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DEDICATION

We dedicate this book to our families—especially our wives, Donna Buja and Barbara Krueger.

Their encouragement and support have been inspirational and fundamental in our work and our lives.
PREFACE

Netter’s Atlas of Human Pathology is intended to provide students with a clear, concise, and compelling presentation of the pathologic basis of the most common human diseases. Pathology is a science and medical discipline that deals with the causes (etiology), mechanisms (pathophysiology), and interrelated anatomical, functional, and clinical manifestations of disease. Pathology is a vast field encompassing all of human disease and expanding geometrically to include information from rapidly evolving advances in the basic biomedical sciences, particularly the elucidation of the human genome. However, understanding human disease will always require a clear understanding of the ultimate expression of disease as anatomical changes in tissues and organs (pathologic anatomy). Therefore, this Atlas provides readily understandable representations of common human diseases, concentrating on pathologic anatomy and relating the anatomical changes to the functional and clinical manifestations of disease and their underlying causes and mechanisms.

The initial chapter covers basic pathologic changes encountered in organs and tissues in many disease processes, including degeneration and atrophy; apoptosis and necrosis; acute and chronic inflammation; immunologic reactions; regeneration, hypertrophy, and hyperplasia; and dysplasia and neoplasia. The following 12 chapters deal with diseases of specific organ systems: the cardiovascular system; respiratory system; gastrointestinal system; liver, gallbladder, and pancreas; kidneys and urinary system; male and female reproductive systems; integumentary (skin) system; hematopoietic and lymphatic systems; bones, joints, and soft tissues; endocrine system; and nervous system. Each chapter begins with a concise summary of the various pathologic processes and diseases to be presented in the chapter. The main body of each chapter consists of illustrations of pathologic processes and diseases accompanied by concise text aimed at clarifying and expanding the information presented in the illustrations. Comparative data about similar disease processes are summarized in tables.

The Atlas is designed to complement a comprehensive textbook of pathology or a course syllabus by providing a vivid visual framework and companion for the study of the causes, pathophysiology, and natural history of disease. The Atlas also can be used as an adjunct when studying gross and microscopic pathology specimens in the laboratory. Additionally, the Atlas can serve as an introduction to new subject matter and as a review after appropriate detail has been learned. Thus, the Atlas is meant to be a useful learning aid for students involved in their first human pathology course and a review for students, medical residents, physicians, and other health care professionals at subsequent stages of their careers.

The distinguishing element of this Atlas is the brilliantly conceived and executed medical illustrations of the famous physician-artist, Frank H. Netter, MD. As a result of a long and productive career, Dr. Netter has left a legacy of a vast collection of medical art familiar to physicians and other health care professionals throughout the world. Dr. Netter’s insight into and understanding of structure-function relations has produced compelling and memorable depictions of the fundamental features of disease processes.

The Netter illustrations are the core of the Atlas. However, in some cases, the Netter drawings have been supplemented with gross photographs and photomicrographs to enhance and complete the picture. The chapters on general pathology, skin, and hematologic disorders use gross and microscopic photographs to illustrate these pathologic processes. Through the combination and integration of the Netter illustrations, gross and microscopic photographs, tables, and text, our goal is to present students with an Atlas that enhances their knowledge, understanding, and appreciation of the pathologic basis of human disease. Pathology is the fundamental bridging discipline linking the basic biomedical sciences to clinical medicine. Therefore, our ultimate goal is for our students to use their knowledge of pathology to become scientifically grounded, effective physicians and health care professionals.

L. Maximilian Buja, MD
Gerhard R.F. Krueger, MD, PhD
ABOUT THE ARTISTS

Frank H. Netter, MD, was born in 1906, in New York City. He studied art at the Art Student’s League and the National Academy of Design before entering medical school at New York University, where he received his MD degree in 1931. During his student years, Dr. Netter’s notebook sketches attracted the attention of the medical faculty and other physicians, allowing him to augment his income by illustrating articles and textbooks. He continued illustrating as a sideline after establishing a surgical practice in 1933, but he ultimately opted to give up his practice in favor of a full-time commitment to art. After service in the United States Army during World War II, Dr. Netter began his long collaboration with the CIBA Pharmaceutical Company (now Novartis Pharmaceuticals). This 45-year partnership resulted in the production of the extraordinary collection of medical art so familiar to physicians and other medical professionals worldwide.

In 2005, Elsevier Inc. purchased the Netter Collection and all publications from Icon Learning Systems. There are now over 50 publications featuring the art of Dr. Netter available through Elsevier Inc. (in the US: www.us.elsevierhealth.com/Netter and outside the US: www.elsevier-health.com)

Dr. Netter’s works are among the finest examples of the use of illustration in the teaching of medical concepts. The 13-book Netter Collection of Medical Illustrations, which includes the greater part of the more than 20,000 paintings created by Dr. Netter, became and remains one of the most famous medical works ever published. The Netter Atlas of Human Anatomy, first published in 1989, presents the anatomical paintings from the Netter Collection. Now translated into 16 languages, it is the anatomy atlas of choice among medical and health professions students the world over.

The Netter illustrations are appreciated not only for their aesthetic qualities, but, more importantly, for their intellectual content. As Dr. Netter wrote in 1949, “… clarification of a subject is the aim and goal of illustration. No matter how beautifully painted, how delicately and subtly rendered a subject may be, it is of little value as a medical illustration if it does not serve to make clear some medical point.” Dr. Netter’s planning, conception, point of view, and approach are what inform his paintings and what makes them so intellectually valuable.


Learn more about the physician-artist whose work has inspired the Netter Reference collection: http://www.netterimages.com/artist/netter.htm

Carlos Machado, MD, was chosen by Novartis to be Dr. Netter’s successor. He continues to be the main artist who contributes to the Netter collection of medical illustrations.

Self-taught in medical illustration, cardiologist Carlos Machado has contributed meticulous updates to some of Dr. Netter’s original plates and has created many paintings of his own in the style of Netter as an extension of the Netter collection. Dr. Machado’s photorealistic expertise and his keen insight into the physician/patient relationship informs his vivid and unforgettable visual style. His dedication to researching each topic and subject he paints places him among the premier medical illustrators at work today.

Learn more about his background and see more of his art at: http://www.netterimages.com/artist/machado.htm
ABOUT THE AUTHORS

L. Maximilian Buja, MD, is Professor of Pathology and Laboratory Medicine and holds the H. Wayne Hightower Distinguished Professorship in the Medical Sciences and the Distinguished Chair in Pathology and Laboratory Medicine at The University of Texas Health Science Center at Houston. He also is Executive Vice President for Academic Affairs, having previously served as Dean of the Medical School and Chairman of the Department of Pathology and Laboratory Medicine at The University of Texas Health Science Center at Houston. He is certified by the American Board of Pathology. Dr. Buja’s scholarly interests are centered on cardiovascular pathology and general principles of disease. Teaching has always been an important part of Dr. Buja’s professional career, and he remains active in the teaching of pathology to medical students, residents, fellows, and graduate students. Dr. Buja’s investigative career encompasses research on the pathogenesis and manifestations of cardiac and vascular diseases, including atherosclerosis, ischemic heart disease, and cardiomyopathies. He has published extensively in his areas of interest. He continues to pursue studies of cardiomyocyte and vascular cell injury and repair.

Gerhard R.F. Krueger, MD, PhD, is Adjunct Professor of Internal Medicine and Pathology and Laboratory Medicine at The University of Texas Health Science Center at Houston. Dr. Krueger formerly served as the Head of the Immunopathology Laboratory, Institute of Pathology, University of Cologne, and as Dean of the University of Cologne Medical School. He holds certificates from the German Board of Pathology and the American Board of Pathology. Throughout his career, Dr. Krueger has been actively engaged in the practice of pathology and the teaching of pathology to medical students, residents, fellows, and graduate students. Dr. Krueger’s investigative career encompasses research in immunopathology, including the pathogenesis of diseases related to herpes viruses and the pathogenesis of lymphomas and other lymphoproliferative diseases. His work has led to an extensive number of publications. His most recent studies have involved computer modeling of T-cell proliferation and differentiation under normal and pathologic conditions.
ACKNOWLEDGMENTS

Our motivation for preparing this Atlas is our mutual passion for the science and practice of pathology and our desire to impart our understanding and appreciation of pathology to students of medicine and other health care fields. Our commitment to pathology was forged early in our careers, including the time we spent at the National Institutes of Health in the early 1970s doing research and training in pathology. Therefore, we want to acknowledge the teachers and mentors who were instrumental in the early stages of our careers, including Dr. Harold Stewart for Dr. Krueger and Dr. Buja, Dr. Victor Ferrans and Dr. William Roberts for Dr. Buja, Dr. Thelma B. Dunn and Dr. Costan W. Berard for Dr. Krueger, and others too numerous to mention. We also want to acknowledge our professional colleagues over the years who have inspired and taught us much. Also, we recognize our students, including medical students and pathology residents, who have challenged us and inspired us to constantly improve as teachers of pathology and medicine.

We thank and appreciate the colleagues and students who have reviewed the draft chapters. Their constructive comments have served to significantly improve the work. We also thank Jean Long, Executive Assistant, for her assistance with assembly of the text. We also acknowledge the review and constructive suggestions we received from Donna Hansel, MD, PhD, of Johns Hopkins University; Richard Sobonya, MD, of the University of Arizona; and Steven Spitalnik, MD, of Columbia University.

Many of Dr. Frank Netter’s illustrations were originally included in the comprehensive multivolume work The Netter Collection of Medical Illustrations, which resulted from Dr. Netter’s long-standing collaboration with the Ciba-Geigy Corporation, now Novartis Pharmaceuticals, Inc. We acknowledge the influence of The Netter Collection series and the contributions of its collaborating authors, who provided extensive descriptive information relevant to the illustrated material. The Collection series served as an important resource for our Atlas.

Finally, we acknowledge our indebtedness to Frank H. Netter, MD, whose incredible ability to capture the structure-function relations at the core of diseases has provided the creative stimulus and drive for our work in developing this Atlas. We have strived to provide explanatory text, photographs, and tables to enhance Dr. Netter’s pictorial insights into disease. We feel fortunate and privileged to have had the opportunity to help extend Dr. Netter’s legacy to future generations of physicians and health care professionals.

L. Maximilian Buja, MD
Gerhard R.F. Krueger, MD, PhD
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Pathologic anatomy, gross and microscopic, is the science of identifying and interpreting morphologic patterns and relating them to the physiologic and pathologic functions of a living organism. Pathology thus helps to elucidate the pathogenesis of diseases and to determine their classification. To correctly register morphologic changes, students of pathology must possess a solid knowledge of the normal composition and appearance of cells and tissues (i.e., normal anatomy and histology). Deviations from such normal appearances require pathologic interpretation. The student also should bear in mind 2 basic principles of pathologic anatomy:

1. All morphologic changes represent a dose-dependent effect in a “time-space window.” That is, first, below a lower-dose threshold of functional alterations, no morphologic lesions occur despite the patient’s apparent illness, and, second, there is a time delay between the occurrence of a functional disturbance and the development of morphologic changes (called morphogenesis). Space refers to the fact that morphologic lesions are most extensive at the site of “toxic impact” and become less severe (and possibly less typical) with increasing distance. This should be kept in mind when taking biopsies for pathologic evaluation.

2. Whatever the quality of injury, the living organism reacts with a limited number of patterns. There are variations to these patterns, which may provide us with clues to the etiology of the injury, but no entirely new reactions can be expected, even when a new pathologic agent (such as human immunodeficiency virus) arises.

Therefore, however clear pathologic anatomical lesions seem to be, the final evaluation with regard to the disease must result from a clinicopathologic correlation, i.e., from the careful evaluation of all the physical, biochemical, and anatomical findings.

GENERAL REACTION PATTERNS

This chapter covers 5 complex reaction patterns that apply equally to all cells, tissues, and organ systems:

1. Degeneration and atrophy
2. Apoptosis and necrosis
3. Inflammation and immunity
4. Regeneration, hypertrophy, and hyperplasia
5. Dysplasia, atypia, and neoplasia

Degeneration is the morphologic cell response to acute injury (i.e., reversible injury), which does not cause immediate cell death. Atrophy of individual cells or of their organized groups (tissues and organs) indicates a persistently catabolic metabolism that is not immediately lethal. Apoptosis and necrosis are distinct forms of cell death after irreversible cell injury. Inflammation is a microvascular response characterized by alterations in blood circulation (hyperemia, prestasis, and stasis), increased vascular permeability, exudation of blood fluids (edema, fibrinous exudates), margination and emigration of blood cell components, and passive expulsion of red blood corpuscles (hemorrhage). Activation of the immune system may result in different morphologic forms of inflammation depending on the nature of the initiating antigen (exogenous or autoimmune, soluble or particulate) and the reacting component of the immune system (T-cell or B-cell system). Regeneration, hypertrophy, and hyperplasia are forms of functional or structural repair or both of damaged cells and tissues. Neoplasia (“new growth”) is a disturbance of physiologic growth regulation with persistent activity of growth-promoting factors or loss of proliferation inhibition functions (or of physiologic apoptosis). It leads to benign or malignant tumorous growth patterns independent of or at the expense of surrounding cells and tissues.

All reaction patterns vary according to differences in composition of the reacting tissue or organ (e.g., extent of vascularization, amount of connective tissue, amount and distribution of parenchymatous cells and their respective regenerative potential) and to the quality and quantity of the (exogenous or endogenous) stimulus. Because the normal tissue composition is known and additional reactive changes can be observed with the unaided eye or with the help of a microscope, the character of the pathologic change reveals the nature of the stimulus and thus of the etiologic agent. Meticulous morphologic interpretation therefore contributes to the elucidation of the etiology and pathogenesis of diseases. This is the essential task and responsibility of the practitioner of general pathology.

The following figures provide examples of the 5 reaction patterns in different tissues and organs.
Degeneration, the reversible cell response to injury, has 2 major forms: cellular swelling (proteinaceous, hydropic or ballooning degeneration) and fatty degeneration (fatty change or steatosis). Ultrastructurally, cells show bleb formation, loss of microvilli, loss of intracellular attachments, and swelling of mitochondria and endoplasmic reticulum with granular and fibrillar disaggregation of nuclear chromatin. Fat vacuoles result from disintegration of lipid membranes (fat phanerosis) or accumulation of metabolic lipids (fat thesauros). Causes include trauma, chemical injury, metabolic and nutritional factors (hypoxidosis, toxic metabolites, malnutrition), and infectious or immunologic injuries. Enhanced influx of calcium ions into the cell and inactivation of the sodium pump (increase of intracellular sodium and loss of potassium) result in increased intracellular water (swelling). Under certain conditions (e.g., sustained acidosis, hypercalcemia), degenerating cells may accumulate precipitated calcium salts, leading to dystrophic calcification.
Atrophy of skin in patient with scleroderma, thinning, contraction, and ulceration of epidermis (left). Thinning of epidermis and loss of skin appendages with fibrosis (right).

Atrophy of skeletal muscle secondary to inherited muscular dystrophy, with replacement of skeletal muscle by fat tissue, cross section (left), interstitial deposition of proteinaceous material in amyloidosis (arrow), longitudinal section (right).

Systemic atrophy of the entire body (cachexia) in a patient with metastatic tumor.

Atrophy of kidney, normal organ size (left) compared to end-stage inflammatory disease (right).

Atrophy of trabecular bone (osteoporosis of vertebra).

**Figure 1-2 Atrophy**

Atrophy of cells or tissues indicates a catabolic metabolism that is not immediately lethal. Cells and organs shrink with or without accumulation of metabolic products (e.g., *lipofuscin*, brown atrophy). Tissue atrophy may be symmetric, with reduction of all tissue components, or asymmetric, with reduction of only some components. Symmetric atrophy is commonly caused by reduced blood supply or old age, whereas asymmetric atrophy suggests a variety of causes, such as decreased workload, nutritional deficiencies, decreased neural or endocrine stimulation, and chronic low-level injury (radiation, chemical toxins). Cellular atrophy (associated with reduction of functional activity) can be reversible on restoration of normal environmental conditions. Cachexia or wasting syndrome refers to systemic catabolic changes and symmetric atrophy of the entire body such as that accompanying advanced tumors or chronic consumptive infections (e.g., tuberculosis, acquired immunodeficiency syndrome [AIDS]).
Apoptosis and Necrosis

**Apoptosis** (programmed cell death) serves the process of physiologic cell turnover in development and aging and the disposal of damaged or functionally incapable cells. It follows the specific stimulation of cell membrane receptors (Fas receptor) or genomic damage and is initiated by activation of endonucleases and caspases, DNA fragmentation, and mitochondrial disruption. In light microscopy, the key morphologic change is nuclear condensation and fragmentation followed by cell shrinkage, engulfment, and further disposal by macrophages. Electron microscopy reveals compartmentalization and dissolution of cytoplasmic organelles. Apoptosis is observed in the lymphocyte turnover in antigenically stimulated germinal centers (apoptotic cells in germinal center macrophages, i.e., tingible body macrophages), developing tissues during ontogenesis, other fast-growing tissues including cancer, virus infection, ionizing radiation, and hormonal or toxic conditions.

**Necrosis**, which follows irreversible cell and tissue injury, starts with cell membrane damage, swelling, denaturation, and coagulation of intracellular proteins with breakdown of organelles. Later stages are accompanied by nuclear pyknosis (shrinkage with condensation), loss of the nuclear membrane, and dissolution of nuclei. **Coagulative necrosis** occurs in tissues with normal protein content, and **liquefaction necrosis** occurs in tissues poor in protein (brain, fat tissue). Necrosis arises from enzymatic autodigestion (autolysis = self digestion; heterolysis = digestion of adjacent cells and tissues by enzymes released from dying cells). Breakdown products induce chemotaxis and cause a neutrophilic inflammation serving the disposal of necrotic debris. Common causes of necrosis are ischemia, physical trauma, chemical toxins, complex biologic injuries (toxins from infections, arthropods, snakes, plants), and immunologic factors.
Acute inflammation describes alterations in microvascular circulation (hyperemia, peristasis, and stasis) with increased vascular permeability and exudation of fluids (edema, fibrinous exudates). After additional toxic effects, local thrombosis or necrosis may complicate the reaction. The type of inflammatory response is determined by the nature of the etiologic agent and its distribution in the body and by the composition of the reacting tissue. Acute neutrophilic inflammation (suppurative inflammation) is commonly caused by bacterial infection. Acute viral infection causes lymphocytic infiltrations (stimulation of the immune system by viruses, virus-infected cells, or both). Bacterial (or fungal) toxins may induce necrosis or abscesses by exotoxins or hemorrhage by endotoxins. Endotoxemia and a systemic inflammatory response can lead to circulatory shock.
Chronic inflammation follows the initiation of repair ("organization") of acute inflammation and is characterized by activation of the immune system and of phagocytosis with subsequent proliferation of new capillaries and fibroblasts, production of collagen, and scarring. Lymphohistiocytic infiltration accompanied by capillaries in an edematous stroma and increasing numbers of fibroblasts is called granulation tissue. When inflammation involves a significant T-cell immune response, as in tuberculosis, salmonellosis, or yersiniosis, granuloma formation may result. The form and course of noninfectious inflammation depends on the toxic dose and duration of the pathologic stimulus. For example, acute low-dose radiation (sun exposure) causes hyperemia, a higher dose (sunburn) causes hyperemia and edema, and a very high dose (sunburn grade III) causes necrosis and secondary inflammation. Chronic low-dose exposure (sun or other radiation) causes mild persistent edema followed by atrophy and fibrosis.
The morphology of immunologically induced inflammation depends on the initiating antigen and the reacting component of the immune system (Table 1-1). Type I B-cell immune reaction (allergy type) is characterized by increased vascular permeability with edema, platelet aggregation, and infiltration by eosinophils (e.g., allergic rhinitis, asthma bronchiale). Type II B-cell reaction causes lysis of the antigenic target cell or necrosis of tissue components (e.g., autoimmune hemolytic anemia, nephrotic glomerulonephritis). Type III B-cell immune reactions or immune complex reactions are characterized by accumulations of...
TABLE 1-1 BASIC TYPES OF B-CELL AND T-CELL IMMUNOREACTIONS*

<table>
<thead>
<tr>
<th>Cell and Coombs Type</th>
<th>Alias</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-cell reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I IR</td>
<td>Allergic IR Atopic IR Anaphylactic IR</td>
<td>Cytophilic antibodies (e.g., IgE) bind to mast cells; antigen binding to these cell-bound antibodies causes mast cell degranulation with release of vasoactive mediators (e.g., histamine), which initiate the microvascular inflammatory response (thrombocytes and eosinophils cooperate).</td>
</tr>
<tr>
<td>Type II IR</td>
<td>Toxic or cytotoxic IR</td>
<td>Complement-binding antibodies (on antigen binding) activate complement cascade, members of which initiate inflammatory response by activating cell chemotaxis and phagocytosis, ultimately causing toxic cell and tissue damage.</td>
</tr>
<tr>
<td>Type III IR</td>
<td>Immunocomplex IR</td>
<td>Persistence of antigen-antibody complexes are recognized by the immune system as foreign and induce the production of secondary anticomplex antibodies (i.e., anti-antibodies, such as rheumatoid factor); these bind and activate complements and cause tissue lesion through complement components (see above).</td>
</tr>
<tr>
<td><strong>T-cell reactions</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Type IV IR           | Cell-mediated IR T-cell cytotoxic IR CTL response | a. Direct destruction of target antigenic cells by binding of CTL, Fas-related induction of apoptosis, and/or release of perforin and granzymes  
  b. T-cell cytokine response activation of macrophages: granulomatous (e.g., IFN-γ, TNF) reaction  
  c. T-cell cytokine response activation of mast cells: basophil reaction (e.g., IL-3, IL-5)  
  d. T-cell cytokine response: activation of vasoproliferative factors (e.g., IL-3, IL-8) |

*CTL indicates cytotoxic T lymphocytes; Fas, cellular apoptosis receptor; Ig, immunoglobulin; IL, interleukin; IFN, interferon; IR, immunoreaction; TNF, tumor necrosis factor.

**FIGURE 1-6 IMMUNOLOGIC INFLAMMATION: B CELL (CONTINUED)**

antigen-antibody complexes and in situ complement activation with subsequent serofibrinous exudates; thickening of basement membranes; and slow, secondary development of granulation tissue at the site of immune complex deposition (e.g., membrano-proliferative glomerulonephritis, certain lesions in lupus erythematosus, and rheumatoid arthritis). More acute reactions cause acute vasculitis with or without microhemorrhage (Arthus-type reaction).
Immune reactions are divided into the lymphocytotoxic reaction (classic type IV reaction or tuberculin-type cellular immune reaction), the granulomatous reaction, the basophil reaction (Jones-Mote-type reaction), and the contact allergy–type reaction (Table 1-1). The lymphocytotoxic reaction is brought about by direct action of cytotoxic T lymphocytes on the cellular antigen, as in acute transplant rejection. Granulomatous reactions are initiated by T-cell–induced accumulation and activation of phagocytes with typical tissue reactions in certain infectious diseases such as tuberculosis. Basophil reactions are caused by secretion of specific T-cell cytokines with attraction of basophils to the site of the antigen deposit. This can be seen in certain arthropod reactions, such as spider bites. The contact allergy–type reaction with production of vasoproliferative factors and other cytokines is caused by antigens such as heavy metals. Eczema is characteristic of contact allergy–type reaction.
Regeneration, hypertrophy, and hyperplasia are forms of functional or structural repair or both of damaged cells and tissues. Regeneration may be complete with restitution of normal structure and function or incomplete. Hypertrophy is an increase in cell mass without cell division (i.e., increase in functional units such as organelles, nuclear ploidy). There are at least 2 identified stimuli for hypertrophy: mechanical triggers (i.e., stretching of cardiac or skeletal muscles) and trophical triggers (i.e., neuroendocrine activation). Compensation for structural or functional deficiency or both by hypertrophy remains limited, and degenerative changes occur when hypertrophic cells can no longer compensate for the increased burden.

Hyperplasia results from an increase in cell division and may follow or coincide with hypertrophy in nonpostmitotic tissues. It is initiated by growth factors produced by cells adjacent to the functionally or structurally damaged area. Hyperplasia compensates for a decrease or loss of cellular function or is a response to increased functional requirement. Examples are hyperplastic intestinal crypts in chronic inflammation, follicular hyperplasia of a lymph node in antigenic stimulation, and axonal proliferation after trauma (traumatic neuroma). Positive effects of hyperplasia are limited by the extent of the blood supply to the newly formed tissue. When hyperplasia becomes out of balance with vascularization, focal degeneration, hypoxidotic necroses, or both occur.
Dysplasia refers to restitution or tissue growth with altered features. Atypia refers to cellular changes. Dysplasia describes an abnormal structural regeneration that may become malignant, such as the adenomatous polyp of the colon. Typical dysplastic changes can be observed in proliferating mucosa of intestinal polyps (adenomas) or in the cervix uteri with chronic inflammation and mucosal regeneration. They are characterized by irregular glandular patterns, occasionally with some loss of cellular polarity. Cellular atypia indicating malignant potential is characterized by nuclear enlargement with hyperchromasia (polyploidy and aneuploidy) with increase in the nuclear/cytoplasmic ratio and irregular nucleoli, loss of cell polarity and contact inhibition, and increased and atypical mitotic figures.

Neoplasia (“new growth”) results from a disturbance of physiologic growth regulation with persistent activity of growth-promoting factors or loss of proliferation inhibition functions (or of physiologic apoptosis). It leads to tumorous growth patterns independent of or at the expense of surrounding cells and tissues. Benign neoplasias (tumors), such as the uterine myoma in the figure, exhibit expansive growth with compression and atrophy of surrounding tissues but no true invasion or metastasis. Benign tumors are often designated by their tissue of origin with the affix -oma, such as myoma, hemangioma, and neurinoma. Although “benign,” such tumors can cause severe disturbances and death when they interfere with the function of other organs, such as by compression (as a meningioma compresses the brain) or obstruction of canalicular structures.
Malignant tumors grow progressively at the expense of other tissues and cause death by damaging vital organs or by causing cachexia and infections. Malignancy is morphologically defined by cellular atypia, invasive and destructive growth, and metastatic spread via lymphatic vessels, hematogenously, or within other canalicular systems and body cavities. Malignant tumors of epithelial origin are carcinomas. Tumors of mesenchymal origin are sarcomas (e.g., squamous cell carcinoma, adenocarcinoma,
Osteogenic sarcoma of femur, gross (left) and microscopic (right) showing poorly differentiated atypical osteoblasts and focal bone formation (arrows).

Rhabdomyosarcoma of foot, gross (left) and microscopic (right) showing poorly differentiated and atypical rhabdomyoblasts (arrow).

**Figure 1-10 Malignant Tumors (continued)**

fibrosarcoma, osteosarcoma). There are exceptions to this nomenclature, such as malignant lymphomas and leukemias for hemolymphatic malignancies and astrocytoma, ependymoma, glioblastoma, and others for malignant brain tumors. The degree of malignancy of a given tumor is assessed by tumor classification and staging, the histologic tumor type, its degree of differentiation, and its local invasion and metastatic spread. Classification and staging determine the choice of treatment and the patient’s prognosis.
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Cardiovascular diseases are common and important causes of morbidity and mortality worldwide, particularly in industrialized countries. In spite of significant advances in primary prevention and therapy, cardiovascular disease, primarily the complications of atherosclerosis and hypertension (HTN), is still the leading cause of mortality in the United States.

### CONGENITAL HEART DISEASE

Congenital malformations of the heart and major blood vessels are produced during embryologic development of the cardiovascular system in the early fetus. They usually arise from randomly occurring defects in embryogenesis, but they sometimes develop as a result of intrauterine infections, such as rubella, or as components of genetic abnormalities such as trisomy 21 (Down syndrome) or cytogenetic disorders of sex chromosomes (Turner syndrome). The 3 major pathophysiologic categories of congenital heart disease are those causing a left-to-right shunt of blood across the circulation (e.g., ventricular septal defect [VSD], atrial septal defect [ASD], patent ductus arteriosus [PDA]), a right-to-left shunt (e.g., tetralogy of Fallot), and obstruction without a shunt (e.g., coarctation of the aorta).

### ATHEROSCLEROTIC DISEASES

Atherosclerosis develops as an inflammatory response of the vessel wall to chronic, multifactorial injury produced by hyperlipidemia, HTN, products of cigarette smoke, diabetes mellitus, and other predisposing factors. The pathogenesis of intimal lesions involves endothelial dysfunction, influx of macrophages and T lymphocytes, vascular smooth muscle proliferation, accumulation of oxidized low-density lipoprotein, and deposition of collagen and elastic tissue. The resultant fibrous (atheromatous) plaques are raised intimal lesions with a fibrous cap and a core containing variable amounts of necrotic, lipid-rich debris, fibrous tissue, calcification, and vascularization from ingrowth of vessels from the vasa vasorum. The plaques involve the aorta and its major distributing branches, including the coronary, cerebral, and iliofemoral arteries, with a propensity for localization adjacent to branch points.

Progression of disease leads to luminal narrowing and the development of complicated lesions as a result of surface ulceration, intraplaque hemorrhage, and superimposed thrombosis. The frequently abrupt transition to a clinically overt state can present as coronary (ischemic) heart disease manifest as angina pectoris, myocardial infarction, or sudden cardiac death; cerebrovascular disease with transient ischemic attacks or cerebral infarcts (stroke); rupture-prone abdominal aortic aneurysm; or iliofemoral atherosclerosis, predisposing to gangrene of the lower extremities.

### CORONARY (ISCHEMIC) HEART DISEASE

The underlying pathologic substrate for clinically apparent myocardial ischemia is coronary atherosclerosis in at least 90% of cases. Narrowing of one or more of the coronary arteries to less than 25% of the luminal area can be slowly progressive, giving rise to recurrent episodes of angina pectoris. Acute changes in plaques associated with platelet aggregation and vasospasm can precipitate myocardial ischemia, ventricular fibrillation, and sudden cardiac death. Sudden luminal occlusion due to thrombosis of an ulcerated plaque can give rise to an acute myocardial infarct, usually of the left ventricle (LV), in the distribution of the occluded coronary artery. Myocardial necrosis begins in the ischemic subendocardial myocardium and progresses in a wave-front fashion over a period of 3 or 4 hours to involve the subepicardial myocardium. Myocardial infarcts undergo organization into granulation tissue over approximately 2 to 3 weeks and complete healing as fibrous scars in 2 to 3 months. Larger healed infarcts can develop into ventricular aneurysms. During the first week to 10 days when healing is minimal, myocardial infarcts are susceptible to developing external rupture, giving rise to cardiac tamponade; rupture across the interventricular septum, producing a VSD; or rupture of a papillary muscle, giving rise to mitral regurgitation. However, such life-threatening complications occur in only approximately 5% of cases. A massive acute myocardial infarct involving 40% or more of the LV can give rise to fatal cardiogenic shock. As myocardium is lost from one or more acute myocardial infarcts, congestive heart failure (CHF) may ensue.

### HYPERTENSIVE DISEASE

Hypertension results from excessive arteriolar constriction and peripheral vascular resistance in relation to the blood volume and, when sustained, leads to hypertensive cardiovascular disease as well as predisposing to atherosclerotic disease. Most patients have primary or essential HTN due to a complex of genetic and environmental influences. Approximately 10% of patients have secondary HTN due to renal, endocrine, or other disease processes. Slowly progressive (“benign”) hypertensive disease presents as mild to moderate blood pressure increase and leads to concentric hypertrophy of the LV and progressive damage to the microvasculature in the form of hyaline arteriolosclerosis. A
leading complication is the development of hemorrhagic stroke. Rapidly progressive (“malignant”) HTN is characterized by marked increase of blood pressure; prominent microvascular damage in the form of hyperplastic arteriolar sclerosis and fibrinoid necrosis; and rapid progression to renal failure, cardiac failure, cerebral edema, and hemorrhagic stroke.

CONGESTIVE HEART FAILURE
Congestive heart failure has many causes that lead to a common final pathway of failure of the heart’s pumping function to provide sufficient blood to meet the metabolic demands of the perfused organs of the body. Initially, compensation to an increased stress is accomplished by ventricular hypertrophy, but when the reserve capacity is exceeded, cardiac failure ensues. Most cases begin as failure of the LV as manifest by fatigue and progressive pulmonary congestion. Failure of the right ventricle (RV) leads to increased central venous pressure, hepatic congestion, pleural and pericardial effusions, and pitting edema of the lower extremities. Cor pulmonale refers to isolated right heart hypertrophy and failure due to pulmonary vascular or parenchymal disease.

ANEURYSMS
An aneurysm is an external bulging of a vascular structure. Severe atherosclerosis is the cause of the relatively common abdominal aortic aneurysm as well as aneurysms of the descending thoracic aorta and iliofemoral arteries. Medial degenerative disease, also known as cystic medial necrosis, gives rise to dissecting hematoma (aneurysm) with origin in the ascending thoracic aorta (type A) or the transverse or descending thoracic aorta (type B), as well as non-dissecting aneurysms of the ascending thoracic aorta. Medial degeneration develops as a result of a genetic defect, as in Marfan syndrome and Ehlers-Danlos syndrome, or as a result of hemodynamic stress accelerated by HTN. Both dissecting and nondissecting aneurysms are prone to external rupture leading to exsanguination. Infections of a major artery can give rise to mycotic (mushroomlike) aneurysms. Cardiovascular syphilis is a form of tertiary syphilis with ascending aortic aneurysm.

VALVULAR HEART DISEASE
Acute rheumatic fever (RF) is an acute multisystem disorder involving the skin, joints, brain, and heart that is triggered by an autoimmune reaction after streptococcal pharyngitis. Most of the inflammation resolves without consequence except for the distortion and subsequent wear and tear on the cardiac valves, particularly the mitral and aortic valves, giving rise months to years later to chronic rheumatic heart disease (RHD).

Infective endocarditis (IE) of the valvular or mural endocardium results from infection with microorganisms (bacteria, fungi, or rickettsiae) that gain access to the bloodstream through the gastrointestinal tract, skin, surgical instrumenta- tion, or other means. Key clinical features of IE are fever and cardiac murmur, and positive blood cultures are confirmatory of the diagnosis. Acute IE is produced by highly virulent organisms, such as Staphylococcus aureus, involving a previously normal valve, whereas subacute IE is characterized by a more indolent clinical course with infection produced by a less virulent organism, such as Streptococcus viridans, often involving a previously diseased valve. In both acute and subacute IE, the infected vegetations produce destruction and incompetence of valves, CHF, and emboli to other organs.

A large variety of entities can produce valvular dysfunction, but the following figure prominently into the differential diagnosis. Mitral valve stenosis is virtually always due to RHD. Mitral valve incompetence (regurgitation) results from RHD, IE, or mitral valve prolapse due to myxomatous degeneration. Aortic valvular stenosis results from chronic RHD involving a tricuspid valve, age-related (senile) sclerosis and calcification of a tricuspid valve, or fibrosis and calcification of a congenitally bicuspid valve. Aortic valvular incompetence can develop from valvular lesions, such as IE, or aortic aneurysms producing distortion of the aortic annulus. Pulmonary and tricuspid valvular disease is produced by congenital defects and, less commonly, acquired causes.

MYOCARDIAL AND PERICARDIAL DISEASES
Myocarditis and pericarditis may be induced by infection with microorganisms (viruses, rickettsiae, bacteria, fungi, and protozoa) or noninfectious, immune-mediated processes. Bacterial infections produce neutrophil-rich supplicative inflammation. Viral infections are associated with lymphohistiocytic infiltrates. Granulomatous inflammation may represent sarcoidosis or tuberculous infection. Myocarditis can produce heart failure or sudden death from arrhythmia. Pericardial involvement is often manifest as fibrinous pericarditis with a pericardial effusion.

Cardiomyopathies are diseases of the heart muscle. Etiologically, primary cardiomyopathies are intrinsic diseases of the heart muscle, and secondary cardiomyopathies develop as a component of a defined disease process usually originating extrinsic to the myocardium. Pathophysiologically, cardiomyopathies are classified as dilated (congestive), hypertrophic, or restrictive. Dilated (congestive) cardiomyopathy is characterized by progressive eccentric hypertrophy, cardiomegaly, and CHF. The condition may have a genetic basis or occur because of an acquired condition, such as viral myocarditis or long-term alcoholism. Hypertrophic cardiomyopathy is due to mutations in contractile protein genes and includes the classic idiopathic hypertrophic subaortic stenosis (IHSS) as well as other variants. Restrictive cardiomyopathy typically has a relatively normal-sized heart coupled with evidence of cardiac failure due to infiltration of the myocardium by amyloid material or severe fibrosis.

Primary tumors of the heart occur at least 10 times less frequently than metastatic tumors of the heart, and most are
Introduction

The most common primary tumor of the heart in infants and children is the **rhabdomyoma**, which can produce a mass effect in the myocardium as well as ventricular cavity obstruction.

benign. The most common primary tumor of the heart in adults is the **myxoma**, which usually occurs in the left atrium and presents with symptoms mimicking mitral stenosis. The most common primary tumor of the heart in infants and children is the **rhabdomyoma**, which can produce a mass effect in the myocardium as well as ventricular cavity obstruction.

### TABLE 2-1 CONGENITAL MALFORMATIONS OF THE HEART AND MAJOR VESSELS

<table>
<thead>
<tr>
<th>A. Left-to-Right Shunts of the Circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular septal defect (VSD), membranous type; ventricular septal defect (VSD), muscular type; patent ductus arteriosus (PDA); atrial septal defect (ASD), ostium secundum (patent foramen ovale) type; atrial septal defect (ASD), sinus venosus type (with partial anomalous pulmonary drainage of right pulmonary veins into right atrium); atrial septal defect (ASD), ostium primum type (partial endocardial cushion defect); atroventricular septal defects (endocardial cushion defects), including complete atroventricular canal defect; anomalous left coronary artery arising from pulmonary trunk; ruptured sinus of Valsalva aneurysm; other.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Right-to-Left Shunts of the Circulation</th>
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</thead>
<tbody>
<tr>
<td>Tetralogy of Fallot; tricuspid atresia with ASD, VSD and/or PDA; total anomalous pulmonary venous connection (TAPVC) with ASD or PDA; transposition of the great vessels (congenital complete transposition of the great vessels) with VSD, ASD and/or PDA; persistent ductus arteriosus; aorticopulmonary septal defect; other.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Obstruction of the Circulation Without Shunt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarctation of the aorta, “infantile” form with tubular hypoplasia and “adult” postductal form; aortic arch and great vessel anomalies producing vascular rings around the trachea and esophagus; pulmonary stenosis; aortic valvular dysplasia and/or stenosis; supravalvular aortic stenosis; discrete subvalvular aortic stenosis; hypoplastic left heart syndrome; other.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D. Other Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebstein’s anomaly of the tricuspid valve; coronary artery anomalies, including origin of the left and right coronary arteries from a single right coronary ostium; other.</td>
</tr>
</tbody>
</table>
Congenital heart disease results from malformations of the heart and major vessels that develop during embryogenesis and are present at birth. A general classification of congenital malformations of the heart and major vessels is presented in Table 2-1. The ventricular septal defect (VSD) is the most common malformation presenting in infancy and childhood. Most VSDs result from defective closure of the membranous interventricular septum, although some are located in the muscular interventricular septum. As a result of the left-to-right shunt, patients present with systolic murmur, CHF, and progressive pulmonary HTN. If not surgically corrected, pulmonary arterial pressure reaches the systemic level, and the shunt becomes predominantly right to left, leading to late onset of cyanosis (Eisenmenger syndrome).
Congenital Malformations

**CARDIOVASCULAR SYSTEM**

**Figure 2-2  Patent Ductus Arteriosus**

The ductus arteriosus is an arterial connection between the origin of the left pulmonary artery and the aorta that normally closes within hours after birth. Failure of this connection to close results in PDA. PDA is another type of high-pressure left-to-right shunt producing symptomatic disease in infants and children. Other anomalies of the aortic arch system, such as an aberrant right subclavian artery, give rise to anatomic variations of the normal pattern of origin of the great arteries. Some of these anomalies produce vascular rings that can compress the trachea and esophagus.
Ostium secundum defect, the most common atrial septal defect (ASD), is located in the middle portion of the interatrial septum in the region of the foramen ovale. This ASD occurs as a result of defective formation of septum primum and septum secundum tissue, which leads to failure of the ostium secundum to close. Sinus venosus defect, located high in the interatrial septum, is the result of defective incorporation of the sinus venosus into the RV.

This ASD is associated with anomalous drainage of the right upper lobe pulmonary veins into the right atrium. Failure of formation of the septum primum and septum secundum results in a common atrium. Because left-to-right shunting occurs at low pressure, patients with ASDs tend to have pulmonary HTN and become symptomatic later in childhood or as adults in contrast to the usual course of patients with VSDs and PDAs.
Atrioventricular septal defects (AVSDs) result from significantly defective formation of endocardial cushion tissue. The ASD component is low in the interatrial septum because of failure of closure of the ostium primum. The VSD component is in the region of the membranous interventricular septum. The partial endocardial-cushion defect is composed of an ostium primum type of ASD, a defective mitral valve with a cleft in the anterior leaflet, and subtle anomalies in the LV, but it is associated with a closed membranous interventricular septum. The complete endocardial-cushion defect, also called a persistent common atrioventricular canal, consists of a large ostium primum ASD, a membranous VSD, and an abnormal common atrioventricular valve straddling the AVSD.
The tetralogy of Fallot is the most common form of cyanotic congenital heart disease, a state characterized by a right-to-left shunt with cyanosis at the time of presentation (i.e., cyanotic congenital heart disease). Depending on the severity of the defects, the presentation may occur in infancy (blue baby syndrome) but is not usually apparent until at least early childhood.

The 4 components of the tetralogy of Fallot are (1) VSD; (2) obstruction of the right ventricular outflow tract, usually as a result of subpulmonic, infundibular stenosis; (3) an aorta that overrides the VSD; and (4) right ventricular hypertrophy. Complete surgical correction of the tetralogy of Fallot includes closure of the VSD and expansion of the right ventricular outflow tract.
Transposition of the great vessels, or more specifically, congenitally complete transposition of the great vessels, is a condition in which the aorta takes origin anteriorly from the RV and the pulmonic trunk arises posteriorly from the LV. Transposition of the great vessels is compatible with postnatal life only when the anomaly occurs in association with one or more other defects, usually VSD, ASD, or PDA. The lower diagram shows the embryological development of transposition. Normally, two pairs of truncal swellings develop. In transposition, the wrong pair of truncal swellings becomes involved in partitioning the truncus, resulting in the abnormal position of the great vessels.
Tricuspid atresia, a severe complex anomaly of the right side of the heart with underdevelopment (hypoplasia) of the RV and a right-to-left shunt through an ASD, a VSD, or a PDA, results in severe cyanotic heart disease in infants. Next to transposition of the great vessels, it is the most common cause of severe cyanosis in the neonatal period, and the degree of cyanosis is usually more marked than in cases of transposition.
Coarctation of the aorta is a common obstructive congenital anomaly. There are 2 major types: (1) an infantile form, with tubular hypoplasia of the aortic arch proximal to a PDA, typically resulting in clinical problems in early childhood; and (2) an adult postductal form, in which there is a discrete ridgelike infolding of the aorta, just opposite the closed ductus arteriosus (the ligamentum arteriosum). The postductal type of coarctation leads to the development of an extensive collateral circulation (top image) to bypass the obstruction. The patient presents with HTN in the upper extremities and normal pressures in the lower extremities. Rib notching (produced by the enlarged collateral arteries) is seen on chest radiograph.
Left ventricular outflow tract (LVOT) obstruction can result from aortic stenosis or atresia. In severe congenital aortic malformation, LVOT obstruction leads to underdevelopment (hypoplasia) of the LV and ascending aorta. There is a dense, porcelain-like endocardial fibroelastosis of the diminutive LV. The ductus arteriosus is open. This constellation of anomalies constitutes the hypoplastic left heart syndrome, a condition that is fatal in the first several days of postnatal life when the ductus closes, unless high-risk surgery is performed. Less severe congenital aortic stenoses are compatible with longer survival. The congenital bicuspid aortic valve occurs in approximately 1% to 2% of the population and can give rise to aortic stenosis in adulthood because of hemodynamic turbulence that leads to fibrosis and calcification.
Atherosclerosis, the most prevalent and important form of arteriosclerosis, is a disease that typically affects the aorta and its major muscular distributing branches. The lesion of established atherosclerosis is the atherosclerotic (fibrous or atheromatous) plaque (gross photo, upper right). The fatty streak is the most obvious precursor lesion (gross photo, upper left). The photomicrographs show the features of atherosclerotic plaques, including fibrous capsule and lipid-rich core containing foam cells and cholesterol crystals.
The major pathologic and clinical effects of **atherosclerosis** involve the brain, the kidneys, the aorta, the peripheral and visceral arteries, and the heart. According to the response to injury hypothesis, atherosclerosis develops as a response of the vessel wall to multifactorial and repetitive injury. Genetic susceptibility, environmental factors, and endogenous metabolic alterations are risk factors that participate in the pathogenesis of atherosclerosis and the formation of **atherosclerotic plaques** in vessels. Atherosclerosis progresses asymptptomatically for years until a clinical threshold is reached. The onset of symptoms may be gradual or abrupt. The major treatable risk factors for development of atherosclerosis are a diet high in saturated fats and cholesterol, HTN, cigarette smoking, and diabetes mellitus.
Coronary heart disease (atherosclerotic or ischemic heart disease), dysfunction and damage to the heart muscle resulting from coronary artery disease (CAD), is usually due to coronary atherosclerosis. coronary atherosclerosis leads to progressive luminal narrowing of one or more of the coronary arteries by atherosclerotic plaques; these frequently have calcification. Coronary reserve is such that angina pectoris usually does not develop until there is at least 75% narrowing of the cross-sectional area. Most symptomatic disease is associated with the development of secondary changes in the plaques, especially surface ulceration, intraplaque hemorrhage, and thrombosis. Coronary thrombi can organize, leading to recanalization of the lumen. Nonatheromatous causes of myocardial ischemia include congenital coronary anomaly, coronary dissection, coronary vasculitis (Kawasaki disease, polyarteritis nodosa, and others), or a systemic hemodynamic problem, such as severe shock or profound anemia.
Angina pectoris, which is due to myocardial ischemia of short duration (approximately 15 minutes), results in reversible myocardial injury. Myocardial infarction, the death of heart muscle due to prolonged, severe ischemia, usually involves the LV. Myocardial necrosis generally begins after 45 minutes of severe ischemia and extends from the subendocardium into the subepicardium in a wave-front fashion over a period of approximately 3 to 4 hours. **Subendocardial (intramural) myocardial infarcts** are limited to the inner half of the wall. **Transmural myocardial infarcts** extend into the outer half of the wall. Lesions of the left anterior descending coronary system give rise to **anterior** and **anteroseptal myocardial infarcts**; lesions of the right coronary artery give rise to **inferior (posteroapical)** and **posterior myocardial infarcts**. Lesions of the left circumflex coronary artery give rise to **lateral myocardial infarcts**.
Healed myocardial infarct. In hypertrophied and dilated heart secondary to hypertension: Right ventricular hypertrophy indicative of heart failure

Healed anteroseptal, subendocardial myocardial infarct. Seen in coronal section of heart

Healed anterolateral infarct. In hypertrophied and dilated heart secondary to hypertension: Right ventricular hypertrophy indicative of heart failure

Healed posterior infarct. With overlying thrombus and acute anteroseptal infarct

Acute myocardial infarction may result in death due to pump failure or ventricular fibrillation. If the patient survives, the infarct undergoes organization and healing. During the first 2 to 3 weeks, the necrotic myocardium is gradually replaced by granulation tissue; during the next 2 to 3 months, the granulation tissue is converted to fibrous scar. This illustration shows various patterns of healed myocardial infarcts. During healing, the thinned infarcted wall may expand to form a ventricular aneurysm. Mural thrombi can form over the infarct and give rise to systemic emboli.
Less than 5% of acute myocardial infarcts rupture. These ruptures involve transmural myocardial infarcts that may rupture during the first 7 to 10 days after onset. Patients at highest risk are those with persistent HTN during their infarcts and those with infarcts in regions without fibrosis; typically, these are first infarcts. Over time, a dissection track develops from the left ventricular chamber through the necrotic myocardium, and the completed process results in abrupt development of hemopericardium, cardiac tamponade, and electromechanical dissociation (electrical rhythm on electrocardiogram [ECG] but no effective cardiac output). This is generally fatal. In some cases, the intramural dissection occurs slowly enough for a pericardial inflammatory reaction to occur and seal off a region of pericardium, containing the rupture. This gives rise to a wide-mouthed pseudoaneurysm that, unlike true aneurysms, is prone to late rupture. Other severe complications of acute myocardial infarction involve rupture of infarcted interventricular septum to produce a VSD and rupture of the head or entire trunk of an infarcted papillary muscle. These complications lead to systolic murmurs and cardiac failure.
Increase of systemic arterial pressure greater than the normal values of 120 mm Hg systolic and 80 mm Hg diastolic leads to a constellation of changes known as **hypertensive cardiovascular disease**. The pathophysiologic basis of HTN is excessive arteriolar constriction leading to increased peripheral vascular resistance. This may be exacerbated by factors promoting increased cardiac output. The fundamental etiology of HTN is unknown in most patients, although genetic predisposition and certain environmental influences, particularly high sodium intake, are known to be important factors. This condition is known as essential, idiopathic, or primary HTN. In approximately 10% of patients, HTN is secondary to a recognizable lesion or disease. Parenchymal renal disease and renovascular disease are the most common of these entities that are amenable to surgical treatment. Endocrine disorders and coarctation of the aorta are less common.
Hypertensive Cardiovascular Disease

The natural history of HTN follows 2 general patterns. **Benign HTN** is characterized by mild to moderate increase of blood pressure and an asymptomatic period of several years before the inevitable onset of symptoms and end-organ damage (hence, the condition is not truly benign). **Malignant HTN** is characterized by marked increase of blood pressure and rapid progression over a few weeks to end-organ failure. Most patients with essential HTN follow the benign pattern, although it may accelerate to malignant HTN. The characteristic vascular lesion of benign essential HTN is widespread hyaline arteriolosclerosis manifest by thickening of the walls of the small arteries and arterioles by amorphous eosinophilic material composed of degenerated smooth cells and deposited plasma proteins. **Hyaline arteriolosclerosis** with associated small cortical scars (hyaline arteriolonephrosclerosis) is commonly seen in the kidneys. Hyperplastic arteriolosclerosis, marked luminal narrowing by cellular intimal proliferation in a lamellar, “onionskin” pattern, is the characteristic lesion of malignant HTN. In severe malignant HTN, fibrinoid necrosis of the glomerular arterioles occurs. An associated ischemic injury develops rapidly, leading to petechial hemorrhages in multiple organs, including the kidneys (hyperplastic arteriolonephrosclerosis).
Hypertension, even of moderate degree, leads rapidly to cardiac hypertrophy, a compensatory increase of mass of the LV. The typical pattern of concentric hypertrophy of the LV, characterized by a thick wall and a relatively small chamber volume, is produced by a pressure load (afterload) on the ventricle. The heart size on cardiac silhouette is relatively normal, but the ECG shows increased voltage. When the limits of compensation are reached, the patient may have progressive cardiac decompensation accompanied by cardiac dilation. Cardiac hypertrophy is an independent risk factor for ventricular arrhythmias and sudden cardiac death.

Electrocardiographic evidence of LV hypertrophy. May or may not be present (tall R waves in V4, V5, and V6; deep S waves in V3R, V1, V2, III, and VR; depressed ST and inverted T in V5, V6, I, II, aVL, and aVF)
Heart failure is a state in which the heart fails as a pump to provide sufficient volume of circulating blood to meet the metabolic demands of the body. Because the dominant symptoms usually result from pulmonary or systemic venous congestion, the condition is termed congestive heart failure (CHF). Most commonly, heart failure is of the low cardiac output variety, but some conditions, including thiamine deficiency (beriberi), thyrotoxicosis, and severe anemia, produce cardiac failure with an increased circulating blood volume (high output cardiac failure), as shown here. The failure may be left-sided, right-sided, or combined left- and right-sided heart failure. This illustration shows the major manifestations of failure of the left and right ventricles. Cardiac transplantation or an artificial heart is the last therapeutic option. The most common conditions necessitating cardiac transplantation are end-stage ischemic heart disease (ischemic cardiomyopathy) and dilated (congestive) cardiomyopathy.
Figure 2-20  The Kidneys in Congestive Heart Failure

Abnormal renal function is important in the pathophysiology of CHF. In response to impaired left ventricular output, renal blood flow is decreased and redistributed from cortical to juxtamedullary nephrons. The subsequent increased glomerular vascular resistance produces increases in filtration fraction and colloid osmotic pressure in peritubular capillaries and also an increase in interstitial hydrostatic pressure secondary to augmented sodium transport, leading to increased sodium and water retention in the peritubular capillaries. The sodium and water retention contribute to the development of edema associated with CHF.
Most cases of CHF result from diseases that affect the LV initially or primarily, most commonly HTN and CAD. In response to chronic stress, the affected part of the heart undergoes compensatory hypertrophy. When the heart reaches a critical weight of 550 g, reserve is lost and progressive cardiac decompensation ensues. Heart failure results in progressive ventricular dilatation superimposed on the hypertrophy, which produces a pattern of so-called eccentric hypertrophy, as shown here. A severe acute load on the heart can produce failure and cardiac dilatation without previous hypertrophy. Stress of the atria can result in atrial fibrillation and formation of mural thrombi. The frequent coexistence of HTN and CAD can result in myocardial infarction of the hypertrophied LV.
**Heart Failure**

**Figure 2-22  Right-Sided Heart Failure: Acute Cor Pulmonale**

Cor pulmonale, the selective or primary impairment of the right heart (RV and right atrium) due to HTN in the pulmonary circulation, is caused by pulmonary vascular or parenchymal disease. Acute strain on the right heart is produced by a massive thromboembolus or by multiple segmental thromboemboli in the pulmonary trunk. A thromboembolus of sufficient magnitude may cause sudden death because the obstruction of the pulmonary vasculature produces pulmonary HTN and acute right-sided heart failure coupled with an impaired return of blood to the left heart with consequent decreased systemic and coronary perfusion and secondary left-sided heart failure. A thromboembolus usually does not result in pulmonary infarction. Because of the dual circulation from the pulmonary arteries and bronchial arteries, most segmental thromboemboli do not produce pulmonary infarcts. Pulmonary infarcts do occur in the presence of thromboemboli and impaired systemic circulation associated with preexistent CHF.
**Cardiovascular System**

**Heart Failure**

Figure 2-23  **Right-Sided Heart Failure: Chronic Cor Pulmonale**

Chronic cor pulmonale typically develops in response to recurring pulmonary thromboembolic disease or chronic pulmonary parenchymal diseases, particularly chronic bronchitis and emphysema. The heart exhibits significant hypertrophy and dilatation of the RV with a normal-sized LV (unless the patient has other diseases, such as systemic HTN or CAD).

**Extensive pulmonary emphysema.** With great distention of pulmonary trunk and main pulmonary arteries, which have pressed the aorta against the trachea; pulmonary arteriosclerosis and right ventricular hypertrophy.

**Figure 2-23** Right-Sided Heart Failure: Chronic Cor Pulmonale

R waves. In leads V₁ and V₂ as well as S, waves in leads I, V₄, V₅, and V₆ are indicative of right ventricular hypertrophy. Prominent P waves in leads II, III, aVF, V₁, and V₂ suggest right atrial enlargement.

X-ray: Chronic obstructive emphysema with cor pulmonale
Atherosclerosis of the aorta is typically most severe in the lower abdominal aorta between the origin of the renal arteries and the aortic bifurcation. The frequent occurrence of abdominal atherosclerotic aortic aneurysms is due to the medial weakening that accompanies the severe atherosclerosis. Less frequently, the entire abdominal aorta and the descending thoracic aorta form a thoracoabdominal atherosclerotic aortic aneurysm. Aortic root and ascending aorta atherosclerotic aneurysms are secondary to end arteriolitis of the vasa vasorum produced years previously by systemic infection by Treponema pallidum (syphilitic or luetic aortitis), unless proven otherwise. Atherosclerotic aneurysms of the iliofemoral arteries also occur. The cavity of the atherosclerotic aneurysm frequently fills with unorganized mural thrombus, and the expanding aneurysms become increasingly susceptible to external rupture and life-threatening exsanguinations.
Primary degenerative disease of the aortic media manifests as cystic medial degeneration, also called cystic medial necrosis. The lesions, which consist of foci of an acid mucopolysaccharide (glycosaminoglycan)–rich ground substance, are devoid of smooth muscle cells and elastic fibers. Severe cystic medial degeneration develops as a component of genetic diseases of connective tissue, specifically, the Marfan syndrome and certain subtypes of the Ehlers-Danlos syndrome. Severe disease gives rise to annuloaortic ectasia, a progressive aneurysmal dilatation of the aortic root, with accompanying aortic valvular incompetence. Myxomatous degeneration of the mitral valve typically develops, which leads to mitral valvular prolapse and mitral incompetence. The aortic and mitral regurgitation place a volume load (preload) on the LV, which causes dilatation and hypertrophy (eccentric hypertrophy). The weakened and dilated aorta is prone to medial dissection or focal perforation with external rupture and fatal exsanguination.
The effects of HTN with excessive hemodynamic trauma on a weakened aortic wall can lead to the formation of a hematoma in the media. The hematoma dissects longitudinally to split the media, which creates a dissecting hematoma or a dissecting aneurysm, a double-barreled aorta with true and false lumens. In most cases, a proximal intimal tear allows blood to enter the false lumen under systemic pressure. In type A dissections, the proximal intimal tear is in the ascending thoracic aorta, whereas in type B dissections, the proximal intimal tear is in the aortic arch or the descending thoracic aorta. Type A dissections, which are prone to external rupture into the mediastinum or pericardial cavity, necessitate surgical intervention. Some dissections develop distal tears and become chronic with the potential for late rupture. Blood pressure control is key in the treatment of any aortic dissection.
Acute RF is a multisystem immunologic illness often resulting in chronic rheumatic heart disease (RHD). RF generally affects children between the ages of 5 and 15 years. Ten to 14 days after infection with group A β-hemolytic streptococci, patients have multisystem manifestations, including skin rash (erythema annulare), subcutaneous nodules, migratory polyarthritis involving the larger joints of the extremities, and acute cardiac failure with mitral regurgitation. In some cases, central nervous system involvement manifests as spontaneous uncoordinated movements of the extremities (Sydenham chorea). The autoimmune attack of the target tissues of the host, which involves both humoral (antibody-mediated) and cellular (activated T lymphocytes) mechanisms, is a result of an immunologic reaction against the streptococci.
Acute rheumatic heart disease.
Rheumatic vegetations on mitral valve

Figure 2-28  Rheumatic Heart Disease

The basic tissue lesion of acute RF consists of fibrinoid necrosis of connective tissue accompanied by inflammatory cellular infiltrates composed of lymphocytes and macrophages. Acute RHD is produced by inflammation of all components of the heart (pancarditis) composed of fibrinous pericarditis, perivascular nodular foci of fibrinoid degeneration of collagen with surrounding granulomatous inflammation (Aschoff bodies), and similar inflammation of the mural endocardium and cardiac valves. The cardiac valvular lesions consist of small, nodular, wartlike fibrin thrombi (verrucae) along the line of closure of the valves, particularly the mitral and aortic valves. The cardiac inflammation leads to depressed myocardial contractile function and dilatation of the cardiac chambers, particularly the LV, and associated mitral valvular regurgitation.
The heart manifests chronic residua at the sites of previous inflammation, including fibrous adhesions, which partially obliterate the pericardial space; perivascular scars in the myocardium; and alterations of the cardiac valves produced by the process of organization and healing. The inflammation of the cardiac valves elicits a granulation tissue response with ingrowth of small blood vessels (neovascularization) and fibroblasts, collagen production, diffuse fibrous thickening, and, later, dystrophic calcification. The organization and healing of the fibrinuous verrucae lead to the partial or complete fusion of one or more of the commissures between adjacent leaflets. These changes distort the anatomy and function of the valves. A vicious cycle of increased hemodynamic turbulence and wear and tear ensues, leading to progressive distortion of valvular anatomy and function, until months to years after the acute RF, the patient becomes symptomatic with chronic RHD.
Chronic RHD accounts for nearly all cases of mitral stenosis. Stenosis and incompetence of the mitral and aortic valve are produced by obstruction of the orifice and regurgitation of blood across the orifice, respectively. In rheumatic mitral stenosis, the shortening and thickening of the mitral leaflets, the fusion and thickening and the shortening of the chordae tendineae, and the fusion of the commissures results in a greatly reduced orifice. This “dam-in-the-stream” effect leads to increased left atrial pressure with subsequent atrial dilatation, formation of atrial mural thrombi, and atrial fibrillation. Increased pulmonary venous pressure, pulmonary congestion, increased pulmonary arterial pressure, and right heart strain leads to right ventricular hypertrophy and dilatation and functional tricuspid regurgitation. There is a characteristic opening snap and diastolic rumbling murmur at the cardiac apex.

**Figure 2-30  Rheumatic Heart Disease: Mitral Stenosis**

Mitral stenosis. Viewed from below and left: minor rheumatic involvement of aortic valve. Thickened stenotic mitral valve. Anterior cusp has typical convexity; enlarged L. atrium; “jet lesion” on L. ventricular wall. Enlargement of R. ventricle. With some thickening of wall resulting from mitral stenosis; pulmonary artery enlarged and thickened with scattered plaques of atheromas.
Systemic lupus erythematosus can produce pancarditis with fibrinous pericarditis and pericardial effusion, multifocal lymphohistiocytic myocarditis, and mural and valvular endocarditis. Valvular inflammation can be extensive, leading to fibrinous verrucae on the upper and lower surfaces of the valvular leaflets, particularly those of the mitral valve. This valvular pathology is known as the atypical verrucous endocarditis of Libman and Sacks. Healing of the inflammation leads to progressive valvular deformity, including fibrous adhesions of the posterior mitral leaflet to the adjacent left ventricular wall with resultant mitral stenosis or regurgitation or both.
Sarcoidosis

Brain + (15%)
Eyes ++ (20%)
Nasal and pharyngeal mucosa, tonsils + (10%)
Salivary glands + (1%)
Lymph nodes ++++ (80%)
Lungs ++++ (80%)
Heart ++ (20%)
Liver ++++ (70%)
Spleen ++++ (15%)
Skin ++ (30%)
Bone ++ (15%)

Relative frequency of organ involvement in sarcoidosis

Scleroderma

Extensive fibrosis (arrows) between and around cardiac muscle fibers and in arterial wall with only moderate lymphocytic and histiocytic infiltration

Progressive systemic sclerosis (scleroderma) can produce interstitial myocarditis and progressive myocardial fibrosis. Sarcoidosis can produce extensive replacement of the myocardium by multiple granulomas with multinucleated giant cells derived from macrophages and associated fibrosis. The process may involve the cardiac conduction system as well as the working myocardium.

**Figure 2-32  Myocarditis in Sarcoidosis and Scleroderma**
Nonbacterial thrombotic endocarditis (NBTE) consists of sterile thrombi that form as vegetations on the superior surfaces of the leaflets of the aortic, mitral, tricuspid, and pulmonic valves as a result of mild inflammation and associated surface endothelial damage. The lesions are frequently associated with disseminated intravascular coagulation. Predisposing illnesses are those that initiate a systemic reaction, including serious infections, shock of various causes, and extensive burns. The valvular lesions also develop with chronic wasting states, particularly in association with malignant tumors, leading to the pseudonym marantic endocarditis. The valvular lesions can be clinically silent or can give rise to serious symptoms due to embolization of the vegetations. After acute illness, the valvular lesions form fibrous tags along the line of closure of the valvular leaflets (Lambl excrescences).
Other Inflammatory Diseases of the Heart

**Common Portals of Bacterial Entry in Bacterial Endocarditis**

- Dental infections
- Genitourinary infections
- Cutaneous infections
- Pulmonary infections

**Bloodstream**

**Common Predisposing Lesions**

**Infective (bacterial) endocarditis** results from direct infection of the valvular or mural endocardium by bacteria or other microorganisms, including fungi and rickettsia. The bacteria or other microorganisms enter the bloodstream from the site of a local infection of the skin, the lungs, the genitourinary system, or the oral cavity. Sometimes there is no obvious site of infection. Some medical or dental procedures may lead to the seeding of the bloodstream with microorganisms. Whether IE follows an acute hectic course or a subtle subacute course depends on whether the virulence of the microorganism is high (Staphylococcus aureus, gram-negative bacteria, fungi, and others) or low (Streptococcus viridans and others), the presence or absence of a preexisting valvular or congenital defect, and the presence or absence of systemic conditions in the host (chronic alcoholism, intravenous drug abuse, immunosuppression).
**Infective endocarditis** generally involves the cardiac valves, unless a congenital cardiac defect, which predisposes to mural endocarditis, is present at the site of a jet lesion. As part of a generalized inflammatory reaction to a bacteremia (or fungemia etc), small thrombi form over foci of endothelial damage on the endocardium, producing lesions similar to those of marantic endocarditis. These thrombi, which are sterile initially, become seeded with microorganisms rapidly, and the influx of neutrophils incites an accelerated inflammatory reaction. The surface thrombi grow to become vegetations. The toxic products of the bacteria and neutrophils produce necrosis of the valvular leaflets, which stimulates further suppurative inflammation.
Progression of the inflammation can lead to the perforation of a valve leaflet or it can spread onto the chordae tendineae, leading to chordal rupture. The inflammation may also invade the valvular annulus, producing a valvular ring abscess. Generally, there is permanent damage to one or more of the cardiac valves, which leads to progressive valvular incompetence and cardiac failure. A major goal of clinical management is to make the diagnosis and institute high-dose intravenous antibiotic therapy to sterilize the vegetations and prevent the spread of the infection beyond the valve leaflets.
Other Inflammatory Diseases of the Heart

Vegetations of bacterial arteritis in pulmonary trunk.
At site of “jet lesion” from patent ductus arteriosus:
multiple infarcts of lungs with overlying pleuritis.

