<table>
<thead>
<tr>
<th>Effector</th>
<th>Parasympathetic Innervation Effects</th>
<th>Sympathetic Innervation Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CARDIOVASCULAR SYSTEM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>Decreases heart rate</td>
<td>Increases heart rate and force of contraction</td>
</tr>
<tr>
<td>Blood vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>None</td>
<td>Vasodilation (β receptors) or vasoconstriction (α receptors)</td>
</tr>
<tr>
<td>To skeletal muscle</td>
<td>None</td>
<td>Vasoconstriction (α receptors)</td>
</tr>
<tr>
<td>Integumentary and most</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>other blood vessels</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>DIGESTIVE SYSTEM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivary glands</td>
<td>Stimulates watery secretion</td>
<td>Stimulates more viscous secretion; ultimately reduces saliva secretion</td>
</tr>
<tr>
<td>GI tract gland secretion</td>
<td>Stimulation</td>
<td>Inhibits</td>
</tr>
<tr>
<td>Smooth muscle in GI tract</td>
<td>Stimulation peristalsis (motility)</td>
<td>Inhibits peristalsis (motility)</td>
</tr>
<tr>
<td>Sphincters</td>
<td>Relax (open, to allow passage of materials)</td>
<td>Contract (close to prevent passage of materials)</td>
</tr>
<tr>
<td>GI tract blood vessels</td>
<td>Vasodilation</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Liver</td>
<td>Stimulates glycogenesis (formation of glycogen from glucose)</td>
<td>Stimulates glycogenolysis (breakdown of glycogen into glucose)</td>
</tr>
<tr>
<td><strong>RESPIRATORY SYSTEM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchi bronchioles of lungs</td>
<td>Bronchoconstriction (airway narrows)</td>
<td>Bronchodilation (airway widens)</td>
</tr>
<tr>
<td><strong>URINARY SYSTEM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidneys</td>
<td>None</td>
<td>Stimulates release of renin (to raise blood pressure)</td>
</tr>
<tr>
<td>Bladder (muscle wall)</td>
<td>Contraction (to facilitate urination)</td>
<td>Relaxation</td>
</tr>
<tr>
<td>Internal urethral sphincter</td>
<td>Relaxation (opens, to facilitate urination)</td>
<td>Contraction (closes, to inhibit urination)</td>
</tr>
<tr>
<td><strong>REPRODUCTIVE SYSTEM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penis</td>
<td>Stimulates erection</td>
<td>Stimulates ejaculation</td>
</tr>
<tr>
<td>Clitoris</td>
<td>Stimulates erection</td>
<td>None</td>
</tr>
<tr>
<td>Uterine muscle</td>
<td>None</td>
<td>Contraction</td>
</tr>
<tr>
<td>Gland secretion</td>
<td>Stimulates</td>
<td>Inhibits</td>
</tr>
<tr>
<td>Vaginal muscular wall</td>
<td>None</td>
<td>Contraction</td>
</tr>
<tr>
<td><strong>INTEGUMENTARY SYSTEM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrector pili</td>
<td>None</td>
<td>Contraction to cause hair elevation (i.e., “goose bumps”)</td>
</tr>
<tr>
<td>Sweat glands</td>
<td>None</td>
<td>Secretion</td>
</tr>
<tr>
<td><strong>EYE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pupil size</td>
<td>Constriction (allows less light into the eye)</td>
<td>Dilation (allows more light into the eye)</td>
</tr>
<tr>
<td>Ciliary muscle</td>
<td>Contraction for near vision</td>
<td>None</td>
</tr>
<tr>
<td>Lacrimal gland</td>
<td>Stimulates secretion</td>
<td>None</td>
</tr>
<tr>
<td><strong>ADRENAL MEDULLA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Stimulates release of epinephrine and norepinephrine</td>
</tr>
<tr>
<td><strong>ADIPOSE CONNECTIVE TISSUE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Stimulates lipolysis (β receptors)</td>
</tr>
</tbody>
</table>
**Figure 15.11 Comparison of the Parasympathetic and Sympathetic Divisions of the ANS.**

(a) The parasympathetic division, also known as the rest-and-digest division, has its preganglionic neurons located in the cranial region of the brainstem and sacral region of the spinal cord. 

(b) The sympathetic division, also known as the fight-or-flight division, contains preganglionic neurons located in the T1–L2 regions of the spinal cord.

**INTEGRATE CONCEPT OVERVIEW**

(a) **Parasympathetic Division**

**The Rest-and-Digest Division**

- **Originate in the cranial and sacral regions of the CNS.**

  - CN III
  - CN VII
  - Pons
  - Medulla
  - CN IX
  - CN X
  - Pelvic splanchnic nerves
  - S2
  - S3
  - S4

- **Tends to have long preganglionic axons and short postganglionic axons; preganglionic axon has few branches and limited divergence**

- **Ganglia lie close to organ or within effector wall (e.g., terminal or intramural).**

  - Terminal ganglia
  - Intramural ganglion
  - Intramural ganglia

- **Neurotransmitters and receptors used**

  - ACh is released from preganglionic axons and binds cholinergic (specifically, nicotinic) receptors.
  - Postganglionic axons release ACh, which binds cholinergic (muscarinic) receptors.

- **Main effects**

  - Pupil constriction
  - Increases motility and activity of digestive system
  - Decreases heart rate and causes bronchoconstriction
  - Stimulates secretion of lacrimal (tear), nasal, and digestive system glands
  - Storage of fuel molecules in liver
  - Returns body to homeostasis

(b) **Sympathetic Division**

**The Fight-or-Flight Division**

- **Originates in the T1–L2 segments of the spinal cord**

- **Ganglia (sympathetic trunk or prevertebral) lie close to the vertebral column.**

- **Short, branching preganglionic axon**

- **Preganglionic neuron**

- **Ganglionic neuron**

- **Long postganglionic axon**

- **Tends to have shorter preganglionic axons and longer postganglionic axons; preganglionic axon has many branches and extensive divergence**

- **Main effects**

  - Pupil dilation
  - Increases heart rate and force of contraction; causes bronchodilation
  - Sweats (sweat gland)
  - Arrector pili
  - Decreases motility and activity of digestive system
  - Stimulates adrenal medulla to secrete epinephrine and NE to prolong sympathetic effects

- **Adrenal gland**

**CN III**

**CN VII**

**CN IX**

**CN X**

**Pons**

**Medulla**

**S2**

**S3**

**S4**

**Pelvic splanchnic nerves**

**S2**

**S3**

**S4**

**Medulla**

**Pons**

**NE**

**ACh**

**Nicotinic receptors**

**Muscarinic receptors**

Target cell
**Release of fuel molecules from liver and adipose connective tissue into the blood**

Originates in the cranial and sacral regions of the CNS. Tends to have long preganglionic axons and short postganglionic axons; preganglionic axon has few branches and limited divergence.

**Intramural ganglia**

Ganglia (sympathetic trunk or prevertebral) lie close to the vertebral column.

