the optic discs surface are visible. (From Rosolens et al., (2001) Ocular fundus images with confocal scanning laser ophthalmoscopy in the dog, monkey and minipig. Veterinary Ophthalmology, 4, 41–45.)
retract the eyelids as well as rotate the globe for best visualization.

Swine Models for Eye Diseases

Experimental Glaucoma

Pigs, and now miniature pigs, have been reported in comparative ophthalmology as models for several eye diseases. Using cautery of three episcleral veins in pigs (as used in rabbits, rats, mice, and nonhuman primates), IOP is elevated. Retinal ganglion cell loss occurred and was greater in the retinal periphery compared to the central retina (Ruiz-Ederra et al., 2005). In another report using minipigs, 4% methylcellulose was injected intracamerally to elevate IOP (Rosolens et al., 2003). The results of the elevated IOP were documented by fundus photography, electroretinography, fluorescein angiography, and scanning laser ophthalmoscopy. By routine histology, the iridocorneal angle was obstructed and significant retinal ganglion cell loss occurred.

Sugar-Induced Cataracts

Cataracts were observed at birth in all offspring of alloxanized Yucatan miniature pig sows (Severin et al., 1976). As these piglets grew, the cataracts regressed as normal cortical development returned. Often limited nuclear opacities were still present in affected pigs after 6 months of age. Cataract surgery in the alloxanized sows yielded excellent results. The postoperative inflammation after extracapsular lens extraction appeared less than observed in the dog.

Retinitis Pigmentosa (RP)

Using an inbred miniature pig, a transgenic animal model for RP was developed using the human P23H RHO gene. Somatic cell nuclear transfer (SCNT) was used to create miniature pigs which expressed the human autosomal dominant P23H RHO mutation (Ross et al., 2012). Using electroretinography in animals with ages from 3 months through 2 years, retinal mRNA was isolated, and the ratio of P23H to wide-type pig RHO was measured. The authors concluded this study served as a novel tool for the study of the pathogenesis and therapeutic intervention of the most common form (autosomal dominant) of adRP.

Retinal and Choroidal Neovascularization (CNV)

A model of retinal and CNV in the Yucatan minipig was developed using a Matrigel™ (BD Biosciences, San Jose, CA) in combination with angiogenic growth factors to induce a retinal and choroidal response when injected subretinally. The model provides the opportunity for testing drugs that may interfere with the neovascularization cascade of AMD (Gum et al., 2010).
CONCLUSION

Over the last decade, considerable advances in laboratory animal ophthalmology have been achieved. It is ironic, however, that many of these advances have been achieved not in animals housed under laboratory conditions, but in individuals kept as companion animals. While studies of disease in large populations are possible in laboratory-based animals as has been obvious in reports of disease prevalence in hundreds of rodents, in-depth evaluation of specific diseases of individual animals is more readily accomplished in veterinary clinics, especially in larger species such as the rabbit and ferret. We can expect further advances in both areas in the future with the genetic basis of many diseases elucidated through gene knockout studies which clearly have their scientific benefits. Improvements in treatments are most likely to be furthered by studies on individual animals or small groups in veterinary clinics directing effort in exotic animal ophthalmology.

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The rabbit has been widely used in ophthalmic research for many years, both in drug and chemical testing using the Draize test (more of which below) and in basic anatomic, physiologic, and pharmacologic work, so much so that Jack H. Prince, Associate Research Professor in the Department of Ophthalmology at Ohio State University, Columbus, Ohio, could devote an entire 650-page book to The Rabbit in Eye Research (Prince, 1964). More recently, the rabbit has moved from being a laboratory model or what some might rather disparagingly term “a mere children’s pet” to becoming, at least in the United Kingdom, the third most commonly encountered pet in small animal practice. A large number of animals are kept as house rabbits as valued companion animals. Associated with this increase in veterinary attention, much has been learned about the healthy and diseased rabbit eye, as detailed here. While in many respects the rabbit eye shares similarities with the more commonly encountered dog and cat eye, there are several differences, and anatomically, the normal rabbit eye has several peculiarities that differentiate it from that of dogs and cats. Thus, while we might place details of rabbit ophthalmology in a text on “exotic” species (Williams, 2012), the rabbit is too commonly seen to be termed exotic, even though its anatomy, physiology, and pathology are still relatively poorly understood by veterinarians in general practice.

The prevalence of various diseases of the rabbit eye differs markedly from those of the eye of species such as the dog and cat, but to date, we have little way of determining disease prevalence in the pet rabbit. Surveys of laboratory rabbit ophthalmic disease have been reported (Jeong et al., 2005), and in a lapine sequel to our survey of eye disease of 1000 guinea pigs (Williams & Sullivan, 2010), we have completed a survey of eye disease in 1000 rabbits but as yet only provided an interim report of the work (Inns & Williams, 2010). In this chapter, the results of the full survey are included where appropriate.

Before Prince had even started his investigations into the rabbit eye, Frederick Allison Davis had published a very useful review of the anatomy of the rabbit eye (Davis, 1929), concentrating on those aspects in which it differed from the human visual organ, some of which we will be aware of—what Davis terms the “sensitive streak” in the retina, Harder’s gland, and the unusual venous drainage of the orbit. Other features may be less familiar—in particular what Davis calls “the practical absence of a lamina cribrosa in the rabbit.” The rabbit orbit is a closed one unlike the open structure of the dog and cat, with significant influence on the globe prolapse occasioned by retrobulbar space-occupying masses whether infectious, neoplastic, or vascular. The orbital glands, including the large harderian gland, produce tears. This perhaps explains the exceptionally slow blink rate in the rabbit which blinks only once or twice per minute (Maurice, 1995), with important consequences on a number of issues from corneal epithelial healing and drug delivery in the clinical patient to toxic substance distribution and epithelial pathology in toxicity studies. The normal tear osmolarity in rabbits is between 300 and 305 mOsm/L (Gilbard & Dartt, 1982), with tear film breakup time of around 20 seconds (Trousdale et al., 2005). The orbit contains a vascular plexus first described by Davis (1929) and termed by him as the orbital sinus. The third eyelid contains no muscles but is passively drawn across by the action of the powerful retractor oculi muscles which can advance it more than two-thirds of the way across the ocular surface. This is important in an animal with so exposed an ocular surface. The lack of an orbital fat pad renders the rest of the orbit filled only by the retrobulbar muscles, the orbital glands, and the globe itself. Of the two other glands, the lacrimal and infraorbital, the lacrimal is much the larger with two portions both covered by orbital fascia. Tear drainage, as noted further below, is through a single slit-like opening 3–4 mm from the eyelid margin. There is no defined lacrimal sac as in the dog, cat and human, but rather an elongated...
dilatation of the nasolacrimal duct, which probably explains the propensity for large amounts of purulent discharge in dacryocystitis.

The globe is a spheroid compressed anterio-ro-posteriorly and, so Davis (1929) reckons, “relatively large compared to the size of the animal.” This is indeed the case with the ratio of volume of a rabbit eye to the weight of the animal around 0.0025, between 3 and 50 times the ratio of eye volume to body weight in other species from cat to cows, respectively, in a short study we have undertaken using data from numerous sources (Table 32.1). Such estimated measurements show the importance of the eye in the rabbit’s ecophysiology.

The sclera is thin as is the cornea with a thickness at its center of 355 µm (Chen et al., 2011) compared with 800–1000 µm in the cat and 600–700 in the small dog (Samuelson, 1999); this is important in understanding the propensity of globe enlargement (buphthalmos) in glaucoma. The cornea is large for the size of eye with a diameter approximately 15 mm and radius of curvature approximately 7 mm, roughly the same radius as that of the sclera. The anterior chamber is deep at its center but shallow at the periphery as the iris bows forward, a feature potentially important in the genesis of glaucoma.

The iris may be darkly pigmented or devoid of pigment depending on coat color and has a pupil almost circular but very slightly oval in the vertical meridian. As noted above, the iris bows forward due to the large almost spherical lens immediately behind it.

The fundus is particularly unusual in the rabbit with its merangiotic arrangement whereby myelinated nerve fibers and blood vessels course horizontally from the optic nerve head. Below this band-like blind spot is a streak of more sensitive retina, the visual streak, with a correspondingly thickened choroid underlying it, which presumably enhances the supply of oxygen and nutrients to the more metabolically active retina adjacent to it, which is thicker (160 µm) than the retina elsewhere in the fundus (from 120 µm to as thin as 40 µm under the myelinated nerve fibers coursing from the disc).

The optic nerve is unusual with a deep normal physiological pit, and it enters the eye above the optic axis, unlike that of other domestic animals or man. The lamina cribrosa is far less obvious than in man or other animals, which may explain the ease with which glaucomatous globes experience optic nerve cupping.

Table 32.1  Estimated Volume and Weight of Several Mammalian Species Showing That the Rabbit Has a Significantly Higher Ratio of Globe Volume to Body Weight Than Other Mammalian Species

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>Volume (mm³)</th>
<th>Weight (g)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horse</td>
<td>45</td>
<td>47,700</td>
<td>500,000</td>
</tr>
<tr>
<td>Cow</td>
<td>40</td>
<td>33,500</td>
<td>300,000</td>
</tr>
<tr>
<td>Sheep</td>
<td>28</td>
<td>11,500</td>
<td>50,000</td>
</tr>
<tr>
<td>Pig</td>
<td>25</td>
<td>8200</td>
<td>50,000</td>
</tr>
<tr>
<td>Dog</td>
<td>23</td>
<td>6400</td>
<td>20,000</td>
</tr>
<tr>
<td>Cat</td>
<td>20</td>
<td>4200</td>
<td>5000</td>
</tr>
<tr>
<td>Rabbit</td>
<td>17</td>
<td>2600</td>
<td>2000</td>
</tr>
</tbody>
</table>

Figure 32.1. Diagram of visual fields in a rabbit. (Reproduced with permission from Hughes, A. (1972) A schematic eye for the rabbit, Vision Research, 12, 123–138.)

WHAT DO RABBITS SEE?

As a prey species, the rabbit has vision which concentrates on the horizon with the ability to gain visual information from this relatively narrow band for almost 360 degrees of circumference but also providing an almost complete visual field dorsally above the rabbit as shown in Hugh’s schematic rabbit eye (Fig. 32.1) (Hughes, 1972). It is difficult to appreciate what this vision “looks” like to the rabbit in the same way we cannot clearly understand what the psychology of a prey species “feels” like. Neurophysiological and electroretinographic reports tell us something as do the visual field studies of researchers in bird vision (Martin, 2009), but in essence, the fact that we can know little of the sensory lives of other species is a philosophical limitation, quite as much as a physiological or psychological one.

The classic view is that rabbits can see both in front and behind them. While this is certainly true of a slim wild animal or pet breed such as a Netherland Dwarf when standing on its...
cycles per degree with an upper cutoff frequency of 3 cycles per degree. This would give the animal a visual acuity of 10 minutes of arc, corresponding to a Snellen acuity of 20/200. Behavioral measurement of grating acuity, in which rabbits chose a horizontal or vertical grating to obtain a food reward, suggested an acuity of between 1.6 and 2.5 cycles per degree although acuity among individuals varied (Vaney, 1980). These all lay within the range noted by van Hof in his 1967 study in which acuity was estimated at between 1.5 and 2.7 cycles per degree (van Hof, 1967). The major limitation with all such measurements is that they use a stationary image. The rabbit's visual system evolved to detect motion, and it may be that local edge detector retinal ganglion cells give a significantly better detection of edge and motion than this low reported visual acuity suggests (van Wyk et al., 2006).

As seen in other herbivorous species, detailed trichromatic color vision is not present in the rabbit. Only 5% of the rabbit's photoreceptors are cones (Davis, 1929). The two populations detecting blue and green light are advantageously placed. These two sets of photoreceptors have maximal absorption at wavelengths of 425 nm and 520 nm corresponding to greatest sensitivity to blue and green, respectively (Juliusson et al., 1994; Nuboer, 1971). In the visual streak, the density of greensensing cones is around 13,000/mm² while in the rest of the retina, cone density is as low as 7500/mm². Below the visual streak lies a second band of cones containing a high proportion of blue-sensitive cones at a density of about 11,000/mm². The rabbit can thus detect birds attacking from the blue sky from above and ground-based predators advancing through the green grass below. We should clearly understand that even
a rabbit’s relatively basic visual system is perfectly suited for its environment and ecology.

**USE OF THE RABBIT EYE IN EXPERIMENTAL RESEARCH**

The rabbit has been used in ocular research for many years. In the preface to his *The Rabbit in Eye Research*, J.H. Prince notes that “The rabbit has been established as the most useful subject for experimental ophthalmology, and the literature discloses investigations in various aspects of this animal’s ocular anatomy as far back as the 17th century.” While there are anatomical and physiological similarities between the rabbit and human eye, there are also significant differences, and today we might wish to distance ourselves from Prince’s assertion of it being a “most useful subject.” A search of PubMed using the terms “rabbit” and “eye” yields over 27,000 papers with 350 being published within the last 12 months. A brief review of the last four of those published within a recent week shows the diversity of research involved. Higher dietary cholesterol was reported to cause pathology similar to macular degeneration in the rabbit eye in the first paper (Dasari et al., 2011). Decreased levels of anti-apoptotic Bcl-2 protein, increased levels of the pro-apoptotic Bax and gadd153 proteins, emergence of TUNEL-positive cells, and increased generation of reactive oxygen species, astrogliosis, and drusen-like debris were all detected in the retinas of cholesterol-loaded animals, so even though the rabbit does not possess a macula, it can be a useful model for such changes. In a second paper, rabbit corneas were used in a study to determine tissue acceptance of hydroxyapatite in keratoprosthesis biointegration into the cornea. Inflammatory cell infiltration was determined showing that hydroxyapatite reduced inflammation and increased biointegration (Wang et al., 2011). A third report described the rabbit cornea as an in vivo model for the new surgical technique of Descemet’s stripping endothelial keratopasty by evaluation with slit lamp biomicroscopy and confocal microscopy (Chen et al., 2011). A fourth paper published used the rabbit eye as a model for treatment of Bacillus cereus endophthalmitis with a fluoroquinolone antibiotic alone or with dexamethasone (Sakalar et al., 2011). These papers not only show the diversity of research using the rabbit eye but also potentially show the severity of pathology and the potential distress caused by such research. Nowhere is this so likely to kindle concern than with regard to the Draize test assessing the toxic effects of cosmetics and other products on the eye.

**THE DRAIZE TEST**

In 1933, a 38-year-old lady used a beauty product (Lash-Lure®) containing paraphenylenediamine, a coal tar derivative. Developing a severe immune reaction, the patient (for that is what she became) was blinded by a scarring keratoconjunctivitis. Her misfortune was reported by several newspapers (Fig. 32.4) and brought before the U.S. senate in support of calls for a strengthening of consumer product regulations (Greenbaum, 1933). Six years later, across the Atlantic, the iconic ophthalmologist Ida Mann, the only female consultant at the world famous Moorfields Eye Hospital, was asked by Britain’s Ministry of Supply to investigate the mechanisms of ocular injury of bis-(2-chloroethyl) sulfide, otherwise known as mustard gas, as Britain faced the outbreak of the World War II. Many hundreds of tons of this noxious vapor, which caused epithelial sloughing and ischemic ulceration to skin and eyes, had been used by both sides in World War I. Mann used the rabbit eye as an in vivo model, hoping to be able to find a method of stopping or resolving such devastating ocular surface pathology (Mann, 1943; Mann & Pullinger, 1941). Her methods were predominantly qualitative but showed the potential value of this model system for assessing ocular toxicity. Back in the United States, John Draize, a chemist working in the Agricultural Experimental Station of the University of Wyoming, was called to the U.S. Army’s Edgewood Arsenal in Maryland where mustard gas was being investigated. Here following the passing of new legislation (Federal Food, Drug and Cosmetic Act of 1938), the Federal Drug Administration’s Division of Pharmacology set up a Dermal and Ocular Toxicology Branch. Jonas S. Friedenwald, Director of the Ocular Pathology Laboratory at the Wilmer Ophthalmological Institute at Johns Hopkins University in Baltimore, was already investigating effects of chemical agents on the eye and suggested the grading of ocular lesions using numerical scales where previously they had been assessed using a dichotomous “±” coding. Draize developed this as a coding method for ocular toxicology: 0.1 mL of test product was applied to the cornea or the inferior conjunctival sac, and the resulting ocular signs were graded using scores for corneal opacity (nature and area involved), iris congestion, injection, hemorrhage and reaction to light, degree of conjunctival hyperemia, chemosis, and ocular discharge. These scores were summed but with different weightings (Draize & Kelley, 1952; Draize et al., 1944). Technically, Draize did not translate this scoring system into an interpretative assessment of severity, but his method of weighting corneal and iridal signs did lead to others assuming that the overall score delineated a defined level of toxicity. The problem was that the same score value could be reached by summation of different degrees of damage to conjunctiva, cornea, or iris, and the degree required to reach the threshold of detection was a matter of subjective observation, not objective assessment. Reproducibility between laboratories, or even between different investigators in the same laboratory, could be remarkably poor. From a statistical perspective, while the score appeared to be a linear continuous measurement, it was in fact nonlinear, ordered, categorical data (Worth & Cronin, 2001). Perhaps the primary problem with the test is the difference between the rabbit and the human eye. The test involves changes associated with epithelial toxicity, transcorneal product absorption, iridal inflammation, and potential systemic effects, many of which will vary between species. One study suggested that the Draize test correctly determined ocular toxicity in the human eye for around 85% of toxic products but overesti-
mated toxicity in the human eye in 10% and underestimated in around 5%. The difficulty is in knowing into which of these groups a specific product falls. All these defects in the scoring system did not stop the Draize test from becoming the main system through which many thousands of products were tested for topical ocular toxic effects. A pictorial guide illustrates the range of ocular pathology scored in the Draize test (Fig. 32.5).

Three individuals, Peter Singer and Henry Spira in the United States and Richard Ryder in the United Kingdom, were instrumental in bringing these experimental techniques into the public gaze. Following Singer’s and Ryder’s book publications (Ryder, 1975; Singer, 1975), Spira mobilized a public campaign in 1978 to initiate discussions with the cosmetic company Revlon, culminating in full-page advertisements in newspapers such as The New York Times. Spira realized that such action should be balanced with calls for the company to not just stop such tests but to develop alternatives. At the end of 1980, Revlon’s chairman announced a $750,000 grant to Rockefeller University’s Laboratory Animal Research Center to investigate safety tests avoiding the use of animals.

More than 20 years before this in the United Kingdom, the University’s Federation for Animal Welfare (UFAW) had commissioned two scientists to develop a monograph promoting the optimal care of laboratory animals (Russell & Burch, 1959). They developed the 3 Rs: refinement, reduction, and replacement. With regard to the Draize test, refinement involved steps to minimize discomfort such as the use of topical anesthetics prior to product placement on the ocular surface (Durham et al., 1992), and techniques to maximize data acquisition such as use of fluorescein dye, standard photography, and eventually, tonometry, pachymetry, and confocal microscopy. With regard to reduction, the standard Draize test used nine animals, reduced in the OECD Good Laboratory Practice manual to five rabbits (but six in many other countries’ testing protocols).

The key R is replacement. Can a nonanimal model or in vitro system be used to test the same sorts of toxicities?
Figure 32.5. Effects of application of irritant agents in the Draize test. (Reprinted from Hobson, D.W., Dermal and Ocular Toxicology: Fundamentals and Methods. Boca Raton, FL: CRC Press, 1991.)
Might an in vitro system or a battery of in vitro models potentially yield greater concordance with actual effects on the human eye than does the rabbit eye? In vitro tests are often used to study effects on particular elements of the cornea, for example, epithelial cell death, effects on inflammatory cascades, interactions with stromal collagen and proteoglycans, and drug–tissue interactions which do not require the entire eye as a model. Several groups sought to develop alternatives to the Draize test, most particularly Michael Balls and the Fund for Replacement of Animals in Medical Experiments (FRAME) (Atkinson et al., 1992, Balls et al., 1983). The red blood cell test or hemoglobin denaturation test can evaluate effects on hemolysis or hemoglobin denaturation (Mitjans et al., 2008), and the hen egg chorioallantoic membrane test (Kishore et al., 2008) demonstrates effects on blood vessels and epithelial monolayers. Work on isolated corneas or isolated eyes allows product assessment without generating ocular pain (Frentz et al., 2008) with utilization of specific irritancy scoring systems (Hackett & McDonald, 1991); however, the sacrifice of healthy animals is necessary to provide animal tissues (Jester et al., 2010). Bovine ocular tissue obtained from abattoirs can be used with caution (van Goethem et al., 2010). The COLIPA European Cosmetics Association ocular irritation program has pioneered methodological development and validation such as the SkinEthic human corneal epithelium model (Cotovio et al., 2010) and the MatTek Epiocular model (Sheasgreen et al., 2009) derived from human corneal keratinocytes. Additional important information may be derived from use of human volunteers and from reports of accidental exposure of humans to commercial products.

**OPHTHALMIC MEASUREMENTS IN THE RABBIT EYE**

For many years the TonoPen® applanation tonometer (Reichet Technology, Buffalo, NY) (Fig. 32.6) has been the preferred device for tonometry in rabbits (Mermoud et al., 1995). More recently, the TonoVet® (Icare, Helsinki, Finland) rebound tonometer (Fig. 32.7) has been found useful by this author. In rabbits, the TonoPen Avia® tonometer (Reichet Technology, Buffalo, NY) measured intraocular pressures (IOPs) consistently higher than the TonoVet® (15.4 ± 2.2 mmHg ± 9.5 ± 2.6 mmHg, respectively) (Pereira et al., 2011). In this study, IOP measured by both tonometers was higher in the morning and decreased throughout the day. Another study found the TonoPen to underestimate IOP slightly compared to manometric measurement, but the pneumotonometer overestimated to a great degree (Abrams et al., 1996). A more recent study found the TonoPen, Perkins, and pneumotonometer all to underestimate IOP (Lim et al., 2005). Another study reported that none of the tonometers are (sic) accurate or reproducible in estimating IOP in rabbits over the tested range (5–50 mmHg) but found the Tonopen to be more accurate at pressures below 30 mmHg while the pneumotonometer overestimated at these low IOPs but was more accurate above 40 mmHg (Bar-Ilan, 1986). There was diurnal and seasonal variation with a daily curve of IOP showing a continuous rise during the day from 18.2 ± 1.7 mmHg at 0800 hours to 20.6 ± 1.8 mmHg at 1700 hours. The key point to note here is that in determining IOP in the rabbit, use of the same tonometer and the same time of day is critical to avoid natural variation. In addition, telemetric tonometery has shown that factors such as handling, drinking water, and the stress of pneumatonometry itself can alter IOP in rabbits substantially (Dinslage et al., 1998).

Measuring tear production in rabbits also has its drawbacks and its variability. A previous study showed that no one Schirmer tear test (STT) value (Fig. 32.8) could be considered a normal level or range for rabbit tear production (Abrams et al., 1990). Their average STT value of 5.3 ± 2.9 mm/min disguised the fact that different breeds of rabbit have very

![Figure 32.6](image1.png) Use of the TonoPen applanation tonometer in the rabbit.

![Figure 32.7](image2.png) Use of the TonoVet rebound tonometer in the rabbit.
different rates of tear production, or of tear drainage, since the STT measures merely the available tears to be taken up by the strip in 1 minute (Williams, 2005).

**OCULAR DISEASE**

**Orbital Disease**

One area in which the rabbit differs markedly from the dog and cat is in the anatomy and hence the diseases of the orbit. An important feature of rabbits is the retrobulbar venous plexus, vital to note during enucleation. Perforation of the orbital venous plexus during globe removal can lead to significant blood loss with hemostasis by digital pressure being difficult to achieve. Performing this surgery transconjunctivally rather than transpalpebrally and remaining as close as possible to the globe during dissection obviates this problem in the vast majority of cases. Another important condition arising from this orbital venous plexus or sinus is that of periodic bilateral exophthalmos when the animal is stroked or picked up (Fig. 32.9a, b) (Pignon & Jardel, 2010; Wagner et al., 2005). Here the problem is that venous return from the head is precluded by a mass around the jugular veins, most commonly a thymoma or thymic carcinoma, so blood fills the orbital sinus and causes a startling exophthalmos, which resolves when the stressful situation ceases. In a recent paper, Kunzel et al. (2012) review 13 rabbits with mediastinal thymomas, 6 of which (46%) exhibited periodic bilateral exophthalmos, while 10 presented with dyspnea and 7 had exercise intolerance. Bilateral prolapse of the third eyelid was also seen in several animals. Of 7 animals which underwent thoracotomy and removal of the tumor, 2 lived 180 and 955 days while 4 were euthanized and the others all experienced perioperative mortality (Kunzel et al., 2012).

**Retrobulbar Abscess**

*Pasteurella* is often associated with retrobulbar abscessation in rabbits, and this condition is often linked to a tooth root abscess (Fig. 32.10a–c). Orbital exenteration is one option in such cases, with the additional use of antibiotic-impregnated methacrylate beads being useful in some circumstances just as they are used in dentistry for infected tooth roots and orthopedics for treatment of osteomyelitis (Henry et al., 1993). The

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**Figure 32.8.** Use of the Schirmer tear test strip in the rabbit.

**Figure 32.9.** (a and b) Exophthalmos during handling of New Zealand white rabbit with thymoma.
Orbital Glands and Associated Disease

Of the three orbital glands present in the rabbit (lacrimal, nictitans, and harderian), any can become hyperplastic, and all but the lacrimal gland can prolapse and protrude out of the orbit (Fig. 32.11a, b). These glands are very heavily vascularized. The normal lacrimal gland is large, lobulated, and pale red in color lying in the lateral orbit. Prince states that “in well nourished animals it protrudes through the sulcus (between the superior orbital ridge and the temporal bone) so that it can be seen under the facial tissue” although this author has not been convinced of this finding. The gland is a serous compound tubular gland supplied by both the lacrimal and the

orbital venous plexus can however, as noted above, yield significant blood loss during such an exenteration and, of course, such surgery results in the loss of a normal visual eye. Given that such abscessation is often, if not always, related to a tooth root, the option of removing the tooth is an attractive one (Ward, 2006). Such a maneuver saves the globe and has the advantage that it yields a sinus tract to the oral cavity through which purulent material can drain; a careful flush of the orbit following the surgery is recommended. Obtaining sufficient access to perform such a procedure can be challenging, and the use of an endoscope to visualize the intraoral structures has been found invaluable by one group (Martínez-Jiménez et al., 2007).

Figure 32.10. a. Exophthalmos from retrobulbar abscess in New Zealand white rabbit. b. Exophthalmos from retrobulbar abscess in dwarf rabbit. c. MRI showing purulent material in retrobulbar space in rabbit shown in part b.
accessory lacrimal arteries, the former arising from the external ophthalmic artery and the latter from the ethmoidal artery. The lacrimal gland probably plays a smaller part in ocular surface lubrication in the rabbit than the harderian gland which is a large structure with white and pink lobules lying in the medial orbit.

Diseases of these structures include tear deficiency (covered with other keratitides below), gland protrusion, hyperplasia, and neoplasia. Because of the considerable volume of the glands in the orbit, any increase in their size is readily noted with protrusion of the gland or much less commonly a degree of exophthalmos. Similar to nictitans gland prolapse in the dog and cat, gland protrusion is seen in the rabbit but with lower frequency than other companion animal species. As with the dog and cat, replacement of the gland is much preferred to excision. We do not know the relative contributions of the orbital glands to the tear film, but removal of any of the glands that contribute to lubrication and nutrition of the ocular surface should be avoided. Another reason to opt for replacement rather than excision is that the glands are intimately enwrapped by the orbital venous plexus, and their removal could provoke uncontrollable hemorrhage. In this author’s experience, the Morgan pocket technique is preferred for gland replacement in the rabbit as in the cat and dog (Fig. 32.12). While the anatomical structures are smaller in the rabbit than in the dog, the technique is identical and can be readily undertaken by any competent ophthalmic microsurgeon. Malignant B-cell lymphoma of the harderian gland has been reported (Volopich et al., 2005).

**ADNEXAL DISEASE**

**Conjunctival Overgrowth**

An unusual and apparently unique abnormality in rabbits is an aberrant overgrowth of conjunctiva producing a type of ankyloblepharon involving conjunctiva covering of the ocular surface (Fig. 32.13a, b). This condition, though widely seen among individual rabbits, is relatively poorly documented in the literature. It was first reported as a congenital condition.
aberrant contractile elements in the leading edge of the conjunctiva.

**Conjunctivitis**

Conjunctivitis is seen commonly in both laboratory and pet rabbits and may have several causes (Fig. 32.15). In one report, severe persistent purulent but sterile conjunctivitis was noted in a number of rabbits and was presumed to be associated with use of overhead hay racks (Buckley & Lowman, 1979). Close examination reveals a mild reddening of the conjunctiva among many rabbits in floor-housed situations.
where hay dust can enter the conjunctival sac. In these cases, topical antibiotic and corticosteroid treatment has been helpful, but the underlying problem with bedding choice and quality should also be corrected (McGarry et al., 1976).

In rabbits, it is important to distinguish conjunctivitis from dacryocystitis (discussed later). Purulent ocular discharge with conjunctival hyperemia often accompanies not only conjunctivitis but also nasolacrimal duct and lacrimal sac infections (Fig. 32.16). The diagnosis of infectious conjunctivitis and dacryocystitis must be approached with appreciation of the normal bacterial flora of the conjunctival sac (Okuda & Campbell, 1974). Pasteurella sp. are considered by many to be the most common bacterial pathogen in the rabbit, but it is important to consider Staphylococcus aureus. In a survey of staphylococcal disease in rabbits, more than 60% had nasal exudate with conjunctivitis (Snyder et al., 1976). In a more recent survey of conjunctival flora in rabbits with conjunctivitis and dacryocystitis, Pasteurella was not the most commonly isolated species: bacteria were isolated from 78% of swabs with staphylococcal species found in 42% of isolates and Pasteurella species detected in 12% (Cooper et al., 2001). Blepharoconjunctivitis characterized by mucopurulent ocular discharge with thickening and crusting of the eyelids has been reported to be associated with localized Staphylococcus aureus infection in one pregnant rabbit (Millichamp & Collins, 1986). Given the periparturient state of this animal, a compromised immune system may have been important in the pathogenesis of this disease, as is the case with the sialodacryoadenitis virus in rodents. In this case, topical and parenteral gentamicin was curative. In other rabbits with staphylococcal conjunctivitis, an autogenous vaccine was useful in ameliorating ocular signs (Hinton, 1977). Haemophilus sp. has also been reported to be conjunctival pathogens in the rabbit (Srivastava et al., 1986). Those authors sought to fulfill Koch’s postulates for the agent by infecting normal rabbits to show that unlike the normal conjunctival flora detected in swabs from the rabbit, the Haemophilus sp. isolated was pathogenic to the normal rabbit eye. Few reports go to these lengths to confirm that an isolated organism is indeed the cause of ocular disease, thereby making it difficult to assess their relevance to other similar situations. It might be argued that such studies in reality are purely academic and cause more suffering to the rabbits involved in the investigation than will be alleviated among those rabbits naturally affected.

Conjunctival disease in the rabbit can be caused by viral as well as bacterial agents. The myxoma virus causes inflammatory and edematous lesions of the lids and conjunctiva as well as of the mouth, anus, and genitals (Fig. 32.17a). Different strains of the virus may cause a variety of presentations (Fenner & Marshall, 1957). In the acute form, death may supervene before any obvious ocular signs occur. Alternatively, conjunctival hyperemia may be the only sign before death. In the more common subacute to chronic forms, conjunctival hyperemia progresses to chemosis with a copious ocular exudate. Edematous and often exudative lesions around the face and anogenital area are pathognomonic of the disease. The profound white ocular exudate in the disease (Fig. 32.17b) may be caused by organisms such as Pasteurella multocida causing dacryoadenitis. The pathogenesis of this disease involves profound immunosuppression and often subsequent multifocal infection with commensal organisms regularly found in nonpathologic carrier status in the nasal turbinates, such as Pasteurella sp. (Fenner & Woodroofe, 1953). In fact, a mixture of different organisms can be detected, including Pasteurella, Pseudomomas, and Staphylococcus in the white ocular discharge in rabbits with myxomatosis; these may also be present in the unaffected rabbit as normal adnexal commensals. Thus, the ocular signs of myxomatosis are a complex mixture of ocular and dermal virally induced signs with sec-
secondary bacterial infections due to a reduced immune response. Further investigation of the exact mechanism of the ocular manifestations is warranted. The diagnosis is made on the basis of clinical signs and microscopic examination of inclusion bodies in mucosal scrapings or histopathologic samples (Patton & Holmes, 1977). The myxoma virus is one of the poxviruses affecting lagomorphs, with the others being the Shope and squirrel fibroma viruses and rabbit pox. These viruses are generally self-limiting in rabbits, but cases of poxviral keratitis in the rabbit with viral induction of adnexal or corneal tumors have been reported (McLeod & Langlinais, 1981).

Myxomatosis in vaccinated rabbits can produce the myxomatous tumors which give the condition its name. These are generally self-limiting and rarely cause ocular surface damage necessitating surgical removal (Fig. 32.17c).

Blepharitis

Blepharitis in the rabbit may be associated with Treponema cuniculi infection, the agent of rabbit syphilis (Fig. 32.18a) transmitted to the neonates by the genitally infected dam (Harkness & Wagner, 1989). The lid lesions can be difficult to differentiate from those of myxomatosis (Fig. 32.18b), and the definitive diagnosis is made on the basis of identifying the spirochete on conjunctival cytology (Fig. 32.18c). Treatment is three injections of penicillin G at 40,000IU/kg given at 7-day intervals. Because prolonged beta-lactam antibiotic therapy can cause fatal dysenterobiosis in rabbits and rodents, this treatment should be given with care and should be stopped if any diarrhea is noted. Squamous cell carcinoma has been reported to mimic treponemal blepharitis (Bagley & Lavach, 1985); squamous cell proliferation seen on cytologic scrape

Figure 32.17. a. Profuse purulent exudate in a case of myxomatosis. b. Lid swelling in myxomatosis in a naive rabbit. c. Periocular myxomas in myxomatosis in a vaccinated rabbit.
samples would be diagnostic. Other causes of lid swelling can be staphylococcal infection (Fig. 32.19) which can lead to entropion and resultant trichiasis. Systemic antibiotic treatment may be indicated combined with hot compresses to reduce swelling.

**Nasolacrimal Duct Abnormalities**

Infection and inflammation of the nasolacrimal duct in the rabbit is not uncommon; 18 of the 27 rabbits seen in this author’s clinic over the past year were diagnosed with dacryocystitis (Fig. 32.16, Fig. 32.20, Fig. 32.21, and Fig. 32.22). Fourteen of the rabbits in our survey of 1000 apparently normal animals were noted to have frank purulent ocular discharge, and 13 had epiphora, perhaps giving a more accurate assessment of true prevalence (D. Williams, personal communication). A previous study of over 500 laboratory
New Zealand white rabbits determined dacryocystitis to be present in only 0.2% of those animals, but they were generally a young rabbit population (Jeong et al., 2005). Affected rabbits in our study of 1000 animals showed an average age of 5.4 ± 1.6 and 5.9 ± 2.0 years for dacryocystitis and epiphora, respectively, this being significantly older than the study population with an average age of 2.2 ± 1.9 years. A recent report of 28 rabbits with dacryocystitis noted an average age of 4.4 years, suggesting that dacryocystitis is a condition seen predominantly in older rabbits, presumably in which dental disease, the most commonly associated condition, occurs more frequently than in young rabbits (Florin et al., 2009).

While most present with a purulent ocular discharge (Fig. 32.16 and 32.20), other rabbits can have a swollen medial canthal area or medial canthal dermatitis that can be severe (Fig. 32.21). The most common initial treatment was topical antibiotic, but flushing of the nasolacrimal duct was performed in 87% of the rabbits; 80% of animals had dental treatment. Only 43% of rabbits in that study showed complete resolution of signs, and 28% were euthanized. Two rabbits continued to display signs of nasolacrimal discharge and were treated symptomatically. In this author’s clinic, a larger proportion fall into this rather unsatisfactory group, but as noted below, continued systemic antibiotic therapy per os may, with care, be an appropriate control measure.

Understanding the anatomic relationship between the nasolacrimal duct, orbit, and roots of the upper incisor and molar arcades is important regarding oculodental disease, particularly in lagomorphs and hystricomorph rodents such as the chinchilla. The rabbit is unusual in having only one nasolacrimal punctum with a nasolacrimal duct that follows a tortuous route through the lacrimal and maxillary bones. Normal duct narrowing results in specific sites at which material can collect and cause obstruction (Fig. 32.23) (Burling et al., 1991; Marini et al., 1996). Obstruction can be caused by oil droplets without infection, in which case epiphora alone is noted (Marini et al., 1996), or with infected purulent material, in which epiphora with dacryocystitis is noted (Petersen-Jones & Carrington, 1988).

The duct passes close to the roots of both the premolar and incisor teeth, and this apposition is important in development of duct obstruction when associated with dental disease or maxillary osseous change secondary to nutritional hyperparathyroidism (Harcourt-Brown, 1996). What appears on first examination to be purulent conjunctivitis in the rabbit is more often than not dacryocystitis, as noted earlier (Fig. 32.16). This can sometimes be shown by expressing purulent material from the nasolacrimal punctum with pressure just ventral to the punctum (Fig. 32.20), cannulation of the nasolacrimal canaliculus, and flushing with sterile saline. Epiphora and dacryocystitis result from the close apposition of the nasolacrimal duct to the incisor and molar roots. Malocclusion of the molar arcades in particular results in retropulsion of the tooth into the weakened maxillary bone, with subsequent nasolacrimal occlusion; incisor malocclusion may perhaps more commonly produce this same result. Culture of nasolacrimal
flushes from affected rabbits showed a wide range of organisms, including *Neisseria* sp., *Moraxella* sp., *Bordetella* sp., *Streptococcus viridans*, *Oligella urethralis*, and *Pseudomonas* sp. (Marini et al., 1996). Note, however, these animals had epiphora rather than dacryocystitis. The same organisms were found in nasolacrimal flushes from unaffected rabbits as well. *P. multocida*, which was the most frequently isolated organism in an earlier study of dacryocystitis (Burling et al., 1991), was not detected. In a more recent study, *Pasteurella* only comprised 12% of isolates (Cooper et al., 2001).

Treatment of dacryocystitis in the rabbit is by cannulation of the single nasolacrimal punctum and flushing of the duct (Fig. 32.24). If cannulation from the ocular punctum is difficult, cannulation of the duct opening at the nasal meatus is possible, but the small diameter of the duct at its nasal end renders this procedure difficult (Fig. 32.25). The proximal end of the nasolacrimal duct can also be difficult to visualize in a rabbit in which dacryocystitis has extended to produce a florid
conjunctivitis (Fig. 32.15). Pressing on the lower eyelid will often expose the duct as a pair of lighter pink lips “pouting” through the darker red, inflamed conjunctiva. Alternatively, the lid can be pulled gently from the ocular surface to reveal the duct (Fig. 32.21). In most cases, cannulation and flushing of the duct with an antibiotic (e.g., ofloxacin, gentamicin) will resolve the problem. When this is ineffective, the duct can be cannulated in a more permanent manner with fine monofilament nylon. There are difficulties and potential hazards with this technique, however, especially given the tortuosity of the rabbit nasolacrimal duct. Nevertheless, sometimes, there is no other option in stubborn cases of dacryocystitis.

As noted above, treatment may need to be protracted. A useful further option may be to suggest to owners that a second rabbit is provided, not as a replacement for the affected animal, but as a companion; in many cases, the second rabbit will lick the discharge off the face of the affected animal and so ameliorate the deleterious effects of continued discharge in the ocular or facial areas. To facilitate this, one highly experienced rabbit veterinarian cannulates the duct from the punctum, ties off the duct where it opens onto the conjunctival surface, and then marsupializes the duct only to facial skin. This can be very useful, but is only appropriate, in this author’s opinion, where another rabbit will clear the discharge for the marsupialized duct opening.

Entropion

Entropion, which is relatively commonly seen in rabbits (Fig. 32.26), is rarely a condition of sufficient interest to warrant reporting in the literature, but the few reports that have appeared confirm this lesion can be severe and is only corrected by surgery (Fox et al., 1979; Yanoff, 1983). Often the lid in-turning leads to corneal ulceration with subsequent increased blepharospasm and worsening ocular surface trauma. In many cases, entropion occurs because of blepharitis and lid swelling with a vicious circle of irritation and further lid deformity ensuing. Staphylococcal blepharitis may lead to entropion, but this form of adnexal abnormality is not generally remedied by simple surgery because lid swelling causes entropion.

Corneal Disease

Corneal disease is commonly seen in rabbits and has been covered well in a review chapter (Andrew, 2002). The most serious corneal condition in rabbits is corneal ulceration. Ulcerative keratitis is not common in rabbits; 8 of the thousand animals in our study had fluorescein-positive epithelial erosions, and 12 showed corneal scarring indicative of previous ulceration (D. Williams, personal communication). Many of these are linear abrasions indicative of trauma most probably from a hay or straw shard (Fig. 32.27). A corneal epithelial erosion after trauma should heal in less than 7 days, but several of the ulcers noted in our study were recalcitrant erosions similar to those seen in the boxer and corgi dog breeds (Bentley et al., 2001; Murphy et al., 2001). The characteristic lip of nonadherent epithelium is present in rabbits with nonhealing ulcers, and debridement of such devitalized tissue will be required before any ulcer healing is possible (Fig. 32.28). Further treatment of these recalcitrant lesions should be performed in an analogous manner to that of the canine equivalent, with a grid keratotomy or anterior stromal puncture (Fig. 32.29). The thin nature of the rabbit cornea (Chan et al., 1983) must be taken into consideration when performing such procedures.

Lipid keratopathy (Fig. 32.30) has been documented in rabbits fed cholesterol-rich diets specifically designed to
Corneal epithelial dystrophy in the rabbit has been reported as a peripheral lesion histopathologically characterized by areas of epithelial thinning adjacent to areas of epithelial cell hyperplasia (Port & Dodd, 1983). Another report described a plaque-like paracentral granular stippling in American Dutch belted rabbits characterized histopathologically by irregularly thickened epithelial basement membrane similar to that seen in epithelial basement membrane dystrophy or Reis-Bucklers’ dystrophy in humans (Moore et al., 1987).

Tear Production and Keratoconjunctivitis Sicca

Clinical keratoconjunctivitis sicca (KCS) is seen rarely in rabbits, but the species is used as a model for human dry eye, and there is extensive literature on the pathology and treatment of aqueous tear deficiency in these animals. The studies have used the New Zealand white rabbit rather than the many breeds kept as companion animals. This is important since the earliest report regarding tear production in rabbits showed significant differences in STT values between rabbits of different breeds (Abrams et al., 1990). Reductions in tear production are seen in rabbits in which their leukocyte population is supplemented with lymphocytes sensitized to lacrimal antigens (Thomas et al., 2008), and CD4 and CD18 cell populations were increased in their lacrimal glands (Zhu et al., 2003). Cyclosporine increases tear production in rabbits with such autoimmune lacrimal adenitis (Thomas et al., 2009). Topical dexamethasone reduced ocular surface pathology in rabbits in which the mitogen concanavalin A was injected into their lacrimal glands to cause resultant inflammation and dry eye. This amelioration of corneal pathology occurred to a greater degree than it does in the dog (Nagelhout et al., 2005).

Rabbits treated with trimethoprim-sulfamethoxazole orally twice daily at a dose of 40mg/kg had significant reductions in STT readings (Shirani et al., 2010). Since such classes of

Figure 32.28. Nonhealing ulcer with devitalized nonadherent epithelial edge in a rabbit.

Figure 32.29. Grid keratotomy being performed in a rabbit with a nonhealing superficial erosion.

Figure 32.30. Corneal lipid arcus in a rabbit fed a high lipid diet.

produce atheromatous lesions for research purposes (Fallon et al., 1988, Kouchi et al., 2006) and is seen in Watanabe rabbits with heritable hyperlipidemia (Garibaldi & Goad, 1988; Roth et al., 1988). It has also been documented in rabbits fed a 10% fish meal maintenance diet (Sebesteny et al., 1985) and in one pet rabbit fed a predominantly milk-based diet (Gwin & Gelatt, 1977).
antibiotics may be given to rabbits quite commonly, it is important to measure tear production before prescribing them and to assess any deleterious effects during treatment.

**Glaucoma**

Hereditary glaucoma in the New Zealand white rabbit has been studied extensively since the early 1960s (Fig. 32.31) (Hanna et al. 1962a, 1962b; Kolker et al., 1963). Neonatal bu/bu homozygotes have normal IOP (15–23 mmHg), but after 1–3 months of age, the pressure rises to between 26 and 48 mmHg (McAaster, 1960). Histopathologic features of these glaucomatous eyes have been well documented as has gonioscopic evaluation, which has shown goniodygenesis involving the pectinate ligaments and trabecular meshwork in affected eyes (Fig. 32.32a, b) (Knepper et al., 1991; Lee, 1968; Tesluk et al., 1982). The eyes become buphthalmic with cloudy corneas. Vision is lost at this stage, but the eyes do not appear painful, probably because of the increase in size accompanying the raised pressure. Over a period of several months, IOP returns to either normal or near-normal associated with ciliary body degeneration. Affected animals rarely show overt ocular or systemic signs of pain or distress. Thus, in the opinion of this author, medical or surgical treatment for this condition, although investigated from the perspective of an experimental model (Vareilles et al., 1980), is rarely particularly effective or necessary. Pain and distress can be difficult to detect and quantify in prey species such as the rabbit (Leach et al., 2011), and glaucoma is known to be painful in other species at least in its acute stage.

The bu gene is a recessive trait that is also semilethal, with heterozygotes giving birth to small litters of unthrifty pups. The New Zealand white rabbit is considered to be the predominant lagomorph strain with the bu/bu trait, but other white strains of pet rabbit have been found to have classic signs of the same condition. In our study of one thousand rabbits, seven animals had glaucoma: three New Zealand whites, two New Zealand white-cross bred rabbits, one Belgian hare, and one Flemish giant (D. Williams, personal communication). The mean age of the affected animals was 3.4 years and the median was 4 years.

**Uveitis**

For many years, inflammatory lesions with vascularization in the rabbit iris were ascribed to infection by *P. multocida*, which produces white, purulent abscesses in other locations in this species. Recent findings are strongly suggestive that many of these lesions are caused by lens-induced uveitis (Fig. 32.33 and 32.34) (Wolfer et al., 1993). This uveitis occurs secondary to capsular rupture caused by intralenticular infection by the protozoan Encephalitozoon cuniculi, demonstrated immunohistochemically in a more recent study (Giordano
et al., 2005). This lens pathology is discussed in more detail later. Because of the lens-induced nature of this inflammation, treatment is lens removal by phacoemulsification with concurrent topical anti-inflammatory medication. Not all anterior uveitis is lens-induced. *Pasteurella* sp.-associated cases may be encountered with a more classic uveitis characterized by episcleral congestion, miosis, and hypopyon (Fig. 32.35). Some *Pasteurella* sp. or *Staphylococcus*-associated iridal inflammation is difficult to differentiate from lens-induced inflammatory disease; in other cases, the yellow purulent material in the anterior chamber is characteristic of a more obvious bacterial infection (Fig. 32.36). Anterior chamber paracentesis may be indicated to acquire a diagnostic sample.

**Cataracts**

Congenital, primarily nuclear, cataracts and persistent pupillary membranes have been documented in a litter of rabbits. Cataracts were shown not to be inherited and appeared similar to those seen occasionally in litters of Cocker spaniels (Gelatt, 1975). In our series of a thousand animals, one colony of rabbits had seven 4-week-old kits with congenital nuclear opacities (Fig. 32.37a) while most animals with cataracts, whether nuclear, cortical (Fig. 32.37b), or posterior subcap-
The sequela of this is lens-induced uveitis.

The Rabbit Fundus

The fundus of the rabbit is merangiotic with a band of blood vessels and myelinated nerve fibers traversing the retina in a horizontal plane from the optic disc (Fig. 32.38 and 32.39). As noted above, the distribution of cone photoreceptors correlates perfectly with the visual ecology of the species, with blue-sensitive photoreceptors ventrally and green-sensitive ones dorsally. As an animal adapted to nocturnal and crepuscular habits as well as daylight vision, the retina is rod
Optic disc cupping is seen in glaucoma in the rabbit (Fig. 32.40), although when mild, it can be difficult to differentiate from the deep physiological cups which can be part of normal variation in this species.

REFERENCES


Chapter 33

Exotic Animal Ophthalmology

Thomas J. Kern and Carmen M. H. Colitz

As public interest in natural history, conservation, and ecology has peaked, demand for competent diagnosis and treatment of the medical disorders of captive nondomestic animals have been thrust upon the veterinary profession. Its response has been timely and comprehensive. Once primarily preventative medicine, nondomestic animal medicine has evolved to incorporate the sophisticated treatment of individual animals commonly available for conventional pet and companion animal species. This trend has fired keen interest in the diagnosis, characterization, research, and management of, among others, the ocular disorders of these once “alien” patients.

The challenges that fish, amphibians, reptiles, birds, and wild mammals present for diagnosis and treatment are potentially daunting. Despite the availability of sophisticated instrumentation and technology to both ophthalmic specialists and nonophthalmologists, the anatomy, physiology, and biology of many creatures seem to defy their practical use. Nonetheless, in the diagnosis and management of ocular disorders of these special species, the clinician is wisely advised to (1) learn and regularly review the ocular anatomy, physiology, and visual ecology of the species of current interest; (2) employ the same quality of complete ocular examination, albeit modified accordingly, performed on conventional species; and (3) articulate the limitations inherent in the examination technique, in order to make a realistic assessment of ocular signs and to formulate specific, directed diagnostic and treatment plans.

OPHTHALMIC EXAMINATION

Despite the aforementioned caveats, a surprisingly complete ocular examination may be performed on many species, especially those with reasonably large eye size. External and anterior segment examination may be facilitated by magnification provided by a slit-lamp biomicroscope, head loupe, or indirect condensing lens, used with bright illumination in the (at least momentarily) immobilized patient. Posterior segment examination is possible in many species with direct or indirect ophthalmoscopy, or both, even without mydriasis (often difficult or impossible to achieve). Indirect condensing lenses in the 28–60 D range facilitate panoramic fundus examination in small eyes and through small pupils. Applanation tonometry is possible in most eyes large enough to accommodate the tonometer’s tip (TonoPen®, Mentor [Colonial Medical Supply, Franconia, NH]). Rebound tonometry (TonoVet®, Tiolat Oy, Finland) utilizes an even smaller tip and may be used on small eyes. Even though normal values may not be well documented in many species of interest, measurements from normal fellow eyes and eyes of other normal individuals of the same species provide good reference values. Similarly, Schirmer tear tests (STTs) and/or phenol red thread tests (PRTTs) may be performed in many species and interpreted by comparison to other normal individuals. Fluorescein dye examinations of cornea and nasolacrimal systems, conjunctival culture collection, and exfoliative cytology may be performed in most species, modified as dictated by eye size and external anatomical features.

Among exotic species, broad variations exist in all parameters of vision: color perception, ultraviolet (UV) wavelength detection, acuity, accommodative ability, motion detection, and stereopsis. Assessment of vision-directed behavior in exotic species presents several challenges. Often, animals are examined outside of their familiar habitats under stressful restraint, precluding observation of the animal’s visual orientation to its environment. Owners and even experienced animal handlers and keepers may be unaware of the normal visual ecology of their charges and thus may not provide dependable observations of behavioral changes. Conversely, their observations and insight may prove more accurate than those of the attending clinicians. The most accurate and reliable assessment of vision-directed behavior in many species is made by observation of them unstressed in familiar and appropriate habitats. Inappropriate husbandry practices may be the ultimate source of ocular complaints.

The important categories of ocular disorders of nondomestic species resemble those of domestic species: congenital

Occlusion occurs most commonly by light-induced vitread migration of melanin within the retinal pigment epithelium. Less commonly retinomotor movement effects occlusion. Elasmobranchs have one or more layers of guanine crystals in the choroid; this tapetum may be occlusible by movement of the pigment epithelial processes themselves over the photoreceptors (Ollivier et al., 2004a). The choroidal gland is a well-developed vascular plexus present within the choroid of many species at the posterior pole, where it wraps around the optic nerve and communicates with an accessory gill (pseudobranch). Its functions presumably include nutrition and local temperature regulation. Indirect ophthalmoscopy has been used to document the fundus morphology of several fish species (Grover & Zigman, 1984; McLaughlin et al., 1996). Adult elasmobranchs possess an entirely avascular retina; it depends completely on the choriocapillaris for its nutrition and there is no accessory vascular organ (choroid gland). The choriocapillaris is supplied by one major artery and is drained by a dorsal and ventral vein (Bellhorn, 1997). Teleosts possess either a falciform process or a membrane, the tunica vasculosa retinae. The falciform process is an infolding of choroid through the fetal fissure into the vitreous (Fig. 33.2). The tunica vasculosa retinae is derived from a branch of the internal ophthalmic artery that enters the eye near the optic disc; it lies in the vitreous in front of the retina (Bellhorn, 1997).

The ciliary body is rudimentary, when present. Ciliary processes are absent. Complete separation of aqueous and vitreous is not present and the mechanisms of aqueous production and loss are poorly understood. The pupil is generally round or pear shaped; the iris is thin and, with few exceptions, immobile. The sphincter and dilator muscles are rudimentary or absent except in elasmobranchs. The very large spherical lens is supported by the zonule and a dorsal suspensory ligament; it consists of a hyaline lens capsule surrounding the lens epithelium, cortex, and nucleus. The anterior surface nearly touches the corneal endothelium, forming a very narrow anterior chamber. The fish lens has the highest refractive index of all vertebrates (−1.69), and the refractive index gradients within it essentially eliminate chromatic and spherical aberration in the image presented to the retina. A posterior muscle, the retractor lentis, is present in teleosts; it arises ventrally from the falciform process of the retina and inserts anterior to the lens equator on the ventral lens capsule. The suspensory ligament/retractor mechanism allows changing the lens position within the pupil as well as alteration of the lens–retina distance. There is an anterior aphakic crescent in the pupil, which aligns with a far temporal fovea; this facilitates binocular vision when the fish targets objects in front of it by tilting the eyes forward, allowing light to obliquely pass through the lens and stimulate the fovea (Schwab, 2011). Predatory fish in general have well-developed accommodation, whereas bottom feeders have little or no accommodative range. A hyper anterior muscle, the protractor lentis, is present in some elasmobranchs.

A anatomic variation in retinal structure and photoreceptor type and morphology exists (Ali, 1976; Nicol, 1989; Schwab, 2011). Both rods and cones are typically present: diurnal species have cone-dominated retinas, deep-sea and nocturnal species have rod-dominated retinas, with gradations dictated by species’ visual ecology. Twin and double cones and oil droplets may be present. A fovea is present. The optic nerve enters the eye via one or more optic discs near the posterior border of the falciform process, where present. Described above, two protective mechanisms have evolved to shield photoreceptors from excessive light promoted by the immobile pupil and lack of eyelids (retinomotor responses). Photoreceptors may contract or elongate between pigmented processes of pigment epithelial cells or alternatively pigment may migrate along the apical processes of pigment epithelium.

**Ophthamlic Examination**

Ocular examination of fish in water is of necessity limited to gross observation. Close examination is facilitated by aerial examination, often under anesthesia. Buffered tricaine methane sulfonate (Finquel MS-222, Argent, Redmond, WA) delivered at 50–200 mg/L depending on species in tank water is usually satisfactory (McLaughlin et al., 1996; Williams & Whitaker, 1997). Gross examination of the external eye and anterior segment may be performed with a focal light source and magnification or by slit-lamp biomicroscopy. Sample collection for culture and cytology of the cornea and lid folds may be done as for other vertebrates, as can fluorescein staining to demonstrate corneal ulceration. Applanation tonometry may be performed only in species with large eyes (TonoPen, Mentor, Norwell, MA). Mean IOP by rebound tonometry in growing koi was 4.9 mm Hg (TonoVet, Tiolat Oy, Finland) (Lynch et al., 2007a). Fundus examination may be possible
by aerial examination using indirect ophthalmoscopy and a 60-D condensing lens. Central corneal thickness was 0.202 mm in channel catfish in which IOPs were not recordable with a TonoPen; fundus evaluation was performed by indirect ophthalmoscopy (McLaughlin et al., 1996).

**Ophthalmic Diseases**

The ocular disorders of fish result from infectious diseases, nutritional deficiencies, trauma, metabolic disorders, degenerations, neoplasia, and teratogenic and spontaneous malformations (Dukes, 1975; Stoskopf et al., 1985; Van Duijn, 1973; Wilcock & Dukes, 1989; Williams & Whitaker, 1997).

Infectious agents include parasites, bacteria, fungi, and viruses. Parasites include ciliated protozoans (Ichtyophthirius Cryptocaryon, Tetrahymena); myxosporidians (the proliferative kidney disease agent; Myxosoma heterospora; Henneuguya; Myxobolus; Sphaerospora; Myxobilus); trematodes (Diplostomum spp. and related genera); crustaceans (copepods, Lernaea spp., Argulus spp.); cestodes (Gilquinia squali) and microsporidia (Glugea). Ichthyophthirius multifiliis, a highly pathogenic ciliated protozoan, afflicts farm-raised food and ornamental fish, infects the skin and gill epithelium as an immature theront, where it matures into a trophozoite, which detaches. Death results from respiratory and excretory exchange problems (Klesius & Rogers, 1995; Pesut & Goldschmidt, 1983). The corneal epithelium or stroma are commonly involved; however, relatively little corneal edema and fibroplasia develop (Dukes & Lawler, 1975; Wilcock & Dukes, 1989). Exophthalmos is a feature of proliferative kidney disease of salmonids (Klesius & Rogers, 1995). Henneuguya lagodon was identified as the cause of periocular cutaneous cysts in pinfish, Lagodon rhomboides (Hall & Iversen, 1967). Dermocystidium gastrostei was identified in the cornea and skin of sticklebacks (Elkan, 1962). Myxobilus and Sphaerophora have been identified in the choroidal rete of fish with exophthalmos and hyphema (Williams & Whitaker, 1997). Myxobilus couseii was associated with iris cyst formations. Metacercariae of Diplostomum spp., a digenetic trematode whose definitive hosts are aquatic birds, infect the eyes of a wide variety of fish, with specific predilection to infect the lens, causing cataract. Several species, at least, of Diplostomum and related genera have been identified in different fish species: Diplostomum scheuringi (brown trout, yellow perch), Ornithodiplodistomum pychocheilus (brassy minnow, creek chub), Neascus spp. (creek chub, brassy and fathead minnows) (Hendrickson, 1978), D. gastrostei (sticklebacks) (Williams, 1956), and Diplostomum spathaceum, from which the classic lenticular lesions were originally described (Ashton et al., 1969; Bylund & Sumari, 1981; Dwyer & Smith, 1989; Karvonen et al., 2004; Palmieri et al., 1976; Shariff et al., 1980; Sweeting, 1974). Successful removal of cataracts caused by a Diplostomum species by phacoemulsification and aspiration from 18 Gulf sturgeons (Acipenser oxyrinchus) has been reported (Bakal et al., 2005). Digenean metacercariae of an unidentified species were found in the corneas and iridocorneal angles of oyster toadfish (Opsanus tau), in which corneal edema and vascularization were prominent features of encystations (Riis et al., 1981). A broad range of ocular lesions may develop in marine and freshwater fish associated with copepod infestation. Some are relatively harmless surface inhabitants of the corneoscleral recess (Wilcock & Dukes, 1989). Some species penetrate only the corneal epithelium, causing only local epithelial and fibrous tissue hyperplasia. A few perforate the eye and embed their mouthparts into the choroid; the Pacific arrowtooth flounder is infected by Phrixocephalus cincinnatus in this manner, causing extensive intraocular damage (Wilcock & Dukes, 1989). A tachment and perforation of the eye with subsequent keratitis, lens rupture, and endophthalmitis were observed associated with attachment of adult anchorworms (Lernaea piscinae) in farm-raised bighead carp (Aristichthys nobilis) in Malaysia (Shariff, 1981). Gilquina squali has been associated with hemorrhagic uveitis, cataract, lens rupture, retinal detachment, and globe rupture (Williams & Whitaker, 1997). Glugea may infect the cornea.

A broad spectrum of pathogenic bacteria infects both marine and freshwater fish. Bacterial septicaemia commonly results in intraocular involvement. Infections with Staphylococcus aureus (Shah & Tyagi, 1986), group B streptococci (Rasheed et al., 1985), Aeromonas, Pseudomonas, and Vibrio (Dukes, 1975; Wilcock & Dukes, 1989) have been documented. Granulomatous uveitis in Atlantic salmon has been reported following intraperitoneal vaccination with a commercial product containing mineral oil adjuvant and antigens of Aeromonas, Moritella, Vibrio, and infectious pancreatic necrosis virus (Koppang et al., 2004). Mycobacterial infections and infection with Nocardia and Flavobacterium cause granulomatous endophthalmitis (Backman et al., 1990; Pesut & Goldschmidt, 1983; Wilcock & Dukes, 1989).

Viral infections with endothelial tropism (e.g., rhabdoviruses) may cause uveitis (Wilcock & Dukes, 1989). At least three epizootic salmonid virus diseases (infectious pancreatic necrosis, infectious hematopoietic necrosis, and viral hemorrhagic septicemia) have exophthalmos as a characteristic sign (Yasutake, 1970). Lymphocystis, caused by a DNA virus, causes primarily verrucose skin lesions of marine and freshwater fish associated with marked hypertrophy of connective tissue cells (Roberts, 1989; Russell, 1974). Ocular lesions have been reported, including orbital involvement causing exophthalmos, uveitis, and corneal invasion (Dukes & Lawler, 1975). Other viruses with reported oral infection include a salmonid retrovirus, a salmonid hepatic herpesvirus, a nodavirus, and a picornavirus (Williams & Whitaker, 1997).

Mycotic ocular disorders of fish include corneal infections, orbital cellulitis, and endophthalmitis. Corneal infection with Saprolegnia usually accompanies multifocal interoculitary mycosis of marine and freshwater fish (Pesut & Goldschmidt, 1983). Experimental infection of tilapia by feeding Aspergillus flavus-contaminated food caused periocular, orbital, and intraocular infection associated with generalized infection (Olufemi & Roberts, 1986). Sarcomycosces cruscatus caused
Nutritional ocular disorders have been extensively described in salmonids and recently in red drum and channel catfish. Deficiencies of riboflavin (Hughes, 1985; Hughes et al., 1981; Poston et al., 1977), thiamine (Hughes, 1985), vitamin A (Hughes, 1985), methionine and cystine (Poston et al., 1977), tryptophan (Poston & Rumsey, 1983), and zinc (Ketola, 1978) produce cataract (Fig. 33.3). In riboflavin-deficient fish, corneal thickening with edema was noted (Hughes et al., 1981). Excess calcium and phosphorus fed to juvenile Chinook salmon produced cataract (Richardson et al., 1986). Thioacetamide fed to rainbow trout produced binding cataract characterized by massive proliferation of lens epithelium (Von Sallman et al., 1966). Multiple ocular lesions were induced by ascorbic acid deficiency in juvenile red drum (Sciaenops ocellatus), including reduced globe size, lack of globe rigidity, vascular congestion, intraocular hemorrhage, lenticular lesions (posterior cortex disorganization and vacuolation, posterior migration of lens epithelium), and severe central retinal degeneration. The retinopathy was suspected to be phototoxic injury enhanced by the deficiency. The causes of the cataract were unclear but were ascribed potentially to direct nutritional effect or indirect result of retinal degeneration (Collins et al., 1993). Nicotin-deficient channel catfish developed exophthalmos (Andrews & M urai, 1978). Corneal edema, cataract, ocular perforation, and phthisis were suspected to be of unspecified nutritional origin in farmed rainbow trout in Malawi (Lee et al., 1976). In farmed Atlantic salmon, high dietary levels of vitamin C and astaxanthin reduced the frequency of spontaneous cataract, whereas high dietary lipid level, iron, and manganese were associated with increased cataract frequency (Waagbo et al., 2003).

Traumatic injury was postulated to occur in Atlantic stingrays (Dasyatis sabina) associated with the turbidity from heavy siting of inshore waters (Nicol, 1981). Corneal ulceration, remodeling, and scarring were noted in histologic specimens. Corneal epithelial erosion was associated with overcrowding during transport in largemouth bass (Brandt & Jones, 1986; Ubels & Edelhauser, 1987). Experimental removal of corneal epithelium from rainbow trout, alewife, and sculpin resulted in transient corneal edema and cataract (Ubels & Edelhauser, 1987). Corneal ulceration due to transport, aggression, and handling is common (Williams & Whitaker, 1997) (Fig. 33.4).

Metabolic disturbances in fish may cause exophthalmos, a common sign in certain infections as well. Gas bubble disease of marine and freshwater fish is a noninfectious, physically induced process caused by uncompensated hyperbaric pressure of total dissolved gases (Bouck, 1980; Dehadrai, 1966; Speare, 1990). When pressure compensation is inadequate, the dissolved gases may form emboli and tissue emphysema. When gas bubbles develop behind the globe, exophthalmos—frequently dramatic and occasionally resulting in total proptosis with loss of the eye—results. Intraocular gas bubble accumulation causes a variety of pathologic changes, including panophthalmitis, synchiae formation, and cataract (Speare, 1990) (Fig. 33.5). Experimental administration of androgens produced exophthalmos in young fish of two species of teleosts; the cause of the exophthalmos was not determined (Mattly et al., 1958).

Ocular neoplasia has been rarely reported in fish. Retinoblastoma was described in a spring cave fish (Chologaster agassizi) (Fournie & Overstreet, 1985), a porkfish (Anisotre­mus virginicus) (Reimschuessel et al., 1989), and a brown bullhead (Ictalurus nebulosus) (Reimschuessel et al., 1989). Of 11 neuronal embryonal tumors of captive marine and freshwater teleost fish reported in one series, eight were ocular; of these, seven were retinoblastoma and one was a teratoid medulloepithelioma (Kagan et al., 2010). Intraocular lymphosarcoma was reported in an Atlantic cod (Gad morhua); a complete necropsy was not performed (Wolke & Wyand, 1969). A medulloepithelioma of the ciliary body was identified in a goldfish (Carassius auratus) (Lahav & Albert, 1978). Bilateral ocular neuroectodermal tumors with central nervous system invasion were diagnosed in a telescope goldfish (Bartlett et al., 2010). A denocarcinoma of the retinal pigment epithelium was reported in a guppy (Fournie et al., 1992). A n iridociliary melanoma causing lens luxation was reported in a long-horned cowfish (Lactoria cornuta) (da Silva et al., 2010).

Degenerations of the lens and retina in fish occur for some of the same reasons as in mammals and associated with a few unusual circumstances. Possibly inherited cataract was reported in aquarium-raised tilapia (Noga et al., 1981). Partially reversible cold cataract has been described in vitro in fish; its relationship to spontaneous cataract development in

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**Figure 33.3.** Rainbow trout. Nutritional deficiency cataract involving nucleus and perinuclear and anterior subcapsular cortex.
Figure 33.4. Fuzzy dwarf lionfish (courtesy of Dr. Carmen Colitz). A. OD: perforated corneal ulcer with flat anterior chamber containing fibrin and hypopyon. B. OS: extensive corneal erosion.

Figure 33.5. Yellowtail rockfish (courtesy of Dr. Carmen Colitz). A. OD: normal. B. OS: gas bubble disease. Globe is buphthalmic with small gas bubbles in anterior chamber, corneal ulcer, and iris disinsertion.

vivo has not been clearly demonstrated (Loewenstein & Bettelheim, 1979). Excessive exposure to sunlight was postulated to cause cataract in hatchery-reared lake trout (Steucke et al., 1968). Retinal degeneration suspected to be phototoxic in origin was reported in wild-caught Atlantic menhaden (Brevoortia tyrannus) after 4 weeks of captivity in an indoor open culture system (Nasisse et al., 1989). Hyphema, iris hemorrhage, and incipient cataract were variably present. Electroretinograms were totally extinguished in all affected fish. Histologically the most extensive retinal lesions occurred in the central retina. Cataract with lens rupture was noted in wolffish (Bjerkas et al., 1998). Cataracts have been noted commonly in both wild and farmed Atlantic salmon (Bjerkas et al., 1996, 2003; Ersdal, 2001; Ferguson et al., 2004; Wall,
1998; Wall & Richards, 1992). Intraocular oxygen tensions were investigated in normal and diseased eyes of farmed halibut (Williams & Brancker, 2004; Williams et al., 1995). Experimental retinal phototoxicity has been documented in several fish species (Penn, 1985; Raymond et al., 1988). Hereditary retinal degeneration was reported in celestial goldfish, a breed with exophthalmos and abnormal globe position in which the iris plane is horizontal (Matsumura et al., 1981). The retina develops fully and normally until 105 days posthatching, when the globes begin to protrude laterally (Sakaue et al., 1987, 1988). Idiopathic cystic degeneration of the choroid causing apparent exophthalmos was noted in five species of captive rockfish (Sebastes spp.) (Engelman et al., 1984). The cysts were filled with fluid, not gas, and associated with minimal inflammation and variable retinal degeneration. Corneal degeneration characterized by corneal thinning, ulceration, and variable rate of perforation were reported in aged captive lake trout (Hoffert & Fromm, 1965). Inherited retinal degeneration occurs in mutant zebrafish (Danio rerio) with cranial malformations, in which the retina begins to develop normally, then undergoes degeneration within 2 days of fertilization in vivo (Daly & Sandell, 2000).

Teratogenic influences of pesticides, heavy metals, fungicides, and polychlorinated biphenyls on developing eyes of embryos of Atlantic silversides (Menidia menidia) have been reported (Hughes, 1985). Spontaneous tyrosinase positive ocular cutaneous albinism has been studied in the goldfish (Abramowitz et al., 1977). Exophthalmos caused by thyroid tissue in the choroid was reported in a Coris gaimard (Schubert, 1969). Orbital exenteration with prosthesis placement has been performed in fish (Nadelstein et al., 1997).

**AMPHIBIANS**

**Ophthalmic Anatomy**

The anatomy of amphibian eyes varies with order (anuran vs. urodele) and stage of development (larval vs. adult). The eyes of larval amphibians resemble teleost fishes. Those of urodeles (tailed amphibians) are poorly developed compared with anurans. The eyes of larval anurans (frogs and toads) have poorly developed eyelids; in adults, the upper lid is immobile and, associated with the lower lid, a false nictitating membrane is formed by an elastic translucent fold of conjunctiva in the lower fornix. When the globe is retracted, it passively covers the eye; this retraction facilitates swallowing because the globe depresses the thin membrane separating the orbit and pharynx, forcing food down the throat. There is no orbital septum separating the two orbits. Superior eyelid glands and a harderian gland are present. The puncta and nasolacrimal duct are present. The retractor bulbi is the most important extraocular muscle, which retracts the globe and aids in swallowing. The globe is spherical with hyaline cartilage in the inner sclera from the posterior pole as far as the equator (Fig. 33.6). Other anurans lack cartilage or have a ring of bones within the sclera. Urodeles lack scleral cartilage. The adult cornea has the mammalian pattern, but larval anurans have a duplex cornea with a dermal portion separated from the sclera. A triangular ciliary body is present with hypertrophied folds dorsally and ventrally that extend to the pupillary border to form pupillary nodules. Two protractor lentis muscles arise from the peripheral cornea to insert on the ciliary folds; contraction causes zonular tension, which moves the lens forward to effect accommodation for distance vision. The lens in tad-
poles is spherical and near the cornea; in adult frogs it is somewhat flattened and positioned more posteriorly, leaving a visible anterior chamber. The urodele lens is large and the anterior chamber is shallow. Urodeles lack ciliary folds and the dorsal protractor lentis muscle. The aqueous is drained through an iridocorneal angle into dorsal and ventral ciliary sinuses. The iris is thin and often highly colored by various stromal pigments; a metallic sheen is associated with the presence of guanine crystals (Fig. 33.7). Myoepithelial sphincter and dilator muscles are present. Iridal arteries have an irregular pattern and communicate with deeper veins. Pupillary excursions are present but limited. Resting pupil size and shape are remarkably variable, but it is spherical when dilated. The avascular retina derives its blood supply from the vascular choroid alone in urodeles and from both the choroid and a membrana vasculosa retinae in the vitreous on the retinal surface in anurans (Bellhorn, 1997). The choroid contains a choriocapillaris but no tapetum, but cells may contain guanine crystals or carotenoid pigments. The optic disc is circular or elongated. The retina contains at least four types of photoreceptors types based on visual pigments in the rods and cones. Oil droplets are present at the distal end of the ellipsoid of some cones. Anuran photoreceptors have been the subject of extensive research involving photochemistry, renewal, and electrophysiology.

**Ophthalmic Diseases**

Considerable research interest has been directed toward amphibian retinal and central visual pathway physiology (Kagan et al., 1973), retinal injury (Kagan et al., 1973; Lolley et al., 1977; Reyer, 1977), and lens injury and repair (Rafferty & Goossens, 1977; Worgul et al., 1982). However, reports of spontaneous ocular diseases of amphibians are scarce. The ophthalmic disorders of amphibians have been reviewed previously (Millichamp, 1991; Williams & Whitaker, 1994). Mycobacterial panophthalmitis was reported in a South American bullfrog (Leptodactylus spp.) (Rowlatt & Roe, 1966). Corneal edema and panophthalmitis have been noted in both natural and experimental infections of leopard frogs (Rana pipiens) with Flavobacterium indologenes (Olsen et al., 1992).

Severe panophthalmitis and otitis interna were reported in a large group of recently imported fire-bellied toads (Bombina orientalis) (Brooks et al., 1983b). Corneal stromal infiltrates, scleritis, hyphema, hypopyon, iridocyclitis, cataract, and chorioraretinitis were prominent. Ophthalmicus, circling, head tilt, and loss of righting reflexes were associated with otitis interna. Several bacteria were cultured from affected eyes and normal viscera, including Aeromonas hydrophila, Citrobacter freundii, Providencia alcalifaciens, Klebsiella oxytoca, and an unidentified oxidase-positive, gram-negative bacillus, resistant to tetracycline. Both A. hydrophila and C. freundii have been implicated as causes of red-leg septicemia in anurans (Glorioso et al., 1974). Treatment of affected fire-bellied toads with oxytetracycline (26 mg/L of water) was not effective but may have prevented infection in normal toads (Fig. 33.8).

Periocular blood-filled blisters were reported in bullfrogs (Rana catesbiana) with classic red-leg septicemia due to A. hydrophila and C. freundii (Glorioso et al., 1974). Conjunctivitis, dacryocystitis, and uveitis have been associated with individual frogs with unspecified systemic infections (Williams & Whitaker, 1994).

Topical treatment of presumptive or proven bacterial ocular infections in amphibians must be undertaken with recognition of the potential for systemic toxicity. Gentamicin diluted to 2 mg/mL has been recommended (Williams & Whitaker, 1994). Parenteral antibiotic or corticosteroid administration may be preferable because an exact dosage may be delivered.
With ulcerative keratitis, the false third eyelid may be sutured to the upper lid for protection (Williams & Whitaker, 1994). Butylcyanoacrylate tissue adhesive has been used to stabilize deep corneal ulcers (Williams & Whitaker, 1994) (Fig. 33.9).

Corneal opacities in amphibians have several potential causes. The most extensively reported and investigated disorder is lipid keratopathy. Originally discovered in Cuban tree frogs (Osteopilus septentrionalis) (Carpenter et al., 1986; Russell et al., 1990), it has since been identified in species of captive hylid, leptodactylid, and ranid frogs either as a corneal and hepatic lesion or as part of a generalized xanthomatosis affecting brain, some viscera, peripheral nerves, periarticular soft tissues, and digital pads (Millichamp et al., 1990). Hypercholesterolemia has been noted in animals with disseminated xanthomatosis (Russell et al., 1990). Clinically, dense white stromal opacities are seen, often raised with corneal thickening and surface epithelial irregularity (Fig. 33.10). Stromal neovascularization and superficial pigmentation may be present (Millichamp et al., 1990). In advanced cases, the densest opacities are in the central cornea. Histologically, empty cholesterol clefts within keratocytes and between corneal collagen lamellae are present with occasional foamy macrophages in the stroma and between epithelial cells. Corneal endothelial vacuolation was present in severely affected frogs. Biochemical analysis of affected corneas and livers showed elevated levels of cholesterol esters. Affected frogs have all been females, many with massive egg development, suggesting that excessive lipid mobilization associated with oogenesis may play a role. Dietary fat has been suggested as a factor, but affected animals have been fed several different diets. In an experimental study of Cuban tree frogs fed normal or high-cholesterol diets, corneal lipidosis was more prevalent in but not confined to frogs on the high-cholesterol diet; affected frogs of both sexes had elevated serum total cholesterol and low-density lipoproteins compared to unaffected frogs. Increased serum cholesterol was not associated with vitellogenesis in female frogs in this study (Shilton et al., 2001).

Buphthalmos with glaucoma was seen in a captive toad 
(Bufo bufo) (Williams & Whitaker, 1994). Globe enlargement prevented complete globe retraction into the orbit, which interfered with swallowing. Because of concerns about swallowing difficulties following enucleation, globe protection was achieved alternatively by suturing the false nictitating membrane across the cornea.

Cataracts have been noted regularly by some observers (Williams & Whitaker, 1994), occurring both in conjunction with other ocular disorders of the anterior segment and alone. Phacoemulsification was successfully performed on a loggerhead sea turtle (Caretta caretta) (Kelly et al., 2005). Dendrobatid frogs receiving 5% dextrose supportive therapy rapidly developed reversible cataract (Williams & Whitaker, 1994).

Reports of neoplasia in amphibians are rare but include an ophthalmic adenocarcinoma in an African clawed frog (Xenopus laevis) (Williams & Whitaker, 1994) and a corneal and retrobulbar epithelioma in a grass frog (Rana temporaria) (Reichenbach-Klinke & Elkan, 1965).

**REPTILES**

**Ophthalmic Anatomy**

Four of the five orders within the class Reptilia have anatomically similar eyes: lizards, chelonians, crocodilians, and the tuatara. The fifth order, snakes, lost the prototype reptilian anatmical pattern during a fossorial period in their evolution, only to reevolve eyes with certain differences from other reptiles. Features of the external eye and adnexa have great clinical significance. In most reptiles, except snakes and certain ablepharine skinks, the upper and lower eyelids are
well developed, the lower being the more mobile. Crocodilians possess a bony tarsus in the upper lid. The eyelids of chameleons are constricted around the cornea and move with the very mobile globe. In some lizards of the families Lacertidae, Scincidae, and Teiidae, the lower lid is variably transparent. Snakes and ablepharine geckos and skinks possess a spectacle covering the cornea, developed from fused eyelids and separated from the cornea by an epithelial-lined subspectacular space. This tertiary spectacle contains an extensive vascular network, optically transparent but demonstrable by microsilicone injection (Mead, 1976). The anterior layers of the spectacle are shed during normal ecdysis with the rest of the skin (Maderson, 1965). Prior to ecdysis, the spectacle becomes cloudy due to thickening and breakdown of skin layers, with accumulation of fluid between the new surface layer of the spectacle and the old. The spectacle is transparent immediately before its surface is shed. During the period the spectacle is cloudy, the animal is blind; many species become more irritable and aggressive during this period. The spectacle is impervious to topically applied medications; thus, topical ocular therapy is ineffective. The biometry of the eyes and spectacles of four species of snakes has been recently described using high frequency ultrasound imaging (Hollingsworth et al., 2007). The ocular surface in reptiles is bathed by fluids secreted by lacrimal (except snakes) and harderian glands. The latter are large in chelonians, especially in marine species; the lacrimal gland functions as an extrarenal site of salt excretion (Dunson, 1976). The nasolacrimal duct, absent in cheloni ans, drains from the medial canthus to the roof of the mouth to emerge at the base of or behind the vomeronasal organ. The detailed anatomy of the head of boa constrictors has been recently described using conventional radiography, computed tomography, and dissection (Banzato et al., 2011). The ocular morphology of the leatherback sea turtle has been described in detail (Brudenall et al., 2008).

A natomic features of the globe that distinguish reptiles include poorly developed rectus muscles (except in lizards), well-developed retractor bulbi muscle (except in snakes), and limited rotational movements (except in chameleons) (Fig. 33.11). Hyaline cartilage is present in the sclera of lizards and chelonians from the equator to the posterior pole, with scleral ossicles extending to the limbus anteriorly from the equator. These form a sclerocorneal sulcus, giving shape to the anterior segment and apposing the ciliary body to the lens equator, which provides leverage for action of the ciliary muscle. Snakes lack both scleral ossicles and cartilage and crocodilians lack scleral ossicles. Morphometric analysis of the corneal endothelium of caiman (Caiman yacare) using scanning electron microscopy showed primarily hexagonal cells, with a cell density similar to crocodiles but higher than that of one gecko species (Pigatto et al., 2004). The soft pliable lens of crocodilians and lizards has an equatorial pad, which is absent in snakes and poorly developed in chelonians.

Accommodation in most reptiles (except snakes) occurs by pressure exerted by the ciliary body, mediated by the ciliary muscle, against the lens equator to increase anteroposterior diameter of the lens. Ciliary processes are fused to the lens equator. The lenses of chameleons (Chamaeleo dilepis) have

**Figure 33.11.** The lacertilian eye (diagrammatic). (Adapted from Duke-Elder Stewart. System of Ophthalmology, Vol 1, The Eye in Evolution, Kimpton, London, 1958.)
a negative refractive power, unlike other vertebrate eyes, and are capable of very rapid accommodation (up to 60 D per second) and very broad accommodative range (up to 45 D) (Ott & Schaeffel, 1995). A accommodation in snakes appears to occur by forward movement of the lens accomplished indirectly by increased pressure on the vitreous applied by a stiff iris (Schwab, 2011). Refractive and anatomic studies of crocodilians suggest that they focus images well in air but are severely defocused underwater, where other sensory systems must be operative for prey location (Fleischman et al., 1988).

The iridocorneal angle resembles the mammalian pattern but is not as well developed. In young growing American alligators (Alligator mississippiensis), mean IOP measured by applanation tonometry (TonoPen II, Oculab, Glendale, CA) was approximately 16 mm Hg (range 5–35 mm Hg) and was inversely correlated to body length and presumably age. Gender differences were not identified (Whittaker et al., 1995). Normal IOP values have been reported for yellow-footed tortoises (Geochelone denticulata), approximately 14 mm Hg (Selmi et al., 2003), red-footed tortoises (Geochelone carbonaria), values similar to yellow-footed tortoises (Selmi et al., 2002), and juvenile loggerhead turtles, values significantly lower than these tortoises (Chittick & Harms, 2001). Iris color, pupil shape, and uveal vascular pattern in reptiles are variable. In general, diurnal lizards have round pupils and nocturnal lizards and crocodiles have vertically elliptical pupils. Ciliary processes are present in all reptiles except lizards. The general pattern of iris vascularity is two arteries entering the iris stroma temporally and inferiorly, running circumferentially, then forming a capillary plexus around the iris sphincter. A radial plexus of superficial iris veins is visible. Both ciliary and iris sphincter muscles are striated; thus, mydriasis is not achieved by parasympathomimetic drugs. Mydriasis can be achieved by general anesthesia or by intracameral injection of curariform drugs. In red-eared slider turtles (Trachemys scripta elegans), topical application of 0.4% vecuronium bromide four times at 15-minute intervals increased pupil size by 28%, whereas atropine had no effect (Dearworth et al., 2007). A parallel trial in the same species documented that topical 2.5% phentolamine administered every 15 minutes for four doses dilated the turtles’ pupils and that a combination of 2.5% phentolamine with 0.4% vecuronium bromide dilated pupils more rapidly but to the same degree as phentolamine alone. These findings suggest the potential presence of a smooth dilator pupillae muscle in turtles that has not been confirmed anatomically (Dearworth & Cooper, 2008).

The avascular retina is supplied by the chorioid in all reptiles. All have a choriocapillaris and, during ocular development, a transient intravitreal hyaloid vascular system (Bellhorn, 1997). In lizards, this is complemented by a vascular conus papillaris derived from the hyaloid vasculature; it projects from the optic nerve head into the vitreous, in some species as far as the posterior pole of the lens and is presumed to have a nutritive function. In alligators, turtles and tortoises, the retina is totally dependent on the choriocapillaris after the hyaloid system regresses; the alligator does have a conus that regresses. Snakes possess a conus during ocular development, but it regresses in most. In a few (e.g., vipers), the conus persists. In all snakes, a permanent preretinal vascular meshwork develops from the embryological hyaloid. In one colubrid (Tarbophis), this meshwork subsequently becomes an intraretinal vascular system known only in eels and few mammals (Bellhorn, 1997). In crocodilians, guanine crystals and calcium salts of guanine in the retinal pigment epithelium form a semicircular superior retinal tapetum (Ollivier et al., 2004b). The relative proportion of rod and cone photoreceptors varies among reptiles, probably correlated with their relative diurnal and nocturnal activity. A fovea is present in lizards and the tuatara. The distal end of the ellipsoid of lizards, but not snakes, contains oil droplets. Chelonians have predominantly cones; crocodilians have predominantly rods, as well as a few cones without oil droplets. Some snakes have a primarily or purely cone retina. Retinal response to dark and light adaptation by cone contraction and pigment epithelial migration is minimal in reptiles.

Ophthalmic Diseases

The important ocular disorders of reptiles have been reviewed (Frye, 1981, 1991; Millichamp et al., 1983; Williams, 1996). The reported ocular disorders of reptiles include malformations, infections, nutritional disorders, degenerations, neoplasia, and trauma.

Ocular Malformations

Malformations include anophthalmos, microphthalmos, cyclopia, exophthalmos, and corneal and pupillary defects. A nophthalmos and corneal and pupillary defects were clinically identified in a wild population of gharial (Gavialis gangeticus), an Indian crocodilian (Singh & Bustard, 1982a, 1982b). Microphthalmos occurs unilaterally and bilaterally alone or with other cranial malformations, including cleft jaw and palate, maxillary hypoplasia, and vertebral abnormalities (Bellairs, 1981; Enslay et al., 1978a; Millichamp et al., 1983). Solitary microphthalmos has been seen in a Nile crocodile (Crocodilus niloticus), an Indian gharial, a Burmese python, and a boa constrictor (Millichamp et al., 1983), and in clutches of red-headed ratsnakes (Elaphe moellendorfii) (Enslay et al., 1978a). In lacertid lizards (Lacerta spp.) and anacondas, microphthalmos was associated with other craniofacial anomalies (Bellairs, 1981). The clinical anophthalmos occasionally described in crocodilians, chelonians, and snakes may represent extreme nanophthalmos insofar as it is an exceedingly rare phenomenon in humans and other animals; unfortunately, histologic confirmation has not accompanied these reports (Frye, 1981; Millichamp, 1991; Singh & Bustard, 1982a). Cyclopia has been reported in pythons and turtles, often associated with microcephaly or other severe somatic abnormalities (Millichamp, 1991; Millichamp et al., 1983). Congenital exophthalmos was reported in a rhinoceros viper (Cooper,
Infections

Viral, bacterial, fungal, and parasitic infections have been reported as causes of ocular disease in reptiles. Herpesvirus infection in mariculture-raised green sea turtles (Chelonia mydas) between 56 days and 12 months of age caused extensive proliferative ulcerative skin lesions frequently involving the eyelids (gray patch disease and fibropapillomatosis). Intranuclear inclusions were noted histologically (Fig. 33.12). Secondary bacterial infections needed antibacterial therapy (Jacobson et al., 1986; Rebell et al., 1975). Herpesvirus infections have been associated with an ocular respiratory syndrome in several tortoise species and in green sea turtles (Coberly et al., 2001; Curry et al., 2000).

Captive spectacled caiman (Caiman crocodilus) infected by poxvirus developed raised skin papules initially confined to the eyelids (Fig. 33.13). Eosinophilic intracytoplasmic inclusions were present histologically. Spontaneous regression occurred (Jacobson et al., 1979). Infection by a herpes-like virus of Argentine and red-footed tortoises (G. chilensis and G. carbonaria, respectively) caused necrotizing stomatitis, ocular discharge (presumably from conjunctivitis), weight loss, and death (Jacobson et al., 1985).

Bacterial Infections

Bacterial infections have been associated with several ocular disorders. Bacterial blepharitis with abscess formation occurs commonly (Fig. 33.14). Abscesses are usually focal and contain inspissated pus. Both gram-negative (Escherichia coli, Pseudomonas) and acid-fast organisms have been implicated (Leonard & Shields, 1970; Millichamp, 1991; Millichamp et al., 1983). Surgical excision or draining and curettage are indicated. Abscesses that dissect through periocular tissues may cause exophthalmos, blepharedema, panophthalmitis, exposure keratitis, ocular perforation, or septicemia. Bacterial conjunctivitis, although rarely documented in the literature, is
probable cause of blepharoconjunctivitis in a laboratory colony of lacertid lizards (Cooper et al., 1980). Pseudomonas was incriminated as the cause of blepharoconjunctivitis in a colony of anoles (Anolis carolinensis). Conjunctivitis in desert tortoises (Gopherus sp.) with respiratory disease was ascribed to Pasteurella infection (Snipes, 1984). Pseudomonas was cultured from a retrobulbar abscess in a Jackson’s chameleon (Chamaeleo jacksoni) (Millichamp et al., 1983). A required surgical drainage was unsuccessful. A periorbital abscess resulting from Pseudomonas infection in another Jackson’s chameleon was successfully treated by excision and antibiotic therapy (Schumacher et al., 1996). Periorbital swelling in chameleons has several causes, including infections, contact irritants, hypovitaminosis A, foreign bodies, metabolic bone disease, and decreased ventilation and humidity (Coke & Couillard, 2002). Uveitis with hypopyon associated with bacteremia/septicemia is seen occasionally in reptiles. Hypopyon in four Tokay geckos (Gekko gekko) was secondary to Klebsiella pneumoniae infection (Bonney et al., 1978). Aeromonas was associated with hypopyon in an alligator (Millichamp et al., 1983) and Pseudomonas was the cause of uveitis in an Indonesian blue-tongue skink (Tiliqua gigas) (Millichamp et al., 1983). Hypopyon in a red-footed tortoise with pneumonia was ascribed to hematogenous spread of the respiratory infection (Tomson et al., 1976).

Subspectacular abscesses develop unilaterally or bilaterally secondary to ascending infection from the oral cavity through the nasolacrimal duct or from penetrating injuries to the spectacle or from systemic infections. Chronic stomatitis may be a predisposing factor in the former. Clinical signs include distension of the spectacle to cause apparent buphthalmos or exophthalmos and cloudiness. White or yellow exudate is often visible below the spectacle. Therapy is directed at establishing drainage by careful excision of a 30° wedge of inferior spectacle, culture and cytology of the expressed exudate for antibiotic sensitivity testing, and flushing of the space with antibiotic solutions (Miller, 1986; Millichamp, 1991; Millichamp et al., 1983). Bacterial isolates have included Pseudomonas and Proteus spp., and Providencia rettgeri (Millichamp et al., 1983). Hemoprotozoa are sometimes identified in the material; their presence is considered incidental, probably facilitated by inflammation of the blood vessels of the spectacle (Millichamp, 1991). Complete physical examination is warranted to identify oral abnormalities and systemic infections. Some cases resolve spontaneously without treatment, while others progress to corneal perforation and panophthalmitis despite appropriate treatment.

Blockage of the nasolacrimal duct occurs in snakes associated with congenital malformation, inflammation associated with necrotic stomatitis and subspectacular infections, and pressure from nearby tumors and granulomas (Millichamp, 1991) (Fig. 33.15). Sometimes termed pseudobuphthalmos (Boniuk & Lauquette, 1963), congenital and some acquired cases may resolve without treatment (Bellairs, 1981; Cooper, 1981) (Fig. 33.16). Discrimination from subspectacular abscess is potentially difficult on inspection, except that simple obstruction causes spectacle distention at first with clear or slightly turbid fluid. Abscess formation may follow simple obstruction. If spontaneous resolution does not occur in a reasonable period, drainage by partial excision of the spectacle to establish drainage is indicated as for subspectacular abscess. Recurrence is possible. Spectacle wound healing in the royal python (Python regius) has been recently studied experimentally. After 25% of each spectacle was surgically removed, regeneration of a normal spectacle in the defect occurred by 3 months postoperatively. The healing process was documented by serial clinical examinations paired with histopathology (Maas et al., 2010). A blood python was treated...
by repeated surgical conjunctivoroastomy with some success (Millichamp et al., 1986). A dacyrocystitis syndrome reported in tortoises with foamy ocular discharge appears to be of questionable validity in view of the reported absence of a nasolacrimal duct in tortoises (Frye, 1981; Millichamp et al., 1983; Williams, 1996).

Panophthalmitis, generalized inflammation of the eye usually associated with infection, develops in reptiles secondary to perforating injuries and infections of the ocular surface and by hematogenous distribution with bacteremia/septicemia. Hypopyon may be extensive and periocular swelling may be dramatic. Any bacteria may be responsible; among others, Staphylococcus has been isolated from a tortoise (Holt et al., 1979). Enucleation may be the most expedient and humane treatment for reptiles without systemic infections. Performed similarly to the procedure in mammals, reptile enucleations may present the challenge of adequate closure of skin over the orbital defect (Zwart et al., 1973). Sliding skin grafts may be necessary (Frye, 1981).

**Fungal Infections**

Fungal infections may cause superficial or deep ocular disease. Fungal infections of the skin may extend onto the spectacle in snakes or the eyelids in chelonians (Millichamp, 1991; Millichamp et al., 1983). Traumas to green sea turtles and damp environments in captive snakes have been identified as predisposing factors. Cultures from skin may not yield growth; skin biopsy may be necessary to identify the nature of the infection. Correction of environmental deficiencies may be adequate treatment; snakes may then shed infected skin with the next ecdysis. Snakes can be soaked in dilute chlorhexidine (0.26 mL/L of water) for 1–2 hours daily. Pacific island boas in a zoologic collection with spectacle involvement by mycotic dermatitis died with fungal pneumonia (Millichamp, 1991). Katoconjunctivitis was unsuccessfully treated by soaking in a 1-inch dichlorvos strip suspended in a perforated container in the cage for 2–3 days followed by cage disinfection and repeat treatment 14 days later (Millichamp, 1991). Alternatively, covering the animal with a thin film of olive oil (to asphyxiate the mites) or spraying with a pyrethroid (not pyrethrins) mite spray have been recommended as safer than organophosphate treatment (Mader, 1996). Ticks occasionally are found in this location in newly imported snakes; manual removal is necessary with local treatment as needed. Unidentified nematode larvae were found densely packed in the choroid of a red-eared slider (Pseudemys scripta elegans) on histologic section (Millichamp et al., 1983). Swollen eyelids associated with infestation with Foleyella, a filarial nematode, were managed in a wild-caught Oustalet’s chameleon (Chamaeleo oustaleti) by incision and removal on two occasions 4 months apart. At each surgery, five adult worms of both sexes were removed. The chameleon had received thiaibendazole as a parasiticide following importation (Thomas et al., 1996). Neopolystoma elizabethae was recovered from the conjunctival sac of Western painted turtles (Chrysemys picta bellii) in Michigan (Platt, 2000).

**Neoplasia**

Fibromas, fibropapilomas, and fibrosarcomas develop on the integument of green sea turtles as part of a proliferative connective tissue response to the eggs of the trematode *Laraedius laraeadii*, which lodge in small vessels of the skin and conjunctiva after hematogenous release from the parasite. Tumors may involve eyelids and conjunctiva (Brooks et al., 1994; Millichamp et al., 1983). A keratoacanthoma involving the entire spectacle associated with multiple retained spectacles was reported in a royal boa (Constrictor constrictor) (Harden et al., 2007). A lacrimal cystadenoma was surgically removed from a Chinese box turtle (*Cuora flavomarginatus*) (Kottwitz et al., 2008). A periocular squamous cell carcinoma in a veiled chameleon (*Chameleo calyptratus*) was treated surgically with good results (Abou-Madi & Kern, 2002).

**Degenerations**

Lenticular degeneration with opacification, cataract, occurs sporadically in reptiles, especially snakes and tortoises, probably for most of the same reasons mammals are afflicted. Cataract in very aged captive specimens has been noted. Secondary cataract caused by uveitis or perforating injuries is common. Posthibernation blindness due to cataract development, vitreal opacification, and central nervous system deficits in European tortoises has been reported (Millichamp, 1991).
Phacoemulsification was performed on an adult savannah monitor lizard (Varanus exanthematicus) (Colitz et al., 2003). Iris cysts were incidental findings at necropsy in a Western fence lizard (Frye, 1991). Dacryops in an aged red-eared slider turtle (Chrysemys scripta elegans) was successfully managed by surgical excision (Allgoewer et al., 2002).

Retinal degenerations have rarely been identified or reported, certainly explained by the difficulty of examination. Focal altered fundus pigmentation and presumed multifocal retinopathy has been observed or suspected by a few clinicians (Frye, 1981; Millichamp, 1991). Retinal degeneration was documented histologically in a reticulated python that died of cerebrovascular thrombosis (Millichamp et al., 1983).

Retained Spectacles

Retained spectacles in snakes present a challenge to manage. The causes of retained spectacles include generalized integumentary disease, dry environment, local injury to the spectacle, mite or tick infestation, and systemic illness. Over several ecdysis cycles, a thick layer of old spectacles accumulates. Spectacle opacification may render the snake blind in one or both eyes and unable or unwilling to feed. Conservative management is often effective and is safest, consisting of increasing humidity in the environment by misting or soaking the snake and lubrication with ophthalmic petrolatum ointment promoting natural shedding during the next cycle. If unsuccessful or if the spectacle has been previously damaged and is unlikely to be shed, application of acetylcysteine (Mucomyst; Mead Johnson Pharmaceutical Division, Evansville, IN) to the spectacle may loosen it enough to allow atraumatic removal with forceps. Extreme care must be taken to avoid corneal injury (Fig. 33.17).

Other Ophthalmic Diseases

Bilateral spectacle opacification in king snakes (Lampropeltis spp.) was suspected to be associated with exposure to organophosphate insecticide (Frye & Gillespie, 1984). Opacification and degeneration of the third eyelid in aged American alligators associated with calcium or other deposition was reported (Millichamp et al., 1983). An idiopathic acquired orbital varix was treated by exenteration in a green iguana (Whittaker et al., 1997). Except for the trematode-induced cutaneous fibromas seen in green sea turtles, spontaneous neoplasia seems very uncommon in reptiles.

Traumatic injury no doubt accounts for a substantial proportion of ocular conditions in reptiles, whether as the only cause or as the inciting reason for infection or inflammation. Ocular lesions in farmed American alligators were ascribed to trauma from handling and overcrowding (Millichamp et al., 1983) (Fig. 33.18). Unilateral phthisis and corneal and anterior segment scarring of presumptive traumatic origin was reported in a small cohort of American crocodiles (Crocodylus acutus) in Costa Rica (Rainwater et al., 2011).

Photodermatitis and photokeratoconjunctivitis were reported in a collection of snakes and skinks associated with excessive exposure to artificial UV light (Gardiner et al., 2009).

Vitamin A Deficiency

Hypovitaminosis A is commonly recognized in chelonians. Most frequent in aquatic species, especially rapidly growing young turtles fed diets of meat and insects, the deficiency causes squamous metaplasia of the orbital glands and their ducts (Elkan & Zwart, 1967). The glands increase in size as desquamated cells block their ducts. The eyelids become

Figure 33.17. Snake (Cnido species) with multiple retained spectacles (courtesy of Dr. Nicholas Millichamp).

Figure 33.18. American alligator. Healed traumatic corneal perforation.
edematous and blepharoconjunctivitis ensues. The palpebral fissure becomes closed, and secondary bacterial conjunctivitis and keratitis are common (Fig. 33.19). Concomitantly, squamous metaplasia of renal, pancreatic, gastrointestinal, and respiratory epithelia progress to fatal consequence. In the early stages of the disease while animals are still eating, a change of diet to commercial trout pellets supplemented with cod liver oil initially can reverse the problem. Later, parenteral vitamin A (1000–5000 IU) (Aquasol-A-USV Pharmaceutical, New York) is recommended weekly until resolution (Millichamp, 1991; Williams, 1996). Topical antibiotic ointment is recommended to control bacterial infection (Millichamp, 1991).

**BIRDS**

**Ophthalmic Anatomy**

Upper and lower eyelid and membrana nictitans are present. The lower lid is more mobile than the upper, usually containing a fibroelastic tarsal plate. The nictitans is well developed, actively mobile, nearly transparent, thin, and covered by a papillary layer of epithelium. Drawn from the medial canthus, the nictitans is moved by contracture of the pyramidalis muscle that originates from the posterior pole sclera where it loops through a sling formed by the quadratus muscle; both are innervated by cranial nerve VI. Both muscles may be derived from the crocodilian retractor bulbi muscles otherwise absent in birds. The oblique and rectus muscles are thin and relatively poorly developed. Melobomian glands are also absent. The lacrimal gland is located inferotemporal to the globe, and a harderian gland is found adjacent to the posterior sclera near the base of the nictitans but not part of it. Two lacrimal puncta drain lacrimal secretions into a nasolacrimal duct and then to the nasal cavity (Wood, 1915). The orbit is typically but not universally incomplete, large, and open; it can be evaluated radiographically (Paul-Murphy et al., 1990). Interspecies variation in orbital bone structure of psittaciform birds has been described in detail. After 27 skulls from 14 species of psittacines were analyzed, they were classified into two groups. One group had a complete enclosed bony orbit formed by the junction of the orbital and postorbital processes forming a suborbital arch. The second group lacked the suborbital arch and had an open incomplete bony orbit typical of most modern birds; even in this group, orbital and postorbital processes were present (Machado et al., 2006).

The globe is very large relative to body size (Fig. 33.20 and Fig. 33.21). The posterior segment is relatively much larger than the anterior segment. Three basic shapes are typical: (1) flat, with a short anteroposterior axis and a flat or partly concave ciliary region (intermediate segment) in the center of which the cornea protrudes, with a hemispheric posterior segment, the most common shape; (2) globose, in which the ciliary region protrudes further from the posterior segment while remaining somewhat concave is present in many diurnal birds needing high-resolution distance vision (e.g., crows, insectivorous wing-feeders, diurnal raptors); and (3) tubular (such as in owls), in which the concave intermediate segment is elongated anteroposteriorly, forming a tube before joining the posterior segment at a sharp angle (Duke-Elder, 1976; Walls, 1942). The shape of the globe is formed and maintained by hyaline cartilage in the sclera of the posterior segment and by 10–18 scleral ossicles (sometimes pneumatic) in the sclera of the intermediate segment. The cornea has the same layers as in mammals. In vivo confocal microscopy of the corneas of five birds of different species confirmed this and identified a Bowman’s-like layer (Kafarnik et al., 2007). Conjunctiva-associated lymphoid tissue in poultry is important in mucosal immunity (Fix & Arp, 1989, 1991). The iris contains striated sphincter and dilator muscles and myoepithelium and smooth muscle, and its stroma harvests several pigments responsible for variable iris coloration (Chiasson & Ferris, 1968; Chiasson et al., 1968; Randall & McLachlan, 1979). The circular pupil is subject to influence from retinal stimulation as well as voluntary control. Iris vascularization is similar to that in lizards. The iridocorneal angle is well developed and drained by two annular channels. The lens is soft, pliable, and of variable shape—spherical in nocturnal species, flattened anteriorly in some diurnal species. An equatorial annular pad formed of modified lens fibers is present and may be very prominent. Between the central body of the lens and the annular pad is a fluid-filled cleft or lenticular space. Though not serving a direct optical role, the annular pad serves an important function in accommodation and may have a nutritive role in lens metabolism. Its size is generally related to the accommodative range of the lens, which varies with species. Except in diving birds, the pad is largest in birds with the widest range of accommodation, (e.g., diurnal birds of prey, other fast-flying species). The smallest are present in nocturnal species with small accommodative ranges. Accommodation in birds involves changes in corneal...
curvature, anterior movement of the lens, and lens deformation. Lens power is increased by contraction of the striated meridional ciliary muscles—Brucke’s muscle posteriorly and Crampton’s muscle anteriorly (which inserts on the peripheral cornea) move the ciliary body axially, compressing the lens by exerting pressure on the annular pad. Crampton’s muscle contraction may flatten the peripheral cornea (Murphy & Dubielzig, 1993). In the chicken and pigeon, changes in corneal curvature account for half or more of the 15- to 17-D accommodative range of the eye (Schaeffel & Howland, 1995). In one investigation of avian accommodation, the accommodative range of 15 species of owls was from 0.7 D to greater than 10 D (Murphy & Howland, 1983). Lower-visual field myopia present in some birds (chickens, pigeons, quail) but absent in raptors allows them to keep the ground in focus while performing other tasks (Murphy et al., 1995). Aquatic birds, in which the corneal accommodative mechanisms are neutralized under water, have accommodative ranges up to 50 D (Katzir & Howland, 2003). In chickens, pigeons, and kestrels, the ciliary muscle fibers predominate in the anterior muscle fiber groups, suggesting an emphasis on corneal accommodation, whereas in the hooded merganser, the majority of fibers are in the internal and posterior muscle fiber groups, suggesting that lenticular accommodation predominates (Pardue & Sivak, 1997). The numerous ciliary processes are tightly fused to the equatorial lens capsule.

In a study of the development of retractive state in the eyes of ostrich chicks, their eyes were 4.5-D myopic at hatching
and by day 7 after hatching, six were slightly hyperopic and changed little after this time point (Ofri et al., 2001b).

The retina is avascular and atapetal but has a well-developed choroid and pecten (Bellhorn, 1997; Duke-Elder, 1976; Walls, 1942). The pecten is a highly vascular pigmented structure of greatly variable size extending into the vitreous from and obscuring examination of the optic nerve head. A vascular mesodermal core overlying neuroectodermal cells, as in reptiles, the avian pecten differs from the purely mesodermal falciform process of fish. The pecten probably has a primary nutritive function but has been credited with over 30 possible functions. Considerable variation in photoreceptor type and density exist. Some species (most domestic species) are afoveate, others are monofoveate, and some are bifoveate (hummingbirds, some raptors and passerines) (Tucker, 2000). The three-dimensional anatomy of the retinas and foveas of four species of raptors has been investigated using ultra-high resolution optical coherence tomography in vivo (Ruggeri et al., 2010). Both rods and cones are present (including double cones with oil droplets); proportions vary with the species’ visual ecology. Some avian species possess UV vision, the function of which is uncertain. One hypothesis is that UV vision functions in orientation for foraging and signaling (Bennett & Cuthill, 1994). Pigment epithelial processes contain pigment granules and respond to light by elongation between rods. The fundus appearance in vivo is a gray or red background speckled with heterogeneous pigmentation through which choroidal vessels may be seen in some species. The choroid of the chicken contains a conspicuous system of thin-walled lacunae not seen in mammalian choroid, which may represent short lymphatic vessels (DeStefano & Mugnaini, 1997). Subcutaneous periocular and cervicothoracic sinuses that communicate with the respiratory system are present in psittacines and some other species (Kern, 1997). Paranasal sinus anatomy of 10 macaws representing four species was investigated using computed tomography, skeletal studies, histology, and deep-frozen tissue sections, and identified two unpaired rostral compartments and eight paired caudal compartments (Artmann & Henninger, 2001).

**Ophthalmic Examination**

Clinical examination of avian eyes utilizes the same instrumentation and diagnostic techniques as in mammals, albeit with modification dictated by the size of the eye and physiological characteristics of the iris. Basic instrumentation should include a bright focal light source (e.g., transilluminator); a low-power magnifying head loupe; from 28-D to 30-D, 40-D, or 60-D indirect condensing lenses (Volk Optical, Mentor, OH) and a direct ophthalmoscope. Acessory diagnostic aids include fluorescein dye strips, STT strips (Iolab Pharmaceuticals, Claremont, CA) phenol red threads (Zone-Quick, Menicon Company, Nagoya, Japan), culture swabs (MiniTip Culturette, Becton-Dickinson, Cockeysville, MD), microscope slides, sterile scalpel blades for conjunctival and corneal cytology collection, and an applanation and/or rebound tonometer (Tono-Pen-VET, Reichert Technologies, Depew, NY; TonoVet, Icare, Finland). When available, slit-lamp biomicroscopy and ocular ultrasonography potentially enhance the diagnostic yield. Complete ocular evaluation of birds includes a history, functional examination, and morphologic examination. The history should include pursuit of management techniques, husbandry, prior health history, and current ocular and systemic signs. It should be revisited, expanded, or investigated further after functional and morphologic ocular assessment.

Avian responses to the eye-related reflexes differ from those of mammals in some respects. Palpebral response is present with the lower lid covering the globe more extensively than the upper lid; membrana nictitans excursions are prominent. Menace responses seem inconsistent even in birds with evidently normal vision; thus, absent menace response has little diagnostic significance. Avoidance behavior is a more reliable indicator of vision than menace reflex. Because retractor bulbi muscles are absent in birds (replaced by the quadratus and pyramidalis muscles that subserve membrana nictitans motility), globe retraction is not a feature of eye-related reflex responses. The corneal reflex is present, manifested by blinking, nictitans excursions, and avoidance behavior. Direct pupil light reflex is present. Its assessment is often problematic owing to presumptive voluntary control of the striated components of the iris musculature and the emotional state of the bird. Slight, intermittent, dynamic anisocoria may be normal. Because of complete decussation of optic nerve fibers, consensual pupillary light responses are not expected in birds (Levine, 1955). A rifactual consensual responses may be induced by inadvertent stimulation of the retina of the fellow eye during elicitation of the direct pupillary response through the posterior pole of the stimulated eye and the thin interosseus septum separating the two orbits (Levine, 1955). Recently, this theory has been challenged by experiments in chicks undergoing unilateral optic nerve transection (Li & Howland, 1996). In operated chicks, pupillary constriction occurred in operated eyes when direct pupillary responses were stimulated in the normal fellow eye.

Posterior segment examination in birds is confounded by difficulty in achieving mydriasis. Parasympatholytic agents are ineffective because of the complex muscular arrangement of the iris. Predominantly striated in nature, the iris muscles may be partially paralyzed by neuromuscular paralyzing agents. Intracameral injection of d-tubocurarine, a nondepolarizing neuromuscular blocking agent, has been reported to cause consistent moderate to maximal mydriasis in pigeons and several raptor species (Murphy, 1987; Verschueren & Lumeij, 1991). Topical application of tubocurarine (3 mg of tubocurarine powder per milliliter of 0.025% benzalkonium chloride solution) instilled three to four times over 20 minutes resulted in partial mydriasis in some species but not others (Bellhorn, 1973). Mydriasis was consistently and safely achieved in European kestrels (Falco tinnunculus) by topical administration of vecuronium bromide (4 mg/mL) (Norcuron, Organon Tekneika, France), two drops every 15 minutes for
three instillations applied to one eye only (Mikaelian et al., 1994). Maximal mydriasis occurred about 1 hour after treatment and was maintained for 4 hours. Alcuronium chloride (5 mg/mL) (Aloferine®, Roche, France) given 1 drop (0.05 mL) unilaterally twice at 15-minute intervals resulted in mydriasis for up to 3 hours, but most birds developed eyelid paralysis; one also developed neck and hind limb paralysis (Mikaelian et al., 1994). Pancuronium bromide (2 mg/mL) (Pavulon®, Organon Tekneika, France) administered unilaterally (two drops twice, 15 minutes apart) had an inconsistent mydriatic effect; most birds did not achieve maximal mydriasis (Mikaelian et al., 1994). Note that the safety of simultaneous bilateral topical ophthalmic administration of these drugs was not investigated in this study. Three curariform (d-tubocurarine, pancuronium, and vecuronium bromide) and two autonomic drugs (atropine and phenylephrine) were evaluated for topical use with and without addition of surface-active penetration agents (saponin or benzalkonium chloride) in three species of large psittacines (Ramer et al., 1996). One mydriatic effect; most birds did not achieve maximal mydriasis (Mikaelian et al., 1994). Note that the safety of simultaneous bilateral topical ophthalmic administration of these drugs was not investigated in this study. Three curariform (d-tubocurarine, pancuronium, and vecuronium bromide) and two autonomic drugs (atropine and phenylephrine) were evaluated for topical use with and without addition of surface-active penetration agents (saponin or benzalkonium chloride) in three species of large psittacines (Ramer et al., 1996). One eye of each bird was tested. Vecuronium (0.8 mg/mL, two drops administered twice 2 minutes apart) without an enhanced penetration agent produced the most consistent and greatest mydriasis with the fewest systemic side effects in all three species. A mazon parrots treated with this protocol developed mild transient systemic side effects. Administration of vecuronium with 1% saponin was fatal to one cockatoo. Topical pancuronium caused mild to severe systemic effects in some cockatoos. Note that the safety and efficacy of bilateral simultaneous administration was not evaluated in this study.

In juvenile double-crested cormorants (Phalacrocorax auritus), mydriasis was best achieved with a combination of 1% topical atropine, 2.5% phenylephrine, and 4 mg/mL of vecuronium (Loerzel et al., 2002).

Topical vecuronium bromide (Esmeron®, Organon Italia S.p.A. Rome, Italy) caused significant mydriasis in tawny owls (Strix aluco), common buzzards (Buteo buteo), and little owls (Athene noctua) after one application in 40–110 minutes (Barsotti et al., 2010a, 2010b).

Variable mydriasis can be fairly consistently achieved under general anesthesia. In raptors, short-acting anesthesia consists of 10–15 mg/kg ketamine hydrochloride (Vetamine®, M allinckrodt Veterinary, M undelein, IL) and 1–2 mg/kg xylazine (Rompun®, Bayer A nimal Helath, Shawnee M ission, K S) (Greenwood & Barnett, 1981).

Tonometry poses certain difficulties in birds. The small size of the eye and cornea of most species of interest makes Schiotz tonometry difficult to impossible. Conventional tonometers have not been validated for use in birds as they have for dogs and cats. High corneal and scleral rigidity compared with mammalian eyes no doubt affects the reliability and interpretive value of the measurements in birds. IOP of normal turkeys measured approximately 25 mm Hg by applanation (Mackay-M arg tonometer, Cooper Vision Systems, Biotronics, Irvine, CA) (Davis et al., 1986). The range of IOPs measured by applanation in a large group of raptors was 11–16 mm Hg (TonoPen II, Oculab, Glendale, CA; Cavitrion Biotronics Ultra-A pplanation Tonometer, BioRad Labs, Rockville Center, NY) (C.J. Murphy, personal communication). In a series of tonometric examinations of 275 normal birds of 39 species and eight orders using the TonoPen device, IOPs measured 9.2–16.3 mm Hg (Korbel, 1993). Reproducible readings were obtained from eyes with a minimal corneal diameter of 9 mm (A mazon parrot eye). Reproducibility was limited to a corneal diameter of 5 mm (cockatiel eye), and below 5 mm (budgerigar eye) measurements were unreliable. In a study of tonometry in raptors, IOPs measured by TonoPen averaged 20.6–21.5 mm Hg in red-tailed and Swainson’s hawks and golden and bald eagles, significantly higher than in great-horned owls (Stiles et al., 1994). For unexplained reasons, consistent measurements could not be obtained in barn owls. IOPs measured by Schiotz tonometry have been reported to be from 15 to 17 mm Hg in hawks and 20 mm Hg in chickens (Schmidt & Seidel, 1988). Reference values for IOP using rebound tonometry in ten raptor species have been reported (Reuter et al., 2011). Compared to applanation tonometry, rebound tonometry significantly overestimated IOP in Eurasian eagle owls (Bubo bubo) (Jeong et al., 2007).

Rebound tonometry demonstrated species-specific deviation from manometric IOP measurements in eight raptor species (Reuter et al., 2010).

STT values without (STT I) and with (STT II) topical anesthesia have been reported in 42 species of birds in seven orders. Values for psittacines (±standard deviation, SD) for STT I and II were approximately from 3 to 7 ± 2 mm/min and from 1.7 to 4.5 ± 2 mm/min, respectively. Values for falconiforms for STT I and II were from 4 to 14 ± 7 mm/min and from 2 to 4 ± 3 mm/min, respectively (Korbel & Leitenstorfer, 1998). Normal values for the PRTT were determined for two groups of large psittacines. Mean PRTT values for the two groups were approximately 20–25 mm/15 seconds but repeatability was low (Holt et al., 2006). STT and PRTTs were performed before and after topical anesthesia in A mazon parrots. Topical anesthesia did not significantly affect PRTT values (mean 12.5 mm/15 seconds) but did affect STT values (mean 7.9 mm/min before and 5.1 mm/min after anesthesia) (Storey et al., 2009).

The ultrasonographic anatomy and biometry of the striped owl’s eye (Rhinoptynx clamator) and the blue-fronted A mazon parrot (A mazona aestiva) have been described (Lehmkuhl et al., 2010; Squarzoni et al., 2010). The examination results of implementation of complete diagnostic protocols to survey ocular disease in captive and free-living raptors have been recently described (Harris et al., 2008; Labelle et al., 2011).

A protocol for electroretinography (ERG) and oscillatory potential recordings of Hispanic A mazon parrots (A mazona ventralis) showed that the latencies of a- and b-waves and amplitudes of dark-adapted b-waves of the parrots were similar to those of normal dogs. The light-adapted a- and b-waves of the parrots had greater amplitudes than the corresponding values of dogs. Oscillatory potentials were composed of three or four peaks (Hendrix & Sims, 2004).
Ophthalmic Diseases

The spontaneous clinical disorders of birds, especially raptors and cage birds, have been the subject of several excellent reviews (Buyukmihci, 1985; Buyukmihci et al., 1988; Greenwood & Barnett, 1981; K ern, 1997; K ern et al., 1996; M urphy, 1987; M urphy et al., 1982a; M ustaffa-B ajbee, 1969; S mall & B urke, 1982; W illiams, 1994). Avian ocular disorders may be generally albeit imperfectly categorized as malformations, inflammations, infections, degenerations, neoplasia, nutritional disorders, and traumatic injuries.

Developmental Malformations

Developmental malformations have been reported infrequently. In one series of ocular anomalies in 16 raptors, the most common lesion was microphthalmia (Buyukmihci et al., 1988). Cataract, microphakia, retinal dysplasia, ciliary body, choroid, pecten malformation, and lentoid formation occurred with undetermined etiology. Bilateral partial upper eyelid agenesis was found in a captive-bred peregrine falcon and was repaired by permanent lateral canthorrhaphy (Kern et al., 1985). Cryptophthalmos occurs sporadically in cockatiels in which surgical correction has usually failed to reconstruct an anatomical eyelid margin and palpebral fissure (Buyukmihci et al., 1990). Congenital symblepharon was reported in a cockatoo chick (Buyukmihci et al., 1990). Corneal dermoids were reported in a goose in which feathers grew from the aberrant skin on the temporal cornea (Busch, 1985). A unilateral corneoonjunctival dermoid was successfully removed from a blue-fronted Amazon parrot (Amazona aestiva) (Leber & Bürge, 1999). Impatent nasolacrimal ducts were suspected in a cockatoo with choanal atresia, and ectropion was diagnosed in cockatiels (Williams, 1994). Cataract and optic nerve hypoplasia of unknown cause in turkey poults was reported in a commercial flock (B arr et al., 1988). Iris colobomas were seen in a flock of rosecomb bantam chickens (Cardona & Plumer, 2004). Photoreceptor dysplasia was diagnosed in two Tippler pigeons (M oore et al., 2004). Broiler chicks were presented blind due to panretinal dysplasia of possible genetic origin (Shivaprasad & K orb, 2003). In albino Japanese quail (Coturnix coturnix japonica), ocular nerve diameter is 25% smaller than in normal quail, with approximately the same number of (thinner) nerve fibers. Different from albinos of many other species, there was no reduction of ipsilateral retinofugal projections (Takatsuji & Nakamura, 1987). The same strain of quail was described with closed-angle glaucoma (Takatsuji et al., 1986). Retinal dysplasia was diagnosed in a hybrid falcon and a prairie falcon (Dukes & F ox, 1983; M urphy et al., 1985). Evidently congenital or perinatal retinal detachment of uncertain cause was found in 3%-5% of captive-raised pheasants (VanderK op, 1993). The rd (retinal degenerate) chicken is behaviorally and electrophysiologically blind at hatching despite an apparently normal-appearing retina (U lshafer & A llen, 1985; U lshafer et al., 1984). Partial retinal dysplasia and subsequent retinal degeneration were investigated in a mutant strain of chicken (rdd) (R andall et al., 1983). Chicks were blind and retinal detachment occurred in adults. Recessive mode of inheritance was suspected. A congenital or perinatal retinopathy purportedly different from the above two was reported in chickens in Britain (Curtis et al., 1987).

Experimental manipulation of environmental factors in growing chickens and turkeys has provided considerable information regarding normal eye growth and the ontogeny of emmetropization and refractive errors. Myopia and hyperopia have been induced in chick eyes of some strains with visual field occlusion, constant darkness, defocusing spectacle lenses, and constant light (K innear et al., 1974; Li et al., 1995), lid suturing (Lauber & Oishi, 1987), induction of thermal gradients within the eye (Hodos et al., 1987), and chemical retinal ablation (Wildsoet & Pettigrew, 1988). Astigmatism also develops with myopia and hyperopia (K ee & D eng, 2008). Raising chicks under constant light results initially in hyperopia (after 3 weeks) that subsequently becomes myopia (after 6 weeks) (Li et al., 1995). Strain differences are important insofar as similar environmental manipulations cause variable refractive errors (Li et al., 1995; Troilo et al., 1995). Turkey poults exposed to constant light developed buphthalmos and heavier eyes but retained normal IOPs (Davis et al., 1986).

Ophthalmic Inflammations and Infections

Ocular inflammation in birds originates from infections, both primary ocular and systemic diseases; nonseptic inflammation, including presumptively immune-mediated processes; and traumatic injuries. Photosensitization in ducks and chickens occurred following ingestion of the methypсорalen-containing plants, Ammi majus and Cymopterus watsonii (Egyed et al., 1975). Blepharoconjunctivitis, chemosis, keratitis, symblepharon, and dyscoria were prominent signs. Inflammation of the nasal salt gland in the superior orbit was noted in range-reared tom turkeys (Riddell & Roepke, 1991). The histological changes were characterized by predominantly nonsuppurative inflammation and epithelial hyperplasia. Etiology was not determined. Chorioretinitis and buphthalmos were found in turkey poults in Britain apparently unassociated with the lighting conditions used on the original turkeys (B arnett et al., 1971). Secondary angle-closure glaucoma was investigated in Slate turkeys in which uveitis developed consistently by 1 day of age and progressed to iris bombé and increased IOP and buphthalmos (de K ater et al., 1986). Severe lens-associated endophthalmitis was reported in a barred owl and a screech owl (A nderson & B uyukmihci, 1983; M iller et al., 1988). A transient idiopathic generally self-limiting punctate keratitis in A mazon parrots was described (K arpinski & Clubb, 1986). Topical antimicrobial therapy was ineffective. A small minority of birds developed deep corneal ulceration and anterior uveitis. Symblepharon developed in two snowy owl chicks (Nyctea scandiaca) following an episode of septicemia (W illiams & Flach, 2003).
The normal external ocular microflora of raptors (Dupont et al., 1994), captive cranes (Miller et al., 1995), psittacines (Zenoble et al., 1983), and a variety of exotic birds in public collections (Wolf et al., 1983) has been surveyed. In 55 of 65 raptors sampled bilaterally, bacteria and/or fungi were cultured (Dupont et al., 1994). Staphylococcus spp. predominated, found in 52% of cultures. Fungi (Aspergillus or Cladosporium) were cultured from only three eyes. In cranes, gram-positive organisms predominated (58% of isolates), represented by Corynebacterium spp., Staphylococcus spp., "hemolytic" Streptococcus spp., and Bacillus spp. The balance (42%) of isolates were gram-negative organisms, most commonly Enterobacter spp. and Pseudomonas spp. A tendency to multiple isolations (more than four) was noted in chicks. No age or species differences were evident. In healthy psittacines, no growth was found in 41% of cultured eyes (Zenoble et al., 1983). Staphylococcus epidermidis and "hemolytic" streptococci predominated. In the study of public collections, 83% of cultures yielded bacteria and 14% yielded fungi (Wolf et al., 1983). Seventy percent of the bacterial isolates were gram positive, with Staphylococcus and Corynebacterium predominating. Mycoplasma were not isolated despite special effort. A wide variety of gram-negative organisms were isolated. The fungal isolates were not specified.

Bacteria, fungi, viruses, protozoa, microsporidia, trematodes, and nematodes cause ocular disease in birds (Abrams et al., 2002) (Fig. 33.22 and Fig. 33.23). A cute severe fibrinopurulent blepharitis and conjunctivitis in chickens and turkeys were associated with infections with Staphylococcus hyicus, E. coli, and Streptococcus spp. (Cheville et al., 1988). Pasteurella multocida caused blepharoconjunctivitis and uveitis in turkeys (Olson, 1980). Panophthalmitis was a prominent feature of natural and experimental infection of broiler chickens with Salmonella arizonae (Silva et al., 1980). Actinobacillus spp. were recovered from native and exotic waterfowl with conjunctivitis (Hacking & Sileo, 1977; Madux et al., 1987). Staphylococcal blepharokeratoconjunctivitis was diagnosed in a large group of newly imported Amazon parrots (Shimakura et al., 1981). In captive Siberian and whooping crane chicks, an outbreak of Pseudomonas aeruginosa keratitis resulted in melting corneal ulceration and perforations (Miller et al., 1994). Visceral and corneal mycobacterial infections were diagnosed in a Maximilian’s parrot (Stanz et al., 1995). Mycobacterium avium was cultured from conjunctival granulomas on the third eyelid of an ostrich (Hood, 1978). Mycobacterial orbital infection was diagnosed in an Amazon parrot (Woerpel & Rosskopf, 1984) and the conjunctiva in two emus (Dromaius novaehollandiae) (Pocknell et al., 1996). The extensive cervicocephalic air sac system of psittacines is commonly involved in respiratory infections, leading to ophthalmic complications (Kern, 1997). Magnetic resonance imaging proved an excellent diagnostic tool for evaluation of intraorbital sinuses in psittacines with chronic sinusitis (Pye et al., 2000). Intraorbital sinus nocardiosis and supraorbital extension of sinusitis due to Pseudomonas aeruginosa were found in Amazon parrots (Baumgartner et al., 1994; Tully & Carter, 1993). Corynebacterium endophthalmitis, glaucoma, and scleral ossicle osteomyelitis were reported in a great-horned owl (MacLaren et al., 1995). Mycoplasma gallisepticum has caused keratoconjunctivitis in layer chickens and has been implicated in an epizootic of conjunctivitis in house finches and other species (Dhondt et al., 1998; Farmer et al., 2002, 2005; Hartup et al., 1998, 2001; Kollias et al., 2004; Ley et al., 1996, 2006; Luttrell et al., 1998; Mashima et al., 1997; Nunoya et al., 1995; Sydenstricker et al., 2005; Weldehan et al., 2001) (Fig. 33.24). In the house finches, treatment with topical ciprofloxacin (Ciloxan®, Alcon Laboratories, Fort Worth, TX) and tylosin tartrate (Tylan®, Eli Lilly and Company, Indianapolis, IN) in drinking water resolved clinical signs. Mycoplasma has been suspected but not proven to

**Figure 33.22.** Cockatiel with blepharoconjunctivitis.

**Figure 33.23.** Spice finch with periocular cellulitis.
Aspergillus was successfully treated with oral itraconazole and topical miconazole (Abrams et al., 2001). Mycotic keratitis was diagnosed in a blue-fronted Amazon parrot (Hoppes et al., 2000). Granulomatous dacryoadenitis of unknown cause in an ostrich resolved with surgical excision (Saroglu et al., 2003).

Avian poxvirus is responsible for the large majority of reported viral infections involving birds’ eyes (Karstad, 1971; Tripathy & Hanson, 1975). A wide variety of species have been affected, including raptors (Fitzner et al., 1985; Graham & Halliwell, 1986), conures (Emanuelson et al., 1978), mynahs (Panigrahy & Senne, 1991), Amazon parrots (Karpinski & Clubb, 1986; McDonald et al., 1981), racing pigeons (Dodd, 1974), bobwhite quail (Davidson et al., 1980; Poonacha & Wilson, 1981), peacocks (Al Falluji et al., 1979), exotic pheasants (Ensley et al., 1978b), a whistling swan (Montgomery et al., 1980), and canaries (Cavill, 1964; Giddens et al., 1971; Johnson & Castro, 1986). Proliferative multifocal keratokonjunctivitis is the characteristic lesion; secondary keratitis and lid deformity may be sequelae to resolution of the lesions (Karpinski & Clubb, 1985). Diagnosis can be confirmed histologically by demonstration of eosinophilic intracytoplasmic inclusions, epidermal hyperplasia, and
intraepithelial vesicles; pox virions can be seen on electron microscopy (Tripathy & Hanson, 1975). Therapy of pox lesions is directed toward prevention of secondary bacterial infection (by administration of topical and systemic antibiotics) and careful attention to hygiene (daily eyewash); vitamin A administration (10,000–25,000 IU per 300 g body weight weekly by intramuscular injection) has also been empirically recommended (Karpinski & Clubb, 1986).

In chickens, cataracts and iridocyclitis have been associated with avian encephalomyelitis infection (Barber & Blow, 1963; Bridges & Flowers, 1958). Marek’s disease causes iridocyclitis and secondary cataract (Rigdon, 1959). Nodular proliferative blepharoconjunctivitis in an African gray parrot was associated with cutaneous infection with a papilloma-like virus demonstrated by electron microscopy (Jacobson et al., 1983). An epidemic of conjunctivitis with respiratory distress and high mortality investigated in a flock of Gouldian finches was ascribed to a cytomegalovirus-like infection (Desmidt et al., 1991). Intranuclear inclusions were found in conjunctival epithelium by electron microscopy. Conjunctivitis in passerine birds has been associated with Newcastle disease virus and paramyxovirus-2 (Kern, 1997). In domestic poultry, infectious laryngotracheitis, duck plague, Newcastle disease, influenza A, infectious bronchitis, quail bronchitis viruses, turkey and pigeon herpesviruses, adenovirus, and pneumovirus cause conjunctivitis (Calnek, 1991). Active and inactive turkey and pigeon herpesviruses, adenovirus, and pneumovirus cause conjunctivitis (Calnek, 1991). A corrective and inactive chorioretinitis have been documented clinically and by histopathology in red-tailed and Cooper’s hawks with naturally acquired West Nile Virus infections (Pauli et al., 2007).

Endophthalmitis and encephalitis due to Toxoplasma gondii was confirmed histologically in two flocks of canaries (Vickers et al., 1992; Williams et al., 2001). Chorioretinitis due to toxoplasmosis was diagnosed in chickens (M usstaffa-B abjee, 1969). Eyelid swelling has been documented with malaria infection (Plasmodium spp.) in canaries and domestic poultry (M usstaffa-B abjee, 1969). Goose parvovirus causes blepharitis and enteritis (K ern, 1997). Papovavirus inclusions were reported from the eyelids of budgerigars (T sai et al., 1993).

Severe conjunctivitis due to cryptosporidiosis has been reported in pheasants (Randall, 1986), a domestic duck (Mason, 1985), and a peacock (Mason & Hartley, 1980). Encephalitozoon bellem was the cause of unilateral keratoconjunctivitis in a cockatoo (Phalen et al., 2006).

Parasitic diseases occasionally cause avian ocular disease (Greve, 1986) (Fig. 33.26). Parasites are sometimes found under the membrane of birds, associated with no clinical signs or conjunctivitis. These include the spirurids Ceratospira and Oxyspirura species in psittacines, mynahs, and domestic and wild birds (Greve, 1986; M urphy, 1987; M usstaffa-B abjee, 1969); the nematodes Thelazia species in a Senegal parrot (B rooks et al., 1983a), a captive oriental white stork (Circonia boyciana) (M urata & A sakawa, 1999), and a Setaria in passerines (K ern, 1997); and the trematode Philothalmus grallii in ostriches, waterfowl, and other species (Greve & H arrison, 1980; Nollen & M urray, 1978; Schmidt & T oft, 1981; Verc a et al., 2009; W illiams, 1994). Treatment of chickens experimentally infected with oxyspirurids from wood partridges with topical ivermectin (0.005–0.5 mg, one dose) was effective in eliminating the nematodes from the conjunctival sac; oral and parenteral ivermectin administration was ineffective (Thomas-Baker, 1986). The life cycle of the oxyspirurids involves ingestion by a bird of an infected cockroach; nematode larvae migrate from crop to esophagus, then into the nasolacrimal duct to the conjunctival sac, where they lay eggs that are swallowed by the host and are expelled in feces (Thomas-Baker, 1986).

In budgerigars and other aviary and pet birds, Knemidoco ptes pilae infestation causes scaly proliferative lesions of the legs, cere, and eyelids; other species cause similar lesions in poultry and wild passerines (Kern, 1997; Williams, 1994). Diagnosis is confirmed by skin scraping that demonstrates the organism. Systemic ivermectin administration is usually curative (Ivomec®, M erck and Company, Inc., West Point, PA), diluted 1:8 in propylene glycol and given at 200 µg/kg subcutaneously or orally (Karpinski & Clubb, 1986). Periocular myiasis occasionally occurs in wild and aviary birds (Kern, 1997). Disseminated mite infection with ocular involvement was described in a juvenile bald eagle (Haliaeetus leucocephalus). Serpiginous retinal scars were noted in one eye. Apparently viable mites of unknown species were found histologically in the retina and episcleral tissues, lungs and liver (Bueno-Padilla et al., 2011).

**Degenerations**

Crystalline corneal degeneration of unknown cause was found at necropsy in 8.7% of birds at a quarantine station, most commonly in cockatiels, budgerigars, ring-necked parakeets,
sive inheritance was postulated in the Yorkshires (Slatter et al., 1983). Spontaneous cataract of unknown cause was identified in a large flock of bobwhite quail, detectable after 3 months of age (Krehbiel, 1972). In Brahma chickens, focal polar cataracts that progressed to maturity by 6 months of age were associated with the concomitant development of crooked toes; inheritance pattern was undetermined (Chmielewski et al., 1993). Spontaneous cataract in chickens and turkeys has been reported (Critchley & Tham, 1983; Rigdon et al., 1959). Maternal vitamin E deficiency in turkeys and dinitrophenol fed to chicks caused cataract (Mustaffa-Babjee, 1969). At a quarantine station, the incidence of uncomplicated cataract was 15.4% (Tsai et al., 1993). Presumptive senile cataract has been documented in aging macaws, an Amazon parrot, and a Bali mynah (Clubb & Karpinski, 1993; Jähne, 1979; Schmidt, 1983). In the captive macaws, most birds over 35 years of age had at least unilateral cataract; many also had iris atrophy, typified by darkening of a normally light-colored iris from exposure of the posterior pigmented iris epithelium (Clubb & Karpinski, 1993). Extracapsular cataract extraction was done in a Mandarin duck and an Andean condor and a black-shouldered kite (Moore et al., 1985; Schmidt, 1983). Phacoemulsification has been performed on raptors and macaws (Hacker & Shifrin, 1988; Kern et al., 1984; Moore et al., 1985; Van Niekerk & Petrick, 1990). Bilateral phacoemulsification was performed successfully with implantation of custom polymethylmethacrylate intraocular lenses in a young great-horned owl. The lenses had a haptic diameter of 17 mm and optic diameter of 10 mm (Carter et al., 2007). In most instances, intracameral injection of a curariform drug prior to surgery facilitated mydriasis. Injection of 0.1–0.3 mL of aqueous tubocurarine chloride (tubocurarine chloride injection, USP, E.R.Squibb, New York), 3 mg/mL, has been effective (Kern et al., 1984). Pupilloplasty was performed to correct pupillary occlusion in a great-horned owl with cataract and a bald eagle with synechiae (Aguilar et al., 1993; Canton et al., 1992). Posttraumatic cataract follows penetrating ocular injury that disrupts integrity of the lens capsule; chronic immune-mediated uveitis often results, even if intraocular infection does not. Trauma and/or chronic inflammation may promote lens luxation; intracapsular extraction was performed in a barred owl with a luxated cataract (Brooks et al., 1983c).