Pleuritis
Vegetations
Infarcts

Vegetations on pulmonary valve and outflow tract of right ventricle

Infection of the right-sided mural endocardium can occur at the site of a “jet lesion” produced by a ventricular septal defect with left-to-right shunting. Infection of the right-sided cardiac valves is also a complication of intravenous drug abuse with contaminated needles and foreign material. The patient may present with severe pneumonia due to seeding of the lungs with infected vegetations.
Embolization of infected vegetations is a serious complication of IE. Small thromboemboli lead to petechial hemorrhages in the skin and internal organs. Larger infected thromboemboli, which result from inflammatory damage to the vessel wall, produce mycotic (mushroom-like) aneurysms. Intraluminal obstruction produces infarcts of the tissue supplied by an end artery. With highly virulent organisms, the affected tissue develops an abscess (infected infarct). Infected emboli to one or more coronary arteries can lead to myocardial infarction or to the formation of myocardial abscesses.

**Figure 2-38 Infective Endocarditis: Remote Embolic Effects**

Embolic infarcts can result in various conditions, including:

- **Infarct of brain with secondary hemorrhage from embolism to right anterior cerebral artery; also small infarct in left basal ganglia**
- **Petechiae of skin and clubbing of fingers**
- **Multiple petechiae of skin and clubbing of fingers**
- **Petechiae and gross infarcts of kidney**
- **Infarct of mucous membranes**
- **Mycotic aneurysms of splenic arteries and infarct of spleen; splenomegaly**
- **Emboli in vessel of ocular fundus (arrow) with retinal infarction; petechiae**
Some infections that originate in the skin or an internal organ can give rise to bacteremia or fungemia. Cardiac involvement, which includes *fibrinopurulent pericarditis* and *multifocal suppurative myocarditis* with abscess formation, can occur in the absence of valvular involvement, or the valves may show lesions of marantic endocarditis (with potential for the development of IE). Systemic fungal infections tend to occur in immunosuppressed patients, and the lesions show much diminished inflammatory cellular infiltrates. The heart may also be involved with various protozoal infections, such as *Chagas disease*. 
Other Inflammatory Diseases of the Heart

Microorganisms (viruses, rickettsiae, bacteria, fungi, and protozoa) or their toxins can produce a pattern of **myocarditis** or myopericarditis that is distinctive but not generally microorganism specific. Pericardial involvement consists of a fibrinous exudate often accompanied by a serous effusion. The type of inflammatory cellular infiltrate provides information about the underlying cause (neutrophils with bacterial infection, lymphocytes with viral infections, eosinophils with allergic reactions). Viral myocarditis is characterized by multifocal infiltration of the interstitium with lymphocytes and some macrophages (histiocytes) and by variable amounts of myocardial necrosis. The extent of inflammatory cellular infiltrate exceeds the amount of necrosis.
Primary (idiopathic) cardiomyopathies develop independently. Secondary cardiomyopathies occur as a component of cardiac disease (not originating in the myocardium) or systemic disease with cardiac involvement. Dilated (congestive) cardiomyopathy, the most common type, is characterized by the progressive development of cardiomegaly, CHF, and often arrhythmias. Pathologically, there is symmetrical hypertrophy and dilatation of the 4 cardiac chambers in the absence of significant coronary, valvular, or congenital cardiac lesions or prominent arteriolonephrosclerosis. Atrial or ventricular mural thrombi or both may form as a result of poor contractile function. The myocardium frequently shows nonspecific degeneration and fibrosis and, occasionally, some inflammatory infiltrates. The likely causes for this disease include previous myocarditis, chronic alcoholism, and genetic mutations often associated with familial disease.
Hypertrophic cardiomyopathy includes the classic IHSS, a condition that produces obstruction of the LVOT at the subvalvular, valvular, or supravalvular level. IHSS is characterized pathologically by asymmetrical ventricular septal hypertrophy (the interventricular septum is at least 1.3 times the thickness of the left ventricular free wall, and, initially, left and right ventricular chambers are small). Myocytes in the affected myocardium have a disorganized, “herringbone” arrangement rather than the normal parallel pattern within muscle bundles. The abnormal pattern of contraction leads to the paradoxical systolic anterior motion of the anterior mitral leaflet toward the bulging interventricular septum, thereby producing functional LVOT obstruction (functional aortic stenosis) and mitral regurgitation. The IHSS phenotype is caused by a variety of genetic mutations of actin, myosin, and other contractile proteins.
Cardiac involvement occurs most frequently in primary systemic amyloidosis and senile cardiac amyloidosis. Myocardial degeneration results from deposits of infiltrative amyloid, which surround the myocytes and cause the classic pattern of low voltage on the ECG. Cardiac amyloidosis and severe fibrosis (collagen deposition) of any cause can produce a restrictive cardiomyopathy. Endomyocardial biopsy is used to distinguish the two conditions and make the diagnosis of amyloidosis. Patients with restrictive cardiomyopathy typically present with symptoms of CHF dominated by those of right-sided failure and a normal-sized heart, which mimic constractive pericarditis on radiographic examination.
Valvular Heart Disease

**Figure 2-44  Rheumatic Heart Disease**

This illustration shows multivalvular disease involving the aortic, mitral, and tricuspid valves produced by chronic RHD. The diffuse fibrosis and variable commissural fusion result in dysfunction dominated by incompetence (insufficiency, regurgitation) or stenosis. **Chronic RHD** results in clinically significant pathology of the mitral valve alone in approximately 40% of cases, the mitral and aortic valves in another 40%, and the aortic valve alone in approximately 20%. Significant rheumatic lesions affect the tricuspid valve in a small percentage of cases, whereas the pulmonic valve is virtually never involved. RHD is only one of a number of diseases that produce significant valvular pathology, which results in incompetence, stenosis, or both of one or more of the valves.
Valvular heart disease may result from congenital cardiac defects or from immunologic, inflammatory, infectious, or degenerative diseases of the heart. In the United States, nonrheumatic causes are responsible for most valvular heart disease necessitating surgical intervention. **Stenosis of a congenital bicuspid aortic valve** in a middle-aged individual and **stenosis due to senile sclerosis** (Mönckeberg) of a tricuspid aortic valve in an older individual are the conditions that lead most commonly to severe isolated aortic valve disease. RHD can produce **aortic stenosis**, which includes the formation of an acquired bicuspid valve due to fusion of one of the 3 commissures. Patients with valvular aortic stenosis experience left ventricular hypertrophy. They present with symptoms of fatigue and angina pectoris and exhibit a systolic ejection murmur along the right sternal border accompanied by diminished carotid pulsations.
The mitral valve leaflets are thickened and elongated due to myxomatous degeneration.

The thickened and redundant mitral leaflets prolapse into the left atrium.

The mitral valve leaflet is thickened and elongated (low magnification).

The thickened mitral leaflet is composed of loose myxomatous connective tissue and the normal dense fibrosa is lost (high magnification).

**Figure 2-46  Mitral Valve Prolapse**

**Myxomatous degeneration of the mitral valve** gives rise to a redundant valve composed of white, glistening myxomatous tissue. Histologically, the normal fibrosa is replaced with myxomatous tissue. The redundant valve prolapses into the left atrium with each systole, which gives rise to mid to late systolic clicks and a short systolic murmur heard at the cardiac apex. The prolapse is readily detected by echocardiography. Some degree of mitral valve prolapse occurs in approximately 2% of the population, with higher frequency in females than in males. The cause is obscure, but there is some evidence that autonomic dysfunction gives rise to an abnormal pattern of cardiac contraction and secondary degenerative change of the mitral valve. A similar lesion is seen with Marfan syndrome. Progression of the mitral degeneration can give rise to progressive mitral regurgitation. Rupture of a chordae tendineae, either spontaneously or due to infection, can give rise to acute severe mitral regurgitation.
Primary tumors of the heart, most of which are benign, occur much less frequently than metastatic tumors of the heart but more often than the rare primary sarcomas of the heart. The most common primary tumor in adults is the **myxoma**, which consists of nondifferentiated small mesenchymal cells in an abundant myxoid stroma. It occurs most commonly in the left atrium and presents with symptoms mimicking mitral stenosis. In infants and children, the **rhabdomyoma** is most common. These tumors may be single or multiple and have a subendocardial, intramural, or subepicardial location. The lesions are composed of primitive myocytes (spider cells). The rhabdomyomas may occur as part of the tuberous sclerosis complex.
**Tumors of the Heart**

**CARDIOVASCULAR SYSTEM**

**Figure 2-48  Metastatic Heart Tumors**

Metastatic cardiac tumors can arise from a number of different malignant neoplasms, including multiple myeloma, bronchogenic carcinoma, breast carcinoma, lymphomas, and leukemias. Various patterns of metastases, including large masses and lymphangitic spread of tumor, are illustrated.
Congestive heart failure produces pericardial effusion consisting of clear fluid with low protein content (a transudate). Viral infections, renal failure (uremia), and noninfectious immunologic diseases result in fibrinous pericarditis that is often accompanied by pericardial effusion. Bacterial infections produce purulent pericarditis. Tuberculosis produces granulomatous pericarditis. Pericardial disease also can result from metastatic tumors. Fluid accumulation in the pericardium can result in impaired cardiac function depending on the rapidity and amount of fluid accumulation. Treatment may involve percutaneous pericardiocentesis or a surgically produced pericardial window.
Healing of acute pericarditis, particularly with abundant fibrinous exudates or hemorrhage, gives rise to adhesive pericarditis. Adhesions may be severe and may be accompanied by calcification. Severe adhesive pericarditis can produce the clinical syndrome of constrictive pericarditis, which necessitates surgical relief. Previously, tuberculous pericarditis was the leading cause of constrictive pericarditis, but currently, most cases are idiopathic. In the age of hemodialysis, chronic renal disease is a relatively common cause of adhesive pericarditis.
Severe crush injury of the chest can result in traumatic damage to the heart muscle known as a cardiac contusion. The lesions show hemorrhagic necrosis of the myocardium. The lesion can be transmural and result in cardiac rupture and cardiac tamponade due to hemopericardium. The lesions can heal with aneurysm formation. Other traumatic lesions include rupture of the interventricular septum, rupture of a papillary muscle, or rupture of a valve cusp. All of these lesions can produce acute cardiac decompensation. Gunshot or stab wounds of the chest can produce lacerations or perforations of various parts of the heart. This leads to severe bleeding into the pericardium and early or delayed cardiac tamponade due to hemopericardium. This life-threatening condition necessitates rapid evacuation of the hemopericardium.
Five major disease categories are presented in this chapter: obstructive and restrictive disorders of gas exchange, vascular diseases of the lung, infectious and inflammatory diseases, and tumors of lungs and pleura.

**OBSTRUCTIVE LUNG DISEASES**

Chronic obstructive pulmonary disease (COPD) is characterized by a reduction of pulmonary air flow as determined by spirometric function tests with normal or increased total lung capacity (TLC) and forced vital capacity (FVC) in combination with decreased forced expiratory volume (FEV). COPD follows either increased resistance to airflow (e.g., by luminal narrowing of air ducts) or the loss of elastic recoil (by passive widening of air spaces). It can be caused by a number of different respiratory diseases, including chronic bronchitis, bronchiolitis and asthma, cystic fibrosis (CF), bronchiectasis, or α1-antitrypsin deficiency. COPD may lead to progressive and destructive emphysema and, eventually, cor pulmonale, characterized by reduced intrapulmonary blood flow, pulmonary hypertension, and right heart insufficiency.

**RESTRICTIVE LUNG DISEASES**

In restrictive lung diseases (RLDs), the lungs have a limited potential to expand, and therefore, compliance is reduced. Although extrapulmonary disorders such as chest abnormalities, intraabdominal masses, and neuromuscular diseases also can limit lung expansion, the term RLD is generally reserved for intrapulmonary parenchymatous diseases. In these cases, spirometric tests show a reduced FVC with normal or proportionately reduced FEV. RLD occurs in acute and chronic forms. Classic examples of acute RLD are the adult respiratory distress syndrome (ARDS) and acute hypersensitivity pneumonitis. Chronic forms include such pathogenetically different entities as idiopathic pulmonary fibroses (fibrosing alveolitis), chronic interstitial pneumonitis in collagen-vascular diseases, pneumoconioses, and sarcoidosis. Only patients in early stages of acute RLD may recover completely; later stages and especially the chronic forms of RLD remit to scarring or progress to extensive interstitial pulmonary fibrosis with honeycombing, pulmonary hypertension, and development of cor pulmonale. Recurrent superimposed infections further complicate the course of RLD.

**VASCULAR LUNG DISEASES**

Most common vascular lung diseases fall into 2 major categories: clotting disorders with secondary vascular occlusion and primary structural diseases of blood vessels. Clotting disorders may cause occlusion of pulmonary vessels by embolization or by in situ thrombosis (e.g., after contraceptive medication with high estrogen content or after clotting disorders in pancreatic carcinoma). In situ pulmonary thrombosis also may be a consequence of primary structural diseases of lung vasculature.

**PULMONARY INFECTIOUS DISEASES**

Infections of the lung present with different pathologic patterns and are classified as bacterial pneumonias, atypical and viral pneumonias, or parasitic (e.g., Pneumocystis carinii pneumonia) or fungal pneumonitis. Most bacterial and viral pneumonias initially are acute inflammatory diseases and, with adequate treatment, may resolve completely. However, pneumonias caused by intracellular bacteria (e.g., Mycobacterium tuberculosis), parasites, or fungi run a protracted and chronic course entailing an immune response and incomplete resolution. They heal with focal or diffuse scarring and the risk of chronic restrictive pulmonary disease.

**TUMORS IN THE LUNGS AND THE PLEURA**

As in other organs, tumors of the lung are identified as carcinomas (e.g., of bronchial epithelium, bronchial glands, or alveolar lining cells) or as sarcomas. They are classified according to their cell of origin (squamous cell carcinoma [SCC], adenocarcinoma [AC], small-cell carcinoma [oat cell carcinoma]) and to their degree of differentiation. Their local extension and metastatic spread determine their prognosis. Consequently, both tumor classification and documentation of its spread (grading and staging) are important responsibilities of diagnostic pathology and form the basis for determining therapeutic intervention. In addition, the lungs are frequent sites of metastases from other locations (e.g., breast, pancreas, testes, bone, malignant melanoma of the skin, and others), which must be distinguished from primary lung tumors.
Respiratory System

Obstructive Lung Diseases

Pulmonary Function in Obstructive Disease

Forced expiratory volume (FEV) and forced expiratory flow (FEF) 25–75% reduced

Obstruction

Normal

Obstructed

Normal

Maximal expiratory flow-volume curves. TLC increased in obstruction but expiratory flow rate decreased. In severe obstruction tidal breathing may coincide with MEFV curve.

Pressure-volume loop. Flow resistance and work of breathing (shaded areas) increased; intrapleural pressure positive on expiration

Figure 3-1 Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is characterized by reduced pulmonary airflow with normal or increased TLC and FVC combined with decreased FEV as determined by spirometric function tests. COPD follows increased resistance to airflow (by luminal narrowing of air ducts) or loss of elastic recoil (and by passive widening of air spaces). COPD is caused by a number of respiratory diseases, including chronic bronchitis, bronchiolitis and asthma, CF, bronchiectasis, and α1-antitrypsin deficiency. COPD results in a progressive and destructive emphysema and reduced intrapulmonary blood flow, pulmonary hypertension, and right heart insufficiency (cor pulmonale).
Chronic bronchitis with persistent and productive cough afflicts up to 25% of persons older than 40 years in smog-ridden cities and up to 15% in smokers. It is accompanied by repeated nonspecific infections, mucosal atrophy with mucoid metaplasia (1 goblet cell per 7 columnar cells changes to 1 goblet cell per 1 columnar cell), reduced dust clearance, and inflammatory destruction of elastic lamellae in the bronchial wall with reactive muscular hypertrophy. Finally, there is degeneration and cylindric bronchiectases, transient fibrotic narrowing of bronchioles (small airway disease), and emphysema.
Pathogenesis of Cystic Fibrosis

In cystic fibrosis (CF) (mucoviscidosis), a primary defect in chloride ion transport across epithelia results in the secretion of abnormally viscous mucus in all secretory glands, including the bronchial glands. Mucus inspissation blocks the airways, causing bronchiectasis and emphysema. Chronic abscess formation, which results from recurrent superinfections (Staphylococcus and Pseudomonas species) can complicate the course of CF. Although CF affects other organs, COPD is the cause of death in 80% to 90% of cases.
Roentgenograms in Chronic Obstructive Pulmonary Disease

Hyperinflation of lungs; depression of diaphragm with its insertion to ribs evident; peripheral attenuation of pulmonary vessels; heart shadow small relative to lungs. Corresponds to “pink puffer.”

Lateral projection of same case as in left. Diaphragm not only depressed but actually concave downward. Retrosternal clear space greatly enlarged.

Bilateral giant apical bullae

No hyperinflation; increased bronchovascular markings, especially at bases; diaphragm well rounded. Patient had chronic CO₂ retention, cor pulmonale, and multiple previous episodes of respiratory failure. Corresponds to “blue bloater.”

**Figure 3-4  Emphysema**

In **emphysema**, overinflation of the alveoli located distal to the terminal bronchioles is caused by the destruction of alveolar walls. The pathogenesis is thought to be an imbalance between increased (inflammatory) elastolysis and decreased antiprotease activity (e.g., in α₁-antitrypsin deficiency). Emphysema is classified by anatomical nature and location in the lobule: **centrilobular (centriacinar) emphysema** affects the upper part of lungs after inhalation of toxic materials; **panlobular (panacinar) emphysema** is commonly found in the lower part of lungs, such as in α₁-antitrypsin deficiency; **paraseptal (distal acinar) emphysema** frequently occurs subpleurally, adjacent to fibrosis; **bullous emphysema** results from enhanced focal destruction of air space walls with confluence of multiple air spaces. **Interstitial emphysema** expands in interstitial septae after acute overinflation of the lungs with rupture and perforation of air spaces into fibrous septae. It may spread to the mediastinum and subcutaneous tissues of the neck.
Asthma bronchiale is caused by an enhanced bronchoconstrictor response to type I (allergic) immune reaction to extrinsic or intrinsic stimuli. The etiology and pathogenesis is multifactorial and includes genetic conditions, psychologic stress, and allergic and infectious stimuli. Severe coughing with expectoration of a characteristic mucoid sputum with masses of eosinophils and their breakdown products (Charcot-Leyden crystals), gyrate mucus clumps (Curschmann spirals), and clusters of epithelial cells (Creola bodies) follows the acute phase of the attack. Histologically, asthmatic bronchitis appears as a mucoid metaplasia of bronchial epithelium, eosinophilic infiltration, hyaline thickening of the basement membrane, and muscular and glandular hypertrophy. Bronchial lumina are often occluded by mucous plugs. Status asthmaticus is a severe persistent bronchoconstriction that does not respond to treatment. It leads to severe hypoxia, acidosis, and hypercapnia and may be fatal.
Restrictive Lung Diseases

**FIGURE 3-6 ADULT RESPIRATORY DISTRESS SYNDROME**

Adult respiratory distress syndrome is defined by reduced arterial oxygenation, decreased lung compliance, and diffuse noncardiogenic pulmonary infiltrates. The morphology is represented by diffuse alveolar damage (DAD). Alveolar and interstitial edema develops subsequent to diffuse alveolar epithelial and vascular endothelial injury with capillary congestion. Alveolar cell necrosis may occur with focal hemorrhage and capillary microthrombosis. The formation of hyaline membranes composed of plasma proteins, cellular debris, and fibrin precipitates is characteristic in ARDS. The decrease in functioning surfactant factor leads to a loss of type I alveolar cells and a reactive proliferation of type II alveolar cells. Progressive fibroblast proliferation leads to fibrosis. The etiology of ARDS/DAD is diverse and often cannot be identified from the morphologic substrate. Causes of ARDS/DAD are summarized in Table 3-1.
Figure 3-7  **Extrinsic Allergic Alveolitis**

Hypersensitivity pneumonitis (extrinsic allergic alveolitis [EAA]), an acute immunologic reaction of the lung to inhaled antigens, is typically caused by occupational exposure to organic dusts (e.g., farmer’s disease bagassosis). Although EAA is classified as an acute RLD, its appearance is distinct from that of ARDS/DAD. EAA may run an acute or a chronic course with lymphoplasmacytic and monocytic interstitial infiltration (rarely eosinophils), mild alveolar exudate, and reactive alveolar cell proliferation (catarrh). There are noncaseating granulomas in approximately one third of cases. EAA is characterized by progressive fibroblast proliferation with interstitial and intraalveolar budding fibrosis and obliterative bronchiolitis. Inflammatory infiltrates usually recede in end-stage disease, leaving the nonspecific scenario of usual interstitial pneumonitis or fibrosis.
Restrictive Lung Diseases

**TABLE 3-2 CLASSIFICATION OF IDIOPATHIC PULMONARY FIBROSIS***

<table>
<thead>
<tr>
<th>Feature</th>
<th>NSIP</th>
<th>UIP</th>
<th>DIP</th>
<th>AIP</th>
<th>LIP</th>
<th>COP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial inflammation</td>
<td>Prominent</td>
<td>Scant</td>
<td>Scant</td>
<td>Scant</td>
<td>Prominent</td>
<td>Scant</td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collagen</td>
<td>Variable, diffuse</td>
<td>Patchy</td>
<td>Variable, diffuse</td>
<td>No</td>
<td>Some areas</td>
<td>No</td>
</tr>
<tr>
<td>Fibroblast foci</td>
<td>Occasional</td>
<td>No</td>
<td>No</td>
<td>Yes, diffuse</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>BOOP</td>
<td>Occasional, focal</td>
<td>Occasional, focal</td>
<td>No</td>
<td>Occasional, focal</td>
<td>No</td>
<td>Prominent</td>
</tr>
<tr>
<td>Intraalveolar macrophages</td>
<td>Occasional, patchy</td>
<td>Occasional, patchy</td>
<td>Yes, diffuse</td>
<td>No</td>
<td>Patchy</td>
<td>No</td>
</tr>
<tr>
<td>Hyaline membranes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes, focal</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>Rare</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Sometimes</td>
<td>No</td>
</tr>
</tbody>
</table>

*AIP indicates acute interstitial pneumonitis; BOOP, bronchiolitis obliterans organizing pneumonitis; DIP, desquamative interstitial pneumonitis; NSIP, nonspecific interstitial pneumonitis; UIP, usual interstitial pneumonitis; LIP lymphocytic interstitial pneumonitis, COP cryptogenic organizing pneumonitis.


**FIGURE 3-8 IDIOPATHIC PULMONARY FIBROSIS (IDIOPATHIC INTERSTITIAL PNEUMONIA)**

Idiopathic pulmonary fibrosis (IPF) refers to a poorly understood chronic inflammatory and progressive fibrosing disorder of the lung. It is not a single entity but a mixture of pathogenetically variable diseases, which may progress in part from an acute RLD (e.g., EAA). **Hamman-Rich syndrome** is the classic description of IPF. The etiology of IPF and its subtypes is often unclear. Potential causes include postinfectious syndromes (e.g., postadenovirus, parainfluenza virus, and influenza B virus infections). The pathogenesis seems to be (auto)immune because the bronchoalveolar lavage contains increased numbers of neutrophils, macrophages, T lymphocytes, and occasionally eosinophils. Tissue biopsy shows expression of major histocompatibility complex (MHC) II antigens in alveolar epithelial cells. Infiltrating lymphocytes show a predominance of CD4+ and CD8+ T cells. Classifications of IPF are shown in Table 3-2.
Restrictive pulmonary disease is evident in up to 70% of patients with systemic lupus erythematosus (SLE), approximately 50% of patients with progressive systemic sclerosis (PSS), and up to 20% of patients with rheumatoid arthritis (RA). Lung involvement in RA is characterized by diffuse interstitial fibrosis (fibrosing alveolitis), bronchiolitis obliterans, sclerosing granulomas and necrotizing nodules, and isolated fibrinous pleuritis. In SLE, characteristic pulmonary changes are DAD, nonspecific interstitial pneumonitis with focal atelectasis, nonspecific infections, leukocytoclastic vasculitis, and focal pulmonary hemorrhage. PSS presents as an IPF (cryptogenic fibrosing alveolitis) with vascular involvement and pleurisy.
Several of the systemic vasculitis syndromes affect the lungs regularly or incidentally. The classic example is **Wegener granulomatosis**, which is characterized by necrotizing granulomatous lesions in the upper and lower respiratory tract accompanied by systemic vasculitis involving arteries and veins and focal necrotizing glomerulitis. Radiographs of the lungs reveal irregular and frequently multiple densities with or without cavitation, which may resemble metastatic disease. Bronchial disease may cause pulmonary atelectases.
Restrictive Lung Diseases

Pneumoconiosis describes a group of chronic RLDs that are caused by inhalation of mineral dusts. The most common forms of these occupational diseases are caused by coal dust, quartz, asbestos, and beryllium. Pneumoconioses are characterized by progressive pulmonary fibrosis, which reflects the dose, particle size, and fibroblastic potential of the individual dust. The dose is a function of dust concentration and duration of exposure. Silicosis, which is caused by inhalation of silica dust, is an example of a common pneumoconiosis. Characteristics of the more common pneumoconioses are shown in Table 3-3.
TABLE 3-3  CLINICAL AND PATHOLOGIC FEATURES OF PNEUMOCONIOSES*

<table>
<thead>
<tr>
<th>Entity</th>
<th>Clinical Appearance</th>
<th>Pathologic Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coal miner’s lung</td>
<td>Black lung disease</td>
<td>Diffusely distributed, small focal anthracosilicosis, initially centriacinar and peribronchiolar with many carbon-laden macrophages and perifocal emphysema; extent of fibrosis depends on admixture of quartz</td>
</tr>
<tr>
<td>Silicosis</td>
<td>Acute silicosis (uncommon)</td>
<td>Alveolar lipoproteinosis and progressive diffuse interstitial fibrosis secondary to inhalation of small particulate silica crystals (e.g., after sand blasting)</td>
</tr>
<tr>
<td></td>
<td>Nodular silicosis (common)</td>
<td>Multiple growing silicotic nodules, usually 2 mm to 1 cm in diameter: fibrosing granulomas with concentric fibrous layering, some anthracotic pigment, small slitlike spaces, and needle-shaped crystalline spicules on polarization; perifocal emphysema</td>
</tr>
<tr>
<td></td>
<td>Progressive massive silicosis</td>
<td>Multiple silicotic granulomas up to 10 cm in diameter, both lungs involved, massive and rapidly progressive fibrosis</td>
</tr>
<tr>
<td>Asbestosis and asbestosrelated</td>
<td>Asbestosis per se</td>
<td>Alveolitis with progressive interstitial fibrosis, deposition of asbestos bodies (golden-brown beaded rods consisting of asbestos fibers coated by ferroproteinaceous material); final stage: honeycombing lung</td>
</tr>
<tr>
<td>diseases</td>
<td>Pleural plaques and</td>
<td>Recurrent pleural fibrinous effusions, pleural fibrosis and pleural plaques (“sugar coating”), focal atelectasis secondary to pleural fibrosis</td>
</tr>
<tr>
<td></td>
<td>rounded atelectasis</td>
<td></td>
</tr>
<tr>
<td>Neoplasms</td>
<td>Malignant mesothelioma (∪ risk of bronchogenic carcinoma)</td>
<td></td>
</tr>
<tr>
<td>Berylliosis</td>
<td>Berylliosis per se</td>
<td>Acute and recurrent pneumonitis, systemic sarcoildike and fibrosing granulomas</td>
</tr>
<tr>
<td>Talcosis</td>
<td>Talcosis per se</td>
<td>Foreign body granulomas with birefringent talcum deposits, micronodular and diffuse interstitial fibrosis</td>
</tr>
</tbody>
</table>

*Caplan syndrome occurs in patients with rheumatoid arthritis and some form of nodular silicosis. Deposition of microparticulate iron causes siderotic macrophage response with secondary focal or diffuse interstitial fibrosis.
Sarcoidosis is a systemic disease of unknown origin characterized by the development of noncaseating epithelioid cell (EC) granulomas with subsequent fibrosis. On radiographs, pulmonary sarcoidosis shows a typical reticulonodular infiltrate with hilar lymphadenopathy. Histologically, multiple noncaseating granulomas are found in the bronchial or bronchiolar submucosa, along intralobular septae or the pleura. Granulomas undergo peripheral and “reticulated” fibrosis with final scarring. Multi-nucleated giant cells similar to Langhans cells may show intracytoplasmic star-shaped or laminar calcified inclusions (asteroid bodies, Schaumann bodies). The course may be acute or chronic persistent or progressive. Approximately one third of cases are complicated by sarcoid vasculitis. Approximately 20% of patients experience repeated recurrences and pulmonary dysfunction; 10% progress to pulmonary fibrosis and cor pulmonale.
Multiple small emboli of lungs

Sudden onset of dyspnea and tachycardia in a predisposed individual is cardinal clue

Dyspnea

Auscultation may be normal or few rales and diminished breath sounds may be noted

Tachycardia

Pleural pain and breathlessness suggest infarction; hemoptysis may also occur

Causative obstructed vessel. A few small scattered emboli without infarction also present in both lungs

Embolism of Lesser Degree Without Infarction

Embolism of Lesser Degree Without Infarction

More than 90% of emboli in the pulmonary arteries arise from venous thromboses of the lower extremities. Approximately 60% to 80% of pulmonary embolisms (PEs) remain silent, presumably because of the small size of the thrombi. PE without infarction occurs without preexisting circulatory insufficiency. The tissue framework and collateral circulation remain intact because the dual arterial blood supply (pulmonary and bronchial arteries) prevents the thrombosis from occluding the pulmonary artery. The lung parenchyma shows severe congestions, with eventual intraalveolar hemorrhage. PE with pulmonary infarction occurs when blood supplied to the lung via the bronchial artery is insufficient, such as in chronic congestive heart failure (CHF) or in chronic pulmonary diseases with reduced vascularization. This hemorrhagic pulmonary infarction causes ischemic necrosis of lung tissue in addition to severe congestion. The infarction appears as a wedge-shaped, dark purple lung lesion with the base pointing toward the pleura and the occluded pulmonary artery at the tip.

Figure 3-13 Pulmonary Embolism
Infection of the lungs cause **pneumonia** (also “pneumonitis”). Following the rules of general inflammation (Chapter 1: Figures 1-5 to 1-8), pulmonary inflammation presents itself as **alveolar pneumonia** (common bacterial), **interstitial lymphocytic pneumonia** (viral, immunological), **granulomatous pneumonia** (Tb, allergic) or mixtures of the latter (certain viruses, protozoal, immunological). Table 3-4 summarizes common infectious agents causing pneumonia. Figures 3-14, 3-15, 3-16, and 3-17 present representative examples. Figures 3-5, 3-7, and 3-8 show examples of immunologic forms of pneumonia. The prognosis of pneumonia depends upon the type of inflammatory reaction in the lungs: acute alveolar pneumonia (serofibrinous, neutrophilic) or pure interstitial lymphocytic pneumonia (common cold virus) may resolve with complete recovery. Structural damage (e.g., abscess formation) or chronic infiltrative diseases (e.g., tuberculosis) always results in scarring, the extent of which will determine the persistence of clinical symptoms.

<table>
<thead>
<tr>
<th>Class</th>
<th>Etiologic Agent</th>
<th>Type of Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Streptococcus pyogenes</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Pseudomonas aeruginosa</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Yersinia pestis</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Legionella pneumophila</em></td>
<td>Legionnaires disease</td>
</tr>
<tr>
<td></td>
<td><em>Peptostreptococcus, Peptococcus</em></td>
<td>Aspiration (anaerobic) pneumonia</td>
</tr>
<tr>
<td></td>
<td><em>Bacteroides</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Fusobacterium</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Veillonella</em></td>
<td></td>
</tr>
<tr>
<td>Actinomycetes</td>
<td><em>Actinomyces israelii</em></td>
<td>Pulmonary nocardiosis</td>
</tr>
<tr>
<td></td>
<td><em>Nocardia asteroides</em></td>
<td>Pulmonary actinomycosis</td>
</tr>
<tr>
<td>Fungi</td>
<td><em>Coccidioides immitis</em></td>
<td>Coccidioidomycosis</td>
</tr>
<tr>
<td></td>
<td><em>Histoplasma capsulatum</em></td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td></td>
<td><em>Blastomyces dermatitidis</em></td>
<td>Blastomycosis</td>
</tr>
<tr>
<td></td>
<td><em>Aspergillus</em></td>
<td>Aspergillosis</td>
</tr>
<tr>
<td></td>
<td><em>Phycomycetes</em></td>
<td>Mucormycosis</td>
</tr>
<tr>
<td>Rickettsia</td>
<td><em>Coxiella burnetii</em></td>
<td>Q fever</td>
</tr>
<tr>
<td>Chlamydia</td>
<td><em>Chlamydia psittaci</em></td>
<td>Psittacosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ornithosis</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td><em>Mycoplasma pneumoniae</em></td>
<td>Mycoplasmal pneumonia</td>
</tr>
<tr>
<td>Viruses</td>
<td><em>Influenza virus, adenovirus, respiratory syncytial virus, etc.</em></td>
<td>Viral pneumonia</td>
</tr>
<tr>
<td>Protozoa</td>
<td><em>Pneumocystis carinii</em></td>
<td><em>Pneumocystis pneumonia</em> (plasma cell pneumonia)</td>
</tr>
</tbody>
</table>
Pulmonary Infectious Diseases

Purulent sputum with pneumococci (diplococci) (Gram stain)

Klebsiella pneumoniae organisms with mucoid capsule

Staphylococci and polymorphonuclear leukocytes in sputum (Gram stain)

**Figure 3-14 Bacterial Pneumonias**

Bacterial pneumonias (Table 3-4) are caused by aerogenic infection (bronchopneumonia, BP) or hematogenous spread of infectious organisms (hematogenous pneumonia, HP). BP starts focally in one lobe with centrifugal spread (pneumococcal or Klebsiella BP), while HP affects both lungs in the peripheral mantle zone with centripetal spread. BP is accompanied by infectious bronchitis, HP rather by infectious (septic) vasculitis. The inflammatory reaction and its extent depend on the nature (toxicity) of the infectious organism and on the host defense status. Necrotizing or hemorrhagic reactions are caused by bacterial exo or endotoxins. Increased coagulation of the exudate may favor abscess formation (staphylococci) and decreased coagulation rapid spread (pneumococci). Segmental pneumonia indicates some defense deficiency. Lobar pneumonia is complicated by a local hypersensitivity reaction. Location, composition, and spread of the inflammatory reaction in pneumonia thus may permit some conclusion of nature and source of the infectious agent.
Varicella Pneumonia

Hemorrhagic chickenpox

Varicella pneumonia. Nodular infiltrates in both lower lobes, more marked and coalescing on right side.

Pulmonary histology. Low power. Alveoli filled with fibrin, fluid, and cellular exudate.

Mononuclear infiltrate in interstitium and fibrin lining alveoli. High power.

Multinucleated giant cell (arrow) with much fluid in alveolus.

Pleural hemorrhagic pocks on lung.

**FIGURE 3-15 VIRAL PNEUMONIAS**

**Viral pneumonitis** is characterized by interstitial lymphocytic infiltration (nonspecific interstitial pneumonitis) combined with variable signs of DAD. Some cases are complicated by bronchiolitis obliterans (influenza virus, respiratory syncytial virus) or by focal necroses and eventual hemorrhage (herpes simplex virus [HSV], varicella-zoster and respiratory syncytial viruses, measles, influenza). Viruses that cause diagnostic cytopathic effects during some stages of infection include measles virus (Warthin-Finkeldey multinucleated giant cells), cytomegalovirus (giant cells with Cowdry type A intranuclear inclusions), other HSVs, and adenoviruses. **Varicella pneumonia**, a typical viral pneumonia, is caused by the varicella zoster virus.
Fungal infections are a major cause for opportunistic pneumonitis in immunodeficient patients (Table 3-5). The most common lesions appear grossly as irregular yellowish-gray infiltrates with a granular dry and firm cut surface. Hemorrhage and occasional regional infarcts may occur in certain infections secondary to vascular involvement (e.g., in mucor mycosis). Some forms closely resemble tuberculosis (TB) (e.g., histoplasma capsulatum infections). Besides cytomegalovirus and various fungi, *P. carinii* organisms are frequently isolated from “opportunistic” pneumonitis. Pathologic changes in *P. carinii pneumonia* show an interstitial plasmacellular (lymphoplasmacytic) pneumonia with alveolar foamy exudate, proliferating type II alveolar cells, and silver-stainable organisms. Certain fungal lung infections that occur in previously healthy persons may be accompanied by severe allergic reactions (e.g., allergic aspergillosis with bronchopulmonary infiltrates, eosinophilia, developing bronchiectasis, and eventual aspergilloma).

**TABLE 3-5  PULMONARY FUNGAL INFECTIONS IN IMMUNOCOMPROMISED PATIENTS**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Pathologic Lesion</th>
</tr>
</thead>
</table>
| *Candida albicans* tropicalis | Participation of the lungs in systemic candidiasis:  
   a. Hematogenous miliary candida abscesses with associated necrotizing focal pneumonitis  
   b. Bronchogenic pneumonia with abscess formation (e.g., after aspiration)         |
| *Aspergillus fumigatus niger flavus*         | Necrotizing bronchopneumonia with eventual hemorrhagic infarcts                   |
| *Mucor (phycomycosis)*            | Necrotizing bronchopneumonia with prominent vascular invasion and hemorrhagic infarction and hemoptysis |
| *Cryptococcus neoformans*        | Alveolar mucoid exudate with organisms and mild foreign body (occasionally tuberculoid) granulomatous reaction |
| *Histoplasma capsulatum*        | Tuberculous granulomatous and necrotizing bronchopneumonia                        |
| *Blastomyces dermatitidis*      | Puriform and bronchopneumonia with abscess formation, chronic cavernous bronchopneumonia |

(A) *P. carinii* pneumonia  
(B) PAS stain (periodic acid-Fuchsin) of pneumocystis organisms  
(C) *P. carinii* (arrow). Methenamine-silver stain of pneumocystis organisms  
(D) Lung in CMV disease with typical fleshy appearance  
(E) Cytomegalovirus pneumonia. Cytomegalic cells (arrow)
Pulmonary tuberculosis (TB) usually results from aerogenic infection with *M. tuberculosis, typus humanus*. The tuberculous granuloma is a classic epitheloid cell (EC) granuloma with palisading of EC around a central caseous necrosis. The EC layer contains multinucleated giant cells with peripherally located nuclei in a “string of pearls” pattern (Langhans-giant cells) surrounded by accumulations of lymphocytes. Tissue reaction to the state of immune reactivity forms for staging the clinicopathologic features of TB (Table 3-6). Infection in immunodeficient patients such as in human immunodeficiency virus (HIV) does not
TABLE 3-6  FORMS AND FEATURES OF PULMONARY TUBERCULOSIS*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Immune Reactivity</th>
<th>Clinicopathologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (primary)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Initial infection</td>
<td>No immunity</td>
<td>Clinically inapparent nonspecific alveolitis</td>
</tr>
<tr>
<td>b. Initial infection</td>
<td>Developing immunity</td>
<td>Ghon’s primary affection: isolated granulomatous reaction, most commonly in right upper lobe</td>
</tr>
<tr>
<td>c. Primary lymphatic spread</td>
<td>Developing immunity</td>
<td>Lymphatic spread of infection to regional lymph nodes with respective granulomas: Ranke’s primary complex</td>
</tr>
<tr>
<td>Stage II (early postprimary generalization)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Lymphatic spread</td>
<td>Good</td>
<td>Isolated subpleural caseous granuloma, upper segments of right upper lobe</td>
</tr>
<tr>
<td>b. Bronchogenic spread</td>
<td>Intermediate</td>
<td>Acinar-nodular pulmonary tuberculosis with progressive caseous granulomas</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>Progressive caseous pneumonia without prominent granulomatous reaction</td>
</tr>
<tr>
<td>c. Hematogenous spread</td>
<td>Intermediate</td>
<td>Systemic hematogenous caseous granulomas of different sizes (i.e., different ages)</td>
</tr>
<tr>
<td>(late postprimary generalization)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Hematogenous spread</td>
<td>Nonimmune → reactive</td>
<td>Miliary tuberculosis with systemic granulomas of uniform size (and age)</td>
</tr>
<tr>
<td>e. Hematogenous spread</td>
<td>A-reactive</td>
<td>Miliary systemic necroses, tuberculocephalosis acutissima, typhobacillosis Landouzy</td>
</tr>
<tr>
<td>(also in early postprimary spread)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III (isolated organ tuberculosis)</td>
<td>High</td>
<td>Limited spread in isolated organs: cavernous pulmonary of renal tuberculosis, isolated tuberculosis (granulomas) in brain, spine, and other organs</td>
</tr>
<tr>
<td>Late generalization</td>
<td>High → low</td>
<td>Local or systemic spread of isolated organ tuberculosis (lymphatic, bronchogenic, or hematogenous)</td>
</tr>
</tbody>
</table>

*The degree of immune reactivity (not resistance to disease) can be monitored by tuberculin skin testing; toxicity of tubercle bacteria is partly determined by “cord factor.”

**Figure 3-17  Pulmonary Tuberculosis (continued)**

Lead to typical tuberculous granulomas but to a nonspecific accumulation of macrophages at the sites of bacterial deposition (mycobacterial histiocytosis). Severe defense deficiencies cause tuberculosis acutissima (typhobacillosis Landouzy), a rapidly progressive and systemic form of TB with extensive caseous pneumonia in the lungs.
Carcinoma of the lung is the most frequent cause of cancer death worldwide (32% of cancer deaths in males, 25% in females). Bronchogenic carcinoma is classified into small-cell lung carcinoma (SCLC) or oat cell and non–small-cell lung carcinoma (NSCLC), which includes squamous cell carcinoma (SCC), large-cell anaplastic carcinoma (LC), and adenocarcinoma (AC). Lung carcinomas vary in their primary location, spread, and overall biologic behavior. They frequently metastasize to regional lymph nodes (hilar, mediastinal) and to extralymphatic sites such as adrenal glands, brain, bone, and liver.

### Classification of Bronchogenic Carcinoma (= 95% of All Lung Carcinoma)

<table>
<thead>
<tr>
<th>Type</th>
<th>Epidermoid (squamous cell)</th>
<th>Small cell anaplastic (oat cell)</th>
<th>Adenocarcinoma</th>
<th>Large cell anaplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>[Image]</td>
<td>[Image]</td>
<td>[Image]</td>
<td>[Image]</td>
</tr>
<tr>
<td><strong>Incidence</strong> (% of all lung carcinoma)</td>
<td>0 50% 100%</td>
<td>0 50% 100%</td>
<td>0 100%</td>
<td>0 100%</td>
</tr>
<tr>
<td><strong>Males vs. females</strong></td>
<td>[Image]</td>
<td>[Image]</td>
<td>[Image]</td>
<td>[Image]</td>
</tr>
<tr>
<td><strong>Location tendency (variable)</strong></td>
<td>Hilar</td>
<td>Hilar, but metastases often present when first discovered</td>
<td>Peripheral (usually &lt;4 cm)</td>
<td>Variable; peripheral or central</td>
</tr>
<tr>
<td><strong>Smoking relation</strong></td>
<td>0 Moderate Great</td>
<td>0 Moderate Great</td>
<td>0 Moderate Great</td>
<td>0 Moderate Great</td>
</tr>
<tr>
<td><strong>Growth rate</strong></td>
<td>Relatively slow</td>
<td>Very rapid</td>
<td>Intermediate</td>
<td>Rapid</td>
</tr>
<tr>
<td><strong>Metastatic tendency</strong></td>
<td>Late; then primarily to hilar nodes</td>
<td>Very early; to mediastinum or distally</td>
<td>Intermediate</td>
<td>Early</td>
</tr>
<tr>
<td><strong>Resectability</strong></td>
<td>Fair</td>
<td>0</td>
<td>Poor</td>
<td>Poor</td>
</tr>
</tbody>
</table>

**Figure 3-18  Lung Cancer**
Small Cell Lung Carcinoma (Oat Cell Carcinoma)

Small-cell lung cancer accounts for 20% of all lung cancers, with a male predominance and relation to cigarette smoking. It presents as a rapidly growing and metastasizing central lung mass occasionally accompanied by a paraneoplastic syndrome (myasthenia of Eaton-Lambert syndrome, ectopic corticotropin production, diabetes insipidus). The tumor consists histologically of sheets of small round or spindle cells with high mitotic index and scattered necroses. SCLC is essentially more sensitive to chemotherapy and therefore separated from all other lung cancers. However, it has the poorest 5-year survival rate (approximately 5%).
Squamous cell carcinoma (SCC) accounts for 30% of all lung cancers and is related to chemical carcinogens and cigarette smoking. SCC usually presents as a central lung mass invading the bronchial wall with rapid spread to local lymph nodes, brain, bone, and liver. Pancoast tumor is a variant of SCC in the apex of the lung that extends into adjacent thoracic and cervical nerves. Microscopically, tumor cells growing in sheets show variable degrees of squamous differentiation with keratinization. Adenocarcinoma (AC) accounts for another 30% of invasive lung cancers. It has a rather peripheral location and early lymphatic spread. There are several histologic subtypes (acinar, papillary bronchioloalveolar) and mixtures of these with variable degrees of differentiation (e.g., large-cell poorly differentiated AC). Large cell carcinoma (LC) accounts for approximately 10% of all lung cancers and may show features of squamous or glandular differentiation or both and pleomorphic or spindle cell variants. LC has the poorest 5-year survival rate of all NSCLCs (approximately 10%).
Tumors in the Lungs and the Pleura

Endocrine Manifestations of Bronchogenic Carcinoma

Corticotropic effects

Oat cell carcinoma of lung

Adrenal cortex hyperplasia

Cortical hormones

Atypical Cushing syndrome with facial edema and cachexia

Hypokalemic alkalosis

Antidiuretic hormone (ADH) effects

Oat cell carcinoma of lung

ADH

High urine osmolality

Low serum osmolality

Hyponatremia

Irritability

Confusion

Weakness

Seizures if extreme

Parathormonelike effects

Squamous cell carcinoma

Parathormonelike substance

Hypercalcemia

Lethargy

Polyuria

Polydipsia

Constipation

Abdominal pain

Coma if extreme

Gonadotropin effects

Squamous cell, oat cell, or adenocarcinoma

Gonadotrophic substance

Gynecomastia

Testicular atrophy

There are several nonmetastatic extrapulmonary manifestations of primary lung carcinoma, which are summarized as paraneoplastic syndromes. In addition to those pictured, these include skin changes, such as acanthosis nigricans, dermatomyositis/polymyositis, and myasthenia. Progressive multifocal leukoencephalopathy, occasionally also described as paraneoplastic syndrome, results from reactivation of latent polyomavirus infection (JC virus), and progressive focal demyelination in the central nervous system as can also be seen in other cases of immune deficiency (e.g., in HIV/acquired immunodeficiency virus [AIDS] and in certain cases of chronic lymphocytic leukemia).
Pancoast tumor characterizes a special growth pattern of bronchogenic carcinoma with early invasion of homolateral soft tissues of the lower neck. The tumor subsequently grows into regional nerves (arm plexus, sympathetic, parasympathetic) and vessels, causing the clinical Horner syndrome: enophthalmos, ptosis, miosis, and anhydrosis (sunken-in eyeball, lowering of upper eyelid, narrowing of pupil, and loss of sweating).

FIGURE 3-22  PANCOAST TUMOR

**Pancoast tumor** Shown in radiograph (arrow)
Mesothelioma of Pleura


Fibrosarcomatous type of tumor

Epithelial cell type of tumor

Mottled shadow over R. lung area with effusion (arrow). In advanced cases, lung may be totally obscured.

FIGURE 3-23  OTHER LUNG TUMORS

Other primary tumors of the lungs include carcinoids (a neuroendocrine tumor), mucoepidermoid and adenoid cystic carcinoma (counterparts to salivary gland tumors of bronchial glands), pulmonary blastoma, angiosarcoma and hemangioendothelioma, and malignant lymphoma. Malignant mesothelioma, a pleural fibrous tumor with adenoid mesothelial structures, may complicate pulmonary asbestosis. This firm tumor encases and compresses the lung (or both lungs) with limited direct invasion of peripheral lung parenchyma. Lymph nodes are rarely affected. The tumor extends locally within the thoracic cavity and along the mediastinum into bones, peritoneum, liver, and adrenals.
Metastases to the lungs occur in approximately 30% of all extrapulmonary malignant tumors. In the absence of a known primary tumor, clinical differential diagnosis may pose a problem. In contrast to a primary lung tumor, (hematogenous) metastases usually occur at multiple sites in both lungs. They are usually well-circumscribed foci, and cavitations occur rarely.

Certain tumors, such as carcinoma of the pancreas and stomach, may show lymphangitic spread in the lungs, giving a characteristic appearance of fine-nodular and linear (reticulonodular) infiltrations. Diagnosis and search for the primary tumor is usually guided by biopsy of a lung metastasis with histologic and immunocytochemical investigation.
Common diseases of the esophagus, the stomach, and the small and large intestines include functional disorders, inflammation, infections, and tumors.

**DISEASES OF THE ESOPHAGUS**
Esophageal diseases of various kinds are characterized by fairly uniform clinical symptoms of dysphagia (swallowing difficulties), heartburn (retrosternal pain), and vomiting (with or without blood). The most frequent causes are inflammatory or neoplastic diseases. Other esophageal problems that should be considered in differential diagnosis include diverticula and fistulas, atresia in the newborn, motility changes (e.g., achalasia), and a number of diseases that affect the esophagus secondarily (e.g., Mallory-Weiss lacerations in alcoholism, varices in hepatic cirrhosis, esophageal sclerosis in primary systemic sclerosis, and bulimia).

**DISEASES OF THE STOMACH**
Congenital diseases of the stomach, such as congenital pyloric stenosis, congenital hernias, diverticula, and cysts, are rare. The 2 most frequent disorders affecting large numbers of patients are inflammation of the stomach (gastritis) and epithelial tumors (carcinoma). These are discussed in more detail here, in addition to the frequent adult hernias, a common cause of reflux esophagitis and, potentially, esophageal cancer.

**NONTUMOROUS DISEASES OF THE SMALL AND LARGE INTESTINES**
Congenital disorders of the intestines are uncommon and are discussed in Table 4-1 and malabsorption syndromes in Table 4-4.

**Infectious enterocolitis** (IEC) and food poisoning are diseases of worldwide prevalence characterized by diarrhea and (gastro)intestinal inflammation with increased intestinal secretion and reduced absorption. Mucosal necrosis, hemorrhage, and ulceration develop according to local or systemic toxic influences of the causative agent. Loss of fluid and toxic side effects are especially dangerous for children and the elderly. Etiologic agents frequently identified in acute IEC are viruses (rotavirus, Norwalk agent) and bacteria (enterotoxic Escherichia coli); however, in up to 50% of cases, no organism is identified. In the United States, the most common causative agents in fatal IEC, in order of frequency, are Salmonellae, Listeria, Toxoplasma, Norwalk agent, E. coli, and Campylobacter.

### TABLE 4-1 DEVELOPMENTAL INTESTINAL DISEASES

<table>
<thead>
<tr>
<th>Disease</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small intestine</td>
<td></td>
</tr>
<tr>
<td>Atresia</td>
<td>Complete occlusion of intestinal lumen secondary to intraluminal diaphragm or disconnected blind ends (occurs in fetuses of mothers with polyhydramnios)</td>
</tr>
<tr>
<td>Stenosis</td>
<td>Partial occlusion (stricture) of the intestinal lumen secondary to incomplete intraluminal diaphragm, external adhesions (e.g., secondary to [transient] volvulus)</td>
</tr>
<tr>
<td>Duplications</td>
<td>Tubular or cystic structures (enteric cysts) that may communicate with the intestinal lumen (most common in ilium; may contain gastric mucosa and cause peptic ulcer similar to Meckel diverticulum)</td>
</tr>
<tr>
<td>Meckel diverticulum</td>
<td>Partial persistence of the vitelline duct, 60–100 cm before the ileocecal valve, with all layers of intestinal or gastric mucosa</td>
</tr>
<tr>
<td>Large intestine</td>
<td></td>
</tr>
<tr>
<td>Malrotation</td>
<td>Abnormal positioning of colon in abdominal cavity (e.g., cecum in left upper quadrant); may give rise to volvulus</td>
</tr>
<tr>
<td>Hirschsprung disease</td>
<td>Congenital megacolon secondary to aganglionic segment (lack of Auerbach and Meissner plexus preferentially in sigmoid colon and rectum)</td>
</tr>
</tbody>
</table>
The most common vascular lesions of the small and large bowel are phlebectases (hemorrhoids) and ischemic and thrombotic disorders; less common are local vasculitis accompanying systemic vasculitis and collagen-vascular diseases as well as angiodysplasia.

TUMORS OF THE SMALL AND LARGE INTESTINES

Benign tumors of the intestines are most often epithelial in nature and are referred to clinically as polyps. They usually are rare in the small intestine but frequent in the large intestine (colonic polyps increase in frequency from approximately 20% before the age of 40 years to 50% beyond the age of 60 years). The clinical entity polyp is subclassified pathologically into polyps as such (i.e., reactive lesions, such as hyperplastic, hamartomatous, or inflammatory polyps) and adenomas (i.e., benign neoplastic lesions, such as tubular or villous adenomas). The pathologic entity polyp does not possess malignant potential, whereas adenomas (also referred to as adenomatous polyps) do. Depending on their size, there is a 10% to 15% risk of cancer development within 5 years in tubular adenomas and a 30% to 40% risk in villous adenomas. The risk of malignancy increases with the number of adenomas; especially prone for malignant change are familial polyposis syndromes (e.g., Gardner syndrome) in which the occurrence of cancer approaches 100% by midlife.

Other more infrequent benign lesions of the intestines are lipomas, leiomyomas, neurofibroma, and hemangioma, which may also impress clinically as polyps and rather rarely may cause complications (e.g., erosion, bleeding and anemia, obstruction, or intussusception).

Malignant tumors of the small intestine account for less than 0.1% of tumors diagnosed at autopsy, or less than 5% of all gastrointestinal (GI) tumors. They consist primarily of adenocarcinomas, malignant lymphomas, and carcinoid tumors (CTs). Even less frequent are stromal tumors, such as leiomyosarcoma and gastrointestinal stromal tumors (GIST). By contrast, adenocarcinomas of the colon and the rectum are among the most common malignant tumors in the Western world, accounting for approximately 15% of all cancer deaths in the United States (approximately 150,000 new cases diagnosed every year, with a peak incidence at the age of 60-70 years). Other malignant tumors of the large bowel include CTs and, rarely, malignant lymphomas and (anal) melanomas. As in the small intestine, stromal tumors occasionally occur.
Esophagitis, which affects up to 20% of people in developed countries, is usually caused by gastric reflux (reflux esophagitis). Reflux esophagitis follows a “chemical” irritation by gastric fluids containing acid and pepsin (peptic esophagitis), which is secondary to improper closure of the lower esophageal sphincter. The tonus of the lower esophageal sphincter may be decreased by hiatal hernia of the stomach; voluminous intake of fatty foods; increased chocolate, alcohol, or nicotine consumption; hormonal factors (estrogen therapy, pregnancy); or treatment with central nervous system (CNS) depressants such as diazepam or opiates. Pathologically, acute reflux esophagitis shows hyperemia and mild degenerative changes such as ballooning of epithelial cells, occasional mild superficial erosion, and occasionally eosinophilic (rarely neutrophilic) infiltration. Chronic disease results in fibrosis and stenosis.
Chronic reflux esophagitis is classified into stages of severity. Stage I is characterized by epithelial hyperplasia and keratosis (clinical finding: leukoplakia) with sparse submucosal lymphocytic infiltrate. Stage II resembles stage I, with the addition of superficial erosion and neutrophilic infiltration. Stage III resembles stage II, with epithelial ulceration and more pronounced epithelial regeneration (elongated epithelial papillae). Complications of chronic reflux esophagitis include fibrous scarring and stenosis, mucosal metaplasia, and cancer. Barrett esophagus (BE) is the focal replacement of stratified squamous epithelium by metaplastic columnar epithelium with goblet cells. BE appears grossly as velvety, pink islands of mucosa in the lower third of the esophagus. Besides the intestinal-type mucosa, gastric mucosal elements (cardia- or fundus-type glands, including parietal and chief cells) are frequent. BE is associated with a greatly increased incidence of adenocarcinoma.

Figure 4-2  Chronic Reflux Esophagitis and Barrett Esophagus
Malignant neoplasms of the esophagus account for up to 2% of cancer deaths in the United States annually. Certain ill-defined genetic predispositions, exposure to food carcinogens (e.g., nitrosamines), tobacco smoke, chronic alcoholism, and chronic esophagitis (especially with BE) seem to be important pathogenic factors. Loss of p53 tumor suppressor gene function is one of the most frequently observed molecular changes in esophageal cancer.

Squamous cell carcinoma usually impresses as a plaquelike or fungating white lesion in the upper or medial part of the esophagus. The tumor infiltrates the esophageal wall deeply, penetrates into the mediastinum, and spreads via lymphatic channels. Invasion of the bronchial tree may occur with fistulation. Severe dysphagia and anorexia cause pronounced cachexia. The 5-year survival rate is 10% for patients with squamous cell carcinoma.
Adenocarcinomas, which account for 25% of cases of esophageal cancer, are pinkish elevated or ulcerative lesions in the lower third of the esophagus. Ulcerative lesions may appear as direct extensions of lesions in the gastric cardia. Onset is usually insidious, and tumors develop slowly. Dysphagia, weight loss, anorexia, and fatigue are the most common symptoms. Surgical removal of the tumor is frequently incomplete because of the early and extensive local metastases within the gastroesophageal wall and into the mediastinum. Even with surgery, the 5-year survival rate is 20% for patients with adenocarcinoma.
There are 2 types of gastric herniation (hiatal hernia) into the thoracic space: sliding (axial) hernias and paraesophageal (nonaxial) hernias. **Sliding hernia** constitutes approximately 95% of hiatal hernias. Systematic radiologic studies reveal sliding hernias in up to 20% of the population, only approximately half of which are symptomatic. Symptoms consist of heartburn and regurgitation of gastric contents and subsequent reflux esophagitis. **Paraesophageal hernia** causes strangulation of parts or all of the stomach incarcerated above the diaphragm. Surgical correction should be considered for both types of hernia.
Paraesophageal hernia

Peritoneal sac

Esophagus

Peritoneal sac

Entire stomach herniated into thoracic cavity

"Upside-down" stomach (advanced paraesophageal hernia)

Herniated stomach

Figure 4-5 Gastric Hernia (continued)
Gastritis is the most common cause of upper abdominal pain in adults. Gastroscopy differentiates the gross features of acute gastritis, erosive gastritis, hypertrophic gastritis, and chronic (atrophic) gastritis. Biopsy and pathologic investigation offer a more exact classification of pathogenesis and prognosis (Table 4-2). Acute gastritis is usually caused by chemical irritation by alcohol, cigarette smoke, or drugs (e.g., aspirin, nonsteroidal antiinflammatory drugs, chemotherapeutics), uremia, or suicidal ingestion of acids or alkali. Severe stress can cause acute gastritis with erosion and ulceration ("stress ulcer"). Systemic infections, shock involving the stomach, loss of pyloric function (e.g., after surgery) or duodenobiliary reflux can initiate acute gastritis. Infection with Helicobacter pylori accounts for 50% to 80% of cases of chronic type B gastritis. Chronic type A gastritis, an autoimmune gastritis, may occur alone or accompany other autoimmune disorders (thyroiditis, insulin-dependent diabetes mellitus, Addison disease).
The pathologic term atrophic gastritis is reserved for chronic gastritis with intestinal metaplasia (i.e., specific crypts of the gastric corpus are replaced by intestinal glands with goblet cells). Glandular necks are markedly elongated with extended epithelial regeneration involving surface epithelium and increasing amounts of dysplastic glands and epithelial atypia. Patients with atrophic gastritis have the highest risk of developing gastric cancer. Table 4-2 summarizes the histologic features and the courses of various types of gastritis.
Peptic ulcers (PUs) of the stomach or duodenum represent approximately 98% of ulcerations in this region. PUs are usually chronic, whereas the less common “stress ulcers,” which may accompany extensive burns, severe trauma, or other situations of excessive stress or the administration of certain drugs (corticosteroids), are acute. The pathogenesis of PU includes excessive action of gastric acid and pepsin, reduced mucosal defense mechanisms (e.g., reduced mucus production, reduced epithelial regeneration such as in tobacco smoking), and, frequently, infection with H pylori. PUs require treatment because of the possibility of complications, including acute or chronic hemorrhage and anemia, perforation, chronic scarring and stenosis (e.g., in pyloric or postpyloric ulcers), penetration into adjacent organs (e.g., into the pancreas with subsequent pancreatitis), and development of carcinoma within the regenerating mucosa adjacent to the ulcer.
Duodenal ulcers are usually located in the anterior or posterior wall of the bulbus and occur secondary to hyperacidification. The mucosa in this area is especially sensitive to acid juices. The pathogenesis and complications of duodenal ulcers resemble those of stomach ulcers, although malignant transformation to cancer is rare.
Carcinomas of the stomach are among the most common tumors in the Western world and Japan. Approximately 50% develop in the antrum or pyloric region, approximately 25% develop in the corpus, and 25% develop in the fundus. Most tumors are located in the lesser curvature. Their gross features vary from mucosal flattening and thickening with erosions to diffuse thickening of the gastric wall (*linitis plastica*), to large ulcers or polypoid-fungating masses. Stomach carcinomas are classified as type I: protruding nodular or polypoid lesion; type II: slightly elevated or depressed flat lesion; and type III: excavated or ulcerated lesion. There are 2 main histologic types of classic carcinoma of the stomach: the intestinal type with tubular glands, which simulates atypical intestinal mucosa, and the diffuse type with extensive mucus production by signet ring cells (signet ring cell carcinoma and linitis plastica including also less mature cells). Polypoid adenocarcinomas are found in the cardia and in rare preexistent adenomas.
Early gastric cancer is a pathologic term for a tumor confined to mucosa or submucosa. It is generally asymptomatic and is detected only by chance. Patients with this tumor have a 10-year survival rate of 95% after surgical intervention; patients with other stomach tumors have a combined survival rate of only 20%. Advanced gastric cancer also may be clinically occult except for undefined abdominal discomfort and weight loss. Large tumors in the prepyloric area may cause obstruction. Acute massive bleeding, even in ulcerated tumors, is uncommon, whereas chronic bleeding with significant anemia is frequently observed.
Mot all gastric carcinomas spread by direct extension to nearby organs or metastasize via lymphatic channels and the bloodstream. Even in early cancer, there is a 5% risk of regional lymphatic metastases at the time of initial tumor diagnosis. The most common sites of metastasis are lymph nodes at the lesser or greater curvature of the stomach, in the subpyloric region, and in the porta hepatis. More distant metastases involve the left supraclavicular lymph nodes (Virchow node), the lungs, the bone marrow, and the ovaries (Krukenberg tumor). The etiology and pathogenesis of gastric cancer are reviewed in Table 4-3.