**Neurotransmitters and receptors used**

- ACh is released from preganglionic axons and binds cholinergic (specifically, nicotinic) receptors.
- ACh binds cholinergic (muscarinic) receptors for sweat glands.
- NE binds adrenergic receptors (all other structures).

Target cell

**Main effects**

- Increases heart rate and force of contraction; causes bronchodilation.
- Increases secretion of sweat glands, contraction of arrector pili.
- Vasoconstricts most blood vessels but vasodilates coronary arteries and arterioles to skeletal muscle.
- Release of fuel molecules from liver and adipose connective tissue into the blood.

**Ganglia (sympathetic trunk or prevertebral)**

Originates in the T1–L2 segments of the spinal cord.

**Ganglia lie close to organ or within effector wall (e.g., terminal or intramural).**

ACh is released from preganglionic axons and binds cholinergic (specifically, nicotinic) receptors.

**Postganglionic axons** release either ACh or NE:

- ACh binds cholinergic (muscarinic) receptors for sweat glands.

**Target cell**

**Adrenal gland**

Stimulates adrenal medulla to secrete epinephrine and NE to prolong sympathetic effects.

**Decreases motility and activity of digestive system**

**Arrector pili**

**Sweat gland**

**Release of fuel molecules from liver and adipose connective tissue into the blood**
Antagonistic Effects

Generally, the effects of parasympathetic and sympathetic innervation to the same organ are antagonistic—that is, they oppose each other. Some variations occur in how antagonistic effects are expressed, as follows:

- **Control of heart rate.** Parasympathetic stimulation slows down the heart rate, whereas sympathetic stimulation speeds up the heart rate (see section 19.9b). The same heart muscle effector cells receive this opposing stimulation. The two divisions are able to cause different responses because cardiac muscle cells contain more than one type of cellular receptor (e.g., muscarinic receptors and β1 receptors).
- **Control of muscular activity in the gastrointestinal tract.** Parasympathetic stimulation of smooth muscle cells in the gastrointestinal tract wall increases their force of contraction and thus increases gastrointestinal tract motility. Conversely, sympathetic stimulation decreases the force of contraction and thus decreases motility. Again, both ANS divisions innervate the same effector cells, but they house two different types of receptors (see section 26.1e).

Cooperative Effects

Cooperative effects are seen when both parasympathetic and sympathetic stimulation cause different responses that together produce a single, distinct result. The best example of cooperative effects occurs in the sexual function of the male reproductive system. The male penis becomes erect as a result of parasympathetic stimulation, and ejaculation of semen from the penis is facilitated by stimulation from the sympathetic division (see section 28.4f). This synergistic effort of ANS divisions facilitates reproduction.

For example, the diameter of most blood vessels is maintained in a partially constricted state by the effects of sympathetic vasomotor tone. A decrease in stimulation below the sympathetic tone causes vessel dilation, whereas an increase above sympathetic tone brings about vessel constriction (see section 20.1b). If the initial level of sympathetic tone were not present, then only vasoconstriction could occur as a result of sympathetic division activity. Another example of autonomic tone results from continued stimulation of the heart pacemaker (sinoatrial node) by the parasympathetic division through vagal tone, which decreases the heart rate (see section 19.6b).

**WHAT DID YOU LEARN?**

20. How does autonomic tone permit the control of blood vessel diameter by sympathetic innervation?

**15.7b Dual Innervation**

**LEARNING OBJECTIVES**

23. Explain dual innervation.

24. Describe the antagonistic and cooperative effects of dual innervation.

Many effectors of the ANS have dual innervation, meaning that they are innervated by postganglionic axons from both parasympathetic and sympathetic divisions. The actions caused by activities of both the divisions on the same organ usually result in effects that are antagonistic or cooperative.

Antagonistic Effects

Generally, the effects of parasympathetic and sympathetic innervation to the same organ are antagonistic—that is, they oppose each other. Some variations occur in how antagonistic effects are expressed, as follows:

- **Control of heart rate.** Parasympathetic stimulation slows down the heart rate, whereas sympathetic stimulation speeds up the heart rate (see section 19.9b). The same heart muscle effector cells receive this opposing stimulation. The two divisions are able to cause different responses because cardiac muscle cells contain more than one type of cellular receptor (e.g., muscarinic receptors and β1 receptors).
- **Control of muscular activity in the gastrointestinal tract.** Parasympathetic stimulation of smooth muscle cells in the gastrointestinal tract wall increases their force of contraction and thus increases gastrointestinal tract motility. Conversely, sympathetic stimulation decreases the force of contraction and thus decreases motility. Again, both ANS divisions innervate the same effector cells, but they house two different types of receptors (see section 26.1e).

Cooperative Effects

Cooperative effects are seen when both parasympathetic and sympathetic stimulation cause different responses that together produce a single, distinct result. The best example of cooperative effects occurs in the sexual function of the male reproductive system. The male penis becomes erect as a result of parasympathetic stimulation, and ejaculation of semen from the penis is facilitated by stimulation from the sympathetic division (see section 28.4f). This synergistic effort of ANS divisions facilitates reproduction.
15.7c Systems Controlled Only by the Sympathetic Division

LEARNING OBJECTIVE

25. Describe the systems innervated only by the sympathetic division and how they function.

In some ANS effectors, opposing effects are achieved without dual innervation. For example, the neurosecretory cells of the adrenal medulla also are innervated only by the sympathetic division. These cells have nicotinic receptors, so upon release of ACh by the postganglionic axon, the adrenal medulla cells are stimulated to release epinephrine and norepinephrine into the blood. There, these molecules act as hormones and prolong the fight-or-flight effects of the sympathetic division.

In addition, many blood vessels are innervated by sympathetic axons only. Increased sympathetic stimulation increases smooth muscle contraction, resulting in increased blood pressure. An analogy is pressing down on a gas pedal to cause a car to accelerate. Decreasing the sympathetic stimulation below the autonomic tone will result in vasodilation, just as lifting your foot off the gas pedal may slow a car down (because you are not supplying the gas). Thus, opposing effects are achieved merely by increasing or decreasing the autonomic tone in the sympathetic division.

Other examples of innervation by only the sympathetic division are seen in sweat glands in the trunk (stimulates sweating) and inner-vation of arrector pili muscles in the skin to cause “goose bumps” (see section 6.2b).

WHAT DID YOU LEARN?

23. What are the body structures innervated by the sympathetic division only?

INTEGRATE

CLINICAL VIEW 15.4

Autonomic Dysreflexia

Autonomic dysreflexia is a potentially dangerous vascular condition that causes blood pressure to rise profoundly, sometimes so high that blood vessels rupture. Specifically, it stimulates a sympathetic division reflex that causes systemic vasoconstriction and a marked increase in blood pressure. Autonomic dysreflexia is caused by hyperactivity of the autonomic nervous system in the weeks and months after a spinal cord injury. Often, the initial reaction to spinal cord injury is spinal shock, which is characterized by the loss of autonomic reflexes. However, paradoxically, this decrease in reflex activities may cause certain viscera to respond abnormally to the lack of innervation, a phenomenon called denervation hypersensitivity. For example, when a person loses the ability to voluntarily evacuate the bladder, the bladder may continue to fill with urine to the point of overdistension. This induces a spinal cord reflex that causes involuntary relaxation of the internal urethral sphincter, allowing the bladder to empty.