Retinal degenerations in birds occur as inherited, postinflammatory, and posttraumatic conditions. Hereditary retinal degeneration in Rhode Island Red chickens appears to follow photoreceptor dysplasia (Ulshafer et al., 1984). Bilateral idiopathic generalized retinal degeneration was diagnosed in a budgerigar (Tudor & Yard, 1978). Retinal degenerations due to inflammation or trauma are focal to multifocal, sometimes extensive enough to cause blindness. Funduscopic appearance is characterized by pigmentary disturbance and asymmetrical fundus pigmentation when both eyes are compared. Retinal and uveal calcifications of unknown cause were found in ring-necked parakeets at necropsy (Tsai et al., 1993). Spontaneous retinal detachment in young pheasants was unexplained (Randall et al., 1986).
Neoplasia

Neoplasia involving the avian eye and adnexa seem relatively uncommon (Dukes & Pettit, 1983; Kern, 1997; Williams, 1994). Marek’s disease of chickens is the most common cause (Ball, 1945; Calnek, 1991; Dukes & Pettit, 1983). Eyelid and conjunctival neoplasia has been rarely reported. Neoplasms include a benign basiloid cell tumor in a budgerigar (Brightman & Burke, 1978), a histiocytic sarcoma of the lower eyelid of a great-horned owl (Sacré et al., 1992), a mastocytoma of the lower eyelid of a chicken (Patnaik & Mohanty, 1970), a chondrosarcoma of the third eyelid of a great white heron (Spalding & Woodard, 1992), a periocular cystadenoma in an African gray parrot (Hochleithner, 1990), and neoplasms of the third eyelid (squamous cell carcinoma in a hawk, basal epithelioma in a parrot, xanthoma in a budgerigar) (Kern et al., 1996). A subconjunctival hibernoma, a benign neoplasm of brown fat, was successfully excised from a domestic goose (Murphy et al., 1986). In addition to herpesvirus-induced ocular lymphomatosis (Marek’s disease) in chickens, primary uveal neoplasia reports include iris melanoma, iris hemangioendothelioma, and anterior uveal rhabdomyosarcoma in chickens (Dukes & Pettit, 1983), medulloepithelioma in two cockatiels (Schmidt et al., 1986), adenocarcinoma in a budgerigar (Tripathy & Hansen, 1975), iris melanoma in a great-horned owl (Kern, 1997), and uveal malignant melanoma with extrascleral extension (Gilger et al., 1995). Periocular swelling was caused by multicentric or metastatic malignant melanoma in an African gray parrot and a pigeon (Paul-Murphy et al., 1985; Rambow et al., 1981). Orbital neoplasia included optic nerve glioma and round cell sarcoma (Williams, 1994). Pituitary adenomas in budgerigars and cockatiels may cause tonic mydriasis and blindness due to optic neuropathy (Curtis-Velasco, 1992; Schlumberger, 1954; Small & Burke, 1982; Spalding & Woodard, 1992). A malignant intraocular teratoid medulloepithelioma was identified in a 3-year-old cockatiel (Bras et al., 2005). Squamous cell carcinoma of the infraorbital sinus was diagnosed at necropsy in a Solomon eclectus parrot (Eclectus roratus solomonensis) with fungal tracheitis (Diaz-Figueroa et al., 2006). Surgical resection of a conjunctival xanthoma from a blue and gold macaw (Ara ararauna) was curative (Souza et al., 2009). Surgical removal of a retrobulbar adenoma suspected to be associated with hypovitaminosis A from an African grey parrot (Psittacus erithacus) was complete with preservation of the globe and vision (Simova-Curd et al., 2009). Intraocular osteosarcoma with orbital extension in an umbrella cockatoo (Cacatua alba) was treated with exenteration and radiation therapy but was euthanized 2 months afterward for neurologic signs. Although axial and appendicular osteosarcoma have been reported in birds, this was believed to be the first report of intraocular osteosarcoma (Fordham et al., 2010).

Vitamin A Deficiency

Hypovitaminosis A, a common subclinical condition in cage birds, may predispose them to diseases of the mucous mem-

branes (e.g., keratitis, conjunctivitis). Clinical deficiency may be manifest as swollen eyelids due to conjunctival hyperkeratosis, mimicking pox lesions. Cytologic and histologic examination of lesions may be used to differentiate the causes. Parenteral and dietary vitamin A supplementation is effective (Koschmann, 1986).

Trauma

Traumatic ocular injury is frequent in raptors (Canton et al., 1992; Davidson, 1997; Greenwood & Barnett, 1981; Lindley et al., 1988; Mclaren et al., 1995; Murphy, 1987; Murphy et al., 1982a; Seruca et al., 2011; Williams et al., 2006) and wild passerine birds. Injuries are often not confined to the eye and ocular injuries may be complex, involving external eye, anterior, and/or posterior segments (Fig. 33.29). Even bony scleral ossicles are subject to injury and fracture (Lindley et al., 1988; Mclaren et al., 1995). Perhaps because of their relatively large eye size, fundus evaluation is relatively easy in raptors; a high prevalence of posterior segment injuries has been found, including retinal edema, tears, and detachment; intravitreal hemorrhage, especially surrounding the pecten; and perforation of the posterior segment (Murphy, 1987; Murphy et al., 1982b). Secondary glaucoma occasionally results; globe enlargement, if present, is usually subtle insofar as the rigid sclera probably limits the extent of buphthalmos development.

Presumptive Horner’s syndrome following cervical trauma has been described in a red-bellied parrot (Poicephalus rufiventris). Ptosis without miosis and ipsilateral facial feather fluffing were the clinical signs, which improved over time (Gancz et al., 2005). Surgical excision of an infraorbital secre-
tory epithelial cyst that developed following trauma was curative in a white cockatoo (Cacatua alba) (Stiles & Greenacre, 2001). Surgical repair of bilateral acquired ankyloblepharon secondary to thermal injury was successful in a young cockatiel (Pinard et al., 2006).

Enucleation in birds may be performed by a lateral or a transaural approach (Murphy et al., 1983). In some birds, incision and collapse of the globe facilitates its removal. In owls, their very large tubular eyes may be more easily enucleated if the auricular skin fold bordering the external ear is transected (Murphy et al., 1983). During enucleation, special care must be taken to avoid traction on the optic nerve; the fellow optic nerve can be avulsed easily because of its close proximity. In addition, careful hemostasis is necessary to prevent hypovolemia, shock, and death, especially in small birds. A lethal oculocardiac reflex was caused by enucleation in a cockatiel (Pipo et al., 1996). After removal of globe, nictitans, conjunctiva, lacrimal and harderian glands, and marginal eyelid skin, closure is accomplished with one cutaneous layer of absorbable or nonabsorbable suture (Murphy et al., 1983). Evisceration with intrascleral prosthesis was performed in a gray parrot (Neumann & Kummerfield, 1983).

Nonhealing corneal ulcers were successfully treated by primary surgical closure of the cornea in two great-horned owls (Gionfriddo & Powell, 2006). Penetrating keratoplasty was performed on a California brown pelican to resolve axial corneal scarring (Lynch et al., 2007b).

Newly imported mynahs developed corneal erosions associated with capture and cage trauma (Williams & Flach, 2003). In most birds, the keratitis resolved uneventfully. Some mynahs developed chronic keratoconjunctivitis with proliferative conjunctival masses, which required excision.

**Penguins**

Penguins (Sphenisciformes) are flightless birds that live in southern oceans and on their coasts. Penguins have a very small lacrimal gland and lack nasolacrimal ducts (Walls, 1942). They also have a supraorbital gland that extracts salt from the blood, excreting it concentrated through the tears (Schmidt-Nielsen & Sladen, 1958). This allows penguins to imbibe salt water and live in both freshwater and saltwater environments. Aerobic bacteria normally inhabit the corneal and conjunctival surfaces of saltwater and freshwater penguins. The most commonly cultured bacteria from both populations was Corynebacterium spp., followed by Staphylococcus spp., then Moraxella spp., Actinomyces canis, and others (Swinger et al., 2009). There were fewer organisms isolated from animals housed in saltwater than from those in freshwater. Possible factors included variations in individual immune defense systems in both habitats, animal density, and differences in each system’s filtration/sanitation systems. Total conform counts were similar in each habitat and were not considered unusual. The average STT value was 6.45 mm/min with a range of 1–12 mm/min. Penguins housed in freshwater had greater tear production (8.5 mm/min) than those housed in saltwater (4.8 mm/min). These differences were thought to be related to either differences in bacterial flora in each habitat or due to changes in their supraorbital glands (Swinger et al., 2009).

Penguins have eyes adapted for underwater vision. However, they reproduce on land, so they must have functional aerial vision to find and protect their young from predators. Their eyes differ in shape from other diving and nondiving birds and it was suggested that a fourth shape category be defined for penguins as quasispherical (Suburo & Scolaro, 1990). The cornea is flattened, making the eye an asymmetric sphere with all equatorial diameters larger than the axial diameter (Howland & Sivak, 1984; M artin & Young, 1984; Sivak et al., 1987). The eyes also differ in vertical and horizontal measurements. The vertical diameter is 85–89% of the horizontal diameter at the equator (Suburo & Scolaro, 1990).

The corneal endothelium of the Magellanic penguin (Spheniscus magellanicus) is similar to that of other vertebrates (Picatto et al., 2005). Penguins’ pupils are rapidly responsive; penguins were initially thought to be myopic in air (Walls, 1942). More recent studies have found that the Gentoo (Pygoscelis papua), the Rockhopper (Eudyptes crestatus), the Magellanic (Spheniscus magellanicus), and the Humboldt (Spheniscus humboldti) are emmetropic in water and air (Howland & Sivak, 1984; Martin & Young, 1984; Sivak et al., 1987). Spheniscus spp., which include Aufric, Galapagos, Humboldt, and Magellanic penguins, do not have binocular vision. The Adlie penguin (Pygoscelis adeliae) can evaluate far objects using binocular vision but, when calmly examining nearby objects, turns the head sideways to look at the object monocularly (Walls, 1942). Penguin lenses are the most spherical lenses among birds (Sivak & Vrablic, 1979) and they are thought to accommodate enough to compensate for loss of corneal refractive power in water (Howland & Sivak, 1984).

IOPs have been measured using applanation tonometry following topical anesthesia in a group of 22 Humboldt penguins. The IOP measurements ranged between 10 and 27 mm Hg with an average of 20.36 mm Hg (Swinger et al., 2009). The only ocular abnormality identified in this group of penguins was cataracts with a 14% incidence. Penguins with cataracts were not included in the reported data. Another study evaluated IOPs in 17 black-footed (African) penguins (Spheniscus demersus) (Mercado et al., 2010). Complete ophthalmologic evaluations were not performed other than noting that one penguin had a cataract oculus sinister (OS) and another had undergone enucleation for previous trauma. Physical examinations including blood sample collections were also performed at the same time as IOP measurements. Rebound tonometry (TonoVet, I care, Helsinki, Finland) was performed in the birds with their heads extended, using both the horse and dog settings on the instrument. Readings taken using the horse calibration found no significant difference in the IOP of either eye (median = 25 mm Hg oculus uterque [OU]), mean 25.06 mm Hg oculus dexter [OD] and 25.05 mm Hg OS), but readings taken using the dog calibration found that the left eye
had a significantly lower IOP than that of the right eye (OD median = 27 mm Hg, mean 30.41 mm Hg; OS median 27 mm Hg, mean 28.13 mm Hg) (Mercado et al., 2010). Colitz has collected IOP values from five species of penguins, although too few from each to publish and all eyes had abnormalities (C.M.H. Colitz, unpublished data). The IOPs ranged between 13 and 35 mm Hg. Abnormalities diagnosed included chronic proliferative keratitis, cataract stages ranging from incipient to hypermature resorbed cataracts, and subluxated and completely luxated cataractous lenses (C.M.H. Colitz, unpublished data) (Fig. 33.30).

Penguins are maintained in a number of facilities with a variety of environmental factors including different salinities, a range of oxidants, and a variation of nutritional management approaches (American Zoo and Aquarium Association, 2005). While eye problems are not major issues in these species a clinician may encounter diseases of the cornea, cataracts, luxated lenses, and trauma. Penguins defend territory with their sharp bills and flapping of their wings, so eyelid trauma and corneal damage, but rarely perforation, are the most common lesions in young birds. Many birds have been raised from eggs. The husbandry involved (food formula variation, restraint, feeding techniques) may cause ocular lesions like keratitis from food particles on the cornea.

Water quality for penguins is often determined by the design of the facility. Like many species they are fairly durable and may do quite well in a variety of systems. In general it is recommended that they be maintained in environmental parameters similar to the wild. Use of oxidants may result in eye damage so systems should be designed to minimize the need for oxidants in the exhibit areas. Penguins housed where water quality was poor developed ocular discomfort and redness that improved when water quality was improved (De Voe, 2000). Penguins undergoing therapy with eye drops may require temporary isolation during the treatment period. Treatments include medications similar to those used for marine mammals.

Cataracts are the most common ocular problem that affects penguins under human care (C.M.H. Colitz, personal observation). Swinger et al. found a 14% incidence in one colony (Swinger et al., 2009). The author (Colitz) has performed phacoemulsification lens extractions in 11 penguins of different species and has diagnosed cataracts of varying stages in 27 penguins from various facilities. Most of these birds are housed indoors; hypothetical causes of cataract include aging and environmental oxidative stressors (C.M.H. Colitz, unpublished data).

Other eye problems seen in penguins include corneal trauma. Penguins can fight among themselves and beaks can cause corneal ulcers and perforations (Fig. 33.31). Penguins are also susceptible to systemic fungal disease as well as fungal keratitis (Fig. 33.32). Salt gland adenitis associated with unidentified gram-negative bacteria at necropsy was identified in three blue penguins (Eudyptula minor) in New Zealand (Suepaul et al., 2010).

MAMMALS

The class Mammalia is comprised of three subclasses: placental mammals (the largest), monotremes, and marsupials. Among the 15 orders of placental mammals, considerable diversity exists in normal anatomy, but in general the eye conforms to the prototypical pattern described in Chapter 2. The other two subclasses show features of evolution from a
retina, the latter possibly functioning to monitor movements of the trunk (Stone & Halasz, 1989). Retinoscopic and keratometric measurements in Asian elephants documented a net spherical refraction of $+0.23$ D with 5 D or greater astigmatism. The mean corneal power by photokeratometry was 21.3 D. Accommodative range was 3 D. Refraction was not affected by cycloplegia, and a thin, meridionally oriented smooth ciliary muscle was observed histologically (Murphy et al., 1992). Refraction studies in the white rhinoceros (Ceratotherium simum) showed moderately poor optical quality of the eye based upon lack of crispness of retinoscopic reflexes; moderately hyperopic at rest ($+1–1.5$ D), rhinos were able to accommodate through a range of 3–4 D (Howland et al., 1993). A study of the ontogeny of refractive state of Thomson’s gazelles (Eudorcas thomsoni) documented that early hyperopia resolved to emmetropia by day 50 (Ofri et al., 2004). The anatomy and physiological optics of the eyes of several cetaceans and pinnipeds have been carefully investigated and described (Cartee et al., 1995; Dawson 1980; Landau & Dawson, 1970; Sivak et al., 1989). A study using Schiotz tonometry in anesthetized lions showed significantly higher IOP in males than in females (24.9 ± 2.0 mm Hg in males; 20.9 ± 2.4 mm Hg in females) (Ofri et al., 1998a). In a different study, elevated serum progesterone during the luteal phase of estrus in lionesses was associated with higher IOP than in nonluteal phase lionesses (27.07 ± 2.15 mm Hg vs. 21.61 ± 2.70 mm Hg) (Ofri et al., 1999b). IOP was significantly associated with increasing age and globe size in lions, with IOP in lions older than 1 year nearly twice that of those less than 1 year of age (Ofri et al., 2008). In a survey of normal beavers, the typical eye had an anangiotic retina IOP of 18 mm Hg, and the normal conjunctival microflora
consisted predominantly of gram-positive organisms (Cullen, 2003). The light microscopic features of the iridocorneal angles and their putative function have been investigated in the West Indian manatee, short-finned pilot whale, hippopotamus, and African elephant (Hatfield et al., 2003). Normal IOPs and STT values were reported in eight captive wild herbivore species in Israel, and tear production was reported in an additional three herbivore species (Ofrim et al., 1998b, 1999a, 2001a, 2002). A study of the iridocorneal angle of the water buffalo included scanning electron microscopy (Kassab et al., 2001). A survey of ocular examinations and conjunctival bacterial flora in North American bison reported similarities to cattle (Davidson et al., 1999). The distribution of lactoferrin and the lack of lysozyme in the lacrimal and other tear glands were also similar in cattle and bison (Pinard et al., 2003a, 2003b).

The comparative ocular anatomy of the western lowland gorilla (Gorilla gorilla gorilla) has been recently reported (Knap et al., 2007). The gross and microscopic findings closely resembled that of the mountain gorilla (Gorilla gorilla beringei) (Rohen, 1962) and another gorilla, species not identified (Heine, 1906). Ophthalmic examinations of six captive gorillas aged 12–48 years yielded the following results: mean spherical equivalent refraction $+1.20 \pm 0.59$ D; mean IOP $12.0 \pm 4.3$ mm Hg Schiotz; mean cup : disc ratio $0.42 \pm 0.11$; mean axial length by A-scan $22.75 \pm 0.71$ mm; and mean keratometry reading of $44.38 \pm 1.64$ D (Liang et al., 2005). Reference values for selected ophthalmic tests of the capuchin monkey (Cebus apella) were also recently reported (Montiani-Ferreira et al., 2008b). STT values were $14.9 \pm 5.1$ min; IOP was $18.4 \pm 3.8$ mm Hg by applanation; and central corneal thickness was $0.46 \pm 0.03$ mm by ultrasonic pachymetry. The normal fundus pigment distribution in rhesus monkeys has been described (Dawson et al., 2004).

STTs, tonometry, and conjunctival flora description have been reported for the red kangaroo (Macropus rufus) (Takle et al., 2010); the capybara (Hydrochaeris hydrochaeris) (Montiani-Ferreira et al., 2008a), and the brown brocket deer ( Mazama gouazoubira) (Martins et al., 2007). STT and IOP values were determined for conscious captive and anesthetized wild koalas (Phascolarctos cinereus) (Grundon et al., 2011). Electoretinographic parameters have been reported for anesthetized western gray kangooroo (Macropus fuliginosus) (Labelle et al., 2010). The ocular parameters of 30 fruit bats of three species (Pteropus vampyrus, Pteropus pumilus, and Pteropus hypomelanus) were determined, including PRTT and tonometric values while hanging upside down, palpebral fissure length, vertical and horizontal corneal diameters, and anterior segment and lens findings from ocular examination (Blackwood et al., 2010). Normal conjunctival flora was described for the North American raccoon (Didelphis virginiana) and raccoon (Procyon lotor) (Pinard et al., 2002).

Malformations, infections, inflammatory disorders, nutritional disorders, neoplasia, and trauma are all important etiologic factors in ocular disorders, of variable importance in different orders of mammals.

### Ophthalmic Malformations

Cyclopia and limb deformity of unknown cause have been reported in a collared peccary (Helfgren et al., 1984). A nophthalmos and microphthalmos were associated with nasomaxillary and central nervous system abnormalities in two unrelated raccoons (Rendel et al., 1983). Unilateral congenital obstruction of the nasolacrimal duct of a young lowland gorilla was successfully treated by temporary stenting with vinyl tubing (Nagashima et al., 1974). Eyelid agenesis was surgically corrected in a Geoffroy’s cat (Millichamp, 1991) and a cougar (Cutler, 2002). A conjunctival dermoid in a captive African lion cub was successfully treated by excision (Robinson & Benirschke, 1981). The brain of a white tiger with strabismus showed abnormal lamination of the lateral geniculate nucleus similar to abnormalities noted in other animals with reduced pigmentation (Guillery & Kaas, 1973). Mink affected with Chediak-Higashi syndrome have pale irides, photophobia, and hypopigment atapetal fundi. An autosomal recessive disorder, it is manifest in several mammalian species as partial oculocutaneous albinism (Collier et al., 1979; Prié & Collier, 1978). Heterochromia iridis was described in a wild koala (Kempster et al., 1996a).

Multiple ocular colobomas (eyelid, optic nerve) and retinal dysplasia of probable genetic origin have been reported in captive snow leopards on two continents (Barnett & Lewis, 2002; Phillips, 1981; Schaffer et al., 1988; Wahlberg & Talkanen, 1980; Wahlberg et al., 1982). Bilateral multiple ocular anomalies including corneal dermoid and cataract were reported in a dromedary camel (Moore et al., 1999).

Congenital cataract afflicted a large proportion of Malayan mouse deer in a European zoo; no familial pattern was detected and vitamin E deficiency was suspected (van der Hage et al., 1989). Microphthalmia and cataract were found in whitetailed deer fawns (Howard et al., 1976). Retinal dysplasia has been reported in wild otters (Lutra lutra) (Williams et al., 2004). Multiple ocular anomalies were described in an infant rhesus macaque (Ribka & Dubielzig, 2008).

### Ophthalmic Inflammations and Infections

Most reported ophthalmic inflammatory disorders have been infectious. A few were not. Ocular nodular fasciitis in an Asiatic black bear was treated by keratectomy and subconjunctival corticosteroid administration (Mäinka & Christmas, 1987). Bilateral chronic superficial keratitis in a Mexican wolf resembling pannus was treated with beta-irradiation and subconjunctival corticosteroids (Harwell et al., 1985). Non- septic uveitis associated with mast cell infiltration was the cause of glaucoma in a lion cub treated by evisceration with silicone prosthesis implantation (Gerding et al., 1987). Idiopathic follicular conjunctivitis was found in 42% of African elephants shot at a national park (McCullagh & Gresham, 1969).

Panophthalmitis was a manifestation of Trypanosoma cruzi and Bacillus piliformis infection in a lesser panda (Bonney &
Keratoconjunctivitis resulting from Chlamydia psittaci has been reported in both wild and captive koalas in Australia (Canfield et al., 1991a; Cockram & Jackson, 1974, 1981; Hirst et al., 1992a, 1992b; Kempster et al., 1996b; Weigler et al., 1988). Experimental and naturally occurring infections follow a similar course (Kempster et al., 1996b). A cute unilateral or bilateral infection may affect up to 30% of wild populations, most commonly in the summer months. Serous ocular discharge, conjunctival injection, and blepharospasm are followed by chemosis with eyelid eversion. By 3 weeks after infection, corneal neovascularization is evident and may progress to vision impairment. Diagnosis is effected by culture of the organism or positive specific immunofluorescence of epithelial cells collected by conjunctival or urogenital swab (Canfield et al., 1991b). Two distinct forms of Chlamydia have been identified (Girjes et al., 1988, 1993).

Infectious keratoconjunctivitis of wild ungulates has many of the same causes as in domestic cattle, sheep, and goats. An epizootic of chlamydial keratoconjunctivitis that affected 60% of bighorn sheep in Yellowstone National Park resulted in significant mortality (Meadger et al., 1992). Keratoconjunctivitis in wild mule deer was associated with infection with Chlamydia, Moraxella spp., and Thelazia californiensis (Taylor et al., 1996). Mycobacterium bovis was isolated from a common waterbuck (Fletcher, 1979) with corneal ulceration and conjunctivitis. Keratitis in red deer responsive to subconjunctival penicillin/streptomycin was suspected to be due to Moraxella spp. (Wilson et al., 1981). Mycoplasma ovis was isolated from mule and deer with severe keratoconjunctivitis in Wyoming (Dubay et al., 2000a).

Keratitis in reindeer in Scandinavia has been extensively investigated (Winqvist & Rehbinder, 1973; Rehbinder 1997). The clinical signs appear identical to infectious bovine keratoconjunctivitis in North America. Summer epizootics occur in forest herds. Microbiologic evaluation has documented the presence of Neisseria ovis, Colesiota-like organisms, and other bacteria, but the definitive causative agent has not been conclusively determined (Kummeneje, 1976; Rehbinder, 1977; Rehbinder & Glatthard, 1977). Corneal injury from first instar larvae of Ceratophyllum trompe, the nostril fly, in the conjunctival sac may act as a predisposing factor. Lesions predominate in calves in which central corneal ulceration may progress to perforation. M. inor superficial ulceration and conjunctivitis are frequent. Ultrastructural examination of infected corneas failed to demonstrate an agent (Winqvist & Rehbinder, 1973).

Necrotizing panophthalmitis and bilateral blindness in a black-tailed deer resulted from plague (Yersinia pestis), proven by culture (Jessup et al., 1989). Conjunctivitis of unknown cause was described in a Grant’s gazelle and a nyala in a zoologic collection (Rehbinder, 1977).

An Indian buffalo developed ulcerative keratomycosis due to Aspergillus fumigatus, perhaps associated with topical antibiotic–corticosteroid treatment; results of therapy were not reported (Pal, 1983).

Keratomalacia associated with yeast and staphylococcal infection was successfully treated both medically and surgically with a conjunctival graft in greater one-horned rhinoceros (Gandolf et al., 2000). In a survey of corneal ulcers in domesticated Asian elephants in Sri Lanka, two-thirds yielded positive bacterial cultures, and more than half of these were concurrently infected with fungi (Kodikara et al., 1999). Exotic felids are susceptible to infection with feline herpesvirus and calicivirus. As in domestic cats, these respiratory pathogens also cause conjunctivitis; ulcerative keratitis may be caused by the rhinotracheitis virus (Fowler, 1986). Facial and eyelid cutaneous ulcers were proven by culture and histopathology to be due to feline herpesvirus-1 infection in a cheetah cub with a history of conjunctivitis and corneal ulceration (Junge et al., 1991).

Uveitis and corneal edema developed in a young maned wolf (Chrysocyon brachyurus) vaccinated 14 days previously with a combination vaccine containing canine hepatitis virus (Thomas-Baker, 1985). Intraocular granulomas associated with disseminated tuberculosis were identified in a rhesus monkey (Kessler & Brown, 1979). Disseminated cryptococcosis with ocular involvement was found in a guenon (Cercopithecus ascanius) (Helmke et al., 2006).

Ocular encephalitozoonosis occurred in blue fox pups farmed in Norway (Arnesen & Nordstoga, 1977). Foxes naturally infected with Encephalitozoon cuniculi had mainly encephalitis, with uveitis and cataracts. Vascular lesions in the eyes resembled polyarteritis nodosa; the posterior ciliary arteries and small vessels of the retina and uvea were involved. The retinas were detached and necrotic and many organisms were seen in the cataractous lenses.

Malignant catarrhal fever (MCF) was fatal to Indian gaur in which it caused pyogranulomatous scleritis and keratitis but not uveitis or retinitis (Zimmer et al., 1981). Nonsuppurative uveitis, scleritis, and keratitis characterized fatal MCF infection in farmed Rusa deer (Denholm & Westbury, 1982; Sanford & Little, 1977). Farmed deer in New Zealand are susceptible to MCF with ocular manifestations (Fletcher, 1982). A n outbreak of blepharoconjunctivitis and uveitis and oral ulceration was ascribed to infection with a virus indistinguishable from bovine herpesvirus-1 in the United Kingdom (Inglis et al., 1983).

Poxviral keratoconjunctivitis and dermatitis were reported in free-ranging mule deer in Wyoming (Williams et al., 1985). Contagious ecthyma in Alaskan musk oxen and Dall sheep caused raised crusted lesions of the eyelids, nostrils, and lips (Dieterich et al., 1981). Diagnosis was confirmed by immunofluorescence and transmission studies to domestic sheep. In the Dall sheep, affected corneas opacified and perforation occurred in one animal.

Bilateral nonsuppurative panuveitis, retinitis, and optic neuritis caused epizootic blindness in eastern and western gray...
kangaroos and red kangaroos in Australia (Durham et al., 1996). A viral etiology was suspected. Subsequently, orbiviruses of the Warrego and Wallall serogroups caused epidemic blindness typified by chorioretinitis and encephalitis in an Australian kangaroo (Durham et al., 1996; Hooper, 1999; Hooper et al., 1999; Raddacliff et al., 1999). Mink develop chronic nongranulomatous iridocyclitis as a manifestation of A leutian disease, an immune complex-mediated glomerulonephritis induced by a parvovirus infection (Hadlow, 1982). Lesions in the posterior segment are less common, primarily a mild choroiditis causing retinal detachment. Cataracts associated with anterior uveitis were described in wild mink, probably associated with A leutian disease (Helgebostad et al., 1979). Disseminated blastomycosis has been reported in a rhesus monkey (Wilkinson et al., 1999).

Wallabies appear to be very susceptible to toxoplasmosis. Uveitis has been noted in captive wallabies, associated with cataract, mild retinitis, and focal outer retinal degeneration (Ashton, 1979). A wallaby succumbed to generalized toxoplasmosis following successful cataract surgery performed by the author (Kern), probably secondary to related stress.

Nematodes infect the conjunctival sacs of deer. Thelazia californiensis was recovered from one-third of black-tailed deer in Oregon, with increased prevalence in females and older animals (Beitel et al., 1974), and from California mule deer with conjunctivitis (Oberhansley, 1940). Thelazia skrjabini, an eyeworm of cattle, was recovered from a white-tailed deer in Alberta (Kennedy et al., 1993). Thelazia californiensis were found in 8–15% of hunter-harvested mule deer and 40–66% of live deer in Utah (Dubay et al., 2000b). The trematode Oculotrema hippopotami was found in the conjunctival sac of hippos without clinical signs (Thurston & Laws, 1965).

The filarid Elaeophora schneideri may cause unilateral or bilateral chorioretinitis in elk. A vascular parasite, the nematode infects and occludes the large arteries of the head and neck, resulting in ischemic necrosis of the brain, eyes, and other tissues of the head. Calves and yearlings are most commonly affected. Blindness occurs with or without neurologic deficits and may be secondary to ocular or central nervous system lesions or both. Retinal and optic nerve atrophy may be visible ophthalmoscopically through tonically dilated pupils. Retinal edema and necrosis, optic neuritis, and optic atrophy are present histologically. Microfilariae may be seen in ocular blood vessels (Adcock & Hibler, 1969). In sheep with elaeophorosis, iridocyclitis has also been noted in addition to the typical lesions in elk (Abdelbaki & Davis, 1972).

Intraocular nematodiasis due to P arelaphostrongylus tenuis resulted in enucleation in an eland antelope in Ohio (Gandolf et al., 2003). In Texas, fire ant bites frequently cause blepharitis and ulcerative keratitis in white-tailed deer fawns. Corneal lesions vary in severity, from pinpoint erosions or subepithelial opacities to melting corneal ulceration and perforation. Topical antibiotic therapy is effective; conjunctival flap placement has been necessary on occasion.

**Corneal Degenerations**

A presumptive corneal endothelial degeneration or dystrophy was described in aged (6–11 years) ranch mink, primarily of the royal pastel coat color. Fifty-three percent of mink were affected, bilaterally in two-thirds. Progressive corneal edema and keratoglobus was not associated with neovascularization or melanosis. Histologically, the endothelium was attenuated or absent, with guttata of a thickened Descemet’s membrane (Hadlow, 1987).

**Cataract Formation**

The causes of cataract include congenital defects, advanced age, trauma, nutritional deficiencies and imbalances, inherited defects of the lens, metabolic disorders, and environmental effects (Fig. 33.33). In a breeding colony of vervet monkeys (Chlorocebus aethiops) more than one-quarter of 55 offspring produced over a 6-year period were diagnosed with cataract; a genetic basis was suspected. Elimination of monkeys related to ones with cataract from the breeding pool resulted in elimination of cataract from the next generation (de Villiers et al., 2001). A high incidence of cataracts was observed in two colonies of gray mouse lemurs (Microcebus murinus)—48% and 21% (Beltran et al., 2007). Bilateral cataract with unilateral ocular perforation was diagnosed in a wild coyote (Pence & Meinzer, 1977). In Sweden, dense cataracts have been observed in wild moose (Kronevi et al., 1977).

Cataracts of suspected nutritional origin in timber wolf pups were ascribed to deficiency or imbalance of arginine (Vainisi et al., 1981). Posterior subcapsular sutural opacification developed first in pups fed a commercial milk replacement diet from 9 to 10 days of age. Anterior cortical cataract followed. By 2.5 weeks on the diet, generalized cataract had developed. When the milk replacement was discontinued in favor of commercial dog food, the lens opacities partially

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**Figure 33.33.** Congenital nuclear cataract in a roan antelope calf.
regressed, leaving perinuclear opacities. Arginine deficiency was suspected after dietary experiments with succeeding litters of wolves. An age susceptibility to cataractogenesis was demonstrated; pups receiving the deficient diet from 5 days of age were more severely affected than those receiving it after 12 days of age. In addition, pups fed lactose in addition to the milk supplement did not develop cataracts, suggesting that lactose may influence arginine absorption or metabolism. Partial bilateral cataract resorption was observed in an 8-month-old timber wolf (Williams et al., 1977).

Bilateral extracapsular cataract extraction was performed with good results on an eland with senile cataracts and a 8-month-old timber wolf (Williams et al., 1977). Bilateral phacoemulsification without intraocular lens implantation has been performed by the author (Kern) on two clouded leopard cubs (Neofelis nebulosa) and a roan antelope calf (Hippotragus equinus). Phacoemulsification was successfully performed without intraocular lens implantation in a mature spider monkey (Ateles geoffroyi), a 3-month-old clouded leopard cub, and a young adult orangutan (Pongo pygmaeus) (Cooley, 2001; Montiani-Ferreira et al., 2010; Whiteley et al., 1980) and with foldable intraocular lens implantation in two young lowland gorillas (de Faber et al., 2004). Galactosemic cataracts have been reported to occur in kangaroos, wallabies, wombats, Austrailian possums, and cuscus (Slatter et al., 1980; Stephens et al., 1974). Affected animals had been orphaned or hand-reared for other reasons and had received cow’s milk. These neonatal marsupials progress through a monogastric phase of gastrointestinal development to a polygastric (ruminant) form of adult digestive system. Prior to maturity, they may be variably deficient in either galactokinase or galactose-1-phosphate uridyl transferase, which limits conversion of galactose in cow’s milk to lactose. Dulcitol accumulation in the lens causes an osmotic cataract. These nutritional cataracts may be prevented by feeding proprietary milk substitutes designed for human infants with inherited galactosemia that lack galactose and lactose. Surgical lensectomy has been generally unsuccessful because most affected animals have vitreous opacified by an unidentified material.

Cataracts were found in 16 of 300 African elephants culled from Tsavo National Park, Kenya (McCullagh & Gresham, 1969); only two were bilateral. Lens luxation and hypermaturity and active and inactive uveitis were noted in some elephants. Cataracts have been recognized in captive elephants as well (Schmidt, 1986).

Cataracts of presumed traumatic origin were noted in Turkish dancing bears from a circus, associated with corneal scarring and phthisis in some animals (F.C. Stades, personal communication).

Diseases of the Ocular Fundus

Central retinal degeneration typical of taurine deficiency in the domestic cat was reported in a white Bengal tiger in the United States and in three unrelated cheetahs in Israel (Beehler et al., 1984; Ofri et al., 1996). Serum taurine level was lower in the white tiger compared with other orange tigers, but not low enough compared with domestic cats with central retinal degeneration to account for the tiger’s retinopathy (Pickett et al., 1990). Levels were not reported for the cheetahs prior to initiation of dietary supplementation (Ofri et al., 1996). Retinal degeneration of uncertain cause has been noted in culled wild African elephants with cataracts (McCullagh & Gresham, 1969) and in captive Asian elephants. The unrelated Asian elephants showed behavioral signs of reduced vision and ophthalmoscopically reduced fundus vascularity; the normal paurangiotic fundus is difficult at best to assess. Retinal degeneration of unknown cause occurred in aged ranch mink (Hadlow, 1984). Presumptive hypertensive retinopathy and uveal vasculopathy were reported in a 40-year-old captive hippopotamus with a pheochromocytoma (Duncan et al., 1994). Histologic lesions included retinal detachment, retinal pigment epithelial degeneration, degeneration of small blood vessels of the uvea with hemorrhage, and hypertrophied tunic media and edematous tunicia adventitia of the larger uveal blood vessels. Idiopathic bilateral optic atrophy has been described in rhesus macaques (Fortune et al., 2005).

Neoplasia

Neoplasia seems relatively uncommon in exotic species. An extensive corneal squamous cell carcinoma in a 5-year-old cheetah was managed by exenteration; the animal was free of local recurrence and radiographic evidence of thoracic metastasis 1 year later (Caligiuri et al., 1988). Intestinal and unilateral ocular lymphosarcoma was reported in a captive adult striped hyena (Porter et al., 1987). The optic nerve, uvea, retina, and vitreous were infiltrated by neoplastic lymphocytes. Bulbar conjunctival ganglioneuromas were diagnosed in two adult Indian water buffalo; clinical signs and outcome were not reported (Gupta & Singh, 1978). An African green monkey (Cercopithecus Chlorocebus pygerythrus) developed extensive bilateral periocular and eyelid squamous cell carcinoma following a long-term carcinogenicity trial (Finchem et al., 1982). A harderian gland adenocarcinoma caused exophthalmos in a Beechey ground squirrel (Spermophilus beechyi) (Morro & day-Lollini, 1990). Bilateral corneal papilloma in a M alayan tapir resolved with repeated subconjunctival injections of 25 mg fluorouracil (Karpinski & Miller, 2002). A transitional cell carcinoma of ovarian origin was metastatic to the eye of a collared peccary (McCowan et al., 2002).

Nutritional Disorders

Nutritional disorders have been relatively rarely implicated in ocular disorders of exotic species. Bilateral retinal liposis occurred in a 2-year-old cottontail rabbit fed an all-milk diet for 20 months (Gwin & Gelatt, 1977). Histologically, lipid deposits were most extensive in the anterior corneal stroma.
and posterior iridal epithelium. Focal lipid depositions were detected in the sclera and choroid. Complete necropsy was not performed. The rabbit is highly susceptible to systemic manifestations of high dietary cholesterol (Gwin & Gelatt, 1977). Ocular lipidosis and aortic atherosclerosis are readily induced by dietary manipulation. In this rabbit, absence of dietary fiber may have enhanced systemic lipidosis (Gwin & Gelatt, 1977).

Nutritional cataracts in wolf pups were investigated and characterized (see previous discussion).

Central retinal degeneration indistinguishable from the taurine deficiency-induced lesion in domestic cats has been reported in cheetahs and a white tiger (Beehler et al., 1984; Ofri et al., 1996) (see previous discussion).

**Trauma**

Traumatic injury is no doubt a frequent cause of ocular disease in nondomestic animals (Fig. 33.34). Extensive epithelial downgrowth was described in the buphthalmic eye of a harbor seal that was postulated to be secondary to a perforating injury (Glover et al., 1995). In addition to extensive anterior synechiae, a layer of stratified squamous epithelium covered the posterior surface of the iris, ciliary body, and retina.

**MARINE AND OTHER AQUATIC MAMMALS**

Marine mammals under human care include pinnipeds, cetaceans, otters, sirensians (manatees and dugongs), and polar bears. Pinnipeds include seals (phocids or true seals), sea lions and fur seals (otariids or eared seals), and walrus (Odobenidae). Cetaceans include whales and dolphins. Otters are typically Asian small-clawed river otters, North American river otters, South American river otters, and sea otters.

**Ophthalmic Examination**

Many aquatic mammals under human care can be examined under behavioral control without sedation but otters are more likely to be examined during physical examinations or anesthetized for examination if needed. Polar bears (Ursus maritimus) are evaluated from protected views such as behind glass or in back areas from a distance or under anesthesia and fortunately do not commonly have eye problems. Unlike with client-owned domestic animals, examination limitations may include the inability to touch the periorcular region or pry their eyelids open manually. Poor dilation of pinniped pupils with topical mydriatic drugs makes fundic examinations challenging. Limited time constraints for ophthalmic evaluation may occur in many cases.

However, it is possible to perform fluorescein staining, slit-lamp evaluation, measure IOPs, measure tear production in some cases, and perform fundic examinations. Darkened conditions are often not practical with cetaceans but pinnipeds, if behaviorally desensitized, can be evaluated in rooms with light control. An alternative for both cetaceans and pinnipeds is to perform examinations outdoors at dusk or dawn. Cetaceans may be trained to station at underwater windows to decrease sun and sky reflection. Viewing the cetacean eye just below the water surface can decrease reflection that is increased on cloudy days. Good digital photography of eyes also contributes to examination findings.

Animals known to bite may still be evaluated through fencing or specially created areas where they can place their heads with eyes near the openings to allow slit-lamp evaluation, fluorescein staining, and tonometry. Specially made transparent Plexiglas shields facilitate safe examinations of unpredictable pinnipeds (Fig. 33.35).

**Pinnipeds**

**Environmental Factors Affecting the Eyes**

In the wild, otariids spend a large part of their lives on land. This would suggest that they are likely to suffer the effects of
the sun in the wild as well as under human care, except that in the wild they typically sleep most of the time. When they do open their eyes on land in the wild they are moving toward the water, mating, or checking their local surroundings. In captivity, pinnipeds are asked to open their eyes to receive food from trainers or the public in feeder pool situations, navigate show and presentation areas, and swim in pools with walls that may be highly reflective. Many of these facilities are not adequately covered to shield their eyes from excessive sunlight exposure. In addition, water type and quality may include natural ocean water, commercial formulations (e.g., Instant Ocean™, Blacksburg, VA), and on-site mixtures of salts, with some formulas containing multiple salts and others containing only sodium chloride or freshwater with no other minerals. Most facilities use some variation of salt water or commercial chemical mixtures if they are away from a coast. In closed systems, salt is continually diluted by rain or lost from systems to backwashing so the salinity levels may fluctuate, exposing the pinnipeds to lower concentrations for periods of time. A few facilities still house pinnipeds in freshwater, usually supplied as city water containing chloride. Pinnipeds that undergo traumatic corneal injury and are in systems with salinity levels lower than seawater (i.e., less than 32–35 parts per thousand) may have more complications such as edema with or without ulcers. Filtration capabilities vary widely and water quality may be maintained with oxidants such as chlorine, ozone, or both. Oxidant management also varies with location, design, financial support, and safeguards such as monitoring of oxidant levels. A dequate safety technology such as automated systems and carbon systems for oxidant removal may not be available.

The animals typically migrate not only to differing depths in the wild but also to many different geographic areas with different temperatures, salinities, and clarity. All of these scenarios cannot be mimicked in captive situations but attempts are made to recreate the environment in which that species lives most of the time. Most animals under human care may be stranded animals that were unable to survive in the wild due to injuries, illness, young age (i.e., neonates and juveniles), or they were born into human care and may be exposed to a wide variation of husbandry and nutritional management systems that may influence ocular health. Some management systems separate captive-born pups from mothers during the nursing period to make weaning easier for both handlers and pups, but this may result in periods of poor growth and nutrition inadequate for ocular health. Generally, the management options for these animals in facilities do not simulate the natural ecology of wild pinniped populations. Wild male pinnipeds, although engaged in intraspecific aggression during breeding season or in groups on shore, are able to move from threats and minimize constant contact and potential eye trauma. Managed pinniped systems may not provide adequate social options to avoid aggression within colonies or small groups as animals mature and engage in territorial or social behavior which can lead to trauma. When an animal presents with an eye problem, the environmental parameters mentioned above should always be investigated by the attending veterinarian and husbandry staff to determine their potential involvement and correlation with eye problems.

**Pinniped Anatomy and Physiology**

Pinnipedia descended from the superfamily Arctoidea within the suborder Caniformia; this suborder also gave rise to Ursidae (bears) and Mustelidae (weasels) (Arnason et al., 2006). There is debate whether walrus and otariids are more closely related to bears and whether phocids are more closely related to weasels. Regardless, approximately 33 million years ago, a split occurred between Otariodea (Otariidae and Odobenidae) and Phocidae, with later divisions between Odobenidae and Otariidae. The transition from a completely terrestrial lifestyle to a combined terrestrial–aquatic lifestyle required numerous adaptations including acquisition of flipper-like appendages, impressive breathing capabilities, and ocular specialization for function in both dry and aquatic environments.

Pinnipeds’ eyelids lack meibomian glands but possess sebaceous glands at the eyelid margin that open onto the outer lid skin (Kelleher Davis et al., 2011). They have a main lacrimal gland located temporally beneath the superior eyelid (Colitz et al., 2011b; Kelleher Davis et al., 2012). The third eyelid has an associated gland that is not a harderian gland, as many previous references have called it. Mucin-type O-glycans have been detected in pinniped tears, which have an overall protein concentration of 0.20–1.2 mg/mL (Kelleher Davis et al., 2010). They lack nasolacrimal excretory systems and are often seen to have a wet area at the lateral aspect of their adnexal region from tear run-off.

Phocids and otariids have large globes relative to their size but walrus do not. The larger the globe, the deeper they can dive. Walrus are different from other pinnipeds not only in body shape (they are less streamlined than the others) but also in behavior; they swim more slowly, dive less deeply to forage for small organisms on the ocean floor, and have smaller globes. Vision may be less important to walrus as they graze along the sea bottom using their impressively sensitive vibrissae to feed on crabs, shrimp, various mollusks (especially clams), and other seafloor inhabitants. Phocids and otariids feed on live fish and crustaceans so they require more effective use of vision for hunting these prey. Vision on land for most pinnipeds is important for mating, reproduction, and lactation; intrapopulation relationship maintenance; and orientation. A adaptation for seeing beneath the surface as well as above has required some novel anatomical and physiological developments. Visual acuity and refractive state have been evaluated in numerous pinniped species including California sea lions (Zalophus californianus), harbor seals (Phoca vitulina), Steller sea lions (Eumetopias jubata), Weddell seals (Leptonychotes weddellii), harp seals (Phoca groenlandica), and spotted seals (Phoca largha) (Feinstein & Rice, 1966; Jamieson & Fisher, 1970; Johnson, 1893; Lavigne & Ronald, 1975; Piggens, 1970; Schusterman, 1968, 1975a, 1975b;
The strongly convex approximately spherical lens is the marine mammal’s main refractive structure used for underwater vision, whereas the cornea is used for vision on land. Because of the location of the dilator muscles at the base of the iris and in the ciliary body, it is probable that the lens moves anteriorly, physically dilating the pupil for underwater vision, and then moves posteriorly for shallow water and land vision. This has been the accepted hypothesis for decades and our recent publication describing the anatomy of the California sea lion globe supports this working hypothesis (Miller et al., 2010). Harbor seals have multifocal lenses; this is also likely in other pinnipeds. Slit pupils are only present in animals with multifocal optical systems (Malmstrom & Kroger, 2006). Characteristics of animals with multifocal optical systems include activity under low light conditions and thick and almost spherical lenses (Kroger et al., 1999). Multifocal lenses have concentric zones of different focal lengths, each focusing a different relevant spectral range onto the retina. The usefulness of the small slit or pinhole pupil with the multifocal lens has been questioned because the lens is largely covered by the iris (Hanke et al., 2008). However, since pinnipeds hunt at depths that have minimal light, the multifocal lenses may be primarily used for underwater activity such as hunting. Another characteristic of animals with multifocal lenses is the presence of several types of cone photoreceptors in the retina with different spectral sensitivities because each focal length of the lens creates a well-focused image for one of the cone types (Hanke et al., 2008). Pinnipeds, however, are L-cone monochromats; the S-cones historically mutated and do not contribute to color vision. This is not the only species with multifocal lenses and limited color vision; nocturnal prosimians are also considered cone monochromats (Malmstrom & Kroger, 2006).

The curvature of the cornea is less than the curvature of a terrestrial canid’s, so the optical features of the anterior surface are similar on land and in the water. This would cause the cornea to be nearly ineffective under water. However, a flat plateau located just inferonasally to the axial cornea (Fig. 33.36) negates any difference in the optical features of the cornea’s curvature between air and water for that area of the cornea (Miller et al., 2010). A recent study performed in harbor seals found that aerial visual acuity was a function of luminance (Hanke & Dehnhardt, 2009). They hypothesized and proved that harbor seals obtained acute aerial visual acuity by the interaction of the vertical slit-shaped (stenopeic) pupil and the flat plateau. Furthermore, aerial visual acuity was comparable to acuity in clear waters if the pupil diameter did not exceed the zone of corneal flattening (Hanke & Dehnhardt, 2009). Previous reports had indicated that pinnipeds were myopic in air and that they had a high degree of against-the-rule astigmatism (Jamieson & Fisher, 1970; Schusterman & Balliet, 1970a, 1970b; Schusterman & Johnson, 1975; Schusterman et al., 1965; Wartzok & McCormick, 1978; Wartzok & Ray, 1976; Wilson, 1970). These studies demonstrated that pinnipeds are capable of resolving visual targets equally well both under water and in air.

Figure 33.36. Left eye of a California sea lion demonstrating the flattened plateau typical of an otariid. The flattened plateau is medial paraxial and round in shape.
should be identified as early in life as possible since they are progressive due to problems with oxidants in the environment. The clinician should closely evaluate the water quality parameters and methods of monitoring oxidants in order to better understand possible etiological factors. Prospectively establishing the normal IOP range in individual normal eyes prior to development of clinically apparent corneal and lens lesions is important to compare with IOP measurements after eyes develop lesions. Lower than normal IOP measurements may indicate lens-induced uveitis. Eyes with anterior lens luxation may have extremely high IOP when measured axially where the lens is touching the corneal endothelium, but when measured via peripheral cornea may be lower due to pinnipeds’ large iridocorneal angle and excellent aqueous outflow dynamics. Chronic presence of cataracts can cause secondary glaucoma. Unilateral primary glaucoma has been diagnosed only once in pinnipeds under human care (C.M.H. Colitz and J. Mejia-Fava, personal observation). The stress of examinations on the animals may cause spuriously elevated IOPs as high as 70 mmHg (C.M.H. Colitz, personal observation). Colitz suspects that animals can contract their extraciliary muscles to elevate IOP and they sometimes hold their breaths as well. Colitz suggests that the trainer work other behaviors prior to remeasuring IOP in order to relax the animal. In addition, the location where the animals are examined may be stressful so understanding each animal’s response to that location is important and an alternate location may be used.

The retina is similar to that of a canid with all the typical layers of a rod-dominant mammalian retina; the ganglion cell layer differs, with larger cells and lower density than terrestrial mammals (Miller et al., 2010). Ganglion cells in California sea lions are large and measure 31 µm, whereas canid ganglion cells measure 28.5 µm (Miller et al., 2010). Ganglion cells in the harp seal are intermediate in size (Nagy & Ronald, 1975). The ganglion cells in walrus and the Northern fur seal are also large, with a maximum size of 35 µm in the fur seal (Mass, 1992). The inner nuclear layer of pinnipeds is disorganized without clear boundaries. The horizontal cells are very large and the giant processes spread farther than in terrestrial mammals. The horizontal cells are in close vicinity to bipolar cells and amacrine cells but not in ordered rows (Supin et al., 2001). Most mammalian retinas have three types of visual pigments, rod opsin and two cone opsins. The two cone opsins are the short wavelength (S, peaks at blue color, 420–440 nm) and the middle/long wavelength (M/L) sensitive opsins (Yokoyama & Yokoyama, 1999). There are actually four cone opsins found in vertebrates, and humans have three of those four, with the long (L) wavelength opsin (peaks at yellowish color, 564–580 nm) being separate from the medium (M) wavelength opsin (peaks at green color, 534–545 nm). All pinnipeds and cetaceans examined to date lack S cones completely, most likely due to a mutational event(s) and may be an adaptation for aquatic vision (Levenson et al., 2006). The M/L cone pigments of pinnipeds are more like those of terrestrial carnivores (maximum sensitivities of 550–560 nm) than those of the bottlenose dolphin (Fasick & Robinson, 1998; Levenson et al., 2006). This may be related to the need for maintenance of effective terrestrial vision. Electrophotographic studies in pinnipeds showed good agreement between rod opsin sequence predictions and ERG spectral sensitivity but there was no evidence of any contribution from cone pigments despite molecular predictions (Levenson et al., 2006). This group hypothesized that there could be too few cones to yield reliable signals, but the numbers of cones (from 7000 to 11,000 per mm²) are similar to some terrestrial carnivores in which ERG cone signals have been successfully recorded.

The tapetum lucidum in pinnipeds, both phocids and otariids, is extensive. The entire fundus is tapetal with pigment only around the extreme periphery (Ninomiya et al., 1998; Levenson et al., 2006). This may be related to the need for maintenance of effective terrestrial vision. Electrophotographic studies in pinnipeds showed good agreement between rod opsin sequence predictions and ERG spectral sensitivity but there was no evidence of any contribution from cone pigments despite molecular predictions (Levenson et al., 2006). This group hypothesized that there could be too few cones to yield reliable signals, but the numbers of cones (from 7000 to 11,000 per mm²) are similar to some terrestrial carnivores in which ERG cone signals have been successfully recorded.

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The lamina cribrosa in pinnipeds is very delicate. A prominent vascular plexus surrounds the optic nerve posterior to the globe (Miller et al., 2010). The function of this prominent vascular plexus for pinnipeds and also cetaceans may be for maintenance of appropriate temperature and oxygen concentration to the delicate tissues of the posterior globe (Ninomiya & Yoshida, 2007).

Ophthalmic Diseases of Pinnipeds

Eyelids/Periocular Region

Eyelid diseases in pinnipeds include dermatopathies and traumatic injuries, including lacerations. The only species encountered so far with periocular skin lesions is the Southern sea lion (Otaria flavescens) which develops intermittent skin lesions on all areas of the body, including the periocular areas. Lesions are characterized by alopecia and superficial skin
ulcerations. Eyelid lacerations are uncommon and if small are usually not surgically repaired (Fig. 33.38).

Older pinnipeds often have eyelid masses that appear benign in behavior (Fig. 33.39). Histopathologic evaluation of one mass showed an intradermal round cell tumor with no detectable mitotic activity. Differential diagnoses included plasmacytoma or mast cell tumor but special staining was negative for mast cell granules.

**Cornea**

Corneal diseases are one of the two main eye problems that occur in both wild and captive pinnipeds. In a previous report, corneal disease was the leading issue in California sea lions (Dunn et al., 1996). This was later confirmed by a survey that reported an incidence of 64.6% in California sea lions and other otariids (Colitz et al., 2010a). California sea lions maintained in freshwater were significantly more predisposed to develop corneal edema than those maintained in salt water ($p < 0.00001$).

**Wild Pinnipeds**

Over 6,000 pinniped cases from two California stranding facilities were recently reviewed for eye disease and concurrent systemic problems (Colitz et al., 2011a). Briefly, the most common eye problems seen in pups were corneal edema and nonspecific opacities, followed by ulcers. The most common concurrent systemic abnormality identified was malnutrition. In yearlings, corneal ulcers were most common and, like pups, malnutrition was the most common concurrent systemic abnormality. Juveniles had the fewest common ocular eye and systemic abnormalities. Corneal perforations and phthisis bulbi were the most common ocular findings and gunshot the most common systemic abnormalities. In subadults, phthisis bulbi was the most common eye problem (Fig. 33.40) and domoic acid toxicity was the most common systemic disease. In adults, corneal edema and corneal ulcers were the most common eye abnormalities and, like subadults, domoic acid toxicity was the most common systemic disease. Malignant neoplasia is very common in pinnipeds, especially stranded California sea lions (Gulland et al., 1996; Ylitalo et al., 2005). It is not possible to evaluate the real frequency of neoplasia in the wild population based on stranded animals. Periocular tumors are also occasionally encountered.

**Pinnipeds under Human Care**

For decades, anterior segment disease has been observed in pinnipeds under human care (Greenwood, 1985; Hirst et al., 1983).

**Exogenous Factors Contributing to Corneal Problems in Pinnipeds under Human Care**

**Otariids** Type of water (i.e., fresh or salinated) varies by facility. Most facilities around the world now use some type of salinated water including synthetic ocean water such as Instant Ocean or city water salinated to approximate the salinity of the ocean (32–35 parts per thousand). A few facilities still maintain pinnipeds in freshwater. Problems with water quality may not be apparent until the acute onset of “otariid keratopathy” (OK) or acute edema in pinniped species in one or more animals at once. Presentation may be mild blepharospasm and corneal edema or as severe as reluctance to open
one or both eyes, loss of appetite, and depressed attitude. Once clinical signs of OK occur, resolution depends on two main factors: correction of the water quality problem and prevention of corneal infection. After these are corrected, affected corneas will remain more sensitive to minor changes in water quality and the environment itself, such as changes in sunlight (UV radiation). This is especially true if the animals live in freshwater. One facility maintains a nonoxidant pool for animals under treatment (M. Walsh, personal communication).

The disease was categorized into three stages based on increasing severity (Table 33.1). In addition, sea lions manifest differently in the initial stages than do fur seals. Differences in latitude may also influence manifestation of the disease in otariids around the world (C.M.H. Colitz, personal observation). California sea lions' initial lesion, Stage 1, occurs just dorso-temporal to the axial cornea, often adjacent to the flattened plateau with perilimbal edema and pigmentation migrating over the limbus (Fig. 33.41). The focal grey lesion is often not visible without proper magnification. Clinical signs of blepharospasm and epiphora occur when the lesion becomes ulcerated. Small fluorescein-positive superficial ulcers at that location should be treated to prevent

<table>
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opportunistic bacterial infections. A common concurrent clinical sign is perilimbal edema that extends temporally from the dorsal aspect around to the ventral aspect. Conjunctival pigmentation also begins to migrate across the limbus. In fur seals, the initial clinical signs of Stage 1 include perilimbal edema, followed by pigment migration across the temporal limbus and, in some cases, vascularization crossing just into the perilimbal area (Fig. 33.42). The dorsotemporal opacity is often absent in fur seals at Stage 1.

In Stage 2, the initial small Stage 1 lesion is larger and often appears as an indolent ulcer or separation of the overlying epithelium from the adjacent stroma (Fig. 33.43). Blepharospasm and epiphora are constant and affected eyes may be held closed most or all of the time. Opportunistic secondary infections are common and must be addressed aggressively to avoid progression to deeper stromal ulcers and perforation. Diffuse edema is present surrounding and throughout the obvious ulcer or nondebrided indolent lesion; perilimbal edema is more apparent and limbal pigmentation is increased, sometimes crossing onto the adjacent cornea. Vascularization may be observed at the temporal or dorsotemporal limbus. Debridement aids in healing. Aggressive use of antibiotics and anticollagenolytic medications such as doxycycline are imperative. Facilities may be reluctant to continue doxycycline therapy for extended periods of time because it is also used to treat bite wounds susceptible to Mycoplasma infections and other conditions, fearing that chronic continual use may lead to endemic bacterial resistance. Plans for short- and long-term antibiotic use should be discussed and developed with the facility’s veterinarian. Since many of the factors that are responsible for eye disease do not change, it is important to promote environmental improvements to decrease future problems and subsequent overuse of antibiotics. Judicious use of systemic nonsteroidal anti-inflammatory medications provides pain relief but prevention of associated gastrointestinal issues is important. Tramadol has variable effects on pinnipeds, including no effect, good pain control, sleepiness, and ataxia. Topical morphine and nalbuphine have been ineffec-

![Figure 33.41](image1.png)

**Figure 33.41.** Stage 1 OK in a California sea lion. There is a small grey superficial corneal opacity located dorsotemporal to the axial cornea that is fluorescein negative (white arrow). There is also mild perilimbal edema evident temporally and a small amount of conjunctival pigment branching onto the temporal limbus. (Legend and photo are from a published paper in *Veterinary Ophthalmology* 2010).

![Figure 33.42](image2.png)

**Figure 33.42.** Stage 1 OK in a South African fur seal. Both corneas demonstrate perilimbal edema. **A.** Right eye has vascularization growing through the limbal region, mild conjunctival depigmentation, and a grey-white corneal opacity located dorsotemporal to the axial cornea. **B.** Left eye has pigmentation that has migrated over the temporal limbus. There is a slightly denser grey-white corneal opacity located dorsotemporal to the axial cornea. Both eyes had incipient cataracts.
The limbal pigmentation becomes sparse and sometimes disappears. In addition, the bulbar conjunctival pigmentation often becomes attenuated with a few focal areas left, like freckles (C.M.H. Colitz, personal observation). Fur seals manifest similarly to sea lions at this stage except that they may retain pigmentation at the limbus and in the cornea (Fig. 33.46).

While most California sea lions develop progressive OK as previously described, a small percentage initially manifest quiescent. Once controlled, a quiescent Stage 2 lesion is grey in appearance without surrounding edema and the eye is comfortable. In fur seals, Stage 2 lesions have dorso temporal corneal involvement as in sea lions but ulcerations appear less common (Fig. 33.44).

In Stage 3, the medium-sized lesion of Stage 2 is deeper and larger and the diffuse edema typically encompasses most of the cornea, with perilimbal edema still denser than the rest of the cornea but sometimes difficult to distinguish (Fig. 33.45). The limbal pigmentation becomes sparse and sometimes disappears. In addition, the bulbar conjunctival pigmentation often becomes attenuated with a few focal areas left, like freckles (C.M.H. Colitz, personal observation). Fur seals manifest similarly to sea lions at this stage except that they may retain pigmentation at the limbus and in the cornea (Fig. 33.46).
Melting ulcers are not common secondary to otariid kerato­
thy or in other pinniped species despite the potentially
pathogenic normal flora that reside in their habitats. Pseu­
donas spp. are present in 60%–70% of fish caught in marine
environments and in biofilms, so elimination of this organism
from their environments is not possible. Animals with melting
ulcers have acute blepharospasm and mucopurulent ocular
discharge. Mucopurulent discharge is uncommon in pinnipeds
with nonmelting corneal ulcers. Aggressive antibiotic therapy
is imperative as is inhibition of stromal melting to avoid per-
foration and vision loss. Surgical intervention may be indi-
cated if enough normal cornea remains.

Successful treatment of OK requires appropriate manage-
ment of the secondary bacterial or yeast/fungal infections.
Doxycycline is used often for its anti-inflammatory and
healing properties (Chandler et al., 2007; Perry et al., 1986).
Doxycycline administered orally can be detected in the tear
film of pinnipeds and achieves concentrations likely to have
antimicrobial and anti-inflammatory effects at the ocular
surface (Freeman et al., 2011). Collaboration with the facility
veterinarian is important to address concerns for extended use
of antibiotics and to investigate the possible factors that may
impede healing such as resistant or new infections.

Phocids The species of phocids under human care include
harbor seals (P. vitulina), harp seals (Pagophilus groenlandi-
cus), grey seals (Halichoerus grypus), and Hawaiian monk
seals (Monachus schauinslandi), with harbor seals comprising
the vast majority. As yet no consistent progressive keratopathy
of harbor seals has been described. Most corneal lesions
appear to be random and due to environmental causes and the
lesions become quiescent after the initial episode is resolved.
Too few harp seals have been evaluated to describe any spe-
cific corneal anomalies other than nonspecific corneal edema.
Grey seals appear to have a consistent progressive corneal
disease. A photograph taken of a grey seal in the wild showed
similar corneal lesions to those in animals under human care.
The lesions include a triangular area of corneal edema with
pigmentation and vascularization (Fig. 33.47). One eye evalu-
ated also had a stromal abscess at the apex of the lesion that
resolved with appropriate medications. Hawaiian monk seals
are predisposed to diffuse corneal edema with intermittent
ulcerations. The current hypothesis for its cause is excessive
exposure to sunlight. The corneal lesions of monk seals that
were moved to shaded areas have improved (B. Doescher,
personal communication).

Phocid pups rescued following stranding frequently
develop diffuse, often unilateral corneal edema. It has been
hypothesized to be due to the manner in which pups are
restrained for feeding since the right eye is almost always
affected. The type of water (salt or fresh) does not affect its
occurrence but may affect the response to treatment. Topical
medications do not seem to improve the condition. Often

with acute to subacute corneal edema with numerous small to
large sized bullae. This manifestation is aggressive and
responds poorly to most medications. Infection must be con-
trolled and final resolution may take up to a year or longer.
Although the underlying cause(s) is/are still unidentified
water quality parameters, salinity, light exposure, oxidants,
infected ulcerated lesions and progressive fibrosis, but can also cause primary keratopathies as in otariids. In addition, the eyelid margins surrounding conjunctiva become depigmented over time.

Corneal Disease Secondary to Lens Luxation
As in other susceptible species, corneal edema and fibrosis secondary to anterior lens luxation are permanent unless the lens is removed immediately. Unfortunately, chronic lens luxations are common. Corneal pathology includes endothelial attenuation, rupture of Descemet’s membrane, hypercellularity of the stroma with fibroblasts, and variable vascularization.

Lens  Cataracts are the other main eye problem that affects both wild and captive pinnipeds (Fig. 33.49). Cataracts are the most common eye problem in phocids (Dunn et al., 1996; Schoon & Schoon, 1992) and are the second most common problem in otariids. Epidemiologic analysis demonstrated a statistically significant association between maintenance of harbor seals in freshwater and an increased risk of cataracts (p < 0.01) (Dunn et al., 1996). The overall prevalence of cataracts in this species was 24%; harbor seals maintained in freshwater were three times more likely to develop cataracts than those in salt water (Dunn et al., 1996). It is possible that uveitis secondary to corneal disease contributes to cataract formation. The most common clinical signs of uveitis in pinnipeds include corneal edema (already present with corneal problems) and miosis (not always apparent due to normal miosis in ambient light).
In the Wild In a recent retrospective study evaluating stranded pinnipeds from two California facilities, the incidence of cataracts was 0.77% overall in all age groups and species (Colitz et al., 2011a). A smaller study evaluated stranded pinnipeds over a 6-year period and found that 0.5% of 765 California sea lions had ocular disease that included cataracts (Gerber et al., 1993), but unfortunately they did not analyze these data by specific diagnosis. In another study evaluating Northern fur seals, 1501 subadult males were examined; 23 had unilateral cataracts (1.5%) and the adult harem bulls had severe corneal fibrosis that precluded lens evaluation (Stoskopf et al., 1985). Further studies of more rookeries would confirm whether 1.5% is an accurate estimate of cataracts in wild pinnipeds.

Under Human Care Of pinnipeds under human care, 15.3% of animals evaluated had both cataracts and lens luxation; 34.2% had cataracts alone (Colitz et al., 2010c). Of 222 eyes evaluated (n = 111 animals), 46.8% had cataracts, lens luxations, or both. The majority of animals in the study were California sea lions due to the populations evaluated. Forty-two percent of eyes of California sea lions were diagnosed with cataract, lens luxation, or both. These percentages are unlikely to be different in other geographic areas of the world. All age groups over 5 years of age had cataracts but since the study was published pups, yearlings and animals up to 5 years of age have also been diagnosed with cataracts (C.M.H. Colitz, personal observation). Cataract incidence increased with age as expected.

Risk factors for cataract development in pinnipeds included increasing age, insufficient access to adequate shade, history of any ocular disease, and history of fighting (Colitz et al., 2010c). The nutritional background of captive-raised pinnipeds may also be a factor. Pups may be separated from their mothers for hand-raising which can result in weight loss or failure to gain weight. One harbor seal that was weaned and went through extensive weight loss developed juvenile bilateral cataracts (M. Walsh, personal communication).

Cataract surgery in pinnipeds has been previously described (Barnes & Smith, 2004; Dutton, 1991; Filer et al., 2003). These reports describe phacoemulsification in two fur seals and a northern elephant seal pup. Others including the author (Colitz) have also found phacoemulsification to be efficient in most young animals but phacoemulsification in a 2-year-old stranded California sea lion with cataracts was unsuccessful. The reasons included complete lens instability and a very dense nucleus. Even relatively young pinnipeds can have issues common in adult animals and the surgeon must be prepared to convert to either an extracapsular approach in incompletely unstable lenses or to intracapsular lens extraction when necessary.

Unlike in most terrestrial mammals, topical mydriatics do not cause pupil dilation in pinnipeds. The anatomy of the dilator muscle differs from terrestrial mammals. It is perpendicular to the sphincter muscle and is most robust near the iris base (Miller et al., 2010). In addition, the dilator muscle extends posteriorly over the widened base of each ciliary process (Miller et al., 2010). Subconjunctival atropine partially dilated the pupils of a fur seal for up to 4 days (Barnes & Smith, 2004). Repeated administration of topical 10% phenylephrine also partially dilated the pupils of a phocid for an hour (C.M.H. Colitz, personal observation). These experiences suggest that the fibrous tunic may impede penetration of the mydriatics or that there may be too few uveal cholinergic and/or adrenergic receptors to effect a response. Intracameral administration of 1:1000 preservative-free epinephrine provides better dilation than topical mydriatics with a maximal pupil diameter of approximately 1 cm, which is about three-quarters dilated compared to a canine patient (C.M.H. Colitz, personal observation).
Section IV

Findings included perilimbal edema, excessive iridal surface structures, and dyscoria as well as suspected cataracts based on leucocoria. The pupils would not dilate under darkened conditions. Ultrasound evaluation found bilateral cataracts and possible persistent hyperplastic primary vitreous (Erlacher-Reid et al., 2011). Other cases have been diagnosed as well (Colitz et al., in preparation).

Glaucoma

Primary glaucoma is rare in captive pinnipeds; only one case has been clinically documented (C.M.H. Colitz, unpublished data). Mild unilateral buphthalmos was diagnosed in a California sea lion at approximately 2 years of age and antiglaucoma medications were suggested. Over the following 5 years the eye became gradually more buphthalmic (Fig. 33.51). The pupil became mydriatic and unresponsive to light with negative menace and dazzle responses and an axial incipient cataract developed.

Secondary glaucoma is uncommon but occurs due to chronic lens-induced uveitis. Anterior lens luxations are common in pinnipeds but buphthalmos is not, presumably due to the mydriatic pupil allowing aqueous humor to continue normal flow into the immense iridocorneal angle. Hyphema following lens removal or trauma can result in secondary glaucoma and buphthalmos. Secondary glaucoma responds well to oral and/or topical carbonic anhydrase inhibitors and appropriate anti-inflammatory medications (C.M.H. Colitz, personal observation).

Fundus

Complete fundic examinations are difficult to perform due to the inability to dilate the pinniped pupil with anticholinergic or sympathomimetic mydriatic drugs. No fundus lesions have been observed when evaluations have been possible.

Cetaceans

Introduction

Cetaceans, the dolphins and whales, evolved from terrestrial ancestors over 50 million years ago and have become the most
dominant group of marine mammals in terms of geographic range, ecological diversity, and taxonomy (Fordyce, 2009). Cetaceans are thought to be derived from common ancestors of artiodactyls, possibly being most closely linked to hippopotamuses, and this has strong genetic support (Boisserie et al., 2011; Nikaido et al., 1999). There are approximately 84 species, with new ones being described and others becoming extinct in our lifetime. They are incredibly diverse in size, natural environments, and diets. Most inhabit oceans, but some inhabit freshwater rivers; some can dive several thousand meters for over an hour like the sperm whale (Physeter macrocephalus) and others are functionally blind like the now extinct Ganges river dolphin (Platanista gangetica). The smallest is the newborn vaquita (Phocoena sinus) and the largest is the adult blue whale (Balaenoptera musculus) at 33 meters in length (Ballance, 2009).

Cetaceans are subdivided into two suborders, the Mysticetes or baleen whales, and the Odontocetes or toothed whales. Baleen whales are generally huge and are not kept under human care. Toothed whales include true dolphins, river dolphins, monodontids (beluga whale and narwhal), porpoises, sperm whales, and beaked whales. Most toothed whales are small to medium sized, except for the sperm and beaked whales. In contrast to baleen whales, odontocetes have one blowhole, possess teeth, and have a large ovoid melon in the anterior part of the facial region used for echolocation. Baleen whales have two blowholes, do not have teeth but instead have a filter-feeding plate mechanism and do not echolocate (Hooker, 2009). Only odontocetes are kept under human care and typically include true dolphins, beluga whales, pilot whales, and porpoises.

In the wild, vision of odontocetes complements echolocation capabilities; under human care and in clear water, cetaceans decrease use of echolocation and increase use of their vision. Vision is used in social interactions, hunting for prey, reproduction, orientation, defense against predators, and for discrimination of individuals based on colors and markings (Mass & Supin, 2009). A recent study supports the use of echolocation in situations where vision is absent. A blind-folded dolphin accurately copied behaviors of another dolphin (Jakkola et al., 2010). Similar to pinnipeds, only one type of cone has been found in bottlenose dolphins and is limited to the blue-green spectrum. However, a recent report found that the Amazon river dolphin’s rhodopsin is shifted toward the red-green end of the spectrum, akin to that of terrestrial mammals rather than that of oceanic cetaceans (Kezmoh, 2011). This may be an adaptation to their natural shallow freshwater environment. Further studies are indicated to assess the color spectrum of other cetacean species.

The lateral position of the eyes provides a visual field of 120–130° and panoramic vision. Despite the eyes being laterally placed on the head they are positioned ventrally. When observing objects in air, eyes of smaller species can move rostrally by 10–15 mm, giving them overlapping visual fields of 20–30° in the frontal sector, suggesting the ability of binocular vision. However, decussation of the optic fibers has not been fully described and uncrossed optic fibers have not yet been identified (Mass & Supin, 2009).

The eyes of cetaceans have adapted to the ocean and its associated risks. Ocean water contains debris and particulates that can damage the eye and there is a vast range of temperatures and visibility conditions and significant light scatter (Mass & Supin, 2009).

### Anatomy and Physiology

Globe dimensions have been measured in several marine mammal species (Miller et al., 2012; West et al., 1991). The outer axial length of the beluga whale globe measured an average of 23.66 mm (20.67–28.75 mm) and the inner axial length measured 22.04 mm (19.64–26.67 mm) (Miller et al., 2012). The horizontal corneal diameter measured an average of 19.26 mm (16.33–22.08 mm) and vertical corneal diameter measured 16.17 mm (14.86–17.08 mm). Bottlenose dolphin globes had an average axial length of 29.13 mm (25–33.28 mm), scleral thickness measured 5.43 mm (5–7.77 mm), horizontal equatorial diameter measured 36.85 mm (36.1–38.71 mm), and vertical equatorial diameter 33.84 mm (32.73–36.28 mm). Horizontal corneal diameter measured an average of 21.45 mm (20.44–22.4 mm) and vertical corneal diameter an average of 18.48 mm (15.71–21.5 mm). Cetaceans’ globes are flattened at the anterior aspect with a small anterior chamber and the eyecup is almost hemispherical. The horizontal diameter is wider than the vertical diameter (Mass & Supin, 2009). The equatorial diameter of the beluga whale lens is 7.9 mm and its axial length is 7.2 mm (West et al., 1991).

The cornea is considerably thicker in the periphery than in the center. This difference makes the cornea a divergent lens under water (Kroger & Kirschfeld, 1993; Mass & Supin, 2007). This is true in both baleen whales and in toothed whales (Mass & Supin, 2007). The cetacean cornea has five layers: epithelium, a variably thick Bowman’s layer, thick collagenous stroma, a very thin Descemet’s membrane, and an endothelial layer. Bowman’s layer thickness varies by species, with the bottlenose dolphin having the thickest (Miller et al., 2012). The tear film of cetaceans lacks the lipid layer found in terrestrial mammals. Recent data have found large glycoproteins, specifically mucin-type O-glycans (Kelleher Davis et al., 2010), in the tears of bottlenose dolphins, supporting the hypothesis that mucins are critical for the protection of the ocular surface of marine mammals (Kelleher Davis & Sullivan, 2008). Tear film analysis has also been performed in the killer whale (Orcinus Orca) (Colitz et al., 2007). Proteins identified included submaxillar apomucin, lysozyme, immunoglobulin V(H), immunoglobulin J chain, immunoglobulin A heavy chain, MUC19, and others. The thick tear film in cetaceans suggests that topical medications may not penetrate efficiently. The addition of acetylcysteine, to a final concentration of 3%, has been clinically useful for the treatment of various diseases (C.M.H. Colitz, unpublished data).
The corneal surface plays a minimal role in underwater light refraction because the refractive index of water is almost identical to that of aqueous humor. The lens is the major refractive structure used in underwater vision and it is described as having lower refractive indices in the outer layers than in the nucleus (Mass & Supin, 2009). The lens is nearly spherical in most cetaceans, like in pinnipeds and fishes, which compensates for the higher refractive index of water and allows for images to be focused onto the retina. Other mysticetes and the beluga whale have a slightly elliptical shaped lens. The total refraction of the cornea and lens of the cetacean eye is emmetropic within ±1D under water (Kroger & Kirschfeld, 1994).

The iris is highly vascularized and has a robust musculature. The ciliary body likewise is highly vascularized, but its musculature is absent or vestigial. The iridocorneal angle is wide with long slim pectinate ligaments and trabeculae (Hatfield et al., 2003; Miller et al., 2012). The iridocorneal angle of the short-finned pilot whale was described and compared to other species. This whale has thin small pectinate ligaments that are taller by two to three times compared to the West Indian manatee, the hippopotamus, and the African elephant. The short-finned pilot whale has a large uveal trabecular meshwork, a small corneoscleral trabecular meshwork with 10–11 layers of trabeculae, and has large vessels in the angular aqueous plexus with an average of three large vessels present (Hatfield et al., 2003). Encapsulated sensory corpuscles (ESCs) were found in most cetaceans evaluated and were present in the anterior uvea, the sclera surrounding the anterior uvea, the trabecular meshwork or any combination of these locations (Miller et al., 2012). ESCs were found throughout the corneoscleral trabecular meshwork in the short-finned pilot whale (Hatfield et al., 2003). ESCs are specialized nerve endings, or mechanoreceptors, with no proven function and are not found in other mammals. However, ESCs could play a role in lens repositioning (D. Samuelson, personal communication). Similar structures have been found in the buccal cavity of the baleen whale, Balaenoptera acutorostrata (de Baker et al., 1997). ESCs have been found adjacent to vessels and may detect changes in vessel volume, pressure, and possibly temperature (Wickham, 1980). It has been proposed that the contraction of the large retractor oculi muscles will increase IOP changes and result in forward movement of the lens (Kroger & Kirschfeld, 1989). Fine-tuning of this potential mechanism for refractive change may be in part autonomically controlled through aqueous humor dynamics in tandem with the ESCs, which could serve to detect IOP changes at the level of aqueous humor outflow (D. Samuelson, personal communication).

Normal IOPs of cetaceans have not been published but they are often referred to as being very high (Dawson, 1980). The author (Colitz) has measured IOPs, using rebound tonometry (TonoVet), in two beluga whales, one harbor porpoise, and 21 bottlenose dolphins. The eyes were clinically normal based on ophthalmologic evaluation. The IOP of a 5-month-old beluga whale was 16 mm Hg OU and that of a 10-year-old beluga whale 25 mm Hg OU. The IOP of the harbor porpoise (Phocoena phocoena) was 29 mm Hg OD and 31 mm Hg OS. The average IOP in the adult Atlantic bottlenose dolphins (Tursiops truncatus) was 40.43 mm Hg OD and 40.57 mm Hg OS. Average IOP in Atlantic bottlenose dolphins using applanation tonometry (TonoPen) was 28.95 mm Hg OD and 29.64 mm Hg OS (M. Yamagata, personal communication). Average IOP in Pacific bottlenose dolphins (Tursiops truncatus gillii) using rebound tonometry was 38.27 mm Hg OD and 36.5 mm Hg OS. Three Pacific bottlenose dolphins were in beached position for ophthalmic evaluation and IOP measurements; the average IOP was 57.67 mm Hg OD and 57.33 mm Hg OS. Based on these data the IOPs of bottlenose dolphins appear to be normally higher than other mammals and tonometry performed in the beached position, though much easier, yields aberrantly elevated IOP measurements. The weight of their bodies on their ventrums is likely the cause.

The retina is holangiatic but differs from ungulates from which cetaceans are derived, in that the vessels do not protrude toward the vitreous. The tapetum covers two-thirds to the entire fundus similar to pinnipeds. The inner plexiform and ganglion cell layers of the cetacean retina differ most from terrestrial mammals. The ganglion cells are large and sparse (Mass & Supin, 2007; Miller et al., 2012). All cetaceans evaluated in one study except the sperm whale had a single row of large ganglion cells; the sperm whale had multiple layers of ganglion cells (Bjerager et al., 2003). Dolphins have two areas of high ganglion cell density, both in the horizontal aspect, with one in the temporal sector and the other in the nasal sector (Mass & Supin, 2007). These zones are connected by an elongated zone of increased cell density, although lower than in the temporal and nasal areas, that runs ventral to the optic nerve, giving the impression of a visual streak (Mass & Supin, 2007).

There is a highly developed rete mirabile, a vascular network located posterior to the globe, that fills much of the orbit. The globe has a very thick sclera and large extraocular muscles. All of these features probably protect the eye from mechanical damage and underwater cooling (Mass & Supin, 2009).

**Ophthalmic Diseases**

Marine mammal veterinarians who work with stranded cetaceans and evaluate wild populations have seen fewer eye lesions than in captive animals that are exposed to environmental factors such as oxidant exposure. Therefore, lesions described are from cetaceans under human care in a variety of habitats. An image of a normal eye from a bottlenose dolphin is shown for comparison to lesions in this chapter and as a reference for the clinician unfamiliar with this species (Fig. 33.52).

There are very few reports in the literature about eye problems in cetaceans; most of the information is a review of clinical issues encountered by the author (Colitz) over the past 9 years.
For clinicians without ophthalmic equipment, ocular evaluations can be challenging. Many systems are outdoors and positioning the animals toward the sun may result in irritation, increasing closure of the eyelids. Training for eye exams and treatment should be a basic part of husbandry of any animal population where eye disease is present. Shade over the eye should be provided if examined in direct sunlight and this may require some desensitization to a hand or object held above their head. On cloudy days, a great deal of reflection on the cornea can make detection of corneal disease difficult and confusing for many clinicians. Animals can be trained to open their eyes for examinations but this approach should not be promoted when staring at direct sunlight. They should also be trained to allow the eye to be positioned slightly under the surface of the water, which removes direct cloud and sun reflection. Most animals are very compliant with their head being gently pushed just below the surface. Although detection of minute detail is lessened, the extent of opacity and other pathology can be better appreciated. Animals that have access to underwater viewing can also be trained to submit to ophthalmic examination where reflection is minimized (Fig. 33.53).

Eyelids/Periocular Region
Eyelid problems in cetaceans are rare but include traumatic injuries like lacerations. Small eyelid lacerations are usually not repaired surgically. If the laceration is large, primary repair may be performed.

Cornea
Corneal diseases are the primary eye problem occurring in cetaceans under human care (Colitz et al., 2010b). Most of the affected animals are bottlenose dolphins (Tursiops spp.), beluga whales (Delphinapterus leucas), and some killer whales (Orcinus orca).

Clinical evaluation of Atlantic and Pacific bottlenose dolphins found three common entities that were named based on their location of lesions of the cornea. Animals evaluated thus far have ranged between 1 and 55 years of age.

Medial Keratopathy
Lesions identified at the medial aspect of the cornea typically have swirling fibrosis, pigmentation, and vascularization entering from the medial limbus and extending into the adjacent cornea (Fig. 33.54). When severe, the lesions extend to the axial cornea and some coincide with horizontal lesions described in the next sections. These lesions develop occasional stromal abscesses that cause acute blepharospasm and a slight focal yellowing within the fibrotic lesion. Often cytologic evaluation of the lesion is not possible or practical. The
The characteristic appearance of horizontal keratopathy is seen in the axial cornea, initially appearing as a linear horizontal grey to white opacity of variable width associated with variable blepharospasm (Fig. 33.56A,B). In addition to bottlenose dolphins, these lesions are also seen in beluga whales (Fig. 33.56C) (C.M.H. Colitz, personal observation). They are often called “speed lines” by many marine mammal veterinarians.

Clinical signs respond to antimicrobial therapy. Medications to alleviate blepharospasm and self-trauma may be used if signs are severe.

The cause of these consistent medial lesions is under investigation but has not been definitively identified. These lesions are more commonly seen in geographical areas where sun is most intense, so perhaps incoming UV radiation enters via the temporal limbus, causing most damage medially due to peripheral light focusing (Coroneo et al., 1991). Direct exposure to UV light is also a possible cause, so trainers’ positioning of animals during feeding and training sessions should consider the relationship of the eyes to the sun.

Temporal Keratopathy
A triangular corneal opacity at the temporal aspect of the cornea has been identified in some dolphins and it has a characteristic appearance. A superficial grey-white triangular lesion originating from the temporal limbus encroaches upon the cornea and may or may not be vascularized (Fig. 33.55). These lesions can also be seen in conjunction with horizontal keratopathy, possibly as an extension of the axial lesions. The underlying cause is unknown but may also be due to peripheral light focusing (Coroneo et al., 1991).

Horizontal Keratopathy
Lesions consistent with horizontal keratopathy occur in the axial cornea, initially appearing as a linear horizontal grey to white opacity of variable width associated with variable blepharospasm (Fig. 33.56A,B). In addition to bottlenose dolphins, these lesions are also seen in beluga whales (Fig. 33.56C) (C.M.H. Colitz, personal observation). They are often called “speed lines” by many marine mammal veterinarians.
SECTION IV: Special Ophthalmology

These “speed lines” are seen in animals as young as under a year of age and in any age group thereafter. Animals continuously exposed to chronic oxidative stress or develop larger/wider lesions, often with stromal loss and a coppery green discoloration, as in rust (Fig. 33.57). Vascularization may be present. These areas are prone to opportunistic infections. The first clinical signs evident with an associated ulcer or stromal abscess are acute blepharospasm and diffuse corneal edema. Lesions with the coppery green hue are usually seen in middle-aged to older dolphins and their origin is unknown. The discoloration may be due to a disruption of iron homeostasis in the cornea. Iron is important for certain functions in the healthy cornea (Loh et al., 2009). In humans, iron is present in the tear film on the corneal surface extracellularly, carried by lactoferrin, which is secreted.

Interestingly, the initial “speed line” is often transient and it is unknown what occurs in the cornea to create the lesion. The lesions typically occur following a water quality imbalance including changes in chlorine or ozone levels, pH, increased debris or turbidity in ocean water habitats, or other similar situations. Young calves are more prone to play in water inflows which can carry higher levels of oxidants and may also carry debris in the water stream at high velocity if the filters are leaking sand. Animals that pattern swim may be likely to pass through concentrated clouds of oxidants. Documentation of oxidant levels may be inaccurate if caretakers are not checking levels at the inflow or if pool designs promote stratification and pockets of elevated oxidants. If chlorine levels are checked only at the side of the pool opposite the inflow, it may result in damaging levels at the inflows. While there is a variation in desired levels of oxidants in different facilities it is important that measurement of both total chlorine and free chlorine be run to better understand the potential involvement of chloramines in the pool system. Total chlorine concentrations of 1 ppm are less likely to cause eye lesions than higher concentrations and provide a margin of safety in case of delayed identification and correction of increases in oxidant levels due to human error, mechanical failure, or environmental shifts that cause chlorine shifts. Clinicians should know all of the variables involved in water quality to effectively treat lesions. These linear lesions occur where the superior and inferior eyelids almost close completely, leaving a small slit through which they see, that is, as if squinting. The current hypothesis for the cause of the linear lesions, which appear elevated and grey-white with slit-lamp evaluation, postulates a buildup of tear film, perhaps with an increased accumulation of mucin formation with focal linear edema. With time and repetitive insults, the lesions become flush with the corneal surface but remain grey-white in color. Slit-lamp evaluation localizes the lesions to the anterior stroma and epithelium, consistent with fibrosis. These usually have diffuse edema surrounding the denser grey-white lesions.

Figure 33.56. Horizontal keratopathy. Both eyes (A and B) of the same Atlantic bottlenose dolphin with irregular horizontal grey-white linear corneal opacities that extend to the temporal limbus. The right eye also has a focal rust-colored opacity at the medial aspect of the horizontal lesion. Both superior eyelids are mildly hyperemic. C. Right eye of a beluga whale with an axial dense horizontal white linear opacity surrounded by a more diffuse opacity. The limbus has numerous small vessels growing through it. The extensive iridal vascularization is normal.

Figure 33.57. Chronic horizontal keratopathy. Left eye of an Atlantic bottlenose dolphin with an axial horizontal grey-white corneal opacity. There is a larger denser grey-white opacity surrounding the most axial aspect of the horizontal lesion, a rim of rust-colored opacity, and diffuse edema of the remainder of the cornea.
by the lacrimal gland’s acinar epithelial cells. Lactoferrin is important for regulating iron levels, strengthening corneal antibacterial defenses by binding to iron, and preventing oxidative damage (Ellison, 1994; Loh et al., 2009). Histopathological characteristics of horizontal keratopathy appear similar to those of keratoconus in humans (Colitz et al., 2012; R. Dubielzig, personal communication). These include thinning of corneal epithelium and stroma, and breaks in Bowman’s layer and in Descemet’s membrane. Investigations are ongoing to better understand the pathophysiology of this condition.

Other Corneal Lesions

Other common findings include axial fibrosis with or without vascularization due to trauma. Dolphins play and interact aggressively at times. They have very sharp teeth that may sometimes cause lacerations of the eyelids and adjacent cornea (Fig. 33.58). Blunt trauma is also common and causes acute blepharospasm that may persist for weeks at a time. Apropriate oral and, if possible, topical antimicrobial medications are indicated to treat or prevent bacterial infection. Actively healing traumatic ulcers and perforations readily vascularize, except in dolphins of advanced age. When perforated, some corneas heal and vision is retained; in severe cases, the entire cornea may be sloughed. When healed, these phthisical eyes are clinically comfortable (Fig. 33.59).

Corneal abscesses have also been identified in animals with other systemic diseases. For example, fungal blowhole infection was diagnosed by culture and cytology in an animal with a corneal stromal abscess. Since the dolphin had a nursing calf, systemic antifungal medications were not used. Instead, topical antifungal drops were compounded with 3% acetyl-cysteine and the abscess resolved. Interestingly, the blowhole infection also resolved; transient positive cultures from the blowhole do not necessarily indicate systemic disease.

Lens

Cataracts causing visual impairment are uncommon but immature cataracts have been identified in bottlenose dolphins and do not appear to impair vision (C.M.H. Colitz, personal observation) (Fig. 33.60). Beluga whales have also been diag-

Figure 33.58. Traumatic fibrosis and medial keratopathy. Right eye of an Atlantic bottlenose dolphin with a vertical irregular grey-white corneal opacity just medial to the axial cornea with a dense rim around an area of stromal loss. Medial to the vertical lesion is an area of grey-white opacity with vascularization and pigmentation.

Figure 33.59. Phthisis bulbi. Healed right eye of an Atlantic bottlenose dolphin following complete loss of the cornea due to a severe infection.

Figure 33.60. Right eye of an Atlantic bottlenose dolphin with an early immature cataract seen with retroillumination. The anterior cortical–anterior perinuclear cataract is surrounded by new normal lens fiber growth. The posterior polar Y suture cataract is seen axially. There is a bubble in the tear film. Medially, there is a faint grey-white corneal opacity with medial perilimbal edema.
nosed with cataracts (C.M.H. Colitz, personal observation) as have pseudorca (Pseudorca crassidens) (M. Walsh, personal communication). Echolocation may compensate for diminished sight in animals with extensive cataract.

**Uvea**

Primary uveal disease is uncommon. Uveitis due to corneal ulcers is likely but not clinically apparent. Corneal edema and opacities often preclude intraocular evaluation. Miosis is normal in these species so it is not a reliable indication of inflammation. One way to evaluate the difference between physiological miosis and clinically important miosis is to observe animals under dim light conditions, where the pupils normally dilate readily. With uveitis, the pupil dilates incompletely or not at all. More common clinical signs of uveitis include corneal edema and/or acute vision loss. Even these clinical signs may be due to corneal disease and secondary uveitis, rather than primary uveitis.

**Fundus**

Complete fundic evaluations are difficult due to the environments in which cetaceans normally live and it is often difficult to evaluate them in the evenings in dim light when pupils dilate naturally. However, to date no clinically abnormal fundus lesions have been identified.

**Ocular Manifestations of Systemic Disease**

As in all species, systemic diseases can affect the eyes. Unfortunately, complete ophthalmologic evaluations may be challenging, especially when a cetacean is ill and possibly unlikely to cooperate. A case of systemic Fusarium oxysporum infection was recently described in a 10-year-old Atlantic bottlenose dolphin (Tursiops truncatus) that died acutely. Necropsy findings included hemorrhage within the right cerebellum, right cerebrum, and the right eye (Staggs et al., 2010). Other cases are likely but are not commonly submitted for publication.

**Sireni ans**

Manatees and dugongs are the only extant herbivorous marine mammals (others are extinct) and are completely aquatic. There are only two genera and four species surviving today. Three species of manatees (Trichechus) live along the Atlantic coasts and rivers of the Americas (Trichechus manatus and Trichechus inunguis) and West Africa (Trichechus senegalensis). Only the Amazonian manatee (T. inunguis) lives in freshwater. The dugong (Dugong dugon) inhabits the Indian and southwest Pacific oceans (Ballance, 2009).

Manatee eyes are small relative to their large physical size. They lack eyelids per se and eyelashes. They constrict the circular sphincter muscle in the skin to cover the eye. The equatorial diameter of the West Indian manatee globe measures 18.8 mm and the axial diameter measures 18.5 mm, making it almost spherical (West et al., 1991).

Manatee corneas are normally vascularized in the fetus as well as the adult with capillaries and occasional venules and arterioles; vessels are located in the anterior stroma with extension into the anterior epithelium (Harper et al., 2005). Depth and area of the corneas that have vascularization vary even between eyes from the same individual and the axial cornea is devoid of vessels (Natiello & Samuelson, 2005). These vessels are not thought to impair vision, but a study evaluating behavior and vision found substantial differences between test subjects in visual acuity, especially in one manatee (Bauer et al., 2003). They hypothesized that the amount of vascularization may differ between manatees and presumably even eyes, depending on their histories in the wild; this difference may cause differences in acuity. Histological evaluation of the manatee cornea found a ridged corneal surface (Ben-Shlomo et al., 2010). The authors hypothesized that the ridges and vascularization are adaptations, allowing manatees to live in both fresh and saltwater environments. The lens is shaped like that of a terrestrial mammal with curvature strong enough for underwater vision without contribution from the cornea (Mass & Supin, 2007).

The resolution potential of the West Indian (Florida) manatee (T. manatus) eye is low based on ganglion cell density distribution (Supin et al., 2001). Dichromatic color vision, with sensitivity in the short (blue) and medium (green) spectra, may compensate for deficiencies in resolution (Cohen et al., 1982; Griebel & Schmid, 1996). Underwater visual acuity was measured in two captive Florida manatees using a grating stimulus system in both fresh and saltwater. It was determined that they had limited visual resolution, effective mostly for intermediate and longer distances (1 meter and greater with no significant near vision (Bauer et al., 2003). The West Indian manatee may have greater visual acuity than the Amazonian manatee as it can often transiently live in clear water (Hatfield et al., 2003). The Amazonian manatee, which lives in murky water, has a rod-dominated retina, high photoreceptor:ganglion cell ratio, some binocular vision at farther distances, and monocular vision with poor near distance focusing ability (Piggins et al., 1983). Manatees are diurnal shallow divers, different from many other marine mammals, which may explain the lack of a tapetum in the West Indian manatee (West et al., 1991).

Like cetaceans, manatees lack ciliary body musculature (Hatfield et al., 2003). In addition, the pectinate ligaments are small and thin, the uveal trabecular meshwork is large, and the corneoscleral trabecular meshwork is small, with seven to eight layers of trabeculae. The vessels in the angular aqueous plexus are large, with an average of six to seven vessels present (Hatfield et al., 2003). M manatees and their closest land relative, the African elephant, lack distinct ciliary processes and a well-defined pars plana. The anterior ciliary process is near the iris but not part of it and several branches of the major arteriole circle not only feed each of the ciliary processes of the manatee’s ciliary body, but the major arteriole circle is located between the posterior end of the iris and the anterior region of the ciliary body (Natiello et al., 2005). Further
analysis has found that each ciliary process is fed by an arterial bed that branches from the major arteriole circle (Natiello & Samuelson, 2005). The venous outflow system is unique to the manatee with a dual vein system. It is proposed that the dual outflow system may be important for regulation of blood flow to the ciliary processes and/or for IOP regulation (Natiello & Samuelson, 2005). Accommodation has not been definitively described but manatees have rapid and efficient control over blood flow to the ciliary body which would allow rapid control over aqueous humor production. These mechanisms may shift the lens position through changes in depth of the anterior chamber and/or change in shape or position of the ciliary body, adaptations necessary in the absence of ciliary musculature (Hatfield et al., 2003; Natiello & Samuelson, 2005; Natiello et al., 2005).

The IOPs in both eyes of nine manatees that were captured for an unrelated survey were measured (Ben-Shlomo et al., 2008). Rebound tonometry (TonoVet) was used in the animals without sedation or anesthesia and eyes had no clinically apparent abnormalities. The mean IOP was 8.5 mm Hg and the median was 9.5 mm Hg.

Review of vision studies in manatees suggests that they are able to focus better at greater than 1 meter from the object of interest. If they are closer than 1 meter they attempt to evaluate the object with each eye separately by shifting their bodies from side to side (Woodyard, 1984). The shifting of the body is most likely due in part to the inability of the eye to rotate as a result of the lack of extraocular muscle attachment to the eyes (Samuelson et al., 2009). Further research is necessary to fully understand the ways in which sirenians interpret and understand their environments; no details are available about dugong vision.

Ocular problems in manatees are more difficult to diagnose since most are not involved with trainers who may notice eye changes. In addition, the small size of their globes and their tendency to keep the eyes closed during handling may make early diagnosis difficult. Manatees examined during health assessments will tend to keep their eyes closed but may open them if water is applied to their head. In facilities where manatees reside long term, the eyes may be examined by holding vegetation close to the surface where they will tend to hold their eyes open. The most common lesions for animals in controlled environments are secondary to trauma, exposure to oxidant variation in controlled environments, and exposure to cold stress in wild juveniles taken in for rehabilitation, in which dermal injury can be extensive and severe. Lesions that have been seen in wild manatees include corneal fibrosis and ulcers (M. Walsh, personal communication) (Fig. 33.61). Manatees captured in nets may show ocular hemorrhage, abrasion of the cornea, and eyelid trauma. Multiple animals undergoing treatment in the same enclosure may develop ocular trauma when animals are in close proximity, with the most common damage from tails in contact with facial areas. Oxidant damage may occur similar to other species with diffuse corneal opacities more prevalent than linear or focal keratopathy. Manatees may also develop blepharedema due to oxidant damage. An adult and juvenile Florida manatee rescued in the Bahamas in salt water both had bilateral corneal opacities similar to lesions seen in captive animals. The cause is unknown but these animals had access to varying levels of

Figure 33.61. A. Eye of a Florida manatee with diffuse grey corneal opacity consistent with fibrosis. B. Eye of a Florida manatee following trauma; there are skin lesions surrounding the eyelid and the third eyelid is edematous and hyperemic. The cornea has an opacity axially. (Images courtesy of Dr. Michael Walsh, University of Florida).
salinity and possible irritants from various levels of water quality. Treatment for eye disease in manatees is very difficult since training for animals that are to be released is not encouraged. Water quality parameters out of the normal range are adjusted to remove inciting variables and animals should be rechecked at similar intervals to other species when possible.

**Otters**

Sea otters (*Enhydra lutris*) and Asian small-clawed river otters (also known as ASCO, *Aonyx cinereus*) are the most common species kept under human care. These animals are terrestrial carnivores that have adapted to an aquatic lifestyle. Sea otters primarily inhabit coastal areas and hunt for prey under water. ASCOs, from Southeast Asia, forage in mangrove forests.

Very little information is published about otter eyes. The most complete data are only available for the sea otter and are briefly summarized here (Murphy et al., 1990). Corneal power measured 3.5 mm (range from 8 to 10 mm). The anterior epithelium of the sea otter cornea comprised one-third of the total corneal thickness and the corneal thickness measured approximately 0.3 mm. Fixed lenses measured 3.5 mm (3.3–3.8 mm) in axial diameter and 7.4 mm (7.2–7.5 mm) in equatorial diameter. The iris sphincter and dilator muscles were well developed, as was the iridocorneal angle and the ciliary cleft extended 1.5 mm posterior to the pectinate ligaments. The ciliary muscle was robust and originated from three locations: the uveal tissue in proximity to the iridocorneal angle most anteriorly, the stromal elements that border the posterior aspect of the ciliary cleft, and the scleral aspect just internal to the corneoscleral venous plexus. All ciliary muscle fibers inserted external to the ciliary body with a few 0.5 mm posterior to the ora ciliaris retinae. Murphy et al. confirmed Walls’ work (Walls, 1942) that otters maintain an emmetropic focus in both water and air. The ability of Asian small-clawed otters to focus in air and water was found to be similar to that of sea otters (Schusterman & Barrett, 1973). The proposed mechanism of accommodation in the sea otter involves the anterior movement of the lens followed by its deformation by contraction of the iris sphincter muscle (Murphy et al., 1990).

Ophthalmic problems are not common in otters under human care. Cataracts have been observed in a sea otter and a geriatric ASCO (C.M.H. Colitz, personal observation). Another ASCO was diagnosed with bilateral corneal opacities consistent with lipid keratopathy (Fig. 33.62). Infectious keratitis is uncommon but can occur secondary to trauma and opportunistic bacterial or fungal organisms.

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**REFERENCES**


Figure 33.62. An Asian small-clawed river otter with an axial diffuse grey-white corneal opacity consistent with lipid.


Chittick, B. & Harms, C. (2001) Intraocular pressure of juvenile loggerhead sea turtles (Caretta caretta) held in different positions. The Veterinary Record, 149, 587–589.


Uganda.


The nervous system is sometimes a daunting system to conceptually consider in a clinical setting. The reasons for this are numerous. The nervous system is divided into central, peripheral, and autonomic components, and these components are, with the exception of the head of the optic nerve and the retina, not readily available for external visual inspection. Instead, however, we rely upon examining the behavior of the animal to various stimuli to indirectly interpret normal from abnormal function of particular pathways within the nervous system. As such, it is important to have a solid foundation in understanding basic neuroanatomy. If one can understand the neuroanatomical basis for particular reflexes and responses to various stimuli, one can begin to deduce where a lesion lies within the nervous system and thereby formulate a neuroanatomic diagnosis. Upon reaching a neuroanatomic diagnosis, and while simultaneously taking into consideration the patient’s signalment and clinical history (anamnesis), an appropriate differential diagnostic list can be created, thus steering an appropriate diagnostic plan.

Neuro-ophthalmology is rather focused with respect to the portion of the nervous system being evaluated. It is of paramount importance to consider the entire clinical picture being provided by the history and clinical signs of the patient when formulating a differential diagnostic list. Of equal importance is the distant examination of every patient. In some instances, especially where systemic disease is suspected, it is essential to complete full physical and neurological examinations.

Finally, and often times ignored in textbooks, it is important to consider the biolifestyle-social history of the patient with respect to its owner when formulating diagnostic and treatment plans (A dams, 2012); that is, careful consideration of how the patient “fits in” with the owner’s life, and understanding the expectations and limitations of the owner, will help to determine appropriate diagnostic and treatment plans. For example, recognizing that the patient is a herd animal and is primarily being raised for food consumption may alter diagnostic planning and may warrant a herd examination and postmortem examination of one or more affected individuals in a herd, while patients who are primarily pets, or considered members of the family, may warrant an exhaustive diagnostic plan aimed at treating the individual.

Though many excellent textbook chapters and review papers have been written about veterinary neuro-ophthalmology, it is a daunting task to provide essential information that does not oversimplify such a complex and important subject. Saying this, we recognize there is much known about the neuroscience of the ophthalmic system, especially vision, that is beyond the scope of this clinically relevant chapter. The scope of this chapter is not to be all encompassing of everything known about neuro-ophthalmology in every species of animal; rather, this chapter provides salient information about neuro-ophthalmology in the clinical setting with a focus on mammalian species. This chapter is divided into the following sections:

1. Gross topographical neuroanatomy
2. The neuro-ophthalmic examination
   (a) Distant examination
      • nystagmus
      • strabismus
      • anisocoria and pupil size
   (b) Reflexes and responses
      • pupillary light reflex (PLR)
      • swinging flashlight test
      • dazzle reflex (photic blink reflex)
      • menace response
      • palpebral reflex
      • corneal reflex
      • vestibulo-ocular reflex and physiologic nystagmus
   (c) Vision testing
      • obstacle course (maze testing)
      • visual placing
   (d) Schirmer tear testing
   (e) Pharmacologic testing of the autonomic nervous system
      • parasympathetic lesions
      • sympathetic lesions
3. Neuroanatomic lesion localization
4. Formulating a differential diagnostic list
5. Neuro-ophthalmic diseases
We wish to acknowledge Drs. Shamir, Ofri, and Scagliotti for their contributions to this chapter from previous editions of this book.

GROSS TOPOGRAPHICAL NEUROANATOMY

Prior to discussing the neuro-ophthalmic examination, and the corresponding neuroanatomic pathways, it is important to have an understanding of gross topographical neuroanatomy. Having an understanding of the general regions and names of portions of the brain and spinal cord helps provide a frame of reference as to where neuronal nuclei, axonal pathways, and so on, are generally located.

General Organization of the Nervous System

The nervous system is divided into the central and peripheral nervous systems (Behan, 2004). Generally speaking, the central nervous system (CNS) comprises any structure covered by meninges, while the peripheral nervous system is not covered by meninges. Accepting this, the CNS is made up of the brain, spinal cord, and optic nerves. Groups of neuronal cell bodies serving a similar function and that are located within the CNS are referred to as nuclei, while groups of cell bodies, subserving a similar function, in the peripheral nervous system are known as ganglia.

The nervous system can also be conceptually divided functionally into the somatic and autonomic nervous systems (Behan, 2004). The somatic portion of the nervous system is concerned with the voluntary control of muscles, while the autonomic portion is concerned with involuntary or visceral functions (e.g., control of cardiac muscle and glands).

With respect to the autonomic nervous system, this system is further subdivided into the parasympathetic, sympathetic, and enteric nervous systems. However, it should be recognized that some classify the enteric nervous system as an entity of its own given that it can function independent of CNS input (Goyal & Hirano, 1996). Given the topic of the present chapter, the enteric nervous system will not be discussed further. Instead, it is important, clinically, to recognize that the parasympathetic and sympathetic nervous systems have a very specific arrangement with regard to the location of their preganglionic neuronal cell bodies. Specifically, preganglionic neuronal cell bodies for the parasympathetic nervous system have a so-called cranio (cranial nerves [CN] III, VII, IX, X)-sacral distribution, while the preganglionic neuronal cell bodies for sympathetic neurons have a thoracolumbar distribution (Jordan, 2012; Llewellyn-Smith, 2012); that is, all sympathetic preganglionic neurons (SPNs) are located within the spinal cord. Preganglionic neuronal cell bodies of the parasympathetic and sympathetic nervous systems extend their axons peripherally to their respective ganglia where they make cholinergic synapses, while postganglionic neurons make either cholinergic or noradrenergic synapses, respectively (Fig. 34.1).

Figure 34.1. Cartoon illustrating some differences between the efferent components of the parasympathetic, sympathetic, and somatic nervous systems. Preganglionic cell bodies for the parasympathetic nervous system are distributed in a craniosacral distribution, while the sympathetic nervous system has a thoracolumbar distribution. Efferent neurons for the somatic nervous system are distributed throughout the central nervous system and make connections directly with the effector organ. Sympathetic and parasympathetic nervous systems have postganglionic neurons that make contact with the effector organ, or in the case of the adrenal medulla, neurotransmitters are dispersed via the bloodstream. GI, gastrointestinal.
The Brain

During development, the CNS is essentially tubular and derived from a tube of neuroectoderm known as the neural tube (Noden & De Lahunta, 1984). The neural tube is the product of fusion of folds of neuroectoderm. The fusion does not occur randomly, however. Instead, the neural folds fuse rostrally and caudally from a region that will ultimately become a region of the brain known as the rhombencephalon (hindbrain) (Noden & De Lahunta, 1984). The caudal portion of the neural tube ultimately becomes the spinal cord, while the rostral portion of the neural tube becomes the brain. One can simplistically think of the neural tube zipping up like a ziplock bag beginning at the center of the zipper, recognizing, of course, that it is not quite this simple. Failure of closure of the neural tube results, clinically, in what are termed neural-tube defects (for review, see Copp & Greene, 2010). Examples of neural tube defects involving the rostral and caudal portions of the neural tube, respectively, include anencephaly and spina bifida (Copp & Greene, 2010).

As neurodevelopment proceeds, the more rostral portion of the neural tube develops into three vesicles, namely, the prosencephalon, the mesencephalon, and the rhombencephalon (Fig. 34.2). The prosencephalon gives rise to the optic vesicles, laterally, which ultimately develop into the adult eyes (see Chapter 1) (Noden & De Lahunta, 1984). Two additional vesicles form rostrally and caudally, giving rise to the telencephalon, ultimately becoming the cerebral hemispheres (see Fig. 34.2). The remaining rostral prosencephalon gives rise to the diencephalon, a structure in the adult containing many nuclei of the thalamus, metathalamus, epithalamus, hypothalamus, and subthalamus (Noden & De Lahunta, 1984). Additionally, the diencephalon also contains the tracts of the optic nerve having originated from the retinal ganglion cells in the retina (Noden & De Lahunta, 1984).

Caudal to the developing diencephalon are the mesencephalon and rhombencephalon (see Fig. 34.2). The mesencephalon is known as the midbrain in the adult, while the rhombencephalon further divides into two vesicles, known rostrally as the metencephalon and caudally as the myelencephalon (Noden & De Lahunta, 1984). The metencephalon ultimately develops dorsally into the cerebellum, while the ventral metencephalon develops into the pons (Fig. 34.2) (Noden & De Lahunta, 1984). The myelencephalon is known commonly in the adult as the medulla oblongata. The midbrain, the pons, and the medulla oblongata are collectively known as the "brainstem" in the adult (see Fig. 34.2).

Remembering that the CNS is an essentially tubular structure, the space within the different regions of the brain becomes the ventricular system (Fig. 34.3) (Noden & De Lahunta, 1984). Specifically, the spaces within the region of the cerebral hemispheres are known as the lateral ventricles; the relatively smaller canal within the diencephalon is known as the third ventricle and is connected to the lateral ventricles by way of the interventricular foramina (De Lahunta & Glass, 2009b). An even smaller space within the mesencephalon, known as the mesecephalic aqueduct, joins the third ventricle with the fourth ventricle, which is located within the rhombencephalon (De Lahunta & Glass, 2009b). The cerebrospinal fluid (CSF), produced by the choroid plexus of the lateral, third, and fourth ventricles (Gomez & Potts, 1981), fills the ventricular system and exits the brain via bilateral lateral openings in the fourth ventricle (lateral apertures), which allow drainage of CSF into the subarachnoid space, thereby bathing the entire CNS (see Fig. 34.3) (De Lahunta & Glass, 2009b). Additionally, CSF flows from the ventricular system caudally in the central canal of the spinal cord. CSF normally is absorbed via structures known as arachnoid villi within the venous sinuses, though alternate pathways (e.g., via cribiform plate) exist (Leeds et al., 1989; Mann et al., 1978). The arachnoid villi act as one-way valves to the flow of CSF. As may be apparent after considering where CSF is produced, and also the flow of CSF from the ventricular system, stenosis or obstruction of connecting portions of the ventricular system,
essential and important information about the neuro-ophthalmic system. Using careful observation of the patient from a distance permits one to not lose sight of the forest for the trees. Information collected during the distant examination should include species and size of the patient, its coat color or coat color pattern, an assessment of the animal’s mental acuity, body condition, gait, head and body posture, ability to navigate, presence of tremor, signs of impaired ocular function (e.g., nystagmus, pupil size at rest in various lighting conditions, and strabismus). All of this information will ultimately be used in conjunction with proximal neuro-ophthalmologic findings to arrive at a neuroanatomic diagnosis. For the purposes of this chapter, however, discussion of the distant examination will be limited to distant clinical examination findings relating to only the eye. The reader is encouraged to consider referring to a textbook relating to veterinary neurology (Bagley, 2005; De Lahunta & Glass, 2009g; Dewey, 2008; Lorenz et al., 2011; Mayhew, 2008; Platt & Olby, 2004; Vite & Braund, 2012) when considering other clinical neurological signs, though we have provided a list of clinical neurological syndromes (later in the chapter) that are useful in arriving at a neuroanatomic diagnosis. Alternatively, partnering or working with someone with expertise in veterinary neurology can oftentimes be invaluable in arriving at a neuroanatomic diagnosis.

Nystagmus

Upon first examining a patient from a distance, it may be clearly evident that the patient exhibits nystagmus, strabismus, or inappropriate pupil size(s). Nystagmus can be described as a rhythmic and involuntary movement of the eyes. Nystagmus may be pendular (spontaneous ocular movements without predilection for a fast or slow movement in any particular direction) and may represent abnormalities of the visual pathway, as is seen sometimes in Siamese, and other pointed-coat colored cats (Kaas, 2005; Webb & Cullen, 2010). Nystagmus may also be in a particular direction and is described as being in the direction of the fast phase of the ocular movement. For example, a left nystagmus is one in which the fast phase of the ocular movement is to the left. Spontaneous, pathologic nystagmus represents dysfunction of the vestibular system (for review, see Pike, 1923) (discussed in detail with vestibulo-ocular reflex testing) and is a result of asymmetric input to the motor nuclei of the cranial nerve nuclei responsible for extraocular muscle control (i.e., CN nuclei III, IV, VI). Vestibular dysfunction can be described as being either central or peripheral in origin. The central vestibular system is that portion of the nervous system located within the CNS and includes the vestibular nuclei and the vestibulocerebellum (i.e., flocculonodular lobe and the fastigial nuclei of the cerebellum) (De Lahunta & Glass, 2009g). The peripheral vestibular system neuroanatomically includes the bilaterally located vestibular apparatus (i.e., the utricle, saccule, three semicircular canals within the petrous temporal bone) and the vestibular portion of the vestibulocochlear
Figure 34.5. F–J, 12. longitudinal cerebral fissure, 13. caudate nucleus, 14. corpus callosum, 25. parietal lobe, 26. parietal bone, 27. lateral ventricle, 28. dorsal sagittal sinus, 29. columns of the fornix, 30. basisphenoid bone, 31. internal capsule, 33. falx cerebri, 36. optic tract, 38. cavernous sinus, 39. third ventricle, 40. hypothalamus, 41. cingulate gyrus, 42. piriform lobe, 43. amygdala, 44. communicating branch of the arterial circle, 45. hypophysis (pituitary gland), 46. pituitary recess/infundibulum, 47. hippocampus, 48. interthalamic adhesion, 49. thalamus, 50. mamillary body, 51. temporal bone, 52. temporal lobe, 53. mesencephalic aqueduct, 54. ventral geniculate body, 55. medial geniculate body, 56. crus cerebri, 57. substantia nigra, 58. caudal cerebral artery, 59. rostral colliculus, 60. caudal colliculus, 61. rostral vermis (at mesencephalic aqueduct), 62. telencephalon; 63. diencephalon; 64. mesencephalon; 65. ventral metencephalon (pons) and myelencephalon. (Reproduced with permission from Leigh et al., 2008.)
Figure 34.6. K–O, 26. parietal bone, 27. lateral ventricle, 55. temporal bone, 69. basilar artery, 74. occipital lobe, 79. tympanic bulla, 80. CN V, 83. sagittal ridge, 84. vermis, 85. rostral vermis, 87. rostral cerebellar peduncle, 88. middle cerebellar peduncle, 89. confluence of cerebellar peduncles, 90. cerebellar hemisphere, 92. reticular formation, 93. CN VIII, 94. pyramid, 95. fourth ventricle, 96. osseous tentorium cerebelli, 97. nodulus, 98. flocculus, 99. cerebellar medulla, 100. membranous labyrinth, 106. occipital bone, 107. vestibular nuclei, 110. choroid plexus in the lateral aperture of the fourth ventricle.  

Telencephalon; dorsal metencephalon (cerebellum); ventral metencephalon (pons) and myelencephalon. (Reproduced with permission from Leigh et al., 2008.)
Figure 34.7. P–T, 1. ethmoturbinates, 3. frontal sinus, 4. olfactory bulb, 6. frontal lobe, 11. optic nerve, 12. longitudinal cerebral fissure, 13. caudate nucleus, 14. corpus callosum, 15. rostral cerebral artery, 18. cruciate sulcus, 20. suprasylvian sulcus, 21. precruciate gyrus, 22. suprasylvian gyrus, 23. ectomarginal gyrus, 24. marginal gyrus, 25. parietal lobe, 27. lateral ventricle, 31. internal capsule, 32. corona radiata, 34. septal nuclei, 35. optic chiasm, 39. third ventricle, 40. hypothalamus, 42. piriform lobe, 44. communicating branch of the arterial circle, 45. hypophysis (pituitary gland), 47. hippocampus, 48. interthalamic adhesion, 49. thalamus, 50. rostral cerebellar artery, 52. tegmentum, 54. mamillary body, 56. temporal lobe, 57. ectomarginal gyrus, 61. lateral geniculate body, 66. internal carotid artery, 67. middle cerebral artery, 68. caudal cerebral artery, 69. basilar artery, 70. rostral colliculus, 71. caudal colliculus, 74. occipital lobe, 76. quadrigeminal cistern, 80. CN V, 84. vermis, 85. rostral vermis, 86. caudal vermis, 90. cerebellar hemisphere, 93. CN VIII, 95. fourth ventricle, 98. flocculus, 101. obex, 102. central canal. **telencephalon; diencephalon; mesencephalon;**, dorsal metencephalon (cerebellum); **ventral metencephalon (pons) and myelencephalon.** (Reproduced with permission from Leigh et al., 2008.)
Figure 34.8. U–V, 1. ethmoturbinates, 2. cribriform plate, 4. olfactory bulb, 5. nasopharynx, 6. frontal lobe, 7. frontal bone, 13. caudate nucleus, 14. corpus callosum, 14a. genu of corpus callosum, 14b. splenium of corpus callosum, 15. rostral cerebral artery, 16. presphenoid bone, 18. cruciate sulcus, 25. parietal lobe, 26. parietal bone, 27. lateral ventricle, 30. basisphenoid bone, 34. septal nuclei, 35. optic chiasm, 39. third ventricle, 45. hypophysis (pituitary gland), 46. pituitary recess/infundibulum, 47. hippocampus, 48. interthalamic adhesion, 49. thalamus, 50. rostral cerebellar artery, 52. tegmentum, 53. lec-tum, 54. mamillary body, 58. mesencephalic aqueduct, 60. body of the fornix, 64. pineal body, 66. internal carotid artery, 68. caudal cerebral artery, 69. basilar artery, 70. rostral colliculus, 71. caudal colliculus, 74. occipital lobe, 76. quadrigeminal cistern, 77. pons, 85. rostral vermis, 86. caudal vermis, 91. arbor vitae, 95. fourth ventricle, 96. osseous tentorium cerebelli, 103. cerebellomedullary cistern, 106. occipital bone, 108. dorsum sellae, 109. rostral commissure, telencephalon; diencephalon; mesencephalon; dorsal metencephalon (cerebellum); ventral metencephalon (pons) and myelencephalon. (Reproduced with permission from Leigh et al., 2008.)
<table>
<thead>
<tr>
<th>Cranial Nerve or Brain Nuclei</th>
<th>Origination</th>
<th>Entry/Exit to/from the Cranial Vault</th>
<th>Termination</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial nerve II (optic nerve)</td>
<td>Retinal ganglion cells in retina</td>
<td>Optic canal</td>
<td>Lateral geniculate nucleus</td>
<td>Vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rostral colliculi</td>
<td>Afferent arm of pupillary light reflex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Thalamic nuclei</td>
<td>Afferent arm of menace response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Note: variable decussation at the optic chiasm (species dependent)</td>
<td>Afferent arm of dazzle reflex</td>
</tr>
<tr>
<td>Motor nucleus of cranial nerve III (oculomotor nucleus)</td>
<td>Tegmentum (floor) of the midbrain</td>
<td>Orbital fissure</td>
<td>Medial, dorsal, ventral recti muscles</td>
<td>Ocular movements (see Table 34.2)</td>
</tr>
<tr>
<td></td>
<td>Caudal to pretectal nucleus</td>
<td></td>
<td>Ventral oblique muscle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rostral to trochlear nucleus</td>
<td></td>
<td>Levator palpebrae superioris muscle</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>All ipsilateral to the nucleus</td>
<td></td>
</tr>
<tr>
<td>Parasympathetic nucleus of cranial nerve III (Edinger–Westphal nucleus)</td>
<td>Tegmentum (floor) of the midbrain</td>
<td>Orbital fissure</td>
<td>Ciliary ganglion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caudal to pretectal nucleus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rostral to trochlear nucleus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor nucleus of cranial nerve IV (trochlear nerve)</td>
<td>Caudal mesencephalon at level of caudal colliculi</td>
<td>Orbital fissure</td>
<td>Dorsal oblique muscle on side opposite the location of the nucleus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Caudal to oculomotor nuclei</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor nucleus of cranial nerve VI (abducens nerve)</td>
<td>Rostral medulla oblongata</td>
<td>Orbital fissure</td>
<td>Lateral rectus and retractor bulbi muscles ipsilateral to the nucleus</td>
<td>Ocular movement and retraction (see Table 34.2)</td>
</tr>
<tr>
<td>Motor nucleus of cranial nerve V (trigeminal nerve)</td>
<td>Pons at level of middle and rostral cerebellar peduncles</td>
<td>Canal for the trigeminal nerve in petrous temporal bone and then exits with the mandibular branch of the nerve via the oval foramen</td>
<td>Masseter, temporal, pterygoid, rostral digastricus and mylohyoideus muscles</td>
<td></td>
</tr>
<tr>
<td>Sensory ganglion of cranial nerve V (trigeminal nerve)</td>
<td>Neuron cell bodies of the mandibular, ophthalmic, and maxillary branches are located in trigeminal ganglion located in the canal for the trigeminal nerve in the petrous temporal bone</td>
<td>Canal for the trigeminal nerve in the petrous temporal bone</td>
<td>Various somatic efferent nuclei within the brainstem</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Receiving sensory information from the head</td>
<td></td>
<td>Spinal tract of the trigeminal nerve</td>
<td></td>
</tr>
<tr>
<td>Motor nucleus of cranial nerve VII (facial nerve)</td>
<td>Rostral medulla oblongata</td>
<td>Stylomastoid foramen via the facial canal in the petrous temporal bone</td>
<td>Muscles of facial expression</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caudal portion of the digastricus muscle</td>
<td>Motor to muscles innervated</td>
</tr>
<tr>
<td>Parasympathetic nucleus of cranial nerve VII</td>
<td>Rostral medulla oblongata</td>
<td>Preganglionic traverse in the facial canal and exit with the maxillary and mandibular branches of the trigeminal nerve</td>
<td>Preganglionic: synapse in pterygopalatine ganglion</td>
<td>Lacrimation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Postganglionic: innervate lacrimal, palatine, and nasal glands</td>
<td></td>
</tr>
<tr>
<td>Cranial nerve VIII (vestibular portion)</td>
<td>Pons and medulla oblongata</td>
<td>Internal acoustic meatus</td>
<td>Rostral, medial, lateral, and caudal vestibular nuclei</td>
<td>Coordinate eye, neck, trunk, and limb position with position and movements of the head</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minority to fastigial nucleus and flocculonodular lobe of the cerebellum</td>
<td>Maintain balance</td>
</tr>
<tr>
<td>Lateral geniculate nucleus</td>
<td>Diencephalon</td>
<td>Not applicable</td>
<td>Visual cortex (lateral, caudal, and medial aspects of the occipital lobe)</td>
<td>Project visual information from optic tracts to visual cortex</td>
</tr>
<tr>
<td>Pretectal nucleus</td>
<td>Mesencephalon</td>
<td>Not applicable</td>
<td>Bilateral projections to parasympathetic nuclei of cranial nerve III (Edinger–Westphal nuclei)</td>
<td>Maintenance of the pupillary light reflex</td>
</tr>
</tbody>
</table>
nerve (De Lahunta & Glass, 2009g). Normally, there is tonic input from the peripheral vestibular apparatus onto the vestibular nuclei which, in turn, exerts control over the nuclei of CN III, IV, and VI. This tonic and equal input results in stationary ocular position when the patient’s head, neck, and body are stationary. If, however, there is asymmetric input onto these CN nuclei, the contralateral side is tonically stimulated more often than the side ipsilateral to the disease process and nystagmus results (see oculocephalic reflex below for more detail about the neuroanatomical basis of spontaneous vestibular nystagmus).

**Strabismus**

With respect to abnormalities of eye position that can be determined during a distant examination, these can be the result of vestibular disease or a disease process involving the extraocular muscles or the cranial nerves innervating the extraocular muscles (CN III, IV, VI) (Fig. 34.9). With respect to vestibular strabismus, this is most often evident when the patient’s head is held in extension (De Lahunta & Glass, 2009g). Normally, the eyes remain in a central position, though animals with vestibular disease may have a strabismus characterized by ventral strabismus ipsilateral to the side of the lesion. It is important to recognize that, in clinically normal horses and ruminants, these animals will not keep their eyes central when holding their head in extension and instead, vestibular strabismus is evident without extending these animals’ heads (Fig. 34.10) (De Lahunta & Glass, 2009g; Mayhew, 2008).

Before discussing strabismus resulting from diseases affecting the extraocular muscles, directly (e.g., extraocular myositis) or indirectly (e.g., orbital disease), or the cranial nerves controlling these extraocular muscles, it is important to consider the anatomy and function of the extraocular muscles (see Chapter 2 for more discussion) and the innervation of these muscles (see Table 34.1 and Table 34.2). It should be noted that all extraocular muscles, referred to herein, are present in common domestic species of animals (Prince et al., 1960).
After considering the function of the various extraocular muscles and their innervations, the direction of the strabismus following primary disease to the muscle(s) or denervation of a muscle is somewhat predictable (see Table 34.3). Worth considering, in arriving at a neuroanatomic diagnosis, are the origins of CN III, IV, and VI nuclei and their course to their point of insertion. Conveniently, the motor nuclei of these cranial nerves are located in chronological order along a rostral to caudal path within the brainstem.

All of the cranial nerve nuclei are paired bilaterally, though we will discuss their location and course taken from an individual nucleus perspective (for anatomic location, see Fig. 34.11, Fig. 34.12, Fig. 34.13, Fig. 34.14, Fig. 34.15, Fig. 34.16, and Fig. 34.17 [Parry & Volk, 2011]). The nucleus of CN III (oculomotor nerve) is located most rostrally. The nucleus of CN III is found within the tegmentum of the midbrain within the ventral part of the periaqueductal gray, that is, a gray matter region that surrounds the mesencephalic aqueduct (De Lahunta & Glass, 2009d). The axons of this nucleus pass ventrally through the reticular formation of the tegmentum, medial to the red nucleus, substantia nigra, and crus cerebri. These axons exit the brainstem as part of the third cranial nerve, at the ventral aspect of the midbrain. Axons exit predominantly on the ipsilateral side in common mammalian species, though one should be cognizant that phylogenetic differences exist (for review, see Buttner-Ennever, 2006; Evinger, 1988). CN III then courses rostrally, lateral to the hypophysis, and enters the orbit through the orbital fissure. After entering the orbit, it sends branches to the ventral oblique and to the dorsal, medial, and ventral rectus muscles, but it also innervates the superior levator palpebral muscle and provides parasympathetic innervation to the iris and ciliary

Table 34.2  Innervation and Function of the Extrinsic Muscles of the Eye

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Innervation</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal rectus</td>
<td>Cranial nerve III (oculomotor nerve)</td>
<td>Rotate globe dorsally</td>
</tr>
<tr>
<td>Ventral rectus</td>
<td>Cranial nerve III (oculomotor nerve)</td>
<td>Rotate globe ventrally</td>
</tr>
<tr>
<td>Medial rectus</td>
<td>Cranial nerve III (oculomotor nerve)</td>
<td>Rotate globe medially</td>
</tr>
<tr>
<td>Ventral oblique</td>
<td>Cranial nerve III (oculomotor nerve)</td>
<td>Extorsion</td>
</tr>
<tr>
<td>Lateral rectus</td>
<td>Cranial nerve VI (abducent nerve)</td>
<td>Rotate globe laterally</td>
</tr>
<tr>
<td>Retractor bulbi</td>
<td>Cranial nerve VI (abducent nerve)</td>
<td>Retract globe</td>
</tr>
<tr>
<td>(absent in primates)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsal oblique</td>
<td>Cranial nerve IV (trochlear nerve)</td>
<td>Intorsion</td>
</tr>
</tbody>
</table>

Table 34.3  Direction of Strabismus due to Unilateral Denervation of Extraocular Muscles

<table>
<thead>
<tr>
<th>Nerve, or Nucleus Affected</th>
<th>Direction of Strabismus</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN III, nucleus of CN III</td>
<td>Ipsilateral, ventrolateral + ptosis</td>
</tr>
<tr>
<td>CN IV</td>
<td>Ipsilateral, extorsion</td>
</tr>
<tr>
<td>Unilateral nucleus of CN IV</td>
<td>Contralateral, extorsion</td>
</tr>
<tr>
<td>CN VI, nucleus of CN VI</td>
<td>Ipsilateral, medial</td>
</tr>
</tbody>
</table>

CN, cranial nerve.

Figure 34.11.  Transverse computed tomography (A) and T2w magnetic resonance (B) image at the level of the most caudal aspect of the optic nerves, just rostral to the optic chiasm. 1, frontal sinus; 2, zygomatic arch; 3, optic canal; 4, hamulus of the pterygoid; 5, lateral ventricle; 6, CN II; 7, CN III, IV, VI and ophthalmic branch of CN V in orbital fissure; 8, maxillary branch of CN V rostral to the rostral alar foramen. (Reproduced with permission from Parry & Volk, 2011.)
body (thus controlling pupillary constriction and lens accommodation, respectively) (De Lahunta & Glass, 2009d).

The motor nucleus of the CN IV (trochlear nerve) is located just caudal to the nucleus for CN III yet still within the midbrain. CN IV is the only cranial nerve in which most of the axons cross over to innervate the contralateral extraocular muscle. In all mammals studied thus far, only a very small percentage (2%–4%) of the motor neurons of CN IV send projections to the ipsilateral dorsal oblique muscle (Buttner-Ennever, 2006). CN IV exits the brain from the dorsal surface of the brainstem just caudal to the caudal colliculus and on the contralateral side from the nucleus the axons arose. After exiting the midbrain, CN IV passes rostroventrally over the side of the midbrain to reach the floor of the cranial vault. Eventually, CN IV exits the cranial vault via the orbital fissure to innervate the dorsal oblique muscle (Buttner-Ennever, 2006; De Lahunta & Glass, 2009d).

The final of the three extraocular motor nuclei, the nuclei of CN VI (abducent nerve), are located just ventral to the floor of the fourth ventricle in the rostral part of the medulla oblongata (De Lahunta & Glass, 2009d). The axons leaving these nuclei course ventrally through the reticular formation (a complex network of neurons believed to be important for arousal [Fuller et al., 2011], modulation of pain [Heinricher et al., 2009], and cardiovascular control [Schreihofer & Sved, 2012]), medially to the nucleus of the trapezoid body, and emerge through the trapezoid body (a portion of the hearing pathway), lateral to the pyramid on both sides of the medulla, as CN VI. CN VI exits the cranial vault via the orbital fissure with CN III and IV, to then innervate the lateral rectus and the retractor bulbi muscles (De Lahunta & Glass, 2009d; Evinger, 1988).

Anisocoria and Pupil Size

Anisocoria, or unequally sized pupils, is a useful finding during the distant examination. The presence of anisocoria, however, should be evaluated in conjunction with history, PLR, and vision testing.
Figure 34.14. Transverse computed tomography (A) and T2w magnetic resonance (B) image at the level of the orbital fissure. 1, zygomatic arch; 2, orbital fissure; 3, hamulus of the pterygoid; 4, CN III, IV, VI; 5, ophthalmic branch of CN V in orbital fissure; 6, maxillary branch of CN V just rostral to the rostral alar foramen. (Reproduced with permission from Parry & Volk, 2011.)

During the distant examination, anisocoria should be observed in normal ambient light (photopic) and in dim light (scotopic) conditions. In so doing, it will become evident which eye is abnormal. For example, anisocoria may be characterized by the right pupil being more mydriatic compared to the left in photopic conditions, though, if the anisocoria resolves in scotopic conditions, this implies that there is a disease process involving the constrictor ability of the right pupil.

In patients without anisocoria, it is important to carefully observe pupil size under photopic and scotopic conditions. A similar approach applies with anisocoria, however, this observation should be noted and only interpreted in conjunction with results of patient history, PLR, and vision testing. For example, the observation of bilaterally symmetric mydriasis under photopic conditions and with history and behavior consistent with not being blind may be misleading if the patient was recently pharmacologically dilated prior to examination. To gain an appreciation why it is important to not consider anisocoria and pupil size in isolation of history, PLR, and vision testing, it is important to discuss the neurologic control of pupil function.

Figure 34.15. Transverse computed tomography (A) and T2w magnetic resonance (B) image at the level of the oval foramen. Note the mandibular branch of the trigeminal (V) nerve within the foramen. 1, oval foramen; 2, temporomandibular joint; 3, thalamus; 4, ophthalmic and maxillary branches of CN V; 5, mandibular branch of CN V descending through the oval foramen. (Reproduced with permission from Parry & Volk, 2011.)
In our common domesticated mammalian species, two groups of antagonistic muscles within the iris control pupil size, shape, and reaction to light. The dilator muscle consists of smooth muscle fibers distributed radially throughout the iris. The smooth iris sphincter muscle forms a ring around the pupillary margin. It has been shown that the iris sphincter and dilator muscles receive double reciprocal innervation by both the sympathetic and the parasympathetic systems (Fig. 34.18) (Yoshitomi & Ito, 1986). This is important biologically because it ensures that an accurate and appropriate amount of pupillary dilation or constriction can occur rapidly depending on the environmental circumstance (e.g., changing light conditions and need to escape from predators). Specifically, it has been shown that cholinergic (parasympathetic) excitatory nerves causing contraction of the iridal sphincter work together with cholinergic inhibitory nerves to cause relaxation of the counteracting dilator muscle (Narita & Watanabe, 1981; Yoshitomi & Ito, 1986). These reciprocal parasympathetic actions result in pupillary constriction. Mydriasis is caused by direct adrenergic (sympathetic) excitatory input to the iris.

Figure 34.16. Transverse computed tomography (A) and T2w magnetic resonance (B) image at the level of the facial canal. 1, facial canal; 2, cochlea; 3, tympanic cavity; 4, CN VII. (Reproduced with permission from Parry & Volk, 2011.)