### Table 4-3 Pathogenesis of Carcinoma of the Stomach

<table>
<thead>
<tr>
<th>Factors</th>
<th>Prevalence and Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional factors</td>
<td>Apparently account for geographic variations in cancer incidence: large amounts of smoked fish, pickled vegetables, highly salted foods; diets low in fruits and vegetables (i.e., in protective antioxidants) Identified carcinogens: nitrosamines, benzpyrene</td>
</tr>
<tr>
<td>Infections</td>
<td>Chronic <em>Helicobacter pylori</em> infection as cofactor (see above)</td>
</tr>
<tr>
<td>Genes</td>
<td>Approximately half of cancer patients possess blood group A No clearcut genetic traits identified Changes in tumor suppressor gene activity (e.g., p53), germline mutations, and genetic mismatch repair similar to cancer of the colon (see there)</td>
</tr>
<tr>
<td>Other factors</td>
<td>Low socioeconomic status (probably related to nutritional factors and infection)</td>
</tr>
</tbody>
</table>
Diverticulosis of the colon is a herniation of the colonic mucosa and submucosa through the intestinal muscular wall, with cystic expansion in the adventitial tissue. In Western countries, it affects up to half of persons older than 60 years. Diverticulosis is found most often in the sigmoid colon, although it may affect any part of the intestine. Diverticula, which develop at sites of weakness in the muscle wall of the intestine (sites of vascular and nerve penetrations), are secondary to increased colon pressure.
Gross bleeding or subclinical chronic bleeding from the diverticula may occur, especially in elderly persons. Stasis of feces in the diverticula is followed by recurrent inflammation (diverticulitis) with adhesions, occasional intestinal distortion, and obstruction. Inflamed diverticula can perforate and induce life-threatening fecal peritonitis. In advanced cases, surgical correction may be necessary.
Malabsorption syndrome (MAS) is characterized by the failure of the intestinal mucosa to absorb nutrients from food. It results from insufficient digestion (luminal and intestinal phases) or transepithelial transport. MAS is a heterogeneous syndrome that can result from a variety of disorders (Table 4-4). Most commonly, MAS results from chronic pancreatitis, Crohn disease, or celiac sprue. Histologically, celiac sprue appears as villous atrophy in the upper small intestine with elongation and arborization of glandular crypts, atrophic and regenerative epithelial changes, mild neutrophilic infiltration, and an increase in immunoglobulin (Ig) G– or IgM-containing plasma cells or both. Whipple disease, in which the intestinal mucosa contains large accumulations of periodic acid-Schiff (PAS) reaction–positive macrophages packed with rod-shaped bacilli, is also associated with clinical
malabsorption. The presentation of MAS is determined by the deficits in nonabsorbed nutrients. General symptoms of weight loss, anorexia, and abdominal distention are combined with specific deficiencies of nutrients such as vitamin B₁₂ or folic acid (megaloblastic anemia), vitamin K deficiency (bleeding with petechiae), vitamin D and calcium deficiency (osteomalacia, tetany), vitamin A deficiency (hyperkeratoses and dermatitis), protein deficiencies (edema, malnutrition), and zinc deficiency (dermatitis and immune defects). Stools are bulky, yellowish gray, and greasy. Treatment, clinical course, and prognosis are based on the primary disorder.
Food poisoning is an acute diarrheal GI disease that follows the ingestion of contaminated food. It is caused by colonization of the GI tract with pathogenic organisms released after ingestion of contaminated food (infection type), by toxins produced in food before ingestion (toxin type), or by a combination of both. The infection type affects the small intestine preferentially. Most cases of food poisoning resolve in 1 to 5 days, except for those caused by *Clostridium botulinum*, which is frequently lethal within 5 days.
Diseases of the Small and Large Intestines

Toxin type
Toxins produced in food *before* ingestion

**Staphylococci**
- Food handlers
- Onset 1 to 7 hours after ingestion
- Pallor, perspiration
- Collaps
- Abdominal pain or cramps
- Diarrhea
- Nausea, vomiting

**Streptococci**
- Creamy pastries
- Custard
- Meats
- Onset 3 to 12 hours after ingestion
- Temperature normal or subnormal

**C. perfringens**
- Meat dishes left standing after cooking
- Onset about 12 hours after ingestion
- C. welchi may also cause enteritis necroticans

**C. botulinum**
- Widely distributed in soil
- Toxins pass to nervous system
- Ocular paresis, diplopia, blepharoptosis
- Aphonia
- Respiratory difficulty
- Muscular weakness
- Vomiting
- Gastrointestinal symptoms may be minor or absent
- Constipation (may be preceded by diarrhea)

Temperature normal or subnormal
- Duration 24 hours; almost never fatal

Days: 1 2 3 4 5

Days: 1 2 3 4 5

Figure 4-15  Food Poisoning (continued)

days. Infection with enterotoxic *E. coli* and with *Salmonella* species (especially in older persons) may cause more frequent deaths. *Salmonella* organisms may persist in asymptomatic carriers after resolution of the acute enteric disease and become the source of future food poisoning cases.
Shigellosis, an enterocolitis, is caused by infection with Shigella organisms. These organisms produce either potent exotoxins, which cause acute disease (S. krusei) or endotoxins, which cause insidious onset of chronic disease (S. flexneri, S. sonnei). The incubation period is usually short (2–4 days). Pathologic lesions in the large intestine consist of irregular patchy pseudomembranous colitis (i.e., fibrinopurulent inflammation with superficial erosions and eventual ulceration) within a markedly hyperemic mucosa and increased mucus production. Clinical symptoms include frequent bowel movements and diarrhea, colicky pains, and, eventually, bloody stools with mucoid streaks. Prognosis is good when fever and fluid loss are promptly controlled and specific antibiotic/sulfonamide therapy is administered. Occasionally, fulminating toxic and lethal conditions may arise in small children and in the elderly.
Typhoid fever (TF), which is prevalent in underdeveloped countries but rare in the Western world, is caused by *Salmonella typhi* Eberthi. The common source of infection is bacteria from contaminated meat, milk, or eggs. A brief transient febrile illness with abdominal discomfort ensues, during which the organisms settle in macrophages and lymphoid tissues with respective stimulation of the immune system. The cyclic infectious disease phase of TF starts after a latent period of 10 days to 3 weeks, during which bacteria spread via lymphatics and blood and immunity is established. Bacteria accumulate in intestinal lymphatic tissues, especially in the Peyer patches, which become inflamed and ulcerated. Transient pseudomembranes shaped like Peyer patches cover these ulcers. TF evolves into a systemic infection through the hematogenous spread of organisms. Immunologically induced granulomas develop at the sites of bacterial colonization such as in the spleen, the liver, the bone marrow, and the spine, and hepatosplenomegaly ensues.
Protozoal infection by *Entamoeba histolytica* (amebiasis) causes up to 10% of human intestinal infections. Ingestion of cysts in food or drink contaminated by human fecal materials, including manure-fertilized vegetables, causes the infection. Flies and other insects that feed on human feces transfer the protozoa to foods. Amebiasis is marked by ulcerating proctosigmoiditis and *colitis*. Typical colonic ulcers contain many amebae with neutrophilic reaction and undermining edges. Infection may cause extensive ulcerating lesions with mucoid and puriform, partially bloody discharges, fever, abdominal pain, and severe tenesmus, or it may remain clinically inapparent for a long period. Rarely, the spread of infection via lymph or blood may cause localized abscesses in the liver, in the lung, or in the brain.
Gastrointestinal tuberculosis, which follows primary infection of the GI tract with *M. tuberculosis bovinum*, is rare in Western countries. Endoscopy reveals typical tuberculous ulcers (granulomas with caseous necrosis and ulceration) perpendicular to the intestinal axis. Bacterial superinfection with puriform ulcers may blur the characteristic features. Intestinal tuberculosis is accompanied by prominent focal peritoneal fibrosis with subsequent adhesions, shrinkage, bowel obstruction, fecal stasis, and perforation. Lymphatic spread of the infection is followed by multiple small peritoneal granulomas, which add to the peritoneal fibrotic process. Occlusion of intramural and mesenteric lymphatic channels may cause malabsorption. Treatment is a combination of tuberculostatic chemotherapy and surgery.

**Figure 4-19  Gastrointestinal Tuberculosis**

- Tuberculous ulcers of small bowel
- Tuberculous peritoneal adhesions
- Complications
  - Intestinal obstruction due to kinking by adhesions
  - Perforation, with “walled-off” or generalized peritonitis

Radiographic appearance in small bowel tuberculosis
Parasitic disease of the GI tract follows infestation with various worms, including human *whipworm* (*Trichocephalus trichuris*), *intestinal roundworm* (*Ascaris lumbricoides*), *human pinworm* (*Oxyuris vermicularis*), *beef tapeworm* (*Taenia saginata*), and *pork tapeworm* (*Taenia solium*). The source of infection is contaminated foods with or without an intermediate animal host. *Oxyuriasis* and *cysticercosis* are shown here. Oxyuriasis occurs in children and can be the cause of poor growth and
Cysticercosis may develop owing to swallowing eggs or autoinfestation by reverse peristalsis.

Detail of scolex (×20)

Adult tapeworm (2 to 7 m long) develops from cysticercus within small intestine of humans (2 to 3 months); and remain there anchored to mucosa.

Figure 4-20 Parasitic Disease of the Gastrointestinal Tract (continued)

development. Pruritus ani (caused by worms leaving the anus) with frequent scratching, eczema, erosions, and eventual superinfection is a common symptom. Cysticercosis is caused by consumption of infested pork meat. Eggs from tapeworms in the small intestine develop into multiple cystic larvae (Cysticercus cellulosae) in organs and tissues, including muscle and the brain. Such isolated cysts may contain multiple “embryos,” which may promote further infestation and should be removed surgically.
Mesenteric artery thrombosis or thromboembolism and venous thrombosis produce hemorrhagic infarction of the intestines because of overlapping vascularization. Arterial thrombosis may follow severe arteriosclerosis, systemic vasculitis, or a dissecting aneurysm. Left cardiac ventricular thrombi secondary to myocardial infarction, cardiac fibrillation, or endocarditis are the common sources of the thromboembolism. Venous thrombosis can follow abdominal trauma or surgery, sepsis, or hypercoagulation states. Whether the infarction is mural or transmural depends on the extent and duration of the vascular occlusion. There is massive hyperemia, hemorrhage, and progressive necrobiosis of tissue components (ischemic injury starts approximately 18 hours after occlusion). Bacteria migrating into the intestinal wall cause severe gangrenous enteritis and peritonitis and eventually perforation of the bowel. Early surgical resection of the infarcted area is the only lifesaving procedure.
Acute appendicitis (AA) (i.e., acute catarrhal or puriform inflammation of the appendix vermiformis) is the most frequent reason for laparotomy. AA is commonly caused by bacterial infections, sometimes after fecal stasis or oxyuriasis (pinworm infection). Acute pain in the right lower quadrant of the abdomen is often accompanied by fever, nausea, vomiting, constipation, or diarrhea. A circumscribed tenderness in the right lower quadrant on palpation and increased blood leukocyte counts complete clinical diagnosis. Surgical removal of the appendix to avoid complications such as penetration of infection and perityphlitic abscess, perforation and generalized peritonitis, and, more rarely, puriform endophlebitis and liver abscesses is the treatment of choice.

Figure 4-22  Acute Appendicitis

- Acute appendicitis
- Gangrenous appendicitis
- Fecal concretions in inflamed appendix
- Inflamed retrocecal appendix with adhesions
- Appendiceal abscess
- Mucocele of appendix
- Carcinoid of appendix

Note: Mucocele, i.e., mucus and debris accumulation secondary to cicatricial occlusion of appendiceal orifice. Carcinoid, i.e., endocrine tumor (see also Figure 4-31).
Acute peritonitis, an inflammation of the peritoneum, is caused by bacterial invasion or chemical irritation. It is usually a complication of perforation of the intraabdominal organs (ruptured appendix, perforated ulcer, diverticula), abdominal surgery, or peritoneal dialysis. Pathologic changes are those of a typical fibrinosupulent, gangrenous, or fecal inflammation with fibrous adhesions and concretions of bowel loops. Symptoms include those of acute abdomen (nausea, vomiting, diffuse abdominal tenderness and pain, abdominal distention, reduction of intestinal motility, or paralytic ileus, with ensuing high fever and septic shock). Treatment consists of antibiotics, surgical drainage, and/or debridement and supportive measures.
Crohn’s disease (enteritis regionalis) is a chronic granulomatous disease of the GI tract, mainly of the terminal ileum. It affects approximately 5 per 100,000 persons per year, with young adults of European ancestry affected most prominently. The etiology remains unknown, although family studies suggest a genetic susceptibility. Characteristic histologic changes are transmural edema (with subsequent fibrosis), nodular and follicular lymphocytic infiltrates, epithelioid cell granulomas, and fistulation. Inflammatory infiltrates are patchy with unchanged intestinum in between (“skip lesions”) and extend to involve the adventitial fat tissue (“creeping fat”) and regional lymph nodes. Symptoms include diffuse abdominal pain, diarrhea, and recurrent fever and malabsorption. Intestinal obstruction and fistulation may necessitate surgery.
Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown etiology. Systemic complications may affect the liver, the joints, the heart, the oral mucosa, and the eyes. The tendency of UC to run in families suggests a genetic predisposition. The association of UC with autoimmune disorders (e.g., sclerosing cholangitis, migratory polyarthritis) suggests an immune component to the disease. Histologic investigation reveals a mucosal, erosive, and ulcerative colitis with neutrophilic infiltration.
(neutrophils in glands: cryptal abscesses), epithelial regenerative changes with elongation of neck area of crypts, and spreading of regenerating cells to the mucosal surface. Increasing epithelial atypia in prolonged disease may lead to adenocarcinoma. In late stages of the disease, epithelial regeneration and formation of pseudopolyps cause a “cobblestone appearance” of the mucosa between ulcerations.

**FIGURE 4-25  ULCERATIVE COLITIS (CONTINUED)**
Obstruction of the bowel (OB) is any mechanical or functional impediment of the normal propulsion of bowel contents. In newborns, congenital abnormalities, including atresias (esophagus, gastric, intestinal, anal), malrotation and volvulus, and aganglionic segments (colon), may cause OB. Mechanical obstruction by meconium (meconium ileus) or, at later age, by hernia, incarceration, and volvulus (peritoneal bands) must be considered. In adults, OB may result from ingested materials, spastic or cicatricial occlusion, compression from the outside (hernia, intussusception, volvulus, tumors), and chronic inflammatory diseases. When OB results in intestinal ileus, no bowel movement sounds are heard on auscultation (“silent abdomen”).
Abdominal radiography shows distended small or large intestinal parts or both with accumulation of gas and fluids. Complications include paralytic ileus, infarction, invasion of the intestinal wall by enterobacteria and peritonitis, perforation, fecal peritonitis, and (septic) shock.
Most polyps and adenomas in the small intestine are benign sessile or pedunculated intraluminal tumors, which cause irregularly arranged intestinal glands and increased mucus production. Solitary tumors are rare. Peutz-Jeghers syndrome (PJS), a heritable small bowel polyposis, consists of multiple hamartomatous polyps in combination with abnormal mucocutaneous (perioral, buccal, perianal) pigmentation. PJS is associated with mutational inactivation of a protein kinase encoded on chromosome 19p (gene \( LKB1 \)). Bleeding, anemia, and intussusception are common complications. Tumor development is very rare, and it does not necessarily occur within the polyps. (See also Fig. 1-10.)
Familial polyposis of the large intestine is an autosomal dominant inherited disease, which, in contrast to PJS, consists of true adenomas (familial adenomatous polyposis) scattered throughout the large bowel. The risk of malignant transformation as early as the age of 40 years approaches 100%. Many adenomas are tubular adenomas; others are tubulovillous or villous adenomas.

The disease is characterized by a germline mutation of chromosome 5 (5q21). Gardner syndrome combines a familial polyposis syndrome with extraintestinal lesions such as soft tissue and bone tumors. Turcot syndrome describes familial polyposis syndrome in combination with malignant tumors of the CNS.
Malignant tumors of the small intestine, which consist of adenocarcinoma, malignant lymphomas, and CTs, constitute approximately 5% of all GI tumors. Adenocarcinoma presents as a circular constricting mass or as an intraluminal polypoid mass. Most adenocarcinomas are located in the duodenum and the jejunum. They are classified as glandular/acinar types, medullary carcinomas, or undifferentiated types based on their histologic characteristics. Chronic inflammatory diseases are a risk factor for the development of adenocarcinoma in the small bowel. Adenocarcinomas in the duodenum are frequently located within the ampulla vater (ampullary carcinoma) and cause obstructive jaundice or pancreatitis or both.
Primary malignant non-Hodgkin lymphoma (NHL) is a common tumor in the small intestine. It occurs in 2 major forms: Mediterranean-type lymphoma (immunoproliferative small intestinal disease [IPSID]), and Western-type malignant NHL. IPSID, with higher incidences in underdeveloped populations, appears infection-related and consists of progressive proliferation of IgA secreting plasmacytoid B lymphocytes (alpha chain disease) with signs of malabsorption. The terminal stage consists of an overt immunoblastic NHL. Western-type NHL tends to develop in the ilium as tumorous plaquelike infiltrates or intraluminal fungating masses, which result in bleeding, obstruction, and occasional intussusception. Histologically, these tumor cells, which consist of the mucosa-associated lymphoid tissue (MALT), are referred to as MALT lymphomas. Follicular center cell lymphomas and other types may also be found.
Carcinoid tumors (CCTs), which account for approximately 20% of small intestine tumors, can occur in other organs, including the intestines, the stomach, the liver, and the lungs. CTs are derived from argentaffine endocrine cells (enterochromaffin cells or Kulchitsky cells). CTs can occur as multiple isolated tumors or as part of a systemic disease (multiple endocrine neoplasia [MEN], type I). CTs less than 1 cm in diameter rarely behave malignantly and usually do not metastasize, whereas 50% or more of tumors 1 cm or larger with the same gross and histologic features metastasize. The tumor spreads most frequently to the liver. Carcinoid syndrome (diarrhea, flushing, bronchospasm, cyanosis, and skin telangiectases) is caused by episodic massive serotonin production by tumor cells. The 5-hydroxyindolacetic acid (5-HIAA) test, which measures 5-HIAA in the urine, is the diagnostic test of choice.
Adenocarcinomas account for 98% of all carcinomas in the colon and the rectum. They may develop de novo or from preexisting adenomas. Adenocarcinomas are located most often in the sigmoid colon and the rectum, followed by the descending colon. They are less frequent in the transverse colon and rare in the ascending colon. The gross appearance of adenocarcinomas of the colon and the rectum is polypoid and ulcerating. Some are plaquelike, infiltrating, and circularly constricting; others are flat but deeply infiltrating and inconspicuous endoscopically. Most tumors are well-differentiated adenocarcinomas with some mucus secretion; a few are mucinous adenocarcinomas or signet ring cell carcinomas. The degree of differentiation influences spread and prognosis. Colonic adenocarcinomas spread by direct extension through the intestinal layers, to regional lymph nodes by invasion of lymph vessels, and to the liver through the portal vein. Tumors in the deep sigmoid colon and rectum spread to the lungs hematogenously via tributaries of the vena cava inferior.
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The liver maintains the physiologic and metabolic balance of the body. Therefore, disease of the liver may have numerous effects throughout the body: it may cause disturbances in carbohydrate, lipid, amino acid, and vitamin metabolism and interfere with protein synthesis, blood clotting, and detoxification of endogenous and exogenous substances (Table 5-1).

**INFLAMMATORY DISEASES OF THE LIVER**

Viral hepatitis is an acute inflammation of the liver, usually caused by the hepatitis viruses (HAV-HGV), rarely by such other viruses as enteroviruses and herpesviruses (CMV, EBV, HHV-6, or HSV). Symptoms do not develop until the onset of immune reactions against the virus or

### Table 5-1 CLINICAL FEATURES OF LIVER FAILURE

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Pathogenesis</th>
</tr>
</thead>
</table>
| Jaundice                                                          | a. Intracellular retention of bilirubin (hepatocyte failure)  
|                                                                  | b. Intercellular and canalicular (bile stasis)       |
| Malabsorption, weight loss, bleeding tendency, muscle wasting     | Bile, enzyme, and vitamin deficiency               |
| Edema, muscle wasting                                             | Decreased protein (albumin) synthesis              |
| Spider nevi, palmar erythema, gynecomastia                        | Disturbed hormone metabolism                       |
| Ascites, splenomegaly, varices (gastroesophageal)                | Portal hypertension                                |
| Hepatic encephalopathy                                           | Toxic metabolites (acetoin, acyloin, ammonia)      |
| Hepatorenal syndrome                                             | Cause unknown (renal vasoconstriction?)            |

### Table 5-2 CHARACTERISTICS OF PRIMARY AUTOIMMUNE DISORDERS OF THE LIVER*

<table>
<thead>
<tr>
<th>Features</th>
<th>AIH</th>
<th>PBC</th>
<th>PSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology (autoantibodies)</td>
<td>Antinuclear (ANA) Anti–smooth muscle (ASMA)</td>
<td>Anti–native DNA Antiribosomal</td>
<td>ANA Antineutrophils (ANCA) Anti–bile duct epithelia</td>
</tr>
<tr>
<td></td>
<td>Anti–liver/kidney membrane (LKM) Antiliver (LSP)</td>
<td>Antimitochondrial (AMA) ASMA Anti–bile proteins Antithyroid LSP</td>
<td></td>
</tr>
<tr>
<td>Genetics</td>
<td>Nonspecific</td>
<td>Female predominance</td>
<td>Male predominance</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis Pernicious anemia Cryoglobulinemia Peripheral neuropathy Hemolytic anemia</td>
<td>Raynaud syndrome Thyroid dysfunction Seronegative arthritis Scleroderma Keratoconjunctivitis</td>
<td>Increased expression: HLA-DR3, HLA-DRW52a, HLA-B8 (DR2,4, DRb12)</td>
</tr>
<tr>
<td>Associated diseases</td>
<td>Rheumatoid arthritis Pernicious anemia Cryoglobulinemia Peripheral neuropathy Hemolytic anemia</td>
<td>Raynaud syndrome Thyroid dysfunction Seronegative arthritis Scleroderma Keratoconjunctivitis</td>
<td>Ulcerative colitis Riedel thyroiditis Retroperitoneal fibrosis Orbital pseudotumor (may be complicated by cholangiocarcinoma)</td>
</tr>
</tbody>
</table>

*AIH indicates autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.  
Overlap syndromes combine features of cholestatic and chronic hepatitic forms of diseases, e.g., AIH + PBC, PBC + PSC, or PBC + sarcoidosis.
virus-infected cells, 2 to 26 weeks after infection (incubation period). Bacteria, fungi, and parasites also may cause hepatitis.

Noninfectious causes of liver inflammation include toxic and immunologic disorders of the liver (see Table 5-2). These are discussed together because certain forms of toxic hepatitis may mimic autoimmune disorders or may be mediated through hypersensitivity reactions. A large variety of substances can cause liver damage, and they are associated with an equally large variety of lesions. A selection is shown in Table 5-3.

There are 3 major groups of autoimmune disorders affecting the liver: primary hepatic autoimmune diseases (Table 5-3), liver diseases with secondary autoimmune component, and systemic autoimmune diseases involving the liver.

METABOLIC DISEASES INVOLVING THE LIVER

A number of metabolic disorders affect the liver, some of which are consequences of inborn errors of metabolism. Major forms discussed in this chapter are hemochromatosis, Wilson disease (WD), and amyloidosis.

PRIMARY TUMORS OF THE LIVER

The most frequent tumors in the liver are metastases, often from the gastrointestinal (GI) tract, the lungs, or the mammary glands. Primary tumors originating in the liver consist of benign hepatic hamartomas and adenomas, bile duct angiomas, and cavernous hemangiomas. Two benign lesions must be distinguished from well-differentiated hepatocellular carcinoma (HCC): hepatocellular adenoma and focal nodular hyperplasia (FNH) of the liver. Adenomas (single or multiple) are well-circumscribed, yellowish masses of liver tissue with a fibrous capsule and histologically lobular architecture devoid of central vein, portal triads, and bile ductules. They occur preferentially in women of reproductive age and seem to be related to the use of oral contraceptives. FNHs, which occur equally in the two sexes, are solitary masses of hypertrophic hepatocellular nodules divided by fibrous septae, with prominent central scarring, large central nutritive vessels, bile ductules and cholestasis, and a pseudocapsule. The most frequent malignant tumors of the liver are HCC and cholangiocarcinoma (CAC). Less frequent are hepatoblastoma (in small children) and hemangiosarcoma.

CHOLELITHIASIS AND CHOLECYSTITIS

Cholelithiasis (CHL) is the formation of stones in the gallbladder and large bile ducts, usually in extrahepatic locations. CHL occurs in up to 20% of the Western population, approximately four fifths of whom have no symptoms (silent CHL). The prevalence of gallstones increases with age, with most patients being older than 40 years. Females experience CHL approximately twice as often as males, suggesting that a role is played by the endocrine system (increased estrogens, oral contraceptives, obesity, and hypercholesterolemia). Additional risk factors are hyperlipidemia, rapid weight loss, inborn errors of bile acid metabolism, and GI diseases such as Crohn ileitis, pancreatic insufficiency, and mucoviscidosis.

TUMORS OF THE GALLBLADDER AND THE BILE DUCTS

Papillomas, adenomas, and adenomyomas of deeper (submucosal) glands may occur in the gallbladder. Most remain clinically apparent except when they cause obstruction (e.g., papillomas in bile ducts or papilla of Vater). The majority of malignant tumors in the gallbladder are adenocarcinomas, which are found in approximately 2% of resected gallbladders. Approximately 5% of malignant tumors in this organ are squamous cell carcinomas.

ACUTE AND CHRONIC PANCREATITIS

Inflammation of the pancreas, usually caused by CHL or alcoholism, is characterized by massive activation of pancreatic enzymes, which, in acute cases, may cause life-threatening autodigestion and shock. Chronic cases cause extensive destruction of pancreatic parenchyma with fibrosis and loss of enzymatic activities.

---

**TABLE 5-3  TOXIC HEPATITIS AND ITS LESIONS**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Lesion</th>
<th>Exemplary Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct and indirect toxicity</td>
<td>Hepatocellular necrosis and steatosis</td>
<td>Alcohol, CCl₄, phosphorus methyl-DOPA, tetracyclines</td>
</tr>
<tr>
<td>Cholestatic</td>
<td>Hepatocanalicular cholestasis</td>
<td>Steroids</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Hepatocellular and hepatocanalicular, necrosis,</td>
<td>Erythromycin, chlorpromazine phenytoin</td>
</tr>
<tr>
<td></td>
<td>cholestasis, granulomatous</td>
<td></td>
</tr>
<tr>
<td>Vasculitis (panarteritis nodosa</td>
<td>Penicillin, allopurinol, sulfathiazole chlorpromazide, diphenylhydantoin, chlorothiazide, methamphetamine</td>
<td></td>
</tr>
<tr>
<td>type)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sclerosing cholangitis type</td>
<td>Floxuridine</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hepatocellular and hepatocanalicular</td>
<td>Isoniazid, halothane</td>
</tr>
</tbody>
</table>
Introduction

**CYSTIC FIBROSIS (MUCOVISCIDOSIS)**

Cystic fibrosis (CF) is the most common autosomal recessively inherited disease in children and young adults, with an incidence in Western populations of 1 in 2000 live births. It is caused by variable mutations of the CF gene on chromosome 7 (7q31-32). The primary defect caused by these mutations is in chloride ion channels, which transport chloride ions across epithelial barriers. Deficient chloride ion transport interferes with sodium and water secretion in exocrine glands, resulting in the production of a viscous mucoid material that obstructs glandular ducts in salivary glands, bronchial glands, the pancreas, and others. (See also Fig. 3-3.)

**NEOPLASMS OF THE PANCREAS**

Benign tumors of the exocrine pancreas are rare and consist essentially of ductal serous or mucinous cystadenomas. They must be distinguished clinically from inflammatory pseudocysts rather than from carcinoma. Carcinoma of the pancreas is the fourth most common tumor in the Western world, is even more frequent in the Pacific region, and is increasing in incidence. Approximately 23,000 new cases are diagnosed every year in the United States; only approximately 1% of these patients survive 5 years. No clear cause of human pancreatic cancer has been identified. Chronic pancreatitis is a recognized risk factor for carcinoma of the pancreas. Dietary factors, such as high fat and meat intake, may be contributory.
Acute viral hepatitis, an inflammatory disease of the hepatic parenchyma, is caused most frequently by the hepatitis viruses (HVs) and less frequently by other viruses (Table 5-4). In the Western world, HBV and HBC are most prevalent. Disease symptoms develop between 2 and 26 weeks after the onset of immune reactions against virus/virus-infected cells. The pathogenesis of liver injury in viral hepatitis is not completely clear, although a cytotoxic T-lymphocyte reaction against hepatocytes presenting viral antigens seems to be the key reaction. Histology shows many lymphocytes invading the liver parenchyma from portal triads, which causes adjacent hepatocellular necroses (piecemeal necroses). Infected hepatocytes change to a ground-glass appearance. In more severe disease, infected hepatocytes show ballooning degeneration. In addition, there are single or multiple hepatocellular coagulation necroses of virus-infected hepatocytes (Councilman bodies) or lytic necroses (dropout necroses).

**TABLE 5-4 MEMBERS AND CHARACTERISTICS OF THE HEPATITIS VIRUSES**

<table>
<thead>
<tr>
<th>Name (Molecule)</th>
<th>Family</th>
<th>Transmission</th>
<th>Incubation, weeks</th>
<th>Disease</th>
<th>Carrier</th>
<th>Chronic</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV (ssRNA)</td>
<td>Picorna</td>
<td>Enteral</td>
<td>2–6</td>
<td>Hepatitis, fulminant hepatitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HBV (dsDNA)</td>
<td>Hepadna</td>
<td>Parenteral</td>
<td>4–26</td>
<td>Hepatitis, fulminant hepatitis, cirrhosis</td>
<td>−1%</td>
<td>−10%</td>
<td>Yes</td>
</tr>
<tr>
<td>HCV (ssRNA)</td>
<td>Flavivirus</td>
<td>Parenteral</td>
<td>2–26</td>
<td>Hepatitis, cirrhosis, extrahepatic disorders</td>
<td>−1%</td>
<td>−50%</td>
<td>Yes</td>
</tr>
<tr>
<td>HDV (ssRNA)</td>
<td>Subviral satellite (HBV helper)</td>
<td>Parenteral</td>
<td>4–7 (super-infection)</td>
<td>Hepatitis, fulminant hepatitis</td>
<td>−10%</td>
<td>−5%</td>
<td>0</td>
</tr>
<tr>
<td>HEV (ssRNA)</td>
<td>Calicivirus</td>
<td>Enteral</td>
<td>2–8</td>
<td>Hepatitis</td>
<td>?</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HGV (ssRNA)</td>
<td>Flavivirus</td>
<td>Parenteral</td>
<td>?</td>
<td>Hepatitis, extrahepatic disorders in drug addicts</td>
<td>−2%</td>
<td>0</td>
<td>?</td>
</tr>
</tbody>
</table>

*ds indicates double-stranded; ss, single-stranded.
The onset of chronic hepatitis is characterized by reticular fibrosis, which surrounds necrobiotic hepatocytes and frequently precedes the formation of collagen fibrils. Collagenous fibrosis replaces damaged liver parenchyma, starting from a simple portal fibrosis and progressing to formation of fibrous septae (septal fibrosis) and final invasion and disruption of the acinus (pseudocacinus formation). The final stage of this fibrotic process is the development of hepatic cirrhosis with diffuse fine-nodular change. The general outcome of infections with HBV and HCV is usually the following: (1) symptomatic acute hepatitis (35% in HBV, 10% in HCV); (2) development of chronic hepatitis (10% in HBV, 50-70% in HCV); (3) development of cirrhosis (10-30% in HBV, at least 35% in HCV); (4) development of HCC (roughly estimated at 5-10% in both HBV and HCV). An additional threat is the high incidence of an asymptomatic carrier state in 70% to 90% of patients.
Cirrhosis of the liver with its extensive scarring and structural and functional alterations constitutes the end stage of various chronic inflammatory liver diseases. Histologically, it is defined by the triad of fibrosis, umbau (reconstruction with pseudoacini), and excess regeneration (hepatocellular nodules, bile duct proliferation). Pseudoacini (pseudolobules) originate from collagen fibers that invade the hepatic acinus, causing it to split. The sections that separate from the hepatic acinus do not contain a central vein and cannot function adequately. This scenario is further complicated by regenerative liver nodules. In the Western world, alcoholic liver cirrhoses constitute approximately 60% to 70% of all cases. Approximately 10% of cases are HV-induced cirrhoses, and 5% to 10% are primary and secondary biliary cirrhoses. Diagnostic gross features of different types of liver cirrhoses are outlined in Table 5-5.

**TABLE 5-5 GROSS FEATURES AS RELATED TO THE PATHOGENESIS OF LIVER CIRRHOSIS**

<table>
<thead>
<tr>
<th>Gross Appearance</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse, finely nodular (classic Laennec type: with atrophy)</td>
<td>Post–hepatitis virus cirrhosis</td>
</tr>
<tr>
<td>Same with or without fatty infiltration</td>
<td>Post–alcoholic cirrhosis</td>
</tr>
<tr>
<td>Diffuse, medium-sized nodular, dark purple (classic Hanot type with hypertrophy)</td>
<td>Chronic congestive (practically only seen in constrictive pericarditis)</td>
</tr>
<tr>
<td>Same with severe jaundice (green liver)</td>
<td>Primary biliary cirrhosis or chronic sclerosing cholangitis</td>
</tr>
<tr>
<td>Same with “dirty” gray-brown appearance (and similarly pigmented pancreas)</td>
<td>Hemochromatosis, Wilson disease</td>
</tr>
<tr>
<td>Diffuse, irregularly nodular, preferentially small- to medium-sized nodular</td>
<td>Autoimmune hepatitis and cirrhosis</td>
</tr>
<tr>
<td>Irregular, medium- to large-sized nodular, with jaundice (green liver)</td>
<td>Secondary biliary cirrhosis (i.e., extrahepatic bile duct obstruction)</td>
</tr>
<tr>
<td>Same with regular color or with fatty infiltration</td>
<td>“Postnecrotic” cirrhosis of variable etiology (e.g., post-HSV + alcoholic or other toxic influences)</td>
</tr>
</tbody>
</table>

*HSV indicates herpes simplex virus.*
Fibrosis and *umbau* cause severe obstruction of intrahepatic blood flow with portal hypertension. Other causes of portal hypertension include thrombosis of major hepatic veins (Budd-Chiari syndrome) and of the portal vein. Symptoms of portal hypertension are splenomegaly, ascites, and gastroesophageal varices. Ascites is usually the result of increased venous pressure, hypoalbuminemia (secondary to hepatocellular damage with reduced protein synthesis), and sodium retention (secondary by hepatocellular damage with diminished inactivation of antidiuretic hormone [ADH] and aldosterone). Bleeding from esophageal varices is a major cause of death in patients with liver cirrhosis and portal hypertension.
Bacterial infections of the liver frequently occur as part of a systemic infection (septic abscesses) or through lymphatic (lymphangitis) or venous (pyelophlebitis) spread from infections of adjacent organs such as appendicitis, infectious cholangitis, diverticulitis, or pancreatitis. Microorganisms entering the liver are taken up by sinusoidal Kupffer cells, which proliferate to form small Kupffer cell nodules intermixed with hematogenous polymorphonuclear leukocytes (neutrophils). The neutrophils are even more pronounced in and around lymph channels and veins. A more toxic inflammatory reaction produces circumscribed necroses and abscesses in the liver.
Liver abscesses are the most common extraintestinal complication of amebiasis. They occur infrequently in the average US population but are more prevalent in homosexual men and especially in populations of tropical and subtropical zones (tropical abscesses). Abscesses impress as large well-circumscribed masses in the liver, which empty a dirty brownish material onto a cut surface. Amebic trophozoites accumulate in the border zone of abscess and viable liver parenchyma. Bacterial superinfection is frequent. Complications are rupture of the abscess into the peritoneal cavity or hematogenous spread of amebae with development of multiple lung and brain abscesses. Mortality in this stage is high (up to 40%).
Granulomatous hepatitis is associated with systemic infections such as tuberculosis, typhoid fever, and sarcoidosis. In addition, brucellosis (Mediterranean fever, undulant fever) is a zoonosis caused by microorganisms of the genus Brucella (B abortus Bang, B melitensis, B suis, B canis). Infection follows direct contact with infected animals or foods. Bacteria invade through the alimentary tract, the lungs, or skin abrasions and localize in cells of the reticuloendothelial tissues. Liver biopsy results reveal a mild nonspecific hepatitis with or without noncaseating granulomas, which are sometimes suppurative and calcifying. Histoplasmosis is a systemic soil-borne fungal infection caused by inhalation of Histoplasma capsulatum. Systemic histoplasmosis affects the liver with epithelioid cell granulomas with or without caseation.
Spirochetal infections of the liver include **Weil disease** and **syphilis**. Weil disease (infectious jaundice) is caused by the spirochete *Leptospira*, a widespread zoonotic inhabitant in wild rats and mice. Liver involvement occurs in 50% of cases with noncharacteristic centrilobular and midzone necroses, Councilman bodies and ballooning degeneration of hepatocytes with signs of regeneration (anisonucleosis, multinucleated cells, mitotic figures), portal inflammation, and Kupffer cell hyperplasia.

The liver appears grossly yellow-green because of combined hepatocellular degeneration, hemolysis, and cholestasis. Leptospira can be identified microscopically in Kupffer cells and especially in renal tubular cells in approximately 65% of patients. Severe disease may be fatal. Syphilitic lesions occur in 2 forms: congenital syphilis, with mild triaditis, mild hepatocellular necrosis, and diffuse fibrosis, and tertiary syphilis, characterized by multiple granulomas (gummas) and scarring.
Parasitic diseases of the liver include infestations by tapeworms of *Echinococcus* species. *Echinococcus infection* is common in the Mediterranean, southern South America, the Middle East, central Asia, and Africa. Incidence is low in the United States. Humans become infected through ingestion of eggs in contaminated food. Approximately 60% of cysts develop in the liver, where they usually remain asymptomatic. Other sites that can be involved are the lungs, the brain, the kidneys, soft tissues, and bone. When cysts grow larger than 10 cm in diameter, they may cause compression of liver tissue with jaundice, portal hypertension, and cholangitis. Resorption of fluid materials from cysts causes immunologic sensitization of patients with secondary arthritis and membranous glomerulonephritis. Rupture of cysts in such conditions can lead to anaphylactic shock.
Schistosomiasis is caused by trematodes of the *Schistosoma* genus. It is endemic in large parts of Africa, the Americas, and the Far East. Humans are the principle hosts for the adult worms, which reside in the intestines, the urinary bladder, and the venous system. Sexual reproduction of worms produces eggs, which infest water and develop into a ciliated intermedia, the *miracidia*. *Miracidia* penetrate into a snail where they reproduce asexually within 4 to 6 weeks to produce hundreds of *cercariae*, which enter humans through the skin when they bathe in infected waters. The *cercariae* migrate to the lungs and mature into adult worms, which travel via blood vessels (veins) to distant organs. Up to 10% of patients in endemic regions develop schistosomiasis of the liver, which consists of granulomatous hepatitis (around schistosomal eggs) with eosinophils and portal fibrosis. Progression to cirrhosis is exceptional.
In Western countries, alcoholism is the most frequent cause of fatty liver (hepatic steatosis) and “toxic” hepatitis. Seventy percent of liver cirrhoses (Table 5-3) are alcoholic cirrhoses. Chronic daily intake of 80 to 160 g ethanol increases peripheral lipolysis and causes influx of fatty acids into the liver, enhances intrahepatic fatty acid and triglyceride synthesis, and reduces fatty acid oxidation and the release of lipoproteins. Hepatic steatosis develops in 3 stages: stage I fatty liver (simple steatosis): 50% or more of hepatocytes show fatty infiltration; stage II fatty liver hepatitis (alcoholic hepatitis): steatosis, focal hepatocellular necrosis/degeneration (fatty and ballooning degeneration of hepatocytes with alcoholic hyaline [Mallory bodies]), and reactive-type hepatitis with or without reticular and septal fibrosis; stage III fatty liver cirrhosis (alcoholic cirrhosis): steatosis (may be absent in later stages) with diffuse micronodular cirrhosis.
Significant fatty infiltration and necrosis result from fungus poisoning (especially with _Amanita muscaria_) or exposure to organic solvents (chloroform) or phosphorus, all of which cause rapidly progressive liver failure and death in _liver coma_. Other toxic injuries to the liver—with or without steatosis—are outlined in Table 5-3. Another toxic condition with extensive hemorrhagic necroses in the liver is eclampsia (_toxemia of pregnancy_), a hypertensive disorder of pregnancy with edema, proteinuria, vascular endothelial injury, and coagulation abnormalities. The latter causes _disseminated intravascular coagulation_, with the most prominent lesions in the liver, the brain, and the kidneys. Patients usually die of cerebral hemorrhages and symptoms of coma and convulsions.
Metabolic Diseases Involving the Liver

Hemochromatosis, a common autosomal recessive disorder, is characterized by iron accumulation in the liver, the heart, the pancreas, and other organs. It affects men 10 times more frequently than women and is based on a genetic change on chromosome 6, gene HLA-H (HFE gene), which controls iron absorption. Iron accumulates in the liver and other organs at a rate of up to 1 g/y; clinical symptoms occur when the body iron stores exceed 20 g (normal, 3–4 g). Liver tissue contains 6000 to 18,000 µg/g dry weight iron as compared with the normal storage of 300 to 1400 µg/g. Hemosiderosis (secondary exogenous hemochromatosis) represents a secondary iron overload syndrome, usually after hypertransfusion with blood.
Wilson disease (WD; hepatolenticular degeneration) is an autosomal recessive disorder of hepatobiliary copper excretion with progressive accumulation of the toxic metal in the liver, the brain, the eyes, and many other organs. The genetic disturbance is located on chromosome 13. The incidence of WD is 1:30,000. First symptoms are usually noted during the second decade of life. Liver pathology shows acute (necrotizing) hepatitis, chronic active hepatitis with cholestasis, or cirrhosis with or without copper deposition (copper usually in excess of 250 µg/g dry weight). Hepatic changes without excess copper are indistinguishable from viral hepatitis and cirrhosis. Of diagnostic value are copper deposits in the corneal limbus, which impress on inspection as brown-greenish rings (Kaiser-Fleischer rings). WD runs a progressive downhill course until copper is reduced by chelating agents, except for rare cases of fulminant hepatitis, which have an unfavorable prognosis.
Amyloidosis of the liver occurs in 2 forms: diffuse perisinusoidal amyloidosis (secondary amyloidosis) after chronic infections, and focal vascular (portal) amyloidosis (primary amyloidosis). **Secondary amyloidosis** causes enlargement of the liver with effacement of the gross lobular structure. The cut surface is smooth and rubbery and of yellowish-brown color. **Primary amyloidosis**, which is not associated with inflammatory diseases of other organs, frequently follows abnormal protein production by plasma cells (plasma cell dyscrasia). Therefore, it is frequently accompanied by diffuse plasmacytosis or malignant plasmacytoma. Vascular (primary) amyloidosis typically involves mesenchymal tissues of other organs such as the myocardium, skeletal muscle, the tongue, the skin, the kidneys, and the spleen. Both forms of liver amyloidosis are part of a systemic process, and involvement of other organs may determine the outcome (e.g., cardiac or renal failure).
Storage diseases (thesaurismoses) affect children preferentially and cause hepatomegaly. Most common are glycogen storage diseases (von Gierke disease and others) and sphingolipidoses (Niemann-Pick, Tay-Sachs, and Gaucher diseases). Nonmetabolized substances accumulate because of genetic mutations of lysosomal hydrolytic enzymes. Glycogen preferentially accumulates in hepatocytes in the liver, whereas other substances are taken up more intensely by cells of the reticuloendothelial (phagocytic) series (Kupffer cells) in the liver. These cells are greatly enlarged, leading to compression and atrophy of hepatocytes. Galactosemia results from deficiency of a transferase that converts galactose into glucose, resulting in deposition of galactose in several organs, such as the liver, the spleen, the kidneys, the central nervous system (CNS), and the eyes. Malnutrition in these infants contributes to diffuse fatty degeneration of hepatocytes with development of liver cirrhosis and portal hypertension.
Hepatocellular carcinoma, which occurs in adults with cirrhotic livers (in children it is seen without cirrhosis), is associated with persistent infection by HBV and HCV, including asymptomatic carriers (i.e., patients with occult liver cirrhosis). Other patients with liver cirrhosis who are at risk for developing HCC are those with hemochromatosis and α1-antitrypsin deficiency. Most patients with alcoholic cirrhosis and HCC are also infected with HCV or HBV. The gross picture of HCC is that of one or several irregular soft yellowish-green nodules in a cirrhotic liver with intrahepatic (parenchymatous, intravascular) spread. The histologic appearance varies from a trabecular and acinar pattern of well-differentiated hepatocytes to a poorly differentiated fibrolamellar tumor or a tumor with cholangiocellular features. The ascites color may change to bloody. Serum levels of α-fetoprotein increase dramatically (400–4000 ng/mL).
Although more rare than HCC, intrahepatic (peripheral) CAC also is associated with cirrhosis. It is derived from small intrahepatic bile canaliculi with lymphatic spread to portal lymph nodes (less frequently than HCC via hepatic vessels). The tumor is usually well differentiated with clearly defined tubular structures and pronounced desmoplasia (tumor fibrosis). Bile pigment is absent.
Cholelithiasis (CL) results from the formation of stones in the gallbladder and in large bile ducts. Bile stones are composed of bile (bile acids, bile pigments, and cholesterol) with various amounts of calcium. Stones are classified as cholesterol stones, pigment stones, and mixed stones according to the prevalent component. More than half of stones are cholesterol stones, which consist of precipitated cholesterol (nutritional hypercholesterolemia, reduced solubilization by bile acids) with crystal formation. Pigment stones are usually smaller and consist of blood pigments (calcium bilirubinate is contained in bilirubin stones). They occur most frequently in patients with some form of hemolytic anemia (e.g., thalassemia, sickle cell anemia) but also occur in patients with infections of the biliary tract. Mixed stones usually result from inflammation and bile stasis.
Only 20% of patients with CHL become clinically symptomatic. Complications usually arise from obstruction of bile passageways by stones, which results in acute severe pain (biliary colic) and inflammation. Obstruction by stones may occur at various sites from the cystic duct to the choledochus and the papilla. Papillary obstruction causes acute pancreatitis in cases of coincident obstruction of the pancreatic duct. Complications of chronic CHL are bile stasis, superinfection with pus accumulation in the bladder (empyema), perforation of a stone into the peritoneum with resultant peritonitis or into the intestines with eventual obstruction (gallstone ileus), and fibrous obstruction of the cystic duct with resorption of bile, which leaves a mucoid intraluminal fluid (mucocele). Stones in the common bile duct or in the major intrahepatic ducts cause obstructive cholestasis in the liver.
Extrahepatic biliary obstruction causes bile casts, which are most prominent in the peripheral part of the lobule. They are usually accompanied by secondary hepatocellular degeneration (feathery degeneration, see Figure 1-1, top right), portal inflammation (neutrophilic and lymphoplasmacytic), and portal and septal fibrosis. The liver is enlarged and dark green but rarely cirrhotic. Intrahepatic cholestasis shows portal and centrilobular bile stasis without major hepatocellular degeneration. Prominent reparative
bile duct proliferation occurs in portal triads with chronic inflammation, progressive fibrosis, and, finally, cirrhosis. Intrahepatic cholestasis usually accompanies other liver diseases, such as viral or toxic hepatitis, but its etiology can remain obscure. In later stages, hepatocytes show ballooning degeneration, and chronic portal inflammation leads to portal and septal fibrosis with regenerative proliferation of bile ducts.
Acute and chronic cholecystitis, diffuse inflammations of the gallbladder wall, are most frequently caused by CHL. They can occur with or without lipid deposits in mucosal macrophages, causing typical foam cells. Cholecystitis not associated with CHL may be seen in infections (sepsis, salmonella), in autoimmune vasculitis (e.g., panarteritis nodosa), or secondary to trauma. Acute cholecystitis is characterized by edematous thickening of the bladder wall with neutrophilic infiltration and eventual hemorrhage. Cholesterol resorption may cause occasional foreign body granulomas (giant cells with cholesterol clefts). Empyema and perforation are possible complications. Chronic cholecystitis shows mucosal atrophy, fibrous thickening of the bladder wall, and hypertrophy and hyperplasia of deeper glands. There may be extensive adhesions of the gallbladder to adjacent organs (e.g., the large intestine).
Adenocarcinoma of the gallbladder, the fifth most common tumor in the GI tract, usually occurs later in life. There are 2 major types: (1) a flat, scirrhous, and infiltrating form (not well differentiated) and (2) a polypoid-fungating form (well differentiated). More than 60% of these cancers are associated with CHL. Nearly all have spread to liver and peribiliary fat tissue at the time of the initial diagnosis so that the mean 5-year survival is only approximately 1%. Biliary adenocarcinoma metastasizes preferentially within the peritoneal cavity to regional lymph nodes and other organs of the GI tract. It spreads to the lungs less frequently.

**Figure 5-23** Cancer of the Gallbladder

Benign papillomata in gallbladder

Carcinoma of fundus with solitary gallstone

Carcinoma of gallbladder invading liver

Carcinoma of neck of gallbladder extending to common bile duct

Hydrohepatosis

Liver

Common bile duct
Adenocarcinoma of extrahepatic bile ducts and of the ampullary region occurs in older patients. It is not usually related to bile stones and is more frequent in areas where infestation with the fluke *Clonorchis sinensis* is endemic. Hepatic pathology secondary to obstruction and bile stasis causes liver enzymes to increase, especially alkaline phosphatase. Early detection while tumors are still small may result in a more favorable prognosis than in cancer of the gallbladder, with a mean 35% five-year survival for patients with ampullary cancers. Common adenocarcinoma of the bile ducts has usually spread at the time of diagnosis, rendering surgical resections incomplete and resulting in an average survival of 18 months.
Acute pancreatitis presents in 3 forms: (1) a mild, self-limited disease with little destruction of acinar cells; (2) a recurrent inflammation, which progresses to chronic pancreatitis; or (3) a life-threatening disease with gross necrosis of pancreatic and fat tissue. The mild form is characterized by interstitial edema with neutrophilic infiltration and occasional acinar cell degeneration. Virally induced pancreatitis occurs as acute or chronic recurrent pancreatitis with a lymphocytic infiltrate, some epithelial necrosis (ductal and acinar), and occasional cytopathic changes (cytomegalic owl eye cells). In the severe form, massive enzymatic digestion by proteases causes extensive necroses and hemorrhage secondary to necrotic blood vessels. Lipases cause extensive necrosis of fat tissue (lipolytic necroses) with precipitation of calcium salts. Fatty acids and calcium form insoluble salts at the site of fatty necroses with a characteristic soapy appearance. There are few neutrophils and, eventually, granulation tissue. Massive necrosis may cause pancreatic pseudocysts on resorption of the necrotic debris.
Chronic pancreatitis with progressive destruction of the parenchyma and fibrosis results from recurrent acute pancreatitis. Various lymphoplasmacytic infiltrates invade disrupted exocrine glandular acini. In end-stage disease, only pancreatic ducts and some islets may remain in the extensive scar tissue. In disease caused by long-term alcohol abuse, there is additional mucus plugging of major pancreatic ducts with secondary calcification (chronic calcifying pancreatitis). Other causes of chronic pancreatitis are mucoviscidosis (CF), which is also characterized by mucus plugging of ducts (chronic obstructive pancreatitis); WD; hemochromatosis; rare forms of hereditary pancreatitis (in childhood); and idiopathic forms. Chronic pancreatitis usually runs a long, debilitating course with a cumulative mortality of 50% in approximately 20 years.
Cystic Fibrosis

More than 80% of patients with CF (mucoviscidosis) have visible secretory abnormalities of the pancreas, which cause mucus inspissation in major ducts and secondary atrophy of exocrine glands. Dilated and plugged ducts may cause multiple cysts, and degrading (sometimes superinfected) mucus leads to chronic resorptive inflammation with lymphoplasmacytic and phagocytic infiltration and progressive collagenous fibrosis. Ductal epithelia may undergo squamous metaplasia (supported by deficient vitamin A resorption). Clinical features are those of malabsorption with abdominal distention, bulky foul stools, and a failure to thrive.
Carcinoma of the pancreas develops from ductal epithelial cells. Approximately 60% of pancreatic cancers are located in the head of the organ, 10% are located in the body, and 5% are located in the tail. The residual tumors show diffuse organ involvement without indication of their initial site. Usually, the tumor has already metastasized at the time of diagnosis. On gross inspection, the carcinoma of pancreas appears as poorly demarcated, white scarred or nodular areas with or without involvement of the common duct, the papilla, or the duodenum. Obstruction of the common bile duct may cause a characteristic dilatation of the gallbladder with jaundice (Courvoisier sign). An important complication of pancreatic cancer is a variable and migrating thrombosis (migratory thrombophlebitis), which may bring patients to clinical attention for multiple pulmonary thromboses and infarcts of unknown origin.
Carcinoma of the Pancreas

Tumors of the pancreas grow into the adjacent peritoneum and organs (duodenum, stomach, liver, colon, spleen) by direct extension and metastasize most commonly to regional lymph nodes and the liver. Lymphangitic metastases to the lungs and hematogenous spread to the bone marrow (occasionally with fatty necroses) are also found. Most tumors are well-differentiated tubular adenocarcinomas with or without mucin secretion and associated fibrosis (desmoplastic tubular carcinoma).

**Figure 5-29** TUMORS OF THE PANCREAS: METASTASES

- Medullary carcinoma
- Carcinoma with ductlike structures
- Anaplastic carcinoma

**Metastases FROM pancreas**
- Most common sites:
  1. Regional nodes
  2. Liver
  3. Lung and pleura
  4. Intestine
  5. Peritoneum
- Moderately common sites:
  6. Adrenal
  7. Bone
  8. Diaphragm
  9. Gallbladder
  10. Kidney

**Metastases TO pancreas**
- Common sources:
  1. Lung
  2. Breast
  3. Thyroid
  4. Kidney
  5. Melanoma (skin)
- Occasional sources:
  6. Ovary
  7. Uterus
  8. Parotid gland
  9. Prostate

**Occasional sites:**
- Heart
- Mediastinum
- Bladder
- Ovary
- Supraclavicular nodes
- Muscles or subcutaneous tissue

**Direct extension:**
- Stomach
- Kidney
- Colon
- Lymph nodes
- Duodenum
- Common bile duct
- Adrenal
The organ system examined in this chapter is the site of numerous diverse conditions, including congenital and hereditary diseases of the kidney, primary disease of the kidney, systemic diseases affecting the kidney, and diseases of the urinary system.

The kidneys are the primary regulators of the internal environment, particularly the volume, tonicity, and compartmental distribution of body fluids. They perform this function by exchanging and excreting water, minerals, and nonmetabolized solutes from the daily diet and end products of nitrogen metabolism (urea and creatinine). To accomplish this task, the kidneys produce an ultrafiltrate of plasma amounting to 180 L per day, reabsorbing more than 99% of it to produce an average of 1.5 L urine per day. Normal kidney function requires well-regulated blood flow through the kidneys, amounting to approximately 20% of the cardiac output, even though both kidneys comprise only approximately 1% of total body weight. Thus, even minor changes in renal structure can cause major functional disturbances and diseases. Consequently, microscopic investigations of the kidneys (e.g., by biopsy) are valuable for the diagnosis and classification of renal diseases.

**PRIMARY DISEASES OF THE KIDNEY**

*Acute renal failure* (ARF), which occurs in approximately 5% of hospitalized patients, is defined as an increase in serum creatinine of 0.5 to 1.0 mg/dL. *Chronic renal failure* (CRF) is a long-standing and usually irreversible impairment of renal function with reduction of the filtration rate, azotemia, and uremia. Common causes of ARF and CRF, as discussed in this chapter, are diverse, and both renal and extrarenal diseases must be considered in differential diagnosis.

The etiopathogenesis of glomerular and tubuloglomerular diseases (e.g., *glomerulonephritis* and *nephrotic syndrome*) is also highly diverse, as reflected in the difficulty in their classification. Many cases follow an autoimmune disorder; therefore, it is necessary to supplement the usual biopsy histology for staging and grading of the disease with immunohistologic procedures, occasionally including serology. Consequently, although the primary manifestation of an autoimmune renal disease may be the kidney, virtually all these conditions should be considered systemic processes (as in postinfectious autoimmune glomerulonephritis). Some, such as *anaphylactoid purpura*, *lupus nephritis*, and *Wegener syndrome* (see below), show systemic organ involvement from the beginning.

**THE KIDNEY AND SYSTEMIC DISEASES**

Many primary systemic diseases affect the kidney, including diabetes mellitus (DM), essential hypertension, various renovascular diseases, and several toxic and metabolic disorders. Progressive renal disease (*diabetic nephrosclerosis, Kimmelstiel-Wilson disease*) is a common complication of DM (see chapter 12) and is responsible for renal failure in 30% to 40% of patients with insulin-dependent DM and 20% of those with non–insulin-dependent DM. Benign and malignant nephrosclerosis are the renal manifestations of *essential hypertension* and must be distinguished from

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**TABLE 6-1 SUMMARY OF SYSTEMIC VASCULITIS SYNDROMES (PRIMARY AND SECONDARY)**

<table>
<thead>
<tr>
<th>Affected Vessel</th>
<th>Entity</th>
<th>Clinical Features</th>
</tr>
</thead>
</table>
| Small           | Wegener disease  
|                 | Microscopic polyangiitis  
|                 | Henoch-Schönlein purpura  
|                 | Leukocytoclastic vasculitis  
|                 | Postinfectious vasculitis (eg, viral) | Microhemituria, purpura,  
|                 |                                               | hemoptyses, perimyocarditis,  
|                 |                                               | episcleritis, vertigo,  
|                 |                                               | polyneuritis, melena |
| Medium          | Pan(poly)arteritis nodosa  
|                 | Churg-Strauss disease  
|                 | Lupus erythematosus  
|                 | Rheumatoid arthritis  
|                 | Progressive systemic sclerosis | Infarction in various organs  
|                 |                                               | including kidneys, hemorrhage  
|                 |                                               | from ruptured microaneurysms,  
|                 |                                               | hypertension, renal failure |
| Large           | Giant cell arteritis  
|                 | Takayasu arteritis | Arterial stenoses,  
|                 |                                               | phlebothromboses, aortic arch  
|                 |                                               | syndrome, subclavian steal  
|                 |                                               | syndrome |
renovascular hypertension, the consequence of renal artery stenosis. Hypertensive vascular diseases affect approximately 20% of the population and, with the complications of myocardial infarction, renal failure, and stroke, constitute a major health hazard. (The cause and pathogenesis of hypertension are discussed in chapter 2.) Systemic vasculitis syndromes frequently affect renal vessels or glomeruli or both (Table 6-1). Toxic nephropathy encompasses a large variety of diseases of different origins causing pathologic changes including cortical necrosis, tubular necrosis, focal hemorrhage, interstitial nephritis, and papillary necrosis. Causative toxins may be exogenous (e.g., drugs, plant toxins, allergens) or endogenic (e.g., toxemia of pregnancy), and the pathogenesis may include immune mechanisms (e.g., Shwartzman-Sanarelli syndrome). Metabolic disturbances such as amyloidosis and hypokalemic and calcium nephropathy also are associated with renal pathology.

DISEASES OF THE URINARY SYSTEM

Common diseases of the urinary system include pyelonephritis, obstructive uropathy, infections (e.g., tuberculosis, parasitic infections, cystitis) nephrolithiasis, some malformations (cystic disease, diverticula), neurogenic bladder, and neoplastic diseases. Obstructive nephropathy and hydronephrosis result from mechanical impediment of urine flow with renal dysfunction, dilatation of the collecting system, and frequent infections. Causes include intraluminal calculi (urolithiasis) and tumors (papilloma), compression (prostatic hypertrophy, pregnancy, retroperitoneal fibrosis or tumors) and ureteral dysfunctions (amyloidosis, malformations, neurogenic conditions). Infections resulting from such functional disturbances are frequent causes of pyelonephritis, a bacterial infection of the renal parenchyma calyces and pelvis. Other frequent and important diseases discussed in this chapter are malignant tumors such as adenocarcinoma and nephroblastoma of the kidney and transitional carcinoma of the urinary tract and bladder. Adenocarcinoma (renal cell carcinoma (RCC)) constitutes approximately 90% of renal malignancies; it occurs in more than 10,000 persons per year in the United States, and its annual incidence is increasing. A few cases occur as hereditary tumors and may be part of a cancer syndrome (e.g., von Hippel-Lindau syndrome). Clinical features are hematuria, pain, and an abdominal mass, which may lead to diagnosis and treatment by surgical resection. The 5-year survival rate of RCC is 40%. Urothelial cell (transitional cell) carcinoma (UCC) of the renal pelvis represents 5% to 10% of all kidney tumors. UCCs are more frequent in the urinary tract and account for 80% of neoplasms in the bladder. As long as the disease is confined to the bladder, as it is in approximately 85% of cases at initial presentation, survival after surgery amounts to 57% and 35% for low-grade and high-grade malignancy tumors, respectively. Nephroblastoma (Wilms tumor (WT)) constitutes the most frequent solid abdominal tumor in children. WTs may develop bilaterally and may accompany various congenital syndromes (e.g., Beckwith-Wiedemann syndrome). Karyotypic analysis reveals characteristic chromosomal changes in sporadic and congenital WTs such as alterations of the tumor suppressor gene WT1 or the susceptibility gene WT2. These changes apparently support the unrestricted growth of the nephrogenic blastoma, resulting in a tumor composed of blastemal, stromal, and epithelial elements. Early diagnosis before the age of 2 years with surgical removal of the tumor, radiation therapy, and chemotherapy may result in long-term survival of up to 90%.
Acute renal failure is a sudden reduction in renal function with accompanying oliguria or anuria and potentially fatal outcome. There are 3 types of ARF: prerenal, renal (parenchymal), and postrenal. In prerenal failure, which is reversible, renal function is reduced by factors extrinsic to the kidney, such as hypotension, salt depletion, dehydration, or an obstruction in the urinary tract. Renal (parenchymal) failure follows malfunction of the nephrons in a wide variety of diseases, including acute glomerulonephritis, acute pyelonephritis, toxic nephropathy, and severe circulatory impairments, with the latter resulting in acute tubulointerstitial nephropathy or “shock kidney.” The pathophysiologic derangements in ARF are complex but include reduced and maldistributed cortical blood flow with resulting local ischemia while total blood flow is partially preserved. Postrenal causes of ARF are various forms of urinary tract obstruction.
The kidneys of patients with **acute renal failure** (ARF) are large and pale, with a pale cortex and a dark, hyperemic medulla. Histologically, the hallmark of the condition is multifocal dilation with epithelial flattening of the distal convoluted tubules and, to some extent, the proximal convoluted tubules. The glomeruli are normal. Tubular epithelial cells exhibit degenerative and hydropic changes. Interstitial edema and focal collections of lymphocytes may be present. Electron microscopy confirms the normal structure of the glomeruli and reveals subcellular degenerative changes of organelles. There is a progressive decrease in urine output and a progressive increase in azotemia, metabolic acidosis, and serum potassium levels. Renal function returns if the underlying disease process is contained and the renal-induced metabolic and electrolyte abnormalities are treated successfully.

**Figure 6-2 Acute Renal Failure II**

Electron microscopic findings in glomerular capillary wall of 61-year-old man with acute renal failure following acute hemorrhagic pancreatitis. Structures essentially normal

- **P** = Foot processes of epithelium
- **BM** = Basement (or basal) membrane
- **E** = Cytoplasm of endothelial cell

**Histologic findings in acute renal failure treated with low-molecular-weight dextran.** Hydropic degeneration of tubular epithelium with intrusion of the transformed epithelium into Bowman capsule.

**Electron microscopic findings following treatment of acute renal failure with low-molecular-weight dextran.** Vacuolization of the proximal tubular epithelium.
Chronic renal failure (CRF) is a marked impairment in renal homeostatic function coupled with abnormalities in composition of body fluids. The most common causes of CRF are various types of glomerulonephritis and other nephritides. The functional and structural consequences of ischemia—obstruction with increased intra-pelvic pressure, infection with microorganisms, or deposition of antigen-antibody-complement complexes—may also result in CRF. Renal insufficiency is characterized by impaired renal adaptive function without major alterations in body fluid composition. Further loss in function results in CRF and culminates in uremia. Changes induced by CRF include secondary hyperparathyroidism and metabolic bone disease. In humans, the common structural basis for renal failure is thought to be a progressive reduction in the number of functioning nephrons, while the remaining nephrons develop hypertrophy and increased work per nephron, until these nephrons also are lost.
Uremia is characterized by multiple clinical and laboratory findings resulting from severe renal failure. Azotemia, a hallmark of renal failure, which is characterized by increased concentration of nonprotein nitrogenous compounds in blood, is measured with the blood urea nitrogen (BUN) test. Reduction in glomerular filtration can be measured by the diminution of creatine clearance and resulting increase of creatinine in the blood.
Nephrotic syndrome may be induced by noninflammatory or inflammatory (glomerulonephritic) conditions. The resultant damage, which may be subtle, produces increased permeability of the glomerular capillaries leading to proteinuria. Clinically, nephrotic syndrome is characterized by proteinuria in excess of 3.5 g/d/1.73 m² body surface area, edema, hypoalbuminemia, and hyperlipidemia. Prolonged massive proteinuria and resultant hypoproteinemia are the common denominators for all consequent metabolic and nutritional defects. Glomerular inflammation also may lead to a decrease in renal blood flow, which may activate the renin-angiotensin system, increasing production of angiotensin II and causing hypertension.
A spectrum of glomerular lesions can produce nephrotic syndrome. Minimal change disease (lipoid nephrosis) shows little or no change by light microscopy. Fused epithelial foot processes and occasional immunoglobulin (Ig) M deposits are seen by electron microscopy. If the disease is complicated by focal and segmental sclerosis, fused epithelial foot processes, capillary collapse, or mesangial expansion with γ-globulin deposits, response to immunosuppressive therapy deteriorates. Membranous nephropathy is characterized by thickened capillary walls, spikes in the basement membrane due to antigen-antibody complexes beneath the epithelial cells (membranous disease), and diffuse granular deposits of IgG and C3 (complement). Mesangioproliferative glomerulonephritis shows thickening of glomerular capillary walls complicated by mesangial proliferation and sclerosis with subendothelial deposits of C3 and IgG in a lumpy, nonlinear pattern. Focal segmental inflammatory necrosis and crescent formation signals a poor response to immunosuppressive therapy.
In anti–glomerular basement membrane (GBM) disease, the antibody is directed against the GBM, the antigen being a normal component of the glomerulus. Anti-GBM disease, whether produced by heterologous antibodies or autoantibodies, has the following features: (1) it is produced by circulating antibodies; (2) the antibodies (γ globulins) and complement are readily detected by immunofluorescence with a distribution along the basement membrane of every glomerulus in a highly distinctive, continuous, linear pattern; and (3) electron microscopy reveals inconspicuous deposits along the endothelial side of the basement membrane. Leukocytes recruited by locally produced chemotactic factors contribute to the glomerular damage. Forms of anti-GBM disease in humans include rapidly progressive, subacute glomerulonephritis and Goodpasture syndrome, which is characterized by lung hemorrhage and severe and rapidly progressive glomerulonephritis.
Acute glomerular injury results when large amounts of immune complexes are delivered to the glomerular capillaries over a short period of time; examples are poststreptococcal glomerulonephritis and the glomerulonephritis associated with subacute bacterial endocarditis. The immune complexes form large deposits on the epithelial side of the basement membranes, which are detected by immunofluorescence as irregular lumpy deposits and by electron microscopy as subepithelial humps in the basement membranes.
The immune complexes stimulate an inflammatory response that leads to acute glomerulonephritis. **Chronic glomerular injury** also results when small amounts of immune complexes are delivered to the glomerular capillaries over a prolonged period, as seen in systemic lupus erythematosus. Electron microscopy and immunofluorescence show extensive deposits of immune complexes along the epithelial side of the basement membrane. The glomerular injury may progress to include proliferative and sclerosing changes.
The kidneys in acute diffuse (poststreptococcal) glomerulonephritis show enlargement and pallor. Abnormally large and cellular glomeruli are seen microscopically; the capillary walls are swollen, and the lumens are narrowed. The hypercellularity is caused by proliferation of mesangial cells with associated increased mesangial matrix. A variable amount of infiltration by polymorphonuclear leukocytes is seen early in the disease. Other changes include casts and erythrocytes in the tubules and interstitial edema and focal inflammation. Electron microscopy reveals swelling of epithelial and endothelial cells and increased numbers of mesangial cells. The presence of semicircular or triangular “humps” (protein deposits) between the basement membrane and epithelial cells are considered to be diagnostic. Rapidly progressive (extracapillary) glomerulonephritis is characterized by the presence of many large cellular crescents consisting of proliferated epithelial cells of Bowman capsules, macrophages, and matrix.