15.8 Autonomic Reflexes

LEARNING OBJECTIVES

26. Discuss how autonomic reflexes help maintain homeostasis.

27. Describe some major examples of autonomic reflexes.

All responses of the autonomic nervous system are regulated through reflexes (below the conscious level of control). Recall from section 14.6b that a reflex is a rapid, preprogrammed response of a muscle or gland to a stimulus, which includes five components arranged in a reflex arc. These components include (1) a receptor (that detects the stimulus); (2) a sensory neuron that relays nerve signals from the receptor to the CNS; (3) an integration center (brain or spinal cord) that integrates the sensory input and initiates motor output; (4) motor neurons that relay nerve signals from the CNS to the effectors; and (5) effectors that bring about a response. Also note that whereas somatic reflexes involve skeletal muscles, autonomic reflexes involve cardiac muscle, smooth muscle, or glands. The autonomic nervous system helps maintain homeostasis through the involuntary activity of autonomic reflexes, also termed visceral reflexes. These reflexes enable the ANS to control visceral function. Autonomic reflexes consist of smooth muscle contractions (or relaxation), cardiac muscle contractions, or stimulation or inhibition of secretion by glands, which are mediated by autonomic reflex arcs in response to a specific stimulus. Some autonomic reflexes are described here. See if you are able to determine the five components of the reflex arc for each of the examples:

- **Cardiovascular reflex.** A classic autonomic reflex involves the reduction of blood pressure. When blood pressure elevates, stretch receptors in the walls of large blood vessels (e.g., aorta) are stimulated and nerve signals are propagated along visceral sensory neurons to the cardiac center in the medulla oblongata. These nerve signals inhibit sympathetic output and activate parasympathetic output to the heart to slow heart rate and decrease the volume of blood ejected, resulting in a decrease in blood pressure (see section 19.5b).

- **Gastrointestinal reflex.** Autonomic reflexes control defecation. Fecal matter entering the rectum causes stretch of the rectal wall. Sensory neurons relay increased nerve signals to the spinal cord, which initiates a change in nerve signals along motor neurons to the rectum and anal sphincter. The rectum contracts and the internal anal sphincter relaxes (see section 26.3d).

- **Micturition reflex.** The mechanism leading to bladder emptying is similar to that for fecal emptying of the colon. In a young child who is not yet toilet trained, stretch receptors send nerve signals to the sacral spinal cord when urine fills the bladder (figure 15.12). The reflex results in contraction of the smooth muscle in the bladder wall and relaxation of the urinary sphincters. (In a toilet-trained individual, sensory nerve signals end at the pons instead of the sacral region of the spinal cord, and urination occurs following voluntary relaxation of the external urethral sphincter. We discuss micturition in greater detail in section 24.8c).

Other autonomic reflexes include changing the size of bronchioles to regulate the amount of air entering the lungs, regulating digestive system activities, and changing pupil diameter.

WHAT DID YOU LEARN?

24. How does the cardiovascular reflex affect blood pressure?
Chapter Fifteen
Nervous System: Autonomic Nervous System

CHAPTER SUMMARY

- The autonomic nervous system controls the internal environment and helps maintain homeostasis.

15.1 Comparison of the Somatic and Autonomic Nervous Systems

- The nervous system can be functionally organized into the somatic nervous system (SNS) and autonomic nervous system (ANS) based upon whether the sensory input and motor output can be consciously regulated.

15.1a Functional Organization

- The somatic nervous system includes sensory input from the special senses, skin, muscles, and joints, and motor output to control skeletal muscle.
- The autonomic nervous system includes involuntary motor output to cardiac muscle, smooth muscle, and glands and responds to sensory input from visceral sensory components.

15.1b Lower Motor Neurons of the Somatic Versus Autonomic Nervous System

- A single motor neuron innervates skeletal muscle fibers in the SNS, whereas the ANS has a two-neuron pathway consisting of preganglionic neurons in the central nervous system (CNS) and ganglionic neurons in the peripheral nervous system (PNS).

15.1c CNS Control of the Autonomic Nervous System

- Autonomic function is regulated by three CNS regions: hypothalamus, brainstem, and spinal cord.

15.2 Divisions of the Autonomic Nervous System

15.2a Functional Differences

- The parasympathetic division is primarily concerned with maintaining homeostasis when the body is at rest, which includes conserving energy and replenishing nutrient stores.
- The sympathetic division is primarily concerned with maintaining homeostasis in conditions of fight-or-flight.

15.2b Anatomic Differences in Lower Motor Neurons

- Parasympathetic preganglionic neurons reside in the brainstem and sacral regions of the spinal cord, whereas sympathetic preganglionic axons reside in the thoracic and lumbar regions of the spinal cord.

15.2c Degree of Response

- The parasympathetic response tends to be discrete and localized, whereas the sympathetic response has the potential to produce a mass activation effect.

---

**Figure 15.12 Autonomic Reflexes.** An autonomic reflex involves stimulation of an automatic effector. Here, the reflex is initiated as baroreceptors in the bladder wall are stretched and nerve signals are transmitted along sensory neurons to interneurons within the CNS. Nerve signals are then transmitted along motor neurons to stimulate the effector. The effector response is the contraction of the urinary bladder wall and relaxation of the internal urethral sphincter.
### 15.3 Parasympathetic Division

- The parasympathetic division is also known as the craniosacral system, because of the location of its preganglionic neurons.

#### 15.3a Cranial Components
- Parasympathetic preganglionic axons extend through the oculomotor, facial, glossopharyngeal, and vagus cranial nerves.

#### 15.3b Pelvic Splanchnic Nerves
- The remaining preganglionic parasympathetic cell bodies are housed within the S2–S4 segments of the spinal cord and form pelvic splanchnic nerves.

### 15.4 Sympathetic Division

- The sympathetic division is also known as the thoracolumbar division, because its preganglionic neurons reside in the T1–L2 segments of the spinal cord.
- A single effector may control one tissue, but many effectors often respond together, a phenomenon called mass activation.

#### 15.4a Organization and Anatomy of the Sympathetic Division
- Preganglionic neuronal cell bodies are housed within the lateral gray horn of the spinal gray matter and their axons extend through white rami communicantes to the sympathetic trunk.
- Gray rami communicantes are composed of postganglionic sympathetic axons from the sympathetic trunk to the spinal nerve.
- Some preganglionic axons pass through the sympathetic trunk without synapsing and form splanchnic nerves that project to the prevertebral ganglia. Postganglionic axons extend from the prevertebral ganglia to the target organ.