Figure 34.17. Transverse computed tomography (A) and T2w magnetic resonance (B) image at the level of the internal acoustic meatus. Note the T2w hyperintense perilymph within the inner ear. 1, vestibular component of the inner ear; 2, tympanic cavity; 3, cerebellar paraflocculus; 4, CN VIII; 5, endolymph and perilymph in the vestibular part of the inner ear. (Reproduced with permission from Parry & Volk, 2011.)
nerves to the dilator cause it to relax, enhancing miosis. (From Scaglotti, sphincter causes it to contract, but at the same time, cholinergic inhibition to the sphincter is inhibited. B. Cholinergic excitation to the its antagonist. A. Mydriasis consists of direct adrenergic excitatory input to

tonation of one of the iris muscles is accompanied by a reciprocal inhibition in its antagonist. A. Mydriasis consists of direct adrenergic excitatory input to the iris dilator muscle, causing it to contract. At the same time, the cholinergic output to the sphincter is inhibited. B. Cholinergic excitation to the sphincter causes it to contract, but at the same time, cholinergic inhibition nerves to the dilator cause it to relax, enhancing miosis. (From Scaglotti, 1999.)

dilator muscle, causing it to contract. At the same time, an adrenergic inhibitory input further relaxes the iris sphincter muscle. The cholinergic (parasympathetic) inhibitory effect on the dilator muscle has been demonstrated in a variety of species including dogs, cats, rats, cattle, and humans (Ehinger et al., 1968; Narita & Watanabe, 1981; Schaeppi & Koella, 1964; Suzuki et al., 1983; Yoshitomi & Ito, 1986). A cholinergic (sympathetic) inhibition of the sphincter muscle has been demonstrated in the canine and bovine iris (Tachado et al., 1989; Yoshitomi & Ito, 1986), though further research is required to decipher the exact role of the various adrenergic receptor subtypes in this response. For a comprehensive comparative description of the autonomic control of the eye, see Neuhuber & Schrodl (2011).

With respect to sympathetic innervation of the iris muscle, the reader is reminded of the thoracolumbar distribution of the sympathetic preganglionic neurons (SPNs). As such, SPNs, important in pupillary constriction, are located in the intermediolateral gray matter of the upper thoracic spinal cord segments (up to approximately the third thoracic spinal cord segment) (De Lahunta & Glass, 2009e; Neuhuber & Schrodl, 2011; Strack & Loewy, 1990). SPNs exit the spinal canal with the ventral spinal nerve roots. Prior to the spinal nerve branching, the SPNs join with the thoracic sympathetic trunk (De Lahunta & Glass, 2009e). The sympathetic trunk ascends through the thorax adjacent to the vertebral bodies and course cranially to the cranial cervical ganglion as a component of the vagosympathetic trunk (located within the carotid sheath). The cranial cervical ganglion is located ventromedial to the tympanic bulla (De Lahunta & Glass, 2009e). The postganglionic sympathetic fibers arising from the cranial cervical ganglion cross the middle ear cavity, enter the carotid sinus, and eventually join the internal carotid artery or the ophthalmic branch of the trigeminal nerve as they enter the orbit (De Lahunta & Glass, 2009e). Together with fibers of the ophthalmic nerve (branch of the CN V [trigeminal nerve]), they course rostrally in the periorbita as the nasociliary nerve and enter the globe via the long ciliary nerve (Christensen, 1936). Therefore, the long ciliary nerve provides both sympathetic efferent fibers and somatosensory afferent fibers (Christensen, 1936). The pupillary sympathetic fibers run in the suprachoroidal space to the ciliary body, iris dilator muscle, and iris sphincter muscle (keep in mind reciprocal iris innervation). Sympathetic fibers also innervate the smooth muscles of the periorbita, Müller’s muscles of the upper and lower eyelids, and the dilator muscle of the iris, and provide inhibitory input to the antagonistic sphincter. Normal sympathetic tone in these smooth muscles keeps the globe slightly protruded, the palpebral fissure opened, the third eyelid retracted, and the pupil partially dilated. Increased sympathetic tone is caused by emotional responses such as fear, excitement, anger, and pain, and these emotions are regulated by the hypothalamus. Given this, and recognizing the importance of the hypothalamus in the “fight or flight” response and that neurons located in a region of the hypothalamus, known as the paraventricular nucleus, make contact with SPNs in the thoracolumbar spinal cord (Ranson et al., 1998), damage to this pathway can ultimately affect sympathetic output and may manifest as first-order Horner’s syndrome (see “Horner’s Syndrome”).

Having just considered the sympathetic innervation of the eye, the following discussion pertains to the parasympathetic innervation of the iris. A utonomic preganglionic nerve fibers for controlling pupillary constriction originate in the parasympathetic nucleus of CN III (oculomotor nerve). This nucleus is also known as the Edinger-Westphal nucleus (see Table 34.1). The parasympathetic nucleus of CN III is located at the most rostral part of the rostral colliculus of the tectum within the central gray substance, next to the midline. Axons from this nucleus course ventrally with the somatic efferent axons of CN III and leave the midbrain medial to the crus cerebri. The crus cerebri is a large ventrally visible band of fibers at the level of the midbrain. The preganglionic parasympathetic efferent fibers are located superficially on the medial side of the oculomotor nerve (Christensen, 1936), where they are susceptible to injuries caused by compression of the nerve from midbrain swelling or displacement. These parasympathetic fibers enter the orbit as part of CN III (oculomotor nerve) and synapse in the ciliary ganglion (De Lahunta & Glass, 2009e). The ciliary ganglion is a collection of postganglionic parasympathetic neuronal cell bodies located lateral to the optic nerve. Axons originating from neurons in the ciliary ganglion form the short ciliary nerve (De Lahunta & Glass, 2009e). The parasympathetic component of the short ciliary nerve innervates the iridal sphincter muscle (Butler & Hodos, 2005) and, because of the presence

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**Figure 34.18.** Double reciprocal innervation of the intraocular musclease. The iris sphincter and dilator muscles receive functional, double reciprocal innervation by both cholinergic and adrenergic systems. Stimulation of one of the iris muscles is accompanied by a reciprocal inhibition in its antagonist. A. Mydriasis consists of direct adrenergic excitatory input to the iris dilator muscle, causing it to contract. At the same time, the cholinergic output to the sphincter is inhibited. B. Cholinergic excitation to the sphincter causes it to contract, but at the same time, cholinergic inhibition nerves to the dilator cause it to relax, enhancing miosis. (From Scaglotti, 1999.)
of dual reciprocal innervation, the iris dilator muscle. As the short ciliary nerve enters the globe, it receives somatosensory contributions from the first division of the nasociliary nerve (a branch of the ophthalmic portion of the trigeminal nerve) (Dakrory & Abdel-Kader, 2011).

Interestingly, there exist many differences among various species of animals with regard to the ciliary ganglion and the ciliary nerves arising from it (for review, see Dakrory & Abdel-Kader, 2011). Specifically, two short ciliary nerves arise from the ciliary ganglion in the cat (Christensen, 1936; Dakrory & Abdel-Kader, 2011). The lateral one is called the malar nerve; the medial one is called the nasal nerve. The malar nerve innervates the lateral half of the iridal sphincter muscle, and the nasal nerve innervates the medial half of the sphincter. Meanwhile, the dog has five to eight short ciliary nerves (as cited by Scagliotti, 1999). Therefore, parasympathetic denervation in the dog will cause pupillary dilation, while in the cat, lesions to either the nasal or the malar short ciliary nerves will result in sphincter hemiplegia and a D-shaped or reversed-D-shaped pupil, respectively.

The sensory innervation of the iris is particularly dense. A fine plexus courses along the blood vessels and among the muscle fibers. This plexus is made up of the sensory fibers of the long ciliary nerve (a branch of the ophthalmic nerve [i.e., CN V] [Neuhuber & Schrodl, 2011]). Additional unmyelinated filaments occur throughout the stroma, from which branches arise to supply the anterior epithelial layer. No fibers have been traced in the posterior pigmented epithelium (Neuhuber & Schrodl, 2011).

**Reflexes and Responses**

Prior to our discussion of reflex and response testing in neuroophthalmology, it is likely important to provide a definition of reflex and how this differs from other stimulus–responses. A reflex is an almost instantaneous, transient, predictable reaction to a given stimulus. A reflex follows a typical reflex arc characterized by some sensory receptor, an afferent neuron, one or more interneurons, and an efferent neuron. Reflexes, unlike responses, are not learned and do not require input from “higher centers” in the brain.

**Pupillary Light Reflex**

The PLR is a reflex where after the retina is stimulated by light a resultant constriction of the pupil ipsilateral (direct PLR) and contralateral (indirect/consensual PLR) to the stimulus results. The PLR is present as early as when the eyes are open after birth (10–16 days postnatally in puppies, 5–14 days postnatally in kittens), albeit PLRs may be initially sluggish and may not react similarly to the adult until maturation of the retina is complete (28 days postnatally in the puppy) (Lavely, 2006). The PLR is present immediately after birth in foals (Adams & Mayhew, 1984).

The afferent pathway of the PLR runs through the CN II (optic nerve) to the optic chiasm to synapse bilaterally on neurons located in the pretectal nuclei (PTN) (Hultborn et al., 1978). These nuclei are located in the transition zone between the diencephalon and the midbrain. Axons from each PTN relay to both the left and the right parasympathetic nucleus of CN III (Hultborn et al., 1978; Dakrory & Abdel-Kader, 2011). Specifically, two short ciliary nerves arise from the ciliary ganglion in the cat (Christensen, 1936; Dakrory & Abdel-Kader, 2011). The lateral one is called the malar nerve; the medial one is called the nasal nerve. The malar nerve innervates the lateral half of the iridal sphincter muscle, and the nasal nerve innervates the medial half of the sphincter. Meanwhile, the dog has five to eight short ciliary nerves (as cited by Scagliotti, 1999). Therefore, parasympathetic denervation in the dog will cause pupillary dilation, while in the cat, lesions to either the nasal or the malar short ciliary nerves will result in sphincter hemiplegia and a D-shaped or reversed-D-shaped pupil, respectively.

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the optic chiasm because it is assumed that the same percentage of fibers that cross over at the optic chiasm cross again between the PTN and the parasympathetic nucleus at the tegmentum (Lowenstein et al., 1953). Following this reasoning, in humans, where the decussation rate is 50%, the direct and consensual PLRs are of equal amplitude. In species such as birds, in which all the optic nerve fibers cross over, there is no consensual PLR (Barbur et al., 2002; Gamlin et al., 1984). However, in some avian species, a thin interorbital septum separating the two eyes may allow light shone into one eye to pass through and stimulate the contralateral retina, resulting in a pseudoindirect PLR (Scagliotti, 1999).

**Swinging Flashlight Test**

The swinging flashlight test is done by moving a focal light source from the tested eye to the opposite eye to check the direct and indirect light reflexes. In a clinically normal animal, the pupil that is not directly stimulated will partially constrict (due to the consensual reflex) and will then constrict further when it is directly stimulated by the swinging flashlight. If the pupil dilates during direct light stimulation instead of performing the expected constriction, the swinging flashlight test is said to be positive for the eye with the dilating pupil. The Marcus-Gunn sign is the name ascribed to the pupillary reflex observed during a positive swinging flashlight test (Pearce, 1996). A positive swinging flashlight test is pathognomonic for unilateral retinal disease or unilateral prechiasmal optic nerve disease (or both). Such a lesion does not prevent the constriction resulting from the indirect PLR when the unaffected eye is stimulated. However, when the flashlight is swung to the affected eye, the loss of the indirect stimulation (combined with lack of direct stimulation) causes mydriasis. Therefore, this test is used to differentiate lesions at these locations from other neurological causes of anisocoria.

The swinging flashlight test is also considered to be positive if, as the light shifts from the normal to the abnormal eye, the direct stimulus is no longer sufficient to maintain the previously evoked degree of pupillary constriction; therefore, both pupils dilate while maintaining the relative anisocoria usually present in domestic animals with optic nerve disease (Scagliotti, 1999). There are two more important tests of pupillary reaction to light. A positive swinging flashlight test should be followed by a cover-uncover test done in a normal room light where the alternation of light stimulus is done by using the examiner’s hand to cover and uncover the examined eye. This test is done to eliminate the influence of scatter illumination.

**Dazzle Reflex (Photic Blink Reflex)**

Another reflex used to evaluate the integrity of a portion of the visual pathway is the dazzle reflex. This reflex is characterized by bilateral, partial eyelid blink in response to a very bright light shone into each eye separately (Burké & Hackley, 1997; Marquis & Hilgard, 1936; Plainis et al., 2006). Closure of the eye contralateral to the eye being stimulated is less obvious, and possibly absent, when compared to the ipsilateral eye (Sherman et al., 1981). Importantly, animals having facial nerve paresis or paralysis may have a reduced or absent dazzle reflex on the ipsilateral side to the facial nerve lesion. The dazzle reflex is present as early as 1–2 days postnatally in puppies and kittens (Lavely, 2006).

Though the anatomical path of the dazzle reflex has not been elucidated in animals, evidence from the human literature suggests that it is present when the optic nerve is intact to the level of the midbrain, and particularly to reflex centers in the rostral colliculi and/or the supraoptic nuclei of the hypothalamus. The reflex also requires association fibers between these nuclei to the facial nuclei in the medulla, as well as intact facial nerves. Results of studies in animals have consistently shown that decerebrate animals blink in response to a bright light (Marquis & Hilgard, 1936; Schaltenbrand & Cobb, 1931). Other studies, conducted in monkeys, following total ablation of the striate cortex, have shown that the dazzle reflex is absent when an ordinary flashlight is used as a stimulus, but an intense light can cause a brisk and highly reliable reflex (Klover, 1942). Likewise in cats, the reflex is maintained following striate cortex ablation (Schaltenbrand & Cobb, 1931). A reflex pathway, based upon known neuroanatomical connections within the brainstem, has been proposed (Fig. 34.20).

The dazzle reflex is particularly useful when the pupils cannot be observed to evaluate the PLR (e.g., in cases of severe corneal edema or hyphema). However, because the exact anatomical pathway of this reflex has not been described, this test should not be used as the only tool for localizing subcortical lesions in the visual pathway.

**Menace Response**

The menace response is performed by making a threatening movement toward the eye being evaluated, remembering to not touch the patient or cause stimulation of the cornea or eyelashes. An appropriate response is characterized by the patient blinking, retracting their globe, and/or turning their head away from the menacing stimulus. As opposed to a simple reflex, the menace response is learned, as is suggested by a recent study demonstrating that calves reared in isolation for prolonged periods of time take longer to develop a menace response compared to those that were raised in a group setting earlier postnatally (Raoofi et al., 2009). Additionally, this response takes longer to develop compared to a simple reflex like the PLR and may not be present for up to 4 weeks postnatally in puppies and kittens (Lavely, 2006), or 8 and 14 days postnatally in lambs and goat kids (Raoofi et al., 2011), respectively. In the foal, the menace response is not complete until 2–3 weeks postnatally (A dams & M ayhew, 1984; E nzerink, 1998). In contrast, the PLR is present in precocial species such as foals, calves, lambs, and goat kids within the first 24 hours after birth (A dams & M ayhew, 1984; E nzerink, 1998; Raoofi et al., 2011), and is present upon eye opening in puppies and kittens (Lavely, 2006).
Prior to discussing the hypothesized neuroanatomic pathway of the menace response, it is important to briefly review the central visual pathway. The afferent component of the central visual pathway consists of optic nerve axons projecting to the lateral geniculate nucleus (LGN) as the optic tract, after having decussated varying amounts (species dependent) at the optic chiasm. After having projected to neurons within the LGN, optic tract axons synapse on neurons within the LGN. In turn, LGN neurons project as the optic radiation to the visual cortex in the occipital lobe where an image is perceived (a more detailed description of this pathway is found in Chapter 4). From the visual cortex, the visual information is transmitted through communication fibers to different regions of the cortex and finally to the primary motor cortex, which initiates the efferent component of the menace response. As suggested earlier, the menace response involves cerebral cortical integration and interpretation and therefore is not a reflex. Rather, it is a cortical response that requires the entire peripheral and central visual pathways, as well as the visual cortex and the facial nucleus of CN VII, to be intact for the response to occur (Scagliotti, 1999).

In addition to the neuroanatomic structures required to elicit a positive menace response, the menace response requires functional integrity of additional neuroanatomical structures. In all domestic species, it has been observed that diffuse cerebellar cortical degenerative lesions cause bilateral absence of the menace response without any associated visual deficits or facial nerve dysfunction (De Lahunta & Glass, 2009h). Varying degrees of this deficit have been observed in horses, cattle, pigs, dogs, and cats with cerebellar cortical lesions (De Lahunta & Glass, 2009a). This implies that the pathway between the visual cortex and the facial nucleus must pass through the cerebellum.
Interestingly, there is a relatively well-studied conditioned eye blink response phenomenon that is used to study the role of various neuroanatomic structures in eyeblinking and also is used as a model of learning and memory in the neurosciences (Freeman & Steinmetz, 2011). Recently, with use of trans-synaptic tracing, using green fluorescent protein (GFP)-expressing pseudorabies virus injected into the mouse orbicularis oculi muscle resulted in labeling of the ipsilateral facial nucleus, bilateral labeling of the red nuclei (with a contralateral predominance) in the midbrain, the interposed nucleus of the cerebellum and Purkinje cells within the cerebellar cortex (Sun & Clark, 2011). Given this, it is possible that the menace response uses the following pathway:

Visual input via the central visual pathway to the contralateral visual cortex → projection fibers rostrally from the visual cortex to the motor cortex contralateral to the eye stimulated → projections from the motor cortex to the pontine nucleus with projections (mossy fibers) from the pontine nucleus projected to the cerebellar nuclei and the granule cell neurons within the cerebellar cortex ipsilateral to the side of visual stimulation (the cerebropontocerebellar pathway) → projections from the Purkinje neurons to the interposed nucleus of the cerebellum → projections from the interposed nucleus to the red nucleus contralateral to the source of visual stimulation → projections from the red nucleus contralateral to the source of visual stimulus to the facial nucleus on the side ipsilateral to the side of visual stimulation.

Though this is only a postulated pathway, it may be that the menace response represents the conditioned eye blink response that is studied experimentally (Freeman & Steinmetz, 2011). The pathway proposed above may account for why unilateral cerebellar lesions cause a deficit of the menace response on the same side as the lesion in otherwise visual patients.

**Palpebral Reflex**

The palpebral reflex is elicited by touching the skin of the lateral and medial canthi of the eye, separately, and by observing an appropriate response after each touch. An expected and appropriate response is a blink of the eyelids following a single touch. The afferent portion of this reflex is via the ophthalmic and maxillary branches of CN V (trigeminal nerve) for medial and lateral canthus stimulation, respectively. The efferent component of the reflex is via CN VII (facial nerve). The palpebral reflex is reportedly present as early as 2–4 days postnatally in the puppy and 1–3 days postnatally in the kitten (Lavely, 2006). Palpebral reflexes are present immediately after birth in foals (Adams & Mayhew, 1984). In order to fully understand the afferent and efferent components of the palpebral reflex, and in order to ultimately be better able to neuroanatomically localize where a disease process is occurring, it is worth considering the neuroanatomy of the afferent and efferent components of this reflex.

CN V (trigeminal nerve) is the main sensory nerve of the face. Its ophthalmic and maxillary divisions are those that provide sensory innervation to the eye and its accessory organs. The ophthalmic nerve (i.e., the ophthalmic branch of the trigeminal nerve) divides into three branches: the frontal, lacrimal, and nasociliary nerves (De Lahunta & Glass, 2009c). The lacrimal nerve innervates the lateral part of the orbit and gives branches to the lacrimal gland, to the upper eyelid, and to the skin in the lateral canthus region of the eye (Konig & Liebich, 2007). The frontal nerve innervates the upper eyelid, the forehead, and the mucosa of the frontal sinus (Konig & Liebich, 2007). The nasociliary nerve, located at the medial side of the optic nerve, gives rise to a sensory root, which passes through the ciliary ganglion to contribute to the short ciliary nerves (Konig & Liebich, 2007). The nasociliary nerve, located at the medial side of the optic nerve, gives rise to two to three branches that join the long ciliary nerves. The latter penetrate the posterior aspect of the eye to innervate the cornea and iris and also contain somatosensory innervation to the ciliary body, trabecular meshwork, and sclera (Konig & Liebich, 2007). A nether division of the nasociliary nerve is the infratrochlear nerve, which provides sensory innervation to the skin and conjunctiva in the medial canthal region (as well as parts of the frontal sinus mucosa) (Konig & Liebich, 2007). In ruminants, the infratrochlear nerve is also the main nerve to supply the horn (M adekurozwa et al., 2000).

The largest branch of the trigeminal nerve is the maxillary nerve (Konig & Liebich, 2007). The maxillary nerve innervates the upper buccal cavity and nasopharynx (Konig & Liebich, 2007). The first branch of the maxillary nerve is the zygomatic nerve. The zygomatic nerve provides the afferent limb of the palpebral reflex resulting from stimulation of the skin at the lateral canthus of the eye (Konig & Liebich, 2007). Specifically, the zygomatic nerve is divided into the zygomatico-facial branch that innervates the skin and conjunctiva of the upper eyelid, and the zygomaticocochlear branch that innervates the skin and the conjunctiva of the lower eyelid (Esteves et al., 2009).

The maxillary and ophthalmic branches of the trigeminal nerve have their cell bodies located within the trigeminal ganglion (Konig & Liebich, 2007). The trigeminal ganglion is situated in the canal of the trigeminal nerve within the petrous temporal bone (see Table 34.1) (De Lahunta & Glass, 2009c). Axons from cells of the trigeminal ganglion enter the brainstem as the trigeminal nerve at the caudolateral aspect of the pons, just rostral to the origin of the facial and vestibulocochlear nerves (De Lahunta & Glass, 2009c). Synaptic connections are then made with various motor nuclei and the large sensory nucleus of the trigeminal nerve (De Lahunta & Glass, 2009c).

The sensory nucleus of the trigeminal nerve extends rostrally from the upper cervical part of the spinal cord, through the medulla, pons, and midbrain (De Lahunta & Glass, 2009c). The sensory trigeminal nucleus is subdivided into three continuous sensory nuclei: the mesencephalic nucleus of the trigeminal nerve, the nucleus of the spinal tract of the trigeminal nerve, and the principal (pontine) sensory nucleus of the trigeminal nerve (Cody et al., 1972; De Lahunta & Glass,
Corneal Reflex

The corneal reflex is elicited by touching the surface of the cornea with a relatively noninjurious object (e.g., cotton-tipped applicator or fiber from a Cochet–Bonnet esthesiometer) and then observing an expected and appropriate eyelid blink. As with the palpebral reflex, the afferent arm of this reflex is mediated via CN V (trigeminal), while the efferent arm is mediated by the CN VII (facial). The cornea is highly sensitive to touch and painful stimuli. Branches of the long ciliary nerves enter the corneal stroma in a radial manner from the sclera, episclera, and conjunctiva (refer to Chapter 2). Once within the stroma, all myelinated fibers lose their myelin sheaths and form an unmyelinated sensory nerve plexus. This plexus provides the cornea with the densest three-dimensional network of sensory nerves in the body. In fact, it has been estimated that the nerve density in the cornea is three to four times higher than that of the finger pad (Roza & Beuerman, 1982).

Though not routinely evaluated in clinical practice, corneal touch threshold (CTT) is measured by determining the minimum amount of force required to stimulate a consistent corneal blink reflex. Humans have the highest number of corneal stromal nerve terminals and therefore possess the greatest corneal sensitivity and lowest CTT. They are followed, in order of decreasing sensitivity, by the cat, rabbit, and dog (Barrett et al., 1991; Blocker & van der Woerd, 2001; Milldot & Larson, 1969; Milldot et al., 1978). In the dog, it has been demonstrated that the central cornea is the most sensitive region, followed by the nasal and temporal cornea (Barrett et al., 1991). This pattern also exists in humans (Milldot et al., 1978). Those regions of the cornea that are less exposed to potential injury (i.e., the dorsal and ventral corneal regions near the lid margins) are the least sensitive. In diseases such as diabetes mellitus, it has been demonstrated that CTT is greater in diabetic compared to nondiabetic patients. This implies that diabetes mellitus likely induces a diabetic neuropathy involving the long ciliary nerve of the cornea, and these patients may be more prone to corneal injury.

Vestibulo-ocular Reflex and Physiologic Nystagmus

The vestibulo-ocular reflex is a reflex that permits stabilization of an image on the retina during movement of the head. Without an appropriate vestibulo-ocular reflex, images would appear blurred. For example, attempt to read this sentence while turning your head. Now, compare your ability to read this sentence, instead, by moving the book and keeping your head stationary. It becomes readily apparent that one is able to read this sentence when the head moves and the book remains stationary. This is because of the vestibulo-ocular reflex. The vestibulo-ocular reflex is present for rotational or translational movement of the head and assists in stabilizing images on the retina (as exemplified in the example above). This reflex results in a rapidly adjusting movement of the eyes in a direction opposite that of the direction of the head movement. For example, for the vestibulo-ocular reflex, if one moves their head in the counterclockwise direction, the person’s eyes move at an appropriate speed in the clockwise direction, that is, until the physical limitations of the eye movement have been met and a compensatory, relatively fast, “resetting” of the eye position occurs (Curthoys, 2002). If this resetting of the eye position does not occur, the eyes would be driven to an extreme position in the orbit, not to mention,
ocular movement is physically limited by the extraocular muscles themselves (Curthoys, 2002). It is this alternation between slow and fast phases that comprises the normal physiologic nystagmus that is evaluated clinically in veterinary medicine. Like the example mentioned above, the vestibulo-ocular reflex is evaluated by inducing a physiologic nystagmus by rotating the patient's head in a clockwise and counterclockwise direction. The expected and normal response is that the patient will slowly move its eyes, relative to the orbit, in a position opposite that of the head being turned. A fast, compensatory, movement of the eyes will occur toward the direction of the head rotation. Similar eye movements occur when the patient's head is rotated dorsally or ventrally, with the fast phase of eye movements being in the direction of head movement. Importantly, it should be noted that the vestibulo-ocular reflex occurs independent of a patient having vision, though visual experience appears necessary for the development of a vestibulo-ocular reflex (Sherman & Keller, 1986). In fact, the vestibulo-ocular reflex is purely driven by the vestibular system. This is evidenced by patients having bilateral disease processes affecting their vestibular system. These patients will lack a vestibulo-ocular reflex, consequently, a nystagmus cannot be induced (e.g., Webb & Neff, 2011; Wilkes & Palmer, 1992). It is worth briefly discussing the basic neuroanatomical pathway of the vestibulo-ocular reflex. In so doing, it will hopefully become more readily apparent as to why spontaneous nystagmus results in patients with unilateral disease processes affecting their vestibular system.

The vestibular system is that portion of the nervous system involved in relaying information about the linear and angular acceleration of the head (Goldberg & Hudspeth, 2000). The vestibular system is found within the peripheral and CNSs (De Lahunta & Glass, 2009f; Goldberg & Hudspeth, 2000). It is because of this that we refer, clinically, to diseases of the vestibular system as being either peripheral or central in nature.

The peripheral vestibular system is made up of the vestibular labyrinth of the inner ear, the corresponding vestibular ganglion, and the vestibular portion of CN VIII (vestibulocochlear nerve) (De Lahunta & Glass, 2009f). The central components of the vestibular system are made up of the vestibular nuclei, which are located within the medulla oblongata, and the flocculonodular lobe of the cerebellum (i.e., vestibulocerebellum) (De Lahunta & Glass, 2009f). Information traveling to and from the vestibulocerebellum does so via the caudal cerebellar peduncle (De Lahunta & Glass, 2009f).

As with all reflexes, there has to be some stimulus that is initially transduced into electrical impulses that can be relayed throughout the reflex pathway. Sensory transduction occurs within the peripheral vestibular system, namely, the vestibular membranous labyrinth, which is located within the petrous temporal bone in close association with the hearing apparatus (i.e., the cochlea) (Goldberg & Hudspeth, 2000). The membranous labyrinth is epithelial lined. Fluid within the membranous labyrinth is known as endolymph (Goldberg & Hudspeth, 2000). Endolymph is high in potassium and low in sodium and calcium, and it is the inward movement of potassium that is responsible for depolarization of hair cells found within the vestibular labyrinth, similar to that seen in the cochlear hair cells (Goldberg & Hudspeth, 2000; Hibino & Kurachi, 2006). The bony component that forms adjacent to the membranous labyrinth is known as the bony labyrinth. Between the membranous and bony labyrinths, there is fluid known as perilymph. Perilymph is similar in its composition to CSF and, as such, it does not intermix with endolymph (Hibino & Kurachi, 2006). The vestibular labyrinth and cochlea are found bilaterally (i.e., right and left sides). The vestibular labyrinth is made up of the utricle, saccule, and three semicircular canals that are orthogonal to each other (De Lahunta & Glass, 2009f; Goldberg & Hudspeth, 2000). The utricle and saccule are located within a bony region called the vestibule. The semicircular canals are found within the respectively named bony semicircular canals (De Lahunta & Glass, 2009f; Goldberg & Hudspeth, 2000).

Semicircular canals are known as the anterior vertical, posterior vertical, and horizontal canals (Goldberg & Hudspeth, 2000). Located at the end of each semicircular canal is a dilatation known as the ampulla (Goldberg & Hudspeth, 2000). Fluid cannot freely move throughout the entirety of a particular semicircular canal, however. Instead, each semicircular canal is bounded by a gelatinous structure known as the cupula (Goldberg & Hudspeth, 2000). The cupula spans the diameter of the ampulla. A thickened epithelial region within the ampulla, known as the ampullary crista, contains hair cells that extend into the cupula. The hair cells are oriented in a similar fashion within the cupula. Rotation of the head causes a mechanical opening or closing of ion channels as stereocilia move toward or away from a single kinocilium on the hair cell. This opening or closing is due to shearing forces generated because of the inertia of the endolymph as the head accelerates or decelerates rotationally (Goldberg & Hudspeth, 2000). Depolarization results in synaptic vesicle release and subsequent stimulation of the bipolar neurons of the vestibular ganglion (i.e., Scarpas ganglion) (Goldberg & Hudspeth, 2000). It is the axonal processes of these bipolar neurons that make up the vestibular portion of CN VIII (vestibulocochlear nerve). The vestibular ganglion is located within the petrous temporal bone of the skull (De Lahunta & Glass, 2009f).

As for detections in linear acceleration or deceleration, these are determined by the utricle and saccule (Goldberg & Hudspeth, 2000). The macula is a region found within each of the utricles and saccules that contains a high abundance of hair cells. The hair bundle for each hair cell is embedded, apically, within a gelatinous mass known as the otolithic membrane. Within and on the surface of the otolithic membrane are calcium carbonate containing particles known as otoconia (Goldberg & Hudspeth, 2000). It is the inertia of the otolithic membrane that causes subsequent movement of stereocilia toward or away from the kinocilium on the hair cell, thus resulting in mechanical opening or closing of the ion channels, respectively (Goldberg & Hudspeth, 2000). Like the
situation for the hair cells of the ampulla, opening of the ion channels results in an influx of potassium within the hair cell with subsequent depolarization of the cell membrane. Given the orientation of the maculae within the utricle and saccule, the saccule relays information pertaining to primarily vertical acceleration, while the utricle relays information predominantly concerned with horizontal acceleration (Goldberg & Hudspeth, 2000). Like the situation described above for the hair cells conveying information about rotational acceleration, the hair cells within the maculae make synaptic contact with primary afferent fibers of vestibular ganglion neurons (Goldberg & Hudspeth, 2000).

Primary afferent neurons of the vestibular ganglion enter the cranial vault via the internal acoustic meatus (De Lahunta & Glass, 2009f). CN VIII (vestibulocochlear nerve) then travels along the lateral aspect of the rostral medulla oblongata at the cerebellomedullary angle. The cerebellomedullary angle is that region between the trapezoid body and the attachment of the caudal cerebellar peduncle (De Lahunta & Glass, 2009f). The vestibular axons enter the medulla oblongata of the brainstem at approximately the level of the caudal cerebellar peduncle. These primary afferent fibers synapse within the vestibular nuclei or within the cerebellum on neurons located within the fastigial nucleus or those located within the cortex of the flocculonodular lobe (De Lahunta & Glass, 2009f). Axons from vestibular nuclei make connections with the cerebellar fastigial nucleus and within the cortex of the flocculonodular lobe (De Lahunta & Glass, 2009f). Additionally, axons from the vestibular nuclei make excitatory or inhibitory connections with neurons located within the motor nuclei for CN III, IV, and VI, among other neurons within the brainstem and spinal cord (De Lahunta & Glass, 2009f). It is these connections that are responsible for the vestibulo-ocular reflex (Fig. 34.21) (Straka & Dieringer, 2004). Please note that axons from neurons within the vestibular nuclei travel rostrally or caudally within a fiber tract known as the medial longitudinal fasciculus (MLF). Please also note that the presence of a vestibulo-ocular reflex and physiologic nystagmus require intact peripheral and central vestibular components, the MLF, and the motor nuclei of CN III, IV, or VI.

The fast phase of physiologic nystagmus occurs at a time point when excitatory and inhibitory burst neurons located just rostral to the abducens nucleus (nucleus of CN VI) are activated. The fast-phase movement is ended by bursting of “pause neurons” that are located just rostral and along the midline relative to the abducens nucleus—this ultimately inhibits firing of excitatory and inhibitory burst neurons (for a detailed review, see Curthoys, 2002).

Of further clinical importance is the pathophysiologic rationale for the direction of the nystagmus seen in pathologic conditions of the peripheral and central portions of the vestibular system. It should be apparent that, at rest, and in the absence of head movement, the eyes remain stationary. This is because normally, there is tonic excitatory input onto the vestibular nuclei, and as such, there is equal input onto motor neurons within CN III, IV, and VI. In the instance of unilateral peripheral vestibular disease, it becomes apparent (after examining Fig. 34.21) that the fast phase of the nystagmus will be toward the side opposite that of the affected side. It is important to recognize that pathologic nystagmus may not be present in patients with subacute or chronic unilateral vestibular disease. This is because of the plasticity of the vestibular system to injury (for review, see Dutia, 2010). In instances of vestibular compensation, however, a pathologic nystagmus can sometimes be elicited by placing the patient on its back or in some other position to cause “decompensation” of the vestibular system. We also mention that patients exhibiting bilateral vestibular disease will lack both a normal physiologic nystagmus and a pathologic nystagmus. Given the pathophysiologic mechanisms accounting for the absence of nystagmus in these patients, however, a pathologic nystagmus cannot be elicited by a change in these animals’ posture.

**Vision Testing**

Prior to discussing clinical tests used for evaluating vision, we provide a brief discussion about anatomy and physiology of the visual pathway. For a more detailed discussion, please see Chapters 2 and 4 (for comparative review of retinal ganglion cells, optic nerve, and optic chiasm, see Brooks et al., 1999). See Figure 34.22 for basic visual pathway.

As with any sensory modality, the ability to sense something is dependent firstly upon stimulating a receptor. In the case of vision, photons of light pass through the cornea, ocular humor, and lens, and finally activate an exquisite cascade of molecular events within the photoreceptors of the retina, ultimately resulting in conversion of transduction of light to electrical activity that can be transmitted to the brain. Once photoreceptor stimulation has occurred, retinal ganglion cells of the retina are stimulated and action potentials are carried by

**Figure 34.21.** Comparison between the neural organizations of the horizontal angular vestibulo-ocular reflex (AVOR) and the horizontal linear vestibulo-ocular reflex (LVOR). (A) Counterclockwise head rotation increases the discharge rate in horizontal canal afferent and in second-order vestibular neurons (2 VN) on the left side, whereas the resting rates decrease in these neurons on the right side. Excitatory 2 VN project across the midline of the brainstem and converge monosynaptically with uncrossed axons from inhibitory 2 VN upon abducens motoneurons and internuclear neurons. The latter contacts monosynaptically medial rectus motoneurons in the contralateral oculomotor nucleus, whereas the former innervates the lateral rectus muscle. (B) A push–pull organization as for the AVOR is not present in the LVOR since inhibitory 2 VN are not activated during linear oscillation. Transverse oscillation activates contralateral abducens motoneurons and internuclear neurons, whereas longitudinal oscillation is assumed to activate ipsilateral medial rectus motoneurons in the oculomotor nucleus directly via fibers in the ascending tract of Deiters (ATD). (Reprinted with permission from Straka & Dieringer, 2004.)
SECTION IV

(A) AVOR

(B) LVOR

midline

Inhibitory 2*VN

HC nerve

ATD ?

UTnerve
Figure 34.22. The visual pathways, demonstrating how each side of the visual field is represented within the opposite occipital (visual) cortex. As the degree of binocular vision in different species decreases, so a greater proportion of optic nerve fibers decussate at the optic chiasm. (Modified and reproduced with permission from Platt & Olby, 2004.)

The visual pathways, demonstrating how each side of the visual field is represented within the opposite occipital (visual) cortex. As the degree of binocular vision in different species decreases, so a greater proportion of optic nerve fibers decussate at the optic chiasm. (Modified and reproduced with permission from Platt & Olby, 2004.)

The optic nerve exits the orbit through the optic foramen/canal of the presphenoid bone and runs beneath the rostroventral aspect of the brain rostral to the optic chiasm (De Lahunta & Glass, 2009h). Axons within the mammalian nerve are grouped into bundles, or fascicles, which are separated from each other by collagen fibers. These fascicles help maintain the structural integrity of the optic nerve during eye movement, allowing the bundles to undulate together as the eye (and nerve) move into extreme positions.

The optic chiasm, at the base of the hypothalamus, is the location where the two optic nerves meet and, in some cases, interdigitate. In many species, there is significant reorganization of the axons at the chiasm before the fibers separate again to form the optic tracts. However, this reorganization, or decussation, varies between species (Herron et al., 1978; Jeffery & Erskine, 2005; Myers, 1901). Broadly speaking, in most fish, amphibian, reptilian, and avian species, all of the fibers cross over to the contralateral side. However, it is important to note there are many exceptions to this generalization, with uncrossing fibers found in avian, amphibian (e.g., the frog), and fish species (e.g., the jawless fish) (Grant et al., 2003; Ward et al., 1995).

In mammalian species, with the evolution of binocular vision, some of the fibers do not cross over. The fibers remaining on the ipsilateral side are invariably those originating in the temporal retina. The proportion of uncrossed (temporal) fibers increases in species with more frontal eyes and with larger binocular fields. However, in all mammals, the proportion of crossing fibers is larger than that of the uncrossing fibers, with the exception of humans, where half the fibers remain on the ipsilateral side. In the horse and other farm animals, 10%–20% of the fibers remain on the ipsilateral side, as do 25% in the dog and 33% in the cat. Because the topography of decussating fibers is characterized by spatial precision, lesions in different areas of the chiasm (or the optic nerve) will cause specific visual deficits.

The bundles exiting the chiasm are called the optic tracts (De Lahunta & Glass, 2009h). As a result of the decussation in the chiasm (in those species in which it occurs), each tract contains fibers from the opposite visual fields of both eyes. For example, the right tract carries information from the two left visual fields. A lesion in the optic tract, therefore, will cause a homonymous hemianopia, or a bilateral opposite visual field deficit. However, the size of these fields varies. In humans, the tract carries fibers from the temporal hemifield of the ipsilateral retina and the nasal hemifield of the contralateral retina. In the retinotopic manner, meaning that the precise spatial arrangement of the retina is maintained within the nerve (Brooks et al., 1999). Fibers from the superior/dorsal retina form the superior/dorsal half of the optic disk, and fibers from the inferior/ventral retina form the inferior/ventral half. Fibers from the central retina are in the center of the nerve, while those from the peripheral retina form the nerve periphery. This precise arrangement is a condition for the subsequent accurate projection of the visual field in both the LGN and the visual cortex.
the cat, it carries one-third of the fibers from the temporal retina and two-thirds of the fibers from the nasal, contralateral retina.

The optic tract courses caudodorsolaterally over the side of the diencephalon to reach the level of the LGN of the thalamus (De Lahunta & Glass, 2009h). At this point, the optic tract diverges into two basic paths: 20% of the fibers project to different brainstem nuclei to enable reflexes connected to visual stimuli; the remaining fibers (80% in the cat) are those that synapse in the LGN (De Lahunta & Glass, 2009h). The fibers that synapse in the LGN (located in the thalamus) project to the visual area of the cortex as the caudal part of the internal capsule in a band called the optic radiation (De Lahunta & Glass, 2009h). These axons terminate in the cerebral visual cortex on the lateral, caudal, and medial aspects of the occipital lobe. The functional retinotopic anatomy and organization of the LGN and visual cortex are discussed in detail in Chapter 4. This pathway from the optic tract to the LGN of the thalamus to the internal capsule and the visual cortex must be intact for normal perception of vision to occur.

Obstacle Course (Maze Testing)

For obstacle course testing, the patient is placed in an unfamiliar environment and is allowed to move freely. Within the environment, there are randomly placed objects that the patient must navigate through during their exploratory behavior. Obstacle course testing is performed in well-lit (photopic) and dimly lit (scotopic) conditions. In instances when the patient is believed to have hemianopia, having the patient navigate the obstacle course with each eye separately blindfolded can be valuable. For canine patients that are seemingly nervous, it is often times valuable to have the owner present and calling the patient’s name on the side of the room opposite that of the patient. The examiner watches for and notes any evidence of the patient bumping into or stumbling over objects, or signs of them being apprehensive while navigating. If such behaviors happen consistently, this leads the examiner to believe there is a problem with the patient’s vision.

Visual Placing

In patients that are small enough, the animal is held up, supporting its sternum and abdomen, and the patient is brought toward the edge of a flat hard surface. Importantly, the flat surface should be able to be seen by the animal. A normal response is for the animal to attempt to place its limbs on the top of the flat surface. If an animal fails to attempt to place its limb on the surface, this implies that the surface was not seen. One must keep in mind that the animal should be alert and strong enough to attempt to place its limb, however. It is important to recognize that the patient’s limb should not touch the edge of the flat surface. Animals that are blind, without any evidence of other neurologic disease, will attempt to step up when their limb makes contact with the edge of the hard surface. When this happens, one is evaluating tactile placing and not visual placing.

Schirmer Tear Testing

Though not traditionally considered a part of the neuro-ophthalmic examination, quantitative testing of tear production provides relevant information concerning the function of the parasympathetic nervous system. Specifically, measurement of tear production can be done by way of the Schirmer tear test type I (see Chapter 10, Section 1). The test involves placing a standardized piece of filter paper in the ventrolateral conjunctival fornix for 1 minute and then measuring the length of wetting along the strip of paper. Though diseases other than those involving the parasympathetic nervous system can affect tear production, this test complements findings where parasympathetic dysfunction is suspected (e.g., patients with diseases affecting the facial nerve or distal trigeminal nerve). To illustrate the utility of Schirmer tear testing in arriving at a neuroanatomic diagnosis, it is important to consider the anatomy of the parasympathetic innervations of the lacrimal gland.

The preganglionic parasympathetic neurons responsible for lacrimal secretion originate from the parasympathetic nucleus of the facial nerve (i.e., the rostral salivatory nucleus) located within the rostral portion of the medulla oblongata (Arenson & Wilson, 1970, 1971; Neuhuber & Schrodl, 2011). The lacrimal gland’s preganglionic parasympathetic fibers run as part of the facial nerve through the facial canal of the petrous temporal bone (Konig & Liebich, 2007). Within the facial canal, some of these preganglionic fibers branch off as the major (greater) petrosal nerve. The major (greater) petrosal nerve exits the temporal bone and synapses on neurons (postganglionic neurons) within the pterygopalatine ganglion (Konig & Liebich, 2007). With respect to lacrimal gland innervations, postganglionic parasympathetic axons join with branches of the trigeminal nerve—the zygomatic nerve (a branch of the maxillary nerve), and the lacrimal nerve (a branch of the ophthalmic nerve). Both zygomatic and lacrimal nerves innervate the lacrimal gland and hence are important in tear production. As is hopefully apparent, some instances of diseases affecting the trigeminal nerve (e.g., trigeminal neuritis) may result in reduced tear production.

Another branch of the facial nerve (branched while still within the facial canal), the chorda tympani, runs through the middle ear and also carries preganglionic parasympathetic fibers, and these fibers join the mandibular branch of the trigeminal nerve to ultimately synapse in the submandibular and sublingual ganglia, which, in turn, send postganglionic fibers to their respective salivary glands (Konig & Liebich, 2007). Given that preganglionic parasympathetic fibers run through the middle ear, it is possible for preganglionic fibers to become affected during diseases like otitis media, thus resulting in neurogenic keratoconjunctivitis sicca (KCS).

Sensory innervation to the lacrimal gland is provided by the lacrimal nerve, the first branch of the ophthalmic nerve after it enters the orbit through the orbital fissure (Konig & Liebich, 2007). The nerve runs to the lateral part of the orbit and gives branches to the lacrimal gland, to other deeper
structures, and then to the skin of the lateral canthus of the eye (Konig & Liebich, 2007). Given that the Schirmer tear test involves quantitatively measuring reflex production of tears, it is important to remember the afferent arm of this measurement involves the trigeminal nerve, while the efferent component involves the parasympathetic output onto the lacrimal gland. As such, conditions causing loss of sensation from the cornea and conjunctiva (e.g., diabetes mellitus) can also result in reduced Schirmer tear test values (Cullen et al., 2005).

Pharmacologic Testing of the Autonomic Nervous System

In some instances, arriving at a neuroanatomic diagnosis, that is, identifying where along the neuroanatomic pathway a lesion is located, one must provocatively test the nervous system pharmacologically. Herein we describe the pharmacologic approach to differentiating between pre- and postganglionic lesions of the parasympathetic and sympathetic nervous systems, respectively. The basis for pharmacologic testing, whether parasympathetic or sympathetic, relies upon (1) the ability of neurotransmitter to be released from the postganglionic neuron or (2) the phenomenon of denervation hypersensitivity (Ramsay, 1986).

Parasympathetic Lesions

In order to differentiate between pre- and postganglionic parasympathetic lesions, the following series of tests can be attempted. The drugs used include the following:

- **Indirect parasympathomimetic drugs such as physostigmine (anticholinesterase).** This class of drug requires an intact postganglionic neuron to induce miosis. The drug acts to extend the action of endogenous acetylcholine being released at the neuromuscular junction by the postganglionic parasympathetic neuron.
- **Direct-acting parasympathomimetic drugs, such as pilocarpine.** These drugs act on the iris sphincter itself by binding to the acetylcholine receptor. These drugs will cause miosis in both pre- and postganglionic lesions. If the lesion is postganglionic, however, there will be an upregulation in the number of acetylcholine receptors at the postsynaptic membrane, resulting in denervation hypersensitivity. Therefore, application of a direct-acting drug in such a patient will cause a more complete and longer constriction than in a patient with a preganglionic neuron lesion.

A drop of 0.5% physostigmine causes rapid pupillary constriction in cases of a preganglionic neuron lesion. A normal eye will constrict more slowly, 40–60 minutes after application of the drug. If no constriction is observed after applying physostigmine, two drops of 2% pilocarpine are administered. Rapid and complete constriction of the pupil will indicate a postganglionic neuron lesion. The direct-acting drugs should only be administered 24 hours after testing the indirect-acting drugs. It has recently been shown that dilute solutions of pilocarpine (0.05%) administered topically can also demonstrate supersensitivity (Ramsay, 1986).

If in both pharmacologic tests the normal pupil constricts but the dilated one does not, then the mydriasis could only be caused by pretreatment with parasympatholytic agents (e.g., atropine) or by an iridal disease. For example, iris degeneration and/or atrophy will cause ipsilateral mydriasis with variable degrees of response to light. This condition is more common in older dogs and in extreme cases may result in complete absence of pupillary constriction. Likewise, glaucoma and annular posterior synechia may cause an ipsilateral mydriasis that is unresponsive both to light and to miotic agents.

Sympathetic Lesions

In order to differentiate between pre- and postganglionic sympathetic lesions, the following series of tests can be attempted (Bistner et al., 1970a). The drugs used include:

- **Indirect-acting sympathomimetic drugs, such as 1% hydroxyamphetamine.** These drugs will induce release of norepinephrine from vesicles in the postganglionic neurons. After application of one to two drops of 1% hydroxyamphetamine, if the lesion is in the central component (i.e., hypothalamospinal pathway) or if the lesion involves the postganglionic neuron, the pupil will dilate immediately and fully. If a lesion involves the postganglionic neuron, norepinephrine cannot or will be minimally released, and therefore treatment will cause minimal or no dilatation of the pupil.
- **Direct-acting sympathomimetic drugs, such as 0.001% epinephrine.** Such a test is based on the fact that a lesion involving the postganglionic neuron causes denervation hypersensitivity of the smooth dilator muscle of the iris. The sensitized muscle will respond to low concentrations of a direct-acting sympathomimetic drug that would be ineffective under normal conditions. For example, 0.001% epinephrine (0.1 mL) will cause mydriasis within 20 minutes following topical administration to a denervated pupil. The same response will take about 40 minutes to occur if the lesion is in the central part of the sympathetic pathway (i.e., hypothalamospinal pathway) or if the lesion involves the preganglionic neuron. Similarly, instillation of 10% phenylephrine will cause mydriasis of a normal eye, or an eye having first-order Horner’s syndrome in approximately 60–90 minutes. Meanwhile, animals with second-order Horner’s syndrome will have pupillary mydriasis between 20 and 60 minutes, and animals with postganglionic (third-order Horner’s syndrome) lesions will respond within 20 minutes (Bistner et al., 1970a). The direct-acting drugs should only be administered 24 hours after testing with indirect-acting drugs. Topical testing with adrenergic agents is less conclusive in most cases (Kern et al., 1989).
Interestingly, a dilute solution of phenylephrine can be used (i.e., 1% phenylephrine) with similar results to using 10% phenylephrine (Ramsay, 1986). The authors commonly use this dilute concentration method.

NEUROANATOMIC LESION LOCALIZATION

Localization of the lesion is, as previously stated, one of the most important steps in reaching a diagnosis. Without an accurate neuroanatomic diagnosis, one will be unable to formulate an appropriate differential diagnostic list or diagnostic plan. The following section aims at not reiterating the neuroanatomy of the various components of the neuro-ophthalmic examination in prose; rather, we have provided a variety of tables and schemata to aid in reaching a neuroanatomic diagnosis. The use of such tables and schemata is intended to aid you, the reader, through deductive reasoning, recognizing the outcome of disease processes involving the neuro-ophthalmic system.

Additionally, we have also provided a list and description of Braund’s neurologic syndromes that may involve abnormalities of the eye and its adnexa (Braund, 1986, 1999, 2003). Understanding such syndromes is helpful when presented with a patient having a constellation of clinical neurologic signs in addition to those detected after completing the neuro-ophthalmic examination. The exact neuroanatomic substrates and pathophysiologic reasoning for the extra-neuro-ophthalmic clinical signs are beyond the scope of this chapter, however, though the reader is directed to an appropriate veterinary neurology textbook for more in-depth discussion (e.g., De Launuta & Glass, 2009g).

Braund’s Syndromes

Behavior can be defined as the motor and autonomic manifestations of physiological processes. Accepting this, specific components of the nervous system are responsible for various behaviors. It is important to recognize, however, that the nervous system is “plastic” and not “hardwired.” Given the plasticity of the nervous system, abnormal behaviors may initially manifest and then be compensated (e.g., nystagmus), or may not manifest until the lesion affecting the nervous system is of sufficient magnitude such that the nervous system cannot compensate for any lost function.

Though first published and revised many years ago, clinical syndromes observed in veterinary neurology are very useful in arriving at a neuroanatomic diagnosis (Braund, 1986, 1999, 2003). Though one may consider such syndromes a simplified approach to arriving at a neuroanatomic diagnosis (i.e., relying heavily on pattern recognition), it is well known that disease processes affecting the central and peripheral nervous systems manifest with a group of characteristic clinical signs (i.e., syndrome). As mentioned previously, arriving at a neuroanatomic diagnosis is key prior to formulating a list of differential diagnoses. Of paramount importance to arriving at a list of differential diagnoses is consideration for the historical severity of the clinical signs (Fig. 34.23).

Though details in the neuroanatomic rationale accounting for clinical syndromes in veterinary neurology are beyond the scope of this chapter (for discussion see deLahunta book), we provide a list of Braund’s clinical syndromes that may include neuro-ophthalmic clinical signs. In addition, we also provide a description of other syndromes important in neuro-ophthalmology. In performing neuro-ophthalmic assessment, it is important to consider clinical signs other than those attained from the neuro-ophthalmic examination itself.

Cerebral Syndrome (Table 34.4)

The cerebral syndrome is a group of clinical signs that may be observed in disease processes involving the cerebral cortex (Braund, 2003). Of course, however, it should be recognized that the cerebral cortex is organized in such a way that it serves sensory, motor, and cognitive functions. That is, the frontal lobe is concerned with executive functions (i.e., integration of sensorimotor behavior for judgement and planning) and motor control, the temporal lobe with hearing, memory, and emotion, and the parietal lobe with somatosensation, and the occipital lobe with vision. Also of importance to recognize, the sensorimotor function of one particular hemisphere of the cerebral cortex is concerned with the contralateral region of the body. This is because of the decussation of fibers running to and from the cerebral cortex from various structures in the body.

Table 34.4 provides a list of clinical signs that comprise the cerebral syndrome. It is important to recognize that a veterinary patient may have only some or all of the clinical signs. A gain, the presence or absence of particular clinical signs varies depending upon the location of the cerebral cortex that is involved and the ability of the cerebral cortex to “compensate” for a particular disease process. It is of paramount importance to recognize that some of the clinical signs of this
syndrome may not be evident in a patient in the hospital setting, though when the patient is in a comfortable “home” setting the behaviors manifest. As such, it is important to carefully glean these atypical behaviors through the clinical history with appropriate use of open- and closed-ended questioning techniques and request, if possible, that video recordings of the animal’s behavior be brought into the appointment for evaluation.

**Diencephalic Syndrome (Table 34.5)**

The diencephalic syndrome is a group of clinical signs that may be observed in disease processes involving the diencephalon (Braund, 2003). The diencephalon is that region of the brain that is home to various structures responsible for autonomic functions such as thermoregulation, state of arousal, sexual activity, sleep-wake cycles, cardiovascular function, emotion, and endocrine functions. As such, disease processes involving this region of the brain can cause abnormal mentation, visual impairment at the level of the optic chiasm (as the diencephalon is where the optic chiasm is located), inability to thermoregulate, and evidence of endocrine disease. Table 34.5 lists clinical signs that can be observed in patients with a disease process involving the diencephalon.

**Midbrain Syndrome (Table 34.6)**

The midbrain syndrome is a group of clinical signs that may be observed in disease processes involving the midbrain (Braund, 2003). The midbrain is home to CN III (oculomotor nerve), parasympathetic nucleus of CN III, and the lateral geniculate nuclei. As such, ocular signs seen in this syndrome may include unilateral or bilateral ventrolateral strabismus, internal opthalmoparesis from involvement of the parasympathetic nucleus of CN III (i.e., dilated pupil), ptosis of the upper eyelid, and menace deficit may be observed contralateral to the lesion if extension of the lesion involves the lateral geniculate nuclei (in the diencephalon). Other clinical signs of this syndrome are related to the motor (i.e., decerebrate rigidity, obstinate progression [walking until coming into contact with object and then head pressing against object]) or respiratory (i.e., rapid regular breathing pattern) systems.

**Vestibular Syndrome (Table 34.7)**

The vestibular syndrome is a group of clinical signs that may be observed in disease processes involving the vestibular system (central or peripheral) (Braund, 2003). This is a common clinical syndrome. As discussed previously, the
central components of the vestibular system are located within the medulla oblongata and the vestibulocerebellum, while the peripheral vestibular system involves CN VIII (vestibulocochlear nerve) and the membranous labyrinth of the vestibular component of the inner ear. See Table 34.7 for clinical signs that are present and help to differentiate central from peripheral vestibular disorders (Webb et al., 2009b). Of course, nystagmus, ventrolateral strabismus, impaired vestibuloocular reflexes (e.g., bilateral vestibular disease) are the principle ocular signs of vestibular disease. However, other signs of vestibular disease may include absent menace response ipsilateral to the lesion in the case of unilateral cerebellar disease, facial paresis/paralysis in cases of peripheral (e.g., otitis media/interna) or central vestibular disease (i.e., involvement of the nucleus of CN VII), or Horner’s syndrome (peripheral vestibular disease only—e.g., otitis media/interna).

### Cerebellar Syndrome

The cerebellar syndrome is a group of clinical signs that may be observed in disease processes involving the cerebellum (Braund, 2003). Important to recall is that the cerebellum is involved in the fine-tuning of coordinated motor movements. As such, disease processes involving the cerebellum oftentimes manifest as over and undershooting of the body during intentional movement of a body part (e.g., truncal sway, intention tremor of the head/neck). In addition, given the importance of the cerebellum in the menace response pathway (without visual field loss) and in the vestibular system, animals with cerebellar disease may lack a menace response ipsilateral to the lesion and may have nystagmus, respectively. Also sometimes seen in cerebellar disease is anisocoria with the dilated pupil being present contralateral to the lesion. Finally, in instances of severe and acute cerebellar disease, patients may present with a characteristic decerebellate posture (i.e., opisthotonus with hind limbs tucked up under the abdomen). Importantly, however, patients with cerebellar disease alone have normal mentation.

### Pontomedullary Syndrome

The pontomedullary syndrome is a group of clinical signs that may be observed in disease processes involving the pons and medulla oblongata (Braund, 2003). Given the location of various cranial nerve nuclei along the pons and medulla
Table 34.9  Pontomedullary Syndrome (Braund, 2003)

Weakness/paralysis observed to involve one of the following:
- All four limbs
- Limbs on the same side of body as lesion
Normal or increased reflexes and muscle tone in all limbs in all limbs
Postural reaction deficits (e.g., impaired knuckling, hopping) in all four limbs or of limbs ipsilateral to the lesion
Possible multiple cranial nerve deficits (CNs V–XII)
Altered ventilatory pattern
Dull mentation (i.e., involvement of the ascending reticular activating system [ARAS])
Partial Horner’s syndrome

Table 34.10  Cervical Syndrome (Braund, 2003)

Weakness/paralysis observed to involve one of the following:
- All four limbs
- Limbs on the same side of body as lesion
- Only one thoracic limb
Normal or increased reflexes and muscle tone in all limbs
\[\pm\] extensor rigidity in limbs ipsilateral to the lesion or in all limbs
Postural reaction deficits (e.g., impaired knuckling, hopping) in all four limbs or of limbs ipsilateral to the lesion
Neck muscle spasms, signs suggestive of pain (e.g., vocalization, impaired voluntary motion of neck, stiff/rigid and low carriage of neck)
Root signature (i.e., thoracic limb held in partial flexion during standing or sitting, seemingly adjusting affected limb to “get comfortable”)
\[\pm\] Ventilatory difficulty
\[\pm\] Horner’s syndrome (partial or complete)

Cervicothoracic Syndrome (Table 34.11)

The cervicothoracic syndrome is a group of clinical signs that may be observed in disease processes involving the cervical spinal cord (spinal cord segments C6-T2) (Braund, 2003). In addition, this region of the spinal cord is home to the SPNs responsible for sympathetic innervation of the eye. As such, animals with a disease process involving the cervicothoracic region of the spinal cord may have lower motor neuron signs (i.e., hypo- to areflexia of the forelimb[s], flaccid paresis/paralysis of the forelimb musculature, varying degrees of neurogenic atrophy of forelimb musculature), upper motor neuron signs to the ipsilateral hind limb with reduction or absence of proprioceptive abilities in the ipsilateral hind limb. In addition, the cutaneous trunci may be absent ipsilateral to the lesion. Finally, ophthalmic signs include partial or complete Horner’s syndrome ipsilateral to the lesion (see Horner’s syndrome below).

Other Syndromes

Horner’s Syndrome (Table 34.12)

The sympathetic innervation of the eye has already been discussed previously in this chapter (see Fig. 34.24 for simplified oblongata (CN V [trigeminal] to CN XII [hypoglossal]), a variety of clinical signs referable to injury to these cranial nerve nuclei can be observed (see Table 34.1, Table 34.2, and Table 34.3). Upper motor neuron signs (i.e., increased muscle tone and hyperreflexia) can be observed in the limbs of patients with pontomedullary syndrome. Given the location of various pattern generators of the respiratory system, various changes in ventilatory patterns can be observed in patients with severe pontomedullary lesions. In addition, alteration in mentation is expected given the involvement of the ascending reticular activating system.
### Table 34.12: Neuroanatomic Localization of Horner's Syndrome

<table>
<thead>
<tr>
<th>Neuroanatomic Location</th>
<th>First-, Second-, or Third-Order Disease</th>
<th>Possible Concurrent Clinical Signs</th>
<th>Potential Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>First</td>
<td>Altered level of consciousness</td>
<td>Neoplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormalities in thermoregulation, eating, drinking, breathing pattern, endocrine function</td>
<td>Inflammatory (primary or secondary)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cranial nerve abnormalities</td>
<td>Vascular</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
<tr>
<td>Cervical spinal cord</td>
<td>First</td>
<td>Ipsilateral hemiparesis/paralysis</td>
<td>Neoplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tetraparesis/quadruplegia</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper motor neuron signs to all four limbs ± Signs of neck pain</td>
<td>Ischemic myelopathy (e.g., fibrocartilagenous embolism)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervertebral disk disease</td>
</tr>
<tr>
<td>T1–T3 spinal cord</td>
<td>Second</td>
<td>Lower motor neuron signs to the forelimb(s)</td>
<td>Neoplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper motor neuron signs to the hind limbs</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper motor neuron bladder</td>
<td>Ischemic myelopathy (e.g., fibrocartilagenous embolism)</td>
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<tr>
<td></td>
<td></td>
<td>Upper thoracic back pain</td>
<td>Intervertebral disk disease</td>
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<tr>
<td></td>
<td></td>
<td>Ipsilateral or bilateral loss of cutaneous trunci reflex</td>
<td></td>
</tr>
<tr>
<td>T1–T3 ventral nerve roots</td>
<td>Second</td>
<td>Lower motor neuron signs to ipsilateral limb</td>
<td>Trauma to brachial plexus</td>
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<tr>
<td></td>
<td></td>
<td>Ipsilateral forelimb lameness</td>
<td>Nerve sheath tumor</td>
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<tr>
<td></td>
<td></td>
<td>Ipsilateral loss of cutaneous trunci reflex</td>
<td></td>
</tr>
<tr>
<td>Sympathetic trunk</td>
<td>Second</td>
<td>Dysphagia</td>
<td>Mediastinal mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cough</td>
<td>Trauma (e.g., IV injection and carotid ligation for surgery in horses)</td>
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<td></td>
<td></td>
<td>Lethargy</td>
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<td></td>
<td></td>
<td>Regurgitation</td>
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<tr>
<td></td>
<td></td>
<td>Cough</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Reduced compressibility of thorax</td>
<td></td>
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<tr>
<td>Middle ear</td>
<td>Third</td>
<td>Ipsilateral signs of peripheral vestibular disease</td>
<td>Otitis media</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipsilateral facial nerve paralysis</td>
<td>Middle ear mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipsilateral keratoconjunctivitis sicca</td>
<td>Guttaral pouch disease</td>
</tr>
<tr>
<td>Cavernous sinus</td>
<td>Third</td>
<td>Internal, external, or complete ophthalmoplegia</td>
<td>Neoplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inflammatory disease (primary or secondary)</td>
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<td></td>
<td></td>
<td></td>
<td>Vascular disease (e.g., aneurysm)</td>
</tr>
<tr>
<td>Retrobulbar</td>
<td>Third</td>
<td>Signs of orbital disease (e.g., exophthalmos and pain upon opening mouth)</td>
<td>Neoplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Involvement of one or more of cranial nerves II, III, IV, V, VI</td>
<td>Abscess</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trauma</td>
</tr>
</tbody>
</table>

Figure 34.24. Cartoon depicting the “three-order” neuron pathway for sympathetic control of the eye. Note that the first-order neuron is located within the hypothalamus and makes connections with the sympathetic preganglionic neurons (SPNs) (second-order neurons) located in the intermediolateral gray matter of the upper thoracic spinal cord. SPNs send projections to third-order neurons located within the cranial cervical ganglion (located adjacent to the tympanic bulla). Neurons within the cranial sympathetic ganglion send postganglionic fibers to the effector organs in the eye and face. Axons of third-order neurons enter the cranial vault and pass near the cavernous sinus prior to exiting the cranial vault via the orbital fissure.
SECTION IV: Special Ophthalmology

Cavernous Sinus Syndrome

Cavernous sinus syndrome is that group of clinical signs that refers to disease processes involving the cavernous sinus (Rossmeisl et al., 2005; Theisen et al., 1996). The cavernous sinus is a venous sinus located bilaterally on the floor of the middle cranial vault and extending from the orbital fissure to the petro-occipital canal. Each cavernous sinus is connected rostrally and caudally by rostral and caudal intercavernous pathways (for reviews and case series, see Van den Broek, 1988; Firth, 1978; Green et al., 1992a; Kern et al., 1989; Morgan & Zanotti, 1989; Simoens et al., 1990; Smith & Mayhew, 1977). Horner’s syndrome is that cluster of clinical signs referable to the loss of ocular sympathetic innervation. Remembering that the sympathetic nervous pathway to the eye essentially involves presympathetic neurons from the brain to the SPNs located in the intermediolateral gray matter of spinal cord segments T1–T3, and finally postganglionic sympathetic neurons located in the cranial cervical ganglion. Postganglionic sympathetic fibers innervate the ciliary body, iris dilator, and iris sphincter muscles (keep in mind reciprocal iris innervations), the smooth muscles of the periorbita, and Müller’s muscles of the upper and lower eyelids. Normal sympathetic tone in these smooth muscles keeps the globe slightly protruded, the palpebral fissure opened, the third eyelid retracted, and the pupil partially dilated. When there is a disease process affecting the sympathetic innervation, however, the following signs are found with variable expression:

- miosis (Fig. 34.25)
- ptosis
- enophthalmus
- protruded third eyelid (Fig. 34.25)
- facial sweating (only in horses) (may see neck sweating if preganglionic lesion is involved) (Fig. 34.26)
- hyperthermia of the facial area
- anhidrosis of the planum nasolabiale in cattle (Fig. 34.27)
- hyperthermia of the ear (ruminants).

Please see Table 34.12 for clinical signs that are seen in Horner’s syndrome depending upon the region of the nervous system affected. To further substantiate the neuroanatomic diagnosis, provocative pharmacologic testing can be used to differentiate first- (presympathetic), second- (preganglionic), and third-order (postganglionic) Horner’s syndrome (see above).

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facial tetany is seen rarely in dogs, though when noticed, it is important to recognize this clinical sign as it a symptom of a disease process of the facial nerve or the nucleus of CN VII. Disease processes having been reported in dogs with hemifacial spasm include degenerative or neoplastic brainstem disease and otitis media/interna. The clinical signs of hemifacial tetany should not be confused with chronic facial nerve paralysis with neurogenic atrophy and fibrosis of the facial muscles. In cases of chronic facial nerve paralysis, these patients will have a diminished or absent palpebral reflex.

Pourfour du Petit Syndrome

Pourfour du Petit syndrome is described in humans as consisting of mydriasis, widened palpebral fissure, exophthalmos, and cool periocular skin with increased sweating (Boydell, 2000). A similar condition has been described in cats having undergone flushing of the middle ear during diagnostic workup of middle ear disease. In these cats, anisocoria was noted with the affected pupil being mydriatic with a brisk but incomplete direct PLR, ipsilateral exophthalmia, and an enlarged palpebral fissure without evidence of third eyelid protrusion. Menace response and palpebral reflexes were normal. Mydriasis resolves within 1 week. Though not known for certain, it is speculated that these clinical signs occur due to a transient irritative (neuritis) lesion to postganglionic sympathetic fibers. In some instances, patients may go on to develop ipsilateral Horner’s syndrome.

### Table 34.13 Cavernous Sinus Syndrome

<table>
<thead>
<tr>
<th>Cranial Nerve</th>
<th>Clinical Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>III (oculomotor) including parasympathetic fibers of CN III</td>
<td>Mydriasis, paralysis or paresis of levator palpebrae, dorsal rectus, medial rectus, ventral rectus, and retractor bulbi muscles</td>
</tr>
<tr>
<td>IV (trochlear)</td>
<td>Paralysis or paresis of the dorsal oblique</td>
</tr>
<tr>
<td>VI (abducens)</td>
<td>Paralysis or paresis of the lateral rectus and retractor bulbi muscles</td>
</tr>
<tr>
<td>V (ophthalmic branch)</td>
<td>Corneal anesthesia, peri orbital and medial canthal anesthesia</td>
</tr>
<tr>
<td>V (maxillary branch)</td>
<td>Periorbital and facial anesthesia</td>
</tr>
<tr>
<td>Postganglionic sympathetic</td>
<td>Horner’s syndrome—ptosis, enophthalmos, miosis, protruding third eyelid</td>
</tr>
</tbody>
</table>

sinuses, respectively. Neuro-ophthalmically important structures that are in close proximity to the cavernous sinus include CN III, IV, VI and the ophthalmic and maxillary branches of CN V. In addition, postganglionic sympathetic axons are also found near the cavernous sinus. It is this close association with the cavernous sinus and the constellation of clinical signs that are referable to these nerves’ dysfunction that this syndrome gets its name. Importantly, however, it should be recognized that disease processes involving the orbit and orbital fissure (i.e., where these cranial nerves exit or have exited) may result in cavernous sinus syndrome. It should be recognized also that cavernous sinus syndrome can be either unilateral or bilateral, albeit bilateral cavernous sinus syndrome is rarer. The clinical signs found in cavernous sinus syndrome typically include

- external and internal ophthalmoparesis
- ptosis
- mydriasis
- reduced corneal sensation
- reduced periorbital and nasofacial sensation
- ± Horner’s syndrome.

### Hemifacial Spasm (Hemifacial Tetany)

The clinical sign of hemifacial spasm is where the facial muscles on one side are in a constant state of contraction (Parker et al., 1973; Roberts & Vainisi, 1967; Van Meervenne et al., 2008). As such, the term hemifacial spasm is more aptly termed hemifacial tetany. Hemifacial tetany may manifest as primarily blepharospasm, ipsilateral deviation of the nasal planum, ipsilateral narrowing of the palpebral fissure, and ipsilateral elevated or caudal displacement of the ear. Other clinical neurologic signs may occur concurrently, especially if there is brainstem involvement. The clinical sign of hemifacial tetany is seen rarely in dogs, though when noticed, it is important to recognize this clinical sign as it a symptom of a disease process of the facial nerve or the nucleus of CN VII. Disease processes having been reported in dogs with hemifacial spasm include degenerative or neoplastic brainstem disease and otitis media/interna. The clinical signs of hemifacial tetany should not be confused with chronic facial nerve paralysis with neurogenic atrophy and fibrosis of the facial muscles. In cases of chronic facial nerve paralysis, these patients will have a diminished or absent palpebral reflex.

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Figure 34.28. Right eye: D-shaped pupil in miosis, fibrinous exudate in the nasal inferior part of the anterior chamber, and moderate rubeosis iridis resulting from anterior uveitis. (From Nell & Suchy, 1998.)
Static Anisocoria (Spastic Pupil Syndrome) and Hemidilated Pupil

Static anisocoria describes a clinical sign seen in cats where miosis, or less commonly mydriasis, of the affected pupil occurs (Nell & Suchy, 1998). In cats with miotic static anisocoria, the miosis does not respond to dark adaptation.

Hemidilated pupil is seen in cats and is characterized by a D-shaped or reverse D-shaped pupil. The proposed pathophysiology of the hemidilated pupil is explained by a lesion involving the malar (lateral) or nasal (medial) short ciliary nerves. Pharmacologic testing with pilocarpine supports this notion. It has been shown, however, that postmortem persistence of this dyscoria could likely be explained by iridal infiltration with lymphosarcoma (Fig. 34.28).

Static anisocoria in the cat can be seen as a result of feline leukemia virus, lymphosarcoma, and feline dysautonomia.

Schemata for Neuroanatomically Localizing Blindness and Anisocoria (Figure 34.29, Figure 34.30, Figure 34.31, and Figure 34.32)

We have provided a variety of schemata (Fig. 34.29, Fig. 34.30, Fig. 34.31, and Fig. 34.32) that can be used to help in arriving at a neuroanatomic diagnosis for patients presenting for visual impairment and/or anisocoria. The intent of these schemata is to provide the reader with varying views in how one might arrive at a neuroanatomic diagnosis for patients presenting with these clinical signs. It is not the intent to provide a “recipe” for lesion localization. There is no substitute for understanding basic neuroanatomy and applied clinical neuroscience when arriving at a neuroanatomic diagnosis for patients who may not “fit” within a particular schema.

FORMULATING A DIFFERENTIAL DIAGNOSIS LIST

Rather than listing every possible disease process that can result in neuro-ophthalmic signs, we discuss the rationale behind arriving at an appropriate differential diagnostic list. Though pattern recognition is a valid approach to arriving at a differential diagnosis, it is important, especially for those patients that do not “fit” a typical pattern, to return to the basics of formulating a list of appropriate differential diagnoses. The first step in formulating a differential diagnostic list is to neuroanatomically localize the problem. In combination with the neuroanatomic diagnosis, it is of utmost importance to consider the signalment and clinical history of the patient. To illustrate, one would not include enrofloxacin toxicity as a differential diagnosis for a dog presenting with a slowly progressive onset of visual disturbance and subacute history of altered mentation.

One must also consider the broad etiologic/pathophysiologic categories of clinical disease:

- vascular
- infectious
- traumatic/toxic
- anomalous
- metabolic
Figure 34.30. An approach to reach a neuroanatomic diagnosis in animals with vision loss with or without pupillary light reflex abnormalities.

Figure 34.31. An approach to reach a neuroanatomic diagnosis in animals with vision loss and having pupillary light reflex abnormalities.

• inflammatory
• neoplastic/nutritional
• degenerative.

In so doing, one can begin to consider some disease processes more likely than others, especially if a clinical sign:time graph is considered (see Fig. 34.23). Though this rudimentary approach is commonly taught early in our careers, it serves a significant function at arriving at an appropriate differential diagnosis list and also aims in creating an appropriate diagnostic plan.

NEURO-OPHTHALMIC DISEASES

Thus far, we have discussed the neuro-ophthalmic examination, pertinent neuroanatomy, a variety of neurologic syndromes where neuro-ophthalmic symptoms may be present, and an approach for formulating a list of differential diagnoses. In the present section, we provide a discussion of various, and important or newly advanced, diseases in which neuro-ophthalmic findings may be found. For diseases of a systemic nature that may manifest neuro-ophthalmically, please refer to Chapter 35. It should be noted, for the purposes of brevity, inborn errors of metabolism, the various inherited retinal degenerative diseases, and other causes of preretinal blindness are discussed elsewhere in this textbook. This section is
Figure 34.32. An approach to reach a neuroanatomic diagnosis in animals with anisocoria.
Chapter 34: Neuro-ophthalmology

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SECTION IV

ral hearing loss ranging from profound elevations in hearing threshold bilaterally to being bilaterally deaf. Cochlear histopathology demonstrates complete degeneration of the organ of Corti. Histopathology of the vestibular labyrinth reveals an absence or abnormality of the otoconia, though no degeneration of vestibular hair cells has been detected. As with any static vestibular disease process, affected animals have variable resolution of clinical signs, though the lack of vestibulo-ocular reflex and hearing loss are persistent. We have recently described this condition to be inherited in an autosomal recessive fashion with a mutation in MYO7A on chromosome 21. Approximately 13% of the population (n = 865) are carriers of the mutation. This disease is a model of human Usher syndrome type 1b (Webb & Neff, 2011).

Hydrocephalus

Hydrocephalus refers to increased amount of CSF within the cranial vault. Congenital hydrocephalus is common in some breeds of dogs, with toy and brachycephalic breeds at highest risk for the disease, thereby suggesting a hereditary basis in many of these dogs (Selby, 1979). The most common cause of congenital hydrocephalus is a primary congenital stenosis or aplasia of the mesencephalic aqueduct associated with fused rostral colliculi (Selby, 1979). Hydrocephalus resulting from impediment of CSF outflow from the ventricular system is referred to as obstructive or noncommunicating hydrocephalus. In cases where there is no associated malformation in the mesencephalic aqueduct, the cause of congenital hydrocephalus remains unknown. Congenital hydrocephalus may produce enlargement of the calvarium and failure of closure of the suture lines of the skull. Consequently, affected puppies may have a persistently open fontanelle. Clinical signs of hydrocephalus include behavioral changes, ataxia,
and seizures. Ventrolateral strabismus is a common ocular manifestation of congenital hydrocephalus due, in part, to enlargement of the calvarium with subsequent impingement on the orbits from the dorsolateral aspects. This consequently pushes the eyes in a ventrolateral direction and produces a “sunset” appearance to the corneas. As well, congenital hydrocephalus may cause cranial nerve compromise and subsequent ventrolateral strabismus. On relatively rare occasions, hydrocephalus may produce papilledema.

Lissencephaly
Lissencephaly is a condition characterized by a lack of gyri and sulci over the cerebral cortex (i.e., a smooth cortex). Affected individuals also have abnormalities in cerebrocortical neuronal organization. The condition is presumed inherited in Lhasa Apsos (Greene et al., 1976; Saito et al., 2002). Affected puppies have abnormal behavior, may be difficult to train, may have evidence of altered postural reactions, and may lack, or have reduced, menace responses. All of these clinical signs are attributed to abnormalities of the cerebral cortex.

Myasthenia Gravis
Myasthenia gravis is a disease affecting the neuromuscular junction (for a complete review, see Shelton, 2002). Myasthenia gravis is either congenital or acquired (for acquired, see under “Acquired” section). Congenital myasthenia gravis occurs when there is a functional disorder or depletion of nicotinic acetylcholine receptors (AChRs) (Shelton, 2002). Congenital myasthenia gravis has rarely been reported in dogs. Congenital myasthenia gravis is inherited as an autosomal recessive trait in Smooth Fox Terriers (Miller et al., 1983), Jack Russell Terriers (Palmer & Goodyear, 1978), and English Springer Spaniels (Johnson et al., 1975; Lohi et al., 2005). Affected puppies have abnormal behavior, may be difficult to train, may have evidence of altered postural reactions, and may lack, or have reduced, menace responses. All of these clinical signs are attributed to abnormalities of the cerebral cortex.

Quadriplegia and Amblyopia
A syndrome of decreased vision with nystagmus, ataxia, and tremors has been described in the Irish Setter. This syndrome is thought to be inherited as a postnatally lethal, autosomal recessive trait (Palmer et al., 1973; Sakai et al., 1994). Most animals are unable to stand at birth, though walking movements are made that propel them in a “seal-like” manner when prone. Vision is difficult to evaluate in a very young animal, but those affected lack fixation responses as well as menace responses and dazzle reflexes. The PLRs are normal. The ocular fundus is normal on fundic examination as well. Electroretinographic (ERG) findings have not been reported. CNS lesions include degeneration and necrosis of the cerebellar cortex, with severe loss of Purkinje cells. Histopathologic findings do not correlate well with clinical neurologic or ocular findings.

Developmental: Dog
Fibrosing Esotropia
Fibrosing esotropia is a progressive esotropia that is seen in juvenile large or giant breed dogs affected by extraocular muscle myositis (Allgoewer et al., 2000). The disease is of unknown origin; it causes fibrosis of the medial rectus and dorsal oblique muscles. The condition can be unilateral but generally is bilateral, and there does not seem to be a sex predilection (Allgoewer et al., 2000). Affected animals may have impaired vision due to the severity of the esotropia.

Forced duction testing (i.e., passive or active manipulation to cause the globe to move in a particular direction) is generally indicative of the problem. Passive forced duction tests are indicative of mechanical restriction, because the globe cannot be forced into the direction of gaze limitation, thereby indicating muscle entrapment or fibrosis of the muscle. Active forced duction tests reveal a lateral rectus capable of pulling the globe caudally but not capable of rotating it laterally. No active contraction can be felt on the medial side of the globe, indicating either entrapment or degeneration of the muscle. Surgical correction may restore eye position and vision in some patients (Allgoewer et al., 2000).

Lafora Disease (Myoclonic Epilepsy)
Lafora disease is an adult onset condition characterized by progressive development of episodic myoclonus of the head, neck, and whole body. The condition has been described in a variety of breeds of dogs, though an expanded repeat mutation in the EPM2B gene has been described in Miniature Wire-Haired Dachshunds and Basset Hounds (Lohi et al., 2005). Though neuro-ophthalmic examination is normal in these patients, patients may present with a complaint of a visual disturbance causing these attacks. Periodic episodes of myoclonus can be triggered by auditory and/or visual stimulation (e.g., stroboscopic light [the flicker from a television or alternating patterns of light and dark as one drives by a row of trees]) (Lohi et al., 2005; Webb et al., 2009). Clinical signs
develop in affected animals between 6 and 9 years of age. Dogs are typically euthanized when clinical signs become so frequent as to deleteriously affect their quality of life. In children, however, signs develop typically in their teens and children typically die within 10 years from the onset of clinical signs. Diagnosis is made based upon signalment, clinical signs, and histopathologic identification of intracellular PAS-staining inclusions (Lafora bodies) (i.e., poorly branched glycogen-like polysaccharides [polyglucosan] intracellular inclusions) within a variety of tissues including liver, muscle, spleen, skin, and retina. Alternatively, a genetic test is available for the mutation described thus far.

Acquired: Dog

Canine Distemper

Canine distemper virus (CDV) is caused by an enveloped, single-stranded RNA Morbillivirus in the Paramyxoviridae family (for review, see Deem et al., 2000). CDV infects a wide variety of families of animals including Canidae (e.g., dogs), Procyonidae (e.g., raccoons), Ursidae (e.g., bears), Mustelidae (e.g., ferrets, skunks), and Hyaenidae (e.g., hyena). The virus is spread mainly by inhalation of viral particles in aerosolized respiratory or other infected secretions such as urine. Wide-spread vaccination of dogs has markedly decreased the incidence of typical disease, and partial immunity may produce disease syndromes characterized more by neurologic signs than catarhal signs of pneumonia and gastroenteritis. Clinical signs of CDV will vary with the strain of virus, immunity, and age of the host.

A cute ocular signs of CDV are usually associated with a bilateral conjunctivitis with serous ocular discharge that progresses to mucopurulent in nature. The palpebral conjunctiva is primarily involved, but the cause of this conjunctivitis may be difficult to diagnose if respiratory and gastrointestinal signs are either minimal or subclinical. The cornea has not been described as being a target for the virus unless a lacrimal adenitis or dehydration has resulted in a marked reduction in tear production (i.e., KCS). The CDV may produce an inflammatory reaction in the lacrimal gland characterized by monocellular and neutrophilic inflammatory infiltration as well as by marked degenerative changes in the glandular tissue (Martin & Kaswan, 1985). Corneal ulceration is often profound with the development of multiple descemetoceles with or without corneal perforations in one or both eyes. KCS usually resolves in 4–8 weeks if the animal recovers from the systemic infection. A nother mechanism for corneal involvement is distemper encephalitis producing a fifth cranial nerve palsy (i.e., neurotrophic keratitis).

CDV often produces a multifocal, nongranulomatous chorioretinitis, which is usually an incidental finding. The incidence of chorioretinitis is unknown but probably varies, as do those of the neurologic signs, with the strain of virus and the immunocompetency of the host. In one study, dogs with neurologic forms of CDV had a 41% overall prevalence of chorioretinal lesions; in contrast, 83% of dogs with chronic leukoencephalopathy syndromes had chorioretinal lesions (Thomas et al., 1993). These lesions are typically multifocal, and they are reportedly more frequent in the peripheral to midperipheral nontapetal fundus (Fischer, 1971). A cute lesions must be differentiated from scars because the latter will not correlate well with acute systemic signs. Active lesions in the nontapetal region are white, somewhat fluffy, and have mildly indistinct borders. A cute lesions progress to scars that are white, flat, and have sharply demarcated borders. In the tapetal region, the acute lesions are subtle, with loss of tapetal detail, and they may have a mild, overlying haziness. With time, these develop into hyperreflective lesions with sharp borders and varying degrees of pigment clumping. Lesions in both the tapetal and nontapetal areas are typically circular to oval in shape and often become confluent with adjacent lesions, thus producing a scalloped pattern. Occasionally, chorioretinal lesions are diffuse, blinding, and may mimic the genetic syndrome of progressive retinal atrophy, with diffuse tapetal hyperreflectivity, optic nerve atrophy, and nontapetal pigment dispersion.

Histopathologic retinal changes are characterized by retinal degeneration with, in some instances, perivascular cuffing. Lesions may be focal or diffuse, characterized by loss of ganglion cells, proliferation and clumping of the retinal pigment epithelium (RPE), focal or diffuse atrophy of photoreceptors, disorganization of retinal layers, focal gliosis, choroidal atrophy, and CDV inclusion bodies in glial cells. A cute cases may have retinal edema, vascular congestion, and perivasculce cuffing (Jubb et al., 1957). The variations in reported ocular lesions may result from the stage of examination, immunocompetence of the animal, and the multiple mechanisms by which the lesions are produced. In the CNS, lesions of acute infections in young or immunocompromised patients are characterized by neuronal necrosis, with a minimal inflammatory reaction. With immunocompetent hosts or chronicity, the CNS lesions are characterized by mononuclear inflammation and secondary demyelization (Thomas et al., 1993).

The most dramatic clinical ocular problem associated with CDV is optic neuritis, which is characterized by an acute onset of bilateral blindness and mydriasis. If inflammation extends rostrally to the optic disk/papilla, ophthalmoscopic signs of peripapillary hemorrhages and edema, retinal vascular congestion, and elevation of the papilla are observed. If the optic neuritis remains retrobulbar, however, the diagnosis is made on the basis of exclusion (i.e., blind eyes with dilated pupils and normal retinal function as tested by electroretinogram [ERG]). The optic neuritis syndrome may be isolated, prodromal, or concurrent with other neurologic signs of CDV. Distemper-associated blindness also may occur with inflammation of the optic tracts, LGN, optic radiation, or occipital cortex.

Ocular signs are suggestive of, but not definitive for, CDV. A cute lesions of chorioretinitis usually correlate well with concurrent systemic disease, but chorioretinal scars may not. CDV inclusions may be identified in infected monocytes,
lymphocytes, neutrophils, or red blood cells during evaluation of a stained peripheral blood smear. Alternatively, positive immunofluorescence by detection of viral antigen from conjunctival swabs/scrapings or blood smears, using methods such as fluorescent antibody (FA) testing may be helpful in diagnosing CDV early in the course of systemic disease (5–21 days postinoculation), but negative findings are inconclusive (Fairchild et al., 1967). This should not inhibit the examiner from performing immunofluorescent antibody testing, however, because one report on encephalomyelitis found an overall positive rate of 54% (and one as high as 75%) despite the mean duration of neurologic signs being 20 days (Fischer, 1971). Further, CDV has immunohistochemically been identified and diagnosed in skin and footpads from infected dogs (Haines et al., 1999). Reverse-transcriptase polymerase chain reaction (RT-PCR) assays have been shown to be both sensitive and specific for detection of experimentally induced CDV (Frisk et al., 1999). Because no specific antiviral therapy against CDV is available, treatment is mainly symptomatic. Conjunctivitis and decreased tear production are treated with topical antibiotics and lubricants. Acute optic neuritis is treated with systemic anti-inflammatory dosages of glucocorticoids if other signs of CDV are absent. Vaccination is the key to preventing CDV. The prognosis for dogs with neurologic disease is considered guarded to poor.

Cerebrovascular Accidents

Cerebrovascular accidents occur much less frequently in dogs than in people (Joseph, 1988; Platt & Garosi, 2003; Thomas, 1996). However, with the ever-increasing access to magnetic resonance imaging, cerebrovascular disease in dogs is being recognized more frequently (Garosi et al., 2005). Cerebrovascular accidents, or strokes, can be the result of cerebral hemorrhage (hemorrhagic stroke) from systemic hypertension, coagulopathies, or trauma. Cerebrovascular accidents can also arise from blockage of blood flow to the brain (ischemic stroke) resulting from thrombosis, embolic events, atherosclerosis, vasculitis, or neoplasia. Regardless of the cause of the cerebrovascular accident, ocular manifestations of impaired brain function may manifest and will vary according to the neuroanatomic location of the cerebrovascular accident. Because cerebrovascular accidents are acute, clinical signs are acute and progressive in nature. Ophthalmic manifestations of cerebrovascular disease may occur at the time of the cerebrovascular accident or develop shortly thereafter. In addition, considering that cerebrovascular accidents typically affect relatively large areas of the brain, abnormal neuro-ophthalmic findings have not been reported as the sole manifestation of cerebrovascular accidents in dogs. For a review on cerebrovascular accidents in dogs, see Garosi (2010) and Garosi & McConnell (2005).

Dysautonomia

Canine dysautonomia is an idiopathic disease resulting from a generalized loss of autonomic function. Dogs affected are typically young adults of medium to large physical stature that typically live in rural areas. It is important to note, however, animals ranging in age from 5 weeks to 15 years of age and of a variety of breeds can be affected (Berghaus et al., 2001; Harkin et al., 2002a). Canine dysautonomia has been reported in Europe (Presthus & Bjerkas, 1987; Rochlitz & Bennett, 1983) and in the United States (Berghaus et al., 2001; Harkin et al., 2002a; Longshore et al., 1996). The disease is prevalent in dogs living in the midwestern United States, specifically in Kansas and Missouri. Affected dogs present with an acute (days) or subacute (2–3 weeks) history of clinical signs referable to loss of autonomic (sympathetic and parasympathetic) function (Berghaus et al., 2001; Harkin et al., 2002a). Common nonocular clinical signs include regurgitation, vomiting, diarrhea, anorexia, weight loss, dry mucous membranes, and purulent nasal discharge (Harkin et al., 2002a; Longshore et al., 1996). Dogs may present with limited clinical signs that progress to involve more signs of autonomic failure during the course of the disease. Ocular signs include ocular discharge, protruding third eyelid, mydriasis, and a reduction in Schirmer tear test values (Harkin et al., 2002a, 2002b; Longshore et al., 1996). Ocular pharmacologic testing with topical 0.05% pilocarpine in dogs with mydriatic pupils, and signalment, history, and clinical signs consistent with dysautonomia provides useful information supporting a diagnosis of dysautonomia. In affected dogs, instillation of 0.05% pilocarpine will cause rapid (<45 minutes) miosis compared to unaffected animals (O’Brien & Johnson, 2002). Severe neuronal degeneration has been reported in a variety of autonomic ganglia including the cranial cervical and ciliary ganglia (Harkin et al., 2002a). In addition, neuronal degeneration of various brainstem nuclei, including the facial, oculomotor, and motor nucleus of the trigeminal nerve, has also been reported (Harkin et al., 2002a). At least 85% of dogs affected with dysautonomia succumb to the disease or are euthanized (Harkin et al., 2002a).

Granulomatous Meningoencephalitis (GME)

GME is an idiopathic nonsuppurative meningoencephalomyelitis seen in dogs (Braud, 1985). Histopathologically, GME is characterized by perivascular cuffing with mononuclear cells (Braud, 1985). One study has demonstrated that perivascular cuffs were composed of a heterogeneous population of major histocompatibility complex (MHC) class-II antigen-positive macrophages and mainly CD3 antigen-positive lymphocytes, supporting a hypothesis of T-cell-mediated, delayed-type hypersensitivity of an organ-specific autoimmune disease (Kipar et al., 1998). Proposed pathogeneses for GME have included a primary immune-mediated phenomenon, precancerous form of lymphoma, and various infectious etiologies. Studies have failed to identify an infectious etiology from the brains of dogs affected by GME (Schatzberg et al., 2005).

The disease is typically seen in young small breeds, although any breed or age of dog may be affected. GME is
characterized typically by neurologic signs suggestive of multifocal central nervous system (CNS) lesions that, at least temporarily, are responsive to systemic corticosteroids or other immunosuppressive therapies. GME is described as being one of three types, namely, (1) disseminated, (2) focal, or (3) ocular. Any combination or permutation of these forms can occur. In the latter form, GME may involve the optic nerves, thus producing a syndrome of acute blindness, papilledema, retinal and peripapillary hemorrhages, and occasionally, extension into the globe, which in turn produces retinal detachments and retinal infiltrates (Fischer & Wi-Kwand, 1971; Smith et al., 1977). Confinement to the retrobulbar optic nerves may limit ocular lesions to blindness and dilated pupils (Braund, 1985; Fischer & Wi-Kwand, 1971; Garmer et al., 1981; Russo, 1979; Thomas & Eger, 1981). A definitive antemortem diagnosis is difficult to make, but multifocal CNS deficits, increased CSF protein levels, pleocytosis with mononuclear cells, and a response to corticosteroids are suggestive (Bailey & Higgins, 1986). Definitive antemortem diagnosis can be made based on the above in concert with brain biopsy (Munana & Luttgen, 1998).

Treatment involves aggressive use of immunosuppressive corticosteroids with or without radiation therapy (Munana & Luttgen, 1998) or immunosuppression using a combination of corticosteroids with one or more of cytosine arabinoside (Mena et al., 2008; Zarfoos et al., 2006), azathioprine (Wong et al., 2010), luffonomide (Gregory et al., 1998), or cyclosporine-A (A damo & O’Brien, 2004; Nuhsbaum et al., 2002). Prognosis for survival varies from weeks to years, but regardless, clinical signs progress and dogs will succumb to the disease (Munana & Luttgen, 1998). Histopathologically, lesions are characterized by dense accumulations of histiocytes, lymphocytes, plasma cells, and monocytes in a perivascular pattern. A aggregates or granulomas may develop from the perivascular cuffs of cells. Lesions can be found in the white matter of the cerebrum, brainstem, cerebellum, and cervical spinal cord, but the gray matter is often involved as well. Granulomatous aggregates may produce space-occupying lesions and have features of neoplasia (Braund, 1985; Thomas & Eger, 1981).

Hypoxia: Cerebral

Hypoxia most commonly occurs during anesthetic episodes, and it may relate to apnea, cardiopulmonary failure, improper intubation, overdose of anesthetic agent, failure of anesthetic equipment, paralysis of the muscles of respiration, and severe systemic hypotension (Gaynor et al., 1999; Jurk et al., 2001; Timm et al., 2008; Wingfield & Van Pelt, 1992). Neurons are more sensitive to hypoxia than other support tissues, and neuronal tissue affected by severe and prolonged hypoxia ± reperfusion will undergo severe cellular metabolic dysfunction leading to apoptosis and ischemic necrosis (Clarkson et al., 2005; Somjen et al., 1993). Clinical signs of cerebral hypoxia include blindness, stupor or coma, paralysis with decerebrate rigidity, seizures, and deafness. PLRs, however, are generally normal. These signs may be either partially or wholly reversible after a period of days to months. Therapy for systemic and cerebral hypoxia depends upon the etiology. In cases of cardiopulmonary arrest, the reader is referred to reviews pertaining to this topic (Hackett, 2001; Marks, 1999; Rieser, 2000; Wingfield & Van Pelt, 1992). Glucocorticoids are not thought to improve neurologic recovery following cardiopulmonary arrest, however (Rieser, 2000).

Idiopathic Facial Nerve Paralysis

The cause of idiopathic facial nerve paralysis is unknown, though it shares clinical features of Bell’s palsy in humans (Tiemstra & Khakhate, 2007). Though viruses have been postulated to play a role in idiopathic facial nerve paralysis, none have been proven to be important in the pathogenesis of this disease. Facial nerve paralysis has been found to be idiopathic in 75% of dogs, while 25% of cases of facial nerve paralysis are due to conditions such as otitis media/interna and hypothyroidism (Kern & Erb, 1987). An important feature of this condition is that patients with idiopathic facial nerve paralysis do not have signs of vestibular dysfunction. Clinical signs of idiopathic facial nerve paresis/paralysis, depending upon when during the course of the disease the patient is examined, include acute paresis/paralysis of the facial muscles, causing a drooping of the lip, reduced or absent menace response, and reduced or absent palpebral reflex, though sensory function is preserved as the trigeminal nerve is not affected. The condition can be unilateral or bilateral in nature. In some instances, reduced tear production may be found, presumably because of involvement of the preganglionic parasympathetic nerve fibers that travel with CN VII. Diagnosis of idiopathic facial nerve paralysis is a diagnosis of exclusion of all potential other causes (e.g., hypothyroidism [Jaggy & Oliver, 1994; Jaggy et al., 1994; Kern & Erb, 1987; Vitale & Olby, 2007] and peripheral nerve sheath neoplasia [Kern & Erb, 1987]). In addition, one should ensure that there is no history of trauma or prolonged anesthesia as both of these can cause facial nerve paralysis. Prognosis is variable with idiopathic facial nerve paralysis. Some patients may have return of facial function within weeks-months or never (Kern & Erb, 1987). As mentioned previously, chronic forms of facial nerve paralysis must be differentiated from hemifacial spasm/tetany.

Idiopathic Vestibular Disease

Idiopathic vestibular disease occurs in approximately 40% of canine cases of acute peripheral vestibular disease (Schunk & Averill, 1983). As the name describes, the cause of this condition is unknown. In dogs having polymerase chain reaction (PCR) evidence of canine herpes virus-1 infection involving the vestibular labyrinth or ganglion, these animals have not had evidence of vestibular dysfunction (Parzefall et al., 2011). Affected animals are 5 years of age and older (Schunk & Averill, 1983). Clinical signs are limited to those seen with
Peripheral vestibular disease and may include spontaneous nystagmus in the horizontal or rotary directions, limb ataxia without evidence of postural reaction deficits, and ventrolateral strabismus (Schunk & Averill, 1983; Troxel et al., 2005). Keep in mind, however, that neuroplastic mechanisms may result in the animal compensating for the static vestibular dysfunction (e.g., spontaneous nystagmus is typically the first clinical sign to resolve despite there being active disease) (Darlington & Smith, 2000). As with any idiopathic condition, diagnosis is based upon excluding other causes of acute onset peripheral vestibular dysfunction (e.g., otitis media/interna [Schunk & Averill, 1983], ototoxicity [Merchant, 1994; Pickrell et al., 1993], neoplasia [Troxel et al., 2005], and hypothyroidism [Higgins et al., 2006; Jaggy & Oliver, 1994; Jaggy et al., 1994]). There is no treatment for this condition. Prognosis for idiopathic vestibular disease is excellent, though recovery may take several weeks and a head tilt may persist (Schunk & Averill, 1983).

Immune-Mediated Retinitis (IMR)
IMR is characterized by a sudden onset of complete blindness or night blindness in dogs and has similar and distinguishing features to sudden acquired retinal degeneration syndrome (SARDS) (see below). Dogs with IMR typically present with sudden blindness, which is often preceded by months to years of sporadic, temporary bouts of decreased vision usually night vision. In addition, dogs with IMR may have a history of abnormal pupillary appearance (pupillary dilation in bright light and/or anisocoria with one pupil being dilated). Most dogs with IMR are reportedly healthy; however, some dogs with IMR (20% in one report) also have concurrent health issues including neoplasia and neurological abnormalities. On ophthalmic examination, dogs with IMR appear blind and lack a menace response, while they tend to blink in response to bright light (positive dazzle reflex). Ophthalmoscopic examination of IMR-affected dogs is generally unremarkable; however, a characteristic pale optic disk due to the presence of vascular attenuation of the optic nerve head may be noted, similar to SARDS-affected patients. When assessing PLRs in IMR-affected dogs using colorimetric PLR testing (blue light vs. red light stimulation; please see “SARDS” section), there is a nearly complete absence of the PLR in response to red light stimulation and a normal PLR when blue light is used. Dogs with IMR have detectable ERG waveforms that can be normal, or reduced or increased in amplitudes, unlike SARDS-affected patients. The pathogenesis of IMR in dogs remains unknown, although it shares similar symptoms to antibody-mediated retinopathies in humans. Retinal autoantibodies have been documented in two of three serum samples from three dogs with IMR. Treatment for dogs with IMR includes oral doxycycline and steroids typically long term. Recovery of the PLR in response to red light stimulation is reported to be the most reliable indicator of therapeutic success. Reevaluation of the ERG waveforms for increases in their amplitudes may also be helpful, as progressive, uncontrolled IMR is often linked with a decrease in retinal electrical activity (Grozdanic et al., 2008).

Masticatory Myositis and Extraocular Myositis
Masticatory myositis (masseter, temporalis, pterygoid muscles) and extraocular myositis are two forms of focal inflammatory myopathies (Carpenter et al., 1989; Evans et al., 2004a; Gilmour et al., 1992). Masticatory myositis typically affects young to middle-aged adult dogs and predominantly medium to large breeds (Evans et al., 2004a; Gilmour et al., 1992). Masticatory myositis may occur concurrently with other immune-mediated diseases including myasthenia gravis (Clooten et al., 2003). Signs include spasm of the masticatory muscles and difficulty in opening the mouth, pain on palpation of the muscles, muscle swelling, or muscle atrophy. Muscular atrophy is a more common clinical sign (72% of cases) than muscle swelling (14% of cases) and is likely due to the chronicity of the disease at presentation of most cases (Gilmour et al., 1992). Ocular signs have been documented in 45% of cases and are variable depending on the chronicity of the disease. Ocular manifestations of acute masticatory myositis include exophthalmos and prolapse of the third eyelid due to swelling of the pterygoid muscle, and possible optic nerve tension/compression causing blindness (Evans et al., 2004a; Gilmour et al., 1992; Lewis, 1994; Smith, 1989). In cases of chronic masticatory myositis, enophthalmos has been reported (Gilmour et al., 1992). Signs are usually, but not invariably, bilateral. Clinical signs, ±peripheral eosinophilia, ±elevated levels of serum creatinine kinase, ±abnormal electromyograms (EMGs), ±presence of circulating antibodies for type 2M fibers, and positive muscle immunohistochemistry for antibodies against type 2M fibers are used to provide a diagnosis of masticatory myositis (Evans et al., 2004a). Predominant histopathologic changes identified in affected muscle biopsies include (1) cellular infiltration with varying degrees of lymphocytes and/or macrophages and/or eosinophils, (2) histologic evidence of muscle atrophy, necrosis, and fibrosis; (3) presence of fibrosis depending upon the chronicity of the disease; and (4) immune complexes bound to type 2M muscle fibers (Evans et al., 2004a; Shelton et al., 1987). Bacteria containing antigenic similarities to type 2M muscle fibers may initiate the immune-mediated myositis (Shelton et al., 1987). Immunosuppressive doses of systemic corticosteroids (prednisone 1–2 mg/kg PO BID) for a minimum of 1 month before tapering are recommended at any stage of the disease. Prognosis is good for dogs treated appropriately with immunosuppressive dosages of corticosteroids, although some dogs may require life-long therapy with these drugs.

The second form of focal inflammatory myositis is extraocular myositis. Extraocular myositis involves only the extraocular muscles and affects predominantly young large and giant breed dogs. Bilateral exophthalmos is the predominant clinical sign in the acute form of the disease (Allgower et al., 2000; Evans et al., 2004a). Chronic extraocular myositis can result in restrictive strabismus and is due to chronic fibrosis.
of the extraocular muscles (Allgoewer et al., 2000). As opposed to masticatory myositis, circulating antibodies to type 2M muscle fibers are not present (Allgoewer et al., 2000; Evans et al., 2004a). Inflammatory infiltrate of affected muscles include lymphocytes and macrophages and fibrosis may be present depending on the chronicity of the disease (Evans et al., 2004a). Immunosuppressive corticosteroid therapy is indicated in cases of extraocular myositis (as for masticatory myositis). Adjunctive corrective strabismus surgery may be useful in some cases of chronic extraocular myositis where the disease is in remission (Allgoewer et al., 2000).

Myasthenia Gravis

Myasthenia gravis is a disease affecting the neuromuscular junction (for a complete review, see Shelton, 2002). Myasthenia gravis is either congenital or acquired. Congenital myasthenia gravis occurs when there is a functional disorder or depletion of nicotinic AChRs. Congenital myasthenia gravis is reported rarely in dogs (Flagstad et al., 1989; Oda et al., 1984; Palmer & Goodyear, 1978) and will not be considered further here (see “Congenital” section). Aquired myasthenia gravis is the most common form of myasthenia gravis occurring in dogs. The acquired condition develops due to an autoimmune destruction of AChRs, which may occur as an autoimmune condition affecting only the AChR (most common [Shelton, 1998]), part of another autoimmune condition (e.g., hypothyroidism [Levine et al., 2005; Shelton, 1998]), or resulting as part of a paraneoplastic syndrome (e.g., thymoma [Lainesse et al., 1996; Paciello et al., 2003]).

Animals with acquired myasthenia gravis can present with either generalized or focal clinical signs. Those animals with generalized myasthenia gravis will have generalized appendicular muscle paresis (weakness) that worsens with prolonged exercise, may have megaesophagus and resultant regurgitation ± aspiration pneumonia, and spinal and cranial nerve reflexes that weaken with repeated testing. Approximately 43% of dogs with myasthenia gravis will have focalized clinical signs in the absence of appendicular muscle weakness (Shelton et al., 1997). Aanimals with the focal form of myasthenia gravis may present with regurgitation, and/or dysphagia, and/or change in character of vocalization because of megaesophagus and pharyngeal or laryngeal paresis, respectively (Dewey et al., 1997; Shelton et al., 1990). With respect to the eye, a paretic menace response and/or palpebral reflex may be the predominant clinical sign(s) (Clooten et al., 2003; Dewey et al., 1997; Webb et al., 1997).

A tentative diagnosis of acquired myasthenia gravis is made based on consistent clinical signs combined with immediate short-term improvement in muscular strength (e.g., improved palpebral reflex [Webb et al., 1997]) following the administration of the short-acting acetylcholinesterase inhibitor, edrophonium hydrochloride (Tensilon). All presumptive cases of acquired myasthenia gravis should be confirmed by demonstrating the presence of circulating muscular AChR autoantibodies (see the Comparative Neuromuscular Laboratory at vetneuromuscular.ucsd.edu/ for testing details).

Neoplasia: CNS

Intracranial neoplasia, whether primary or secondary, often produces ocular and/or orbital signs. All animals with a suspected space-occupying CNS lesion should undergo ophthalmoscopy to determine whether papilledema, optic neuritis, or optic nerve atrophy is present.

The neuro-ophthalmic signs associated with intracranial neoplasia are highly variable and dogs may present with signs as subtle as internal ophthalmoparesis as the predominant clinical sign or with ophthalmic signs associated with abnormalities of multiple cranial nerves and abnormal changes in mentation and/or gait (Cullen et al., 2002; Larocca, 2000; Rossmeisl et al., 2005; Webb et al., 2009a). Intracranial neoplasia frequently produces visual deficits and papilledema in association with neurologic signs (Palmer et al., 1974). Because of the great variation in myelination of the canine papilla/optic disk, early papilledema is difficult to detect unless it is asymmetrical or there is a definite rim of peripapillary edema. Intracranial tumors may also produce blindness, which may be acute in nature. Diffuse or multifocal disease may produce blindness by involving multiple sites in the visual pathways and, as a result, may produce other neurologic deficits as well (Braud et al., 1977; Palmer et al., 1974). A solitary mass involving the optic chiasm may produce blindness without obvious neurologic signs. Tumors at the base of the brain in the middle cranial or rostral fossa may be varied, but pituitary carcinomas that are nonfunctional, optic nerve gliomas, and meningiomas are likely candidates for optic chiasmal involvement (Davidson et al., 1991; Safaty et al., 1988). Papilledema was not a feature of these lesions perhaps because of their relatively small size. Clinically, blindness is often acute. In reality, it is progressive, and partial visual deficits are not generally noted by owners. Because blindness is accompanied by afferent pupillary defects with a normal ocular fundus, the syndrome must be differentiated from SARDS using electroretinography (ERG). Early diagnosis and aggressive therapy may result in the return of some vision (Davidson et al., 1991).

Neurogenic KCS

KCS is a progressive inflammation of the cornea and conjunctiva caused by neurogenically derived tear production deficiency. Lesions anywhere along the efferent path, including the parasympathetic nucleus of the facial nerve, the main trunk of the facial nerve, geniculate ganglion, major petrosal nerve, the nerve of the pterygoid canal, the pterygopalatine ganglion, or the postganglionic parasympathetic fibers, will reduce tear production and result in neurogenic KCS.

Lesions to the preganglionic parasympathetic fibers may be caused by otitis (media or interna) or by petrositis (i.e., inflammation of the petrous temporal bone) (Kern & Erb,
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In such cases, the reduced tear production may be accompanied by signs of facial paralysis and Horner’s syndrome if the adjacent facial nerve motor neurons or sympathetic fibers are involved. Neurogenic KCS may also present without signs of facial paralysis if the major petrosal nerve is damaged distal to the geniculate ganglion of the facial nerve.

Preganglionic parasympathetic denervation can also occur due to erosive lesions involving the floor of the middle fossa of the skull and affecting the major petrosal nerve. In such cases, the trigeminal nerve may frequently be involved, and the KCS will be accompanied by facial anesthesia and xeromycteria (i.e., dry nasal mucosa).

Lesions involving the pre- and postganglionic parasympathetic fibers, as well as the pterygopalatine ganglion itself, result from diseases affecting the pterygopalatine fossa. Causes include peri orbital myositis or cellulitis (frequently caused by maxillary dental disease) or drainage of dental abscesses (Ramsey et al., 1996). Such diseases may be accompanied by pericocular anesthesia and xeromycteria. Preganglionic parasympathetic lesions are most commonly caused by orbital trauma (Matheis et al., 2011). As the postganglionic fibers course together with the zygomatic nerve (the first branch of the maxillary division of the trigeminal nerve), pericocular anesthesia may also occur. A recent retrospective study of canine neurogenic KCS has identified that a number of cases may be idiopathic in nature and that some of these idiopathic cases may enter spontaneous remission (Matheis et al., 2011).

Regardless of the cause of neurogenic KCS, patients with primary neurogenic KCS are unlikely to respond to immunomodulating drugs such as cyclosporine (Matheis et al., 2011). However, denervation hypersensitivity occurring after postganglionic lesions makes patients with neurogenic KCS responsive to direct-acting parasympathomimetic drugs. Treatment with oral pilocarpine is advocated in these cases (Matheis et al., 2011).

Otitis Media/Interna

As the name implies, otitis media/interna is characterized by inflammation of the middle and inner ears, respectively. Otitis interna represents the most common cause of peripheral vestibular disease in dogs (Schunk & Averill, 1983). The causative agents of otitis media/interna in dogs include primarily bacteria, fungi, and yeast. Otitis media is thought to develop primarily from extension of a preexisting otitis externa (Webb, 2011). Alternatively, otitis media can result from inoculation via the Eustachian tube or via hematogenous spread (Webb, 2011). Neurologic signs of otitis media include aural pain, head shaking, facial nerve paresis/paralysis, Horner’s syndrome, and neurogenic KCS. Signs consistent with peripheral vestibular syndrome exist only if there is otitis interna but not if only otitis media is present alone (Webb, 2011). Diagnosis is based upon aural examination, evidence of conductive hearing loss based upon clinical signs and results of brainstem auditory evoked response (BAER) testing, cross-sectional imaging (CT or MR imaging), and myringotomy with aspiration of middle ear contents (Webb, 2011). Treatment is based upon choosing and implementing an appropriate antimicrobial based upon culture and sensitivity results. Surgical curettage and drainage of the middle ear may be necessary. Prognosis is variable and depends upon the chronicity of the disease and other predisposing factors (Webb, 2011). Importantly, other disease processes that may cause similar clinical signs include neoplasia, nasopharyngeal polyps, and trauma.

Pupillotonia (Adie’s Pupil)

Presumed pupillotonia has been rarely described in dogs. It is thought that pupillotonia is similar to that observed in humans affected with Holmes–Adie syndrome. The condition in dogs is characterized by a dilated pupil that has a diminished PLR. Affected dogs do not have evidence of other neurologic signs (Gerding et al., 1986; Goldfarb & Swann, 1984; Spiess, 1988). A tentative diagnosis is made based upon postganglionic supersensitivity using provocative pharmacologic testing with pilocarpine (see provocative pharmacologic testing in this chapter). Recognizing, however, that supersensitivity of the iris to pilocarpine administration, may not be different between pre- and postganglionic lesions (Jacobson & Vierkant, 1998). Though people afflicted with Holmes–Adie syndrome also have concurrent decreased or absent segmental spinal reflexes, this has not been demonstrated in dogs. The etiology of pupillotonia in dogs is unknown. It should be mentioned that pupillotonia alone may be the only clinical sign presented by patients with intracranial neoplasia in-hospital, and that careful attention to history and complete workup of cases, including transverse imaging of the skull be performed on any patient presenting with pupillotonia as the primary clinical sign (Webb et al., 2005). Idiopathic pupillotonia requires no treatment and the condition is benign.

Sudden Acquired Retinal Degeneration Syndrome (SARDS)

SARDS is an idiopathic blinding condition consisting of acute blindness in the absence of funduscopic disease (early in disease), and clinical signs suggestive of an underlying metabolic disease. SARDS has been recognized among dogs in the United States for over two decades (Vainisi et al., 1983). Nevertheless, the cause of SARDS is unknown, and epidemiologic questionnaires have not been suggestive of any common thread for an environmental toxin (Acland et al., 1984). Preliminary investigations into excitotoxins (e.g., glutamate) have found increased levels in the vitreous of affected animals, but the significance of this is unknown (Abrams et al., 1995). Circulating antiretinal antibodies have been found in dogs with SARDS; however, antiretinal antibodies are also found in clinically normal dogs (Bellhorn et al., 1988; Gilmour et al., 2004). Attempts to link SARDS with paraneoplastic processes, as has been shown in human cancer-associated retinopathy, has proven unrewarding (Gilmour et al., 2004). Recently, analysis of tissues from SARDS-affected dogs revealed the
presence of immunoglobulin-producing plasma cells in affected retinas, which may account for localized intraretinal production of autoantibodies and subsequent development of an antibody-mediated retinopathy (Grozdanic et al., 2008). In addition, strong complement activity has been documented in the retinas of dogs with SARDS which may account for antibody-mediated neuronal damage (same ref above).

In one study, 40%–60% of dogs affected with SARDS were reported to have had systemic signs and altered clinico-pathological test results (van der Woerdt et al., 1991). Animals are characteristically presented with acute blindness and a normal to near-normal ocular fundus (van der Woerdt et al., 1991). Because of the acute onset, most dogs are quite disoriented. In most patients, vision loss occurs over the course of 1–2 weeks, and nyctalopia may be observed (van der Woerdt et al., 1991). The mean age of affliction is 8.5–10.0 years (Miller et al., 1998; van der Woerdt et al., 1991). The syndrome occurs predominantly in neutered females, in both pure and mixed breeds, and with a predisposition for Dachshunds (Acland & Aquirre, 1986; Acland et al., 1984; Vainisi et al., 1983, 1985; van der Woerdt et al., 1991). A seasonal incidence has been reported as well, with 46% of cases occurring in December and January (Acland et al., 1984). Many affected dogs have polyuria (PU), polydipsia (PD) (28%–36% of cases), and polyphagia (39%), as well as a history of weight gain (57%). As well, systemic hypertension (4 of 10 dogs) and proteinuria (7 of 10 dogs) have been reported in dogs with SARDS (Carter et al., 2009). Laboratory values are variable, but lymphopenia (30% of cases), lymphopenia with neutrophilia (21%), and abnormal biochemical profiles (68%) may be present. Elevated levels of alkaline phosphatase (30%–40% of cases) and cholesterol (42%) are the most common biochemical changes. A drenocorticotropic hormone (ACTH) stimulation or a low-dose dexamethasone suppression test may be abnormal (van der Woerdt et al., 1991). Overall, 12%–17% of patients have adrenal profile changes compatible with those of Cushing’s disease, but these changes may be adaptations to other diseases as well (Acland et al., 1984; Carter et al., 2003; Mattson et al., 1992; van der Woerdt et al., 1991). These associated alterations in pituitary function have led to the hypothesis that elevations in melanocyte-stimulating hormone (MSH) may accompany an increased ACTH level. Increased MSH may then lead to increased melanin production by the RPE, which may impair RPE phagocytosis of photoreceptor outer segments and, consequently, result in retinal degeneration (van der Woerdt et al., 1991). Most recently, serum cortisol and sex hormone concentrations were measured prior to and following ACTH stimulation in 13 dogs with SARDS (Carter et al., 2009). Serum cortisol was elevated in 9 of 13 dogs; elevations in one or more sex hormones were found in 11 of 13 patients with SARDS while only one dog had normal ACTH stimulation results (Carter et al., 2009).

On ophthalmic examination, dogs with SARDS appear blind and lack a menace response, while they tend to blink in response to bright light (positive dazzle reflex). The pupils are usually dilated at rest and demonstrate sluggish PLRs (van der Woerdt et al., 1991). Ophthalmoscopic changes during the acute stages are very minimal, with mild retinal vascular attenuation or variability in retinal vascular caliber and changes in tapetal reflectivity. In the early stages, all dogs with SARDS have a characteristic pale optic disk due to the presence of vascular attenuation of the optic nerve head (Grozdanic et al., 2008). In patients with SARDS of typically greater than 2 months in duration, subtle tapetal hyporeflective spots may be observed with these hyporeflective spots having been detected in some affected dogs only 7 days following the onset of acute blindness (Grozdanic et al., 2008). After several weeks to months, more advanced retinal vascular attenuation and tapetal hyperreflectivity become apparent. The funduscopic appearance in chronic SARDS is similar to that of inherited retinal degeneration (van der Woerdt et al., 1991). Histopathologic changes have been infrequently reported, but cases of early SARDS have a diffuse loss of photoreceptor outer segments, with more subtle changes in swelling of the dendritic processes and cell bodies in the amacrine, bipolar, and ganglion cells. With chronicity, the entire neuroretina degenerates, and the RPE becomes attenuated and loses its apical processes (Acland et al., 1984; Miller et al., 1998; Vainisi et al., 1985; van der Woerdt et al., 1991).

Optical coherence tomography (OCT) has been used to analyze the structural thickness of retinas of dogs with SARDS; OCT revealed significant retinal thinning even for retinas that appeared relatively normal on funduscopic examination with primary damage of the nerve fiber layer and decreased retinal thickness of the ventral retina early on in this disease and progressing to involve thinning of all retinal layers, including the photoreceptor layer, in the dorsal and ventral quadrants (Grozdanic et al., 2008).

Electroretinography (ERG) is considered the gold standard for establishing a diagnosis of SARDS. The ERG response is extinguished with SARDS (van der Woerdt et al., 1991). Recently, a study documented the spectral properties of the PLR in eyes of healthy dogs compared to eyes of SARDS-affected dogs (Grozdanic et al., 2007). Dogs that have SARDS have complete pupillary constriction in response to blue light of a narrow wave length (480 nm) and high light intensity (200 kcd/m2) most likely due to stimulation of a photosensitive pigment, melanopsin, located in a subpopulation of retinal ganglion cells that can drive PLRs in the absence of photoreceptor activity. When red light of a given wavelength (630 nm) and high light intensity (200 kcd/m2) was used to evaluate PLRs in SARDS-affected patients, the pupils remained fixed and dilated as this wavelength of red light does not activate the melanopsin pathway but rather activates the photoreceptor-mediated pathway which is absent in dogs with SARDS. A portable, diode-based light source with narrow wavelengths for blue and red light that matches the spectral properties of canine visual pigments is available for colorimetric PLR testing (Melan-100 unit; BioMed Vision Technologies, Inc., Ames, IA) (Grozdanic et al., 2008).

SARDS has long been considered an untreatable, irreversible blinding disease of dogs. However, recently, experimental
use of intravenous human immunoglobulins (IV Ig) has resulted in restoration of limited visual behavior in some SARDS-affected dogs in the early stages of this disease (Grozdanic et al., 2008). Many dogs diagnosed with SARDS would not be suitable candidates for IV Ig due to advanced retinal thinning at the time of diagnosis. Most dogs with SARDS still make acceptable house pets provided they adjust well to being blind.

Trigeminal Neuropathy (Trigeminal Neuritis)

Trigeminal neuropathy is an acute to subacute, bilateral, idiopathic condition involving inflammation of primarily the mandibular branch of the trigeminal nerve (efferent to muscles of mastication) (Mayhew et al., 2002). Patients with this disease may present with clinical signs of variable degrees of masticatory muscle atrophy and reduced facial sensation, dropped jaw, facial nerve paralysis/paresis, and Horner’s syndrome (Mayhew et al., 2002). In some instances, lack of facial sensation may be the predominant clinical sign. As such, some patients with trigeminal neuropathy may have reduced/absent palpebral reflexes, lack of menace response, evidence of enophthalmos due to atrophy of the pterygoid muscles, corneal anesthesia, and Horner’s syndrome (presumably due to involvement of the postganglionic sympathetic axons as they course alongside the trigeminal ganglion and the ophthalmic branch of the trigeminal nerve). As with other idiopathic conditions, a diagnosis of idiopathic trigeminal neuropathy is made after excluding other possible causes of bilateral trigeminal nerve dysfunction including infectious (e.g., rabies), traumatic, hematopoetic neoplasms (e.g., lymphosarcoma), and idiopathic polyneuritis. Prognosis for this condition is good and the disease is self-limiting with patients recovering anywhere from 0.7 to 9.0 weeks after onset of symptoms (Mayhew et al., 2002). Treatment is purely supportive and there is no evidence to support the use of corticosteroids (Mayhew et al., 2002).

Vitamin A Deficiency

Vitamin A (retinol), a fat-soluble vitamin, is derived from its precursors (carotenoids) which are found in plants (for a review, see vonLintig & Vogt, 2004). With regard to the importance of vitamin A in the ocular system, vitamin A (retinol) is stored and transformed into retinol which is translocated between the RPE and the photoreceptors (Thompson & Gal, 2003). Within the photoreceptors, retinal combines with opsin (a protein) to form the visual pigment rhodopsin (Thompson & Gal, 2003). Vitamin A deficiency has been produced experimentally in young dogs, but it does not appear to be a naturally occurring clinical syndrome (Tvedten & Whitehair, 1977). The earliest sign of such deficiency in young dogs, however, is vestibular disease, but blindness may also be an early manifesting sign (Tvedten & Whitehair, 1977). Papilledema has been noted in some dogs with a deficiency in vitamin A; however, the resultant papilledema could not be correlated with increased CSF pressure (Tvedten & Whitehair, 1977).

Congenital: Feline

Anomalies of the Visual System and Forms of Albinism

Visual system abnormalities associated with forms of albinism have been reported in animals for years (Creel et al., 1982b). A commonly studied model is the Siamese cat, demonstrating a form of partial albinism with retinal hypopigmentation. In particular, Siamese cats possess a mutant allele of the albino series at the C locus (c^c) (Creel, 1971; Creel et al., 1982b). Siamese cats, therefore, have reduced ocular pigmentation including a lack of stromal pigmentation of the iris or choroid, and a reduction in pigment of the iridal and retinal pigment epithelia (Thibos et al., 1980). The retinal hypopigmentation in these cats is the critical factor resulting in misrouting of many of the projections of the retina to the brain, the nature of the projection error, and the developmental consequences of the relay of the misrouted retinal inputs to the visual cortex (Kaas, 2005; LaVail et al., 1978; Sanderson et al., 1974). The abnormal retinogeniculate projections in Siamese cats was first described by Guillery in 1969 (Guillery, 1969). Since this study, several reports regarding the visual system of the Siamese cat have been published (Creel, 1971; Guillery & Kaas, 1971; Hubel & Wiesel, 1971; Kalil et al., 1971). Specifically, Siamese cats have reduced ipsilateral retinal projections since many axons originating in the temporal retina which normally project ipsilaterally project contralaterally in Siamese cats. As a consequence, each LGN contains an abnormally greater representation of the ipsilateral visual field (Cooper & Blasdell, 1980). Convergent strabismus with or without involuntary horizontal or rotary nystagmus are possible ocular manifestations as a result of this retinogeniculate misdirection (Fig. 34.34) (Blake & Crawford, 1974; Rengstorff, 1976).

Hydrocephalus

Hydrocephalus refers to increased amount of CSF within the cranial vault. The most common cause of congenital hydrocephalus is a primary congenital stenosis or aplasia of the mesencephalic aqueduct associated with fused rostral colliculi. Mesencephalic aqueductal stenosis has been reported in kittens following in utero exposure to griseofulvin (Scott et al., 1975), and following transplacental infection with feline panleukopenia virus (Csiza et al., 1971). Congenital hydrocephalus may produce enlargement of the calvarium and failure of closure of the suture lines of the skull. Consequently, affected kittens may have dome-shaped heads and a persistently open fontanelle. Clinical signs of hydrocephalus include behavioral changes, ataxia, compulsive circling, and seizures (Coates & Sullivan, 2001). Ventrolateral strabismus is a common ocular manifestation of congenital hydrocephalus due, in part, to enlargement of the calvarium with subsequent cranial vault.
impingement on the orbits from the dorsolateral aspects (Coates & Sullivan, 2001). This consequently pushes the eyes in a ventrolateral direction and produces a “sunset” appearance to the corneas. As well, congenital hydrocephalus may cause cranial nerve compromise and subsequent ventrolateral strabismus.

**Developmental: Feline Chédiak-Higashi Syndrome**

Chédiak–Higashi syndrome (CHS) is an autosomal recessive disorder of cats and other species (Prieur & Collier, 1978, 1981). In cats, CHS is characterized by partial oculocutaneous albinism, increased susceptibility to infections, and bleeding tendencies (Collier et al., 1984). To date, CHS has only been reported in the Persian breed. Ocular manifestations of CHS in cats include photophobia, pale irides, hypopigmentation of the nontapetal fundus, tapetal degeneration, cataracts ranging from incipient posterior suture line associated to mature cataracts, and spontaneous nystagmus (Collier et al., 1979, 1985b; Creel et al., 1982a). The ocular hypopigmentation in affected cats is thought to result from fusion of premelanosomes with lysosomes, with resultant destruction of the premelanosomes (Collier et al., 1985a). Melanin granules that do remain in the eyes of cats with CHS are nonuniform in distribution and irregular in shape (Collier et al., 1984). The tapetum develops normally in CHS-affected kittens, but it later rapidly degenerates, so that by 56 days of age, tapetal rods have disappeared and tapetal cells are disorganized (Collier et al., 1985b). Ophthalmoscopically, the tapetum of affected cats is not visible. Abnormal retinal projections to the LGN (similar to those in the Siamese breed) have also been found in CHS-affected cats, thus accounting for the nystagmus (Creel et al., 1982a). The disease is characterized histologically by giant cytoplasmic granules within lysosomes, melanocytes, and neutrophils. When eyes from older CHS-affected cats were examined histologically and ultrastructurally, lysosomes and residual bodies were found within the RPE (Collier et al., 1986). The residual bodies formed drusen-like mounds beneath the RPE, and RPE cells had detached and moved into the interphotoreceptor space. A diagnosis of CHS is made based upon identifying enlarged melanin granules histologically within hair shafts of cats combined with clinical signs suggestive of the disease.

**Acquired: Feline Dysautonomia (Key-Gaskell or Dilated Pupil Syndrome)**

Feline dysautonomia, which is also known as Key–Gaskell or dilated pupil syndrome, was first reported in England in 1982 (Key & Gaskell, 1982). The disease, which produces widespread autonomic nervous system dysfunction, has since been reported in many cats throughout Europe,(Cave et al., 2003; Rochlitz, 1984; Sharp et al., 1984), but the number of documented cases in the United States remains small (Bromberg & Cabaniss, 1988; Canton et al., 1988; Guilford et al., 1988; Levy et al., 1994). The cause of dysautonomia has not been determined. No evidence of infectious agents has been found, and the lesions are unlike those reported with known toxins (Sharp et al., 1984; Symonds et al., 1995). Interestingly, a recent study reported 6/8 pet cats in a closed colony developed overt signs of dysautonomia over the course of 7 days (Cave et al., 2003). However, the closed nature of this cat colony and biosecurity cautions taken by the owners made an infectious etiology unlikely (Cave et al., 2003). Interestingly, it has recently been reported that toxicoinfectious Clostridium botulinum may be important in the pathogenesis of feline dysautonomia, an etiology seriously being considered in equine dysautonomia (Nunn et al., 2004).

Common systemic signs of feline dysautonomia include general malaise, dehydration, reduced appetite or anorexia, dysphagia, vomiting or regurgitation, xerostoma, bradycardia, urinary bladder distention, and constipation (Cave et al., 2003). Ocular signs that have been reported most consistently include dilated unresponsive pupils, decreased tear production, and protruding nictitating membranes (Bromberg & Cabaniss, 1988; Canton et al., 1988; Guilford et al., 1988; Levy et al., 1994; Sharp et al., 1984; Symonds et al., 1995). Vision is unaffected, and photophobia is variable. Pharmacologic testing with ocular autonomic stimulants can aid in establishing the diagnosis of feline dysautonomia. Results of these tests are based on denervation supersensitivity. As such, the dysautonomic eye will respond to dilute concentrations of drugs that will not affect a normal eye. Pilocarpine, which is a direct-acting parasympathomimetic agent, at a concentration of 0.1% will produce constriction of
the pupil. Epinephrine, which is a direct-acting sympathomimetic agent, at a concentration of 1:10,000 will induce retraction of a prolapsed third eyelid. Echotiothiophate iodide, which is an irreversible cholinesterase inhibitor, at a concentration of 0.06% will reportedly cause miosis in a normal cat but have no effect on a dysautonomic pupil (Canton et al., 1988). The same response has been seen with phystostigmine, which is a reversible cholinesterase inhibitor, at a concentration of 0.25% (Guilford et al., 1988). The finding of decreased urinary catecholamines can also support the diagnosis of dysautonomia (Levy et al., 1994).

However, a definitive diagnosis of dysautonomia is rarely made antemortem as it involves the histopathologic examination of autonomic ganglia (Cave et al., 2003). Histopathologic examination of affected cats has shown widespread reduction of neurons within both sympathetic and parasympathetic autonomic ganglia, inconsistent neuronal degeneration, and increased numbers of non-neuronal nuclei (Bromberg & Cabaniss, 1988; Canton et al., 1988; Guilford et al., 1988; Levy et al., 1994; Sharp et al., 1984; Symonds et al., 1995). Ultrastructural studies of the ganglia and axons have shown degeneration and disorganization (Griffiths et al., 1985). The membrane glycoprotein, synaptophysin, has recently been shown to be increasingly accumulated in degenerating neurons of both equine and feline dysautonomia cases (Hilbe et al., 2005). The prognosis for cats with dysautonomia must be viewed as being guarded to poor, though some cats have been maintained long-term on supportive therapy (Bromberg & Cabaniss, 1988; Rochlitz, 1984) or have even recovered after a prolonged period (Sharp et al., 1984).

**Feline Coronavirus (Feline Infectious Peritonitis)**

Feline coronavirus infection in cats may lead to no clinical disease, enteric disease, or feline infectious peritonitis (FIP), which is a disseminated pyogranulomatous vasculitis (Addie & Jarrett, 1992; Addie et al., 1995; Kipar et al., 2005). FIP replicates within macrophages resulting in the deposition of virus-laden macrophages within the endothelium of small blood vessels (Kipar et al., 2005). FIP is a fatal arthus-type disease, enteric disease, or feline infectious peritonitis (FIP), which is a disseminated pyogranulomatous vasculitis (Addie et al., 1995; Kipar et al., 2005). FIP most commonly occurs in young cats, and it may manifest by an effusive or wet form of the disease, which includes fibrin-rich fluid within the abdominal and peritoneal cavities, or as a noneffusive or dry form of the disease. Ocular and neural lesions are more likely to be present with the noneffusive form (Andrew, 2000; Foley et al., 1998). Neuro-ophthalmic signs vary according to the region of the brain that is affected.

For a consensus statement regarding the diagnosis, treatment, and prevention of feline infectious peritonitis the reader is directed to recommendations from an international workshop on feline infectious peritonitis (Addie et al., 2004).

**Feline Leukemia Virus (FeLV)**

Anisocoria or dyscoria may arise due to neurological effects of FeLV on the ciliary ganglia and short ciliary nerves of affected cats. Alternatively, dyscoria may result from lymphocytic infiltration of the ciliary body and iris (Nell & Suchy, 1998). In particular, spastic pupil syndrome, involving a static anisocoria during dark adaptation, has been reported in FeLV-positive cats. A nisocoria may have been noted by the patient’s owner over time, alternating with periods of normal pupil behavior. Other ophthalmic abnormalities are absent, however, and vision is unaffected. These cats are positive for FeLV but may have no other clinical signs when the anisocoria is noted (Brightman et al., 1977; Scagliotti, 1980). C-type viral particles have been identified in the ciliary ganglia and short ciliary nerves of these cats, however, which is suggestive that the virus has invaded these nerves. The prognosis for long-term survival in these cats is poor.

**Fluoroquinolones**

Enrofloxacin, a fluoroquinolone antibiotic, has recently been associated with a rare adverse ophthalmic reaction causing an acute, typically irreversible, retinal degeneration in cats (Gelatt et al., 2001; Giuliano & van der Woerd, 1999; Grahn et al., 2002; Wiebe & Hamilton, 2002). In addition, this reaction has reportedly been seen with other fluoroquinolones including marbofloxacin and orbifloxacin (Ramirez et al., 2011). A affected cats develop signs of partial, temporary, or total blindness. The reported estimated incidence of this adverse reaction is 1 in 122,414 treated cats or 0.0008% (Wiebe & Hamilton, 2002). The association of enrofloxacin, retinal degeneration, and blindness in cats was first described in a retrospective study in which 5 of 26 cats with diffuse retinal degeneration had received oral enrofloxacin (Giuliano & van der Woerd, 1999). Subsequently, another retrospective study documented the association between enrofloxacin administration and the acute onset of retinal degeneration in 17 cats (Gelatt et al., 2001). All cats were domestic shorthair breed with ages ranging from 3 to 16 years old. All affected cats had variable medical ailments for which enrofloxacin was administered including lymphoma and pancreatitis, otitis, urinary tract disorders, dermatitis, bowel perforation, diarrhea, and upper respiratory infection. The daily enrofloxacin dosages these cats received were highly variable ranging from 4.6 mg/kg PO once daily to 27 mg/kg PO twice daily. Cats in this study generally presented with signs of mydriasis and acute blindness. All cats had generalized retinal degeneration, and vision only returned in a few cases. Five of 17 affected cats underwent electroretinography which revealed no observable responses in any case. Histological assessment of two affected globes showed mainly outer retinal degeneration as evidenced by a diffuse loss of the photoreceptor and outer nuclear layers,
and hypertrophy and proliferation of the RPE. Given the findings in this study, the adverse retinal reaction to enrofloxacin in cats appears to be a rare, idiosyncratic reaction. Adherence to the manufacturer’s current recommendation for enrofloxacin dosage in cats of 5 mg/kg PO q 24 hours is advisable. It is, however, unclear as to whether a dosage of 5 mg/kg PO q 24 hours is safe in geriatric cats, especially those with renal or hepatic dysfunction, as safety studies performed by the manufacturer were conducted in young healthy cats (Wiebe & Hamilton, 2002).