**Figure 6-9 Acute Glomerulonephritis**
Chronic glomerulonephritis is characterized pathologically by sclerosis of many glomeruli and clinically by manifestations of renal insufficiency. The disease progresses because of inflammation leading to sclerosis of glomeruli and scarring. The kidney may be normal or slightly increased or decreased in size and is often pale yellow with smooth or slightly granular surfaces. On cut section, the cortex is often pale and swollen as a result of lipid in the tubules and interstitial edema. In proliferative and sclerosing glomerulonephritis, the glomeruli typically exhibit cellular proliferation and deposition of intercellular material with an approximate balance between proliferation of cells and sclerosis. In contrast, in membranous glomerulonephritis, cell proliferation and sclerosis are absent, and the histologic changes are limited to the capillary walls, at least in the early stages.
Mesangiocapillary glomerulonephritis (membranoproliferative, lobular, or hypocomplementemic glomerulonephritis) occurs most often in children and young adults. Patients present with components of the nephrotic syndrome and, usually, depression of serum complement. Typically, the disease progresses slowly. Histologically, the glomeruli are enlarged and moderately cellular, and the lobular centers are expanded as a result of proliferation of the mesangial cells and matrix. Ingrowth of the mesangium into the capillary wall causes capillary wall thickening, separates the endothelium from the basement membrane, and narrows the lumen. Immunofluorescence reveals deposits of complement (C3) and small amounts of γ globulin (IgG, IgM) within the mesangial matrix.
Membranous glomerulonephritis is common in adults but not in children. Characteristic changes in the capillary basement membranes are seen by electron and light microscopy (silver stains). Small, dense protein deposits that contain γ globulin (IgG) and complement are located between the basement membrane and the overlying, fused epithelial cell foot processes (see Fig. 6-6). The deposits are interrupted by focal thickening or by projections (spikes) of the basement membrane. Late chronic glomerulonephritis represents an end-stage common pathway of many glomerular diseases. Pathologically, it is characterized by the predominance of scarring and atrophy of both glomeruli and tubules with secondary arteriolosclerosis.
Focal segmental glomerulonephritis refers to disease processes in which some but not all glomeruli are involved, portions but not the entirety of each glomerulus are involved, or both. Etiologic or associated conditions include streptococcal and nonstreptococcal infections; autoimmune and immunologically mediated diseases, including systemic lupus erythematosus and Henoch-Schönlein purpura; and various vasculitides, including polyarteritis nodosa. A variety of pathologic lesions ranging from mild or moderate to severe focal glomerular damage may be found. Clinical findings may include hematuria, azotemia, hypertension, and nephrotic syndrome. The clinical course and outcome range from self-limited disease to death.

<table>
<thead>
<tr>
<th>Etiologic or associated conditions</th>
<th>Nonstreptococcal infection</th>
<th>Streptococcal infection</th>
<th>Systemic lupus erythematosus</th>
<th>Henoch-Schönlein purpura</th>
<th>Polyarteritis nodosa</th>
<th>Unknown systemic disease</th>
<th>Completely unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types of lesions that may be found in variable number of glomeruli, with others normal or almost normal</td>
<td>Erythrocytes in Bowman space</td>
<td>Focal glomerulitis</td>
<td>Subsiding focal glomerulitis</td>
<td>Focal lobular scars</td>
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<tr>
<td>Variable clinical findings</td>
<td>Hematuria (gross or microscopic) most common, often recurrent, associated with nonspecific infection</td>
<td>Proteinuria, often</td>
<td>Nephrotic syndrome, in some</td>
<td>Hypertension, in late stages</td>
<td>Azotemia, in late stages</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variable outcome of source</td>
<td>Complete recovery</td>
<td>Continued mild hematuria and/or proteinuria</td>
<td>Continued or progressive nephrotic syndrome</td>
<td>Chronic diffuse glomerulonephritis</td>
<td>Progressive azotemia, proteinuria, and hypertension; death</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 6-13 Focal Segmental Glomerulonephritis**
Anaphylactoid purpura (Henoch-Schönlein disease), a hypersensitivity disorder with renal involvement, usually affects children. The disorder closely resembles serum sickness in humans and experimental animals. Multiple allergens may be involved. Skin lesions include urticaria, maculopapular rash, petechiae, and purpura. Joints may become inflamed, painful, and swollen. Other features may include central neurologic signs, gastrointestinal involvement, and anemia. Renal manifestations are dominated by hematuria and nephrotic syndrome, which in severe cases may be accompanied by hypertension and azotemia. Renal biopsies show variable involvement of most of the glomeruli, with focal changes consisting of proliferation of endothelial and mesangial cells and accumulation of periodic acid-Schiff (PAS) reaction-positive matrix material.
Primary Diseases of the Kidney

Systemic lupus erythematosus, an autoimmune disease that occurs predominantly in young women, involves many tissues and organs. Important renal abnormalities involving the glomeruli include swelling and proliferation of endothelial and mesangial cells, fibrinoid necrosis, thrombi, neutrophil infiltration, crescent formation, increased mesangial matrix, and thickening. Deposits of antigen-antibody complexes in the basement membrane often appear as “wire-loop” lesions. Focal proliferative lupus nephritis (class III) is characterized by focal involvement of some of the glomeruli, swelling and proliferation of endothelial and mesangial cells, neutrophil accumulation, and necrosis.
### Histologic and Clinical Classification of Lupus Nephritis

<table>
<thead>
<tr>
<th>Pathology (findings by light microscopy)</th>
<th>Clinical course</th>
<th>Prognosis</th>
</tr>
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</table>
| Only portions (segmental) of some (focal) glomeruli are affected; the majority appear normal. In affected areas there are swelling and proliferation of mesangial and endothelial cells, capsular adhesions, and localized periglomerulitis, as shown in H and E section above. Necrosis, deposits of fibroinoid, and crescent formation may occur, as in the azocarmine section to the right. Occasionally, “wire loops” and intracapillary thrombi may be seen (not illustrated). | Microscopic hematuria  
Proteinuria, usually slight but occasionally heavy  
Nephrotic syndrome, rarely  
Moderate hypertension, occasionally  
BUN elevation, rarely  
Remission usually complete, either spontaneously or in response to corticosteroid therapy.  
Relapses respond to treatment except in rare cases of transition to diffuse proliferative type. | Patients usually survive for many years  
Do not ordinarily develop renal insufficiency or nephrotic syndrome. |
| Glomerular abnormalities are similar to those of focal proliferative, but all or almost all glomeruli are involved, and larger portions of glomeruli are affected. In H and E section above, there are severe, irregular swelling and proliferation of endothelial and mesangial cells, with obliteration of capillaries, necrosis, and karyorrhexis. Hematoxylin bodies and crescents may sometimes be seen. | Gross hematuria  
Heavy proteinuria  
Nephrotic syndrome, usually  
Hypertension, usually  
Renal insufficiency and azotemia, usually  
Remission may occur but is rarely complete  
Relapses common  
Usually does not respond to treatment. | Renal insufficiency and nephrotic syndrome progress  
Death commonly occurs within 5 years but may come much earlier; death usually due to other aspects of SLE or its complications rather than to uremia. |
| Characterized by diffuse, fairly uniform thickening of glomerular capillary walls, as illustrated in H and E section above. Necrosis, neutrophil infiltration, or crescents are not found, and only mesangial cell proliferation is present. If intracapillary cell proliferation is prominent, the condition is classified as diffuse proliferation. In azocarmine section at right, diffuse thickening of capillary wall is seen to be due mainly to deposits of carminophilic material along outer side of basement membrane. | Gross hematuria  
Heavy proteinuria  
Nephrotic syndrome, almost invariably  
Hypertension, usually  
Renal insufficiency, occasionally  
May remit with treatment but usually relapses  
Usually characterized by heavy proteinuria with little or no renal insufficiency. | Most patients survive for many years  
In some, complete remission may be maintained for long periods  
Death in uremia rare. |

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**FIGURE 6-15 LUPUS NEPHRITIS (CONTINUED)**

Diffuse proliferative lupus nephritis (class IV) is characterized by involvement of most glomeruli coupled with more prominent accumulation of basement membrane material and more severe and widespread interstitial inflammation. **Diffuse membranous lupus nephritis** is characterized by diffuse abnormalities of the basement membranes resembling those of idiopathic membranous nephropathy.
Acute diffuse interstitial nephritis, although uncommon, is an important cause of acute oliguric renal failure. It usually occurs as a manifestation of a hypersensitivity reaction to sulfonamides, penicillins, or other drugs (drug reaction). The characteristic features are fever, rash, eosinophilia, hematuria, oliguria, and azotemia. The kidneys are enlarged and may be 3 times their normal weight. Microscopy reveals pronounced edema and cellular infiltration by lymphocytes, eosinophils, and, occasionally, plasma cells. Parenchymal damage is minimal and is usually limited to focal tubular necrosis.
In diabetic glomerulosclerosis, a characteristic lesion occurs in diffuse and nodular (Kimmelstiel-Wilson) forms when increased amounts of PAS basement membrane material accumulate in the mesangium (intercapillary glomerulosclerosis) and the capillary walls. The pathogenesis of the glomerulopathy seems to involve accelerated degeneration and turnover of connective tissue cells coupled with abnormal glycosylation of matrix proteins. The capillary walls, although thickened, become porous, giving rise to nephrotic syndrome. Similar degeneration and accumulation of glycosylated proteins occurs in the walls of the microvasculature, giving rise to hyaline thickening (arteriolosclerosis) of both the afferent and efferent glomerular arterioles. Other lesions include hyaline, lipoproteinaceous deposits in the parietal layer of Bowman capsules, lipohyaline deposits in glomerular capillaries, thickening of the tubular basement membranes, and glycogen-filled epithelial cells in the distal, straight portion of the proximal tubule (the Armanni-Ebstein lesion).
Benign essential hypertension is a poorly defined condition of multifaceted origin characterized by persistent, moderate increase of systemic blood pressure. Over time, progressive damage occurs to the resistance vessels, leading to hyaline arteriolosclerosis in the kidneys and other organs. The small and medium intrarenal arteries become involved, which leads to fibrosis, hyalinization (sclerosis), and narrowing of the lumen. The hyaline material is composed of degenerated vascular cells and plasma proteins that have leaked into the vessel. Fibrosis results from active laying down of collagen by vascular cells. The narrowing of the arterioles and small arteries results in multifocal ischemia and small scars throughout the renal cortex giving rise to a thinned cortex and a finely granular surface. These changes lead to progressive renal insufficiency.
Malignant hypertension is closely associated with renal ischemia due to parenchymal or renovascular abnormalities or to rapid progression of renal changes in essential hypertension. The kidney may be of normal size with minimal granularity or shrunken and scarred, depending on the extent and duration of preexistent moderate hypertension. The characteristic gross feature of malignant hypertension is the presence of multiple petechial hemorrhages, reflective of multifocal severe ischemia, which produce the “flea-bitten” kidney. Hyperplastic arteriolar-sclerosis, the characteristic microscopic lesion in widespread obliterative fibroelastosis of arterioles and small arteries, is accompanied by glomerular and interstitial hemorrhage and fibrin deposition. Severe malignant hypertension produces fibrinoid necrosis of the afferent glomerular arterioles.
Various stenosing or obstructing lesions of the extrarenal vasculature, especially stenosis of the main renal artery, often result in hypertension. Such lesions include arteriosclerotic plaques, various forms of fibromuscular dysplasia, obstruction, and trauma. An appropriate evaluation is needed to determine whether the lesion is unilateral and whether the hypertension is likely to be relieved by surgery. The renin-angiotensin system has an important role in both extrarenal renovascular hypertension and hypertension due to intrarenal disease. Renal ischemia leads to increased renin excretion, which is followed by production of increased levels of angiotensin I and II and increased release of aldosterone. In primary hyperaldosteronemia, aldosterone is increased, and levels of renin and angiotensin are low.
Intravascular coagulation and thrombotic microangiopathy (hemolytic-uremic syndrome [HUS]) is characterized by hemolysis, thrombocytopenia, intravascular coagulation, hypertension, and renal failure. HUS occurs as an idiopathic disease, usually in infants and young children, or during the course of systemic disease (e.g., malignant hypertension, eclampsia, and disseminated carcinomatosis). The histologic picture is dominated by fibrin-platelet thrombi in many glomerular capillaries and in small arteries, which sometimes exhibit fibrinoid necrosis. The accumulation of pale, finely granular or fibrillar material between the endothelium and the capillary basement membranes of the glomeruli is an important feature of HUS. Immunofluorescence shows that the deposits contain fibrinogen and globulin. The affected capillary walls are thick, and the lumens are narrow. The combination of arteriolar thrombosis and capillary wall thickening constitutes the entity of thrombotic microangiopathy.

**Figure 6-21 Hemolytic-Uremic Syndrome**

Cortical necrosis due to intravascular coagulation. Multiple grayish-yellow necrotic areas rimmed by hyperemic margins in cortex (confluent or patchy); subcapsular zone spared; pyramids congested.

Glomerulus. Thrombi (stained pink) in capillary lumina (H and E stain, ×100).

Small artery in kidney obstructed by fibrin thrombus. (stained purple) (phosphotungstic acid, hematoxylin stain, ×100).

Pyramids

Cortical necrosis in kidney

Necrotic areas in cortex

Pyramids

Necrotic areas in cortex

Cortical necrosis due to intravascular coagulation. Multiple grayish-yellow necrotic areas rimmed by hyperemic margins in cortex (confluent or patchy); subcapsular zone spared; pyramids congested.
The kidneys are frequently involved in various forms of amyloidosis. Marked proteinuria is the usual mode of presentation, and overt nephrotic syndrome occurs in most cases. Homogeneous hyaline deposits of amyloid involve the arterioles and the glomeruli. When examined under polarized light, Congo red-stained sections show typical apple-green birefringence as a result of the β-pleated sheet configuration of the amyloid protein. Electron microscopy reveals that amyloid deposits are composed of masses of nonbranching fibrils of 7.5 to 10 nm in diameter, which are much smaller than collagen fibrils found in the foci of ordinary fibrosis.
Progressive systemic sclerosis (scleroderma) is a systemic disease characterized by the accumulation of excess collagen and the presence of vascular lesions with little inflammation. The classic form exhibits widespread involvement of skin and internal organs. Vascular lesions are particularly striking in the kidneys. Medium-sized renal arteries exhibit variable combinations of mucoid swelling of the intima and fibroelastic intimal proliferation, similar to the onion-skinning seen in malignant hypertension. When renal involvement becomes clinically apparent, it progresses rapidly, and malignant hypertension, retinopathy, encephalopathy, and renal failure ensue. Renal involvement in rheumatoid arthritis is less common and usually less severe than in other autoimmune diseases. The basic lesion, a multifocal vasculitis, involves small arteries and veins.
Polyarteritis nodosa refers to a constellation of inflammatory and necrotizing disease processes that involve medium and small arteries, most commonly in the kidneys, the gastrointestinal tract, and the heart. Classical polyarteritis nodosa produces multifocal involvement of medium or larger arteries. The kidneys may be coarsely nodular and irregularly scarred as a result of regional areas of ischemia and infarction of various ages. Acute lesions are characterized by fibrinoid necrosis of the arterial wall with inflammatory cellular infiltration by polymorphonuclear leukocytes and plasma cells in the adventitia extending into the media. Healing lesions exhibit medial fibrosis, focal destruction of the internal elastic lamella, and intimal fibrosis. The hypersensitivity type of polyarteritis nodosa is dominated by fibrinoid necrosis and inflammation of small arteries. In the kidney, Wegener granulomatosis shows segmental and focal necrotizing glomerular lesions and a granulomatous and necrotizing arteriolitis.
Toxic nephropathy encompasses any adverse functional or structural change in the kidney produced by a chemical or biological product. The renal tubules are a frequent target of injury. Nephrotoxins include heavy metals (mercury, lead), organic chemicals (carbon tetrachloride, ethylene glycol), drugs (many antibiotics, analgesics), pesticides (e.g., chlorinated hydrocarbons), physical agents (radiation), and products of metabolic disturbances, including hyperuricemia, hypercalcemia, and hypokalemia. Nephrotoxins may act directly on the nephrons or may produce hypersensitivity reactions, which result in vasculitis, nephritis, or nephrotic syndrome. With the toxic nephropathy resulting from excessive intake of mixed analgesic tablets, especially those containing phenacetin, the pathologic process is one of chronic interstitial nephritis with inflammatory cellular infiltration and fibrosis and a tendency for papillary necrosis.
Renal vein thrombosis is an uncommon cause of nephrotic syndrome. It may occur as a complication of previously existing renal disease or as a primary disease after trauma, particularly in individuals predisposed to venous thrombosis, or as a result of compression of the renal vein by tumors or adhesions. In infants and children, severe dehydration may lead to acute renal vein thrombosis producing renal cortical necrosis and severe renal insufficiency. In adults, the typical presentation is nephrotic syndrome with severe proteinuria. The kidneys become extremely enlarged as a result of interstitial edema, and their surfaces may exhibit small, dilated veins. By electron microscopy, the glomeruli show fusion of epithelial foot processes and the presence of dense osmiophilic deposits on both sides of and sometimes within the basement membrane. These deposits have been shown to consist of IgG, IgM, complement, and fibrin-fibrinogen.
Lung purpura with nephritis (Goodpasture syndrome) is an acute condition involving the lungs and the kidneys. The characteristic feature is profound hemoptysis, which may lead to severe anemia and very low serum iron levels. Chest radiography typically shows cardiomegaly and striking pulmonary opacities. The pathologic counterpart is a hemorrhagic alveolitis. Kidney involvement, which may develop simultaneously with or subsequent to the pulmonary lesion, manifests clinically by gross or microscopic albuminuria and pathologically by necrotic and proliferative lesions. Hypertension generally does not develop.
Hypokalemic nephropathy may result from excessive fluid loss through the gastrointestinal tract, excess fluid loss in the urine, excessive sterol levels, or miscellaneous conditions. Renal dysfunction includes impaired urinary concentrating ability, impaired bicarbonate excretion, alkalosis with paradoxical aciduria, and sodium retention. The characteristic histologic finding is marked vacuolization of renal tubular epithelium, which is more marked in the proximal convoluted tubules than in the distal. Clinical manifestations include focal myocarditis, muscle weakness or paralysis, and ileus.

**Figure 6-28 Hypokalemic Nephropathy**
A variety of metabolic states and systemic diseases may result in an excess calcium load to the kidneys. Clinical findings include decreased urinary concentrating ability; increased sodium and chloride excretion; hematuria; mild proteinuria; and, in severe cases, azotemia, anorexia, stupor, and coma. Pathologically, multifocal calcification of interstitial tissue, distal convoluted tubules, and collecting ducts may be seen. Glomeruli frequently show partial or complete hyalinization, and chronic inflammatory changes are frequently present.
Multiple myeloma is a part of the clinical spectrum of paraproteinemias in which neoplastic plasma cells infiltrate bone, lymph nodes, and various soft tissues and elaborate abnormal serum proteins. These proteins typically produce a monoclonal γ-globulin spike on serum electrophoresis. Approximately 15% of individuals with multiple myeloma also have amyloidosis. In at least 60% of cases, with or without amyloidosis, the kidneys excrete immunoglobulin fragments known as Bence Jones proteins into the urine. The kidneys exhibit glomerular lesions associated with proteinuria as well as markedly dilated tubules containing proteinaceous casts.
Obstructive uropathy, a common cause of severe or fatal renal failure, is caused by pathologic changes in the urinary tract produced by obstruction to the flow of urine. It may be unilateral or bilateral, depending on the site of obstruction. The likelihood of complications is greatly increased by urinary tract infection, a common finding of obstruction. Acute urinary tract obstruction is often associated with obvious clinical symptoms, whereas chronic obstruction may be insidious or clinically silent. Hydro-

Hydronephrosis, a dilatation of the renal collecting system resulting from severe obstruction to the flow of urine, may be bilateral depending on the site of obstruction. Severe hydronephrosis with renal parenchymal atrophy is unusual except in persons with congenital hydronephrosis. Asymptomatic or silent hydronephrosis, which occurs in adults, may become clinically significant because it increases susceptibility to trauma and infection.
Cystitis results from an inflammation of the urinary bladder. Cystitis usually is a self-limited condition or one easily treated with antibiotics. In some circumstances, such as poorly controlled DM or chronic urinary tract obstruction, cystitis is a severe condition that progresses to involve the upper urinary tract and kidneys and leads to renal failure. In adult women, cystitis is usually limited to the trigone and rarely develops into a severe ulcerative or hemorrhagic disease. In adult men and in children of both sexes, cystitis usually signifies the presence of an underlying anatomical or physiologic abnormality. On cystoscopy, various patterns of involvement may be seen, including cystitis cystica, which is manifest as multiple epithelial-lined cysts. The chief complication of cystitis is spread of infection to the kidneys.
Pyelonephritis, an infectious disease of the kidney, is usually induced by pyogenic microorganisms, particularly *Escherichia coli* and other gram-negative bacteria. The primary process is inflammation of the renal interstitium and the tubules. In **acute pyelonephritis**, the swollen kidney exhibits multiple small abscesses seen as linear, yellowish areas radiating continuously from the corticomedullary junction to the surface and sometimes extending through the medulla into the papillae. Microscopically, the yellow lesions correspond to a heavy interstitial infiltrate of polymorphonuclear leukocytes, with pus formation and liquefaction necrosis. The lesions are generally patchy with preserved glomeruli and vessels. The characteristic gross feature of **chronic pyelonephritis** is a coarsely granular contracted kidney with significant loss of renal parenchyma in the cortex and the medulla. Chronic interstitial inflammation (lymphocytes, macrophages) is widespread; many tubules are destroyed, and those remaining are dilated, lined by flattened epithelium, and filled with proteinaceous casts.
When coagulation necrosis of the renal papillae and portions of the medulla occurs, the necrotic tissue may be sloughed into the renal pelvis and passed into the ureter. The patient typically becomes ill with fever, renal colic, hematuria, oliguria, and azotemia, which may progress to fatal uremia. In some patients, particularly those with long-standing azotemia, sloughing of the papillae may occur over a prolonged period without overt ARF.

**Papillary necrosis** occurs most often in older people and in those with DM or pyelonephritis, particularly if there is lower urinary tract obstruction. In such individuals, a zone of neutrophilic infiltration at the periphery of the necrotic papilla is usually present. In patients who ingest excessive amounts of analgesic drugs, the papillary necrosis seems to result from a chemical toxicity without significant inflammation.
Renal carbuncle and perirenal abscess are septic conditions caused by infections with *Staphylococcus* species. These conditions, which may begin as an innocuous skin furuncle, reach the renal or perirenal tissue by hematogenous or lymphogenous spread. A renal carbuncle is an abscess in the renal cortex that typically results from the confluence of several smaller abscesses. This lesion occasionally produces a perirenal abscess through rupture into the collecting system or through the capsule. The perirenal abscess usually develops as a primary abscess in the perirenal fat inside the Gerota fascia. Both renal carbuncle and perirenal abscess produce a marked leukocytosis of the blood, with variable findings on urinalysis. An intrarenal or perirenal mass lesion is detected by imaging studies.
Tuberculosis of the urinary tract develops as a consequence of hematogenous dissemination of the tubercle bacilli (usually *Mycobacterium tuberculosis*). Urinary tract involvement has a peak incidence between the ages of 30 and 50 years and occurs more frequently in males. Bilateral involvement, particularly of the upper poles of the kidneys, is common. After the initial involvement of the kidneys, spread may occur to other components of the urinary tract. In countries where the dairy industry is closely regulated, the infecting organism is usually the human strain, but infection by the bovine strain is prevalent in other parts of the world. The lesions are those of a caseating granulomatous process with predisposition to cavitation and calcification. The kidneys are a common site of involvement in miliary tuberculosis in children.
Blood fluke parasites have a worldwide distribution. Infection with *Schistosoma haematobium* leads to urinary schistosomiasis. In the acute phase of the infection, cercarial penetration produces local skin erythema and itching, which is usually followed in 4 to 6 weeks by a febrile and toxic illness with eosinophilia. Spontaneous clinical resolution occurs, although the adult worm continues to lay eggs. Chronic illness resulting from lesions caused by the eggs occurs months or years later. Initially, a granulomatous reaction occurs around schistosome eggs, producing pseudotubercles. Dystrophic calcification of the eggs and adjacent tissue is common. The progression of the lesions is toward a fibrotic stage, which is frequently associated with anatomical distortion of the genitourinary tract. The chronic infection predisposes to the development of carcinoma of the urinary bladder. The disease may progress to bilateral obstructive uropathy with renal dysfunction.
Clinically significant complications of urinary calculi involve up to 10% of the population. The calculi affect men more than women, with peak occurrence between 20 and 50 years of age. The etiology is poorly defined, although factors leading to highly concentrated urine predispose to stone formation. Most stones originate in the kidney and are composed of calcium oxylate and other calcium salts embedded in an organic matrix. Certain metabolic diseases (hyperoxaluria and disorders of amino acid metabolism) predispose to stone formation. Renal calculi may remain in the pelvis of the kidney (staghorn calculus) or pass down the ureter, which produces the severe pain of renal colic. Destruction of renal parenchyma may result from progressive growth of the calculus, obstruction, or infections. Occasionally, calculi form in the ureter or urinary bladder as a result of urinary stasis secondary to various congenital or acquired anomalies.
A general classification of renal cystic diseases is as follows: (1) autosomal dominant (adult) polycystic disease of the kidney; (2) autosomal recessive (childhood) polycystic disease of the kidney; (3) unilateral multicystic disease of the kidney (unilateral renal dysplasia); (4) simple cysts (single, multiple, and multilocular); and (5) cysts of miscellaneous origin, such as retention or inflammatory cysts, and cysts secondary to hematomata, Echino-
coccus infections, pyelonephritis, and other specific diseases. Simple cysts may be solitary or multiple, thin walled or thick walled, trabeculated or multilocular. The cystic fluid may be clear or hemorrhagic, and the wall may occasionally have foci of dystrophic calcification. Rarely, adenocarcinoma of the wall may occur. Simple cysts are usually located in the cortex and bulge through the renal capsule. Sometimes, the cysts may be more deeply located and produce obstruction to urine outflow. Cysts must be kept in mind in the differential diagnosis of mass lesions in the kidney.
Adult polycystic kidney disease has an autosomal dominant inheritance pattern, with individual cases resulting from a mutation of the \textit{PKD1} gene on chromosome 16, the \textit{PKD2} gene on chromosome 4, or a yet-to-be-localized \textit{PKD3} gene. In contrast, infantile or childhood polycystic disease has an autosomal recessive inheritance pattern and represents a severe form of renal dysplasia. Adult polycystic kidney disease is relatively common, occurring in 1 of 400 to 1000 live births and accounting for approximately 10\% of chronic renal failure in adults. Kidney damage is a slowly developing but progressive process that eventually reaches clinical significance in all affected individuals surviving into the ninth decade of life. In the more advanced stages, destruction of renal tissue results in azotemia and physical discomfort from the sheer size of the large cystic masses. Hypertension occurs frequently, as do urinary tract infections. Associated conditions include intracranial berry aneurysms. The patients inevitably become dependent on hemodialysis and are candidates for kidney transplantation.
Benign tumors of the kidney may mimic malignant tumors and should be considered in the differential diagnosis of a renal cyst. **Renal adenomas** are typically small cortical nodules, which often grow within small cysts. They are usually papillomatous structures but may have a tubular or alveolar growth pattern. Occasionally, a large, single adenoma is found. The cells of adenomas are usually cuboidal and show well-differentiated cytology and growth pattern. The adenoma should be considered premalignant and prone to give rise to clones of malignant cells. Tumors larger than 3 cm in diameter are likely to metastasize. Connective tissue tumors that arise in the kidney include fibroma, lipoma, myoma, hemangioma, and angiomyolipoma (hamartoma), the latter occurring as part of the tuberous sclerosis complex.
Malignant tumors of the kidney may be primary tumors originating in the parenchyma, pelvis, or capsule or they may be metastatic, usually with bilateral involvement. Fibrosarcoma, myosarcoma, liposarcoma, and angioendothelioma are rare primary tumors. **Renal adenocarcinoma**, which encompasses all malignant epithelial renal tumors, accounts for approximately three fourths of all renal malignancies, usually occurs in middle age, and affects males twice as often as females. Typically, the unilateral and solitary tumor, which is usually encapsulated, firm, and solid, arises from either pole or the central region of the kidney. Renal vein invasion is common. Growth of the primary lesion may lead to a mass in the flank, microscopic or gross hematuria, and renal colic.
Subtypes of renal cell adenocarcinoma (in order of frequency) are clear cell carcinoma (70 to 80%), papillary carcinoma (10 to 15%), chromophobe renal carcinoma (5%), and collecting duct carcinoma (1%). Histologically, adenocarcinoma shows a variety of patterns, including vacuolated clear cells, granular cells, and anaplastic cells. The extent of local spread and the presence of metastases are more important than the histological pattern. Renal cell carcinoma often metastasizes via the blood, but lymphatic spread also occurs.
Tumors of the renal collecting system, which usually arise from the epithelium as urothelial cell (transitional cell) papillomas or urothelial cell carcinomas, comprise approximately 10% of renal tumors. Squamous cell carcinoma, adenocarcinoma, and metastases are less common. Urothelial cell papilloma is cytologically bland but must be considered premalignant, whereas urothelial cell carcinomas exhibit overt cytologic atypia. Urothelial cell tumors of the renal pelvis, ureter, and bladder occur predominately in older men. They may be single or multiple and are usually papillomatous and unilateral. Squamous cell (epidermoid) carcinoma is frequently associated with renal calculi and infection. The lesions, which are usually flat and firm and often ulcerated, are likely to invade the renal parenchyma and metastasize early. These tumors usually present with microscopic or gross hematuria.
Urinary bladder tumors typically arise from the mucosa and are composed of urothelial cells. The full spectrum of lesions includes papillomas, papillary lesions of low malignant potential, flat urothelial carcinoma, and papillary carcinomas. Other forms of bladder cancer include undifferentiated carcinomas, squamous (epidermoid) carcinomas (in areas of leukoplakia), adenocarcinoma (which may be mucin producing), and the rare epithelial mesenchymal tumors. The lesions occur principally in older adults, mostly males, and in 25% of cases are multiple. Exposure to and ingestion of environmental toxins are important in the pathogenesis of these lesions. The prognosis for patients with bladder tumors is strongly influenced by the degree of tumor infiltration of the bladder wall, or tumor stage (Jewett classification), but histologic grading of the degree of differentiation and cytologic atypia also provides useful information (Broder classification).

**Figure 6-44 Tumors of the Bladder**
The differential diagnosis of an upper abdominal mass in an infant or child includes the more common benign conditions such as ureteropelvic junction obstruction, with or without associated pyelonephritis, multicystic kidney disease, and malignant tumors, particularly neuroblastoma and nephroblastoma (Wilms tumor, WT). Nephroblastoma is a usually unilateral, intrinsic renal neoplasm containing both epithelial and connective tissue elements with various degrees of cellular differentiation. It is thought to arise from the metanephrogenic blastoma. Definitive differential diagnosis and rapid treatment are important because the tumor has a propensity for metastasis, primarily to lungs, the liver, the lymph nodes, and, less frequently, the bones. The prognosis has improved with the combined use of chemotherapy, radiation therapy, and surgery.
Diverticula of the bladder begin as small outpouchings or evaginations of the bladder wall between hypertrophied muscle bundles in the setting of bladder outlet obstruction. As obstruction progresses, weakening of the detrusor muscle, the external muscle layer of the bladder, gradually allows the formation of one or more true diverticula. The opening of the diverticulum is usually narrow, the lumen is covered with urothelium, and the wall is constructed primarily of connective tissue with focal strands of muscle fibers. The incidence of bladder diverticula is much greater in men and is usually a consequence of bladder outlet obstruction resulting from prostatic enlargement. Congenital diverticula are likely secondary to obstruction.
Neurologic impairment of bladder function may result from a variety of conditions. The site of the injury or disease determines the nature of the abnormality because the innervation of different parts of the bladder arises from different portions of the nervous system. Treatment of neurogenic bladder is aimed at prevention of eventual damage to the upper urinary tract from infection, urolithiasis, and obstruction. When effective control is absent, chronic neurogenic bladder may cause chronic urinary infection with secondary stone formation, leading to deterioration of kidney function and eventual uremia. Prevention includes use of indwelling urinary catheters, good hydration to maintain high urine volume, bladder irrigation to dissolve calcium salts, and treatment with antibiotics.
DISEASES OF THE MALE REPRODUCTIVE SYSTEM

The male reproductive system develops in close relation with the urinary tract, and the two are usually thought of as the urogenital system. After formation of the metanephric duct and the induction of nephrons, a distal part of the meso-nephric (Wolffian) duct becomes integrated into the lateral walls of the urogenital sinus with separation into ureters and male ejaculatory channels. The testes develop from the gonadal ridge, and their seminiferous tubules combine with the secretory channels formed by the Wolffian duct. The prostate develops from epithelial invaginations in the distal urethra. Therefore, congenital diseases of the genital system may also be associated with disorders of the urinary tract. A summary of the many infectious and inflammatory diseases of the male reproductive system is shown in Table 7-1.

DISEASES OF THE PENIS AND THE URETHRA

A variety of disorders may result in urinary or sexual dysfunction: structural and functional anomalies, including malformations; urethral stenosis and phimosis; fibromatosis (Peyronie disease); and priapism. In addition, the penis is a frequent site of inflammatory diseases, including sexually transmitted diseases (STDs) and some benign and malignant tumors. STDs and related infections, such as papilloma virus and candidiasis, have recently received considerable attention because of their rising incidence, association with HIV infection, and copathogenetic effects in the development of certain cancers. Squamous cell carcinoma (SCC) of the penis represents only 0.5% of all cancers in men in the United States but is significantly more frequent in some parts of Africa and Asia. Most penile SCCs are confined to the penis and can be cured by amputation. Delayed diagnosis or the presence of occult metastases at initial presentation, however, worsens the prognosis.

DISEASES OF THE PROSTATE GLAND AND THE SEMINAL TRACTS

Prostatitis occurs fairly frequently in men older than 50 years and is usually nonbacterial. In all ages, bacterial prostatitis usually follows urinary tract infection, but hematogenous forms may occur. Among the more common causative organisms are Escherichia coli, Chlamydia species, Mycoplasma, and Trichomonas vaginalis.

Benign prostatic hyperplasia (BPH) is common in older men, affecting more than 50% at the age of 60 years and more than 75% at the age of 80 years. The etiology of BPH is unknown, but recent studies suggest a relation with disturbed 5-dihydrotestosterone synthesis. Clinical features result from compression of the prostatic urethra with resultant obstruction of urine outflow, muscular hypertrophy of the bladder, and retrograde back pressure, ultimately causing hydroureter and hydronephrosis.

Cancer of the prostate (adenocarcinoma, ACP) is among the most frequent malignant tumors in men, causing approximately 30,000 deaths per year in the United States. One of 10 American men has clinically apparent prostate cancer during his life. The etiology of ACP is unknown. Hormonal imbalances (estrone to testosterone ratio) and exogenous carcinogens may play important roles in the pathogenesis. ACP constitutes 98% of prostatic neoplasias. Because the clinical features of ACP are similar to those of BPH, with which it often coexists, only 10% of patients with ACP present at an early stage. Demonstration of prostate-specific antigen (PSA) in serum and/or biopsy specimens may be helpful in the primary diagnosis and follow-up. The treatment and prognosis of ACP are stage dependent.

MALE INFERTILITY

Three mechanisms account for most reproductive problems in males. The most common is testicular damage from radiation, alcohol, varicocele, cryptorchism, or orchitis. Genetic disorders with gonadal dysgenesis include Klinefelter syndrome and Turner syndrome. Blockage of excretory ducts may result from infections or occlusion.

TESTICULAR DISORDERS

Testicular tumors are divided into 2 major classes: germ cell tumors and gonadal stromal tumors (sex cord tumors). More than 90% of testicular tumors are germ cell tumors, most frequently seminoma, embryonal carcinoma, and teratoma. Seminoma accounts for approximately one half of all germ cell tumors. The so-called classic type, occurring at the ages of 25–55 years, is radiosensitive and, after treatment of solitary tumors, is associated with 5-year survival greater than 90%. Embryonal carcinoma, which occurs at younger ages (20–35 years), is the second most common germ cell tumor. It is histologically more pleomorphic and may include human chorionic gonadotropin- (β-HCG) or α-fetoprotein–producing cells (transition to choriocarcinoma or teratoma). These tumors tend to respond well to chemotherapy; in localized cases, 5-year survival may exceed 95%. Sex cord tumors include Sertoli cell tumor and Leydig cell tumor.
### TABLE 7-1 INFECTIOUS AND INFLAMMATORY DISEASES OF THE MALE REPRODUCTIVE SYSTEM

<table>
<thead>
<tr>
<th>Diseases of the Glans Penis and Prepuce (Balanis, Balanoposthitis)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Simple balanitis (infants, older men)</td>
<td>Congenital or acquired phimosis, secondary bacterial infection</td>
</tr>
<tr>
<td>Balanoposthitis (adults)</td>
<td>Adhesions, phimosis secondary to obstruction (edema, cancer, elephantiasis), trauma, chemical irritation, sexually transmitted infections</td>
</tr>
<tr>
<td>Erosive balanitis</td>
<td>Phimosis, anaerobic organisms (spirochetes, vibrios)</td>
</tr>
<tr>
<td>Gangrenous balanitis</td>
<td>Phimosis, anaerobic organisms (spirochetes, vibrios)</td>
</tr>
<tr>
<td>Vesicular or ulcerative balanitis</td>
<td>Herpes progenitalis due to herpes simplex virus (HSV) type 2, histoplasmosis, keratosis blenorrhagia, pemphigus, scabies</td>
</tr>
<tr>
<td>Atrophic (leukoplakic) balanoposthitis</td>
<td>Dysplasia of epithelium</td>
</tr>
<tr>
<td>Venereal warts (Condylomata accuminata)</td>
<td>Human papilloma viruses (HPV), especially types 6, 11, 42, and 44</td>
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<thead>
<tr>
<th>Diseases of the Uretha</th>
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<tbody>
<tr>
<td>Acute and subacute urethritis</td>
<td>Neisseria gonorrhoeae (gonorrhoeal urethritis), Trichomonas vaginalis, Chlamydia trachonatis serotypes D-K, other infections</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Diseases of the Penis, Scrotum, and Inguinal Lymph Nodes</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Chancre of glans, penile body, scrotum</td>
<td>Syphilis due to Treponema pallidum</td>
</tr>
<tr>
<td>Ulcerative lesions with lymphadenopathy</td>
<td>Chancroid (Haemophilis ducreyi), lymphogranuloma venereum (Chlamydia trachomatis serotypes L1, L2, L3), Granuloma inguinale (Calymmatobacterium granulomatis)</td>
</tr>
<tr>
<td>Elephantiasis</td>
<td>Wuchereria bancrofti (filaria), nonfilarial elephantitis (lymphedema)</td>
</tr>
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<thead>
<tr>
<th>Diseases of the Prostate</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Acute prostatitis</td>
<td>Neisseria gonorrhoeae, staphylococci (instrumentation), nonspecific</td>
</tr>
<tr>
<td>Prostatic abscesses</td>
<td>Complication of urethritis and prostatitis, systemic infections</td>
</tr>
<tr>
<td>Chronic prostatitis</td>
<td>Insidious onset or extension of acute prostatitis, various pyogenic bacteria, tuberculosis (Mycobacterium tuberculosis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diseases of the Scrotum</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea crus (jock itch)</td>
<td>Superficial fungal infection (Epidermophyton and Trichophyton groups)</td>
</tr>
<tr>
<td>Erythrasma</td>
<td>Nocardia minutissima</td>
</tr>
<tr>
<td>Dermatitis venenata and other contact dermatoses</td>
<td>Chemical irritants, drug eruption (Dermatitis medicamentosa)</td>
</tr>
<tr>
<td>Eczema (chronic)</td>
<td>Allergic reactions, atopic dermatitis</td>
</tr>
<tr>
<td>Intertrigo</td>
<td>Erythema due to chemical irritation with secondary infection with cocci and fungi</td>
</tr>
<tr>
<td>Scabies</td>
<td>Mite infestation (Sarcoptes scabiei)</td>
</tr>
<tr>
<td>Pediculosis pubis (phthiriasis)</td>
<td>Crab louse infestation (Phthirius pubis)</td>
</tr>
<tr>
<td>Furuncle (abscess) of the scrotum</td>
<td>Pyogenic bacteria, esp. Staphylococcus aureus</td>
</tr>
<tr>
<td>Erysipelas of the scrotum</td>
<td>Pyogenic bacteria, esp. Streptococcus pyogenes</td>
</tr>
<tr>
<td>Gangrene of the scrotum</td>
<td>Mechanical, chemical or thermal injuries with secondary infection, idiopathic gangrene (Fournier’s gangrene)</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Diseases of the Testis</th>
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</thead>
<tbody>
<tr>
<td>Orchitis, epididymitis, epididymoorchitis</td>
<td>Multiple organisms, spread from local or systemic infections</td>
</tr>
<tr>
<td>Acute pyogenic orchitis, abscess of the testis</td>
<td>Pyogenic bacteria</td>
</tr>
<tr>
<td>Mumps orchitis</td>
<td>Mumps virus</td>
</tr>
<tr>
<td>Epididymitis</td>
<td>Specific (gonorrhoeal, syphilitic, etc.), nonspecific, traumatic</td>
</tr>
<tr>
<td>Granulomatous orchitis</td>
<td>Syphilitic orchitis, syphilitic gumma, tuberculosis (M. tuberculosis)</td>
</tr>
</tbody>
</table>
The 3 gonadotrophic hormones of the pituitary adenohypophysis are (1) follicle-stimulating hormone (FSH); (2) luteinizing hormone (LH) of the female, known as interstitial cell–stimulating hormone (ICSH) in the male; and (3) luteotropin (prolactin, LTH). These pituitary hormones determine the development of the male and female gonads. The germinal epithelia of the testes and ovaries are responsible for the production of sperm and ova, respectively. Various stromal cells of the gonads are responsible for the production of the androgen and estrogen hormones, which act on the organs of the reproductive tract, the secondary sex organs, and other parts of the body. There is a feedback loop for interdependent regulation of the production of the gonadal and pituitary hormones.
True hermaphroditism, defined as the presence of both testicular and ovarian tissue in the same patient, is rare. The chromosomal karyotype usually is euploid, with either a 46, XX or a 46, XY pattern, but may be aneuploid (45X/XY). Complex alterations in sex chromosomal gene expression lead to abnormal development of the gonads, including the formation of 1 or 2 ovotestes, an ovary on one side and a testis on the other, or a combination of these arrangements. The internal and external genitalia and secondary sexual characteristics correlate with the composition of the gonadal structures. Male pseudohermaphrodites have gonads with the histologic features of testes and varying degrees of feminine characteristics. Female pseudohermaphrodites have ovaries, but their external genitalia appear male. Male and female pseudohermaphroditism both generally result from a spectrum of neoplastic and nonneoplastic endocrine disorders.
Certain congenital anomalies of the urinary bladder and urethra are clinically important. **Congenital valves** of the posterior urethra are thin folds of mucosa that develop in the prostatic urethra and extend from the verumontanum to the sides of the urethra. Obstruction to urine flow leads to bladder hypertrophy and dilatation, bilateral hydronephrosis, and, ultimately, fatal renal failure. **Epispadia** is a rare anomaly of the male urethra that involves the dorsum of the penis and can range from minimal deformity (glanular epispadia) to moderate deformity (penile epispadia) to complete epispadia. **Hypospadia**, which are more common, develop on the ventral aspect of the penis because of the failure of the genital folds to close fully and can be a component of pseudohermaphroditism. Epispadia and hypospadia are often associated with developmental anomalies of the urinary tract (extrophy of the urinary bladder, undescended testicles), infections, and sterility.
Phimosis is the presence of a redundant prepuce that cannot be retracted over the glans penis. If the condition is not relieved, fibrous adhesions may develop between the prepuce and the glans. Infection can significantly complicate the condition by producing an inflammatory exudate and edema. Paraphimosis is a retained retraction of a tight foreskin behind the coronary sulcus. Compression of the constricted veins and lymphatics leads to marked edematous swelling of the distal prepuce and glans. Strangulation may result from constriction of the penis by external devices, such as metal rings.
Peyronie disease (fibrous cavernitis, or plastic induration of the penis), a chronic, self-limiting disease of middle or older age, can be mistaken for malignancy. The position of the erect penis is distorted, and penile erection is painful because of the deposition of inelastic fibrous tissue (plaques) in the tunicae or intracavernous septum of the corpora cavernosa of the penis. Priapism, a painful and persistent erection of sudden onset, may be idiopathic or may occur in association with a systemic disorder, such as leukemia, gout, or sickle cell anemia, or with neoplastic or inflammatory lesions of the nervous system. True priapism is erection of the corpora cavernosa without erection of the glans penis or corpora spongiosum. A major complication of persistent erection is thrombosis of the corpora cavernosa. The organization of the thrombus into fibrous tissue leads to permanent impairment of penile erection.

**Figure 7-5** PEYRONIE DISEASE, PRIAPISM, AND THROMBOSIS

Peyronie disease, Priapism, and Thrombosis of corpora cavernosa (intense engorgement and priapism).
Balanitis is inflammation of the glans penis. Balanoposthitis is a similar process involving the glans and the prepuce, usually associated with congenital or acquired phimosis, which predispose to growth of anaerobic microorganisms. Simple balanitis is a superficial infection presenting as a swollen, hyperemic, tender, and itchy lesion, whereas erosive balanoposthitis is characterized by the formation of painful necrotic erosive lesions. Gangrenous balanoposthitis is a rapidly progressive form of erosive balanoposthitis. In herpes progenitalis, which is caused by herpesvirus type 2, red papules on the glans penis develop into vesicles that rupture, leaving superficial ulcers. The lesions heal but tend to recur. Recurring episodes of any form of balanitis may lead to formation of thickened white epithelium, so-called atrophic (leukoplakic) balanoposthitis.
Urethritis results from infections with *Neisseria gonorrhoea*, *Trichomonas vaginalis*, *Chlamydia trachomatis*, or, less commonly, other microbes. In gonorrheal urethritis, a superficial infection of the urethral mucosa is followed by extension into the crypts and glands of the penile urethra, leading to involvement of the entire urethra, with an inflammatory exudate and purulent discharge in response to toxins released by the organisms. Complications include infections of the corpus spongiosum and posterior urethra, resulting respectively in painful erections and frequent, painful urination. Infection can extend from the prostate and posterior urethra down the spermatic cord to involve the epididymis. A rare complication is bacterial endocarditis due to gonococcal sepsis. Other forms of urethritis are usually more contained infections. Nonspecific urethritis can occur in isolation or with acute conjunctivitis and arthritis as Reiter syndrome.
The initial stage of syphilis is characterized by the development of a painless chancre, the hallmark primary lesion. The chancre, which usually develops slowly as an eroded papule, often accompanied by enlargement of the inguinal lymph nodes, heals gradually over several weeks. Definitive diagnosis is made by detection of the *Treponema pallidum* organism by darkfield examination of fluid from the primary lesion or a lymph node because the serologic test results for syphilis are often negative during the initial phase of infection. In untreated cases, secondary syphilis quickly follows, with systemic dissemination of organisms and skin rash. After a latent period, tertiary syphilis develops, involving the cardiovascular system, the nervous system, or both.
Chancroid (soft chancre) usually develops on the penis as a result of venereal infection with *Haemophilus ducreyi*. The infection spreads to the inguinal lymph nodes, producing secondary infection, extensive necrosis, pain, and tenderness. Lymphogranuloma venereum is caused by *Chlamydia trachomatis* serotypes L1, L2, and L3, usually transferred during sexual intercourse. The small, inconspicuous vesicle or papule that typically develops on the glans penis is followed by inguinal lymphadenitis and perilymphadenitis, which often progress to a chronic, persistent infection, with suppuration of the inguinal lymph nodes, fistulae, and multiple skin abscesses. Syphilis, chancroid, and lymphogranuloma venereum can coexist. Granuloma inguinale is a chronic disease of the genitalia characterized by ulcer formation. Prevalent in the tropics, this disease is not necessarily of venereal origin. The lesion, caused by *Calymmatobacterium granulomatis*, is recognizable as Donovan bodies in inflammatory cells.
Strictures may involve any portion of the urethra, including the meatus and the penile, bulbous, membranous, and prostatic urethra. Narrowing in the urethral lumen may be long or short, single or multiple, and slight or severe. Strictures may develop after urethritis as a result of venereal and other infections or secondary to indwelling urinary catheters. Posttraumatic strictures develop after severe blows, straddle injuries, and various punctures and tears related to instrumentation. Urethral strictures may be accompanied by infection elsewhere in the genitourinary tract, including prostatitis, epididymitis, cystitis, and pyelonephritis. Urethral abscess and urinary sinuses or fistulae are particularly serious complications. Symptoms include difficulty in urination, hematuria, and pyuria.
Venereal warts (condyloma acuminatum, verrucae) caused by human papillomaviruses (HPVs) usually occur around the base of the glans with a phimotic prepuce. Erythroplasia of Queyrat, a premalignant lesion of the glans penis, consists of slightly raised, red, velvety plaques composed of hypertrophied epidermis. Leukoplakia, a premalignant complication associated with chronic inflammation and glycosuria, can involve the entire prepuce or the glans. It develops as patches of indurated, leathery, blue-white skin. Early carcinoma of the penis starts as a.
small growth around the corona of the glans penis. The lesion often becomes ulcerated; untreated, it develops into a large fungating mass. Almost all penile cancers are squamous cell carcinomas (SCCs). At least half of patients have nodal metastases at the time of presentation because the initial lesion is painless and may be obscured by a phimotic prepuce.
Papillomas (polyps) and verrucae (condylomas) are benign tumors of the urethra that usually develop just within the urethral meatus in the fossa navicularis as a result of inflammation in the urethral glands. They can cause urinary urgency, frequency and pain, hematuria, and disturbances in sexual function. Primary carcinoma of the urethra, a rare malignancy with an indolent course and an unfavorable prognosis, usually occurs in older men. The lesions develop equally often in the penile urethra and in more proximal portions of the urethra. Patients often present with a perineal abscess or a urethral stricture that is suspiciously increasing in size. Undetected tumors most commonly metastasize to regional inguinal lymph nodes.
**DISEASES OF THE MALE REPRODUCTIVE SYSTEM**

**Diseases of the Prostate Gland**

**Acute prostatitis** develops as an occasional complication of urinary tract instrumentation. The offending organisms are staphylococci or gram-negative bacilli; acute gonococcal prostatitis is uncommon in the antibiotic era. Polymorphonuclear leukocytes infiltrate the prostatic acini and the stroma. Prostatic abscess is a rare complication.

**Chronic prostatitis**, with or without chronic seminal vesiculitis, usually develops without a history of an acute phase and presents as urinary or sexual dysfunction, sometimes with a thin, mucopurulent urethral discharge. Predisposing conditions include indwelling catheters, urinary tract instrumentation, urinary tract infection, spread of infection from distant foci, and prolonged sexual activity. There is a mixed neutrophilic and lymphocytic infiltrate, and foci of fibrosis may develop. Although a mixed population of bacteria may be identified, lack of demonstrable bacteria is more common. Granulomatous lesions representing tuberculous prostatitis occur rarely.

**Prostatic abscess.** The arrows show routes of spread of infection outside the prostate.
**Nodular hyperplasia** of the prostate is a disease associated with aging. Benign prostatic hypertrophy or hyperplasia (BPH) describes the benign proliferation (hyperplasia) of prostatic acinar epithelium and stroma with variable fibromuscular and epithelial predominance. Hyperplastic lesions typically arise in short glands adjacent to the proximal urethra in the middle lobe of the prostate (transitional zone). As the nodules increase in size, they compress the normal tissue of the more peripherally situated lateral and posterior lobes into a thin rim adjacent to the capsule. Formation of a median bar is one mechanism by which hyperplastic tissue obstructs the outlet of the urinary bladder. Significant BPH is confirmed by the detection of an enlarged, firm,
rubbery prostate gland on rectal examination. BPH can adopt a number of gross configurations that obstruct the bladder outlet, including the median bar, the bilobular pattern (2 lateral lobes), and the trilobular pattern (2 lateral lobes plus median lobe). The pathogenesis of BPH involves hormonally driven proliferation and growth of prostatic tissue in the setting of androgen and estrogen imbalance. BPH leads to progressive urinary dysfunction, recurrent urinary tract infections, and obstructive uropathy. Surgical intervention is usually palliative if not curative.
American men older than 50 years have a lifetime risk of clinical carcinoma of the prostate of approximately 10%. It occurs twice as frequently in African-Americans as in whites. This malignant tumor typically originates in the posterior lobe of the gland, with or without coexistent benign hyperplasia. Prostate cancer is frequently an adenocarcinoma composed of atypical epithelium (single cell layer without basal cells), which form small acini that grow in a crowded and disorganized pattern intermixed with abundant fibrous stroma (scirrhous form). Prostate cancer is scored on architecture by the Gleason scoring system. The unusual soft medullary type may elude early detection. Occult carcinomas are small lesions found incidentally at autopsy, in tissue resected for BPH, or in biopsy tissue for elevated prostate-specific antigen (PSA). Other prostatic cancers grow progressively to infiltrate much of the parenchyma of the gland, including eventually the posterior capsule. Perineural invasion is probably
important in local extension and development of metastases. Prostatic cancer extends initially by contiguous spread to the bladder and surrounding tissues. It spreads eventually to distant sites by invasion of the bloodstream and lymphatics. Approximately two thirds of patients with advanced disease have bony metastases. Typically, the metastatic foci stimulate bone growth, producing osteoblastic metastases that manifest as radiodense lesions, although radiolucent, osteoclastic metastases occur rarely. Lymph node and visceral metastases can be localized or widespread. Because androgens stimulate the growth of normal and neoplastic prostatic epithelium, carcinogenesis likely relates to an imbalance in production of androgens and estrogens. However, of utmost importance for cure of prostatic cancer is early detection and treatment before the malignancy has extended beyond the prostatic capsule to involve adjacent pelvic structures or spread to distant sites.
Diseases of the Scrotum and Testis

Hydrocele, an accumulation of serous fluid in the 2 peritoneal layers of the tunica vaginalis, results from abnormalities in the descent of the testicles from the retroperitoneal position in the abdominal cavity to the scrotum. The common simple hydrocele is a distended, fluid-filled segment of a normally formed tunica vaginalis. Congenital hydrocele, with or without hernia, involves a communication with the abdominal cavity. Hydrocele of the cord develops as a circumscribed sac of peritoneum localized in the cord. Acute hydrocele typically occurs secondary to trauma, tumors, or infection of the testicle and epididymis, particularly gonorrhea and tuberculosis. Chronic hydrocele may or may not have an apparent underlying cause. A spermatocele is a cyst within the scrotum that develops due to obstruction of the sperm transporting system. Rarely, enlargement of the spermatic cord is due to a malignant tumor, typically some type of sarcoma.
**Varicocele**, a collection of dilated, tortuous veins of the pampiniform plexus in the scrotum, is nearly always left sided and asymptomatic. Most varicoceles occur in young males and are without demonstrable etiology. The sudden onset of varicocele after the age of 30 years is secondary to retroperitoneal disease, such as tumors, hydronephrosis, or vascular anomalies. **Hematocele** is due to hemorrhage into the tunica vaginalis caused by an injury to the spermatic vessels, particularly trauma or operation, or it may occur spontaneously related to underlying vascular disease, infection, or neoplasm. **Torsion** (twisting) of the spermatic cord results in compression of the vasculature followed by infarction or complete gangrene of the testicle. Excessive mobility of the testis due to various developmental anomalies is the common predisposing factor. Torsion of the tiny vestigial appendix testis may cause acute pain in the scrotum, which can simulate acute epididymitis or can even mimic acute appendicitis from a referred pain pattern.
Reduced air circulation and evaporation of sweat in a tight space, irritation of scrotal skin by rubbing against adjacent structures, and ready access to bacteria are common causes of infection in the scrotum. Furuncles develop from hair follicles or sweat glands infected with *Staphylococcus aureus*. **Scrotal erysipelas**, a widespread superficial infection of scrotal skin, is usually caused by *Streptococcus pyogenes*. **Gangrene of the scrotum** with extensive necrosis and sloughing of skin can develop as a result of extravasation of infected urine into the subcutaneous tissues or mechanical, chemical, or thermal injuries to the scrotum, particularly in individuals with diabetes mellitus, alcoholism, or other chronic diseases. Abrupt onset and rapid progression of gangrene in apparently healthy individuals are initiated by an occult infection (idiopathic or Fournier gangrene). Prompt debridement and antibiotic therapy are mandatory.
Hypogonadism connotes testicular deficiency in androgen production by the interstitial (Leydig) cells, although failure of the sperm-producing germinal cells is also involved. Eunuchism and eunuchoidism are, respectively, the absence of the testis and severe reduction of androgen production. Primary testicular failure, which typically begins in the prepubertal or very early pubertal period, is the result of various intrinsic developmental defects in the testis with intact pituitary function. This picture is characterized as primary or hypergonadotropic eunuchoidism or hypergonadotropic hypogonadism. Testicular atrophy also can occur from acquired causes, such as infections (e.g., mumps) and trauma. Klinefelter syndrome, a genetic disease with a sex chromosomal abnormality, usually XXY, presents at puberty with small testes with hyalinized seminiferous tubules and features of eunuchoidism.
**Figure 7-20 Testicular Failure: Secondary Hypogonadotropic Hypogonadism**

Testicular deficiency is secondary to failure of the pituitary to produce gonadotrophic hormones (secondary hypogonadotropic hypogonadism) in approximately 80% of hypogonadal male patients. Although the exact cause of the hypofunction is often unknown, it is important to rule out a pituitary tumor (chromophobe adenoma) or a hypothalamic tumor or other intracranial lesion. Histologically, the testis is immature, with small tubules containing undifferentiated spermatogonia and Sertoli cells and few interstitial Leydig cells. The phenotype may be eunuchoid with a specific pituitary gonadotropic deficiency or that of a pituitary dwarf with panhypopituitarism. Many patients present with hybrid features of both primary and secondary hypogonadism.
Sexual precocity involves not only premature enlargement of the penis, pubic hair, and testes (macrogenitosomia), but also growth of the skeleton, muscles, body hair, and other structures. Sexual precocity may result from premature development or abnormalities of the hypothalamus and pituitary. Histology of the testis shows a mature pattern with significant development of both tubules and interstitial cells. Urinary gonadotropins and 17-ketosteroids are usually excessive for age. The endocrine type (pseudosexual precocity) results from an adenoma, carcinoma, or hyperplasia of the adrenal cortex or an interstitial cell (Leydig cell) tumor of the testis. These patients can combine the macrogenitosomia and premature musculoskeletal development with Cushing syndrome, hypertension, or both. The testes remain infantile in both germinal and interstitial development.
Orchitis may develop alone but more commonly occurs secondary to epididymitis. It may also result from systemic infections or be caused by bacterial toxins from distant localized infections, such as tonsillitis, sinusitis, or cellulitis. Acute pyogenic orchitis (epididymoorchitis) may progress to involve the testis, resulting in a large abscess. Mumps orchitis, which complicates approximately 20% of postpubertal mumps cases, progresses from transitory edema to marked interstitial inflammation (lymphocytes, macrophages, and plasma cells). If severe, it can result in tubular sclerosis and testicular atrophy. Most cases are unilateral, and sterility is rare. Epididymitis without orchitis is common in adults. It may result from a specific infection (e.g., gonorrhea, syphilis, or tuberculosis), a nonspecific inflammation, or trauma. The source of organisms can be infected urine, prostate, or seminal vesicles, with spread via the vas deferens to the epididymis.
Malignant neoplasms of the testis, which usually occur in men aged 15-40 years, are more frequent in undescended testicles. **Seminomas** are nonencapsulated but well circumscribed tumors with a lobulated architecture and a yellow, orange, or pink color. Histologically, they are composed of uniform cells with single, prominent, central nuclei arranged in compact lobules separated by thin fibrous septa. The stroma typically contains lymphocytes and plasma cells. These tumors are highly radiosensitive and curable if they do not contain a malignant trophoblastic component. **Embryonal carcinomas** have foci of hemorrhage and necrosis in a yellow lobulated mass. Histologically, they are composed of primitive cells with prominent nuclei that grow in glandular, lobular, or tubular patterns and, occasionally, exhibit chorioepitheliomatous tissue. Embryonal carcinoma usually has relative radioresistant elements, may have spread beyond the testis at diagnosis, and carries a guarded prognosis.
Choriocarcinomas are highly malignant neoplasms that occur most often as focal components of embryonal carcinomas and teratocarcinomas. They rarely occur as pure primary tumors. Histologically, choriocarcinomas consist of atypical syncytial and cytотrophoblastic cells surrounding blood spaces, which form structures resembling chorionic villi. Teratomas have a variable gross appearance with solid and cystic areas and a variable histologic appearance reproducing various mature glandular and solid tissues derived from the 3 germ layers. However, mature (adult) teratomas in males should be considered to have malignant potential because of the frequent occurrence of cryptic foci of poorly differentiated elements. Teratocarcinoma represents a group of tumors in which malignant elements of embryonal carcinoma, chorioepithelioma, and seminoma are present in conjunction with differentiated teratoid structures.
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Female sex organs develop from the same primitive structures as male sex organs. The ovary evolves from the embryonic urogenital ridge, and the Wolffian (mesonephric) duct remains vestigial without male stimulation. Paramesonephric ducts (müllerian ducts) form the anlage of the fallopian tubes, uterus, and vagina. External genitalia are essentially female in design and develop male features only when stimulated by dihydrotestosterone.

Common diseases of the female reproductive system are discussed in the following chapter according to their anatomical sites. They comprise congenital alterations, inflammation, and infections (Table 8-1); benign and malignant tumors; and pregnancy-related disorders.

DISEASES OF THE VULVA

The vulva includes such structures as the mons pubis, the labia majora and minora, the clitoris, and the introitus (vestibule). Diseases of the vulva affect the skin (e.g., vulvitis, tumors) and the adnexal glands (cysts, Bartholinitis, tumors).

DISEASES OF THE VAGINA

The vagina connects the uterus with the vestibule and is lined by a hormone-sensitive squamous epithelium. Consequently, loss of estrogen stimulation favors infections and causes atrophic vaginitis. Diseases of the vagina involve the epidermis (e.g., inflammation, polyps, squamous cell carcinoma [SCC]), the adnexal glands (adenosis, adenocarcinoma), or ductal remnants (Gartner duct cysts).

DISEASES OF THE UTERUS

The uterus is subdivided for diagnostic and therapeutic reasons into the uterine cervix, the endometrium, and the myometrium. Common diseases include functional disturbances, inflammation, and neoplasia. Cervicitis, which often results from sexually transmitted disease (STD), is common, whereas endometritis is rather rare. STDs include infections by papilloma virus, herpes simplex virus type II, syphilis, and gonorrhea (also see chapter 7). Chlamydia species cause infections of the female reproductive system with increasing frequency.

Cervical intraepithelial neoplasia (CIN) is a common atypical proliferation of squamous epithelium, frequently related to infection with certain papilloma viruses (human papillomaviruses [HPVs] 16 and 18), which carries the risk of progressing to SCC. Early diagnosis of CIN by exfoliative cytology (PAP smear) followed by appropriate treatment has helped to decrease the annual incidence of SCC by 50% to 85%.