#### 15.4b Sympathetic Pathways
- In the spinal nerve pathway, the postganglionic axon enters the spinal nerve through the gray ramus and extends to target organs (blood vessels and glands of the skin of the neck, torso, and limbs).
- In the sympatheic sympathetic nerve pathway, the postganglionic axon extends from the sympathetic trunk and projects directly to the target organs (e.g., head, neck viscera, and thoracic viscera).
- In the splanchnic nerve pathway, the preganglionic axon passes through the sympathetic trunk and travels to the prevertebral ganglia, where it synapses with a ganglionic neuron, which extends to the target organs (most abdominal and pelvic viscera).
- In the adrenal medulla pathway, the preganglionic axon extends through both a sympathetic trunk ganglion and a prevertebral ganglion without synapsing. It synapses on secretory cells in the adrenal medulla that release epinephrine and norepinephrine.

### 15.5 Autonomic Plexuses and the Enteric Nervous System

#### 15.5a Autonomic Plexuses
- Autonomic plexuses are meshworks of sympathetic postganglionic axons and parasympathetic preganglionic axons, as well as some visceral sensory axons.

#### 15.5b Enteric Nervous System
- The gastrointestinal (GI) tract has an enteric nervous system to regulate digestive functions.
- The enteric nervous system may operate independently, although ANS divisions may stimulate or inhibit this system.

### 15.6 Comparison of Neurotransmitters and Receptors of the Two Divisions

#### 15.6a Overview of ANS Neurotransmitters
- Acetylcholine (ACh) is the neurotransmitter released by cholinergic neurons, which include all preganglionic neurons as well as all ganglionic parasympathetic neurons. ACh also is used by some ganglionic sympathetic neurons to sweat glands.
- Norepinephrine (NE) is the neurotransmitter released from adrenergic neurons, which include all other sympathetic postganglionic neurons.

#### 15.6b Cholinergic Receptors
- Nicotinic receptors are located on all ganglionic neurons and cells in the adrenal medulla, and they are always excitatory (stimulatory).
- Muscarinic receptors are located on all parasympathetic target cells, on sweat glands in the skin, and on blood vessels in skeletal muscle. Their effect may be excitatory or inhibitory depending upon the muscarinic receptor subtype.

#### 15.6c Adrenergic Receptors
- Adrenergic receptors include α and β receptors. There are several subsets for both α and β types.

### 15.7 Interactions Between the Parasympathetic and Sympathetic Divisions

#### 15.7a Autonomic Tone
- Both ANS divisions maintain some continual activity, which is called the autonomic tone for that division.

#### 15.7b Dual Innervation
- Many visceral effectors have dual innervation, meaning they are innervated by both ANS divisions. The actions of the divisions mostly are antagonistic (having opposite effects on a target organ), but a few are cooperative (working together to cause a single result).

#### 15.7c Systems Controlled Only by the Sympathetic Division
- The adrenal medulla, most blood vessels, and sweat glands of the skin are innervated by sympathetic axons only.

### 15.8 Autonomic Reflexes

- The autonomic nervous system helps maintain homeostasis through autonomic reflexes, which are also called visceral reflexes.
A splanchnic nerve in the sympathetic division of the ANS:

a. connects neighboring sympathetic trunk ganglia.

b. controls parasympathetic functions in the thoracic cavity.

c. is formed by preganglionic axons that extend to prevertebral ganglia.

d. travels through parasympathetic pathways in the head.

Some parasympathetic preganglionic neuron cell bodies are housed within the:

a. hypothalamus.

b. sacral region of the spinal cord.

c. cerebral cortex.

d. thoracolumbar region of the spinal cord.

Which of the following is a function of the parasympathetic division of the ANS?

a. increases heart rate and breathing rate

b. prepares for emergency

c. increases digestive system motility and activity

d. dilates pupils

Maintaining a resting level of ANS activity in a cell is called:

a. autonomic tone.

b. cooperative effect.

c. dual innervation.

d. antagonistic effect.

Sympathetic division preganglionic axons travel to the _______ ganglia via the _______ rami.

a. terminal, white

b. sympathetic trunk, gray

c. prevertebral, gray

d. sympathetic trunk, white

All parasympathetic division synapses use _______ as a neurotransmitter.

a. dopamine

b. acetylcholine

c. norepinephrine

d. epinephrine

Which autonomic nerve plexus innervates the pelvic organs?

a. cardiac plexus

b. esophageal plexus

c. hypogastric plexus

d. inferior mesenteric plexus

A sympathetic postganglionic axon is

a. long and unmyelinated.

b. short and myelinated.

c. short and unmyelinated.

d. long and myelinated.

Nicotinic receptors are located on which of the following?

a. plasma membranes of ganglionic neurons

b. target cells that receive parasympathetic innervation

c. blood vessels in skeletal muscles

d. sweat glands

Which of the following is accurate about a beta receptor?

a. It binds acetylcholine.

b. Its effects are excitatory (stimulatory) only.

c. It causes general vasoconstriction.

d. It increases heart rate.

What are the three CNS regions that regulate autonomic function?

For the following ganglia, identify the location and the division of the ANS each is a part of:

- sympathetic trunk ganglia
- prevertebral ganglia
- terminal ganglia.

Compare and contrast the postganglionic axons of the parasympathetic and sympathetic divisions. Examine the axon length, myelination (or lack thereof), and the neurotransmitter used.

Compare and contrast sympathetic and parasympathetic innervation effects on digestive system structures.

Explain responses of nicotinic receptors and muscarinic receptors to simulation by ACh.

Describe the differences between cooperative effects and antagonistic effects in dual innervation of target organs.

Describe how the general functions of the sympathetic and parasympathetic divisions of the ANS differ.

What may occur with the mass activation of the sympathetic division of the ANS?

Describe the process of the micturition reflex.

How does sympathetic innervation regulate vasoconstriction or vasodilation in the same blood vessels?

Can You Apply What You’ve Learned?

Use the following paragraph to answer questions 1 and 2.

Arlene was crossing the street when a car ran a red light and nearly hit her. Arlene was not hurt, but she was very frightened and was in a heightened state of alertness well after the incident.

1. Arlene likely experienced all of the following physiologic effects except:

   a. increased heart rate.

   b. pupil constriction.

   c. goose bumps.

   d. sweaty palms.
2. Arlene was in a heightened state of alertness well after the incident because
   a. the adrenal medulla secreted epinephrine and norepinephrine.
   b. the parasympathetic division stimulated regions of the brain.
   c. the sympathetic division decreased overall autonomic tone of blood vessels.
   d. All of these are correct.