Safety studies evaluating the incidence of retinal degeneration with orbifloxacin, another veterinary-labeled fluoroquinolone, revealed a dose- and concentration-dependent adverse ophthalmic reaction, with cats receiving higher doses of the medication developing focal retinal degeneration (Kay-Mugford et al., 2002). Safety studies conducted on marbofloxacin, another veterinary-approved fluoroquinolone, did not demonstrate any ocular lesions following oral administration of up to 20 times the minimum recommended daily dosage. Nonetheless, the manufacturer of marbofloxacin indicates that it is a prudent precaution to consider that all fluoroquinolones may have the potential to induce feline ocular lesions, therefore all fluoroquinolones should be used with caution in this species (Wiebe & Hamilton, 2002).

Recently, it has been shown that cats have four specific amino acid sequence differences in P-glycoprotein, ABCG2, in comparison to that of other mammals (Ramirez et al., 2011). ABCG2 is a member of the ATP-binding cassette superfamily of proteins and is located in a variety of tissues including the endothelium comprising the blood-retinal barrier. These proteins transport a variety of molecules, including fluoroquinolones, across cell membranes. As such, this protein acts to regulate the concentration of drugs, such as the fluoroquinolones, within the retina. Fluoroquinolones produce reactive oxygen species when exposed to light. When HEK-293 cells are modified to contain either (1) no ABCG2, (2) human-specific ABCG2, or (3) feline-specific ABCG2, and are subsequently exposed to ultraviolet light, 50% of cells not containing ABCG2 die when exposed to 1–10 µmol/L of enrofloxacin, 50% of cells with feline specific ABCG2 will die when exposed to 10 µmol/L enrofloxacin, and 50% of cells with human ABCG2 will die when exposed to 50 µmol/L enrofloxacin (Ramirez et al., 2011). These results demonstrate that feline-specific ABCG2 is ultimately ineffective at transporting enrofloxacin from within the cells, thus likely explaining the fluoroquinolone-related retinal toxicity described clinically in cats.

Current recommendations to help decrease the risk of retinal degeneration in some cats receiving enrofloxacin include: (1) using split dosing (i.e., 2.5 mg/kg PO q 12 hours) on exact body weight; (2) avoidance of rapid intravenous infusions of the drug and drug interactions; and (3) avoidance of UVA light during active treatment may also be beneficial. Owners of a cat receiving parenteral fluoroquinolone therapy should be instructed to monitor their cat for mydriasis and to consult their veterinarian immediately should this sign develop. The pharmacokinetics of parenteral enrofloxacin in neonatal kittens compared with the pharmacokinetics of this medication in young and adult cats have recently been reported (Seguin et al., 2004). Ophthalmic examinations were not conducted on animals in this study, however.

**Griseofulvin Teratotoxicity**

Griseofulvin is a fungistic agent used in cats to treat dermatophytosis. Griseofulvin is teratogenic in the cat. Ocular anomalies reported in affected offspring of cats having received griseofulvin in the first half of gestation include cyclopia, anophthalmia, optic nerve aplasia, and rudimentary optic tracts (Scott et al., 1975). Mesencephalic aqueductal stenosis has also been reported in kittens following uterine exposure to griseofulvin (Scott et al., 1975). Other widespread malformations also accompany the ocular abnormalities. One adult cat was thought to have retinal degeneration secondary to griseofulvin toxicity (Rottman et al., 1991).

**Hypoxia: Cerebral**

Hypoxia most commonly occurs during anesthetic episodes, and it may relate to apnea, cardiopulmonary failure, improper intubation, overdose of anesthetic agent, failure of anesthetic equipment, paralysis of the muscles of respiration, and severe systemic hypotension (Gaynor et al., 1999; Jurk et al., 2001; Wingfield & Van Pelt, 1992). Neurons are more sensitive to hypoxia than other support tissues, and neuronal tissue affected by severe and prolonged hypoxia ± reperfusion will undergo severe cellular metabolic dysfunction leading to apoptosis and ischemic necrosis (Clarkson et al., 2005; Somjen et al., 1993). Clinical signs of cerebral hypoxia include blindness, stupor or coma, paralysis with decerebrate rigidity, seizures, and deafness. PLRs, however, are generally normal. These signs may be either partially or wholly reversible after a period of days to months. Therapy for systemic and cerebral hypoxia depends upon the etiology. In cases of cardiopulmonary arrest, the reader is referred to reviews pertaining to this topic (Hackett, 2001; Marks, 1999; Rieser, 2000; Wingfield & Van Pelt, 1992). Glucocorticoids are not thought to improve neurologic recovery following cardiopulmonary arrest, however (Rieser, 2000).

**Ischemic Encephalopathy in Felines**

Ischemic encephalopathy occurs when the arterial supply to part of the brain is disrupted. A portion of one side of the cerebrum supplied by the middle cerebral artery is most often involved, thereby resulting in necrosis. The cause is unknown in most cases, however, there is some evidence that Cuterebra infection may play a role in some cases (Williams et al., 1998). In the cat, the condition manifests by a sudden onset of behavior change, seizures, ataxia, and motor deficits (Shell, 1996; Zaki & Nafe, 1980). Visual deficits may accompany other neurologic signs and are usually cortical in origin. Occasionally, the optic chiasm may be involved, thus resulting in
dilated unresponsive pupils (De Lahunta, 1977). Anisocoria has been noted as well (Bernstein & Fiske, 1986).

Treatment involves supportive care with improvement in clinical signs typically occurring over days to weeks. Alterations in behavior and seizures may persist, and repeated episodes may occur (De Lahunta, 1977; Quesnel et al., 1997; Williams et al., 1998).

**Nictitating Membrane Protrusion**

Idiopathic bilateral protrusion of the feline nictitating membranes is a common, poorly understood ophthalmic disorder (Gruffydd-Jones et al., 1977). Retraction of the nictitating membranes following instillation of topical adrenergic drugs, in affected cats, is suggestive of a loss of sympathetic innervation such as that seen in Horner’s syndrome; however, other ophthalmic signs of Horner’s syndrome are absent. Cats with this syndrome have normal intraocular structures, and vision is unaffected unless the nictitating membranes protrude to the extent that they cover the pupil.

Affected cats often have concurrent watery diarrhea that precedes nictitating membrane protrusion. Some cats may have diarrhea for weeks. Many cats, however, recover from diarrhea quickly, yet will still have nictitating membrane protrusion. A Tora-like virus has been isolated from the feces of several affected cats in England (Muir et al., 1990). In that study, 17 of 45 cats had nictitating membrane protrusion for more than 4 weeks, and 16 of 41 cats had diarrhea for more than 4 weeks. In 87% of the cases from multicat households, more than one cat was affected, suggesting an infectious etiology.

The prognosis for this condition is good. The diarrhea and nictitating membrane protrusion are self-limiting, although clinical signs may be long-lasting. Therapy is not indicated, but if the nictitating membrane protrusion is severe, a topical adrenergic agent may be helpful.

**Neoplasia: CNS**

Blindness associated with intracranial neoplasia has been reported in cats (Davidson et al., 1991; Dunho et al., 2000; Gordon et al., 1994; Nafe, 1979; Sant’Ana et al., 2002; Troxel et al., 2003). In one study, an acutely blind, 12-year-old cat with afferent pupillary deficits was found to have a pituitary carcinoma that encroached on the optic chiasm (Davidson et al., 1991). In a series of 36 cats with meningoimias, blindness or visual field deficits were found in 7 (Nafe, 1979). Six of these 7 cats had unilateral visual deficits, whereas the remaining cat was completely blind, with dilated pupils from compression of the optic chiasm by a third-ventricle meningioma. Six cats also had positional nystagmus, and one cat with tentorial herniation had anisocoria, with the smaller pupil being contralateral to the tumor. It is also important to keep in mind that cranial nerve disturbances will also be apparent with some cases of feline intracranial neoplasia.

**Otitis Media/Interna**

As the name implies, otitis media/interna is characterized by inflammation of the middle and inner ears, respectively (Webb, 2011). Otitis interna represents a common cause of peripheral vestibular disease in cats (Negrin et al., 2010). The causative agents of otitis media/interna in cats include primarily bacteria, fungi, yeast, and parasites. Otitis media is thought to develop, primarily from extension of a preexisting otitis externa. Alternatively, otitis media can result from inoculation via the Eustachian tube or via hematogenous spread. Otitis interna typically results from extension of otitis media. Neurologic signs of otitis media include aural pain, head shaking, facial nerve paresis/paralysis, Horner’s syndrome, and neurogenic KCS (Kern & Erb, 1987; Kern et al., 1989; Schlicksup et al., 2009; Shanaman et al., 2011), it has been suggested that subclinical otitis media is relatively common, however (Schlicksup et al., 2009; Shanaman et al., 2011). Signs consistent of peripheral vestibular syndrome exist only if there is otitis interna but not when only otitis media is present alone.

Diagnosis is based upon aural examination, evidence of conductive hearing loss based upon clinical signs and results of brainstem auditory evoked response (BAER) testing, cross sectional imaging (CT or MR imaging) and myringotomy with aspiration of middle ear contents (Webb, 2011).

Treatment is based upon choosing and implementing an appropriate antimicrobial based upon culture and sensitivity results. In some patients, surgical curettage and drainage of the middle ear may be necessary.

Prognosis is variable and depends upon the chronicity of the disease and other predisposing factors. Importantly, other disease processes that may cause similar clinical signs include neoplasia, nasopharyngeal polyps, and trauma.

**Rabies**

Rabies continues to be one of the most feared zoonotic diseases in the world. Rabies, a bullet-shaped RNA virus, is a Lyssavirus in the family Rhabdoviridae (Woldehiwet, 2002). Transmission of rabies occurs via a bite by a rabid animal, although infections through aerosols have been documented (Constantine, 1966; Winkler et al., 1973). The virus can infect any warm-blooded animals, with dogs and cats being the main vectors of human infection (Woldehiwet, 2005). Clinically, rabies infection can be divided into three phases: (1) prodromal, (2) furious, and (3) paralytic phases (Bedford, 1976). In its early stages, rabies in cats can be difficult to diagnose. In one study, the main signs of rabies in cats reported by veterinarians included changes in behavior, gait abnormality, wound or injury within the past 6 months, and an unusual look in the eyes, while the most frequently reported signs by owners included aggressiveness, gait abnormality, and, once again, an unusual look in the eyes (Fogelman et al., 1993). Although the unusual expression in the eyes was not further characterized in this study, it may have arisen due to alterations in pupil
size (i.e., mydriasis) from rabies-induced neurologic dysfunction. The reader is referred to current internal medicine textbooks for a detailed discussion on rabies.

**Thiamine Deficiency**

Thiamine deficiency may occur in cats eating large amounts of raw fish, which contains thiaminases, or in cats eating processed commercial foods in which thiamine has been destroyed by heat processing and not replaced adequately. Thiamine deficiency has also been reported in cats being fed commercial food containing sulfur dioxide as a food preservative (Malik & Sibraa, 2005; Steel, 1997; Studdert & Labuc, 1991). Further, cats with severe gastrointestinal disease may not absorb sufficient amounts of thiamine. Clinical signs of thiamine deficiency include initial inappetence and occasional vomiting, followed by papillary dilatation without visual deficits, ataxia, and ventroflexion of the head and neck (Davidson, 1992; Loew et al., 1970; Martin, 1971). A final and irreversible stage of thiamine deficiency is characterized by a progression of clinical signs culminating in a semicomatose state, which is characterized by crying, opisthotonos, and extensor rigidity.

The diagnosis can be made on the basis of dietary history, clinical signs, and measurement of thiamine concentration in food as well as in blood. Normal blood thiamine levels for cats are approximately 32 μg/dL. Before development of a comatose state, cats will respond favorably to parenterally administered vitamin B complex preparations containing 50 to 75 mg of thiamine per dose every 8 hours. A supplementation should be provided via a nasogastric or gastrostomy tube. Improvement is usually seen within 3 days, though ataxia may be present for 2 weeks. Once the cat is eating, oral vitamin supplementation can be instituted, and the diet should be corrected to include an adequate thiamine intake.

**Equine: Congenital**

**Congenital Stationary Night Blindness**

A condition long thought to be related to the incompletely dominant leopard spotting (LP) allele is congenital stationary night blindness (CSNB) in Appaloosa horses (Joyce & Witzel, 1977; Rebhun et al., 1984; Witzel, 1977; Witzel et al., 1977, 1978). The condition is nonprogressive; affected animals have cautious behavior in dim-light conditions and may be difficult to train. Neuro-ophthalmic signs may include bilateral dorsomedial strabismus, spontaneous nystagmus, and a dark-adapted ERG lacking a b-wave (Sandmeyer et al., 2007, 2012).

Congenital stationary night blindness has been reported in a variety of breeds of horses including Appaloosa, Miniature Horses, Thoroughbred, and Paso Fino (Nunnery et al., 2005; Rebhun et al., 1984; Sandmeyer et al., 2007, 2012; Witzel, 1977; Witzel et al., 1977). CSNB is most commonly documented in breeds with the LP allele (Sandmeyer et al., 2007, 2012). Specifically, it has been shown that of the cases of CSNB occurring in breeds with the LP allele, CSNB is only found in those animals homozygous for LP (i.e., LP/LP) (Sandmeyer et al., 2007, 2012). Animals with LP are characterized along a spectrum of white patterning (very little white patterning to significant white patterning) (as discussed in Webb & Cullen, 2010). In heterozygous animals (LP/lp), there is typically more “spotting” within the white-patterned regions of the body. Animals homozygous for LP (LP/LP) typically have little to no spotting in the areas of white patterning.

It has been shown, phenotypically, that animals homozygous for LP, but not heterozygous (LP/lp) or noncarriers (ip/ip), are affected by CSNB (Sandmeyer et al., 2007, 2012). Additionally, decreased expression of transient receptor potential cation channel member 1 (TRPM1) gene in the skin and retina has been described in horses homozygous for LP and having CSNB (Bellone et al., 2008). Recently, three single nucleotide polymorphisms (SNPs) have been identified as completely associating with CSNB and LP (Bellone et al., 2010). Though the causative mutation for CSNB and LP is presently unknown, these SNPs can be used as a genetic test for CSNB and LP (Bellone et al., 2010).

**Multiple Congenital Ocular Anomaly Syndrome (MCOAS)**

Multiple congenital ocular anomaly syndrome (MCOAS) was described in Rocky Mountain Horses in 1999 (Ramsey et al., 1999a). Since this time, MCOAS has been described in crossbred Rocky Mountain Horses, Kentucky Mountain Horses, Moun tain Pleasure horse, Morgans, Belgians, American miniature Horses, and Icelandic Horses (Andersson et al., 2008, 2011a, 2011b; Grahn et al., 2008; Komaromy et al., 2011; Plummer & Ramsey, 2011; Ramsey et al., 1999a). MCOAS exists in 2 phenotypes, namely, (1) cyst phenotype, and (2) MCOA phenotype. Animals with the cyst phenotype have cysts arising from the ciliary body, peripheral retina, and/or iris. These patients may also have concomitant retinal dysplasia and/or retinal detachment. Animals with the MCOA phenotype have all of the anomalies seen within the cyst phenotype but also have varying severity and combination of congenital cataracts, cornea globosa, iris hypoplasia, iridocorneal angle abnormalities, lens subluxation, microphthalmia, and macropalpebral fissures (Ramsey et al., 1999a, 1999b). Neuro-ophthalmic abnormalities consist of miotic pupils, abnormal PLRs with pupils that respond poorly to pharmacologically induced mydriasis (Ramsey et al., 1999a). A affected individuals also have varying degrees of vision loss (Grahn et al., 2008; Ramsey et al., 1999a). Congenital ocular abnormalities observed in Rocky Mountain Horses are, in part, related to coat color (Ramsey et al., 1999a).

Mane and tail colors were found to be associated with the presence of multiple ocular abnormalities. Specifically, 45% of Rocky Mountain horses with chocolate-colored coats with white manes and tails had multiple ocular abnormalities including megalocornea, congenital miosis, ciliary cysts, and retinal dysplasia (Ramsey et al., 1999a). Meanwhile, only
12%, 6%, and 4% of horses with chocolate-colored coat with flaxen mane and tail, chestnut-colored coat, or some other coat color, respectively, had multiple ocular abnormalities (Ramsey et al., 1999a). Moreover, Rocky Mountain horses with white manes and tails were more likely to have multiple ocular abnormalities compared to animals with nonwhite manes and tails (Ramsey et al., 1999a). It has been shown that a genetic mutation occurring at the Silver Dapple locus is responsible, in part, for the multiple ocular abnormalities seen in Rocky Mountain horses (Ramsey et al., 1999a). A recent study has narrowed the M COAS locus to 208-kb on chromosome 6 (Andersson et al., 2011b). In particular, this narrow region contains 15 genes requiring further investigation into their role in M COAS; one of these genes is P M E L17 (gene responsible for silver coloration) (Andersson et al., 2011b).

**Equine: Acquired**

**Borna Disease**

Borna disease is caused by a single-stranded, enveloped, RNA virus of the Flaviviridae family and is serologically distinct from Eastern equine encephalomyelitis, Western equine encephalomyelitis and Venezuelan equine encephalomyelitis (for a review, see Richt et al., 2000; Rott et al., 2004). The disease is considered endemic in Germany and has been reported in the Netherlands, France, Poland, United States, Iran, and Japan (Rott et al., 2004). Clinical signs are similar to those of the other equine viral encephalitides and include altered PLRs and central blindness. Diagnosis of Borna disease is based on serum and CSF antibody titers, and the mortality rate varies from 37% to 94% (Rott et al., 2004).

**Dysautonomia (Equine Grass Sickness)**

Equine dysautonomia, commonly known as equine grass sickness, has been defined as a “fatal dysautonomia of horses associated with severe neuronal damage, especially in affected autonomic ganglia” (Timoney & Wernery, 2003). The cause of equine dysautonomia remains unknown, although a variety of theories exist. Recently favored hypotheses include: (1) overgrowth of C. botulinum type C within the gastrointestinal tract (Hunter et al., 1999; McCarthy et al., 2004) and (2) ingestion of cyanogenic producing plants (McGorum & Kirk, 2001). The highest incidence of equine dysautonomia is in Scotland but has been reported elsewhere in Europe and in South America. In Europe, the disease is most likely to be seen between April and July in young horses kept on pastures (French et al., 2005; Newton et al., 2004).

Clinical signs associated with equine dysautonomia are related to degeneration of autonomic ganglia and the enteric nervous system including pharyngeal and esophageal dysfunction, colic, sweating, tachycardia, and dry nasal mucosa (Milne et al., 2005). The most consistent ocular manifestation of equine dysautonomia is ptosis (Hahn & Mayhew, 2000). Ptosis in equine dysautonomia may result from a primary inability to move the upper eyelid effectively or may occur secondary to abnormal globe position within the orbit (Hahn & Mayhew, 2000). Severe degeneration of neurons in the cranial cervical ganglion (resulting in Horner’s syndrome) or abnormally functioning CN III and/or VII, as indicated by chromatolytic neurons in the nuclei of these nerves, may contribute to the ptosis observed in equine dysautonomia (Hahn & Mayhew, 2000).

Presumptive diagnosis of equine dysautonomia is made based on consistent clinical signs, geographic location of the animal, and time of year. Recently, it has been demonstrated that horses with equine dysautonomia and ptosis have a positive response to ocular administration of topical 0.5% phenylephrine compared to horses not afflicted with equine dysautonomia (Hahn & Mayhew, 2000).

Specifically, animals with equine dysautonomia treated with 0.5% phenylephrine will have a wider vertical palpebral fissure opening, as determined by evaluating the angle of the eyelashes relative to the head (opening of palpebral fissure in eye treated with phenylephrine subtracted from the opening of palpebral fissure in eye not treated with phenylephrine), compared to those animals without equine dysautonomia (Hahn & Mayhew, 2000). Definitive diagnosis of equine dysautonomia is typically made by postmortem examination of affected ganglia and gastrointestinal system. Therapy is aimed at supportive and intensive nursing care. Prognosis is poor to grave.

**Electrocution**

Electric shocks and lightning strikes can produce direct ocular sequelae and also cause injury to the CNS (may manifest as blindness, papilledema, cranial nerve palsies) (for review on pathogenesis and human manifestation see [Norman et al., 2001]). Three horses suspected of being hit by lightning and four horses electrocuted because of a faulty electrical transformer have been reported (Bedenice et al., 2001; Evans et al., 2011; Novales et al., 1998). In some instances, affected animals may die acutely because of peracute heart failure (Bedenice et al., 2001; Evans et al., 2011). Affected animals can become recumbent and exhibit thrashing and/or have exuberant muscle contractions after being struck by lightning or electrocuted. Affected animals may manifest with a variety of neurological signs.

With respect to ocular findings, affected horses have been reported to have ulcerative keratitis (unsure as to cause—i.e., may be secondary to trauma from thrashing on ground), blindness, corneal edema and hydrops, signs of vestibular disease (spontaneous nystagmus), signs of facial nerve paralysis (including ptosis, and absent palpebral reflex and menace response), and absent PLRs (Bedenice et al., 2001). Fundic lesions were not found in one horse after being struck by lightning (Bedenice et al., 2001). In another horse, however, choroidal hemorrhage and retinal detachment and atrophy were present (Evans et al., 2011). Electric shocks and lightning strikes of a severe nature may produce cataracts that manifest months later.
Although not reported in horses, cataracts are likely to be produced by electrical shocks to the head. The appearance of clinical and experimentally induced electric cataracts are quite similar, and they consist initially of vacuoles that are present bilaterally in the midperipheral anterior cortical lens (Fraunfelder & Hanna, 1972; Thomas & Hanna, 1974). Ultrastructurally, the vacuoles are extracellular and transient, lasting several weeks. The lens vacuoles are prognostic indicators of later cataract formation. The lens epithelium subsequently proliferates, thereby producing multilayered plaques of lens capsule and lens fibers in the central anterior capsular region. Severe electric shock (e.g., from lightning) may produce both anterior and posterior cortical lenticular opacities (Norman et al., 2001).

Therapy for electrocuted horses is supportive and symptomatic. Horses surviving lightning strike or electrocution may have persistent neurological deficits or return to normal following the incident (Bedenice et al., 2001; Novales et al., 1998).

**Equine Protozoal Myeloencephalitis (EPM)**

EPM is a multifocal, progressive disease of the CNS caused by infection with Sarcocystis neurona (for reviews, see Dubey, 2004; Dubey et al., 2001; Furr et al., 2002). The disease has been reported only in horses born and raised in the Americas including Canada, United States, Brazil, and Panama, with young horses being affected more than older horses and a breed predilection for Standardbred, Thoroughbred, and Quarter Horses (Dubey, 2004). The parasite causes inflammation and necrosis of the caudal brainstem and spinal cord. The cerebrum and peripheral nerves may be affected as well. Clinical signs include ataxia, tetraparesis, head tilt, facial paralysis, circling, nystagmus, and blindness (with or without pupillary light abnormalities). Horner’s syndrome has also been seen in horses with EPM (Mayhew, 1980). Severe temporalis and masseter muscle denervation and atrophy may lead to prominence of the supraorbital fossa, ptosis, and varying degrees of enophthalmos (Mayhew, 1989).

Diagnosis of EPM is made based upon demonstrating anti-Sarcocystis neurona antibody titers within the CSF, immunohistochemical detection of parasites in the CNS, and detection of S. neurona DNA by PCR in conjunction with consistent clinical signs (Furr et al., 2002). Treatment of EPM has been most successful with long-term therapy using combinations of pyrimethamine and trimethoprim (Dubey et al., 2001). Patients with severe inflammatory disease should also be given anti-inflammatory therapy at the start of antimicrobial therapy.

**Equine Viral Encephalomyelitis**

Viruses of the family Togaviridae are insect-transmitted and cause encephalitis in the horse. The most pathogenic of these viruses are called alphaviruses, and these include Eastern, Western, and Venezuelan equine encephalomyelitis (EEE, WEE, and VEE, respectively) viruses, all of which occur in the Americas (for a review, see Weaver et al., 1999). All of these viruses are transmitted by biting insects, especially mosquitoes. Also important to note, these viruses are considered zoontic.

Early clinical signs, regardless of the type of virus, include fever, stuporous state, ataxia, and hyperesthesia. Later signs include aggression, head pressing, blindness, paralyzed tongue and pharynx, nystagmus, strabismus, and pupillary dilatation. Diagnosis of equine viral encephalomyelitis is made based upon time of year (are mosquitoes present?), consistent clinical signs, rising serum antibody titers, and in acute cases, isolation of the virus from CSF or demonstration of the virus using RT-PCR (Calisher et al., 1983, 1986; Lambert et al., 2003; Linssen et al., 2000). Treatment is nonspecific and supportive in nature. The mortality rate is high, but horses can recover from viral encephalitis. Most will have residual neurologic signs, though complete recoveries have been reported (Devine & Byrne, 1960). Prevention of equine viral encephalomyelitis is through routine vaccination schedules and by controlling the mosquito population.

**Guttural Pouch Disease**

The guttural pouch is essentially a diverticulum of the Eustachian tube whose function is related to brain cooling (Baptiste et al., 2000). Regardless, there are several nerves located in close proximity to the guttural pouch including the cervical sympathetic trunk, the cranial cervical ganglion, mandibular branch of CN V (trigeminal), CN VII (facial), CN IX (glossopharyngeal), CN X (vagus), CN XI (spinal accessory), and CN XII (hypoglossal) (Manglai et al., 2000). As such, a myriad of clinical signs can emerge when disease processes affect the guttural pouch. Clinical signs of guttural pouch disease may include mucopurulent nasal discharge, nonexercisive associated epistaxis, and varying signs of dysphagia. Neuro-ophthalmic signs may include signs related to facial nerve paresis/paralysis (i.e., reduced or absent palpebral aspect of the menace response, reduced or absent palpebral reflex, ptosis, Horner’s syndrome, and peripheral vestibular syndrome) (if involvement of the temporal bone). Prognosis and treatment of guttural pouch disease is dependent upon the underlying cause. For discussion of guttural pouch disease and the neurologic manifestations of guttural pouch disease see (Borges & Watanabe, 2011).

**Neoplasia: Primary CNS**

There are few reports of intracranial neoplasms with ophthalmic manifestations in the horse. A pituitary mass in one aged horse resulted in blindness caused by degeneration of the optic nerves, optic chiasm, and optic tracts up to the lateral geniculate bodies (De Lahunta & Cummings, 1967). A morgan horse with a large intracerebral mass diagnosed as a microglioma had metastasis of the tumor to both eyes, with neoplastic cells being found within the vitreous humor and retina (Finn & Tennant, 1971).
Plants
Numerous plants may be toxic to the horse, and Table 34.14 lists toxic plants along with their systemic and ophthalmic effects. Historically, chronic selenium toxicity has been associated with “blind staggers” in the horse, but horses fed pure selenium compounds fail to develop the blindness, ataxia, or respiratory failure characteristic of blind staggers (Traub-Dargatz & Hamar, 1986). Thus, it has more recently been hypothesized that the toxic effects of alkaloids or other compounds in plants cause blind staggers, and that the condition does not relate directly to the selenium contained within these plants.

Many plants also have teratogenic effects in the horse, especially if they are eaten during the first trimester (Lewis, 1995). Pregnant mares may produce foals with a centrally placed, single eye if they eat Veratrum eschscholtzii during early pregnancy, much as ewes will produce such lambs if they eat Veratrum californicum on day 14 of gestation (Binns et al., 1962, 1963).

Polyneuritis Equi
Polyneuritis equi is an idiopathic, inflammatory disease of the spinal and cranial nerve roots and peripheral nerves (Mayhew, 2009). The condition is characterized initially by a nonsupplicative neuritis that progresses to a proliferative and granulomatous perineuritis later in the course of the disease (Mayhew, 2009). Polyneuritis equi is thought to be immunemediated, though it is unknown whether this is a primary or secondary immune-mediated disease (Aleman et al., 2009; Cummings et al., 1979; Kadlubowski & Ingram, 1981; Rousseaux et al., 1984). Affected animals can present with clinical signs of cauda equina involvement predominantly (cauda equina syndrome) or in combination with cranial nerve involvement. Clinical signs referable to unilateral or bilateral involvement of CNs III, V (trigeminal), VII (facial), VIII (vestibulocochlear), IX (glossopharyngeal), X (vagus), XII (hypoglossal), can be seen in severe cases (Aleman, 2011). As with all idiopathic diseases, the diagnosis of polyneuritis equi is a diagnosis of exclusion and is made based upon patient history, clinical signs, demonstration of a mononuclear pleocytosis within the CSF, and failure to identify an infectious or traumatic etiology. Treatment relies upon supportive care and immunosuppressive therapy may slow the progression of the clinical signs (Alemán, 2011). Prognosis is poor (Mayhew, 2009).

Temporohyoid Osteoarthropathy
Temporohyoid osteoarthropathy is a condition that involves the bony proliferation of the bones of the temporohyoid joint, namely the stylohyoid and petrous temporal bones (Walker et al., 2002; Yadernuk, 2003). The pathogenesis of temporohyoid osteoarthropathy remains unknown, although it is thought that otitis media or degenerative joint disease of the temporohyoid joint may be important in the pathogenesis of this disease (Walker et al., 2002; Yadernuk, 2003). Temporohyoid osteoarthropathy is commonly associated with facial (CN VII) and vestibulocochlear (CN VIII) nerve dysfunction (Walker et al., 2002; Yadernuk, 2003). Horses with this condition may also exhibit head shaking, hyperesthesia of the ears, and avoidance of bit placement (Yadernuk, 2003). Ocularly, temporohyoid osteoarthropathy commonly manifests secondarily through involvement of the parasympathetic fibers of CN VII (neurogenic KCS), CN VII (facial nerve paralysis), and the vestibular labyrinth and/or vestibulocochlear nerve (signs of peripheral vestibular disease) (Blythe, 1997; Verdegaal et al., 2003; Walker et al., 2002; Yadernuk, 2003). Diagnosis is made based upon consistent clinical signs combined with endoscopic, radiographic, or magnetic resonance or computerized tomographic evidence of asymmetry, inflammation, or osseous proliferation of the temporohyoid joint or stylohyoid bone (Walker et al., 2002). Therapy of temporohyoid osteoarthropathy involves appropriate antimicrobial therapy. Prophylactic partial stylohyoidostectomy is used in some instances (Blythe, 1997; Newton & Knottenbelt, 1999; Pease et al., 2004; Walker et al., 2002). Prognosis for this condition is good; however, maximal resolution of clinical signs is not observed for up to 2 years and many animals will have residual neurological signs (Walker et al., 2002).

Thiamine Deficiency
Thiamine deficiency occurs in horses primarily because of the ingestion of plants containing the catabolic thiamine enzyme, thiaminase. Plants such as bracken fern (Pteridium aquilinum) and horse tails (Equisetum arvense) contain thiaminases, and equine thiamine deficiencies have been attributed to chronic ingestion of these particular plants (Carpenter et al., 1950; Evans et al., 1951; Henderson et al., 1952; Roberts et al., 1949). Amprolium, a coccidiostat, has been used to induce thiamine deficiency in horses experimentally (Cymbaluk et al., 1978). Clinical signs of thiamine deficiency in the horse include ataxia, blindness, bradycardia, heart block, muscle fasciculations, weight loss, diarrhea, and hypothermia of the extremities. Diagnosis of thiamine deficiency is made based upon demonstrating exposure to thiaminase-containing plants and demonstrating low serum thiamine or by response to therapy. Therapy includes removal of access to thiaminases and parenteral treatment with thiamine. Clinical signs, including blindness, are reversible if the animal is not in the late stages of deficiency.

Traumatic Optic Neuropathy
Traumatic optic neuropathy in the horse is often times caused by blunt head trauma, commonly from the animal flipping over backward or other means of blunt head trauma (Bogg & Marc, 1990; Martin et al., 1986; Reppas et al., 1995; van Schaik et al., 1998). Such injury causes injury to orbital structures and optic nerve damage. Optic nerve damage is thought to result from shearing and compressive forces applied to the optic nerve at the level of the optic canal. As with any
### Table 34.14  Toxic Plants That May Lead to Systemic and Ophthalmic Disease in Horses

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Scientific Name</th>
<th>Plant Toxin</th>
<th>Systemic Signs</th>
<th>Ophthalmic Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field bindweed or morning glory</td>
<td><em>Convolvulus arvensis</em></td>
<td>Tropane alkaloid</td>
<td>Colic</td>
<td>Mydriasis</td>
</tr>
<tr>
<td>Jimsonweed</td>
<td><em>Datura stramonium, D. metaloides</em></td>
<td></td>
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<tr>
<td>Belladonna</td>
<td><em>Atropa belladonna</em></td>
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<tr>
<td>Fiddleneck or tarweed</td>
<td><em>Amsinckia spp.</em></td>
<td>Pyrrolizidine alkaloid</td>
<td>Hepatic failure, photosensitization, weight loss, neurologic signs, anemia</td>
<td>Cortical blindness</td>
</tr>
<tr>
<td>Rattlepod, rattlebox</td>
<td><em>Crotolaria spp.</em></td>
<td></td>
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<tr>
<td>Hound's tongue</td>
<td><em>Cynoglossum officinale</em></td>
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<tr>
<td>Salvation Jane, Patterson's curse</td>
<td><em>Echium spp.</em></td>
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<tr>
<td>Heliotrope, stickseed</td>
<td><em>Heliotropium spp., Trichodesma spp.</em></td>
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<tr>
<td>Tansy ragwort, stinking willie</td>
<td><em>Senecio spp.</em></td>
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<tr>
<td>Lamb's tongue groundsel</td>
<td><em>Equisetum arvense</em></td>
<td>Thiaminase</td>
<td>Weakness, ataxia, diarrhea or constipation, bradycardia, muscle fasciculations</td>
<td>Cortical blindness</td>
</tr>
<tr>
<td>Wooly or threadleaf groundsel</td>
<td><em>Pteridium aquilinum</em></td>
<td></td>
<td></td>
<td>Mydriasis</td>
</tr>
<tr>
<td>Poison hemlock</td>
<td><em>Conium maculatum</em></td>
<td>Piperidine alkaloid</td>
<td>Salivation, colic, muscle tremors, ataxia, cyanosis, respiratory paralysis, sudden death</td>
<td>Mydriasis</td>
</tr>
<tr>
<td>Serviceberry or Saskatoon berry</td>
<td><em>Amelanchier alnifolia</em></td>
<td>Cyanogenic glycoside</td>
<td>Bright red venous blood, cyanotic membranes, labored breathing, frothing at the mouth, ataxia, seizures, sudden death</td>
<td>Mydriasis</td>
</tr>
<tr>
<td>Wild blue flax</td>
<td><em>Linum spp.</em></td>
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<td>Chokecherry</td>
<td><em>Prunus virginiana</em></td>
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<td>Elderberry</td>
<td><em>Sambucus spp.</em></td>
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<tr>
<td>Johnson grass</td>
<td><em>Sorghum halepense</em></td>
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<tr>
<td>Sudan grass, or broom or kafir corn</td>
<td><em>Sorghum sudanense</em></td>
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<tr>
<td>Arrow, pod, or goosegrass</td>
<td><em>Triglochin spp.</em></td>
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<tr>
<td>Blind grass (Australia)</td>
<td><em>Stypandra spp.</em></td>
<td>Not defined</td>
<td>Ataxia, weakness</td>
<td>Optic nerve and retinal degeneration</td>
</tr>
</tbody>
</table>

- **Colic**
- **Mydriasis**
- **Cortical blindness**
traumatic injury to the CNS, the optic nerve sustains not only primary injury but also secondary injury (i.e., secondary to primary insult). Such secondary injury is characterized by varying degrees of inflammation, altered permeability to blood vessels, etc. Ultimately, retinal ganglion cell fibers are damaged and varying degrees of optic nerve degeneration occur over weeks and months. Such degeneration is evidenced by optic nerve atrophy and varying degrees of retinal degeneration. Neuro-ophthalmic findings vary from acute to subacute progressive visual field deficits or blindness, variably dilated pupils, reduced or absent PLRs, inconsistent to absent dazzle reflexes and menace responses. Treatment is aimed at reducing edema of the CNS and maintaining oxygenation. Prognosis is typically poor, though those animals not sustaining basilar skull fractures and having some evidence of vision at the time of injury may develop improved visual function (Irby, 2011).

**Vitamin A Deficiency**

Vitamin A (retinol), a fat-soluble vitamin, is derived from its precursors (carotenoids) which are found in plants (for a review, see Fraser & Bramley, 2004; von Lindig & Vogt, 2004). With regard to the importance of vitamin A in the ocular system, vitamin A (retinol) is stored and transformed into retinal which is translocated between the RPE and the photoreceptors (Thompson & Gal, 2003). Within the photoreceptors, retinal combines with opsin (a protein) to form the visual pigment rhodopsin (Thompson & Gal, 2003). Early signs of vitamin A deficiency, include reduced feed intake and growth rate; a dull and brittle, long haircoat; and in foals, an increased incidence of respiratory and diarrheal diseases. A diagnosis of vitamin A deficiency, in the horse, is suspected in horses with excessive tearing and night blindness (Lewis, 1995). An important differential diagnosis for vitamin A deficiency is congenital stationary night blindness in Appaloosa horses (the latter is present from birth, is nonprogressive, and has no clinically evident ocular lesions). Ocular lesions and night blindness occur only if vitamin A deficiency is severe (Green et al., 1992b; Hudson et al., 1996). Night blindness occur only if vitamin A deficiency is severe (Green et al., 1992b; Hudson et al., 1996). Ocular signs indicative of infection of the central components of the visual and oculomotor systems including blindness, nystagmus, and strabismus may develop (Green et al., 1992b; Hudson et al., 1996). During the clinical course of the disease clinical signs worsen and the animal eventually succumbs to the disease. A ntemporal diagnosis can be made by demonstrating antigen, using immunochemical methods or by detecting the virus using RT-PCR, in skin, corneal impressions, or saliva (Woldehiwet, 2005). Definitive diagnosis is made at postmortem by detecting the virus in brain tissue using immunochemical techniques or RT-PCR (Woldehiwet, 2005). Eosinophilic intracytoplasmic inclusion bodies (Negri bodies) may be observed in neurons throughout the CNS, including retinal ganglion cells (Haltia et al., 1989). It is important to note, however, that not all cases of rabies will have Negri bodies present; hence, the reason other more specific tests are used. Prevention of rabies is aimed at routine vaccinating of susceptible animals.

**West Nile Virus (WNV)**

WNV is single-stranded RNA virus of the family Flaviviridae that is maintained in the environment by a bird-mosquito relationship (for a review, see Garg & Jampol, 2005; Ostlund et al., 2000). Birds are the reservoir host while mosquitoes transmit the virus to a variety of animal species, including birds, horses, cats, dogs, bats, alligators, and humans (Garg & Jampol, 2005; Kulasekera et al., 2001; Nasel et al., 2001; Turell et al., 2002). Horses are similar to humans in that they are considered dead-end hosts (cannot transmit the disease), although transfusion of infected blood products can result in transmission of the disease to the recipient (Pealer et al.,...
persistent pupillary membranes, and vitreous hemorrhage have been associated with hydrocephalus (Leipold et al., 1971, 1974). The cause has not been determined, but it has been postulated to be genetic (Leipold et al., 1971).

**Pendular Nystagmus**

Benign pendular nystagmus has been reported in Holstein, Jersey, Ayrshire, and Guernsey breeds of cattle (McConnon et al., 1983; Nurmio et al., 1982; Rebhun, 1979). The condition is characterized by vertical, horizontal, or rotary pendular nystagmus (i.e., spontaneous nystagmus occurring with no clear fast or slow phase). The condition is presumed inherited, though this has not been confirmed.

**Food Animals: Developmental**

**Bilateral Convergent Strabismus with Exophthalmos (BCSE)**

BCSE is an inherited disease affecting German Flackvieh, German Holstein, German Brown, and Jersey breeds of cattle (for review, see Momke & Distl, 2007). The condition is characterized by a progressive, bilaterally convergent strabismus and mild to severe exophthalmos (Fig. 34.35). Affected animals can become blind due to severe strabismus. Clinical signs are first noticed as early as 6 months of age, or much more commonly just prior to an animal’s first breeding. The disease typically affects young adult horses, although any age of horse can have a clinically relevant infection. In humans, however, WNV infection manifests ocularly as chorioretinitis, uveitis, retinal vasculitis, and optic neuritis (Garg & Jampol, 2005). It is possible that horses, too, have similar ocular lesions though complete ophthalmic examinations may not routinely be performed or such lesions have not been reported.

Diagnosis of WNV infection is made based upon determining IgM concentrations in the serum and/or CSF, amplifying WNV DNA using PCR, or isolating the virus (Schuler et al., 2004; Weese et al., 2003). Therapy for WNV infection involves supportive care and administering systemic anti-inflammatory drugs to reduce cerebral edema (Weese et al., 2003). Prognosis is variable. Older horses, horses not vaccinated for WNV, and horses that are recumbent are more likely to succumb to the disease (Schuler et al., 2004; Weese et al., 2003). Specifically, up to approximately 80% of WNV-infected and recumbent horses will succumb to the disease (Schuler et al., 2004). Prevention is aimed at implementing a routine vaccination schedule. In addition, the percent mortality for animals that develop clinical signs of the disease yet are vaccinated (when used according to the manufacturers instructions) is 4% while the mortality of unvaccinated animals has been reported to be 33% (Schuler et al., 2004).

**Food Animals: Congenital**

**Hydrocephalus**

Hydrocephalus refers to increased amount of CSF within the cranial vault. Bovine hydrocephalus is a commonly encountered congenital defect for which concurrent ocular lesions are rarely reported (Greene & Leipold, 1974; Leipold et al., 1971, 1974). In Shorthorn calves, multiple ocular anomalies including microphthalmia, cataracts, retinal detachment, retinal dysplasia, optic nerve, optic chiasm and optic tract hypoplasia,
fashion in German Brown dairy cattle. There is no treatment or cure for this disease. The suspected causative mutation in German brown dairy cattle has been localized to chromosome 18, though the causative mutation has yet to be identified (Momke et al., 2008).

**Food Animals: Acquired**

**Bovine Virus Diarrhea (BVD)**

BVD results from a pestivirus with a worldwide distribution that infects cattle, sheep, goats, and wild ruminants. It is transmitted via inhalation or ingestion of infective secretions or excretions, semen, and transplacentally. Results of a recent study showed that BVD virus can also be transmitted to susceptible animals if they come into contact with fetal fluids during the birth of persistently infected calves (Lindberg et al., 2004). BVD virus has been implicated with causing abortion, and cerebellar and ocular disease. In cattle, in utero infection with BVD virus between 76 and 150 days of gestation may result in congenital defects of the eye and brain. In addition, following experimentally induced BVD infection, persistently infected calves have minor skeletal abnormalities including short limbs, narrow skull with bulging eyes and/or prognathism (Stokstad & Loken, 2002). CNS lesions include microencephaly, cerebellar hypoplasia, hydranencephaly, and hydrocephalus (Baker, 1987). Ocular lesions of cataracts, retinal degeneration and retinal dysplasia, optic nerve gliosis, optic neuritis, and microphthalmia have also been described with experimentally induced disease (Bistner et al., 1970b; Scott et al., 1973). At ophthalmoscopy, the tapetal coloration is altered, and pigment clumping is visible. Cataracts and optic nerve lesions may not be present in naturally occurring cases of BVD; this may relate to the stage of gestation during which the pregnant dam became infected (Bistner et al., 1970b). A acute histopathologic ocular lesions detected in fetuses taken 17–21 days following inoculation of their dams at 150 days’ gestation included mild to moderate retinitis atrophy suggestive of compression in the optic canal. Retinal lesions have developed blindness, paresis, and paralysis. Lesions have consisted of bilateral, symmetric edema of the CNS white matter with destruction of myelin, and the optic nerve develops gliosis. The intracanalicular portion of the optic nerve subsequently undergoes fibrosis and atrophy suggestive of compression in the optic canal. Retinal lesions include degeneration and loss of photoreceptor outer segments, mainly in the nontapetal fundus. The RPE is hyperplastic and migrates into the neurosensory retina (van der Lugt et al., 1996).

**Brain Abscessation**

Central blindness has been diagnosed in a 3.5-year-old cross-bred steer diagnosed with multiple brain abscesses (Strain et al., 1987). In particular, clinical signs in this steer included depression, head pressing, and circling to the left. Ocular manifestations in this animal included ptosis and absent menace response of the right eye; direct and consensual PLRs were normal in both eyes. Electrodiagnostic testing was performed and revealed essentially normal brainstem auditory evoked potentials and ERGs, while visual evoked potentials (VEPs) were greatly diminished for the right eye and absent for the left eye. On postmortem examination, the brain abscesses were located in the left thalamus, left caudal cerebrum, and right frontal cerebrum (Strain et al., 1987).

**Bracken Fern Poisoning (Bright Blindness)**

Ingestion of bracken fern (Pteridium aquilinum) in chronic, low-level amounts has been suspected of causing the syndrome of bright blindness among sheep and cattle in the United Kingdom (Barnett & Watson, 1968, 1970; Hirono et al., 1993; Watson et al., 1965, 1972). The syndrome manifests as a retinal degeneration with blindness. Retinal lesions are most severe centrally and involve degeneration of the rods and cones. Ophthalmoscopic findings include retinal vascular attenuation, tapetal hyperreflectivity, and optic nerve atrophy (Barnett & Watson, 1968). The active chemical in bracken to cause progressive retinal degeneration following Pteridium sp. ingestion is ptaquiloside, a carinogenic norsequiterpene (Hirono et al., 1993) (for a review pertaining to ptaquiloside see [Yamada et al., 2007]).

**Bullous Empyema**

Bullous empyema causing peripheral vestibular syndrome has recently been described in a pregnant heifer. Clinical signs in this heifer included generalized ataxia, wide-based stance of the hind limbs, abnormal behavior, circling to the left, and left head tilt. In addition, ocular lesions included strabismus to the left, and nystagmus with the fast phase to the right (Braun et al., 2004b).

**Helichrysum argyrosphaerum Poisoning**

In Africa, sheep and cattle grazing on pastures mainly consisting of H. argyrosphaerum have developed blindness, paresis, and paralysis. Lesions have consisted of bilateral, symmetric edema of the CNS white matter with destruction of myelin, and the optic nerve develops gliosis. The intracanalicular portion of the optic nerve subsequently undergoes fibrosis and atrophy suggestive of compression in the optic canal. Retinal lesions include degeneration and loss of photoreceptor outer segments, mainly in the nontapetal fundus. The RPE is hyperplastic and migrates into the neurosensory retina (van der Lugt et al., 1996).

**Electrocution**

Electric shocks and lightning strikes can produce direct ocular sequelae and also cause injury to the CNS (may manifest as blindness, papilledema, cranial nerve palsies) (for
Lead poisoning is commonly diagnosed in cattle, and to a lesser extent, sheep and horses. Cattle, especially young calves, are very susceptible to lead poisoning (Neathery & Miller, 1975). The cause of lead poisoning is accidental ingestion of sources of lead compounds (e.g., automobile battery) or of feed containing lead from environmental pollution. Lead poisoning in food animals is of public health significance due to the risk to humans through ingestion of contaminated meat and milk products from affected animals (Rumbeiha et al., 2001). In addition, the half-life of blood lead is variable (ranging from 48 to 2507 days) and, hence, difficult to predict in accidental cases of lead poisoning in cattle (Rumbeiha et al., 2001). In acute lead poisoning of cattle, clinical signs include staggering, muscle tremors (mainly of the head and neck), clamping of the jaws, frothing at the mouth, in addition to ocular signs such as snapping of the eyelids, rolling of the eyes, and blindness. In the acute syndrome, death usually results during a convulsion as a result of respiratory arrest.

**Hypocalcemia (Bovine Parturient Paresis, Milk Fever)**

Bovine parturient paresis is a complex metabolic disorder resulting in an acute to peracute flaccid paralysis and/or somnolence of lactating dairy cows which usually occurs at the onset of lactation (Horst et al., 1997). The hypocalcemia arises due to a rapid increase in milk production and subsequent acute depletion of serum ionized calcium. Parturient paresis is divided into three main clinical stages of which stage two hypocalcemia is characterized by depression, anorexia, an inability of the animal to stand, tachycardia, gastrointestinal stasis, and ocular signs of mydriasis with absent or sluggish PLRs (Murray et al., 2008). Recommended treatment for parturient paresis is prompt intravenous therapy with a calcium solution (Murray et al., 2008).

**Hypomagnesemia (Grass Tetany)**

Hypomagnesemia results from a primary dietary deficiency of magnesium. Hypomagnesemia is a highly fatal condition of ruminants. Clinical signs in lactating cows affected with grass tetany (i.e., occurs mainly in winter and spring when grasses which are low in magnesium comprise the diet) include anorexia, hyperexcitability, muscle fasciculations, head and neck tremors, followed by poorly coordinated gait and lateral recumbency. In addition, ocular manifestations of grass tetany include nystagmus and a rapid, snapping eyelid retraction. Confinement-housed dairy cows on a controlled feeding program can also develop hypomagnesemia (Donovan et al., 2004). Prevention of hypomagnesemia involves both continuous provision of adequate levels of dietary magnesium and improving absorption of this essential mineral by the ruminal epithelium (Martens & Schweiigel, 2000). The reader is referred to current internal medicine textbooks for a detailed discussion on hypomagnesemia in ruminants.

**Listeriosis**

Listeriosis is caused by a small rod-shaped, gram-positive bacterium belonging to the genus *Listeria*. The most common and important organism causing disease in domesticated animals is *Listeria monocytogenes*. Spoiled or incompletely fermented corn or hay silage is the main source of infection. Small wounds in the lips and oral and nasal mucosae, and the conjunctiva permit entry of the causative agent (Braun et al., 2002). In addition, venereal transmission in ruminants has been described (Wiedmann et al., 1999). For further details regarding the transmission and pathogenesis of listeriosis in food animals, the reader is referred to a current textbook in food animal infectious disease and/or internal medicine.

Listeriosis of the CNS (i.e., meningoencephalitic form) is most likely to be associated with ocular signs in food animal species. The main clinical manifestations of listeriosis include CNS disease with vestibular ataxia and unilateral cranial nerve deficits. Involvement of the brainstem may be associated with facial nerve paralysis and KCS. Keratitis is the main ocular lesion, though varying degrees of hypopyon and anterior uveitis may also be present. Purulent endophthalmitis may result as well (Saunders & Rubin, 1975). A variety of ocular lesions have been reported in sheep and goats with listeriosis including scleral hyperemia, unilateral keratitis with or without corneal ulceration, bilateral mydriasis, vertical or horizontal nystagmus, ventrolateral or ventromedial strabismus, unilateral or bilateral diminished or absent menace response, lack of palpebral reflex, and diminished or absent PLRs (Braun et al., 2002; Gerros, 1998). In cattle, ocular lesions have been reported to be the most common clinical manifestation of listeriosis, followed by neurologic signs (Erdogan et al., 2001). Recently, listerial ocular infections (conjunctivitis, keratitis, and uveitis) in ruminants have also been related to environmental or host factors, such as direct ocular exposure of susceptible animals to high numbers of the agent (Evans et al., 2004b). In swine, listeriosis usually occurs in newborn pigs, among which oral exposure results
in focal necrosis of the parenchymatous organs, lymphoreticular tissue, and a necrotizing vasculitis and septic choroiditis (Busch et al., 1971).

A diagnosis of listeriosis is made based upon consistent clinical signs, and culturing and identifying the organism from body fluids (e.g., CSF) and tissues. Suggested treatments include systemic administration of appropriate antimicrobials (e.g., penicillin or oxytetracycline), supportive therapy, and isolation of affected animals. L. monocytogenes can cause serious disease in people including meningitis and sepsis, and, in pregnant women, spontaneous abortion and stillbirth can result (Low & Donachie, 1997).

**Locoweed Poisoning**

Ingestion of locoweed (Astragalus spp.) by cattle, sheep, and horses may produce ocular signs of blindness and a “dull” eye. Histopathologic changes of marked vacuolation of the retinal ganglion and bipolar cells, ciliary epithelial cells, and lacrimal acinar cells have been described in research animals (Van Kampen & James, 1971).

**Male Fern Poisoning**

Male fern (Dryopteris filix-mas) consumption by cattle is associated with lethargy, constipation, and blindness. A cutely blind cattle have dilated pupils and ophthalmoscopic lesions of papilledema, as well as retinal and preretinal hemorrhages. Most animals recover when removed from pastures containing male fern, but some do not. Chronically blind animals develop optic nerve atrophy and vascular attenuation. At histopathology, the retrobulbar optic nerves are twice the normal diameter, myelin sheaths are fragmented and invaded by Gitter cells, and axons are decreased in number. The peripheral nerve, however, is relatively spared. The process appears to be a retrobulbar neuropathy that destroys the myelin sheaths of the nerve (Rosen et al., 1971).

**Paramyxovirus (Blue Eye Disease)**

Pig paramyxovirus of the blue eye disease (PPBED) is a new member of the Paramyxoviridae family that infects swine. This disease emerged in 1980 in central Mexico (Stephano, 1990). PBPED is characterized by corneal opacity, CNS disorders, and reproductive failure. CNS manifestations (e.g., fatal encephalitis) and corneal opacity are the main signs in piglets 2–21 days old (Ramirez-Herrera et al., 1997, 2001; Stephan et al., 1988; Stephano & Gay, 1984). Older pigs appear more resistant and corneal opacity is a commonly observed feature (Stephan et al., 1988). PBPED in pregnant sows has been linked with reproductive failure and infertility. Piglets 2–15 days of age are most susceptible. Affected piglets become prostrate, and develop progressive neurologic signs. The affected animals may be blind, with dilated pupils and nystagmus. In addition, PBPED-affected pigs may develop conjunctivitis with epiphora, swollen eyelids, and ocular discharge adherent to the eyelids. Piglets older than 30 days of age may have respiratory signs and corneal opacities, or they may strictly have corneal opacities. Up to 30% of affected piglets have either unilateral or bilateral corneal opacities, which tend to resolve spontaneously. Histopathologically, ocular lesions consist of corneal edema and anterior uveitis. The cellular reaction is mononuclear, with some neutrophils and intracytoplasmic inclusions possibly being present in the epithelial cells (Hornedo & Gutierrez, 1986; Stephano, 1990). PBPED has also been shown to bind to pig neuronal tissue of the brainstem, hippocampus, olfactory bulb, cerebellum, and frontal, temporal and parietal lobes of the cerebral cortex in newborn, 60-day-old, and adult pigs (Mendoza-Magana et al., 2001). Clinical signs of encephalitis and corneal edema in piglets, or reproductive failure in adults, are suggestive of the diagnosis. The diagnosis is confirmed on the basis of virus isolation and hemagglutination-inhibition tests. At present, there is no specific therapy.

**Polioencephalomalacia (PEM) (Cerebrocortical Necrosis)**

PEM is a disorder of the CNS of ruminants that results in necrosis of the cortical gray matter (Gould, 1998; Newsholme & O’Neill, 1985). PEM has a worldwide distribution. There are several causes of PEM including altered thiamine (vitamin B₃) status caused by such factors as excessive ruminal consumption of thiamine by bacterial thiaminases, and ingestion of plants with thiaminolytic activity, among others. However, PEM may also be induced by other neural metabolic disturbances such as water deprivation-sodium ion toxicosis, lead poisoning (see “Lead” under “Systemic Toxicities” section), and high sulfur intake. (Gould, 1998) Early clinical signs of PEM in affected animals include anorexia, incoordination, muscle tremors, holding the head in an erect position, and appearing blind. As PEM progresses, animals develop blindness, head-pressing, dorsomedial strabismus, miosis, variable nystagmus, excitement, facial twitching, repetitive chewing, and recumbency and opisthotonus (McGuirk, 1987). In addition, a lack of menace responses and reduced palpebral reflexes have been described in PEM-affected cattle (Haydock, 2003). Death usually arises following 3–4 days if the affected animal is not treated.

Electrodiagnostic visual testing (ERG and VEP) has been performed on five ruminants (three lambs, one kid, and one steer) with thiamine-responsive PEM (Strain et al., 1990). The lambs and kid had typical clinical signs of PEM, including blindness. The ERG in these animals was normal but the VEP was abnormal. Follow-up recordings in the kid and one lamb indicated an improvement in VEP recordings subsequent to thiamine treatment and a gradual return of vision. According to the owners, all animals had complete return of vision. The steer did not have signs of blindness, and the ERG and VEP were normal (Strain et al., 1990). The reader is referred to current internal medicine textbooks for a detailed discussion on PEM.
**Prion Disease**

Scrapie is a neurodegenerative disease of the group of transmissible spongiform encephalopathies (TSEs) affecting sheep and goats. Sheep are regarded as the natural reservoir for scrapie. The incubation period is typically between 2.5 and 3.5 years. According to the prion hypothesis, which explains most of the biological features pertaining to the scrapie agent, scrapie lesions are triggered by the conversion of the cellular prion protein (PrP<sup>c</sup>) into the abnormal isoform (PrP<sup>sc</sup>) resulting in its pathological accumulation (Hunter, 1998). Scrapie produces progressive neurological signs, the lesions of which consist mainly of vacuoles within the nervous system, and eventual death. In particular, clinical signs are categorized into three main groups including: (1) sensation abnormalities, namely, pruritis; (2) changes in mental status including apprehension and occasional aggression and stupor; and (3) postural and locomotion changes such as low carriage of the head, wide-based or cross-legged stance, pacing (Braun et al., 2004a), and ataxia (for a review of scrapie, please refer to Bradley & Verwoerd, 2004).

One study examining the neuroophthalmic manifestations of naturally occurring scrapie using 17 affected animals and 6 age-matched control animals has been published (Regnier et al., 2011). In this study there was no evidence of anisocoria, pupil size aberrations, PLR abnormalities, or corneal or palpebral reflex abnormalities. Three affected animals, however, had inconsistent menace responses, though one control animal also had an inconsistent menace response. As such, it is unclear from this study whether sheep with scrapie develop altered vision. Interestingly, however, all scrapie-affected sheep had histopathological changes consistent with retinal degeneration. Future studies would need to examine a larger population of animals to more clearly identify whether visual field deficits exist in sheep affected by scrapie.

Ocular manifestations of scrapie infection of sheep and goats include multifocal, round tapetal lesions that can be as large as the optic disk. Histologically, these lesions are focal retinal detachments resulting from subretinal accumulations of eosinophilic material characterized as lipid (Barnett & Palmer, 1971). These fundic lesions are typical enough to be suggestive of the diagnosis when combined with chronic, progressive neurologic disease. Importantly, however, not all animals with scrapie-affected sheep had histopathological changes consistent with retinal degeneration. Future studies would need to examine a larger population of animals to more clearly identify whether visual field deficits exist in sheep affected by scrapie.

There is no effective treatment for scrapie. Animals suspected of having scrapie should be euthanized, and their brain should be submitted for laboratory examination.

**Pseudorabies (Aujeszky’s Disease)**

Pseudorabies is caused by Aujeszky’s disease virus, a neurotropic alphaherpesvirus. Pseudorabies epizootics in swine are noted with drastic climatic changes, and they are characterized by blindness, depression, head pressing, and death. Death or recovery tends to occur by day 3, with blindness occurring as a permanent sequela in recovered animals. Histopathologically, ocular lesions include decreased numbers of retinal ganglion cells, degeneration of retinal ganglion cells, and perivascular cuffing with mononuclear cells and neutrophils in the optic nerve (Howarth & De Paoli, 1968). In addition, rapidly progressive punctate corneal ulcers associated with blepharospasm, follicular conjunctivitis, corneal anesthesia, transient blindness, iridal edema, miosis, and fever, have been produced following experimental inoculation of traumatized porcine corneas with Aujeszky’s disease virus (Schneider & Howarth, 1973). There is no treatment for the disease. Vaccines against Aujeszky’s disease virus have been developed (Pastoret & Jones, 2004; Pensaelt et al., 2004).

**Rabies**

Rabies continues to be one of the most feared zoonotic diseases in the world. Rabies, a bullet-shaped RNA virus, is a Lyssavirus in the family Rhabdoviridae (Woldehiwet, 2002). Transmission of rabies occurs via a bite by a rabid animal, although infections through aerosols have been documented (Constantine, 1966; Winkler et al., 1972, 1973). The virus can infect any warm-blooded animals, with dogs and cats being the main vectors of human infection (Woldehiwet, 2005). Clinically, rabies infection can be divided into three phases: (1) prodromal, (2) furious, and (3) paralytic phases (Bedford, 1976). Cattle are most commonly affected among livestock. A recent study documented that cases of rabies infection reported in the United States in cats, dogs, horses and mules, and sheep and goats decreased 12.5%, 19.7%, 31.8%, and 16.7%, respectively, whereas cases reported in cattle increased 174% (Krebs et al., 2005). Rabies virus is likely the most important cause of bovine encephalitis because of the public health implications (Callan & Van M etre, 2004). The clinical signs of rabies infection in livestock are variable. Clinical manifestations of the prodromal form of rabies in animals include depression, inappetance, pyrexia, significant ataxia, and facial musculature flaccidity, among others. In addition, other signs, including ocular manifestations, may be seen prior to death such as circling, head-pressing, strabismus, nystagmus, and blindness. The reader is referred to current internal medicine textbooks for a detailed discussion on rabies.

**Vitamin A Deficiency**

Vitamin A deficiency has been studied extensively among cattle, both in spontaneous cases and with experimental induction. In young, growing animals, vitamin A deficiency produces clinical signs when the vitamin A levels fall to less than 20 µg/DL of plasma and less than 2 µg/g of liver (Kohlmier & Burroughs, 1979). A sexual predilection for males has been noted in two clinical reports (Divers et al., 1986; Paulsen et al., 1989). A lag period of 3–12 months may be necessary...
before the effects of vitamin A deficiency are noted, and these effects depend on age of onset, degree of deficiency, and the amount of liver stores. Animals younger than 6 months of age are more susceptible and more likely to have blindness as a presenting sign because of sphenoid bone overgrowth constricting the optic nerve (Barnett et al., 1970; Blakemore et al., 1957; Booth et al., 1987; Divers et al., 1986; Hayes et al., 1968; Paulsen et al., 1989; Spratling et al., 1965; Van Donkersgoed & Clark, 1988; Wetzel & Moore, 1940). Blindness, with or without convulsions, is the first outward sign noted in most cases among young, growing animals (Barnett et al., 1970; Divers et al., 1986; Spratling et al., 1965). Seizures are short and tonic-clonic in nature (Divers et al., 1986). Upon critical examination of animals, night blindness, the first clinical sign noted in experimentally affected animals, may be noted, but it is unlikely to be noted under typical husbandry conditions (Barnett et al., 1970). Blindness is accompanied by fixed, dilated pupils, and on ophthalmoscopy, papilledema will be present. Papilledema occurs well before blindness in both adult- and young-onset deficiencies. Papilledema presumably results from increased CSF pressure, which develops from fibrosis and thickening of the dura mater that, in turn, results in decreased absorption of the CSF by the arachnoid villi. Increased CSF pressure is the first change noted with vitamin A deficiency (Hayes et al., 1968).

Causes of blindness will vary with age of onset for the deficiency. Blindness may result from retinal degeneration at all ages or constrictive and ischemic necrosis of the optic nerve at the optic foramen in growing animals. Eventually, optic nerve atrophy develops (Barnett et al., 1970). Day blindness has not been reversible, but night blindness or papilledema detected before blindness occurs has been responsive to therapy (Spratling et al., 1965). A ditional changes in the fundus are papillary and peripapillary hemorrhages as well as disruption of pigment in the nontapetal region. Retinal degeneration primarily occurs in the nontapetal region (Barnett et al., 1970; Booth et al., 1987; Divers et al., 1986; Paulsen et al., 1989; Van Donkersgoed & Clark, 1988). Tapetal color alterations have not been noted in experimental or in clinical reports until late in the deficiency. A ditional ocular lesions that have been attributed to vitamin A deficiency include exophthalms (origin not understood), epiphora, nystagmus, and corneal ulceration. Though described clinically, corneal lesions have not usually been observed experimentally in calves, but decreased corneal sensitivity has been observed (Barnett et al., 1970). Recently, 25% of calves born to heifers which experienced prolonged hypovitaminosis A during pregnancy had several congenital ocular abnormalities including microphthalmos, ocular dermoids covering the external surfaces of the eyes, and single chambered globes each lacking a uveal tract, lens (i.e., aphakia) and aqueous humor (Mason et al., 2003).

Histopathologic examination of the affected eyes revealed severe retinal dysplasia with retinal rosettes, retinal folds, and a generalized loss of retinal cells. In addition, the optic nerves were more cellular and paler staining than normal (Mason et al., 2003). Concurrent systemic signs will vary depending on the source of nutrition, duration of the deficiency, and age of the affected animal. In general, severe vitamin A deficiency will be accompanied by unthriftiness, diarrhea, poor growth, decreased appetite, and pneumonia.

The pathogenesis of the optic nerve lesions associated with vitamin A deficiency in calves has been extensively studied (Blakemore et al., 1957; Hayes et al., 1968; Wetzel & Moore, 1940). In calves made deficient for vitamin A from 35 days onward and examined at 5.5–6.0 months of age, the optic foramen of the sphenoid bone became deformed into a narrow, horizontal aperture. Normal development of the optic foramen results from new bone growth across the dorsomedial aspect of the optic canal and resorption of bone ventrally, which results in the progressive ventral displacement of the canal. In vitamin A-deficient calves, osteoblastic activity persisted both dorsally and ventrally, thus resulting in the two surfaces growing toward each other and a narrowed, horizontal slit for an optic canal (van der Lugt & Prozesky, 1989). In addition, the dura mater becomes thicker, and the combination produces compression within the canal, thereby compromising the vascular supply for the optic nerve. Optic nerve changes result mainly from ischemic necrosis, but in some instances when vascularity is maintained, the optic nerve pathology is subtle and may result from retinal degeneration. Constriction of the optic canal could not be produced in 2-year-old animals (Hayes et al., 1968), and the retinal histopathology has been reported in both naturally and experimentally deficient calves. Experimentally, degenerative changes were limited to the outer retinal layers and the RPE and occurred preferentially in the ventral nontapetal retina. Clinically, not only outer retinal degeneration but focal areas of full-thickness retinal degeneration and detachments have been reported (Barnett et al., 1970; Booth et al., 1987; Paulsen et al., 1989; Van Donkersgoed & Clark, 1988).

The clinical signs, history, and ophthalmoscopic signs are very suggestive of hypovitaminosis A. If vitamin supplementation has not been instituted, plasma blood levels of less than 20 µg/dL of vitamin A will confirm the diagnosis (Divers et al., 1986; Kohlmier & Burroughs, 1979; Paulsen et al., 1989). Vision will not be restored in calves that are day blind, but animals with vision and papilledema as well as older animals may benefit from parenteral administration of vitamin A at 440 IU/kg (Divers et al., 1986).

Vitamin A deficiency in pregnant sows has, both experimentally and clinically, been responsible for a high incidence of varying degrees of microphthalmos and blindness in piglets. In extreme cases, anophthalmia was present as well. In the clinical setting, the gilts are usually normal, though slow-healing skin wounds may be noted. Milder deficiencies have additional manifestations of hyperkeratotic facial lesions, posterior limb incoordination, inability to fully extend the carpal joint, and a high neonatal morality rate. In extreme experimental deficiencies of vitamin A, anomalies of cleft palate, accessory ears, and subcutaneous cysts have been produced (Hale, 1935; M aneely, 1951; Watt & Barlow, 1965).


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Wunschmann, A., Shivers, J., Bender, J., et al. (2004) Pathologic findings in red-tailed hawks (Buteo jamaicensis) and Cooper’s hawks (Accipiter cooperi) naturally infected with West Nile virus. Avian Diseases, 48, 570–580.
Ocular examination of animals with systemic disease is an essential diagnostic component of a complete physical examination that can help reduce the list of probable differential diagnoses and can assist in organizing such a differential diagnostic list from most to least likely. In addition, the visual prognosis for the animal may be crucial to owners when deciding how aggressively they wish to pursue diagnostic and therapeutic alternatives.

Diseases affecting the vascular and nervous systems are particularly prone to ocular manifestation. Inspection of the uvea and retina and optic disc of the animal through the transparent cornea and lens permits evaluation of both the peripheral vasculature and central nervous system (CNS), respectively. Since the rate of ocular blood flow is very high, there is increased likelihood that the uveal and retinal vasculature will be exposed to, and possibly filter out, hematogenously spread neoplastic cells and/or infectious organisms.

For the purposes of this chapter, ocular manifestations of systemic disease include any disorder not of primary ocular origin that manifests as ocular clinical signs. Systemic diseases have been categorized according to species (dog; cat; horse; food animals), stage of onset (congenital; developmental; or acquired), and have been alphabetically arranged according to the mechanism and/or cause of the systemic disease (cardiovascular; hematologic; idiopathic; immune-mediated; infectious; metabolic; neoplastic-CNS vs. systemic; nutritional; toxicities). A miscellaneous category has been included for those conditions for which the mechanism underlying the systemic disease is poorly, or not yet, understood.

**CONGENITAL**

**Coat Color-Related Diseases/Conditions**

Complete albinism (complete lack of pigmentation) or partial or localized albinism (an absence or reduction in the degree of pigmentation) is associated with not only the phenotypic appearance of an animal’s coat and skin color but is also associated with conditions affecting the ear and eye. Albinism or partial albinism may result from the failure of migration of neural crest cells (precursors to melanocytes) and hence result in reduced numbers of melanocytes in a nonpigmented area, or may result because of impaired production of pigment due to some intrinsic deficiency in melanin production (e.g., tyrosinase deficiency) but where the number of melanocytes in nonpigmented or hypopigmented areas is normal.

Inherited sensorineural deafness and ocular abnormalities have been linked to coat color genes in many breeds of dogs. Hearing loss related to coat color in dogs typically results from cochleosaccular degeneration and can be associated with the absence of pigment within the stria vascularis of the cochlea (Steel & Barkway, 1989). Coat color is often associated not only with deafness but also with heterochromia iridis, blue irides, and lack of retinal pigment (Strain et al., 1992).

Coat color genetics soon becomes complicated when one considers all of the combinations and permutations of coat colors seen in the numerous breeds of dogs that have been developed. Briefly, the S-gene (white spotting gene) determines body pigmentation pattern. The S-gene has been identified more specifically as the microphthalmia-associated transcription factor (MITF) (Karlsson et al., 2007). There are thought to be four alleles of the S-gene, including the dominant S-allele, and the recessive s* (Irish spotting), s* (piebald), and sw* (extreme-white piebald) alleles (Strain, 2004). Consequently, solid colored animals have at least one copy of the S-allele; colored Bull Terriers must have s’s, breeds like Dalmatians and white Bull Terriers must have two copies of the extreme-white piebald gene (s”s”), while the Whippet and Boston Terrier can be s’s, s”s”, or s”s” (Karlsson et al., 2007; Strain, 2004). Animals homozygous for the recessive S-alleles are predisposed to developing congenital sensorineural deafness. A positive correlation between inherited sensorineural
deafness and blue irides has been reported in the Dalmatian, English Setter, and English Cocker Spaniel (Strain, 2004). This association has a relevant clinical impact, given that approximately 30% of Dalmatians in the United States are unilaterally or bilaterally deaf (blue eyes permitted in breed standard) (Strain et al., 1992), while the incidence of deafness in Dalmatians from Europe is lower (blue eyes not allowed in breed standard) (Wood & Lakhani, 1997). The mode of inheritance of inherited sensorineural deafness associated with white coat colors still remains elusive (Cargill et al., 2004).

A nother gene known as the M- or merle-gene (Clark et al., 2006) has both a dominant (M) and recessive (m) allele and is associated with deafness and ocular abnormalities (see later discussion) (Strain, 2004). In individuals of breeds known to have the dominant merle-gene, including Collies, Shetland Sheepdogs, Great Danes, and Long-haired Dachshunds, heterozygote (MM)—merle colored) animals can be predisposed to unilateral or bilateral inner ear defects resulting in deafness (Gwin et al., 1981; Strain, 2004; Strain et al., 2009). Dogs homozygous for the dominant merle allele (MM)—typically have more white than heterozygotes, or may be completely white) are typically deaf, blind with microphthalmic eyes, and may be sterile (Dausch et al., 1978).

The Australian Shepherd has been studied rather extensively, and the mode of inheritance for the ocular lesions in the merle dog has been demonstrated to be a recessive trait with incomplete penetrance (Gelatt et al., 1981). The embryogenesis of the ocular defects stems from a primary abnormality of the retinal pigment epithelium (RPE) or outer layer of the optic cup (Cook et al., 1991). Ocular lesions described in these dogs include microphthalmia of varying degrees, persistent pupillary membranes, iridal colobomas, dyscoria, corectopia, corneal epithelial dysplasia, scleral staphylomas, goniodysgenesis, cataracts, lenticular colobomas, choroidal colobomas, choroidal hypoplasia, retinal dysplasia, retinal detachments, and retinal fibrosis (Bertram et al., 1984; Gelatt & McGill, 1973). Pituitary and adrenal cysts as well as congenital cardiac anomalies may also be observed inconsistently in the Australian Shepherd (Gelatt & McGill, 1973).

Dwarfism (Skeletal Dysplasia-Osteochondrodysplasia)

Osteochondrodysplasias are disorders characterized by abnormalities in growth and development of bone, cartilage, or both. These forms of skeletal dysplasia have been described in several breeds of dogs. In particular, a syndrome of short appendages with a normal axial skeleton (i.e., short-limbed dwarfism) and ocular lesions, so-called ocular-skeletal dysplasia, has been recorded as being inherited in the Labrador Retriever and the Samoyed (Aroch et al., 1996; Farnum et al., 1992; Meyers et al., 1983). In particular, in both breeds the complete phenotype, including skeletal and ocular defects, is transmitted as an autosomal recessive trait, while ophthalmoscopic findings have indicated a semidominant mode of inheritance in which skeletally normal, heterozygous dogs can have no ophthalmoscopic abnormalities or multiple retinal folds, vitreal membranes, or vitreous degeneration (Goldstein et al., 2010).

The syndrome in the Labrador Retriever was once felt to be recessive for the skeletal lesions and incomplete dominant trait for the ocular lesions (Carrig et al., 1988). Most recently, the causative locus in ocular-skeletal dysplasia of the Labrador Retriever has been termed drd1 and it is mapped to canine chromosome 24, and an insertional mutation in exon 1 of the gene COL9A3 cosegregates with the disease (Goldstein et al., 2010). In this breed, skeletal changes consist of the following: short limbs with the forelimbs being more affected than the hind limbs; prominent elbows and carpi; paws deviated laterally; shortening and bowing of the radius and ulna; hyperextended hind limbs; short and wide tubular bones with thin cortices and flattened and flared metaphyses; delayed development of epiphyseal plates; and renal anomalies (Fig. 35.1.1) (Carrig et al., 1977, 1990). Ocular lesions associated with this syndrome in the Labrador Retriever vary from mild (e.g., retinal folds) to blinding (e.g., retinal detachment), and they typically occur in field-trial lines. In general, those animals manifesting skeletal dysplasia have more severe ocular lesions, but the affected litter may have a spectrum of mild to severe lesions. To date, whether two distinct genetic forms of retinal dysplasia exist in the Labrador Retriever (i.e., one linked with skeletal dysplasia and one distinct from this syndrome) remains unresolved (Barnett et al., 1970). Heterozygous animals may or may not have retinal lesions. Heterozygous individuals may manifest with focal or geographic retinal...
dysplasia (Fig. 35.1.2), which is typically observed as hyper-reflective areas having pigment clumping dorsal to the optic disc. Animals with focal retinal lesions may exhibit a loss of central vision as evidenced by failing to mark downed birds or stationary handlers. Milder degrees of retinal manifestation may have smaller, branching retinal folds and be located in other fundic regions (Nelson & McMillan, 1983). A nimals may be presented as puppies with retinal detachments, or such detachments may occur during the first 2–3 years of life (see Fig. 35.1.2). The emphasis has been placed clinically on the retinal dysplasia. The mechanism of retinal detachment is probably unrelated, however, because many detached retinas have minimal, if any, lesions of dysplasia. Peripheral retinal dialysis occurs and is associated with vitreous traction. Once retinal dialysis occurs, proliferative cellular responses by the ciliary epithelium, RPE, glial cells, and macrophages produce cellular migration onto the vitreous face, which in turn produces contracting forces that detach the retina (Blair et al., 1985a, 1985b). Homozygous dogs inconsistently exhibit a variety of ocular lesions, including those of axial myopia, superficial corneal opacities, varying degrees of cataract formation, prominent hyaloid artery remnants, tapetal hypoplasia, and alterations in optic nerve color and size (see Fig. 35.1.2).

The Samoyed syndrome of ocular-skeletal dysplasia is an autosomal recessive trait (Goldstein et al., 2010). In particular, the causative locus in ocular-skeletal dysplasia of the Samoyed has been termed drd2, and it is mapped to canine chromosome 15 and cosegregates with a 1267bp deletion mutation in the 5′ end of COL9A2 (Goldstein et al., 2010). Skeletal lesions in the Samoyed consist of the following: short forelimbs; premature closure of ulnar growth plates; bowed radius; varus deformity of elbows; valgus deformity of carpi; and domed forehead (Aroch et al., 1996; Meyers et al., 1983). Ocular lesions in this breed consist of focal cortical cataracts, multifocal retinal dysplasia, retinal detachments, prominent hyaloid remnants, and red tapetal fractures or fissures (Meyers et al., 1983). Retinal detachment usually occurs during the first 6 months of life, and it may occur in retinas with no obvious lesions of dysplasia.

Dogs homozygous for drd1 or drd2 can typically be identified by experienced clinicians on physical examination, based upon their skeletal abnormalities (Goldstein et al., 2010). However, dogs heterozygous for drd1 or drd2 may or may not have retinal folds/dysplasia (Goldstein et al., 2010). In addition, some Labrador Retrievers diagnosed clinically as affected with short-limbed dwarfism were confirmed normal when tested for the drd1 mutation, indicating that in this breed, there are likely further, as yet, undetermined genetic mutations to account for retinal folds and/or dwarfism (Goldstein et al., 2010).

**Ehlers–Danlos Syndrome**

Ehlers–Danlos syndrome, or cutaneous asthenia, has been reported in the dog. It is a congenital, inherited syndrome involving collagen, and it is characterized by fragile and easily torn skin. Some animals have excessive joint laxity as well. The mode of inheritance of this syndrome in the dog is autosomal dominant (Barnett & Cottrell, 1987). If the complete syndrome is manifest, ocular lesions may occur. Dogs with the complete syndrome have ocular lesions consisting of lax eyelids, corneal edema, thin sclera, cataracts, bilateral lens luxation, and diffuse cortical cataracts (Barnett & Cottrell, 1987; Matthews & Lewis, 1990). In one case, the lenses were subluxated dorsally and were colobomatous ventrally (Barnett & Cottrell, 1987).

A diagnosis of Ehlers-Danlos syndrome is made based upon a clinical syndrome of skin hyperextensibility, clinical signs associated with skin fragility including easily torn skin, and skin histopathology (routine histopathology with Masson’s trichome staining and ultrastructural examination) (Paciello et al., 2003a). Determination of skin hyperextensibility can be objectively assessed by calculating the extensibility index (Paciello et al., 2003a; Patterson, 1977). The extensibility index is determined by dividing the vertical height of a skin fold (extending a skin fold over the dorsal lumbar area maximally without eliciting pain) by body length (measured from occipital crest to base of tail), then multiplying by 100. A skin extensibility index greater than 14.5% is considered hyperextensible.

Ehlers–Danlos syndrome is incurable and because of its hereditary nature, owners should be advised not to use affected dogs for breeding. Therapy for affected dogs is directed at preventing skin abrasions and pressure sores.

**Hydrocephalus**

Hydrocephalus refers to increased amount of cerebrospinal fluid (CSF) within the cranial vault. Congenital hydrocephalus is common in some breeds of dogs, with toy and brachycehalic breeds at highest risk for the disease, thereby suggesting a hereditary basis in many of these dogs (Selby, 1979). The most common cause of congenital hydrocephalus is a primary congenital stenosis or aplasia of the mesencephalic aqueduct associated with fused rostral colliculi (Selby, 1979). Hydrocephalus resulting from impediment of CSF outflow from the ventricular system is referred to as obstructive or noncommunicating hydrocephalus. In cases where there is no associated malformation in the mesencephalic aqueduct, the cause of congenital hydrocephalus remains unknown. Congenital hydrocephalus may produce enlargement of the calvarium and failure of closure of the suture lines of the skull. Consequently, affected puppies may have a persistently open fontanelle. Clinical signs of hydrocephalus include behavioral changes, ataxia, and seizures. Ventrolateral strabismus is a common ocular manifestation of congenital hydrocephalus due, in part, to enlargement of the calvarium with subsequent impingement on the orbits from the dorsolateral aspects. This consequently pushes the eyes in a ventrolateral direction and produces a "sunset" appearance to the corneas (Fig. 35.1.3). As well, congenital hydrocephalus may cause cranial nerve...
compromise and subsequent ventrolateral strabismus. On relatively rare occasions, hydrocephalus may produce papilledema (Fig. 35.1.4).

**Keratoconjunctivitis Sicca (KCS) and ichthyosiform dermatosis (ID)**

A syndrome of congenital keratoconjunctivitis sicca (KCS) and ichthyosiform dermatosis (ID) (KCSID) has been described in the Cavalier King Charles Spaniel (Barnett, 2006; Hartley et al., 2011). This condition is also known as dry eye and curly coat syndrome. Affected animals present with a congenital atypical hair coat characterized by being rough/curly (Fig. 35.1.5) (Barnett, 2006; Hartley et al., 2011). Clinical signs of KCS are present at onset of eyelid opening. Affected animals will go on to develop progressive dermatologic signs including scaling of the skin over the dorsum and involving the flanks, a harsh/curly hair coat with alopecia, and hyperkeratinized footpads (Hartley et al., 2011). Older animals often have signs of intermittent lameness associated with cracked foot pads and/or sloughed nails with exposure of the nail beds (Hartley et al., 2011). Anecdotally, patients with KCSID have concurrent dental disease, though this has not been specifically examined (Forman et al., 2012).

It is unknown why affected animals develop KCS, though histopathologic examination of the lacrimal glands does not reveal inflammation and, therefore, immune-mediated mechanisms likely do not account for this component of the syndrome (Hartley et al., 2011). Other suggested explanations accounting for KCS in these animals include neurogenic causes, obstruction through lacrimal ductules (Hartley et al.,...
Myasthenia Gravis

Myasthenia gravis is a disease affecting the neuromuscular junction (for complete review, see Shelton, 2002). Myasthenia gravis is either congenital or acquired (for acquired, see “Acquired Immune-Mediated” section). Congenital myasthenia gravis occurs when there is a functional disorder or depletion of nicotinic acetylcholine receptors (AChRs) (Shelton, 2002). Congenital myasthenia gravis has been rarely reported in dogs. Congenital myasthenia gravis is inherited as an autosomal recessive trait in Smooth Fox Terriers (Miller et al., 1983), Jack Russell Terriers (Palmer & Goodyear, 1978), and English Springer Spaniels (Johnson et al., 1975). Given that congenital myasthenia gravis is inherited, owners should be made aware that the dam and sire of affected animals are carriers and should not be used for breeding. Clinical signs associated with congenital myasthenia gravis include generalized muscle weakness that worsens with exercise, possible megaesophagus, facial weakness, and tendon reflexes that weaken with repeated testing. It is also possible, as has been reported in the acquired form, that facial weakness, including a weakened palpebral reflex, may be observed. Animals with congenital myasthenia gravis are seronegative for AChR antibodies (Miller et al., 1983). Diagnosis of congenital myasthenia gravis requires detailed histopathological, immunohistopathological, and ultrastructural examination of skeletal muscle neuromuscular junctions. Prognosis for dogs with congenital myasthenia gravis is poor in most instances. However, clinical signs have been reported to spontaneously resolve at 6 months of age in a manifestation of congenital myasthenia gravis affecting Smooth Miniature Dachshunds (Dickinson et al., 2005). Most animals do not live to reach reproductive maturity and are euthanized because of aspiration pneumonia resulting from megaesophagus.

Quadriplegia and Amblyopia

A syndrome of decreased vision with nystagmus, ataxia, and tremors has been described in the Irish Setter. This syndrome is thought to be inherited as a postnatally lethal, autosomal recessive trait (Palmer et al., 1973; Sakai et al., 1994). Most animals, however, are unable to stand at birth, though walking movements are made that propel them in a “seal-like” manner when prone. Vision is difficult to evaluate in a very young animal, but those affected lack fixation responses as well as menace responses and dazzle reflexes. The pupillary light reflexes (PLRs) are normal. The ocular fundus is normal on fundic examination as well. Electoretinographic findings have not been reported. CNS lesions include degeneration and necrosis of the cerebellar cortex, with severe loss of Purkinje cells. Histopathologic findings do not correlate well with clinical neurologic or ocular findings.
DEVELOPMENTAL INBORN ERRORS OF INTERMEDIARY METABOLISM

Tyrosinemia

Tyrosinemia arises as a result of deficiency in hepatic tyrosine aminotransferase. Tyrosinemia has been described in a young dog presented for dermatologic and ocular problems (Kunkle, 1984). The syndrome was characterized by markedly elevated serum and urine tyrosine levels. Dermatologic lesions consisted of ulcerative lesions of the nasal planum, tongue, footpads, and around the nails (Kunkle, 1984). Ocular lesions consisted of small globes (possibly microphthalmos), conjunctivitis with mucopurulent ocular discharge, superficial corneal scarring and vascularization (possibly from a previous ulcer), axial superficial corneal crystals, and cataracts (Kunkle, 1984).

Lysosomal Storage Diseases

Many lysosomal storage diseases have been identified in dogs. These inborn errors of metabolism are, however, relatively rare diseases that have received a disproportionate amount of investigation, because they represent potential animal models for human syndromes. Storage diseases are characterized by an accumulation of metabolic by-products within lysosomes, the cellular organelles which degrade complex macromolecules. The substrates for catabolism within lysosomes include glycoproteins, mucopolysaccharides, oligosaccharides, proteins, and sphingolipids (Jolly & Walkley, 1997; Skelly & Franklin, 2002). Storage diseases result from a deficiency in a specific catabolic enzyme (i.e., acid hydrolases), which allows the enzyme substrate to accumulate in the lysosomes within cells. Consequently, lysosomal storage diseases are subclassified based upon the type of storage product. Important groups include the glycoprotein storage diseases (MPs), oligosaccharidosis, proteinoses, and the sphingolipidoses (Jolly & Walkley, 1997; Skelly & Franklin, 2002). Specific lysosomal storage diseases are normally named according to the specific accumulated product. Because this excess material is a normal component, the histopathologic changes result from physical distortion of affected cells rather than from a toxic effect. Most lysosomal storage diseases, with known mode of inheritance, are inherited as an autosomal recessive trait. When homozygous, the syndromes are usually severe, thus resulting in neurologic disease and, eventually, death. The eyes in most patients have histopathologic lesions, but clinical ophthalmologic lesions may not be visible (Aguirre et al., 1986; Evans, 1989). Reviews pertaining to lysosomal storage diseases in animals should be consulted for details regarding the clinical signs and diagnosis of lysosomal storage diseases in dogs (see Jolly & Walkley, 1997; Skelly & Franklin, 2002). Antemortem diagnosis of a lysosomal storage disease can be confirmed by lysosomal enzyme analysis (e.g., Lysosomal Disease Testing Laboratory, Jefferson Medical Center, Philadelphia, PA, www.jefferson.edu/lysolab/index.cfm) or with genetic testing for specific canine lysosomal storage diseases. For a relatively complete listing of genetic tests and the laboratories offering testing, please see the Orthopedic Foundation for Animals website (www.offa.org/dna_alltest.html).

Ceroid Lipofuscinosis (CL)

Ceroid lipofuscinoses (CLs) are a group of inherited proteinoses characterized by accumulation of proteins in neurons and other tissues, including the retina. These storage products demonstrate an autofluorescence similar to ceroid and lipofuscin, lipopigments that accumulate normally with aging. However, ceroid and lipofuscin are not detected in appreciable quantities in these diseases. Subunit c of mitochondrial adenosine triphosphate (ATP) synthase and sphingolipid activating proteins (SAPs)-A and SAP-D have been identified as major constituents of the lysosomal storage products in human forms of CL (Palmer et al., 1992; Tynela et al., 1993). SAP-A and SAP-D accumulation, but not the subunit c of ATP-synthase, has been described in an adult onset form of CL in Miniature Schnauzers (Palmer et al., 1997).

Ceroid lipofuscinosis has been described in cats, cattle, dogs, goats, humans, mice, and sheep (Jolly & Walkley, 1997). Clinical signs can manifest at <6 months of age, as is observed in Dalmatians (Goebel et al., 1988), or may develop into adulthood as is seen in English Setters and Tibetan Terriers. Longevity of affected dogs is variable. Affected Tibetan Terriers can live up to 10 years of age while other breeds of dogs, including the English Setter, develop acute clinical signs at approximately 1 year of age and die approximately 1 year later (Koppang, 1988). Diminished vision, most noticeable in dim-light conditions, is typically the first presenting sign of CL. Over time, blindness develops in most instances, except for individuals with a late-onset, adult form (e.g., Tibetan Terriers) (Katz et al., 2005b). Additional abnormalities also evident with CL include confusion, nervousness, unprovoked aggression toward people, inappropriate urination/defecation, difficulty prehending food or water, wide-based stance, ataxia, and hypermetria. Nonambulatory tetraparesis may be observed in later stages of CL (Evans et al., 2005).

The English Setter and Tibetan Terrier have been studied extensively, but the disease has been observed and described in the American Bulldog, American Cocker Spaniel, American Staffordshire Terrier, Australian Blue Heeler, Australian Shepherd, Border Collie, Chihuahua, Dachshund, Dalmatian, Miniature Schnauzer, Polish Owczarek Nizinny, and Saluki (Abitbol et al., 2010; Evans et al., 2005; Jolly et al., 1994; Koppang, 1970; Nakamoto et al., 2011; Narfstrom et al., 2007; O’Brien & Katz, 2008; Sisk et al., 1990; Smith et al., 1996; Wrigstad et al., 1995). In the English Setter, clinical signs of blindness, seizures, and decreased mentation develop at approximately 12–14 months of age. Although the animals are blind, electroretinogram (ERG) amplitudes are only diminished...
by 30%-40% (Berson & Watson, 1980). Histopathologically, cellular inclusions of stacked membranes are present in the RPE, ganglion cells, and other retinal neuronal cells (Neville et al., 1980). Despite these latter findings, ophthalmoscopic lesions have not been noted in the English Setter. In the Polish Owczarek Nizinny breed, fundic lesions may be normal or may consist of grayish plaque-like spots in the central tapetal and in the nontapetal fundus, areas of tapetal hyperreflectivity, and generalized vascular attenuation in advanced cases (Fig. 35.1.6) (Narfstrom et al., 2007). In the Miniature Schnauzer, mild tapetal hyperreflectivity, mild retinal vascular attenuation, and optic disc pallor have been noted as early as 2.5 years of age (Smith et al., 1996). Peroxidase activity is decreased in the retina and leukocytes, but the exact enzymatic deficiency has yet to be defined (Armstrong et al., 1978; Siakotos et al., 1978). A genetic mutation has been identified as the cause of CL in English Setters (Katz et al., 2005a).

In Tibetan Terriers, abnormal behavioral signs develop at approximately 4-6 years of age, while abnormal retinal function has been reported as early as 7 weeks of age. A study has demonstrated both light and dark-adapted ERG responses to be reduced in amplitude in 7- to 10-year-old dogs (Katz et al., 2005b), while another study reported that ERG responses were nearly undetectable in dogs that were 4-6 years of age (Riis et al., 1992). Behaviorally, Tibetan Terriers with CL have moderate visual impairment in low-light and good vision in bright-light conditions (Katz et al., 2005b). Specifically, poor performance in maze testing and following falling cotton balls and hand movements has been observed in scotopic conditions (Katz et al., 2005b). In dogs ranging between 7 and 10 years of age, ophthalmoscopic examination revealed normal to moderately advanced generalized retinal degeneration. Electoretinography reveals depressed rod cell function in affected dogs. Autofluorescent storage bodies can be observed in Muller cells and neurons within the retina and cerebral and cerebellar cortices (Fig. 35.1.7). Typical ultrastructural characteristics for CL are also observed.

There is no treatment of CL, though experimental therapies have been attempted without clinical success (Vuillemenot et al., 2011). Various genetic tests have been developed for CL in dogs including the American Bulldog, American Staffordshire Terrier, Austrailian Shepherd, Border Collie, Dachshund, English Setter, and Tibetan Terrier (see the Orthopedic Foundation for Animals website, www.offa.org/dna_alltest.html).

**Fucosidosis**

Fucosidosis is an autosomal recessive glycoproteinosis occurring in the English Springer Spaniel (Healy et al., 1984; Kelly et al., 1983). The disease is produced by a deficiency of the lysosomal enzyme α-L-fucosidase. Some glycolipid and oligosaccharide moieties of glycoproteins contain the sugar, fucose. Deficiency of lysosomal α-L-fucosidase causes the accumulation of these glycolipids and oligosaccharides. The disease is characterized by a progressive decrease in mentation, which begins at approximately 4 months of age. Temp-
perament changes, ataxia, hearing impairment, and ocular signs of diminished vision and nystagmus develop, and death occurs by 4 years of age. Vision impairment usually occurs later, though it may be the presenting complaint. While retinal ganglion cells are vacuolated from the accumulation of substrate, ophthalmoscopic lesions have not been reported with the visual impairment in the English Springer Spaniel (Healy et al., 1984; Keller & Lamarre, 1992; Kelly et al., 1983). The diagnosis is confirmed on the basis of determining α-1-fucosidase activities in plasma and leukocytes and/or through genetic testing (Skelly et al., 1999). Experimental treatment with intrathecal administration of recombinant α-1-fucosidase has demonstrated decreased oligosaccharide accumulation in the CNS, peripheral lymph nodes, and liver, though clinical success of this treatment is unknown (Kondagari et al., 2011).

Galactocerebrosidosis (Globoid Cell Leukodystrophy, Krabbe’s Disease, Galactosylceramide Lipidosis)

Galactocerebrosidosis, or globoid cell leukodystrophy or Krabbe’s disease, is a member of the inherited sphingolipidoses described in the dog that results from a deficiency in β-D-galactocerebrosidase (GALC) activity (Skelly & Franklin, 2002). The substrate galactocerebroside (i.e., galactosylceramide), a constituent of myelin, and another metabolite of myelin turnover, psychosine (galactosyl sphingosine), accumulate. Psychosine is highly cytotoxic to oligodendroglia and is thought to be the primary metabolite involved in the pathogenesis of the disease ( Miyatake & Suzuki, 1972). Consequently, to the buildup of these toxic metabolites, leukodystrophy results. Galactocerebrosidosis is pathologically characterized by bilaterally symmetric demyelination of the white matter of the brain, spinal cord, spinal nerve roots, and peripheral nerves, and by the accumulation of globoid cells (multinuclear globoid macrophages), predominantly perivascularly. Galactocerebrosidosis is an autosomal recessive trait in West Highland White and Cairn Terriers (Capucchio et al., 2008; Wenger et al., 1999), Australian Kelpies ( Fletcher et al., 2010), and Irish Setters ( McGraw & Carmichael, 2006). Galactocerebrosidosis in Irish Setters has been characterized by an insertion mutation of 78 base pairs (bp’s) in the sequence of the GALC cDNA consisting of 16bp of insertion site duplication and 62 bp of sequence derived from the U4 small nuclear RNA ( McGraw & Carmichael, 2006).

Clinical signs of globoid cell leukodystrophy in dogs are generally rapidly progressive (2–6 months) and develop at a young age (2–6 months of age). Cerebellar signs or progressive paraparesis and paraplegia are the predominant clinical manifestations. Visual deficits and blindness may result late in the course of disease, but ophthalmoscopic lesions have not been observed ( Aquirre et al., 1986). Genetic testing can be used to identify homozygotes and heterozygotes of the mutation for galactocerebrosidosis in West Highland White and Cairn Terriers ( Wenger et al., 1999) and Irish Setters ( McGraw & Carmichael, 2006).

**GM 1-Gangliosidosis**

GM 1-gangliosidosis is a member of the sphingolipidoses. A deficiency of lysosomal hydrolase, β-galactosidase, produces an accumulation of GM1-ganglioside in the cerebral cortex and visceral organs. Such deficiencies have been reported in cats, cattle, humans, mice, and sheep. With respect to dogs, GM 1-gangliosidosis is an autosomal recessive condition seen in Alaskan Huskies, English Springer Spaniels, mixed breed-Beagles, Portuguese Water Dogs, and Shiba Inus ( Altroy et al., 1992; Muller et al., 2001; Yamato et al., 2003). Abnormal ophthalmoscopic findings in dogs with this disease are limited to (1) central corneal clouding observed in Shiba Inus and Portuguese Water Dogs; (2) vision disturbances seen in Shiba Inus and Portuguese Water Dogs; (3) strabismus observed in mixed breed- Beagles and Alaskan Huskies; and (4) nystagmus observed in English Springer Spaniels, Portuguese Water Dogs, and Alaskan Huskies. For a complete tabular comparison of clinical signs observed between breeds of dogs with GM 1-gangliosidosis, see Yamato et al. (2003). Affected Shiba Inus develop anterior corneal opacities at approximately 10 months of age which arise from accumulation of neutral carbohydrates in the lysosomes of keratocytes with swelling and dysfunction of keratocytes, and subsequent irregular arrangement of collagen fibrils in the cornea (Nagayasu et al., 2008). Histopathologic lesions of membrane-bound inclusions have been demonstrated throughout the brain, spinal cord, and retinal ganglion cells, but only in cattle and cats have clinical ophthalmoscopic lesions been observed. Those ophthalmoscopic lesions were multifocal, white, small spots that probably resulted from elevations of the internal limiting membrane by swollen ganglion cells. Affected animals typically live to 14–15 months of age. Separate genetic mutations have been identified, and genetic tests have been developed for Alaskan Huskies (Kreutzer et al., 2005), Portuguese Water Dogs ( Wang et al., 2000), and Shiba Inus ( Chang et al., 2010; Yamato et al., 2004).

**GM 2-Gangliosidosis**

GM 2-gangliosidosis is caused by a deficiency of hexosaminidase (for review, see Jeyakumar et al., 2002). Hexosaminidase has two subunits, α and β, each coded for by HEXA and HEXB genes, respectively. There are three types of hexosaminidase—hexosaminidase S (αα dimer), hexosaminidase A (αβ dimer), and hexosaminidase B (ββ dimer). In addition, there is a GM 2-activator protein coded for by the GM 2A gene which is necessary for degrading GM 2 ganglioside in concert with hexosaminidase A. In humans, deficiency in the α subunit, and therefore depletion of hexosaminidase A and S, results in classical GM 2-gangliosidosis (Tay-Sachs disease or B-variant). A deficiency in the β subunit, depleting both hexosaminidase A and B, is known as Sandhoff disease or the O-variant. Furthermore, deficiencies in GM 2-activator protein result in GM 2-activator deficiency, also known as the AB-variant. Variant forms of GM-2 gangliosidosis have been reported in...
the Japanese Spaniel (A B variant gangliosidosis) (J eyakumar et al., 2002), the German Shorthair Pointer (Tay-Sachs disease) (Singer & Cork, 1989), and also in the Golden Retriever and Toy Poodle (Sandhoff disease) (Tamura et al., 2010; Yamato et al., 2002). The Golden Retriever with Sandhoff disease demonstrated abnormal neurological signs including vision loss commencing at 11 months of age (Yamato et al., 2002). A 15-month-old affected Golden Retriever presented with progressive neurological abnormalities including blindness, bilaterally weak palpebral reflex, and miosis with absent PLRs bilaterally (Matsuki et al., 2005). Magnetic resonance imaging (M R I) of this dog’s brain demonstrated lesions similar to M R I reports in humans affected with Sandhoff’s disease. In particular, M R I showed bilaterally symmetrical T2 hyperintensity and T1 hypointensity in the nucleus caudatus, and cerebrocortical atrophy, primarily in the temporal lobe of this affected dog (Matsuki et al., 2005).

Mucopolysaccharidoses

The M P Ss are a group of diseases characterized by defective metabolism of mucopolysaccharides (glycosaminoglycans). Five types of M P S have been identified in dogs (M P S I, II, III, VI, and VII).

MPS I (Hurler syndrome) has been described in the Plott Hound, and other breeds of dogs, as a deficiency of α-L-iduronidase (Shull et al., 1982). The result of this enzyme deficiency is the tissue accumulation and urinary excretion of dermatan and heparan sulfate (glycosaminoglycans) (Jolly & Walkley, 1997). Affected dogs have stunted growth, excessive joint laxity, multiple degenerative joint disease, and cardiac valvular disease, and develop diffuse corneal opacities from the accumulation of substrate in the keratocytes. High-dose intravenous enzyme replacement therapy (IVERT) has been shown to reduce glycosaminoglycan accumulation within the corneal stroma (Newkirk et al., 2011). High-dose IVERT is also more beneficial if begun earlier in the course of the disease (Newkirk et al., 2011).

MPS II (Hunter syndrome) has been reported in a Labrador Retriever and results from a deficiency in iduronate-2-sulfate sulfatase (Wilkerson et al., 1998). MPS II is unusual, in comparison to the autosomal modes of inheritance of most lysosomal storage diseases, as it is inherited as an X-linked trait. As is seen in MPS I, dermatan and heparan sulfate accumulate in tissues and are excreted in the urine (Wilkerson et al., 1998). One affected dog reported to have MPS II was 3 years of age with a history of progressive incoordination (Wilkerson et al., 1998). The dog was thin yet well-muscled, had labial mucosal thickening, premature graying of hair on the face and the withers, coarse facial features, hyperextended carpi, and macrodactylyia. Neurologically, the animal demonstrated asymmetric ataxia, proprioceptive deficits. With regard to ophthalmic findings, this animal demonstrated positional vertical and rotary nystagmus, multifocal corneal opacities in one of its eyes, and an exaggerated PLR with hippos. This animal had hepatomegaly and generalized osteopenia of its axial skeleton. Light microscopy revealed intracytoplasmic vacuoles of various cell types, including the iris pigment epithelium. Definitive diagnosis was made biochemically by comparing iduronate-2-sulfatase activity in fibroblasts from the affected dog and two normal dogs.

MPS III (Sanfilippo syndrome) is a storage disease that develops due to a lack of one of four different enzymes which include heparan sulfate sulfamidase (MPS IIIA), α-N-acetylg glucosaminidase (MPS IIIB), acetylc0A:α-glucosaminide-N-acetyl transferase (MPS IIIC), and N-acetylg glucosamine 6 sulfatase (MPS IIID). Each of these enzymes acts on heparan sulfate, and their deficiency results in cellular accumulation and urinary excretion of heparan sulfate. MPS III has been reported, and the genetic mutation identified, in Wire-haired Dachshunds (MPS IIIA) (Aronovich et al., 2000), Schipperkes (MPS IIIB) (Ellinwood et al., 2003), and New Zealand Huntaway Dogs (Yogalingam et al., 2002); however, no ocular abnormalities have yet been observed in dogs with MPS III. Clinical signs generally develop from 18 months of age and manifest as mainly cerebellar disease. A recent pathologic study of MPS IIIA disease in Huntaway dogs documented histopathological and ultrastructural abnormalities in affected dogs as a means of characterizing them as a model for testing therapeutic methodologies for the analogous disorder in children (Jolly et al., 2007).

MPS VI (Maroteaux-Lamy syndrome), caused by a deficiency of the lysosomal enzyme arylsulfatase-B, has been reported in Chesapeake Bay Retrievers (Haskins et al., 2002), Miniature Schnauzers, Miniature Pinschers, and Welsh Corgis (Neer et al., 1995). Aaryl sulfatase-B hydrolyzes dermatan sulfate; therefore, lack of this enzyme results in lysosomal accumulation and urinary excretion of dermatan sulfate. Corneal opacities are seen with this condition in dogs. Thickening of the sclera and the optic nerve sheath with atrophy of the optic nerve are seen in addition to corneal opacities in humans.

MPS VII (Sly syndrome) resulting from a deficiency of β-D-glucuronidase, has also been described in two puppies (Haskins et al., 1984) and has subsequently been developed as an experimental canine model (Haskins et al., 1984). β-D-glucuronidase deficiency results in impaired catabolism of chondroitin, dermatan, and heparan sulfates (Schuchman et al., 1989). Consequently, these glycosaminoglycans accumulate in tissues and are excreted in the urine (Silverstein et al., 2004). Corneal opacification and systemic lesions are similar to cases of MPS I. Hepatomegaly may be present, and corneal lesions have a diffuse, fine granular appearance with some peripheral edema and focal central cholesterol deposits (Silverstein et al., 2004). Histopathologically, vacuolated cytoplasmic inclusions have been detected in cells of the corneal stroma, and RPE (Silverstein et al., 2004) and retinal degeneration have been reported in one dog affected with MPS VII (Haskins et al., 1984). Enzymatic and DNA-based tests are used to diagnose this condition (Ray et al., 1999; Silverstein et al., 2004). Studies suggest that intravenous gene therapy may be useful for the treatment of this disease (Ponder et al., 2002; Wang et al., 2006).
Chapter 35: Ocular Manifestations of Systemic Disease

SECTION IV

Howard & Nielsen, 1965; Leblanc et al., 2011; Littman et al., 1988; Sansom & Bodey, 1997). Secondary hypertension is now recognized as being a common complication of renal disease (60%–80% of cases), hyperadrenocorticism (59%–86% of cases), pheochromocytoma (>50% of cases), diabetes mellitus, primary aldosteronism, hypothyroidism, and hyperthyroidism (Dimski, 1988; Howard & Nielsen, 1965; Leblanc et al., 2011; Ortega, 1996). The consequence of experimental ocular vascular hypertensive changes is an initial vascular constriction in the retinal arterioles in response to increased blood pressure; when sustained, it results in occlusion and ischemic necrosis of the vessel walls, with resultant increased vascular permeability. Serous retinal exudates, hemorrhages, and edema also result. Choroidal vascular changes result in subretinal fluid and retinal detachment (Keyes, 1937). Ocular lesions associated with canine hypertension include tortuous retinal vessels, variable-sized retinal and preretinal hemorrhages, papilledema, variable degrees of retinal detachment (Fig. 35.1.8), and tapetal reflectivity changes. Potential complications of systemic hypertension include anterior segment and vitreous hemorrhage, uveitis, and glaucoma (Kern & Riis, 1980; Keyes, 1937; Paul & Ward, 2003; Rubin, 1975). Hypertension should therefore be ruled out when presented with intraocular hemorrhage or bullous retinal detachment of unknown origin.

The goals of antihypertensive therapy include lowering blood pressure and slowing the progression of target organ damage caused by chronic hypertension. Successful therapy requires good client compliance with frequent reassessment.

ACQUIRED
Cardiovascular Diseases
Cerebrovascular Accidents

Cerebrovascular accidents occur much less frequently in dogs than in people (Joseph, 1988; Platt & Garosi, 2003; Thomas, 1996). However, with the ever-increasing access to MRI, cerebrovascular disease in dogs is being recognized more frequently (Garosi et al., 2005). Cerebrovascular accidents, or strokes, can be the result of cerebral hemorrhage (hemorrhagic stroke) from systemic hypertension, coagulopathies, or trauma. Cerebrovascular accidents can also arise from blockage of blood flow to the brain (ischemic stroke), resulting from thrombosis, embolic events, atherosclerosis, vasculitis, or neoplasia. Regardless of the cause of the cerebrovascular accident, ocular manifestations of impaired brain function may manifest and will vary according to the neuroanatomic location of the cerebrovascular accident. Because cerebrovascular accidents are acute, clinical signs are acute ± progressive in nature. Ophthalmic manifestations of cerebrovascular disease may occur at the time of the cerebrovascular accident or develop shortly thereafter. In addition, considering that cerebrovascular accidents typically affect relatively large areas of the brain, abnormal neuro-ophthalmic findings have not been reported as the sole manifestation of cerebrovascular accidents in dogs. For review on cerebrovascular accidents in dogs, see Garosi, (2010) and Garosi & McConnell (2005).

Hypertension

Systemic arterial blood pressure is the product of cardiac output (CO) (CO = heart rate × stroke volume) and total peripheral resistance. Any factor causing persistent elevation in one or more of these three parameters of blood pressure can cause systemic hypertension. When hypertension is associated with an underlying causative disease, it is called secondary hypertension. Hypertension in veterinary patients is typically secondary hypertension. It should be noted, however, that primary (essential) hypertension has been described, although rarely, in dogs (Bovee et al., 1989; Littman et al., 1988). Primary hypertension is hypertension resulting from unknown reasons. Previously, the high “normal” range of systolic blood pressure for dogs was reported to be between 160 and 180 mmHg. Renal damage in dogs has been reported to progress with systolic blood pressures in this range, however (Finco, 2004). Consequently, systemic hypertension is defined as a calm animal having repeatable systolic blood pressure measurements greater than 160 mmHg and/or diastolic blood pressure measurements greater than 100 mmHg (Stepien, 2005). It should be noted, however, that results of a large epidemiological study that evaluated blood pressure in clinically normal dogs found that sight hounds had higher blood pressures compared to other breeds (Bodey & Michell, 1996).

Hypertension-induced (hypertensive) retinopathy has been described, not uncommonly, in the dog (Gwin et al., 1978; Howard & Nielsen, 1965; Leblanc et al., 2011; Littman et al., 1988; Sansom & Bodey, 1997). Secondary hypertension is now recognized as being a common complication of renal disease (60%–80% of cases), hyperadrenocorticism (59%–86% of cases), pheochromocytoma (>50% of cases), diabetes mellitus, primary aldosteronism, hypothyroidism, and hyperthyroidism (Dimski, 1988; Howard & Nielsen, 1965; Leblanc et al., 2011; Ortega, 1996). The consequence of experimental ocular vascular hypertensive changes is an initial vascular constriction in the retinal arterioles in response to increased blood pressure; when sustained, it results in occlusion and ischemic necrosis of the vessel walls, with resultant increased vascular permeability. Serous retinal exudates, hemorrhages, and edema also result. Choroidal vascular changes result in subretinal fluid and retinal detachment (Keyes, 1937). Ocular lesions associated with canine hypertension include tortuous retinal vessels, variable-sized retinal and preretinal hemorrhages, papilledema, variable degrees of retinal detachment (Fig. 35.1.8), and tapetal reflectivity changes. Potential complications of systemic hypertension include anterior segment and vitreous hemorrhage, uveitis, and glaucoma (Kern & Riis, 1980; Keyes, 1937; Paul & Ward, 2003; Rubin, 1975). Hypertension should therefore be ruled out when presented with intraocular hemorrhage or bullous retinal detachment of unknown origin.

The goals of antihypertensive therapy include lowering blood pressure and slowing the progression of target organ damage caused by chronic hypertension. Successful therapy requires good client compliance with frequent reassessment.

of the blood pressure. If an underlying cause of the hypertension has been identified, the primary condition should be addressed therapeutically, when possible. However, even if the presumed underlying cause of the hypertension is controlled, antihypertensive therapy is typically required long term. The number of dogs that are naturally hypertensive is small when compared to the number of cats. As such, there is limited information available regarding effective antihypertensive medications in hypertensive dogs. The current first-line antihypertensive agents of choice in the dog are angiotensin-converting enzyme inhibitors or calcium channel blockers (usually amlodipine).

**Hematologic Diseases**

**Anemia**

Anemia is the reduction in red blood cells (RBCs) per volume of whole blood. Anemia is classified as regenerative if there has been a normal bone marrow response to erythropoietin (e.g., usually occurs with blood loss or hemolytic disease), or nonregenerative if the normal reticulocyte response is lacking (e.g., may occur with chronic extra-narrow disease which reduces RBC survival time, selective erythropoietin depression, insufficient erythropoietin release, or a combination of these factors) (Rebar et al., 2005a). Severe anemia often manifests systemically as varying pallor of mucous membranes, cool mucous membranes, tachycardia, polyptemia, weakness, as well as signs specific to the underlying primary condition. Conjunctival pallor is even used as an indicator of anemia due to gastrointestinal parasitism in sheep and goats (Kaplan et al., 2004; Vatta et al., 2001). Ocular manifestations of severe anemia include pale retinal vasculature, varying degrees of retinal hemorrhage, and subtle changes in tapetal reflectivity. Retinal hemorrhages are more likely to be observed, however, and are more dramatic if accompanied by thrombocytopenia (Carraro et al., 2001; Shelah-Goraly et al., 2009). Small intraretinal hemorrhages are typical and may reabsorb quickly with correction of the anemia, but pigmentary disturbances may be a residual retinal alteration. The pathogenesis of the retinal hemorrhage is postulated to be from hypoxia to the vessel walls as a consequence of the anemia (Carraro et al., 2001). Extreme pallor to the retinal vessels may mimic the appearance of generalized/diffuse retinal degeneration/atrophy, with the exception of the marked tapetal hyperreflectivity present in the latter syndrome. In a recent prospective study evaluating the prevalence and severity of ocular lesions in dogs with anemia and/or thrombocytopenia compared to healthy dogs, both the prevalence and severity of ocular lesions were significantly associated with thrombocytopenia but not with anemia (Shelah-Goraly et al., 2009). In particular, of the 17 dogs with anemia alone, 15 out of 17 had no ocular lesions while only 1 out of 17 had focal retinal edema and 1 out of 17 had subconjunctival pectchial while no dogs with anemia alone had severe ocular lesions.

**Hyperlipidemia**

Hyperlipidemia refers to an elevation in plasma concentrations of cholesterol and/or triglycerides, and arises due to a disturbance in plasma lipoprotein metabolism (Watson, 1993). Hyperlipidemia represents an abnormal finding in fasted dogs and, when present, is indicative of either increased production or reduced degradation of lipoproteins (Watson, 1993). Because triglycerides are transported in the blood by various proteins, the term hyperlipoproteinemia is often used. Post-prandial hyperlipidemia is a common cause of hyperlipidemia in the dog. It has been demonstrated that chronic obesity also results in elevations in serum cholesterol and triglycerides (Jeuette et al., 2005). Pathologic elevations in plasma lipids and lipoproteins are classified as primary (i.e., familial or genetic origin) or secondary (i.e., develop as a consequence of an underlying disease) (Crispin, 1993; Rogers et al., 1975; Watson, 1993). Primary hyperlipidemia/hypercholesterolemia has been described in various breeds including the Beagle, Briard, Collie, Miniature Schnauzer, and Shetland Sheepdog (Jeuette et al., 2004; Manning, 1979; Sato et al., 2000; Watson et al., 1993; Whitney, 1987). Hyperlipidemia is seen in a variety of systemic diseases including hypothyroidism, diabetes mellitus, hyperadrenocorticism, pancreatitis, and renal (e.g., nephrotic syndrome) as well as hepatic (e.g., cholestasis) diseases (Watson, 1993). Common diseases associated with secondary hypercholesterolemia in the dog are hypothyroidism, diabetes mellitus, and pancreatitis.

Depending on the quantity and class of elevated lipoprotein, hyperlipidemia may produce ocular lesions. In the dog, high-density lipoprotein (HDL) is the major carrier of cholesterol, whereas the triglycerides are carried by chylomicrons, very low-density lipoprotein (VLDL), or both. Visible lipemia in the dog is produced by elevations of triglyceride levels, and it can be detected in the ocular vessels of the conjunctiva and retina (i.e., lipemia retinalis) as pink, engorged vessels (Wyman & McKissick, 1973). It is most easily observed in the retinal vessels over the nontapetal region (Sigler, 1977; Wyman & McKissick, 1973). Hyperlipidemia may also manifest with lipids in the anterior chamber (Crispin, 1993; Kern & Riis, 1980; Nell et al., 1995). A prerequisite for gaining access to the anterior chamber by the large, lipid-laden molecules is alteration of the blood–aqueous barrier, presumably resulting from preexisting uveitis. It is unclear, however, whether the lipids incite or are the result of uveitis. The syndrome is usually unilateral, which would argue against hyperlipidemia-inciting uveitis.

Hyperlipidemia characterized by elevated cholesterol levels may result in corneal lipidosis with varying patterns. A rapid, rather diffuse, and bilateral corneal stromal syndrome has been observed in association with elevated cholesterol levels in hypothyroid dogs. Ocular irritation appears to accompany this syndrome as well, because marked conjunctival hyperemia has been noted (Kern & Riis, 1980). Animals with lipid keratopathy or depositions of superficial plaque-like lesions associated with vascularization often have elevated
Hyperviscosity Syndrome

Hyperviscosity syndrome comprises single or multiple clinicopathologic abnormalities resulting from increased serum viscosity. The severity of hyperviscosity syndrome is linked to the size, shape, type, and concentration of large molecules (e.g., immunoglobulins [Ig]) in the bloodstream. This syndrome is seen with IgA, IgG, or IgM macroglobulinemia (Braund et al., 1978; Center & Smith, 1982; Couto et al., 1984; Giraudel et al., 2002; Hammer & Couto, 1994; Peterson & Meininger, 1997; Ramaiah et al., 2002).

The underlying cause is usually a malignancy, such as lymphoma, chronic lymphocytic leukemia, plasmacytoma, or multiple myeloma, but infectious diseases such as ehrlichiosis may also produce the syndrome (Braund et al., 1978; Center & Smith, 1982; Giraudel et al., 2002; Hammer & Couto, 1994; Harrus et al., 1998; Hendrix et al., 1998; Hoskins et al., 1983; Kirschner et al., 1988; Sansom & Dunn, 1993). The mechanism of producing clinical signs is perhaps multifactorial and is not well understood. Hemorrhage may occur from multiple causes, such as sludging of blood in small vessels, ineffective delivery of oxygen and nutrients to vessel walls, hypertension, coagulation abnormalities as a result of elevated protein levels interfering with clotting factors and platelet function, and thrombocytopenia. The ocular lesions most frequently noted include dilated, tortuous retinal vessels, which may develop kinking or “box carrying,” or venous dilatation and sacculation; papilledema; retinal hemorrhages; intraretinal cysts; and bullous retinal detachments (Fig. 35.1.9). Anterior segment complications such as anterior uveitis and glaucoma may develop as well (Center & Smith, 1982; Hendrix et al., 1998; Kirschner et al., 1988; Sansom & Dunn, 1993).

The diagnosis of hyperviscosity syndrome is made on the basis of demonstrating the hyperproteinemia on serum biochemistry profile combined with serum and urine protein electrophoresis and immunoelectrophoresis. A detailed medical workup is necessary to determine the cause of the hyperproteinemia.

Plasmapheresis may be used to treat the hyperviscosity (Matus et al., 1983). In addition, appropriate antineoplastic
therapy directed at the underlying cause is indicated (Hendrix et al., 1998).

Icterus

Icterus or jaundice is a condition characterized by hyperbilirubinemia and deposition of bile pigments in the skin, sclera, and mucous membranes, causing them to appear a shade of yellow. The sclera is the classic location for detection of icterus given its relative lack of pigmentation. The yellow appearance of icterus may be detected in the intraocular structures as well (e.g., blue irides may turn green (Fig. 35.1.10), and yellow hues may be imparted on the tapetum).

Intravenous Fluid Overload

Ophthalmologists performing consultations for internists may note bullous retinal detachments associated with isotonic fluid administration to patients having varying degrees of renal compromise. This condition begins with multiple, small, subretinal bullae forming in both eyes. The small bullae coalesce to form larger detachments, and eventually, they progress to total retinal detachments associated with a clear subretinal fluid. Retinal hemorrhages are absent, and affected animals have normal blood pressure (Martin, 1999). When observed early in the course of disease, internists are looking for retinal signs of hypertension; when observed late in the course of disease, patients are examined for dilated pupils. Correction of the underlying renal problem or decreasing the fluid intake will cause the fluid to be reabsorbed and the retinas to reattach, even though retinal folds may persist. The exact pathogenesis is unknown, but leakage of solutes into the choroidal extracellular space with drawing of fluid into the interstitium is postulated. A breakdown of the blood-retinal barrier at the RPE is also necessary for subretinal fluid to accumulate. Impaired renal function is another prerequisite, but affected animals are not usually anuric.

Finding bullous retinal detachments without hemorrhages or exudates in animals receiving intravenous fluids for renal disease is suggestive of the disease. The systemic blood pressure is either normal or low on repeated examinations. Therapy should concentrate on decreasing fluid administration, regaining renal compensation, or both.

Polycythemia

Polycythemia is classified as relative or absolute (primary and secondary forms). Relative polycythemia is an increased packed cell volume with normal RBC mass occurring as a result of a reduction in plasma volume as may arise from external losses of body fluids (e.g., diarrhea; burns).

Absolute polycythemia is an increase in total RBC mass, and it may be classified as either primary or secondary (appropriate and inappropriate). A absolute primary polycythemia (i.e., polycythemia vera) has been described in dogs and is an absolute increase in erythropoiesis without an increase in erythropoietin (for review, see Campbell, 1990). The underlying molecular basis of polycythemia vera has yet to be elucidated.

Absolute secondary polycythemia results from altered erythropoietin homeostasis and is described as being appropriate or inappropriate. A absolute secondary appropriate polycythemia occurs as a consequence of persistent hypoxia, and is seen in animals with conditions such as congenital cardiac defects causing right-to-left shunting of blood (Moore & Stepien, 2001). A absolute secondary inappropriate polycythemia, however, results from disease processes which lead to inappropriate secretion and elevation of erythropoietin or an erythropoietin-like substance in the absence of systemic hypoxia. Causes of absolute secondary inappropriate polycythemia include diseases that result in the production of erythropoietin or that cause local hypoxia and trigger erythropoietin synthesis, including malignancies (e.g., cecal leiomyosarcoma (Sato et al., 2002) and renal disease (e.g., renal neoplasia, amyloidosis, inflammation, infection), respectively (Crow et al., 1995; Snead, 2005; Waters & Prueter, 1988).

Polycythemia may manifest as dark, ruddy colored conjunctival and retinal blood vessels that are dilated and tortuous. In addition, bilateral anterior uveitis with concurrent unilateral chorioretinitis has been described in a dog with polycythemia vera (Gray et al., 2003). Treatment varies according to the cause of the polycythemia. In one case of polycythemia vera, treatment with phlebotomy and oral hydroxyurea resulted in resolution of both systemic and ocular signs (Gray et al., 2003). If left untreated, however, retinal detachment and ocular hemorrhage may occur with persistent polycythemia (Lombard & Twitchell, 1978; Martin et al., 1972b).

Thrombocytopenia and Thrombopathies

Thrombocytopenia results from either decreased platelet production, increased removal, sequestration, or any combination
of these (Rebar et al., 2005b). The most common causes of thrombocytopenia include infectious diseases, neoplasia, drug-induced reactions, and immune-mediated diseases (Grindem et al., 1991). In particular, the numerous pathogens implicated in causing infectious thrombocytopenia in dogs include arthropod-borne agents (e.g., Babesia, Borrelia, Cytaxuxoon, Dirofilaria spp., Ehrilichia spp., Leishmania, Rickettsia), viral agents (e.g., canine distemper virus, herpesvirus, parvovirus, adenovirus), and fungal and bacterial organisms (e.g., Candida, Histoplasma, Leptospira spp.). Thrombocytopenia is also seen in association with (1) many forms of neoplasia including lymphoma, leukemia, and multiple myeloma; (2) medications which impair platelet production, or cause secondary immune destruction of the platelets (e.g., chloramphenicol, azathioprine, cyclophosphamide, doxorubicin); or (3) it may develop as an idiopathic or primary immune-mediated condition. In a recent prospective study evaluating the prevalence and severity of ocular lesions in dogs with anemia and/or thrombocytopenia compared to healthy dogs, both the prevalence and severity of ocular lesions were significantly associated with thrombocytopenia but not with anemia (Shelah-Goraly et al., 2009). In particular, of the 36 dogs with thrombocytopenia alone, 9 out of 36 had mild ocular lesions, including conjunctival (n = 3), iridal (n = 1) or retinal petechiae (n = 3), focal retinal edema (n = 2), and 6 out of 36 had severe ocular lesions, including hyphema (n = 5) and retinal hemorrhage (n = 1) (Shelah-Goraly et al., 2009).

Thrombopathies are blood coagulation disorders as a result of platelet dysfunction and are either acquired or inherited (Rebar et al., 2005b). Disease processes associated with thrombopathies include anemia, disseminated intravascular coagulation (DIC), liver failure, and uremia (Rebar et al., 2005b). Regardless of the origin, both thrombocytopenia and thrombopathies are rather frequent causes of ocular and periocular hemorrhage. The presence of bleeding signs at a given platelet level varies between individuals, but platelet counts are usually less than 50,000 cells/µL when ocular petechiae form. A cute loss of platelets is more likely to manifest as hemorrhage at a given level than is a gradual loss of platelets. Petechiae in the ocular fundus are often present without visible petechiae in the skin and other mucous membranes. Therapy is directed at the underlying cause, and if bleeding signs are severe, transfusion of fresh whole blood or platelet-rich plasma is indicated.

**Idiopathic Systemic Diseases**

**Canine Idiopathic Granulomatous Disease**

Idiopathic granulomatous disease in the dog is considered to be immune-mediated because of the absence of any demonstrable infectious agent and because favorable responses to immunsuppressive doses of corticosteroids or other immunsuppressive drugs have been reported (Carpenter et al., 1987; Collins et al., 1992; Gionfriddo et al., 2003). Syndromes of sterile granulomatous inflammation are poorly defined and are relatively rare. An idiopathic perianidnexal multinodular granulomatous dermatitis syndrome has been described that, in one instance, was associated with anterior uveitis (Collins et al., 1992). Multiple sterile granulomas of the eyelids, conjunctiva, and sclera that accompanied dermal granulomas have been described in another case (Collins et al., 1992). Bilateral orbital granulomatous disease that was very responsive to corticosteroids and required therapy indefinitely for remission has been noted (Martin, 1999). Eventually, while this animal was off therapy, massive granulomatous disease developed in the chest and abdomen. Necropsy and histopathology did not reveal the cause of the granulomas. A case of idiopathic ocular and nasal granulomatous disease in a dog without dermatologic lesions has been described and may be a different form of the classically described canine idiopathic granulomatous disease (Gionfriddo et al., 2003). In this case, bilateral limbal and intranasal granulomatous masses were observed. These masses were predominantly T-cell rich granulomatous reactions, and the dog responded favorably to immunsuppressive doses of oral prednisolone, topical prednisolone acetate, and azathioprine.

**Dysautonomia**

Canine dysautonomia is an idiopathic disease resulting from a generalized loss of autonomic function. Dogs affected are typically young adults of medium to large physical stature that typically live in rural areas. It is important to note, however, animals ranging in age from 5 weeks to 15 years of age and of a variety of breeds can be affected (Berghaus et al., 2001; Harkin et al., 2002a). Canine dysautonomia has been reported in Europe (Presthus & Bjerkas, 1987; Rochlitz & Bennett, 1983) and the United States (Berghaus et al., 2001; Harkin et al., 2002a; Longshore et al., 1996). The disease is prevalent in dogs living in the midwestern United States, specifically, Kansas and Missouri. Affected dogs present with an acute (days) or subacute (2–3 weeks) history of clinical signs referable to loss of autonomic (sympathetic and parasympathetic) function (Berghaus et al., 2001; Harkin et al., 2002a). Common nonocular clinical signs include regurgitation, vomiting, diarrhea, anorexia, weight loss, dry mucous membranes, and purulent nasal discharge (Harkin et al., 2002a; Longshore et al., 1996). Dogs may present with limited clinical signs that progress to involve more signs of autonomic failure during the course of the disease. Ocular signs include ocular discharge, protruding third eyelid, mydriasis, and a reduction in Schirmer tear test (STT) values (Harkin et al., 2002a, 2002b; Longshore et al., 1996). Ocular pharmacologic testing with topical 0.05% pilocarpine in dogs with mydriatic pupils, and signalment, history, and clinical signs consistent with dysautonomia, provide useful information supporting a diagnosis of dysautonomia. In affected dogs, instillation of 0.05% pilocarpine will cause rapid (<45 minutes) miosis compared to unaffected animals (O’Brien & Johnson, 2002). Severe neuronal degeneration has been reported in a variety of autonomic ganglia, including the cranial cervical and ciliary.
ganglia (Harkin et al., 2002a). In addition, neuronal degeneration of various brainstem nuclei, including the facial, oculomotor, and motor nucleus of the trigeminal nerve, has also been reported (Harkin et al., 2002a). At least 85% of dogs affected with dysautonomia succumb to the disease and are euthanized (Harkin et al., 2002a).

**Granulomatous Meningoencephalitis**

Granulomatous meningoencephalitis (GME) is an idiopathic nonsuppurative meningoencephalomyelitis seen in dogs (Braund, 1985). Histopathologically, GME is characterized by perivascular cuffing with mononuclear cells (Braund, 1985). One study has demonstrated that perivascular cuffs were composed of a heterogeneous population of major histocompatibility complex (MHC) class-II antigen-positive macrophages and mainly CD3 antigen-positive lymphocytes, supporting a hypothesis of T-cell-mediated, delayed-type hypersensitivity of an organ-specific autoimmune disease (Kipar et al., 1998). Proposed pathogenesis for GME have included a primary immune-mediated phenomenon, precancerous form of lymphoma, and various infectious etiologies. Studies have failed to identify an infectious etiology from the brains of dogs affected by GME (Schatzberg et al., 2005).

The disease is typically seen in young small breeds, although any breed or age of dog may be affected. GME is characterized typically by neurologic signs suggestive of multifocal CNS lesions that, at least temporarily, are responsive to systemic corticosteroids or other immunosuppressive therapies. GME is described as being one of three types, namely: (1) disseminated; (2) focal; or (3) ocular. Any combination or permutation of these forms can occur. In the latter form, GME may involve the optic nerves, thus producing a syndrome of acute blindness, papilledema, retinal and peripapillary hemorrhages, and occasionally, extension into the globe, which in turn produces retinal detachments and retinal infiltrates (Fischer & Wi-K wand, 1971; Smith et al., 1977). Confinement to the retrobulbar optic nerves may limit ocular lesions to blindness and dilation of pupils (Braund, 1985; Fischer & Wi-K wand, 1971; Garmer et al., 1981; Russo, 1979; Smith et al., 1977; Thomas & Eger, 1981). A definitive antemortem diagnosis is difficult to make, but multifocal CNS deficits, increased CSF protein levels, pleocytosis with mononuclear cells, and a response to corticosteroids are suggestive (Bailey & Higgins, 1986). Definitive antemortem diagnosis can be made based on the above in concert with brain biopsy (M unana & Luttgen, 1998).

Treatment involves aggressive use of immunosuppressive corticosteroids with or without radiation therapy (M unana & Luttgen, 1998) or immunosuppression using a combination of corticosteroids with one or more of cytosine arabinoside (Menaut et al., 2008; Zarfoss et al., 2006), azathioprine (Wong et al., 2010), leflunomide (Gregory et al., 1998), or cyclosporine-A (Adamo & O’Brien, 2004; Nuhsbaum et al., 2002). Prognosis for survival varies from weeks to years, but regardless, clinical signs progress and dogs will succumb to the disease (M unana & Luttgen, 1998). Histopathologically, lesions are characterized by dense accumulations of histiocytes, lymphocytes, plasma cells, and monocytes in a perivascular pattern. Aggregates or granulomas may develop from the perivascular cuffs of cells. Lesions can be found in the white matter of the cerebrum, brainstem, cerebellum, and cervical spinal cord, but the gray matter is often involved as well. Granulomatous aggregates may produce space-occupying lesions and have features of neoplasia (Braund, 1985; Thomas & Eger, 1981).

**Sudden Acquired Retinal Degeneration Syndrome (SARDS)**

Sudden acquired retinal degeneration syndrome (SARDS) is an idiopathic blinding condition consisting of acute blindness in the absence of funduscopy disease (early in disease) and clinical signs suggestive of an underlying metabolic disease. SARDS has been recognized among dogs in the United States for over two decades (Vainisi et al., 1983). Nevertheless, the cause of SARDS is unknown, and epidemiologic questionnaires have not been suggestive of any common thread for an environmental toxin (Acland et al., 1984). Preliminary investigations into excitotoxins (e.g., glutamate) have found increased levels in the vitreous of affected animals, but the significance of this is unknown (Abrams et al., 1995). Circulating antiretinal antibodies have been found in dogs with SARDS; however, antiretinal antibodies are also found in clinically normal dogs (Bellhorn et al., 1988; Gilmour et al., 2004). Attempts to link SARDS with paraneoplastic processes, as has been shown in human cancer-associated retinopathy, has proven unrewarding (Gilmour et al., 2004). Recently, analysis of tissues from SARDS-affected dogs revealed the presence of immunoglobulin-producing plasma cells in affected retinas which may account for localized intra-retinal production of autoantibodies and subsequent development of an antibody-mediated retinopathy (Grozdanic et al., 2008). In addition, strong complement activity has been documented in the retinas of dogs with SARDS which may account for antibody-mediated neuronal damage (Grozdanic et al., 2008).

In one study, 40%–60% of dogs affected with SARDS were reported to have have systemic signs and altered clinicopathological test results (van der Woerd et al., 1991). Animals are characteristically presented with acute blindness and a normal to near-normal ocular fundus (van der Woerd et al., 1991). Because of the acute onset, most dogs are quite disoriented. In most patients, vision loss occurs over the course of 1–2 weeks, and nyctalopia may be observed (van der Woerd et al., 1991). The mean age of affliction is 8.5–10 years (M iller et al., 1998; van der Woerd et al., 1991). The syndrome occurs predominantly in neutered females, in both pure and mixed breeds, and with a predisposition for Dachshunds (Acland & Aguierre, 1986; Acland et al., 1984; Vainisi et al., 1983, 1985; van der Woerd et al., 1991). A seasonal incidence has been reported as well, with 46% of cases occur-
Many affected dogs have polyuria (PU), polydipsia (PD) (28%–36% of cases), and polyphagia (39%), as well as a history of weight gain (57%). As well, systemic hypertension (4 of 10 dogs) and proteinuria (7 of 10 dogs) have been reported in dogs with SARDS (Carter et al., 2009). Laboratory values are variable, but lymphopenia (30% of cases), lymphopenia with neutrophilia (21%), and abnormal biochemical profiles (68%) may be present. Elevated levels of alkaline phosphatase (30%–40% of cases) and cholesterol (42%) are the most common biochemical changes. A drenocorticotrophic hormone (ACTH) stimulation or a low-dose dexamethasone suppression test may be abnormal (van der Woerdt et al., 1991). Overall, 12%–17% of patients have adrenal profile changes compatible with those of Cushing’s disease, but these changes may be adaptations to other diseases as well (Acland et al., 1984; Carter et al., 2003; Matson et al., 1992; van der Woerdt et al., 1991). These associated alterations in pituitary function have led to the hypothesis that elevations in melanocyte-stimulating hormone (MSH) may accompany an increased ACTH level. Increased MSH may then lead to increased melanin production by the RPE, which may impair RPE phagocytosis of photoreceptor outer segments and, consequently, result in retinal degeneration (van der Woerdt et al., 1991). Most recently, serum cortisol and sex hormone concentrations were measured prior to and following ACTH stimulation in 13 dogs with SARDS (Carter et al., 2009). Serum cortisol was elevated in 9 of 13 dogs; elevations in one or more sex hormones were found in 11 of 13 patients with SARDS while only one dog had normal ACTH stimulation results (Carter et al., 2009).