Squamous cell carcinoma of the cervix is the second or sixth most common tumor of females (depending on the efficiency of cervical cytologic screening). There are 15 new cases annually per 100,000 women in the United States. The chief clinical feature of SCC is vaginal bleeding after intercourse or douching; it may be silent in sexually inactive women. The 5-year survival after treatment is stage-dependent and ranges from 90% in patients diagnosed in International Federation of Gynecology and Obstetrics (FIGO) stage I to 10% in those diagnosed in stage IV.

Endometrial hyperplasia and endometrial adenocarcinoma (EAC) represent a continuum of proliferative diseases (hyperplasias) that start as a benign disturbance and proceed stepwise to malignancy. Atypical hyperplasia with complex glandular crowding and cytologic atypia signals the transition to carcinoma. Afflicting approximately 34,000 women per year in the United States, EAC is the fourth most frequent cancer in women. The incidence decreased recently when the administration of menopausal estrogens was reduced, suggesting that prolonged estrogenic stimulation may support its pathogenesis. The essential clinical feature of EAC is perimenopausal or postmenopausal bleeding. The prognosis for patients with EAC depends on the tumor stage and additional risk factors; the 10-year survival rate is approximately 65%.

DISEASES OF THE FALLOPIAN TUBES

Inflammation (salpingitis) and ectopic pregnancy (EP) are the most common diseases in this region. Salpingitis caused by Escherichia coli, chlamydia, or gonorrhea, frequently as STD, may cause abscesses, adhesions, obstructions, and infertility. EPs may be related to preceding salpingitis and occur in the United States at a rate of approximately 1.5 per 100 live births. More than 95% of EPs are located in the fallopian tubes. They constitute life-threatening diseases because of their risk of tubal rupture and massive hemorrhage. Adenocarcinoma of the salpinx is a rare disease.

DISEASES OF THE OVARY

Besides various endocrinopathies, ovarian tumors are the most important diseases in this region. There are more than 25 types of ovarian tumors and many subtypes. They are classified into major groups: tumors of the germinal epithelium (e.g., serous and mucinous cystadenoma/carcinoma), tumors of the germ cell (dysergminoma, teratoma, chorio-carcinoma), tumors of the gonadal stroma (granulosa cell tumor, Sertoli-Leydig cell tumor, thecoma), and benign hilus
Introduction

PREGNANCY AND ITS DISEASES

Diseases discussed in this section comprise a large variety of disorders: structural and functional alterations (placenta previa, EP, abortion), various infections and tumors, diseases of the fetus (erythroblastosis fetalis), and toxemia of pregnancy and eclampsia.

TABLE 8-1 INFECTIOUS AND INFLAMMATORY DISEASES OF THE FEMALE REPRODUCTIVE SYSTEM

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatoses of the vulva</td>
<td></td>
</tr>
<tr>
<td>Folliculitis and furunculosis</td>
<td><em>Staphylococcus aureus</em>, mixed organisms</td>
</tr>
<tr>
<td>Herpes genitalis (progenitalis)</td>
<td>Herpes simplex virus type 2</td>
</tr>
<tr>
<td>Intertrigo</td>
<td>Chafing plus dermatophytosis (fungal infection)</td>
</tr>
<tr>
<td>Tinea cruris</td>
<td>Ringworm of the groin, usually <em>Epidermophyton floccosum</em></td>
</tr>
<tr>
<td>Molluscum contagiosum</td>
<td>Poxvirus</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Systemic noninfectious inflammatory disorder</td>
</tr>
<tr>
<td>Infections and other lesions of the vulva, vagina, and cervix</td>
<td></td>
</tr>
<tr>
<td>Diabetic vulvitis</td>
<td>Mycotic (fungal) infection</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td><em>Neisseria gonorrhoeae</em></td>
</tr>
<tr>
<td>Syphilis</td>
<td><em>Treponema pallidum</em></td>
</tr>
<tr>
<td>Chancroid</td>
<td><em>Haemophilus ducreyi</em></td>
</tr>
<tr>
<td>Lymphogranuloma venereum</td>
<td><em>Chlamydia trachomatis</em> types L1, L2, L3</td>
</tr>
<tr>
<td>Granuloma inguinale</td>
<td><em>Calymmatobacterium granulomatis</em> (originally <em>Donovania</em> species)</td>
</tr>
<tr>
<td>Bartholin gland cyst and abscess</td>
<td><em>Neisseria gonorrhoeae</em>, other pathogenic bacteria</td>
</tr>
<tr>
<td>Common vulvovaginitis, urethritis, and cervicovaginitis</td>
<td><em>Candida albicans</em> (moniliasis), <em>Chlamydia trachomatis</em> (serotypes D-K), <em>Trichomonas vaginalis</em>, other organisms, including gram-positive and -negative bacteria (nonspecific vaginitis)</td>
</tr>
<tr>
<td>Genital (venereal) warts (condylomata acuminata)</td>
<td>Human papillomaviruses, especially types 6, 11, 42, and 44 (low risk for cervical cancer)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td><em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Chemical vaginitis</td>
<td>Douches (high-concentration chemicals)</td>
</tr>
<tr>
<td>Traumatic vaginitis</td>
<td>Foreign bodies, pessaries</td>
</tr>
<tr>
<td>Pelvic inflammatory disease</td>
<td></td>
</tr>
<tr>
<td>Vulvitis, cervicitis, endometritis, salpingitis, oophoritis</td>
<td><em>Neisseria gonorrhoeae</em>, <em>Chlamydia trachomatis</em>, polymicrobial puerperal infections — staphylococci, streptococci, coliform bacteria, <em>Clostridium perfringens</em></td>
</tr>
<tr>
<td>Puerperal infections</td>
<td></td>
</tr>
<tr>
<td>Endometritis, vaginitis, sepsis</td>
<td><em>Streptococcus</em> species, <em>Staphylococcus</em> species, gram-negative bacteria</td>
</tr>
</tbody>
</table>
PATHOLOGY OF THE MAMMARY GLAND

The female breast, like the endometrium and the cervical-vaginal epithelium, responds sensitively and with varying histology to alterations in female sex hormones during adolescence, the menstrual cycle, pregnancy, and menopause. Knowledge of the normal histologic reaction patterns in the breast gland is essential for the interpretation of pathologic changes. The most frequent disorders today are various forms of hyperplasia (fibrocystic disease) and mammary carcinoma (MCa). MCa is the most frequent tumor in females of the Western world, with a lifetime incidence of approximately 1 woman in 9. Approximately one third of patients die of the disease.

Genetic factors play a significant role in breast cancer, and its risk is significantly increased among first-degree relatives of affected individuals. Several genes, including BRCA1 and 2, have been implicated. In addition, there are obvious hormonal and environmental influences on the pathogenesis of MCa. Because the initial growth of the tumor usually remains clinically inapparent or is camouflaged by preexistent fibrocystic disease, regular breast examination is essential for early diagnosis and survival.
The skin of the vulva can be involved by the same spectrum of dermatoses that affect the skin of the rest of the body. Some common dermatoses are shown here, and the causes are listed in Table 8-1. **Folliculitis** is a papular or pustular inflammation involving the apertures of the hair follicles, and **furuncles** are larger and more deeply seated lesions with a central core of purulent exudate. **Herpes genitalis or progenitalis** is a recurring, localized condition, beginning as groups of vesicles on an edematous, erythematous base and subsequently forming small ulcers that dry, crust, and heal. **Intertrigo** and **tinea cruris** are superficial dermatoses associated with fungal infection. Vulvar lesions of psoriasis, a systemic noninfectious inflammatory disorder, are typically pruritic, red, and covered with silvery-white scales. The presence of similar lesions on the scalp and extensor surfaces of the extremities and nail changes help to establish the diagnosis.
Presenting features of vulvitis or vulvovaginitis include pruritus vulvae, vaginal discharge, burning on urination, and dyspareunia. Diabetic vulvitis is characterized by an inflamed, dark-red or beefy appearance with a superimposed superficial fungal infection. The vulvovaginitis produced by *Trichomonas vaginalis* has a thick, odoriferous, bubbly discharge in the vestibule. Vulvovaginitis caused by *Candida albicans* and related yeast fungi (moniliasis) is characterized by white, cheesy, irregular plaques, partially adherent to the congested mucosa of the vagina and cervix (vaginal thrush). Acute gonorrhea often presents with vaginitis beginning 1 to several days after contact; occasionally, the disease may not manifest until after the following menses, when ascending infection has resulted in acute salpingitis. Examination of the external genitalia may reveal a congested vestibule with a purulent discharge and inflammation of the urethra, Skene ducts, and Bartholin ducts.
The painless ulcerated **chancre**, the primary lesion of **syphilis**, typically develops on the labia majora or vaginal mucosa approximately 3 to 4 weeks after infection and is easily overlooked. Inguinal lymphadenopathy develops slowly and is usually well demarcated 6 weeks after infection. Histologically, the chancre shows edema, congestion, and infiltration with lymphocytes, plasma cells, epithelioid macrophages, and multinuclear giant cells. The diagnosis is made by the demonstration of the spirochetes of *Treponema pallidum* by dark field examination of wet preparations of the lesions. **Condylomata lata**, the lesions of secondary syphilis, are slightly elevated, disk-shaped papules with depressed centers. **Condyloma acuminata** (genital or venereal warts) are caused by an infection with HPVs, often not the precancerous 16 and 18. The confluent, cauliflowerlike growths of squamous epithelium form multiple soft, pointed, watery excrescences about the labia and perineum.
Chancroid, a venereal infection caused by the Ducrey bacillus (*Haemophilus ducreyi*), is a painful ulcerated, inflamed lesion that develops 3 to 10 days after infection. It is associated with suppurative inguinal nodes or buboes. **Lymphogranuloma venereum**, which is caused by strains of *Chlamydia trachomatis*, begins as a papule, a pustule, or an erosion on the vulva or within the vagina. Lymphatic spread leads to the development of inguinal adenitis, a painful matted mass of glands with periadenitis and occasional suppuration and draining sinuses. Complications include rectal stricture. **Granuloma inguinale** is a chronic infectious disease that is widespread in the tropics and common in the southern United States. After a variable incubation period, the primary lesion develops as a vivid, circumscribed, granulomatous nodule involving the vulva, the vaginal mucosa, or the cervix. Healing occurs slowly, with the lesion persisting for many months or years.
Varicose veins of the vulva are associated with varicose veins of the lower extremities that develop as a result of retarded venous flow caused by increased intrapelvic pressure during pregnancy. Angioneurotic edema is a transient recurrent allergic reaction that manifests as painless swelling of the vulva and other areas of the body. Bartholin cysts result from obstruction of the excretory duct or one of its subdivisions due to specific or nonspecific infections and accidental or operative trauma. Sebaceous cysts result from occlusion of a sebaceous duct, which causes sebum and epithelial debris to be retained in the gland. Benign tumors of the vulva include the fibroma, fibromyoma, lipoma, papilloma, urethral caruncle, hydradenoma, angioma, myxoma, neuroma, and endometrial growths. Fibromas, which arise from vulvar connective tissue, become pedunculated as they increase in size and weight. Lipomas of the vulva are soft proliferations of benign adipose tissue.
Primary vulvar lesions account for approximately 5% of the malignant tumors of the female genital tract. **Primary carcinoma of the vulva or clitoris** almost always develops in elderly women. Most are SCCs, and approximately 50% are preceded by leukoplakia. The typical course is the development of a small, firm nodule that progressively enlarges and ulcerates. Lymphatic extension to the regional inguinal nodes occurs early, but distant metastases are rare. Basal cell carcinoma or adenocarcinoma of a Bartholin gland or other glandular tissue is less common. **Secondary carcinoma** of the vulva is uncommon, but it may occur particularly with renal cell carcinoma (hypernephroma), choriocarcinoma of the uterus, and carcinoma of the uterine body or cervix. **Sarcoma** of the vulva, which includes fibrosarcoma, spindle cell carcinoma, lymphosarcoma, myxosarcoma, and liposarcoma, is also uncommon, but it is usually very malignant.
Most congenital anomalies of the uterus and vagina are caused by a failure of the müllerian ducts to fuse completely or to develop after fusion. Absence of the vagina (gynatresia) results from complete lack of union of the müllerian ducts. Each ovary, because it is derived from a different embryonic structure, is normal; the fallopian tubes may be rudimentary. A less extreme failure in müllerian development leads to a double vagina. The partial septate vagina is a milder degree of congenital malformation caused by a failure of the core of solid müllerian epithelium to slough completely at its lowermost portion. Another variation is a rudimentary second vagina. Failure of proper interaction and development of the lower müllerian ducts and the urogenital sinus can lead to an imperforate hymen (external gynatresia).
The decline in estrogen levels after the onset of menopause leads to vulvar and **vaginal atrophy**. The vagina is narrowed, especially near the apex, making visualization of the cervix difficult. The thin mucosa exhibits pallor and petechial hemorrhages, and some ulcerations may be present. *Trichomonas* or mixed bacterial infections may be present. As the condition advances, attempts at regeneration and repair lead to the formation of adhesions. Histologically, the epithelium is thin and focally interrupted, and the stroma is edematous and contains focal infiltrates of lymphocytes and polymorphonuclear leukocytes. Cytology of a cervical smear shows atrophic epithelial cells and neutrophils. Senile vaginitis is a common cause of postmenopausal bleeding.
DISEASES OF THE FEMALE REPRODUCTIVE SYSTEM

Diseases of the Vagina

A **cystocele**, a hernialike structure, occurs when the spreading and tearing of the principal muscular supports of the vagina and rupture of pelvic fascia during childbirth cause the bladder to push forward and downward through the anterior vaginal wall. **Fistulae** may develop between the vagina and urinary bladder and rectum, diverting the urinary or fecal streams and causing incontinence. The extent of the defect depends on the number and difficulty of previous deliveries and the quality of prepartum and postpartum care. A severe cystocele may produce urinary retention leading to recurrent attacks of **cystitis** with dysuria, frequency, nocturia, and stress incontinence and may necessitate surgical repair. The consequences of unrepaired posterior obstetric lacerations of the vagina depend on the direction and extent of the tear. **Rectocele** and varying degrees of prolapse of the pelvic floor may occur in subsequent months. Rectoceles are graded according to size; third degree is a hernia to or beyond the introitus.

**Figure 8-9  Cystocele and Rectocele**

![Diagram of cystocele and rectocele](image-url)
Nonspecific or simple vaginitis occurs when the normal vaginal flora of microorganisms proliferate, stimulated by conditions such as age, debility, systemic disease, ovulation, menstruation, or pregnancy. Characteristic features of the infection caused by the protozoan parasite *Trichomonas vaginalis* are a vaginal and cervical epithelium with small petechial hemorrhages producing a “strawberry” appearance and a thin, greenish-yellow discharge containing many small bubbles, producing a foamy appearance.
Vaginal infection due to the fungus *C. albicans* (moniliasis) causes an aphthous ulcerative infection with patchy, white exudate that leaves a raw, bleeding surface when it is removed. Predisposing factors are diabetes and previous use of antibiotics. Vaginitis can be produced by chemical irritation from substances in douches and from foreign bodies in the vagina.
In the vagina, the syphilis chancre, with its raised indurated border surrounded by a shallow ulceration, is most likely to be near the vestibule, and inguinal lymphadenopathy may be present. In the primary stage, serologic test results are often negative, and dark field examination results of a smear from the lesion are positive for treponemes. In late syphilis, white mucosal patches that coalesce and ulcerate focally may be present in the vagina and the external genitalia. Gonorrhea involves the cervix, but spares the vagina during reproductive life because the vaginal epithelium is resistant to infection by Neisseria gonorrhoeae. Gonorrheal vaginitis is a recognized but rare clinical entity in the postmenopausal period and in childhood. Tuberculosis, which rarely affects the vagina, is secondary to tuberculosis of the fallopian tubes, the uterus, and the cervix. Typical ulcerated lesions usually involve the posterior vagina.
Most vaginal tumors are **benign cysts**. **Gartner duct cysts** are formed from embryonic epithelial remnants of Wolffian ducts, are located on the anterolateral vaginal walls, may be simple or multiple, and occasionally attain large enough size to produce pain and other symptoms. Congenital cysts of müllerian origin (**inclusion cysts**) may occur in the fornices or lower in the vagina. Malignant tumors include **primary carcinoma of the vagina**, which is usually an SCC that begins as a small growth of the...
posterior vaginal wall and progresses to infiltrate the vagina and eventually the adjacent pelvic viscera and regional lymphatics, and the rare vaginal sarcomas, fibrosarcoma, and variants in adults and sarcoma botryoides in children. Melanoma of the vagina is unusual, but can occur as an apparently primary lesion or, more commonly, as part of metastatic disease.
Approximately 60% of vaginal malignant tumors are secondary to other tumors, most often carcinomas of the cervix or endometrium. After hysterectomy for endometrial carcinoma, the vaginal vault is a common site of recurrence. Vulvar carcinomas may involve some or most of the vagina. The vagina is the most frequent site of metastases from uterine choriocarcinoma and may be the earliest clinical manifestation. A history of recent pregnancy may be elicited. The dark-purple hemorrhagic gross appearance and the histologic picture are characteristic. The lesion is made up of clusters of syncytiotrophoblasts and cytotrophoblasts, with the trophoblastic cells exhibiting large, hyperchromatic nuclei and frequent mitoses. Renal cell carcinoma, or hypernephroma, may metastasize to the vagina, forming a nodular, yellow tumor mass, usually composed of clear cells with hyperchromatic nuclei. Metastases or extensions may involve the vagina before or after treatment of carcinomas of the ovary, the bladder, or the rectum.
Endometriosis is characterized by the presence of hormonally responsive endometrial glands or stroma in abnormal locations outside the uterus. Endometrial tissue can result from retrograde menstruation through the fallopian tubes, metaplasia of coelomic epithelial implants, or vascular or lymphatic dissemination of tissue from the endometrium. Vaginal endometriosis is associated with similar lesions in the ovary and rectovaginal septum. The sagittal section shows a distribution of endometriosis on the surface of the ovary and other implants on the adjacent peritoneum of the posterior cul-de-sac and the lateral pelvic wall. Blue-domed endometrial cysts extend down the rectovaginal septum, which causes the anterior rectal wall to adhere to the posterior surface of the uterus. Occasionally, there may be involvement of the vulva or perineum and, rarely, a Bartholin gland.
A variety of congenital anomalies are related to the embryologic derivation of the female genital tract from the müllerian ducts. Complete failure of fusion of the müllerian ducts results in the formation of 2 separate genital tracts with completely independent uteri and a fallopian tube attached to the lateral angle of each uterus (uterus didelphys). Each uterus can function separately and sustain a normal pregnancy. More frequently, partial fusion of the müllerian ducts takes place, as is the case in the uterus duplex bicornis. If failure of fusion occurs only at a higher level, the result is 2 uterine bodies with a single cervix, the uterus bicornis unicollis. In some cases, the uterine cavities are completely or partially separated by a thin septum, giving rise to uterus septus or uterus subseptus, respectively. Uterus unicornis is a half uterus arising from only 1 formed müllerian duct. Uterine aplasia with blind fallopian tubes also is known to occur.
Displacement of the uterus occurs when it becomes fixed or rests chronically in an abnormal position. The anatomical configurations are retroversion, retroflexion, retrocession, and anteflexion. Prolapse refers to descent of the uterus down the vaginal canal so that it lies below its normal position. Some degree of retroversion is present. Usually, this occurs after parturition when the stretched uterine ligamentous supports cannot counteract the usual intraabdominal pressure and the involuting uterus lacks normal myometrial tone. In first-degree prolapse, the cervix does not protrude at the introitus. In second-degree prolapse (procidentia), the cervix protrudes. In complete procidentia, the entire uterus

**Figure 8-16 Displacements and Prolapse**

Displacement of the uterus occurs when it becomes fixed or rests chronically in an abnormal position. The anatomical configurations are retroversion, retroflexion, retrocession, and anteflexion. Prolapse refers to descent of the uterus down the vaginal canal so that it lies below its normal position. Some degree of retroversion is present. Usually, this occurs after parturition when the stretched uterine ligamentous supports cannot counteract the usual intraabdominal pressure and the involuting uterus lacks normal myometrial tone. In first-degree prolapse, the cervix does not protrude at the introitus. In second-degree prolapse (procidentia), the cervix protrudes. In complete procidentia, the entire uterus
protrudes. Cystocele and rectocele are frequent complications. Spontaneous rupture of the uterus is a rare complication of parturition or may occur during procedures such as dilatation and curettage, especially when there is preexisting displacement with anatomical malposition of the uterus.
Lacerations of the external cervical os are common after parturition, and, barring infection, most heal spontaneously. More complex lacerations penetrate deeply into the endocervical stroma or extend into the lateral fornix, which permits eversion of the lining of the endocervical canal, predisposing to infection. Stricture of the internal cervical os, which can result in hematometra (retained menstrual flow and endometrial debris), occurs after posttraumatic or postinfectious scarring, after radiation therapy, and in rare cases of partial or complete congenital atresia. The uterine mucosa can form polyps, which differ from endometrial polyps etiologically and clinically. Endocervical polyps, which are usually benign, typically contain all the elements of the endocervical mucosa (columnar epithelium, fibrous stroma, and glands). As the polyps grow to produce protruding soft, red, granular lesions, they can produce mild vaginal bleeding. The etiology of cervical polyps is unknown.
Endometrial hyperplasia occurs under conditions that produce a constant stimulus of estrogen, which prevents the progestational or secretory phase of the menstrual cycle to take place. The gross appearance of endometrial hyperplasia is a thickened and edematous mucosa. Estrogenic stimulation produces an overgrowth of glands, stroma, and microvessels. In long-standing cases, the glands show irregular cystic dilatation with a lining of low cuboidal epithelium, which leads to the “Swiss cheese” pattern. The exuberant growth may be difficult to distinguish from well-differentiated adenocarcinoma. Atypical hyperplasia is defined as complex glandular crowding and cytologic atypia. Endometrial hyperplasia may give rise to single or multiple endometrial polyps. The diagnosis of endometrial hyperplasia usually is made from pathologic examination of endometrial curettings from a woman with abnormal uterine bleeding. Occasionally, examination reveals an infectious process, including tuberculosis. Tuberculous endometritis is characterized by caseating granulomas in the endometrial stroma.

**FIGURE 8-18  ENDO METRIAL HYPERPLASIA AND POLYPS AND TUBERCULOUS ENDOMETRITIS**
Exposure of the mucous glands in the endocervical canal, which is often due to erosions from congenital defects or childbirth injuries, is a key factor in initiating cervical infections. The even, concentric appearance of congenital erosions contrasts sharply with the jagged papillary granulomas that usually result from inadequately treated lacerations of childbirth. Spontaneous healing does not occur because the inward growth of squamous epithelium does not cover the infected areas. In areas where healing has occurred, the covering epithelium blocks the exit of previously exposed glands, which produces retention cysts of various sizes (nabothian cysts).
Gonorrheal infection caused by the gram-negative diplococcus Neisseria gonorrhoeae is the most common cause of **acute cervicitis**. The infection begins in the lower genital tract and does not ascend to the adnexa until the next menstruation. Initially, acute infection involves the deeply branching cervical and endocervical glands, the urethra and the Skene glands, and the Bartholin glands in the vulva. At the time of menses, the gonorrheal infection ascends through the uterus to the fallopian tubes, which become swollen, inflamed, and tortuous. Inflammation of the endosalpinx leads to extrusion of pus from the edematous fimбриae into the posterior cul-de-sac, causing pelvic peritonitis. Lymphatic involvement of the mesosalpinx can predispose to bacteremia and septicemia. A minority of cases of acute cervicitis is caused by pyogenic infections of cervical glands exposed by unhealed lacerations of childbirth. Gram staining of smears may reveal a mixed bacterial population and neutrophils.
Uterine myomata, the most common tumors in the female pelvis, have an incidence of approximately 4% to 11% in adult women. Commonly called fibroids, these tumors are composed of benign proliferations of uterine smooth muscle cells with a typical whorled pattern on histologic examination and are, therefore, leiomyomata. The tumors, which vary in size, location, and position (intramural, subserous, or submucosal), occur most frequently in the fifth decade of life and are more common in black women. Leiomyomata also are found in the cervix and broad ligament (intraligamentary myoma). The most common symptom, profuse or prolonged uterine bleeding, occurs in approximately 50% of cases. The uterine bleeding and the growth of the leiomyomata may have a common cause in excess estrogen stimulation, so that excision of the leiomyoma may or may not cure the uterine bleeding.
DISEASES OF THE FEMALE REPRODUCTIVE SYSTEM

Diseases of the Uterus

The evaluation of infertility should take uterine leiomyomata into account, particularly if there are submucous myomas. Indications for surgery, either removal of the leiomyoma (leiomyectomy) or hysterectomy, include recurrent uterine bleeding, pelvic pressure, pelvic pain, and rapid growth suggesting sarcomatous transformation. Pedunculated submucous leiomyomas are prone to torsion of the pedicle, cutting off the blood supply and causing sloughing and necrosis. Occasionally, a myoma on a long pedicle can prolapse through the cervix and cause complete inversion of the uterus. Large leiomyomas sometimes exceed their blood supply, leading to cystic degeneration and calcification. Leiomyomas may not affect a successful pregnancy but, if located in the cervix, may obstruct the passage of the fetal head through the birth canal. During pregnancy, the vascular supply to an interstitial leiomyoma may become compromised, leading to necrosis and hemorrhage, so-called red degeneration, which may become a serious complication.

Figure 8-22  LEIOMYOMA: SECONDARY CHANGES

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Sarcoma of the uterus accounts for approximately 3% to 4% of malignancies of the female genital tract. Uterine sarcomas, whether primary or secondary to a preexisting fibroid (rate of sarcomatous degeneration is approximately 1%), grow rapidly and have a grave prognosis. Sarcomas arising in a fibroid appear grossly as soft, meaty areas, often with foci of central necrosis or hemorrhage due to an inadequate blood supply. The size and extent of tumor are more important for prognosis than is location or histologic characteristics. Histologically, the sarcoma cells may be spindle-shaped or round and show nuclear pleomorphism and mitoses. Occasionally, uterine polyps show sarcomatous degeneration. Sarcoma botryoides ("grape" sarcoma) is a rare and almost invariably fatal condition that occurs only in young children.
Cervical carcinoma, a slow-growing neoplasm confined for several years to the surface epithelium as a noninvasive growth, is caused by infection by strains of HPV, including HPV-16, 18, 31, and 33. The in situ lesions in the early stage of the disease can be detected by screening with exfoliative cytology of cervical scrapings and vaginal smears (Pap smear) and confirmed by cervical biopsy. In cytologic preparations, cells of the squamous epithelium are classified as basal, parabasal, intermediate, precomified, cornified (keratinizing), and hypercomified. These epithelial cells show a variety of changes during inflammatory processes. The squamous cells show changes generally classified as CIN, ranging from mild dysplasia (CIN grade I) to carcinoma in situ (CIN III), and invasive cancer. These changes are characterized by progressive nuclear enlargement, hyperchromasia, atypia, loss of maturation, and anaplasia. Viral changes may be especially prominent in CIN I.
Surface carcinoma, CIN grade III, typically originates at the squamocolumnar junction of the cervix and appears histologically as a complete lack of normal basal to surface maturation of the epithelium, coupled with marked nuclear atypia of the cervical epithelial cells. Invasive SCC is characterized by the extension of sheets of atypical squamous cells forming foci of keratinization (epithelial pearls) into the cervical stroma. Adenocarcinoma arises from the endocervical glands and invades the stroma by atypical glandular epithelium. Cervical cancer follows a standard pattern of extension involving the lymphatic channels and direct invasion of adjacent organs. It is characterized histologically according to degree of differentiation (anaplasia) from grade I to grade IV and clinically according to spread of disease from stage 0 to stage IV. Death is more common from uremia secondary to obstructions from local disease than from late metastases to the liver, the lungs, or the bones.
The differential diagnosis of abnormal vaginal bleeding or discharge, particularly in postmenopausal women, should include adenocarcinoma of the uterus. Detection of endometrial carcinoma in a curettage specimen is diagnostic. Stage 0 designates lesions limited to focal areas of the mucosa. Stage I refers to tumor involving the full thickness of the mucosa, with invasion of the myometrium but limited to the uterus. Stage II indicates tumor that has involved the corpus uteri and the cervix. Stage III and IV designate a cancer that has extended beyond the uterus, including direct extension through the uterine wall or transmigration of cancer cells through the fallopian tubes with implantation on the ovaries. Fractional curettage defines the site of origin of the carcinoma: (1) those that involve only the corpus, (2) those arising only from the endocervix, and (3) those involving both the corpus and endocervix. The importance of the site of origin for staging and therapy reflects different routes of lymphatic spread and invasion.
The histopathologic diagnosis of adenocarcinoma can be difficult, particularly differentiation from an atypical adenomatous hyperplasia of the endometrium. Foci of adenocarcinoma are characterized by crowded, back-to-back glands lined by thickened layers of epithelial cells exhibiting nuclear hyperchromasia and atypia. Most lesions are pure adenocarcinomas, but some lesions, termed adenoacanthomas, have islands or sheets of squamous carcinoma intermingled with the malignant glands. Location and stage of disease are of paramount importance prognostically, but the more anaplastic tumors may be expected to grow more rapidly and to metastasize earlier than the more mature adenocarcinomas. Successful therapy depends on surgical removal of the disease while it is confined to the uterus. Radiation treatment is used as adjunct therapy. Death from distant metastases to vital organs occurs more often in endometrial carcinoma than in cervical neoplasms.
Normal desquamation of the uterine mucosa with menstrual bleeding is controlled through a delicate balance of pituitary and ovarian hormones and the response of the target tissue, the endometrium. Steroid withdrawal bleeding is often associated with persistent estrogen phases and anovulatory cycles. It may follow a state of estrogen-progesterone imbalance, which produces an abnormal secretory endometrium. Excess estrogen produces hyperplastic and anaplastic endometrium, while an estrogen deficiency produces a hypoplastic endometrium. The major categories of pathologic states that can cause or be accompanied by menorrhagia (heavy or prolonged menstrual flow) or metrorrhagia (spotting or bleeding between menstrual flows) are illustrated.
Because the fallopian tubes traverse between the uterus and the ovaries, infection can spread from either the uterus or the ovaries to involve the fallopian tubes producing an **acute salpingitis**. The opening of the tubes into the peritoneal cavity predisposes the tubes to peritoneal infections, especially appendicitis. Infection by the hematogenous route also may occur as in tuberculosis. Gonococci and most other bacteria reach the tubes by way of the mucous membranes of the vagina and the uterus. Gonococci produce a relatively superficial infection of the mucosa, whereas streptococci and staphylococci typically spread from the mucosa into the uterine wall and invade the adjacent lymphatics, blood vessels, and adjacent pelvic connective tissue, where the most prominent changes with these infections occur. These changes constitute a **purulent parametritis**, lymphangitis, and thrombophlebitis. Occasionally, a parametrial abscess forms.
Acute salpingitis is characterized by an edematous, hyperemic, and tortuous fallopian tube with thickened mucosal folds, pus-filled lumen, and a fibrinous or fibrinopurulent exudate on the serosa (perisalpingitis). In gonorrheal salpingitis, the infiltrate is located chiefly in the mucosa. In nongonorrheal salpingitis, the entire wall is inflamed. The loss of epithelium and inflammatory exudate often leads to adhesions of the edematous folds of mucosa. The acute stage is followed by a subacute and eventually by a chronic inflammatory stage. Complications include unilateral or bilateral partial or complete closure of the ampullary ostium, the uterine end, or both the uterine and ampullary sections of the tubes. The closure leads to progressive distention of the tube, forming a sausage-shaped structure called a pyosalpinx. The thick contents of the tube liquefy gradually to become serous or serosanguinous fluid, thus transforming the pyosalpinx into a hydrosalpinx.
Pelvic peritonitis can result from spillage of the purulent contents of an infected fallopian tube with a patent ampullary ostium or, with obstructed tubes, from spread of tubal lymphangitis and perisalpingitis or rupture of a tube. The severity and extent of the peritonitis depend on the type and virulence of the pathogenic bacteria, the resistance of the patient, and the efficacy of treatment. A pelvoperitoneal abscess, or abscess of pouch of Douglas, results when the pus that has accumulated in the cul-de-sac between the uterus and the rectum becomes sealed off from the rest of the peritoneal cavity by fibrous adhesions between the pelvic organs and the overlying intestinal loops. Pelvic peritonitis usually results in formation of multiple adhesions, which can lead to uterine retroflexion and accompanying pelvic symptomatology. Kinking and fibrosis of the fallopian tubes can lead to infertility.
Salpingo-oophoritis is an inflammatory disease involving the ovaries and the fallopian tubes. A tuboovarian abscess forms when a pyosalpinx communicates with a ruptured ovarian follicle or corpus luteum. The ovary may be the site of a bacterial infection or may be involved secondarily from inflammation of the adjacent tube. Generally, follicular or luteal abscesses develop as complications of pelvic peritonitis, whereas ovarian stromal abscesses are usually due to hematogenous dissemination of bacteria. In rare cases, a tuboovarian abscess may gradually become a tuboovarian cyst, which consists of the dilated tube in communication with a large ovarian cyst. The pelvis also may contain mesonephric cysts (congenital cysts) and multiple loculated cysts from Echinococcus infestations (the tapeworm, Echinococcus granulosus).
Hematogenous dissemination of *Mycobacterium tuberculosis*, usually from a primary focus in the lungs or hilar lymph nodes, can result in tuberculous infection of the uterus, tubes, and pelvic peritoneum. Usually, both tubes are involved in association with tuberculous peritonitis, and the uterus is involved in approximately half of the cases. Grossly, multiple small nodules consistent with the miliary pattern of tuberculosis are observed. The tubes exhibit caseous necrosis and granulomatous inflammation. The pelvic infectious process can be insidious, and the diagnosis can be difficult to make. The disease process can be exacerbated if diffuse peritonitis develops or if a secondary pyogenic bacterial infection occurs.
Salpingitis isthmica nodosa, a benign proliferation of stroma and glands similar to uterine adenomyosis, results in an enlargement with stenosis of the inner, isthmic portion of the tubes. Primary neoplasms of the uterine tubes are uncommon and may arise from epithelium (papillomas, adenomas, carcinomas, choriocarcinomas) or the mesenchymal tissue (fibromas, angiomas, leiomyomas, myomas). The carcinomas may be primary in the tubal mucosa or may occur as a metastasis from a primary carcinoma of the ovary, the uterus, or the gastrointestinal tract. The primary carcinomas have the appearance of a distended tube filled with a protuberant growth of neoplastic tissue with multiple papillary projections. The lesions spread by peritoneal implantation as well as by lymphatic and hematogenous metastases. Diagnosis is usually late, and the prognosis is poor.

**FIGURE 8-34  SALPINGITIS ISTHMICA NODOSA AND CARCINOMA**

Salpingitis isthmica nodosa, a benign proliferation of stroma and glands similar to uterine adenomyosis, results in an enlargement with stenosis of the inner, isthmic portion of the tubes. Primary neoplasms of the uterine tubes are uncommon and may arise from epithelium (papillomas, adenomas, carcinomas, choriocarcinomas) or the mesenchymal tissue (fibromas, angiomas, leiomyomas, myomas). The carcinomas may be primary in the tubal mucosa or may occur as a metastasis from a primary carcinoma of the ovary, the uterus, or the gastrointestinal tract. The primary carcinomas have the appearance of a distended tube filled with a protuberant growth of neoplastic tissue with multiple papillary projections. The lesions spread by peritoneal implantation as well as by lymphatic and hematogenous metastases. Diagnosis is usually late, and the prognosis is poor.
Turner syndrome (ovarian agenesis, ovarian dwarfism) is due to a major defect in ovarian development. This syndrome results from complete or partial monosomy of the X chromosome with a 45, XO karyotype in most subjects and various deletions in 1 of the 2 X chromosomes in the remaining subjects. Turner syndrome is characterized by short stature, infantile genitalia, primary amenorrhea, failure of development of secondary sex features, and multiple congenital abnormalities (web neck, shieldlike chest, cubitus valgus, coarctation of the aorta). The ovaries are rudimentary and consist of stroma without germ cells or follicles. Less common developmental anomalies include absence of one ovary and tube, ectopic ovary, and accessory ovaries.
Most small and simple cysts in the ovary represent variations of the normal ovulatory cycle. These cysts are derived from ovarian follicles and corpora lutea and are nonneoplastic but may be mimicked by a small neoplastic ovarian cyst. A corpus luteum of pregnancy can become large and cystic and can be suspected of being an EP. Follicle cysts are distended atretic follicles up to 1 cm in diameter. A polycystic ovary contains multiple cystic follicles. Hydrops folliculi refers to an unusually large follicle cyst that is several centimeters in diameter. A follicle cyst hematoma may result from bleeding into the cyst from the vascularized perifollicular thecal zone. A similar mechanism can produce a corpus luteum hematoma. Resorption of the hematoma produces a corpus luteal cyst, which can convert to a corpus albicans cyst lined by dense collagen. A ruptured Graafian follicle or hemorrhagic corpus luteum gives rise to intraabdominal bleeding.
Pelvic endometriosis results from the nonneoplastic growth of aberrant or ectopic endometrium in response to stimulation by estrogen and progesterone. Pelvic lesions result from periodic proliferation of the aberrant tissue, infiltration of local structures, recurrent bleeding, and fibrosis. Symptoms include sterility, dysmenorrhea, sacral and pelvic pain, and abnormal uterine bleeding. Endometriosis of the ovary occurs as small surface implants, small hemorrhagic cysts within the cortex, or large dark-brown cysts filled with old blood with the appearance of thick chocolate (chocolate cysts). The distribution of the cysts and associated fibrous adhesions render them prone to rupture on manipulation with escape of large quantities of thick, chocolate-colored fluid. The cyst wall may exhibit a lining of typical endometrial stroma and glands, but older lesions may show little evidence of endometrial tissue.
Cystadenomas comprise a group of common benign ovarian neoplasms. Serous cysts include a connective tissue and an epithelial component, with variable predominance of these components. The simple serous cyst (serous cystoma) is a unilocular cyst lined by a simple cuboidal layer of serous epithelium. It is usually unilateral, smooth surfaced, and grayish-white and contains clear, serous, watery fluid. The multilocular serous cystadenoma is a unilocular or multilocular serous cyst of the ovary that contains glandlike, epithelial foci in its wall. These lesions are frequently bilateral and are composed of multiple interconnected cysts of various sizes. Histologically, the cyst walls are lined by a single layer of cuboidal or low columnar ciliated epithelium.

**Figure 8-38  SEROUS CYSTOMA AND SEROUS CYSTADENOMA**
Papillary serous cystadenomas are serous cysts that are typically bilateral and multilocular and exhibit intracystic or extracystic papillary and adenomatous growths, which indicates an increased proliferative tendency. The lesions have the potential to spread slowly in the peritoneal cavity and recur after surgery, thus fitting into the borderline malignant category. The papillary excrescences are the most striking feature of these tumors.

Histologically, the cyst wall is composed of fibrous tissue with an inner lining of a single cell layer of serous epithelium. Focal calcifications or psammoma bodies may be present. The cysts and papillae may show focal areas of piling of epithelium or cytologic atypia. They usually occur during the reproductive years (age 20-50 years).
Mucinous cystadenomas are cystic ovarian neoplasms lined with mucous-producing epithelium. Typically, they are unilateral and smooth surfaced, are composed of multiple distended lobules, and occur during the reproductive years. They vary in size, some becoming so large as to distend the abdomen. Microscopically, benign, variants of mucinous cystadenomas show the connective tissue capsule and dividing septa lined by a single layer of tall columnar cells with clear cytoplasm and uniform basal nuclei. More aggressive borderline malignant and malignant lesions exhibit localized, firm infiltrations of the cyst wall with papillary projections on the interior of the cyst. Pseudomyxoma peritonei arises from a mucinous ovarian lesion or, more commonly, from a primary mucinous tumor of the appendix, with subsequent implantation and growth of pseudomucinous epithelium in the peritoneal cavity and progressive enlargement of the abdomen leading to increased abdominal pressure and impairment of bladder and bowel function.
The dermoid cyst (benign teratoma of the ovary) is a common benign cystic neoplasm of germ cell origin with well-differentiated components of the 3 germ layers. The tumors, which are sometimes bilateral and can vary in size, are round or oval, are heavy, have a smooth, gray-white or yellow surface, and contain variable combinations of fatty sebaceous material and strands of hair. Histologically, the wall is lined by squamous epithelium; contents include well-differentiated tissues of ectodermal, mesodermal, and endodermal origin. Malignant transformation, most often as SCC, occurs in approximately 2% of cases. Solid (embryonal) teratomas are rare malignant neoplasms occurring typically in younger women. On cut section, malignant teratomas have a variegated appearance with foci of necrosis, hemorrhage, and cystic degeneration. Microscopically, well-differentiated areas coexist with poorly differentiated elements showing embryonal, undifferentiated, sarcomatous, or carcinomatous features.
The **granulosa cell tumor** is a usually benign, but occasionally malignant feminizing neoplasm composed of cells with features and organizational pattern of granulosa cells of the **Graafian follicle**, including small glandlike structures mimicking immature follicles (**Call-Exner bodies**). Grossly, the tumors are usually unilateral, soft, and yellow, with focal cystic areas. These hormone-producing tumors occur with approximately equal frequency in young adult and postmenopausal women and may occasionally occur in prepubertal girls, leading to precocious pseudopuberty. **Theca cell tumors** are benign, unilateral, solid, estrogen-producing neoplasms composed of cells resembling the theca interna. They occur in menopausal and postmenopausal women and rarely in young adults. Histologically, the tumor is composed of interlacing bands of elongated, stromal cells with oval nuclei and vacuolated fat-containing cytoplasm (theca cell features) separated by collagenous bands.
The **arrhenoblastoma** (Sertoli–Leydig cell tumors) is composed of cells that show features of testicular differentiation in the maturing gonad. Most of these tumors occur in young to middle-aged women; 25% are malignant. The tumors are unilateral, solid, smooth, lobulated, encapsulated, gray-yellow neoplasms with numerous foci of necrosis, hemorrhage, and cystic change in cut section. Several patterns occur, including cuboidal or columnar cells forming tubules or glands (Sertoli cells), large polygonal interstitial or Leydig cells, and, in some, more primitive areas with poorly organized spindle-shaped or epithelioid cells.

**Adrenal rest tumors** may arise from aberrant adrenal rests in the ovary. These rare tumors are composed of large polygonal cells with central nuclei and clean cytoplasm. Leydig cell tumors are rare neoplasms derived from the hilus cells of the ovary. Virilism associated with these neoplasms includes hypertrophied clitoris, hirsutism, acne, and increased muscularization.

**Figure 8-43  Masculinizing Neoplasms: Arrhenoblastoma and Adrenal Rest Tumor**

- **Arrhenoblastoma**: Tumor composed of glandlike structures lined by crowded columnar cells (Sertoli cell pattern).
- **Adrenal rest tumor**: Tumor composed of large cells with clear cytoplasm.
- **Hypertrophied clitoris**: Sparse, inactive glands.
- **Masculinization**: Inactive endometrium with amenorrhea.
Stein-Leventhal syndrome, characterized by amenorrhea, sterility, hirsutism, and obesity, is often associated with polycystic ovaries. Grossly, the ovaries are enlarged symmetrically and contain many cystic follicles, 2 to 15 mm in diameter, just below the outer, thickened tunica albuginea. Microscopically, there is evidence of hyperthecosis. The theca interna layer surrounding many of the atretic follicles shows prominent proliferation and luteinization, whereas the ovarian parenchyma is hyperplastic with increased cellularity. Stein-Leventhal syndrome is an endocrinologic disturbance involving increased production of luteinizing hormone of the anterior pituitary and ovary (increased luteinizing hormone stimulating the theca cells to produce androgens). Bilateral wedge resection of one half to two thirds of each ovary can lead to renewed menses and fertility in some cases.
The 

dysgerminoma

is a unilateral, malignant epithelial tumor analogous to the seminoma of the testis. It may be associated with gonadal maldevelopment or pseudohermaphroditism. Most occur in young adults. The dysgerminoma is a solid oval tumor of variable size composed of cords or nests of large, round or polygonal cells with centrally placed, round, uniform nuclei with prominent nucleoli, mitoses, and often an interspersed infiltrate of lymphocytes. Dysgerminomas are malignant but exhibit variability in aggressive growth and spread beyond the capsule.

These tumors are radio-sensitive. The 

Brenner tumor

is an uncommon, benign, unilateral, fibroepithelial neoplasm composed of masses of polyhedral cells surrounded by connective tissue that resemble transitional cells of the urinary bladder. Microscopically, the masses of epithelial cells resemble a pavement epithelium. Multiple or solitary small cysts may be present. Most Brenner tumors occur after the age of 40 years or postmenopausally.
Ovarian fibromas, benign tumors of ovarian stroma, may be small surface pedunculated lesions or large pelvic masses. They are usually unilateral, although a single ovary may show multiple tumors. Most fibromas are found in postmenopausal women, but they can occur at any age. The ovarian fibroma is the most common tumor associated with Meigs syndrome of hydroperitoneum (ascites) and hydrothorax. Fibromas are well-encapsulated, solid, oval, grayish-white tumors composed of dense, white, interweaving bundles of connective tissue and, in the larger neoplasms, focal areas of cystic degeneration and hemorrhage. Microscopically, the tumor is composed of interlacing whorls of spindle-shaped cells with uniform, small nuclei. Removal of the pelvic tumor typically results in resorption of the hydrothorax and hydroperitoneum. Fibrosarcoma of the ovary is a rare neoplasm composed predominantly of spindle cells with irregular hyperchromatic nuclei. Extension may be by direct invasion or via the vasculature.

**Figure 8-46  Stromatogenous Neoplasms: Fibroma, Meigs Syndrome, and Sarcoma**

- **Fibroma.** Cystic degeneration and hemorrhage, sectioned open
- **Meigs syndrome.** The association of hydrothorax and ascites with fibroma of the ovary
- **Fibroma.** Spindle cell sarcoma
Ovarian carcinomas are either primary or secondary (metastatic) carcinomas. The primary carcinomas may be solid or cystic. **Ovarian carcinoma** is a major category of malignancy of the female genital tract, ranking next to carcinoma of the cervix and uterine fundus. Most ovarian carcinoma occurs between 40 and 60 years of age. Most ovarian carcinomas are papillary SACs. **Mucinous cystadenocarcinoma** is less common, and mucinous cysts are less likely to be malignant than are papillary lesions. Most ovarian carcinomas are relatively large at the time of diagnosis. Histologic features of malignancy include crowding and piling up of cells with marked nuclear atypia. Bilateral ovarian involvement occurs in one third to one half of cases, depending on the type of malignancy. SACs are more likely to be bilateral than are pseudomucinous cystadenocarcinomas. SCCs may develop in a dermoid cyst.
Primary solid ovarian carcinomas, also designated as the undifferentiated or unclassified group, are classified as solid adenocarcinoma, medullary carcinoma, scirrhouos carcinoma, alveolar carcinoma, plexiform carcinoma, and adenocarcinoma with squamous cell metaplasia (adenocanthoma) on the basis of the pattern and arrangement of the epithelial and connective tissue elements. Carcinoma of the ovary spreads by various routes, including local infiltration, to involve adnexal structures, metastatic spread via retroperitoneal channels to the opposite ovary, lymphatic extension to other pelvic organs and lymph nodes, implantation on the peritoneal lining of the abdominal cavity, and spread to distant organs by either lymphatic or hematogenous routes. Prognosis is strongly influenced by the type of tumor and the extent of involvement at the time of diagnosis.
Diseases of the Ovary

The ovary is a common site of metastatic invasion by carcinoma. The primary sites include the breast, lungs, stomach, colon, pancreas, liver, uterus, tubes, opposite ovary, and urinary bladder. Metastatic ovarian carcinoma occurs most frequently from the fourth to the sixth decades of life. Ascites is a common finding. There is bilateral involvement in up to 75% of cases, and lesions can vary in size from minute to large. The cut surface may be solid and uniform or cystic and mottled, depending on the extent of hemorrhage and necrosis. Other abdominal foci of tumor may be present. The histologic features generally mirror the primary lesion. *Krukenberg tumor* is a secondary ovarian carcinoma containing characteristic signet ring cells in which the nucleus is flattened to one side by secretion, distending the cell and creating clean cytoplasm. Primary carcinoma of the stomach metastatic to the ovary is a classic cause of Krukenberg tumor. The prognosis in secondary ovarian carcinoma is generally grave.
In **placenta previa**, the placenta is implanted in the lower uterine segment so that it partially or totally obstructs the cervical canal. In **abruptio placenta**, the normally implanted placenta separates prematurely from its uterine attachment in the late second or third trimester of pregnancy. Placenta previa and abruptio placenta are major causes of uterine bleeding during the last trimester of pregnancy. The bleeding from placental detachment may be internal or external, depending on whether the blood remains
concealed between the placenta and the uterine wall because of incomplete detachment of the placenta or obstruction of the cervical canal by the fetus. Most cases of abruptio placenta are associated with toxemia of pregnancy or with chronic hypertension complicating the pregnancy, with associated placental ischemia as often is manifest by a large number of placental infarcts. Abruptio placenta is treated by rapid emptying of the uterus and blood transfusions.
Uteroplacental apoplexy (Couvelaire uterus) is usually associated with severe forms of abruptio placentae. The process is characterized by extensive hemorrhage into the myometrium, the tubes, and the ovaries compounded by defibrination and impaired clotting of the blood. Lifesaving hysterectomy is often necessary to stop the continuous bleeding because the uterus remains atonic after being emptied of the fetus. Rupture of the uterus, which may be traumatic or spontaneous, occurs before (rare) or during labor and often results in death of both the mother and the fetus. Maternal pulmonary embolism by cellular debris containing amniotic fluid is the apparent cause of some cases of sudden obstetric death, with the typical setting being in multiparas with excessive uterine contractions. The clinical course is one of dyspnea, cyanosis, shock, and death within a few hours.
Ectopic pregnancy is the implantation of a fertilized ovum outside the uterine cavity, which occurs in approximately 1 of 150 to 200 pregnancies. Previous pelvic inflammatory disease with chronic salpingitis is a significant predisposing factor. The site of implantation determines the type: tubal (by far the most common), ovarian, abdominal or peritoneal, and cervical. The subtypes of tubal ectopics—interstitial, isthmic, ampullar, and infundibular—refer to the portion of the tube in which implantation takes place. Ampullar implantation is most common, although the interstitial form has more serious clinical consequences. Early development of an EP is the same as that of a uterine pregnancy, but tubal pregnancy usually ends in abortion through the tube into the peritoneal cavity, or the trophoblast erodes the tubal wall, leading to tubal rupture. A typical presentation is amenorrhea of several weeks followed by bleeding and abdominal pain. It necessitates immediate surgical attention.
Abortion is the interruption of pregnancy in the first trimester before fetal viability. After viability, early end of pregnancy is called premature labor. Maternal or fetal factors, or both, may contribute to an abortion. Maternal factors include systemic infections and toxic agents in the maternal organism. Fetal factors include fetal malformations and congenital abnormalities. Rh incompatibility is an example of combined maternal and fetal factors. Signs and symptoms of abortion are vaginal bleeding followed by expulsive uterine contractions and cervical dilation. Abortion is complete when the entire fetus, placenta, and membranes are expelled and incomplete when the fetus is expelled but all or part of the placenta is retained in the uterus. In missed abortion, the fetus dies, but the placenta is not detached, and the fetus undergoes mummification. In the various types of inevitable abortion, the uterus must be completely evacuated to prevent recurrent hemorrhage and infection.
In various high-risk populations, syphilis remains a common cause of late fetal death. The fetus becomes infected through the placenta from the mother. At delivery, the placenta is enlarged, excessively lobulated, pale, and edematous. The cord and membranes are discolored and pale. Most syphilitic fetuses are born dead, but if the fetus is born alive, congenital syphilis soon becomes manifest. A syphilitic fetus is usually shorter than expected and has maceration of the skin. At autopsy, inflammatory and degenerative changes are usually present in the lungs, liver, spleen, kidneys, and other organs. There is a characteristic osteochondritis with signs of disordered cartilage formation and endochondral ossification. Silver stains can reveal spirochetes of *T. pallidum* in fetal tissues and the placenta.
Puerperal infection is infection with various microorganisms of the birth canal in the postpartum period. Most cases of puerperal infection are caused by anaerobic and aerobic nonhemolytic varieties of streptococci. However, hemolytic streptococcus, introduced from the outside, is the most common cause of the fulminating and severe forms of puerperal infection. A similar pathophysiology is operative in nonpregnant women with toxic shock syndrome. Less common causes of puerperal infection are staphylococci and anaerobic and coliform bacteria. Blood loss and birth trauma are the most important predisposing factors for puerperal infection. Avoidable factors include faulty aseptic technique during labor and delivery. Endometritis may develop and give rise to puerperal sepsis. Pelvic thrombophlebitis as well as thrombophlebitis of the leg veins also may develop. Distant spread of infection from septic emboli may occur. Rapid diagnosis and antibiotic therapy can prevent a fatal outcome.

**Figure 8-55** Puerperal Infection

Dissemination of septic endometritis following puerperal infection
1. Peritonitis
2. Parametritis (via lymphatics)
3. Pelvic thrombophlebitis
4. Femoral thrombophlebitis
5. Pulmonary infarct or abscess (septic embolus)
Hydatidiform mole and choriocarcinoma arise from trophoblastic tissues and cause rapid uterine enlargement, vaginal bleeding, and significantly increased urine and serum levels of human chorionic gonadotropic (HCG) hormone. Beginning as a pregnancy with a defective ovum, a hydatidiform mole is composed of abnormal chorionic villi that appear as grapelike clusters of vesicles and consist of branching structures covered with 2 or more layers of trophoblastic cells but lacking fetal blood vessels. Partial moles have embryo present and contain mixtures of normal and abnormal villi. Complete moles are composed entirely of abnormal villi with no identifable embryo. A benign or malignant character to the mole is indicated primarily by the degree of cellular atypia of the villi. Choriocarcinoma (chorioepithelioma) is a rare but very malignant tumor composed of both syncytial and cytotrophoblastic cells arranged in a disordered pattern without forming chorionic villi. The neoplasm invades the uterine wall aggressively and metastasizes early, particularly to the lungs. Treatment includes evacuation of the contents of the uterus, surgery, and chemotherapy. Chorioangioma is a rare benign lesion.
Erythroblastosis fetalis results from the progressive destruction of fetal erythrocytes by Rh factor antibodies produced by an Rh-negative mother (approximately 15%) and passed through the placental circulation to the fetus. Predisposing factors include transfusion or intramuscular injection of Rh-positive blood or carrying an Rh-positive fetus in utero. The major features of the disease are hemolytic anemia, icterus, and hydrops. Hydrops, the most severe form, results in an enlarged, boggy placenta and a macerated, stillborn infant. This must be distinguished from neonatal syphilis. The icteric type occurs in live infants with severe hemolytic anemia. In these infants, fetal blood contains many nucleated red blood cells, and the organs have prominent foci of extramedullary erythropoiesis. In less severe cases, anemia is milder, but the destruction of erythrocytes still leads to icterus and increased indirect bilirubin.

Injection of Rh immune globulin to induce immunologic tolerance in the mother may prevent erythroblastosis fetalis.

Erythroblastosis fetalis (hemolytic disease of the newborn) results from the progressive destruction of fetal erythrocytes by Rh factor antibodies produced by an Rh-negative mother (approximately 15%) and passed through the placental circulation to the fetus. Predisposing factors include transfusion or intramuscular injection of Rh-positive blood or carrying an Rh-positive fetus in utero. The major features of the disease are hemolytic anemia, icterus, and hydrops. Hydrops, the most severe form, results in an enlarged, boggy placenta and a macerated, stillborn infant. This must be distinguished from neonatal syphilis. The icteric type occurs in live infants with severe hemolytic anemia. In these infants, fetal blood contains many nucleated red blood cells, and the organs have prominent foci of extramedullary erythropoiesis. In less severe cases, anemia is milder, but the destruction of erythrocytes still leads to icterus and increased indirect bilirubin. Injection of Rh immune globulin to induce immunologic tolerance in the mother may prevent erythroblastosis fetalis.
Toxemia of pregnancy is a generic term for a syndrome of pregnancy characterized by hypertension, proteinuria, and edema with the potential for convulsions or coma. Toxemia includes preeclampsia and eclampsia, and is distinct from essential hypertension associated with pregnancy. Acute toxemia develops during the third trimester of pregnancy—presenting as progressive weight gain, blood pressure higher than 140/90 mm Hg, and proteinuria—and disappears promptly after delivery. Eclampsia is characterized by convulsions and coma, and these manifestations may develop independent of the magnitude of hypertension. Regular, prompt care is the key to prevention.
The pathologic effects of preeclampsia and eclampsia in various organs are qualitatively similar but vary in severity in relation to the clinical course. The liver and other organs can exhibit swollen and multiple foci of hemorrhage and necrosis. The most characteristic renal lesion consists of narrowing of the lumens of glomerular capillaries caused by thickening of the glomerular membranes due to endothelial cell swelling. Obstruction of blood flow through the glomerular tufts can lead to distal tubular necrosis. Bilateral cortical necrosis, a less common but severe lesion, is caused by severe vasoconstriction and necrosis of the intralobular arteries. The characteristic changes in the brain include edema, petechial hemorrhages, and, in severe cases, larger foci of hemorrhagic necrosis. All of this organ pathology is driven by vasoconstriction often complicated by microthrombosis due to disseminated intravascular coagulation (DIC).
There is a close correlation between the occurrence of acute toxemia and conditions that predispose to a decrease in the maternal circulation to the placenta, the decidua, or both. Severe reduction of maternal blood flow causes true infarction of one or more of the placental cotyledons. True infarcts are found on the maternal aspect of the placenta, in contrast to other incidental placental lesions. Microscopically, the characteristic feature is necrotic chorionic villi. Acutely, the lesions are hemorrhagic infarcts that become pale as they age and heal without organization (i.e., without formation of granulation tissue and fibrosis). Placental ischemia is considered the major event in the pathogenesis of acute toxemia because it leads to increased production of angiotensin and other vasoconstrictors and decreased production of nitric oxide and other vasodilators. In turn, the placental ischemia may be caused by abnormal formation and implantation of the placenta (placentation).
Painful engorgement of the breast usually occurs within the first few days postpartum, before the onset of lactation, or later when active lactation is interrupted. Because of vascular stasis, the breasts become engorged, firm, warm, and painful. Acute mastitis occurs during lactation after entry of infectious agents by way of a cracked or traumatized nipple, most commonly in primiparous women. The clinical manifestations are fever, leukocytosis, tenderness, and induration. There are 3 subtypes of mastitis: subareolar, glandular, and interstitial, the latter giving rise to a retromammary abscess. Rare infections of the breast, usually in nonpregnant women, are tuberculosis and syphilis with chancre formation.
Chronic cystic disease or fibrocystic disease of the breast is a mammary disease complex with underlying endocrine disturbance, which comprises 3 principal types of abnormalities: cyst formation, often with apocrine metaplasia, fibrosis, and adenosis. True mastodynia, or intrinsic mammary pain, can be the first manifestation. Palpation typically reveals a swollen granular zone of increased density, which is most frequently located in the upper lateral quadrant, often bilaterally. On biopsy, the painful mammary tissue grossly is more dense and fibrous than normal, and histologically, the lobules are stunted or irregularly shaped, with small cystic dilatations, and they are surrounded by immature, proliferating connective tissue. The defective lobule formation relates to some disturbance of integrated action of the ovarian hormones on the mammary gland, increased estrogen production, inadequate progesterone secretion, or a combination of these.
Some cases of fibrocystic disease are dominated by cystic changes. In some subjects, a single cyst of 1 to several centimeters in diameter develops. In other cases, the cysts are multiple, and often but not uniformly, both breasts are affected. The larger cysts have a characteristic blue dome, which bulges into the subcutaneous fat and contains cloudy straw-colored fluid, and a thin, fibrous wall, which may have an epithelial lining of duct cells. The cyst wall is embedded in dense, fibrous stroma. Multiple smaller cysts have similar features.

**Figure 8-63  FIBROCYSTIC DISEASE: CYSTIC CHANGES**

Solitary “blue dome” cyst

Nipple

Cysts

Cross section of breast showing multiple cysts
Pathology of the Mammary Gland  DISEASES OF THE FEMALE REPRODUCTIVE SYSTEM

Adenosis is characterized by the development, in one or both breasts, of multiple nodules, varying from 1 mm to 1 cm in size and usually distributed about the periphery of the breast, creating a nodular breast with a saucerlike edge. The affected mammary tissue contains dense fibrous tissue, numerous cysts, and foci of epithelial proliferation. Lobule formation is considerably distorted. Some of the terminal tubules form solid plugs of basal cells, which, on cross section, appear as duct adenomas. Other tubules have greatly enlarged lobular structures, which are penetrated by dense strands of fibrous tissue, giving the appearance of an orderly proliferation of small ductules and acini, known as sclerosing adenosis. The incidence of cancer in patients with fibrocystic disease and accompanying ductal proliferative changes is approximately twice as high as is the incidence in the general female population.
The fibroadenoma, the most common benign mammary tumor of the female breast, usually occurs in young adult women. The typical presentation is a firm, well circumscribed, nodular, freely movable, gradually enlarging mass. On excision, the tumor appears as a lobular mass and consists of well-developed ducts surrounded by marked overgrowth of periductal connective tissue. The growth of fibroadenoma is rapid in early adolescence, in pregnancy, or toward menopause, when estrogenic secretion is increased. Benign intracystic papillomas are fleshy epithelial growths occurring within a mammary duct or a dilated acinus, usually at or near menopause, in the central zone of the breast. They cause either a sanguinous discharge from the nipple or a lump associated with moderate tenderness. Intracystic papillomas are encapsulated tumors that contain branching epithelial projections and rest on a fibrous stalk. Multiple papillomas may occur in one or both breasts.
Giant mammary myxoma, also known as phyllodes tumor or cystosarcoma phyllodes, is a fibroadenoma that typically occurs near menopause and grows to large size. The tumors are heavy, massive, lobulated, fleshy growths with cystic areas; they remain encapsulated and moveable. Microscopically, the lesions are composed of myxomatous and fibrous connective tissue lined by epithelial cells and containing abundant stromal cells. Most of these tumors behave in a benign fashion. Mammary sarcoma is rare among the mammary tumors. Most of these sarcomas are fibrocellular lesions arising in the stroma of the breast or from the stroma of preexisting fibroadenomas. The lesions are characterized by rapid growth, large size, firm consistency, and, commonly, ulceration of the skin, with fungation of the mass.
Approximately 15% to 30% of mammary carcinomas are in situ, and 70% to 85% are invasive. Approximately 80% of invasive lesions are infiltrating ductal carcinoma (scirrhous carcinoma or carcinoma simplex). They present as a palpable mass and may be associated with nipple retraction. Grossly, these are dense, yellowish-white, stellate, irregular masses with a gritty consistency. Microscopically, the tumor cells have a relatively uniform size; exhibit prominent, hyperchromatic nuclei; grow in small nests or cords; and are accompanied by growth of fibrous tissue producing the scirrhous feature of the lesions. Invasive lobular carcinoma (5-10% of breast carcinomas) tends to be multicentric in the same breast, to involve both breasts at a high frequency (approximately 20%), and to be hard to detect because of a diffusely invasive pattern. Prognosis is influenced by growth pattern of the tumor; degree of organization and cellular differentiation; expression of various gene products, including estrogen receptors and BRCA1 and BRCA2; and the presence of regional axillary lymph node and distant metastases.
Inflammatory or acute fulminant carcinoma usually presents as a rapidly widening area of inflamed skin. The dermal inflammation usually correlates with retrograde spread of the cancer cells through the lymphatics of the skin. The skin is reddened, edematous, and rough, producing the characteristic orange peel effect. The carcinomatous spread is accompanied by a localized and systemic inflammatory process with low-grade fever, increased leukocyte count, and enlarged axillary lymph nodes. The most frequent site of local recurrence of breast cancer is the scar in the chest wall, followed by the axilla and the supraclavicular regions.
Approximately one fourth of mammary carcinomas have features of well-differentiated adenocarcinomas. These lesions include papillary adenocarcinomas, carcinomas with gelatinous, mucoid degeneration, and comedocarcinoma, a type of intraductal carcinoma that forms plugs and circumscribed rings of carcinoma cells in preexisting ducts. These lesions tend to bulge out from the breast rather than retract inwardly as with the infiltrating carcinomas. Skin and axillary node involvement occur much later in the course than with infiltrating scirrhous carcinoma. The tumors typically progress slowly and often reach large size. The majority are detected and removed by mastectomy before metastasis occurs. The lesions may have central foci of necrosis or hemorrhage.
Paget disease of the nipple is produced by carcinomatous invasion of the nipple or areola and the mouths of the larger ducts by large malignant cells with hyperchromatic or vesicular nuclei and pale staining cytoplasm. Usually, involvement of the nipple precedes the detection of a small primary tumor in the breast. The disease is occasionally bilateral. The involved nipple has a red granular or an exuding crusted appearance and eventually undergoes ulceration. Eventually, a hard mass, which is often associated with enlarged axillary lymph nodes, is palpable.
The usual classification of skin diseases differs slightly from the terminology used in general pathology: both the gross appearance of lesions and, at least in part, their pathogenesis determines their class in dermatopathology.