3. George has hypertension (high blood pressure). His physician prescribed the drug propranolol, which is described as a beta-blocker, to reduce his blood pressure. What could be a side effect of propranolol?
   a. reduced heart rate
   b. increased blood clotting
   c. vasoconstriction of blood vessels to the skin
   d. bronchodilation

4. Albuterol is a drug designed to counteract the effects of asthma—namely, the medication, which may be used in an inhaler, facilitates bronchodilation. What receptors would you expect this drug to bind?
   a. $\alpha_1$ receptors
   b. $\alpha_2$ receptors
   c. $\beta_1$ receptors
   d. $\beta_2$ receptors

5. One surgical treatment for gastric ulcers is a selective vagotomy, where branches of the vagus nerve to the upper GI tract are cut. How would you suppose a vagotomy would help the treatment of a gastric ulcer?
   a. It would stimulate vasodilation of the blood vessels serving the stomach.
   b. It would reduce gastric gland secretion.
   c. It would promote faster movement of materials through the stomach.
   d. All of these are correct.

Can You Synthesize What You’ve Learned?

1. Our body expends a lot of energy activating and propagating the mass activation response of the sympathetic nervous system. Why is it necessary for us to have such an “expensive” mechanism at our disposal?

2. When you were younger, your parents may have told you to wait until 1 hour after you’ve eaten before you go swimming. Based on what you’ve learned about the ANS, can you hypothesize why swimming right after a meal may be problematic?

3. Some faculty dislike teaching lecture classes after lunch, complaining that the students do not pay attention at this time. From a physiologic viewpoint, what is happening to these students?
We are barraged continuously with sensory information about the environment—both outside and inside our bodies. This information is detected by various sensory receptors and then transmitted to the brain and spinal cord so that it can be interpreted and the appropriate responses initiated. The sensory information comes in many different forms. Touch receptors react to physical contact, pressure receptors within blood vessels respond to stretch, taste receptors detect chemicals in the food we eat, visual receptors respond to light, and hearing receptors detect and react to sound waves. In this chapter on the senses, we first provide an introduction to sensory receptors and describe the structure and function of the general senses. We then examine in detail the special senses (smell, taste, vision, hearing, and equilibrium).
16.1 Introduction to Sensory Receptors

Sensory receptors (recipio = to receive) are components of the nervous system that provide us with information about our external and internal environments. Here we describe the general function and structure of sensory receptors, the type of information they provide, and how the various types of sensory receptors are classified.

16.1a General Function of Sensory Receptors

LEARNING OBJECTIVE

1. Describe the general function of sensory receptors as transducers.

The general function of all sensory receptors is to respond to a stimulus (stim’û-lus; pl., stimuli; a goad) and initiate sensory input to the central nervous system (CNS). This involves converting stimulus energy into an electrical signal. The original energy form detected is specific to the type of sensory receptor (e.g., light energy is detected by the eye, sound energy by the ear, and mechanical energy by blood vessels). However, the form the energy is transduced, or changed, to is always electrical energy, and it is sent along a sensory neuron. This sensory information is propagated as nerve signals; see section 12.8c) to the CNS for interpretation. It is because sensory receptors transduce stimulus energy to electrical energy that sensory receptors are referred to as transducers (trans-z’dû-sér; trans = across, duco = to lead).

Two features are critical to allow sensory receptors to function as transducers: (1) Sensory receptors, like neurons and muscle cells, establish and maintain a resting membrane potential (RMP) across their plasma membrane (see section 4.4). (2) Sensory receptors contain modality gated channels within their plasma membranes. A modality gated channel opens in response to a stimulus other than a neurotransmitter or a voltage change at the plasma membrane. (Recall that chemically gated channels open in response to a neurotransmitter and voltage-gated channels open in response to a voltage change; see section 12.6a). The specifics for the various types of sensory receptors and the opening of their specialized modality gated channels are explained in detail throughout the later sections of this chapter.

WHAT DID YOU LEARN?

How does a sensory receptor function as a transducer?

16.1b General Structure of Sensory Receptors

LEARNING OBJECTIVE

2. Describe the general structure of a sensory receptor, and explain the significance of a receptive field.

Sensory receptors range in complexity from the relatively simple, bare dendritic endings of a single sensory neuron (e.g., some touch receptors; see figure 16.2) to specialized, complex structures called sense organs (e.g., the eye; see figure 16.10). Regardless of their anatomic complexity, however, all are functionally connected to the CNS by sensory neurons. This provides the means of relaying sensory information from the sensory receptors to the brain and spinal cord.

A receptive field is the area within which the dendritic endings of a single sensory neuron are distributed. The concept of a receptive field and its significance is most clearly shown with a comparison of receptive fields within the skin (figure 16.1). Note the relative amount of area that sensory neurons of the skin are distributed in two different regions of the body—the skin of the fingertips and the skin of the upper back. The size of the receptive field will determine the ability of the CNS to identify the exact location of a stimulus. A small receptive field provides us with the ability to identify the stimulus location more specifically. In contrast, a large receptive field allows us to determine only the general region of the stimulus.

Although it might seem advantageous for all sensory neurons to have small receptive fields (because it would provide us with...
enhanced perceptive abilities), the number of sensory neurons in the body would have to markedly increase for us to gain this advantage. This greater number of sensory neurons would require a significant increase in body size, and the energy costs to maintain their activity would be enormous.

**WHAT DID YOU LEARN?**

1. Describe the general range in structural complexity of sensory receptors, and identify what is associated with all sensory receptors.

**16.1c Sensory Information Provided by Sensory Receptors**

**LEARNING OBJECTIVES**

1. Describe the general range in structural complexity of sensory receptors, and identify what is associated with all sensory receptors.

Sensory input is relayed from sensory receptors to the CNS for interpretation. Whether we consciously perceive a stimulus is dependent upon which specific region of the CNS receives that sensory information. Only nerve signals that reach the cerebral cortex of the brain result in our conscious awareness. A stimulus that we are consciously aware of is called a sensation. A sensation occurs when we recognize a child’s face or realize that the room is too warm. Although your body is constantly bombarded by numerous sensory stimuli, you are consciously aware of only a fraction of them. Much of the sensory input is relayed to other areas of the CNS (e.g., the hypothalamus, brainstem, spinal cord), where a response is initiated without your awareness. Sensory stimuli regarding your blood pressure, blood carbon dioxide levels, and chemical composition of material within the small intestine are examples of sensory information that is detected and responded to on a subconscious level.

A sensory receptor must be able to provide the CNS with several characteristics regarding a stimulus (whether it is consciously perceived or not). These characteristics include its modality, location, intensity, and duration. The modality (mō-dal’-i-tē; modus = a mode) or form of a stimulus is provided by a given type of sensory receptor relaying sensory input along designated sensory neurons to specific regions of the CNS. For example, the sensory receptors of the eye (the retina) initiate nerve signals along the optic nerve to the occipital lobe (visual cortex), and sensory receptors of the ear (spiral organ) initiate nerve signals along the cochlear branch of the vestibulocochlear nerve to the temporal lobe (auditory cortex). In comparison, baroreceptors within the aorta send nerve signals along the vagus nerve to the cardiovascular center within the brainstem as part of blood pressure regulation. The brain is like a switchboard, and it interprets the source based upon which “line” the signal arrived.