On ophthalmic examination, dogs with SARDS appear blind and lack a menace response, while they tend to blink in response to bright light (positive dazzle reflex). The pupils are usually dilated at rest and demonstrate sluggish PLRs (van der Woerdt et al., 1991). Ophthalmoscopic changes during the acute stages are very minimal, with mild retinal vascular attenuation or variability in retinal vascular caliber and changes in tapetal reflectivity. In the early stages, all dogs with SARDS have a characteristic pale optic disc due to decreased retinal thickness of the ventral retina early on in this disease and progressing to involve thinning of all retinal layers, including the photoreceptor layer, in the dorsal and ventral quadrants (Grozdanic et al., 2008).

Optical coherence tomography (OCT) has been used to analyze the structural thickness of retinas of dogs with SARDS; OCT revealed significant retinal thinning even for retinas that appeared relatively normal on funduscopic examination with primary damage of the nerve fiber layer and decreased retinal thickness of the ventral retina early on in this disease and progressing to involve thinning of all retinal layers, including the photoreceptor layer, in the dorsal and ventral quadrants (Grozdanic et al., 2008).

Electroretinography is considered the gold standard for establishing a diagnosis of SARDS. The ERG response is extinguished with SARDS (van der Woerdt et al., 1991). A recent study documented the spectral properties of the PLR in eyes of healthy dogs compared to eyes of SARDS-affected dogs (Grozdanic et al., 2007). Dogs that have SARDS have complete pupillary constriction in response to blue light of a narrow wavelength (480 nm) and high light intensity (200 kcd/m2) most likely due to stimulation of a photosensitive pigment, melanopsin, located in a subpopulation of retinal ganglion cells that can drive PLRs in the absence of photoreceptor activity. When red light of a given wavelength (630 nm) and high light intensity (200 kcd/m2) was used to evaluate PLRs in SARDS-affected patients, the pupils remained fixed and dilated as this wavelength of red light does not activate the melanopsin pathway but rather activates the photoreceptor-mediated pathway which is absent in dogs with SARDS. A portable, diode-based light source with narrow wavelengths for blue and red light that matches the spectral properties of canine visual pigments is available for colorimetric PLR testing (Melan-100 unit; BioMed Vision Technologies, Inc., Ames, IA) (Grozdanic et al., 2008).

SARDS has long been considered an untreatable, irreversible blinding disease of dogs. However, recently, experimental use of intravenous human immunoglobulins (IVIg) has resulted in restoration of limited visual behavior in some SARDS-affected dogs in the early stages of this disease (Grozdanic et al., 2008). Many dogs diagnosed with SARDS would not be suitable candidates for IVIg due to advanced retinal thinning at the time of diagnosis. Most dogs with SARDS still make acceptable house pets provided they adjust well to being blind.

Immune-Mediated Diseases

Dermatologic Diseases

Immune-mediated and allergic skin diseases often produce a facial dermatitis involving the eyelids and conjunctiva. Immune-mediated skin diseases are divided into two main categories: primary autoimmune diseases, in which the disease results from an attack against self-antigens, and secondary immune-mediated disease, in which the disease results from exogenous material inducing autoimmune disease. Such
causes of secondary immune-mediated diseases include bacteria, drugs, and viruses.

The pemphigus complex consists of five autoimmune skin diseases: (1) pemphigus vulgaris, (2) pemphigus vegetans, (3) pemphigus foliaceus, (4) pemphigus erythematosus, and (5) bullous pemphigoid. The pemphigus complex is characterized by autoantibodies directed against intercellular substances. In most cases, facial lesions involve the mucocutaneous regions and are characterized by pustules and vesicles that eventually rupture, thereby leaving erosions and ulcers, crusting, scaling, and hypopigmentation. Discoid lupus erythematosus, a primary autoimmune disease, is also associated with facial dermatitis, consisting of crusts, depigmentation, erosions, and ulcers, which predominantly affects the nasal planum and muzzle; oral ulcers are also described with this disease. Systemic lupus erythematosus, a complex syndrome involving autoimmunity with or without the presence of antinuclear antibodies (ANA), may produce a facial dermatitis and may also be associated with intraocular disease through vasculitis, thrombocytopenia, and severe anemia (Ihrke et al., 1985; Maning et al., 1980; Miller, 1979; Scott, 1981; Scott et al., 1980; Walton et al., 1981).

Allergic dermatitis, urticaria, may arise as a result of flea or food allergies, atopy, drug reactions, or insect bites (Carlotti & Jacobs, 2000; Scott & Miller, 1999; Trepanier, 1999; Zur et al., 2002). Allergic reactions to systemic or topical drugs or drug eruptions often involve the mucocutaneous and cutaneous regions of the head. When caused by a topical drug, the reaction is usually limited to the point of contact, but systemic absorption may produce a generalized reaction. A topry or clinical allergy to environmental antigens involves the face in approximately 80% of cases, and 50% have conjunctivitis (Martin, 1999). Episodes of conjunctivitis frequently exacerbate with flare-ups of skin lesions (Martin, 1999).

The pattern of skin lesions may be suggestive of the diagnosis, but a specific diagnosis of the immune-mediated disease is made on the basis of patient history, skin biopsy with histopathologic and immunofluorescent testing, and autoantibody tests (e.g., the ANA and lupus erythematosis [LE], preparations for systemic and discoid lupus erythematosus). Intradermal skin tests may find specific antigens to which the atopic patient is sensitive (Zur et al., 2002). For a discussion of appropriate treatments for each of these conditions, the reader should consult current dermatology references.

**Juvenile Pyoderma/Cellulitis (Puppy Strangles)**

Juvenile sterile granulomatous dermatitis (i.e., pyoderma/cellulitis) and lymphadenitis is a syndrome of dogs which usually manifests in animals less than 8 months of age (Basset et al., 2005; Hutchings, 2003; Mason & Jones, 1989; Reimann et al., 1989; White et al., 1989). A dult dogs, however, may become affected by this condition (Jeffers et al., 1995; Neuber et al., 2004). One or more puppies in a litter may be involved. Predisposed breeds include the Dachshund, Golden Retriever, Labrador Retriever, Gordon Setter, and Lhasa Apso (Mason & Jones, 1989; Reimann et al., 1989; White et al., 1989). A cute pyoderma affecting mainly the head manifests as pustules which then fistulate and drain, thereby creating a moist, crusty lesion of the pinna, muzzle, and periocular skin (Fig. 35.1.11). Though the lesions appear to be induced by bacteria, they are actually sterile and cannot be transmitted. A bacterial hypersensitivity has been postulated to explain the response to corticosteroids and the explosive course of the disease. During the early stages, a puppy may be presented with only eyelid pustules, but within a few days, the pyoderma may extend to the ears and nose. Regional lymph nodes, particularly the mandibular lymph nodes, become markedly enlarged, and a severe otitis externa is typical as well. Occasionally, puppies will develop a more generalized pyoderma.

Even if the patient is presented with only a blepharitis, the diagnosis should be suspected because of the age of the dog and the bilateral eyelid involvement. Without systemic therapy, the lesions will progress to involve other typical areas. Immunosuppressive doses of systemic corticosteroids, tapered following 3–4 weeks after resolution of the clinical signs, and systemic broad-spectrum antibiotics to treat the secondary bacterial pyoderma, are indicated. Some clinicians prefer treatment with antibiotics for a few days before initiating corticosteroids. Nursing care, consisting of gentle cleansing or soaking of the skin lesions, may also be attempted. With appropriate therapy, prognosis is excellent.
Immune-Mediated Retinitis (IMR)

Immune-mediated retinitis (IMR) is characterized by a sudden onset of complete blindness or night blindness in dogs and has similar and distinguishing features to SARDS (see “SARDS” section). Dogs with IMR typically present with sudden blindness, which is often preceded by months to years of sporadic, temporary bouts of decreased vision, usually night vision. In addition, dogs with IMR may have a history of abnormal pupillary appearance (pupillary dilation in bright light and/or anisocoria with one pupil being dilated). Most dogs with IMR are reportedly healthy; however, some dogs with IMR (20% in one report) also have concurrent health issues including neoplasia and neurological abnormalities. On ophthalmic examination, dogs with IMR appear blind and lack a menace response, while they tend to blink in response to bright light (positive dazzle reflex). Ophthalmoscopic examination of IMR-affected dogs is generally unremarkable; however, a characteristic pale optic disc due to the presence of vascular attenuation of the optic nerve head may be noted, similar to SARDS-affected patients. When assessing PLRs in IMR-affected dogs using colorimetric PLR testing (blue light vs. red light stimulation; please see “SARDS” section), there is a nearly complete absence of the PLR in response to red light stimulation and a normal PLR when blue light is used. Dogs with IMR have detectable ERG waveforms which can be normal, or reduced, or increased in amplitudes, unlike SARDS-affected patients. The pathogenesis of IMR in dogs remains unknown, although it shares similar symptoms to antibody-mediated retinopathies in humans. Retinal autoantibodies have been documented in two of three serum samples from three dogs with IMR. Treatment for dogs with IMR includes oral doxycycline and steroids typically long term. Recovery of the PLR in response to red light stimulation is reported to be the most reliable indicator of therapeutic success. Reevaluation of the ERG waveforms for increases in their amplitudes may also be helpful, as progressive, uncontrolled IMR is often linked with a decrease in retinal electrical activity (Grozdanic et al., 2008).

Keratoconjunctivitis Sicca (KCS)

Keratoconjunctivitis sicca (KCS) is a condition characterized by a decrease in the aqueous tear film beyond that which is compatible with conjunctival and corneal health (Fig. 35.1.12). KCS in the dog has several causes, but one of the most common underlying causes appears to be a multiglandular inflammatory destruction that is most likely immune mediated. Evidence of immune-mediated glandular inflammation is provided by the presence of circulating autoantibodies (i.e., rheumatoid factor [RF] and/or ANA) in a significant number of animals (34% and 40%, respectively), breed specificity, glandular pathology, and the presence of a variety of other diseases in 40% of KCS patients that may have an immune-mediated component. The salivary and thyroid glands are two of the glands that are often involved (in 20% of cases each) concurrently with involvement of the lacrimal glands (Kaswan et al., 1983, 1985; Quimby et al., 1979). Anecdotally, KCS often improves when other systemic problems in the animal improve.

A presumptive diagnosis of suspected immune-mediated KCS is made on the basis of STT results (Hamor et al., 2000), breed predisposition, lack of any history of sulfa administration (for review, see Trepanier, 1999, 2004) or third-eyelid gland excision, and perhaps, involvement of other systems. Recommended treatment is the use of a topical immunosuppressive agent such as cyclosporine (Olivero et al., 1991; Salisbury et al., 1990; Sansom et al., 1995), tacrolimus (Adkins et al., 2003; Berdoulay et al., 2005), or pimecrolimus (Nell et al., 2005), as needed.

Myasthenia Gravis

Myasthenia gravis is a disease affecting the neuromuscular junction (for a complete review, see Shelton, 2002). Myasthenia gravis is either congenital or acquired. Congenital myasthenia gravis occurs when there is a functional disorder or depletion of nicotinic AChRs. Congenital myasthenia gravis is reported rarely in dogs (Flagstad et al., 1989; Oda et al., 1984; Palmer & Goodyear, 1978) and will not be considered further here (see “Congenital” section). Aquired myasthenia gravis is the most common form of myasthenia gravis occurring in dogs. The acquired condition develops due to an autoimmune destruction of AChRs which may occur as an autoimmune condition affecting only the AChR (most common; e.g., Shelton, 1998), part of another autoimmune condition (e.g., hypothyroidism; Levine et al., 2005; Shelton, 1998), or resulting as part of a paraneoplastic syndrome (e.g., thymoma; Lainsese et al., 1996; Paciello et al., 2003b).
Animals with acquired myasthenia gravis can present with either generalized or focal clinical signs. Those animals with generalized myasthenia gravis will have generalized appendicular muscle paresis (weakness) that worsens with prolonged exercise, may have megaesophagus and resultant regurgitation ± aspiration pneumonia, and spinal and cranial nerve reflexes that weaken with repeated testing. A approximately 43% of dogs with myasthenia gravis will have focalized clinical signs in the absence of appendicular muscle weakness (Shelton et al., 1997). Animals with the focal form of myasthenia gravis may present with regurgitation, and/or dysphagia, and/or change in character of vocalization because of megaesophagus, pharyngeal, or laryngeal paresis, respectively (Dewey et al., 1997; Shelton et al., 1990). With respect to the eye, a paretic menace response and/or palpebral reflex may be the predominant clinical sign(s) (Clooten et al., 2003; Dewey et al., 1997; Webb et al., 1997).

A tentative diagnosis of acquired myasthenia gravis is made based on consistent clinical signs combined with immediate short-term improvement in muscular strength (e.g., improved palpebral reflex (Webb et al., 1997) following the administration of the short-acting acetylcholinesterase inhibitor, edrophonium hydrochloride (Tensionon). All presumptive cases of acquired myasthenia gravis should be confirmed by demonstrating the presence of circulating muscular AChR autoantibodies (see the Comparative Neuromuscular Laboratory at vetneuromuscular.ucsd.edu/).

The mainstay of therapy for acquired myasthenia gravis is the administration of anticholinesterase drugs. Therapy must be tailored according to the individual’s response to therapy (for details pertaining to treatment recommendations, see Shelton, 2002). Untoward side effects of anticholinesterase drug therapy are similar to clinical signs observed in animals with organophosphate exposure, including excessive salivation, lacrimation, and gastrointestinal signs, including nausea and diarrhea. Furthermore, animals may become paretic because of exuberrant depolarization and/or desensitization of the postsynaptic (skeletal muscle) membrane. The administration of corticosteroids concurrently with anticholinesterase drug therapy is warranted when the response to monomodal anticholinesterase therapy is less than ideal. Corticosteroid therapy may, however, be inappropriate if underlying disease processes such as aspiration pneumonia are evident. Of course, other important aspects of therapy for canine myasthenia gravis include good supportive care (e.g., feeding regimens for dogs with megaesophagus), including appropriate antimicrobial therapy for any secondary complications arising from the disease (e.g., aspiration pneumonia).

Complete spontaneous remission occurring from 1 to 18 months following the diagnosis of acquired myasthenia gravis is possible and has been seen in 47 of 53 dogs with the disease (Shelton & Lindstrom, 2001). Prognosis for canine myasthenic patients is, however, a likely variable depending on the form (focal vs. generalized), severity (mild, moderate, or severe fulminating generalized myasthenia gravis), and other underlying disease processes (e.g., neoplasia) (Shelton, 2002).
Ocular signs have been documented in 45% of cases and are variable depending on the chronicity of the disease. Ocular manifestations of acute masticatory myositis include exophthalmos and prolapse of the third eyelid due to swelling of the pterygoid muscle, and possible optic nerve tension/compression causing blindness (Evans et al., 2004; Gilmour et al., 1992; Lewis, 1994; Smith, 1989). In cases of chronic masticatory myositis, enophthalmos has been reported (Gilmour et al., 1992). Signs are usually, but not invariably, bilateral. Clinical signs, ± peripheral eosinophilia, ± elevated levels of serum creatinine kinase, ± abnormal electromyograms (EMGs), ± presence of circulating antibodies for type 2M fibers, and positive muscle immunohistochemistry for antibodies against type 2M fibers are used to provide a diagnosis of masticatory myositis (Evans et al., 2004). Predominant histopathologic changes identified in affected muscle biopsies include (1) cellular infiltration with varying degrees of lymphocytes, and/or macrophages, and/or eosinophils; (2) histologic evidence of muscle atrophy, necrosis, and fibrosis; (3) presence of fibrosis depending upon the chronicity of the disease; and (4) immune complexes bound to type 2M muscle fibers (Evans et al., 2004; Shelton et al., 1987). Bacteria containing antigens similar to type 2M muscle fibers may initiate the immune-mediated myositis (Shelton et al., 1987). Immunosuppressive doses of systemic corticosteroids (prednisone 1–2 mg/kg PO BID) for a minimum of 1 month before tapering are recommended at any stage of the disease. Prognosis is good for dogs treated appropriately with immunosuppressive dosages of corticosteroids, although some dogs may require life-long therapy with these drugs.

The second form of focal inflammatory myositis is extraocular myositis. Extraocular myositis involves only the extraocular muscles and affects predominantly young large-breed dogs. Bilateral exophthalmos is the predominant clinical sign in the acute form of the disease (Allgoewer et al., 2000; Evans et al., 2004). Chronic extraocular myositis can result in restrictive strabismus and is due to chronic fibrosis of the extraocular muscles (Fig. 35.1.13) (Allgoewer et al., 2000). As opposed to masticatory myositis, circulating antibodies to type 2M muscle fibers are not present (Allgoewer et al., 2000; Evans et al., 2004). Inflammatory infiltrate of affected muscles include lymphocytes and macrophages, and fibrosis may be present depending on the chronicity of the disease (Evans et al., 2004). Immunosuppressive corticosteroid therapy is indicated in cases of extraocular myositis (as for masticatory myositis). Adjunctive corrective strabismus surgery may be useful in some cases of chronic extraocular myositis where the disease is in remission (Allgoewer et al., 2000).

Uveodermatologic Syndrome (Vogt-Koyanagi-Harada-Like Syndrome)

Vogt-Koyanagi-Harada (VKH) syndrome describes an idio pathic condition in humans characterized by uveitis, poliosis, vitiligo, ± changes in hearing ability, and meningitis (for review, see Herrera & Duchene, 1998; Laus et al., 2004; Morgan, 1989). A similar syndrome is recognized in the dog, except that meningitis is rarely reported (Denerolle et al., 2000), hence the terms uveodermatologic or VKH-like syndrome have been applied. One hypothesis regarding the etiology of the condition is that it results from an immune-mediated destruction of melanocytes (Yamaki et al., 2000). A relatively recent study examining ocular and dermatologic tissue from two dogs with VKH-like syndrome has suggested that skin lesions are the result of a Th1-mediated inflammatory response while ocular lesions are the result of a Th2-mediated inflammatory response (Carter et al., 2005). Furthermore, the role of certain dog leukocyte antigen (DLA) class II gene alleles may be important regarding the pathogenesis of VKH-like syndrome in Akitas (Angles et al., 2005).
Skin biopsy specimens have lichenoid dermatitis, histiocytes, and small mononuclear cell as well as giant cell infiltrations. The level of melanin in the epidermis and hair follicles is decreased. Enucleated eyes have a marked panuveal infiltrate of macrophages, plasma cells, and lymphocytes (Lindley et al., 1990).

The prognosis for dogs affected with uveodermatologic syndrome is guarded, and therapy should be considered to be life-long. Relapses are frequent if therapy is stopped or tapered. Because of the immunosuppressive therapy, periodic rechecks as well as blood and liver evaluations are necessary. Initial therapy involves immunosuppressive doses of oral prednisone ± azathioprine or cyclophosphamide. Azathioprine has a lag period of 3–5 weeks before it becomes effective; thus, tapering of corticosteroids should not be attempted before this period (Beale, 1988). Maintenance therapy may require one or both drugs at a markedly reduced dose. Topical corticosteroids may be used for anterior segment lesions.

Infectious Diseases

Algal Diseases

Protothecosis

Protothecosis is a rare disease in humans and a variety of animals caused by a colorless, ubiquitous, saprophytic alga of the genus Prototheca. Prototheca spp. have a wide geographic distribution and are found in soil, water, sewage, and some vegetable matter (Pier et al., 2000). Prototheca spp. are thought to be achlorophyllous mutants of green algae. Three species have been recognized, but only Prototheca wickerhamii and Prototheca zopfii are known to be pathogens. P. zopfii is usually isolated from disseminated cases, whereas P. wickerhamii produces a cutaneous syndrome. Prototheca spp. appear in tissue as thick-walled, nonbudding, round to ovoid, yeast-like cells (Font & Hook, 1984; Hosaka & Hosaka, 2004). The disease is not considered to be transmissible, and a decrease in cell-mediated immunity may be responsible for the disease itself (Perez et al., 1997; Rakich & Latimer, 1984). Large breeds of dogs may be overrepresented, and ≥50% of animals with protothecosis may have ocular involvement (Migaki et al., 1982). As well, in a review of protothecosis in 17 Australian dogs, females (12/17 cases) and Boxer dogs (7/17 cases) were overrepresented (Stenner et al., 2007). A study from North Carolina, USA found that 2 out of 18 cases of infectious uveitis were due to protothecosis (Massa et al., 2002). Most ocular syndromes are associated with systemic signs, but in some instances, the systemic signs are occult. Tissues most commonly affected include the eyes, digestive tract, kidney, heart, bone, and brain. Histopathologic lesions may be characterized by minimal inflammation of a mononuclear to pyogranulomatous nature (Migaki et al., 1982).

Ocular lesions include a granulomatous, posterior uveitis or panuveitis that is often bilateral and blinding (Fig. 35.1.15).
Bacterial

Any sporadic bacteremia may result in seeding of the uveal tract and create various degrees of inflammation, but only a few bacterial syndromes are relatively consistent regarding involvement of the eye. Sporadically, bacteremia from bacterial infections involving other organ systems (e.g., peritonitis (Ramsey et al., 1996), pyometra (Schwink & Barstad, 1986)) may result in varying degrees of focal chorioretinal lesions consisting of hemorrhage or exudates (or both), which often go unnoted. Typically, these lesions are associated with the end-arterioles or small vessels in the retina. In small animals, they may develop into a fulminating endophthalmitis, but this appears to be rare (Massa et al., 2002).

Furthermore, bacterial infection of the CNS, causing a meningitis or meningoencephalitis, can result in ocular signs that are related to the region of the brain involved. Importantly, bacterial meningitis/ meningoencephalitis of dogs and cats typically results from local extension or penetration of the CNS by bacterial organisms, while bacterial meningitis/ meningoencephalitis is typically due to hematogenous spread of bacteria in large animal species (Fecteau & George, 2004; Meric, 1988).

Bartonellosis

Canine bartonellosis results from infection with the gram-negative, intracellular bacilli, or cocccobacilli bacterium, Bartonella spp. There are numerous species of Bartonella. Bartonella henselae (causative agent of cat scratch disease), Bartonella vinsonii (berkhoffii), Bartonella clarridgeiae, and Bartonella elizethae are known or likely to cause naturally occurring disease in dogs (Barnes et al., 2000; Breitschwerdt et al., 1995, 1999, 2004; Michau et al., 2003; Pappalardo et al., 2000), and B. vinsonii (berkhoffii) appears to be an important species to cause clinical disease in dogs (Baneth et al., 1998; Breitschwerdt et al., 2004; Suksawat et al., 2001).

Tick transmission of Bartonella spp. is thought to be an important mode of infection in dogs as seroreactivity for bartonellosis is often found concurrently with other tick-borne infectious agents (Breitschwerdt et al., 1998; Kordick et al., 1999; Mylonakis et al., 2004).

Clinical presentation is variable (see Breitschwerdt et al., 2004 for complete listing of clinicopathological abnormalities). Nevertheless, canine bartonellosis has been associated with numerous pathological conditions including anterior uveitis, hyphema, retinal detachment due to systemic hypertension, and choroiditis (Fig. 35.1.16) (Breitschwerdt et al., 2004; Michau et al., 2003), endocarditis (Breitschwerdt et al., 1999), cutaneous vasculitis (Breitschwerdt et al., 2004), granulomatous lymphadenitis (Pappalardo et al., 2000), myocarditis (Breitschwerdt et al., 1995, 1999), and polyarthritis (Breitschwerdt et al., 2004). Treatment of canine bartonellosis consists of systemic antimicrobial therapy. An appropriate antimicrobial must be efficacious against Bartonella spp. and should achieve high intracellular concentrations (Breitschwerdt et al., 2004). An appropriate antimicrobial include...
macrolides (e.g., azithromycin), fluoroquinolones (e.g., enrofloxacin), and doxycycline (recommended to be used at high dosages [10 mg/kg q 12 hours for 4–6 weeks]) (Breitschwerdt et al., 2004; Kordick et al., 1997; Michau et al., 2003).

Borreliosis (Lyme Disease)

Lyme disease, or borreliosis, is a tick-borne spirochetosis produced by Borrelia burgdorferi, which comprises several species that affect humans and dogs worldwide. Borrelia organisms, like most spirochetes, are small, 25 µm long and 0.2 µm in diameter, corkscrew-shaped, motile microaerophilic bacteria of the order Spirochaetales (Fritz & Kjemtrup, 2003). Borrelia organisms do not survive free-living in the environment, but rather depend on hosts and are transmitted between vertebrate reservoir hosts and blood-sucking arthropod vectors (Fritz & Kjemtrup, 2003). In particular, B. burgdorferi is transmitted primarily by ticks of the Ixodes sp., but Amblyomma americanum has also been associated with outbreaks (Fritz & Kjemtrup, 2003). The primary reservoirs for B. burgdorferi include small rodents and birds (Fritz & Kjemtrup, 2003). Tick larvae acquire B. burgdorferi when feeding on the mouse and nymph, and adult ticks then transmit the organism to a variety of hosts (Fritz & Kjemtrup, 2003). Successful transmission of the agent relates directly to contact time of the tick on the host, requiring 48–72 hours for a 38%–92% transmission rate (Appel, 1990; Fritz & Kjemtrup, 2003; Levy et al., 1993). Once inside the host, these organisms rarely spread hematogenously, but rather use their flagella to move through connective tissue (Fritz & Kjemtrup, 2003).

In the dog, the horse, and humans, B. burgdorferi may produce ocular lesions. In a retrospective review of 132 seropositive dogs, five had a primary complaint of ocular lesions (Cohen et al., 1990). Ocular lesions were undoubtedly underrepresented, however, because of the study design and the difficulty in making a definitive diagnosis of borreliosis. Documented ocular lesions included conjunctivitis, corneal edema, anterior uveitis, retinal petechia, chorioretinitis, and retinal detachment. In addition to these ocular lesions, dogs with borreliosis may also present with orbital disease (Raya et al., 2010).

Numerous problems exist regarding antibody testing for borreliosis. Specifically, there is no current standardization for antigen preparations, techniques, or interpretations across different laboratories (Fritz & Kjemtrup, 2003; Jacobson et al., 1996). In addition, vaccination against borreliosis using whole cell bacterin results in positive results using enzyme-linked immunosorbent assay (ELISA) and indirect fluorescent antibody (IFA) for months to years following immunization, and further confirmation regarding whether the antibody response is due to vaccination must be obtained using Western immunoblotting (Jacobson et al., 1996). As well, paired serologic titers are not useful in the diagnosis of borreliosis because high antibody titers for IgM persist for months in naturally Borrelia-infected dogs, thus a positive IgM titer does not confirm current infection or recent exposure (Jacobson et al., 1996).

Because of the limitations of current tests that measure antibody response, other confirmatory tests must be performed including the Western blot assay and the C6 ELISA (Levy, 2002). The C6 ELISA is used by veterinarians in endemic areas (Levy, 2002). Despite higher sensitivity and specificity than whole-cell ELISA or IFA, both the Western blot analysis and C6 ELISA do not predict clinical borreliosis, but rather indicate natural exposure to the causative organism. The method of choice for serodiagnosis of borreliosis today involves utilizing two-tiered laboratory testing involving an ELISA to filter out negative samples with high sensitivity followed by immunoblotting (Western blotting) to further characterize positive samples or to differentiate between infected or vaccinated animals (Branda et al., 2011). Polymerase chain reaction (PCR) for B. burgdorferi can be conducted on skin, synovia, and connective tissue samples (Littman, 2003; Salinas-Melendez et al., 1995). A presumptive diagnosis of borreliosis can be made on the basis of compatible signs (usually lameness, joint pain, pyrexia, and lymphadenopathy of lymph nodes of the limbs), ruling out other causes of systemic disease in endemic areas, and on the basis of response to antibiotic therapy (Fritz & Kjemtrup, 2003; Littman et al., 2005). Vaccination, and tick control, both in the environment and on the animal, are important for preventing infection (Fritz & Kjemtrup, 2003; Littman et al., 2005). In particular, amitraz-impregnated collars may help decrease transmission of Borrelia spirochetes in dogs (Elfassy et al., 2001). Various antimicrobials including tetracyclines, some cephalosporins (e.g., ceftriaxone), and macrolides are useful for treating borreliosis (Littman et al., 2005). Doxycycline is one of the first-line antimicrobials of choice. It is presently advised that animals with borreliosis be treated for
at least 30 days (Littman et al., 2005), and in cases of chronic borrellosis, experimental evidence indicates that longer term therapy would be needed (for current consensus statement regarding the diagnosis, treatment, and prevention of Lyme disease in dogs, see Littman et al., 2005; Straubinger et al., 2000). Topical atropine and nonsteroidal anti-inflammatory drugs would be indicated for anterior uveal inflammation.

Botulism
Botulism results from the neurotoxin produced by Clostridium botulinum. C. botulinum is a gram-positive, spore-forming, saprophytic, anaerobic, rod-shaped bacterium. There are 8 subtypes (A — Ca, Cb— G) of C. botulinum, and they are differentiated from each other based upon the type of neurotoxin they produce. Dogs have been affected with only C. botulinum types C and D (Barsanti et al., 1978; Borst et al., 1986; Doutre, 1982, 1983; Fain-Binda et al., 1998; Farrow et al., 1983; M arlow & Smart, 1982; Pommier, 1988; Richmond et al., 1978; Tjalsma, 1990; Wallace & McDowell, 1986).

Clinical signs develop following ingestion of the bacterium in contaminated food including carrion and raw meat (Barsanti et al., 1978; Fain-Binda et al., 1998; Farrow et al., 1983; M arlow & Smart, 1982; Pommier, 1988). After ingestion of contaminated meat, the toxin, botulin toxin, is absorbed in the gut and prevents the release of acetylcholine at cholinergic synapses. Consequently, clinical signs are suggestive of skeletal muscular weakness and autonomic dysfunction. Signs include symmetrical ascending limb paresis leading to paralysis, depressed or absent tendon reflexes, abnormal motor responses during cranial nerve testing, and excessive salivation. Ocular signs that manifest include mydriasis due to loss of parasympathetic/sympathetic balance on the iris. Definitive diagnosis is made based on finding the toxin, through use of the neutralization test in mice, in the food, vomitus, feces, or serum. Treatment consists of supportive care and antitoxin administration (to prevent further binding of toxin). Prognosis is variable and is dependent upon the severity of the disease and whether secondary complications (e.g., pneumonia) occur (Barsanti et al., 1978; M arlow & Smart, 1982; Pommier, 1988).

Brucellosis
The etiologic agent of canine brucellosis is Brucella canis (for review, see Wanke, 2004). B. canis is a zoonotic aerobic, gram-negative coccobacillus. B. canis naturally infects dogs by penetrating mucous membranes such as occurs via coitus. Aside from venereal transmission, Brucella spp. can be transmitted via fomites such as cages or equipment (Wanke, 2004). Following penetration of mucous membranes, bacteremia ensues. Brucella sp. are intracellular bacteria that persist for extended periods in mononuclear phagocytes and produce a prolonged bacteremia (Carmichael, 1976).

B. canis has been isolated from the eye and is recognized as a cause of uveitis or endophthalmitis in both experimental and naturally occurring brucellosis (Gordon et al., 1985; Gwin et al., 1980a; Ledbetter et al., 2009c; Riecke & Rhoades, 1975; Saegusa et al., 1977; Vinayak et al., 2004). Infected dogs are often times not systemically ill. Because of the insidious nature of the systemic disease, infected dogs are often presented for ocular disease rather than for systemic signs. A review of records submitted to the Veterinary Medical Data Base at Purdue University revealed that approximately 14% of all brucellosis cases have ocular signs (Vinayak et al., 2004). Some of the more common ocular diagnoses reported included endophthalmitic uveitis, chronic uveitis, hyphema, chorioretinitis, and posterior synechia (Fig. 35.1.17) (Vinayak et al., 2004). Ocular inflammation associated with ocular brucellosis is typically chronic and slowly progressive (Vinayak et al., 2004). Brucellosis should be suspected in any dog with a smoldering or recurrent uveitis, and though the syndrome typically occurs in intact animals, neutered animals remain at risk of brucellosis because of the prolonged bacteremia.

Bacteriological isolation of the microorganism is the only means of definitively diagnosing brucellosis (Wanke, 2004). Serological testing for brucellosis is problematic. Nevertheless, serological testing is the most commonly used diagnostic technique for the diagnosis of brucellosis. Many of these antibody tests have not been widely evaluated and may result in false-positives and negatives depending upon the stage of the disease (Wanke, 2004). The preferred in-hospital screening procedure is the 2-mercaptoethanol rapid slide agglutination test (ME-RSAT) (D-Tec CB; Synbiotics, San...
Leptospirosis

The causative agent of canine leptospirosis is *Leptospira interrogans* sensu lato (Bolin, 1996). More than 200 serovars have been identified (Levett, 2001). Members of the genus *Leptospira* are motile spirochetal bacteria (Levett, 2001). Predominant serovars responsible for causing clinical disease in dogs include canicola, icterohemorrhagiae, grippotyphosa, pomona, Bratislava (Birnbaum et al., 1998). It appears, however, that the disease causing serovars, namely grippotyphosa, pomona, and bratislava, are becoming more prevalent (Andin & Cowgill, 2000; Birnbaum et al., 1998; Brown et al., 1996; Ward et al., 2004a). The bacterium is maintained in host-adapted species that act as reservoir hosts and is shed in the urine. Contamination of the environment with the bacterium is thought to be important in the development of outbreaks. It has been shown in one study, for example, that dogs living in periurban areas (increased contact with wildlife) are at higher risk for leptospirosis (Ward et al., 2004b). Direct transmission can occur through contact with infected urine, bites, ingestion of infected material, and contact with contaminated water. Leptospirosis is a significant zoonotic disease with worldwide distribution that causes human disease and death, mostly in regions of Asia and South America (Goldstein, 2010).

After infection, the organism multiplies, and bacteremia ensues. Leptospires sequester in various organs, particularly kidneys, liver, spleen, CNS, and the eyes. Involvement of a particular organ results in expected clinical signs including acute renal or hepatic failure/dysfunction. Nevertheless, in the acute phase of infection, conjunctivitis, scleritis, and anterior uveitis may present in concert with other systemic signs (Dziezyc & Stiles, 2000; Thirunavukkarasu et al., 1995). Additional reports of naturally occurring leptospirosis have documented nonspecific ocular signs including mucopurulent ocular discharge or scleral injection in 42%-45% of cases (Andin & Cowgill, 2000; Birnbaum et al., 1998).

Diagnosis of leptospirosis is dependent on consistent clinical signs and detection of antibodies using the microscopic agglutination test (MAT) or ELISA and/or evidence of the presence of the organism in urine using darkfield microscopy, or by visualizing the organism in histological preparations, directly culturing the organism, or by detecting organismal DNA using PCR (Bolin, 1996; Goldstein, 2010).

Treatment of leptospirosis is directed at (1) eliminating the bacteremia by initially using penicillins, specifically ampicillin and amoxicillin (Prescott, 1991), and (2) eliminating the carrier state by administering tetracyclines (Birnbaum et al., 1998; Brown et al., 1996; Kalin et al., 1999; Prescott, 1991). Antibacterial therapy should be commenced as soon as the disease is suspected and the samples have been drawn (if using PCR) to eliminate the bacteremia and the risk of live organisms in the urine that pose a zoonotic risk to humans (Goldstein, 2010). Prognosis for complete recovery is variable depending on the severity of renal injury and development of complications such as DIC (Andin & Cowgill, 2000; Birnbaum et al., 1998). Given that leptospirosis is zoonotic, it is important to use necessary precautions when handling infected animals and contaminated material (e.g., urine soaked blankets).

Tetanus

Tetanus is caused by the neurotoxin produced by the bacterium *Clostridium tetani*. *C. tetani* is a motile, gram-positive,
nonencapsulated, anaerobic, rod-shaped, spore-forming bacterium (for review, see Acke et al., 2004; Merrett, 1993). Dogs and cats are naturally resistant when compared to other species such as humans and horses. Clinical signs of tetanus develop when spores of C. tetani enter the body through skin wounds or during surgical procedures (Bagley et al., 1994). Spores become vegetative and a toxin, tetanospasmin, retrogradely migrates along axons of motor nerves to the CNS. However, it should be noted that tetanospasmin, the principle neurotoxin, is only one of three toxins produced by the bacterium (Acke et al., 2004). The toxin then prevents inhibitory neurotransmission to motor neurons, thereby resulting in the classical signs associated with tetanus. Clinical effects on the autonomic nervous system have also been described (Panciera et al., 1988).

Clinical signs may be localized or generalized (Fig. 35.1.18). In the localized form, increases in stiffness of specific muscle groups or a given limb may be noted. The localized form is described more commonly in cats compared to dogs. In the generalized form, affected dogs will initially have a characteristic smiling/sneering appearance (risus sardonicus) and a stiff gait that may progress to megaesophagus ± hiatal hernia, complete rigid paralysis with the appearance of periodic generalized convulsive-type behavior (Acke et al., 2004). Respiratory compromise may result in death. Ocular signs seen in a tetanic animal include protrusion of the third eyelid and enophthalmus resulting from globe retraction due to the hypertonicity of the extracocular muscles (Acke et al., 2004).

Diagnosis is made based upon consistent physical examination findings (presence of a wound) and clinical signs. However, culture of the organism from the wound and/or measuring circulating serum antibodies against tetanospasmin may help to confirm the diagnosis. Treatment is aimed at administering tetanus antitoxin and penicillin-G and/or metronidazole to prevent binding of any unbound toxin and to destroy any remaining bacteria, respectively. Tetanus antitoxin therapy should be done only after intradermal testing with this antitoxin as there is a strong likelihood of anaphylaxis following systemic administration (Acke et al., 2004). Supportive care and wound management are also indicated. Prognosis is variable depending upon the severity of the clinical signs and secondary complications (e.g., aspiration pneumonia).

Mycotic

Acremoniosis

Acremoniosis is a systemic mycotic infection caused by Acremonium spp. Acremoniosis has been reported in an adult dog (Simpson et al., 1993). Systemic signs in this dog were similar to those seen in cases of disseminated aspergillosis. Clinical signs include various general malaise, weight loss and anorexia, lymphomegaly, neurological signs (depending on the neuroanatomic focus of the principle pathologic process), and various ocular signs. Ophthalmologic signs include chemosis, corneal edema, anterior uveitis, focal chorioretinitis, and bullous retinal detachments (Simpson et al., 1993). Postmortem examination of a dog with acremoniosis revealed pyogranulomatous and necrotizing myocarditis, pericarditis, hepatitis, and nephritis (Simpson et al., 1993). Granulomatous lymphadenitis, endometritis, meningoencephalitis, and retinitis have also been noted (Simpson et al., 1993). Treatment is similar to that for systemic aspergillosis, and, as such, supportive therapy combined with systemic itraconazole administration is utilized (Simpson et al., 1993). Because of the relative paucity of cases of acremoniosis, prognosis is difficult to determine.

Aspergillosis

Aspergillosis is caused by the filamentous fungus Aspergillus spp. Aspergillus spp. are considered ubiquitous in the environment, and animals are infected opportunistically after inhaling Aspergillus spores (Gelatt et al., 1991). Infection
with Aspergillus spp. is either localized or disseminated. Localized aspergillosis involves colonization of the respiratory sinuses and nasal mucosa. Secondary CNS infection may result from erosion of the cribriform plate. Disseminated infection occurs typically in the immunocompromised patient and involves a whole host of organ systems, although history of respiratory involvement is not typically documented (Lehmann, 1985).

Disseminated aspergillosis occurs frequently in German Shepherd dogs (Day et al., 1986; Gelatt et al., 1991; Kabay et al., 1985; Neer, 1988). It is likely that this breed is predisposed due to an inherited impairment in their immune system (Day et al., 1985, 1986; Day & Penhale, 1988; Griot-Wenk et al., 1999; Whitbread et al., 1984). In general, the most common clinical signs relate to multiple organ system involvement, and include general malaise, pyrexia, anorexia and weight loss, and bone pain. Other signs are attributed to involvement of the liver, kidneys, CNS, and eyes. Disseminated aspergillosis has been reported to cause panuveitis, choriotretinitis, exudative retinal detachments, and endophthalmitis (Gelatt et al., 1991; Render et al., 1982; Watt et al., 1995). Diagnosis is made based on identification and culture of urine sediment, serum, synovial fluid, vitreous, lymph node, or intervertebral disc centesis specimens (Gelatt et al., 1991; Render et al., 1982; Watt et al., 1995). Treatment is directed at eliminating the organism by administering amphothercin B, itraconazole, or fluconazole intravenously. Long-term therapy with oral azoles may be required. Regardless, the prognosis for recovery from disseminated aspergillosis is poor.

**Blastomycosis**

Blastomycosis is a systemic mycotic infection caused by the dimorphic fungus, *Blastomyces dermatitidis*. *B. dermatitidis* is a thick-walled yeast that reproduces by budding in infected tissues (i.e., yeast phase), and in nature, is most likely a soil saprophyte which produces infective spores called conidia (i.e., mycelial phase). The tissue-budding yeast form is 5–20 µm in size, with a thick, double-contoured wall. *B. dermatitidis* is endemic in North America, India, and Africa (Axtell & Scalarone, 2002; M C Cullough et al., 2000).

Young, large breed sporting dogs and hounds living near water are at increased risk of blastomycosis, presumably because of outdoor exposure (Render et al., 1982; Rudmann et al., 1992; Wolf, 1989). The group at highest risk is usually reported to be 2- to 4-year-old intact male dogs, but during an outbreak in Wisconsin, blastomycosis occurred almost exclusively in females (Czuprynski et al., 1988; Legendre et al., 1981; Rudmann et al., 1992). Breeds including Bluetick Coonhounds, Treeing-walker Coonhounds, Pointers, and Weimaraners have been reported to have the highest risk of *B. dermatitidis* infection (Rudmann et al., 1992).

Blastomycosis is not a contagious or zoonotic disease but has been transmitted to a person through an accidental needlestick with a syringe and needle used for pulmonary aspiration from a dog with *B. dermatitidis* infection (Ramsey, 1994). Typically, blastomycosis develops following the inhalation of organism spores. Afer inhalation of the infective conidia by the host, these infective spores become phagocytized by alveolar macrophages and transform from the mycelial phase to the yeast phase. The common *B. dermatitidis*-infected organs in dogs are the skin, eyes, bones, lymph nodes, subcutaneous tissues, prostate, brain, and testicles (Arceneaux et al., 1998; Bloom et al., 1996; Hendrix et al., 2004; Legendre et al., 1981, 1996).

Clinical signs in dogs with blastomycosis vary significantly due to the multisystemic nature of the disease. Nonspecific signs of anorexia, lethargy, depression, fever, weight loss, and cachexia are common. Pulmonary signs are seen in 43%–88% of dogs affected with blastomycosis, ranging from mild respiratory distress during physical exertion to severe dyspnea at rest (Arceneaux et al., 1998; Legendre et al., 1981). Nearly 60% of dogs with blastomycosis develop lymphadenopathy (Arceneaux et al., 1998), while cutaneous lesions are reported in approximately 30% of affected dogs (Arceneaux et al., 1998; Legendre et al., 1981). Ocular involvement has been reported in as many as 48% of dogs with blastomycosis (Bloom et al., 1996). Ocular signs have been reported as the sole indicator of *B. dermatitidis* infection in up to 3.0% of diagnosed cases (Bloom et al., 1996). Approximately 50% of the ocular lesions caused by *B. dermatitidis* are bilateral (Bloom et al., 1996). For prognostic purposes, the ocular lesions have been divided into anterior segment only (5%–30%), anterior and posterior segment lesions (endophthalmitis, 26%–72%), and posterior segment (22%–43%) (Bloom et al., 1996; Buyukmihci, 1982; Legendre et al., 1981). Buyukmihci & Moore (1987) postulate that the initial lesion is a pyogranulomatous chorioiditis arising as a result of hematicogenous spread of the *B. dermatitidis* to the choroid, thereby producing a pyogranulomatous lesion that may not be initially visible. During this initial phase, the first visible ocular signs are often those of anterior uveal inflammation including conjunctival hyperemia, miosis, synchiae, and flare. Progression of the choroiditis produces an extension into the subretinal space and focal subretinal granulomas, which in turn may progress to exudative retinal detachments (Buyukmihci & Moore, 1987). Severe anterior uveitis, accompanied by secondary glaucoma, is indicative of endophthalmitis even if the posterior segment cannot be visualized. Though anterior segment inflammation may be severe, *B. dermatitidis* is infrequently found in the anterior uvea, and this anterior uveal inflammation has been attributed to a diffusible substance from the posterior segment (Buyukmihci & Moore, 1987). A ditional ocular lesions of canine blastomycosis are optic neuritis, retinal and vitreal hemorrhages, and orbital cellulitis (Bloom et al., 1996).

Granulomatous chorioretinitis occurring concurrently with systemic signs such as weight loss, cough, fever, skin lesions, or lameness in an endemic area is suggestive of *B. dermatitidis* infection. Thoracic radiographic assessment is often very useful in the diagnostic evaluation of a dog with suspected blastomycosis. In particular, 70% of canine cases...
demonstrate an interstitial pulmonary pattern on thoracic radiographs including classical nodular (41% of cases), diffuse (24%), or broncho (5%)-interstitial patterns (Walker, 1981). Definitive diagnosis of this disease is made by identification of the *B. dermatitidis* organism via cytology, histopathology, or fungal culture. Blastomycosis is typically easy to diagnose given the large numbers of characteristic yeast found within infected tissues, particularly lesions involving the skin, lymph nodes, and eyes (Arceneaux et al., 1998; Kerl, 2003). The yeast organisms lack a capsule, thereby aiding in differentiation of *B. dermatitidis* from *Cryptococcus*. Examination of tissue aspirates (including ocular cente­sis) usually demonstrates the causative organism. Specifically, skin lesions yield a diagnostic sample (i.e., *B. dermatitidis* organisms) 85% of the time, vitreal aspirates yield organisms from nearly all affected eyes, while lymph node aspirates yield organisms approximately 67% of the time (Arceneaux et al., 1998). If the yeast cannot be seen following repeated tissue imprints or aspirates, or histologically in biopsy specimens, serology and/or identification of Blastomyces spp. DNA using PCR should be used (Bialek et al., 2003). A n agar-gel immunodiffusion (A G I D) test is the most commonly used serologic test for blastomycosis. This test detects antibodies directed against the *B. dermatitidis* organism and has a sensitivity and specificity of approximately 67% and 100%, respectively (Klein et al., 2000). When used in combination, a positive AGID test for the fungal organism and compatible thoracic radiographs are indicative of blastomycosis. It has been found that a radioimmunooassay (RIA) for anti-W1-1 antibodies is superior to the AGID test. The sensitivity of the RIA test is 92%, while the specificity of this test is 100% (Klein et al., 2000).

Therapy for systemic mycoses, no matter what etiology, is a financial dilemma. Therapy becomes prohibitively expensive for many owners because most of the affected dogs are large breeds, therapy may be very protracted, and imidazole medications are very costly. Currently, itraconazole is considered the drug of choice for the treatment of blastomycosis (Legendre et al., 1996). Blastomycosis can be clinically cured in approximately up to 80% of appropriately treated dogs (Legendre et al., 1996). However, the degree of pulmonary involvement is the main determinant of successful response to therapy for blastomycosis (Legendre et al., 1996). Relapse occurs in approximately 20% of treated dogs. Recurrence may occur from months to years following the cessation of therapy (Legendre et al., 1996). Relapses should be treated as new blastomycosis infections.

Many affected dogs are working hunting dogs, and the visual prognosis is often critical for the owner’s decision as to whether or not to attempt treatment. Therapeutic success rates for ocular blastomycosis have been reported to be 42% with oral itraconazole, 5 mg/kg twice a day for 60 days (Brooks et al., 1991), and 40% with a protocol of amphotericin B, 0.5–1.0 mg/kg intravenously every 48 hours for a cumulative dose of 4–6 mg/kg, and ketoconazole, 10–20 mg/kg every 24 hours for 30–90 days (Bloom et al., 1996). The majority of dogs with anterior segment disease (65%) have the affected eye enucleated (Brooks et al., 1991), while eyes of dogs with posterior segment disease have an increased likelihood (76%) of recovering (Brooks et al., 1991). In instances where there is CNS involvement, including the presence of optic neuritis, prognosis is guarded to grave (Brooks et al., 1991; Legendre et al., 1996). The use of fluconazole has been successfully used to treat a dog with CNS involvement, however (Arceneaux et al., 1998). A recent retrospective study evaluating the visual outcome of dogs with ocular blastomycosis showed that the use of systemic corticosteroids in combination with systemic antifungals did not appear to adversely affect survival rate and may have improved the preservation of vision in the majority of affected dogs (Finn et al., 2007). In particular, 14/19 affected eyes (all eyes with mild to moderate lesions and 5/10 severely affected eyes) retained vision at their final reexamination (Finn et al., 2007). Treatment of anterior segment lesions is nonspecific, involving the use of topical atropine and prostaglandin inhibitors (Bloom et al., 1996; Brooks et al., 1991). Carbonic anhydrase inhibitors may be used to treat elevated intraocular pressures, but such eyes are candidates for enucleation, given that eyes with secondary glaucoma have been reportedly unresponsive to treatment and had endophthalmitis at histopathologic examination (Bloom et al., 1996). Enucleation is also indicated for blind, painful eyes. Enucleation to remove a nidus of infection that might disseminate and produce relapses has no basis in the published, factual information.

**Coccidioidomycosis (Valley Fever; San Joaquin Valley Fever)**

Coccidioidomycosis is caused by the dimorphic fungus *Coccidioides immitis*. The organism is found in sandy, alkaline soils of the dry regions of the southwestern United States, western Mexico, and Central and South America (Wolf, 1989). *Coccidioides* spp. produce mycelia during seasonal rainfall. As the soil dries, arthrospores develop and become airborne under dry and windy conditions. The major route of *Coccid­ioides* spp. infection is via inhalation (Wolf, 1989). Cutaneous entry of the organism through a penetrating skin wound is possible but occurs rarely (Wolf, 1989).

Coccidioidomycosis may produce a wide variety of clinical diseases, depending on the immunocompetence of the host, ranging from a mild, subclinical respiratory disease to a severe multisystemic disseminated disease. *Coccidioides* spp. may produce disease in a wide variety of domestic and wild animals as well as in humans. In the lung, the arthrospores transform into their parasitic form, spherules, which gradually enlarge to 200 µm in diameter. These spherules contain endospores that, when released following rupture of the spherule at maturity, form new endosporulating spherules. The incubation period from inhalation to the appearance respiratory signs is 1–3 weeks in experimental animals (Hugenholtz et al., 1958). If the infection spreads beyond the respiratory system, the disease is considered to be disseminated. Dissemination may
SECTION IV: Special Ophthalmology

Cryptococcosis

Cryptococcosis is caused by Cryptococcus neoformans or Cryptococcus gattii (previously C. neoformans var. gattii) (Wolf, 1989). C. neoformans is associated with high nitrogen-containing environments such as avian feces or soil enriched with avian feces (O’Brien et al., 2004). Hence, birds such as pigeons are considered to be significant vectors of Cryptococcus spp. C. gattii, however, is associated with Eucalyptus and fir trees in Australia and Canada, respectively (O’Brien et al., 2004). In infected tissue, and often when cultured using standard laboratory conditions, C. neoformans is a variably sized yeast-like organism (3.5 to 7 μm) which typically contains a thick capsule.

Cryptococcosis has been described in a variety of mammals as well as in humans. Importantly, cryptococcosis is not contagious. Rather, inhalation of the yeast-like organism is the likely mode of infection (Wolf, 1989). Dissemination occurs through hematological spread. The predominant signs of cryptococcosis vary with the affected species, immune status of the patient, and perhaps, the strain of organism (Faggi et al., 1993).

Canine cryptococcosis is uncommonly reported in comparison to other systemic mycotic infections such as blastomycosis and in comparison to feline cryptococcosis (Berthelin et al., 1994a; Bistner et al., 1971; Faggi et al., 1993; Gelatt et al., 1973; Kurtz & Finco, 1970; Malik et al., 1995; O’Brien et al., 2004; Rubin & Craig, 1965; Tiches et al., 1998). As with other systemic mycoses, dogs with medium to large physical stature are typically affected, including American Cocker Spaniels, Doberman Pinschers, Great Danes, and Labrador Retrievers. Young adult dogs are generally affected with cryptococcosis. Clinical manifestations of canine cryptococcosis pertain mainly to CNS involvement (Berthelin et al., 1994a; O’Brien et al., 2004), and ocular, upper respiratory, or cutaneous lesions (Malik et al., 1995; O’Brien et al., 2004). Common, non-specific clinical signs of canine cryptococcosis include anorexia, lethargy, and depression. Fever is not a common clinical finding in dogs with C. neoformans infection. Twenty to forty percent of dogs with cryptococcosis have ocular and/or periorbital involvement (Malik et al., 1995). The most common ocular lesion of cryptococcosis is granulomatous to
Figure 35.1.19. Labrador Retriever with tetraparesis and Cryptococcus in the cerebrospinal fluid. Optic neuritis and multiple retinal hemorrhages are present, and a granuloma adjacent to the disc is obscured by a hemorrhage. Vasculitis is evident, with multiple hemorrhages, perivascular infiltrate around smaller vessels, and marked hyperemia. (Reprinted with permission from Martin, C.L. (1999) Ocular manifestations of systemic disease: Part 1: The dog. In: Gelatt, K.N., ed., Veterinary Ophthalmology, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 1401–1448.)

Identification of the causative agent permits confirmation of the diagnosis of cryptococcosis. Ocular lesions are suggestive of mycotic chorioretinitis, and vitreous or subretinal fluid centesis, or CSF tap (in CNS-infected cases) will usually reveal the causative organism on cytological assessment (Berthelin et al., 1994b; Render et al., 1982). Histopathological evaluation of infected tissues is also helpful for definitive diagnosis. The thin wall and large capsule of Cryptococcus allow ready differentiation from Blastomyces. Cryptococcal organisms can also be readily cultured on Sabouraud’s agar from infected tissue, CSF, exudate, blood, urine, and joint fluid (Malik et al., 1995). However, positive culture of specimens taken from the nasal cavity may occur in animals without clinical disease (Malik et al., 1997).

Alternatively, the latex agglutination test for C. neoformans is an antigen test against a cryptococcal capsular antigen (Malik et al., 1996b). This antigen test can be used to make the diagnosis of cryptococcosis using CSF, urine, or serum, as well as to follow the animal’s response to therapy. Since most C. neoformans-infected animals fail to mount a humoral immune response, antibody titers are not useful diagnostically.

Treatment of cryptococcosis involves subcutaneous, diluted amphotericin B in combination with oral flucytosine (especially helpful for treating CNS-infected cases) or azole therapy (Malik et al., 1995, 1996a, 1996c). Fluconazole is recommended for cases of ocular or CNS cryptococcosus (Berthelin et al., 1994b; Malik et al., 1995). Therapy should be monitored both by clinical improvement and by monitoring C. neoformans antigen titers. Therapy should be continued until titers have dropped to 1:10 or less (Jacobs et al., 1997). Ideally, treatment should be continued until the titer is negative or for an additional two or more months after the clinical signs have resolved (Berthelin et al., 1994b; Jacobs et al., 1997). The prognosis is guarded in most affected dogs because of increased likelihood of CNS involvement.

Dermatophytosis

Dermatophytosis, or cutaneous infections with fungi, are usually caused by Microsporum canis, Microsporum gypseum, Trichophyton mentagrophytes, or some combination of these in dogs (for review, see Moriello, 2004). Young animals are more frequently infected by dermatophytosis. Because dermatophytes are a cause of facial dermatitis, they frequently involve the eyelids, typically producing a dry, crusty, periorcular alopecia. The condition is diagnosed on the basis of direct microscopic examination of skin scrapings from lesions, Wood’s light examination, or more frequently, direct fungal culturing with dermatophyte test medium. Therapy, if necessary, is oral griseofulvin for 4–6 weeks and environmental decontamination. When treating facial dermatophytes with one of a variety of antifungal shampoos, it is important to avoid getting these cleansing agents in the animal’s eyes.

Histoplasmosis

Histoplasmosis is caused by a dimorphic fungus, Histoplasma capsulatum, which exists in various river bottoms as a mycelial-phase, soil saprophyte. H. capsulatum grows best in nitrogen-rich organic matter, such as bat and bird feces (Wolf, 1989). Though quite widespread in North and South America, endemic areas are in the Ohio, Missouri, and Mississippi River valleys (Howard, 1984). The life cycle of H. capsulatum is similar to that of Blastomyces and Coccidioides spp., with a mycelial phase in the soil that produces conidia, which once in the pulmonary system convert to a budding yeast phase (Wolf, 1989). Histoplasma organisms can then be disseminated via hematogenous or lymphatic spread.
Histoplasmosis has been observed commonly in dogs and cats (Clinkenbeard et al., 1988; Gwin et al., 1980b; Kerl, 2003; Rowley et al., 1954; Sano & Miyaji, 2003). Experimentally, ocular lesions have been identified in 66% of dogs and occurred preferentially in the anterior choroid, iris, ciliary body, and sclera (Salfelder et al., 1965). Young hunting breeds of dogs may have an increased risk (Kerl, 2003). Histoplasmosis typically originates in the lungs and potentially the gastrointestinal tract, then the organism disseminates via monocytes if the exposure is overwhelming or the host is immunocompromised.

Most infections are probably subclinical respiratory infections. Alternatively, clinical signs may be limited to the respiratory system, but if the organism disseminates, the digestive tract and reticuloendothelial system become involved. Clinical signs include pyrexia, inappetence and weight loss, general malaise, and coughing (Kerl, 2003). With respect to ocular signs, the choroid appears to be the target. Pyogranulomatous inflammation extending into the subretinal space producing focal or coalescing lesions and retinal detachment has been observed (Gwin et al., 1980b; Huss et al., 1994). Optic neuritis and anterior uveitis may also occur. Histoplasmosis-induced granulomatous chorioretinitis is similar in appearance, ophthalmoscopically, to chorioretinal lesions associated with other causes of systemic mycoses (Fig. 35.1.20). Unlike other mycotic infections, H. capsulatum organisms are relatively few in number and are small (2–4 µm in diameter), round to oval, intracellular (typically within phagocytic cells of the mononuclear phagocyte system) yeast cells. H. capsulatum organisms may, therefore, require enhancement with Gomori methenamine-silver (GMS) staining to visualize them and establish the diagnosis (Render et al., 1982). Cytological and biopsy specimens of infected tissues may establish the diagnosis. Culture of the organism can be performed by plating biological fluid, including CSF, on Sabouraud’s dextrose agar. Serologic diagnosis of histoplasmosis using an AGID test is 80% sensitive and almost 100% specific (Huss et al., 1994). A negative test result does not rule out the disease, however, and a positive test result may only indicate previous exposure in endemic areas. Similar to other systemic mycoses, pulmonary forms of histoplasmosis without dissemination have a better prognosis. Dogs with ocular lesions typically do not respond to antifungal therapy. Long-term therapy and a propensity for relapse are characteristic. Readers are referred to current internal medicine or infectious disease textbooks for further details regarding therapy for canine histoplasmosis.

**Parasitic: Dipteric Larvae**

**Ophthalmomyiasis**

Ophthalmomyiasis interna has been observed in the dog and the cat, and refers to either the intraocular (ophthalmomyiasis interna) or external (ophthalmomyiasis externa) migration of fly (Diptera) larvae. Animals present with one of three different forms of ophthalmomyiasis. The three forms are named according to location of the larvae and include (1) ophthalmomyiasis externa, where the larvae are found in the orbital and extraocular tissues; (2) ophthalmomyiasis interna anterior, where the larvae are found in the anterior chamber of the eye; and (3) ophthalmomyiasis interna posterior, where larvae are found in the posterior segment of the eye (Crumley et al., 2011; Harris et al., 2000; Wyman et al., 2005). The point of entry of the fly larvae is unknown, but it is postulated that fly larvae cross the conjunctival surfaces. Ophthalmomyiasis may be presented in the acute stages if an anterior uveitis is produced, but more commonly, the syndrome is noted as an incidental finding in the chronic stages. The characteristic ophthalmoscopic lesions are wandering, curvilinear tracts that frequently intersect and are associated with retinal and preretinal hemorrhages in the acute stage. If the larva is observed, it is typically photosensitive, moving away from a strong light (Gwin et al., 1984; Kaswan & Martin, 1984).

Manual removal of externally located organisms with appropriate anti-inflammatory and antimicrobial therapy, along with correcting any extraocular conformational defects, have shown positive outcomes (Crumley et al., 2011).

With regard to treatment of ophthalmomyiasis interna, direct visualization of the larvae in either the anterior or the posterior segment of the eye has been reported, but more commonly, the finding is of typical wandering tracts in the ocular...
fundus. Only acute cases warrant therapy, and topical or systemic corticosteroids are indicated depending on the location of the lesion (or lesions). If the larva is present, laser energy may be attempted to kill the larva, even though it is not pigmented. Physical removal of the larva from the anterior chamber has also been performed (Harris et al., 2000). Pars plana vitrectomy has also successfully been used to treat intra-vitreal ophthalmyiasis (Ollivier et al., 2006). Systemic organophosphates have been used as well to treat ophthalmyiasis interna, but because the condition spontaneously improves in most instances, the efficacy of this treatment is unknown. Killing the larva may incite more intraocular inflammation, however, and waiting for spontaneous departure of the larva from the eye may be prudent.

**Parasitic: Mites**

Demodicosis

Canine demodicosis is caused by the parasitic mite *Demodex canis*. *Demodex* spp. live as commensals in the skin of most mammals, including dogs. Most species of *Demodex*, including the *D. canis* mite, spend their entire life cycle in the hair follicles and sebaceous glands of their host, while a few species are found within the epidermis. *Demodex* mites, present in small numbers, are part of the normal skin fauna (for review, see M ueller, 2004; Nutting, 1976). For unknown reasons, *Demodex* spp. mites may multiply to produce either local or generalized demodicosis. Generalized demodicosis is either juvenile onset or adult onset (M ueller, 2004). Predisposing factors contributing to overgrowth of *Demodex* include poor nutrition, concurrent parasites/infectious disease, short hair coat, nonenrollment into preventive wellness plan, stress, immunosuppressive drug therapy (L emarie et al., 1996; Plant et al., 2011). Localized demodicosis typically develops in young dogs (3–6 months of age), starting preferentially around the eyes, lips, and forelegs. Skin lesions are typically circumscribed, dry, scaly, and hairless. Most are nonpruritic, but bacterial infection and self-trauma may create moist, erythematous lesions.

Skin scrapings are the main method of establishing a diagnosis, and the mites are typically easy to find (M ueller, 2004). All forms of blepharitis should indicate the need for skin scrapings, and demodicosis should be an important differential diagnosis in young dogs with blepharitis.

Dogs with normal immune systems will typically have self-limiting local demodicosis (generally resolves in 6–8 weeks, with or without therapy), but the lesions should be observed for progression to generalization. Local lesions may heal, and new skin lesions may develop over a period of several months. Treatment of canine demodicosis involves the use of amitraz dips and/or oral ivermectin or milbemycin administration (M ueller, 2004). Use of avermectin drugs should be limited to animals lacking mutation for the P-glycoprotein gene (M DR1) (see “Ivermectin” in “Systemic Toxicities” section). For current treatment recommendations, see M ueller et al. (2012).

**Parasitic: Nematodes**

Angiostrongylosis (Heartworm of France; French Heartworm)

Angiostrongylosis is caused by the nematode *Angiostrongylus vasorum*. *A. vasorum* inhabits the pulmonary arteries and right heart of dogs and wild carnivores in parts of Europe, Africa, and Asia (for review, see B olt et al., 1994; M organ et al., 2005). A case of *A. vasorum* infection in a dog from northeastern Canada has been described (B ourque et al., 2002; C onboy, 2004). Dogs are infected by eating intermediate hosts such as snails and slugs. Third-stage larvae pass from the gut
to the liver, molt to fourth-stage larvae, and then migrate to the heart and the pulmonary arteries. Larvae are coughed, swallowed, and passed in the feces. Migrating larvae may become aberrant and may be found in the eye (King et al., 2005). Severe granulomatous uveitis and secondary glaucoma have been observed with chronic involvement (King et al., 2005; Perry et al., 1991). A. vasorum infection may also manifest in acute cases as a free nematode in the anterior chamber (King et al., 2005; Perry et al., 1991).

Coughing and right-heart failure are the usual signs of severe A. vasorum infestation. A history of exposure to an endemic area should prompt utilization of the Baermann technique or fecal flotation to detect larvae in the feces. False negative results may arise as A. vasorum larvae are not shed continuously. Both the worm and the presenting clinical signs need to be differentiated from Dirofilaria immitis-induced disease.

Standard therapy for infection with A. vasorum is oral levamisole. Treatment with other anthelminthics such as ivermectin or fenbendazole are reported (Bolt et al., 1994; Bourque et al., 2002; Chapman et al., 2004). Oral milbemycin oxime has also been demonstrated to relieve clinical signs and prevent fecal shedding of larvae (Conboy, 2004).

Dirofilariasis (Canine Heartworm Disease)

Dirofilariasis, canine heartworm infection, caused by Dirofilaria immitis, is the most commonly reported intracocular nematode among dogs in North America (Carastro et al., 1992). Heartworm disease is widely distributed. Dirofilariasis is recognized in dogs worldwide. Approximately 240,000 cases of heartworm disease were diagnosed in 2001 in the United States (Atkins, 2005). In Canada, dirofilariasis is relatively infrequent and limited to the southernmost portions of the country (Klotins et al., 2000). The disease has been reported in the tropics in northern and southern temperate zones, and in the subtropics. Dirofilariasis infects numerous species of canids, cats, ferrets, sea lions, and humans (Atkins, 2005).

Transmission of D. immitis is by mosquitoes. The life cycle of D. immitis is complex, thus readers are referred to current internal medicine or infectious disease textbooks for further details. D. immitis completes its life cycle within 184–210 days under ideal conditions (Atkins, 2005). The canine host usually develops microfilaremia 6–7 months following infection (Atkins, 2005). Adult heartworms are known to live up to 5 years, while microfilaria live up to 30 months in dogs (Atkins, 2005).

Ocular involvement with D. immitis is postulated to arise as a result of aberrant migration of fourth-stage larvae from the subconjunctival space into the eye, with subsequent development to immature adults or fifth-stage larvae (Carastro et al., 1992; Dantas-Torres et al., 2009). Approximately half of these infected dogs do not have microfilaremia or are occult. In a retrospective study, the German Shepherd represented 33% of D. immitis-infected dogs in a series of 21 dogs (Carastro et al., 1992). All ocular involvement was unilateral. The worm was in the anterior chamber in 20 of the 21 cases, but it may also be found in the vitreous (Carastro et al., 1992). Anterior uveitis was a consistent ocular manifestation, and ocular discomfort was exacerbated by examination of the affected eye with a light, which stimulated parasitic movement (Carastro et al., 1992). With this disease, corneal edema may be severe and may hinder examination of deeper intraocular structures. The uveitis and corneal edema are postulated to be associated with mechanical trauma from the worm, toxic metabolic by-products from the worm, or an immune reaction to the worm (Beller, 1962; Bellhorn, 1973; Blanchard & Thayer, 1978; Brightman et al., 1977; Carastro et al., 1992; Guterbock et al., 1981; Medcalf & Jordan, 1982; Miller & Cooper, 1987).

The diagnosis of intraocular dirofilariasis is established by finding the worm, usually present in the anterior chamber of dogs in areas endemic for heartworm (Fig. 35.1.21). Severe corneal edema, however, may preclude visualization of the parasite. Approximately 50% of the affected dogs are occult for microfilaria; thus, occult heartworm testing and thoracic radiography may be needed as well (Carastro et al., 1992).

Therapy has involved removal of the D. immitis worm through a limbal incision and has been successful in 90% of patients so treated. Preoperative treatment with a topical cholinesterase inhibitor may decrease parasite movement, as may avoiding bright surgical lights until required. A retrospective study has demonstrated preservation of vision in 89% of cases, but vision was usually lost when glaucoma was a complication (Carastro et al., 1992). The most commonly reported ocular complication is corneal edema that was persistent in only 4 of 21 cases of intraocular dirofilariasis (Carastro et al., 1992). Corneal edema was more likely to be persistent if the history was chronic (Carastro et al., 1992). Anterior uveitis, in cases of intraocular dirofilariasis, should be treated with topical corticosteroids and atropine.

**Figure 35.1.21.** Heartworm filaria within the anterior chamber of a dog’s eye. (Reprinted with permission from Carastro, S.M., Dugan, S.J. & Paul, A.J. (1992) Intraocular dirofilariasis in dogs. Compendium on Continuing Education for the Practicing Veterinarian, 14, 209–217.)
Onchocerciasis (Onchocercosis)

Ocular onchocerciasis is caused by the nematode, *Onchocerca* spp. (for review, see Sreter & Szell, 2008; Sreter et al., 2002; Zarfoss et al., 2005). The exact species of *Onchocerca* causing canine ocular onchocerciasis is speculative, and consensus has yet to be reached (Zarfoss et al., 2005). The life cycle of *Onchocerca lupi* is not completely understood, but is likely similar to that of other *Onchocerca* spp. (Sreter et al., 2002). Larval maturation is thought to occur in black flies (*Simulium*) or gnats/midges (*Culicoides*), the intermediate hosts (Sreter et al., 2002; Zarfoss et al., 2005). Larvae are then transmitted to the definitive host (dog in this case) via blood feeding of the insect (Zarfoss et al., 2005). The parasites then mature, mate, and produce microfilariae that are ingested by the intermediate host, and so on (Zarfoss et al., 2005). To date, canine ocular onchocerciasis has only been reported in dogs from Germany, Greece, Hungary, Portugal, and the western United States (Eberhard et al., 2000; Faisca et al., 2010; Gardiner et al., 1993; Hermesilla et al., 2005; Komnenou et al., 2002, 2003; Orihel et al., 1991; Szzel et al., 2001a, 2001b; Zarfoss et al., 2005). The majority of these cases have originated from Greece. Dogs are of medium to large physical stature. No age or gender predilection has been reported. The condition may present unilaterally or bilaterally. Clinically, there are two forms of ocular onchocerciasis, namely acute and chronic ocular onchocerciasis (Sreter et al., 2002). In acute cases, ocular onchocerciasis is characterized by conjunctivitis, chemosis, and periorbital swelling. In some cases, parts of the parasite are observed on the conjunctival surface or other periocular tissues (Sreter et al., 2002). In chronic cases, parasite-containing granulomatous nodules are found in various parts of the eye and periocular tissues (Fig. 35.1.22). Nodules are histopathologically characterized by being highly vascular, containing parasites, and are composed of eosinophils, plasma cells, histiocytes, and fibroblasts (Sreter et al., 2002). Diagnosis is made based on consistent clinical examination findings and, in acute cases, by identifying the presence of worm fragments on the conjunctiva or in periocular tissues. In chronic cases, diagnosis is made by grossly and/or histopathologically identifying *Onchocerca* spp. within the granulomatous nodules or within the periocular tissues. Therapy for ocular onchocerciasis involves, in part, surgical removal of the granulomatous nodules and other tissues containing the worm (Komnenou et al., 2002). *Onchocerca* spp. have endosymbiotic bacteria, Wolbachia, that are required for survival of the parasite (Sreter et al., 2002). Consequently, administration of antimicrobials effective against the endosymbiont (tetracyclines) may be useful at eliminating the parasite. Antiparasitic agents such as ivermectin and diethylcarbamazine are not effective against adult worms but are effective against dirofillaria (Sreter et al., 2002). A successful therapeutic regimen resulting in complete destruction of the worm and resolution of clinical signs involves the surgical removal of the parasite containing granulomas followed by immediately administering prednisolone (0.5 mg/kg PO BID) for 9–12 days and doxycycline (5 mg/kg PO BID) for 1 month. One week after surgical debulking, melarsomine (2.5 mg/kg IM SID) is administered for 2 days followed by ivermectin (50 µg/kg SC) 1 month after surgery (Komnenou et al., 2002; Zarfoss et al., 2005). Recurrence of ocular onchocerciasis has not been reported with up to 1 year of follow-up with this therapy (Komnenou et al., 2002; Zarfoss et al., 2005).

Strongyliasis (Hookworms)

Strongyliasis is caused by the aberrant migration of strongyles (order Strongylida) (Gaunt et al., 1982). The most common routes of infection of a common strongyle of dogs, *Ancylostoma* sp., is through ingestion of larvae or direct penetration of larvae through intact skin (Gaunt et al., 1982). Infection may also occur through transplacental migration to the fetus (Gaunt et al., 1982). A berrant migration is more common following direct penetration of skin compared with following ingestion of the larva (Gaunt et al., 1982).

A 3-month-old Beagle with ocular strongyliasis has been described with granulomatous endophthalmitis and secondary glaucoma (Gaunt et al., 1982). The eye was enucleated and submitted for histopathology. Histopathologic examination of the affected eye revealed an adult *Strongylida* worm in the posterior chamber, which was identified as *Ancylostoma caninum*, although *Uncinaria* sp. could not be ruled out. Successful therapy for this nematode has not been reported.
Toxocariasis (Roundworm Ascarids)

Toxocariasis is caused by the nematode Toxocara canis (for review, see Despommier, 2003). T. canis is an extremely common roundworm or ascari of the dog, and is thought to be responsible for migrating larvae that may, occasionally, aberrantly migrate to the eye of humans and dogs. Roundworms most often cause disease in young animals. T. canis can be transmitted across the placenta and through the milk. Toxocariasis can also occur by ingestion of the eggs or of other infected hosts, such as rodents. Infective eggs of T. canis have the second-stage larva, which when ingested, normally migrates through the gut wall, enters the portal system to reach the liver, and then passes via the blood to the lungs. In the lungs, they molt to third- and fourth-stage larvae, after which they then migrate up the trachea to be swallowed and mature in the small intestine. T. canis larvae also migrate to the uterus to infect the prenatal liver of puppies and then continue their migration to the lungs after birth. Migrating juvenile T. canis can cause hepatic, pulmonary, and less commonly, ocular damage.

Both visceral and ocular larval migrans as a result of T. canis pose a public health problem. Ocular larval migrans is migration of nematode larvae through the eye. A aberrant migration of T. canis to the canine eye has been described as an incidental finding manifesting as small (one-fourth to one-sixth disc diameter), solitary focal granulomas in the posterior segment in four dogs (Rubin & Saunders, 1965). Two dogs had granulomas originating from the choroid that broke into the subretinal space, thus producing focal retinal detachment, and two dogs had granulomas affecting the optic nerve (Rubin & Saunders, 1965).

Although ocular larva migrans is considered to be a rare syndrome, two outbreaks in working herding dogs have been reported (Hughes et al., 1987; Johnson et al., 1989). In rural New Zealand, 39% of 1448 dogs had lesions characterized by multifocal hyperreflective tapetal lesions, with central pigment clumping, focal depigmentation of the nontapetal fundus, and some mild vitreal clouding that may have been associated with Toxocara sp. (Hughes et al., 1987). A approximately half of these animals had bilateral ocular lesions. Ocular examination of young dogs revealed active, hazy, inflammatory changes of the posterior segment that evolved into the characteristic, sharply demarcated lesions. Severely T. canis-affected dogs had diffuse tapetal hyperreflectivity and retinal vascular attenuation.

Histopathologic examination of 47 affected eyes with inflammatory lesions revealed three categories of posterior segment lesions: (1) those from dogs 3 years of age or younger with active inflammation of the posterior segment (four dogs in this group had Toxocara sp. larvae identified); (2) those with diffuse retinal atrophy and retinitis, with localized retinal necrosis; and (3) those with chronic, low-grade retinitis and variable atrophy, in which the dogs were usually older than 3 years of age (Hughes et al., 1987). Lesions in the young dogs had focal granulomas similar to those in the original description of ocular larval migrans. The second histologic category involved dogs that were blind, most of which were older than 3 years. The retinitis was typically a perivascular plasma cell infiltrate, with peripapillary retinal necrosis. It was postulated that young, severely affected dogs progressed to category-two dogs and, if less severely affected, retained function and appeared as category-three dogs (Hughes et al., 1987). Further study is needed to prove this hypothesis, because larvae were not found in any of the dogs with advanced lesions or in the older animals with lesions. Rural dogs were thought to be at risk either through massive contamination of the environment or through eating raw mutton with migrating larvae (Hughes et al., 1987). A study involving two litters of Border Collies from the same pig farm in the United States provided a compelling association between lesions very similar to those observed in New Zealand and ocular larval migrans (Johnson et al., 1989). A case of ocular larva migrans causing orbital cellulitis has also been described in a dog (Laus et al., 2003).

Rural dogs with environmental exposure or those that are fed raw meat, demonstrating asymmetrical retinal atrophy, focal granuloma formation, and occasionally, the observation of an intraocular larva, would be suggestive of possible ocular larval migrans syndrome. Either ophthalmoscopic or histopathologic observation of T. canis larvae is the only means of establishing a definitive diagnosis, thus differentiating this syndrome from other causes of chorioretinitis. Differentiation from genetic retinal atrophy would be made on the basis of focal lesions superimposed on diffuse retinal atrophy, age, asymmetric lesions, and histopathologic differences.

Attempts at therapy for T. canis-associated ocular larval migrans have not been reported in dogs. However, prevention by adequately cooking the meat fed to dogs, good kennel hygiene, and routine deworming should keep the worm burden down and, thus, minimize the occurrence of this condition.

Parasitic: Protozoal

Hepatozoonosis

Hepatozoonosis in dogs is a tick-borne disease caused by the protozoans Hepatozoon canis and Hepatozoon americanum (Baneth et al., 2000, 2003; Vincent-Johnson et al., 1997). Hepatozoonosis has a worldwide distribution (Baneth et al., 2003). H. americanum is transmitted by the gulf coast tick (Amblyomma maculatum), while the H. canis is transmitted by the brown dog tick (Rhipicephalus sanguineus) (Baneth et al., 2003; Mathew et al., 1998). Unlike most tick-borne diseases where infection results from the bite of an infected tick, infection of a dog with Hepatozoon spp. occurs following ingestion of an infected tick (Baneth et al., 2003). A fter ingestion, sporozoites of Hepatozoon spp. infect phagocytic leukocytes, endothelial cells, and the bone marrow. Circulating organisms can further infect various tissues including skeletal muscle and hemolymphatic organs (Baneth et al., 2003; Panciera et al., 1999).

Infection with H. canis results in somewhat less severe clinical signs compared to animals infected with H. american-
num (Baneth & Weigler, 1997; Vincent-Johnson, 2003; Vincent-Johnson et al., 1997). Dogs infected with H. canis can be febrile, have signs of general malaise, and may have a leukocytosis.

H. americanum infection manifests as a febrile disease, with generalized emaciation, inappetance, stiff gait, bilateral mucopurulent ocular discharge, and severe generalized hypesthesia especially along the epaxial musculature (Macintire et al., 2001; Vincent-Johnson, 2003). Most dogs are young adults, and there is no gender or breed predisposition to developing the disease (Macintire et al., 2001). Animals infected with H. americanum may also have concurrent infection with other tick-borne diseases including Rickettsia rickettsii, Anaplasma platys, and E. canis (Macintire et al., 2001). In a series of 22 dogs, chronic, mucopurulent ocular discharge was present in 77% of cases (Macintire et al., 1997). On ocular examination, KCS was present in 36% of cases, retinal scars in 14% of cases, papilledema in one dog, and active uveitis in one dog (Macintire et al., 1997). A didirectional systemic signs of joint and back pain, paresis and ataxia, and generalized weakness were also common (Macintire et al., 1997). Clinical signs of hepatozoonosis may be intermittent and recurrent.

Chronic fever with loss of condition during the tick season in a dog from an endemic area is suggestive of a tick-borne disease. Neutrophilic leukocytosis, often extreme, with a left shift and a nonregenerative anemia, are the most common hematologic findings (Macintire et al., 2001). Biochemistry profiles are typified by an elevated alkaline phosphatase level, hypoglycemia, and hypoalbuminemia (Macintire et al., 2001).

Definitive diagnosis of hepatozoonosis is made upon identifying the organism in circulating leukocytes or muscle biopsy specimens (Macintire et al., 2001). Outside of the United States, gametes are frequently observed in the cytoplasm of peripheral leukocytes and in the bone marrow (Macintire et al., 2001). In one study, the presence of serum antibodies (via ELISA) against H. americanum was compared to tissue biopsy results (Mathew et al., 2001). The sensitivity and specificity of using serum antibodies to diagnose hepatozoonosis were 93% and 96%, respectively (Mathew et al., 2001). A newer ELISA used for detecting antibodies against H. canis has been shown to have a sensitivity and specificity of 86% and 97%, respectively (Gonen et al., 2004).

There is no therapy to effectively eliminate H. americanum or H. canis from the body of infected dogs. A retrospective study has demonstrated that a 14-day treatment regimen with trimethoprim-sulfadiazine (15 mg/kg PO q 12 hours), clindamycin (10 mg/kg PO q 8 hours), and pyrimethamine (0.25 mg/kg PO q 24 hours) demonstrated favorable response for only 6 months (Macintire et al., 2001). In the same study, it was found that administration of a similar 14-day regimen of trimethoprim-sulfadiazine, clindamycin, and pyrimethamine followed by administration of decoquinate (10-20 mg/kg PO q 12 hours) for 3–33 months results in longer term survival of dogs (Macintire et al., 2001). Other therapies used in the treatment of canine hepatozoonosis include subcutaneous imidocarb dipropionate, 5 mg/kg in two doses at 14-day intervals (drug of choice for H. canis), and primaquine phosphate (Macintire et al., 2001). Tick control is important in preventing relapses as well as initial infections.

Leishmaniasis

Leishmania spp. are diphasic protozoal parasites that infect a wide range of vertebrates, including dogs and humans (for reviews, see Alvar et al., 2004; Desjeux, 2004; Solano-Gallego et al., 2011). Dogs and others are primary reservoirs of Leishmania spp., and sandflies (Phlebotomus spp. or Lutzomyia spp.) are the vectors (Alvar et al., 2004). Leishmania infantum is the species responsible for endemic leishmaniasis in dogs from Greece, Spain, Portugal, Turkey, parts of Africa, Central and South America, and India (Koutinas et al., 1999; Pasa et al., 2005; Pena et al., 2000; Solano-Gallego et al., 2001). Alterations in socioeconomic and possible climate factors have resulted in changes in the distribution in L. infantum in Europe (Solano-Gallego et al., 2011). In particular, canine leishmaniasis has been reported in northern Italy (Marioli et al., 2008) and of the Pyrenees in France (Chamaille et al., 2010) as well as northwestern Spain (Amusategui et al., 2004). Travel of many dogs to southern Europe or their importation from endemic areas has increased the number of affected dogs in nonendemic countries such as Germany (Menn et al., 2010) and the United Kingdom (Shaw et al., 2009). Leishmaniasis caused by Leishmania donovani has been reported in the United States and is considered endemic in Oklahoma, Texas, and Ohio (Eddlestone, 2000; Sellon et al., 1993; Swenson et al., 1988). L. donovani or Leishmania spp. infection has been documented in over 30 Foxhound kennels in 20 states and Ontario, Canada, indicating a competent vector for spread of leishmaniasis exists in North America (Gaskin et al., 2002). It is important to note, however, that the seroprevalence of antibodies for Leishmania spp. in North American dogs is, however, low (Gaskin et al., 2002).

As previously mentioned, one mode of transmission to vertebrates is via bites from infected sandflies. Furthermore, sandflies are infected by reservoir hosts during feeding. Approximately 90% of infected dogs ultimately develop clinical disease, usually before 5 years of age. The incubation period may be a few months to between 3 and 4 years (Kontos & Koutinas, 1993). Consequently, a thorough travel history needs to be investigated in suspect cases of canine leishmaniasis. A recent study documented vertical transmission of L. infantum in naturally infected dogs in North America, emphasizing that this novel means of transmission could possibly sustain infection within populations (Boggia et al., 2011).

Leishmania spp. cause cutaneous, mucocutaneous, and visceral diseases (Koutinas et al., 1999; Pena et al., 2000). Dogs will typically develop a combination of these forms of leishmaniasis (Pena et al., 2000). The disseminated disease produces emaciation with muscular weakness, chronic renal failure, and chronic, nonpruritic skin lesions. The cutaneous lesions begin on the head, thereby producing a blepharitis characterized by scaliness and loss of hair that begin at the
medial canthus (Pena et al., 2000). A vesicular-bullous blepharitis similar to pemphigus complex may also develop, which results in ulcerative/erosive lesions (Pena et al., 2000). Focal granulomatous blepharitis is also a typical eyelid reaction. Most recently, the LeishVet group has developed a staging system that divides canine leishmaniasis into four stages ranging from mild disease to very severe disease aimed at helping the clinician determine appropriate therapeutic and monitoring strategies, as well as assisting with prognostication. The reader is referred to Solano-Gallego et al. (2011) for further details regarding these LeishVet guidelines. Most recently, splenic lymphoid tissue atrophy and germinal center disruption, and low CXCL13 expression have been reported in dogs with severe visceral leishmaniasis (Silva et al., 2012).

Many studies have been recently conducted assessing the presence of numerous cytokines in tissues from dogs with naturally acquired leishmaniasis to help determine which cytokines may play a role in protection against this infection versus progression of the disease (Alves et al., 2009; Panaro et al., 2009). In one such study, prescapular lymph nodes of asymptomatic dogs had the highest expression of IFN-gamma and TNF-alpha and low parasite burden, indicating that these cytokines play a role in protection against infection. Highest expression of IL-10 and TGF-beta and high parasite burden were observed in symptomatic dogs, suggesting a role for these cytokines in the progression of disease (Alves et al., 2009).

Ocular manifestations of leishmaniasis occur in up to 81% of dogs with the disease (Naranjo et al., 2005). Ocular manifestations of leishmaniasis consist of blepharitis, simple or granulomatous conjunctivitis (Fig. 35.1.23), scleritis, superficial or deep keratitis, anterior uveitis (Fig. 35.1.24), KCS, and secondary glaucoma; signs are typically bilateral (Naranjo et al., 2005; Pena et al., 2000). The anterior vitreous may have an inflammatory reaction, but the posterior choroid and retina are usually spared. The inflammation is mononuclear, and the organism can be found in histiocytes (Giles et al., 1975; McConnell et al., 1970; Roze, 1986). Leishmania spp. and associated granulomatous inflammatory infiltrates have been recently described in intraocular, extracocular, and adnexal smooth and striated muscles in affected dogs (Fig. 35.1.25).
Neosporosis

Neosporosis is caused by the coccidian protozoan Neospora caninum. The organism is morphologically similar to Toxoplasma gondii (for review, see Buxton et al., 2002). Canine neosporosis has been reported in many countries worldwide. Dogs are both the definitive and intermediate hosts of this protozoan (McAlisters et al., 1998). The sexual cycle of N. caninum is completed in the gastrointestinal tract of dogs (definitive host), following ingestion of tissue cysts, and oocytes are shed in feces. Oocysts sporulate in the environment and are then infective. After being ingested in an intermediate host, the oocysts release sporozoites in the gut. Sporozoites change into tachyzoites which then spread throughout the body, leading to tissue cyst (bradyzoite) formation. Transmission of neosporosis by the transplacental route occurs (Dubey et al., 1990); consequently, reports of canine neosporosis commonly involve neonatal infections. Clinical disease is most often reflective of neuromuscular disease in dogs, however, but other clinical signs of polymyositis, myocarditis, hepatitis, and dermatitis may manifest following infection.

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Definitive diagnosis is made based upon identifying the organism in CSF, tissue, or feces using routine cytological/histopathological techniques. However, it should be noted that oocyst shedding has not been described in cases of clinically active neosporosis. Given the similar morphologic appearance of N. caninum with T. gondii, neosporosis may be misdiagnosed as toxoplasmosis at histopathologic examination. However, given that the two organisms are antigenically dissimilar and have unique DNA sequences, N. caninum can be distinguished from T. gondii by using immunohistochemistry and PCR (Lindsay & Dubey, 2000). An IFA test can also differentiate N. caninum from T. gondii. Clinical signs suggestive of neosporosis combined with positive serology or the presence of antibodies in the CSF, with exclusion of similarly presenting disease such as T. gondii, should result in a presumptive diagnosis of neosporosis. Therapy is similar to that for toxoplasmosis. In particular, trimethoprim-sulfadiazine combined with pyrimethamine, sequential treatment with clindamycin, trimethoprim-sulfadiazine, and pyrimethamine, or clindamycin alone have been used to treat neosporosis (Lindsay & Dubey, 2000). The prognosis is grave for dogs with severe neosporosis-induced neuromuscular disease.
has a worldwide distribution. Cats are both definitive and intermediate hosts of *T. gondii*. Because cats are definitive hosts, they are the only species that can shed oocysts. It should be noted, however, that dogs can pass *T. gondii* oocysts in their feces after the ingestion of infected feline feces (Lindsay et al., 1997). Many mammalian species can act as intermediate hosts. In the cat, ingested *T. gondii* bradyzoites (from tissue cysts) undergo a typical coccidian intestinal life cycle, and infected cats excrete oocysts in their feces that, after 1–5 days, sporulate and become infectious sporozoites (Dubey, 2004). The oocysts are resistant to environmental conditions, and they may remain infectious for months to years (Dubey, 2004). Ingestion of the oocysts by a susceptible host results in rapid division of sporozoites in the gut epithelium. The resultant tachyzoites are 4–8 µm by 2–4 µm, and are spread throughout the body via blood and lymphatics, and encyst in the brain, skeletal, and cardiac muscles, as well as the liver. The encysted forms, termed bradyzoites, survive in tissues for the life of the host. Ingestion of bradyzoites by a new host dissolves the cyst wall and transforms them into tachyzoites, which ultimately encyst again. Transmission of *T. gondii* may occur transplacentally in cats following ingestion of oocysts in contaminated food or water, or from ingestion of tissues containing bradyzoites (Dubey, 1986).

Ocular disease associated with *T. gondii* is more commonly observed in cats than in dogs, and, in the dog, it is usually not associated with systemic manifestations of the disease. In both experimental and natural canine infections with *T. gondii*, the reported ocular lesions (in order of decreasing frequency) were a mononuclear anterior uveitis (35 of 60 dogs), retinitis (27 of 60), choroiditis (18 of 60), extraocular myositis (12 of 60), scleritis (3 of 60), optic neuritis (3 of 60), and keratoconjunctivitis (Piper et al., 1970; Swinger et al., 2009). Systemic disease in dogs with *T. gondii* is relatively rare, but when it occurs, it is usually associated with other diseases, such as canine distemper virus, or with other systemic, debilitating or immunocompromising states (Dubey, 1985; Dubey et al., 1989; Piper et al., 1970; Webb et al., 2005b). *T. gondii* appears to be a very significant cause of ocular lesions in systemically healthy dogs and cats on the basis of correlating lesions with positive serologic results. Because of the ubiquitous presence of *T. gondii*, it should be considered in the differential diagnosis of endogenous anterior uveitis and chorioretinitis regardless of whether systemic signs are present (Busanschan & Rootman, 1985; Dubey, 1985, 1986; Dubey et al., 1989; Piper et al., 1970).

A definitive diagnosis of toxoplasmosis can be made if the organism is detected in tissue. However, bradyzoites or tachyzoites are rarely detected in tissues, effusions, or fluids including aqueous humor and CSF. A diagnosis of toxoplasmosis is usually made on the basis of serologic tests using an ELISA for *T. gondii*-specific immunoglobulin (Ig) M and IgG. Paired serum samples at 2- to 3-week intervals are preferred for determining rising titers or seroconversion from IgM to IgG titers. However, *T. gondii*-specific antibodies can be detected not only in the blood of clinically ill dogs, but also in normal dogs. A positive IgM titer is correlated more with clinical toxoplasmosis than is the IgG titer because IgM antibodies are rarely detected serologically in clinically healthy animals. However, a fourfold or greater increase in IgG titer against *T. gondii* is also suggestive of recent or active toxoplasmosis.

Toxoplasmosis may be a self-limiting disease that does not require therapy, but if systemic signs or active intraocular inflammation is present, systemic therapy is usually advised. Oral clindamycin, 25 mg/kg every 12 hours for 21–30 days, and topical corticosteroids as well as atropine are recommended for ocular surface and anterior uveal inflammation. Clindamycin and oral corticosteroids are recommended for posterior uveal inflammation.

Toxoplasmosis is a significant zoonotic disease (Dubey, 2004). Clinical signs of toxoplasmosis may develop in the fetus of pregnant mothers experiencing a primary *T. gondii* infection. Ocular disease, and other manifestations such as stillbirth, may be noted in infected fetuses. As such, prevention of toxoplasmosis is recommended. Restricting the dog’s ability to hunt and the dog’s exposure to cat feces will help prevent canine toxoplasmosis. In addition, litter boxes for cats should be changed daily (pregnant women should avoid this task), and dogs (and humans) should not be fed raw or incompletely cooked meat.

**Trypanosomiasis**

Trypanosomiasis is caused by the hemoparasitic protozoan of the genus Trypanosoma. Transmission of Trypanosoma infection is by the tsetse fly; however, dogs may also become infected with the disease by ingesting Trypanosoma-infected meat.

Common clinical manifestations of trypanosomiasis in dogs include weakness, anorexia, emaciation and fever. Ocular signs have been reported in dogs with trypanosomiasis as well. *T. venezuelense* has been reported to produce blepharitis, conjunctivitis, keratitis, and endophthalmitis in a dog (Garcia et al., 1983). The organism was present in the eye as well as the blood of the affected dog (Garcia et al., 1983). T. brucei infections in the dog and cat frequently produce corneal opacification, blepharitis, conjunctivitis, and keratitis (Ikede, 1974; Mortelmans & Neetens, 1975; Nwosu & Ikeme, 1992).

The diagnosis of trypanosomiasis is made by identification of the organism on evaluation of blood smears or lymph node aspirates (Bradley et al., 2000; Garcia et al., 1983). Other methods such as IFA and ELISA, and PCR may also be used to diagnose the disease (Bradley et al., 2000; Desquesnes & Davila, 2002). In cases of anterior segment ocular disease, aqueous centesis may demonstrate the trypanosomes.

Chemotherapy for trypanosomiasis is dependent on the species of Trypanosoma causing the infection in the animal (for human reviews, see Sra et al., 2004; Urbina & Docampo, 2003). Drugs used in canine cases include diminazene (infected with *T. Evansii*; Varshney et al., 2003 and nifurti-
Canine ehrlichiosis is a tick-borne disease caused by Ehrlichia chaffeensis, Ehrlichia ewingii, and Anaplasma phagocytophilum. Prognosis for animals with trypanosomiasis is considered poor. Infection with Trypanosoma is life-long.

**Rickettsial Diseases**

Members of the bacterial order Rickettsiales are the cause of numerous conditions in numerous species of vertebrates (for comprehensive review, see Parola et al., 2005; Raoult & Roux, 1997). All members of the order Rickettsiales are obligate intracellular parasitic bacteria that require host cells to replicate (McQuiston et al., 2003; Parola et al., 2005). The development of molecular taxonomic methods has resulted in the reclassification of several species of rickettsia (Dumler et al., 2001). Rickettsial diseases are transmitted via an arthropod, typically fleas or ticks (Parola et al., 2005). Two common groups of diseases still considered rickettsial diseases in veterinary medicine include (1) rickettsioses caused by bacteria of the genus Rickettsia, and (2) ehrlichioses and anaplasmoses caused by bacteria in the family Anaplasmataceae (Parola et al., 2005). Many rickettsial diseases are considered zoonotic (McQuiston et al., 2003). Because of these unique features of bacteria of the order Rickettsiales, we consider them here separately from other bacterial diseases that manifest, in part, with ocular disease.

**Canine Cyclic Thrombocytopenia**

Canine cyclic thrombocytopenia is caused by A. platys (formerly Ehrlichia platys), a bacterial organism which strictly replicates in platelets, and is not considered zoonotic (McQuiston et al., 2003; Sainz et al., 1999). A tick vector is the presumed mode of transmission of A. platys (Neer et al., 2002). A. platys is distributed in the southeastern United States, southern Europe (Greece, Italy, France), and South America (Neer et al., 2002).

A. platys replicates within platelets, resulting in diminished platelet survival and thrombocytopenia. The disease follows a cyclical course. Specifically, platelet counts decline dramatically within a few days of A. platys infection, and then they rise within a few days, thereby following a cyclical course at 1- to 2-week intervals. A. platys has been described as producing uveitis in a dog, but the syndrome was mild and improved rapidly (Glaze & Gaunt, 1986). Diagnosis of A. platys depends upon observing the organism within platelets, detecting serum antibodies for the organism or by detecting the presence of organismal DNA via PCR (Neer et al., 2002). Treatment is aimed at eliminating the bacteria by using doxycycline as the first drug of choice (Neer et al., 2002). Topical ocular therapy for an underlying uveitis includes use of topical corticosteroids and atropine. Clinical improvement is typically noted within 24-48 hours after commencement of antimicrobial therapy (Neer et al., 2002).

**Canine Ehrlichiosis**

Canine ehrlichiosis is a tick-borne disease produced by E. canis, Ehrlichia chaffeensis, Ehrlichia ewingii, Ehrlichia equii, A. platys (formerly E. platys), Anaplasma phagocytophilum (formerly Ehrlichia phagocytophila), and Neorickettsia risticii (formerly Ehrlichia risticii) (Dumler et al., 2001; Mylonakis et al., 2004b). As mentioned in the introduction to this section, Ehrlichia spp. and Anaplasma spp. are small, gram-negative, pleomorphic, obligate intracellular bacteria (McQuiston et al., 2003; Parola et al., 2005). The distribution of canine ehrlichiosis is related, in part, to the geographical distribution of ticks that act as vectors for these bacteria (Neer et al., 2002). In particular, E. canis is transmitted by the brown dog tick, Rhipicephalus sanguineus, while transmission of E. chaffeensis and E. ewingii is via the lone star tick, Amblyomma americanum (for a list of worldwide geographic distribution of rickettsial diseases and their vectors, see Neer et al., 2002). Animals may be coinfected with more than one rickettsial agent (Mylonakis et al., 2004a).

Canine ehrlichiosis is divided into an acute disease phase (2-4 weeks), a subclinical phase (months to years), and a chronic disease phase (Mylonakis et al., 2004b). As such, a dog with chronic, subclinical infection may be moved from an endemic to a nonendemic area and develop signs of the disease years after the initial infection (Gould et al., 2000). A cute disease phase clinical signs, including general malaise, anorexia, fever, and ocular and nasal discharge, are typically transient, and animals will typically recover spontaneously without treatment. Hematological findings in the acute phase of the disease also include thrombocytopenia, leucopenia, and nonregenerative anemia (Panciera et al., 2001). During the chronic disease phase of ehrlichiosis, common clinical signs include general malaise, bleeding tendencies, anorexia, pale mucous membranes, fever, lymphadenopathy, splenomegaly, and uveitis (Mylonakis et al., 2004b). Hematological features of dogs presenting with the chronic phase of the disease also include nonregenerative anemia, thrombocytopenia, and leucopenia (Mylonakis et al., 2004b).

Ocular signs may be present in all stages, but animals are not usually presented for diagnosis until the chronic stage. Experimental inoculation of E. canis in dogs has resulted in the development of chorioretinitis and anterior uveitis in addition to meningitis during the acute phase of the disease (Panciera et al., 2001). Meanwhile, inoculation of E. ewingii or E. chaffeensis or A. phagocytophilum in dogs did not result in the development of ocular or meningeal pathology (Panciera et al., 2001).

The prevalence of ocular lesions in canine ehrlichiosis has been reported as 10%-37%; when present, such ocular lesions can produce devastating ocular disease that is typically bilateral (Leiva et al., 2005; Swanson & Dubielzig, 1986; Troy et al., 1980). It has also been reported that approximately 18% of the cases of uveitis in North Carolina, USA are the result of some infectious etiology (Massa et al., 2002). Of these infectious causes of uveitis, nearly 40% of them are associated with E. canis infection (Massa et al., 2002). The ocular lesions themselves result from either a platelet deficiency or, more commonly, a vasculitis (or both). In a recent retrospective study of dogs with ocular manifestations of canine monocytic
ehrlichiosis, uveitis was the most common ocular diagnosis with 58/90 (64.5%), 8/90 (8.9%), and 24/90 (26.6%) of affected dogs having anterior, posterior, or panuveitis, respectively (Komnenou et al., 2007). Massive orbital and ocular hemorrhages have been observed, but more commonly, a uveitis with hemorrhagic overtones is the basic lesion (Fig. 35.1.26 and Fig. 35.1.27). Retinal vessels may be engorged and have perivascular infiltrates. Retinal hemorrhages are common, and retinal detachments may be observed, either from massive subretinal hemorrhage or from exudates (Fig. 35.1.28 and Fig. 35.1.29) (Leiva et al., 2005). Optic neuritis with engorged retinal vessels and papillary hemorrhages may also occur. In addition, corneal ulceration, necrotic scleritis, 

Figure 35.1.26. Photograph of the right eye of a 7-year-old, male mixed-breed dog with monocytic ehrlichiosis. Note the conjunctival hemorrhage, hyphema, and slight miosis. (Reprinted with permission from Leiva, M., Naranjo, C. & Pena, M.T. (2005) Ocular signs of canine monocytic ehrlichiosis: a retrospective study in dogs from Barcelona, Spain. Veterinary Ophthalmology, 8, 387–393.)

Figure 35.1.27. Photograph of the left eye of a 5-year-old, male, mixed-breed dog with monocytic ehrlichiosis. Note the conjunctival hyperemia, rubecosis iridis, and iridal hemorrhages. (Reprinted with permission from Leiva, M., Naranjo, C. & Pena, M.T. (2005) Ocular signs of canine monocytic ehrlichiosis: a retrospective study in dogs from Barcelona, Spain. Veterinary Ophthalmology, 8, 387–393.)


Figure 35.1.29. Left fundus of a 4-year-old, female German Shepherd dog with monocytic ehrlichiosis. Note the exudative retinal detachment and vitreous hemorrhage. (Reprinted with permission from Leiva, M., Naranjo, C. & Pena, M.T. (2005) Ocular signs of canine monocytic ehrlichiosis: a retrospective study in dogs from Barcelona, Spain. Veterinary Ophthalmology, 8, 387–393.)
low tear production, and orbital cellulitis have been reported (Komnenou et al., 2007). Experimentally, discrete perivascular infiltrates have been described during the subacute stage, but such infiltrates have not been described in clinical cases (Ellet et al., 1973). An atypical form of ocular lesion of canine ehrlichiosis involving bilateral, melting scleral lesions associated with uveitis, and resultant subconjunctival uveal prolapse was described (Martin, 1999). Histopathologically, the ocular lesions are typically a mononuclear perivasculitis.

Diagnosis of ehrlichiosis involves the direct visualization of morulae in peripheral blood smears (only been found in 11% of dogs with chronic ehrlichiosis), detection of E. canis antibodies, or PCR amplification of Ehrlichia spp. DNA (Belanger et al., 2002; Mylonakis et al., 2004b; Neer et al., 2002; Waner et al., 2001; Wen et al., 1997).

The mainstay of therapy for canine ehrlichiosis includes the administration of doxycycline or tetracycline (Neer et al., 2002; Sainz et al., 2000). The short-term prognosis for ehrlichiosis in dogs is typically good during the acute phase or mild chronic phase of the disease; however, long-term prognosis of chronic canine ehrlichiosis is variable to grave (Mylonakis et al., 2004b; Neer et al., 2002). Consensus on treatment of the ocular signs associated with canine ehrlichiosis has not been made. Nevertheless, therapy for ocular lesions associated with canine ehrlichiosis should include topical corticosteroids and atropine for anterior uveitis. In addition, a recommendation for systemic administration of anti-inflammatory dosages of corticosteroids in the presence of posterior segment disease has been made (Stiles, 2000).

Rocky Mountain Spotted Fever

Rickettsia rickettsii, a small coccobacillary, gram-negative, obligate intracellular bacterium, is the causative agent of Rocky Mountain spotted fever (RM SF) (for review, see Parola et al., 2005; Warner & Marsh, 2002). Rodents and other small mammals serve as reservoirs for R. rickettsii (Warner & Marsh, 2002). R. rickettsii is transmitted by ticks; the vector and reservoir ticks are Dermacentor andersoni (Rocky Mountain wood tick), D. variabilis (American dog tick), Amblyomma americanum (Lone star tick), Amblyomma cajennense (Cayenne tick), Rhiciphealus sanguineus (brown dog tick), and Haemaphysalis leporispalustris (rabbit tick) (Warner & Marsh, 2002).

Incubation time varies from 2 to 14 days following infection via a tick bite (Warner & Marsh, 2002). R. rickettsii invade small blood vessels and subsequently replicate in endothelial cells, thereby damaging these cells and causing vasculitis and activation of primary and secondary hemostasis systems (Warner & Marsh, 2002). Systemic signs of RM SF include fever within 4–5 days of tick attachment (Warner & Marsh, 2002). Hemorrhages (i.e., petechiae and ecchymoses) occur commonly and are often seen on mucous membranes including those surrounding the eye (Warner & Marsh, 2002). Common clinicopathologic findings include thrombocytopenia, leukocytosis, hypoalbuminemia, and proteinuria (Mikszewski & Vite, 2005). Ocular and neurologic involvement is common with R. rickettsia infection, and clinical findings are consistently due to vasculitis. Signs of conjunctivitis, chemosis, petechiae of the conjunctiva, iris and retina, hyphema, mild anterior uveitis, retinal edema, and retinal vasculitis are common, occurring in 9 of 11 dogs in one series of dogs infected with RM SF (Davidson et al., 1989). In another study, fundic examination revealed chorioretinal lesions and retinal hemorrhage (Mikszewski & Vite, 2005). In experimentally infected dogs, uveitis was noted 14–21 days after onset of the signs of acute infection (Davidson et al., 1990). Fluorescein angiography in these experimentally infected cases revealed increased retinal vascular permeability which developed within 1–2 days after the onset of fever (Davidson et al., 1990). Leakage of vessels peaked during the second week of infection and persisted past the point of clinical and clinico-pathologic recovery. The permeable areas involved venules more than arterioles, and smaller vessels were affected more frequently than larger vessels. These areas of retinal vascular leakage developed too early to be associated with immune complexes (Davidson et al., 1990). Other ocular abnormalities that may be noted on ocular examination are found when the CNS is affected. For example, one study found that some dogs with RM SF had abnormal nystagmus (spontaneous or positional nystagmus) and/or loss of menace response (Mikszewski & Vite, 2005).

Diagnosis of RM SF is made based upon consistent history, clinical and hematological findings consistent with RM SF, and identifying R. rickettsii through immunofluorescent testing (tissue), presence of circulating antibodies, or by identifying organism DNA using PCR (Warner & Marsh, 2002). A fourfold increase in circulating IgG, from acute to convalescent (≥3 weeks apart) measurements, is diagnostic for recent infection (Warner & Marsh, 2002). Similarly, an increase in circulating IgG in acute to convalescent sera is diagnostic for RM SF. Importantly, a single IgG titer is non-definitive because IgG may remain high for several years after infection (Warner & Marsh, 2002). If the disease is suspected, trial therapy with tetracyclines or chloramphenicol is warranted until test results are available (Warner & Marsh, 2002). Response to therapy is usually rapid and may be used in establishing a presumptive diagnosis (Mikszewski & Vite, 2005; Warner & Marsh, 2002). The inflammatory lesion of the anterior ocular segment should be treated with topical corticosteroids and atropine. The ocular lesions of RM SF usually resolve quickly with therapy. Immunity following infection with R. rickettsii is long lasting and provides protection against subsequent reinfection (Warner & Marsh, 2002). Reducing the dog’s exposure to ticks and prompt removal of attached ticks are helpful to prevent RM SF (Warner & Marsh, 2002).

Viral

Canine Distemper

Canine distemper virus (CDV) is caused by an enveloped, single-stranded RNA Morbillivirus in the Paramyxoviridae
family (for review, see Deem et al., 2000). Several lineages or genotypes of CDV exist that are variously distributed throughout many continents (Demeter et al., 2007; Martella et al., 2006, 2008). CDV infects a wide variety of families of animals including Canidae (e.g., dogs), Procyonidae (e.g., raccoons), Ursidae (e.g., bears), Mustelidae (e.g., ferrets, skunks), and Hyaenidae (e.g., hyaena). The virus is spread mainly by inhalation of viral particles in aerosolized respiratory or other infected secretions such as urine. Widespread vaccination of dogs has markedly decreased the incidence of typical disease, and partial immunity may produce disease syndromes characterized more by neurologic signs than catarrhal signs of pneumonia and gastroenteritis. Clinical signs of CDV will vary with the strain of virus, immunity, and age of the host.

Acute ocular signs of CDV are usually associated with a bilateral conjunctivitis with serous ocular discharge that progresses to mucopurulent in nature. The palpebral conjunctiva is primarily involved but the cause of this conjunctivitis may be difficult to diagnose if respiratory and gastrointestinal signs are either minimal or subclinical. The cornea has not been described as being a target for the virus unless a lacrimal adenitis or dehydration has resulted in a marked reduction in tear production (i.e., KCS). The CDV may produce an inflammatory reaction in the lacrimal gland characterized by mononuclear and neutrophilic inflammatory infiltration as well as by marked degenerative changes in the glandular tissue (Martin & Kaswan, 1985). A recent study revealed that the histopathological changes in conjunctival samples obtained from dogs with CDV-induced KCS were similar to those with noninfectious KCS (de Almeida et al., 2009). In particular, a predominant lymphoplasmacytic infiltration, and acantholysis and keratinization of the ocular surface were described (de Almeida et al., 2009). Corneal ulceration is often profound with the development of multiple descemetoceles with or without corneal perforations in one or both eyes. KCS usually resolves in 4–8 weeks if the animal recovers from the systemic infection. A noster mechanism for corneal involvement is distemperencephalitis producing a fifth cranial nerve palsy (i.e., neurotrophic keratitis).

CDV often produces a multifocal, nongranulomatous chorioretinitis, which is usually an incidental finding. The incidence of chorioretinitis is unknown but probably varies, as do those of the neurologic signs, with the strain of virus and the immunocompetency of the host. In one study, dogs with neurologic forms of CDV had a 41% overall prevalence of chorioretinal lesions; in contrast, 83% of dogs with chronic leukoencephalopathy syndromes had chorioretinal lesions (Thomas et al., 1993). These lesions are typically multifocal, and they are reportedly more frequent in the peripheral to midperipheral nontapetal fundus (Fischer, 1971). A cute lesions must be differentiated from scars, because the latter will not correlate well with acute systemic signs. Active lesions in the nontapetal region are white, somewhat fluffy, and have mildly indistinct borders (Fig. 35.1.30). A cute lesions progress to scars that are white, flat, and have sharply demarcated borders. In the tapetal region, the acute lesions are subtle, with loss of tapetal detail, and they may have a mild, overlying haziness. With time, these develop into hyperreflective lesions with sharp borders and varying degrees of pigment clumping. Lesions in both the tapetal and nontapetal areas are typically circular to oval in shape and often become confluent with adjacent lesions, thus producing a scalloped pattern. Occasionally, chorioretinal lesions are diffuse, blinding, and may mimic the genetic syndrome of progressive retinal atrophy, with diffuse tapetal hyperreflectivity, optic nerve atrophy, and nontapetal pigment dispersion.

Histopathologic retinal changes are characterized by retinal degeneration with, in some instances, perivascular cuffing. Lesions may be focal or diffuse, characterized by loss of ganglion cells, proliferation and clumping of the RPE, focal or diffuse atrophy of photoreceptors, disorganization of retinal layers, focal gliosis, choroidal atrophy, and CDV inclusion bodies in glial cells. Acute cases may have retinal edema, vascular congestion, and perivascular cuffing (Jubb et al., 1957). The variations in reported ocular lesions may result from the stage of examination, immunocompetence of the animal, and the multiple mechanisms by which the lesions are produced. In the CNS, lesions of acute infections in young or immunocompromised patients are characterized by neuronal necrosis, with a minimal inflammatory reaction. With immunocompetent hosts or chronicity, the CNS lesions are...
characterized by mononuclear inflammation and secondary demyelination (Thomas et al., 1993).

The most dramatic clinical ocular problem associated with CDV is optic neuritis, which is characterized by an acute onset of bilateral blindness and mydriasis. If inflammation extends rostrally to the optic disc/papilla, ophthalmoscopic signs of peripapillary hemorrhages and edema, retinal vascular congestion, and elevation of the papilla are observed (Fig. 35.1.31). If the optic neuritis remains retrobulbar, however, the diagnosis is made on the basis of exclusion (i.e., blind eyes with dilated pupils and normal retinal function as tested by ERG. The optic neuritis syndrome may be isolated, prodromal, or concurrent with other neurologic signs of CDV. Distemper-associated blindness also may occur with inflammation of the optic tracts, lateral geniculate nucleus, optic radiation, or occipital cortex.

Ocular signs are suggestive of, but not definitive for, CDV. Acute lesions of chorioretinitis usually correlate well with concurrent systemic disease, but chorioretinal scars may not. CDV inclusions may be identified in infected monocytes, lymphocytes, neutrophils, or RBCs during evaluation of a stained peripheral blood smear. Alternatively, positive immunofluorescence by detection of viral antigen from conjunctival swabs/scrapings or blood smears, using methods such as fluorescent antibody (FA) testing may be helpful in diagnosing CDV early in the course of systemic disease (5–21 days postinoculation), but negative findings are inconclusive (Fairchild et al., 1967). This should not inhibit the examiner from performing immunofluorescent antibody testing, however, because one report on encephalomyelitis found an overall positive rate of 54% (and one as high as 75%) despite the mean duration of neurologic signs being 20 days (Fischer, 1971). Furthermore, CDV has immunohistochemically been identified and diagnosed in skin and footpads from infected dogs (Haines et al., 1999). Reverse-transcriptase polymerase chain reaction (RT-PCR) assays have been shown to be both sensitive and specific for detection of both experimentally induced CDV (Frisk et al., 1999) and naturally induced CDV. In particular, CDV RNA has been detected in urine, tonsils, whole blood, and conjunctival swabs from dogs with natural infections with CDV (Elia et al., 2006; Saito et al., 2006). A semi-nested PCR system with specific probes now permits characterization of major CDV lineages and distinction between certain field- and vaccine-associated CDV strains (Martella et al., 2007). Ribavirin, a purine nucleoside analogue, was shown to be highly effective at inhibiting replication of CDV in vitro (Elia et al., 2008). However, because no specific antiviral therapy against CDV is, as yet, commercially available, treatment is mainly symptomatic. Conjunctivitis and decreased tear production are treated with topical antibiotics and lubricants. A cute optic neuritis is treated with systemic anti-inflammatory dosages of glucocorticoids if other signs of CDV are absent. Vaccination is the key to preventing CDV. The prognosis for dogs with neurologic disease is considered guarded to poor.

Herpesviruses

Canine Herpesvirus Canine herpesvirus is an enveloped, double-stranded DNA virus of the Alpha-herpesviridae family and infects all canids. Transmission of the virus can occur in utero or during parturition. Puppies make contact with the virus in infectious secretions on passing through the birth canal of an infected bitch or may contract viral infection from contact with other infected puppies. Canine herpesvirus replicates in epithelial cells of the oropharynx and mucosa of the tonsils following oronasal exposure of neonatal puppies. The virus then enters macrophages which spread the infection hematogenously. The virus may remain latent in sensory ganglia and lymphoid tissue (Miyoshi et al., 1999). Litters of stillborn puppies or abortions may occur following transplacental infections. Young puppies (<2–3 weeks of age) most frequently develop clinical signs of canine herpesvirus, while infection tends to be confined to the respiratory and genital tracts in older dogs (Hill & Mare, 1974).

For further details on CHV infection, the reader is referred to a recent review of CHV (Evermann et al., 2011) which documents the clinical features of five forms of CHV-associated infections including the ocular form. Ocular manifestations of CHV infection are dependent on the age and immune competence of the host and may arise during both primary and recurrent infections (Evermann et al., 2011).
Canine herpesvirus infection in adults tends to be restricted to ocular surface diseases affecting the cornea, conjunctiva, and eyelids including combinations of blepharitis, conjunctivitis, and keratitis (ulcerative and nonulcerative). In primary CHV ocular infections, lesions tend to be bilateral and are not always symmetrical, and most resolve spontaneously without permanent scarring. Naturally acquired recrudescent CHV ocular infections are reported in dogs with immunocompromising systemic diseases and those receiving immunosuppressive medications. In immunocompetent dogs, CHV ocular infection is frequently mild and self-limiting, although it may recur. Canine herpesvirus infection has produced a transient conjunctivitis and vaginitis of 4–5 days’ duration (Hill & Mare, 1974). The marked follicular reaction in the vagina raised speculation regarding whether it might be responsible for conjunctival syndromes characterized by follicular hyperplasia, but this has been discounted by the lack of transmissibility, inability to culture, and failure to demonstrate canine herpesviral antigen from dogs with this syndrome (Jackson & Corstvet, 1975, 1980). Conjunctival petchiae are frequently reported in dogs with CHV and are uncommon with most other causes of canine conjunctivitis, and hence, this lesion should be considered suggestive of CHV (Ledbetter et al., 2009a, 2009b; Malone et al., 2010). Two adult dogs were diagnosed with canine herpesvirus-associated dendritic corneal ulcers (Ledbetter et al., 2005). Dendritic corneal ulcers are strongly indicative of CHV infection in the dog (Evermann et al., 2011). A recent report described an outbreak of CHV infection in a colony of 27 young adult laboratory Beagles with conjunctivitis, ulcerative keratitis (ranging from punctate to dendritic to geographic in appearance) and nonulcerative keratitis being detected in 100%, 26%, and 19% of affected dogs, respectively (Ledbetter et al., 2009b).

Until recently, canine herpesvirus has been thought of almost exclusively as a disease of the neonate, in which it is usually fatal. Puppies dying of herpesvirus infection have been reported to have bilateral panuveitis with keratitis, synchiae, cataracts, retinal necrosis and disorganization, retinal atrophy and dysplasia, and optic neuritis as well as atrophy. Because of the high fatality rate, the clinical implication of these lesions is unknown.

Diagnosis of canine herpesvirus is by identifying clinical signs suggestive of the disease in young puppies combined with necropsy lesions. Definitive confirmation of canine herpesvirus involves identification of virus, viral antigen, or viral DNA by transmitting electron microscopy, immunohistochemical methods, or PCR of infected tissues, respectively.

Therapy for canine herpesvirus is largely supportive; however, neonatal fatalities are common. Topical ophthalmic antiviral agents such as 0.1% idoxuridine, 1% trifluridine, and cidofovir 0.5% have been used to treat CHV ocular disease. There is no current commercial vaccine for canine herpesvirus.

**Pseudorabies**

Pseudorabies is caused by an enveloped, double-stranded DNA virus of the Alpha-herpesviridae family (for review, see Mettenleiter, 2000). This virus is capable of infecting a variety of animals, including the cat, cow, dog, and pig. Pigs are the main reservoirs of pseudorabies. Most infected dogs have a history of ingestion of infected raw pork. A after ingestion of the virus, pseudorabies enters peripheral nerve endings in the mucosa and spreads along axons to the brain.

Clinical signs of pseudorabies include variable neurologic disturbances including ataxia, cervical rigidity, and ptosis. Once clinical signs of pseudorabies have manifested, death from pseudorabies usually occurs quickly in dogs. In particular, 94% of dogs have been reported to die within 48 hours of the onset of signs of pseudorabies (Monroe, 1989). Ocular manifestations of this disease have been attributed to neurologic lesions, and include blindness, miosis, mydriasis, anisocoria, abnormal PLRs, ptosis, facial paralysis, and epiphora (Monroe, 1989).

Presumptive diagnosis of pseudorabies is made based on clinical signs and history of the dog having been exposed to pigs or infected raw pork. The definitive diagnosis of pseudorabies is confirmed based on identification of the virus by in situ hybridization, immunohistochemistry, or PCR of infected brain or tonsil (Cao et al., 2005; Quiroga et al., 1998).

Therapy for canine patients infected with pseudorabies is supportive, but most dogs do not survive the infection. There is no approved vaccine available for dogs against pseudorabies.

**Infectious Canine Hepatitis (Canine Adenovirus Type-1)**

Canine adenovirus type-1 (CAV-1), a nonenveloped, double-stranded DNA virus in the Adenoviridae family, is the causative agent of infectious canine hepatitis (ICH). ICH produces clinical disease in dogs, foxes, and bears. The virus replicates in regional lymph nodes and tonsils, following which the viremia develops resulting in infection of other tissues. In particular, CAV-1 has a predilection for liver parenchyma, vascular endothelium, and the reticuloendothelial system. The ocular lesions of ICH have mostly become a historical footnote since Rubarth described them in 1947 (Rubarth, 1947). CAV-1 may produce ocular lesions of anterior uveitis and corneal edema (Fig. 35.1.32 and Fig. 35.1.33) and has been estimated to produce ocular lesions in approximately 20% of dogs during the recovery phase of a natural infection (Carmichael, 1965). More troubling was the modified-live strains of CAV-1 used in vaccine production that were also capable of producing ocular lesions (Fig. 35.1.34), with an estimated prevalence of 0.4% or less (Curtis & Barnett, 1973b). The universal use of canine adenovirus type-2 (CAV-2) for immunization against ICH, however, has all but eliminated this complication of vaccination. ICH and its ocular manifestations still occur in countries without routine ICH immunizations.

Ocular lesions of CAV-1 manifest approximately 7–21 days after virus inoculation. Subcutaneous inoculation with
If the response is incomplete, immune complexes form, which, with a balance of antibody and antigen in the presence of complement, stimulate leukocytic, chemotactic, and other inflammatory factors. The resultant neutrophilic and monocytic responses release lysosomal enzymes that, when directed at viral antigen in the corneal endothelium, result in endothelial damage and corneal edema. The histopathologic response is a nongranulomatous anterior uveitis that spares the posterior segment (Carmichael et al., 1975).

The ocular reaction is bilateral in up to approximately 30% of cases. The most visible ocular lesion is corneal stromal edema. Occasionally, however, a dog will have blepharo-spasms, miosis, hypotony, and aqueous flare 1–2 days before the corneal edema manifests. Corneal edema begins near the limbus, and it may remain focal or progress rapidly to generalized edema. A marked hypotony combined with altered corneal rigidity may result in keratoconus. The conjunctiva and episclera are usually hyperemic, and though the corneal edema may obscure deeper examination, anterior uveitis may manifest, with iris texture changes, plasmoid aqueous, and miosis. Most reactions occur in young animals that have endothelial regenerative capabilities, so the corneal edema is usually transient, taking from a few days to between 2 and 3 weeks to clear. In some instances, the edema is either permanent or may require several months to clear. If the edema persists, eventually scarring and pigmentation develop in the cornea; the Afghan Hound is reported to have an increased risk for persistent corneal edema (Curtis & Barnett, 1981). The anterior uveitis is notable for the lack of residual synchiae. Glaucoma, which is the most significant ocular sequela of CAV-1, usually results in blindness, because it is masked.

CAV-1 produces ocular lesions 2–3 weeks after administration, and intravenous inoculation produces lesions in 7–14 days. This correlates with the observation of ocular lesions developing in the recovery phase of clinical disease. The most apparent ocular lesions are observed after clinical infection, but the virus invades the eye earlier (4–8 days postinoculation) and may produce a mild, subclinical anterior uveitis (Carmichael, 1965; Carmichael et al., 1975; Curtis & Barnett, 1973b).

The ocular lesions, whether resulting from natural infection or induced by vaccine, are considered to be due to an immune-complex, Arthus, reaction that occurs 10–21 days after vaccination or in the recovery stage of natural infection. The events suggest that if the virus persists in the anterior segment, it stimulates a local immune response that either restricts growth or, if incomplete, allows for viral persistence.
during the early stages by the preexisting corneal edema and conjunctival hyperemia (Carmichael, 1965; Curtis & Barnett, 1973a, 1973b).

Tentative CAV-1 infection is diagnosed on the basis of the typical ocular lesions combined with a history of recent vaccination or illness (i.e., acute hepatic disease in a dog with poor vaccination) in a puppy or young (<2 years of age) dog. Definitive diagnosis is made based upon immunohistochemistry for CAV-1 and detection of viral DNA using PCR in infected tissue (Caudell et al., 2005; Chouinard et al., 1998).

Therapy of CAV-1 is symptomatic and similar to that for other forms of nonseptic anterior uveitis. Specifically, therapy includes topical corticosteroids, atropine, prostaglandin inhibitors, and perhaps, hypertonic salt solution or ointment.

**Papillomavirus**

Papillomaviruses are nonenveloped, double-stranded DNA viruses in the family Papillomaviridae (for review, see Nichols & Stanley, 1999). Two forms of papillomaviruses (oral form and conjunctival form) have been associated with causing papillomas involving the canine eye and adnexa. Papillomaviruses are usually species-specific and antigenically distinct. Oral papillomas, which are usually found in young animals, result from infection with a canine oral papillomavirus (COPV), and the solitary skin lesions of older animals result from infection with a cutaneous papilloma-producing virus. The COPV may, in addition to causing oral papillomas, produce lesions on the eyelids, conjunctiva, and cornea. Not all ocular papillomas result from the COPV, but lesions in dogs younger than 2 years of age or with multiple lesions probably do (Bonney et al., 1980a, 1980b; Hare & Howard, 1977; Sansom et al., 1996).

Papillomas develop 4–8 weeks following infection with COPV, and they usually regress within 4–8 weeks after their development as T cells migrate into the papilloma from a cell-mediated immunity response (Nicholls & Stanley, 1999). Despite spontaneous regression of most viral papillomas, the ocular forms may not. Ocular viral papillomas have been reported in dogs as old as 9 years of age (Hare & Howard, 1977). Lesions are characteristically pedunculated and have a cauliflower-like surface. A conjunctival form that is distinct from the large cauliflower lesions has also been described; it typically manifests as a solitary lesion on the dorsal to lateral bulbar conjunctiva, in proximity to the limbus, and is often pigmented, slightly nodular, and has fronds on the surface (Sansom et al., 1996). Most lesions in older animals are solitary, but multiple lesions may develop as well (Bonney et al., 1980b; Hare & Howard, 1977; Sansom et al., 1996). Physical irritation from the lesion may preclude observation and awaiting its spontaneous regression. Excision should involve minimal handling of the papilloma, wide excision (if possible), and perhaps, cryotherapy at the base of the lesion (Bonney et al., 1980a, 1980b; Collier & Collins, 1994; Hare & Howard, 1977). There is no vaccine to prevent canine papillomaviruses.

**Tick-Borne Encephalitis Virus**

Tick-borne encephalitis virus (TBEV) is a single-stranded, enveloped RNA virus belonging to the genus Flavivirus (for review, see Gritsun et al., 2003). TBEV is seen in Europe and Asia. The virus is transmitted to humans and animals via the bite of an infected tick (Ixodes ricius—central Europe; Ixodes persulcatus—Ural, Siberia, Far East) (Gritsun et al., 2003). Several cases of TBEV infection have been reported in dogs, most of which are relatively recent and indicate an emerging disease (Gresikova et al., 1972a; Stadtbaurer et al., 2004; Tipold et al., 1993; Weissenbock & Holzmann, 1996; Weissenbock et al., 1998). It has been demonstrated that 16.4% and 24% of dogs have been exposed to the virus in Norway and Austria, respectively (Csango et al., 2004; Leschnik et al., 2002). Clinical signs develop after 5–9 days following infection with the virus (Gresikova et al., 1972b). Dogs infected with TBEV can either (1) seroconvert without clinical signs, or (2) manifest with peracute (death within 1 week), acute (animals recover, clinical signs improve within 3 weeks), or chronic disease (clinical signs resolve between 1 and 6 months) (Leschnik et al., 2002; Stadtbaurer et al., 2004; Weissenbock & Holzmann, 1996).

Clinical signs are representative of the neuropathologic changes seen in the CNS and include pyrexia, general malaise, seizures, tetraparesis, anisocoria, and neck or back pain. TBEV has been reported as a possible cause of optic neuritis in one dog (Fig. 35.1.35) (Stadtbaurer et al., 2004). Diagnosis of TBEV is made based on measuring acute and convalescent serum and CSF IgG for TBEV using an ELISA or by using immunohistochemistry on CNS tissue (Stadtbaurer et al., 2004; Weissenbock et al., 1998). Treatment of dogs with TBEV infection is purely supportive as there is no virucidal therapy for the disease. Prognosis is variable depending on the clinical form of the disease.

**Metabolic Diseases**

**Diabetes Mellitus**

Diabetes mellitus is the most common disorder of the endocrine pancreas in dogs, resulting from an absolute or relative insulin deficiency due to deficient insulin secretion by the β cells of the islets of Langerhans. Two clinically recognized forms of diabetes mellitus exist in dogs: insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). The most common form of canine diabetes mellitus is IDDM which is characterized by permanent hypoinsulinemia, thereby necessitating exogenous insulin to maintain glycemic regulation. The cause of IDDM in dogs is likely multifactorial, including genetic predispositions and pancreatitis, among others.

Ocular manifestations of both experimental and spontaneous diabetes mellitus in the dog have long been used as a model for human diabetic ocular complications (Gepts & Toussaint, 1967). In particular, the galactosemic dog has been used to study diabetic complications because of the acceler-
Chapter 35: Ocular Manifestations of Systemic Disease

Section IV

Diabetic cataractous dogs have significantly lower STT values and significantly higher corneal touch thresholds (CTTs) than nondiabetic noncataractous dogs. They also have significantly lower mean tear film breakup times (TFBUTs) than nondiabetic cataractous and nondiabetic noncataractous dogs. Conjunctival epithelial dysplasia and/or squamous metaplasia occur in 5/7 dogs. Reductions in goblet cell densities are observed in 4/7 diabetic dogs. Tear glucose concentrations are also elevated in diabetic dogs.

Ocular manifestations of diabetes mellitus in dogs include cataract formation, corneal endothelial cell loss, corneal endothelial pleomorphism and polymegathism, and retinal vascular damage such as microaneurysms. Reduced corneal sensitivity and significantly altered keratoconjunctival parameters have also been reported in diabetic dogs. In particular, diabetic cataractous dogs have (1) significantly lower STT values and significantly higher corneal touch thresholds than nondiabetic noncataractous dogs; (2) significantly lower mean tear film breakup times than nondiabetic cataractous and nondiabetic noncataractous dogs; (3) conjunctival epithelial dysplasia and/or squamous metaplasia in ventral palpebral conjunctival biopsy specimens of 5/7 dogs; (4) reductions in goblet cell densities in 4/7 diabetic dogs; and (5) elevations in tear glucose concentrations compared to...

Figure 35.1.35. Tick-borne encephalitis virus in a 3-year-old, spayed female Siberian Husky. Fundus photographs on day 0. (A) OD: The optic disc is swollen with mild peripapillary edema. (B) OS: The optic disc is markedly swollen and elevated. The peripapillary retina is detached. Note some peripapillary hemorrhages. (Reprinted with permission from Stadtbaumer, K., Leschnik, M.W. & Nell, B. (2004) Tick-borne encephalitis virus as a possible cause of optic neuritis in a dog. Veterinary Ophthalmology, 7, 271–277.)

Figure 35.1.36. (A) Photomicrograph of a section of ventromedial palpebral conjunctiva from a nondiabetic cataractous dog. Note the abundance of periodic acid-Schiff (PAS)-positive goblet cells and normal epithelial architecture (PAS; scale bar = 35 µm). (B) Photomicrograph of a section of ventromedial palpebral conjunctiva from a diabetic cataractous dog. Note the epithelial thinning and absence of goblet cells (PAS; scale bar = 35 µm). (Reprinted with permission from Cullen, C.L., Ihle, S.L., Webb, A.A. & McCarville, C. (2005) Keratoconjunctival effects of diabetes mellitus in dogs. Veterinary Ophthalmology, 8, 215–224.)
both the noncataractous nondiabetic and cataractous nondiabetic dogs, which did not appear to affect conjunctival microbial isolates (Cullen et al., 2005).

The most common ocular manifestation of diabetes mellitus in the dog is cataract formation (Basher & Roberts, 1995; Ling et al., 1977). Diabetic cataract formation varies with the species affected, individual, age of disease onset, duration of the diabetes, and severity of hyperglycemia. The young dog is very susceptible, and the cat resistant, to diabetic cataract formation (Wyman et al., 1988). Cataracts were present at the initial examination of almost 60% of spontaneous canine diabetics, whereas no cataracts were noted in a series of 30 cats (Ling et al., 1977; Schaefer, 1977). This percentage of cataracts in the dog increases even after the diagnosis of diabetes is established, because diabetic control is usually erratic. In particular, a study reported that 75% of the canine population diagnosed with diabetes mellitus developed cataracts by approximately 12 months, while approximately 80% of the affected population formed cataracts by approximately 16 months (Beam et al., 1999).

Research into both ocular and nonocular complications of diabetes now focuses on the role of aldose reductase in the sorbitol or polyol metabolic pathway. The increase in blood sugar (either glucose or galactose) results in diffusion of increased amounts of sugar into the lens. The principal energy pathway of the lens is anaerobic glycolysis, and the first enzyme in the glycolytic pathway is hexokinase, which is in limited supply. When there is an increased supply of sugar, it becomes shunted to the sorbitol pathway, which normally supplies only 5% of the glucose metabolism. Aldose reductase is the first enzyme in this pathway, which forms polyols (i.e., sorbitol with glucose; dulcitol with galactose) that do not diffuse through the cell membranes as well and thus accumulate in the lens. This results in an osmotic gradient that draws water into the lens, which in turn results in swelling of lens fibers and opacification of the lens. Sorbitol is slowly metabolized to fructose, which can slowly diffuse across cellular membranes, whereas dulcitol is not further metabolized, thereby resulting in more rapid changes. The speed of the process depends on sugar concentrations and endogenous levels of aldose reductase (Engerman et al., 1982; Wyman et al., 1988). One of the reasons for variations in susceptibility among species, ages, and individuals to diabetic cataracts is the lenticular activity of aldose reductase (Engerman et al., 1982). Cataractous changes are initially observed as vacuoles in the equatorial cortex that extend into the anterior and posterior cortex (Engerman et al., 1982). The cortical sutures may be accentuated as well (Fig. 35.1.37). The process progresses to complete cortical opacification of the lens, and the sutures are often either fractured or widened because of water imbibition. Cataracts from a variety of causes may progress rapidly, but diabetes should be considered when a dog is presented with rapidly progressive bilateral cataracts.

The cells of the corneal endothelium in diabetic dogs, when examined with specular microscopy, have more pleomorphism and a wider variation in size (Yee et al., 1985). These changes directly relate to the degree of diabetic control, but the significance of this in the dog has not been documented (Yee et al., 1985).

Early diabetic retinopathy, which is characterized by microaneurysms, has been demonstrated in both spontaneous and experimental diabetes as well as in the galactosemic canine model. Diabetic retinopathy takes approximately 3–5 years to develop, and almost invariably in this period, cataracts will develop that obscure this change. In the galactosemic model, microaneurysms develop by 27 months. The background retinopathy, or nonproliferative stage, is characterized by the following sequence of events: thickening of the basement membrane of the retinal capillaries, dilation of retinal veins, loss of pericytes, microaneurysms, areas of capillary nonperfusion, retinal hemorrhages, infarction of the nerve fiber layer, and edematous residues. The pericytes are thought to support the capillaries, and their loss is thought to be responsible for the dilation and microaneurysm formation (Engerman & Bloodworth, 1965; Wyman et al., 1988). Pericyte loss is linked to aldose reductase activity in these cells, and it can be retarded with use of aldose reductase inhibitors (Kador et al., 1990).