**Acute inflammatory diseases** of the skin, commonly lasting a few days to several weeks, are numerous and pathogenetically inhomogeneous. Like other dermatologic diseases, they are classified according to the location of changes (i.e., in different strata of epidermis, dermis, and subcutis) and according to their composition and quality (edematous, vesicular, neutrophilic, lymphocytic, mast cell, necrotic, hemorrhagic, vascular, etc). Consequently, there are several classification schemes for dermatologic diseases, and the examples in this chapter do not favor any particular one.

Chronic inflammatory diseases of the skin (chronic inflammatory dermatoses), lasting for several months to years, are also pathogenetically inhomogeneous but have in common signs of chronic inflammation with thickening of the skin, keratinic scale formation, and desquamation (shedding). Among them is systemic lupus erythematosus, which because of its complexity cannot be described in detail here but is discussed in texts on clinical immunology and immunopathology.

Vesicular and bullous dermatoses are characterized by epidermal or dermal-epidermal separation (dyshesive diseases) with formation of vesicles or bullae (blisters). They are classified according to the site where blisters form: epidermolytic blisters comprise superficial intradermal or acantholytic separation and suprabasal epidermal separation, junctional blisters are found below the basal cell layer and dermal lamina densa, and dermolytic blisters form in the upper subepithelial dermis. Although the etiology of these diseases remains obscure, most if not all bullous dermatoses seem to have an autoimmune pathogenesis. Different types of autoantibodies (e.g., immunoglobulin [Ig] A) to basement membrane antigen or other structures are demonstrable by immunofluorescence studies.

There exists a large variety of dermatologic infections, the pathologic changes of which are similar to those in other organs and tissues (taking into account the structural peculiarities of the site of infection): neutrophilic inflammation with or without necrosis and hemorrhage (bacteria, fungi), lymphoplasmacytic infiltration (virus or autoimmune component), and granulomatous (intracellular organisms, fungi, parasites, or autoimmune component). Lesions may be localized (site of entry, lymphatic spread) or systemic (hematogenous spread), occur in superficial or deep parts of the skin, and are usually painful. Infection with certain organisms (Candida, zoster and other herpes viruses, papilloma virus, and others) may suggest that the patient has immune deficiency (opportunistic infections).

**Tumors of the skin** may be benign or malignant. Hyperplastic changes of the skin consist primarily of hyperplastic scars (keloids) or hyperplastic glands (sebaceous hyperplasia). Benign tumors of the skin are common, and only exceptional cases of conditions such as actinic keratosis (AK) and some forms of nevi progress to malignancy. Benign tumors are usually derived from surface epithelium (seborrheic keratosis, keratoacanthoma, epithelioma of Malherbe), ductular cells of skin appendages (sebaceous adenoma, syringoma, various cysts), or neuroectodermal cells (nevi). Some benign tumors are associated with viral infections (verruca vulgaris, molluscum contagiosum). Benign mesenchymal tumors in the dermis include hemangiomas, lymphangiomas, and fibromas, including skin tags (dermatofibroma, fibrous histiocytoma), neurofibromas, and lipomas.

The most frequent malignant tumors of the skin are epidermal neoplasms (squamous cell carcinoma [SCC], basal cell carcinoma [BCC]), melanocytic tumors (malignant melanomas [MMs]), and malignant lymphomas. Less frequent are tumors of the skin appendages (sebaceous cell carcinoma, sweat gland carcinoma), other neuroectodermal tumors (malignant neuroectodermal tumor, Merkel cell tumor), and mesenchymal neoplasms (fibrosarcoma, liposarcoma, hemangiosarcoma, lymphangiosarcoma).
Acute Dermatitis

Urticaria (hives), an acute pruritic disease of short duration, is caused by a type I immune reaction (allergic, IgE-mediated) that results in local accumulation and degranulation of mast cells with histamine release and edema (pruritic nodule, edematous swelling and plaques, formation of bullae). Urticaria is caused by substances such as drugs, household stuffs, insect bites, and foods that elicit a type I immune reaction. Chronic urticaria lasting more than 6 weeks suggests persistent exposure to food additives, dyes, drugs, dust, or diseases such as thyroiditis or systemic lupus erythematosus. Acute eczematous dermatitis is characterized by erythema, edema, and vesicle formation. In later stages, oozing lesions may become crusted with scaling plaques. The etiopathogenesis is similar to urticaria (IgE-dependent immune reaction), but microscopy shows distinct eosinophilia and epidermal spongiosis. Fungal infection (dermatophytosis) must be excluded in the differential diagnosis.
Acute Dermatitis

INTEGUMENTARY SYSTEM (SKIN)

Erythema multiforme (EMF), a common hypersensitivity syndrome with associated vasculitis, may coincide with other diseases (e.g., various infections). EMF may occur after the administration of certain drugs (sulfonamides, barbiturates, salicylates) or may accompany malignant diseases (carcinoma, lymphoma) and collagen-vascular disorders (e.g., systemic lupus erythematosus). It represents a hypersensitivity reaction (CD8+ cellular immune reaction), although the immediate causative agent is unknown. Skin eruption is frequently preceded by malaise, fever, and itching or burning sensations. Typical skin changes consist of target lesions with centrifugal growth, dusky red plaques, and macules and papules on the feet and the extensor surfaces of the arms and legs. Individual lesions heal within 1 to 2 weeks and show variable hyperpigmentation and hypopigmentation. Urticarial changes may add to the polymorphism (hence the term multiforme).

**Figure 9-2** Erythema Multiforme

Erythema multiforme frequently affects the palms.

Erythema multiforme exudativum
**FIGURE 9-3 LICHEN PLANUS AND PSORIASIS**

Lichen planus (LP) is a papulosquamous dermatosis. LP affects skin and mucous membranes and consists of small (2-10 mm) polygonal, white to pink, flat pruritic papules with a crisscrossed surface (Wickham striae). Externally, the papules are located on the flexor surfaces of the wrists, arms, and legs; internally, they appear on the tongue and buccal mucosa as nonerosive or erosive plaques. Malignant transformation of oral LP to SCC has been reported. Microscopy shows liquefaction degeneration of basal cells with subepithelial lymphocytic infiltration. Rete pegs are elongated with hyperparakeratosis, tissures, and single cell keratinization (Civatte bodies). LP is a cellular immune reaction against unidentified epithelial antigens. Psoriasis is a chronic inflammatory dermatosis of epidermis and dermis with epidermal hyperplasia and hyperkeratosis and parakeratosis. A deregulated epidermal cell proliferation with disturbed microcirculation has been hypothesized. Skin lesions are large (4-5 cm), demarcated, pink plaques with silver-white keratotic scales showing pinpoint hemorrhages (Auspitz sign). Microscopy shows epidermal thickening with elongated rete pegs (acanthosis), loss of the stratum granulorum and parakeratosis, thinning of suprapapillary plates with hyperemic vessels in dermal papillae, and a mixed cellular subepidermal-epidermal inflammatory infiltrate.
Dermatitis herpetiformis is a pruritic vesicular dermatosis often related to gluten-sensitive enteropathy (celiac disease). Burning and itching lesions on the extensor surfaces, the knees and elbows, the back, and the buttocks show a herpeslike (herpetiform) pattern. Microscopy shows subepidermal cleft formation with dense neutrophilic infiltration and microabscess formation. Dermoeepidermal separation causes blister formation. Immuno-fluorescence shows granular or fibrillar IgA deposits in dermal papillae, and antiendomysial IgA antibodies can be demonstrated. Pemphigus vulgaris, a potentially lethal autoimmune dermatosis, involves skin and mucous membranes, primarily in older patients. It occurs everywhere on the skin except the palms and soles, with blisters that can be laterally dislocated (Nikolsky sign). Healing occurs with hyperpigmentation and scarring. Microscopy shows vesicle formation within the stratum spinosum with acantholytic epithelial cells and few lymphocytes, macrophages, or eosinophils. Serum IgG autoantibodies against desmoglein III (intercellular desmosomal component) can be demonstrated. Death occurs in approximately 10% of cases.
Impetigo, a superficial staphylococcal infection of the skin, occurs after minor injury. Lesions consist of pustular, vesicular, or bullous eruptions with surrounding erythema and development of honey-yellow adherent crusts. The infection usually heals within a few weeks or months. Cellulitis is an acute streptococcal infection of the deeper dermis and subcutaneous tissue that can spread to cover a large area of skin. Lesions consist of poorly demarcated painful erythematous swellings, occasionally complicated by blisters, hemorrhage, or abscess formation. Erysipelas is an acute superficial form of cellulitis with demarcated margins and prominent lymphangitis usually caused by type A streptococci. Patients experience malaise, anorexia, fever, and chills. Blood culture results may be positive in cases with high fever. Lesions clear within 2 to 3 weeks, with frequent recurrences in immunocompromised patients.
Infectious Diseases

INTEGUMENTARY SYSTEM (SKIN)

Along with varicella zoster virus and herpes genitalis, herpes simplex virus is among the more common viruses causing acute vesicular dermatitis. Acute primary infection by respiratory droplets or direct contact causes transient stomatitis and pharyngitis associated with mild lymphadenopathy. Grouped vesicles on an erythematous background appear at various sites, including the mucous membranes. Lesions heal spontaneously without scarring within 2 to 6 weeks. Some areas show only erythematous spots or plaques. Reactivated herpes simplex or varicella zoster in immunodeficient patients can cause severe systemic herpes with generalized necrotic and hemorrhagic lesions and life-threatening internal disease (hemorrhagic enteritis and encephalitis, necrotizing and hemorrhagic hepatitis).
Other viral infections of the skin produce a proliferative epidermal reaction with or without overt inflammatory response. These include verrucae vulgares (common warts) and condylomata acuminata (genital warts) caused by human papillomavirus (HPV) and molluscum contagiosum (Milker nodule) caused by an unclassified poxvirus. There are more than 70 subtypes of HPV, some of which may be oncogenic, including HPV-5, implicated in epidermodysplasia verruciformis; HPV-6, in genital warts; HPV-16, in penile carcinoma; HPV-16 and HPV-18, which in a subset of cases may lead to the development of dysplasia (cervical intraepithelial neoplasia) or carcinoma. The occurrence of proliferative viral infections and their malignant sequelae increase significantly in immunodeficient patients.
Dermal candidiasis is a fungal infection that occurs frequently in patients with metabolic or immunodeficiency disorders (e.g., diabetes mellitus, long-standing steroid or antibiotic treatment, HIV, inherited immune deficiency). Yeasts, such as Candida species, belong to the normal flora of skin and mucous membranes close to the skin (oral cavity, vagina, anus). If the host defense is disturbed, these organisms become pathogenic, causing mucositis and eventual hematogenous spread. Initially, warm, moist areas, such as the axillae, the groin, and other intertriginous regions, show moist erythematous plaques and papules with red denuded areas and glistening, cigarette paper–like scaling. Fungal organisms can be scraped from lesions and shown with histologic stains or by cultivation.
Lyme disease is caused by the spirochete *Borrelia burgdorferi*, which is acquired through tick bites. Ticks invade the skin, causing erythema migrans. Starting at the site of the tick bite, erythematous patches develop and spread in an irregular pattern while the center will return to normal. Lyme disease progresses through several stages, including an acute influenzalike illness, cardiac and neurologic symptoms, and, finally, arthritis and persistent neuropsychiatric disorders.

**Figure 9-9  Lyme Disease**

Lyme disease is caused by the spirochete *Borrelia burgdorferi*, which is acquired through tick bites. Ticks invade the skin, causing erythema migrans. Starting at the site of the tick bite, erythematous patches develop and spread in an irregular pattern while the center will return to normal. Lyme disease progresses through several stages, including an acute influenzalike illness, cardiac and neurologic symptoms, and, finally, arthritis and persistent neuropsychiatric disorders.
Seborrheic keratosis is a common, benign, sharply demarcated, flat or raised, epidermal proliferation with a pink to brownish-black, pigmented, smooth or lobulated surface. A sudden outgrowth of multiple seborrheic keratoses may be associated with malignancies of internal organs (Leser-Trélat sign). Microscopy shows epidermal thickening by multiple layers of small basaloid cells and various degrees of melanin pigmentation and hyperkeratosis. Some pigmented lesions must be distinguished from MM. AK is a benign lesion that may eventually progress to SCC. Excessive keratinization frequently produces cutaneous horns. AK develops at sites of chronic sun exposure and shows progressive epithelial dysplasia. Some may be pigmented (spreading pigmented actinic keratosis) and are difficult to distinguish from lentigo maligna or superficial spreading MM.

**Figure 9-10 Keratoses**

Seborrheic keratosis is a common, benign, sharply demarcated, flat or raised, epidermal proliferation with a pink to brownish-black, pigmented, smooth or lobulated surface. A sudden outgrowth of multiple seborrheic keratoses may be associated with malignancies of internal organs (Leser-Trélat sign). Microscopy shows epidermal thickening by multiple layers of small basaloid cells and various degrees of melanin pigmentation and hyperkeratosis. Some pigmented lesions must be distinguished from MM. AK is a benign lesion that may eventually progress to SCC. Excessive keratinization frequently produces cutaneous horns. AK develops at sites of chronic sun exposure and shows progressive epithelial dysplasia. Some may be pigmented (spreading pigmented actinic keratosis) and are difficult to distinguish from lentigo maligna or superficial spreading MM.
Nevi (common moles) are benign skin tumors of melanocytic origin. Dysplastic nevi describe nevi with cellular atypia without invasion. Nevi erupting de novo in areas of the body not exposed to the sun and occurring after the age of 30 years should always be evaluated for malignancy. Microscopy shows bands or nests of melanocytes in the epidermis (epidermal) or epidermal junction (junctional nevus) or both (compound nevi). Dermal nevi do not show epidermal involvement. Deep dermal nevi are referred to as blue nevi. A gross change to asymmetry and partial poor demarcation with spread and discoloration may indicate malignant transformation.
**Malignant Tumors**  

**INTEGUMENTARY SYSTEM (SKIN)**

Superficial basal cell carcinoma. Slightly scaly pink to red patch. These tumors are slow growing and occur on chronically sun-exposed skin.

Nodular basal cell carcinoma. Pearly plaque with telangiectatic central ulceration, and rolled border.

**Figure 9-12 Basal Cell Carcinoma**

Basal cell carcinoma is a primary epidermal malignancy that does not metastasize but shows progressive invasion without sparing even skull bones (*ulcus rodens*). BCC is frequent in the skin of the face, scalp, ears, and neck. In addition, there exists a rare familial basal cell nevus syndrome with multiple tumors on the back and other non–sun-exposed sites. BCC appears as flat, yellowish-pink circumscribed nodules ("pearly" appearance) with prominent telangiectasia and occasional white keratotic scaling. Microscopy shows the replacement of regular squamous epithelium with atypical basal cells with peripheral palisading and signs of invasion. After surgical removal, 92% of patients with primary tumors and 60% with recurrences achieve 5-year survival.

**Figure 9-13 Squamous Cell Carcinoma**

Squamous cell carcinoma, derived from keratinocytes, is one of the most common malignant tumors in the sun-exposed skin (head, neck, hands) of older people. Chemical carcinogens in tars, oils, arsenicals, and ionizing radiation also may cause SCC. Primary SCC appears as sharply circumscribed, soft or firm red nodules with a "crusted" hyperkeratotic or eroded center spreading within the skin and extending into the dermis along perivascular or perineural spaces (*conduit spread*). Ultimately, tumors metastasize to regional lymph nodes. Microscopy shows variable differentiation and keratinization of squamous cells, with disorganized growth and single cell keratosis, focal or total loss of stratification, and overt invasion. Tumors larger than 2 cm in diameter with deep (0.4 cm) dermal invasion are at risk for metastasis, which occurs in approximately 2% to 6% of tumors in well-vascularized regions and 20% to 30% in other areas (lips, ears, scar tissue). The 5-year mortality in patients with regional metastases is approximately 50%.
INTEGUMENTARY SYSTEM (SKIN)

Malignant Tumors

Malignant lymphomas of the skin include non-Hodgkin lymphomas and Hodgkin lymphomas. The most frequent non-Hodgkin lymphoma of the skin is the T-cell lymphoma identified as mycosis fungoides (MF), preferentially affecting people aged 30 to 50 years. MF is a distinct CD4+ T helper cell lymphoma that may secondarily involve lymph nodes and internal organs. It develops in stages from pre-MF eczematoid or psoriasis-like lesions to a patch stage, a plaque stage, and a tumor stage.

Microscopy shows a bandlike polymorphous dermal infiltrate with small to medium lymphoid cells, including approximately 10% to 40% atypical cells with cerebriform nuclei (MF cells) and pronounced epidermotropism. Atypical cells invade the epidermis to form small aggregates referred to as Pautrier abscesses. The median survival time is 5 years, although if lesions are ulcerated and MF invades lymph nodes, the survival time decreases to 1 year.

Figure 9-14 Malignant Lymphomas

Mycosis fungoides. Eczematous (left), tumorous (middle), and plaquelike (right) infiltrations of skin

Microscopy. Epidermal invasion (left) and atypical giant cells in touch prep (right)
Malignant melanoma, an increasingly common melanocytic neoplasm, comprises approximately 4% of all cancers, with greatest incidence in the sun-exposed skin of red- or fair-haired persons. MM is clinically asymptomatic except for the warning signs: enlargement of a preexisting nevus with irregular border or change in color; itching and pain; or sudden development of pigmented lesions in adults in sites not often exposed to the sun. Late-stage changes are tenderness, bleeding, and ulceration. The types of MM are lentigo maligna melanoma, superficial spreading melanoma, nodular melanoma, and amelanotic melanoma. Microscopy shows poorly formed nests of nevus cells with atypia (enlarged nuclei with prominent nucleoli and mitoses), overt signs of invasion, adjacent chronic inflammatory reaction, and lymphatic spread. Size and vertical spread determine clinical staging and prognosis. After lesion removal, the 5-year survival rate is 80% to 95% in patients with early MM and less than 20% in patients with advanced disease.
Cells of the hematopoietic and lymphatic tissues serve vital functions of host defense, internal homeostasis, and bodily intactness. They all originate from the same stem cell population and in their functional activities interact in various ways (see chapter 1). Disorders in one cell population may thus cause reactions in the other. For this reason, the hematopoietic and lymphatic systems are discussed together. Just as there are a large number of different cell populations with various differentiation stages and functional activities, so are there a multitude of human diseases of the blood and lymphatic systems. The most common and important are discussed in this chapter. The most common leading symptoms of all these diseases are infection, hemorrhage or thrombosis, and anemia.

**RED BLOOD CELL DISORDERS**

Red blood cell (RBC) disorders manifest themselves by either a decrease (anemia) or an increase (erythrocytosis) of RBCs, the latter being reactive or neoplastic in nature. These disorders preferentially affect oxygen transport to tissues; excessive erythrocytosis may be complicated by increased intravascular thrombosis.

**WHITE BLOOD CELL DISORDERS (NONLYMPHATIC)**

White blood cell (WBC) disorders (nonlymphatic) include reactive and neoplastic changes of hematopoietic tissues. Reactive changes may be either hyperplastic (leukocytosis) or hypoplastic/aplastic (leukopenia). They arise in response to exogenous or endogenous stimuli and generally are reversible. Neoplastic changes (myelodysplastic or myeloproliferative syndromes, leukemia) also may occur in response to certain stimuli (e.g., carcinogens, radiation, viral infection) but become autonomous and thus practically irreversible.

**NONNEOPLASTIC LYMPHATIC DISORDERS**

Lymphatic tissues are the body’s main carriers of host defense, both specific and nonspecific. Consequently, nonneoplastic changes in the lymphatic system may result from functional alterations in the immune system as well as from inflammatory, necrotic, or metabolic disorders. Changes in lymph nodes or spleen may be secondary to other disorders, as when the lymph system or bloodstream transports disease products from a primary disease focus (e.g., lymphadenitis in the neck developing secondary to a dental abscess or septic splenitis secondary to bacterial enterocolitis). Investigation of a patient with some form of lymphatic disease therefore must always include a search for a primary cause.

**NEOPLASTIC LYMPHATIC DISORDERS**

Malignant neoplasias of the lymphatic tissues are collectively identified as malignant lymphomas (MLs) or, when malignant cells circulate in the blood, lymphocytic leukemias. There are 2 major groups of MLs: Hodgkin lymphomas (lymphogranulomatosis) and non-Hodgkin lymphomas (NHLs). Hodgkin lymphoma, or Hodgkin disease (HD), is distinguished from NHL by its polymorphic features, including certain inflammatory components such as fibrosis and occasional regression simulating nonneoplastic diseases, which eventually may progress to ML. Although it is a lymphatic malignancy, it is accompanied by a large number of associated nonneoplastic cells, which may influence the course and progression of the disease. NHL, by contrast, begins as malignant clonal proliferations. Transition from HD to NHL and combinations of HD with certain types of NHL have been observed (HD and chronic lymphocytic leukemia [CLL] or follicular center cell lymphoma [FCC]; see Table 10-4).

Along with diagnosing an ML as HD or NHL and determining the subclassification based on histologic, immunologic, and cytogenetic markers, staging of disease extent helps to determine the appropriate treatment and the life expectancy of the patient. Staging of all lymphomas is similar: stage I indicates involvement by lymphoma of 1 lymph node site (e.g., axillary, neck); stage II indicates involvement of 2 lymph node sites on the same side of the diaphragm (e.g., neck and axillary, or left and right inguinal); stage III indicates involvement of lymph nodes on both sides of the diaphragm; and stage IV indicates involvement of lymphatic and extralymphatic sites (e.g., liver, spleen, bone marrow). ML may arise from sites other than the lymph nodes. These are grouped together as extranodal lymphomas and have different staging.
Classification of anemias by immediate cause is shown in Table 10-1. Acute blood loss initially causes blood volume depletion; normochromic anemia becomes overt 24 to 48 hours later, after some volume is replaced. Chronic blood loss (e.g., in intestinal ulcers, polyposis, hypermenorrhea) with depletion of the body’s iron stores causes hypochromic anemia. Erythrocyte destruction causes several anemias. Immunohemolytic anemia arises spontaneously after infection or drug treatment or in erythroblastosis fetalis, the incompatibility of erythrocyte antigens between an Rh-negative mother and her Rh-positive fetus. Microangiopathic hemolytic anemia (MAHA) is caused by mechanical shear forces from fibrin strands in small vessels (hemolytic uremic syndrome, disseminated intravascular coagulation, or multiple hemangiomas) or from artificial devices in the bloodstream (e.g., cardiac valvular prostheses). Peripheral blood smears show fragmented erythrocytes (schistocytes, fragmentocytes).

### Table 10-1 Classification of Anemias

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<thead>
<tr>
<th>Category</th>
<th>RBCs</th>
<th>Characteristics</th>
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<tr>
<td>Blood loss, acute</td>
<td>Initially: normochromic, normocytic Later: hypochromic reticulocytosis</td>
<td>Acute volume depletion RBC reduction secondary to fluid influx Rapid RBC regeneration</td>
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<td>Blood loss, chronic</td>
<td>Hypochromic</td>
<td>Reduced iron stores</td>
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<td>Increased Destruction of Erythrocytes</td>
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<td>Bone marrow: significant erythropoietic hyperplasia Splenomegaly</td>
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<tr>
<td></td>
<td></td>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trauma by intracardiac artificial devices</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple hemangiomas (e.g., hepatic)</td>
</tr>
<tr>
<td>Hereditary</td>
<td>Spherocytosis Elliptocytosis Sickle cells</td>
<td>RBC membrane and cytoskeleton deficiencies</td>
</tr>
<tr>
<td></td>
<td>Hypochromic, microcytic Heinz bodies</td>
<td>Hemoglobinopathies: sickle cell anemia, thalassemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enzyme deficiencies (e.g., of hexose monophosphate shunt)</td>
</tr>
<tr>
<td>Deficient Erythropoiesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Stem cell” defect</td>
<td>Normochromic, Normocytic to mildly macrocytic</td>
<td>Aplastic anemia (with pancytopenia), pure red cell aplasia secondary to myelofibrosis (with thrombocytopenia, splenomegaly)</td>
</tr>
<tr>
<td>Maturation defect</td>
<td>Megaloblastic Anisocytic Hyperchromic Poikilocytic</td>
<td>Pernicious anemia (vitamin B12 deficiency), folate deficiency, anemia, iron deficiency (infection, tumor, chronic blood loss)</td>
</tr>
<tr>
<td>Hb synthesis defect</td>
<td>Sideroblasts</td>
<td>Sideroblastic anemia</td>
</tr>
</tbody>
</table>

*Hb indicates hemoglobin; RBC, red blood; normochromic: normal color (i.e., normal Hb content); normocytic: normal size and shape of RBC; hemolytic: red cell lysis.
Hereditary anemias with structural abnormalities of RBC membranes, cytoskeleton, or hemoglobin (Hb) show spherocytes (hereditary spherocytosis), elliptocytes (hereditary elliptocytosis), sickle cells (sickle cell anemia), or poikilocytosis, anisocytosis, microcytosis, hypochromasia, and reticulocytosis. Vulnerable RBCs are sequestered in the spleen and undergo hemolysis. Many hereditary anemias thus have clinical features of hemolytic anemia: splenomegaly, bone marrow hyperplasia, and tissue siderosis. Thalassemias entail defective synthesis of Hb α or β chains (α, β-thalassemia). A severe form (Cooley anemia) shows a reduction or absence of Hb β chains, predominance of fetal hemoglobin, reactive bone marrow hyperplasia and splenomegaly, enhanced iron resorption, and iron overload syndrome (hemosiderosis, hemochromatosis). In sickle cell anemia, rigid sickle cells undergo hemolysis and cause vasoocclusive disease (capillary stasis and thrombosis) with infarcts in many organs.
Aplastic anemia is characterized by anemia, neutropenia (reduced number in neutrophils), and thrombocytopenia (reduced number in platelets) and may transform to leukemia. The bone marrow is hypocellular. Patients show pallor, petechial hemorrhages, and increased susceptibility to infection.

Pernicious anemia (megaloblastic anemia) arises from a deficiency of vitamin B₁₂, folate, or both secondary to reduced resorption in atrophic gastritis or chronic liver diseases. Myelocytes and megakaryocytes in the bone marrow show nuclear abnormalities (e.g., “horseshoe myelocytes,” hypersegmented megakaryocytes).

Sideroblastic anemia is an X chromosome–linked or acquired deficiency of Hb synthesis. It is a hypochromic microcytic anemia with ferric phosphate or hydroxide deposits in mitochondria of erythroblasts (ring sideroblasts). Resistant cases necessitate multiple transfusions and thus may be complicated by iron overload syndrome with secondary hemochromatosis, cardiac failure, and diabetes mellitus.
A chronic myeloproliferative disease with autonomous clonal proliferation of myelopoietic stem cells in bone marrow and extramedullary sites (liver, spleen), **polycythemia vera** (PCV, primary erythrocytosis) must be distinguished from other chronic myeloproliferative diseases, such as chronic myelogenous leukemia (CML), primary thrombocythemia (PTH), and osteomyelofibrosis (OMF). The bone marrow in PCV shows panhyperplasia with erythropoietic predominance, depletion of bone marrow iron stores, progressive fibrosis, and clusters of macromegakaryocytes. Clinical features include splenomegaly, erythrocytosis of 6 to 10 million cells/µL, Hb level greater than 20 g/dL, and hematocrit greater than 60%. Serum erythropoietin is reduced. Patients show a typical red facies and report headaches and dizziness. Disturbances in blood flow may result in **angina pectoris**, **claudicatio intermittens**, upper intestinal ulcerations, or life-threatening thrombotic complications. Twenty percent to 50% of PCV patients progress to preleukemia and acute leukemia.
Plasmodium protozoa (P vivax, P malariae, P ovale, and P falciparum) are carried by the female Anopheles mosquito, whose bite transfers sporozoites to the blood. After infecting hepatocytes, they transform to merozoites and infect erythrocytes. The 4 species cause diseases of different cycles and severity. P vivax and P ovale cause tertian malaria, P malariae causes quartan malaria, and P falciparum causes falciparum malaria, the most lethal form. Initial symptoms are anorexia, headache, bone pain, and chills. Episodic destruction of RBCs by schizogony and release of merozoites causes spiking fevers and shaking chills every third day in tertian and falciparum malaria and every fourth day in quartan malaria. Pathologic changes are hemolytic anemia, reticuloendothelial (RE) cell hyperplasia (liver, lymph nodes, spleen), obstruction of capillaries by infected RBCs (lungs, liver, kidneys, bone marrow, brain), and deposits of malaria pigment in RE cells and vascular endothelia.

**FIGURE 10-5 MALARIA**
Decrease or loss of peripheral blood neutrophilic WBCs (neutropenia or agranulocytosis) is caused either by enhanced removal or destruction of cells or by their reduced production (i.e., by bone marrow hypoplasia). Increased destruction may result from toxins or infections (e.g., drugs, overwhelming infections), autoimmune reactions (e.g., autoimmune neutropenia or agranulocytosis), or increased removal in enlarged spleens (i.e., hypersplenism with neutrophilic sequestration). In these cases, the bone marrow shows reactive hyperplasia without cytologic abnormalities. In cases of toxic destruction, peripheral blood neutrophils may show toxic granulations in their cytoplasm and hypersegmented or fragmented nuclei. The 3 characteristic clinical consequences of hematopoietic hypoplasia are anemia, hemorrhage (in thrombocytopenia), and infection (in neutropenia or agranulocytosis).

Hematopoietic hyperplasia in the bone marrow and reactive leukocytosis in the blood occur in response to various inflammatory stimuli or to certain cellular and metabolic deficiencies and may progress to simulating neoplasia (leukemoid reaction). Hematopoietic hyperplasia is accompanied by release from the bone marrow of less mature cells (shift to the left) with increased numbers of immature neutrophils, metamyelocytes, or even myelocytes. Different from neoplasia, reactive hyperplasia is usually transient and subsides when the causative stimulus is terminated (Table 10-2).

### Table 10-2  Reactive Hematopoietic Hyperplasia (Nonlymphatic)

<table>
<thead>
<tr>
<th>Involved Cell Compartment</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrophilic, neutrophilic, and megakaryopoiesis</td>
<td>Blood loss or transient myelotoxic agents</td>
</tr>
<tr>
<td>Preferentially neutrophilic</td>
<td>Pyogenic bacterial infections, extensive tissue necroses Less extensive: drugs such as SCF, steroids</td>
</tr>
<tr>
<td>Neutrophilic and histiocytic (frequently with lymphocytes and eventual granuloma formation)</td>
<td>Chronic infections such as by intracellular organisms (e.g., <em>Rickettsia</em>, <em>Yersinia</em>, <em>Salmonella</em>, mycobacteria), mycoses, collagen-vascular diseases (e.g., lupus erythematosus)</td>
</tr>
<tr>
<td>Preferentially histiocytic</td>
<td>Protozoal infection (e.g., malaria) Suggestive viral infection (hemophagocytic syndrome) Phagocytosis defects (infantile septic granulomatosis, Chediak-Higashi syndrome, and others) Metabolic (various storage diseases: morbus Gaucher, morbus Niemann-Pick, and others)</td>
</tr>
<tr>
<td>Eosinophilic</td>
<td>Allergic diseases Parasitic infestations Viral infections with immune complex reaction (e.g., Hodgkin disease) Treatment with IL-2</td>
</tr>
<tr>
<td>Basophilic</td>
<td>Certain allergic diseases (e.g., food allergies) Certain endocrine disorders (e.g., myxedema) Estrogen treatment</td>
</tr>
</tbody>
</table>

SCF indicates colony stimulating factor; IL, interleukin.

**Figure 10-6  Hematopoietic Hypoplasia**

Marrow hypoplasia. Following cancer chemotherapy

Marrow hypoplasia and focal fibrosis (arrow) in autoimmune agranulocytosis
Myelodysplastic syndrome (MDS) is a form of hematopoietic hyperplasia and dysplasia with peripheral cytopenia. MDS originates from hematopoietic stem cell defects with multiple genetic abnormalities and clonal proliferation of hematopoietic cells, T lymphocytes, and clonal or polyclonal B lymphocytes. Several stages are identified: (1) refractory anemia (RA), with less than 5% blasts in the bone marrow; (2) refractory anemia with ringed sideroblasts (RARS), with less than 5% blasts; (3) refractory anemia with excess blasts (RAEB), with 5% to 20% bone marrow blasts; and (4) refractory anemia with excess blasts in transformation (RAEB-T), with 20% to 30% bone marrow blasts and more than 5% blasts in the blood. Anemia and fatigue are early symptoms, followed by neutropenia, infections, thrombocytopenia, and bleeding. Bone marrow aspirates show a megaloblastic erythropoiesis with ring sideroblasts, increased myeloblasts, and hypolobulated megakaryocytes. Transition to acute myelogenous leukemia (AML) occurs in 40% to 50% of advanced cases.
Chronic myeloproliferative diseases, clonal neoplastic disorders with variable myelofibrosis and a terminal blastic phase, include PCV, osteomyelofibrosis, CML, and PTH (primary thrombocytopenia). Osteomyelofibrosis, also referred to asagnogenic myeloid metaplasia, myelosclerosis, and idiopathic myeloid metaplasia, occurs primarily in older populations exposed to viral infections or toxic chemicals. Patients report fatigue, fever and night sweats, weight loss, upper abdominal fullness (splenomegaly, hepatomegaly), and bleeding. Peripheral blood shows “teardrop” poikilocytosis (dacryocytes), normoblasts, immature myeloid cells and megathrombocytes with the bone marrow in early hematopoietic hyperplasia, and predominance of mega-karyocytes and granulocytes. Megakaryocytes include many pleomorphic giant forms with nuclear atypia, naked nuclei, and cytoplasmic fragments. Life expectancy varies according to risk factors (low Hb level and low WBC count) from 93 months to 13 months.
Chronic myelogenous leukemia (CML), another chronic myeloproliferative disease, is defined by myeloid hyperplasia, leukocytosis, basophilia, and splenomegaly. CML is associated with a characteristic chromosomal t(9,22)(q34;q11) translocation, the Philadelphia chromosome, which provides the mutated cells with a proliferative advantage. Clinical features are fatigue, weight loss, sweats, bone pain, anemia, hepatosplenomegaly, and petechial hemorrhages. An initial chronic phase of CML (<10% blasts in bone marrow) is followed by an accelerated phase with final inevitable and fatal blast crisis (>30% blasts in the bone marrow with promyelocytes). Variants of CML include chronic myelomonocytic leukemia (CMoML), which must be distinguished from MDSs. The life expectancy of patients with CML depends on disease progression and type of treatment; 45% to 65% of patients survive 5 years.
Primary thrombocythemia (PTH) is a chronic myeloproliferative disease with progressive megakaryocytic hyperplasia, peripheral thrombocytosis (>600,000/mL), splenomegaly, and hemorrhagic and thrombotic complications. The bone marrow contains partially clustered giant megakaryocytes and promegakaryocytes with mitoses, cytoplasmic fragments, and prominent emperipoleisis (engulfment of a cell by a cell other than phagocytes). Clinical features may include hemorrhagic or thrombotic episodes or both, headache, dizziness, paresthesias, and other neurologic symptoms. Microvascular occlusions cause microinfarcts in several organs and occasional digital gangrene. Large vessel thrombosis occurs most frequently in femoral, renal, coronary, gastrointestinal (GI), and other arteries. In approximately 3% to 10% of patients, blastic transformation with features of myelogenous, myelomonocytic, megakaryocytic, or even lymphoblastic leukemia is reported. The 10-year survival rate for patients with PTH is 65% to 80%.
Acute myelogenous leukemia (AML) is an acute myeloproliferative disease (Table 10-3) representing approximately 90% of all acute leukemias. Approximately 22% of cases develop in patients with MDSs. Patients usually present with malaise and fatigue, frequently after a flulike illness, and may have resistant skin infections, unusual pallor, and bleeding from the gums and the nose. Blood smears show leukopenia of 1000 WBCs/mL or excessive leukocytosis up to 200,000 WBCs/mL with increase in immature cells. The liver and the spleen are enlarged and infiltrated by atypical blasts. Additional symptoms result from metabolic and electrolyte derangements (hypokalemia, hypercalcemia), agranulocytosis (necrotizing enterocolitis), or rapid lysis of leukemic blasts (tumor lysis syndrome: urate nephropathy, hyperphosphatemia, muscle cramps, arrhythmias). Survival rates for all AML subtypes combined are 40% at 15 months and approximately 20% at 50 months.

**TABLE 10-3** CLASSIFICATION IN SUBTYPES OF ACUTE MYELOPROLIFERATIVE DISEASES*

<table>
<thead>
<tr>
<th>FAB Class</th>
<th>Subtype Name</th>
<th>Abbreviation</th>
<th>Proportion of Acute Myeloproliferative Diseases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>Acute myeloblastic leukemia, stem cell (i.e., minimal differentiation)</td>
<td>AML</td>
<td>3-5</td>
</tr>
<tr>
<td>M1</td>
<td>Acute myeloblastic leukemia without maturation</td>
<td>AML</td>
<td>15-20</td>
</tr>
<tr>
<td>M2</td>
<td>Acute myeloblastic leukemia with maturation</td>
<td>AML</td>
<td>25-30</td>
</tr>
<tr>
<td>M3</td>
<td>Acute promyelocytic leukemia</td>
<td>APL</td>
<td>5-20</td>
</tr>
<tr>
<td>M4</td>
<td>Acute myelomonocytic leukemia</td>
<td>AMML</td>
<td>20-30</td>
</tr>
<tr>
<td>M5</td>
<td>Acute monoblastic leukemia</td>
<td>AMOL</td>
<td>2-9</td>
</tr>
<tr>
<td>M6</td>
<td>Acute erythroleukemia</td>
<td>AEL</td>
<td>3-5</td>
</tr>
<tr>
<td>M7</td>
<td>Acute megakaryoblastic leukemia</td>
<td></td>
<td>3-12</td>
</tr>
</tbody>
</table>

*Acute myeloproliferative diseases are clonal neoplastic disorders of hematopoietic stem cells, the classification of which is determined by their preferential cytologic differentiation.

FAB indicates French-American-British classification.

Acute myelogenous leukemia (AML)–M0 and AML-M1 constitute the most immature types of AML and can be difficult to distinguish from acute lymphoblastic leukemia or monoblastic or megakaryoblastic leukemia. They present with more than 30% blasts with hardly any positive myeloperoxidase reaction. AML-M0 cells are usually positive for terminal deoxynucleotidyl transferase (TdT) and CD34 (hematopoietic stem cell marker). AML-M1 types show approximately 10% promyelocytes, suggesting some myelopoietic differentiation. The prognosis is poor. AML-M2 shows signs of maturation beyond promyelocytes. There are more than 30% blasts, and promyelocytes account for 3% to 20% of leukemic cells with occasional maturation of eosinophils and basophils. Maturing cells contain intracytoplasmic red rodlike structures (Auer rods) and stain strongly for chloroacetate esterase and peroxidase enzyme activities. The 50% of patients who have t(8;21) chromosomal translocations have a slightly better prognosis than those without translocations.
Acute myelomonocytic leukemia (AML-M4) is characterized by cells differentiating toward granulocytes and monocytes. Atypical blasts in the bone marrow (>30%) include myeloblasts, monoblasts, and promonocytes, the latter staining positive for (fluoride inhibitable) nonspecific esterase enzyme activity. There may be abnormal eosinophils with the appearance of monoblasts and eosinophil crystals in the cytoplasm, which may carry CD2+ T-cell markers (M4EO subtype). Clinical features include extramedullary disease with multiple organ involvement including the skin and the central nervous system (CNS). Pronounced hepatosplenomegaly and blood cell counts of 30,000 to 100,000 cells/mL are common. Karyotypic changes on chromosome 16 (inversions and translocations) may be found. The response rate to chemotherapy is 65% or greater.

Acute promyelocytic leukemia (AML-M3) is characterized by atypical promyelocytes in the bone marrow and hypergranular cells with multiple Auer rods (Auer bundles). Patients with M3 leukemia are generally younger (median age, 31 years) and have lower WBC counts than patients with more common leukemias. They frequently have coagulation disorders with hemorrhage and disseminated intravascular coagulation (DIC). There are diagnostic chromosomal t(15q+;17q-) translocations, which cause a fusion of the retinoic acid receptor-α region on chromosome 17 to a region in chromosome 15 (PML-RARα) and seem to account for a differentiation blockage of the myeloid lineage. Differentiation can be induced by administration of all-trans retinoic acid, with complete remission of disease in 70% to 85% of patients.

Acute myelomonocytic leukemia (AML-M4) is characterized by cells differentiating toward granulocytes and monocytes. Atypical blasts in the bone marrow (>30%) include myeloblasts, monoblasts, and promonocytes, the latter staining positive for (fluoride inhibitable) nonspecific esterase enzyme activity. There may be abnormal eosinophils with the appearance of monoblasts and eosinophil crystals in the cytoplasm, which may carry CD2+ T-cell markers (M4EO subtype). Clinical features include extramedullary disease with multiple organ involvement including the skin and the central nervous system (CNS). Pronounced hepatosplenomegaly and blood cell counts of 30,000 to 100,000 cells/mL are common. Karyotypic changes on chromosome 16 (inversions and translocations) may be found. The response rate to chemotherapy is 65% or greater.

Acute monocytic leukemia (AML-M5) is characterized by more than 80% cells of the monocytic series with positive cytoplasmic α-naphthyl acetate esterase reaction. It may occur in young age groups and is associated with a poor prognosis.
Acute megakaryoblastic leukemia (AML-M7) follows OMF or CML in up to half of patients. Megakaryoblasts (>30% of cells) are undifferentiated round cells reacting positively with antibodies against platelet glycoproteins or factor VIII–related antigens. WBC counts are usually 5,000 cells/mL or less. Secondary AML-M7 shows prominent hepatosplenomegaly. Advanced marrow fibrosis causes marrow aspirates to be inadequate for diagnosis (“dry tap”). Response to chemotherapy is usually poor. Acute erythroleukemia (AML-M6) is characterized by more than 50% abnormal erythroblasts with mixed proportions (30%) of myeloid and monocytic precursors. Peripheral blood smears show abnormal erythrocytes with prominent basophilic granules but rarely atypical blasts. Patients with acute erythroleukemia are usually older than 50 years and have anemia, hepatosplenomegaly, and occasionally rheumatic symptoms, polyclonal gammopathy, and Coombs-positive hemolytic anemia.
After preferred homing of cells in secondary lymphatic tissues and the subdivision of these tissues into functional T- and B-cell units, hyperplasia or aplasia in these units reflects T- or B-cell activities. Functional stimulation of the B-cell system leads to follicular hyperplasia, with prominent plasmacytosis in later stages. Stimulation of the T-cell system leads to paracortical hyperplasia and activation of phagocytosis to sinus histiocytosis or diffuse reticulohistiocytosis. Under physiologic conditions of stimulation by compound antigens, these units react together. Loss of reactivity (e.g., hypoplasia or atrophy) of one of these units indicates deficiency. Hyperplastic changes indicating functional activation of lymphatic tissues are found in various viral infections and are most pronounced in infections by lymphotropic viruses (e.g., Epstein-Barr virus, human herpesvirus types 6 and 7, cytomegalovirus). They cause clinical disorders such as infectious mononucleosis.
Pathologic aberrations from “physiologic” lymphatic hyperplasia are found in autoimmune diseases (e.g., systemic lupus erythematosus and rheumatoid arthritis) and are characterized by B-cell hyperactivity combined with selective T-cell deficiency. Typical lymph node changes consist of prominent follicular hyperplasia and plasmacytosis with paracortical lymphoid depletion. Regressive changes appear and may include degenerating and fibrotic germinal centers (burnt-out follicles), atrophy and fibrosis, or postcapillary venules and paracortical zones. Plasmacytosis increases. In some systemic autoimmune diseases, such as lupus erythematosus, the thymus shows an unusual B-cell hyperplastic reaction with follicular hyperplasia, germinal center formation, and plasmacytosis. Excessive and pathologic reactions in lymphatic tissues affect the phagocytic system, as occurs in storage diseases (thesauropathies, thesaurismoses), such as Niemann-Pick disease and Gaucher disease.
Bacterial infections (excluding organisms with intracellular replication) commonly cause suppurative inflammation; depending on their toxin production, they may cause necrosis, abscess formation, or hemorrhage. These are usually secondary infections after puriform infections in their lymphatic drainage area or septicemia. Lymphadenitis or splenitis with abscess formation is also common in acute fungal infections such as those caused by Candida species. If superficial (mucosal) lymphoid organs are involved, localized erosions, ulcerations, and pseudomembranous inflammation may result, as is typically observed in streptococcal and diphtheric tonsillitis or in Peyer patches with salmonella infections (typhoid fever).
Infections with intracellular organisms persist for a long period, stimulating the T-cell immune system and phagocytosis. Consequently, granulomatous inflammation arises in lymphatic tissues just as it would in other organs. Depending on the toxicity of the etiologic agent, necrosis and abscess formation may occur together. Granulomatous lymphadenitis caused by Mycobacterium tuberculosis, Salmonella species, or fungi of the Histoplasma genus is an example of such a reaction. Combinations of follicular granulomas and centrally located abscesses are found in such diverse infections as Yersinia lymphadenitis, lymphogranuloma venereum, tularemia, and cat-scratch disease. Some toxic fungal infections, such as histoplasmosis and mucormycosis, may cause similarly combined necrotic and granulomatous reactions.
Viral infections may cause hyperplastic reactions in lymphatic tissues. Specific viral infections can be identified only by characteristic cytopathic effects (e.g., Warthin-Finkeldey cells in measles virus infection or cytomegalic inclusion disease in cytomegalovirus infection) or by immunologic and molecular techniques for viral antigens and nucleic acids. Except for the lymphotropic viruses, such as Epstein-Barr virus, where such techniques may occasionally be helpful, viral infections are proven by observing their characteristic diseases in nonlymphatic organs and by serologic testing or viral isolation. Lymphotropic viruses cause a prominent paracortical T-zone hyperplasia with release of stimulated T and B cells into the bloodstream (mononucleosis cells, plasmablastoid B cells). Human immunodeficiency virus (HIV) infection causes rapid loss of cells from the paracortical T-cell zone, structural disruption of cortical follicles, and reactive polyclonal B-cell proliferation.
Immune deficiency disorders (IDDs) may be inherited or acquired. Either may affect the B- or T-cell systems or both, with thymic atrophy, paracortical and cortical atrophy of lymph nodes, or follicular atrophy of the spleen and other lymphoid tissues. Reticular dysgenesis (DeVaal-Seynhaeve syndrome), the most extensive form of inherited IDD, affects the T- and B-cell systems and hematopoiesis. Other classic examples, all incompatible with life, are DiGeorge syndrome of the T-cell system and of the parathyroid glands, Bruton disease of the B-cell system, and severe combined immune deficiency (SCID) of T and B cells.
Acquired immune deficiency syndrome (early AIDS) in lymph node.
Follicular disruption (arrows) and mixed paracortical hyperplasia (right, red cells: B lymphocytes)

Late AIDS. Diffuse atypical lymphoproliferation in lymph node (left) with opportunistic CMV infection (note giant cells with nuclear inclusions) and severe splenic atrophy (right)

**Figure 10-22  Acquired Immune Deficiency Disorders**

Acquired immune deficiency disorders are caused by toxic drugs (chemotherapeutics, steroids, analgesics, and others), ionizing radiation, endocrine and metabolic disturbances, chronic alcoholism, and viral infections such as congenital rubella and HIV, which is characterized by a combination of T-cell deficiency and polyclonal B-cell proliferation. The diagnosis and classification of IDDs follows detailed immunologic testing.

Pathologic studies with immunologic T- and B-cell quantification show hypoplasia or atrophy of the T-cell system (i.e., thymus and paracortical area of lymph nodes, periarteriolar sheath of spleen), hypoplasia or atrophy of the B-cell system (i.e., lymph node and splenic follicles, plasma cell maturation), or combinations of these features. Clinical consequences of IDDs include opportunistic infections and neoplasia (e.g., MLs).
Graft-versus-host reaction (GVHR) is the “rejection” of the recipient (host) by a transplant (graft). It may occur whenever genetically foreign immunocompetent cells are transplanted into an immunodeficient recipient, especially in bone marrow allotransplantation. It also may occur in patients with leukemia or other IDDs who receive multiple blood transfusions. Transfused immunocompetent T lymphocytes recognize and destroy such allogeneic host cells as epidermal cells, hepatocytes, bile duct epithelia, intestinal epithelial cells, and cells of hemolymphatic tissues. Microscopically, a typical acute GVHR shows a T-cell immune reaction in the skin, the liver, and the upper intestines combined with growth inhibition and atrophy of hemolymphatic tissues. Severe acute GVHR has a high mortality secondary to severe ulcerating enteritis with superinfection, diarrhea, and fluid loss; severe hepatitis with hepatocellular necroses; or systemic viral disease and bacterial septicemia.
Hodgkin disease is characterized histologically by mixed proliferations of lymphoid cells with various numbers of histiocytes, eosinophils, and the diagnostic Hodgkin cells or Reed-Sternberg cells. Lymph nodes may show focal or diffuse involvement with effacement of the architecture and invasion beyond their capsule. HD cells are mononuclear histiocytoid blasts with vesicular nuclei and large prominent nucleoli. Reed-Sternberg cells are essentially similar but binucleated blasts. HD are classified into 4 major groups according to their overall cell composition: lymphocyte-predominant type, mixed-cellularity type, nodular-sclerosing type, and lymphocyte-depleted type. The most frequently affected lymph nodes are in the mediastinum (59%), the neck (55-58%), the axillae (13-14%), and the lung hilus (11-12%). Multimodal radiation therapy and chemotherapy can result in stage-dependent disease-free survival of up to 94% at 10 years.
Non-Hodgkin lymphomas are a diverse group of monoclonal T- or B-cell proliferative diseases recently classified according to the Revised European American Lymphoma (REAL) classification, shown in Table 10-4, which categorizes them based on cytology, histologic growth pattern, immunologic phenotype, and cytogenetic markers and includes consideration of clinical course and prognosis. Immunologically, there are B-cell lymphomas, T-cell lymphomas, T-cell–rich B-cell lymphomas, B-cell–rich T-cell lymphomas, and natural killer (NK) cell lymphomas. The etiology of most NHLs is unknown. Some are related to viral infection; Epstein-Barr virus is implicated in Burkitt and Burkitt-type lymphoma, and human T-cell leukemia virus (HTLV-1) is implicated in adult T-cell leukemia (ATL). Many NHLs show genetic mutations with unusual oncogene activation (e.g., c-myc, BCL-2, BCL-1, BCL-6, PAX-5, NPM/ALK) or inactivation of tumor suppressor genes (p53, p16).
### TABLE 10-4  CLASSIFICATION OF LYMPHOMA (NHL) ENTITIES

*Revised European American Lymphoma (REAL) Classification*

<table>
<thead>
<tr>
<th>B-Cell Lymphomas</th>
<th>T-Cell and NK-Cell Lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Precursor B-Cell Neoplasias</strong></td>
<td><strong>Precursor T-Cell Neoplasia</strong></td>
</tr>
<tr>
<td>1. Precursor B-lymphoblastic lymphoma (B-LBL)</td>
<td>1. Precursor T-lymphoblastic lymphoma (T-LBL)</td>
</tr>
<tr>
<td>2. Precursor B-lymphoblastic leukemia (B-ALL)</td>
<td>2. Precursor T-lymphoblastic leukemia (T-ALL)</td>
</tr>
<tr>
<td><strong>Peripheral B-Cell Neoplasias</strong></td>
<td><strong>Peripheral T-Cell and NK-Cell Lymphomas</strong></td>
</tr>
<tr>
<td>1. B-cell chronic lymphatic leukemia (B-CLL) or prolymphocytic leukemia (B-PLL)</td>
<td>1. T-cell chronic lymphatic leukemia (T-CLL) or T-cell prolymphocytic leukemia (T-PLL)</td>
</tr>
<tr>
<td>2. Small cell lymphocytic lymphoma</td>
<td>2. Large granular cell lymphocytic leukemia (LGL)</td>
</tr>
<tr>
<td>3. Lymphoplasmacytoid lymphoma (LPL) or immunocytoma (IC)</td>
<td>• Subtype: T-cell type</td>
</tr>
<tr>
<td>4. Mantle cell lymphoma</td>
<td>• Subtype: NK-cell type</td>
</tr>
<tr>
<td>5. Follicular center cell lymphoma, follicular pattern (FCCf)</td>
<td>3. <em>Mycosis fungoides/Sezary’s syndrome (MF/SS)</em></td>
</tr>
<tr>
<td>• Grade I small cell</td>
<td></td>
</tr>
<tr>
<td>• Grade II mixed small and large cell</td>
<td></td>
</tr>
<tr>
<td>• Grade III large cell</td>
<td>4. Peripheral T-cell lymphoma NOS (not otherwise specified)</td>
</tr>
<tr>
<td>6. Follicular center cell lymphoma, small cell, diffuse pattern (FCCd)</td>
<td>• Subtype: Subcutaneous panniculitic T-cell lymphoma</td>
</tr>
<tr>
<td>7. Marginal zone lymphoma (MZL)</td>
<td>• Subtype: Hepatosplenomegalic gamma/delta T-cell lymphoma</td>
</tr>
<tr>
<td>• Subtype I extranodal MZL of MALT-type with or without mononcytoid cells</td>
<td></td>
</tr>
<tr>
<td>• Subtype II nodal MZL with or without monocytoid cells</td>
<td></td>
</tr>
<tr>
<td>8. Marginal zone lymphoma of the spleen (SLVL)</td>
<td>5. Angioimmunoblastic T-cell lymphoma (AILD)</td>
</tr>
<tr>
<td>9. Hairy cell leukemia (HCL)</td>
<td>6. Angiocentric lymphoma</td>
</tr>
<tr>
<td>12. Burkitt lymphoma</td>
<td>9. Anablastic large cell lymphoma (ALCL), CD30+, T- or 0-Cell Type</td>
</tr>
</tbody>
</table>

**Figure 10-25  Non-Hodgkin Lymphomas, Microscopic (continued)**
Patients with NHL present with persistent indolent lymphadenopathy with or without splenic enlargement and **B-symptoms** (night sweats, fever, weight loss). Internal and extranodal lymphomas cause symptoms only by compression or infiltration of adjacent organs (e.g., abdominal discomfort, uncharacteristic GI problems). Hypersplenism or direct invasion of the bone marrow may be followed by anemia, thrombocytopenia, and pancytopenia. Treatment of NHL is adjusted according to its histologic classification and clinical stage. Follicular lymphomas and small-cell lymphomas are usually less aggressive and have a better prognosis than large-cell and diffuse lymphomas. In certain lymphomas, however, relapses have been described after periods as long as 15 years.
Lymphocytic leukemias are characterized by hematogenous circulation of malignant cells and lymphomatous infiltration of bone marrow, lymphatic organs, or extralymphatic sites. CLL, in approximately 90% of cases a B-cell malignancy, is the most common form of leukemia. Immunodeficiency and autoimmune reactions (autoimmune hemolytic anemia) may accompany CLL, rendering the patient susceptible to infections. The disease course is slowly progressive but rapid when chemotherapy becomes necessary. Acute lymphocytic leukemia (ALL; cytologic subtypes L1-L3 according to cell size) is preferentially a childhood leukemia. Approximately 80% of cases of childhood ALL consist of monoclonal B-precursor cells, and approximately 15% consist of cells from the T-cell lineage. Clinical features are anemia (pallor, fatigue), thrombocytopenia (hemorrhage), and mature leukocytopenia (infections). Combination chemotherapy and radiation therapy have resulted in long-term disease-free survival of 70% to 80% of children.
Multiple myeloma is a neoplastic clonal proliferation of plasma cells (plasmacytoma) usually at multiple sites in the bone marrow. It frequently is accompanied by the production of unusual immunoglobulin components (gammopathy, monoclonal M protein in serum, and Bence Jones protein in urine). Clinical features include bone pain, anemia, bleeding, hypercalcemia, hyperglobulinemia (myeloma kidney), and susceptibility to infection. Systemic amyloidosis develops in later stages of the disease. With treatment, the life expectancy is approximately 2.5 to 3 years. Waldenström disease (WD) is another form of mature B-cell neoplasia with respective lymphoplasmacytic infiltration of the bone marrow and immunoglobulin (Ig) M macroglobulinemia. Other frequently involved sites are lymph nodes, spleen, GI tract, lungs, and skin. Clinical features are hyperviscosity, cryoglobulinemia, bleeding, renal disease, peripheral neuropathy, and amyloidosis. The median survival of patients with WD is 5 years.
The skeletal system provides structural support and protection to the human body and its internal organs, serves as primary home for blood-forming tissues, and stores several vital minerals, above all, calcium. This chapter focuses on alterations of the bony (structural support) part of the skeletal system. Calcium metabolism is also discussed with the endocrine system (chapter 12), and blood-forming tissues are treated separately in the chapter about hematopoietic and lymphatic tissues (chapter 10).

METABOLIC BONE DISEASES

Metabolic bone diseases include diseases of increased bone resorption, such as osteoporosis, and of calcium metabolism, such as rickets, osteomalacia, hyperparathyroidism, and renal osteodystrophy. Primary osteoporosis is an age-related disorder preferentially affecting women that ultimately may cause a loss of 35% to 50% of cortical or trabecular bone mass. It is related to hormonal influences (e.g., estrogen deficiency), reduced physical activity, and nutritional and genetic factors. Secondary osteoporosis follows a large variety of diseases, including malabsorption or malnutrition, endocrine disorders (e.g., hyperparathyroidism or hypoparathyroidism, hypogonadism, and type 1 diabetes) and neoplastic diseases, such as multiple myeloma and bony metastases. Disorders in calcium homeostasis cause reduced matrix mineralization with osteopenia. Primary and secondary hyperparathyroidism (with the latter related to renal insufficiency) are characterized by increased osteoclastic bone resorption with features of dissecting osteitis and osteitis fibrosa cystica (von Recklinghausen disease of the bone).

INFECTIOUS DISEASES

Osteomyelitis (OM), an acute or chronic inflammation of the bone marrow cavity and bone, usually has an infectious cause. OM may originate from hematogenous spread of infectious organisms (i.e., secondary to pyemia or septicemia) or from their direct invasion through penetrating wounds (including from orthopaedic procedures) or open fractures. Despite readily available antibiotic drugs, infectious OM still constitutes a serious clinical problem for several reasons: First, OM is rarely a primary disease but more often a complication of an undiagnosed or inadequately treated infection. Second, OM responds poorly to antibiotic treatment (causative organisms may be drug resistant) and may run a chronic course with complications such as amyloidosis. Third, OM may be the source of additional hematogenous spread causing septic shock, hemorrhage, or abscesses in vital organs (brain, myocardium). Therefore, treatment must be radical, combining antibiotic and surgical intervention.

NONINFECTIOUS ARTHRITIC DISEASES

Osteoarthritis (OA) is an extremely common cause of disability, especially in people aged older than 75 years, 85% of whom show clinical evidence of the disorder. Despite its ubiquity, primary OA is of unknown etiology, although it is thought to result from intrinsic defects of cartilage. Abnormal mechanical forces on the cartilage, decreased water bonding of cartilage, increased stiffness of subcartilaginous bone, and biochemical abnormalities such as decrease in proteoglycans and shortening of glucosaminoglycans have been implicated. The latter decreases cartilaginous water binding in favor of its binding by collagen fibers. Mutations of the collagen type II gene may be involved. Secondary OA occurs in patients with such underlying causes as malformations, trauma, and metabolic diseases with or without crystalline deposits.

PAGET DISEASE

Excessive osteoblastic bone formation with abnormal structure and impaired stability characterize Paget disease (PD; osteitis deformans). After the age of 40 years, the disease increases in incidence to affect 4% to 10% of the population, primarily in white populations of Northern Europe, North America, Australia, and New Zealand, more often in men than women. It may occur in a monostotic form (in only one bony site) or in polyostotic forms (i.e., systemically). Head bones become enlarged; patients report headache, back pain, deafness, and visual disturbances; long bones (especially of the lower extremities) become tender; and deformities and fractures occur. The disease course is complicated by osteosarcoma (OS) in approximately 1% of patients.

TUMORS OF THE SKELETAL SYSTEM

Tumors of the skeletal system comprise a large variety of benign and malignant lesions, including bone cysts. They are classified according to their tissue of origin and are further identified by the age of the patient and the site. Primary tumors of bone are less common than metastatic lesions to the skeletal system, which always should be considered in differential diagnosis (usually, radiographic findings of primary and metastatic lesions are quite characteristic). The extraskeletal malignant neoplasms most likely to metastasize to the skeleton are carcinomas of the prostate, the breast, the lungs, the gastrointestinal tract, the kidneys, and the thyroid. Such metastases may be osteoblastic (e.g., prostate) or osteolytic.
Other primary tumors with secondary involvement of the bony skeleton are those of the hematopoietic bone marrow or lymphatic tissues (e.g., plasmacytoma, Hodgkin disease). They are discussed in chapter 10.

**SOFT TISSUE DISORDERS**

*Soft tissue* refers to the widely distributed interstitial tissue of mesodermal origin filling spaces between ectodermal, endodermal, and skeletal structures. It includes differentiated tissues such as fibrous tissue, fat, and skeletal muscle. Although all pathologic reaction patterns are represented in diseases of soft tissue, including necrosis and degeneration, infection and inflammation, and hyperplasia and neoplasia, only a few examples can be discussed here. We focus on such important disorders as *compartment syndrome*, *collagen-vascular diseases* (CVDs), and benign and malignant tumors.
Osteoporosis refers to a condition of reduced mass of mineralized bone secondary to an imbalance between catabolic (↑) and anabolic (↓) bone metabolism. The loss of skeletal mass can reach a state where the mechanical stability of affected parts is no longer maintained and fractures occur. There are primary and secondary forms of osteoporosis, and localized or systemic changes are identified. The most well-known and frequent type of primary osteoporosis is old age osteoporosis (senile osteoporosis). Inactivity osteoporosis (immobilization osteoporosis) is a localized form of secondary osteoporosis. Other pathogenetic categories of osteoporosis are summarized in Table 11-1.

**TABLE 11-1 PATHOGENETIC FORMS OF OSTEOPOROSIS**

<table>
<thead>
<tr>
<th>Category</th>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary, type 1</td>
<td>Increased osteoclast activity</td>
<td>Postmenopausal (estrogen withdrawal)</td>
</tr>
<tr>
<td>Primary, type 2</td>
<td>Decreased osteoblast activity</td>
<td>“Old age” osteoporosis</td>
</tr>
<tr>
<td>Secondary</td>
<td>Endocrine disorders</td>
<td>Hyperparathyroidism, hyperthyroidism or hypothyroidism, hypogonadism, Cushing syndrome, Addison disease, acromegaly</td>
</tr>
<tr>
<td>Hematologic diseases</td>
<td></td>
<td>Multiple myeloma, systemic mastocytosis, some leukemias and lymphomas</td>
</tr>
<tr>
<td>Malabsorptive</td>
<td>Malabsorption syndromes, malnutrition, gastrectomy, hepatic diseases, vitamin D and C deficiencies</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Inactivity osteoporosis, chemotherapy and other drugs, chronic alcoholism, certain metabolic diseases</td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 11-1 OSTEOPOROSIS**

Marked kyphosis is evident. Anterior wedge and biconcave (codfish) deformities are present.

Multiple grade 3 compression fractures are evident in the thoracic vertebral bodies, resulting in marked kyphosis.
The anatomical and clinical manifestations of osteoporosis are dependent on the maximal bone mass (peak bone mass), which is genetically determined. It is higher in men than in women and lower in white populations than in others. Therefore, a white female is at highest risk. Bone mass is commonly determined by radiographic measurement of bone density, which is highest at the ages of 25 to 35 years and decreases gradually thereafter by approximately 0.7% per year. Gross and microscopic features of osteoporosis show a diffuse rarefaction of trabecular bone and a symmetric thinning of trabecular and cortical bone. The ratio of mineralized bone to osteoid remains normal. In postmenopausal osteoporosis, disruption of trabecular bone adds significantly to the instability of the skeleton. The most common fractures resulting from primary osteoporosis are hip fractures, compression fractures of vertebral bodies (8 times more frequent in females), and fractures of the distal radius.
In rickets and osteomalacia, mineralization of osteoid is reduced while bone mass remains normal. Rickets affects the growing bones of children, and osteomalacia affects the newly formed bone matrix in adults. Responsible metabolic disturbances are vitamin D deficiency, phosphate deficiency, and mineralization defects (Table 11-2). Growing bone is severely changed in children with rickets because inadequate mineralization of osteoid matrix leads to overgrowth and distortion of epiphyseal cartilage projecting into the medullary space, disruption of osteoid/cartilage replacement, and reactive proliferation of capillaries and fibroblasts. Loss of structural stability causes skeletal bone deformations (thoracic kyphosis, lumbar lordosis, coxa vara, genu varum). Osteocartilaginous thickening of ribs produces characteristic rachitic rosary. Adults with osteomalacia experience only mild bowing of long bones; however, stress resistance of bones is reduced, and gross or microscopic fractures may occur.