The specific location of a stimulus is able to be determined by the CNS because sensory information is relayed either from different regions of a sensory receptor or from different locations within the body along designated sensory neurons within a given nerve that reaches specific regions of the CNS. For example, the optic nerve (see figure 16.10) is composed of many sensory neurons that extend from different portions of the retina of the eye to communicate with designated regions within the visual cortex of the occipital lobe. The inner ear has a similar anatomic arrangement between the different regions of the spiral organ (see figure 16.27) and designated regions within the auditory cortex of the temporal lobe. Recall that the specific location of sensory receptors of the skin relay sensory input to designated regions of the postcentral gyrus of the parietal lobe for interpretation, a concept visually represented in the sensory homunculus (see figure 13.13).

The CNS is able to interpret the relative intensity of the stimulus because of the change in number of nerve signals that are arriving along a designated nerve. A greater or more intense stimulus results in both the most sensitive sensory receptors initiating nerve signals more frequently and the less sensitive sensory receptors (which are not typically active) initiating nerve signals. A lesser stimulus would result in fewer nerve signals being relayed by its associated sensory neurons. For example, a bright light results in a greater frequency of nerve signals relayed along the optic nerve to the visual cortex, whereas a softer sound results in a lesser frequency of nerve signals relayed along the vestibulocochlear nerve to the auditory cortex.

The CNS is able to determine the duration of stimulus because all sensory receptors become less sensitive to a constant stimulus and initiate a progressive decrease in nerve signals. This decrease in sensitivity to a continuous stimulus is called adaptation. However, the rate of decrease is different for the various types of sensory receptors. This difference in adaptation is used to categorize sensory receptors as either tonic receptors or phasic receptors. Tonic receptors demonstrate limited adaptation. In response to a constant stimulus, tonic receptors continuously generate nerve signals and only slowly decrease the number relayed to the CNS. Examples of tonic receptors include sensory receptors within the inner ear that determine head position and proprioceptors in the joints and muscles that provide information of where your body is in space. In addition, all pain receptors are tonic receptors so as to provide the motivation to address the cause of the pain and hopefully eliminate it so that the pain will stop. In comparison, phasic receptors exhibit rapid adaptation to a constant stimulus. Phasic receptors generate nerve signals only in response to a new (or changing) stimulus and quickly decrease the number of nerve signals relayed to the CNS. Examples include the deep pressure receptors that sense the increased pressure when we first sit down in a chair. We are immediately aware of the pressure increase wherever our body contacts the chair. But soon, we do not notice this pressure because adaptation has occurred in these receptors. You may have experienced adaptation after placing your glasses on the top of your head and then forgetting that they were there. It is advantageous for us to not be continuously bombarded by this type of sensory information.

**WHAT DID YOU LEARN?**

3. Explain how sensory receptors provide input regarding the modality, location, intensity, and duration of a stimulus.

**16.1d Sensory Receptor Classification**

**LEARNING OBJECTIVES**

5. Identify and describe the three criteria used to classify receptors.

6. Classify the various types of sensory receptors based upon each of the three criteria.

Three criteria are used to categorize sensory receptors—receptor distribution, stimulus origin, and modality of stimulus. These classification criteria are summarized in table 16.1.

**Sensory Receptor Distribution**

Sensory receptors may be classified based upon their distribution in the body. The two distribution types are the general senses and the special senses.

**General sense** receptors are distributed throughout the body and are simple in structure. The receptors for general senses are subdivided into two categories based upon their location in the body and include somatic sensory receptors and visceral sensory receptors. **Somatic sensory** (or somatosensory) receptors are tactile receptors housed within both the skin and mucous membranes, which line the nasal cavity, oral cavity, vagina, and anal canal. These sensory receptors monitor...
Table 16.1 Criteria for Classifying Sensory Receptors

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory receptor distribution (location of receptor)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General senses</td>
<td>Distributed throughout the body; structurally simple</td>
<td>Tactile (touch) receptors, Joint receptors, muscle spindles, Golgi tendon organs</td>
</tr>
<tr>
<td>Somatic sensory receptors</td>
<td>Located in skin and mucous membranes</td>
<td>Tactile (touch) receptors, Joint receptors, muscle spindles, Golgi tendon organs</td>
</tr>
<tr>
<td>Visceral sensory receptors</td>
<td>Located within walls of viscera and blood vessels</td>
<td>Stretch receptors in stomach wall, chemoreceptors in blood vessels</td>
</tr>
<tr>
<td>Special senses</td>
<td>Located only in the head; structurally complex sense organs</td>
<td>Sensory receptors for smell, taste, vision, hearing, and equilibrium</td>
</tr>
<tr>
<td>Stimulus origin (location of stimulus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exteroceptors</td>
<td>Detect stimuli in the external environment</td>
<td>Sensory receptors within skin or mucous membranes, Sensory receptors for smell, taste, vision, hearing, and equilibrium</td>
</tr>
<tr>
<td>Interoceptors</td>
<td>Detect stimuli within the body</td>
<td>Sensory receptors within walls of viscera and blood vessels</td>
</tr>
<tr>
<td>Proprioceptors</td>
<td>Detect stimuli within joints, skeletal muscles, and tendons that sense body or limb movement</td>
<td>Joint receptors, muscle spindles, Golgi tendon organs</td>
</tr>
<tr>
<td>Modality of stimulus (stimulating agent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemoreceptors</td>
<td>Detect chemicals (molecules or ions) dissolved in fluid</td>
<td>Taste receptors, receptors in blood vessels that monitor carbon dioxide levels</td>
</tr>
<tr>
<td>Thermoreceptors</td>
<td>Detect changes in temperature</td>
<td>Sensory receptors within skin and hypothalamus</td>
</tr>
<tr>
<td>Photoreceptors</td>
<td>Detect changes in light intensity, color, and movement</td>
<td>Retina of the eye</td>
</tr>
<tr>
<td>Mechanoreceptors</td>
<td>Detect physical deformation of the plasma membrane due to touch, pressure, vibration, and stretch; subtypes include baroreceptors, proprioceptors, tactile receptors, and other specialized cells such as the hair cells in the cochlea of the ear</td>
<td>Tactile receptors in the skin</td>
</tr>
<tr>
<td>Nociceptors</td>
<td>Detect painful stimuli</td>
<td>Pain receptors present in almost all organs</td>
</tr>
</tbody>
</table>

Sensory receptors can also be classified based upon where the stimulus originates. These classifications include exteroceptors, interoceptors, and proprioceptors.

Exteroceptors (eks′ter-ō-sep′ter, -tōr; exterus = external) detect stimuli from the external environment. Exteroceptors include the somatic sensory receptors of the skin and mucous membranes, as well as the receptors of the special senses. All of these types of sensory receptors respond to a stimulus that is outside of the body.

Interoceptors (in′ter-ō-sep′ter; inter = between) detect stimuli from within our internal environment. Interoceptors include the visceral sensory receptors within the wall of internal organs and blood vessels. Interoceptors keep our CNS informed about the changes that are occurring within our bodies.