Proliferative diabetic retinopathy, which is devastating to human vision, was difficult to produce experimentally in the diabetic dog (because of the induction time), but it can be produced experimentally in the galactosemic dog by 74–80 months post induction. Preretinal hemorrhages were noted by 56 months and soft exudates and neovascularization by 60 months. Neovascularization was limited to the disc area. Descriptions of diabetic retinopathy in clinical cases usually have relied on postmortem, flat-mount preparations of the retinal vessels. In a clinical series of diabetic dogs, retinal alterations of venous dilation, tortuosity and sacculation,
microaneurysm, retinal hemorrhages, color and reflection changes in the tapetum, and exudates were described (Fig. 35.1.38 and Fig. 35.1.39) (Landry et al., 2004; Monti et al., 1976). Background retinopathy may be suspected at ophthalmoscopy, but fluorescein angiography is necessary for confirmation. Unlike in human diabetics where elevations in aqueous humor levels of vascular endothelial growth factor (VEGF) have been correlated with the severity of diabetic retinopathy, diabetic dogs do not have elevations in aqueous humor levels of VEGF compared to nondiabetic dogs which may explain the low prevalence and severity of diabetic retinopathy in this species (Abrams et al., 2011).

All dogs undergoing evaluation for cataract surgery should have their blood and urinary glucose levels determined. As well, serum fructosamine and/or glycosylated hemoglobin levels help to determine the degree of glycemic control over 2–3 weeks, and 3 months, respectively (Jensen, 1995).

Cataract surgery is the only available therapy for diabetes-induced cataract formation in dogs. The success rate in diabetic animals is approximately the same as that for cataract extraction in nondiabetic dogs (Bagley & Lavach, 1994). Lens-induced uveitis is often present and, if possible, should be controlled before performing surgery, but in severe cases, this may not be an option. With regard to the keratoconjunctival effects of diabetes mellitus, diabetic dogs may be at risk of developing ulcerative keratitis following procedures requiring general anesthesia. Afterall, diabetic dogs have (1) reduced corneal sensation; (2) reduced STT values; (3) accelerated TFBUTs; and (4) altered conjunctival goblet cell numbers and general anesthesia has been shown to alter tear film properties (Cullen et al., 2005). Consequently, the authors recommend that tear supplements be used in diabetic dogs following, and occasionally prior to, procedures requiring anesthesia (such as cataract extraction).

**Hyperadrenocorticism (Cushing’s Syndrome)**

Hyperadrenocorticism, or Cushing’s syndrome, is one of the most common endocrinopathies in dogs. Hyperadrenocorticism is pathophysiological divided into three forms: (1) pituitary-dependent hyperadrenocorticism; (2) hyperadrenocorticism from functional adrenocortical tumors; and (3) iatrogenic hyperadrenocorticism. Affected dogs are typically 6 years of age or older. The clinical and laboratory findings associated with canine Cushing’s syndrome are mainly attributable to chronic glucocorticoid excess and, to a much lesser degree, overproduction of adrenal androgens.

Hyperadrenocorticism has been associated with ocular lesions of progressive corneal ulceration, nonhealing corneal ulceration, corneal calcification, cataracts, KCS, lipemia retinalis, and lesions associated with systemic hypertension (Lorenz, 1982; Ward et al., 1989; Williams et al., 2007). Hyperlipidemia may produce lipemia retinalis or lipids in the aqueous humor. An association with KCS has also been
observed in a series of cushinoid dogs, in which 11 of 57 cushinoid dogs had KCS (though the STT was not routinely performed) and 18% had corneal ulcers (Lorenz, 1982). The corneal ulcers were typically deep, chronic, and often, the presenting complaint. Tear production and ulcerations often improved with mitotane (o,p. DDD) therapy and remission of the hyperadrenocorticism. In general, high endogenous corticosteroid levels are thought to aggravate the healing of corneal ulcers rather than to cause ulcers, but spontaneous ulceration has been observed when relapse of the hyperadrenocorticism occurs. The incidence of cataracts may relate more to complications of diabetes mellitus than to elevated levels of corticosteroids.

Any nonhealing corneal stromal ulcer or sterile progressive corneal ulcer should prompt consideration of endogenous predisposing factors, of which elevated corticosteroid levels (either endogenous or exogenous in origin) should be kept in mind. In most instances, clinical signs of Cushing’s syndrome will be evident. Readers are advised to consult a current internal medicine textbook for a detailed discussion on the diagnosis and therapy for hyperadrenocorticism.

Hypothyroidism

Hypothyroidism develops as a result of decreased production of thyroxine (T4) and triiodothyronine (T3) by the thyroid gland. Hypothyroidism is uncommonly occurring diseases in dogs, with reported prevalence rates of 0.2%–0.8% (Dixon & M ooney, 1996; M ilne & H ayes, 1981). The mean age of dogs diagnosed with hypothyroidism is 7 years.

There is a clinical association between hypothyroidism and a variety of ocular lesions, though experimental dogs that were made hypothyroid for 9 months did not develop any ophthalmic lesions. As many as 20% of dogs with hypothyroidism have been reported to have KCS (P eruccio, 1982). The presence of reduced tear production has been described in another study of hypothyroid dogs, though whether these animals go on to develop clinical KCS requires further investigation (W illsiams et al., 2007). The association between KCS and hypothyroidism has been thought to be one of multifaceted, immune-mediated inflammation. The lack of decreased STT values in experimental hypothyroidism, however, supports an indirect association rather than hypothyroidism per se (M iller & P anciera, 1994). Because hypothyroidism results in vascular disease characterized by atherosclerosis, the association with retinal lesions of hypertension and arteriosclerosis is not surprising, nor is it consistent. Hypertensive retinal changes of retinal hemorrhages and, less frequently, bullous retinal detachments may be observed (G win et al., 1978; L iu et al., 1986; M annin g, 1979; M iller & P anciera, 1994; R ubin, 1975). The retinal vasculature may provide evidence of arteriosclerosis, with straight, narrow vessels that, when advanced, become irregular and opaque. Hyperlipidemia with hypothyroidism may manifest as lipemia retinalis, corneal lipid degeneration, and lipids in the aqueous humor (K ern & R iis, 1980; N ell et al., 1995). Corneal lipid deposits with hypothyroidism may take various forms as well, from diffuse and rapidly developing opacities at all levels of the cornea to the characteristic, peripheral arcus lesion adjacent to the limbus (C rispin, 1993).

In addition to the keratoconjunctival effects, and evidence of hypertension and/or hyperlipidemia, patients with hypothyroidism may also manifest with a variety of neurologic signs. Specifically, hypothyroidism has been associated with the development of various neurologic signs including signs of stupor/coma, appendicular lower motor neuron disease (manifesting as generalized weakness), cranial nerve deficits (e.g., facial nerve paresis/paralysis, peripheral and central vestibular disease), laryngeal paresis/paralysis, and megaesophagus (B ichsel et al., 1988; H iggins et al., 2006; J agg y et al., 1994; V itale & O lby, 2007). Of these clinical manifestations, patients most likely will present for ophthalmic assessment based upon demonstration of signs of cranial nerve dysfunction of vestibular disease (e.g., nystagmus, strabismus, facial nerve paresis/paralysis, etc.), though other hypothyroid-associated concurrent clinical signs may be present.

The gold standard for the diagnosis of canine hypothyroidism is made on the basis of comparing resting T4 levels with those occurring after administration of thyrotropin-stimulating hormone (P anciera, 1999). Because of the limited availability of thyrotropin-stimulating hormone, however, diagnosis of hypothyroidism is made based upon consistent clinical signs in association with measuring serum levels of total thyroxine, canine thyroid stimulating hormone, and free thyroxine. Readers are advised to consult a current internal medicine textbook for a detailed discussion on the diagnosis of and therapy for canine hypothyroidism.

Ionic Disturbances

Hypocalcemia

Hypocalcemia in dogs may be caused by several conditions including hypoparathyroidism, postparturient hypocalcemia, acute or chronic renal failure, acute pancreatitis, vitamin D toxicity, severe nutritional secondary hyperparathyroidism (rare in dogs fed diets containing low calcium-to-phosphorus ratios), and intestinal malabsorption syndromes, among others (for review, see D hupa & P roulx, 1998). Neurologic signs of restlessness, muscular fasciculations, and tonic-clonic seizures occur with a total serum calcium level of 6–7 mg/dL or a serum-ionized calcium level of less than 2.5 mg/dL. (B ruyette & F eldman, 1988). The cause of the hypocalcemia can be determined with renal function tests, radiography, and parathyroid hormone assays.

Hypocalcemia in the dog has been documented, both experimentally and clinically, to be associated with focal punctate to linear opacities in the anterior and posterior cortices of the lens (J ones & A lley, 1985; K orneyag et al., 1980; L ettow et al., 1966). The lenticular opacities may occur at different levels in the cortex, and they may reflect different episodes of hypocalcemia. The degree and duration of hypocalcemia necessary to produce cataracts is unknown,
but the appearance of the cataracts is quite suggestive of hypocalcemia.

Treatment of hypocalcemia involves correction of the underlying disease, if possible, and calcium supplementation with vitamin D₂, D₃, or dihydrotachysterol. Additional focal cataracts may manifest for a period after correction of the hypocalcemia, and the existing lenticular opacities will remain.

Neoplasia: Central Nervous System

Intracranial neoplasia, whether primary or secondary, often produces ocular and/or orbital signs. All animals with a suspected space-occupying CNS lesion should undergo ophthalmoscopy to determine whether papilledema, optic neuritis, or optic nerve atrophy is/are present.

The ophthalmic signs associated with intracranial neoplasia are highly variable, and dogs may present with signs as subtle as internal ophthalmoparesis as the predominant clinical sign or with ophthalmic signs associated with abnormalities of multiple cranial nerves and abnormal changes in mentation and/or gait (Cullen et al., 2002; Larocca, 2000; Rossmeisl et al., 2005; Webb et al., 2005a). Intracranial neoplasia frequently produces visual deficits and papilledema in association with neurologic signs (Palmer et al., 1974). Because of the great variation in myelination of the canine papilla/optic disc, early papilledema is difficult to detect unless it is asymmetrical or there is a definite rim of peripapillary edema. Intracranial tumors may also produce blindness, which may be acute in nature. Diffuse or multifocal disease may produce blindness by involving multiple sites in the visual pathways and, as a result, produce other neurologic deficits as well (Braud et al., 1977; Palmer et al., 1974). A solitary mass involving the optic chiasm may produce blindness without obvious neurologic signs. Tumors at the base of the brain in the middle cranial or rostral fossa may be varied, but pituitary carcinomas that are nonfunctional, optic nerve gliomas, and meningiomas are likely candidates for optic chiasmal involvement (Davidson et al., 1991; Safaty et al., 1988).

Papilledema was not a feature of these lesions, perhaps because of their relatively small size. Clinically, blindness is often acute. In reality, it is progressive, and partial visual deficits are not generally noted by owners. Because blindness is accompanied by afferent pupillary defects with a normal ocular fundus, the syndrome must be differentiated from SARDS using electroretinography. Early diagnosis and aggressive therapy may result in the return of some vision (Davidson et al., 1991).

Cavernous Sinus Syndrome

The cavernous sinus is a paired venous sinus anatomically located on the floor of the cranial vault and extending from the orbital fissures to the petro-occipital canals. Cranial nerves III, IV, VI, and the ophthalmic and maxillary branches of V lie in close proximity to the cavernous sinus. Consequently, diseases (including neoplasia) involving the region of the cavernous sinus can result in deficits in any or all of these cranial nerves. The constellation of abnormal clinical signs attributed to dysfunction of cranial nerves III, IV, V1 and at least one of the first two branches of cranial nerve V is known as cavernous sinus syndrome (Rossmeisl et al., 2005). Cavernous sinus syndrome can be either unilateral or bilateral (Rossmeisl et al., 2005; Theisen et al., 1996). Clinical signs related to deficits of these cranial nerves may include a fixed and dilated pupil on testing direct and consensual PLRs, ptosis, decreased corneal sensation, decreased ability to retract the globe, and complete (i.e., internal and external) ophthalmoplegia. The most common cause of cavernous sinus syndrome in dogs is neoplasia (Rossmeisl et al., 2005). Consequently, prognosis for cavernous sinus syndrome is considered guarded to poor (Rossmeisl et al., 2005).

Neoplasia: Systemic

Lymphosarcoma

Lymphosarcoma is the most common secondary intraocular neoplasia of dogs, and it usually affects both eyes. In most cases, systemic involvement is obvious at the physical examination, but ocular disease may be the presenting complaint. Very rarely, the systemic disease is occult and the ocular lesion is the primary clinical sign. In one large prospective study, 37% of cases of lymphosarcoma had ocular lesions (Krohne et al., 1994). Of these ocular lesions, 49% were anterior uveitis, 9% posterior uveitis, 14% panuveitis, 23% retinal hemorrhages only, and 6% adnexal diseases (Krohne et al., 1994). Most animals with ocular lesions were in the advanced stages of lymphoma (i.e., stage V), and 78% of the cases with leukemia involved ocular disease. This study did not report secondary glaucoma as a presenting feature, though previous authors have noted this as being a common complication of intraocular lymphosarcoma (Barron et al., 1963; Cello & Hutcherson, 1962). This may represent the difference between ocular lesions detected following presentation of a case for ocular complaints and those found prospectively by screening patients with lymphosarcoma. Regardless, lymphosarcoma with ocular involvement equates to advanced disease and translates to a shorter survival period for the dog.

A variety of mechanisms may cause retinal hemorrhages, but the cause is often not obvious. Retinal hemorrhages may be associated with inflammation, thrombosis, severe anemia, thrombocytopenia, hypoxia, vasculitis, and interference with clotting factors. The retinal hemorrhages associated with lymphosarcoma may be multifactorial and may not necessarily represent leukemic invasion, but uveitis represents tumor invasion of the eye (Krohne et al., 1994).

A relatively rare syndrome involving rapidly fulminating lymphosarcoma in young dogs, with dramatic orbital and ocular involvement has been observed (Martín, 1999). The orbital involvement produces marked bilateral exophthalmos, chemosis, and exposure keratitis. Rarely, lymphoma will be...
diagnosed on the basis of a diffusely enlarged third eyelid that has no obvious accompanying systemic lesions.

Lymphadenopathy combined with endogenous bilateral uveitis or hemorrhages should prompt fine needle aspirations of enlarged lymph nodes or other affected organs to confirm the diagnosis of lymphosarcoma cytologically.

For current therapeutic options, the reader should consult appropriate internal medicine textbooks for lymphosarcoma protocols. Lesions affecting the anterior segment of the eye, however, do respond to conventional anterior uveitis therapy using topical corticosteroids. The intraocular pressure should be monitored, and glaucoma should be treated if it develops.

**Other: Metastases**

Though relatively rare, a variety of carcinomas and sarcomas have been described as metastasizing to the eye and orbit. Bilateral ocular involvement may occur, because most tumors spread via a hematogenous route. The typical site of ocular metastasis is the uveal tract, and, specifically, the ciliary body. The neoplasms may be masked by intraocular hemorrhage, inflammation, and glaucoma; thus, intraocular neoplasia, whether primary or secondary, should be included in the differential diagnosis of undetermined spontaneous intraocular hemorrhage or secondary glaucoma. Ocular metastasis is usually a late occurrence, so the history and/or physical examination of the affected dog will often be indicative of significant systemic disease.

The incidence of ocular metastasis is probably underreported. Systemic and/or neoplastic processes involving the eye include intravascular lymphoma; hemangiosarcoma (Fig. 35.1.40); malignant melanoma; adenocarcinoma of the pancreas, mammary, salivary, sweat, and thyroid glands; squamous cell carcinoma; transitional carcinoma; mastocytoma; and canine transmissible venereal tumor (Bush et al., 2003; Cullen et al., 2000; Dubielzig, 1990; Habin & Else, 1995; Kilrain et al., 1994; Ladds et al., 1970; Lavach, 1984; Millar et al., 1990; Pereira et al., 2000; Szymanski et al., 1984).

**Nutritional Disorders**

**Milk Replacer-Induced Disease**

Cataract formation has been recognized in puppies and a variety of other species fed commercial or homemade orphan milk formulas. Levels of arginine have been found to be deficient in canine and feline formulas, and supplementation has prevented cataracts in wolf cubs, puppies, and kittens (Remillard et al., 1993; Vainisi et al., 1981). Various attempts to correct commercial milk formulas, however, still result in cataract formation (Glaze & Blanchard, 1983; Martin & Chambreau, 1982; Ranz et al., 2002). Different breeds have been suggested to be more susceptible, but there is no documentation to support this idea. It has been shown that large breeds with rapid growth may need more supplementation with methionine and arginine (Ralston et al., 1990). In order to develop nutrition-related cataracts, milk-replacer diet must be ingested during the first week postpartum, and lenticular changes will be noted by 3 weeks. Lenticular changes begin as vacuolar changes separating the anterior and posterior cortices from the nucleus and outlining the sutures. At 5 weeks following milk-replacer supplementation, a lenticular opacity remains as a white, posterior subcapsular opacity. With growth, this opacity occupies the fetal nucleus and appears as a spheroidal or ring-shaped fetal nuclear opacity (Martin & Chambreau, 1982). In exotic or wild animals, lenticular opacities have been more complete, appearing as a diffuse, anterior subcapsular cortical opacity and producing at least a temporary blindness (Vainisi et al., 1981). Because these cataracts rarely produce blindness in the dog, the dilemma lies in differentiating nutritional from inherited congenital cataracts or cataracts due to other noxious agents. The history of milk replacer supplementation, normal ocular examination in parents of affected dogs, and location of the lenticular opacity usually suggest the nutritional source of the cataract.

**Vitamin A Deficiency**

Vitamin A (retinol), a fat-soluble vitamin, is derived from its precursors (carotenoids) which are found in plants (for review, see von Lintig & Vogt, 2004). With regard to the importance of vitamin A in the ocular system, vitamin A (retinol) is stored...
and transformed into retinal which is translocated between the RPE and the photoreceptors (Thompson & Gal, 2003). Within the photoreceptors, retinal combines with opsin (a protein) to form the visual pigment rhodopsin (Thompson & Gal, 2003). Vitamin A deficiency has been produced experimentally in young dogs, but it does not appear to be a naturally occurring clinical syndrome (Tvedten & Whitehair, 1977). The earliest sign of such deficiency in young dogs, however, is vestibular disease, but blindness may also be an early manifesting sign (Tvedten & Whitehair, 1977). Papilledema has been noted in some dogs with a deficiency in vitamin A; however, the resultant papilledema could not be correlated with increased CSF pressure (Tvedten & Whitehair, 1977).

**Vitamin E Deficiency**

The antioxidant action of vitamin E limits lipid peroxidation and production of free radicals, which are very damaging to cellular constituents. The major sites of oxidant damage are the membranes of subcellular organelles. Phospholipids are a significant structural component of the photoreceptors, and normal shedding and phagocytosis by the RPE produces a peroxidized lipoprotein or lipofuscin from the lysosomes in the cell. Lipofuscin is a yellow-brown, autofluorescent pigment.

Ocular consequences of vitamin E deficiency in the dog have been described in both clinical and research animals (Davidson et al., 1998; Hayes et al., 1970; McLellan et al., 2002, 2003; Riis et al., 1981). Systemic lesions consist of muscular and testicular degeneration, reproductive problems, hemolytic anemia, and weak and dying puppies. Ocular lesions in both clinical and research animals occur only with prolonged deficiency, and they consist of cataracts, decreased vision to blindness, and retinal degeneration. The retinal degeneration has been described in detail and is first noted on ophthalmoscopy as a fine stippling in the central deep retina. The mottling increases in intensity, with brown accumulations and night blindness later developing. After 6 months on a vitamin E-deficient diet, the tapetum develops central hyperreflectivity, and retinal vascular attenuation is noted. Eight to twelve months of deficiency results in discrete, yellow-brown, multifocal accumulations in the tapetal fundus, tapetal hyperreflectivity, and attenuated retinal vessels with focal constrictions (Fig. 35.1.41). In one report, the ERG response was extinguished after 3 months of deficiency, though the animals were not blind at this time (Riis et al., 1981).

Histopathologic changes are more severe in the central retina, beginning as RPE hypertrophy with inclusions of lipofuscin. With chronicity, the lipofuscin increases in amount and radiates out from the central retina, and degenerative changes develop preferentially in the rods (though cones also degenerate). With time, the retinal degeneration progresses to involve all layers, and lipofuscin is present in the retina (Riis et al., 1981).

Clinical reports of vitamin E deficiency and retinal pigment epitheliopathy or central retinal degeneration closely parallel those of experimental models (Davidson et al., 1998; McLellan et al., 2002, 2003). The clinical appearance of multifocal, yellowish-brown accumulations in the tapetal retina with modest tapetal hyperreflectivity and vascular attenuation is suggestive of the diagnosis. Furthermore, neurological signs including ataxia, generalized paresis, proprioceptive deficits, and abnormal spinal reflexes may be present (McLellan et al., 2003). Diagnosis is made based upon identifying characteristic clinical signs and identifying low serum concentrations of vitamin E (McLellan et al., 2002). Therapy is directed at supplementation with vitamin E (McLellan et al., 2003).

**Zinc Deficiency**

Zinc deficiency may result from either reduced intestinal absorption or by consuming a diet deficient in zinc. Zinc deficiency has been implicated in dogs with dermatitis characterized by dry, scaly skin, erythema, alopecia, and change in hair coloration (White et al., 2001). Young, adult Alaskan Malamutes and Siberian Huskies are predisposed to zinc-responsive dermatosis (White et al., 2001). The distribution of cutaneous lesions caused by zinc deficiency involves perioral and periloral regions, mucocutaneous junctions, and...
Sulfa Drugs

Idiosyncratic reactions (non dose-dependent) to sulfonamides result in a variety of medical conditions including polyarthropathy, hepatopathy, blood dyscrasias, skin eruptions, and ocular disease (for review, see Trepanier, 2004). One of the most common clinical findings in dogs with idiosyncratic reactions to potentiated sulfonamides is KCS (Trepanier et al., 2003). The lacrimotoxicity is thought to result from the sulfonamides' nitrogen-containing pyridine ring, and the toxicity is not unique to sulfadiazine. The incidence of KCS may be as high as 4%–15% among animals overall, but as many as 63% of animals on the drug may have decreased STT values compared with their baseline, pretreatment levels. The decrease in tear production may occur in a matter of a few days after sulfa therapy is initiated, and though 50% will develop it within 30 days, the average duration has varied from 41 to 91 days of therapy. The resultant KCS may be either unilateral or bilateral (Berger et al., 1995; Diehl & Roberts, 1991; Morgan & Bachrach, 1982; Slatter & Blogg, 1978).

To date, the lacrimotoxicity in dogs has not been related to breed, age, or dose of medication. Improvement in the KCS with cessation of the sulfa therapy and cyclosporine stimula-


Pressure points (Fig. 35.1.42) (White et al., 2001). Other ocular manifestations of experimental zinc deficiency in dogs, other than blepharitis, include mucopurulent exudation, and keratitis (Roberston & Burns, 1963). Diagnosis of zinc-responsive dermatosis is made based upon consistent clinical signs, histopathological examination of skin lesions, and response to oral zinc supplementation. Most dogs respond favorably to oral zinc supplementation (White et al., 2001).

Toxicities

Antimicrobials

Ketoconazole

The imidazole drug, ketoconazole, is a widely used antifungal agent. Long-term use of ketoconazole has been found to be associated with the development of bilateral cataracts (Da Costa et al., 1996). Most dogs affected by ketoconazole-induced cataracts are young (<5 years) and have medium to large physical stature. There does not appear to be any gender predisposition. Cataracts develop anywhere from 3.5 to 37 months after initiating ketoconazole therapy. The pathogenesis of ketoconazole-induced cataract formation remains unknown.
Johnson syndrome may produce a facial dermatitis involving the eyelids and mucocutaneous junctions as well as KCS (M. C. M. urdy, 1990; M. edleau et al., 1990).

**Anti-Parasitic Drugs**

**Disophenol**

Disophenol (2,6-diiodo-4-nitrophenol) was a popular, injectable anthelmintic for ancylostomiasis during the 1970s. In young neonatal or weanling puppies, either debilitated or overdosed toxic signs might develop, relating to an increased metabolic rate. Experimentally, cataracts could be routinely produced with three times (30 mg/kg) the recommended parenteral dose. The onset of cataracts is within 24–36 hours and is typically a vacuolar lesion beginning at the equator of the lens, then progressing axially, both anteriorly and posteriorly, in the superficial lenticular cortex. In most cases, resolution of the cataracts occurs within 3–7 days (Martin et al., 1972a).

**Ivermectin**

Ivermectin is an antiparasitic drug that exerts its antiparasitic actions by activating ligand-gated chloride channels in a variety of invertebrates (Cully et al., 1994; Kane et al., 2000). Activation of chloride channels prevents synaptic transmission thereby causing paralysis of the invertebrate parasite (Campbell et al., 1983; Wang & Pong, 1982). Ivermectin concentrations do not typically reach toxic levels within the mammalian CNS when administered at therapeutic antiparasitic dosages. The reason for this is that the mammalian CNS vascular endothelial cell of the blood–brain barrier has a specific ATP-dependent transporter, known as P-glycoprotein, that prevents a variety of molecules (drugs) from entering the CNS. This attribute of the blood–brain barrier prevents the toxic or therapeutic accumulation of a variety of drugs, including ivermectin, within this body compartment (for review on P-glycoprotein, see Mealey, 2004; for review on the blood–brain barrier, see Webb & Muir, 2000). It should be noted, however, that a variety of tissues will express P-glycoprotein (Mealey, 2004). Other drugs that are actively removed by P-glycoprotein include doxorubicin, methylprednisolone, doxycycline, digoxin, and various phenothiazines (Mealey, 2004).

P-glycoprotein is coded for by the multiple drug resistance gene (MDR-1). It has been known for some time that herding dogs, especially Collies, are sensitive to therapeutic dosages of ivermectin (Houston et al., 1987; Paul et al., 1987; Seward, 1983; Tranquilli et al., 1987). A genetic defect in MDR-1 has been found as the cause of ivermectin sensitivity (Mealey et al., 2001). The mutant allele (gene) is thought to have descended from a common ancestor in Great Britain sometime in the 19th century (Neff et al., 2004). Breeds having been found to carry the mutant MDR-1 allele include the Australian Shepherd, Miniature Australian Shepherd, Collie, English Shepherd, Longhaired Whippet, M. C. N. ab, Old English Sheepdog, Shetland Sheepdog, and Silken Windhound (Neff et al., 2004).
2004). Animals homozygous for the mutant MD1-1 allele are highly sensitive to ivermectin toxicity (100 µg/kg), heterozygotes may be sensitive to dosages greater than 100 µg/kg, and noncarrier animals are not predisposed to ivermectin toxicity at recommended therapeutic dosages (Meadle, 2004). Assessment of MD1-1 mutations in dogs is possible (Veterinary Clinical Pharmacology Laboratory, College of Veterinary Medicine, Washington State University, www.vetmed.wsu.edu/depts-VCL/). Ivermectin toxicosis can occur with gross overdosages of the drug (Hopkins et al., 1990). Ivermectin toxicosis resulting from increased inhibition of neurons within the CNS manifests as impaired level of consciousness (depression to coma), muscle tremors, ± hyper- or hypothermia, and a variety of abnormal neuro-ophthalmic findings including absent menace response, mydriasis (in normal ambient lighting) ± positive PLRs, and various types of strabismus. Blindness may occur without marked CNS signs, and this is usually accompanied by mydriasis in normal ambient lighting. Blindness has also been observed with normal PLRs and a normal fundus. Ophthalmoscopic findings may include papilledema and retinal edema with folds and low-lying retinal separations (Kenny et al., 2008). Residual pigment disruption may be visible in the nontapetal fundus with recovery. Electroretinography may show extinguished or attenuated a- and b-waveforms (Kenny et al., 2008). Vision loss is temporary, with recovery in 2–10 days (Hopkins et al., 1990; Kenny et al., 2008; Ketting, 1990).

Diagnosis of ivermectin toxicosis is based on clinical signs (adverse signs appear within hours of administration or accidental ingestion) and a history of recent administration or ingestion of ivermectin. Therapy for ivermectin toxicosis is aimed at supportive nursing care. Recently, however, use of intravenous lipid emulsion has been used successfully in a dog with ivermectin toxicosis (Clarke et al., 2011). Intensive care may be required if clinical signs become severe. Animals typically make full recoveries. However, complete recovery may be prolonged (weeks), and affected dogs may die of severe respiratory/cardiovascular depression in severe cases.

**Cardiovascular Drugs**

**Amiodarone**

Amiodarone is a class III antiarrhythmic drug used in dogs with dilated cardiomyopathy and ventricular arrhythmias (Calvert et al., 2000; Jacobs et al., 2000). Adverse reactions to this drug include hepatotoxicosis and blood dyscrasias. (Bicer et al., 2002b; Calvert et al., 2000). As well, it has been demonstrated, experimentally, that corneal opacities may develop following long-term use of amiodarone in dogs (Bicer et al., 2002a). Only one of six dogs treated with amiodarone, however, developed corneal opacities in this study. Considering that these dogs were housed indoors, and that amiodarone-induced corneal opacity development is dependent somewhat on ultraviolet light exposure, the incidence of corneal opacities in dogs receiving amiodarone therapy may increase if dogs have exposure to sunlight (Bicer et al., 2002a).

**Tocainide**

Tocainide is an oral, antiarrhythmic agent that has been used in veterinary cardiology. When used in 12 Doberman Pinschers with cardiomyopathies at recommended doses for more than 2 months, however, a bilateral, progressive corneal edema developed in three of the animals that was irreversible when well-established. When advanced, the edema was severe enough to hinder vision. Early withdrawal of the drug may reverse the edema (Gratzek et al., 1993).

**Electricity**

Electric shocks and lightning strikes can produce direct ocular sequelae and also cause injury to the CNS (may manifest as blindness, papilledema, cranial nerve palsies) (for review on pathogenesis and human manifestation, see Norman et al., 2001). Electric shocks and lightning strikes of a severe nature may produce cataracts that manifest months later. Cataracts are more likely to be produced by electrical shocks to the head. The appearance of clinical and experimentally induced electric cataracts are quite similar, and they consist initially of vacuoles that are present bilaterally in the midperipheral anterior cortical lens (Fraunfelder & Hanna, 1972; Thomas & Hanna, 1974). Ultrastructurally, the vacuoles are extracellular and transient, lasting several weeks. The lens vacuoles are prognostic indicators of later cataract formation. The lens epithelium subsequently proliferates, thereby producing multilayered plaques of lens capsule and lens fibers in the central anterior capsular region. Severe electric shock (e.g., from lightning) may produce both anterior and posterior cortical opacities (Norman et al., 2001). A typical electric cataract has been described in one dog 18 months after chewing on an electric cord (Fig. 35.1.44) (Brightman et al., 1984).

**Insect Bites**

Insect bites or envenomation from hornets, bees, fire ants, and spiders may occur on the eyelids or cornea of all animals. A cute, severe blepharedema is the usual extent of bites to the eyelids, though bites from insects such as the brown spider or multiple fire ant bites may result in tissue sloughing (Joyce, 1983; Rakich et al., 1993). A cute, focal corneal necrosis with rapid melting of the corneal stroma is not a rare event because of the deposition of proteolytic enzymes. The diagnosis is often presumptive unless multiple bites on the animals are present or insects were observed while biting. Lysis of the corneal stroma may require surgical repair with conjunctival flaps.

**Hypolipidemic Drugs**

Hypolipidemic compounds of the hydroxymethylglutaryl-coenzyme A reductase inhibitor group, when administered at
high dosages, produce cataracts in the dog. These cataracts typically begin as posterior subcapsular equatorial opacities and, occasionally, anterior equatorial cortical cataracts. In one report, cataracts were noted 9–28 weeks after the initiation of therapy and began around the suture lines (Gerson et al., 1990). Continuation of therapy did result in complete cortical cataracts. Not all animals developed opacities, however. The dose used for cataract induction was 40–60 times the clinical dose, and chronicity of administration of the drug did not increase the incidence of cataracts. Therefore, such cataracts are unlikely to be of clinical importance. The genesis of the cataract was not determined, but it was thought to result from inhibition of cholesterol synthesis in the lens fiber’s cellular membrane.

**Ionizing Radiation**

The ocular effects of ionizing radiation are similar no matter the source. Both the ocular effect(s) and the time to develop ocular disease depend on the dose, age of the animal, and the species being studied. In a long-term study of burros, swine, and cattle receiving gamma and mixed neutron-gamma radiation, the swine and burros were resistant to radiation-induced cataracts, but cattle were about as equally susceptible as humans (Brown et al., 1972). The most common source of ionizing radiation-induced ocular lesions is from radiation therapy for neoplasms of the head. All dogs develop a blepharitis at 1 month or less after radiation therapy. In three series involving cobalt-60 radiation therapy and megavoltage therapy for neoplasms of the head, ocular complication rates were between 76% and 84% (Jamieson et al., 1991; Roberts et al., 1987; Theon et al., 1993). Approximately 45%–59% of these complications were sight-threatening or chronic in nature. The mildest sign was a self-limiting conjunctivitis (35% of cases), but more severe and chronic signs of keratoconjunctivitis, KCS, and ulcerative keratitis were more common (64%–78%) and occurred either during or 2–3 months after therapy. Anterior uveal changes such of miosis, hypotony, and flare were relatively uncommon (8%–10%) and occurred within 1 month after therapy. They were also unresponsive to anti-inflammatory drugs. Cataract formation was delayed for 1.0–9.6 months and occurred in 11%–26% of patients. Cataracts were typically in the equatorial and posterior subcapsular region, but they may be diffuse. Multifocal retinal hemorrhages were delayed from 1 to 6 months and present in 19% of the patients. Optic nerve damage from irradiation was not documented in these three clinical studies, though in one study, four dogs developed blindness 2–6 months after therapy, with no evidence of cataracts or retinal disease. A separate, histopathologic study reported seven dogs that developed optic nerve axonal degeneration 6–24 months after radiation therapy (Ching et al., 1990). A dditional late-onset lesions noted at histopathology, but not clinically, included retinal atrophy and tapetal atrophy (Ching et al., 1990).

Histopathologically, several ocular lesions have been identified (Ching et al., 1990). Conjunctivitis is characterized by...
epithelial and subepithelial infiltrate of neutrophils, plasma cells, and lymphocytes with vascular congestion; keratitis with mixed inflammatory cells, with or without neovascularization; and corneal epithelial atrophy and thinning. Radiation-induced cataracts are characterized by disorganized lens epithelium in the lens bow, posterior migration of nuclei, disorganized lens fibers, bladder cells, and vacuoles. These latter changes occur predominantly at the equator and posterior subcapsular region. Mononuclear infiltration into the anterior uvea as well as tapetal atrophy and retinal hemorrhages can also be present. Degenerative vasculopathy of retinal and choroidal vessels progresses to replacement of smooth muscle with fibrous tissue. There is also inner retinal degeneration, with decreased numbers and degeneration of ganglion cells, and axonal degeneration in the optic nerve (Ching et al., 1990).

**Miscellaneous Diseases**

**Systemic Histiocytosis**

Systemic histiocytosis is a familial disease of Bernese Mountain Dogs and also occurs less frequently in other breeds (Moore, 1984; Moore & Rosin, 1986; Padgett et al., 1995; Paterson et al., 1995). As opposed to malignant histiocytosis (disseminated histiocytic sarcoma), systemic histiocytosis is considered a nonneoplastic, generalized histiocytic proliferative disease that causes prominent skin lesions identical to those reported with cutaneous histiocytosis, however, ocular and nasal mucous membranes, and other organs such as the lungs, bone marrow, and peripheral lymph nodes may also be frequently affected. Young to middle-aged dogs (2–8 years of age) are mainly affected by this disease.

Systemic histiocytosis is characterized histologically by multisystemic, perivascular infiltration of large histiocytes, and variable numbers of lymphocytes, neutrophils, and eosinophils (Moore, 1984). Systemic signs vary but include anorexia, depression, weight loss, cutaneous nodules, and nasal infiltration (Moore, 1984; Scherlie et al., 1992). Ulceration of the skin overlying the cutaneous nodules is common. Ocular lesions occurred in three of six affected animals, manifesting as eyelid masses, episcleral masses, exophthalmos, corneal edema, anterior and posterior uveitis, retinal detachment, and glaucoma (Fig. 35.1.45) (Moore, 1984).

Cellular atypia is lacking, and systemic histiocytosis has not been proven to be neoplastic but, rather, has been postu-

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### Nonsteroidal Anti-Inflammatory Drugs

**Etodolac**

Etodolac is a nonsteroidal anti-inflammatory drug that selectively inhibits cyclooxygenase-2 and is used in the management of pain in a variety of conditions, especially osteoarthritis (Jones & Budsberg, 2000). KCS has been reported with its use in dogs (Klauss et al., 2007). The mean age of affected dogs is 10 years, and there does not appear to be a breed or gender predisposition (Hampshire et al., 2004). Etodolac-induced KCS is severe and may be irreversible (Klauss et al., 2007; Stiles, 2004), though shorter duration of etodolac administration has been associated with improved outcome (Klauss et al., 2007).

**Phenazopyridine**

Phenazopyridine has been used as a urinary analgesic, and in the dog, it has a unique lacrimal toxicity. Within 7–10 days after doses of 25 mg/kg in the dog, the STT decreased below 10 mm/min, and signs of KCS developed. Cats, rabbits, and humans do not develop lacrimal toxicity to phenazopyridine. The lacrimal glands develop a grossly visible, brown-black discoloration within 48 hours of drug administration. The product is present only in the lacrimal glands, and the material is found in the secretory granules that fuse into larger degenerative granules with subsequent cellular degeneration. Adjacent acinar cells may have normal secretory granules. Early cessation of therapy may reverse the process (Bryan & Slatter, 1973; Slatter & Davis, 1974; Slatter et al., 1982).

**Rodenticides (Anticoagulant Rodenticides)**

In all species, coumarin poisoning may manifest with ocular or orbital hemorrhages. In the dog, the source of coumarin is typically found in anticoagulant rodenticides. When hemorrhages are limited to the orbit, hemorrhages may not be obvious unless the hemorrhage dissects anteriorly into the subconjunctival space. Orbital hemorrhage may be confused with other causes of acute orbital disease (e.g., orbital cellulitis).

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**Figure 35.1.45.** Exophthalmos and cutaneous lesions of the nasal region associated with systemic histiocytosis. A temporary partial tarsorrhaphy is evident on the left eye. (Reprinted with permission from Scherlie, P.H., Jr., Smedes, S.L., Feltz, T., Dougherty, S.A. & Riis, R.C. (1992) Ocular manifestation of systemic histiocytosis in a dog. *Journal of the American Veterinary Medical Association, 201*, 1229–1232.)
lated to be an immunoregulatory disorder involving dermal dendritic cells (Affolter & Moore, 2000). Immunohistochemical staining may help to differentiate cutaneous and systemic histiocytosis from malignant histiocytosis. Specifically, cutaneous and systemic histiocytosis stain positively for Thy-1 (CD90) and CD4 markers for dermal dendritic cells and activated antigen presenting cells, respectively (Affolter & M oore, 2000). Malignant histiocytosis, however, does not stain for CD4 and inconsistently stains for Thy-1 (Affolter & Moore, 2002). Furthermore, the clinical behavior and response of systemic histiocytosis to immunosuppressive therapy with agents that profoundly inhibit T-cell activation have solidified the concept of disorderly immune regulation resulting from defective interaction of dendritic antigen presenting cells and T-cells (Affolter & M oore, 2000).

Systemic histiocytosis is a progressive disease that may wax and wane, especially early in the course of the disease, but typically necessitates continuous immunosuppressive therapy such as corticosteroids. Immunosuppressive doses of systemic cyclosporine A or leflunomide, both potent inhibitors of T-cell activation, are often warranted to treat intractable cases of systemic histiocytosis (Affolter & Moore, 2000). However, in severe cases, lesions may become persistent and fail to respond to therapy.

A recent study has shown that histiocytic sarcomas of Bernese Mountain Dogs and Flat-coated Retrievers present with highly aberrant genome-wide DNA copy number profiles, many of which are identified in human histiocytic neoplasia (Hedan et al., 2011). These results suggest that histiocytic sarcomas in Bernese Mountain Dogs and Flat-coated Retrievers are a model for human histiocytic tumors (Hedan et al., 2011). Furthermore, these results afford the opportunity to understanding the pathophysiologic and genetic mechanisms of histiocytic neoplasia in these breeds of dogs (Hedan et al., 2011).

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Chapter 35

Ocular Manifestations of Systemic Disease

Part 2: The Cat

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CONGENITAL

Coat Color-Related Diseases/Conditions

Chédiak–Higashi Syndrome

Chédiak–Higashi syndrome (CHS) is an autosomal recessive disorder of cats and other species (Prieur & Collier, 1978, 1981). In cats, CHS is characterized by partial oculocutaneous albinism, increased susceptibility to infections, and bleeding tendencies (Collier et al., 1984). To date, CHS has only been reported in the Persian breed. Ocular manifestations of CHS in cats include photophobia, pale irides, hypopigmentation of the nontapetal fundus, tapetal degeneration, cataracts ranging from incipient posterior suture line associated to mature cataracts, and spontaneous nystagmus (Collier et al., 1979, 1985b; Creel et al., 1982a). The ocular hypopigmentation in affected cats is thought to result from fusion of premelanosomes with lysosomes, with resultant destruction of the premelanosomes (Collier et al., 1985a). Melanin granules that do remain in the eyes of cats with CHS are nonuniform in distribution and irregular in shape (Collier et al., 1984). The tapetum develops normally in CHS-affected kittens, but it later rapidly degenerates, so that by 56 days of age, tapetal rods have disappeared and tapetal cells are disorganized (Collier et al., 1985b). Ophthalmoscopically, the tapetum of affected cats is not visible. Abnormal retinal projections to the lateral geniculate nucleus (similar to those in the Siamese breed) have also been found in CHS-affected cats, thus accounting for the nystagmus (Creel et al., 1982a). The disease is characterized histologically by giant cytoplasmic granules within lysosomes, melanocytes, and neutrophils. When eyes from older CHS-affected cats were examined histologically and ultrastructurally, lysosomes and residual bodies were found within the retinal pigment epithelium (RPE) (Collier et al., 1986). The residual bodies formed drusen-like mounds beneath the RPE, and RPE cells had detached and moved into the interphotoreceptor space. A diagnosis of CHS is made based on identifying enlarged melanin granules histologically within the hair shafts of cats combined with clinical signs suggestive of the disease.

Visual System Anomalies and Forms of Albinism

Visual system abnormalities associated with forms of albinism have been reported in animals for years (Creel et al., 1982b). A commonly studied model is the Siamese cat, demonstrating a form of partial albinism with retinal hypopigmentation. In particular, Siamese cats possess a mutant allele of the albino series at the C locus (c^c^) (Creel, 1971; Creel et al., 1982b). Siamese cats, therefore, have reduced ocular pigmentation including a lack of stromal pigmentation of the iris or choroid, and a reduction in pigment of the iridal and retinal pigment epithelia (Thibos et al., 1980). The retinal hypopigmentation in these cats is the critical factor resulting in misrouting of many of the projections of the retina to the brain, the nature of the projection error, and the developmental consequences of the relay of the misrouted retinal inputs to the visual cortex (Kaa, 2005; LaVail et al., 1978; Sanderson et al., 1974). The abnormal retinogeniculate projections in Siamese cats was first described by Guillery (1969). Since this study, several reports regarding the visual system of the Siamese cat have been published (Creel, 1971; Guillery & Kaas, 1971; Hubel & Wiesel, 1971; Kalil et al., 1971). Specifically, Siamese cats have reduced ipsilateral retinal projections since many axons originating in the temporal retina that normally project ipsilaterally, project contralaterally in Siamese cats. As a consequence, each lateral geniculate nucleus contains an abnormally greater representation of the ipsilateral visual field (Cooper & Blasdel, 1980). Convergent strabismus with or without involuntary horizontal or rotary nystagmus are possible ocular manifestations as a result of this retinogeniculate misdirection (Blake & Crawford, 1974; Rengstorff, 1976).
White Coat Color, Blue Irides, and Deafness

Complete albinism (complete lack of pigmentation) or partial or localized albinism (an absence or reduction in the degree of pigmentation) is associated not only with the phenotypic appearance of an animal’s coat and skin color but also with conditions affecting the ear and eye (Creel et al., 1983). Albinism or partial albinism may result from the failure of migration of neural crest cells (precursors to melanocytes) and hence result in reduced numbers of melanocytes in a nonpigmented area, or may result because of impaired production of pigment due to some intrinsic deficiency in melanin production (e.g., tyrosinase deficiency) but where the number of melanocytes in nonpigmented or hypopigmented areas is normal.

Domestic cats with white coat color and blue irides have been reported to have a dominantly inherited deafness characterized by alterations to the membranous labyrinth and bony modiolus (Bergsma & Brown, 1971). The syndrome results from an autosomal dominant gene, W, that is fully dominant with complete penetrance in producing white fur, with incomplete penetrance of deafness, and is incompletely dominant in producing blue irides (Bergsma & Brown, 1971). The blue iris is also conditioned by other genes that produce high degrees of white spotting that are allelic to gene W and by other independent genes (Bergsma & Brown, 1971). Importantly, therefore, not all blue-eyed white cats are deaf while white cats with nonblue irides may also be deaf (Bamber, 1933). However, in one study, white cats with bilateral blue eyes were more frequently deaf than were heterochromic white cats, which in turn were more frequently deaf than were white cats with bilateral “brown” eyes (Bergsma & Brown, 1971). Different manifestations of cochlear pathology have been described in deaf white cats (Ryugo et al., 2003). The deafness in this colony of cats was not progressive and occurred either unilaterally or bilaterally; however, iris color was not described.

Ehlers–Danlos Syndrome

Ehlers-Danlos syndrome, or cutaneous asthenia, has been reported in cats. It is a congenital, inherited syndrome involving collagen, and it is characterized by fragile, hyperextensible, and easily torn skin. The mode of inheritance of this syndrome in cats is autosomal dominant (Patterson & Minor, 1977). In contrast to the dominant forms of Ehlers-Danlos syndrome reported in humans in which excessive joint laxity may be seen in addition to the skin lesions, affected cats only demonstrate fragility and hyperextensibility of the skin thereby suggesting differences in the underlying genetic defect and/or in metabolism of dermal and skeletal collagen in cats compared with humans (Patterson & Minor, 1977). Ocular manifestations of Ehlers-Danlos syndrome reported in cats have been linked to excessive laxity of the eyelid skin and include entropion with secondary blepharospasm and keratoconjunctivitis (Patterson & Minor, 1977).

A diagnosis of Ehlers-Danlos syndrome is made based on a clinical syndrome of skin hyperextensibility, clinical signs associated with skin fragility including easily torn skin, and skin histopathology (routine histopathology with Masson’s trichome staining and ultrastructural examination). Determination of skin hyperextensibility can be objectively assessed by calculating the extensibility index (Patterson & Minor, 1977). The extensibility index is determined by dividing the vertical height of a skin fold (extending a skin fold over the dorsal lumbar area maximally without eliciting pain) by body length (measured from occipital crest to base of tail), then multiply by 100. A skin extensibility index greater than 14.5% is considered hyperextensible.

Ehlers–Danlos syndrome is incurable and because of its hereditary nature, owners should be advised not to use affected cats for breeding. Therapy for affected cats is directed at preventing skin lacerations (i.e., declawing fore- and hindpaws).

Hydrocephalus

Hydrocephalus refers to increased amount of cerebrospinal fluid (CSF) within the cranial vault. The most common cause of congenital hydrocephalus is a primary congenital stenosis or aplasia of the mesencephalic aqueduct associated with fused rostral colliculi. Mesencephalic aqueductal stenosis has been reported in kittens following in utero exposure to grisulfulin (Scott et al., 1975), and following transplacental infection with feline panleukopenia virus (FPV) (Csiza et al., 1971). Congenital hydrocephalus may produce enlargement of the calvarium and failure of closure of the suture lines of the skull. Consequently, affected kittens may have dome-shaped heads and a persistently open fontanelle. Clinical signs of hydrocephalus include behavioral changes, ataxia, compulsive circling, and seizures (Coates & Sullivan, 2001). Ventrolateral strabismus is a common ocular manifestation of congenital hydrocephalus due, in part, to enlargement of the calvarium with subsequent impingement on the orbits from the dorsolateral aspects (Coates & Sullivan, 2001). This consequently pushes the eyes in a ventrolateral direction and produces a “sunset” appearance to the corneas. As well, congenital hydrocephalus may cause cranial nerve compromise and subsequent ventrolateral strabismus. For a review of hydrocephalus in cats as well as dogs, the reader is referred to Thomas (2010).

Myasthenia Gravis

Myasthenia gravis is a disease affecting the neuromuscular junction (for a complete review, see Shelton, 2002). Myasthenia gravis is either congenital or acquired (for acquired, see section on acquired immune-mediated conditions). Congenital myasthenia gravis occurs when there is a functional disorder or depletion of nicotinic acetylcholine receptors (AChRs) (Shelton, 2002). Congenital myasthenia gravis has been reported in two cats (Indrieri et al., 1983; Joseph et al., 1988)
and is most likely caused by an inherited depletion of AChRs. There is no breed or sex predisposition for feline congenital myasthenia gravis, and clinical disease generally manifests in 3- to 4-month-old cats (Indrieri et al., 1983; Joseph et al., 1988). Clinical signs associated with congenital myasthenia gravis include generalized muscle weakness that worsens with exercise, dysphagia and/or regurgitation, changes in voice, and head ventroflexion. It is also possible, as has been reported in the acquired form of myasthenia gravis in dogs, that facial weakness, including a weakened palpebral reflex, may be observed. Diagnosis of congenital myasthenia gravis requires detailed histopathological, immunohistopathological, and ultrastructural examination of skeletal muscle neuromuscular junctions. Oral anticholinesterase therapy (e.g., pyridostigmine bromide) should be attempted in cases of confirmed myasthenia gravis. Neuromuscular weakness was resolved in the two cats reported to have congenital myasthenia gravis following appropriate therapy (Indrieri et al., 1983; Joseph et al., 1988).

**Myotonia**

Myotonia is characterized by muscle spasm and stiffness as the result of continued active contraction of a muscle following cessation of voluntary effort (Gaschen et al., 2004). Myotonia may be a primary disorder or can develop secondary to other disorders such as endocrinopathies and muscular dystrophies. Primary congenital myotonia has been described in cats (Hickford et al., 1998; Toll et al., 1998). An autosomal recessive mode of inheritance is suspected for feline congenital myotonia. In most species, the underlying abnormality of myotonia involves a defect in chloride conductance in the sarcolemma (Vite et al., 1998). The clinical signs associated with myotonia in cats include a stiff awkward gait and generalized muscle hypertrophy, and, when startled, affected kittens may stiffen, fall into lateral recumbency, and develop spasms of the facial muscles and eyelids (Hickford et al., 1998).

**DEVELOPMENTAL**

**Lysosomal Storage Diseases**

Many lysosomal storage diseases have been identified in cats (Aguirre et al., 1986; Alroy et al., 1991; Blakemore, 1986; Breton et al., 1983; Burditt et al., 1980; Cork et al., 1977, 1978; Cowell et al., 1976; Cummings et al., 1988; Haskins et al., 1979a, 1979b, 1979c, 1980a, 1980b, 1982; Jezyk et al., 1977, 1986; Langweiler et al., 1978; Lowenthal et al., 1990; Mazrier et al., 2003; M urray et al., 1977; Neuwelt et al., 1985; Nowakowski et al., 1988; Sheridan et al., 1994; Stramm et al., 1985, 1986; Vandeveld et al., 1982; Vine et al., 1981). These inborn errors of metabolism are, however, relatively rare diseases that have received a disproportionate amount of investigation, because they represent potential animal models for human syndromes. Storage diseases are characterized by an accumulation of metabolic by-products within lysosomes, the cellular organelles that degrade complex macromolecules. The substrates for catabolism within lysosomes include glycoproteins, mucopolysaccharides, oligosaccharides, proteins, and sphingolipids (Jolly & Walkley, 1997; Skelly & Franklin, 2002). Storage diseases result from a deficiency in a specific catabolic enzyme (i.e., acid hydrolases), thus causing the enzyme substrate to accumulate in the lysosomes within cells. Consequently, lysosomal storage diseases are subclassified based on the type of storage product. Important groups include the glycoproteinoses, mucopolysaccharidoses (MPS), oligosaccharidoses, proteinoses, and the sphingolipidoses (Jolly & Walkley, 1997; Skelly & Franklin, 2002). Specific lysosomal storage diseases are normally named according to the specific accumulated product. Because this excess material is a normal component, the histopathologic changes result from physical distortion of affected cells rather than from a toxic effect. Most lysosomal storage diseases, with known mode of inheritance, are inherited as an autosomal recessive trait. When homozygous, the syndromes are usually severe, thus resulting in neurologic disease and, eventually, death. The eyes in most affected animals have histopathologic lesions, but clinical ophthalmic lesions may not be visible (Aguirre et al., 1986; Evans, 1989). Antemortem diagnosis of a lysosomal storage disease can be confirmed by lysosomal enzyme analysis (e.g., Lysosomal Disease Testing Laboratory, Jefferson Medical Center, Philadelphia, PA, http://www.jefferson.edu/lysolab/index.cfm) or with genetic testing for specific feline lysosomal storage diseases (http://www.vgl.ucdavis.edu/services/cat).

**Alpha-Mannosidosis**

Alpha (α)-mannosidosis is a member of the inherited oligosaccharidoses described in Persian, domestic shorthair, and domestic longhair cats, which results from a deficiency in acidic α-mannosidase (Cummings et al., 1988; Maenhout et al., 1988; Raghavan et al., 1988). Specifically, the disease in cats is caused by a four base-pair deletion in the feline α-mannosidase gene (Berg et al., 1997). Systemic manifestations of α-mannosidosis in cats include stunted growth, skeletal deformities, emaciation, hepatomegaly, and neurologic dysfunction including tremors, ataxia, dysmetria, and progressive weakness (Maenhout et al., 1988). Ocular abnormalities described in affected cats include progressive corneal opacity and lenticular opacification (Alroy et al., 1991), and resting nystagmus (Vite et al., 2005). Visual evoked potentials revealed asymmetry in latency and shape of signal conduction as well (Alroy et al., 1991). Histologic and histochemical ocular findings in eyes of cats with α-mannosidosis revealed cytoplasmic vacuolation of numerous ocular cell types including keratocytes and lens epithelial cells, and positive staining of these cells with Concanavalis ensiformis agglutinin (Con A) and wheat germ agglutinin (WGA). Two phenotypic variants of feline α-mannosidosis have been recognized. Clinical signs of α-mannosidosis in domestic longhair cats were milder and slower to progress than those observed in affected Persian
and domestic shorthair cats, and did not include prominent skeletal deformities, hepatomegaly, or ocular lesions reported in the aforementioned breeds (Cummings et al., 1988). Feline α-mannosidosis can thus be categorized into severe acute and milder chronic forms (type I and type II α-mannosidosis in humans, respectively) (Cummings et al., 1988). Gene therapy in brains of cats with α-mannosidosis, using multiple intracerebral injections and adeno-associated virus vector, was evaluated experimentally (Vite et al., 2005). Significant improvements in neurological signs and brain myelination were noted in treated cats (Vite et al., 2005).

Globoid Cell Leukodystrophy (Krabbe’s Disease)

Globoid cell leukodystrophy, or Krabbe’s disease, is a member of the inherited sphingolipidoses described in cats, which results from a deficiency in galactocerebrosidase (GALC) activity (Salvadori et al., 2005). The substrate galactocerebroside (i.e., galactosylceramide), a constituent of myelin, and another metabolite of myelin turnover, psychosine (galactosyl sphingosine), accumulate. Psychosine is highly cytotoxic to oligodendroglia and is thought to be the primary metabolite involved in the pathogenesis of the disease (Miyatake & Suzuki, 1972). Consequent to the buildup of these toxic metabolites, leukodystrophy results. Globoid cell leukodystrophy is pathologically characterized by bilaterally symmetric demyelination of the white matter of the brain, spinal cord, spinal nerve roots, and peripheral nerves, loss of oligodendrocytes, and the accumulation, predominantly perivascularly, of globoid cells (multinuclear globoid macrophages) containing nonmetachromatic, nonsudanophilic, periodic acid-Schiff (PAS)-positive material (Suzuki & Suzuki, 2002). The mode of inheritance of globoid cell leukodystrophy in cats has yet to be determined.

Globoid cell leukodystrophy in cats is generally characterized by an early onset, rapidly progressive, and severe disease, which has pathological lesions identical to those reported in other domestic animals (Salvadori et al., 2005). Clinical signs are characterized by early posterior dysmetria and ascending incoordination, and generalized tremors, in association with paraplegia and inability to perceive deep pain (Salvadori et al., 2005). Cerebellar signs or progressive paraparesis and paraplegia are the predominant clinical manifestations. Ocular manifestations of this disease in cats include lack of vestibular ocular reflexes, and signs associated with visual deficits including diminished pupillary light reflexes and reduced menace responses (Salvadori et al., 2005). The optic tracts and optic radiation are among the most severely affected regions of the white matter of the brain of cats with globoid cell leukodystrophy (Salvadori et al., 2005), thereby accounting, in part, for the visual deficits. The definitive diagnosis of globoid cell leukodystrophy involves genetic testing to document the mutation in the GALC gene or biochemical assays to demonstrate the enzymatic deficiency. Although genetic testing has been developed to diagnose globoid cell leukodystrophy in West Highland White and Cairn Terriers (Victoria et al., 1996), this test is not useful in cats as the feline GALC gene has yet to be cloned (Salvadori et al., 2005).

Gangliosidoses

GM 1-Gangliosidosis

GM 1-gangliosidosis is caused by a deficiency of lysosomal hydrolase, β-d-galactosidase, which produces an accumulation of GM 1-ganglioside in the cerebral cortex and visceral organs. Such deficiencies have been reported in cats, dogs, cattle, and sheep (De Maria et al., 1998). The mode of inheritance of feline GM 1-gangliosidosis is autosomal recessive. GM 1-gangliosidosis is characterized by mild (3–7 months of age) to severe (>7 months of age) progressive neurological disease and early death (Cox et al., 1998). In particular, clinical manifestations of feline GM 1-gangliosidosis include discrete head and/or limb tremors, ataxia with hypermetria, and progressive paraparesis (De Maria et al., 1998), often with blindness and seizures (Cox et al., 1999). GM 1-mutant cats have also been shown to have greatly reduced body weight and premature thymic involution (Cox et al., 1998), and electrophysiological abnormalities including abnormal brainstem auditory evoked responses and spinal evoked potentials (Steiss et al., 1997). Histopathologic lesions of membrane-bound inclusions are present throughout the brain, spinal cord, and retinal ganglion cells, but only in cats and cattle have clinical ophthalmoscopic lesions been observed. Those ophthalmoscopic lesions were multifocal, white, small spots that probably resulted from elevations of the internal limiting membrane of the retina by swollen ganglion cells. Lesions described outside the central nervous system (CNS) of affected cats include empty cytoplasmic vacuoles in specific cells of some visceral organs, including hepatocytes and renal cortical cells, and in peripheral ganglia (De Maria et al., 1998). Cats with GM 1-gangliosidoses have also been reported to have a unique, faint corneal opacity associated with intracellular vacuoles (Aguirre et al., 1986). Most recently, a mutation in exon 14 of the β-galactosidase gene (GLB1) has been identified in Korat and Siamese cats with GM 1-gangliosidoses (Martin et al., 2008). A genetic test is now commercially available for the detection of this single-base substitution in the GLB1 gene that causes GM 1-gangliosidosis in Korat and Siamese cats (http://www.vgl.ucdavis.edu/services/cat/).

GM 2-Gangliosidosis (Sandhoff Disease, Tay-Sachs Disease, AB-Variant GM 2-Gangliosidosis)

GM 2-gangliosidosis is caused by a deficiency of hexosaminidase. Hexosaminidase has two subunits, α and β, each coded for by HEXA and HEXB genes, respectively. There are three types of hexosaminidase—hexosaminidase S (an αα dimer), hexosaminidase A (an αβ dimer), and hexosaminidase B (a ββ dimer). In addition, there is a GM 2-activator protein coded for by the GM2A gene that is necessary for degrading GM2 ganglioside in concert with hexosaminidase A. In humans, deficiency in the α subunit, and therefore depletion of hexosaminidase A and S, results in classical GM 2-gangliosidosis
(Tay–Sachs disease or B-variant). A deficiency in the β subunit, depleting both hexosaminidase A and B, is known as Sandhoff disease or the O-variant. Furthermore, deficiencies in GM 2-activator protein results in GM 2-activator deficiency, also known as the AB-variant. Feline GM 2-gangliosidosis (Sandhoff disease or O-variant) has been reported in domestic shorthair cats (Baker et al., 1979; Cork et al., 1977) and Korat (Muldoon et al., 1994; Neuwelt et al., 1985). The mode of inheritance of feline GM 2-gangliosidosis is autosomal recessive. The causative mutation of GM 2-gangliosidosis in the domestic shorthair cat has been documented as a 25 base-pair inversion at the extreme 3’ end of the β-subunit (HEXB) coding sequence (Martin et al., 2004). Affected cats show clinical signs of early onset (4–7 weeks of age), progressive neurological dysfunction initially characterized by fine head tremors with or without lacrimation, followed by ataxia, immobility, blindness, and dysphagia, and finally, seizures or generalized myoclonus (5 months of age), quadriplegia (6 months of age), and death prior to 8 months of age (Neuwelt et al., 1985). The definitive diagnosis of GM 2-gangliosidosis involves biochemical confirmation of the enzyme deficiency. Although GM 2-gangliosidosis is mainly a neuronal disease (i.e., gray matter disease), magnetic resonance (MR) imaging of brains of affected cats can demonstrate alterations in myelinization of white matter tracts that may arise secondary to the neuronal damage (Kroll et al., 1995). MR imaging may provide a noninvasive method of monitoring response to treatment once therapeutic strategies are developed for feline GM 2-gangliosidosis (Kroll et al., 1995). In Burmese and Korat cats, the disease is caused by a mutation in the feline hexosaminidase β-subunit (HEXB) gene (Bradbury et al., 2009; Muldoon et al., 1994). Genetic tests are now commercially available for the detection of the 15 base-pair deletion of HEXB and the 1 base deletion in the HEXB gene that cause GM 2-gangliosidosis in Burmese and Korat cats, respectively (http://www.vgl.ucdavis.edu/services/cat/).

**Mucolipidosis II (Inclusion Cell Disease)**

Mucolipidosis II, or inclusion cell (I-cell) disease, is caused by deficient activity of the enzyme N-acetylglucosamine-1-phosphotransferase. Unlike other forms of lysosomal storage diseases, mucolipidosis II results from an error in trafficking of enzymes into lysosomes rather than a deficiency of a specific lysosomal hydrolase (Mazrier et al., 2003). As a result, affected lysosomes are secondarily deficient in multiple acid hydrolases (Lightbody et al., 1971, as cited by Mazrier et al., 2003). Clinical signs in affected kittens initially include facial dysmorphism and failure to thrive, with death or euthanasia due to disease progression being reported to occur between the first postnatal day and 216 days of age (mean = 47 days) (Mazrier et al., 2003). Neurologic signs in affected cats included dull, quiet behavior, and progressive hindlimb ataxia. Skeletal deformities, such as carpal valgus or varus, were also described. Congenital facial abnormalities in affected cats included thickened eyelids, hypertelorism (widely spaced eyes), depressed nasal bridge, a flat broad face, frontal bossing, and low-set ears (Fig. 35.2.1a) (Mazrier et al., 2003). Ocular abnormalities detected in cats affected with mucolipidosis II included, from early to late lesions, absent menace response and diminished pupillary light reflexes, and dilated pupils by 4 months of age. Initially, retinal development appears normal until 2.5 months of age at which time dorsal retinal degeneration developed followed by progressive end-stage generalized retinal degeneration and blindness by 3.5 months of age (Fig. 35.2.1b) (Mazrier et al., 2003).

**Mucopolysaccharidosis**

The MPS are a group of diseases characterized by defective metabolism of mucopolysaccharides (glycosaminoglycans). Three types of MPS have been identified in cats (MPS I, VI, and VII). Defects in the degradation of glycosaminoglycans and other proteoglycans result in accumulation of these compounds in many cell types including cells of the most severely affected axial and appendicular skeleton.

MPS I (Hurler syndrome), caused by a deficiency of the lysosomal enzyme α-L-iduronidase, has been reported in domestic shorthair cats (Haskins et al., 1983a). The result of this enzyme deficiency is the tissue accumulation and urinary excretion of dermatan and heparan sulfate (Jolly & Walkley, 1997). Affected cats have an abnormal gait due to bony dysplasia, vertebral fusion and polyarthropathies, stunted growth, joint immobility, cardiac valvular disease, facial deformities, and develop corneal clouding.

MPS VI (Maroteaux–Lamy syndrome), caused by a deficiency of the lysosomal enzyme arylsulfatase-B, has been reported in cats (Crawley et al., 2003; Haskins et al., 1983b). MPS VI is one of the more prevalent inherited diseases in cats and occurs commonly in cats with Siamese ancestry (Crawley et al., 2003). Arylsulfatase-B hydrolyzes dermatan sulfate; therefore, lack of this enzyme results in lysosomal accumulation and urinary excretion of dermatan sulfate. Clinical signs in affected cats are similar to those in cats with MPS I including corneal opacities, but also include severe spondylosis and kyphosis, widened intervertebral disk spaces, and severe facial dysmorphism. MPS VI-affected cats also have a high incidence of degenerative joint disease (Crawley et al., 2003). In addition, feline MPS VI results in lysosomal accumulation of dermatan sulfate within connective tissue cells of the cornea, sclera, conjunctiva, uvea, and RPE, with corneal clouding being the most debilitating ocular manifestation (Aguirre et al., 1983). The enzyme defect was partially corrected following allogenic bone marrow transplantation in feline MPS VI, thereby resulting in improved clinical signs including clearing of the corneal opacities (Gasper et al., 1984). Recombinant adeno-associated virus-mediated subretinal delivery of feline 4-sulfatase has been shown to correct the histopathologic lesions of RPE cells of feline MPS VI (Ho et al., 2002). Improvements in the clinical signs of feline MPS VI have been reported following enzyme replacement therapy in a feline model of MPS VI (Crawley et al., 1997).
Corneal clouding associated with feline MPS I and VI is felt to be due, in part, to accumulation of substrate in the keratocytes (Mollard et al., 1996). Corneal endothelial cells of MPS I-affected cats were shown to function normally in affected cats, despite these cells having numerous vacuolated lysosomal inclusions or a granular matrix (Mollard et al., 1996). Structural alterations in the corneal stroma, including abnormal spacing, size, and arrangement of collagen fibrils in feline models, of MPS I and VI were also reported to account, in part, for the corneal cloudiness observed in affected cats (Alroy et al., 1999).

MPS VII (Sly syndrome) resulting from a deficiency of β-glucuronidase, has also been described in domestic short-haired cats (Gitzelmann et al., 1994; Schultheiss et al., 2000). β-Glucuronidase deficiency results in impaired catabolism of chondroitin, deramatin, and heparan sulfates (Schuchman et al., 1989). Consequently, these glycosaminoglycans accumulate in tissues and are excreted in the urine (Silverstein et al., 2004). Clinical signs of feline MPS VII include corneal clouding, facial abnormalities, an awkward gait due to multiple skeletal deformities, stunted growth, paraparesis, tracheal hypoplasia (Gitzelmann et al., 1994; Schultheiss et al., 2000), and, atypically, generalized seizures, which were inducible following cutaneous stimulation over the dorsum of one cat (Gitzelmann et al., 1994). In one such cat, the corneal clouding developed in both eyes by 9 months of age, but had
nearly resolved by 21 months of age despite progressive systemic signs and death 2 weeks later (Schultheiss et al., 2000).

**Sphingomyelin Lipidosis (Niemann–Pick Disease)**

In humans, there are six types of Niemann–Pick diseases (NPDs; types A–F), with types A, B, and F demonstrating a deficiency in sphingomyelinase (Summers et al., 1995), while a feline model of NPD type C exhibited a defect in cholesterol transport (Brown et al., 1994). Sphingomyelin lipidosis, or NPD, is characterized by sphingomyelin and cholesterol accumulation in tissues. NPD type A has been reported in Siamese and Balinese cats (Baker et al., 1987; Snyder et al., 1982).

Clinical manifestations of this disease include head tremors and bobbing, and dysmetria by 3–4 months of age, followed by paresis later in the disease. Cats with NPD type A may also exhibit hepatomegaly (Baker et al., 1987; Snyder et al., 1982).

NPD type C has been reported in domestic shorthair cats (Brown et al., 1994; Lowenthal et al., 1990; March et al., 1997; Munana et al., 1994). Clinical signs in NPD type C–affected cats involve progressive neurological dysfunction including intention tremors at 8–12 weeks of age, followed by ataxia, hypermetria, lack of menace response with intact vision, and occasionally, positional nystagmus. In addition, other common manifestations of this disease include hepatosplenomegaly and elevations in serum alkaline phosphatase and alanine aminotransferase. Feline NPD type C is generally fatal by 8–10 months of age (Brown et al., 1994; Lowenthal et al., 1990; March et al., 1997; Munana et al., 1994).

**ACQUIRED**

**Cardiovascular Diseases**

**Hypertension**

Systemic arterial blood pressure is the product of cardiac output (CO) (CO = heart rate x stroke volume) and total peripheral resistance. Any factor causing persistent elevation in one or more of these three parameters of blood pressure can cause systemic hypertension. When hypertension is associated with an underlying causative disease, it is called secondary hypertension. Hypertension in veterinary patients is typically secondary hypertension. It should be noted, however, that primary (essential) hypertension has been described, although less commonly, in cats (Maggio et al., 2000). Primary hypertension is hypertension resulting from unknown reasons. A previous definition of the high "normal" range of systolic blood pressure for cats was between 160 and 200 mmHg. Renal damage in dogs has been reported to progress with systolic blood pressures in this range, however (Brown et al., 2000; Finco, 2004). Consequently, systemic hypertension is defined as a calm animal having repeatable systolic blood pressures measurements greater than 160 mmHg and/or diastolic blood pressure measurements greater than 100 mmHg (Stepien, 2005). Measurement of blood pressure in cats is most easily accomplished in a clinical setting by indirect measurement using an oscillometric or ultrasonic detection device. Cats aged 11 years and older have been noted to have significantly higher systolic, diastolic and mean arterial, and pulse pressures than cats under 11 years of age (Bodey & Sansom, 1998).

Systemic hypertension is a relatively common disease of older cats, and it has most consistently been associated with chronic renal failure and hyperthyroidism (Kobayashi et al., 1990; Littman, 1994; Maggio et al., 2000; Morgan, 1986; Sansom et al., 1994; Stiles et al., 1994). A recent study reported that 20/103 cats (19.4%) with chronic renal failure were hypertensive (Syme et al., 2002). Other conditions associated with feline hypertension include diabetes mellitus, primary aldosteronism, chronic anemia, and high-salt diet (Maggio et al., 2000; van de Sandt et al., 2003).

The ocular manifestations of systemic hypertension can be severe and lead to blindness. The consequence of ocular vascular hypertensive changes is an initial vascular constriction in the retinal arterioles in response to increased blood pressure; when sustained, it results in occlusion and ischemic necrosis of the vessel walls, with resultant increased vascular permeability (Garner, 1982; Garner et al., 1975; Keys, 1937; Keyes & Goldblatt, 1938). Serous retinal exudates, hemorrhages, and edema also result. Choroidal vascular changes result in subretinal fluid and retinal detachment. Ocular lesions associated with feline hypertension include retinal hemorrhages, retinal detachments, retinal edema, retinoschisis, varying degrees of retinal degeneration, and papilledema (Fig. 35.2.2 and Fig. 35.2.3) (Littman, 1994; Maggio et al., 2000; Morgan, 1986; Sansom et al., 1994; Stiles et al., 1994; Turner et al., 1990). The fundus abnormalities in feline hypertension can be separated into three categories: (1) hypertensive retinopathy, which comprises retinal edema, “pseudonarrowing” of the retinal arterioles due to the effects of retinal edema, followed by narrowing and increased tortuosity of the retinal arterioles due to arteriosclerosis, and retinal hemorrhages; (2) hypertensive choroidopathy, which involves retinal detachments that may be single or multiple, flat, bullous or total detachments, and degenerative RPE lesions (Fig. 35.2.4); and (3) hypertensive optic neuropathy, which includes papilledema, and optic atrophy following end-stage retinal degeneration (Crispin & Mould, 2001). Potential complications of systemic hypertension include anterior segment and vitreous hemorrhage, uveitis, and glaucoma (Littman, 1994; Morgan, 1986; Sansom et al., 1994; Stiles et al., 1994; Turner et al., 1990). Hypertension should therefore be ruled out when presented with intraocular hemorrhage or bullous retinal detachment of unknown origin. Hypertensive cats have been shown to have a greater prevalence of retinal lesions (48%) compared with normotensive cats (3%) (Chetboul et al., 2003). In addition, cats with retinopathies had higher blood pressure (262 ± 34 mmHg) than hypertensive cats without retinal lesions (221 ± 34 mmHg) (Chetboul et al., 2003).

The goals of antihypertensive therapy include lowering blood pressure and slowing the progression of target organ damage caused by chronic hypertension. Successful therapy
Figure 35.2.2. Photographs of the ocular fundi of cats with systemic hypertension and associated retinal lesions. (A) Preretinal hemorrhage near a major retina venule (arrow) and focal intraretinal edema (arrowhead). (B) Multifocal intraretinal and subretinal edema (arrows) and mild retinal vascular tortuosity. (C) Complete infundibular retinal detachment with substantial serous subretinal fluid and focal intraretinal hemorrhage (arrow). (D) Diffuse retinal degeneration and vascular attenuation. Notice the substantial tapetal hyperreflectivity (arrows) and focal hemorrhage (arrowhead). (E) Multifocal intraretinal edema (arrows). (F) Same eye as (E), 2 weeks after treatment with amlodipine besylate (0.625 mg PO q 24 hours). Notice the substantial resolution of edema. (Reprinted with permission from Maggio, F., DeFrancesco, T.C., Atkins, C.E., Pizzirani, S., Gilger, B.C. & Davidson, M.G. (2000) Ocular lesions associated with systemic hypertension in cats: 69 cases (1985–1998). *Journal of the American Veterinary Medical Association*, 217, 695–702.)
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Antihypertensive agents used in cats include β-blockers such as propranolol or atenolol; diuretics such as spironolactone/thiazide, furosemide, and hydrochlorothiazide; and angiotensin-converting enzymes such as captopril (Littman, 1994; Morgan, 1986). Amlodipine, a calcium channel blocker, has been shown to be an effective antihypertensive agent in cats and is now considered a mainstay of therapy for feline hypertension (Elliott et al., 2001; Henik et al., 1997; Komaromy et al., 2004; Maggio et al., 2000; Tissier et al., 2005).

Hypertensive retinopathy in many cats is a slow, insidious process. Vision may be spared if the process is identified and controlled before severe ocular disease develops (Stiles et al., 1994). Consequently, cats with diseases such as chronic renal failure and hyperthyroidism should be screened for systemic hypertension.

Periarteritis Nodosa

Periarteritis nodosa, an infrequently reported disease in cats, is characterized by fibrinoid necrosis of the media, adventitia, and endothelium of both small- and medium-sized arteries. Eventually, granulation tissue forms, and vessels become obstructed and nonfunctional. Tissues supplied by these vessels then become ischemic.

Few reports in the literature describe this disease in cats (Altera & Bonasch, 1966; Campbell et al., 1972; Lewis et al., 1965). Ocular lesions of periarteritis nodosa have included unilateral iritis in one cat (Altera & Bonasch, 1966). A mother cat, which was euthanized, had bilateral panuveitis with infiltration of lymphocytes and plasma cells and hyalin necrosis of the ciliary processes (Campbell et al., 1972). Fibrinous exudates were present in the ocular chambers, and cyclitic membranes spanned the globes. Retinal detachments were also present in both eyes.

In humans, periarteritis nodosa is now accepted to be an immune complex-mediated vasculitis. In some cases, it is associated with viral infections, particularly hepatitis B. Ocular lesions are not uncommon, and treatment often includes immunosuppression with glucocorticoids or azathioprine. In cats, the diagnosis has usually been made on the basis of necropsy findings.

Anemia

Anemia is the reduction in red blood cells (RBCs) per volume of whole blood. A anemia is classified as regenerative if there has been a normal bone marrow response to erythropoietin (e.g., usually occurs with blood loss or hemolytic disease), or nonregenerative if the normal reticulocyte response is lacking (e.g., may occur with chronic extra-marrow disease that reduces RBC survival time, selective erythropoietin depression, insufficient erythropoietin release, or a combination of these factors) (Rebar et al., 2005). Severe anemia requires good client compliance with frequent reassessment of the blood pressure. If an underlying cause of the hypertension has been identified, the primary condition should be addressed therapeutically, when possible. However, even if the presumed underlying cause of the hypertension is controlled, antihypertensive therapy is typically required long term.
often manifests systemically as pale mucous membranes, cool mucous membranes, tachycardia, polyneuropathy, weakness, as well as signs specific to the underlying primary condition. Ocular manifestations of severe anemia include pale retinal vasculature, varying degrees of retinal hemorrhage, and subtle changes in tapetal reflectivity. Retinal hemorrhages are more likely to be observed, however, and are more dramatic if accompanied by thrombocytopenia (Carraro et al., 2001). Small intraretinal hemorrhages are typical and may reabsorb quickly with correction of the anemia, but pigmented disturbances may be a residual retinal alteration. In one study of 26 cats with anemia and hemoglobin values of less than 5 g/dL, 20/26 affected cats had retinal hemorrhages (Fischer, 1970). Causes of anemia in these cats included Mycoplasma haemofelis (previously Haemobartonella felis) infection, thrombocytopenia, autoimmune hemolytic anemia, aplastic anemia, lymphosarcoma, and bleeding duodenal ulcer (Fischer, 1970). In retrospect, some of the cats in this study were likely infected with the feline leukemia virus (FeLV), which was not widely known at that time. Though noted only infrequently in the literature (Brightman et al., 1991), cats with FeLV infections and profound anemia commonly have retinal hemorrhages. Furthermore, ehrlichiosis and anaplasmosis have been suspected as causes of thrombocytopenia and anemia in cats (Breitschwerdt et al., 2002; Peavy et al., 1997; Shaw et al., 2005).

The mechanism of retinal hemorrhage in anemic cats may be multifactorial (Fischer, 1970). Lack of RBCs render vascular endothelial cells hypoxic, thereby increasing vascular fragility. Thrombocytopenia may accompany anemia as well, thus decreasing platelet aggregation in areas of microvascular trauma.

Hyperlipidemia

Hyperlipidemia refers to an elevation in plasma concentrations of cholesterol and/or triglycerides, and arises due to a disturbance in plasma lipoprotein metabolism (Watson & Barrie, 1993). Hyperlipidemia can occur in cats for several reasons, including postprandial hyperlipidemia, diabetes mellitus, exogenous corticosteroid administration, megestrol acetate administration, nephrotic syndrome, lipoprotein lipase deficiency, idiopathic hyperchylomicronemia, and familial hypertriglyceridemia (Crispin, 1993). Familial hyperlipidemia in cats arises due to production of an inactive lipoprotein lipase resulting in a fasting chylomycronemia with a slight increase in very low-density lipoprotein (VLDL) (Jones et al., 1983). If lipemia persists in a fasted blood sample, serum triglyceride and cholesterol levels should be measured. In addition, lipoprotein electrophoresis and ultracentrifugation to determine lipoprotein fractions can be performed.

Lipemia retinalis has infrequently been described as an ocular manifestation of hyperlipidemia in cats (Crispin, 1993; Wyman & McKissick, 1973). The term lipemia retinalis describes excess lipid within the retinal vessels, thus giving them a pale appearance. In both cats and dogs, it is the large, triglyceride-rich lipoproteins (e.g., low-density lipoproteins) that produce a visible lipemia (Crispin, 1993). Hyperlipidemia may also manifest with lipids in the anterior chamber. A prerequisite for gaining access to the anterior chamber by the large, lipid-laden molecules is alteration of the blood–aqueous barrier, presumably resulting from preexisting uveitis. It is unclear, however, whether the lipids incite or are the result of uveitis. The syndrome is usually unilateral, which would argue against hyperlipidemia inciting uveitis. Persistent lipemia was induced in kittens with high-dose parenteral methylprednisolone (Wyman & McKissick, 1973), and a primary inherited/familial hyperchylomicronemia has been described (Bauer & Veriander, 1984), as has idiopathic hyperchylomicronemia (Jones et al., 1983). The inherited disorder is accompanied by skin masses that, histopathologically, were characteristic of lipogranulomas. Feeding a low-fat diet controls the clinical signs. One recent report described several unrelated litters of kittens with idiopathic transient hyperlipidemia and anemia as well as lipemia retinalis (Gunn-Moore et al., 1997). Many of these kittens died, but those that survived improved rapidly on a low-fat diet.

Hyperviscosity Syndrome

Hyperviscosity syndrome comprises single or multiple clinicopathologic abnormalities resulting from increased serum viscosity. The severity of hyperviscosity syndrome is linked to the size, shape, type, and concentration of large molecules (e.g., immunoglobulins [Igs]) in the bloodstream. The underlying cause is usually a malignancy, such as lymphoma, chronic lymphocytic leukemia, plasmacytoma, or multiple myeloma (Forrester et al., 1992; Hribernik et al., 1982; K ruth & Carter, 1990). Hyperviscosity syndrome in cats has most frequently been associated with multiple myeloma, in which a certain class of Ig is produced in excess (Forrester et al., 1992; Hribernik et al., 1982; Patel et al., 2005).

Clinical signs are variable, but they often include listlessness, pale mucous membranes, neurologic signs, and lameness. Ocular manifestations are common. Reported ocular lesions in the cat include retinal hemorrhages, dilated and tortuous retinal vessels, retinal detachment, perivascular effusion, papilledema, and retinal degeneration (Forrester et al., 1992; Hawkins et al., 1986; Hribernik et al., 1982; Lane et al., 1993). The mechanism of producing clinical signs is perhaps multifactorial and is not well understood. Hemorrhage may occur from multiple causes, such as sludging of blood in small vessels, ineffective delivery of oxygen and nutrients to vessel walls, hypertension, coagulation abnormalities as a result of elevated protein levels interfering with clotting factors and platelet function, and thrombocytopenia.

The diagnosis of hyperviscosity syndrome is made on the basis of demonstrating the hyperproteinemia with serum electrophoresis and immunoelectrophoresis, to detect a mono- or polyclonal spike and to categorize the type of gammopathy. A detailed medical workup is necessary to determine the cause of the hyperproteinemia.
Treatment is aimed at defining and treating the underlying disease process, if possible. Reducing serum viscosity by plasmapheresis is sometimes helpful as well.

Hypoxia

Hypoxia most commonly occurs during anesthetic episodes, and it may relate to apnea, cardiopulmonary failure, improper intubation, overdose of anesthetic agent, failure of anesthetic equipment, paralysis of the muscles of respiration, and severe systemic hypotension (Gaynor et al., 1999; Jurk et al., 2001; Wingfield & Van Pelt, 1992). Neurons are more sensitive to hypoxia than other support tissues, and neuronal tissue affected by severe and prolonged hypoxia ± reperfusion will undergo severe cellular metabolic dysfunction leading to apoptosis and ischemic necrosis (Clarkson et al., 2005; Somjen et al., 1993). Clinical signs of cerebral hypoxia include blindness, stupor or coma, paralysis with decerebrate rigidity, seizures, and deafness. Pupillary light reflexes, however, are generally normal. These signs may be either partially or wholly reversible after a period of days to months. Therapy for systemic and cerebral hypoxia depend on the etiology. In cases of cardiopulmonary arrest, the reader is referred to recent reviews pertaining to this topic (Hackett, 2001; Marks, 1999; Rieser, 2000; Wingfield & Van Pelt, 1992). Glucocorticoids are not thought to improve neurologic recovery following cardiopulmonary arrest, however (Rieser, 2000).

Icterus

Icterus or jaundice is characterized by hyperbilirubinemia and deposition of bile pigments in the skin, sclera, and mucous membranes causing them to appear a shade of yellow. Jaundice typically becomes present when serum bilirubin concentrations are greater than 5- to 10-fold above "normal" reference range (Sherding, 2000). The sclera is the classic location for detection of icterus given its relative lack of pigmentation. The yellow appearance of icterus may be detected in the intraocular structures as well (e.g., blue irides may turn green). For a review of icterus in cats, see Sherding (2000).

Polycythemia

Polycythemia is classified as relative or absolute (primary and secondary forms). Relative polycythemia is an increased packed cell volume with normal RBC mass occurring as a result of a reduction in plasma volume as may arise from external losses of body fluids (e.g., diarrhea; burns).

Absolute polycythemia is an increase in total RBC mass, and it may be classified as either primary or secondary (appropriate and inappropriate). A absolute primary polycythemia (i.e., polycythemia vera) has been described in cats and is an absolute increase in erythropoiesis without an increase in erythropoietin (Evans & Caylor, 1995; Foster & Lothrop, 1988; Nett et al., 2001; Queensel et al., 1997; Reed et al., 1970). A n underlying molecular basis of polycythemia vera has yet to be elucidated.

Absolute secondary polycythemia results from altered erythropoietin homeostasis and is described as being appropriate or inappropriate. A absolute secondary appropriate polycythemia occurs as a consequence of persistent hypoxia, and is seen in animals with conditions such as congenital cardiac defects causing right-to-left shunting of blood (Kirby & Gillick, 1974). A absolute secondary inappropriate polycythemia, however, results from disease processes that lead to inappropriate secretion and elevation of erythropoietin or an erythropoietin-like substance in the absence of systemic hypoxia. Causes of absolute secondary inappropriate polycythemia include diseases that result in the production of erythropoietin or that cause local hypoxia and trigger erythropoietin synthesis including malignancies and renal disease (e.g., renal neoplasia), respectively (Hasler & Giger, 1996; Henry et al., 1999). Polycythemia may manifest as dark, ruddy-colored conjunctival and retinal blood vessels that are dilated and tortuous. In addition, bilateral anterior uveitis with concurrent unilateral chorioretinitis has been described in a dog with polycythemia vera (Gray et al., 2003). Treatment varies according to the cause of the polycythemia. If left untreated, however, retinal detachment and ocular hemorrhage may occur with persistent polycythemia.

Thrombocytopenia and Thrombopathies

Thrombocytopenia is an acquired hemostatic defect of cats. Thrombocytopenia results from either decreased platelet production, increased platelet removal, sequestration of platelets, or any combination of these. The most common causes of thrombocytopenia include infectious diseases, neoplasia, drug-induced reactions, and immune-mediated disease. In particular, the numerous pathogens implicated in causing infectious thrombocytopenia in cats include arthropod-borne agents (e.g., Babesia [Schoeman et al., 2001], Cytauxzoon [Hoover et al., 1994], Ehrlichia spp. [Breitschwerdt et al., 2002; Peavy et al., 1997], viral agents, e.g., feline immunodeficiency virus (FIV) [Shelton et al., 1990b], panleukopenia virus [Peterson et al., 1995], and fungal and bacterial organisms, e.g., histoplasmosis [Bromel & Sykes, 2005b]). Thrombocytopenia is also seen in association with (1) many forms of neoplasia including lymphoma, leukemia, and multiple myeloma (Patel et al., 2005; Peterson et al., 1995); (2) medications that impair platelet production, or cause secondary immune destruction of the platelets (e.g., propylthiouracil [Peterson et al., 1984]); or (3) may develop as an idiopathic or primary immune-mediated disease (Garon et al., 1999; Tasker et al., 1999).

Thrombopathies are blood coagulation disorders resulting from platelet dysfunction. Disease processes associated with thrombopathies include anemia, disseminated intravascular coagulation (DIC) liver failure, and uremia. Regardless of the origin, both thrombocytopenia and thrombopathies are rather frequent causes of ocular and periocular hemorrhage. The presence of bleeding signs at a given platelet level vary between individuals, but platelet counts are usually less than 50,000 cells/µL when ocular petechiae form. Petechiae in
the ocular fundus are often present without visible petechiae in the skin and other mucous membranes. Therapy is directed at the underlying cause, and if bleeding signs are severe, transfusion of fresh whole blood or platelet-rich plasma is indicated.

Idiopathic Systemic Diseases

Dysautonomia (Key-Gaskell or Dilated Pupil Syndrome)

Feline dysautonomia, which is also known as Key-Gaskell or dilated pupil syndrome, was first reported in England in 1982 (Key & Gaskell, 1982). The disease, which produces widespread autonomic nervous system dysfunction, has since been reported in many cats throughout Europe (Cave et al., 2003; Rochlitz, 1984; Sharp et al., 1984), but the number of documented cases in the United States remains small (Bromberg & Cabaniss, 1988; Canton et al., 1988; Guilford et al., 1988; Levy et al., 1994). The cause of dysautonomia has not been determined. No evidence of infectious agents has been found, and the lesions are unlike those reported with known toxins (Sharp et al., 1984; Symonds et al., 1995). Interestingly, a recent study reported 6/8 pet cats in a closed colony developed overt signs of dysautonomia over the course of 7 days (Cave et al., 2003). However, the closed nature of this cat colony and biosecurity cautions taken by the owners made an infectious etiology unlikely (Cave et al., 2003). Interestingly, it has been reported that toxico-infectious Clostridium botulinum may be important in the pathogenesis of feline dysautonomia, an etiology seriously being considered in equine dysautonomia (Nunn et al., 2004).

Common systemic signs of feline dysautonomia include general malaise, dehydration, reduced appetite or anorexia, dysphagia, vomiting or regurgitation, xerostoma, bradycardia, urinary bladder distention, and constipation (Cave et al., 2003; Sharp et al., 1984). Ocular signs that have been reported most consistently include dilated unresponsive pupils, decreased tear production, and protruding nictitating membranes (Bromberg & Cabaniss, 1988; Canton et al., 1988; Guilford et al., 1988; Levy et al., 1994). Vision is unaffected, and photophobia is variable.

Pharmacologic testing with ocular autonomic stimulants can aid in establishing the diagnosis of feline dysautonomia. Results of these tests are based on denervation supersensitivity. As such, the dysautonomic eye will respond to dilute concentrations of drugs that will not affect a normal eye. Pilocarpine, which is a direct-acting parasympathomimetic agent, at a concentration of 0.1% will produce constriction of the pupil. Epinephrine, which is a direct-acting sympathomimetic agent, at a concentration of 1:10,000 will induce retraction of a prolapsed third eyelid. Echothiophate iodide, which is an irreversible cholinesterase inhibitor, at a concentration of 0.06% will reportedly cause miosis in a normal cat but have no effect on a dysautonomic pupil (Canton et al., 1988). The same response has been seen with physostigmine, which is a reversible cholinesterase inhibitor, at a concentration of 0.25% (Guilford et al., 1988). The finding of decreased urinary catecholamines can also support the diagnosis of dysautonomia (Levy et al., 1994).

However, a definitive diagnosis of dysautonomia is rarely made antemortem as it involves the histopathologic examination of autonomic ganglia (Cave et al., 2003). Histopathologic examination of affected cats has shown widespread reduction of neurons within both sympathetic and parasympathetic autonomic ganglia, inconsistent neuronal degeneration, and increased numbers of non-neuronal nuclei (Bromberg & Cabaniss, 1988; Canton et al., 1988; Guilford et al., 1988; Levy et al., 1994; Sharp et al., 1984; Symonds et al., 1995). Ultrastructural studies of the ganglia and axons have shown degeneration and disorganization (Griffiths et al., 1985). The membrane glycoprotein, synaptophysin, has been shown to be increasingly accumulated in degenerating neurons of both equine and feline dysautonomia cases (Hilbe et al., 2005). The prognosis for cats with dysautonomia must be viewed as being guarded to poor, though some cats have been maintained long term on supportive therapy (Bromberg & Cabaniss, 1988; Rochlitz, 1984) or have even recovered after a prolonged period (Sharp et al., 1984).

Generalized Osteosclerosis

Generalized osteosclerosis is a rare, poorly understood condition that has been reported in several species. Osteosclerosis involves any abnormal hardening of the bones. In cats, osteosclerosis is a poorly understood, presumably acquired disorder. Some affected cats are anemic due to FeLV infection (Hoover & Kociba, 1974; Onions et al., 1982), while others are negative for FeLV (Kramers et al., 1988). Generalized osteosclerosis has been reported in a domestic longhair cat with presenting history involving inspiratory stertor and epiphora of 6 months duration (Hanel et al., 2004). Radiographs and computed tomography of the cat's thorax, right femur and stifle, and skull and pelvis, respectively, revealed generalized osteosclerosis, including complete destruction of the nasal turbinates. Nasalalarical duct obstruction was also detected and was deemed to be the cause of the epiphora.

Ischemic Encephalopathy

Ischemic encephalopathy occurs when the arterial supply to part of the brain is disrupted. A portion of one side of the cerebrum supplied by the middle cerebral artery is most often involved, thereby resulting in necrosis. The cause is unknown in most cases; however, there is some evidence that cuterebra infection may play a role in some cases (Williams et al., 1998). In cats, the condition manifests by a sudden onset of behavior change, seizures, ataxia, and motor deficits (Shell, 1996; Zaki & Nafe, 1980). Visual deficits may accompany other neurologic signs and are usually cortical in origin. Occasionally, the optic chiasm may be involved, thus resulting in dilated unresponsive pupils (de ahunta, 1977). Anisocoria has been noted as well (Bernstein & Fiske, 1986).
Treatment involves supportive care with improvement in clinical signs typically occurring over days to weeks. Alterations in behavior and seizures may persist, and repeated episodes may occur (delahunta, 1977; Quesnel et al., 1997; Williams et al., 1998).

Nictitating Membrane Protrusion

Idiopathic bilateral protrusion of the feline nictitating membranes is a common, poorly understood ophthalmic disorder (Fig. 35.2.5) (Gruffydd-Jones et al., 1977). Retraction of the nictitating membranes following instillation of topical adrenergic drugs, in affected cats, is suggestive of a loss of sympathetic innervation such as that seen in Horner’s syndrome; however, other ophthalmic signs of Horner’s syndrome are absent. Cats with this syndrome have normal intraocular structures, and vision is unaffected unless the nictitating membranes protrude to the extent that they cover the pupil.

Affected cats often have concurrent watery diarrhea that precedes nictitating membrane protrusion. Some cats may have diarrhea for weeks. Many cats, however, recover from diarrhea quickly, yet will still have nictitating membrane protrusion. A Tora-like virus has been isolated from the feces of several affected cats in England (Muir et al., 1990). In that study, 17 of 45 cats had nictitating membrane protrusion for more than 4 weeks, and 16 of 41 cats had diarrhea for more than 4 weeks. In 87% of the cases from multicat households, more than one cat was affected, suggesting an infectious etiology.

The prognosis for this condition is good. The diarrhea and nictitating membrane protrusion are self-limiting, although clinical signs may be long lasting. Therapy is not indicated, but if the nictitating membrane protrusion is severe, a topical adrenergic agent may be helpful.

Immune-Mediated Diseases

Dermatologic Diseases

Several immune-mediated skin diseases may affect the eyelids of cats, usually accompanying other head lesions and with variable lesions on the rest of the body. These include pemphigus foliaceus, pemphigus erythematosus, pemphigus vulgaris, food hypersensitivity, and feline atopy (Carlotti et al., 1990; Chalmers & Medleau, 1994; Preziosi et al., 2003; Scott et al., 1980, 1983). However, pemphigus foliaceus is the most common immune-mediated dermatologic condition affecting the feline eyelid (Sousa, 1995). Biopsy is necessary to establish the diagnosis of pemphigus complex diseases. Food hypersensitivity may be diagnosed on the basis of food elimination trials, whereas atopy may be best diagnosed on the basis of skin testing. Treatment is aimed at the underlying disease process, but it often includes anti-inflammatory therapy, either topically or systemically, as well. For further details regarding each of these dermatologic conditions, the reader should consult current dermatology references.

Myasthenia Gravis

Myasthenia gravis is a disease affecting the neuromuscular junction (for a complete review, see Shelton, 2002). Myasthenia gravis is either congenital or acquired. Congenital myasthenia gravis occurs when there is a functional disorder or depletion of nicotinic AChRs. Congenital myasthenia gravis has been reported in two cats (Indrieri et al., 1983; Joseph et al., 1988) and will not be considered further here (see “Congenital” section earlier). Although an uncommon disorder of cats, acquired myasthenia gravis is the most common form of myasthenia gravis occurring in this species. The acquired condition develops due to an autoimmune destruction of AChRs, which may occur as an autoimmune condition affecting only the AChR (most common), part of another autoimmune condition (e.g., hypothyroidism), or resulting as part of a paraneoplastic syndrome (e.g., thymoma). In cats, naturally occurring hypothyroidism is extremely rare and has not been associated with feline myasthenia gravis (Shelton et al., 2000). However, myasthenia gravis was described in five cats receiving treatment for hyperthyroidism with methimazole. Abyssinians, including Somalis, are at highest risk for myasthenia gravis, thereby suggesting a hereditary basis for this autoimmune condition (Shelton et al., 2000).

Animals with acquired myasthenia gravis present with either generalized or focal clinical signs. One study reported that the two most common clinical manifestations of myasthenia gravis in cats were (1) generalized weakness without megaesophagus (28.6% of affected cats) and (2) generalized weakness associated with a cranial mediastinal mass (25.7% of affected cats). Cats with the focal form of myasthenia gravis may present with dropped jaw, regurgitation and/or dysphagia, and/or change in character of vocalization because of megaesophagus and pharyngeal or laryngeal paresis, respectively (Shelton et al., 2000). With respect to the eye, a
diminished or lack of palpebral reflex may be the predominant clinical sign (Shelton et al., 2000).

Important features regarding acquired myasthenia gravis in cats include the increased frequency with which thymomas are diagnosed in affected cats (19%–25.7%) compared with dogs (3.4%) (Shelton, 1999; Shelton et al., 2000), and the possibility of methimazole-induced myastenia gravis in hyperthyroid cats that develop weakness following commencement of this therapy (Shelton et al., 2000). Diagnosis of acquired myasthenia gravis in cats is based on demonstrating circulating antibodies to the AChRs. Treatment for feline acquired myasthenia gravis includes anticholinesterase and immunosuppressive agents, nutritional and possibly respiratory support, and antibiotics for aspiration pneumonia due to regurgitation. The reader is referred to current internal medicine textbooks for further details regarding the diagnosis and treatment of myasthenia gravis in cats.

**Sjögren’s-Like Syndrome**

Sjögren’s syndrome is a condition in humans, affecting mainly women, characterized by xerophthalmia and xerostomia as a result of lymphocytic infiltration and destruction of exocrine glands (Bell et al., 1999). Sjögren’s syndrome is a systemic autoimmune disorder that can affect numerous exocrine glands and internal organs resulting in intermittent fever, salivary gland hypertrophy, pulmonary disease, and dermatologic, gastroenterologic, nephrologic, dental, rheumatologic, gynecologic, and neurologic disorders (Bell et al., 1999). The syndrome may be a primary autoimmune-mediated disease or part of another immune-mediated connective tissue disease. Sjögren’s-like syndrome has been reported in a female domestic shorthair cat (Canapp et al., 2001). The presenting clinical signs in this cat included dysphagia and weight loss, mild enlargement of all salivary glands, and ocular signs including blepharospasm and conjunctival hyperemia. Diagnostic testing revealed Schirmer tear test (STT) values of 0 mm/min for both eyes, and a lack of salivation in response to atropine placed on the cat’s tongue (Canapp et al., 2001). Over time, the affected cat also developed corneal ulceration, and a corneal sequestrum despite treatment with topical cyclosporine 2% solution and administration of pilocarpine solution (gradually increased from 2% to 6%) on the food with some improvements in tear production and salivation noted (Canapp et al., 2001).

A diagnosis of Sjögren’s syndrome in humans requires documenting the presence of xerophthalmia and xerostomia, and requires histologic examination of salivary gland biopsy specimens. In particular, lymphocytic infiltrates in a least four salivary lobules (a grade of 4/4) is required to confirm the diagnosis of Sjögren’s syndrome. Laboratory evidence of a systemic autoimmune disease (e.g., positive antinuclear antibody [ANA] test, rheumatoid factor, or anti-Ro or anti-La antibody titers) may also be useful in supporting a diagnosis of this syndrome (Fox et al., 1986). The diagnosis of Sjögren’s-like syndrome was made in a cat based on the clinical signs of xerophthalmia and xerostomia, combined with histologic diagnosis of lymphocytic sialoadenitis (Canapp et al., 2001). Fluorescent ANA tests were deemed to be negative at a titer <1:40 (Canapp et al., 2001). Treatment of Sjögren’s syndrome in humans is primarily symptomatic. The most common treatment is pilocarpine, a direct-acting parasympathomimetic that stimulates tear production and salivation (Bell et al., 1999; Fox et al., 1986). Systemic immunosuppressive therapy is used to treat the most severe complications of Sjögren’s syndrome in humans including pulmonary manifestations such as obstructive airway disease, bronchectasis, and interstitial pulmonary disease (Fox et al., 1999); however, the sicca conditions tend not to respond favorably to this form of therapy (Bell et al., 1999).

**Infectious Diseases**

**Bacterial**

Any bacteremia may result in seeding of the uveal tract and create various degrees of inflammation, but only a few bacterial syndromes are relatively consistent regarding involvement of the eye. Sporadically, bacteremia arising from bacterial infections involving other organ systems (e.g., periodontitis or endodontic disease [Ramsey et al., 1996]) may result in varying degrees of focal chorioretinal lesions consisting of hemorrhage or exudates (or both), which often go unnoted. Typically, these lesions are associated with the end arterioles or small vessels in the retina. In small animals, they may develop into fulminating endophthalmitis, but this appears to be rare (Massa et al., 2002).

Bartonellosis

Bartonella spp. are fastidious, hemotropic, short, pleomorphic, gram-negative rod-shaped bacteria identified in a wide range of domestic and wild animals (Chomel et al., 2004). Bartonella organisms are considered emerging zoonotic agents (Chomel et al., 2004). Bartonella henselae, the causative agent for human “cat scratch disease” (CSD), is the prototypic Bartonella disease, which was originally recognized in humans in 1889. Domestic cats are important reservoir hosts for the following five Bartonella spp.: B. henselae, Bartonella clarridgeiae, Bartonella elizabethae, Bartonella koehlerae, and Bartonella weissii (Breitschwerdt & Kordick, 2000; Clarridge et al., 1995; Jameson et al., 1995). Bartonella quintana DNA has been recovered from the dental pulp of a domestic cat thereby suggesting that cats may also be an emerging source of B. quintana infection in humans (La et al., 2005). In cats, infection with B. henselae is common with 55%–81% of cats being seropositive for the bacterium; however, many infected cats do not show clinical signs (Lappin & Black, 1999). Bartonella spp. are typically vector borne with the vector varying according to the species of Bartonella (Chomel et al., 2004). Cat (Rolain et al., 2003) and dog fleas and, less commonly, dog and deer ticks carry the bacteria and act as vectors for transmitting Bartonella from
cat to cat, and as potential vectors for transmitting the organism from cats to humans (Ketting et al., 2004).

Systemic manifestations of bartonellosis in cats include fever, lymphadenopathy, lethargy, anorexia, CNS disorders, urologic diseases, and endocarditis (Chomel et al., 2003, 2004). Ocular lesions associated with CSD in humans include Parinaud’s oculoglandular syndrome as manifested by regional lymphadenopathy and unilateral ocular redness, epiphora, and ulceration of the bulbar conjunctiva (Cunningham & Koeher, 2000). Human manifestations of ocular bartonellosis may also include retinochoroiditis and neuroretinitis (for a review, see Cunningham & Koeher, 2000). Five to 10% of B. henselae-infected patients have ocular signs (Cunningham & Koeher, 2000; Wade et al., 2000). Uveitis in cats has been reported to be associated with Bartonella spp. (Fontenelle et al., 2008; Lappin & Black, 1999; Lappin et al., 2000). Additional ocular diseases associated with Bartonella in cats include blepharitis, conjunctivitis, keratitis, and chorioretinitis (Ketting et al., 2004). One cat was reported to develop a transient unilateral focal equatorial cataract and mild perilimbal viretal degeneration following experimental blood inoculation with B. henselae (Kordick & Breitschwerdt, 1997). Bartonella-infected cats may also show concurrent inflammatory disease including gingivitis, stomatitis, dermatitis, gastroenteritis, and upper respiratory disease that may or may not be linked to Bartonella infection (Ketting et al., 2004).

Bartonella spp. are slow growing and extremely difficult to culture. As such, the diagnosis of Bartonella-associated ocular diseases in cats is often based on eliminating other causes, positive serology for Bartonella, response to therapy, reduction in Bartonella antibody titers following therapy, and, in certain cases, lymphocytic-plasmacytic uveitis diagnosed histologically with no other apparent cause (Ketting et al., 2004). Bartonella-associated feline uveitis has also been reported following positive serology for Bartonella, and detection of Bartonella antibodies and DNA (i.e., via polymerase chain reaction [PCR]) in samples of aqueous humor (Lappin & Black, 1999; Lappin et al., 2000). However, the findings in most recent studies support that it is not possible to correlate clinical signs of ocular and/or systemic disease in cats with positive serology or culture for Bartonella spp. when this infectious agent is so widespread in the cat population and is not typically associated with signs of clinical disease. Recently, a study evaluated serum from 113 cats with uveitis, 156 clinically ill cats without uveitis, and 97 healthy cats (Fontenelle et al., 2008). The healthy group of cats had the highest percentage of serum samples (68 of 97 [70%]) that were enzyme-linked immunosorbent assay (ELISA) positive for Bartonella spp. IgG antibodies. As well, a recent study used immunofluorescent antibody (IFA) and blood culture to detect Bartonella spp. serum antibody and DNA in 298 ill cats (Sykes et al., 2010). Five of these 298 cats had uveitis and only one such cat was seropositive and culture positive for Bartonella spp. A third recent study compared serum antibodies and PCR DNA amplification from blood and aqueous humor for Bartonella spp. and two other infectious agents in 104 cats with uveitis and 19 healthy shelter cats (Powell et al., 2010). Once again, a higher percentage of healthy cats (84%) had positive serum antibody titers than did the group of cats with uveitis (54%). Furthermore, no cats with uveitis had Bartonella spp. DNA detected from the aqueous humor, while the aqueous humor from one healthy cat was positive for Bartonella spp. DNA.

Treatment of bartonellosis in cats is challenging. The intermittent bacteremia regarding bartonellosis, makes documenting clearance of the organism, even in experimental infections, challenging (Stiles, 2011). Currently, there is no antibiotic regime that has proven effective for definitively eliminating feline bartonellosis (Greene et al., 1996).

Treatment of bartonellosis in cats involves the use of systemic antibiotics such as azithromycin or doxycycline. There is, however, information to support that azithromycin may have limited efficacy against Bartonella and resistance in vitro has been documented (Biswas et al., 2010). The current recommendation for treating ill cats with bartonellosis is using doxycycline at a dose of 10–22 mg/kg PO q 12 hours for 2–6 weeks, with the dose being adjusted (up or down) to permit administration of a whole tablet to avoid esophageal irritation (Breitschwerdt et al., 2010). In one cat with Bartonella-associated uveitis, treatment with topical or oral steroids failed to resolve the ocular disease; the uveitis responded to treatment with oral doxycycline (Lappin & Black, 1999). The reader is referred to Stiles (2011) for a review entitled “Bartonellosis in cats: a role in uveitis?”

Chlamydophilosis

Chlamydophilosis is caused by gram-negative, obligate intracellular bacteria of the genus Chlamydia (for a review, see Sykes, 2005). Chlamydophila psittaci (formerly Chlamydia psittaci) primarily infects birds, and is a common pathogen of cats (formerly Chlamydia psittaci var felis), although the strain affecting cats has been renamed Chlamydia felis (Cello, 1967, 1971; Everett, 2000; Hoover et al., 1978; Johnson, 1984; Shewen et al., 1978; Studdert et al., 1981; Wills et al., 1984). The pathogenesis of chlamydophilosis in cats remains largely unknown, although C. felis appears to have a predilection toward conjunctival epithelial cells (Sykes, 2005). Chlamydophilosis is naturally transmitted by direct contact with other infected cats, aerosols (Sykes, 2005), and by fomites. The incubation period is approximately 3–5 days (Sykes, 2005).

C. felis is endemic in house cats worldwide, mainly causing acute and chronic conjunctivitis (Hoover et al., 1978; Johnson, 1984; Sykes, 2005). The organism can also infect the respiratory tract causing rhinitis and respiratory problems, (Everett, 2000) and it has been isolated from the gastrointestinal (O’Dair et al., 1994) and reproductive (Everett, 2000) tracts of cats. Chlamydophilosis has been associated with lameness in experimentally infected cats (TerWee et al., 1998). Two weeks following the development of conjunctivitis, lameness occurred in 10 of 19 infected cats (TerWee et al., 1998).
The acute phase of C. felis infection results in conjunctival hyperemia, chemosis, serous ocular discharge, and blepharo-spasms. Mild nasal discharge and sneezing may also occur in some cats (O’Dair et al., 1994; Sykes, 2005). Conjunctivitis is often unilateral initially, and then progresses to involve the contralateral eye during the next few days. Ocular disease results from host cell lysis that occurs during the release of Chlamydia spp. elementary bodies (Wyrick & Richmond, 1989). If untreated, infection with C. felis can produce chronic conjunctivitis (O’Dair et al., 1994). Asymptomatic carrier states can exist and are likely significant in spreading the organism within a population (Storz & Kaltenboeck, 1993). Persistence of the organism in the genital and gastrointestinal systems may also contribute to the spread of chlamydophilosis (Wills et al., 1987).

C. felis infection, unlike chlamydial infections in other species, is rarely associated with keratitis in cats. Concurrent infection with feline herpesvirus type 1 (FHV-1) should be suspected in C. felis-positive cats with keratitis. Other non-C. felis chlamydiae, including Neochlamydia hartmannellae, were detected in cats with ocular disease (von Bomhard et al., 2003). Further investigations are, however, required to confirm whether or not N. hartmannellae is a causative agent of feline conjunctivitis. In addition, N. hartmannellae does not appear more likely to cause keratitis than C. felis (Sykes, 2005), despite being found within the amoeba Hartmannella vermiformis, and being a suspected cause of amoebic keratitis in humans (Kinnear, 2003).

Chlamydophilosis may be complicated by coinfection with other microorganisms including Mycoplasma spp., Bordetella bronchiseptica (Shewen et al., 1980b; Sykes, 2005), feline calicivirus (FVC) (Wills et al., 1988), FHV-1 (von Bomhard et al., 2003), and FIV (O’Dair et al., 1994). In one study, coinfection with FIV led to a prolonged duration of clinical signs and the development of chronic conjunctivitis (O’Dair et al., 1994). In this same study, clinical signs of conjunctivitis in control cats were resolved by day 109 after infection with Chlamyphila spp., whereas cats with FIV and Chlamyphila spp. cats still had conjunctivitis up to day 200. Chlamyphila spp. were excreted from the conjunctival sac for up to 270 days in FIV-infected cats but for only 70 days in control cats. Both FIV-infected and control cats excreted Chlamyphila spp. from the gastrointestinal tract for 35 days.

Natural exposure of cats to C. felis, as evaluated by serum antibody titers, appears to vary. The prevalence of seropositive cats in England has ranged from 9% among healthy cats (Gunn-Moore et al., 1995) to 69% in those with conjunctivitis (Wills et al., 1988). A further study of cats in England reported a 45% rate of positive antibody titers in a group that included both asymptomatic cats as well as those afflicted with conjunctivitis (Gethings et al., 1987). Reported antibody titers of cats in Japan ranged from no seropositive cats (Yamaguchi et al., 1996) to a 2% seropositive rate, (Fukushi et al., 1985) though the presence or absence of conjunctivitis was not reported in these studies. In northern Italy, the prevalence of seropositive cats ranged from 21% and 21.3% of the free-living feral cats and household cats, respectively, to 64% of cattery cats (Di Francesco et al., 2004), although the presence of clinical signs suggestive of chlamydophilosis was not recorded. Studies evaluating the prevalence of C. felis in cats using PCR on conjunctival swabs resulted in estimates of 14.3% in Australian cats with upper respiratory tract disease (Sykes et al., 1999a); 17.7% in British cats with ocular signs (McDonald et al., 1998); 20% in Italian cats with conjunctivitis (Rampazzo et al., 2003); and 11.5% in Swiss cats with ocular signs (von Bomhard et al., 2003). The prevalence of C. felis in asymptomatic cats is low with estimates of <5% in studies using PCR (Rampazzo et al., 2003; von Bomhard et al., 2003) in comparison to prevalence estimates of non-C. felis chlamydial infection in asymptomatic cats of 20% (von Bomhard et al., 2003).

C. felis is considered to be a zoonotic agent. Transmission of this agent from cats to humans has been reported in an HIV-positive man with chronic conjunctivitis (Hartley et al., 2001). C. felis has been associated with other diseases in humans including respiratory tract disease, endocarditis, gonococcal conjunctivitis, and hepatitis (Marrie et al., 2003; Regan et al., 1979). The rate of transmission from cats to humans is, however, probably low, but maintaining hygienic conditions and prompt treatment of infected cats is warranted to help prevent human disease.

Traditionally, the diagnosis of chlamydophilosis has been established by using a variety of ELISA antigen kits with varying sensitivities (25%–80%) and specificities (80%–90%) or using cell culture, the “gold standard” for the diagnosis of chlamydial infection (Sykes, 2005). Chlamyphila spp. can be cultured in many types of mammalian and avian cells (O’Dair et al., 1994; Storz & Kaltenboeck, 1993). However, isolation of the agent in cell culture is technically challenging, expensive, and time-consuming (Sykes, 2005). Finding the characteristic inclusion body within the conjunctival epithelial cell cytoplasm on cytologic examination of Giemsa-stained conjunctival smears may be helpful in lending support for a diagnosis of chlamydophilosis (Fig. 35.2.6). However, inclusions are typically only detectable during early infection, and in some cases not at all. In particular, chlamydial inclusion bodies are present in conjunctival cells from the third day after inoculation, and they persist in decreasing numbers for 2 weeks (Storz & Kaltenboeck, 1993). Relatively recently, PCR assays have become available for the diagnosis of C. felis. These PCR assays are typically more rapid and sensitive, and less expensive than traditional diagnostic tests such as ELISA and culture (Sykes, 2005). Broad-spectrum chlamydial PCR assays, available in certain research laboratories, are used to test for non-C. felis chlamydial organisms including N. hartmannellae (von Bomhard et al., 2003). A definitive association between feline conjunctivitis and these agents is necessary prior to routinely screening affected cats for non-C. felis chlamydial organisms.

Chlamydial organisms are sensitive to tetracyclines, erythromycin (Johnson et al., 1983), rifampin, fluoroquinolones,
SECTION IV: Special Ophthalmology


and azithromycin (Sykes, 2005). Topical administration of tetracycline three to four times daily to both eyes for 1–2 weeks after resolution of conjunctivitis is sufficient in some cats. However, given that chlamydiopholisis may be systemic, topical therapy alone may be ineffective in certain cats. Oral administration of tetracycline or doxycycline may be necessary to treat refractory infections, and may also be necessary to clear the gastrointestinal tract of latent infection (O’Dair et al., 1994). In experimentally infected cats, oral doxycycline alone (5 mg/kg q 12 hours) for 3 weeks effectively eliminated the C. felis infection (Sykes et al., 1999b). However, a recent study reported that in some cases, 3 weeks of treatment with oral doxycycline (10 mg/kg/day) did not eliminate C. felis infection. In fact, at least 4 weeks of therapy with oral doxycycline may be required to ensure elimination of the organism (Dean et al., 2005). Systemic doxycycline has been reported to produce more rapid clinical and microbiological resolution of chlamydiosis than topical chlorotetracycline used twice daily (Sparks et al., 1999). In another study, oxytetracycline, 50 mg twice daily for 60 days, cleared FIV-infected cats of both conjunctival and gastric mucosal infections (O’Dair et al., 1994). In contrast, administration of oral azithromycin (10–15 mg/kg) daily for 3 days and then twice weekly, resulted in rapid resolution of the clinical signs and lack of isolation of C. felis early in treatment similar to doxycycline; however, C. felis was re-isolated in four of five azithromycin-treated cats from 6 to 14 days into treatment (Owen et al., 2003). Even daily administration of azithromycin to chronically C. felis-infected cats failed to clear the infection (Owen et al., 2003). Amoxicillin-clavulanic acid of 4 weeks duration successfully eliminated C. felis in experimentally infected cats, with no recurrent infection 6 months following the cessation of therapy (Sturgess et al., 2001).

Both humoral and cell-mediated immunity appear necessary for the resolution of chlamydiosis. As such, kittens that have obtained colostrum from previously exposed queens appear to be protected from chlamydial infection by maternal antibodies until they reach 2–3 months of age. Both modified live and inactivated cell culture vaccines for C. felis have been used in the United States (Sykes, 2005). Vaccination with a live chlamydial vaccine provides the best clinical protection (Shewen et al., 1980a; Wills et al., 1987). When challenged by conjunctival and nasal routes, vaccinated cats develop milder ocular and upper respiratory tract signs compared with those in unvaccinated cats. Some vaccinated cats did shed organisms, however, from the eye and respiratory tract, but for a shorter duration than unvaccinated cats. Although vaccination for chlamydia does not prevent infection, it may be beneficial in catteries with endemic chlamydiosis.

Mycobacteriosis

Mycobacteria are aerobic, non-spore-forming, nonmotile, acid-fast staining bacteria (Greene & Gunn-Moore, 1998). Mycobacteria have been associated with causing tuberculosis characterized by internal tubercular granulomas, leprosy characterized by cutaneous nodules, or progressive subcutaneous inflammation (Greene & Gunn-Moore, 1998). The incidence of mycobacterial infections in cats has decreased dramatically since the decline in bovine tuberculosis (Mycobacterium bovis) and pasteurization of milk, although new cases still occur. Feline mycobacteriosis has been reported to be caused by M. bovis, Mycobacterium tuberculosis, Mycobacterium simiae, Mycobacterium genavense, and Mycobacterium avium (Dietrich et al., 2003; Greene & Gunn-Moore, 1998; Gunn-Moore et al., 1996; Hughes et al., 1999; Snider et al., 1971; Studdert & Hughes, 1992). Ocular lesions involve primarily of the posterior segment and include retinal hemorrhage, retinal detachment, and granulomatous choroiditis associated with large numbers of tubercle organisms within the eye (Formston, 1994). Unilateral granulomatous chorioretinitis with subretinal hemorrhage, exudation, and retinal detachment has been described in a domestic shorthair cat with disseminated M. simiae, a less commonly encountered nontuberculous mycobacteria (Dietrich et al., 2003). Periocular skin lesions were reported in an FIV-positive cat diagnosed with disseminated M. genavense infection; however, these cutaneous lesions were likely due to numerous mites (Demodex cati), which were observed in skin scrapings of the periocular region (Hughes et al., 1999). Interestingly, a conjunctivocorneal granuloma was recently described in a young European shorthair cat (Fig. 35.2.7), and histological examination confirmed a granulomatous lesion with acid-fast bacilli within macrophages (Lamagna et al., 2009). Mycobacterium 16S rRNA gene-specific PCR was positive in this case (Lamagna et al., 2009).

A presumptive diagnosis of mycobacterial infection can be made on the basis of identifying acid-fast bacilli from aspiration samples or tissue sections using special stains such as...
Ziehl–Neelsen or Kinyoun stains (Jordan et al., 1994). Culture of the organism is required for speciation, but few laboratories are equipped to grow these agents. PCR tests are also available for Mycobacterium spp. (Hughes et al., 1999).

Treatment of cats with mycobacterial infections requires long-term combination therapy, and perhaps even lifelong therapy. Zoonotic potential should also be considered. Standard therapies include combinations such as isoniazid and rifampin, plus ethambutol or pyrazinamide if the disease is disseminated (Greene & Gunn-Moore, 1998). These drugs have potential hepatotoxicity, however, and ethambutol can cause optic neuritis. Newer therapies for mycobacterial infections have fewer potential side effects and include combinations of a systemic fluoroquinolone (i.e., enrofloxacin, ciprofloxacin), clarithromycin (i.e., a macrolide), and rifampicin (Dietrich et al., 2003; Gunn-Moore et al., 1996). It should be noted that enrofloxacin should be administered according to the manufacturer’s recommendations in cats (2.5 mg/kg PO q 12 hours) as this medication has been reported to cause retinal degeneration and blindness in cats, even if administered at low doses (Gelatt et al., 2001).

Mycoplasmosis

Mycoplasma spp. are the smallest free-living organisms, and they are classified as prokaryotes. Mycoplasma felis, Mycoplasma gatae, and Mycoplasma arginini have all been isolated from both sick and healthy cats (Tan & Miles, 1974; Tan et al., 1977b). The role of Mycoplasma spp. as a cause of conjunctivitis in cats has been controversial because the organism has been isolated from the eyes of normal cats (Blackmore et al., 1971; Cole et al., 1967; Tan et al., 1977a) as well as from those of cats with conjunctivitis (Blackmore et al., 1971; Campbell et al., 1973; Cole et al., 1967; Haesebrouck et al., 1991; Tan et al., 1977a). Experimentally, M. felis has caused conjunctivitis among kittens in some studies (Haesebrouck et al., 1991; Tan, 1974) but not in others (Blackmore & Hill, 1973). Experimental infection has not resulted in conjunctivitis in adult cats (Blackmore & Hill, 1973).

Most Mycoplasma spp. that normally inhabit the upper respiratory tract have been isolated at necropsy from the lungs of cats with pneumonia, but they are not normally present in the lungs of normal cats (Spradbrow et al., 1970; Tan et al., 1977a). Mycoplasma spp. inhaled from the upper respiratory tract probably establish infection in a lung that is already compromised by another pathogen. The same view may hold true for the eye, in which another pathogen, such as feline herpesvirus (Schneck, 1972, 1973) or C. felis, create an environment in which Mycoplasma spp. may thrive. Because these organisms have only been shown experimentally to cause conjunctivitis in kittens, an altered or immature immune system may also be a factor in allowing establishment of disease.

The diagnosis of mycoplasmosis can be established on the basis of culturing the organism on special media or finding the characteristic, small coccoid inclusions within the cytoplasm of the epithelial cells (Fig. 35.2.8). Mycoplasma spp. are sensitive to many routinely used ophthalmic antibiotics.

Tetanus

Tetanus is caused by the neurotoxin produced by the bacterium Clostridium tetani. C. tetani is a motile, gram-positive, nonencapsulated, anaerobic, rod-shaped, spore-forming bacterium (for an overview, see Ake et al., 2004). Dogs and cats are naturally resistant when compared with other species such...
as humans and horses. Clinical signs of tetanus develop when spores of C. tetani enter the body through skin wounds or during surgical procedures (Bagley et al., 1994). Spores become vegetative and a toxin, tetanospsamin, retrogradely migrates along axons of motor nerves to the CNS. Although, it should be noted that tetanospsamin, the principle neurotoxin, is only one of three toxins produced by the bacterium (Acke et al., 2004). The toxin then prevents inhibitory neurotransmission to motor neurons thereby resulting in the classical signs associated with tetanus. Clinical effects on the autonomic nervous system have also been described (Panciera et al., 1988).

Clinical signs may be localized or generalized. In the localized form, increases in stiffness of specific muscle groups or a given limb may be noted (Polizopoulou et al., 2002). The localized form is described more commonly in cats compared with dogs as a result of an inherent inability of the toxin to penetrate and bind to nervous tissue. In the generalized form, affected cats may have a stiff gait, an outstretched or dorsally curled tail, or be recumbent with profound rigidity of the limbs (De Risio & Gelati, 2003). A characteristic smiling/sneering appearance (risus sardonicus) may be seen in affected cats as a result of spasms of the facial muscles causing a drawing back of the lips, and a wrinkling of the forehead (Baker et al., 1988). Respiratory compromise may result in death. Ocular signs seen in a tetanic animal include protrusion of the third eyelid and enophthalmus resulting from globe retraction due to the hypertonicity of the extraocular muscles (Acke et al., 2004).

Diagnosis is made based on consistent physical examination findings (presence of a wound) and clinical signs. Although, culture of the organism from the wound and/or measuring circulating serum antibodies against tetanospsamin may help to confirm the diagnosis. Treatment is aimed at administering tetanus antitoxin (usually unnecessary in localized forms of tetanus) and penicillin G and/or metronidazole to prevent binding of any unbound toxin and to destroy any remaining bacteria, respectively. Tetanus antitoxin therapy should be done only after intradermal testing with this antitoxin as there is a strong likelihood of anaphylaxis following systemic administration (Acke et al., 2004).

Symptomatic therapy with muscle relaxants such as diazepam may or may not be helpful in protracted cases. Supportive care and wound management are also indicated. Prognosis is variable depending on the severity of the clinical signs and secondary complications.

**Mycotic**

**Blastomycosis**

Blastomycosis is a systemic mycotic infection caused by the dimorphic fungus, Blastomyces dermatitidis. B. dermatitidis is a thick-walled yeast that reproduces by budding in infected tissues (i.e., yeast phase) and, in nature, is most likely a soil saprophyte, which produces infective spores called conidia (i.e., mycelial phase). The tissue budding yeast form is 5–20 μm in size, with a thick, double-contoured wall. B. dermatitidis is endemic to various river valleys in the United States, Canada, Europe, Mexico, Latin America, and Africa (Bromel & Sykes, 2005a; McCullough et al., 2000).

Blastomycosis is not typically considered a zoonotic disease but has been transmitted to a person through an accidental needlestick with a syringe and needle used for pulmonary aspiration from a dog with B. dermatitidis infection (Ramsey, 1994). Typically, blastomycosis develops following the inhalation of organismal spores. After inhalation of the infective conidia by the host, these infective spores become phagocytized by alveolar macrophages and transform from the mycelial phase to the yeast phase. B. dermatitidis has been reported in cats, though to a much lesser extent than it has been reported in dogs (Alden & Mohan, 1974; Breider et al., 1988; Davies & Troy, 1996; Jasmin et al., 1969; McEwen & Hulland, 1984; Meschter & Heiber, 1989; Miller et al., 1990; Nasisse et al., 1985; Sheldon, 1966). The distribution of lesions is similar between species, with the lungs, eyes, skin, bone, CNS, and visceral organs being commonly involved. Reported ocular lesions in cats include retinal detachment, pyogranulomatous chorioretinitis, and panophthalmitis (Alden & Mohan, 1974; Miller et al., 1990; Nasisse et al., 1985). The posterior segment of the globe is more commonly affected than the anterior segment (Miller et al., 1990).

A diagnosis of blastomycosis is made based on the cyto logic identification of the organism. A positive agar-gel immunodiffusion test is considered to be highly suggestive of disease (Bromel & Sykes, 2005a). PCR and in situ hybridization for the organism are becoming important in the clinical diagnosis of blastomycosis (Bromel & Sykes, 2005a).

Few cases in the literature include treatment for blastomycosis in cats. Two cats have been successfully treated, however, one with a combination of amphotericin B and ketoconazole, and one with ketoconazole alone (Miller et al., 1990). Three other cats with advanced disease died despite attempted treatment with amphotericin B (Breider et al., 1988; Nasisse et al., 1985). Itraconazole has been used successfully to treat dogs with ocular and systemic blastomycosis (Brooks et al., 1991; Legendre et al., 1996). Itraconazole has also been recommended for treatment of blastomycosis in cats at the same dose as that used for cryptococciosis (Bromel & Sykes, 2005a).

**Candidiasis**

Candida albicans is a dimorphic fungus that may cause either localized or generalized disease. Local proliferation of Candida spp. within wounds or mucosal surfaces is the first step in the spread of infection, and it generally occurs in immunosuppressed or debilitated cats (Pressler et al., 2003). Panuveitis resulting from candidiasis has been reported in cats (Gerdig et al., 1994; Miller & Albert, 1988). In one case, ophthalmic examination of a diabetic cat revealed corneal ulceration, from which the yeast was observed at cytology (Gerdig et al., 1994). This same cat later developed bilateral panuveitis and had disseminated candidiasis at necropsy. A
second cat with bilateral panuveitis at presentation was in a generalized debilitated condition, but specific immunosuppression was not documented (Miller & Albert, 1988). Histopathology of the eyes in both cases revealed pyogranulomatous inflammation, and organisms were found within the retina and vitreous humor. The cat with corneal ulcers had large numbers of organisms within the corneal stroma as well.

Coccidioidomycosis

Coccidioidomycosis is caused by the dimorphic fungus Coccidioides immitis. The organism is found in sandy, alkaline soils of the dry regions of the southwestern United States, western Mexico, and Central and South America (Wolf, 1989). Coccidioides spp. produce mycelia during seasonal rainfall. As the soil dries, arthrospores develop and become airborne under dry and windy conditions. The major route of Coccidioides spp. infection is via inhalation (Wolf, 1989). Cutaneous entry of the organism through a penetrating skin wound is possible but occurs rarely (Wolf, 1989). Coccidioidomycosis has been reported in cats (Angell et al., 1985; Davies & Troy, 1996; Foureman et al., 2005; Greene & Troy, 1995). In a retrospective study of 48 cats, 19% had ocular signs that, though not described in detail, included retinal detachments, uveitis, and iritis (Greene & Troy, 1995). The most common systemic signs of systemic coccidioidomycosis in cats are skin lesions, respiratory disease, and bone lesions (Greene & Troy, 1995). The most reliable means of diagnosis is identification of the organism from fluid or tissue aspirates. In the above-mentioned study, 39 of these 48 cats were evaluated with serologic tests (agar-gel immunodiffusion or complement-fixing antibody titers), and all were positive at some point in the course of their disease (Greene & Troy, 1995). Forty-four of these cats were treated, 40 with ketoconazole and four with fluconazole and itraconazole. Thirty-two cats became asymptomatic, though relapses were common in cats treated with ketoconazole (Greene & Troy, 1995).

One report has described unilateral pyogranulomatous endophthalmitis in a cat with coccidioidomycosis (Angell et al., 1985). This cat did not have detectable systemic disease, and serologic tests for coccidioidomycosis were negative. The cat was clinically normal for a follow-up period of 2 years after enucleation, with no antifungal therapy administered. Most recently, three cases of feline ocular coccidioidomycosis have been described (Tofflemire & Betbeze, 2010). Two cats presented for subpalpebral or peri-orbital periocular swellings (Fig. 35.2.9) with systemic signs including weight loss, lethargy, and unkempt hair coat. One cat presented for bilateral red, swollen eyes and apparent blindness with no systemic signs (Fig. 35.2.10). Clinical ophthalmologic abnormalities were bilateral in each cat and included hyperemic, conjunctival masses; fluid-filled periorbital swellings; granulomatous chorioretinitis, nonregmatogenous retinal detachments; and anterior uveitis. In this case series, a combination of corticosteroids and fluconazole was found to be effective in treating ocular coccidioidomycosis, although long-term fluconazole
therapy may be needed in cases of persistent chorioretinal granulomas.

Cryptococcosis

Cryptococcosis is caused by Cryptococcus neoformans or Cryptococcus gattii (previously C. neoformans var gattii) (Wolf, 1989). C. neoformans is associated with high nitrogen-containing environments such as avian feces or soil enriched with avian feces (O’Brien et al., 2004). Hence, birds such as pigeons are considered to be significant vectors of Cryptococcus spp. C. gattii, however, is associated with Eucalyptus and fir trees in Australia and Canada, respectively (O’Brien et al., 2004). In infected tissue, and often when cultured using standard laboratory conditions, C. neoformans is a variably sized yeast-like organism (3.5–7 µm), which typically contains a thick capsule.

Cryptococcosis has been described in a variety of mammals as well as in humans. Importantly, cryptococcosis is not contagious. Rather, inhalation of the yeast-like organism is the likely mode of infection (Wolf, 1989). Dissemination occurs through hematological spread. The predominant signs of cryptococcosis vary with the affected species, immune status of the patient, and perhaps, the strain of the organism.

C. neoformans is the most commonly reported feline mycotic infection. The most frequent sites of disease are the nasal passages, skin, and CNS. Chorioretinitis with granulomatous inflammation and retinal detachments (Fig. 35.2.11), anterior uveitis, and exophthalmos have been reported (Dye & Campbell, 1981; Fischer, 1971; Gerds-Grogan & Dayrell-Hart, 1997; Gwin et al., 1977; Rosenthal et al., 1981), and optic neuritis may also occur, particularly if the CNS is involved. One case of adnexal cryptococcus in a cat without intraocular or systemic lesions has been described (Martin et al., 1996).

A diagnosis of cryptococcosis is made on the basis of cytologic identification of the organism aspirated from affected tissue. Antigen can be identified in the serum by latex cryptococcal agglutination kits (M edleau et al., 1990b), and serum antigen titers can be used to monitor the response to therapy (Jacobs et al., 1997; M edleau et al., 1995).

Cats with cryptococcosis have been successfully treated with itraconazole (Jacobs et al., 1997; Martin et al., 1996; M edleau et al., 1995), which seems to cause less side effects than ketoconazole or amphoteracin B in this species (M edleau et al., 1990a, 1995). The recommended dose for itraconazole in cats is 5 mg/kg every 12 hours, and the drug is well-tolerated by most cats. Anorexia and hepatic toxicosis can occur, however, and blood chemistry profiles should be monitored. The capsules can be opened and placed on canned cat food, because ingestion with a fatty meal enhances intestinal absorption of the drug. Therapy should be continued for at least 1 month after the resolution of clinical disease, but also until a decrease in antigen titer by at least two orders of magnitude has been demonstrated and, preferably, until serum antigen is undetectable (Jacobs et al., 1997). This may mean that cats remain on itraconazole for months after clinical disease becomes inapparent (M artin et al., 1996). Fluconazole, 50 mg given orally every 12 hours, has also been used successfully and without side effect in cats with cryptococcosis (Malik et al., 1992).

Dermatophytosis (Ringworm)

Dermatophytosis, or ringworm, is a cutaneous infection with fungi, and in cats, it may be caused by one of several species of Microsporum or Trichophyton (Cafarchia et al., 2004). The most common species affecting the cat is Microsporum canis. Lesions, which are characterized by alopecia with or without scales, most commonly affect the head, pinnae, and paws, but they may also involve the eyelids, typically producing a dry, crusty, periocular alopecia. Lesions can become ulcerated as well. Cats are typically less than 5 years of age and any breed or gender can be affected (Cafarchia et al., 2004; Lewis et al., 1991; Scott & Paradis, 1990). The condition is diagnosed on the basis of direct microscopic examination of skin scrapings from lesions, Wood’s light examination, or more frequently, direct fungal culturing of the affected hair and scales with dermatophyte test medium (Cafarchia et al., 2004).