**TABLE 11-2 PATHOGENETIC MECHANISMS OF RICKETS AND OSTEOMALACIA**

<table>
<thead>
<tr>
<th>Category</th>
<th>Mechanism</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiencies</td>
<td>Decreased synthesis in skin</td>
<td>Insufficient sun exposure from 7-dehydrocholesterol</td>
</tr>
<tr>
<td></td>
<td>Decreased intestinal absorption</td>
<td>Dietary lack, malabsorption syndromes (intestines, pancreas, bile)</td>
</tr>
<tr>
<td></td>
<td>Decreased synthesis of 25(OH)-D</td>
<td>Liver diseases</td>
</tr>
<tr>
<td></td>
<td>Enhanced degradation of 25(OH)-D</td>
<td>Various drugs inducing cytochrome and P450 enzymes</td>
</tr>
<tr>
<td></td>
<td>Decreased synthesis of 1,25(OH)-D</td>
<td>Advanced renal disease</td>
</tr>
<tr>
<td>Phosphate deficiency</td>
<td>Increased excretion</td>
<td>Renal tubular disorders (e.g., Fanconi syndromes)</td>
</tr>
<tr>
<td></td>
<td>Decreased absorption</td>
<td>Phosphate-binding drugs (e.g., antacids)</td>
</tr>
<tr>
<td></td>
<td>Disturbed reabsorption</td>
<td>Tumor associated (e.g., prostate cancer, neurofibromatosis)</td>
</tr>
<tr>
<td>Mineralization defects</td>
<td>Target organ resistance</td>
<td>Congenital lack of receptors (type II rickets)</td>
</tr>
</tbody>
</table>

*1,25(OH)-D indicates 1,25-dihydroxyvitamin-D, active form after second hydroxylation in renal tubule; 25(OH)-D, 25-hydroxyvitamin-D, major circulating metabolite hydroxylated in the liver.*
Renal osteodystrophy, which is most common in patients undergoing long-term dialysis for chronic renal failure, combines the changes of osteomalacia with focal soft tissue, bone resorption, and vascular calcifications (metastatic calcification). Tumorlike calcium deposits are observed in some cases. While osteomalacic changes suggest renal tubular damage, additional focal osteoclastic bone resorption is caused by secondary hyperparathyroidism. Therapeutic planning must focus on treating the chronic renal disease, replacing 1,25(OH)_{2}-D, substituting for hypophosphatemia, and partially resecting hyperplastic parathyroid glands.
Primary hyperparathyroidism causes generalized bone resorption by focal osteoclastic activities (as described in osteitis fibrosa cystica) combined with an increased incidence of stone formation (e.g., nephrolithiasis). Osteoclastic hyperactivity starts at subperiosteal and endosteal surfaces, cutting into the bone and replacing respective splits and holes by connective tissue (dissecting osteitis). Areas of hemorrhage and microfracture may occur. Larger cystic spaces occur eventually, hemorrhage expands, and resorptive giant cell granulomas develop (“brown tumors” in osteitis fibrosa cystica). These must be distinguished from aneurysmal bone cysts (ABCs), giant cell tumor (GCT) of bone, and telangiectatic OS. Characteristic radiographic changes in hyperparathyroidism are found preferentially in the hands (radial phalanges of the second and third fingers), with signs of focal calcinosis in the spine and the cartilage of major joints.
Infectious Diseases

Although osteomyelitis (OM) can easily be suspected from persistent purulent secretion from deep open wounds or fistulas extending to the bone, the clinical manifestations of hematogenous OM are more difficult to identify. Obscure back pain, low-grade fever, malaise, and moderate blood leukocytosis are among uncharacteristic general symptoms. If localized signs appear, such as circumscribed bone pain, reddening and swelling of the covering skin or mucous membranes, or even fistula formation with purulent discharge, radiographic procedures and tissue biopsies may reveal the real nature of the disease. The most common organisms causing OM are Staphylococcus aureus (e.g., after long-standing infected intravenous catheters, endocarditis, or complicated wound healing), various gram-negative rods, pneumococci (in neonates), salmonellae, and Mycobacterium tuberculosis.

**FIGURE 11-6  OSTEOMYELITIS**

Fever (>75% of acute cases) may be mild, high, or absent. Less common in chronic cases and in adults.

- Pain, tenderness 75%
- Warmth, tenderness < 50%
- Swelling > 50%
- Drainage (later stage)
- Effusion in adjacent joint < 50%
- Limitation of motion < 50%

**Vertebral involvement.** Systemic manifestations usually milder. Pain may be principal manifestation, especially in adults.

**Blood culture and bone aspiration** or open biopsy required to establish diagnosis and identify organism for choice of antibiotic therapy.

**Radiographic signs delayed.** Lytic lesions usually first evidence. Sclerosis appears only after disease has progressed more than 2 months.

**Indium-labeled leukocyte scintigram.** Showing focal signal increase (arrow) and can be useful in early diagnosis.
Infectious Diseases

At the site of bacterial nesting in the bone, usually at well-vascularized metaphyseal sites, acute endotheliitis/vasculitis with subsequent neutrophilic exudation and necrosis of adjacent bone develops. Necrosis may follow local vascular occlusion by thrombosis, compression and hypoxemia, or both. Infection spreads through the marrow cavity and cortical bone, extending subperiosteally, transperiosteally, and through soft tissues, creating draining sinuses (fistulas). Progression to chronic OM adds focal osteoclastic bone resorption and fibrous repair mechanisms. Bony cavities may contain fragments of necrotic bone (bony sequestrum) surrounded by hyperostotic bone (involucrum). Persistent abscesses are surrounded by condensed sclerotic bone (Brodie abscess). Periosteal and osteal hyperostosis on radiograph may signal underlying chronic OM. Microscopic features include decreased neutrophils, persistent edematous swelling, scattered plasmacytic infiltrates, and progressive fibrosis.
Infectious arthritis is an acute or chronic inflammation of a joint or joints, usually caused directly or indirectly by specific infectious organisms. Infectious arthritis is caused directly by seeding of such pyogenic organisms as gonococci, staphylococci, meningococci, and pneumococci. Infection results in a characteristic edematous and neutrophilic infiltration of the synovialis with hemorrhage or necrosis (according to endotoxin or exotoxin activities) and with subsequent lymphoplasmacytic infiltration, capillary proliferation, and fibrosis, depending on the duration of the process. Destruction of cartilage and fibrous adhesions may cause final joint dysfunction and ankylosis.
Tuberculous arthritis is characterized by granulomatous reaction and runs a primary chronic course. It is the consequence of hematogenous spread of organisms, usually during early or later phases of stage II tuberculosis (early or late post–primary tuberculosis). Infection usually affects only one joint, most frequently the spine, the hip, the knee, the elbow, or the ankle. The onset of symptoms is insidious; frequent local muscle spasms at night may be the first suspicious sign of the disease. Walking may be problematic if the spine is involved (Pott disease). Radiographic changes and strong positive tuberculin skin test results are helpful in establishing the diagnosis. Diagnostic proof is given by tissue biopsy and the demonstration of acid-fast bacilli in the granulomatous inflammation as well as by culture or polymerase chain amplification reaction (PCR) techniques.
Osteoarthritis (OA) is the most common degenerative joint disease causing physical disabilities in persons aged older than 65 years. Initial changes, which become overt by the age of 20 years in 4% of the population, increase steadily to affect more than 85% of persons by the age of 75 years. Primary OA is thought to result from intrinsic defects of cartilage. Secondary OA results from conditions such as malformations, trauma, and metabolic diseases with or without crystalline deposits. Several pathogenetically important factors may contribute to the development of OA: abnormal mechanical forces on the cartilage (increased unit load), decreased water bonding of cartilage (decreased resilience), increased stiffness of subcartilaginous bone, and biochemical abnormalities such as decrease in proteoglycans and shortening of glucosaminoglycans. The latter decreases cartilaginous water binding in favor of binding by collagen fibers. Genetic factors may favor mutations of the collagen type II gene.
Signs and symptoms of osteoarthritis (OA)—morning stiffness and pain, rubbing sounds (crepitus), and tenderness and swelling of soft tissues covering joints—develop gradually, most often in the knees, the hips, the lumbar and cervical spine, and the finger joints, leading eventually to muscle contracture and compromised joint mobility. Early microscopic findings are loss of cartilaginous metachromatic staining (loss of proteoglycans), loss of chondrocytes, reactive hypertrophy and grouping of residual chondrocytes, and fibrillation and splitting of the cartilage surface. Fibrillation favors infiltration by synovial fluid with further enzymatic damage, inflammation, and cartilage destruction. Granulation tissue and fibrosis replace cartilage, and erosions result in open bony surfaces. Reactive new bone formation (osteophytes) and fibrous adhesions in border zones limit movement. Circumscribed areas of destruction with fragments of cartilage, dead bone, and synovial fluid may expand into the adjacent bone, forming debris-laden subchondral cysts.

**FIGURE 11-11  OSTEOLTHRITIS: CLINICAL MANIFESTATIONS**
Rheumatoid arthritis (RA) is a systemic chronic progressive inflammatory disease with symmetric involvement of small joints. Variants are Still disease in children (juvenile arthritis) and ankylosing spondylitis (Bechterew disease) preferentially involving the vertebral column and the sacroiliacal joints. RA is representative of a group of autoimmune disorders referred to as collagen-vascular diseases, which include lupus erythematosus, primary systemic sclerosis, polymyositis, and dermatomyositis. The etiology of RA is unknown; however, its pathogenesis includes genetic factors (prevalence of HLA-DR4 and HLA-DR1 genes and others), autoimmune reactions (possibly postinfectious), and local factors such as mechanical stress and specifics of tissue reactivity.

**FIGURE 11-12  RHEUMATOID ARTHRITIS**

Advanced hand involvement

Hand deformities. Marked ulnar deviation of metacarpophalangeal joints, boutonniere deformity of thumb, synovitis of wrist

Radiograph. Cartilage thinning at proximal interphalangeal joints, erosion of carpus and wrist joint, osteoporosis, and finger deformities

Crippling involvement of metacarpophalangeal and interphalangeal joints of both hands. Swan-neck deformity of many fingers, boutonniere deformity of thumbs, and numerous subcutaneous nodules

Radiograph (left). Early loss of articular cartilage and osteopenia (arrow)

Same patient after 14 years (right). Carpus, wrist joint, and ulnar head completely eroded (arrow).

Nodule
Microscopic features of **rheumatoid arthritis** (RA) are progressive villous hypertrophy of the synovialis secondary to fibrinous swelling, proliferation of synovial lining cells, and lymphoplasmacytic infiltration. With increasing chronicity, acute inflammatory reactions are replaced by granulation tissue and fibrosis covering and eroding the cartilaginous surface of the joints (pannus formation). Joint mobility is severely inhibited with grossly impressive deviations (subluxation) of joints. End-stage disease is characterized by complete fibrous obliteration of the joints. Adjacent soft tissues may contain focal granulomas with binucleated giant cells (Aschoff cells) surrounding soft tissue fibrinoid necrosis (rheumatic nodule). Although 25% of patients with RA may recover completely, 50% experience terminal severe incapacitation. Death usually occurs from complications such as infections, gastrointestinal hemorrhage, or cardiovascular or pulmonary involvement.
Paget disease (osteitis deformans) is characterized by excessive osteoblastic bone formation with abnormal structure and impaired stability. It occurs with increasing incidence after the age of 40 years (4-10% of the population), primarily in white populations, more often in men than in women. PD may occur in a monostotic form (one bony site) or in a systemic polyostotic form. In the initial stage, ostoclast hyperactivity with increased lacunar bone resorption is seen; the presence of respective inclusion bodies and viral transcripts (resembling paramyxovirus) suggests it is stimulated by infection with a slow virus. In the second stage, marked osteoblastic hyperactivity compensates and then overcompensates for the osteoclast function, and excessive disorderly new bone with irregular cement lines (mosaic bone) is produced. The final stage (“cold” or burnt-out phase) is characterized by marked thickening of densely mineralized bone (osteosclerotic phase) with minimal cellular activity.
Early phases of Paget disease (PD) are asymptomatic, although incidentally increased serum alkaline phosphatase levels may suggest a skeletal disorder. In more advanced cases, incidental radiographic findings may suggest the disease. Typical features are enlargement of head bones, headache, deafness and visual disturbances, deformation and tenderness of long bones (especially of the lower extremities), back pain, and fractures (vertebra, chalk-stick-type cross-fractures of long bones). OS develops in approximately 1% of patients.
Fibrous dysplasia (FD) is a tumor-imitating developmental abnormality of bone that consists of circumscribed mixed fibrous and osseous lesions. FD may be associated with endocrine abnormalities and skin pigmentation such as precocious puberty and café au lait spots (McCune-Albright syndrome), acromegaly, and Cushing syndrome. Monostotic and polyostotic forms frequently occur in the proximal femur, the tibia, the ribs, and the mandible. Polyostotic forms (25%) also may involve the pelvis, the hands, or the feet. Growing lesions cause pain, deformation of bones, and pathologic fractures. Characteristic radiographic findings show a ground-glass, slightly “multivesicular” (“soap bubble”) appearance with distinct borders. Microscopy shows a dense whorled fibrous tissue containing spicules of woven bone. The prognosis of FD is good, and management should prevent complications such as fractures. Rarely, malignant sarcomas may complicate the course of FD. See Table 11-3.
Aneurysmal bone cysts are not a true neoplasm but a reactive tumorlike lesion arising suggestively from previous trauma or degeneration of another underlying disease (e.g., osteoblastoma, FD, GCT, and others). Grossly, ABCs appear as circumscribed masses of spongy, bloody tissue with fibrous septae, thinning the cortical bone, and bulging through the periosteum. Part of the bone may be replaced by granulation tissue with microscopic multinucleated giant cells and osteoid bone formation. Although lesions usually enlarge rapidly, there are slow-growing types of ABC that must be distinguished from the malignant telangiectatic osteosarcoma and giant cell tumor of bones. Bone scans and computed density measurements may be helpful in the differential diagnosis, but biopsy and pathologic investigation are necessary to confirm ABCs. Local curettage with grafting of trabecular bone is the treatment of choice. See Table 11-3.
### TABLE 11-3  BENIGN PRIMARY TUMOROUS LESIONS OF THE SKELETAL SYSTEM AND JOINTS

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Ages</th>
<th>Usual Location</th>
<th>Gross Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonossifying fibroma (fibrous cortical defect)</td>
<td>Children</td>
<td>Metaphysis, long bones (tibia, fibula)</td>
<td>Eccentric cortical lesion with well-demarcated sclerotic margins</td>
</tr>
<tr>
<td>Solitary bone cyst</td>
<td>Children, adolescents</td>
<td>Humerus, femur (adjacent to growth plate)</td>
<td>Well-demarcated epiphyseal lesion</td>
</tr>
<tr>
<td>Aneurysmal bone cyst</td>
<td>Children, young adults</td>
<td>Long bones, vertebra (essentially everywhere)</td>
<td>Rapidly expanding cyst (previous trauma?)</td>
</tr>
<tr>
<td>Fibrous dysplasia (monostotic or polyostotic)</td>
<td>Adolescents, young adults</td>
<td>Long bones</td>
<td>Diaphyseal “soap bubble” translucencies</td>
</tr>
<tr>
<td>Osteoma (eburneum) (probably not a real neoplasm)</td>
<td>Adults</td>
<td>Skull, tibia</td>
<td>Exophytic solid mass</td>
</tr>
<tr>
<td>Osteoid osteoma</td>
<td>Children, young adults</td>
<td>Tubular bones, lower extremity</td>
<td>Diaphyseal cortex “nidus”</td>
</tr>
<tr>
<td>Osteoblastoma</td>
<td>Children, young adults</td>
<td>Vertebra, spinal, transverse process</td>
<td>Similar to osteoid osteoma (“nidus”)</td>
</tr>
<tr>
<td>Osteochondroma (exostosis)</td>
<td>Young adults</td>
<td>Long bones</td>
<td>Bony exostoses with cartilaginous cap</td>
</tr>
<tr>
<td>Chondroma (enchondroma)</td>
<td>Adults</td>
<td>Tubular bones metacarpal, phalanges</td>
<td>Intraosseous, solitary well-circumscribed lesion</td>
</tr>
<tr>
<td>Chondroblastoma</td>
<td>Children, young adults</td>
<td>Long bones femur,ibia, humerus</td>
<td>Epiphysis, paraarticular well-circumscribed lesion</td>
</tr>
<tr>
<td>Chondromyxoid fibroma</td>
<td>Children, young adults</td>
<td>Femur, tibia</td>
<td>Excentric lucent defect, delicate sclerotic border</td>
</tr>
<tr>
<td>Synovial chondromatosis (self-limited)</td>
<td>Young adults (men)</td>
<td>Large joints</td>
<td>Hyaline cartilage nodules and floating free bodies</td>
</tr>
<tr>
<td>Villonodular synovitis Pigmented</td>
<td>Young adults</td>
<td>Knee, hip, ankles, feet, fingers</td>
<td>Synovial lining cell proliferation with hemosiderin deposits</td>
</tr>
</tbody>
</table>

### TABLE 11-4  MALIGNANT PRIMARY TUMOROUS LESIONS OF THE SKELETAL SYSTEM AND JOINTS

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Ages</th>
<th>Usual Location</th>
<th>Gross Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteogenic sarcoma (osteosarcoma)</td>
<td>Adolescents, children</td>
<td>Femur, tibia, fibula, and others</td>
<td>Irregular bone destruction, reactive periosteal new bone (see text for variants)</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>Adults (fourth to sixth decades of life)</td>
<td>Pelvis, shoulder, proximal femur, ribs</td>
<td>Often bulky destructive lesion with calcification or bone formation (see text for variants)</td>
</tr>
<tr>
<td>Giant cell tumor (locally aggressive, potentially malignant)</td>
<td>Adults</td>
<td>Long bones, epimetaphyseal junction</td>
<td>Slowly growing lytic lesion with periosteal reaction, circumscribed, painful</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>Children, adolescents</td>
<td>Long bones, mid shaft metaplasia, humerus, femur, tibia</td>
<td>Lytic lesion in medulla and inner cortex, periosteal reaction</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>Adolescents, young adults</td>
<td>In vicinity of joints, 10% intraarticular</td>
<td>Soft tissue tumor associated with tendons, bursae, joint capsule</td>
</tr>
</tbody>
</table>
Enchondroma (EC) is a benign intraosseous tumor of well-differentiated cartilage occurring primarily in adults and adolescents. It most frequently affects small tubular bones of the hands and feet but can develop anywhere in the skeleton. The monoclonality of chondrocytes in EC suggests a benign neoplasm. EC may occur in multiplicity (enchondromatosis, Ollier disease). Rarely, EC transforms to secondary chondrosarcoma (CS). EC is usually asymptomatic except for certain “obscure” pain sensations. Incidental radiographs show well-defined radiolucent lesions with slightly pronounced bony margins and sometimes calcification. Microscopy reveals a somewhat disorganized, well-differentiated cartilage with stippled calcification. Larger lesions may undergo pseudocystic degeneration. The prognosis for small benign ECs is good, and lesions may be followed without intervention. Surgical intervention is suggested for mechanical reasons or when suspicion of malignancy arises. See Table 11-3.
Osteochondroma (osteocartilaginous exostoses), which constitute approximately one third of benign bone tumors, are not tumors as such but rather developmental dysplasias of the growth plate. Osteochondroma presents as a solitary lobulated metaphyseal outgrowth, polyostotic, or rarely as a familial disorder (multiple hereditary exostosis) and consists of mature trabecular bone with a cartilaginous cap. Common locations are the proximal and distal femur, the proximal humerus and tibia, and the pelvis and scapula. Radiographic and gross changes are characteristic. Rapidly growing lesions in adults may indicate a (rare) risk of malignant transformation to secondary chondrosarcoma. These lesions must be distinguished from parosteal osteosarcoma. The prognosis of solitary exostosis is excellent, with approximately 5% recurrence after surgical removal. See Table 11-3.
Giant cell tumor of bone (osteoclastoma) occurs preferentially between the ages of 20 and 40 years. Typically, the lesion is located at the epimetaphyseal junction of long bones such as the femur, the tibia, the humerus, the radius, and the fibula, presenting as a slowly growing lytic lesion causing persistent intraosseous pain, reactive effusions, and eventual fractures. Radiographs reveal large radiolucent lesions with surrounding reactive bone formation, cortical thinning, trabecularization, and bony separation. Grossly, they appear as soft, friable, reddish-brown tissue resembling a bloody sponge. There may be areas of aneurysmal cavitation. Microscopically, they show a mixed-cell proliferation of stromal mononuclear cells and multinucleated (osteoclastic) giant cells in a markedly vascularized stroma and focal hemorrhages. Up to 10% (usually the incompletely removed tumors) metastasize; the neoplastic component is the mononuclear stromal cells. Treatment by curettage alone results in 50% recurrence. See Table 11-3.
Osteosarcoma (osteogenic sarcoma) is the most common malignant bone tumor, occurring in endosteal, cortical or parosteal juxtacortical forms, usually during the second decade of life. Most frequent sites (75%) are metaphyseal areas adjacent to knee or shoulder (e.g., tibia, fibula, humerus), hands, feet, skull and jaws. Radiographs show localized lytic or osteoblastic lesions with fuzzy borders and prominent subperiosteal reactive bone formation (Codman triangle). The cut surface depends on the histologic variant of the tumor: it is whitish soft or bony hard, pseudocystic with focal necroses or hemorrhages and freely invades into adjacent soft tissues. Parosteal OS may resemble exostoses with well-differentiated bone or fibrous tissue components. Histologic variants include degrees of differentiation of chondroblastic areas or of giant cell components and overtly telangiectatic or fibroblastic forms. OS readily metastasizes into the lungs and pleura, less frequently to other organs. See Table 11-4.
Chondrosarcoma arises from cartilage rests or preexisting ECs. There are several gross variants: central, juxtacortical and peripheral (the latter arising outside the bone). CSs occur in older persons with a peak in the sixth decade of life, usually in central portions of the skeleton such as shoulder, pelvis, proximal femur and ribs. Radiographic images show a bulky osteodestructive lesion with a characteristic pattern of calcification (“salt and pepper” or “popcorn”). Gross lesions show a smooth whitish glistening cut-surface that is occasionally lobulated and focally calcified. Histologic appearances vary from well differentiated cartilaginous tumors to undifferentiated and mesenchymal forms. Well-differentiated OS can be hard to distinguish from EC. Criteria of malignancy are the grouping and polymorphism of chondrocytes, their nuclear atypia, multinucleate cells and occasional mitoses. CSs metastasize preferentially to the lungs. See Table 11-4.
Ewing sarcoma (ES), after OS the second most common bone tumor in children, accounts for approximately 5% of all bone tumors and has a peak incidence in the second decade of life. Although its histogenesis remains unclear, frequent genetic mutations (t[11;22]p13;q12) suggest a relationship of malignant cells in ES to primitive neuroectodermal cells. Unlike other bone tumors, ES frequently presents with fever and pain simulating an inflammatory disease. The diagnosis is confirmed by biopsy and microscopic investigation. The characteristic dense small cell tumors must be distinguished from cell tumors such as neuroblastoma and malignant lymphoma. Long bones including midshaft humerus, tibia and femur are the sites most frequently affected. Grossly, the tumor impresses as osteolytic soft grayish-white masses with focal hemorrhage which may penetrate the perios teum and invade adjacent soft tissues. ES commonly metastasizes to lungs, brain and other bony sites such as the skull. See Table 11-4.
Compartment syndrome (CS) results from increased pressure in one or more (osteofascial) compartments. Sustained increase of tissue pressure from local edema reduces capillary perfusion below the level necessary for sustaining tissue viability; irreversible muscle and nerve damage results in a few hours. Partial burial, trauma, burns, or exercise may cause CS. Pathogenetic mechanisms are increased fluid accumulation, decreased tissue volume (compartment constriction), and restricted volume expansion secondary to external compression (e.g., casts). In conscious patients, pain is disproportionate to the obvious injury and increases with passive stretching of muscles. Loss of sensation from nerves running through affected compartments may occur. Microscopic changes are intense soft tissue edema with progressive degeneration and necrosis, hemorrhage, and, in delayed cases, slowly developing granulation tissue and fibrosis. There is high risk of superinfection, and secondary septicemia exists.
Collagen-vascular disease (CVD) refers to a group of systemic autoimmune disorders with overlapping signs and symptoms that affect several organ systems (e.g., skin, kidneys, lungs). CVDs include systemic lupus erythematosus, RA, primary systemic sclerosis, dermatomyositis, polymyositis, and certain “overlap syndromes” (Table 11-5). Although the etiologies of CVDs are unknown, the pathogenesis is characterized by various autoimmune reactions with demonstration of respective autoantibodies,
Soft Tissue Disorders

Microscopy of RA. With acute synovitis (left) and chronic tenovaginitis (right)

Microscopy of systemic lupus erythematosis. With acute (left) and chronic arthritis/synovialitis (right)

TABLE 11-5 FEATURES OF EXEMPLARY MEMBERS OF COLLAGEN-VASCULAR DISEASES

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Autoimmunity*</th>
<th>Features†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Autoantibodies against native ds-DNA, denatured ss-DNA, histones, and histone complexes T-, NK-cell, and cytokine abnormalities, circulating immune complexes</td>
<td>Rash, arthritis/arthritis, glomerulonephritis, proteinuria, thrombocytopenia, hemolytic anemia, pleural effusions, pulmonary fibrosis, pericarditis, endocarditis, psychosis, seizures Vasculitis and thrombosis</td>
</tr>
<tr>
<td>Primary systemic sclerosis</td>
<td>Autoantibodies against small RNA protein (SS-A/ Ro), topoisomerase 1 (Scl-70), 45K RNA protein (SS-B/La)</td>
<td>Hallmark: scleroderma, Raynaud syndrome, proliferative arteritis and fibrosis, capillary malformations such as telangiectasia and bleeding; esophagus and lower GI tract: fibrosis and muscular atrophy with motility problems and dysphagia, interstitial pneumonitis, shrinking lung disease, pulmonary hemorrhage; heart: conductive and ventricular dysfunction, renal vasculitis and hypertension</td>
</tr>
<tr>
<td>Polymyositis, dermatomyositis</td>
<td>tRNA synthetases: Jo-1, PL-7; protein complex (PM-Scl)</td>
<td>Muscle weakness: segmental myofiber necrosis with inflammatory infiltrate, fever, myoglobinuria, skin rash, erythema of hands (knuckles), interstitial pneumonitis, approximately 25% associated with malignancies</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Denatured ss-DNA Rheumatoid factor, CIC, antikeratin, collagen antibody, T-cell “activation”</td>
<td>Chronic relapsing synovitis, arthritis, small joints of hands, symmetrical, tenosynovitis, soft tissue rheumatic nodules, pleuritis, pericarditis, vasculitis, interstitial pneumonitis, bronchiolitis obliterans, polyneuritis, mononeuritis, Felty syndrome</td>
</tr>
</tbody>
</table>

CIC indicates circulating immune complexes; ds, double-stranded; GI, gastrointestinal; ss, single-stranded.
*Selective antibodies only.
†See text for additional microscopy.

circulating immune complexes, or both. The essential pathologic features in all CVDs are chronic inflammatory infiltration (lymphoplasmacellular) of connective tissue, edema, fibrinoid necroses, vasculitis, and progressive fibrosis. The extent and composition of these features vary among the different CVDs and with their type of autoimmune reaction (autoantibodies, circulating immune complexes, T-cell immune reaction).
Benign tumors of soft tissue may occur at any age and are classified according to the tissue where they arise: fibromas, lipomas, rhabdomyomas, leiomyomas, or mixtures of these, and composite tumors with additional tissue components (angiolipomas, fibrous histiocytoma, neurofibroma, myelolipoma). **Subcutaneous lipomas**, the most frequent benign tumors, are slowly enlarging well-circumscribed yellowish masses with a histology indistinguishable from normal fat tissue. Fibrous tumorlike lesions (nodular fasciitis, fibromatosis) are not considered real tumors, although some show locally aggressive behavior. **Fibrous histiocytomas** are dermal tumors of interlacing fibrous strands and collections of lipid- and iron-containing histiocytes. **Benign neurofibromas** occur in dermis and in part in the submucosa of the alimentary tract. They may cause bleeding or mild obstruction. Leiomyomas are common in the uterus but also are found in the gastrointestinal tract or originating from blood vessels.
Sarcomas spread by hematogenous metastases rather than through lymphatic channels. They are classified according to the tissue from which they derive, or in a more descriptive way if their histogenesis is unclear. Variants include liposarcomas, fibrosarcomas, malignant fibrous histiocytoma (MFH), neurofibrosarcomas, rhabdomyosarcomas, leiomyosarcomas, and alveolar soft part sarcomas or epithelioid sarcomas. Fibrosarcoma, usually arising from fascia, tendons, periosteum, or scar tissue of the thigh, the knee, or the trunk, is not a common malignancy, but its “pleomorphic cousin,” MFH, is the most common soft tissue sarcoma. MFH is a highly malignant tumor of deep fascia, skeletal muscle, and the retroperitoneal space, preferentially occurring in patients aged 50 to 70 years. Postradiation fibrosarcoma is classified as MFH. Prognosis depends on the degree of atypia and the polymorphism of its cells. Approximately 50% of MFHs metastasize early to the lungs. Liposarcomas arise...
preferentially in the deep subcutaneous tissues of the thighs, the abdomen, and the retroperitoneum of persons aged older than 50 years. There are several morphologic variants (e.g., well-differentiated, myxoid, pleomorphic, and round cell forms), some of which show mutational chromosomal abnormalities of their adipocytes. Rhabdomyosarcoma is a tumor of children and young adults. It is thought to derive from primitive mesenchyme or embryonic muscle tissue and has corresponding appearances: embryonal rhabdomyosarcoma, alveolar rhabdomyosarcoma, and pleomorphic rhabdomyosarcoma. Well-differentiated forms contain plump cells resembling striated muscle. Leiomyosarcomas are malignant tumors of smooth muscle, occurring most commonly in the uterus and gastrointestinal tract. Neurofibrosarcoma and neurolemmal sarcoma (malignant schwannoma) are tumors of peripheral nerves that are more common in adults. Epithelioid sarcomas and alveolar soft part sarcomas are rare, highly malignant tumors of uncertain histogenesis.
THE ENDOCRINE SYSTEM

The endocrine system consists of a number of organized glands, groups of cells, and dispersed solitary cells that control the functional balance of internal organs by means of chemical messengers called hormones. Organized endocrine glands include the pituitary, the thyroid and parathyroid, the adrenal cortex and medulla, and the endocrine pancreas. In addition, sex organs such as the ovary and testis produce certain hormones (see chapters 7 and 8).

HYPOTHALAMUS-PITUITARY AXIS

Endocrine function responds to feedback control. Because the nervous system “supervises” the endocrine organs, particularly the hypothalamus, it is more appropriate to speak of the neuroendocrine system. In fact, almost all neuroendocrine stimuli exert feedback control, so one could speak of, for example, a neuroendocrine-immunologic axis. All such actions and reactions follow a circadian rhythm, controlled by light, which is the subject of the science of chronobiology.

THYROID GLAND

The thyroid gland, which responds with peripheral feedback control to the hypothalamus and pituitary, is the key endocrine organ controlling energy metabolism (carbohydrate and lipid catabolism, stimulation of protein synthesis). It acts primarily through the effects of 2 hormones, thyroxin (tetraiodothyronine; T4) and triiodothyronine (T3), which bind to receptors on various peripheral cells and stimulate their metabolic activities. These hormones are coupled to thyroglobulin and are stored in follicular colloid. Proteolytic enzymes release T4 and T3 and make it available in the periphery as active hormones. This process is accompanied morphologically by signs of follicular activation such as paraepithelial resorptive vacuoles in the colloid, epithelial swelling (cuboidal size), and proliferation (focal stratification to form Sanderson cushions and papillae).

PARATHYROID GLANDS

In most people, 4 separate parathyroid glands lie in close proximity to the posterior part of the thyroid gland. Their hormone, parathyroid hormone (PTH), controls the calcium balance of the body as it responds to feedback mechanisms independently of hypothalamic-hypophysial supervision. One third of the normal parathyroid gland consists of fat tissue, and the balance contains the pale PTH-producing chief cells and pink oxyphilic cells. Any increase in weight above the normal 130 mg or replacement of fat tissue by glandular cells indicates hyperplasia/hyperfunction. Hyperparathyroidism independent of feedback control (i.e., autonomous) usually is caused by adenomas or carcinomas of the gland. Hypoparathyroidism (lack of PTH) is rare, usually follows surgical resection of the glands in thyroidectomies, and causes severe hypocalcemia. Familial autosomal recessive forms of hypoparathyroidism may occasionally occur as part of a multiglandular deficiency or in combination with T-cell immune deficiency (e.g., DiGeorge syndrome). The ionized serum calcium level provides the stimulus for PTH secretion. PTH stabilizes the serum calcium level by inhibiting renal tubular phosphate reabsorption and calcium/phosphate absorption in the bone and by enhancing calcium absorption in the intestines.

ADRENAL CORTEX (SUPRArenal CORTEX)

The adrenal cortex is composed of 3 microscopically identifiable zones, each of which engages in the production of different hormones: the zona glomerulosa (outer zone), the zona fasciculata (intermediate zone), and the zona reticularis (inner zone adjacent to adrenal medulla). The latter 2 zones respond to stimulation by hypophyseal corticotropin, whereas the zona glomerulosa functions independently of it. This zone produces the hormone aldosterone in response to increases in potassium levels and angiotensin or decreases in atrial natriuretic peptide or somatostatin. The 2 inner zones produce glucocorticoids and androgens in response to corticotropins. Increased functional activity in either zone is associated with microscopic hyperplasia, adenoma, or carcinoma; decreased functional activity is associated with atrophy (e.g., in malnutrition), necrosis (e.g., in septicemia, tuberculosis, or viral infection), or autoimmune adrenalitis.

ADRENAL MEDULLA

The major organs of the sympathetic neuroendocrine system are the adrenal medulla and less compact collections of neuroendocrine cells in paraganglia, including the carotid body and the organ of Zuckerkandl. All consist of chromaffin cells (which have an affinity to chromium salts and stain dark on oxidation), which produce the catecholamines epinephrine and norepinephrine. Several tumors of chromaffin catecholamine-producing cells, such as pheochromocytoma and paragangliomas, exaggerate the physiologic functions of the organs. In addition, ganglionic cells in these regions may give rise to neuroblastomas. Approximately 10% of pheochromocytomas are part of a familial syndrome.
called multiple endocrine neoplasia (MEN). Several forms of MEN are autosomal dominant diseases with mutations on chromosomes 10 and 11. Patients with an identified adenoma or carcinoma at one of these organ sites and their families must therefore be screened for other endocrine abnormalities.

ENDOCRINE PANCREAS

The endocrine pancreas consists of the islets of Langerhans. These are composite fabrication sites composed of different cells that produce and secrete several hormones. The greatest proportion (60-70%) are insulin-producing β cells; α cells (15–20%) produce the “insulin antagonist” glucagon. There are several clones of δ cells (e.g., D cells, D1 cells) which secrete somatostatin or vasoactive intestinal polypeptide (VIP) as well as cells that produce substance P, human pancreatic polypeptide, or gastrin (G cells). Consequently, pancreatic endocrine adenomas or carcinomas (e.g., gastrinoma, vasoactive intestinal polypeptide–secreting tumor [VIPoma], somatostatinoma, and others) can affect multiple endocrine activities. This chapter focuses only on the more common types of hyperinsulinism and hypoinsulinism (diabetes mellitus).
Endocrine function is supervised by the nervous system, especially the hypothalamus. Several nuclei of the hypothalamus secrete hypothalamic hormones that stimulate peripheral endocrine tissues via the pituitary (hypophysis). These hormones include corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), luteinizing hormone-releasing hormone (LHRH), and growth hormone-releasing hormone (GHRH). In addition, there are several direct- and indirect-acting hypothalamic hormones, including arginine vasopressin (AVP), somatostatin, and dopamine. Hypothalamic function responds to extraneous physical and emotional stimuli as well as to internal feedback control.
The pituitary gland controls the functional activity of peripheral endocrine tissues by secreting a large number of hormones, including thyroid-stimulating hormone (TSH), corticotropin (adrenocorticotropic hormone [ACTH]), follicle-stimulating hormone (FSH), luteinizing hormone (LH), interstitial cell-stimulating hormone (ICSH), luteotropic hormone or prolactin (LTH), somatotropic hormone (STH), and melanocyte-stimulating hormone (MSH). Hypothalamic damage from viral or other infections, granulomatous diseases (e.g., sarcoidosis), degenerative disorders, or tumor metastases has pathologic effects on the function of other peripheral tissues and endocrine organs. Such relations exist in obesity or anorexia nervosa, hypogonadism (e.g., pubertas tarda, sterility, amenorrhea), and certain rare polysymptomatic syndromes (Prader-Labhart-Willi syndrome, Laurence-Moon-Bardet-Biedl syndrome).
The pituitary gland consists of an anterior lobe (adenohypophysis) and a posterior lobe (neurohypophysis), which has a stalk that connects the organ to the infundibulum hypothalami. The anterior lobe develops from an ectodermal outgrowth of the oral cavity, whereas the posterior lobe with the stalk represents a downward extension of the brain. The neurohypophysis (posterior lobe) serves as a reservoir for AVP (antidiuretic hormone [ADH]) and oxytocin, both of which are secreted from the hypothalamus by unmyelinated nerve endings. The adenohypophysis, which composes approximately 80% of the organ, is the major hormone-producing part of the pituitary gland. The epithelial cells of the adenohypophysis are classified as acidophilic, basophilic, and chromophobe cells, depending on their hormonal functions.
Acidophilic or chromophobe adenomas may secrete excessive somatotropin (growth hormone [GH]), which produces gigantism in prepubertal children or acromegaly in postpubertal individuals. Exposure to excessive GH before epiphyseal closure leads to symmetric giant growth. After symphyseal fusion, excessive GH causes asymmetrical growth affecting the nose, the chin, the hands, and the toes. Persons with acromegaly show hyperostosis, cardiomegaly and visceromegaly, thickened skin, and other endocrine abnormalities. Clinical features include arthralgia, muscle weakness, neuropathy, and hypertension in approximately one third of patients. Patients are at high risk for cardiovascular and respiratory failure and cerebrovascular death unless the adenoma is removed by surgery or radiation.
Basophil adenomas are uncommon, usually small, and located within the normal-sized gland. They may secrete corticotropins (corticotropin adenoma) or related peptides, such as lipotropin and endorphins. **Crooke hyaline**, homogeneous hyaline globules consisting of densely packed, keratin-positive paranuclear intermediate filaments, is characteristic of basophil adenomas. Crooke hyaline is seen when Cushing disease is caused by primary adrenal tumors or in prolonged corticotropin therapy.

Clinical features of functioning corticotrophic adenomas are described as **Cushing syndrome**: truncal obesity with **moon facies**, systemic hypertension, muscle weakness (decreased muscle mass), hyperglycemia, and thirst. Osteoporosis, hirsutism (male-type hair distribution in females) and amenorrhea, mood swings, and depression are also characteristic. The diagnosis is further confirmed by elevated free cortisol in the 24-hour urine.
Chromophobe adenomas, the most common pituitary tumors, constitute approximately 15% of all intracranial tumors. They occur in both sexes, usually in later life (sixth decade). Chromophobe adenomas, which may remain microscopic for long periods, most often compress the optic chiasm, causing subsequent bitemporal hemianopsia when they expand. Vision impairment is often the initial clinical sign. Functioning chromophobe adenomas produce a variety of hormones, including prolactin (lactotrophic adenomas), somatotropin (somatotropic adenomas), LH and FSH (gonadotropic adenomas), and, rarely, TSH (thyrotropic adenomas). Clinical features differ according to adenoma type with signs of hypogonadism and virilization, acromegaly, hypothyroidism, and others. Some adenomas produce more than 1 hormone including corticotropins.
Hypopituitarism refers to deficiencies in hormone production by the adenohypophysis (anterior lobe of pituitary). The lack of hormone affects the function of peripheral endocrine tissues. Hypopituitarism is caused by destruction of the gland by tumor metastases, local tumors extending into the *sella turcica*, infiltrative processes such as infections (e.g., tuberculosis), metabolic disorders (e.g., hemochromatosis, Hand-Schüller-Christian disease), ischemic postpartum necrosis (Sheehan syndrome), hemorrhagic infarction (pituitary apoplexy), or, rarely, hypophyseal atrophy secondary to subarachnoid space herniation (empty sella syndrome). Symptoms develop slowly and occur when approximately 75% of the adenohypophysis is lost. Hormone replacement is the therapy of choice. The underlying disease causing the hypopituitarism determines the prognosis.
Deficient hormone release by the neurohypophysis (posterior lobe of pituitary) results in inadequate ADH availability. Diabetes insipidus, characterized by uncontrolled water diuresis, polyuria, and polydipsia (excessive thirst), ensues. Although patients consume large amounts of water daily, they may experience life-threatening dehydration. Diabetes insipidus is caused by a variety of processes (head trauma, infection, neoplasm), but many cases develop without recognizable underlying disease. Cranio-pharyngioma, a dysontogenetic tumor derived from displaced epithelium of the Rathke pouch, is one of the more common tumors that compresses and destroys the neurohypophysis.

**Figure 12-8  Diabetes Insipidus**

Deficient hormone release by the neurohypophysis (posterior lobe of pituitary) results in inadequate ADH availability. Diabetes insipidus, characterized by uncontrolled water diuresis, polyuria, and polydipsia (excessive thirst), ensues. Although patients consume large amounts of water daily, they may experience life-threatening dehydration. Diabetes insipidus is caused by a variety of processes (head trauma, infection, neoplasm), but many cases develop without recognizable underlying disease. Cranio-pharyngioma, a dysontogenetic tumor derived from displaced epithelium of the Rathke pouch, is one of the more common tumors that compresses and destroys the neurohypophysis.
In the thyroid follicular epithelial cells, iodide, which is absorbed in the gastrointestinal (GI) tract, is oxidized to I\(_2\), which serves for the stepwise iodination of tyrosine. The combination of 2 molecules of diiodotyrosine produces T\(_4\) (L-thyroxin). The coupling of 1 molecule of monoiodotyrosine to 1 molecule of diiodotyrosine results in T\(_3\). T\(_4\) and T\(_3\) are the main thyroid hormones. They are coupled to thyroglobulin and are stored in follicular colloids. Proteolytic enzymes release T\(_4\) and T\(_3\) into the circulation as active hormones when stimulated. Proteolysis, the follicular epithelial resorption and release of the hormone by these cells, is accompanied morphologically by such signs of follicular activation as paraepithelial resorptive vacuoles in the colloid and epithelial swelling (cuboidal size) and proliferation (focal stratification to form Sanderson cushions and papillae). Various steps in iodine/hormone metabolism can be blocked by chemicals, which thus can be used to treat thyroid functional aberrations.
Hyperthyroidism is associated pathologically with diffuse or nodular goiter, Graves disease (morbis Basedow), thyroid adenoma and carcinomas, and certain forms of early thyroiditis. The etiology of Graves disease, the most common cause of hyperthyroidism, remains obscure. The diagnosis is confirmed by scintigraphic demonstration of increased T4, T3 uptake in the thyroid gland. Autoantibodies against follicular epithelial membranes, which may bind to the TSH receptor and thus contribute to thyroid stimulation, are frequently observed. The thyroid, which is grossly enlarged, firm, and red (struma parenchymatosa), shows histologically diffuse follicular activation and hyperplasia with resorption of colloid and eventual lymphocytic infiltration. The clinical course is variable, with exacerbations, remissions, and final hypothyroidism after secondary chronic nonspecific thyroiditis.
Hypothyroidism is characterized by a reduction of the physiologic thyroid function with respectively reduced thyroid hormone excretion. Congenital hypothyroidism is related to developmental defects and may occur endemically. In addition, there exists a sporadic, intrauterine post-inflammatory or post-toxic hypothyroidism with unresponsiveness of the thyroid gland to TSH stimuli and deficient thyroid hormone synthesis. Patients are of short stature, with thick yellowish skin and a characteristic facial expression. Eyelids are puffy, the nose is flat and thick, and the tongue is enlarged and protruding. The neck is short and
Primary myxedema

- Hair dry, brittle
- Lethargy, memory impairment, slow cerebration (psychoses may occur)
- Edema of face and eyelids
- Thick tongue, slow speech
- Deep coarse voice
- Sensation of coldness
- Diminished perspiration
- Heart enlarged, poor heart sounds, precordial pain (occasional)
- Hypertension (frequently)
- Skin coarse, dry, scalding, cold (follicular keratosis), yellowish (carotenemia)
- Pulse slow
- Ascites
- Menorrhea (amenorrhea may occur late in disease)
- Weakness
- Reflexes, prolonged recovery

Pituitary myxedema (differential features)

- Hair finer, softer
- Loss of axillary hair
- Heart small
- Hypotension
- Skin less dry, not scaly
- Loss of pubic hair
- Amenorrhea

PBI and BEI; low—no rise after TSH

- Low, but rise after TSH

- 1\(^{131}\); 24-hour uptake low—no rise after TSH

- Low, but rise after TSH

- Cholesterol; elevated (usually)

- Normal (usually)

- Uric acid; elevated in males and postmenopausal females

- Same

- Urinary gonadotropins; positive

- Absent

- 17-Ketosteroids; low

- Lower

- BMR; usually low, but very variable

- Same

---

BMR, basal metabolic rate; BEI, butanol-extractable iodine; PBI, protein-bound iodine; TSH, thyroid-stimulating hormone.

**FIGURE 12-11 CONGENITAL HYPOPHYROIDISM AND MYXEDEMA (CONTINUED)**

thick. Adult hypothyroidism manifests as myxedema. Patients experience tiredness and lethargy. Their hair is dry and brittle, their skin is thickened (myxedema), and the face resembles to a certain extent that in cretinism. The heart rate is usually decreased, and some patients have psychotic crises (myxedema madness). Laboratory tests show a decrease of T4 levels in the blood, whereas TSH is significantly increased.
Goiter (struma) refers to an enlargement (usually nodular) of the thyroid related to either hyperthyroidism or hypothyroidism. Goiter in combination with hyperthyroidism, as is seen in Plummer syndrome (toxic goiter), is usually autonomous but not cancerous. Goiter can be caused by low dietary intake of iodine but is usually caused by increased levels of TSH in response to a defect in hormone synthesis in the thyroid gland. Patients with goiter usually remain asymptomatic except for progressive swelling of the neck with potential airway obstruction and dysphagia or compression of the recurrent nerve with hoarseness. Microscopically, there is diffuse or nodular crowding of enlarged follicles. In time, regressive changes with chronic reactive inflammation and fibrosis develop. Focal intrafollicular hemorrhage and siderosis and follicle rupture with signs of colloid resorption and foreign body granulomatous reaction may occur.
There are several forms of primary thyroiditis (Table 12-1). The thyroid gland is usually enlarged (except in Riedel thyroiditis, in which the gland is small to undetectable) and tender with radiating pain. Regional lymph nodes are enlarged, suggesting an inflammatory disease. Patients may be euthyroid with eventual hyperthyroidism related to follicle destruction (hashitoxicosis in Hashimoto disease) but eventually have hypothyroidism. Thyroid autoantibodies and cytotoxic T lymphocytes often can be shown.
### TABLE 12-1 PRIMARY INFLAMMATION OF THE THYROID GLAND (THYROIDITIS)

<table>
<thead>
<tr>
<th>Entity</th>
<th>Pathology</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphofollicular thyroiditis (Hashimoto thyroiditis), chronic</td>
<td>Lymphocytic/plasmacellular infiltrate with lymph follicles, follicle destruction, oxyphilic metaplasia of follicle cells (Hürthle or Askanazy cells)</td>
<td>T-cell autoimmune reaction (TPO, TMA), genetic predisposition</td>
</tr>
<tr>
<td>Granulomatous thyroiditis (de Quervain thyroiditis), subacute</td>
<td>Microfocal neutrophilic infiltrates, follicle destruction with secondary giant cell granulomatous reaction, marked lymphoplasmacellular infiltrates</td>
<td>E.g., virus infection: coxsackie, adenovirus, mumps, and others, secondarily autoimmune</td>
</tr>
<tr>
<td>Chronic sclerosing thyroiditis (Riedel thyroiditis)</td>
<td>Lymphocytic thyroiditis with progressive glandular atrophy and fibrosis extending to adjacent tissues</td>
<td>Suggestively autoimmune*</td>
</tr>
<tr>
<td>Painless subacute thyroiditis</td>
<td>Lymphocytic infiltrates with eventual follicular destruction, usually self-limited, hyperthyroid</td>
<td>Unknown HLA-DR3 associated</td>
</tr>
</tbody>
</table>

TMA indicates thyroid microsomal antigen; TPO, thyroid peroxidase antigen.
*Associated with primary sclerosing cholangitis

### FIGURE 12-13 THYROIDITIS (CONTINUED)

Some cases of autoimmune thyroiditis are part of systemic autoimmune disorders such as collagen-vascular diseases. Consequently, careful examination of the patient with primary thyroiditis is recommended. The nature of the autoimmune process usually determines the prognosis of the thyroiditis.
Autonomous proliferative diseases of the thyroid consist of adenomas (benign) and carcinomas (malignant), either of which may be hormone-producing tumors. Adenomas (usually autonomous nodules in a nodular goiter) show signs of hyperthyroidism, tachycardia, shortness of breath, nervousness, weight loss, and emotional instability, although they are usually less pronounced than in Graves disease. Iodine uptake is increased in the adenoma (scintigram), and blood iodine is moderately increased (protein-bound as well as butanol-extractable forms). Certain forms of adenoma are difficult to distinguish from well-differentiated follicular carcinoma (atypical adenoma with cellular atypia, mitoses, or even vascular invasion); therefore, adenomas should be removed and studied histologically (see also Table 12-3).
The 4 major types of thyroid carcinomas (Table 12-2) differ histologically, in their routes of metastasis, and in their prognosis. Papillary, follicular, and anaplastic carcinomas are derived from follicular epithelial cells. Medullary carcinoma is an endocrine tumor from calcitonin-producing interstitial C cells. This tumor may occur in combination with other related endocrine tumors forming familial MEN syndromes, such as MEN-2 with associated pheochromocytoma. The clinical features of such tumors are determined by the combination of different neoplasms. Medullary carcinoma may show symptoms of carcinoids (flushing, watery diarrhea), Cushing syndrome, hyperparathyroidism (HPPT), and episodic hypertension. The life expectancy of patients with MEN is generally shorter than that of patients with solitary medullary carcinoma.
There are 2 major forms of hyperparathyroidism (HPPT), primary and secondary, as well as combinations of the two. Eighty-four percent of primary HPPT (autonomous HPPT) is caused by parathyroid adenomas, 12% is caused by hyperplasia, and 4% is caused by parathyroid carcinomas. Secondary HPPT follows chronic renal insufficiency (renal rickets, renal osteodystrophy) with hyperphosphatemia and decreased ionized serum calcium. Parathyroid glands show diffuse or nodular hyperplasia. Long-standing secondary HPPT may be complicated by development of autonomous adenomas, thus adding a form of primary HPPT. Clinical features of HPPT are variable combinations of serum hypercalcemia with calcium deposits (kidney stones, GI mucosa, blood vessels, soft tissues, etc.) and enhanced bone resorption (osteitis cystica fibrosa, dissecting fibroosteolasia) (see also Table 12-3).
Hypoparathyroidism is a rare condition that may follow surgical resection of parathyroid glands in thyroidectomy. It causes severe hypocalcemia with paresthesias, muscle spasms, and seizures. There are occasional familial autosomal recessive forms of hypothyroidism that occur as part of a multi-glandular deficiency or in combination with T-cell immune deficiency (DiGeorge syndrome). The ionized serum calcium level provides the stimulus for PTH secretion. PTH stabilizes the serum calcium level by inhibiting renal tubular phosphate resorption and calcium/phosphate absorption in the bone. In addition, calcium absorption in the intestines may be enhanced. Calcitonin or thyrocalcitonin of thyroid interstitial C cells counteracts calcium absorption by decreasing the serum calcium level.
The adrenal cortex is composed of the zona glomerulosa (outer zone), the zona fasciculata (intermediate zone), and the zona reticularis (inner zone adjacent to adrenal medulla). The 2 inner zones respond to stimulation by hypophysial corticotropin. The outer zone functions independently of corticotropin. This zone produces the hormone aldosterone in response to potassium and angiotensin (↑) or atrial natriuretic peptide and somatostatin (↓). The inner zones produce glucocorticoids and androgens in response to corticotropins. Increased functional activity may be caused by hyperplasia, adenoma or carcinoma, and decreased functional activity by atrophy (e.g., in malnutrition), necrosis (e.g., in septicemia, tuberculosis, viral infection), or autoimmune adrenalitis. Hyperplasia of glucocorticoid-producing parts results in Cushing disease as caused by excessive corticotropin stimulation. Corticotropin-independent forms of Cushing syndrome occur in autonomous cortical adenomas or carcinomas (see also Table 12-3).
Adrenogenital syndrome (congenital and adult forms) is caused by a form of adrenal cortical hyperplasia or tumors with excessive production of 17-ketosteroids (dehydroepiandrosterone, etiocholanolone, and androsterone). In addition to androgen abnormalities, the syndrome may be complicated by alterations in sodium metabolism, glucocorticoid deficiency, or both. Clinically, there are signs of masculinization in females (hirsutism, clitoral hypertrophy, oligomenorrhea) and precocious puberty and enlargement of genitalia in males. Some forms of congenital adrenal cortical hyperplasia occur with androgen deficiency and cause pseudohermaphroditism in males. Ninety-five percent of patients with congenital adrenal hyperplasia show defects in 21-hydroxylase, which results from mutations on chromosome 6.

**Figure 12-18 Adrenogenital Syndrome**

Adrenogenital syndrome (congenital and adult forms) is caused by a form of adrenal cortical hyperplasia or tumors with excessive production of 17-ketosteroids (dehydroepiandrosterone, etiocholanolone, and androsterone). In addition to androgen abnormalities, the syndrome may be complicated by alterations in sodium metabolism, glucocorticoid deficiency, or both. Clinically, there are signs of masculinization in females (hirsutism, clitoral hypertrophy, oligomenorrhea) and precocious puberty and enlargement of genitalia in males. Some forms of congenital adrenal cortical hyperplasia occur with androgen deficiency and cause pseudohermaphroditism in males. Ninety-five percent of patients with congenital adrenal hyperplasia show defects in 21-hydroxylase, which results from mutations on chromosome 6.
Adrenal cortical adenomas that simulate structures of the zona glomerulosa cause primary hyperaldosteronism (Conn syndrome). Excessive aldosterone secretion causes potassium depletion (increased potassium loss from kidneys and other exocrine glands), sodium retention, decreased plasma renin activity, and hypertension. Secondary hyperaldosteronisms in response to stimulation by the renin-angiotensin mechanisms show increased plasma renin activity. Adenomas in primary hyperaldosteronism usually remain small (less than 6 g) and can be difficult to identify clinically. Patients experience a metabolic alkalosis and muscle weakness.
Acute adrenal cortical insufficiency (adrenal crisis, Waterhouse-Friderichsen syndrome) follows the acute necrosis and hemorrhage of the adrenal cortex secondary to bacterial septicemia, usually meningococcal septicemia, and sometimes Pseudomonas, pneumococci, and Haemophilus influenzae. Bacterial toxins (endotoxins) are thought to cause diffuse vascular damage with intravascular coagulation and hemorrhage, which destroy large parts of the adrenal cortex. Other conditions that may be associated with similar adrenal hemorrhage and necrosis are birth trauma, treatment with anticoagulants, and almost all causes of disseminated intravascular coagulation (DIC). The resulting acute adrenal crisis is attributed primarily to the sudden loss of glucocorticoids.
Chronic adrenal cortical insufficiency, Addison disease, is a clinical syndrome characterized by progressive weakness and fatigue, hypotension, weight loss, skin and mucosal hyperpigmentation, and abdominal problems. Laboratory test results show hyperkalemia, hyponatremia and volume depletion (decrease in mineralocorticoids such as aldosterone), and, occasionally, hypoglycemia (decrease in glucocorticoids). Patients without adequate replacement therapy die in coma. The underlying disease is a progressive shrinking (collapse) of the adrenal cortex secondary to epithelial atrophy and chronic inflammation (lymphocytic or granulomatous). In approximately two thirds of cases, autoimmune adrenalitis is responsible for these changes. Other cases are associated with infections (tuberculosis, fungal) or tumor metastases. Sarcoidosis, amyloidosis, and hemochromatosis are less frequent causes.
The adrenal medulla consists of typical chromaffin cells (affinity to chromium salts with dark staining on oxidation), which produce the catecholamines epinephrine (80% in the adrenal medulla) and norepinephrine. Tumors of chromaffin, catecholamine-producing cells, include pheochromocytoma and paragangliomas. Pheochromocytomas, smooth yellowish-tan nodules or large hemorrhagic masses of several kilograms, may be bilateral. Nests of amphophilic chromaffin cells with a finely granular, silver-stainable cytoplasm are seen microscopically. Approximately 10% of pheochromocytomas are found in extraadrenal locations. Clinical features are headaches, intermittent hypertension, palpitation, and sweating. Approximately 10% of pheochromocytomas are part of a familial syndrome called multiple endocrine neoplasia, autosomal dominant diseases with mutations on chromosomes 10 and 11, such as 11q13 (MEN type I) and 10q1.2 (MEN types II and III).
The endocrine pancreas consists of the islets of Langerhans, which are composed of insulin-producing β cells (60-70%), α cells (15-20%), which produce the “insulin-antagonist” glucagon, several clones of δ cells (e.g., D cells, D1 cells), which secrete somatostatin or vasoactive intestinal peptide (VIP), and other substances. Hyperinsulinism caused by β-cell adenomas or carcinomas constitutes 75% of pancreatic endocrine neoplasms.

Clinical features are spontaneous hypoglycemia with hunger, tremor, perspiration, confusion, anxiety, convulsions, and coma. In nesidioblastosis, which occurs in rare cases of reactive hypoglycemia, pancreatic β cells are hypertrophic and increased in number. Islet cell carcinomas (10% of insulin-producing tumors) are less well demarcated, metastasize early, preferentially to the liver, and generally are associated with a poor prognosis.
Insulin-dependent diabetes mellitus (IDDM, type 1) is a complex disorder of carbohydrate, lipid, and protein metabolism caused by hypoinsulinism and multiorgan disease. In IDDM, the progressive destruction of β cells in pancreatic islets usually begins before the age of 20 years. Microscopically, pancreatic islets show scattered lymphocytic infiltration (predominance of cytotoxic CD8+ T lymphocytes and anti-islet cell antibodies in up to 80%) with loss of β cells and mild fibrosis. Besides genetic predisposition, virus infections such as coxsackievirus are considered the initiating events for IDDM. The metabolic disturbance is characterized by hyperglycemia with mobilization of fat and protein, negative nitrogen balance, and acidosis. Polyuria leads to loss of electrolytes and dehydration, mobilization of fat and proteins, weight loss, and hunger.
Non–insulin-dependent diabetes mellitus (NIDDM, type 2), the most common form of diabetes, is characterized by an initial decreased sensitivity of peripheral tissues to insulin (insulin resistance) followed by alterations in insulin secretion by β cells. Pancreatic islets show amyloid deposits, cell atrophy, and progressive fibrosis. The incidence of NIDDM increases with obesity and the consumption of glucose (in all nutritional forms).

Metabolic disturbances, especially hyperglycemia, cause a number of complications and secondary diseases, including progressive microangiopathy with diabetic retinopathy, renal glomerular nephrosclerosis (Kimmelstiel-Wilson disease), peripheral neuropathy, ulcer cruris, and gangrene. Many patients have severe hypertensive cardiovascular disease, which is the leading cause of mortality in this population.

Diabetic retinopathy can be easily detected during a dilated eye examination and is the leading cause of blindness among adults in the United States. Visual loss can be prevented with early recognition and treatment of retinopathy.

Diabetic nephropathy

Diabetes mellitus. Leading cause of end-stage renal disease in the Western world.

**Figure 12-25**  **Non–Insulin-Dependent Diabetes Mellitus**
The nervous system is an exceedingly complex entity responsible for the sensory, motor, and cognitive activities of the human body. The nervous system contains groups of neurons organized anatomically and specialized functionally for specific activities. The neurons are supported by the glia—the astrocytes, oligodendroglia, microglia, and ependyma in the central nervous system and the Schwann cells in the peripheral nervous system. This chapter examines a spectrum of diseases of the nervous system and their role in the differential diagnosis of common neurologic clinical presentations, including headache, vertigo, seizures (epilepsy), hydrocephalus, stroke, and coma.

### NEUROLOGIC DISORDERS OF INFANCY AND CHILDHOOD

Many neurologic disorders of infancy and childhood result from birth trauma, prematurity predisposing to hemorrhage within the germinal matrix of the brain, and a wide spectrum of development defects involving abnormalities in the formation of the neural tube (anencephaly, encephalocele), neural proliferation and migration (microcephaly), and neural organization and myelination (porencephaly). The chronic motor dysfunction known as cerebral palsy often develops in surviving infants.

### CEREBROVASCULAR DISEASE

Cerebrovascular disease presents as a transient ischemic attack or the more severe and persistent neurologic deficit of stroke. It stems from underlying pathology of the extracranial or intracranial cerebral vasculature. The major categories are ischemic strokes due to thrombosis, embolism or hypoxia, and hemorrhagic strokes due to rupture of a cerebral vessel. Global cerebral ischemia is caused by hypotension, hypoperfusion, and low flow states and results in multifocal infarcts in the border zones (watershed areas) at the interface between the perfusion zones of 2 major arteries or more diffuse encephalopathy.

Significant obstruction of a component of the carotid or vertebrobasilar arterial trunks leads to focal cerebral ischemia or infarction. In situ thrombosis of a cerebral artery is usually secondary to atherosclerosis or, less commonly, arteritis associated with infections or collagen-vascular diseases. Other cases of cerebral infarction are due to emboli to the cerebral vasculature from thrombi formed in a diseased heart, the aorta, or a major extracranial cerebral artery. The effects of arterial occlusion can be mitigated to a variable extent by the collateral circulation, particularly through the circle of Willis at the base of the brain. Pale, nonhemorrhagic infarcts are produced by in situ thrombosis, whereas hemorrhagic infarcts due to influx of blood from collateral vessels are produced with cerebral emboli. The distinction between infarction due to in situ thrombosis versus embolization is important for optimal clinical treatment, which does not call for the use of anticoagulants in cases of hemorrhagic infarcts due to cerebral emboli.

Hypertension is the most common and important cause of primary intracerebral (intraparenchymal) hemorrhage. Other causes include vascular malformations and hematologic disorders. Hypertension produces cerebral arteriolar sclerosis and Charcot-Bouchard microaneurysms. Rupture of the microaneurysm leads to hemorrhage into the brain parenchyma, with frequent extension into the ventricles and subarachnoid space. Hypertensive hemorrhages originate in the basal ganglia in approximately 75% of cases and other sites in the remainder. The most common cause of a major primary subarachnoid hemorrhage is the rupture of a saccular (or berry) aneurysm, located at bifurcation sites of the arteries of the circle of Willis.

### TRAUMA

Traumatic brain injuries include concussion, contusion, skull fracture, and hemorrhage, which may be epidural, subdural, subarachnoid, or intraparenchymal. Epidural hematoma results from rupture of a meningeal artery and follows a hyperacute course, whereas subdural hematoma results from rupture of bridging veins and follows an acute or a chronic course, depending on the severity of the injury. Trauma of the spinal cord produces a variety of neurologic deficits not only from direct neurologic trauma, but also from direct and delayed damage to the vasculature, with resultant paraplegia or quadriplegia, depending on the level of injury.

### BRAIN TUMORS

Tumors of the central nervous system are either primary or metastatic. The more common metastatic brain tumors may take origin from virtually any primary neoplasm, but the most frequent are lung, breast, melanoma, kidney, and colon. The primary tumors of the central nervous system are classified as gliomas and nonglial neoplasms, including neuronal tumors and meningiomas. The gliomas are the most common primary tumors of the brain and include astrocytomas, oligodendrogliomas, and ependymomas. In children, most brain tumors arise in the posterior fossa and include astrocytomas and medulloblastomas of the
cerebellum and gliomas of the brainstem, whereas in adults, most brain tumors arise in the cerebral hemispheres. The distinction between benign and malignant lesions is blurred because of the infiltrative growth pattern, frequent involvement of vital structures, and the tendency for lower-grade lesions to transform over time to higher-grade lesions, including the glioblastoma multiforme. Meningiomas are typically benign tumors of adults that arise from the meningoeipithelial cells of the arachnoid, become attached to the dura, and produce symptoms by compression of adjacent structures. Most tumors of peripheral nerves are derived from Schwann cells. Acoustic neuroma is a single lesion that produces a mass effect in the cerebellopontine angle. Neurofibromatosis, or von Recklinghausen disease, is the prototype of a group of inherited disorders known as phacomatoses, in which defects of the neural crest lead to multifocal lesions of the nervous system and the skin.

DEGENERATIVE DISEASES
Degenerative diseases are characterized by loss of neurons in various regions of the gray matter in selective patterns. These patterns characterize the various clinicopathologic conditions that have obscure etiologies. Dementia, or progressive loss of cognitive function, is a major manifestation of the degenerative diseases. Alzheimer disease is characterized by cerebral atrophy, most pronounced in the frontal, temporal, and parietal lobes and associated with the microscopic findings of neurofibrillary tangles, senile (neuritic) plaques, and amyloid angiopathy. Huntington disease is inherited with an autosomal dominant pattern and is characterized by dementia plus uncoordinated movements (chorea) and by atrophy of the frontal lobes and the caudate nucleus. Creutzfeldt-Jakob disease is characterized by spongiform degeneration of the cerebral cortex, with the pathogenesis involving mutated proteins called prions. Parkinsonism, as seen in idiopathic Parkinson disease and related conditions, is a clinical syndrome with impaired facial and voluntary muscle movements, intention tremor, rigidity, and shuffling gait. The underlying mechanism is impairment of the nigrostriatal dopaminergic system, with prominent neuronal degeneration in the substantia nigra and the locus ceruleus.