Proprioceptors (prō′pre-ō-sep′ter; proprius = one′s own) detect body and limb movements and include only the somatic sensory receptors within joints, muscles, and tendons.

Modality of Stimulus

Sensory receptors may also be classified according to the stimulus they respond to, which is called the modality of stimulus, or the stimulating agent. Thus, some sensory receptors respond only to temperature changes, whereas others respond to chemical changes. There are five groups of sensory receptors, based upon their modality of stimulus: chemoreceptors, thermoreceptors, photoreceptors, mechanoreceptors, and nociceptors.

- Chemoreceptors (kē′mō-rē-sep′tōr, -ter) detect chemicals, either molecules or ions dissolved in fluid. These chemicals include the food and drink we have ingested, the composition of our body fluids, and the relative components of our inhaled air. The sensory receptors in the taste buds on our tongue are chemoreceptors, because they respond to the specific molecules and ions in our ingested food to provide information to us about what is present in what we are eating. Likewise, chemoreceptors in some of our blood vessels monitor the...
INTEGRATE

LEARNING STRATEGY

When you eat a very spicy meal, your mouth stings because the nociceptors in your mouth are somatic nociceptors. When you swallow and the food moves through your gastrointestinal (GI) tract, you may not experience a stinging, burning sensation because visceral nociceptors respond only to abnormal muscle stretch, oxygen deprivation, or chemical imbalance in the tissue. When the waste products from that spicy meal are expelled from the body, the anus may sting because the nociceptors around the anus and inferior anal canal are somatic nociceptors.

©Getty Images/Stockbyte RF

Classifying a Sensory Receptor

A given sensory receptor is described based upon each classification criterion: receptor distribution, stimulus origin, and modality of stimulus. The eyes, for example, are special senses because they are located in the head (sensory receptor distribution); exteroceptors because they detect stimuli outside the body (stimulus origin); and photoreceptors because they detect light (modality of stimulus). In comparison, sensory receptors that detect stretch of blood vessels are classified as general senses because they are distributed throughout the body, interoceptors because they detect stimuli within the body, and mechanoreceptors (specifically, baroreceptors) because they detect changes in distension of the organ wall.

We use sensory receptor distribution (general senses versus special senses) as the criterion for organizing the remaining sections in this chapter on the senses. General senses are first described in section 16.2, followed by the details of the special senses in sections 16.3 to 16.5.

WHAT DID YOU LEARN?

4. Describe the following sensory receptors based upon the three classification criteria: the ear and the sense of hearing, the tongue and the sense of taste, and stretch receptors in the urinary bladder wall.

16.2 The General Senses

Receptors for general senses, as described in section 16.1, are organized into somatic sensory receptors (tactile receptors of the skin and mucous membranes and proprioceptors) and visceral sensory receptors. Here we discuss somatic sensory receptors (tactile receptors only) and referred pain. (Proprioceptors are discussed in sections 14.4b and 14.6d, and visceral sensory receptors are included throughout the text when discussing the physiology of the various body systems.)

16.2a Tactile Receptors

LEARNING OBJECTIVE

7. Compare and contrast unencapsulated and encapsulated tactile receptors.
Tactile (tak’til; tango = to touch) receptors are the most numerous type of sensory receptor (figure 16.2). They are mechanoreceptors located in the skin and mucous membranes. The dendritic endings that compose these sensory receptors are either unencapsulated or encapsulated (table 16.2).

**Unencapsulated Tactile Receptors**

Unencapsulated tactile receptors are simply dendritic endings of sensory neurons with no protective covering. The three types of unencapsulated receptors are free nerve endings, root hair plexuses, and tactile discs.

Free nerve endings are the least complex of the tactile receptors and reside closest to the surface of the skin, usually in the papillary layer (superficial layer) of the dermis (see section 6.1b). Often, some branches extend into the deepest epidermal strata and terminate between the epithelial cells. Free nerve endings are also located in mucous membranes. These tactile receptors primarily detect temperature and pain stimuli, but some also detect light touch and pressure. Free nerve endings can be either tonic receptors (adapt slowly) or phasic receptors (adapt quickly).

Root hair plexuses are specialized dendritic endings of sensory neurons that form a weblike sheath around hair follicles in the reticular layer (deeper layer) of the dermis. Any movement or displacement of the hair changes the arrangement of these dendritic endings, initiating nerve signals. These phasic receptors quickly adapt; thus, although we feel the initial contact of a long-sleeved shirt on our arm hairs when we put on the garment, our conscious awareness subsides immediately until we move and the root hair plexuses are restimulated.

Tactile discs, previously called Merkel discs, are flattened dendritic endings of sensory neurons that extend to tactile cells (Merkel cells), which are specialized epithelial cells located in the stratum basale (deepest layer) of the epidermis. These discs function as tonic receptors for light touch. (Note that tactile cells are the only specialized tactile receptor cells; the remaining tactile receptors are simply the dendritic endings of sensory neurons.)

**Encapsulated Tactile Receptors**

Encapsulated tactile receptors are dendritic endings of sensory neurons that are wrapped either by connective tissue or by connective tissue and specialized glial cells called neurolemmocytes (previously called Schwann cells; see section 12.4b). Encapsulated tactile receptors include end bulbs, lamellated corpuscles, bulbous corpuscles, and tactile corpuscles.

End bulbs, or Krause bulbs, are dendritic endings of sensory neurons ensheathed in connective tissue. They are located both in the dermis of the skin and in the mucous membranes of the
Table 16.2  Types of Tactile Receptors

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>Free Nerve Ending</th>
<th>Root Hair Plexus</th>
<th>Tactile Disc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Dendritic endings of sensory neurons</td>
<td>Dendritic endings of sensory neurons that surround hair follicles</td>
<td>Flattened dendritic endings of sensory neurons that end adjacent to specialized tactile cells</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Closest to skin surface (papillary layer of the dermis and some dendritic endings extend into the deepest layers of the epidermal strata); mucous membranes</td>
<td>Reticular layer of the dermis</td>
<td>Stratum basale of epidermis</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Detects temperature, pain, light touch and pressure</td>
<td>Detects movement of the hair</td>
<td>Detects light touch</td>
</tr>
<tr>
<td><strong>Rate of Adaptation</strong></td>
<td>Phasic or tonic</td>
<td>Phasic</td>
<td>Tonic</td>
</tr>
</tbody>
</table>

**ENCAPSULATED TACTILE RECEPTORS**

<table>
<thead>
<tr>
<th>Receptor Type</th>
<th>End Bulb</th>
<th>Lamellated Corpuscle</th>
<th>Bulbous Corpuscle</th>
<th>Tactile Corpuscle</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>Dendritic endings of sensory neurons ensheathed in connective tissue</td>
<td>Dendritic endings of sensory neurons ensheathed with an inner core of neurolemmocytes and outer concentric layers of connective tissue</td>
<td>Dendritic endings of sensory neurons within connective tissue</td>
<td>Highly intertwined dendritic endings of sensory neurons enclosed by modified neurolemmocytes and dense irregular connective tissue</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Dermis, mucous membranes of oral cavity, nasal cavity, vagina, and anal canal</td>
<td>Reticular layer of the dermis; hypodermis of the palms of the hands, soles of the feet, breasts, and external genitalia; and walls of some organs</td>
<td>Dermis and subcutaneous layer</td>
<td>Dermal papillae, especially in lips, palms, eyelids, nipples, and genitals</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Detects light pressure and low-frequency vibration</td>
<td>Functions in coarse touch; detects continuous deep pressure and high-frequency vibration</td>
<td>Detects continuous deep pressure and skin distortion</td>
<td>Discriminative touch for distinguishing texture and shape of an object; light touch</td>
</tr>
<tr>
<td><strong>Rate of Adaptation</strong></td>
<td>Tonic</td>
<td>Phasic</td>
<td>Tonic</td>
<td>Phasic</td>
</tr>
</tbody>
</table>
oral cavity, nasal cavity, vagina, and anal canal. End bulbs are tonic receptors that detect light pressure stimuli and low-frequency vibration.