Treatment includes clipping the hair in the affected region, which is followed by topical (i.e., lime sulfur, enilconazole, or miconazole) or systemic (i.e., griseofulvin, itraconazole, terbinafine) antifungal therapy that continues until two to four negative cultures have been obtained at weekly or biweekly time points (for a review, see Moriello, 2004).
Histoplasmosis

Histoplasmosis is caused by a dimorphic fungus, Histoplasma capsulatum, which exists in various river bottoms as a mycelial-phase, soil saprophyte. H. capsulatum grows best in nitrogen-rich organic matter, such as bat and bird feces (Wolf, 1989). Though quite widespread in North and South America, endemic areas are in the Ohio, Mississippi, and Mississipi river valleys (Bromel & Sykes, 2005b). Two cats with histoplasmosis have also been reported in San Joaquin Valley, a non-endemic region of California (Johnson et al., 2004). The life cycle of H. capsulatum is similar to that of Blastomyces and Coccidioides spp., with a mycelial phase in the soil that produces conidia, which once in the pulmonary system convert to a budding yeast phase (Wolf, 1989). Histoplasma organisms can then be disseminated via hematogenous or lymphatic spread.

Histoplasmosis has been observed in cats and dogs (Bromel & Sykes, 2005b; Clinkenbeard et al., 1987; Gwin et al., 1980; Huss et al., 1994; Johnson et al., 2004; Kabli et al., 1986; Rowley et al., 1954; Wolf, 1987). Cats in endemic areas commonly have asymptomatic pulmonary infections, but may develop disseminated disease when the organism extends beyond the lungs. Common sites of infection in disseminated disease include bone, skin, and visceral organs (Clinkenbeard et al., 1987). Ocular lesions include granulomatous chorioretinitis, anterior uveitis, retinal detachment, and optic neuritis (Gwin et al., 1980; Hodges et al., 1994; Johnson et al., 2004; Mahaffey et al., 1977; Peiffer, 1979; Percy, 1981).

A diagnosis of histoplasmosis is made based on the cytologic identification of the fungal organism and culture of the organism. Positive serological tests can also be supportive of the diagnosis; however, many cats with disseminated histoplasmosis have negative serologic tests (Johnson et al., 2004). Cats with histoplasmosis have been successfully treated with itraconazole without adverse effect during treatment (Hodges et al., 1994; Johnson et al., 2004). In one study, eight cats were reportedly cured of histoplasmosis with the use of itraconazole, though two cats relapsed and required additional therapy (Hodges et al., 1994). Readers are referred to current internal medicine or infectious disease textbooks for further details regarding therapy for feline histoplasmosis.

Sporotrichosis

Sporotrichosis is caused by the dimorphic fungus, Sporothrix schenckii, which exists in soil rich in decaying organic matter (Schubach et al., 2004b). The organism is endemic worldwide and grows as a mold at 25–30°C and as a yeast at 37°C (Schubach et al., 2004b). Sporotrichosis typically develops from direct cutaneous inoculation of the fungus through contact with soil or plants, or, less commonly, via inhalation of infective conidia (Rippon, 1988). Localized cutaneous and subcutaneous infections with S. schenckii occur most frequently, while disseminated sporotrichosis occurs rarely.

Despite its worldwide distribution, feline sporotrichosis is reported to occur only sporadically but is an important zoonosis responsible for causing human epidemics in some instances (Davies & Troy, 1996; de Baroni et al., 1998; de Lima Barros et al., 2001; de-Oliveira-Nobre et al., 2001; Schubach et al., 2004b, 2005). Cats experimentally infected with S. schenckii have been shown to develop both the localized and disseminated forms of the disease (Barbee et al., 1977). In naturally occurring infections, S. schenckii primarily affects younger intact male cats (<4 years of age) (Davies & Troy, 1996; Schubach et al., 2004b). In a recent study, clinical signs observed in affected cats ranged from subclinical infection to a self-regressing solitary cutaneous lesion to fatal disseminated forms (Schubach et al., 2004b). Cutaneous and subcutaneous lesions included focal crustured areas, subcutaneous nodules that eventually drained purulent material, exudative ulcers, and large regions of necrosis exposing underlying muscle and bone. Sporotrichosis preferentially affects the face, neck, and extremities (Davies & Troy, 1996; Schubach et al., 2004b). One study reported cutaneous lesions involving mainly the head and hindlimbs in 56.8% and 13.8% of cats, respectively (Schubach et al., 2004b). Mucosal lesions, including ulcerated conjunctival granulomas, were observed in 34.9% of cats (Fig. 35.2.12) (Schubach et al., 2004b). Systemic signs were present in 57.1% of cats and included poor body condition, anorexia, vomiting, and most frequently, respiratory signs such as sneezing and dyspnea. Affected cats may also be FIV and/or FeLV positive, although no differences in presenting clinical signs were noted in FIV-FeLV-positive versus -negative cats (Schubach et al., 2004b).

Diagnosis of sporotrichosis involves isolation or demonstration of the causative agent, S. schenckii from affected tissues (e.g., nasal or oral swabs, secretions form cutaneous lesions) via mycologic culture, histopathologic examination...
of a skin biopsy, or via detecting organismal DNA using PCR (Kano et al., 2005). The presence or absence of granuloma formation in the cutaneous biopsy specimens has reportedly affected whether or not S. schenki was detected histologically. The fungal organisms were observed in 57.8% of specimens in which granulomatous inflammation was not present, but in only 4.4% of samples that contained granulomas (Schubach et al., 2004b).

Cats with sporotrichosis have been successfully treated with itraconazole, combinations of itraconazole and fluconazole or intraconazole and terbinafine, terbinafine, sodium iodide, or ketoconazole. In one study, treatment duration ranged from 16 to 80 weeks (median = 36 weeks) (Schubach et al., 2004b). A diverse treatment effects were seen in 40.5% of cats treated with sodium iodide and 13.7% of cats receiving the other treatment regimes (Schubach et al., 2004b). Readers are referred to current internal medicine or infectious disease textbooks for further details regarding therapy for feline sporotrichosis.

Parasitic: Dipteric Larvae

Ophthalmomyiasis Interna/Externa

Ophthalmomyiasis interna refers to the intraocular migration of fly (Diptera) larvae. The syndrome has been observed in cats and in dogs. The syndrome is quite characteristic, but it is uncommon to determine the type of fly larvae present. The point of entry is unknown but postulated to be across mucous membrane-lined sites such as the conjunctival surfaces, oral cavity, nasal cavity, skin, or other body orifice or wound. The syndrome may be presented in the acute stages if an anterior uveitis is produced, but usually the syndrome is noted as an incidental finding in the chronic stages. The characteristic ophthalmoscopic lesions are wandering, curvilinear tracts that frequently intersect and are associated with retinal and preretinal hemorrhages in the acute stage.

These curvilinear retinal lesions have been reported in cats (Brooks et al., 1984; Gwin et al., 1984; Kaswan & Martin, 1984), and in one case, a larva was visualized migrating within the retina (Gwin et al., 1984). This cat had bilateral disease, with retinal hemorrhage in one eye and retinal detachment in the other. Only acute cases warrant therapy, and topical or systemic steroids are indicated depending on the location of the lesion (or lesions). If the larva is present, laser energy may be attempted to kill the larva, even though it is not pigmented. Systemic organophosphates have been used as well, but because the condition spontaneously improves in most instances, its efficacy is unknown. Killing the larva may incite more inflammation, however, and waiting for spontaneous departure may be prudent.

Three cases of intracameral *Cuterebra* spp. larvae in cats have also been reported (Harris et al., 2000; Johnson et al., 1988; Stiles & Rankin, 2006). In one case, severe panophthalmitis was present, and even though the larva was surgically removed from the anterior chamber, the eye was blind (Johnson et al., 1988). In another affected cat, the *Cuterebra* larva had directly penetrated the sclera resulting in severe anterior uveitis characterized by a large fibrin clot followed by generalized retinal degeneration and blindness noted 6 weeks following surgical removal of the larva from the anterior chamber (Harris et al., 2000). In the third case, the parasite was surgically removed from the anterior chamber with preservation of vision reported at 6 months postoperatively (Stiles & Rankin, 2006). Ophthalmomyiasis interna in which the *Cuterebra* spp. was found in the vitreous slightly lateral to the optic nerve has been described (Fig. 35.2.13 and Fig. 35.2.14) (Wyman et al., 2005). The larva was demonstrated histologically as were coagulation necrosis and hemorrhage of the optic nerve, retina and choroid, and anterior uveitis. In addition, cerebrospinal cuterebrasis has been reported as a cause of blindness in 6 of 10 affected cats (Williams et al., 1998). A another report involved an adult *Metastrongylidae* sp. nematode within the globe of a cat (Bussanich & Rootman, 1983). This nematode could not be removed surgically, however, and uveitis necessitated enucleation (Bussanich & Rootman, 1983).

Ophthalmomyiasis externa refers to the extraocular migration of fly larvae. Migration of *Cuterebra* spp. larvae in the subcutaneous tissues of the cat is common, and the eyelids or conjunctiva may be affected. In addition, *Cuterebra* have been found within the feline orbit (Harris et al., 2000). Removal of the larva is indicated. Care must be taken not to crush the larva, however, because a severe inflammatory response may occur.

**Figure 35.2.13.** Cuterebrasis in a cat. Fundus photograph of the organism in the vitreous with vitreal hemorrhage overlying the optic disk. The black cuticular spines can be observed. (Reprinted with permission from Wyman, M., Starkey, R., Weisbrode, S., Filko, D., Grandstaff, R. & Ferreeb, E. (2005) Ophthalmomyiasis (interna posterior) of the posterior segment and central nervous system myiasis: *Cuterebra* spp. in a cat. *Veterinary Ophthalmology*, 8, 77–80.)
Chapter 35: Ocular Manifestations of Systemic Disease

SECTION IV

Notoedric Mange

The causative agent of feline scabies is *Notoedres cati*, but cats may also be infected with the mite that causes canine scabies, *Sarcoptes scabiei var canis* (Bornstein et al., 2004; Delucchi & Castro, 2000; Hawkins et al., 1987; Itoh et al., 2004). Importantly, feline mange is zoonotic and owners of affected cats may become infected (Chakrabarti, 1986). Typically, lesions begin around the medial edge of the ear pinna, then progress to involve the upper ear, face, eyelids, and neck. Intense pruritus is characteristic, and the diagnosis is suggested by location of the lesions and intense pruritus. The diagnosis is confirmed on the basis of cutaneous scrapings of the lesion(s), which are examined under low-level light at 10× magnification for the small mite. Treatment should include clipping of all hair and application of a 3% lime sulfur solution every seventh day until the lesions have resolved. All other cats on the premises must be treated as well. The avermectins are highly effective at treating notoedric mange in cats. Ivermectin, although not approved for use in cats, has been shown to be effective for use in cats (Oliva & Baldi, 1988; Song, 1992). Ivermectin use in kittens, however, has a low safety margin (Lewis et al., 1994; Muhammad et al., 2004). Doramectin (290 µg/kg SQ) administered as a single dose and selamectin (6–12 mg/kg topically) have also been shown to be effective in the control of notoedric mange in cats (Delucchi & Castro, 2000; Itoh et al., 2004). Selamectin apparently has a wide safety margin and has not been associated with adverse effects in kittens older than 6 weeks of age (Itoh et al., 2004).

Parasitic: Mites

Demodicosis

An uncommon disease, feline demodicosis results from three species of mites: *D. cati*, *Demodex gatoi*, and a third species of *Demodex* that has not yet been named (Chesney, 1988; Desch & Stewart, 1999; Guaguere et al., 2004; Lowenstein et al., 2005; Medleau et al., 1988; Wilkinson, 1983). Affected animals typically have a concurrent medical condition. Lesions usually affect the eyelids, pericentral area, head, and neck (Fig. 35.2.15). They are variably pruritic, and they are characterized by alopecia, erythema, crusting, and scaling. Demodicosis may be associated with other concurrent cutaneous lesions. A cat with multiple cutaneous xanthomas and concurrent mild demodicosis and dermatophytosis affecting the head and neck has been described (Vogelnest, 2001). The diagnosis of demodicosis is established on the basis of cutaneous scrapings of the lesion(s) and identification of the mite. A thorough review of the literature has identified lime sulfur dips (1.6%–2% every 5–7 days for 4–6 weeks) and amitraz rinses (0.0125%–0.025% twice weekly or every other week for 2–4 weeks) as being the most reliable treatment for feline demodicosis (Mueller, 2004). It should be mentioned, however, that favorable response to treatment of feline demodicosis has been seen with subcutaneous administration of doramectin (Johnstone, 2002). The use of ivermectin was not successful in one cat with concurrent infection with *D. cati* and an unnamed mite species (Lowenstein et al., 2005).
The life cycle of *Onchocerca lupi* is not completely understood, but is likely similar to that of other *Onchocerca* spp. (Sreter et al., 2002). Larval maturation is thought to occur in black flies (*Simulium*) or gnats/midges (*Culicoides*), the intermediate hosts (Sreter et al., 2002; Zarfoss et al., 2005). Larvae are then transmitted to the definitive host via blood feeding of the insect (Zarfoss et al., 2005). The parasites then mature, mate, and produce microfilariae that are ingested by the intermediate host, and so on (Zarfoss et al., 2005). Most recently, two domestic shorthair cats residing in the southwestern United States were confirmed histologically and by molecular identification to have feline ocular onchocerciasis due to infection with *O. lupi* (Labelle et al., 2011). The ophthalmic findings reported in one cat included chemosis and conjunctivitis, opacity within the anterior chamber and dyscoric pupil with progression to secondary glaucoma and eventual enucleation following 2 years. Histopathologic assessment of this globe revealed a multinodular, predominantly granulomatous inflammatory infiltrate centered on these parasites affecting the posterior episclera and orbital tissues (Fig. 35.2.16). The second affected cat had persistent conjunctivitis, ipsilateral facial nerve paralysis, facial hypalgnesia, and corneal ulceration that resulted in subsequent enucleation. The main histopathologic findings for this eye revealed female parasites in the posterior episclera and orbit surrounded by small numbers of macrophages, lymphocytes, and plasma cells with mild fibrosis. Rare lymphocytes and plasma cells were noted within the iris stroma and ciliary body, and there was evidence of glaucomatous retinal and optic nerve damage. Ocular onchocerciasis should be included in the differential diagnosis list for cats with conjunctivitis and orbital disease. The antiparasitic treatment commenced in the two *O.* lupi-affected cats was empirical, and consisted of two broad-spectrum parasiticides, including an avermectin class parasiticide, selamectin, that were selected, in part, based on known safety in cats (Labelle et al., 2011). Further investigation into therapies for onchocerciasis in cats is warranted.

**Parasitic: Protozoal**

**Leishmaniasis**

Leishmania spp. are diphasic protozoal parasites that infect a wide range of vertebrates, including dogs, cats, and humans (for reviews, see Aivar et al., 2004; Desjeux, 2004). Dogs are considered important primary reservoirs of Leishmania spp., and sandflies (*Phlebotomus* spp. or *Lutzomyia* spp.) are the vectors (Aivar et al., 2004). Naturally occurring leishmaniasis has traditionally been uncommonly recognized in cats but has been increasingly reported in the last decade (de Souza et al., 2005; Grevot et al., 2005; Hervas et al., 1999, 2001; Leiva et al., 2005; M orsy & A bou el Seoud, 1994; Ozon et al., 1998; Passos et al., 1996; Pennisi et al., 2004; Poli et al., 2002; Rufenacht et al., 2005; Schubach et al., 2004a). Feline leishmaniasis is generally caused by different Leishmania spp. than those affecting dogs including Leishmania mexicana in Texas, Leishmania major in Egypt, and Leishmania (*Viannia*) panamensis in Brazil (Rufenacht et al., 2005). Although, Leishmania infantum, a causative agent of feline leishmaniasis in southern France and Italy, also causes leishmaniasis in dogs in the “Old World.”

As previously mentioned, transmission to vertebrates is via bites from infected sandflies. Furthermore, sandflies are infected by reservoir hosts during feeding. The incubation period may be a few months to between 3 and 4 years (Kontos & Koutinas, 1993). Consequently, a thorough travel history needs to be investigated in suspect cases of feline leishmaniasis.

Leishmania spp. cause cutaneous, mucocutaneous, and visceral diseases (Pena et al., 2000). Dogs will typically develop a combination of these forms of leishmaniasis (Pena et al., 2000). Visceral forms of leishmaniasis are not typically described in cats, although reports of Leishmania-induced cutaneous lesions have been more commonly described. Cutaneous lesions are variable but typically involve an ulcerative dermatitis on the face, pinnae, neck, thorax, and bony protuberances. In addition, generalized alopecia and scaling, and cutaneous nodules on the head and extremities have been reported. Ocular manifestations of leishmaniasis occur in at least 25% of affected dogs (Pena et al., 2000). However, ocular manifestations of feline leishmaniasis have only been described in three cats, two of which had panuveitis (Hervas et al., 2001; Laruelle-Magonal & Toga, 1996; Leiva et al., 2005). A case of ocular and visceral leishmaniasis has been reported in a cat (Leiva et al., 2005). This affected cat had bilateral melting ulcerative keratitis, exudative panuveitis and

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**Figure 35.2.16.** Histopathologic section of the orbital tissues stained with hematoxylin and eosin (magnification ×200). A section of the parasite (*Onchocerca lupi*) is bordered by mild fibrosis (bold arrow). The section includes one of the paired uteri that contains numerous microfilariae. Cuticular ridges are visible (arrow). (Reprinted with permission from Labelle, A.L., Daniels, J.B., Dix, M. & Labelle, P. (2011) *Onchocerca lupi* causing ocular disease in two cats. *Veterinary Ophthalmology*, 14, 105–110.)
secondary glaucoma, diabetes mellitus, and macrophages with intracytoplasmic Leishmania detected cytologically on bone marrow aspirates (Leiva et al., 2005). Leishmaniasis has also been reported in cats with coinfections with FeLV and/or FIV (Grevot et al., 2005; Pennisi et al., 2004; Poli et al., 2002), and in one cat with concurrent pemphigus foliaceus (Rufernacht et al., 2005).

The diagnosis of feline leishmaniasis may be difficult since serology and serum protein electrophoresis patterns are usually less specific than in affected dogs (Merchant & Taboada, 1995). The diagnosis if confirmed on the basis of finding the organisms (i.e., amastigotes), which are round to oval and 2.5–5.0 µm by 1.5–2.0 µm in size, in bone marrow aspirates, lymph node aspirates, or skin impression smears stained with Wright’s or Giemsa stains. Other means of identifying the Leishmania organism include histopathologic or immunoperoxidase evaluation of cutaneous or organ biopsy specimens, PCR performed on anticoagulated blood, or bone marrow or lymph node aspirates, or culture inoculation of hamsters (Ashford et al., 1995; Manna et al., 2004; Solano-Gallego et al., 2001; Vitale et al., 2004). Serologic tests are available that use ELISA and indirect fluorescent antibody (FA) testing.

Leishmania spp. are difficult to eliminate from the body and recurrences are common (Cavaliere et al., 1999). A variety of drugs have been used for the treatment of leishmaniasis (Noli & Auxilia, 2005). Due to the limited number of reported cases of feline leishmaniasis, treatment is not clearly defined. Readers are advised to consult a current internal medicine textbook for further details regarding the treatment of feline leishmaniasis.

Toxoplasmosis

Toxoplasmosis is caused by the obligate intracellular protozoal parasite, Toxoplasma gondii (for a review, see Dubey, 2004). T. gondii has a worldwide distribution. Cats are both definitive and intermediate hosts of T. gondii. Because cats are definitive hosts, they are the only species that can shed oocysts, which in turn are infective to other species. Cats shed oocysts for approximately 1 week, beginning 3–5 days after the initial infection, and then are immune to reshedding oocysts unless they are reinfected. Even when reinfected, however, cats inconsistently reshed oocysts (Dubey, 1995). Many mammalian species can act as intermediate hosts. In cats, ingested T. gondii bradyzoites (from tissue cysts) undergo a typical coccidian intestinal life cycle, and infected cats excrete oocysts in their feces that, after 1–5 days, sporulate and become infectious sporozoites (Dubey, 2004). The ookysts are resistant to environmental conditions, and they may remain infectious for months to years (Dubey, 2004). Ingestion of the oocysts by a susceptible host results in rapid division of sporozoites in the gut epithelium. The resultant tachyzoites are 4–8 µm by 2–4 µm, and are spread throughout the body via blood and lymphatics, and encyst in the brain, skeletal, and cardiac muscles, as well as the liver. The encysted forms, termed bradyzoites, survive in tissues for the life of the host. Ingestion of bradyzoites by a new host dissolves the cyst wall and transforms them into tachyzoites, which ultimately encyst again. Transmission of T. gondii to cats may occur from ingesting food or water contaminated with oocysts, from ingesting infected prey, or transplacentally from the queen (Dubey & Carpenter, 1993b; Dubey et al., 1995; Sato et al., 1993).

Ocular disease associated with T. gondii is more commonly observed in cats than in dogs, and, in cats, it is commonly associated with systemic disease including anorexia, fever, hepatitis, myositis, pneumonia, gastrointestinal signs, and neurological signs (Davidson & English, 1998). A recent case report also describes the first antemortem association of toxoplasmosis with pericardial effusion and infiltrative myocardial disease, presumed to be myocarditis, in a cat (Simpson et al., 2005). Clinical feline toxoplasmosis may also manifest initially as cutaneous nodules (Anfray et al., 2005). T. gondii has been implicated as being a major contributor to feline uveitis (Chavkin et al., 1992; Dubey & Carpenter, 1993a; Lappin et al., 1989b, 1992a, 1992b), yet its role in causing anterior uveitis in an otherwise asymptomatic cat is unclear (Davidson & English, 1998). The uveitis may be anterior, posterior, or both (Fig. 35.2.17). However, chorioretinitis is the most common ocular manifestation (Fig. 35.2.18) (Davidson, 2000; Davidson & English, 1998; Dubey & Carpenter, 1993a). In addition, optic neuritis has also been reported in affected cats.
Uveitis secondary to toxoplasmosis may result from rapid replication of tachyzoites within ocular tissue (Dubey & Carpenter, 1993a) or from deposition of immune complexes within uveal tissue (Dernouchamps, 1981; Dernouchamps et al., 1977). Intraocular production of antibodies specific for T. gondii has been documented (Chavkin et al., 1994; Lappin et al., 1992b, 1995), and the organism has been identified within the uveal tract by histopathology (Dubey & Carpenter, 1993a) and in the aqueous humor by PCR (Burney et al., 1998; Lappin et al., 1996). Uveitis may occur secondarily to recent infection by T. gondii. In humans, reactivation of the dormant tissue phase (i.e., bradyzoites) of the organism leads to retinochoroiditis. It is unclear, however, whether uveitis occurs from reactivation in cats, although it is likely that it does. Stressors that may relate to reactivation include coinfection with agents such as FIV (Davidson et al., 1993) or with immunosuppressive doses of corticosteroids (Dubey & Frenkel, 1974). However, a study investigating the factors that trigger development of uveitis in some T. gondii-infected cats, reported that experimental inoculation with B. henselae followed by FHV-1 did not reactivate ocular toxoplasmosis (Powell et al., 2002). In another study, latently infected cats that received weekly injections of methylprednisolone redeveloped serum IgM titers and circulating antigenemia, but they did not resed oocysts or develop clinically apparent disease (Lappin et al., 1991). Correlations have been made between seropositivity for FIV and toxoplasmosis (see the discussion under “Feline Immunodeficiency Virus”) (Chavkin et al., 1992; Lappin et al., 1989b, 1992a; O’Neil et al., 1991; Witt et al., 1989).

A diagnosis of ocular toxoplasmosis in an otherwise asymptomatic cat is difficult, and histologic demonstration of the parasite is the sole definitive means of confirmation. The diagnosis of toxoplasmosis-related uveitis is, however, generally established on the basis of a positive serum T. gondii-antibody titer, though PCR tests to identify T. gondii DNA in biologic samples have also been developed (Lappin et al., 1996; Stiles et al., 1996). Laboratory tests that measure both T. gondii-specific IgM and IgG are most helpful, because levels of the IgM class of antibody rise and fall over approximately 3–4 months after infection, whereas those of the IgG class of antibody may rise more slowly and remain elevated in cats for years after exposure to T. gondii (Lappin et al., 1989a). In addition, cats coinfected with FIV and T. gondii may develop a positive IgM antibody titer, whereas the IgG antibody titer in these same cats remains negative (Lappin et al., 1992b). T. gondii-specific IgA has been demonstrated in the serum, but these levels rose more slowly than those of IgM or IgG, being detected 34 weeks after experimental infection (Burney et al., 1995). Detection of T. gondii-specific antibodies in aqueous humor may aid in establishing an accurate diagnosis (Chavkin et al., 1994; Hill et al., 1995; Lappin et al., 1992b, 1995). The overall seroprevalence of T. gondii-specific antibodies (IgM, IgG, or both) in clinically ill cats across the United States was reported to be 31.6% (Vollaire et al., 2005). In particular, the percentage of cats seropositive for T. gondii antibodies ranged from 16.1% to 43.5% in the southwestern and northeastern United States, respectively. A nother report documented no significant differences in seroprevalence of antibodies to T. gondii in stray (50%) versus client-owned (36%) cats, or indoor (26%) versus outdoor (39%) cats (DeFeo et al., 2002). A recent study compared serum antibodies and PCR DNA amplification from the blood and aqueous humor for T. gondii in addition to Bartonella spp. and FHV-1 in 104 cats with uveitis and 19 healthy shelter cats (Powell et al., 2010). Results supported the addition of the PCR assay to the diagnostic workup for cats with uveitis to increase the detection of both T. gondii and FHV-1, although the diagnostic usefulness of this added information remained unclear.
Current treatment recommendations for cats with toxoplasmosis-induced uveitis include oral clindamycin hydrochloride, 12.5 mg/kg twice daily for 21–30 days, in addition to treatment with a topical corticosteroid, such as 1% prednisolone acetate every 6 hours, and atropine (as needed to maintain mydriasis) (Chavkin et al., 1992; Lappin et al., 1989b). Despite treatment with clindamycin, uveitis in cats with positive T. gondii serum antibody titers may be chronic or recurring, and long-term use of topical prednisolone acetate may be needed to control the uveitis.

Toxoplasmosis is a significant zoonotic disease (Dubey, 2004). Clinical signs of toxoplasmosis may develop in the fetus of pregnant mothers experiencing a primary T. gondii infection. Ocular disease, and other manifestations such as stillbirth, may be noted in infected fetuses. As such, prevention of toxoplasmosis is recommended. Restricting the cat’s ability to hunt (i.e., maintaining the cat indoors) will help prevent feline toxoplasmosis. In addition, litter boxes for cats should be changed daily (pregnant woman should avoid this task), and cats (and humans) should not be fed raw or incompletely cooked meat.

Trypanosomiasis
Trypanosoma brucei, which is a parasitic, flagellate protozoa, is the cause of sleeping sickness. It is also highly pathogenic to a number of species. Experimental infection of cats with T. brucei leads to marked anterior uveitis and formation of ciliary epithelial cysts containing the organism. Trypanosomes have also been found free within the anterior chamber (Mortelmans & Neetens, 1975).

Prions
Feline Spongiform Encephalopathy
Feline spongiform encephalopathy (FSE) is a transmissible spongiform encephalopathy (TSE) caused by the conversion of the cellular prion protein (PrPc) into an insoluble protease-resistant isoform (PrPSc) (Wyatt et al., 1991). This is a fatal neurodegenerative disease that is associated with the ingestion of bovine spongiform encephalopathy (BSE)-contaminated food. FSE was first documented in 1990 in the United Kingdom during the epizootic of BSE. Since 1990 to present, there have been nearly 100 reported cases of FSE with the majority of cases in Great Britain, including one case each from Northern Ireland, Norway, Liechtenstein (Hilbe et al., 2009), and Portugal, and two cases in Switzerland (Hilbe et al., 2009; Imran & Mahmood, 2011; Iulini et al., 2008).

Domestic cats with FSE typically range in age from 4 to 9 years (mean of 6.6 years) (Wyatt et al., 1991). Other felids have also been reported with FSE including the cheetah (Bencsik et al., 2009; Eidon et al., 2010), ocelot, puma (WilloUGHBY et al., 1992), A si an golden cat, lion, and tiger (Imran & Mahmood, 2011; kirkwood & Cunningham, 1994). The clinical manifestations of FSE involve progressive neurological signs not readily distinguished from those of other, more common feline neurological diseases, and include depression, restlessness, locomotor dysfunction including abnormal or hypermetric gait and ataxia of mainly the hindlimbs, and severe behavioral changes such as fear, uncharacteristic aggressiveness or timidity. As well, affected cats often demonstrate poor judgment of distance and hyperesthesia to noise and/or touch, and some affected cats stare vacantly, develop tremors, a head tilt, or circle. In addition, excessive salivation, polyphagia, polydipsia, and dilated pupils have been reported in some FSE-affected cats (Hilbe et al., 2009; Imran & Mahmood, 2011; Salvadori et al., 2007). FSE is typically fatal after 3–8 weeks of clinical onset of the disease in domestic cats.

The confirming diagnosis of FSE is made only at postmortem by histological, immunohistochemical, or Western blot examination of brain tissue to identify the typical spongiosis and PrPSc deposition. For a review of prion diseases in animals, the reader is referred to Imran & Mahmood (2011).

Viral
Calicivirus
FCV, a picornavirus, is primarily a respiratory tract pathogen of cats but may cause oral ulcers and polyarthritis (Bennett et al., 1989; Hoover & Kahn, 1975; Ormerod et al., 1979). One study reported that FCV had become a major viral pathogen of the upper respiratory tract of cats in Japan with increased prevalence over FHV-1 (Mochizuki et al., 2000). Compared with FHV-1, FCV has a low pathogenicity for the conjunctiva, though it can cause conjunctivitis (Kahn & Gillespie, 1971; Tan & Miles, 1974). In one experimental study, only 2 of 10 FCV strains tested caused conjunctivitis in cats (Hoover & Kahn, 1975). In another study using only a single strain of FCV, 67% of kittens exposed developed conjunctivitis, which lasted for as long as 2 weeks (Kahn & Gillespie, 1971). A case of FCV and coinfection with FPV was reported in a cat with systemic signs including ocular discharge (Camero et al., 2004). More virulent forms of FCV are, however, emerging and resulting in outbreaks of infection in various regions (Hurley et al., 2004; Pedersen et al., 2000).

Cats may be asymptomatic while shedding FCV in ocular and nasal discharges, saliva, and feces (Hurley et al., 2004). In particular, a study in Sweden reported that FCV was isolated using virus isolation (VI) from 2.6% of clinically healthy cats from breeding catteries (Holst et al., 2005). Interestingly, these cats had all demonstrated signs of respiratory disease or conjunctivitis several years previously.

The diagnosis of FCV can be made using laboratory techniques such as VI, immunofluorescence (IF), and PCR assay. A novel nested PCR (nPCR) assay for the detection of FCV DNA has been developed and performed on 47 conjunctival swabs from 47 cats of which 18 ocular swabs were FCV positive (Marsilio et al., 2005). This nPCR was determined to be more sensitive than both VI and reverse transcriptase (RT)-PCR in the diagnosis of FCV.

Vaccination with standard inactivated trivalent vaccine including FCV has been correlated with resistance to infection
and clinical disease (Lappin et al., 2002; Scott & Geissinger, 1999). Furthermore, a study has reported that most vaccinated cats develop a serologic response to all three viral antigens (FPV/FCV/FHV-1) that surpasses presumed protective levels, lasting up to and beyond 2 years (Mouzin et al., 2004).

**Feline Coronavirus (Feline Infectious Peritonitis)**

Feline coronavirus (FCoV) infection in cats may lead to no clinical disease, enteric disease, or feline infectious peritonitis (FIP), which is a disseminated pyogranulomatous vasculitis (Addie & Jarrett, 1992; Addie et al., 1995; Kipar et al., 2005). FIP replicates within macrophages resulting in the deposition of virus-laden macrophages within the endothelium of small blood vessels (Kipar et al., 2005). Interestingly, the FIP virus has been recently shown to enter target macrophages/monocytes by first binding to the cell surface and then being internalized by a clathrin- and caveolae-independent and dynamin-dependent endocytosis (Van Hamme et al., 2008). FIP is a fatal arthus-type immune reaction of cats to infection with the virus (Foley et al., 1998). Large multicat indoor environments are known to favor feline enteric coronavirus (FECV) infection and FIP (Pedersen et al., 2008). Sexually intact cats and purebred cats are more likely to develop FIP (Pesteanu-Somogyi et al., 2006). A recent study evaluating the prevalence of FIP in individual breeds reported increased risk of development of disease in Abyssinians, Bengals, Birmans, Himalayans, Ragdolls, and Rexes (Pesteanu-Somogyi et al., 2006). As well, FIP most commonly occurs in young cats, and it may manifest by an effusive or wet form of the disease, which includes fibrin-rich fluid within the abdominal and peritoneal cavities, or as a non effusive or dry form of the disease. Ocular and neural lesions are more likely to be present with the non effusive form (Andrew, 2000; Foley et al., 1998).

The most common ocular manifestation of FIP is bilateral granulomatous anterior uveitis, often with large, mutton-fat keratic precipitates and a fibrinous exudate into the anterior chamber. Chorioretinitis is also frequently observed, and a pyogranulomatous exudate sheathing the retinal vessels may be present as well. Additional findings may include retinal hemorrhages, detachments, and optic neuritis (Campbell & Reed, 1975; Doherty, 1971; Montali & Strandberg, 1972; Slauson & Finn, 1972). Recently, FIP was diagnosed in a 7-month-old intact male domestic shorthair cat with unilateral anterior uveitis and pyrexia (Declercq et al., 2008). Interestingly, non pruritic cutaneous lesions, characterized by slightly raised intradermal papules over the dorsal neck and over both lateral thoracic walls, were recognized at the end stage of the disease in this cat and facilitated a diagnosis of FIP (Declercq et al., 2008).

Histologically, lesions in FIP consist of granulomas comprising mixtures of neutrophils, lymphocytes, plasma cells, and large, spindle-shaped histiocytes. Ocular lesions include focal or diffuse granulomatous inflammation of the uvea, retina, and meninges of the optic nerves. Fibrinocellular exudates may be present in the ocular chambers (Krebiel et al., 1974; Montali & Strandberg, 1972).

Current evidence is indicative that the FIP virus develops as a simple mutation of FECV during primary infection (Poland et al., 1996; Vennema et al., 1998). The acquisition of macrophage tropism appears to be an essential aspect in the transformation of an FECV to an FIP virus. A epidemiologic study of 820 cats with positive coronavirus titers determined that cats were just as likely to develop FIP in households without other FIP-affected cats as were cats in households with other FIP-affected cats, and that the risk of developing FIP decreased with time (Addie et al., 1995). Many cats even became seronegative and, apparently, cleared the virus. Experimental infection of FIV-positive cats with FECV resulted in the development of FIP through mutation of the FECV (Poland et al., 1996). The delayed and reduced antibody titers produced by FIV-positive cats may select for such a mutation.

In many cases, the definitive diagnosis of FIP antemortem is difficult (Addie et al., 2004). Confirming a diagnosis of FIP infection based on the measurement of several variables within the serum, including serum coronavirus titers, is impossible (Foley et al., 1997; Hartmann et al., 2003). Many cats with FIP have low antibody titers, and fluctuating or high titers may, in fact, be more likely among cats with chronic re exposure to FECV in the environment. This would be especially relevant in a cattery situation. One study documented that the utility of the serum albumin to globulin ratio to diagnose FIP was greater than the utility of serum total protein and γ-globulin concentrations, especially when performed on effusions (Hartmann et al., 2003). Tests using PCR to identify coronaviruses have been developed, but still cannot differentiate between FIP virus and FECV (Herrewegh et al., 1995; Li & Scott, 1994). However, RT-PCR conducted on effusion samples was accurate in diagnosing FIP in five cats with histologically confirmed FIP and was negative in the cat with a different disease (Kinnear, 2003). A PCR test was recently developed to solely detect forms of the viral RNA that were present during the replication stage of FIP virus, in order to help increase the sensitivity and specificity of this form of testing (Simons et al., 2005). The rationale was such that replicating forms of the viral RNA would only be found in blood cells of FIP-affected cats. In particular, the test amplified subgenomic mRNA of the highly conserved M gene. In the study by Simons et al., 2005, almost 50% of the 651 cats suspected of having FIP were positive for the replicating form of FCoV mRNA in their peripheral blood cells, whereas only 5% of the healthy cats (n = 424 cats) were positive. However, when this PCR test was performed on other groups of cats suspected of having FIP and/or on healthy cats, many healthy cats were also noted to be positive for FCoV (Can-Sahna et al., 2007; Rottier et al., 2005), indicating that FCoVs may be present not only in the blood samples from cats with clinical FIP but also in the blood samples of healthy cats.

There is no effective treatment at present for FIP. Elimination of FIP from a cattery is only possible by total elimination of endemic FECV infection. The most important method for
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• 2007

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though some of these cats will have concurrent sneezing or other mild signs of respiratory tract infection (FECV is the elimination of chronic FECV shedders (Addie et al., 2004; Foley et al., 1997).

Treatment of ocular disease is symptomatic and includes use of topical, subconjunctival, or systemic corticosteroids as well as topical atropine. Temporary amelioration of ocular disease may occur, but such disease will usually rebound in a short period of time. For a recent consensus statement regarding the diagnosis, treatment, and prevention of FIP, the reader is directed to recommendations from an international workshop on FIP (Addie et al., 2004). For a detailed review of FIP virus infection, the reader is referred to Beals (2009).

Feline Herpesvirus Type 1

FHV-1, a double-stranded DNA virus and a member of the alphaherpesvirus subfamily, is highly species specific. Infection with FHV-1 is common, and the virus is widespread among cat populations. Studies have estimated that over 90% of cats are seropositive to the virus (Maggs et al., 1999b) with as much as 80% of infected cats remaining latently infected on a lifelong basis, and with approximately 45% of these latently infected cats shedding virus throughout life (Gaskell & Povey, 1977; Townsend et al., 2004). The virus is spread from cat to cat either by direct contact, fomites, or by aerosolization of virus. FHV-1 infects the epithelial surfaces of the respiratory tract and conjunctiva and, to a lesser degree, the corneal epithelium, thereby causing necrosis of these tissues as the virus replicates and invades the adjacent cells (Hoover et al., 1970; Nasisse et al., 1989b). The virus then ascends by axons of sensory neurons to the trigeminal ganglion to establish lifelong latency (Maggs, 2005). Cats may therefore develop chronic or recurrent ocular disease associated with FHV-1. Though cats can be reinfected with FHV-1 despite previous infection or vaccination, recurrent ocular disease is most likely to be associated with recrudescence of latent virus (Bistner et al., 1971; Bodle, 1976).

FHV-1 produces disease via at least two mechanisms (Maggs, 2005). The first mechanism involves cytolytic infection during active viral replication. Cell rupture can occur during primary FHV-1 infection or following viral reactivation from latency. FHV-1 infection can also induce disease via a second mechanism, immune-mediated inflammation. Primary FHV-1 disease in kittens generally produces upper respiratory and ocular diseases, and is characterized by malaise, fever, inappetence, sneezing or coughing, and nasal as well as ocular discharge. Polymorphonuclear cell infiltrate is marked and results in purulent ocular and nasal discharge, even if secondary bacterial infection is not present. Primary respiratory tract and conjunctival FHV-1 infection usually lasts for 10–14 days and resolves spontaneously, but the course can be variable (Stiles, 2000). Clinical ophthalmic manifestations of FHV-1 cytolytic infection are numerous and include conjunctivitis characterized by hyperemia, blepharospasm, chemosis, and ocular discharge. Conjunctivitis, whether unilateral or bilateral, is probably the most common FHV-1-related ocular disorder in adult cats without active respiratory disease, though some of these cats will have concurrent sneezing or other mild signs of respiratory tract infection (Fig. 35.2.19). Keratoconjunctivitis sicca (KCS) has been reported in cats with FHV-1-related conjunctivitis as well (Andrew, 2001; Stiles, 1995). FHV-1 is the sole documented viral cause of keratitis in cats (Andrew, 2001). Corneal ulcers, whether dendritic or geographic, are thus a common manifestation of cytolytically induced FHV-1 ocular disease usually accompanied by conjunctivitis (Fig. 35.2.20). If both the cornea and conjunctiva are ulcerated due to the cytolytic effects of FHV-1, corneal stroma and conjunctival substantia propria become exposed, thereby facilitating adhesion formation between these tissues (i.e., symblepharon). Neonatal ophthalmia may
be caused by FHV-1, either from maternal transmission to the kitten or infection shortly after birth (Andrew, 2001; Bistner et al., 1971). Raised, plaque-like lesions on the eyelids of a cheetah cub with FHV-1 have also been reported (Junge et al., 1991).

Clinical disease caused by the immunopathological mechanism of FHV-1 is an uncommon response to the viral infection (Maggs, 2005). Stromal keratitis results from immune-mediated response to viral antigen, and is probably the most serious ocular manifestation of FHV-1. Subconjunctival dexamethasone predisposed experimentally infected cats to develop stromal keratitis (Nasisse et al., 1989b). Stromal keratitis is often secondary to chronic ulceration and is characterized by deep corneal vascularization, edema, and cellular infiltrates. Stromal keratitis may be a source of chronic pain, and it can lead to significant corneal scarring as well (Nasisse et al., 1995).

Corneal sequestration is a common disorder in cats, particularly in the Persian and Himalayan breeds (Fig. 35.2.21) (Featherstone & Sansom, 2004). The cause in many cats remains undetermined, but sequestra may occur after chronic corneal ulcers or keratitis caused by infection with FHV-1 (Morgan, 1994; Startup, 1988). The condition is characterized by an area of corneal degeneration with a brown-to-black discoloration. The lesions vary from pinpoint sequestra to those occupying more than half the cornea. Vascularization may be intense or absent, and ocular pain ranges from none to marked. Corneal sequestration has been noted to occur after topical corticosteroid use in cats experimentally infected with FHV-1 (Nasisse et al., 1989b) as well as in naturally infected cats. In a study that analyzed 28 kerectectomy specimens from Persian and Himalayan cats with corneal sequestra by PCR for the presence of FHV-1 DNA, five samples were positive (Stiles et al., 1997a). In a recent study, four of nine corneal sequester keratectomy specimens were positive for the presence of FHV-1 DNA using PCR, and one of these four corneal sequestra was also positive for T. gondii DNA (Cullen et al., 2005b). In another study, three conjunctival swabs from 2 of 11 cats with sequestra were positive for FHV-1 using PCR (Grahn et al., 2005). In addition, a retrospective study detected FHV-1 DNA, via PCR, in 5.9% (1/17) of corneas from clinically normal cats, 55.1% (86/156) of corneal sequestra, and 76.3% (45/59) of scraping specimens from cats with proliferative (eosinophilic) keratitis (Nasisse et al., 1998). Like stromal keratitis, corneal sequestration can be one of the most serious and potentially blinding sequela of FHV-1 infection. The necrotic cornea can be surgically removed by keratectomy, and placement of a conjunctival graft after keratectomy may help to prevent recurrence (Blogg et al., 1989; Morgan, 1994). However, a recent retrospective study reported no significant difference in rate of recurrence between globes receiving a graft procedure (n = 5) and eyes that did not (n = 11) (Featherstone & Sansom, 2004).

Establishing an accurate diagnosis of FHV-1-related ocular disease in adult cats without respiratory tract disease has been problematic. Diagnostic tests such as virus isolation and FA test, both of which are widely available, are relatively insensitive in cats with chronic or recurrent ocular disease (Nasisse et al., 1993; Stiles et al., 1997b). In addition, serum antibody titers are only potentially useful in unvaccinated cats, and even then, such titers may not rise in a predictable manner (Nasisse, 1990). More recently available techniques to identify viral DNA, such as the PCR assay, are more sensitive and will likely become the preferred diagnostic tests. In a study of 50 cats with either acute or chronic conjunctivitis, 54% were positive for FHV-1 DNA by PCR (Stiles et al., 1997a). In another study, however, only 19% of 91 cats with chronic conjunctivitis could be positively identified as being infected with FHV-1 when evaluated by VI and FA (Nasisse et al., 1993). When the techniques of nPCR, VI, and FA were compared in three groups of cats (conjunctivitis only, respiratory tract disease and conjunctivitis, or clinically normal), PCR was found to be much more sensitive than VI or FA in cats with conjunctivitis only and in cats with respiratory tract disease and conjunctivitis (Stiles et al., 1997b). An RT-PCR assay has been developed to detect FHV-1 latency-associated transcripts (Townsend et al., 2004). Results of this study revealed that a high percentage of cats that did not have clinical signs of ocular disease had detectable FHV-1 DNA in their corneas and trigeminal ganglia using this RT-PCR assay, indicating this assay may serve to improve our current understanding of the biologic characteristics of FHV-1 (Townsend et al., 2004).

Several recent studies have been published that have evaluated ocular samples from clinically healthy or diseased feline

Figure 35.2.21. Corneal sequestrum in an adolescent brachycephalic cat. Note the superficial corneal vascularization encroaching upon the darkly pigmented sequestrated corneal tissue, and the overlying corneal ulcer.
eyes for the presence of FHV-1 using PCR. In particular, conjunctival swabs for FHV-1 PCR screening, among other agents, were collected from eyes of young healthy cats (Cullen et al., 2005a) and cats with conjunctivitis (Lim & Cullen, 2005) following tear film breakup time (TFBUT) and STT evaluations. In the young healthy cats, 5 of 18 cases were FHV-1 positive in the blood, and three conjunctival samples from three eyes of these five cats were FHV-1 positive (Cullen et al., 2005a). However, TFBUT and STT values obtained from these clinically healthy cats were not correlated with the blood or conjunctival PCR findings (Cullen et al., 2005a). Blood samples from 9 of 14 cats with conjunctivitis tested positive for FHV-1 (Lim & Cullen, 2005). Mean TFBUTs (±SD) from these cats were significantly lower (mean TFBUT = 6.8 [±3.1] seconds) than mean TFBUTs for affected cats from which no such DNA was isolated from the blood (mean TFBUT = 11.4 [±5.5] seconds) (Lim & Cullen, 2005). Most recently, a study reported that FHV-1 also induced qualitative tear film abnormalities in experimentally infected cats, as measured by TFBUT and goblet cell density (GCD) (Lim et al., 2009). In another study, a significant association was found between viral presence and epithelial keratitis, but no significant association was noted between viral presence and conjunctivitis (Volopich et al., 2005). Specifically, FHV-1 DNA was detected in 3 of 7 cats with conjunctivitis, and 5 of 6 cats with epithelial keratitis, 3 of 11 cats with stromal keratitis, and 3 of 12 cats with corneal sequestration. Furthermore, one study concluded that using the presence of FHV-1 DNA alone for the diagnosis of FHV-1-associated conjunctivitis is not suitable since their results demonstrated FHV-1 DNA in 33% of cats with conjunctivitis and 20% of control cats in northern Italy (Rampazzo et al., 2003). FHV-1 has also been shown to infect feline intraocular tissues and may be associated with uveitis in some cats (Maggs et al., 1999a). In particular, 22 of 44 cats with idiopathic uveitis and 11 of 29 cats with toxoplasma-associated uveitis had evidence of intraocular FHV-1 antibody production, while 12 cats had FHV-1 DNA detected in the aqueous humor, of which 11 had uveitis. Another recent study compared serum antibodies and PCR DNA amplification from the blood and aqueous humor for FHV-1 in addition to T. gondii and Bartonella spp. in 104 cats with uveitis and 19 healthy shelter cats (Powell et al., 2010). Results supported the addition of the PCR assay to the diagnostic workup for cats with uveitis to increase the detection of both FHV-1 and T. gondii, although the diagnostic usefulness of this added information remained unclear. For a review regarding ocular manifestation of FHV-1 including its diagnosis and treatment options, the reader is referred to Gould (2011).

Treatment of recurrent FHV-1 ocular disease may, or may not, be required. Many cats with transient conjunctivitis recover spontaneously and need no therapy. The combined results of two in vitro studies (Maggs & Clarke, 2004; Nasisse et al., 1989a) have shown FHV-1 to be susceptible to the following antiviral agents, which are listed in order of decreasing effect:

1. trifluridine,
2. idoxuridine = ganciclovir,
3. cidofovir = penciclovir,
4. vidarabine,
5. bromovinyldeoxyuridine,
6. acyclovir = foscarnet.

An additional in vitro study further demonstrated the efficacy of cidofovir against FHV-1 infection of a primary culture of feline corneal epithelial cells (Sandmeyer et al., 2005a). However, cidofovir also had cytostatic effects on cultured cells at concentrations of 0.05 mg/mL. In another in vitro study, (S)-9-(3-hydroxy-2-phosphonylmethoxypropyl) adenine (HPMPA) was found to have the greatest antiviral activity against FHV-1, acyclovir was least active, and penciclovir and bromovinyldeoxyuridine had intermediate activity (Williams et al., 2004).

Certain medications (e.g., topical trifluridine, idoxuridine, and vidarabine) have been widely tested and used in cats with FHV-1 infection, while the clinical efficacy and safety of others remain unknown. Recent studies have evaluated the effectiveness and safety of an oral antiviral medication in cats called famciclovir. Recently, oral administration of famciclovir at 90 mg/kg q 8 hours for 21 days improved outcomes for not only ophthalmic but also systemic, clinicopathologic, virologic, and histologic variables in cats experimentally infected with FHV-1 (Thomasy et al., 2011). Famciclovir, a produg to penciclovir, has been used in client-owned cats with FHV-1 ocular disease at wide dosing rates and frequencies (25–90 mg/kg q 8–24 hours). There is some supportive evidence to indicate that a dose of 90 mg/kg PO at a frequency of q 8 hours is safe and warranted pharmacokinetically in cats; however, the pharmacokinetics of this medication are complex. Most recently, a pilot study evaluating the pharmacokinetics of famciclovir and penciclovir in tears of cats with suspected FHV-1-associated disease revealed that oral administration of 40 mg of famciclovir/kg q 8 hours resulted in a tear penciclovir concentration–time profile that approximated the plasma penciclovir concentration–time profile and frequently achieved a penciclovir concentration at the ocular surface likely to be effective against FHV-1 (Thomasy et al., 2012).

Treatment of cats with viral corneal ulcers should include debridement to reduce the number of viral particles (Missotten, 1994) and an ophthalmic antiviral medication, both to hasten healing and to prevent the development of keratitis or sequestration. Antiviral agents can be used in cats with chronic conjunctivitis as well, though the results in these cases are variable. Many cats are irritated by topical antiviral agents. Treatment for KCS in cats with FHV-1 conjunctivitis can include topical 0.2% cyclosporine ointment in addition to antiviral therapy. In rabbits experimentally infected with herpes simplex virus, intramuscular administration of cyclosporine resulted in more severe and persistent stromal disease (Meyers-Elliott et al., 1987b) and both greater incidence and recovery of virus from the cornea (Meyers-Elliott et al., 1987a). A other study reported that concomitant topical use
of cyclosporine and ganciclovir decreased the severity of herpetic stromal keratitis in rabbits (Naibo et al., 1991), and the use of topical cyclosporine and trifluridine also resulted in reduced stromal keratitis in a rabbit model (Bojsjoly et al., 1984). If an anti-inflammatory agent such as a corticosteroid or cyclosporine is used to treat FHV-1-related ocular disease, an antiviral medication should also be used concurrently.

Recombinant interferon has been used in cats with herpesvirus-related ocular disease, though studies to document its effectiveness have been limited. In one report, natural oral human interferon at a dose of 5 and 25 IU reduced the severity of clinical signs in experimentally infected cats when given on days 1 and 2 of infection (Nasissi et al., 1996). In addition, synergistic antiviral activity of recombinant and natural human interferon and acyclovir on FHV-1 replication has been shown in vitro (Weiss, 1989), though the effectiveness of this combination has not been reported in cats.

Topical administration of interferon has been used for herpetic keratitis in humans (McLeish et al., 1990; Sundmacher et al., 1978, 1987). Good results were achieved when topical trifluridine was combined with high-titer (30 million IU/mL) α- or γ-interferon given once daily or with moderate-titer (2 × 0.3 million IU/mL) mixtures of the two interferons (Sundmacher et al., 1987). Patients were treated for only 3–4 days with interferon. Interferon has no effect on infected cells, but it may prevent healthy cells from becoming infected, thus shortening the course of disease (Missetten, 1994). Recently, α-interferon was shown not to have cytotoxic effects on feline corneal epithelial cells at concentrations ranging from 10² to 10⁴ IU/mL (Sandmeyer et al., 2005b). In the same study, α-interferon, at a concentration of 10³ IU/mL, significantly reduced FHV-1 titers and the viral-induced cytopathic changes in cultured corneal epithelial cells.

Treatment with oral lysine has been of some benefit among humans in accelerating recovery from herpes simplex infection and in suppressing recurrence (Griffith et al., 1978). An in vitro study has shown lysine to be effective at reducing FHV-1 synthesis, in conjunction with low arginine levels, by antagonizing the availability of arginine, an essential amino acid used for viral synthesis (Maggs et al., 2000). Recent clinical studies reveal that oral lysine is safe (Fascetti et al., 2004), and reduces both the severity of conjunctivitis in cats with primary FHV-1 infection (Stiles et al., 2002) and the ocular viral shedding rate in FHV-1 latently infected cats (Maggs et al., 2003). Recently, a study evaluated the effect of dietary lysine supplementation fed to 261 adult cats housed in an animal shelter for 4 weeks (Drazenovich et al., 2009); this study revealed that cats fed the lysine-supplemented diet (5.7% dietary lysine compared with controls fed 1.7% dietary lysine) had increased severity of FHV-1 disease and increased detection of FHV-1 DNA at given time periods throughout the study (Drazenovich et al., 2009). Despite this varying information regarding lysine and its effectiveness in cats with FHV-1, there are no current studies evaluating its effectiveness in client-owned cats (Maggs, 2010). Current recommendations for lysine administration in cats are 500 mg as a bolus PO twice daily (not as a dietary supplement) (Maggs, 2010): (1) during active FHV-1 disease and (2) as a long-term prophylactic treatment in cats with chronic recurrent herpes viral episodes. For a review regarding antiviral therapy for FHV-1, the reader is referred to Maggs (2010).

**Feline Immunodeficiency Virus**

FIV is a lentivirus. The transmission of FIV is most likely via bites between animals (Pedersen et al., 1989). However, FIV has been detected in semen from acutely and chronically infected male cats, indicating that FIV may also potentially be transmitted to queens via infected semen (Jordan et al., 1995, 1999). Earlier in the course of disease, FIV infection results in progressive loss of CD4⁺ T-helper cells, followed by depletion of CD8⁺ T cells in the advanced stages of the disease (English et al., 1994). FIV was first reported in 1987 (Pedersen et al., 1987) and has subsequently been related to a number of diseases in cats, including ocular manifestations. The virus causes ocular lesions via (1) direct damage of ocular tissues, (2) inciting secondary immune phenomena, and/or (3) by promoting opportunistic ocular infections (English et al., 1994). In one experimental study, 3 of 20 cats developed anterior uveitis and conjunctivitis after infection with FIV (Callanan et al., 1992). In a study of nine cats with naturally occurring FIV infection, all cats had ocular disease, with anterior uveitis being the most frequent clinical diagnosis (English et al., 1990). In addition, pars planitis was seen in four of these nine cats, being evidenced by anterior vitreal, white infiltrates presumed to be inflammatory cells. In a retrospective study of cats with lens luxations, FIV infection was diagnosed in tested cases more often than any other infectious disease (Olivero et al., 1991). A nother report, using PCR, did not detect FIV in any of 36 formalin-fixed, uveal melanomas, suggesting that FIV does not appear to play a role in naturally occurring feline uveal melanomas (Stiles et al., 1999).

Correlations have been made between FIV and seropositivity for toxoplasmosis. Positive serum antibody titers for toxoplasmosis have been found more frequently in FIV-positive cats than in FIV-negative cats (O’Neil et al., 1991; Witt et al., 1989). In a study of 54 clinically ill cats seropositive for antibody to FIV, 19 had ocular disease, and 76% of these 19 were also positive for T. gondii-specific serum antibodies. Anterior uveitis and chorioretinitis were the most common ocular findings (O’Neil et al., 1991). Of cats coinfected with both FIV and T. gondii, 43% had positive T. gondii-specific IgM serum antibody titers without a positive T. gondii-specific IgG titer, thus emphasizing the need for a laboratory test that includes both classes of antibody.

The diagnosis of FIV infection has depended on the use of positive antibody results in ELISA, Western blot, or IFA tests (Levy et al., 2004). This has made it difficult to reliably assess the FIV infection status of cats using current serological tests because the antibodies produced in response to vaccination against FIV are indistinguishable from those used to diagnose FIV infection (Levy et al., 2004). As a result, various PCR...
assays have been developed for the diagnosis of FIV infection (Steinrigl & Klein, 2003; Uhl et al., 2002). Unfortunately, currently marketed PCR assays for the detection of FIV vary significantly in accuracy with sensitivities reportedly ranging from 41% to 93%, and false-positive results being higher in FIV-vaccinated than unvaccinated cats (Crawford et al., 2005).

Treatment of uveitis in cats with both FIV and toxoplasmosis should be the same as that for toxoplasmosis. Cats with uveitis associated only with FIV, however, should be treated with a topical corticosteroid, such as prednisolone acetate 1%, and atropine 1% (as the uveitis dictates). Some cats may also benefit from oral prednisolone, and long-term use of topical prednisolone acetate may be needed to control the anterior uveitis. Response of pars planitis to oral and topical prednisolone, however, is often poor.

**Feline Leukemia Virus**

FeLV is a retrovirus that replicates in many epithelial tissues. Transmission of FeLV is primarily through saliva. FeLV infection eventually results in malignant transformation or cytopathic depletion of specific lymphocytic/hematopoietic cell lines (Onions et al., 1982; Rojko et al., 1979). Infection with FeLV appears to cause little in the way of ocular disease, with primarily the exception of its role in lymphosarcoma (Brightman et al., 1991). The uveal tract is a common site for metastasis of neoplastic lymphocytes, probably via hematogenous spread. Cats with ocular lymphosarcoma may present initially with signs of mild uveitis, including miosis, aqueous flare and keratic precipitates, or subtle iridal masses. As the disease progresses, the iris becomes greatly thickened and distorted with the infiltration of tumor cells (Fig. 35.2.22), and glaucoma is a common sequela as tumor cells infiltrate the irido-corneal angle (Corcoran et al., 1995). In association with neoplastic invasion of the anterior uvea, iris motility becomes restricted (Willis, 2000). Aqueous centesis may be helpful in establishing the diagnosis, because neoplastic lymphocytes exfoliate into the aqueous humor.

Anisocoria or dyscoria may also arise due to neurological effects of FeLV on the ciliary ganglia and short ciliary nerves of affected cats. In particular, spastic pupil syndrome, involving a static anisocoria during dark adaptation, has been reported in FeLV-positive cats. Anisocoria may have been noted by the patient’s owner over time, alternating with periods of normal pupil behavior. Other ophthalmic abnormalities are absent, however, and vision is unaffected. These cats are positive for FeLV but may have no other clinical signs when the anisocoria is noted (Brightman et al., 1977; Scagliotti, 1980). C-type viral particles have been identified in the ciliary ganglia and short ciliary nerves of these cats, however, which is suggestive that the leukemia virus has invaded these nerves. The prognosis for long-term survival in these cats is poor.

In one experimental study, kittens were infected with FeLV either systemically in utero or intraocularly on the day after birth (Albert et al., 1977). The most consistent ocular abnormalities with both routes of infection were retinal dysplasia and diffuse uveitis. One kitten developed an intraocular neoplasm of probable retinal origin. FeLV may also induce anemia, which could result in secondary retinal hemorrhages (Brightman et al., 1991; Fischer, 1970).

Recent studies have investigated the role of FeLV/feline sarcoma virus (FeSV) in the tumorigenesis of feline uveal melanomas and ocular sarcomas (Cullen et al., 1998, 2002; Stiles et al., 1999). Two studies reported a lack of detection of FeLV/FeSV in either intraocular tumor type based on negative immunohistochemical staining for FeLV gp 70 and negative PCR results of formalin-fixed, paraffin-embedded tissue samples (Cullen et al., 1998, 2002). A nother report, using nPCR, detected FeLV/FeSV in 3 of 36 formalin-fixed, uveal melanomas, suggesting a possible link between FeLV/FeSV and certain naturally occurring feline uveal melanomas (Stiles et al., 1999). FeLV antigens and proviral DNA have also been detected in normal corneal tissues from FeLV-infected cats, suggesting the importance of screening potential feline corneal donors for FeLV (Herring et al., 2001).

**Feline Panleukopenia Virus**

FPV is a parvovirus. Transmission of FPV occurs most commonly by direct contact with infected cats or their excretions (e.g., feces, urine, saliva, and vomitus). Fleas may also transmit FPV from infected to susceptible cats. As well, the virus may be spread by contact with fomites, such as food bowls, litter pans, bedding, and cages. Kittens infected with FPV during gestation or shortly after birth develop cerebellar hypoplasia and retinal dysplasia (Csiza et al., 1971; Kilham et al., 1967, 1971; Percy et al., 1975; Schatzberg et al., 2003). Mesencephalic aqueductal stenosis has been reported in kittens following transplacental infection with FPV (Csiza et al.,

The cerebellar disease becomes apparent at approximately 3–4 weeks of age (i.e., when the kittens begin walking). Hypermetria and ataxia are apparent as well. Retinal dysplasia, which is characterized by thinning of neural tissue, loss of normal architecture, and rosette formation, has also been reported in a naturally infected kitten (Percy et al., 1975).

**Feline Sarcoma Virus**

FeSV is a naturally occurring, replication-defective, acute, transforming FeLV that has incorporated one of several cellular oncogenes (Cullen et al., 1998). These viruses can be transmitted either horizontally or vertically, and they can cause spontaneous tumors in cats (Essex, 1975; Shelton et al., 1990a). In experimental models, injection of the virus into the feline anterior chamber has resulted in the formation of malignant uveal melanomas (Albert et al., 1981; Shadduck et al., 1981). In structure, these melanoma cells have been spindle-shaped and epithelioid, much like naturally occurring feline uveal melanomas (Albert et al., 1981; Niederkorn et al., 1981; Shadduck et al., 1981). In one study, enucleation of eyes with melanomas induced by FeSV resulted in a high percentage of cats developing secondary tumors (Niederkorn et al., 1982). This finding was interpreted to result from local transformation of virus shed from the intraocular neoplasm, not from metastases. In cats that developed uveal melanomas, production of antibodies against feline oncornavirus-associated cell membrane antigen was much higher in cats with nonprogressive lesions than in those with progressive melanomas (Niederkorn et al., 1981). Subcutaneous injection of FeSV leads to fulminant anterior uveitis in cats (Lubin et al., 1983), and limbal fibrosarcomas have also been produced at the site of such injection (Shadduck et al., 1981). The role of FeSV in naturally occurring feline uveitis is unknown. Recent studies have, however, investigated the role of FeLV/FeSV in the tumorigenesis of naturally occurring feline uveal melanomas and ocular sarcomas (Cullen et al., 1998, 2002; Stiles et al., 1999). Two studies reported a lack of detection of FeLV/FeSV in either intraocular tumor type based on negative immunohistochemical staining for FeLV gp 70 and negative PCR results of formalin-fixed, paraffin-embedded tissue samples (Cullen et al., 1998, 2002). A further report, using nPCR, detected FeLV/FeSV in 3 of 36 formalin-fixed, uveal melanomas, suggesting a possible link between FeLV/FeSV and certain naturally occurring feline uveal melanomas (Stiles et al., 1999).

**Rabies**

Rabies continues to be one of the most feared zoonotic diseases in the world. Rabies, a bullet-shaped RNA virus, is a lyssavirus in the family Rhabdoviridae (Woldehiwet, 2002). Transmission of rabies occurs via a bite by a rabid animal, although infections through aerosols have been documented (Constantine, 1966; Winkler et al., 1973). The virus can infect any warm-blooded animals, with dogs and cats being the main vectors of human infection (Woldehiwet, 2005). Clinically, rabies infection can be divided into three phases: (1) prodromal, (2) furious, and (3) paralytic phases (Bedford, 1976). In its early stages, rabies in cats can be difficult to diagnose. In one study, the main signs of rabies in cats reported by veterinarians included changes in behavior, gait abnormality, wound or injury within the past 6 months, and an unusual look in the eyes, while the most frequently reported signs by owners included aggressiveness, gait abnormality, and, once again, an unusual look in the eyes (Fogelman et al., 1993). Although the unusual expression in the eyes was not further characterized in this study, it may have arisen due to alterations in pupil size (i.e., mydriasis) from rabies-induced neurologic dysfunction. The reader is referred to current internal medicine textbooks for a detailed discussion on rabies.

**Metabolic Diseases**

**Diabetes Mellitus**

Diabetes mellitus is a relatively common endocrine disorder of cats. It has been estimated that 1 in 400 cats are affected by diabetes mellitus (Panciera et al., 1990). Two clinically recognized forms of diabetes mellitus exist in cats: insulin-dependent diabetes mellitus (IDDM)—type I, and non-insulin-dependent diabetes mellitus (NIDDM)—type II. The most common form of feline diabetes mellitus is type II diabetes mellitus, although many cats are insulin dependent upon initial diagnosis (Rand & Marshall, 2005). Results of a recent study suggest that up to nearly 2/3 of cats with diabetes mellitus may have type II form of the disease (Bennett et al., 2005). The cause of diabetes mellitus in cats is multifactorial.

The most common ocular manifestation of diabetes mellitus in dogs is cataract formation (Basher & Roberts, 1995; Ling et al., 1997). Diabetic cataract formation varies with the species affected, individual, age of disease onset, duration of the diabetes, and severity of hyperglycemia. The young dog is very susceptible, and the cat resistant, to diabetic cataract formation (Wyman et al., 1988). Cataracts were present at the initial examination of almost 60% of spontaneous canine diabetics, whereas no cataracts were noted in a series of 30 cats (Ling et al., 1977; Schaer, 1977). Aldose reductase plays a role in the formation of cataracts when glucose levels are elevated in diabetes mellitus. One of the reasons for variations in susceptibility among species, ages, and individuals to diabetic cataracts is the lenticular activity of aldose reductase (Engerman et al., 1982). Older cats are not susceptible to diabetic cataracts since the level of intralenticular aldose reductase is low in comparison to that of dogs (Richter et al., 2002). Younger cats (<4 years of age) do, however, have elevated levels of aldose reductase in their lenses (Richter et al., 2002), but since diabetes mellitus is rarely reported in younger cats, feline diabetic cataracts are uncommon (Thoresen et al., 2002). One case of diabetes mellitus and related secondary bilateral nuclear and cortical cataracts has been reported in a kitten (Fig. 35.2.23A, B) (Thoresen et al., 2002).
Diabetic retinopathy has been described in two cats that developed diabetes mellitus following long-term treatment with megestrol acetate for dermatologic disease (Thoresen et al., 2002). Both cats had bilateral retinal hemorrhage and retinal detachment, and in one cat, microaneurysms were seen. Cessation of the drug resulted in the resolution of the retinal hemorrhages, but the cats were blind because of retinal detachment, retinal degeneration, or cataract. The role that systemic hypertension may have played was not addressed. Systolic blood pressure was measured in 14 diabetic cats. None of these cats had evidence of hypertensive retinopathy, and systolic blood pressures were all <180 mmHg, suggesting that hypertension does not occur or rarely occurs in cats with diabetes mellitus (Sennello et al., 2003).

Hyperthyroidism

Hyperthyroidism is the most common endocrine disease of cats. Feline hyperthyroidism usually develops as a result of functional adenomatous hyperplasia, or less commonly adenoma, of one or both thyroid lobules. Hyperthyroidism causes systemic hypertension in cats (Kobayashi et al., 1990), which in turn, causes hypertensive retinopathy (see the “Hypertension” section) (Maggio et al., 2000; van der Woerdt & Peterson, 2000). In one study, only 1 of 13 hyperthyroid cats had ocular disease as evidenced by retinal arterial tortuosity and focal retinal degeneration (Stiles et al., 1994). Retinal hemorrhages and retinal detachment have also been reported in hyperthyroid cats secondary to systemic hypertension (Littman, 1994; Sansom et al., 1994). One retrospective study reported active retinal lesions in five eyes of only 3 of 100 hyperthyroid cats (van der Woerdt & Peterson, 2000). Another study described hyphema in 1 of 25 hyperthyroid cats, but complete ophthalmic examinations were not performed in these cases (Bucknell, 2000). As well, neither of these two particular studies evaluated systemic blood pressure in the affected cats (Bucknell, 2000; van der Woerdt & Peterson, 2000). The reader is referred to current internal medicine textbooks for further details regarding feline hyperthyroidism.

Ionic Disturbances

Hypocalcemia

Hypocalcemia in cats may be caused by several conditions including hypoparathyroidism, postparturient hypocalcemia, acute or chronic renal failure, acute pancreatitis, vitamin D toxicity, severe nutritional secondary hyperparathyroidism, and following surgical thyroidectomy, among others (for a review, see Dhupa & Proulx, 1998). Neurologic signs of restlessness, muscle fasciculations, and tonic-clonic seizures occur with a total serum calcium level of 6–7 mg/dL or a serum ionized calcium level of less than 2.5 mg/dL. The cause of the hypocalcemia can be determined using a combination...
Hypocalcemia in cats has been documented clinically to be associated with focal punctate to linear opacities in the anterior and posterior cortices of the lens (Bassett, 1998; Stiles, 1991). The lenticular opacities may occur at different levels in the cortex, and they may reflect different episodes of hypocalcemia. The degree and duration of hypocalcemia necessary to produce cataracts is unknown, but the characteristic appearance of the cataracts is quite suggestive of hypocalcemia.

Treatment of hypocalcemia involves correction of the underlying disease, if possible, and calcium supplementation with vitamins D₂, D₃, or dihydrotachysterol. A dditional focal cataracts may manifest for a period after correction of the hypocalcemia, and the existing lenticular opacities will remain.

Neoplasia: CNS

Blindness associated with intracranial neoplasia has been reported in cats (Davidson et al., 1991a; Dunihoo et al., 2000; Gordon et al., 1994; Nafe, 1979; Sant’An a et al., 2002; Troxel et al., 2003). In one study, an acutely blind, 12-year-old cat with afferent pupillary deficits was found to have a pituitary carcinoma that encroached on the optic chiasm (Davidson et al., 1991a). In a series of 36 cats with meningiomas, blindness or visual field deficits were found in 7 (Nafe, 1979). Six of these seven cats had unilateral visual deficits, whereas the remaining cat was completely blind, with dilated pupils from compression of the optic chiasm by a third ventricle meningioma. Six cats also had positional nystagmus, and one cat with tentorial herniation had anisocoria, with the smaller pupil being contralateral to the tumor. It is also important to keep in mind that cranial nerve disturbances will also be apparent with some cases of feline intracranial neoplasia.

Neoplasia: Systemic

Lymphosarcoma

Only a few reports of feline systemic neoplasia with ocular metastases have appeared in the literature. The most common disease of this nature is probably lymphosarcoma (Carlton, 1976; Corcoran et al., 1995; Davidson et al., 1991b; Menicke, 1966; Peiffer & Wilcock, 1991). In a retrospective study of 49 cats with lymphosarcoma confirmed at histopathology, ocular manifestations of disease preceded systemic disease in most cases (Corcoran et al., 1995). The uveal tract was involved in all eyes, and nodular iris lesions were the most common manifestation, being present in 35 of 50 eyes. Seventeen of these cats were tested for FeLV, and seven were positive. Survival ranged from 0 days to 31 months, with a mean survival of 14 months. A ggressive treatment of cats with ocular lymphosarcoma using topical corticosteroids, such as 1% prednisolone acetate, as well as using systemic therapy with corticosteriods or other chemotherapeutic protocols, is indicated.

Other: Metastases

A denocarcinomas have been reported to metastasize to the feline eye, with the site of origin being the lungs (Gionfriddo et al., 1990), mammary tissue (West et al., 1979), uterus (Bellhorn, 1972; O’Rourke & Geib, 1970), and disseminated adenocarcinoma of undetermined origin (Murphy et al., 1989a). Four cases of feline pulmonary carcinoma have been reported to metastasize to the posterior segment of the eye (Cassotis et al., 1999). A case of a soft-tissue fibrosarcoma with widespread metastasis including the eye has been reported as well (Fulton et al., 1991). One retrospective study reported 55 cases of extraskeletal osteosarcoma (ESOS), 4 of which were orbital (Heldmann et al., 2000). Forty-five of the 55 cases (80%) were also detected in subcutaneous sites, 54% of which were consistent with sites used for vaccination. Squamous cell carcinoma has also been reported to invade intraocular structures, either by direct extension from the head (Hayden, 1976; M urphy et al., 1989b) or via hematogenous spread (Cook et al., 1984; Hamilton et al., 1984) from a more distant site. Plasmacytomas may also invade the orbit and globe. One report described a plasma cell tumor of the orbit in a cat that had originated from the masticatory muscle (Ward et al., 1997). Another study reported an extramedullary plasmacytoma in the iris and ipsilateral mandibular lymph node; however, no other evidence of disseminated disease was noted in this cat (Michau et al., 2003). As well, ocular manifestations of multiple myeloma in cats are reported and include intraocular hemorrhage (two of nine cats) (Hanna, 2005), and ocular lesions associated with associated hyperviscosity syndrome such as retinal hemorrhages, dilated and tortuous retinal vessels, retinal detachment, perivascular effusion, papilledema, and retinal degeneration (Forrester et al., 1992; Hawkins et al., 1986; Hribernik et al., 1982; Lane et al., 1993) (see the “Hyperviscosity Syndrome” section).

Nutritional Disorders

Milk Replacer-Induced Disease

Cataracts have been reported in growing kittens fed a commercial milk-replacer diet (Remillard et al., 1993). The low serum arginine concentration in these kittens was thought to relate to the diet and, possibly, to the cataract formation. A study of growing kittens documented cataract development in kittens fed diets containing less than 3.0g of histidine per kilogram of body weight (Quam et al., 1987).

Taurine Deficiency

Feline central retinal degeneration (FCRD) was first described by Bellhorn et al. in 1970 and 1974. The lesion was characterized as a focus of outer retinal layer degeneration in the area centralis. A few years later, taurine-deficiency retinopathy was
Taurine is essential for photoreceptor survival, and it is highly concentrated in the inner and outer segments. Possible functions of taurine in the retina include protection of the photoreceptors from light and chemical damage, regulation of calcium ion transport, and regulation of signal transduction (Militante & Lombardini, 2002, 2003a, 2003b, 2004; Lombardini 1991). Ultrastructural studies of the taurine-deficient feline retina show initial disorganization and vesiculation of rod and cone outer segment lamellar disks in the area centralis (Hayes et al., 1975b). Subsequent loss of outer segments and photoreceptor nuclei occurs in the area centralis as well as in the midperipheral retina. Electroretinographic findings are of progressive loss of rod and cone amplitudes and a delay in the temporal aspects of the cone response. The early receptor potential is preserved, however, even when the a- and b-waves are substantially reduced (Berson et al., 1981; Hayes et al., 1975b). In cats with minimal to moderate degeneration, supplementation with taurine returned both rod structure and rod function to normal, whereas some abnormalities of cone structure and cone function remained.

A cause for the geographic distribution of the lesion in taurine-deficiency retinopathy has not been definitively elucidated. Early work suggested that the lesions followed cone cell distribution (Bellhorn et al., 1974). There is evidence that cones are preferentially damaged in the area centralis during the early stage of disease (Hayes et al., 1975b), but there is no evidence for a band of cone cell density in the horizontal streak, where lesions are seen during a later stage (Leon et al., 1995). Areas containing the highest retinal concentrations of the visual pigment rhodopsin in cats have a similar distribution to the areas that preferentially degenerate (Jacobson et al., 1987). Rhodopsin has been documented to diminish following this pattern in taurine-deficient cats, and this has been suggested to cause the characteristic geographic lesion. This theory, which involves preferential light damage to areas of high rhodopsin concentration, was not supported in one study, however, in which unilateral tarsothromaphy of taurine-deficient cats still resulted in characteristic lesions (Leon et al., 1995).

Cats with area centralis lesions have demonstrable deficits in visual acuity (Blake & Bellhorn, 1978), but in a normal home environment, these cats usually do not have discernible problems. The finding of an area centralis lesion does not indicate current taurine deficiency, because the lesions will remain for the life of the cat. Measurement of plasma taurine levels is the best way to determine a deficient animal. Plasma levels of 20 nmol/mL are critically low; to be safe, cats with values of less than 40 nmol/mL should be switched to a different diet, one that is known to support higher plasma taurine levels (Pion & Kittleson, 1990). Because commercial cat foods today contain much more taurine than they did 10 years ago, active cases of taurine deficiency are likely to occur in cats fed inappropriate diets or in those with intestinal diseases that alter proper nutrient absorption. A recent study documented that the dietary requirement for taurine in cats is dependent on dietary protein concentration and quality.
(Backus et al., 1998). Increasing the dietary protein concentration increases the need for taurine, as does a reduction in protein quality.

**Thiamine Deficiency**

Thiamine deficiency may occur in cats eating large amounts of raw fish, which contains thiaminases, or in cats eating processed commercial foods in which thiamine has been destroyed by heat processing and not replaced adequately. Thiamine deficiency also has been reported in cats being fed commercial food containing sulfur dioxide as a food preservative (Malik & Sibraa, 2005; Steel, 1997; Studdert & Labuc, 1991). Furthermore, cats with severe gastrointestinal disease may not absorb sufficient amounts of thiamine. Clinical signs of thiamine deficiency include initial inappetence and occasional vomiting, followed by pupillary dilatation without visual deficits, ataxia, and ventroflexion of the head and neck (Davidson, 1992; Loew et al., 1970; Martin, 1971). A final and irreversible stage of thiamine deficiency is characterized by a progression of clinical signs culminating to a semicoma state, which is characterized by crying, opisthotonos, and extensor rigidity.

The diagnosis can be made on the basis of dietary history, clinical signs, and measurement of thiamine concentration in food as well as in blood. Normal blood thiamine levels for cats are approximately 32 µg/dL. Before the development of a comatose state, cats will respond favorably to parenterally administered vitamin B complex preparations containing 50–75 mg of thiamine per dose every 8 hours. Alimentation should be provided via a nasogastric or gastroscopy tube. Improvement is usually seen within 3 days, though ataxia may be present for 2 weeks. Once the cat is eating, oral vitamin supplementation can be instituted, and the diet should be corrected to include an adequate thiamine intake.

**Systemic Toxicities**

**Antimicrobials**

Fluoroquinolones

Enrofloxacin, a fluoroquinolone antibiotic, has been associated with a rare adverse ophthalmic reaction causing an acute, typically irreversible, retinal degeneration in cats (Gelatt et al., 2001; Giuliano & van der Woerd, 1999; Grahn et al., 2002; Wiebe & Hamilton, 2002). In addition, this reaction has reportedly been seen with other fluoroquinolones including marbofloxacin and orbifloxacin (Ramirez et al., 2011).

Affected cats develop signs of partial, temporary, or total blindness. The reported estimated incidence of this adverse reaction is 1 in 122,414 treated cats or 0.0008% (Wiebe & Hamilton, 2002). The association of enrofloxacin, retinal degeneration, and blindness in cats was first described in a retrospective study in which 5 of 26 cats with diffuse retinal degeneration had received oral enrofloxacin (Giuliano & van der Woerd, 1999). Subsequently, another retrospective study documented the association between enrofloxacin administration and the acute onset of retinal degeneration in 17 cats (Gelatt et al., 2001). All cats were domestic shorthair breed with ages ranging from 3 to 16 years old. All affected cats had variable medical ailments for which enrofloxacin was administered including lymphoma and pancreaticitis, otitis, urinary tract disorders, dermatitis, bowel perforation, diarrhea, and upper respiratory infection. The daily enrofloxacin dosages these cats received were highly variable ranging from 4.6 mg/kg PO once daily to 27 mg/kg PO twice daily. Cats in this study generally presented with signs of mydriasis and acute blindness. All cats had generalized retinal degeneration, and vision only returned in a few cases (Fig. 35.2.25A–C). Five of 17 affected cats underwent electroretinography, which revealed no observable responses in any case. Histological assessment of two affected globes showed mainly outer retinal degeneration as evidenced by a diffuse loss of the photoreceptor and outer nuclear layers, and hypertrophy and proliferation of the RPE. Given the findings in this study, the adverse retinal reaction to enrofloxacin in cats appears to be a rare, idiosyncratic reaction. A adherence to the manufacturer’s current recommendation for enrofloxacin dosage in cats of 5 mg/kg PO q 24 hours is advisable. It is, however, unclear as to whether a dosage of 5 mg/kg PO q 24 hours is safe in geriatric cats, especially those with renal or hepatic dysfunction, as safety studies performed by the manufacturer were conducted in young healthy cats (Wiebe & Hamilton, 2002).

Safety studies evaluating the incidence of retinal degeneration with orbifloxacin, another veterinary-labeled fluoroquinolone, revealed a dose- and concentration-dependent adverse ophthalmic reaction, with cats receiving higher doses of the medication developing focal retinal degeneration (Kay-Mugford et al., 2001). Safety studies conducted on marbofloxacin, another veterinary-approved fluoroquinolone, did not demonstrate any ocular lesions following oral administration of up to 20 times the minimum recommended daily dosage. Nonetheless, the manufacturer of marbofloxacin indicates that it is a prudent precaution to consider that all fluoroquinolones may have the potential to induce feline ocular lesions; therefore, all fluoroquinolones should be used with caution in this species (Wiebe & Hamilton, 2002).

 Recently, it has been shown that cats have four specific amino acid sequence differences in P-glycoprotein, ABCG2, in comparison to that of other mammals (Ramirez et al., 2011). A BCGB2 is a member of the ATP-binding cassette superfamily of proteins and is located in a variety of tissues including the endothelium comprising the blood-retinal barrier. These proteins transport a variety of molecules, including fluoroquinolones, across cell membranes. As such, this protein acts to regulate the concentration of drugs, such as the fluoroquinolones, within the retina. Fluoroquinolones produce reactive oxygen species when exposed to light. When HEK-293 cells are modified to contain either (1) no ABCG2, (2) human-specific ABCG2, or (3) feline-specific ABCG2, and are subsequently exposed to ultraviolet light, 50% of cells not containing ABCG2 die when exposed to 1–10 µmol/L of enrofloxacin, 50% of cells with feline-specific ABCG2 will
Figure 35.2.25. Acute retinal degeneration in a 15-year-old, male castrated cat after 196 days of enrofloxacin administration. (A) Tapetal changes characterized by loss of retinal vessels, focal increased tapetal reflectivity, and large gold- to rust-colored foci scattered throughout the tapetal fundus. (B) Pigment loss and clumping within the nontapetal fundus. (Reproduced with permission from Gelatt, K.N., van der Woerdt, A., Ketring, K.L., Andrew, S.E., Brooks, D.E., Biros, D.J., Denis, H.M. & Cutler, T.J. (2001) Enrofloxacin-associated retinal degeneration in cats. Veterinary Ophthalmology, 4, 99–106.) (C) Fundus photograph from a mature domestic shorthair cat following 5 days of enrofloxacin therapy. Note the tapetal granularity, focal tapetal hyperreflectivity, and moderate generalized retinal vessel attenuation.

die when exposed to 10 µmol/L enrofloxacin, and 50% of cells with human ABCG2 will die when exposed to 50 µmol/L enrofloxacin (Ramirez et al., 2011). These results demonstrate that feline-specific ABCG2 is ultimately ineffective at transporting enrofloxacin from within the cells, thus likely explaining the fluoroquinolone-related retinal toxicity described clinically in cats.

Current recommendations to help decrease the risk of retinal degeneration in some cats receiving enrofloxacin include (1) using split dosing (i.e., 2.5 mg/kg PO q 12 hours) on exact body weight; (2) avoidance of rapid intravenous infusions of the drug and drug interactions; and (3) avoidance of ultraviolet (UV) light during active treatment may also be beneficial. Owners of cats receiving parenteral fluoroquinolone therapy should be instructed to monitor their cats for mydriasis and to consult their veterinarian immediately should this sign develop. The pharmacokinetics of parenteral enrofloxacin in neonatal kittens compared with the pharmacokinetics of this medication in young and adult cats have been reported (Seguin et al., 2004). Ophthalmic examinations were not conducted on animals in this study, however.

Griseofulvin
Griseofulvin is a fungistatic agent used in cats to treat dermatophytosis. Griseofulvin is teratogenic in cats. Ocular anomalies reported in affected offspring of cats having received griseofulvin in the first half of gestation include cyclopia, anophthalmia, optic nerve aplasia, and rudimentary optic
tracts (Scott et al., 1975). M esencephalic aqueductal stenosis has also been reported in kittens following in utero exposure to griseofulvin (Scott et al., 1975). Other widespread malformations also accompany the ocular abnormalities. One adult cat was thought to have retinal degeneration secondary to griseofulvin toxicity (Rottman et al., 1991).

Ivermectin

Ivermectin is a broad-spectrum anthelmintic that has been used in cats for the treatment of ear mites and notoedric mange. Ivermectin toxicosis has been reported mainly in kittens, but this also occurs in adult cats. Signs of toxicosis typically become apparent within 1–12 hours of administration of the ivermectin and include altered behavior, lethargy, weakness, ataxia, recumbency, coma, and death (Lewis et al., 1994). Ocular manifestations of feline ivermectin toxicosis include apparent blindness, and alterations in pupil size including mydriasis and miosis (Houston, 1985; Lewis et al., 1994; Rowley, 1988; Tudury & Lorenzoni, 1987).

Ethylene Glycol

Ethylene glycol intoxication is a common cause of poisoning in small animals, including cats. The lethal dose of 95% ethylene glycol in cats is 1.4 mL/kg. A single report in the literature describes a cat with acute renal failure secondary to ethylene glycol intoxication (Barclay & Riis, 1979). This cat developed bilateral retinal detachments and edema, which was thought (but not confirmed) to be secondary to oxalate crystals within the retina. Systemic blood pressure was not evaluated in this cat, and hypertension may have contributed to the retinal disease.

Ionizing Radiation

The ocular effects of ionizing radiation are similar no matter the source (see “Ionizing Radiation” in “Part 1: The Dog”). Both the ocular effect(s) and the time to develop ocular disease depend on the dose, age of the animal, and the species being studied. The most common source of ionizing radiation-induced ocular lesions is from radiation therapy for neoplasms of the head. Three of 16 cats undergoing irradiation for nasal or paranasal neoplasia developed chronic ocular conditions (Theon et al., 1994).

Megestrol Acetate

Megestrol acetate is a synthetic derivative of progesterone. It is generally used in the treatment of dermatologic disorders, and has been used to treat proliferative (eosinophilic) keratoconjunctivitis in cats (Bedford & Cotchin, 1983; Kunkle, 1984; Spiess et al., 1991). Two cats treated with long-term megestrol acetate for dermatologic disease developed diabetes mellitus and diabetic retinopathy (Heritage et al., 1985). Both cats had bilateral retinal hemorrhage and retinal detachment, and in one cat, microaneurysms were seen. Cessation of the drug resulted in resolution of the retinal hemorrhages, but the cats were blind because of retinal detachment, retinal degeneration, or cataract. The role that systemic hypertension may have played was not addressed.

Tissue Plasminogen Activator

Tissue plasminogen activator (tPA) is a thrombolytic enzyme available for clinical use in facilitating clot dissolution. In veterinary ophthalmology, intracameral injection of tPA is most common. However, a recent experimental study reported a dose-dependent retinal toxicity in feline eyes having received intravitreal injections of commercial tPA (Hrach et al., 2000). Specifically, eyes receiving doses of tPA greater than 50µg/0.1 mL had fundus pigmentedary changes. Electoretinography revealed diminished mean b-wave amplitudes in eyes of cats receiving ≥50µg of tPA. Histologic findings in affected globes involved regions of photoreceptor loss with necrosis and proliferation of the RPE.

Miscellaneous Diseases

Dental Disease

Varying degrees of focal chorioretinal lesions consisting of hemorrhage or exudates (or both) have been reported from bacterial infections involving organ systems including periodontitis or endodentine disease (Ramsey et al., 1996). Recently, chronic ocular discharge in the form of epiphora and mucopurulent discharge of the left eye has been described in a 10-year-old cat with severe periodontal disease and a fractured upper left canine tooth (Anthony et al., 2010). Dental radiographs revealed findings consistent with a tooth root abscess at the apex of the upper left canine tooth. Dacryocystorhinography revealed narrowing of the nasolacrimal duct above the root of the fractured upper left canine tooth. Following the removal of the fractured canine tooth, the ocular discharge was resolved. The suspected tooth root abscess reportedly resulted in extralumenal compression of the nasolacrimal duct.

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Chapter 35

Ocular Manifestations of Systemic Disease

Part 3: The Horse

Cheryl L. Cullen and Aubrey A. Webb

CONGENITAL

Coat Color-Related Diseases/Conditions

Complete albinism (complete lack of pigmentation) or partial or localized albinism (an absence or reduction in the degree of pigmentation) is associated with not only the phenotypic appearance of an animal’s coat and skin color but is also associated with conditions affecting the eye and other organ systems. Albinism or partial albinism may result from the failure of migration of neural crest cells (precursors to melanocytes) and hence result in reduced numbers of melanocytes in a nonpigmented area, or may result because of impaired production of pigment due to some intrinsic deficiency in melanin production (e.g., tyrosinase deficiency) but where the number of melanocytes in nonpigmented or hypopigmented areas is normal. In any case, albinism or partial albinism may manifest ocularly as something as benign as pale blue irides and/or subalbinotic fundi or be associated with generalized systemic disease such as lethal white foal syndrome.

Congenital Stationary Night Blindness (CSNB)

A condition long thought to be related to the incompletely dominant leopard spotting (LP) allele is congenital stationary night blindness (CSNB) in Appaloosa horses (Joyce & Witzel, 1977; Rebhun et al., 1984; Witzel, 1977; Witzel et al., 1977, 1978). The condition is nonprogressive, and affected animals that have cautious behavior in dim-light conditions may be difficult to train. Neuro-ophthalmic signs may include bilateral dorsomedial strabismus, spontaneous nystagmus, and a dark-adapted electroretinogram lacking a b-wave (Sandmeyer et al., 2007, 2012).

Congenital stationary night blindness has been reported in a variety of breeds of horses including Appaloosa, Miniature Horse, Thoroughbred, and Paso Fino (Nunnery et al., 2005; Rebhun et al., 1984; Sandmeyer et al., 2007, 2012; Witzel, 1977; Witzel et al., 1977). Recognizing, of course, CSNB is most commonly documented in breeds with the LP allele (Sandmeyer et al., 2007, 2012). Specifically, it has been shown that of the cases of CSNB occurring in breeds with the LP allele, CSNB is only found in those animals homozygous for LP (i.e., LP/LP) (Sandmeyer et al., 2007, 2012). Animals with LP are characterized along a spectrum of white patterning (very little white patterning to significant white patterning) (as discussed in Webb & Cullen, 2010). In heterozygous animals (LP/lp), there is typically more “spotting” within the white-patterned regions of the body. Animals homozygous for LP (LP/LP) typically have little to no spotting in the areas of white patterning.

It has been shown, phenotypically, that animals homozygous for LP, but not heterozygous (LP/lp) or noncarriers (lp/lp), are affected by CSNB (Sandmeyer et al., 2007, 2012). Additionally, decreased expression of transient receptor potential cation channel member 1 (TRPM1) gene in the skin and retina has been described in horses homozygote for LP and having CSNB (Bellone et al., 2008). Recently, three single nucleotide polymorphisms (SNPs) have been identified as completely associating with CSNB and LP (Bellone et al., 2010). Though the causative mutation for CSNB and LP is presently unknown, these SNPs can be used as a genetic test for CSNB and LP (Bellone et al., 2010).

Lethal White Foal Syndrome (Lethal White Overo Syndrome)

In horses, coat color is oftentimes associated with iris color and heterochromia iridis. For example, it is not uncommon to see Paint horses with one blue eye and one darkly pigmented eye or with two blue eyes. A condition known as lethal white foal syndrome (an equine model of Hirschsprung Disease in humans) is seen in white, typically blue-eyed foals with typically two overo-colored parents (McCabe et al., 1990;
Trommershausen-Smith, 1977; Vonderfecht et al., 1983). In this instance, these foals are born with two copies (homozygous) of a mutated endothelin-B receptor gene (Metallinos et al., 1998; Santschi et al., 1998; Yang et al., 1998). Endothelin-3, a ligand for the endothelin-B receptor, is a signaling molecule important in the maturation and migration of neural crest cells (McCallion & Chakravarti, 2001). Neural crest cells are precursors to melanocytes and neurons in the peripheral nervous (including enteric) systems. In addition, neural crest cells also migrate to the inner ear and are important in maintenance of normal hearing ability. Consequently, foals afflicted with lethal white foal syndrome are not only white with blue eyes but also have aganglionic colon resulting in gastrointestinal motility dysfunction and may also be deaf (Fig. 35.3.1 and Fig. 35.3.2) (Magdesian et al., 2009; McCabe et al., 1990; Trommershausen-Smith, 1977; Vonderfecht et al., 1983).

Lethal white foal syndrome is inherited as an autosomal recessive trait and therefore both parents of affected foals are carriers of the affected gene. Specifically, coat colors associated with heterozygotes for the endothelin receptor-B mutation include frame overo, highly white calico overo, and frame blend overo (Santschi et al., 2001). Heterozygous animals with tobiano, sabino, minimally white calico overo, splashed white overo, nonframe overo, and breeding-stock solid coat colors may also exist, however (Santschi et al., 2001). Importantly, however, not all white foals of Paint horse breeding with blue eyes will be homozygous for the endothelin-B receptor gene mutation, and consequently will not have lethal white foal syndrome. A genetic test has been developed to screen for carrier animals or to test white blue-eyed foals and thereby reduce the prevalence of this condition in the American Paint horse population and prevent the premature euthanasia of white, blue-eyed foals (Metallinos et al., 1998; Santschi et al., 1998, 2001). Genetic testing for lethal white foal syndrome is commercially available (Animal Genetics Incorporated (www.horsetesting.com/LWO.htm); Veterinary Genetics Laboratory, University of California at Davis (www.vgl.ucdavis.edu)).

Multiple Congenital Ocular Anomaly Syndrome (M COAS)

Multiple congenital ocular anomaly syndrome (M COAS) was described in Rocky Mountain Horses in 1999 (Ramsey et al., 1999a). Since this time, M COAS has been described in cross-bred Rocky Mountain Horses, Kentucky Mountain Horses, Mountain Pleasure Horse, Morgans, Belgians, American Miniature Horses, and Icelandic Horses (Andersson et al., 2008, 2011a, 2011b; Grahn et al., 2008; Komaromy et al., 2011; Plummer & Ramsey, 2011; Ramsey et al., 1999a). M COAS
exists in two phenotypes, namely, (1) cyst phenotype and (2) MCOA phenotype. Animals with the cyst phenotype have cysts arising from the ciliary body, peripheral retina, and/or iris. These patients may also have concomitant retinal dysplasia and/or retinal detachment. Animals with the MCOA phenotype not only have all of the anomalies seen within the cyst phenotype but also have varying severity and combination of congenital cataracts, cornea globosa, iris hypoplasia, iridocorneal angle abnormalities, lens subluxation, microphthalmia, and macropalpebral fissures (Ramsey et al., 1999a, 1999b). Neuro-ophthalmic abnormalities consist of miotic pupils, abnormal pupillary light reflexes with pupils that respond poorly to pharmacologically induced mydriasis (Ramsey et al., 1999a). Affected individuals also have varying degrees of vision loss (Grahn et al., 2008; Ramsey et al., 1999a). Congenital ocular abnormalities observed in Rocky Mountain horses are, in part, related to coat color (Ramsey et al., 1999a).

Mane and tail color was found to be associated with the presence of multiple ocular abnormalities. Specifically, 45% of Rocky Mountain Horses with chocolate-colored coats with white manes and tails (Fig. 35.3.3) had multiple ocular abnormalities including megalocornea (Fig. 35.3.4), congenital miosis (Fig. 35.3.5), ciliary cysts (Fig. 35.3.6), and retinal dysplasia (Fig. 35.3.7) (Ramsey et al., 1999a). Meanwhile, only 12%, 6%, and 4% of horses with chocolate-colored coat with flaxen mane and tail, chestnut-colored coat, or some other coat color, respectively, had multiple ocular abnormalities (Ramsey et al., 1999a). Moreover, Rocky Mountain Horses with white manes and tails were more likely to have multiple ocular abnormalities compared to animals with nonwhite manes and tails (Ramsey et al., 1999a). It has been shown that a genetic mutation occurring at the Silver Dapple locus is responsible, in part, for the multiple ocular abnormalities seen in Rocky Mountain horses (Ramsey et al., 1999a).

A recent study has narrowed the MCOAS locus to 208-kb on chromosome 6 (Andersson et al., 2011b). In particular, this narrow region contains 15 genes requiring further investigation into their role in MCOAS; one of these genes is PMEL17 (gene responsible for silver coloration) (Andersson et al., 2011b).

**Griseofulvin Teratogenicity**

Griseofulvin is a commonly used antifungal agent used especially for dermatomycosis (Schutte & van den Ingh, 1997). Griseofulvin can readily cross placental membranes and has

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**Figure 35.3.3.** Photograph of a Rocky Mountain Horse with a chocolate coat color and a white mane and tail. Ophthalmic lesions appear to be more common in this breed of horse with this coat coloration. (Courtesy of D. Ramsey.)

**Figure 35.3.4.** Profile photographs of the right cornea of two age- and gender-matched Rocky Mountain Horses. A. Megalocornea is characterized by a grossly observable, excessively large corneal optical diameter with a short radius of curvature, and a notably globular contour of the cornea with atypical and excessive protrusion. B. Profile photograph of a normal cornea from an age- and gender-matched Rocky Mountain Horse. (Reprinted with permission from Ramsey, D.T., Ewart, S.L., Render, J.A., et al. (1999) Congenital ocular abnormalities of Rocky Mountain Horses. *Veterinary Ophthalmology*, 2, 47–59.)
been associated with microphthalmia, brachygnathia superior (shortened maxilla), and palatocheiloschisis (cleft lip and palate) in a foal born to a dam that was administered griseofulvin at 48 days of gestation (Schutte & van den Ingh, 1997). The foal was born without complication but was euthanized due to malformations that rendered the foal blind and unable to nourish itself. A side from the forementioned abnormalities, there was a notable absence of third eyelids. The use of griseofulvin in pregnant animals should not be advised.

**Hereditary Equine Regional Dermal Asthenia (HERDA) (Cutaneous Asthenia, Dermatosparaxis, Ehlers-Danlos Syndrome, Hyperelastosis Cutis)**

Hereditary equine regional dermal asthenia (HERDA) has been reported most commonly in purebred and partbred Quarter Horses although it has been reported sporadically in other breeds (Brounts et al., 2001; Gunson et al., 1984; Mochal et al., 2010; Solomons, 1984; White et al., 2004; Witzig et al., 1984). In Quarter Horses, HERDA is a congenital disorder of collagen inherited as an autosomal recessive trait that is char-

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**Figure 35.3.5.** A. Photograph of the eye of a Rocky Mountain Horse with congenital miosis and megalocornea. Abnormalities include a miotic pupil, stromal hypoplasia with a flattened, circumferentially oriented granula iridica at the pupillary ruff, visible sphincter pupillae muscle, an absence of a discernable collarette. Radially oriented deep stromal strands of iris tissue extend from the pupillary ruff toward the ciliary zone of the iris. B. Photograph of a normal iris of an age- and gender-matched Rocky Mountain Horse. (Reprinted with permission from Ramsey, D.T., Ewart, S.L., Render, J.A., et al. (1999) Congenital ocular abnormalities of Rocky Mountain Horses. *Veterinary Ophthalmology*, 2, 47–59.)

**Figure 35.3.6.** Photograph of the right eye of a Rocky Mountain Horse. Note the large, translucent cystic structure arising from the ciliary body. (Courtesy of D. Ramsey.)

**Figure 35.3.7.** Fundus photograph of the left eye of a Rocky Mountain Horse. Note the multiple, darkly pigmented curvilinear streaks of retinal pigment epithelium in the peripheral tapetal fundus. (Courtesy of D. Ramsey.)

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gous for the trait. Therapy for affected horses is directed at preventing skin abrasions and pressure sores (e.g., sores from tack).

**Severe Combined Immunodeficiency**

Severe combined immunodeficiency is a condition that manifests as lymphopenia (both combined B and T lymphocyte deficiency) and lack of lymphocytes in lymph nodes and the spleen, subsequent lack of immunoglobulin synthesis, and thymic hypoplasia (for a review of the condition, see Perryman, 2004). The condition is inherited as an autosomal recessive trait in purebred and partbred Arabian foals (Perryman & Torbeck, 1980), with as many as 25% of Arabian horses being carriers (Bernoco & Bailey, 1998; Poppie & McGuire, 1977; Studdert, 1978). The prevalence is estimated to be 2.3% in foals of Arabian descent. Affected foals may survive as long as 4 months provided they have developed passive immunity from ingesting the dam’s colostrum. Clinical signs include general malaise, serous to mucopurulent nasal and/or ocular discharge, coughing, diarrhea, and nonresponsiveness to antimicrobial therapy. Affected foals may have uveitis secondary to sepsis or other disseminated opportunistic pathogens. Diagnosis is made based on measuring serum immunoglobulin levels and detecting a persistent lymphopenia. Prognosis is grave. The cause of death is usually adenoviral pneumonia, other secondary infections, or both. Considering that the condition is inherited, carrier animals should be identified and culled from the breeding population.

**DEVELOPMENTAL Immunoglobulin-M Deficiency**

Deficiency of immunoglobulin (Ig) M is common in all breeds of horse, especially Arabians and Quarter Horses (for review, see Perryman, 2000). It may occur as a primary genetic disorder or as a result of immunosuppression (Crisman, 1988; Perryman et al., 1977). Most commonly, foals will present at 4–8 months of age with respiratory tract infection or enteritis. As opposed to severe combined immunodeficiency, foals with IgM deficiency will have a normal blood lymphocyte count (both B and T cells) but will have reduced or absent serum IgM concentrations. Affected foals may have uveitis resulting from this inherited immunodeficiency.

**ACQUIRED Hematologic Diseases**

**Anemia**

Anemia is the reduction in red blood cells per volume of whole blood. Anemia is classified as regenerative if there has been a normal bone marrow response to erythropoietin (e.g., usually occurs with blood loss or hemolytic disease), or...
nonregenerative if the normal reticulocyte response is lacking (e.g., may occur with chronic extra-marrow disease which reduces red blood cell survival time, selective erythropoietin depression, insufficient erythropoietin release, or a combination of these factors) (Rebar et al., 2005). Severe anemia often manifests systemically as varying pallor of mucous membranes, cool mucous membranes, tachycardia, polyneuropathy, weakness, as well as signs specific to the underlying primary condition. Conjunctival pallor is even used as an indicator of anemia due to gastrointestinal parasitism in sheep and goats (Kaplan et al., 2004; Vatta et al., 2001).

\section*{Icterus (Jaundice)}

Icterus or jaundice is a condition characterized by hyperbilirubinemia and deposition of bile pigments in the skin, sclera, and mucous membranes causing them to appear a shade of yellow. The causes of icterus in the horse are numerous and include any condition where hyperbilirubinemia results. The conjunctiva is the classic location for detection of icterus given its relative lack of pigmentation. The yellow appearance of icterus may be detected in the intraocular structures as well (e.g., blue irides may turn green, and yellow hues may be imparted on the tapetum).

\section*{Neonatal Isoerythrolysis (Alloimmune Hemolytic Anemia of Foals, Isoimmune Hemolytic Anemia of Foals)}

Neonatal isoerythrolysis is an acquired immune-mediated phenomenon observed in foals (Bailey, 1982; MacLeay, 2001; Traub-Dargatz et al., 1995). This condition is considered the most common cause of icterus in neonatal foals (Boyle et al., 2005). The condition results from the ingestion of colostrum containing antibodies directed at the antigenically distinct foal’s red blood cells (inherited from sire) (Boyle et al., 2005). The dam typically develops these antibodies following exposure to the specific red blood cell antigen during a previous pregnancy or blood transfusion or via transplacental exposure of fetal red blood cell antigen during pregnancy. Affected foals develop clinical signs following exposure to the specific red blood cell antigen during a previous pregnancy or blood transfusion or via transplacental exposure of fetal red blood cell antigen during pregnancy. Affected foals develop clinical signs including general malaise, tachypnea, tachycardia, mucous membrane pallor, and icterus (Boyle et al., 2005). Affected foals are typically less than 1 week of age (Boyle et al., 2005). Ocular signs include conjunctival pallor and jaundice, and hemorrhages affecting the conjunctiva and sclera (Lavach, 1992). Hyphema may also result (Lavach, 1992).

Diagnosis of neonatal isoerythrolysis is made based upon consistent clinical signs and hemolytic crossmatch between the dam’s serum or colostrum with the foal’s red blood cells (Becht et al., 1983). Treatment is aimed at providing supportive care and transfusing compatible blood (Boyle et al., 2005). Prognosis for recovery with appropriate medical care is considered good (Boyle et al., 2005). The owner should be made aware of the pathogenesis of the condition and instructed to not repeat the same breeding. Also, the dam should not be bred to stallions with the same incriminating red blood cell antigen.

\section*{Dystocia}

Although not a systemic disease, dystocia is related, in part, to the physical stature of the foal. A study examining the prevalence of retinal hemorrhages in Thoroughbred foals found that approximately 16% of foals had either unilateral or bilateral retinal hemorrhages occurring in the tapetal fundus or at the optic disc (Munroe, 2000). Thoroughbred foals weighing greater than 51 kg are more likely to have retinal hemorrhage than foals weighing less than 51 kg (Munroe, 2000). Furthermore, it has been shown that prolonged second-stage parturition, related to size of the foal, is associated with retinal hemorrhage in Thoroughbred foals. Various factors contributing to increased intracranial and intravenous pressures (presumably the pathophysiological phenomena responsible for congenital retinal hemorrhage) likely include the force of maternal contraction, the length of the second stage of labor, disparity between fetal and maternal size, excessive traction during assisted delivery, and the size of the foal’s cranium and/or chest (Munroe, 2000). Alternatively, ischemia (important in neonatal maladjustment syndrome) may play an important role in the pathogenesis of neonatal retinal hemorrhage (Munroe, 2000). Nevertheless, foals that acquire retinal hemorrhage due to dystocia are otherwise clinically healthy, and retinal hemorrhages resolve within 10 days (Munroe, 2000).

\section*{Idiopathic Systemic Diseases}

\subsection*{Dysautonomia (Equine Grass Sickness)}

Equine dysautonomia, commonly known as equine grass sickness, has been defined a “fatal dysautonomia of horses associated with severe neuronal damage, especially in affected autonomic ganglia” (Timoney & Wernery, 2003). The cause of equine dysautonomia remains unknown, although a variety of theories exist. Favorable hypotheses include (1) overgrowth of Clostridium botulinum type C within the gastrointestinal tract (Hunter et al., 1999; McCarthy et al., 2004) and (2) ingestion of cyanogenic producing plants (McGorum & Kirk, 2001). The highest incidence of equine dysautonomia is in Scotland but it has been reported elsewhere in Europe and in South America. In Europe, the disease is most likely to be seen between April and July in young horses kept on pastures (French et al., 2005; Newton et al., 2004).

Clinical signs associated with equine dysautonomia are related to degeneration of autonomic ganglia and the enteric nervous system including pharyngeal and esophageal dysfunction, colic, sweating, tachycardia, and dry nasal mucosa (Moline et al., 2005). The most consistent ocular manifestation of equine dysautonomia is ptosis (Hahn & Mayhew, 2000). Ptosis in equine dysautonomia may result from a primary inability to move the upper eyelid effectively or may occur secondary to abnormal globe position within the orbit (Hahn et al., 2003).
et al., 2000; Rua-Domenech et al., 1997). There is no effec-
denervation (Kyles et al., 2001; Palencia et al., 2005; Polack
similar to that seen in dogs with vitamin E deficiency (Riis
may have fundic changes characterized by a honeycomb
ophthalmic signs, horses with equine motor neuron disease
characters and weight loss. In
when standing in one position and have evidence of varying
will also frequently shift their body weight between limbs
(paresis) and lower motor neuron disease. Affected animals
disease can be observed in North America and Europe.
degeneration (Divers et al., 1997). Equine motor neuron
treated with 0.5% phenylephrine will have a
wider vertical palpebral fissure opening, as determined by
evaluating the angle of the eyelashes relative to the head
(opening of palpebral fissure in eye treated with phenyleph-
mine subtracted from the opening of palpebral fissure in eye
not treated with phenylephrine), compared with those animals
without equine dysautonomia (Hahn & Mayhew, 2000).
Definitive diagnosis of equine dysautonomia is typically made
by postmortem examination of affected ganglia and gastroin-
testinal system. Therapy is aimed at supportive and intensive
nursing care. Prognosis is poor to grave.

Equine Motor Neuron Disease

Equine motor neuron disease is an idiopathic condition char-
acterized by spinal and brainstem motor neuron loss and
degeneration (Divers et al., 1997). Equine motor neuron
disease can be observed in horses of any breed, age, or gender.
The disease has been reported in North America and Europe.
Clinical signs are typically attributed to muscular weakness
(paresis) and lower motor neuron disease. Affected animals
will often have a short-strided gait and will have muscular
fasciculations that worsen following exercise. These animals
will also frequently shift their body weight between limbs
when standing in one position and have evidence of varying
degrees of generalized muscle atrophy and weight loss. In
more severe cases, horses are unable to stand. With regard to
ophthalmic signs, horses with equine motor neuron disease
may have fundic changes characterized by a honeycomb
pattern of yellow/brown pigment within the tapetal fundus
similar to that seen in dogs with vitamin E deficiency (Riis
et al., 1999; Verhulst et al., 2001). This yellow/brown pigment
has been identified as accumulation of ceroid/lipofuscin. In
some instances, pupillary light reflexes may be abnormal
(Verhulst et al., 2001).

Although the etiology of this condition is unknown, serum
vitamin E levels are not uncommonly reduced (Polack et al.,
2000; Rua-Domenech et al., 1997). Diagnosis of equine
motor neuron disease is made based on consistent clinical
findings, reduced serum vitamin E concentration, and
electromyography and muscular histopathology consistent with
denervation (Kyles et al., 2001; Palencia et al., 2005; Polack
et al., 2000; Rua-Domenech et al., 1997). There is no effec-
tive therapy for this condition, and prognosis is grave in most
instances.

Photic Headshaking

Photic headshaking is a condition characterized clinically by
excessive and possibly violent movement of the head in the
vertical, horizontal, or rotary directions (Wilkins, 1997). The
underlying pathophysiology of photic headshaking in horses
remains unknown. Photic headshaking is thought to be similar
to photic sneezing in humans. Specifically, photic headshak-
ing is oftentimes stimulated by exposure to bright light and
the behavior improves when ocular exposure to light is dimin-
ished (Madigan et al., 1995). In one study of seven horses, six
experienced the onset of signs during the spring months
(Madigan et al., 1995). Diagnosis of photic headshaking is
made based upon consistent history and by ruling out other
causes of headshaking including otitis and guttural pouch
disease. Treatment with cyproheptadine, an antihistamine
and serotonergic antagonist, has successfully eliminated head-
shaking in five of seven treated horses in one study, but the
exact mechanism of its apparent clinical efficacy is unknown
(Madigan et al., 1995). Surgical therapy for photic headshak-
ing includes bilateral infraorbital neurectomy, but this is con-
sidered a salvage procedure (Mair, 1999; Mair et al., 1992;
Wilkins, 1997).

Immune-Mediated Diseases

Dermatologic Diseases

The pemphigus groups of dermatoses are immune-mediated
diseases characterized by vesiculobullous skin lesions. Pem-
phigus foliaceus is a rare immune-mediated skin disease
occurring in a variety of species including the horse (for case
series and review of the literature, see Vandenabeele et al.,
2004). Although rare, pemphigus foliaceus is the most
common autoimmune skin disease occurring in the horse
(Vandenabeele et al., 2004). There are no breed or sex predi-
lections for developing pemphigus foliaceus in horses (Van-
denabeele et al., 2004). Lesions are typically observed on the
head (including palpebrae), limbs, and ventrum, and they are
characterized initially by vesicles, erosions, epidermal col-
larettes, scaling, and crusting (Fig. 35.3.9). Pruritus and pain
are variable (Vandenabeele et al., 2004). Affected animals
may show signs of general malaise, weight loss, poor appetite,
and pyrexia.

Diagnosis of pemphigus foliaceus is made based upon
characteristic clinical and dermatohistopathologic findings.
Direct immunofluorescence testing reveals diffuse intercel-
lular deposition of immunoglobulin and, occasionally, com-
plement within the epidermis (George & White, 1984; Scott,
1987). Therapy requires immunosuppression, usually with
high doses of oral glucocorticoids possibly combined with
chrysotherapy (therapy with gold compounds) or azathioprine
(Vandenabeele et al., 2004). Chrysotherapy has been success-
ful in horses with pemphigus (Power et al., 1982; Vandenabeele
Urticaria, or hives, refers to the sudden onset of transient focal erythema, edema, and pruritus (Rufenacht et al., 2005). Urticaria may develop due to type I (most common), II, or III hypersensitivity reactions or may be complement-mediated (Byars, 1984; Rufenacht et al., 2005). Consequently, urticaria may be associated with anaphylaxis. Eyelid edema and chemosis frequently accompany generalized wheal (focal swellings of skin and mucous membranes) formation. Factors contributing to urticaria are numerous, but a variety of allergens and/or drug-related causes including penicillin, phenylbutazone, aspirin, and tetracyclines have been implicated. Diagnosis of urticaria is based upon consistent clinical signs (Fig. 35.3.10), intradermal skin testing, elimination trials, and consistent dermatohistopathologic findings (Jose-Cunilleras et al., 2001; Rufenacht et al., 2005). Treatment consists of eliminating the offending drug or environmental condition, if possible. Corticosteroids to control the acute condition are helpful as are antihistamines (Rees, 2001; Rufenacht et al., 2005).

Infectious Diseases

Bacterial

Borrelliosis (Lyme Disease)

Lyme disease is a tick-borne disease caused by Borrelia burgdorferi, a spirochete bacteria (Litman et al., 2005). Borreliosis is transmitted to vertebrates by Ixodes spp. and Amblyomma americanum (Fritz & Kjemtrup, 2003; Levine, 1995). Typically, ticks must remain attached for more than 24 hours in order to transmit the spirochaete (Piesman et al., 1987). Horses in endemic areas show serologic evidence of exposure to B. burgdorferi, but most are clinically unaffected (Bernard et al., 1990; Magnarelli & Anderson, 1989; Marcus et al., 1985). Clinical signs reported in association with equine Lyme disease include arthritis and lameness, encephalitis, limb edema, dermatitis, abortion, and foal mortality (M adigan, 1993b; Parker & White, 1992). B. burgdorferi spirochetes have been found using silver stain and immunofluorescent antibody within the eye of a pony with arthritis and panuveitis (Burgess et al., 1986). In endemic areas, Lyme disease may be responsible for cases of equine uveitis but may go unrecognized or underreported.
Diagnosis of Lyme disease is made based upon consistent clinical signs, positive serologic tests (e.g., immunofluorescent antibody, enzyme-linked immunosorbent assay [ELISA], or Western blot), and positive response to therapy (M adigan, 1993b; Parker & White, 1992). Detection of B. burgdorferi DNA using polymerase chain reaction (PCR) for B. burgdorferi on skin, synovia, and connective tissue samples may be useful in diagnosing borreliosis (Littman, 2003; Salinas-Melendez et al., 1995). Treatment for Lyme disease should include systemic antibiotics. Tetracyclines, amoxicillin, cephalaxine, and imipenem are effective against B. burgdorferi. Treatment of borreliosis-related uveitis is nonspecific, but should include systemic nonsteroidal anti-inflammatory drugs, topical corticosteroids, and/or nonsteroidal anti-inflammatory drugs, and atropine.

Botulism (Forage Poisoning)

Botulism results from the neurotoxin, botulinum, produced by Clostridium botulinum. C. botulinum is a gram-positive, spore-forming, saprophytic, anaerobic, rod-shaped bacterium. There are eight distinct subtypes (A, B, Ca,Cb, D, E, F, G) of C. botulinum, and they are differentiated from each other based upon the type of neurotoxin they produce (Wilkins & Palmer, 2003a). A side from causing botulism, there is growing evidence incriminating C. botulinum as an important etiology of equine dysautonomia (see “Dysautonomia (Equine Grass Sickness)” under “Idiopathic Systemic Diseases” section). Horses are most commonly affected by types B and C (Haagsma et al., 1990; Kelly et al., 1984; Kinde et al., 1991; MacKay & Berkhoff, 1982; Mitten et al., 1994; Ricketts et al., 1984; Swerczek, 1980; Wichtel & Whitlock, 1991; Wilkins & Palmer, 2003a). The mechanism of action of the neurotoxin is via blocking presynaptic acetylcholine release (Kao et al., 1976). The toxin or organism may be ingested in contaminated forage or commercial feed or may gain entry through wounds (Haagsma et al., 1990; Kelly et al., 1984; Kinde et al., 1991; MacKay & Berkhoff, 1982; Mitten et al., 1994; Ricketts et al., 1984; Swerczek, 1980; Wichtel & Whitlock, 1991; Wilkins & Palmer, 2003a). Clinical signs develop within 1–7 days and are variable depending on the stage and/or severity of the disease. Nevertheless, clinical signs in adult horses include weakness, dysphagia, drooling, and inability to retract the tongue, ptosis, mydriasis (with slow pupillary light reflexes), dyspnea, and generalized paresis/paralysis (Ricketts et al., 1984). In foals affected by botulism (shaker foals), foals are initially alert, but progression occurs from a stiff gait with muscle trembling to complete recumbency. Foals may have sluggish pupillary light reflexes, ptosis, and other lower motor neuron signs (MacKay & Berkhoff, 1982; Swerczek, 1980; Wilkins & Palmer, 2003a).

The diagnosis of botulism may be difficult to establish. Identification of the toxin in serum, gastrointestinal contents, or food is definitive. A positive neutralization test in mice is also definitive (Sippel, 1972). Culture of C. botulinum from feedstuffs is usually difficult. Therapy involves supportive nursing care, administration of antitoxin, and appropriate antimicrobials including metronidazole. Antimicrobials associated with neuromuscular dysfunction (e.g., aminoglycosides) should be avoided. Some horses will recover from botulism, and although mortality in foals has been thought to be traditionally high, a study has demonstrated that greater than 96% of foals less than 6 months of age will survive with appropriate intensive care (Wilkins & Palmer, 2003a, 2003b).

Leptospirosis

Leptospirosis is caused by systemic infection by spirochetal bacteria of the genus Leptospira (Levet, 2001). More than 200 serovars have been identified (Levet, 2001). Of these serovars, those most commonly isolated in horses include Leptospira autumnalis, Leptospira bratislava, Leptospira icterohaemorrhagiae, and Leptospira pomona (for review, see Bernard, 1993). The bacterium is commonly excreted in the urine of infected animals, but any bodily secretion may contain the bacteria during the acute stage of the disease (Bernard, 1993). The organism may survive in warm and moist conditions for several weeks. Horses typically become infected by ingesting water or feed previously contaminated by a carrier host’s urine (e.g., wildlife, cattle). The organism may enter the vascular system via conjunctival, nasopharyngeal, oral, esophageal, small intestinal, and genital mucous membranes (Hanson, 1982; Thiermann, 1984). Exposure of open wounds to the bacterium may also be an important route of infection in some instances. Horses with leptospirosis may have clinical signs attributed to acute renal failure, abortion, and hepatitis in foals (Divers et al., 1992; Frazer, 1999; Hathaway et al., 1981; Hodgkin et al., 1989; Twigg et al., 1971; van den Ingh et al., 1989). Leptospirosis is also highly incriminated in equine recurrent uveitis (ERU) (for review see Chapter 28, “Equine Ophthalmology”). Specifically, anterior uveitis and peripapillary chorioretinitis may be seen in association with leptospirosis (Williams et al., 1971), and corneal opacities as well as binding of leptospiral antibodies to the cornea have also been reported among experimentally infected horses (Parma et al., 1985, 1987).

Leptospira interrogans serovar pomona has been the strain most frequently associated with uveitis in the horse, though the serovars icterohaemorrhagiae, grippotyphosa, canicola, and hardjo have also been reported (Davidson et al., 1987; Sillerrud et al., 1987). In both experimental and naturally occurring infections, ocular lesions develop 12–24 months after the primary infection (Roberts, 1958; Roberts et al., 1952; Williams et al., 1971).

Diagnosis of leptospirosis is made by identifying the organism in the urine using dark-field microscopy, demonstrating the presence of circulating anti-Leptospira antibodies using the microscopic agglutination test or ELISA, and culturing the organism from urine or blood. The finding of specific leptospiral antibody titers in the aqueous humor that are higher than those in the serum or detecting DNA of leptospiral organisms in the aqueous humor, however, support a diagnosis of
leptospirosis as a cause of ERU (Davidson et al., 1987; Faber et al., 2000; Halliwell et al., 1985). In a recent study, however, only 1 horse of 52 with ERU had non-ERU inflammation had definitive intraocular production of antibodies against Leptospira organisms (Gilger et al., 2008). Most recently, Leptospira spp. were reported to be the trigger of ERU, in a likely autoimmune disease, in the majority of European cases (Spiess, 2010).

Therapy for equine leptospirosis includes appropriate antimicrobial therapy using penicillins or tetracyclines. Fencing off streams, ponds, and marshes as well as controlling access of wildlife to farm structures are means by which the spread of disease can be controlled and contained (Hanson, 1982). A variety of therapies and prevention strategies have been attempted and studied for leptospirosis-related ERU (Gilger, 2010; Lowe, 2010; Spiess, 2010) (see Chapter 28, “Equine Ophthalmology,” for current review).

**Rhodococcus equi**

Rhodococcus equi is a soil-dwelling, gram-positive, catalase-positive, aerobic, coccal bacteria. This bacterium is well-known, worldwide, to cause pneumonia in foals (for review, see Prescott, 1991). Adult horses are typically spared from R. equi infection. Immunocompromised foals (e.g., foals having failure of passive transfer and severe combined immunodeficiency), however, are susceptible to infection with R. equi infection. Foals will typically present with pyrexia, nasal discharge, and other signs of respiratory tract infection. In addition to respiratory illness, foals may have clinical signs related to gastrointestinal, orthopedic, or ocular disease. The bacteria have been cultured from the eye of a foal, and the resultant uveitis resulted in blindness (Blogg et al., 1983). Foals with R. equi infection may develop uveitis, panophthalmitis, or keratouveitis (Giguere & Prescott, 1997; Reuss et al., 2009). However, a recent study reported the prevalence of ocular signs in foals with R. equi infection was low with 16 of 150 (11%) of foals with R. equi pneumonia reported to have uveitis (Reuss et al., 2009).

Diagnosis of R. equi infection is made based upon culturing the organism from fluid obtained from transtracheal wash or bronchoalveolar lavage, although as previously mentioned, the organism may be cultured antemortem via aqueous centesis. Treatment of R. equi infection typically involves supportive nursing care and antimicrobial therapy using erythromycin, clarithromycin, or azithromycin combined with rifampin (Davis et al., 2002; Giguere et al., 2004; Jacks et al., 2001, 2003). A retrospective study found that clarithromycin-rifampin therapy was superior to erythromycin-rifampin or azithromycin-rifampin for the treatment of R. equi-associated pneumonia in foals (Giguere et al., 2004). Ocular therapy, when indicated, should include frequent topical administration of corticosteroids (e.g., prednisolone acetate or dexamethasone) and atropine. Prognosis for foals with R. equi infection is variable depending upon the severity of the disease and the duration of illness prior to commencing therapy.

**Salmonellosis (Paratyphoid)**

Salmonellosis is caused by gram-negative motile rod-shaped bacteria of the genus Salmonella. Salmonellosis frequently occurs in the horse, and it is a commonly diagnosed infectious cause of diarrhea among adult horses. Salmonella spp. are frequently present in the environment, and disease occurs mainly among stressed animals or in those with altered host defenses (Spier, 1993). Diarrhea results from malabsorption secondary to gut epithelial cell destruction and host inflammatory response to bacterial endotoxin.

Ocular manifestations of salmonellosis may include iridocyclitis and hypopyon, and such manifestations are most likely to be seen in bacteremic animals. The organism has been cultured from the anterior chamber of affected horses (Whitley & Gelatt, 1981). The diagnosis of salmonellosis is established on the basis of positive cultures from fecal samples, blood, or tissues (Hyatt & Weese, 2004). The reader is referred to a recent internal medicine textbook for discussion of treatment, control, and prevention strategies used for salmonellosis. Nevertheless, treatment of salmonellosis-related uveitis should be aimed at controlling intraocular inflammation, preventing synechia formation, and reducing ocular pain by administering topical corticosteroids and atropine.

**Sepsis**

Sepsis is defined as the presence of pathogenic microorganisms or their toxins in the blood or other tissues (Blood & Studdert, 1990). With respect to bacterial sepsis, specifically bacteremia, a variety of bacteria cause clinical disease in foals and adult horses, and include R. equi, Streptococcus equi subsp., Leptospira spp., Mycobacteria avium, Salmonella spp., and Clostridium spp. to name a few (for special mention, see specific bacteria mentioned in this chapter). Particular etiologies of bacteremia are, in part, dependent on the age and concurrent disease-status of the animal. Clinically, animals with bacteremia will present with a variety of clinical signs depending on the organ system(s) affected. With respect to ocular conditions, a variety of manifestations of bacteremia may occur either during the active stages of bacteremia or after the bacteremia has been treated or has subsided (e.g., leptospirosis-associated ERU). Often, ocular signs will accompany clinical signs of other organ involvement. Uveitis, keratitis, chorioretinitis, optic neuritis, or endophthalmitis may manifest secondarily to systemic bacterial disease or disease disseminating from a primary infectious nidus. Ocular signs may present unilaterally or bilaterally. For example, unilateral uveitis, optic neuritis, and concomitant meningoencephalitis has been reported as a secondary complication of bacterial endocarditis in adult horses (Hatfield et al., 1987; Kaplan & M oore, 1996).

Definitive diagnosis of bacteremia is made by identifying the causative organism in the blood and/or multiple organs (e.g., transtracheal wash samples from the lungs, joint fluid samples, aqueous, and/or vitreous from clinically affected eyes) using current bacterial culture methods. Antimicrobial
susceptibility should be performed on isolated organisms and appropriate systemic therapy implemented. Topical use of anti-inflammatory drugs and atropine should be instituted for general management of uveitis. Further symptomatic management and appropriate nursing and supportive care should be implemented. Prognosis is variable depending on the cause of the bacteremia and whether management of concurrent clinical disease is possible (e.g., Arabian foals with severe combined immunodeficiency vs. adult case of equine strangles).

**Streptococcus equi** (Strangles, Distemper)

*S. equi* var. *equi* is a gram-positive coccoid bacterium. Infection occurs via direct contact from infected horses’ nasal secretions or from coming in contact with fomites, including feed and water troughs and housing. *S. equi* var equi colonizes within the pharyngeal and nasal mucosae and then drains into regional lymph nodes and in some instances can result in bacteremia (for review, see Sweeney et al., 2005; Timoney, 1993, 2004). *S. equi* var equi infection is relatively common and is often observed as an outbreak on a farm or in a stable. Clinical signs of *S. equi* var equi infection include pyrexia, general malaise, anorexia, serous (initial) and purulent (later) nasal discharge, pharyngitis manifesting as an inability to swallow, and pharyngeal, submaxillary, and parotid lymphadenitis that may become abscessed. In some instances, clinical signs related to multiple organ involvement (bacterial strangies) may occur. Ocular abnormalities associated with strangies include initially serous and later mucopurulent ocular discharge (Knight et al., 1975; Yelle, 1987), panophthalmitis (Barratt-Boytes et al., 1991), and chorioretinitis (Roberts, 1971). In some cases, blindness may occur because of the development of brain abscessation (Audi et al., 2004; de la Hunta & Cummings, 1967; Spoormakers et al., 2003).

Diagnosis of *S. equi* var. *equi* infection is made based on characteristic clinical signs and positive culture of *S. equi* from abscesses. Therapy for *S. equi* var. *equi* infection is controversial, and the reader is referred to recent internal medicine textbooks and a recent consensus statement made by the American College of Veterinary Internal Medicine (Sweeney et al., 2005).

**Tetanus**

Tetanus is caused by the neurotoxin produced by the bacterium, *Clostridium tetani*. *C. tetani* is a motile, gram-positive, nonencapsulated, anaerobic, rod-shaped, spore-forming bacterium. The organism is prevalent in soil worldwide, and spores typically enter the body through an open wound. Incubation times vary from 10 days to 1 month. Spores become vegetative and a toxin, tetanospasmin, retrogradely migrates along axons of motor nerves to the central nervous system (CNS). However, it should be noted that tetanospasmin, the principal neurotoxin, is only one of three toxins produced by the bacterium (Acke et al., 2004). The toxin then prevents inhibitory neurotransmission to motor neurons thereby resulting in the classical signs associated with tetanus.

Clinical signs include initial stiffness progressing to generalized spasticity. Infected horses generally have a sawhorse stance, retraction of the ears and lips, elevation of the tail, and rapid retraction of the globe, thereby resulting in prolapse of the third eyelids. In one study of 20 horses, hyperesthesia and third eyelid prolapse were the most common signs (Green et al., 1994). Death can occur from respiratory and cardiac failure.

Therapy for tetanus consists of providing muscle relaxation, providing an appropriate substrate footing and bedding, eliminating infection by treatment with penicillin, neutralizing unbound toxin by administering tetanus antitoxin, maintaining hydration and nutritional status, and immunization with tetanus toxoid to stimulate an immune response. Prognosis is poor to grave. Prevention is attained by vaccinating animals with tetanus toxoid.

**Mycotic**

**Aspergillosis**

Aspergillosis is caused by the filamentous fungus Aspergillus spp. Aspergillus spp. are considered ubiquitous in the environment, and animals are infected opportunistically after inhaling Aspergillus spores (Gelatt et al., 1991). Infection with Aspergillus spp. is either localized or disseminated. Localized aspergillosis involves colonization of the respiratory sinuses, guttural pouch, and nasal mucosa. Secondary CNS involvement may result from erosion of the cribriform plate. Disseminated aspergillosis occurs typically in the immunocompromised patient and involves a whole host of organ systems, although history of respiratory involvement is not typically documented (Lehmann, 1985; Shoham & Levitz, 2005).

Clinical manifestations of Aspergillus infection include mycotic rhinitis (Koren et al., 1994), mycotic pneumonia (Blue et al., 1987; Hattel et al., 1991; Slocombe & Slauzon, 1988; Sweeney & Habecker, 1999), otitis media (Newton & Kottenbelt, 1999), and guttural pouch mycosis (Hatziolos et al., 1975; Johnson et al., 1973; Lepage et al., 2004; Ludwig et al., 2005; Rawlinson & Jones, 1978). Aspergillus spp. are also isolated from the cases of equine keratomycosis (Brooks et al., 1998; Gaarder et al., 1998; Grahn et al., 1993; Kern et al., 1983; Peiffer, 1979). Horner’s syndrome and optic neuritis may result secondarily from guttural pouch mycosis (Cook, 1968; Hardy et al., 1990; Hatziolos et al., 1975).

**Cryptococcosis**

Cryptococcosis is caused by Cryptococcus neoformans or Cryptococcus gattii (previously C. neoformans var. gattii) (Wolf, 1989). *C. neoformans* is associated with high-nitrogen containing environments such as avian feces or soil enriched with avian feces (O’Brien et al., 2004). Hence, birds such as pigeons are considered to be significant vectors of Cryptococcus spp. *C. gattii*, however, is associated with eucalyptus and fir trees in Australia and Canada, respectively (O’Brien et al., 2004). In infected tissue, and often when cultured using
standard laboratory conditions, \( C. \) neoforms it is a variably sized yeast-like organism (3.5–7 \( \mu m \)) which typically contains a thick capsule.

\( C. \) neoforms is less commonly reported in the horse compared to the dog or the cat. Clinically, \( C. \) neoforms has been reported to cause abdominal abscessation, abortion, infection of the upper and lower respiratory tract, and meningoceitis (B arclay & deL ahunta, 1979; B egg et al., 2004; Bl anchard & Filkins, 1992; B oulton & William son, 1984; Ch o et al., 1986; Dick son & M eyer, 1970; Freeman et al., 1990; Pear son et al., 1983; Petrit es-Mur phy et al., 1996; Riley et al., 1992; Ryan & Wyand, 1981; Sc ott et al., 1974; St eckel et al., 1982).

The incidence of cryptococcosis appears to be somewhat higher in western Australia than that in other regions of the world (Dick son & M eyer, 1970; Riley et al., 1992). Ocular lesions have not been reported in most cases of equine cryptococcosis. There is one instance, however, of Cryptococcus causing choriorretinal lesions and frontal sinuitis with a mass within the retrobulbar space causing exophthalmos and peri orbital distention (Scott et al., 1974).

Diagnosis of equine cryptococcosis is based upon identifying the organism histologically, cytopathologically, or via culture of infected tissue. Prognosis is very poor in cases of equine cryptococcosis (Riley et al., 1992), although some animals may survive with appropriate medical therapy, including treatment with an appropriate antifungal drug such as amphotericin-B (B egg et al., 2004).

**Dermatophytosis (Ringworm)**

Dermatophytosis is a mycotic skin infection, and in the horse, it may be caused by Microsporum equinum, Microsporum gypseum, Trichophyton equinum, Trichophyton mentagrophytes, Trichophyton verrucosum, and Trichophyton quincke num (C arter, 1966; C arter et al., 1970; C on Hole, 1973; G eorg et al., 1957; K ane et al., 1982; K apl an et al., 1957). A higher incidence of dermatophytosis is seen in hot, humid climates. Lesions are characterized by alopecia, with or without crusts and often with a brownish color, and they may affect any part of the body, including the head and eyelids. Pruritus and pain vary from none to intense.

Diagnosis of dermatophytosis is made based upon positively culturing the etiologic fungus. Histopathologic examination of skin biopsy specimens may also identify dermatophytes. Dermatophytosis in the horse is generally self-limiting and may not require treatment. Topical therapy with amphotericin-B (Begg et al., 2004).

**Histoplasmosis (Epizootic Lymphangitis)**

Histoplasmosis is caused by the fungal organism Histoplasma capsulatum. Histoplasmosis is not uncommonly reported in the horse. Pulmonary infections, placentitis with abortion, and disseminated disease have been reported (al A ni, 1999; A meni & Siyoum, 2002; C ornick, 1990; J ohnston et al., 1995; R ezbak et al., 1993).

Epizootic lymphangitis is a chronic and contagious disease caused by Histoplasma farciminosum (for review, see al A ni, 1999). This disease is endemic in West, North, and East Africa as well as the Middle East, India, and the Far East. Epizootic lymphangitis is transmitted between horses via insects (biting flies) feeding on open wounds or some other transmission of infected secretions into traumatized skin or conjunctiva. Soil does not appear to be a source of the organism, and infection does not occur in normal, undamaged tissue. Outbreaks have occurred in which large numbers of horses were housed together. In most areas of the world, this is a reportable disease.

Clinical signs include skin nodules that eventually erupt into draining lesions located along the subcutaneous lymphatics. Ocular lesions begin as serous and then purulent ocular discharge, with blepharitis. Later, papules on the conjunctival surfaces develop and ulcerate, thus leading to a thick, purulent ocular discharge. Diffuse swelling of the eyelids occurs, and lesions may erupt on the epidermal palpebral surface. Horses may not be able to open their eyes, and the nasolacrimal duct may become occluded (Singh, 1956). Palpebral granulomas have been seen (Singh, 1963), and keratitis may occur secondary to the conjunctival disease (A l-A ni & A l-D ela ima, 1986).