INFECTIOUS DISEASES
Infections of the central nervous system may develop as a result of seeding of microorganisms via the hematogenous route, direct implantation from trauma or medical intervention, local spread from a contiguous site such as the paranasal sinuses, or retrograde spread along a peripheral nerve, as is the case with certain viral infections such as herpes simplex and rabies. Infectious meningitis of the leptomeninges and the cerebrospinal fluid (CSF) presents with fever, somnolence, and stiff neck. Examination of the CSF is important to differentiate acute pyogenic bacterial meningitis (numerous white blood cells with neutrophil predominance, high protein, low glucose) from aseptic (viral) meningitis (lymphocytic pleocytosis, moderate protein increase, normal glucose) and chronic forms of meningitis, including tuberculous meningitis (pleocytosis with mononuclear cells or mixed mononuclear cells and neutrophils, markedly increased protein level, and moderately reduced or normal glucose level). Parameningeal infections consist of brain abscess, subdural empyema, and spinal epidural abscess. Neurosyphilis occurs late in the course of approximately 10% of untreated patients and may be manifest as meningeval-meningovascular disease, dementia paralytica (general paresis), or tabes dorsalis. A number of viruses can produce encephalitis or encephalomyelitis, characterized by meningeal and parenchymal, particularly perivascular, inflammation. The viruses include arthropod-borne viruses (e.g., eastern and western equine encephalitis), herpes simplex virus (HSV) types 1 and 2, varicella-zoster virus, cytomegalovirus, poliomyelitis, rabies, human immunodeficiency virus types 1 and 2, and viruses responsible for so-called slow virus infections, including progressive multifocal leukoencephalopathy. Immunosuppressed patients are particularly susceptible to fungal infections such as Candida albicans, Mucor species, Aspergillus fumigatus, and Cryptococcus neoformans and protozoal infections such as Toxoplasma gondii.

DEMYELINATING DISEASES
Multiple sclerosis is a classic chronic demyelinating disease in which multiple areas of demyelination produce spatially separated plaques in the cerebral white matter that are associated with temporally separated episodes of clinical neurologic deficits. The pathogenesis involves inflammatory damage to the oligodendroglia and white matter, with altered immunity contributing to the process. The disease has a 2:1 female-to-male prevalence and is characterized by multiple exacerbations and remissions.

DISORDERS OF THE SPINAL CORD, NERVE ROOT, AND PLEXUS
Spinal cord dysfunction can be produced by primary or metastatic tumors in or about the cord, vascular occlusion, epidural abscess, transverse myelitis (acute demyelinating disorder), cervical or lumbar disc herniation, syringomyelia (a developmental or degenerative defect), and toxic and metabolic disorders, including subacute combined degeneration caused by vitamin B12 deficiency. Amyotrophic lateral sclerosis combines manifestations of lower motor neuron degeneration leading to muscular weakness with upper motor neuron and corticospinal tract degeneration leading to muscle spasticity.

DISORDERS OF THE MOTOR NEURON, PERIPHERAL NERVE, NEUROMUSCULAR JUNCTION, AND SKELETAL MUSCLES
Peripheral neuropathies manifest as subacute or chronic sensory and motor dysfunction resulting from metabolic, toxic, or nutritional disorders or vasculitis, particularly polyarteritis nodosa (PAN). Guillain-Barré syndrome is an acute,
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rapidly progressive, ascending paralysis due to inflammatory demyelination of peripheral nerves, with potential for reversal. *Myasthenia gravis* is manifest as muscle weakness due to autoimmune attack on acetylcholine receptors at the neuromuscular junction. *Muscular dystrophies* are a heterogeneous group of inherited diseases manifest as progressive muscle weakness and degeneration of skeletal muscle, usually with onset in childhood (e.g., Duchenne muscular dystrophy). *Polymyositis* and *dermatomyositis* are autoimmune, inflammatory disorders producing proximal muscle weakness with or without skin rash.
In the newborn, certain forms of intracranial hemorrhage are usually related to birth trauma, and these include subdural hemorrhage, subarachnoid hemorrhage, and posterior fossa hemorrhage. However, other factors, particularly prematurity and asphyxia, are involved in periventricular and intraventricular hemorrhage. **Periventricular-intraventricular hemorrhage** originates in the germinal matrix and occurs with increasing frequency in relation to the degree of prematurity of the infant. Such bleeding causes a high mortality rate. Surviving infants often develop cerebral palsy.

**Figure 13-1 Cranial Hemorrhage**

Intracranial Hemorrhage in Newborn

CT scan. Showing subdural hematoma due to tentorial tear

Large subdural hemorrhage. Over convexity of right cerebral hemisphere; subarachnoid hemorrhage on left side

Tear of tentorium and great cerebral vein (of Galen). With massive subdural hemorrhage in posterior fossa

CT scan. Subdural and subarachnoid hemorrhage

Periventricular-intraventricular hemorrhage. Filling and distending lateral and 3rd ventricles, passing through cerebral aqueduct (of Sylvius) into 4th ventricle, then via lateral and median apertures into cerebellomedullary cistern of posterior fossa

Unilateral periventricular-intraventricular hemorrhage. Originating in germinal center over head of caudate nucleus, distending frontal and temporal horns of lateral ventricle, and passing through interventricular foramen (of Monro) into 3rd ventricle

Intracerebellar hemorrhage. Ruptured into 4th ventricle

CT scan. Showing periventricular-intraventricular hemorrhage
The time of onset of prenatal injury predicts the type of maldevelopment and resultant prenatal encephalopathy characterized by defects in the formation of the neural tube (first trimester), neural proliferation and migration (second trimester), and neural organization and myelination (third trimester). Defects in neural tube formation in the first trimester result in anencephaly, encephalocele, or holoprosencephaly (arhinencephaly), the latter characterized by a single ventricle with defective olfactory and optic systems, and impairment of caudal closure results in meningomyelocele. During the phase of neuronal proliferation, a decrease in number of neurons leads to microcephaly, whereas an increase results in megalencephaly. With defective neuronal migration, gyral formation does not occur, resulting in lissencephaly (smooth brain) or other lesions, such as agenesis of the corpus callosum. Abnormalities in intrauterine cerebral blood flow, if severe, can result in the rare disorder of hydranencephaly and, if less severe, porencephaly characterized by cystic spaces in the brain parenchyma.
Spinal dysraphism includes several conditions characterized by congenital failure of fusion of the midline structures of the spinal column. The resultant clinical spectrum ranges from an asymptomatic bony abnormality (spina bifida occulta) to severe and disabling malformation of the spinal column and spinal cord (meningomyelocele). Lesions in the lumbosacral region and higher may produce paraplegia and loss of bowel and bladder control; hydrocephalus develops in approximately 90% of cases. The hydrocephalus is related to a congenital deformity of the hindbrain, known as the Arnold-Chiari malformation, in which the posterior fossa structures are downwardly displaced into the spinal canal and interfere with the circulation and absorption of CSF.

**Figure 13-3  Spinal Dysraphism**

Spina bifida occulta

Dermal sinus

Meningocele

Meningomyelocele

Spina bifida. With central cicatrix

Fat pad overlying spinal bifida occulta. Tuft of hair or only skin dimple may be present, or there may be no external manifestation. Dermal sinus also present in this case (arrow).
Hydrocephalus, characterized by enlargement of the ventricles of the brain, results from increased formation or decreased absorption of CSF (communicating hydrocephalus) or from blockage of one of the normal outflow paths of the ventricular system (obstructive hydrocephalus). Obstructive hydrocephalus often results from a congenital stenosis of the cerebral aqueduct of Sylvius, but a brainstem tumor or a posterior fossa tumor encroaching on the fourth ventricle that obstructs one of the medial or lateral apertures can produce the same effect. In adults, brain tumors are the usual cause of obstructive hydrocephalus. Communicating hydrocephalus may occur in premature infants after intraventricular hemorrhage. In children and adults, communicating hydrocephalus with increased intracranial pressure may follow an intracranial hemorrhage or infection. Adults also may have normal-pressure hydrocephalus, which must be differentiated from ventricular dilatation secondary to brain atrophy (hydrocephalus ex vacuo).
Hypotonia is an important clinical sign of neurologic problems in infants and young children. Classically, the infant hangs like a rag doll when lifted under the abdomen and exhibits weakness and flaccidity of all muscles. Muscle weakness coexisting with hypotonia indicates involvement of the peripheral nervous system, whereas the presence of brisk reflexes and a positive Babinski sign indicate involvement of the central nervous system. Friedreich ataxia, which is inherited in an autosomal recessive fashion, is the most common of the spino cerebellar degenerations in older children. The differential diagnosis includes various congenital myopathies and connective tissue diseases. Neurologic disease in infants and young children can also result from several inherited single gene defects of lipid metabolism (Niemann-Pick disease, Gaucher disease, and metachromatic leukodystrophy).
Brain tumors in children are found most commonly in the posterior fossa. The more common astrocytomas and medulloblastomas develop from the parenchyma of the cerebellum. Symptoms include evidence of cerebellar dysfunction (ataxia of the trunk and extremities) and obstruction of CSF flow, leading to headache, nausea, and vomiting. Other tumors include ependymomas, which originate from the ependymal cells lining the ventricular system, and brainstem gliomas. Treatment of posterior fossa tumors involving a combination of surgery, radiation therapy, and chemotherapy, can yield a favorable prognosis, whereas the prognosis for brainstem gliomas is generally poor.

**Figure 13-6  Brain Tumors in Children**

Brain tumors in children are found most commonly in the posterior fossa. The more common astrocytomas and medulloblastomas develop from the parenchyma of the cerebellum. Symptoms include evidence of cerebellar dysfunction (ataxia of the trunk and extremities) and obstruction of CSF flow, leading to headache, nausea, and vomiting. Other tumors include ependymomas, which originate from the ependymal cells lining the ventricular system, and brainstem gliomas. Treatment of posterior fossa tumors involving a combination of surgery, radiation therapy, and chemotherapy, can yield a favorable prognosis, whereas the prognosis for brainstem gliomas is generally poor.
Tuberous Sclerosis is a neurocutaneous syndrome caused by a genetic mutation that occurs spontaneously or is inherited as an autosomal dominant trait. Tuberous Sclerosis is characterized by the formation of tubers, foci of abnormal neural tissue growth, in the nervous system and retina. The clinical features in childhood are dominated by epilepsy and mental retardation, although some patients may have neither manifestation. Cutaneous manifestations include adenoma sebaceum, depigmented nevi, a shagreen patch in the lumbar area, and subungual fibromas. Some patients have cardiac tumors, known as rhabdomyomas, or angiomyolipomas in the kidneys or both. Sturge-Weber disease, which occurs sporadically, presents with a characteristic port-wine nevus that is apparent at birth. Brain lesions consist of hypervascularity and calcification in the leptomeninges and gray matter. The course is progressive, with increasing seizures and hemiparesis.

**Figure 13-7 Neurocutaneous Syndromes**

- **Tuberous Sclerosis**: Consisting of many astrocytes, scanty nerve cells, some abnormal sites.
- **Multiple small tumors**: Caudate nucleus and thalamus projecting into ventricles.
- **CT scan**: Showing calcified lesions in periventricular area.
- **Adenoma sebaceum**: Over both cheeks and bridge of nose.
- **Facial nevus**: CT scan, showing calcifications and atrophy in temporoparietal area.
- **Sturge-Weber disease**: X-ray film showing “railroad” calcification.
- **Calcific deposits and hypervascularity**: In leptomeninges and gray matter of brain.
The headache syndromes include migraine (vascular headache), cluster headache (a migraine variant), muscle contraction headache (often stress related), and headache due to temporal (giant cell) arteritis. Temporal (giant cell) arteritis is an inflammatory disease that occurs in older individuals and affects the temporal branches of the external carotid artery. A steady, aching pain in the temporal and occipital regions, often accompanied by malaise and fever, is symptomatic. The temporal and occipital arteries are firm, tender, and pulseless. Histologically, the arteries are infiltrated by lymphocytes, plasma cells, and giant cells, and the lumen is occluded by organized thrombus. Intracranial vessels are affected occasionally, and blindness can result when ophthalmic arteries are involved. The generalized malaise, muscle pain and stiffness, fever, and other symptoms constitute an associated syndrome of polymyalgia rheumatica.
Dizziness is a general term used to describe a variety of feelings related to a disturbed sense of relation to space, including unsteadiness and giddiness. Vertigo refers more specifically to a sensation of exterior motion, often described as spinning, turning, or rotating of the external environment in relation to the person. Vertigo may be caused by dysfunction of any of the structures that are involved in sound detection or the relay of signals from the vestibular apparatus of the ear to the brain. Useful clues to localization include an analysis of effect of movement or change in position, features of the motion, abnormal symptoms or signs related to dysfunction of adjacent structures, previous attacks, nystagmus, and laboratory tests such as electroencephalography, audiometric tests, computed tomography (CT), and magnetic resonance imaging (MRI).
Seizures are triggered by the sudden and intense increase in the discharge of neurons and constitute the symptomatic expression of epilepsy. **Primary seizures** are of unknown etiology and are typically generalized without (petit mal) or with tonic-clonic muscle contractions (grand mal). **Secondary seizures**, which may be focal or generalized, result from an identifiable pathologic lesion or disease process, which may be either intracranial or extracranial. The most common intracranial lesions causing seizures are tumors, vascular lesions, head trauma, infectious diseases, congenital defects, and biochemical or degenerative diseases affecting the brain. Extracranial causes of seizures include various metabolic, electrolyte, and biochemical disturbances; fever; inborn errors of metabolism; anoxia; hypoglycemia; toxic processes; and drugs or abrupt withdrawal from drugs or alcohol.

**Figure 13-10  Causes of Seizures**
Coma results from loss of consciousness as indicated by the complete absence of awareness of the environment or response to environmental stimuli. Confusion and stupor represent lesser degrees of impairment of consciousness. Consciousness is maintained by coordinated neural activity in both cerebral hemispheres reinforced by the reticular activating system located in the tegmentum of the brainstem. Consciousness is diminished or lost by major impairment of the reticular activating system or extensive damage to both cerebral hemispheres. The basic pathophysiologic mechanisms for loss of consciousness are (1) bilateral cerebral hemisphere disease, (2) unilateral cerebral hemisphere lesion with compression of the brainstem, (3) primary brainstem lesion, and (4) cerebellar lesion with secondary brainstem compression. These should be differentiated from nonorganic or feigned stupor.

**Figure 13-11 Differential Diagnosis of Coma**
Stroke refers to a constellation of disorders in which brain injury is caused by a vascular disorder. The 2 major categories of stroke are ischemic, in which inadequate blood flow due to thrombosis, embolism, or generalized hypoxia causes one or more localized areas of cerebral infarction, and hemorrhagic, in which bleeding in the brain parenchyma or subarachnoid space causes damage and displacement of brain structures. The clinical spectrum of focal cerebral ischemic events includes transient ischemic attacks, residual ischemic neurologic deficit, and completed infarction.
Atherosclerosis is characterized by the development of foci of intimal thickening composed of variable combinations of fibrous and fatty material and known as fibrous (atheromatous) plaques. Such lesions tend to form adjacent to branch points in arteries. The fibrous plaques may remain static, regress, progress, become calcified, or develop into complicated atheromatous lesions called dangerous or vulnerable plaques because they are responsible for clinical disease. Complications include loss of endothelial integrity, overt surface ulceration, aggregation of platelets and fibrin on the eroded plaque surface, hemorrhage in the plaque, formation of mural thrombi, embolization of plaque contents or thrombotic material or both, and total arterial occlusion by thrombus. The consequences of thrombotic occlusion are variable and unpredictable depending on the extent of disease and the amount of preexisting collateral blood flow. Thrombotic occlusion often results in tissue infarction.
Stenosis or occlusion of a carotid artery accounts for a high percentage of strokes. The most common location for atherosclerosis in the carotid system is at the bifurcation of the common carotid artery into the internal and external carotid arteries. Atherosclerotic stenosis at the origin of the common carotid artery is rare, but aortic arch arteritis (Takayasu disease) can occlude the proximal common carotid artery and other aortic branches. The extracranial pharyngeal portion of the internal carotid artery is usually spared of atherosclerosis but is subject to fibromuscular dysplasia and medial dissection. Atherosclerosis can affect the siphon portion of the carotid artery and the site of bifurcation of the internal carotid artery into anterior and middle cerebral arteries after it has begun its intracranial course. Ischemia in the internal carotid territory can lead to visual field defects, language defects, and hemiparesis or hemiplegia.
Collateral circulation occurs by blood flow from the vasculature supplied by one major blood vessel into the vascular branches of another major blood vessel through small vascular channels that connect the two systems. Occlusion of the internal carotid artery can be partially ameliorated through collateral circulation. The major extracranial pathways of collateral circulation are anastomoses between the ophthalmic artery and branches of both external carotid arteries. The major intracranial pathways of collateral circulation are the anastomoses formed by the circle of Willis at the base of the brain. The amount of collateral circulation is determined by the specific anatomy of the vascular connections and the extent and distribution of vascular disease.
The internal carotid artery bifurcates within the cranial cavity into the anterior cerebral artery (which supplies the anterior parietal cerebral hemisphere) and the larger middle cerebral artery (which supplies the lateral cerebral hemisphere and most of the basal ganglia) after giving origin to the ophthalmic, anterior choroidal, and posterior communicating artery branches. The middle cerebral artery contributes penetrating lenticulostriate branches that arise from its horizontal main stem and trifurcates near the lateral cerebral (sylvian) fissure into major superior and inferior trunks and a small anterior temporal artery. Occlusion of the main stem of the middle or anterior cerebral artery or their superficial branches is usually caused by an embolus from the heart or the proximal vessels, particularly the internal carotid artery.
Atherosclerosis involves large- and medium-sized cerebral arteries, whereas hypertension produces disease of small penetrating arteries of the brain. Progressive arteriolosclerosis develops in the small vessels. Hyaline and fibrinoid material thickens the wall and obliterates the lumen. The lacunae (holes), the small, round lesions deep in the brain parenchyma, are commonly found in the brain at autopsy. Some lesions are clinically significant. A small infarct in the base of the pons or internal capsule can produce a pure motor hemiplegia with contralateral weakness of the face, the arm, and the leg but no sensory, visual, or intellectual defects. Other lesions can produce pure sensory strokes. Lacunar lesions in the pons can produce several syndromes, including hemiparesis coupled with ataxia.

**Figure 13-17  Lacunar Infarction**

A small (100 μm) artery within brain parenchyma. Showing typical pathologic changes secondary to hypertension. Vessel lumen almost completely obstructed by thickened media. Pink-staining fibrinoid material within walls.

Lacunar infarcts in base of pons. Interrupting some corticospinal (pyramidal) fibers. Such lesions cause mild hemiparesis.

Multiple bilateral lacunae and scars of healed lacunar infarcts. In thalamus, putamen, globus pallidus, caudate nucleus, and internal capsule. Such infarcts produce diverse symptoms.
Ischemia in the vertebrobasilar territory accounts for approximately a fifth of all cerebrovascular accidents. Ischemia in the vertebrobasilar system may produce impairment of the brainstem, the cerebellar hemispheres, or the occipital lobes of the cerebral hemispheres. Symptoms and signs include altered consciousness, ataxia, vertigo, motor and sensory deficits of the extremities, visual field defects, and palsy of one or more of the cranial nerves. This illustration shows the relation between areas of the brain affected by various sites of vascular pathology and the associated neurologic symptoms. Atherosclerosis of the basilar artery and posterior cerebral arteries is a common cause of strokes in this region. Also, atherosclerosis and pulseless disease (Takayasu arteritis) may involve the subclavian artery and its right or left vertebral artery branches. Ischemia also can result from trauma of the third segment of the vertebral artery as it enters the posterior fossa.
The classic presentation of a stroke of embolic cause is the abrupt loss of neurologic function confined to the distribution of a major cerebral vessel or one of its major branches without previous transient ischemic episodes. In various studies, findings suggestive of an embolic origin have been identified in as many as 50% of patients presenting with stroke. The major sites of origin of cerebral emboli are carotid artery atheromas and a variety of cardiac lesions. Atrial fibrillation is an important pathophysiologic alteration that can give rise to intracardiac thrombus formation and subsequent cerebral emboli. Atrial fibrillation develops most often in patients with arteriosclerotic heart disease and congestive heart failure of various causes. Emboli also can arise from thrombi forming on prosthetic valves, from vegetations of bacterial endocarditis, and from mural thrombi at sites of acute myocardial infarction or ventricular aneurysms.
Less common but treatable mechanisms should be considered before concluding that stroke is due to cerebral atherosclerosis, including cardiomyopathy, mitral valve prolapse, atrial myxoma, marantic vegetations (nonbacterial thrombotic endocarditis), and paradoxical emboli across a probe-patent foramen ovale. Echocardiography and angiography are important diagnostic procedures to detect cardiac or unusual carotid or intracerebral arterial disorders. Also included in the differential diagnosis are conditions that may be associated with markers of inflammation (erythrocyte sedimentation rate, C-reactive protein), such as intracranial temporal arteritis, other vasculitides, bacterial endocarditis, or atrial myxoma. Abnormal cerebrovascular fluid examination results may lead to a diagnosis of bacterial meningitis or other forms of nervous system infection. Abnormalities affecting platelets or red blood cells may contribute to stroke, and consideration should be given to drug-induced mechanisms of stroke.
Hypertension is the most common and important etiologic factor in intracerebral hemorrhage. Over time, degenerative changes of the small arteries lead to the formation of microaneurysms. The penetrating lenticulostriate branches of the middle cerebral artery are most commonly involved, but similar changes can occur in other parts of the brain, especially lobar white matter, thalamus, pons, and cerebellum. Hemorrhages tend to dissect through white matter pathways, thereby disrupting the cerebral cortex. The enlarging hematoma may extend onto the cerebral surface, producing subarachnoid hemorrhage or rupture into the ventricles. **Hypertensive hemorrhage** typically occurs in regions where small lacunar lesions develop (see Fig. 13-17) and involve, in descending order of frequency, the putamen, the cerebral white matter, the thalamus, pons, the cerebellum, and the caudate nucleus. Hemorrhages usually begin while the patient is awake and engaged in daily activity. As the hematoma expands, the focal neurologic deficit gradually increases during a period of minutes or a few hours.
Cerebrovascular Disease

Symptoms and specific signs of neurologic deficit relate to the site and size of the intracerebral hemorrhage. Hypertension-induced damage of small arteries is the most common cause of intracerebral hemorrhage. Other causes include arteriovenous malformations (AVMs), bleeding diatheses (natural disease or anticoagulant induced), trauma, drug abuse (amphetamines or cocaine), and amyloid angiopathy (a degenerative vasculopathy seen in elderly patients). CT and MRI confirm the diagnosis of intracerebral hemorrhage. The hemorrhages appear as round, well-circumscribed lesions of uniform high density on CT scans. Large hemorrhages are often fatal. Small hemorrhages can resolve if blood pressure is controlled. Surgical drainage of medium-sized hemorrhages can occasionally be lifesaving.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>CT scan</th>
<th>Pupils</th>
<th>Eye movement</th>
<th>Motor and sensory deficits</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate nucleus (blood in ventricle)</td>
<td></td>
<td>Conjugate deviation to side of lesion. Slight ptosis.</td>
<td>Contralateral hemiparesis, often transient</td>
<td>Headache, confusion</td>
<td></td>
</tr>
<tr>
<td>Putamen (small hemorrhage)</td>
<td>Normal</td>
<td>Conjugate deviation to side of lesion</td>
<td>Contralateral hemiparesis and hemisensory loss</td>
<td>Aphasia (if lesion on left side)</td>
<td></td>
</tr>
<tr>
<td>Putamen (large hemorrhage)</td>
<td></td>
<td>Conjugate deviation to side of lesion</td>
<td>Contralateral hemiparesis and hemisensory loss</td>
<td>Decreased consciousness</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td>Both lids retracted. Eyes positioned downward and medially. Cannot look upward.</td>
<td>Slight contralateral hemiparesis, but greater hemisensory loss</td>
<td>Aphasia (if lesion on left side)</td>
<td></td>
</tr>
<tr>
<td>Occipital lobar white matter</td>
<td>Normal</td>
<td>Normal</td>
<td>Mild, transient hemiparesis</td>
<td>Contralateral hemianopsia</td>
<td></td>
</tr>
<tr>
<td>Pons</td>
<td></td>
<td>Constricted, reactive to light bilaterally</td>
<td>No horizontal movements. Vertical movements preserved.</td>
<td>Quadriplegia</td>
<td>Coma</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Slight constriction on side of lesion</td>
<td>Slight deviation to opposite side. Movements toward side of lesion impaired, or 6th cranial nerve palsy.</td>
<td>Ipsilateral limb ataxia. No hemiparesis.</td>
<td>Gait ataxia, vomiting</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 13-22  Intracerebral Hemorrhage: Clinical Manifestations Related to Site**
Vascular malformations are congenital anomalies that can cause intracerebral or subarachnoid hemorrhage. There are 4 categories: (1) AVMs characterized by direct connections between arteries and veins, with the veins becoming arterialized by exposure to high pressure; (2) capillary angiomas, or telangiectases, consisting of malformations of arterioles and capillaries; (3) cavernous angiomas, consisting of dilated abnormal vessels of various sizes, with no intervening neural tissue; and (4) venous angiomas, consisting of large aggregates of veins (caput medusae). Complications include headache, epileptic seizures, and bleeding. Treatment may involve surgical ablation or ablation by various interventional neuroradiologic procedures.
Although saccular (berry) aneurysms are generally referred to as congenital aneurysms, they are actually caused by a combination of congenital and acquired factors. The congenital defect is a focal absence of the media, particularly at arterial bifurcations. Hemodynamic forces cause the intima to bulge into the adventitia creating the aneurysm, followed by intimal proliferation. Atherosclerosis and hypertension accelerate the process. The relative distribution of aneurysms involving arteries of the circle of Willis and distributing branches is illustrated. Complications of a rupture include subarachnoid hemorrhage, intracerebral hemorrhage, infarction, and vasospasm. The onset of symptoms after aneurysm rupture is abrupt and rapid, with sudden, severe headache and alteration in consciousness. The mortality rate from rupture is high; rapid diagnosis and surgical intervention are essential to prevent death.
Cardiac arrest or severe cardiac failure leads rapidly to generalized hypoperfusion of the brain and hypoxic brain injury. The extent, severity, and location of hypoxic brain damage are influenced by the degree and duration of circulation collapse (full cardiac arrest or hypotension, with some preserved cardiac pump function) and other factors, such as accompanying respiratory failure. Persistent hypotension usually leads to border zone ischemic lesions, whereas cardiac arrest causes more extensive cortical necrosis, which may include the cerebral gray matter, brainstem nuclei, and the hippocampus. Regions of the brain most susceptible to ischemic damage are the Purkinje cells of the cerebellum, the hippocampus, and border zone (watershed) regions at the boundaries of the territories of major arteries supplying the cerebral cortex. Severe ischemia sets in motion a chain of events leading to irreversible brain death.

**Figure 13-25  Hypoxic Brain Damage and Brain Death**

Cardiac arrest or severe cardiac failure leads rapidly to generalized hypoperfusion of the brain and hypoxic brain injury. The extent, severity, and location of hypoxic brain damage are influenced by the degree and duration of circulation collapse (full cardiac arrest or hypotension, with some preserved cardiac pump function) and other factors, such as accompanying respiratory failure. Persistent hypotension usually leads to border zone ischemic lesions, whereas cardiac arrest causes more extensive cortical necrosis, which may include the cerebral gray matter, brainstem nuclei, and the hippocampus. Regions of the brain most susceptible to ischemic damage are the Purkinje cells of the cerebellum, the hippocampus, and border zone (watershed) regions at the boundaries of the territories of major arteries supplying the cerebral cortex. Severe ischemia sets in motion a chain of events leading to irreversible brain death.

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Traumatic brain injuries include concussion, contusion, skull fracture, and, in a small percentage of major head injuries, epidural hematomas. Usually, the bleeding is from arterial injury. Common locations of epidural hematomas are the temporal fossa, the subfrontal region, and the occipital-suboccipital area. The temporal fossa epidural hematoma, which results from damage to the middle meningeal artery, is the most common epidural hematoma. The classic course is a period of unconsciousness due to a concussion, a period of lucidity as the dura mater initially slows the leakage of blood, and a rapid deterioration of consciousness. An aggressive diagnostic and surgical approach is required to save the patient.
A subdural hematoma usually results from an acute venous hemorrhage caused by rupture of cortical bridging veins. Acute subdural hematomas, which are often associated with skull fractures, usually develop within hours after injury. Associated massive cerebral or brainstem contusions or both contribute to a high mortality rate. Common signs are depressed consciousness, ipsilateral pupillary dilatation, and contralateral hemiparesis. Chronic subdural hematomas in infants can occur as a result of birth trauma. In adults, they are more common in the elderly, patients with chronic alcoholism, and patients receiving long-term anticoagulant therapy or who have a blood dyscrasia. The precipitating trauma is often trivial. Brain atrophy with an

**Figure 13-27 Acute and Chronic Subdural Hematoma**
Catheter tunneled subcutaneously to help avoid infection, then angled downward through drill hole into hematoma for drainage.

Twist-drill craniostomy at 45° angle over hematoma containing xanthochromic fluid.

Chronic subdural hematoma in infant

Enlarged head and bulging fontanelle. Aspiration via lateral angle of anterior fontanelle; should be done bilaterally. Repetitive aspiration may be curative in infant.

Increase in the subdural space is a predisposing factor. A vascular membrane forms around the lesion within 2 weeks after the initial hemorrhage fills the available subdural space. The hematoma enlarges slowly until it produces symptoms. The clinical course can be subtle, with waxing and waning signs and symptoms. The differential diagnosis includes stroke, infection, or psychosis.
Spinal cord injuries are produced by motor vehicle accidents, other types of accidents, and missile or knife wounds. Spinal cord injury, which involves direct neuronal trauma and direct and delayed injury to the vasculature, can result in a variety of neurologic deficits. The most frequent injuries occur at the levels of the lower cervical vertebrae and the thoracolumbar junction. The resulting neurologic deficits comprise complete functional interruption, partial functional interruption, nerve root deficit, Brown-Séquard syndrome, central cord damage, and other deficits. Initial treatment is aimed at reducing the extent of damage by preventing the delayed component of injury. Currently, there is great expectation that neuronal regeneration can be achieved to treat patients with paraplegia and other deficits from spinal cord injury.
Patients with brain tumors present with symptoms resulting from either increased intracranial pressure or focal brain dysfunction. Gliomas, the most common tumors of the brain, arise from the glial supporting tissue rather than the neurons. The tumors show differentiation toward any of the normal glial components (astrocytoma, oligodendroglioma, ependymoma, and ganglieneuroma). The tumors of each cell type range from moderately well-differentiated, slow-growing neoplasms to pleomorphic, rapidly growing tumors, the most common of which is the glioblastoma multiforme. The glioblastomas are characterized by vascular proliferation and necrosis and cellular pleomorphism. The prognosis, which varies with the location and type of tumor, is difficult to determine because glioblastomas may show a mixed pattern with high-grade areas adjacent to low-grade areas, and low-grade tumors tend to progress over time to high-grade lesions.
Certain common neoplasms, particularly carcinomas of the lung and the breast, as well as less common neoplasms, including carcinoma of the kidney and melanoma, have a propensity to metastasize to the brain or spinal cord. Metastatic brain tumors are more common than primary brain tumors. Brain metastases may be the first manifestation of an aggressive tumor such as lung cancer. Most metastatic tumors reach the brain through the bloodstream (hematogenous metastases) and become localized at the border between white and gray matter, although occasionally a tumor may spread directly to the brain by local extension from a head and neck cancer or via Batson venous plexus. Metastatic tumors are usually well demarcated and solid, but they may be cystic. Some tumors may be hemorrhagic at the time of presentation, confusing the real diagnosis. The lesions are frequently multiple. CSF examination may yield evidence of meningeal carcinomatosis.
Meningiomas are the most common of the benign brain tumors. Their incidence increases with age, with a moderate female preponderance. Meningiomas, which arise from arachnoid cells in the meninges, are nearly always benign, but rare malignant variants occur. Most meningiomas are composed of groups of cells arranged in a whorled pattern without identifiable cell membranes (syncytial type), sometimes containing large numbers of calcified psammoma bodies (psammomatous type). Fibroblastic and transitional variants also occur. The symptoms depend on location of the tumor, the growth rate, and adherence to adjacent structures rather than on histologic type. Meningiomas may extend into venous structures, such as the superior sagittal sinus, or erode into the bone of the skull.
Pituitary tumors of the adenohypophysis are classified on both a functional and an anatomical basis. With the use of standard histology, the tumors are classified as eosinophilic adenoma, basophilic adenoma, and chromophobe adenoma. The eosinophilic adenoma is associated with acromegaly, and the basophilic adenoma is associated with Cushing syndrome. The chromophobe adenoma, the most common type of tumor, may be nonfunctioning. A more accurate classification can be obtained by immunocytochemical staining for specific hormones. Clinically important features include the degree of sella turcica enlargement and erosion and the type of suprasellar extension. Precise delineation of tumor extent can be obtained with a combination of CT and MRI scans and angiography.
Craniopharyngiomas are the most common parasellar tumors in children, but they also occur in adults. Craniopharyngiomas arise from remnants of the Rathke pouch derived from the embryonic pharynx. The lesion is composed of clusters of columnar and cuboidal epithelial cells. The tumor may be solid or cystic because of formation of degenerative areas containing oily fluid, calcium, and keratin. The tumor routinely extends to the optic chiasm. A craniopharyngioma produces visual symptoms secondary to compression of the optic tract. Approximately 50% of patients have endocrine dysfunction, with diabetes insipidus, panhypopituitarism, and gonadal deficiency in adults and growth retardation and obesity in children. Hydrocephalus, often with papilledema, also can develop in children with this tumor.
The pineal gland has a strategic central location in the brain surrounded by vital structures, including the posterior third ventricle. Symptoms result from compression or involvement of these vital structures by the pineal tumor. Pineal tumors can be classified into tumors of germ cell origin, tumors of the pineal parenchyma, and a miscellaneous group. **Tumors of germ cell origin** are germinomas and teratomas. **Germinomas**, which comprise approximately half of all pineal tumors, are most common in adolescents and have a marked predilection for males. **Teratomas** have a similar male predilection. These tumors usually present with endocrine abnormalities. The germinoma usually spreads via the CSF but is radiosensitive, whereas teratomas are not invasive. **Pinealcytoma** is well circumscribed and noninvasive. It occurs at any age and has no sex predilection. The **malignant pineal blastoma** is composed of primitive cells resembling medulloblastoma and spreads within the CSF. Other pineal tumors include benign meningiomas and cysts.
Acoustic neuromas cause characteristic symptoms resulting from a mass effect in the cerebellopontine angle. The acoustic neuroma typically arises from the Schwann cells of the vestibular nerve, and the tumor slowly impairs the vestibular and cochlear nerves. Undiagnosed, the tumor can continue to expand and produce brainstem compression and hydrocephalus. In addition to hearing loss and tinnitus, early symptoms of acoustic neuroma may include tic douloureux, ataxia, facial sensory loss, or, occasionally, even dementia. A hearing loss for high tones, with impaired speech discrimination, frequently occurs. Involvement of the facial (VII) and trigeminal (V) nerves indicates a large tumor.
Neurofibromatosis, or von Recklinghausen disease, is the most common of a group of inherited disorders known as phacomatoses that involve tissues derived embryologically from the neural crest, including the nervous system and components of the skin. Pathologic lesions of neurofibromatosis consist of café-au-lait spots representing cutaneous patches formed by melanin-containing cells derived from the neural crest and neurofibromas formed from neural crest–derived Schwann cells involving the cranial and peripheral nerves. Gliomas and meningiomas also occur with increased frequency in neurofibromatosis. Peripheral neurofibromatosis is characterized by multiple subcutaneous tumors of the peripheral nerves but without apparent central nervous system involvement. The various forms of neurofibromatosis represent a common group of human genetic mutations, with autosomal dominant inheritance. Bilateral acoustic neuromas and other intracranial lesions can produce debilitating disease.
Intraventricular tumors are a heterogeneous group that shares a unique position within the brain. These lesions produce symptoms by local pressure and invasion, with the common finding being hydrocephalus. Tumors of the lateral ventricles may arise from the choroid plexus (meningioma and choroid plexus papilloma) or from the brain parenchyma (ependymoma, astrocytoma, subependymoma, and the giant cell tumor of tuberous sclerosis). Anterior third ventricle tumors are colloid cysts, giant craniopharyngioma, and pituitary adenoma. Posterior third ventricle tumors are pineal gland tumors. Tumors of the posterior cranial fossa can be subdivided into 3 groups. The extracerebral tumors are acoustic neuroma, meningioma, and cholesteatoma. Cerebellar hemispheric tumors are cystic astrocytoma and medulloblastoma in children and metastases and astrocytoma in adults. Tumors of the fourth ventricle are ependymoma and subependymoma.
Alzheimer disease, a distinctive form of senile dementia, is a progressive neurologic disorder usually presenting in older adults and characterized by slowly progressive loss of higher intellectual capacity and memory followed by more severe cerebral dysfunction. The distinctive pathologic lesions are the so-called senile plaques, composed of argyrophilic fibers surrounding a central core of amyloid material, and the argyrophilic neurofibrillary tangles in neurons. Granulovacuolar inclusions may also be seen in some neurons. The process results in progressive loss of neurons and cerebral atrophy. The regions of the brain most involved in Alzheimer disease correspond to pathways of neurotransmitter transport, specifically acetylcholine. Certain brain regions, the precentral, postcentral, and some occipital gyri and perisylvian regions, for example, are spared, whereas the prefrontal, superior parietal, and inferior temporal gyri become severely atrophied, eventually involving the frontal lobes.
Degenerative Disorders of the Central Nervous System

Normal-pressure hydrocephalus is a disease of the elderly that develops over a period of several months or more insidiously. Most symptoms relate to enlargement of the anterior horns and loss of frontal lobe white matter. The clinical course is dominated by the triad of dementia, abnormalities of gait, and incontinence. If more CSF is produced than is absorbed, the ventricles and subarachnoid space become distended with CSF. Conditions that cause scarring of the piaarachnoid membranes, such as meningeal infection, subarachnoid hemorrhage, or bleeding from past traumas, can cause hydrocephalus by decreasing the effectiveness of CSF absorption. However, in most elderly patients, communicating hydrocephalus has no easily identifiable cause.

**Figure 13-39 Normal-Pressure Hydrocephalus**

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Chorea is a term applied to rapid, complex, and varied movements of the body, especially the distal limbs. The differential diagnosis includes Sydenham chorea (acute rheumatic fever), systemic lupus erythematosus, chorea gravidarum (in pregnant women), drug effects, and Huntington chorea. Abnormal facial and limb movements, behavioral disturbances, and progressive dementia characterize Huntington disease, a degenerative disorder with an autosomal dominant inheritance pattern, with onset usually after the age of 40 years. The genetic mutation is carried by approximately 50% of the offspring of an affected individual. Autopsy reveals severe shrinkage of the caudate nucleus and cortical atrophy, especially of the frontal lobes.
Parkinsonism is a clinical syndrome characterized by impaired facial expression, slow voluntary movements, intention tremor, and characteristic gait with increasingly shortened, quickened steps. Impairment of the nigrostriatal dopaminergic system is the underlying mechanism for the variety of conditions that produce the characteristic motor alterations. The pathology of Parkinson disease is characterized by degeneration of the substantia nigra with loss of the normal black pigmentation. Microscopic examination shows loss of neuronal cells and mild reactive gliosis in the substantia nigra, the locus ceruleus, the substantia innominata, and certain reticular nuclei. Many neurons contain distinctive eosinophilic spherical inclusions known as Lewy bodies.
Meningitis, or inflammation of the leptomeninges and CSF, is usually caused by spread of a microorganism through the bloodstream from another site, such as the ears, the throat, the lungs, or the skin. Less frequent causes include contiguous spread of infection from the paranasal sinuses or the mastoid process or from penetrating trauma. The most likely infectious agents vary according to the age of the patient. Predisposing factors include defects causing leakage of spinal fluid, sickle cell anemia, alcoholism, cirrhosis of the liver, immunodeficient states, and asplenia. The disease usually progresses rapidly with symptoms...
Infectious Diseases

Inflammation and suppurative process. On surface of leptomeninges of brain and spinal cord

Thrombophlebitis of superior sagittal sinus and suppurative ependymitis, with beginning hydrocephalus

Kernig sign. Patient supine, with hip flexed 90°. Knee cannot be fully extended.

Neck rigidity (Brudzinski neck sign). Passive flexion of neck causes flexion of both legs and thighs.

**Figure 13-42** Bacterial Meningitis (continued)

including diffuse headache, fever, vomiting, stiff neck, lethargy, and diminished consciousness. A spinal tap with examination and culture of the CSF can provide definitive information to distinguish suppurative (bacterial) meningitis from other conditions. Meningitis can progress to produce severe neurologic damage, particularly if there is obstruction to drainage of CSF, cerebral arteritis, or thrombophlebitis.
Brain abscesses develop from hematogenous spread from a distant site of infection, particularly the heart (infectious endocarditis, congenital heart disease) and the lungs (bronchiectasis, chronic infections), from direct extension from an adjacent focus, such as a middle ear infection, or from penetrating trauma. Direct extension is the usual cause of subdural abscesses as well. Patients with brain abscesses present with severe headache usually accompanied by focal neurologic signs and often with fever. Responsible microbes are usually aerobic bacteria, most commonly streptococci, staphylococci, or gram-negative bacteria, but some cases involve anaerobic microorganisms or multiple organisms. An epidural abscess is a purulent or granulomatous process within the spinal epidural space that may encroach on the spinal cord, the nerve roots, and the nerves. Predisposing conditions include vertebral osteomyelitis and hematogenous spread of infections from the skin, the mouth, and the respiratory tract.

**FIGURE 13-43 PARAMENINGEAL INFECTIONS**

- **Scar of healed brain abscess**, with collapse of brain tissue into cavity
- **CT scan** shows brain abscess with thin enhancing rim and central necrosis
- **Osteomyelitis of skull**, with penetration of dura to form subdural “collar button” abscess
- **Epidural abscess**
  - Anterior spinal artery
  - Dura
  - Arachnoid
  - Dura
  - Posterior spinal arteries
  - Venous plexus
  - Fat in epidural space
  - Abscess in epidural space compressing spinal cord and its blood supply
- **Myelogram**: block at T9-10 due to spinal epidural abscess
Syphilis of the central nervous system occurs late in the course of a primary infection with Treponema pallidum in approximately 10% of patients. Invasion of the spirochete elicits a lymphocytic inflammatory process involving the meninges, the brain, and the spinal cord (meningoencephalitis), often accompanied by endarteritis and degenerative and gummatous lesions. Neurosyphilis can occur in several forms: syphilitic meningitis, meningo-vascular syphilis, tabes dorsalis, dementia paralytica (general paresis), and gumma (rare). CSF analysis shows modest lymphocytosis, a moderately increased protein level, and a normal glucose level. Of key importance, results of serologic tests for syphilis, such as the Venereal Disease Research Laboratory (VDRL) test and the fluorescent treponemal-antibody absorption test, are positive in serum and CSF. Prolonged treatment with penicillin is indicated to arrest the progression of disease.
Tuberculous meningitis usually begins with a focus of meningeal seeding by hematogenous spread followed by discharge of infection into the subarachnoid space from the caseous focus. The meningitis sometimes results from contiguous spread from a tuberculoma or parameningeal granuloma with rupture into the subarachnoid space. As the infection spreads, an intensive inflammatory reaction at the base of the brain leads to obliterative endarteritis with thrombosis of small vessels and secondary brain infarction, compression of cranial nerves, and obstruction of the flow of CSF. The clinical course of tuberculous meningitis is usually florid, with rapid progression to neurologic defects and coma. Classically, the CSF glucose level is low, the protein level is high, and the cell count is increased with predominantly lymphocytes. Acid-fast smears may be positive but often are not, so cultures must be performed. Other forms of tuberculous disease are the isolated tuberculoma and vertebral tuberculosis (Pott disease).
Infectious Diseases

**Poliomyelitis** represents a well-characterized neurologic disease caused by poliovirus infection and a disease successfully prevented by vaccination. Poliovirus, an RNA virus of the picorna group of enteroviruses, is propagated by oral-fecal transmission. Poliomyelitis begins as an acute febrile illness. In a small minority of infected individuals, viremia is followed by propagation in the nervous system, leading to a lower motor neuron type of paralysis, which may be accompanied by respiratory and vasomotor disturbances caused by neuronal lesions in the medulla. Outcomes ranging from an abortive minor illness or nonparalytic
illness to paralytic illness depend on individual susceptibility and the neurovirulence of the infecting virus. The incidence of paralytic polio in the United States has progressively and dramatically declined, initially after the introduction of the subcutaneously administered formalin-inactivated poliovirus vaccine (Salk type) and, subsequently, the live, attenuated oral poliovirus vaccine (Sabin type).
Herpes zoster (shingles), a relatively common infection of the peripheral nervous system, occurs most often in immunocompromised individuals. **Herpes zoster** is an acute neuralgia with a characteristic painful vesicular rash confined to the distribution of a specific spinal nerve root or cranial nerve. The primary site of infection is the dorsal root ganglion, and the infectious agent is the DNA-containing varicella-zoster virus, the same virus that causes chickenpox. The virus migrates up the peripheral nerve to the dorsal root ganglion after an attack of chickenpox and then remains dormant until an immunologic imbalance allows it to become active again. On reactivation, an acute inflammatory reaction occurs in the dorsal root ganglion, and the virus then spreads down the nerve root and the peripheral nerve to the skin, producing the characteristic rash. Patients with ophthalmic herpes zoster are at risk for blindness.
Herpes simplex encephalitis (HSE) is a relatively common and serious acute viral disease of the brain. The infection is associated with a high mortality, and survivors often have significant neuropsychiatric sequelae. Neonates usually are infected with HSV-2, and children and adults usually are infected with HSV-1. The virus likely reaches the brain via the olfactory tract or the trigeminal (V) nerve and leads to a primary infection or a subsequent reactivation event. Encephalitis most often involves the medial temporal and frontal lobes. The histologic features are hemorrhagic necrosis, inflammatory infiltrates, and neurons containing intranuclear inclusions. Rabies is an acute viral disease of the central nervous system caused by an RNA virus of the Rhabdoviridae family transmitted by inoculation of a wound contaminated by saliva of a rabid animal. Paralytic disease begins 1 to 3 months after infection. Although clinical manifestations are severe, neuropathologic findings consist of mild inflammation plus neurons showing the pathognomonic cytoplasmic eosinophilic inclusion, the Negri body.

**Figure 13-48  Herpes Simplex Encephalitis and Rabies**
Infectious Diseases

NERVOUS SYSTEM

Slow virus infections refer to progressive and fatal neurologic syndromes that arise months or years after an initial viral infection. Immunosuppressed patients are particularly susceptible. Examples are progressive multifocal leukoencephalopathy caused by the JC papovavirus and subacute sclerosing panencephalitis caused by reactivation of a measleslike virus. Spongiform encephalopathies are known to be caused not by a virus but by a unique mechanism involving mutated proteins called prions. The human diseases caused by these agents are Creutzfeldt-Jakob disease, which has a worldwide distribution, and kuru, linked to cannibalistic practices in the New Guinea highlands. The pathology of both diseases is characterized by neuronal loss, neuronal vacuolization, and astrocytosis without inflammatory infiltrates. The human form of mad cow disease is a variant of Creutzfeldt-Jakob disease. The clinical hallmarks are progressive dementia and myoclonus.
Multiple sclerosis is a relatively common disease that is characterized by clinical neurologic defects that are separated over time and are linked to the development of demyelinating lesions of the white matter that are separated spatially in the brain. Multiple sclerosis typically occurs in adults aged younger than 50 years and occurs approximately twice as frequently in women as men. The pathogenesis involves inflammation in response to an undefined trigger and possibly involving an autoimmune component. Lymphocytes and macrophages produce focal destruction of myelin and loss of oligodendroglia while sparing axons, and then microglia and astrocytes phagocytose the myelin. The resulting areas of demyelination with variable amounts of glial scar are known as plaques, and these lesions are the hallmark of the disease. The symptoms and signs of multiple sclerosis depend on the number and the location of the plaques. The course of the disease is characterized by multiple exacerbations and remissions and has highly variable outcomes.
Disorders of the Spinal Cord, Nerve Root, and Plexus

NERVOUS SYSTEM

Acute spinal cord damage is often produced by a mass lesion that reaches a critical size in the confined space of the spinal canal. Differential diagnosis includes metastatic carcinoma, infarction due to a vascular occlusion, epidural abscess, and transverse myelitis. Transverse myelitis is a syndrome of acute spinal cord dysfunction due to a demyelinating disorder similar to acute disseminated encephalomyelitis. Prompt diagnosis and treatment of an acute spinal cord lesion may prevent paraplegia.

Figure 13-51 Acute Spinal Cord Syndromes: Pathology, Etiology, and Diagnosis

Acute spinal cord damage is often produced by a mass lesion that reaches a critical size in the confined space of the spinal canal. Differential diagnosis includes metastatic carcinoma, infarction due to a vascular occlusion, epidural abscess, and transverse myelitis. Transverse myelitis is a syndrome of acute spinal cord dysfunction due to a demyelinating disorder similar to acute disseminated encephalomyelitis. Prompt diagnosis and treatment of an acute spinal cord lesion may prevent paraplegia.
Tumors involving the spine are found external to the spinal cord (extradural tumors) or they involve the spinal cord (intradural). Extradural tumors are usually metastases to the spine that invade the epidural space. Most occur via hematogenous spread, but direct extension from extravertebral soft tissue also occurs. The most common primary tumors are lung, breast, prostate, kidney, and thyroid. Most produce osteolytic lesions in the vertebrae, but lesions of prostatic cancer are often osteoblastic. There also are primary bone tumors such as osteogenic sarcoma and giant cell tumor and the hemangioma of bone. **Multiple myeloma** is a neoplastic proliferation of plasma cells that typically produces multiple osteolytic lesions in bone. The neoplastic clones typically produce a monoclonal γ-globulin component detectable in serum and in urine as Bence Jones protein.
Intradural extramedullary tumors arise in the meninges and include the isolated benign meningioma and neurilemmoma and neurofibromas associated with neurofibromatosis. Progressive compression of the spinal cord can lead to local back pain and radicular pain and eventually cause serious spinal cord defects. Intramedullary tumors usually involve a discrete short segment of...
**Myelographic and CT Characteristics of Spinal Tumors**

- **Lymphoma.** Invading spinal canal via intervertebral foramen, compressing dura mater and spinal cord.

- **Frontal (left) and lateral (right) metrizamide myelograms.** Show complete obstruction just above T6-7. Spinal cord displaced forward and to right, with similar displacement of arachnoid, which suggests that mass is extradural.

- **CT scan.** More graphically displays left and posteriorly situated soft-tissue mass within spinal canal and its extension through left intervertebral foramen. Absence of bony involvement confirmed.

- **Meningoma.** Compressing spinal cord and distorting nerve roots.

- **Frontal (left), lateral (center), and oblique (right) metrizamide myelograms.** Show right lateral displacement of spinal cord and complete obstruction. Frontal view shows injection from above; lateral and oblique views show interior margin of intradural mass, separate from spinal cord, defined by injection from below.

- **CT scan.** At C2 shows only small amount of contrast medium posteriorly. Tumor is more dense than spinal cord, which is displaced to right and severely deformed and compressed.

- **Astrocytoma.** Exposed by longitudinal incision in bulging spinal cord.

- **Frontal (left) and lateral (right) metrizamide myelograms.** With injection from below show high-grade stenosis caused by nearly symmetric expansion of spinal cord beginning at T12.

- **Myelogram.** With injection from above shows extension of tumor to upper cervical level.

- **CT scan.** Of lower thoracic region showing rounded, expanded spinal cord that is nearly twice normal sagittal diameter.

**Figure 13-53 Tumors of the Spinal Cord (continued)**

The spinal cord but may be more extensive, involving much of the length of the spinal cord. The 2 most common intramedullary tumors are the astrocytoma and the ependymoma. Intradural tumors of the lumbar spine can involve the specialized structures of this region, the conus medullaris, the filum terminale, and the cauda equina.
Syringomyelia is a rare disorder produced by the development of a cylindrical cavity, or syrinx, in the central area of the spinal cord, most frequently in the cervical and upper thoracic segments. The pathogenesis is poorly understood but seems to be developmental, degenerative, or both in nature. Other defects may be present, including the Arnold-Chiari malformation. Gradual expansion of the syrinx in the central area of the spinal cord produces neuronal and nerve tract damage. Symptoms usually develop in adults aged 20 to 50 years. The classic sign of syringomyelia is a dissociated loss of pain and temperature sensation in the upper extremities with preservation of light touch sensation and proprioception without motor deficits. The disease is characterized by progressive incapacitation due to spinal cord damage.
Subacute combined degeneration of the spinal cord is a process of degeneration of the posterior and lateral tracts of the spinal cord resulting from vitamin B₁₂ deficiency. Most cases are the result of pernicious anemia due to an autoimmune chronic atrophic gastritis leading to an absence of intrinsic factor needed for vitamin B₁₂ absorption or, less often, from other conditions in which vitamin B₁₂ absorption is impaired or its dietary intake is insufficient. The most common neurologic symptoms relate to involvement of the posterior columns with loss of the sense of vibration of particular diagnostic significance. Lateral column dysfunction usually occurs later. The neurologic signs and symptoms may precede the appearance of anemia. Folate ingestion may mask the anemia but may not prevent the progressive neurologic damage. Proper diagnosis and administration of B₁₂ is needed to prevent permanent neurologic damage.
Cervical disc herniation is a common disorder usually caused by degenerative disease (osteoarthritis) rather than trauma. Severe degenerative cervical disc disease (spondylosis) can result in rupture of an intervertebral disc or osteophytes developing on the vertebrae from osteoarthritis. Osteophytes or ruptured discs produce symptoms when they compress the spinal cord or nerve roots against posteriorly located structures of the spinal column, including the posterior nerve root foramen and the ligamentum flavum. Neurologic examination focusing on motor, reflex, and sensory findings in the upper extremities usually reveals a diagnostic grouping of symptoms and signs pointing to the location of the pathologic lesion. Surgical therapy is indicated only if conservative management is unsuccessful.

**Figure 13-56  Cervical Disc Herniation: Clinical Manifestations**

<table>
<thead>
<tr>
<th>Level</th>
<th>Motor signs (weakness)</th>
<th>Reflex signs</th>
<th>Sensory loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>Deltoid</td>
<td>0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C6</td>
<td>Biceps brachii</td>
<td>Weak or absent reflex</td>
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<tr>
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<tr>
<td>C7</td>
<td>Biceps brachii</td>
<td>Weak or absent reflex</td>
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<tr>
<td>C8</td>
<td>Interossei</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Homer syndrome</td>
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</table>

Spurling maneuver. Hyperextension of neck and rotation away from side of lesion cause radicular pain in neck and down arm.
Lumbar disc disease causing low back pain and nerve root pain is a common problem. The lumbar spine is a compact anatomical region composed of the 5 lumbar vertebrae and the sacrum, which are separated by the normally tough and compact intervertebral discs. With aging, the fibrocartilaginous disc degenerates and fragments; in the process, the adherence to the adjacent vertebrae is weakened. Mechanical forces can then cause the fragments to move, usually in a posterolateral direction toward the exit sites of the nerve roots. Pain and neurologic deficits develop from the ensuing pressure on the nerve roots. The various clinical features of a herniated nucleus pulposus of a lumbar intervertebral disc are shown here. Surgical intervention is often needed to relieve the problem.
Disorders of the Motor Neuron, Peripheral Nerve

The motor neurons of the spinal cord and the cranial nerves serve as the final common path for transmission of neural impulses through the axon and neuromuscular junction to the skeletal musculature. Diseases of the motor-sensory unit typically occur without impairment of mental function. In diseases of the neuromuscular junction, particularly in myasthenia gravis, cranial nerve abnormalities, especially those producing diplopia or ptosis or both, occur frequently. Bulbar motor neuron disease may present with dysphagia. Careful evaluation of gait and the pattern of muscle weakness are important in the differential diagnosis. In general, the deep tendon reflexes are either normal or reduced in most disorders of the motor-sensory unit. A sensory examination and pattern of sensory deficit also are important to determine the underlying pathology because sensation is usually intact in motor neuron disease, neuromuscular junction disorders, and primary myopathies, whereas distal sensory loss is typical of peripheral neuropathies.

**Figure 13-58  Diseases of the Motor-Sensory Unit: Regional Classification**

The motor neurons of the spinal cord and the cranial nerves serve as the final common path for transmission of neural impulses through the axon and neuromuscular junction to the skeletal musculature. Diseases of the motor-sensory unit typically occur without impairment of mental function. In diseases of the neuromuscular junction, particularly in myasthenia gravis, cranial nerve abnormalities, especially those producing diplopia or ptosis or both, occur frequently. Bulbar motor neuron disease may present with dysphagia. Careful evaluation of gait and the pattern of muscle weakness are important in the differential diagnosis. In general, the deep tendon reflexes are either normal or reduced in most disorders of the motor-sensory unit. A sensory examination and pattern of sensory deficit also are important to determine the underlying pathology because sensation is usually intact in motor neuron disease, neuromuscular junction disorders, and primary myopathies, whereas distal sensory loss is typical of peripheral neuropathies.

**Motor neuron**
- Primary motor neuron diseases
  - Progressive muscular atrophy
  - Primary bulbar palsy
  - Amyotrophic lateral sclerosis
  - Werdnig-Hoffman disease
  - Poliomyelitis
  - Tetanus

**Dorsal root ganglion**
- Herpes zoster
- Friedreich ataxia
- Hereditary sensory neuropathy

**Spinal nerve (dorsal and ventral roots)**
- Disc extrusion or herniation
- Tumor

**Plexus**
- Tumor
- Trauma
- Idiopathic plexopathy
- Diabetic plexopathy

**Peripheral nerve**
- Metabolic, toxic, nutritional, idiopathic neuropathies
- Arteritis
- Hereditary neuropathies
- Infectious, postinfectious, inflammatory neuropathies (Guillain-Barré syndrome)
- Entrapment and compression syndromes
- Trauma

**Neuromuscular junction**
- Myasthenia gravis
- Lambert-Eaton syndrome
- Botulism

**Muscle**
- Duchenne muscular dystrophy
- Myotonic dystrophy
- Limb-girdle muscular dystrophy
- Congenital myopathies
- Polymyositis/dermatomyositis
- Potassium-related myopathies
- Endocrine dysfunction myopathies
- Enzymatic myopathies
- Rhabdomyolysis
Primary motor neuron diseases have varied clinical manifestations. Patients may present with progressive muscular atrophy (primary asymmetric lower motor neuron disease), primary bulbar palsy (dysfunction of motor neurons originating in the brainstem), or the syndrome of amyotrophic lateral sclerosis (upper motor neuron disease with corticospinal tract involvement superimposed on primary muscular atrophy or primary bulbar palsy). Amyotrophic lateral sclerosis (Lou Gehrig disease) typically presents with manifestations of lower motor neuron disease, particularly dysfunction of muscle movements. These manifestations eventually join with symptoms of degeneration of the corticospinal or corticobulbar tract, including muscle spasticity. Electromyography reveals a characteristic pattern of abnormalities.
A variety of metabolic, toxic, or nutritional conditions can produce subacute or chronic peripheral neuropathies that tend to involve multiple nerves in a symmetric pattern. Some cases are idiopathic, and in others, the family history suggests a hereditary basis. Typically, the patient presents with symptoms of symmetric numbness, tingling, burning, or constriction of the extremities and a cautious gait. Physical examination usually shows changes first evident in the legs and feet. There is a symmetric hyporeflexia, with distal weakness. Pathologic changes on nerve biopsy may be nonspecific and consist of patchy loci of demyelination and axonal degeneration or may show more specific findings, such as amyloid deposits and, in patients with diabetes, hyaline arteriolosclerosis.
There are a number of conditions that compromise the circulation to a specific nerve acutely. The neurologic presentation resembles the acute onset of pressure or traumatic lesions but without evidence of such lesions. The acute onset of foot drop is a common presentation. The illness progresses by recruitment of additional peripheral nerves, usually in an asymmetric fashion. The presentation may even mimic a diffuse, symmetric polyneuropathy but with a much more rapid course. Acute lesions are more commonly caused by disorders affecting small-sized arterioles, and this occurs relatively often in patients with diabetes. Also to be considered are PAN, an acute necrotizing vasculitis with multisystem involvement, and the arteritises associated with systemic lupus erythematosus or Churg-Strauss syndrome. Other diagnostic considerations are cardiac embolic lesions from bacterial endocarditis or atrial myxoma; dysproteinemias, a paraneoplastic syndrome associated with some carcinomas; and leprosy.

**Figure 13-61  Mononeuritis Multiplex With Polyarteritis Nodosa (PAN)**
Myasthenia gravis is an acquired autoimmune disease characterized by production of antibodies to acetylcholine receptors linked to marked reduction of junctional folds and decrease in acetylcholine receptors at the neuromuscular junction, thereby impairing the transmission of nerve impulses. Myasthenia gravis is frequently associated with other autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, and pernicious anemia. Abnormalities of the thymus are common, which is manifest in most cases as thymic hyperplasia and in approximately 10% as a thymoma. Myasthenia gravis has a worldwide distribution and occurs in all age groups but with a strong female preponderance. Myasthenia gravis may be generalized or limited to ocular myopathy. There also are congenital, neonatal, and drug-induced forms. Lambert-Eaton syndrome is a condition resembling myasthenia gravis occurring as a paraneoplastic syndrome in patients with an underlying carcinoma, often oat cell carcinoma of the lung.
Guillain-Barré syndrome is an acute, rapidly progressive, ascending paralysis that spreads from the distal limbs to involve more proximal muscle groups, including facial and respiratory muscles. The disease affects motor function primarily, leading to total loss of reflexes and function. Predisposing conditions include a recent viral infection in most patients or impaired immune function. The syndrome results from inflammatory attack of the peripheral nerves, probably triggered by an autoimmune

**Figure 13-63  GUILLAIN-BARRÉ SYNDROME**

**Stage I.** Lymphocytes migrate through endoneural vessels and surround nerve fiber, but myelin sheath and axon not yet damaged.

**Stage II.** More lymphocytes extruded and macrophages appear. Segmental demyelination begins; however, axon not yet affected.

**Stage III.** Multifocal myelin sheath and axonal damage. Central chromatolysis of nerve cell body occurs and muscle begins to develop denervation atrophy.

**Stage IV.** Extensive axonal destruction. Some nerve cell bodies irreversibly damaged, but function may be preserved because of adjacent less-affected nerve fibers.

**Clinical phase 1**

Tingling of hands and feet

**Phase 2**

Difficulty in arising from chair

**Phase 3**

Areflexia, weakness, distal sensory loss
Disorders of the Motor Neuron, Peripheral Nerve

The inflammation leads to demyelination and, in severe cases, secondary axonal damage. Patients may present with progressive symmetric paralysis with cranial nerve dysfunction, particularly Bell palsy, sensory ataxia, or pure autonomic dysfunction. Differential diagnosis includes acute spinal cord lesions; toxic, metabolic, or infectious processes; poliomyelitis; diphtheria; botulism; porphyria; and myasthenia gravis. Guillain-Barré syndrome is self-limiting in most patients.
Muscular dystrophies are a heterogenous group of inherited diseases characterized by progressive muscle weakness due to progressive degeneration of skeletal muscle, often with onset in childhood. There are various inheritance patterns, including the most common X-linked pattern of Duchenne muscular dystrophy and Becker muscular dystrophy, a milder variant. The disease is marked by progressive development of muscle weakness, especially of pelvic girdle muscles, marked lordosis, and enlargement of the calves, so-called pseudohypertrophy due to muscle swelling. Pathologic changes are those of multifocal muscle fiber degeneration and necrosis, removal of necrotic muscle by phagocytic leukocytes, regenerative changes in surviving muscle fibers, fibrofatty replacement of muscle, and muscle atrophy. The illness progresses relentlessly, and the majority of patients die during the late second or third decade of life.
Polymyositis is a relatively common condition characterized by weakness of the proximal musculature with usual onset in middle-aged persons. Polymyositis seems to develop on an autoimmune basis, and it can be associated with other connective-tissue diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and systemic vasculitis, or, occasionally, with an underlying malignancy. The onset is often insidious but may be rapid. Many patients have an accompanying rash, and the combination of conditions is known as dermatomyositis. In patients with recent onset of symmetric proximal muscle weakness, with or without a rash, the diagnosis of an inflammatory myopathy can be confirmed by evidence of increased serum markers of muscle damage, especially creatine kinase, typical electromyographic changes, and positive muscle biopsy with inflammatory cellular infiltrates and immunoglobulin deposits by immunofluorescence. The prognosis ranges from complete recovery to frequent recurrence to fatality in approximately 25% patients even with treatment with steroids.
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