Diagnosis of epizootic lymphangitis is made based upon identifying the organism cytologically or via culture (Sel im et al., 1985). Fluorescent antibody and ELISA tests have been described (G abal & M ohammed, 1985; G abal et al., 1983). Frequently, no treatment is allowed, and affected horses are euthanized. Mildly affected horses may recover, however, and are reportedly immune to reinfection. Antifungal agents such as amphotericin-B are considered useful for treating epizootic lymphangitis (al A ni, 1999). Prognosis for horses with epizootic lymphangitis is variable but it may be fatal. Vaccination of horses living in endemic areas is recommended (al A ni, 1999).

**Parasitic: Lice and Mites**

**Demodicosis**

Demodex equi and Demodex caballi have both been reported as causing dermatologic disease in this species, though not with the frequency of demodicosis in some other species (B en nison, 1943; B esch & G riffiths, 1956). Demodex spp. live as commensals in the skin of most mammals, including horses. Most species of Demodex, including D. equi and D. caballi, spend their entire life cycle in the hair follicles and sebaceous glands of their host, while a few species are found within the epidermis. Demodex mites, present in small numbers, are part of the normal skin fauna (for review, see M ueller, 2004; N utting, 1976). Consequent pathologic sequelae of these mites probably relates in some way to immunocompromise. Lesions are characterized by alopecia and scaling, and the development of small nodules and pustules, especially over the face, neck, shoulders, and forelimbs. D. caballi tends to inhabit the eyelids and the muzzle, whereas D. equi affects the entire body. The diagnosis is established on the basis of identifying the mite in
Intraocular migration of Dirofilaria immitis probably occurs less frequently in the horse than it does in carnivores. There is one report of successful surgical removal of a nematode from the anterior chamber of a horse; the parasite was identified as an adult D. immitis (Moore et al., 1983).

**Habronemiasis (Habronemiosis, Summer Sores, Swamp Cancer)**

Habronemiasis is a parasitic disease caused by the aberrant migration by larvae of the nematodes Habronema muscae, Habronema majus, and Draschia megastoma (Moore et al., 1983; Pusterla et al., 2003). Habronemiasis is seen in tropical and temperate climates worldwide. These nematodes normally are found within the stomach of horses. Flies, including Musca domestica (house fly) and Stomoxys calcitrans (stable fly), are used as the intermediate host (Pusterla et al., 2003). Larvae are passed in the feces and are consumed by maggots of the intermediate host. When the adult fly emerges, the third-stage larvae (L3) within the fly are infective, and horses become infected by ingesting the fly or the L3 larvae that have been deposited near the mouth of the horse. Habronema or Draschia larvae may be deposited on wounds or near the eye, and larval migration through these tissues results in a granulomatous inflammatory response. Habronemiasis is commonly seen in young and middle-aged adult horses, although any age may be affected (Pusterla et al., 2003). There is no gender predilection for developing habronemiasis (Pusterla et al., 2003). Pale-colored horses (e.g., gray, palomino) appear more likely to be affected, and this may be due to flies being attracted to light rather than to dark colors (Pusterla et al., 2003). Lesions are typically concurrent with the fly season and may regress with cold weather only to resume when the weather becomes warm again (Pusterla et al., 2003). Lesions may affect the conjunctiva or the periocular area, and the papules have a raised, irregular, yellow (i.e., “sulfur granules”) appearance (Fig. 35.3.11) (Gasthuys et al., 2004; Glaze, 1983; Pusterla et al., 2003; Rebhun et al., 1981). A affected tissue tends to bleed easily, and pruritus and self-trauma may be evident.

**Diagnosis** of cutaneous habronemiasis is made based upon consistent clinical signs and histopathologically consistent features observed in biopsy specimens. Specifically, granulomatous inflammatory infiltrate with eosinophils and mast cells is seen, along with collagenolysis (Rebhun et al., 1981). Larvae may not be identified histopathologically. In fact, nematode larvae are only present in 44%–50% of biopsy specimens (Pusterla et al., 2003). Therapy is aimed at destroying the nematodal larvae by administering systemic doses of ivermectin (Gasthuys et al., 2004; Herd & Donham, 1981; Pusterla et al., 2003). Debunking large nodules may be necessary. Furthermore, topical or systemic anti-inflammatory drugs may be used to control inflammatory responses to dead and dying larvae (Gasthuys et al., 2004; Pusterla et al., 2003). Control of the fly population by removal of horse manure and implementing appropriate fly control measures is useful in reducing habronemiasis in the horse population.
The prevalence of *O. cervicalis* microfilariae among U.S. horses appears to be high. On the basis of skin biopsy findings, prevalence rates of approximately 50%–77% have been reported in horses from the western, midwestern, and southeastern United States (Cummings & James, 1985; Rabalais et al., 1974; Stannard & Cello, 1975); prevalence rates of as high as 76% in the Gulf Coast area and 82% in Louisiana have also been reported (Klei et al., 1984). The prevalence in the United Kingdom appears to be less than that in the United States, with reports of positive skin biopsy specimens between 2.3% and 24% (Attenburrow et al., 1983; Mellor, 1973). The prevalence of ocular microfilariae has been reported to be 18% in 292 horses from the eastern, southeastern, and midwestern United States (Moran & James, 1987), 11% in 368 eyes of horses from the midwestern United States (Schmidt et al., 1982a), and 49% in 121 horses from the eastern United States (Lloyd & Soulsby, 1978). The most common sites of ocular microfilariae are the conjunctiva and eyelids, followed by cornea/sclera and the intraocular structures or aqueous humor.

As alluded to already, ocular manifestations of onchocerciasis include anterior and posterior uveitis, peripapillary chorioretinitis, keratitis, keratoconjunctivitis, and lateral conjunctival vitiligo (Attenburrow et al., 1983; Cello, 1971; Hammond et al., 1983; M unger, 1983; Schmidt et al., 1982a). Diagnosis of onchocerciasis is made based upon histologically identifying the nematode in biopsy specimens of affected tissues, including conjunctiva and skin.

Treatment of onchocerciasis has been most effective with systemically administered ivermectin (0.2 mg/kg) or moxidectin (0.4 mg/kg) (Herd & Donham, 1983; Mancebo et al.,...
1997). It is important to note, however, that there is no efficacious therapy for destroying the adult nuchal ligament-residing nematodes. Further, concurrent treatment of ocular signs should be implemented to control ocular inflammatory responses because dead and dying microfilaria may exacerbate ocular disease. Systemic nonsteroidal anti-inflammatory agents as well as topical or subconjunctival corticosteroids should be used.

**Parelaphostrongylus**

Parelaphostrongylus spp. are metastrongylid nematodes; there are three species of Parelaphostrongylus, all of which are extrapulmonary parasites of definitive ungulate hosts, including cervids and bovids. Among these three parasites, Parelaphostrongylus tenuis (meningeal worm) is relatively large with males ranging from 31 to 62 mm in length, and equipped anatomically with spicules that typically exceed 200 μm in length, and a gubernaculum of >100 μm in length (Reinstein et al., 2010). P. tenuis is considered to be a common neurotropic parasite in white-tailed deer, the definitive host, in parts of the United States, including eastern to central North America. Noncervid domestic livestock, including llamas, goats, sheep, and cattle, are also susceptible. In white-tailed deer, the larvae of this parasite migrate cranially through the grey matter of the spinal cord and into the brain where they mature into adult parasites. A dull meningeal worms reside in the meninges of white-tailed deer and rarely cause clinical signs of disease. For details regarding the life cycle of this parasite, the reader is referred to Pugh et al. (1995). Successful surgical extraction of P. tenuis from the anterior chamber of a horse (Fig. 35.3.12) has been recently reported (Reinstein et al., 2010).

**Setaria**

Setaria spp. are nematodes of the superfamily Filarioidea and, consequently, are transmitted to their hosts by blood-feeding insects. Like *Dirofilaria* spp., Setaria spp. can be found within circulating blood by examining blood smears. Setaria digitata and *Setaria equina* are the species known to migrate to the equine eye. Although uncommonly reported, Setaria spp. are the most commonly reported intraocular nematode infecting the horse (Jemelka, 1976; Schwartz, 1927). Successful surgical removal of *S. digitata* from the anterior chamber of a horse has been reported (Jemelka, 1976). A recent study reported successful treatment of equine ocular setariais with ivermectin (Muhammad & Saqib, 2007).

**Parasitic: Protozoal**

**Babesiosis (Equine Piroplasmosis, Biliary Fever)**

Equine babesiosis is caused by the tickborne, intraerythrocytic, protozoal parasites *Babesia equi* and *Babesia caballi* (for review, see Bruning, 1996; De Waal & Van Heerden, 2004). The disease occurs in tropical and subtropical climates. Tick vectors for equine babesiosis belong to a variety of genera, including *Dermacentor*, *Hyalomma*, *Amblyomma*, *Boophilus*, *Anocentor*, and *Rhipicephalus* (Battsetseg et al., 2002a, 2002b; De Waal, 1990; De Waal & Potgieter, 1987; Potgieter et al., 1992; Teglas et al., 2005; Ueti et al., 2005). The incubation period is from 5 to 28 days, and clinical signs include pyrexia, hemolytic anemia, jaundice, hemoglobinuria, and death.

Ophthalmic signs include swelling of the eyelids as well as icterus of the conjunctiva and sclera. The color of the conjunctiva varies from yellow to dark brown, often with petechial and ecchymotic hemorrhages over the third eyelid and other conjunctiva (Sippel et al., 1962). Red-colored, serous ocular discharge has also been noted in some horses, and distention of the supraorbital fossa may be seen.

Diagnosis of equine babesiosis is made based upon identifying the organism within erythrocytes on a blood smear. Other more sophisticated, and in some instances, more reliable diagnostic tests include blood culture, ELISA, Western blot, immunofluorescent and complement fixation antibody tests, and detecting DNA of the infectious agent using PCR (Alhassan et al., 2005; Bose & Daemen, 1992; Bose & Peymann, 1994; Holman et al., 1993; Kappmeyer et al., 1999; Posnett et al., 1991; Rampersad et al., 2003; Weiland, 1986). Consensus regarding appropriate therapeutic regimes for the treatment of equine babesiosis has not been reached (for current therapeutic strategies, see Bruning 1996; De Waal & Van Heerden, 2004). A variety of drugs including diminazene diaceturate (11 mg/kg IM), amicarbalide diisethionate (9 mg/kg IM), and imidocarb dipropionate (2 mg/kg SQ or IM) are...
effective against both *B. caballi* and *B. equi* (De Waal & Van Heerden, 2004). Attempts to eliminate the carrier state of *B. equi* originating in Eastern Europe have been unsuccessful (Kuttler et al., 1987; Zaugg & Lane, 1989, 1992). Consequently, repeated treatments are required.

**Sarcocystis neurona (Equine Protozoal Myeloencephalitis)**

Equine protozoal myeloencephalitis (EPM) is a multifocal, progressive disease of the CNS caused by infection with *Sarcocystis neurona* (for reviews, see Dubey, 2004a; Dubey et al., 2001; Furr et al., 2002). The disease has been reported only in horses born and raised in the Americas, including Canada, United States, Brazil, and Panama, with young horses being affected more than older horses and a breed predilection for Standardbred, Thoroughbred, and Quarter Horses (Dubey, 2004a). The parasite causes inflammation and necrosis of the caudal brainstem and spinal cord. The cerebrum and peripheral nerves may be affected as well. Clinical signs include ataxia, tetrarapheusis, head tilt, facial paralysis, circling, nystagmus, and blindness (with or without pupillary light abnormalities). Horner’s syndrome has also been seen in horses with EPM (Mayhew, 1980). Severe temporalis and masseter muscle denervation and atrophy may lead to prominence of the supra-orbital fossa, ptosis, and varying degrees of enophthalmos (Mayhew, 1989).

Diagnosis of EPM is made based upon demonstrating anti-*S. neurona* antibody titers within the cerebrospinal fluid (CSF), immunohistochemical detection of parasites in the CNS, and detection of *S. neurona* DNA by PCR in conjunction with consistent clinical signs (Furr et al., 2002). Treatment of EPM has been most successful with long-term therapy using combinations of pyrimethamine and trimethoprim (Dubey et al., 2001). Patients with severe inflammatory disease should also be given anti-inflammatory therapy at the start of antimicrobial therapy.

**Toxoplasmosis**

Toxoplasmosis is caused by the protozoan *Toxoplasma gondii* (for review, see Dubey, 2004b). *T. gondii*, similar to *Neospora caninum*, has a worldwide distribution. Cats are both definitive and intermediate hosts of *T. gondii*. Because cats are definitive hosts, they are the only species that can shed oocysts. It should be noted, however, that dogs can pass *T. gondii* oocysts in their feces after the ingestion of infected feline feces (Lindsay et al., 1997). Many mammalian species can act as intermediate hosts. In the cat, ingested *T. gondii* bradyzoites (from tissue cysts) undergo a typical coccidian intestinal life cycle, and infected cats excrete oocysts in their feces that, after 1–5 days, sporulate and become infectious sporozoites (Dubey, 2004b). The oocysts are resistant to environmental conditions, and they may remain infectious for months to years (Dubey, 2004b). Ingestion of the oocysts by a susceptible host results in rapid division of sporozoites in the gut epithelium. The resultant tachyzoites are 4–8 µm by 2–4 µm, and are spread throughout the body via blood and lymphatics, and encyst in the brain, skeletal and cardiac muscles, as well as the liver. The encysted forms, termed bradyzoites, survive in tissues for the life of the host. Ingestion of bradyzoites by a new host dissolves the cyst wall and transforms them into tachyzoites, which ultimately encyst again. The reported prevalence of serum antibodies, indicating exposure to *T. gondii*, among horses ranges from 1% in Sweden (Uggla et al., 1990), 12% in India (Chhabra et al., 1985), 17%–37% in Nigeria (Aganga et al., 1983; Osyemi et al., 1985), to <1%–34% in North America (Dubey et al., 1999; Eugster & Joyce, 1976; Riemann et al., 1975).

Uveitis has been reported in association with positive *T. gondii* serum antibody titers (Eugster & Joyce, 1976; McDonald & Cleary, 1970), and the organism itself has been identified by PCR in the retina, choroid, and sclera of a pony without apparent ocular disease (Turner & Savva, 1991). In one study of 130 horses with uveitis in Germany, a correlation could not be made with serum antibody titers for *T. gondii*, but a correlation could be made with titers to *Leptospira* sp. (Alexander & Keller, 1990).

Horses experimentally infected via the oral route with *T. gondii* oocysts did not develop clinical disease, but they did develop low-level serum antibody titers, as determined on the basis of a modified agglutination test (Dubey & Desmonts, 1987). Persistence of the encysted form of *T. gondii* in muscles and other tissues, including the eye of one horse, was demonstrated even months after inoculation (Dubey, 1985). Because the organism has been isolated from the equine eye, toxoplasmosis is a likely etiology in some instances of uveitis. Its role in ERU, if any, remains undefined.

**Parasitic: Tapeworms**

**Echinococcus granulosus (Hydatid Disease)**

Equine hydatid disease is caused by infection with the tapeworm *Echinococcus granulosus* subspecies equinus. Hydatid disease is relatively common in the horse, but reports of ocular hydatid disease are uncommon (Barnett et al., 1988; Capatina et al., 1969; Summerhays & Mantell, 1995). Domestic and wild canids are the definitive hosts of *E. granulosus* ssp. equinus, while horses and mules are this species’ intermediate hosts. With respect to ocular disease, hydatid cysts have been reported in the equine orbit and these animals present with signs of orbital disease (Barnett et al., 1988; Capatina et al., 1969; Summerhays & Mantell, 1995). Ultrasonography may aid in the presumptive diagnosis of hydatid disease in the horse (Summerhays & Mantell, 1995). Treatment is aimed at enucleation and surgical excision of the hydatid cyst in the case of blind eyes (Barnett et al., 1988). Alternatively, vision has been maintained in a horse by aspirating the cyst contents and concurrently administering systemic albendazole (10 mg/kg for 7 days, then 7 days of no treatment, repeat this cycle of therapy 6 times) (Summerhays & Mantell, 1995). Diagnosis of retrobulbar hydatid disease is established on the basis of a positive histopathologic examination of excised tissue
C) (Barnett et al., 1988). It should be mentioned, however, that diagnosis may be confirmed via microscopically identifying portions of the worm within fluid aspirated from the cyst (Summerhays & Mantell, 1995).

**Rickettsial Diseases**

Members of the bacterial order Rickettsiales are the cause of numerous conditions in numerous species of vertebrates (for comprehensive review, see Parola et al., 2005; Raoult & Roux, 1997). All members of the order Rickettsiales are obligate intracellular parasitic bacteria that require host cells to replicate (McQuiston et al., 2003; Parola et al., 2005). The development of molecular taxonomic methods has resulted in the reclassification of several species of rickettsia (Dumler et al., 2001). Rickettsial diseases are transmitted via an arthropod, typically fleas or ticks (Parola et al., 2005). Two common groups of diseases still considered rickettsial diseases in veterinary medicine include (1) rickettsioses caused by bacteria of the genus Rickettsia and (2) ehrlichioses and anaplasmoses caused by bacteria in the family Anaplasmataceae (Parola et al., 2005). Many rickettsial diseases are considered zoonotic (McQuiston et al., 2003). Because of these unique features of bacteria of the order Rickettsiales, we consider them here separately from other bacterial diseases that manifest, in part, with ocular disease.

**Ehrlichiosis (Equine Granulocytic Ehrlichiosis, Equine Anaplasmosis)**

Equine granulocytic ehrlichiosis is caused by the rickettsial organism Anaplasma phagocytophilum (previously Ehrlichia equi) (Dumler et al., 2001). As mentioned above, equine granulocytic ehrlichiosis is transmitted to horses via ticks, specifically ticks of the genus Ixodes (Reubel et al., 1998; Richter et al., 1996). Clinically, horses have general malaise and are pyrexic, anorexic, and icteric (can be observed periocularly). Limb edema, mucosal petechiation (including conjunctiva), and ataxia are also observed. Animals are also thrombocytopenic and leukopenic. Ocular manifestations of equine granulocytic ehrlichiosis include those already mentioned and uveitis (Ziemer et al., 1987).

Diagnosis of equine granulocytic ehrlichiosis is made based upon consistent clinical findings, identifying the organism within the cytoplasm of granulocytic leukocytes (neutrophils and eosinophils), detecting DNA within the blood of affected animals, and demonstrating circulating anti-Anaplasma antibodies (Magnarelli et al., 1999). Therapy is aimed at eliminating the organism by administering tetracyclines. Prognosis is good in uncomplicated cases of equine granulocytic ehrlichiosis (Madigan, 1993a).

**Viral**

**Adenovirus**

Adenoviral infection is primarily a problem in immunodeficient A rabian foals (McChesney et al., 1974). Affected animals develop fever, pneumonia, and leukopenia (McChesney et al., 1973, 1974). Clinical signs include a thick, yellow discharge from the eyes and nares that adheres to the eyelids, muzzle, and forelegs, as well as dyspnea, cough, and diarrhea. Necrosis of the epithelial surfaces occurs, including the conjunctiva and epithelium of the lacrimal glands. Microscopic lesions in the uvea have been seen, as has panuveitis. The conjunctiva may contain intranuclear inclusion bodies as well (McChesney et al., 1973). The diagnosis is established on the basis of virus isolation results, serum antibody titers, and viral inclusions in exfoliated epithelial cells. Therapy is supportive in nature, though demonstrated benefit from blood or serum with a high antibody titer has been reported. The mortality rate is high among foals with marked leukopenia.

**African Horse Sickness**

African horse sickness (AHS), an infectious but not contagious disease, is caused by a virus named African horse sickness virus, and this virus belongs to the family Reoviridae, genus Orbivirus (for review, see House, 1993; Mellor & Hamblin, 2004). There are nine serotypes which are transmitted by Culicoides sp. (biting midges) and, possibly, mosquitoes. AHS typically affects equidae in sub-Saharan Africa, but it has also been reported in the Middle East, Spain, and Portugal. There are four syndromes associated with AHS:

1. the peracute or pulmonary form;
2. the subacute, edematous or cardiac form;
3. the acute or mixed form; and
4. the horse sickness fever form.

In the peracute or pulmonary form, the clinical signs are fever followed by vascular congestion of the conjunctiva and mucous membranes, sweating, and cough. The mortality rate with this form of AHS is very high; death often occurs in 1–3 days.

The subacute or cardiac form has the early clinical signs of fever and vascular congestion of the conjunctiva and mucous membranes. Subcutaneous edema (from localized damage by the virus) develops in multifocal areas, including the eyelids and the supraorbital fossa, which may bulge (Maurer, 1961). Bulging of the supraorbital fossa is considered to be pathognomonic for the cardiac form. Petechial hemorrhages of the conjunctiva and ventral tongue may occur as well. The mortality rate is approximately 50%, with death occurring between 4 and 8 days after the onset of signs.

The acute or mixed form is the most common form of AHS, and it has the clinical signs of both the pulmonary and the cardiac forms. The mortality rate ranges from 50% to 95%, with death occurring from 3 to 6 days after the onset of fever.

The horse sickness fever form is the mildest form of AHS, and it may even go undetected. Clinical signs include low-grade fever, conjunctival vascular congestion, mild depression, and anorexia. Affected animals make a full recovery. The diagnosis of AHS is established on the basis of virus isolation, demonstration of the organism using molecular probes or...
Equine Viral Arteritis

Equine viral arteritis is a contagious equine disease caused by a togavirus known as equine viral arteritis virus (for review, see Del Piero, 2000; Timoney & McCollum, 1993a). Equine viral arteritis virus is transmitted via inhalation of the virus and through sexual contact. The virus causes a panvasculitis, with necrotizing arteritis of the small arteries of muscles commonly being seen (Del Piero, 2000). Outbreaks and serologic evidence of the virus have been reported from many countries around the world. Clinical signs include fever, depression, coughing, nasal and ocular discharge (Fig. 35.3.13 and Fig. 35.3.14), and abortion. Periorbital and peripheral edema, conjunctivitis, corneal opacity, and photophobia have also been described (Fig. 35.3.15) (Jones, 1969; Timoney & McCollum, 1993b; Traub-Dargatz et al., 1985). Diagnosis of equine viral arteritis is made based on consistent clinical signs, detecting a rising serum titer and/or isolation of the virus, and/or detecting the organism using RT-PCR (Del Piero, 2000). Treatment is aimed at supportive care, and most adult horses make a full recovery although stallions may become chronic carriers of the virus (Del Piero, 2000).

Figure 35.3.13. Photograph of the left eye of a horse with equine viral arteritis. Note the serous ocular discharge from the medial canthus. (Courtesy of R. Holyoak.)
Toes. Also important to note, these viruses are considered zoonotic.

Early clinical signs, regardless of the type of virus, include fever, stuporous state, ataxia, and hyperesthesia. Later signs include aggression, head pressing, blindness, paralyzed tongue and pharynx, nystagmus, strabismus, and pupillary dilatation. Diagnosis of equine viral encephalomyelitis is made based upon time of year (are mosquitoes present?), consistent clinical signs, rising serum antibody titers, and in acute cases, isolation of the virus from CSF or demonstration of the virus using RT-PCR (Calisher et al., 1983, 1986; Lambert et al., 2003; Linssen et al., 2000). Treatment is nonspecific and supportive in nature. The mortality rate is high, but horses can recover from viral encephalitis. Most will have residual neurologic signs, though complete recoveries have been reported (Devine & Byrne, 1960). Prevention of equine viral encephalomyelitis is through routine vaccination schedules and by controlling the mosquito population.

Influenza

Equine influenza is caused by infection with orthomyxoviruses of the influenza A type (for review, see van Maanen & Cullinane, 2002; Wilson, 1993). Influenza is highly contagious, and it is transmitted through aerosolized virus. Clinical signs include sudden onset of a harsh, dry, and nonproductive cough, fever, lethargy, and anorexia. Ocular signs include conjunctival hyperemia and excessive tearing. Treatment is symptomatic, with rest in a clean, well-ventilated area being important. Horses generally recover in 3–4 weeks.

Rabies

Rabies is caused by rabies virus, an enveloped RNA rhabdovirus (for review, see Woldehiwet, 2002). Rabies virus is purely a neurotropic virus and the source of the infection is another infected animal. Rabies virus is transmitted through inoculating infected saliva by biting a “naïve” animal. Interestingly, however, infection may occur via inhalation or ingestion of the virus (Gibbons, 2002). Common vector species include bats, foxes, raccoons, and skunks (Woldehiwet, 2002). After an animal has been bitten by an infective rabid animal, virus enters the CNS by migrating up peripheral nerves by binding to rabies virus receptors at the neuromuscular junction (for review, see Lafon, 2005). Consequently, the time from being bitten to showing brain dysfunction is related to the distance of the bite from the head (i.e., the further away the bite from the head, the longer it takes to see signs of brain dysfunction). Once the virus has reached the CNS, a nonsuppurative polioencephalomyelitis and ganglionitis develop and account, in part, for the development of clinical signs (Green et al., 1992; Hudson et al., 1996). With respect to clinical signs, classical “dumb” and “furious” forms of rabies have been described and are indicative of whether the limbic system is unaffected or affected, respectively.

Clinical signs of equine rabies are highly variable but include behavioral changes, ataxia and paresis of the hind
limbs, pharyngeal paralysis, recumbency, and signs of colic (Green et al., 1992; Hudson et al., 1996). Ocular signs indicative of infection of the central components of the visual and oculomotor systems, including blindness, nystagmus, and strabismus, may develop (Green et al., 1992; Hudson et al., 1996). During the clinical course of the disease, clinical signs worsen, and the animal eventually succumbs to the disease. A ntemortem diagnosis can be made by demonstrating antigen, using immunochemical methods or by detecting the virus using RT-PCR, in skin, corneal impressions, or saliva (Woldehiwet, 2005). Definitive diagnosis is made at postmortem by detecting the virus in brain tissue using immunochemical techniques or RT-PCR (Woldehiwet, 2005). Eosinophilic intracytoplasmic inclusion bodies (Negri bodies) may be observed in neurons throughout the CNS, including retinal ganglion cells (Haltia et al., 1989). It is important to note, however, that not all cases of rabies will have Negri bodies present; hence, the reason other more specific tests are used. Prevention of rabies is aimed at routine vaccination of susceptible animals.

West Nile Virus

West Nile virus (WNV) is a single-stranded RNA virus of the family Flaviviridae that is maintained in the environment by a bird–mosquito relationship (for review, see Garg & Jampol, 2005; Ostlund et al., 2000). Birds are the reservoir host while mosquitoes transmit the virus to a variety of animal species, including birds, horses, cats, dogs, bats, alligators, and humans (Garg & Jampol, 2005; Kulasekera et al., 2001; Nasci et al., 2001; Schuler et al., 2004; Turell et al., 2002). Horses are similar to humans in that they are considered dead-end hosts (cannot transmit the disease), although transfusion of infected animals has been reported to be 33% (Schuler et al., 2004). Prevention is aimed at implementing a routine vaccination schedule. In addition, the percent mortality for animals that develop clinical signs of the disease yet are vaccinated (when used according to the manufacturer’s instructions) is 4% while the mortality of unvaccinated animals has been reported to be 33% (Schuler et al., 2004).

Metabolic Diseases

Hypothyroidism

Hypothyroidism develops as a result of decreased production of thyroxine (T4) and triiodothyronine (T3) by the thyroid gland. Hypothyroidism is a rare condition in adult horses, and the prevalence of this endocrinopathy is unknown (Messer & Johnson, 2007). Clinical signs in horses with naturally occurring hypothyroidism are reportedly more subtle and vague than those in experimentally thyroidectomized horses which include lethargy, low exercise tolerance, and poor quality of the haircut (Messer & Johnson, 2007). A recent case report documented bilateral keratoconjunctivitis sicca and dry nares attributable to parasympathetic nerve dysfunction, headshaking syndrome with paresthesia and dysesthesia of the face attributable to sensory trigeminal nerve disorder, and hypothyroidism in a 6-year-old German Warmblood gelding (Schwarz et al., 2008). The two nerve dysfunctions were considered peripheral neuropathies that were most likely caused by the hypothyroidism. Readers are advised to consult a current large animal internal medicine textbook for a detailed discussion on the diagnosis of and therapy for equine hypothyroidism.

Pituitary Pars Intermedia Dysfunction (Equine Cushing’s Disease)

Pituitary pars intermedia dysfunction (PPID) is a condition seen in geriatric equids (for review, see Schott, 2002). It has been shown that hyperplasia of the pars intermedia likely results from loss of inhibition by neuronal degeneration of dopaminergic neurons (McFarlane et al., 2005). Because
dopamine normally is inhibitory to melanotropes of the pitu-
itary pars intermedia, and this inhibitory input is lost in horses 
with pars intermedia dysfunction, elevations in corticotropin, 
α-melanocyte stimulating hormone (α-M SH), endorphin, and 
corticotropin-like intermediate lobe peptide are seen in the 
serum of affected horses (Orth et al., 1982). A approximately 
0.001%–0.5% of horses, of any age, are estimated to be 
affected by PPID (Brosnan & Paradis, 2003; van der Kolk 
et al., 1993). The prevalence of PPID is estimated to be at 
least 10% of the geriatric equine cases seen in one referral 
institution, however (Brosnan & Paradis, 2003).

Clinical signs of PPID in equids include generalized muscle 
wasting, hirsutism, hyperhidrosis, impaired wound healing 
(may increase susceptibility to nonresponsive ulcerative kera-
titis), laminitis, and polyuria/polydypsia. With respect to 
ocular manifestations of equine PPID, bulging to the supraor-
bital fat pad may occur (due to presumed disease-related fat 
redistribution) and blindness (with or without concurrent neu-
rological signs) may also develop in cases of optic nerve 
compression due to the hyperplastic pars intermedia of the 
pituitary (Brosnan & Paradis, 2003; Donaldson et al., 2002).
Further, although not definitively proven, it is suspected that 
senile retinopathy may be related to PPID in horses and ponies 
(Chandler et al., 2003). Clinically, senile equine retinopathy 
manifests as an accumulation of linear or geographic depig-
mented areas combined with heavily pigmented regions in the 
nontapetal fundus with the tapetal fundus only rarely involved 
(Cutler, 2002). Senile retinopathy is characterized histologi-
ously by a loss of retinal pigment epithelium, loss of rods and 
cones, and a cystic degeneration of the inner layers of the 
peripheral retina (Barnett, 1972).

Diagnosis of PPID is made based upon consistent historical 
and clinical findings combined with positive results of a dexa-
methasone suppression test or by demonstrating elevated 
serum adrenocorticotropin hormone (ACTH). It should be 
noted, however, that laboratory diagnosis of PPID may be 
hindered by season (Donaldson et al., 2005). Treatment of 
equine PPID involves medically managing the disease by 
administering dopamine agonists, such as pergolide, or sero-
tonin antagonists such as cyproheptadine (Schott, 2002). 
Furthermore, it is important to implement appropriate husbandry 
and feeding regimes in addition to managing complications 
that may arise secondarily to PPID. Given the nature of the 
disease, therapy is needed for the duration of the animal’s life. 
Secondary complications, including susceptibility to various 
infections, are more likely in some horses with PPID.

Neoplasia: Central Nervous System

There are few reports of intracranial neoplasms with ophthal-
mic manifestations in the horse. A pituitary mass in one aged 
horse resulted in blindness caused by degeneration of the optic 
nerve, optic chiasm, and optic tracts up to the lateral genicu-
late bodies (deLahunta & Cummings, 1967). A another horse 
with a large intracerebral mass diagnosed as a microglioma 
had metastasis of the tumor to both eyes, with neoplastic cells 
being found within the vitreous humor and retina (Finn & 
Tennant, 1971).

Neoplasia: Systemic

Lymphosarcoma

Lymphosarcoma is the most common systemic neoplastic 
disease affecting the equine eye, but the disease in the horse 
occurs much less frequently than in the dog or the cat. Reported 
ocular manifestations of equine lymphosarcoma include 
eyelid swelling, third eyelid masses, uveitis (Fig. 35.3.16), 
chemosis and conjunctivitis, corneoscleral masses, and orbital 
lymphosarcoma (Blodi & Ramsey, 1967; Germann et al., 
2008; Glaze et al., 1990; Lavach & Severin, 1977; Murphy 
et al., 1989; Rebhun & Bertone, 1998; Rebhun & Del Piero, 
1998).

Nutritional Disorders

Thiamine Deficiency

Thiamine deficiency occurs in horses primarily because of the 
ingestion of plants containing the catabolic thiamine enzyme, 
thiaminase. Plants such as bracken fern (Pteridium aquilinum) 
and horse tails (Equisetum arvense) contain thiaminas, and 
equine thiamine deficiencies have been attributed to chronic 
ingestion of these particular plants (Carpenter et al., 1950; 
Evans et al., 1951; Henderson et al., 1952; Roberts 
et al., 1949). Amprolium, a coccidiostat, has been used to 
induce thiamine deficiency in horses experimentally (Cymba-
luk et al., 1978). Clinical signs of thiamine deficiency in the 
horse include ataxia, blindness, bradycardia, heart block,
Vitamin A Deficiency

Vitamin A (retinol), a fat-soluble vitamin, is derived from its precursors (carotenoids) which are found in plants (for review, see Fraser & Bramley, 2004; von Lintig & Vogt, 2004). With regard to the importance of vitamin A in the ocular system, vitamin A (retinol) is stored and transformed into retinal which is translocated between the retinal pigment epithelium and the photoreceptors (Thompson & Gal, 2003). Within the photoreceptors, retinal combines with opsin (a protein) to form the visual pigment rhodopsin (Thompson & Gal, 2003). Early signs of vitamin A deficiency include reduced feed intake and growth rate; a dull and brittle, long haircoat; and in foals, an increased incidence of respiratory and diarrheal diseases. A diagnosis of vitamin A deficiency in the horse is suspected in horses with excessive tearing and night blindness (Lewis, 1995). A n important differential diagnosis for vitamin A deficiency is CSNB in Appaloosa horses (the latter is present from birth, is nonprogressive, and has no clinically evident ocular lesions). Ocular lesions and night blindness occur only if vitamin A deficiency is severe and long-standing (Howell et al., 1941). Complete blindness from retinal degeneration eventually occurs if the horse remains on a vitamin A-deficient diet; at that point, the pupils will be dilated and unresponsive to light. In addition, horses with vitamin A deficiency may have hyperkeratinization of the cornea and reduced numbers of conjunctival goblet cells.

Diagnosis of vitamin A deficiency is made based upon documenting low levels of serum retinol and by using the relative dose response test (Grewe-Crandell et al., 1995). Horses consuming good-quality, green pasture grasses and hay are unlikely to suffer from vitamin A deficiency (Lewis, 1995). Therapy is aimed at providing adequate levels of vitamin A in the diet.

Toxicities

Electrocution

Electric shocks and lightning strikes can produce direct ocular sequelae and also cause injury to the CNS (may manifest as blindness, papilledema, cranial nerve palsies) (for review on pathogenesis and human manifestation, see Norman et al., 2001). Three horses suspected of being hit by lightning and four horses electrocuted because of a faulty electrical transformer have been reported (Bedenice et al., 2001; Evans et al., 2011; Novales et al., 1998). In some instances, affected animals may die acutely because of peracute heart failure (Bedenice et al., 2001; Evans et al., 2011). Affected animals can become recumbent and exhibit thrashing and/or had exuberant muscle contractions after being struck by lightning or electrocuted. Affected animals may manifest with a variety of neurological signs.

With respect to ocular findings, affected horses have been reported to have ulcerative keratitis (unsure as to cause—i.e., may be secondary to trauma from thrashing on ground), blindness, corneal edema and hydrops, signs of vestibular disease (spontaneous nystagmus), signs of facial nerve paralysis (including ptosis and absent palpebral reflex and menace response), and absent pupillary light reflexes (Bedenice et al., 2001). Fundus lesions were not found in one horse after being struck by lightning (Bedenice et al., 2001). In another horse, however, choroidal hemorrhage and retinal detachment and atrophy were present (Evans et al., 2011). Electric shocks and lightning strikes of a severe nature may produce cataracts that manifest months later.

Although not reported in horses, cataracts are likely to be produced by electrical shocks to the head. The appearance of clinical and experimentally induced electric cataracts are quite similar, and they consist initially of vacuoles that are present bilaterally in the midperipheral anterior cortical lens (Fraunfelder & Hanna, 1972; Thomas & Hanna, 1974). Ultrastructurally, the vacuoles are extracellular and transient, lasting several weeks. The lens vacuoles are prognostic indicators of later cataract formation. The lens epithelium subsequently proliferates, thereby producing multilayered plaques of lens capsule and lens fibers in the central anterior capsular region. Severe electric shock (e.g., from lightning) may produce both anterior and posterior cortical lenticular opacities (Norman et al., 2001).

Therapy for electrocuted horses is supportive and symptomatic. Horses surviving lightning strike or electrocution may have persistent neurological deficits or return to normal following the incident (Bedenice et al., 2001; Novales et al., 1998).

Fungal

Fusarium moniliforme (Blind Staggers, Moldy Corn Disease, Equine Leukoencephalomalacia)

Equine leukoencephalomalacia (EL) is a disease caused by the ingestion of a toxin, produced by F. moniliforme, fumonis sin (for review, see Uhlinger, 1997; Cole, 1973; Wilson & Maronpot, 1971). F. moniliforme is found in moldy corn. The disease has been reported worldwide, and it results in liquefaction necrosis of the white matter of one or both cerebral hemispheres (Wilson et al., 1985). Clinical signs appear suddenly and may affect a group of horses if all are fed from the same food source. Signs include depression, ataxia, recumbency, central blindness (with or without abnormal pupillary light reflexes), head pressing, circling, seizures, or frantic running behavior (Naranjo et al., 1996; Shanks et al., 1995; Wilkins et al., 1994).
Diagnosis is made antemortem based upon identifying clinical signs consistent with EL and by identifying a chronic exposure of the affected horse to moldy corn. Hepatic encephalopathy is clinically indistinguishable from leukencephalomalacia. Field corn has been most commonly implicated in this disease, but commercial feed rations may also be sources of F. moniliforme (Wilson et al., 1985). Culture of F. moniliforme and isolation of fumonisin toxins should be performed if the feed source is available (Naranjo et al., 1996; Wilkins et al., 1994). Aside from supportive therapy, there is no treatment for EL. Prognosis for horses affected with EL is commonly grave (Naranjo et al., 1996; Wilkins et al., 1994).

Plants

Numerous plants may be toxic to the horse (see Table 34.13 of Chapter 34, “Neuro-ophthalmology,” for additional information, including their systemic and ophthalmic effects). Historically, chronic selenium toxicity has been associated with “blind staggers” in the horse, but horses fed pure selenium compounds fail to develop the blindness, ataxia, or respiratory failure characteristic of blind staggers (Traub-Dargatz & Hamar, 1986). Thus, it has more recently been hypothesized that the toxic effects of alkaloids or other compounds in plants cause blind staggers, and that the condition does not relate directly to the selenium contained within these plants.

Many plants also have teratogenic effects in the horse, especially if they are eaten during the first trimester (Lewis, 1995). Pregnant mares may produce foals with a centrally placed, single eye if they eat Veratrum eschscholtzii during early pregnancy, much as ewes will produce such lambs if they eat Veratum californicum on day 14 of gestation (Binns et al., 1962, 1963).

Miscellaneous Diseases

Hyperkalemic Periodic Paralysis

Hyperkalemic periodic paralysis (HyPP) is a condition resulting from an abnormality of skeletal muscle sodium channel alpha-subunit and is inherited as an autosomal dominant condition (Naylor et al., 1992; Spier et al., 1993). It has been shown that descendents of the Quarter Horse stallion named “Impressive” are affected by this condition (Naylor, 1994). Consequently, HyPP should be considered in Quarter horses and crosses and breeds of horses with Quarter horse lineage (e.g., American Paint horses, and Appaloosas) with consistent clinical signs. As previously mentioned, HyPP is the result of a genetic mutation in a gene coding for a particular skeletal muscle sodium channel subunit (Cannon et al., 1995; Hanna et al., 1996; Rudolph et al., 1992a, 1992b). A result of this sodium channel defect in skeletal muscle membrane potential is predominantly a failure of sodium channel inactivation (Cannon et al., 1995; Hanna et al., 1996; Rudolph et al., 1992b). In conditions where the serum potassium concentration is elevated (e.g., high intensity exercise, renal failure), the membrane potential rises, threshold for an action potential is met, in HyPP-affected horses sodium channels fail to inactivate, and persistent depolarization of the skeletal muscle membrane occurs. The clinical consequence of persistent sodium channel inactivation is intermittent episodes of muscular fasciculation and weakness that oftentimes result in recumbency. During attacks, serum potassium levels are oftentimes, although not always, elevated (Naylor, 1994; Spier et al., 1990, 1993; Stewart et al., 1993).

Ocular manifestations of HyPP include third-eyelid protrusion secondary to retraction of the globe. Definitive diagnosis of HyPP is made based upon demonstrating the genetic defect (see the following genetic testing laboratories: Veterinary Genetics Laboratory, University of California at Davis, www.vgl.ucdavis.edu; Aimal Genetics Incorporated, www.horse testing.com/HYPP.htm; Healthgene Corporation, www.health gene.com/veterinary-testing/genetic-dna-testing/large animals/). A cute therapy for severe episodes is aimed at facilitating intracellular movement of potassium by administering intravenous calcium gluconate, glucose, or bicarbonate during attacks resulting in rapid recovery (M eyer et al., 1999; Naylor, 1997). Management practices involve reducing dietary potassium intake (avoiding potassium-rich alfalfa-based feed), enhancing renal excretion of potassium (e.g., acetazolamide administration), and avoiding metabolic states associated with elevated potassium (e.g., exercise). Owners of affected animals should be educated about the inheritance of this condition and should be discouraged from using the animal for breeding.

Temporohyoid Osteoarthropathy

Temporohyoid osteoarthropathy is a condition that involves the bony proliferation of the bones of the temporohyoid joint, namely the stylohyoid and petrous temporal bones (Walker et al., 2002; Yadernuk, 2003). The pathogenesis of temporohyoid osteoarthropathy remains unknown, although it is thought that otitis media or degenerative joint disease of the temporohyoid joint may be important in the pathogenesis of this disease (Walker et al., 2002; Yadernuk, 2003). Temporohyoid osteoarthropathy is commonly associated with facial (CN VII) and vestibulocochlear (CN VIII) nerve dysfunction (Walker et al., 2002; Yadernuk, 2003). Horses with this condition may also exhibit head shaking, hyperesthesia of the ears, and avoidance of bit placement (Yadernuk, 2003). Ocularly, temporohyoid osteoarthropathy commonly manifests secondarily through involvement of the parasympathetic fibers of cranial nerve VII (neurogenic keratoconjunctivitis sicca), cranial nerve VII (facial nerve paralysis), and the vestibular labyrinth and/or vestibulocochlear nerve (signs of peripheral vestibular disease) (Blythe, 1997; Verdegaal et al., 2003; Walker et al., 2002; Yadernuk, 2003). Diagnosis is made based upon consistent clinical signs combined with endoscopic, radiographic, or magnetic resonance or computerized tomographic evidence of asymmetry, inflammation, or osseous proliferation of the temporohyoid joint or stylohyoid bone...
(Walker et al., 2002). Therapy of temporohyoid osteoarthropathy involves appropriate antimicrobial therapy. Prophylactic partial stylohyoidostectomy is used in some instances (Bylythe, 1997; Newton & Knottenbelt, 1999; Pease et al., 2004; Walker et al., 2002). Prognosis for this condition is good; however, maximal resolution of clinical signs are not observed for up to 2 years, and many animals will have residual neurological signs (Walker et al., 2002).

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Chapter 35

Ocular Manifestations of Systemic Disease

Part 4: Food Animals

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CONGENITAL

Coat Color-Related Diseases/Conditions

Complete or Incomplete Albinism

Complete albinism (complete lack of pigmentation) or incomplete or partial albinism (an absence or reduction in the degree of pigmentation) is associated with not only the phenotypic appearance of an animal’s coat and skin color but is also associated with conditions affecting the eye. Albinism or incomplete albinism may result from the failure of migration of neural crest cells (precursors to melanocytes) and hence result in reduced numbers of melanocytes in a nonpigmented area, or may result because of impaired production of pigment due to some intrinsic deficiency in melanin production (e.g., tyrosinase deficiency) but where the number of melanocytes in nonpigmented or hypopigmented areas is normal.

Complete albinism, although rare in cattle, has been reported in several breeds including Swiss Brown “Braunvieh” in Europe (Winzenreid & Lauvergne, 1970), a Guernsey (Leipold et al., 1968) and Shorthorns (Greene et al., 1973) in the United States, and Murboden in Austria (Schlegler, 1959). Inheritance of complete albinism in these breeds appears to be recessive. Clinical and ophthalmoscopic manifestations of complete albinism in cattle include white coat, photophobia, blepharospasm, nystagmus, and nonpigmented irides and ciliary processes (Greene et al., 1973). In contrast, forms of dominant incomplete albinism in these breeds appear to be recessive. Clinical and ophthalmoscopic manifestations of complete albinism in cattle include white coat, photophobia, blepharospasm, nystagmus, and nonpigmented irides and ciliary processes (Greene et al., 1973).

Chediak–Higashi Syndrome

Chediak–Higashi syndrome (CHS) is an autosomal recessive disorder described in cattle and also in cats, minks, and mice (Ogawa et al., 1997; Prieur & Collier, 1978, 1981). Animals have a partial oculocutaneous albinism, an increased susceptibility to infection, a tendency for prolonged bleeding, and enlarged cytoplasmic granules in most, but not all, granule-containing cells. Ocular manifestations of CHS include photophobia, light or pale irides, pale tapetal fundus, and fundic hypopigmentation (Fig. 35.4.1). In affected cattle, the corpora nigra are also absent (Collier et al., 1979).

Ehlers–Danlos Syndrome (Dermatosparaxis, Hyperelastosis Cutis, Cutaneous Asthenia)

Ehlers–Danlos syndrome, or cutaneous asthenia, has been reported in sheep and cattle. It is a congenital, inherited syndrome involving collagen, and it is characterized by fragile and easily torn skin. Some animals have excessive joint laxity as well. The mode of inheritance of this syndrome in both sheep and cattle is autosomal recessive. If the complete syndrome is manifest, ocular lesions may occur. Dogs with the complete syndrome have ocular lesions consisting of lax eyelids, corneal edema, thin sclera, cataracts, bilateral lens luxation, and diffuse cortical cataracts (Barnett & Cottrell, 1987; Matthews & Lewis, 1990). The lenses were subluxated dorsally and were colobomatous ventrally (Barnett & Cottrell, 1987). A variant form of Ehlers–Danlos syndrome has been reported in a Holstein calf consisting of a genetic defect of the core protein of dermatan sulfate proteoglycan which caused the functional abnormality in cutaneous tissues (Tajima et al., 1999).
A diagnosis of Ehlers-Danlos syndrome is made based upon a clinical syndrome of skin hyperextensibility, clinical signs associated with skin fragility including easily torn skin, and skin histopathology (routine histopathology with Masson’s trichome staining and ultrastructural examination) (Paciello et al., 2003).

Ehlers-Danlos syndrome is incurable, and because of its hereditary nature, owners should be advised to not use affected animals for breeding.

**Hydrocephalus**

Hydrocephalus refers to increased amount of cerebrospinal fluid (CSF) within the cranial vault. Bovine hydrocephalus is a commonly encountered congenital defect for which concurrent ocular lesions are rarely reported (Greene & Leipold, 1974; Leipold et al., 1971, 1974). In Shorthorn calves, multiple ocular anomalies including microphthalmia, cataracts, retinal detachment, retinal dysplasia, optic nerve, optic chiasm and optic tract hypoplasia, persistent pupillary membranes, and vitreous hemorrhage have been associated with hydrocephalus (Leipold et al., 1971, 1974). The cause has not been determined, but it has been postulated to be genetic (Leipold et al., 1971).

**Marfan Syndrome**

Marfan syndrome is a condition characterized in cattle, and humans, by joint/tendon laxity, spinal curvature, long thin limbs, aortic dilatation and mitral valve malformation, myopia, microspherophakia, and lens luxation (Fig. 35.4.2) (Besser et al., 1990; Pessier & Potter, 1996; Potter & Besser, 1994; Singleton et al., 2005). Affected animals may succumb to the disease in early adulthood due to rupture of major cardiovascular structures (e.g., aorta). Like human Marfan syndrome, a genetic defect in the gene encoding fibrillin-1 (i.e., FBN1), a protein important in extracellular microfibrils, has been demonstrated (Hirano et al., 2012; Singleton et al., 2005).

**Multiple Ocular Defect Syndrome**

Multiple ocular defect syndrome (M ODS) is inherited as an autosomal recessive trait. This syndrome has been reported in Japanese black cattle and is characterized by congenital blindness, unilateral or bilateral medial strabismus, lenticular hypoplasia and/or dysplasia, retinal dysplasia and detachment, persistence of the hyaloid artery, persistence of the primary vitreous, and microphthalmia (Uchida et al., 2006). The genetic mutation for M ODS has been identified in the WFDC1 gene on chromosome 18, thus providing evidence of WFDC1’s importance in ocular development (Abbasi et al., 2009).

**DEVELOPMENTAL**

**Lysosomal Storage Diseases**

Lysosomal storage diseases have been identified in cattle and sheep, and occasionally in goats. These inborn errors of metabolism are, however, relatively rare diseases that have received a disproportionate amount of investigation, because they represent potential animal models for human syndromes. Storage diseases are characterized by an accumulation of metabolic by-products within lysosomes, the cellular organelles which degrade complex macromolecules. The substrates for catabolism within lysosomes include glycoproteins, mucopolysaccharides, oligosaccharides, proteins, and sphingolipids (Jolly & Walkley, 1997; Skelly & Franklin, 2002). Storage...
syndromes are usually severe, thus resulting in neurologic disease and, eventually, death. The eyes in most patients have histopathologic lesions, but clinical ophthalmic lesions may not be visible (Aguirre et al., 1986; Evans, 1989).

**Ceroid Lipofuscinosis**

Ceroid lipofuscinoses (CLs) are a group of inherited proteinoses characterized by accumulation of proteins in neurons and other tissues, including the retina. These storage products demonstrate an autofluorescence similar to ceroid and lipofuscin, lipopigments that accumulate normally with aging. However, ceroid and lipofuscin are not detected in appreciable quantities in these diseases. Subunit c of mitochondrial
adventitious triphosphate (ATP) synthase and sphingolipid activating proteins (SAPs)-A and -D have been identified as major constituents of the lysosomal storage products in human forms of CL (Hall et al., 1991; Palmer et al., 1992; Tyynela et al., 1993). CL has been described in cattle, sheep, and goats, as well as cats, dogs, humans, and mice (Harper et al., 1988; Jolly, 1995; Jolly & Walkley, 1997). This condition is inherited as an autosomal recessive trait (Prieur et al., 1990). CL is classified on the basis of age at onset. Clinical signs include a slowly progressive ataxia and animals will eventually succumb to the disease. Blindness develops in most instances, except with the late-onset adult form.

The sheep model has been studied most extensively (Jolly et al., 1994; Koppang, 1970; Sisk et al., 1990; Smith et al., 1996). Hampshire sheep present with blindness and, in advanced cases, manifest slight retinal vascular attenuation (Jolly & Palmer, 1995). In one report, Devon cattle in Australia with lipofuscinosis manifested visual and neurologic signs by 14 months of age, and they had ophthalmoscopio signs of altered tapetal reflectivity, optic disc pallor, and depigmentation of the nontapetal region (Smith & Harper, 1987). A autofluorescing lysosomal storage products accumulate in neural tissue including the retinal photoreceptors (Armstrong & Jolly, 1986). Peroxidase activity is decreased in the retina and leukocytes, but the exact enzymatic deficiency has not yet been defined (Armstrong et al., 1978; Jolly & Palmer, 1995; Siakotos et al., 1978).

**Galactocerebrosidosis (Globoid Cell Leukodystrophy, Krabbe’s Disease, Galactosylceramide Lipidosis)**

Galactocerebrosidosis, or globoid cell leukodystrophy or Krabbe’s disease, is a member of the inherited sphingolipidoses described in dogs, cats, and sheep that results from a deficiency in β-D-galactocerebrosidase (GALC) (aka galactosylceramidase) activity (Pritchard et al., 1980; Skelly & Franklin, 2002). The substrate galactocerebroside (i.e., galactosylceramide), a constituent of myelin, and another metabolite of myelin turnover, psychosine (galactosyl sphingosine), accumulate. Psychosine is highly cytotoxic to oligodendroglia and is thought to be the primary metabolite involved in the pathogenesis of the disease (Miyatake & Suzuki, 1972). Consequent to the buildup of these toxic metabolites, leukodystrophy results. A progressive, diffuse neurologic syndrome develops at a young age, and death occurs within a few months. Visual deficits and blindness may result late in the disease, but ophthalmoskopic lesions have not been observed (Aguirre et al., 1986). Globoid cell leukodystrophy is pathologically characterized by bilaterally symmetric demyelination of the white matter of the brain, spinal cord, spinal nerve roots, and peripheral nerves, and by the accumulation of globoid cells (multinuclear globoid macrophages), predominantly perivascularly.

**Generalized Glycogenosis**

Generalized glycogenosis (glycogen storage disease type II; Pompe’s disease) is caused by a deficiency of acidic 1,4-α-glucosidase (AAG) and has an autosomal recessive mode of inheritance (Reichmann et al., 1993). The disease has been described in humans, dogs, quail, sheep, and Shorthorn and Brahman or Brahman-type cattle in Australia. The disease occurs just prior to or after weaning at approximately 6 months of age in Brahman cattle. Affected cattle usually live less than 12 months (Reichmann et al., 1993). The earliest presenting clinical signs typically include failure to thrive and muscular weakness. As the disease progresses, the calves develop a wide-based stance, concave arch of the neck, and apparent enopthalmos.

Histopathologic lesions in affected calves include diffuse swelling and cytoplasmic vacuolation of neurons in the brain and spinal cord, and marked vacuolation in skeletal muscle fibers (Reichmann et al., 1993). In this same study, 2 of 96 affected Brahman or Brahman-type calves displayed apparent congenital blindness. The eyes of one such affected blind calf were examined histologically and had mild vacuolation of the retinal ganglion cells and glial cells in the optic nerves, similar to histopathologic lesions noted in two older affected calves with vision (Reichmann et al., 1993). Given these results, it remains unclear as to whether or not the blindness in these calves was directly related to generalized glycogenosis. Polymerase chain reaction (PCR) restriction enzyme-based assays have been developed for genotyping Brahman cattle for loss-of-function alleles within the AAG gene (1057deltaTA and 1783T) associated with generalized glycogenosis in this breed (Dennis et al., 2002). In addition, amplification procedures using leukocytes and hair roots as sources of target DNA have been effective for genotyping Shorthorns for generalized glycogenosis (Dennis & Healy, 2001).

**GM1-Gangliosidosis**

GM1-gangliosidosis is a member of the sphingolipidoses. A deficiency of lysosomal hydrolase, β-galactosidase, produces an accumulation of GM1-ganglioside in the cerebral cortex and visceral organs. Such deficiencies have been reported in cats, cattle, dogs, humans, mice, and sheep. With respect to food animals, the condition has been reported to occur in Friesian cattle and sheep (Donnelly & Sheahan, 1981; Donnelly et al., 1973; Murnane et al., 1989a, 1989b, 1991; Sheahan et al., 1978). Histopathologic lesions of membrane-bound inclusions have been demonstrated throughout the brain, spinal cord, and retinal ganglion cells, but only in cattle have clinical ophthalmoskopic lesions been observed consisting of multifocal tiny white spots. These ophthalmoscopic lesions were resultant from elevations of the internal limiting membrane by swollen retinal ganglion cells (Sheahan et al., 1978). Wallerian degeneration has also been reported in the optic nerves of affected calves (Sheahan et al., 1978). Affected animals typically live up to approximately 15 months of age.
GM 2-Gangliosidosis (Tay-Sachs Disease, Sandhoff Disease)

GM 2-gangliosidosis is caused by a deficiency of hexosaminidase (for review, see Jayakumar et al., 2002). Hexosaminidase has two subunits, α and β, each coded for by HEXA and HEXB genes, respectively. There are three types of hexosaminidase—hexosaminidase S (αα dimer), hexosaminidase A (αβ dimer), and hexosaminidase B (ββ dimer). In addition, there is a GM 2-activator protein coded for by the GM 2A gene which is necessary for degrading GM 2 ganglioside in concert with hexosaminidase A. In humans, deficiency in the α subunit, and therefore depletion of hexosaminidase A and S, results in classical GM 2-gangliosidosis (Tay-Sachs disease or B variant). A deficiency in the β subunit, depleting both hexosaminidase A and B, is known as Sandhoff disease or the O variant. Furthermore, deficiencies in GM 2-activator protein results in GM 2-activator deficiency, also known as the AB variant. GM 2-gangliosidosis has been reported in Yorkshire pigs (Read & Bridges, 1968). Clinical signs in affected pigs include ataxia after 3 months of age, reduced growth, and gray-white spots within the retina.

Mannosidosis

Mannosidosis, a member of the inherited oligosaccharidoses, is a recessively inherited deficiency of mannosidase resulting in the excessive storage of mannose-rich glycoproteins, glycopeptides, and oligosaccharides. Deficiencies of alpha (α) and beta (β) forms of mannosidase have been described. A α-mannosidosis has been described in Angus, Murray Grey, and Galloway cattle, and Nubian goats (Borland et al., 1989, 1992). Nevertheless, affected calves have a domed-shaped skull, mild prognathism, and vertically narrowed palpebral fissures, although the globes are normal-sized compared to age-matched unaffected calves. In bovine β-mannosidosis, the positioning, size, and shape of the pinnae, the external auditory meatus, and the tympanic bullae are also abnormal (Render et al., 1992). A side from nystagmus and narrowed palpebral fissures, clinical ophthalmic examination of affected calves is unremarkable.

Histopathologically, similar to affected goats, most ocular cells are distended with intracytoplasmic vacuoles (Jones et al., 1983; Render et al., 1989), except cattle with β-mannosidosis also have vacuolation of both the inner and outer ciliary epithelial cells (Render et al., 1992). Optic nerve hypomyelination is also reported in calves with β-mannosidosis (Patterson et al., 1991).

ACQUIRED

Hematologic Diseases

Anemia

Anemia is the reduction in red blood cells (RBCs) per volume of whole blood. Anemia is classified as regenerative if there has been a normal bone marrow response to erythropoietin (e.g., usually occurs with blood loss or hemolytic disease), or nonregenerative if the normal reticulocyte response is lacking (e.g., may occur with chronic extra-marrow disease which reduces RBC survival time, selective erythropoietin depression, insufficient erythropoietin release, or a combination of these factors) (Rebar et al., 2005a). Severe anemia often manifests systemically as varying pallor of mucous membranes, cool mucous membranes, tachycardia, polypnea, weakness, as well as signs specific to the underlying primary condition. Conjunctival pallor is even used as an indicator of anemia due to gastrointestinal parasitism in sheep and goats (Kaplan et al., 2004; Vatta et al., 2001). Ocular manifestations of severe anemia include pale retinal vasculature, varying degrees of retinal hemorrhage, and subtle changes in tapetal reflectivity. Retinal hemorrhages are more likely to be observed, however, and are more dramatic if accompanied by thrombocytopenia (Carraro et al., 2001). Small intraretinal hemorrhages are typical and may reabsorb quickly with correction of the anemia, but pigmentary disturbances may be a residual retinal alteration. The pathogenesis of the retinal hemorrhage is postulated to be from hypoxia to the vessel walls as a consequence of the anemia (Carraro et al., 2001). Extreme pallor of the retinal vessels may mimic the appearance of generalized/diffuse retinal degeneration/atrophy, with the exception of the marked tapetal hyperreflectivity present in the latter syndrome.
Icterus

Icterus or jaundice is a condition characterized by hyperbilirubinemia and deposition of bile pigments in the skin, sclera, and mucous membranes causing them to appear a shade of yellow. The sclera is the classic location for detection of icterus given its relative lack of pigmentation. The yellow appearance of icterus may be detected in the intraocular structures as well (e.g., blue irides may turn green and yellow hues may be imparted on the tapetum).

Polycythemia

Polycythemia is classified as relative or absolute (primary and secondary forms). Relative polycythemia is an increased packed cell volume (PCV) with normal RBC mass occurring as a result of a reduction in plasma volume as may arise from external losses of body fluids (e.g., diarrhea; burns).

Absolute polycythemia is an increase in total RBC mass, and it may be classified as either primary or secondary (appropriate and inappropriate). Absolute primary polycythemia (i.e., polycythemia vera) is an absolute increase in erythropoiesis without an increase in erythropoietin, and appears to be rare in food animals (Fowler et al., 1954). The underlying molecular basis of polycythemia vera has yet to be elucidated.

Absolute secondary polycythemia results from altered erythropoietin homeostasis and is described as being appropriate or inappropriate. Absolute secondary appropriate polycythemia occurs as a consequence of persistent hypoxia, and is seen in animals with conditions such as congenital cardiac defects causing right-to-left shunting of blood (Cote & Ettinger, 2001; Lombard et al., 1989; Moore & Stepion, 2001) and certain forms of chronic pulmonary disease. In large animals, congenital cardiac defects causing right-to-left shunts, such as tetralogy of Fallot and ventricular septal defect, are common causes of absolute secondary appropriate polycythemia (Bayly et al., 1982; Martin et al., 1972). Absolute secondary inappropriate polycythemia, however, results from disease processes which lead to inappropriate secretion and elevation of erythropoietin or an erythropoietin-like substance in the absence of systemic hypoxia. Causes of absolute secondary inappropriate polycythemia include diseases which result in the production of erythropoietin or which cause local hypoxia and trigger erythropoietin synthesis including renal (e.g., renal neoplasia, cystic disease, and hydropnephrosis), hepatic, or endocrine disease, especially that caused by neoplasia (e.g., hepatocellular carcinoma and interstitial nephritis) (Beech et al., 1967). The most prominent ocular manifestations of polycythemia reported in animals include engorged and tortuous, dark, ruddy colored conjunctival and retinal blood vessels. In addition, varying degrees of papill edema, retinal hemorrhage, and occlusion of the retinal veins caused by increased blood viscosity may occur. A heifer with absolute secondary appropriate polycythemia resulting from congenital cardiac disease developed hyphema and vitreous hemorrhage later in the course of the disease (Martin et al., 1972). Treatment varies according to the cause of the polycythemia. In one case of secondary appropriate polycythemia, treatment with two phlebotomies, performed 3 days apart, resulted in short-term relief followed by recurrent systemic signs, miosis and hyphema, and euthanasia 2 months later (Martin et al., 1972). If left untreated, however, retinal detachment and ocular hemorrhage may occur with persistent polycythemia (Lombard & Twitchell, 1978; Martin et al., 1972).

Thrombocytopenia and Thrombopathies

Thrombocytopenia results from either decreased platelet production, increased removal, sequestration, or any combination of these (Rebar et al., 2005b). The most common causes of thrombocytopenia in food animals include infectious diseases, immune-mediated disease, and drug-related or toxin-related causes. In particular, the numerous pathogens implicated in causing infectious thrombocytopenia in food animals include bovine viral diarrhea (BVD) virus (Hamers et al., 2000), Theileria annulata (Omer et al., 2002; Singh et al., 2001), Babesia bovis (Yeruham et al., 2003), and classical swine fever (CSF) (Bautista et al., 2002; Gomez-Villamandos et al., 2003). Thrombocytopenia is also seen (1) as an idiopathic (Hoyt et al., 2000; Yasuda et al., 2002) or primary immune-mediated thrombocytopenia; or (2) due to medications which impair platelet production, or cause secondary immune destruction of the platelets.

Thrombocytopenias are blood coagulation disorders as a result of platelet dysfunction and are either acquired or inherited (Rebar et al., 2005b). Disease processes associated with thrombopathies may include anemia, disseminated intravascular coagulation (DIC), liver failure, and uremia (Irma k & Turgut, 2005; Rebar et al., 2005b). Inherited thrombopathies are seen in cattle affected with CHS or may be inherited as a primary disorder in Simmental and Japanese black cattle (Akuzawa et al., 1991; Mapleton et al., 2000; Searcy et al., 1990). Regardless of the origin, both thrombocytopenia and thrombopathies are rather frequent causes of ocular and periocular hemorrhage. A case of idiopathic thrombocytopenia, diagnosed in a Japanese Black cow, resulted in sudden severe subconjunctival hemorrhage and hemorrhage under the mucous membranes of the vagina (Yasuda et al., 2002). The presence of bleeding signs at a given platelet level vary between individuals, but platelet counts are usually less than 50,000 cells/μL when ocular petechiae form. A cute loss of platelets is more likely to manifest as hemorrhage at a given level than is a gradual loss of platelets (Breitschwerdt, 1988). Therapy is directed at the underlying cause, and if bleeding signs are severe, transfusion of fresh whole blood or platelet-rich plasma is indicated.

Idiopathic Diseases

Idiopathic Bovine Uveitis (Bovine-Specific Ophthalmia)

An idiopathic uveitis affecting cattle has been described (Davidson et al., 1992; Marolt, 1968). As the name of this
condition implies, the cause of this condition remains elusive. Clinical signs of idiopathic bovine uveitis are compatible with uveitis and, in addition, chorioretinal edema and hemorrhage may be noted. Therapy for this condition is aimed at ameliorating intraocular inflammation. Prognosis is unknown given the paucity of clinical reporting of this disease.

Immune-Mediated Diseases

Allergic Conjunctivitis

Allergic conjunctivitis has been reported in food animals (Fledderus et al., 1988; Krahwinkel et al., 1988; Wiseman et al., 1982). Allergic conjunctivitis is mediated by immunoglobulin-E (IgE) and subsequent activation of histamine receptors by mast cell degranulation (Rosenwasser et al., 2005). Exuberant lacrimation, ocular pruritus, and hyperemic and edematous conjunctiva are common clinical signs of allergic conjunctivitis. Allergic conjunctivitis has been described in a herd of cattle with familial allergic rhinitis (Krahwinkel et al., 1988) and in veal calves being fattened with cow’s milk or milk replacer (Fledderus et al., 1988). The veal calves fattened with milk replacer showed signs of increased severity of diarrhea, hyperemia of the conjunctiva and nose, and skin hypersensitivity compatible with food allergy (Fledderus et al., 1988). Allergic conjunctivitis is typically diagnosed in food animals after excluding all other causes of conjunctivitis. Treatment is aimed at identifying and removing the inciting allergen.

Infectious Diseases

Bacterial

Botulism

Botulism is an intoxication resulting from the neurotoxin produced by Clostridium botulinum. C. botulinum is a gram-positive, spore-forming, saprophytic, anaerobic, rod-shaped bacterium. There are eight subtypes (types A, B, C-alpha and C-beta, D, E, F, G) of C. botulinum, and each is differentiated from the other based upon the type of neurotoxin they produce. Cattle, sheep, goats, and horses are considered to be quite susceptible to botulism compared to dogs, cats, and swine. Livestock are predominantly affected by C. botulinum type C or D, and less commonly type A or B (Kriek & Odendaal, 2004).

Clinical signs in livestock typically develop following ingestion of food, water, and soil contaminated by decomposed organic materials (e.g., carrion and putrid bones) containing neurotoxins produced by the bacterium (Kriek & Odendaal, 2004). In addition, nutritionally deprived animals may directly ingest infected carrion. After ingestion, the botulinum toxin is absorbed in the gut and subsequently prevents the release of acetylcholine (ACh) at cholinergic synapses. Consequently, clinical signs are suggestive of skeletal muscular weakness and autonomic dysfunction, regardless of the food animal species affected.

Clinical signs vary depending on the type and quantity of toxin ingested. General clinical signs include symmetrical ascending limb paresis leading to flaccid paralysis, depressed or absent tendon reflexes, abnormal motor responses during cranial nerve testing, excessive salivation, regurgitation of feed and water, and depressed ruminal movements. Sensory perception and reflexes associated with the eye persist for a significant period of time following the onset of skeletal muscular paralysis (Kriek & Odendaal, 2004). Ocular signs that may manifest include mydriasis due to loss of parasympathetic/sympathetic balance on the iris, and diminished pupillary light reflexes. Definitive diagnosis is made based on finding the toxin, through use of the neutralization test in mice, in the food, vomitus, feces, or serum. Treatment consists of supportive care and the administration of hyperimmune serum specific to the toxin type involved (to prevent further binding of toxin). Prognosis is variable and is dependent upon the severity of the disease and whether secondary complications (e.g., pneumonia, compartmental syndrome) occur. In cases of herd outbreaks, it is important to identify the source of food, water, and/or soil contamination.

Chlamyphophilosis

Several strains of bacteria in the family Chlamydiaceae cause disease in food animals. In particular, this family contains two genera, Chlamydia and Chlamydophila, each containing three and six species, respectively (Andersen, 2004). Chlamydial diseases in ruminants and swine are mainly caused by the species Chlamydophila pecorum, Chlamydophila abortus, and Chlamydia suis. However, C. pecorum is the main chlamydial pathogen responsible for disease in domestic ruminants. Hence, the term chlamyphophilosis will be subsequently used throughout this section to refer to chlamydial disease in food animals.

Chlamyphophilosis is caused by gram-negative, obligate intracellular bacteria that multiply in cytoplasmic inclusions in the cytoplasm of eukaryotic cells. The intestine is the natural habitat of this organism, and transmission is via fecal contamination, aerosol, and contact with infected secretions. It has been suggested that if contact is by aerosol, pneumonia and keratoconjunctivitis are the clinical manifestations (Ldsse, 1984). Factors influencing the clinical signs that manifest include the strain of chlamydiae (each strain has a predilection for different tissues and hence causes different disease(s)), age of animal, route of infection, and perhaps, the means of transmission. C. pecorum may produce a wide range of diseases in cattle, sheep, and swine including encephalomyelitis, enteritis, polyarthritis, metritis, pneumonia, and conjunctivitis (Andersen, 2004; Longbottom, 2004). Outbreaks of this particular disease are typically sporadic and usually affect young animals. In swine, C. suis strains have also been isolated from the conjunctiva, and intestinal and respiratory tracts in association with conjunctivitis, enteritis, and pneumonia. In severe cases of conjunctivitis, lymphofollicular hyperplasia of the palpebral conjunctiva is common. However, C. suis strains
Chlamydophilosis among lambs and kids may produce both ocular signs and polyarthritis (Hopkins et al., 1973). Up to 85% of affected lambs may develop polyarthritis as evidenced by a stiff gait or lameness. Lambs may be febrile, gaunt, and spend most of their time lying down. The infection may reach epidemic proportion in flocks as a result of being transmitted by close contact. The ocular signs are bilateral in 80% of cases. Conjunctival lesions include conjunctivitis, petchial hemorrhages, epiphora and mucopurulent exudation, and conjunctival lymphoid follicular proliferation which become confluent, thereby producing folds. The cornea may become involved in advanced cases with peripheral edema and neovascularization (preferentially of the dorsal region) (Fig. 35.4.3). Rarely, the entire cornea may become opacified, and corneal ulceration may develop. In uncomplicated cases, the condition is self-limiting, with resolution occurring within 2–3 weeks (Hopkins et al., 1973).

A definitive diagnosis of chlamydophilosis is made based upon the isolation or demonstration of the organism from infected tissues, combined with the presence of consistent clinical and/or pathological findings. Chlamydial agents may be demonstrated by conjunctival cytology, which may be positive for chlamydial inclusions in 35% of cases, and culture of Chlamydophila spp. which may be positive in 42% of cases. Isolation of the agent by cell culture is the method of choice; however, C. pecorum strains grow better in embryonated chicken eggs (Andersen, 2004). In addition, enzyme-linked immunosorbent assay (ELISA) kits are available for the detection of chlamydiae, but the sensitivity and specificity of these tests require further evaluation. There are also reports documenting the use of PCR techniques for the detection of various species of chlamydia (Everett et al., 1999; Kaltenboeck et al., 1992). Differentiation of chlamydial agents from Mycoplasma spp. may be achieved on the basis of culture results, fewer inflammatory cells at conjunctival cytology with Mycoplasma spp., lack of follicle formation with Mycoplasma spp., and tendency toward bilateral ocular involvement with Chlamydophila/Chlamydia spp.

Chlamydial organisms are ubiquitous in the livestock population. Hence, vaccination (available for ovine abortion strain [C. abortus] only) and antibiotic therapy are the main methods of control (Andersen, 2004). Treatment usually includes topical or systemic tetracycline therapy.

Hemophilus somnus (Thromboembolic Meningoencephalitis [TEM E], Sleeper Calves)

Hemophilus somnus is caused by infection with a nonencapsulated, gram-negative bacterium, H. somnus (Stephens & Little, 1981). H. somnus produces a peracute to chronic septicemia of yearling cattle, usually in feedlots, though pastured animals have also experienced outbreaks. Most infections occur during the early winter months, and mortality rates may be as high as 95%. The infection produces a vasculitis with thrombosis.

Clinical signs reflect the body system that is affected. H. somnus can cause mastitis, meningoencephalitis, myocarditis, otitis, orchitis, metritis, pneumonia, polyneuritis, and vulvitis (for review, see Harris & Janzen, 1989). Peracute cases are found either dead or with neurologic signs. Cranial nerve deficits are often present. Blindness may also be present, as may strabismus and nystagmus. Blindness may result from ocular disease or be central in origin due to multifocal hemorrhage and necrosis within the brain (MacDonald et al., 1973; Panciera et al., 1969; Stephens et al., 1981). Ocular lesions of conjunctivitis and, less commonly, corneal opacities and anterior uveitis may occur, but the most characteristic lesions are in the fundus. Ocular fundus lesions characteristic of TEM E are varying degrees of retinal hemorrhages and focal exudates, so-called cotton spots, associated with end-arterioles (Fig. 35.4.4). Focal retinal detachments may be associated with the exudates as well, and modest papilledema is often present.

Histopathologically, thrombosis of the retinal vessels, focal retinal necrosis, focal neutrophilic exudates in the retina, focal detachments, cystoid bodies in the nerve fiber layer, degeneration and neutrophilic inflammation of the vitreous, and an optic neuritis are typical lesions. The cellular reaction is mainly neutrophilic, but mononuclear perivascular reactions in the retina and choroid are also present. In the later stages
of the disease, fibrous chorioretinal adhesions are also seen (Dukes, 1971; Little & Sorensen, 1969).

Peracute to acute deaths with neurologic signs as well as retinal hemorrhages and exudates in feedlot cattle are highly suggestive of the diagnosis. Demonstration of elevated circulating serum antibodies for H. somnus can be helpful in the diagnosis of TEME (Stephens et al., 1981). Lesions of fibrinopurulent meningitis and multifocal hemorrhagic necrosis of the brain at necropsy are “pathognomonic.” PCR detection of H. somnus has been reported (Christensen et al., 2003).

Early treatment before the animal is recumbent using appropriate antimicrobials may prevent death. Vaccination is available.

Listeriosis
Listeriosis is caused by a small rod-shaped, gram-positive bacterium belonging to the genus Listeria. The most common and important organism causing disease in domesticated animals is Listeria monocytogenes. Spoiled or incompletely fermented corn or hay silage is the main source of infection. Small wounds in the lips and oral and nasal mucosae, and the conjunctiva permit entry of the causative agent (Braun et al., 2002). In addition, venereal transmission in ruminants has been described (Wiedmann et al., 1999). For further details regarding the transmission and pathogenesis of listeriosis in food animals, the reader is referred to a current textbook in food animal infectious disease and/or internal medicine.

Listeriosis of the central nervous system (CNS) (i.e., meningoencephalitic form) is most likely to be associated with ocular signs in food animal species. The main clinical manifestations of listeriosis include CNS disease with vestibular ataxia and unilateral cranial nerve deficits. Involvement of the brain stem may be associated with facial nerve paralysis and keratoconjunctivitis sicca. Keratitis is the main ocular lesion, though varying degrees of hypopyon and anterior uveitis may also be present. Purulent endophthalmitis may result as well (Saunders & Rubin, 1975). A variety of ocular lesions have been reported in sheep and goats with listeriosis including scleral hyperemia, unilateral keratitis with or without corneal ulceration, bilateral mydriasis, vertical or horizontal nystagmus, ventrolateral or ventromedial strabismus, unilateral or bilateral diminished or absent menace response, lack of palpebral reflex, and diminished or absent pupillary light reflexes (Braun et al., 2002; Gerros, 1998). In cattle, ocular lesions have been reported to be the most common clinical manifestation of listeriosis, followed by neurologic signs (Erdogan et al., 2001). Listerial ocular infections (conjunctivitis, keratitis, and uveitis) in ruminants have also been related to environmental or host factors, such as direct ocular exposure of susceptible animals to high numbers of the agent (Evans et al., 2004). In swine, listeriosis usually occurs in newborn pigs, among which oral exposure results in focal necrosis of the parenchymatous organs, lymphoreticular tissue, and a necrotizing vasculitis and septic choroiditis (Busch et al., 1971).

A diagnosis of listeriosis is made based upon consistent clinical signs, and culturing and identifying the organism from body fluids (e.g., CSF) and tissues. Suggested treatments include systemic administration of appropriate antimicrobials (e.g., penicillin or oxytetracycline), supportive therapy, and isolation of affected animals.

L. monocytogenes can cause serious disease in people including meningitis and sepsis, and, in pregnant women, spontaneous abortion and stillbirth can result (Low & Donachie, 1997).

Mycobacterium bovis (Bovine Tuberculosis)
Bovine tuberculosis, caused by Mycobacterium bovis, is a zoonotic disease which affects cattle worldwide. M. bovis also infects other animals, both domesticated and wild, thereby complicating attempts to control or eradicate the disease in cattle. Furthermore, bovine tuberculosis most commonly presents as apparently healthy cattle showing an immunologic response to tuberculin rather than animals with clinical disease (Collins, 2006). Ocular tuberculosis has rarely been observed as part of systemic disease in cattle, and swine; however, the ocular syndrome has been observed most frequently in cattle. As with most systemic infections, tuberculosis initially involves the choroid to eventually cause subretinal exudation and retinal detachment. Ocular tuberculosis may also progress to involve the anterior uvea, thus
resulting in an endophthalmitis. Ocular lesions are granulomatous, and hence, similar to systemic tubercles for the species (Saunders & Rubin, 1975).

Often, affected small animals are in farm settings and drinking unpasteurized milk. History as well as vitreous centrifugation with cytology and culture would establish a definitive diagnosis. Bovine tuberculosis is a reportable disease in many developing countries and large-scale eradication programs have been implemented and are effective in many countries (for review, see Collins, 2006; Cousins, 2001). Improved vaccines against bovine tuberculosis are also being developed and are likely to show promise in disease control and eradication strategies (Buddle et al., 2005).

Mycoplasmosis
Mycoplasmosis occurring in sheep and goats is caused by members of the genus Mycoplasma including Mycoplasma conjunctivae, Mycoplasma mycoides, Mycoplasma agalactiae, and Mycoplasma arginini (al-Aubaidi et al., 1973; Arbuckle & Bonson, 1980; Baaas et al., 1977; Bar-Moshe & Rapaport, 1981; Jones, 1983; McCauley et al., 1971; Rodriguez et al., 1995; Trotter et al., 1977; Whitley & Albert, 1984). The disease may be seen in individual animals or may be seen as an epidemic. Mycoplasmosis in sheep and goats has been reported to cause keratoconjunctivitis as a sole manifestation of infection or in association with various other systemic abnormalities including respiratory disease, arthritis, and mastitis. Mycoplasmosis has also been reported to cause an anterior uveitis, choroiditis, and hyalitis.

In cattle, Mycoplasma bovis has been reported to cause systemic disease including pneumonia, arthritis, mastitis, meningitis, infertility, and subcutaneous abscesses. M. bovis may also cause keratoconjunctivitis in affected cattle (Behrens et al., 1996; Kirby & Nicholas, 1996; Levisohn et al., 2004). Diagnosis of mycoplasmosis is made based upon consistent clinical signs, identifying the organism cytologically from conjunctival swabs, positively culturing the organism from conjunctival swabs and/or body fluids (e.g., synovial fluid), or identifying organismal DNA from affected animals (Bashiruddin et al., 2005; Thomas et al., 2004). Treatment is aimed at appropriate topical and/or systemic antimicrobial therapy (e.g., tetracyclines) (Rosenbusch et al., 2005).

Neonatal Septicemias
Neonatal septicemias in calves, piglets, kids, and lambs may arise from umbilical infections or ingestion of bacteria. Neonatal septicemias may be associated with polyarthritis, meningitis, and/or diarrheal signs, and may sporadically involve the eye. A variety of organisms may be associated with these syndromes, including Streptococcus sp., Escherichia coli, Corynbacterium pyogenes, Salmonella sp., Actinobacillus sp., Klebsiella sp., and Pasteurella sp. The usual ocular signs relate to the anterior segment, such as episcleral and conjunctival injection, fibrin clots in the anterior chamber, hypopyon or hyphema, and miosis (Fig. 35.4.5). Posterior segment lesions may be observed if the anterior segment is spared, and they are typical embolic lesions of multifocal hemorrhages, exudates, and focal retinal detachments. Many anterior segment lesions resolve with treatment, but the end result may be a fulminating endophthalmitis.

Figure 35.4.5. Photograph of the left eye of a septicemic goat with uveitis. Note the intracameral fibrin and corneal edema. (Courtesy of R. Hamor.)

Tetanus
Tetanus is caused by the neurotoxin produced by the bacterium, Clostridium tetani. C. tetani is a motile, gram-positive, nonencapsulated, anaerobic, rod-shaped, spore-forming bacterium. The organism is prevalent in soil worldwide, and spores typically enter the body through an open wound (Herd & Riches, 1964; O’Connor et al., 1993; Ramsay, 1973; Robinson, 1968). In some cattle, exuberant gastrointestinal growth of C. tetani may also be associated with causing the disease (Ellison, 1992; Ramsay, 1973; Wallis, 1963). Incubation times vary from 10 days to 1 month. Spores become vegetative and a toxin, tetanospasmin, retrogradely migrates along axons of motor nerves to the CNS. However, it should be noted that tetanospasmin, the principle neurotoxin, is only one of three toxins produced by the bacterium (Acke et al., 2004). The toxin then prevents inhibitory neurotransmission to motor neurons, thereby resulting in the classical signs associated with tetanus.

Clinical signs include initial stiffness progressing to generalized spasticity and paralysis. Infected animals generally have a sawhorse stance, retraction of the ears and lips, elevation of the tail, and rapid retraction of the globe, thereby resulting in prolapse of the third eyelids (McGuirk, 1983;
mammals (pigs), and rum canis (sheep), immune to reinfection. Facial involvement is common and may manifest as dry, crusty, periocular alopecic, and nonpruritic lesions. Lesions may be localized or generalized and involve the periocular and nonpruritic lesions. Lesions of the anterior chamber and iris as well as the ciliary body. Therapy for tetanus consists of providing muscle relaxation, providing an appropriate substrate for footing and bedding, eliminating infection by treatment with penicillin, neutralizing unbound toxin by administering tetanus antitoxin, maintaining hydration and nutritional status, and immunization with tetanus toxoid to stimulate an immune response (McGuirk, 1983). Prognosis is poor to grave (Ansari & Matros, 1982). Prevention is attained by proper hygiene and disinfection of surgical instruments during surgical procedures such as castration. Vaccinating animals with tetanus toxoid, although cost-effective, likely precludes vaccinating entire flocks of sheep or herds of cattle (Maru et al., 1986).

Mycotic

Dermatophytosis, or clinically relevant cutaneous infections with fungi, is usually caused by the following dermatophytes: Trichophyton verrucosum (bovids, goats, and sheep), Trichophyton ovis (sheep), Microsporum canis (pigs), Microsporum nanum (pigs), and Trichophyton mentagrophytes (pigs) (for review, see Picard & Vismen, 2004). Importantly, dermatophytosis is contagious and zoonotic. The severity and extent of experimentally induced dermatophytosis in calves caused by T. verrucosum was shown to be directly dependent on the degree of cutaneous damage at the site of mycotic inoculation (Oborilova & Rybnikar, 2005). In cattle, goats, and sheep, facial involvement is common and may manifest as dry, crusty, periocular alopecic, and nonpruritic lesions. Lesions may be localized or generalized and involve the periocular skin. The disease is typically self-limiting, and animals are immune to reinfection.

Diagnosis of dermatophytosis is made based upon consistent clinical signs typically affecting more than one animal in a group, microscopically identifying the organism on skin scrapings, and positively culturing the organism from skin scrapings on an appropriate culture medium (causing a “positive” color change in the culture media). Therapy is typically not implemented in food animals because of the expense incurred by treating a group of animals. In valuable individuals, however, appropriate antifungal drugs (e.g., griseofulvin) are administered and animals can be bathed in appropriate antifungal shampoos. Careful disinfection of affected animals’ housing is necessary to prevent spread of the disease, and a commercially available vaccine is effective and available for use in cattle (Gudding & Lund, 1995; Gudding & Naess, 1986).

Disseminated Rhizopus

Rhizopus is an opportunistic fungus. Although rare, systemic infections with opportunistic fungi, such as Rhizopus, occur most commonly in immunocompromised animals. In adult cattle, systemic mycoses typically arise due to pulmonary or alimentary invasion (Dion et al., 1987). In calves, systemic mycotic infection is rare, and is thought to arise due to hematogenous spread to the fetus from placental infection of the dam (Cordes et al., 1967). A calf with disseminated Rhizopus infection has been described with bilateral ocular lesions including endophthalmitis and intumescent immature cataracts (Vasconcelos & Grahn, 1995). Histopathologic ocular abnormalities included vasculitis, suppurative keratitis, anterior uveitis and chorioretinitis, and extensive subcapsular cataracts. Hyphae, most numerous adjacent to blood vessels, and numerous neutrophils were noted in all ocular tissues (Vasconcelos & Grahn, 1995).

Parasitic: Flagellates

Trypanosomiasis

African trypanosomes cause sleeping sickness in humans and trypanosomiasis in livestock. Sleeping sickness is caused by Trypanosoma brucei, an extracellular eukaryotic flagellate parasite. Livestock trypanosomiasis is caused by closely related Trypanosoma spp., and mainly affects animals in sub-Saharan Africa where the tsetse fly vector is common, but also occurs in Asia and South America (Berriman et al., 2005). Experimental T. brucei infection in sheep has produced an initial bilateral epihora, photophobia, and mucous exudation; ocular lesions were more likely to develop the longer the animals survived. Late in the course of disease, hypopyon may develop, which spontaneously improves and then relapses. The cornea may remain clear or develop a mild keratitis. Eyelid edema develops late in the course of disease and is part of extensive subcutaneous edema (Ikede, 1974). Histopathologic examination reveals trypanosomes in the fibrin of the anterior chamber and iris as well as the ciliary body. The anterior uvea is edematous, with a mononuclear inflammatory infiltrate. The retina and choroid have perivascular mononuclear cuffing, and optic neuritis is common. Extraocular muscles often have intense mononuclear inflammation, with trypanosomes being visible. Brain and eye involvement in goats with T. brucei and Trypanosoma vivax infections are thought to act as niduses of infection, from which relapses may originate after chemotherapy or spontaneous improvement (Whitelaw et al., 1988). Aqueous centesis may demonstrate the trypanosomes, and suramin, pentamidine, and benenil have been advocated for therapy.

Parasitic: Metazoaons

Cysticercosis

Cysticercosis is a zoonotic disease caused by the larval form of Taenia solium (pork tapeworm). Swine are the natural intermediate host of T. solium. Previously, humans were thought to be the sole definitive hosts and tapeworm carriers, and hence the source of infective eggs through which oral-fecal transmission causing cysticercosis would arise in humans and...
pigs. An alternative pig-to-pig route of transmission consisting of secondhand transmission of *T. solium* eggs has been reported (Gonzalez et al., 2005b). In humans, these metacestodes invade the brain (neurocysticercosis) and are responsible for most cases of adult-onset epilepsy in the world (Gonzalez et al., 2005b). The larval stage of *T. solium* may also invade the eye and orbit of various species. Among 39 abattoir swine diagnosed with cysticercosis, 17 had orbital cysts (Cardenas et al., 1984). The parasite stimulates a fibrous sheath, which is formed by the host, which initially does not have inflammatory cells. Macrophages accumulate around the cyst, however, with a halo of lymphocytes and plasma cells that, eventually, surround the parasite (Cardenas et al., 1984). In particular, the active inflammatory response against the metacestode of *T. solium* in swine includes the participation, in sequence, of CD4+, CD8+, and IgM+ lymphocytes (Perez-Torres et al., 2002). Strategies aimed at avoiding disease transmission have involved chemotherapy of infected pigs (e.g., albendazole sulfoxide at 15 mg/kg q 24 hours for 8 days) (Peniche-Cardena et al., 2002) and vaccination to prevent infection of the pig intermediate host (de Aluja et al., 2005; Gonzalez et al., 2005a).

Setariasis

Adult *Setaria digitata* are found free within the abdominal cavity of many ungulates including cattle and sheep (Shin et al., 2002). The larvae of *Setaria spp.* can migrate into the CNS of animals such as sheep and goats and cause serious disease (Innes & Shooh, 1953). Typically, the adult worms of *Setaria spp.* within the abdominal cavity of cattle are mainly harmless. Heterotropic parasitism of cattle with *Setaria spp.*, although rare, has been reported to the cavity of a cystic corpus luteum (Nair et al., 1993) and the eye (Shin et al., 2002). In particular, two cattle in Korea each had a single opaque, blind eye with the presence of motile white worms in the aqueous humor, which were later identified as *S. digitata* in one such case.

**Parasitic: Mites**

Demodicosis

Demodex spp. live as commensals in the skin of most mammals. In cattle, demodicosis is caused by a burrowing mite, *Demodex bovis*, which lives in the hair follicles. The clinical signs associated with *D. bovis* typically include tiny to egg-sized nodules, containing mites in a purulent material, with generalized distribution over the forelimbs and withers (Nutting, 1976). Demodicosis may also affect the eyelids. Diffuse, firm swellings beneath both eyes, causing disfigurement of the ventral eyelids, have been reported in a heifer (Gearhart et al., 1981). Biopsy of the diseased palpebra revealed chronic eosinophilic granulomatous cellulitis and degenerate D. bovis. Regression of these lesions occurred within 3 months without treatment.

**Parasitic: Protozoa**

Besnoitiosis

Besnoitiosis, elephant skin disease, is a relatively common disease of cattle caused by the protozoan parasite Besnoitia besnoiti. The infection may be clinically apparent or, in its severe form, it manifests as two sequential stages: (1) the acute stage characterized by fever and anasarca, and orchitis in bulls, and (2) the chronic stage as evidenced by scleodermatia, alopecia, and hyperkeratosis. Fever is the initial clinical sign followed, a few days later, by hyperemia of the muzzle, peri orbital skin, and scrotum in pale-skinned animals (for review, see Bigalke & Prozesky, 2004).

Leishmaniasis

Leishmania spp. are diphasic protozoal parasites that infect a wide range of vertebrates, mainly dogs and humans. Dogs are primary reservoirs of Leishmania spp., and sandflies (*Phlebotomus spp.* or *Lutzomyia spp.* ) are the vectors. The cutaneous form of leishmaniasis has been described in sheep from South Africa (van der Lugt et al., 1992). Clinical signs included severe swelling and diffuse cutaneous thickening and crusty exudate of one pinna, and small cutaneous crusts around the external nares, upper lip, muzzle, lateral aspects of the face, as well as the eyes. Alopecia, hyperpigmentation, hyperkeratosis, and crust formation have also been described in affected sheep in the periorcular skin, and the skin along the dorsum of the nose and both ears.

Neosporosis

Neospora caninum is a protozoal parasite, having structural and biological similarities to *Toxoplasma gondii*, that can infect livestock. Neosporosis can be transmitted vertically and horizontally. In naturally infected cattle, sheep, and goats, *N. caninum* can be transmitted transplacentally. In adult cows, abortion is the sole observable clinical sign (Dubey, 1999). However, N. caninum-infected calves may be born underweight with neurological signs including inability to rise, ataxia, and loss of conscious proprioception (Barr et al., 1993; Dubey et al., 1990). Ocular manifestations of neosporosis in affected calves, such as exophthalmia or an asymmetrical appearance of the eyes, may also be observed.

Sarcocystis

Sarcocystis is caused by tissue cyst-forming coccidia, Sarcocystis spp. Cattle are intermediate hosts. Sarcocystosis has been reported in the ocular musculature of cattle in India infected with *Sarcocystis cruzi*, with a prevalence of 71.5% (Juyal et al., 1982). The affected ocular musculature contained a heavy concentration of cysts, and appeared to be the preferred site for the development of sarcocystosis in this species, second only to cardiac musculature. Sarcocysts have also been reported in the ocular muscles of sheep experimentally infected with *S. ovicanis* sporocysts from dogs (Leek & Fayer, 1978).
**Prions**

**Scrapie**

Scrapie is a neurodegenerative disease of the group of transmissible spongiform encephalopathies (TSEs) affecting sheep and goats. Sheep are regarded as the natural reservoir for scrapie. The incubation period is typically between 2.5 and 3.5 years. According to the prion hypothesis, which explains most of the biological features pertaining to the scrapie agent, scrapie lesions are triggered by the conversion of the cellular prion protein (PrPc) into the abnormal isoform (PrPSc) resulting in its pathological accumulation (Hunter, 1998). Scrapie produces progressive neurological signs, the lesions of which consist mainly of vacuoles within the nervous system, and eventual death. In particular, clinical signs are categorized into three main groups including (1) sensation abnormalities, namely pruritis, (2) changes in mental status including apprehension and occasional aggression, and stupor, and (3) postural and locomotion changes such as low carriage of the head, wide-based or cross-legged stance, pacing (Braun et al., 2004a), and ataxia (for a review of scrapie, please refer to Bradley & Verwoerd, 2004).

One study examining the neuro-ophthalmic manifestations of naturally occurring scrapie using 17 affected animals and 6 age-matched control animals has been published (Regnier et al., 2011). In this study, there was no evidence of anisocoria, pupil size aberrations, pupillary light reflex abnormalities, or corneal or palpebral reflex abnormalities. Three affected animals, however, had inconsistent menace responses, though one control animal also had an inconsistent menace response. As such, it is unclear from this study whether sheep with scrapie develop altered vision. Interestingly, however, all scrapie-affected sheep had histopathological changes consistent with retinal degeneration. Future studies would need to examine a larger population of animals to more clearly identify whether visual field deficits exist in sheep affected by scrapie.

Ocular manifestations of scrapie infection of sheep and goats include multifocal, round tapetal lesions that can be as large as the optic disc. Histologically, these lesions are focal retinal detachments resulting from subretinal accumulations of eosinophilic material characterized as lipid (Barnett & Palmer, 1971; Fig. 35.4.6). These fundic lesions are typical enough to be suggestive of the diagnosis when combined with chronic, progressive neurologic disease. Importantly, however, not all animals with scrapie have retinal changes that can be observed ophthalmoscopically (Regnier et al., 2011).

Electrophysiologically, sheep affected by scrapie have reduced a- and b-wave amplitudes, though waveforms are similar between affected and unaffected animals, and there are no differences in implicit times between affected and unaffected animals (Regnier et al., 2011).

There is no effective treatment for scrapie. Animals suspected of having scrapie should be euthanized, and their brain should be submitted for laboratory examination.

**Figure 35.4.6.** Retinal photograph from scrapie-affected sheep showing raised blister-like areas scattered in the tapetal fundus. (Reprinted with permission from Barnett, K.C. & Palmer, A.C. (1971) Retinopathy in sheep affected with natural scrapie. *Research in Veterinary Science*, 12, 383–385.)

**Viral**

**African Swine Fever**

African swine fever (ASF), caused by ASF virus, is the only member of the newly named Asfaviridae and the only known DNA arbovirus (in Dixon et al., 2000 as by Zsak et al., 2005). There are several disease forms of ASF ranging from a highly lethal hemorrhagic disease of domestic swine to subclinical infections (Mebus, 1988). Ocular lesions have been reported in affected pigs, including conjunctival hemorrhages, and serous to mucopurulent conjunctival and nasal discharges in the early and latter stages of ASF, respectively. In addition, blindness in phthisical globes with keratitis has also been reported in ASF-infected pigs (Vestre, 1984). A diagnosis of ASF is made based upon detection of the infectious virus, viral antigens, and specific antibodies, and by using PCR assays for the detection of genomic DNA (King et al., 2003).

**Bluetongue**

Bluetongue is caused by an arbovirus. The virus is transmitted by Culicoides gnats and causes disease in ruminants. Clinical signs of bluetongue in cattle include fever and vasculitis, and severe conjunctivitis accompanied by mucosal lesions, lami-nitis, and edema of the lips. In sheep, attenuated, modified live vaccine strains of bluetongue virus may produce deformed lambs, brain deformities, and ocular lesions when injected.
during the 8th-11th week of pregnancy. The ocular lesions from such injections are primarily a choroiditis and retinitis centered around retinal vessels, with retinal necrosis and retinal dysplasia. Similar lesions have not been reported with natural infections (Silverstein et al., 1971). PCR techniques are being developed for the surveillance of bovine arboviruses, including bluetongue virus, in field specimens (Ohashi et al., 2004).

Bovine Herpesvirus-Type 4

Bovine herpesvirus-type 4 (BHV-4), a gammaherpesvirus, is another widespread herpesviral pathogen of cattle. Clinical signs associated with BHV-4 include conjunctivitis, pneumonia, metritis, enteritis, cutaneous mummification, and tumors of the rumen and urinary bladder (Goyal & Naem, 1992). BHV-4 has also been isolated from conjunctival swabs in cases of naturally occurring BHV-4 keratoconjunctivitis (B artha et al., 1966). One study has detected BHV-4 DNA, using a nested PCR assay, in the conjunctiva and cornea of experimentally infected calves at 62 days postinfection, indicating contributions by these ocular tissues in the persistence BHV-4 infection (Egyed & Bartha, 1998).

Bovine Leukosis

Bovine leukemia virus (BLV) is an oncogenic retrovirus with worldwide distribution. In adult cattle, lymphosarcoma is commonly caused by BLV. Cattle sometimes experience a syndrome of orbital involvement with lymphosarcoma that results in a progressive, bilateral, or unilateral exophthalmos. For more information regarding this syndrome, the reader is referred to “Lymphosarcoma” under the “Neoplasia: Systemic” section later.

Bovine Viral Diarrhea

Bovine viral diarrhea (BVD) results from a pestivirus with a worldwide distribution that infects cattle, sheep, goats, and wild ruminants. It is transmitted via inhalation or ingestion of infective secretions or excretions, semen, and transplacentally. Results of one study showed that BVD virus can also be transmitted to susceptible animals if they come into contact with fetal fluids during the birth of persistently infected calves (Lindberg et al., 2004). BVD virus has been implicated with causing abortion, and cerebellar and ocular disease. In cattle, in utero infection with BVD virus between 76 and 150 days of gestation may result in congenital defects of the eye and brain. In addition, following experimentally induced BVD infection, persistently infected calves have minor skeletal abnormalities including short limbs, narrow skull with bulging eyes, and/or prognathism (Stokstad & Loken, 2002). CNS lesions include microencephaly, cerebellar hypoplasia, hydrencephaly, and hydrocephalus (Baker, 1987). Ocular lesions of cataracts, retinal degeneration and retinal dysplasia, optic nerve gliosis, optic neuritis, and microphthalmia have also been described with experimentally induced disease (Bistner et al., 1970; Scott et al., 1973). At ophthalmoscopy, the tapetal coloration is altered, and pigment clumping is visible. Cataracts and optic nerve lesions may not be present in naturally occurring cases of BVD; this may relate to the stage of gestation during which the pregnant dam became infected (Bistner et al., 1970). A cute histopathologic ocular lesions detected in fetuses taken 17-21 days following inoculation of their dams at 150 days gestation included mild to moderate retinitis causing destruction of the retinal layers, mononuclear cuffing of the inner retinal vessels, proliferation of the retinal pigment epithelium, and choroiditis (Brown et al., 1975).

Ocular lesions of tapetal color alterations, optic nerve atrophy and cataracts, and cerebellar hypoplasia are suggestive of BVD. A diagnosis of BVDV is further confirmed based upon the demonstration of the virus via microtiter virus isolation (VI) or sandwich ELISA (S-ELISA) using serum. Serotesting must be performed beforecolostrum is ingested, however, and immunotolerance may produce a lack of antibody response. A n S-ELISA kit has been reported to be effective for the detection of cattle persistently infected with BVDV (Saliki et al., 2000). At present, there is no therapy for BVDV.

Hog Cholera

Hog cholera is a highly contagious viral disease of swine caused by hog cholera virus (HCV), a member of the genus Pestivirus. The organism has a close antigenic relationship with BVD virus and border disease virus. The pig is the only natural reservoir of HCV. Blood, tissues, secretions, and excretions from an infected animal contain HCV. Transmission typically occurs by the oral route, though infection can occur through the conjunctiva, mucous membranes, a skin abrasion, insemination, and percutaneous blood transfer (e.g., common needle). Transplacental infection with viral strains of low virulence often results in persistently infected piglets, which constitute a major cause of virus dissemination to non-infected farms.

Hog cholera occurs in several forms including acute, subacute, chronic, or persistent. In the acute form, the disease is characterized by high fever, depression, multiple superficial and internal hemorrhages, and high morbidity and mortality. In the chronic form, the signs of depression, anorexia, and fever are less severe than in the acute form, and recovery is occasionally seen in mature animals. In the acute form of hog cholera, conjunctivitis is frequent and is manifested by copious ocular discharge, periocular crusting, and the eyelids may adhere together as a result of the exudate. Histopathologic ocular lesions of mononuclear inflammation of the retina and uvea may develop with hog cholera if the animal survives for 1 week or more. In addition, iridociliary congestion, edema, and, less frequently, hemorrhage may develop (Vestre, 1984). Anterior uveitis, focal choroiditis, retinitis with perivascular cuffing and gliosis, and optic neuritis may also occur with time (Saunders et al., 1958).

For details regarding the diagnosis and control and prevention of hog cholera, the reader should consult a current large animal internal medicine or infectious disease textbook.
Infectious Bovine Rhinotracheitis

Infectious bovine rhinotracheitis (IBR), caused by bovine herpesvirus-type 1 (BHV-1), a member of the alphaherpesvirus family, is an important pathogen of cattle. Infection with BHV-1 typically arises ocularily or via the nasal cavity. Following acute infection, the primary site for BHV-1 latency is within sensory neurons in the trigeminal ganglia (Lovato et al., 2003). Sporadically, reactivation of the virus from latency occurs, causing viral shedding and transmission to susceptible cattle. The persistence and reactivation of BHV-1 has also been reported within the germinal centers of pharyngeal tonsil of latently infected calves (Winkler et al., 2000). Depending on the strain of virus involved, IBR can cause various forms of disease including conjunctivitis/keratitis, severe respiratory infection, abortion, vulvovaginitis, balanoposthitis, and systemic infection in neonatal calves (Wylor et al., 1989). BHV-1 is also one of several agents linked with “shipping fever” or bovine respiratory complex (Tikoo et al., 1995). Outbreaks usually consist of a predominant form. The ocular form may be the only sign or it may be associated with respiratory signs. The ocular lesions of IBR are either unilateral or bilateral and may be confined to the conjunctiva. Conjunctivitis is thus the most common ocular manifestation of IBR, and may be characterized by raised, red to white plaques of lymphocyte follicles in chemotic bulbar and palpebral conjunctivae (A binati & Plumer, 1961; Rebhun et al., 1978). The ocular discharge is initially serous, following which it progresses to become mucopurulent. A nonulcerative keratitis of varying degrees may develop in some animals. The keratitis is characterized by peripheral edema and deep neovascularization that spreads centrally. In severe cases, the cornea becomes completely opaque from the edema and leukocytic infiltration, thereby producing blindness. Anterior uveitis, which is evidenced by miotic pupils and thickened irises, may accompany the keratitis. The course of the conjunctivitis is approximately 2 weeks, but as with other herpesvirus infections, latent carrier states develop, and such animals may become symptomatic with stress. One study has demonstrated that a latency-related protein promotes ocular viral shedding during acute IBR infection in calves (Inman et al., 2001). In addition, anti-apoptotic properties of the latency-related gene were thought to play an important role during the establishment of BHV-1 latency (Lovato et al., 2003). IBR may also produce ocular lesions of conjunctivitis and keratitis with respiratory disease in goats (Mohanty et al., 1972). The diagnosis of IBR is established on the basis of viral isolation and fluorescent antibody testing of conjunctival scrapings. PCR techniques are also being used. Specific antiviral therapy is usually not given as cattle typically recover spontaneously from the conjunctival form of the disease. Genistein, an inhibitor of tyrosine kinase activity found in soya products, has resulted in inhibition of BHV-1 replication in vitro (A kula et al., 2002). Vaccines are available to prevent and control the disease in susceptible animals.

Maedi-Visna

Maedi-visna is a systemic disease of sheep caused by a lentivirus, maedi-visna virus (MVV). Transmission of MVV is generally by pulmonary aerosols, semen, or colostrum. MVV mainly affects the lungs, CNS, and other tissues including joints and the mammary glands. MVV proviral DNA has been detected, via nested PCR, in the third eyelid of sheep naturally infected with maedi-visna (Capucchio et al., 2003). In particular, maedi-visna viral DNA has been detected in situ within macrophages, and glandular, ductal, and surface epithelia in the third eyelid of affected sheep. In this same study, a moderate to severe lymphoproliferative inflammation was also noted in the third eyelids of all MVV-infected sheep (Capucchio et al., 2003).

Malignant Catarrhal Fever

Malignant catarrhal fever (MCF), caused by ovine herpesvirus-2 or alcelaphine herpesvirus-1, is an often fatal and communicable disease in cattle. The disease may affect other cloven-hoofed animals including some wild ruminants and occasionally domestic pigs as well. It may produce either sporadic disease affecting one or more animals in a herd or epizootics involving large numbers of animals. It typically produces an acute syndrome of pansystemic vasculopathy that results in death from 1 to 10 days after the onset of clinical signs.

Four to five variations in clinical signs have been described. The most prominent clinical manifestations of MCF are pyrexia, profuse nasal and/or ocular secretions, hyperventilation, and death (Brenner et al., 2002). The “head-and-eye” form of MCF is the classic manifestation, and when this is observed, the diagnosis can be established on the basis of clinical signs (Pierson et al., 1973, 1978; Zemljic et al., 2012). Ocular lesions associated with this form of MCF include corneal edema, uveitis, exophthalmos, bilateral blindness, photophobia, nystagmus, severe lacrimation (Brenner et al., 2002; Zemljic et al., 2012). Corneal edema is the most obvious ocular lesion and develops within 36 hours of the onset of disease (Fig. 35.4.7). The edema may vary from mild, peripheral edema to dense, diffuse edema. Epithelial erosion is common and may occur from either subepithelial bullae or degenerative changes in the epithelium. If the cornea is clear, an anterior uveitis is evident by fibrin, cells, and flare in the anterior chamber as well as by miosis and iris texture changes (Fig. 35.4.8) (Whiteley et al., 1985; Zemljic et al., 2012). Histopathologically, panophthalmitis is present, with lesions being characterized by marked lymphocytic vasculitis, and this characteristic proliferation results in lymphocytes and lymphoblasts within the lesions. Lymphocytic ciliary neuritis and optic meningoitis were detected, although less commonly (Whiteley et al., 1985). As well, corneal endothelial degeneration secondary to endothelialitis has been described (O’Toole et al. 1997). The pathogenesis of the lesions is speculated to be immune-mediated.

The clinical signs are diagnostic if classical, but other clinical variations must be diagnosed on the basis of the classical
ized by corneal opacity, CNS disorders, and reproductive failure. CNS manifestations (e.g., fatal encephalitis) and corneal opacity are the main signs in piglets 2–21 days old (Ramirez-Herrera et al., 1997, 2001; Stephan et al., 1988; Stephan & Gay, 1984). Older pigs appear more resistant and corneal opacity is a commonly observed feature (Stephan et al., 1988). PR infection in pregnant sows has been linked with reproductive failure and infertility. Piglets 2–15 days of age are most susceptible. Affected piglets become prostrate, and develop progressive neurologic signs. Affected animals may be blind, with dilated pupils and nystagmus. In addition, PR-affected pigs may develop conjunctivitis with epiphora, swollen eyelids, and ocular discharge adherent to the eyelids. Piglets older than 30 days of age may have respiratory signs and corneal opacities, or they may strictly have corneal opacities. Up to 30% of affected piglets have either unilateral or bilateral corneal opacities, which tend to resolve spontaneously.

Histopathologically, ocular lesions consist of corneal edema and anterior uveitis. The cellular reaction is mononuclear, with some neutrophils and intracytoplasmic inclusions possibly being present in the epithelial cells (Hornedo & Gutierrez, 1986; Stephan, 1990). PR has also been shown to bind to pig neuronal tissue of the brain stem, hippocampus, olfactory bulb, cerebellum, and frontal, temporal, and parietal lobes of the cerebral cortex in newborn, 60-day-old, and adult pigs (Mendoza-Magana et al., 2001). Clinical signs of encephalitis and corneal edema in piglets, or reproductive failure in adults, is/are suggestive of the diagnosis. The diagnosis is confirmed on the basis of virus isolation and hemagglutination-inhibition tests. At present, there is no specific therapy.

Pseudorabies (Aujeszky’s Disease)

Pseudorabies is caused by Aujeszky’s disease virus, a neurotropic alphaherpesvirus. Pseudorabies epizootics in swine are noted with drastic climatic changes, and they are characterized by blindness, depression, head pressing, and death. Death or recovery tends to occur by day 3, with blindness occurring as a permanent sequela in recovered animals. Histopathologically, ocular lesions include decreased numbers of retinal ganglion cells, degeneration of retinal ganglion cells, and perivascular cuffing with mononuclear cells and neutrophils in the optic nerve (Howarth & De, 1968). In addition, rapidly progressive punctate corneal ulcers associated with blepharospasm, follicular conjunctivitis, corneal anesthesia, transient blindness, iridal edema, miosis, and fever, have been produced following experimental inoculation of traumatized porcine corneas with Aujeszky’s disease virus (Schneider & Howarth, 1973). There is no treatment for the disease. Vaccines against Aujeszky’s disease virus have been developed (Pastoret & Jones, 2004; Pensaert et al., 2004).

Rabies

Rabies continues to be one of the most feared zoonotic diseases in the world. Rabies, a bullet-shaped RNA virus, is a
lyssavirus in the family Rhabdoviridae (Woldehiwet, 2002). Transmission of rabies occurs via a bite by a rabid animal, although infections through aerosols have been documented (Constantine, 1966; Winkler et al., 1972, 1973). The virus can infect any warm-blooded animals, with dogs and cats being the main vectors of human infection (Woldehiwet, 2005). Clinically, rabies infection can be divided into three phases: (1) prodromal, (2) furious, and (3) paralytic phases (Bedford, 1976). Cattle are most commonly affected among livestock (Blanton et al., 2011). Rabies virus is likely the most important cause of bovine encephalitis because of public health implications (Callan & Van, 2004). The clinical signs of rabies infection in livestock are variable. Clinical manifestations of the prodromal form of rabies in animals include depression, inappetence, pyrexia, significant ataxia, and facial musculature flaccidity, among others. In addition, other signs, including ocular manifestations, may be seen prior to death such as circling, head-pressing, strabismus, nystagmus, and blindness. The reader is referred to current internal medicine textbooks for a detailed discussion on rabies.

**Metabolic Diseases**

**Ionic Disturbances**

**Hypocalcemia (Bovine Parturient Paresis, Milk Fever)**

Bovine parturient paresis is a complex metabolic disorder resulting in an acute to peracute flaccid paralysis and/or somnolence of lactating dairy cows which usually occurs at the onset of lactation (Horst et al., 1997). The hypocalcemia arises due to a rapid increase in milk production and subsequent acute depletion of serum ionized calcium. Parturient paresis is divided into three main clinical stages of which stage two hypocalcemia is characterized by depression, anorexia, an inability of the animal to stand, tachycardia, gastrointestinal stasis, and ocular signs of mydriasis with absent or sluggish pupillary light reflexes (Murray et al., 2008). Recommended treatment for parturient paresis is prompt intravenous therapy with a calcium solution (Murray et al., 2008).

**Hypomagnesemia (Grass Tetany)**

Hypomagnesemia results from a primary dietary deficiency of magnesium. Hypomagnesemia is a highly fatal condition of ruminants. Clinical signs in lactating cows affected with grass tetany (i.e., occurs mainly in winter and spring when grasses which are low in magnesium comprise the diet) include anorexia, hyperexcitability, muscle fasciculations, head and neck tremors, followed by poorly coordinated gait and lateral recumbency. In addition, ocular manifestations of grass tetany include nystagmus and a rapid, snapping eyelid retraction. Confinement-housed dairy cows on a controlled feeding program can also develop hypomagnesemia (Donovan et al., 2004). Prevention of hypomagnesemia involves both continuous provision of adequate levels of dietary magnesium and improving absorption of this essential mineral by the ruminal epithelium (Martens & Schweigel, 2000). The reader is referred to current internal medicine textbooks for a detailed discussion on hypomagnesemia in ruminants.

**NEOPLASIA: CENTRAL NERVOUS SYSTEM**

**Neoplasia: Systemic**

**Lymphosarcoma**

Bovine lymphosarcoma occurs as a sporadic or an adult form. The adult, or enzootic, form is the most common neoplastic disease of cattle, usually affecting cattle greater than 4 years of age. However, cattle as young as 2 years of age may also be affected. A dult lymphosarcoma is typically associated with BLV infection. The disease is very rare in cattle uninfected with BLV (Burridge et al., 1982). Cattle sometimes experience a syndrome of orbital involvement with lymphosarcoma that results in a progressive, bilateral, or unilateral exophthalmos. The resultant exposure keratitis may be severe, but intraocular involvement is rare. Systemic involvement of the peripheral or the visceral lymph nodes is usually present (Rebhun, 1982). A case of bilateral conjunctival involvement without obvious orbital involvement has also been observed. The clinical appearance in this case mimicked that of chemosis; however, the conjunctiva contained solid cellular infiltration rather than edema (Joyce, 1973).

A general physical examination will usually find lymphadenopathy or other organ involvement and, thus, fine needle aspiration or biopsy of the affected tissues is warranted. A complete blood count demonstrating lymphocytosis and a positive BLV agar-gel immunodiffusion test are also supportive of the diagnosis (Rebhun, 1982).

**Other: Metastases**

A strain of Miniature Sinclair swine has a high incidence (54%) of congenital cutaneous melanomas. As the animals mature, further tumor development occurs, until approximately 85% of the animals have melanomas. The tumors may metastasize, but most animals have spontaneous regression of both primary and secondary tumors, which is accompanied by depigmentation (80%). Depigmentation occurs not only at the tumor site but in other melanin-containing structures, such as skin, hair, and eyes. Though intraocular melanomas have not been described, the depigmentation of the uveal tract results in an inflammatory cascade that often produces blindness. Ocular depigmentation is usually detectable by 4–5 weeks of age. This is accompanied by an invasion of macrophages into the eye and mononuclear cells into the ciliary body. The macrophages accumulate pigment and cluster around veins. The pigment epithelium of the iris, ciliary body, and the pigment in the choroid are destroyed, but the retinal pigment epithelium is spared. Approximately 50% of the animals with uveal depigmentation have photoreceptor degeneration. Calcification of the cornea or band keratopathy eventually develops in approximately 9% of the animals that develop severe depigmentation.
Severity of the ocular changes correlates with the tumor burden and speed of tumor regression (Feeney-Burns et al., 1988).

**Nutritional Disorders**

**Polioencephalomalacia (Cerebrocortical Necrosis)**

Polioencephalomalacia (PEM) is a disorder of the CNS of ruminants that results in necrosis of the cortical gray matter (Gould, 1998; Newsholme & O’Neill, 1985). PEM has a worldwide distribution. There are several causes of PEM including altered thiamine (vitamin B₁) status caused by such factors as excessive ruminal consumption of thiamine by bacterial thiaminases, and ingestion of plants with thiaminolytic activity, among others. However, PEM may also be induced by other neural metabolic disturbances such as water deprivation-sodium ion toxicosis, lead poisoning (see “Lead” under “Systemic Toxicities” section), and high sulfur intake (Gould, 1998). Early clinical signs of PEM in affected animals include anorexia, incoordination, muscle tremors, holding the head in an erect position, and appearing blind. As PEM progresses, animals develop blindness, head-pressing, dorsomedial strabismus, miosis, variable nystagmus, excitement, facial twitching, repetitive chewing, and recumbency and opisthotonos (McGuirk, 1987). In addition, lack of menace responses and reduced palpebral reflexes have been described in PEM-affected cattle (Haydock, 2003). Death usually arises following 3–4 days if the affected animal is not treated.

Electrodiagnostic visual testing (electroretinogram [ERG] and visual-evoked potential [VEP]) have been performed on five ruminants (three lambs, one kid, and one steer) with thiamine-responsive PEM (Strain et al., 1990). The lambs and kid had typical clinical signs of PEM, including blindness. The ERG in these animals was normal, but the VEP was abnormal. Follow-up recordings in the kid and one lamb indicated an improvement in VEP recordings subsequent to thiamine treatment and a gradual return of vision. According to the owners, all animals had complete return of vision. The steer did not have signs of blindness, and the ERG and VEP were normal (Strain et al., 1990). The reader is referred to current internal medicine textbooks for a detailed discussion on PEM.

**Vitamin A Deficiency**

Vitamin A deficiency has been studied extensively among cattle, both in spontaneous cases and with experimental induction. In young, growing animals, vitamin A deficiency produces clinical signs when the vitamin A levels fall to less than 20 µg/dL of plasma and less than 2 µg/g of liver (Kohlmiér & Burroughs, 1979). A sexual predilection for males has been noted in two clinical reports (Divers et al., 1986; Paulsen et al., 1989). A lag period of 3–12 months may be necessary before the effects of vitamin A deficiency are noted, and these effects depend on age of onset, degree of deficiency, and the amount of liver stores. Animals younger than 6 months of age are more susceptible and more likely to have blindness as a presenting sign because of sphenoid bone overgrowth constricting the optic nerve (Barnett et al., 1970; Blakemore et al., 1957; Booth et al., 1987; Divers et al., 1986; Hayes et al., 1968; Paulsen et al., 1989; Spratling et al., 1965; Van Donkersgoed & Clark, 1988; Wetzel & Moore, 1940). Blindness, with or without convulsions, is the first outward sign noted in most cases among young, growing animals (Barnett et al., 1970; Divers et al., 1986; Spratling et al., 1965). Seizures are short and tonic-clonic (Divers et al., 1986). On critical examination of animals, night blindness, the first clinical sign noted in experimentally affected animals, may be noted, but it is unlikely to be noted under typical husbandry conditions (Barnett et al., 1970). Blindness is accompanied by fixed, dilated pupils, and on ophthalmoscopy, papilledema will be present (Fig. 35.4.9A, B and Fig. 35.4.10). Papilledema occurs well before blindness in both adult- and young-onset deficiencies. Papilledema presumably results from increased CSF pressure, which develops from fibrosis and thickening of the dura mater that, in turn, results in decreased absorption of the CSF by the arachnoid villi. Increased CSF pressure is the first change noted with vitamin A deficiency (Hayes et al., 1968).

Causes of blindness will vary with age of onset for the deficiency. Blindness may result from retinal degeneration at all ages or constriction and ischemic necrosis of the optic nerve at the optic foramen in growing animals. Eventually, optic nerve atrophy develops (Fig. 35.4.11) (Barnett et al., 1970). Day blindness has not been reversible, but night blindness or papilledema detected before blindness occurs has been responsive to therapy (Spratling et al., 1965). Additional changes in the fundus are papillary and peripapillary hemorrhages as well as disruption of pigment in the nontapetal region (Fig. 35.4.12). Retinal degeneration primarily occurs in the nontapetal region (Barnett et al., 1970; Booth et al., 1987; Divers et al., 1986; Paulsen et al., 1989; Van Donkersgoed & Clark, 1988). Tapetal color alterations have not been noted in experimental or in clinical reports until late in the deficiency. Additional ocular lesions that have been attributed to vitamin A deficiency include exophthalmos (origin not understood), epiphora, nystagmus, and corneal ulceration. Though described clinically, corneal lesions have not usually been observed experimentally in calves, but decreased corneal sensitivity has been observed (Barnett et al., 1970). Twenty-five percent of calves born to heifers which experienced prolonged hypovitaminosis A during pregnancy had several congenital ocular abnormalities, including microphthalmos, ocular dermoids covering the external surfaces of the eyes, and single-chambered globes each lacking a uveal tract, lens (i.e., aphakia), and aqueous humor (Mason et al., 2003).

Histopathologic examination of the affected eyes revealed severe retinal dysplasia with retinal rosettes, retinal folds, and a generalized loss of retinal cells. In addition, the optic nerves were more cellular and paler staining than normal (Mason et al., 2003). Concurrent systemic signs will vary depending on the source of nutrition, duration of the deficiency, and age.
Figure 35.4.9. A. Normal fundus appearance of a Friesian calf. Note the presence of the conus vestigialis, the obvious difference between arteries and veins, and the color and clear outline of the optic disc. B. Papilledema due to vitamin A deficiency in a calf of comparable age and breed. Note the size of the disc, the indistinct and raised border and the small flame shaped hemorrhage at 11 o’clock. (Courtesy of K. Barnett.)

Figure 35.4.10. Marked papilledema in a steer that was blind and experiencing periodic seizures because of vitamin A deficiency. (Reprinted with permission from Martin, C.L. (1999) Ocular manifestations of systemic disease: Part 4: Food animals. In: Gelatt, K.N., ed., Veterinary Ophthalmology, 3rd ed., Philadelphia: Lippincott Williams & Wilkins, 1492–1504.)

Figure 35.4.11. Optic and early retinal atrophy following papilledema in a vitamin A-deficient calf. (Courtesy of K. Barnett.)
of the affected animal. In general, severe vitamin A deficiency will be accompanied by unthriftiness, diarrhea, poor growth, decreased appetite, and pneumonia.

The pathogenesis of the optic nerve lesions associated with vitamin A deficiency in calves has been extensively studied (Blakemore et al., 1957; Hayes et al., 1968; Wetzel & Moore, 1940). In calves made deficient for vitamin A from 35 days onward and examined at 5.5–6 months of age, the optic foramen of the sphenoid bone became deformed into a narrow, horizontal aperture. Normal development of the optic foramen results from new bone growth across the dorsomedial aspect of the optic canal and resorption of bone ventrally, which results in the progressive ventral displacement of the canal. In vitamin A-deficient calves, osteoblastic activity persisted both dorsally and ventrally, thus resulting in the two surfaces growing toward each other and a narrowed, horizontal slit for an optic canal (van der Lugt & Prozesky, 1989). In addition, the dura mater becomes thicker, and the combination produces compression within the canal, thereby compromising the vascular supply for the optic nerve. Optic nerve changes result mainly from ischemic necrosis, but in some instances when vascularity is maintained, the optic nerve pathology is subtle and may result from retinal degeneration. Constriction of the optic canal could not be produced in 2-year-old animals (Hayes et al., 1968), and the retinal histopathology has been reported in both naturally and experimentally deficient calves. Experimentally, degenerative changes were limited to the

Systemic Toxicities

Antimicrobials

Hygromycin B

Hygromycin B is an aminoglycoside antibiotic that has been used in the swine industry as a feed additive to control gastrointestinal helminths. The mixture is fed at 13.2 gm per 1000 kg of feed for 8 weeks on, and then 8 weeks off, the mixture. Cataracts developed experimentally after 10–11 months on continuous feed with elevated levels of hygromycin B and after 14 months at the recommended level. The cataracts begin as axial, posterior subcapsular opacities and then progress to complete cortical cataracts. The opacities are often asymmetric as well. In the field, cataracts developed only in sows, but this predilection may result from their increased feed consumption, with farrowing and culling of the boars at an earlier age (Sanford & Dukes, 1978; Sanford et al., 1981).

Arsanilic Acid

Arsanilic acid has been used in swine both as a growth stimulant and as a therapy for swine dysentery. Arsanilic acid poisoning has occurred from its long-term administration, errors in feed formulation, or when water has been restricted. Clinical signs of blindness and pupillary dilation occur with toxicity, and additional signs of ataxia, torticollis, and paralysis may develop as well. Optic disc atrophy is noted ophthalmo-
scopically in affected swine. The electroretinogram in affected animals is normal, whereas the visual evoked response is nonrecordable. Histopathologic examination of eyes of these pigs reveals optic nerve degeneration and atrophy (Witzel et al., 1976).

Electricity

Electric shocks and lightning strikes can produce direct ocular sequelae and also cause injury to the CNS (may manifest as blindness, papilledema, cranial nerve palsies) (for a review on pathogenesis and human manifestation, see Norman et al., 2001). Electric shocks and lightning strikes of a severe nature may produce cataracts that manifest months later. Cataracts are more likely to be produced by electrical shocks to the head. In one report, a herd of Holstein-Friesian cattle experienced lightening strike while kept on pasture (Boeve et al., 2004). Following the lightening strike, 8 of the 18 cattle had an unsteady, swinging gait, 9 calves had visual impairment as evidenced by an absent menace response, and 3 calves showed nystagmus. Four of the nine blind calves underwent ophthalmic examination which revealed normal pupillary light reflexes and no morphologic ocular lesions. Histopathologic examination of the brain of affected animals, including one of the blind calves, revealed cerebrocortical necrosis (Boeve et al., 2004).

Insect Bites

Insect bites, or envenomation, from hornets, bees, fire ants, and spiders may occur on the eyelids or cornea of all animals. A cute, severe blepharedema is the usual extent of bites to the eyelids, though bites from insects such as the brown spider or multiple fire ant bites may result in tissue sloughing (Joyce, 1983; Rakich et al., 1993). A cute, focal corneal necrosis with rapid melting of the corneal stroma is not a rare event because of the deposition of proteolytic enzymes. The diagnosis is often presumptive unless multiple bites are present on the animal or insects were observed while biting. Lysis of the corneal stroma may require surgical repair with conjunctival flaps.

Insecticides

Organophosphorus Compounds and Carbamates

Organophosphorus (OP) and carbamate insecticides are used commonly to control pests of crops and animals. These compounds are toxic, and livestock poisoning has occurred from mistaken addition of unused insecticide to feeds and animal access to materials which have been improperly disposed. The toxicologic effects of OP and carbamate insecticides arise due to the inactivation of cholinesterase (ChE) resulting in an increase in ACh in tissues. The accumulation of ACh results in uninhibited impulse transmission of the parasympathetic nervous system and of the postganglionic cholinergic nerves of the sympathetic nervous system. The toxic effects of these compounds therefore mimic the muscarinic and nicotinic responses of ACh administration. There is typically increased sensitivity of young animals to this toxicity. Clinical signs of OP or carbamate insecticide poisoning include muscarinic signs of salivation, excessive lacrimation, frequent urination, and diarrhea. In addition, signs pertaining to the nicotinic effects of these insecticides include muscle tremors followed by weakness and paralysis. Miosis with subsequent vision impairment may be observed as well. A diagnosis of OP or carbamate insecticide poisoning is made based on demonstrating clinical signs and history that are consistent with this toxicity. In addition, detection of the chemical compound in stomach or rumen contents and tissues, and demonstration of the adverse biological effect, ChE inhibition, also help confirm the diagnosis (Meerdink, 1989).

Ionizing Radiation

The ocular effects of ionizing radiation are similar regardless of the source. Both the ocular effect(s) and the time to develop ocular disease depend on the dose, age of the animal, and the species being studied. In a long-term study of burros, swine, and cattle receiving gamma and mixed neutron-gamma radiation, both the swine and the burros were resistant to radiation-induced cataracts, but the cattle were about as equally susceptible as humans (Brown et al., 1972). The most common source of ionizing radiation-induced ocular lesions is radiation therapy for neoplasms of the head.

Lead

Lead poisoning is commonly diagnosed in cattle and, to a lesser extent, sheep and horses. Cattle, especially young calves, are very susceptible to lead poisoning (Neathery & Miller, 1975). The cause of lead poisoning is accidental ingestion of sources of lead compounds (e.g., automobile battery) or of feed containing lead from environmental pollution. Lead poisoning in food animals is of public health significance due to the risk to humans through ingestion of contaminated meat and milk products from affected animals (Rumbeiha et al., 2001). In addition, the half-life of blood lead is highly variable (ranging from 48 days to 2507 days) and, hence, difficult to predict in accidental cases of lead poisoning in cattle (Rumbeiha et al., 2001). In acute lead poisoning of cattle, clinical signs include staggering, muscle tremors (mainly of the head and neck), clamping of the jaws, frothing at the mouth, in addition to ocular signs such as snapping of the eyelids, rolling of the eyes, and blindness. In the acute syndrome, death usually results during a convulsion as a result of respiratory arrest.

Phenothiazine

Cattle on a low plane of nutrition may develop a photochemical reaction within 24 hours after being dosed with phenothiazine as a dewormer. After subsequent exposure to sunlight, diffuse corneal edema results and is typically in the lower two-thirds of the cornea. Corneal ulceration may develop
secondary to the edema, and recovery may occur in 1 week (if the animal is restricted indoors) or be prolonged for 2–3 months (if the animal is kept out on pasture). Uveitis is not present, nor is there any reaction in the eyelids or skin. Susceptibility to the photodynamic reaction varies between species because of the variable conversion of phenothiazine in the gut to phenothiazine sulfoxide, which is absorbed by the portal system. If phenothiazine sulfoxide is incompletely metabolized in the liver, it reaches the systemic circulation and the aqueous humor, where it then acts as a photoreactive agent. A similar syndrome has also been described in pigs (Bistner et al., 1980; Clare et al., 1947). However, affected pigs may also develop eyelid edema (Swales et al., 1942).

Plants

Food animals are subject to the adverse effects from poisonous plants, which are not infrequently encountered in their environment. The clinical effects of some of these plants primarily involve the visual system.

**Bracken Fern Poisoning (Bright Blindness)**

Ingestion of bracken fern (*Pteridium aquilinum*) in chronic, low-level amounts has been suspected of causing the syndrome of bright blindness among sheep and cattle in the United Kingdom (Barnett & Watson, 1968, 1970; Hirono et al., 1993; Watson et al., 1965, 1972). The syndrome manifests as a retinal degeneration with blindness. Retinal lesions are most severe centrally and involve degeneration of the rods and cones. Ophthalmoscopic findings include retinal vascular attenuation, tapetal hyperreflectivity, and optic nerve atrophy (Fig. 35.4.13A, B) (Barnett & Watson, 1968). The active chemical that is bracken to cause progressive retinal degeneration following *Pteridium* sp. ingestion is ptaquiloside, a carcinogenic norsequiterpene (Hirono et al., 1993) (for a review pertaining to ptaquiloside, see Yamada et al., 2007).

**Helichrysum argyrosphaerum Poisoning**

In Africa, sheep and cattle grazing on pastures mainly consisting of *Helichrysum argyrosphaerum* have developed blindness, paresis, and paralysis. Lesions have been bilateral, symmetric edema of the white matter with destruction of myelin, and the optic nerve has developed gliosis. The intracanalicular portion of the optic nerve later undergoes fibrosis and atrophy suggestive of compression in the optic canal. Retinal lesions include degeneration and loss of photoreceptor outer segments, mainly in the nontapetal fundus. The retinal pigment epithelium was hyperplastic and migrated into the neurosensory retina (van der Lugt et al., 1996).

**Locoweed Poisoning**

Ingestion of locoweed (*Astragalus* sp.) by cattle, sheep, and horses may produce ocular signs of blindness and a "dull" eye. Histopathologic changes of marked vacuolation of the retinal ganglion and bipolar cells, ciliary epithelial cells, and lacrimal acinar cells have been described in research animals (Van Kampen & James, 1971).

**Male Fern Poisoning**

Male fern (*Dryopteris filix-mas*) consumption by cattle is associated with lethargy, constipation, and blindness. A cutely blind cattle have dilated pupils and ophthalmoscopic lesions of papilledema, as well as retinal and preretinal hemorrhages. Most animals recover when removed from pastures containing male fern, but some do not. Chronically blind animals...
develop optic nerve atrophy and vascular attenuation. At histopathology, the retrobulbar optic nerves are twice the normal diameter, myelin sheaths are fragmented and invaded by Gitter cells, and axons are decreased in number. The peripheral nerve, however, is relatively spared. The process appears to be a retrobulbar neuropathy that destroys the myelin sheaths of the nerve (Rosen et al., 1970).

Veratrum Poisoning in Sheep
Cyclopia in lambs may be produced by ingestion of Veratrum californicum or skunk cabbage in pregnant ewes on day 14 of gestation (Binns et al., 1965). Exposure to Veratrum after day 14 increases the fetal death rate, but the embryos are normal. The teratogenic dose is less than the toxic dose to the ewes. The steroid alkaloids primarily responsible for the teratogenic effects of Veratrum are cyclopamine and jervine. These teratogens were found mainly in the green leaves, stems, and especially the roots. The toxicity of Veratrum may vary widely, both from year to year and from pasture to pasture. The teratogenic effect is limited mainly to the head, with distortion of the bones of the upper jaw and cranium, fusion of the cerebrum, hydrocephalus, cyclopia, and anophthalmia. Usually, a protrusion from above the eye on the midline is also present. Anomalies may be present in one twin even though the other is normal. The incidence of anomalies may be as high as 25% (Binns et al., 1963). An ELISA has been developed to detect cyclopamine and jervine (Lee et al., 2003).

Rodenticides
In all species, coumarin poisoning may manifest with ocular or orbital hemorrhages. The source of coumarin may be rodenticides or sweet-clover poisoning in cattle, sheep, pigs, and horses. When hemorrhages are either limited or predominantly located in the eye and orbit, the diagnosis may be less obvious. Unless the orbital hemorrhage is visible by dissecting anteriorly to the subconjunctival space, orbital hemorrhage may be confused with other causes of acute space-occupying lesions, such as orbital cellulitis. Unless a definitive history or evidence of ocular/head trauma is present, other causes of spontaneous hemorrhage should always be considered (Heider & Hart, 1993).

Miscellaneous Diseases
Brain Abscess
Central blindness has been diagnosed in a 3.5-year-old crossbred steer diagnosed with multiple brain abscesses (Strain et al., 1987). In particular, clinical signs in this steer included depression, head pressing, and circling to the left. Ocular manifestations in this animal included ptosis and absent menace response of the right eye; direct and consensual pupillary light reflexes were normal in both eyes. Electrodiagnostic testing was performed and revealed essentially normal brainstem auditory evoked potentials and electroretinograms, while visual evoked potentials (VEPs) were greatly diminished for the right eye and absent for the left eye. On postmortem examination, the brain abscesses were located in the left thalamus, left caudal cerebrum, and right frontal cerebrum (Strain et al., 1987).

Bullous Empyema
Bullous empyema (left-sided) causing peripheral vestibular syndrome has been described in a pregnant heifer. Clinical signs in this heifer included generalized ataxia, wide-based stance of the hind limbs, abnormal behavior, circling to the left, and left head tilt. In addition, ocular lesions included strabismus to the left, and nystagmus with the fast phase to the right (Braun et al., 2004b).

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