**Lamellated** (lam‘e-lät-ed; lamina = leaf) **corpuscles** (corpus = body), previously called Pacinian corpuscles, are large, leaf-shaped tactile receptors composed of several dendritic endings ensheathed with an inner core of neurolemmocytes and outer concentric layers of connective tissue. They are phasic receptors found deep within the reticular layer of the dermis of the skin; in the hypoderms of the palms of the hands, soles of the feet, breasts, and external genitalia; and in the walls of some organs. The structure and location of lamellated corpuscles allow them to function in coarse touch, and sensing continuous deep-pressure and high-frequency vibration stimuli.

**Bulbous corpuscles**, or **Ruffini corpuscles**, are dendritic endings of sensory neurons ensheathed within connective tissue that are housed within the dermis and subcutaneous layer. They are tonic receptors that detect both continuous deep pressure and distortion in the skin.

**Tactile corpuscles**, previously called Meissner corpuscles, are receptors formed from highly intertwined dendritic endings of sensory neurons enclosed by modified neurolemmocytes, which are then covered with dense irregular connective tissue. They are housed within the dermal papillae (which are projections of the dermis; see section 6.1b), especially in the lips, palms, eyelids, nipples, and genitals. Tactile corpuscles are phasic receptors for discriminative touch to distinguish texture and shape of an object and for detecting light touch.

**WHAT DID YOU LEARN?**

What are the three types of unencapsulated tactile receptors, and where are they located within the integument?

### 16.2b Referred Pain

**LEARNING OBJECTIVE**

8. Define referred pain, and explain its significance in diagnosis.

**Referred pain** occurs when sensory nerve signals from certain viscera are perceived as originating not from the organ, but from somatic sensory receptors within the skin and skeletal muscle (see section 14.5a). Numerous somatic sensory neurons and visceral sensory neurons conduct nerve signals on the same ascending tracts within the spinal cord (Figure 16.3). As a result, the somatosensory cortex in the brain (see section 13.3c) is unable to accurately determine the actual source of the stimulus, and thus the stimulus may be localized incorrectly.

Clinically, some common sites of referred pain are useful in medical diagnosis (Figure 16.4). For example, cardiac problems are often a source of referred pain because the heart receives its sympathetic innervation from the T1–T5 segments of the spinal cord (see section 15.4). Pain associated with a myocardial infarction (heart attack) may be referred to the skin innervated by the T1–T5 spinal nerves, which lie along the pectoral region and the medial side of the arm. Thus, some individuals who are experiencing heart problems may perceive pain along the medial side of the left upper limb where the T1 spinal nerve innervates (see Clinical View 19.5: “Coronary Heart Disease, Angina Pectoris, and Myocardial Infarction”). By the same token, kidney and ureter pain may be referred along the T10–L2 spinal nerves, which typically overlie the inferior abdominal wall in the groin and loin regions (see Clinical View 24.7: “Renal Calculi”).

Visceral pain is usually referred along the sympathetic nerve pathways, but sometimes it can follow parasympathetic pathways as well. Referred pain from the urinary bladder often can follow the parasympathetic pathways (via the pelvic splanchnic nerves; see section 15.3b). Because the pelvic splanchnic nerves lie in the S2–S4 region of the spinal cord, pain may be referred to the S2–S4 spinal nerves, which overlie the medial buttocks regions (see Clinical View 24.8: “Urinary Tract Infections”).

**WHAT DID YOU LEARN?**

Explain the clinical significance of referred pain.
Chapter Sixteen
Nervous System: Sense

Figure 16.4 Common Sites of Referred Pain
Note: Appendicitis typically refers pain to the umbilical region. It is only in the later stages of appendicitis, when the pain becomes localized (due to the parietal peritoneum becoming inflamed as well), that the pain may be felt in the lower right abdominal quadrant.

16.3 Olfaction and Gustation
Both olfaction (the sense of smell) and gustation (the sense of taste) occur through sensory receptors in the head that detect dissolved chemicals in the air and in our food, respectively. Thus, both of these receptors are classified as special senses, exteroceptors, and chemoreceptors. We cover these together because as you will see later, the appreciation of taste also involves our sense of smell.

16.3a Olfaction: The Sense of Smell

LEARNING OBJECTIVES
9. Name the components of the olfactory receptors, and discuss their mode of action.
10. Describe the olfactory pathways that relay sensory input to the brain.

Olfaction (ol-fak’shən; olfacio = to smell) is the sense of smell, whereby volatile molecules (called odorants) must be dissolved in the mucus in our nasal cavity to be detected by chemoreceptors. We use this sense to sample our environment for information about the food we will eat, the presence of other individuals in the room, or potential danger (e.g., spoiled food, smoke from a fire).

Compared to many other animals, our olfactory ability is much less sensitive and not as highly developed. Consequently, we do not rely as greatly on olfactory information to find food or communicate with others. Yet we do have the ability to distinguish one odor among thousands of different ones, a capability that we may appreciate as we walk through a garden of flowers.

Olfactory Epithelium
The sensory receptor organ for smell is the olfactory epithelium. This epithelium lines the superior region of the nasal cavity, covering both the inferior surface of the cribriform plate and superior nasal conchae of the ethmoid bone (see figure 8.12a). The olfactory epithelium is composed of three distinct cell types (figure 16.5):

- **Olfactory receptor cells** (also called olfactory neurons), which detect odors
- **Supporting cells** (also called sustentacular cells), which sustain the olfactory receptor cells
- **Basal cells**, which function as neural stem cells to continually replace olfactory receptor cells

Olfactory receptor cells are one of the few neuronal types that are replaced. Olfactory receptor neurons are regenerated every 40 to 60 days by basal cells within the olfactory epithelium. This process decreases with age, and the olfactory receptor cells that remain lose their sensitivity to odors. Thus, an elderly individual has a decreased ability to recognize odor molecules.

Internal to the olfactory epithelium is an areolar connective tissue layer called the lamina propria (lam’i-nə prō’prē-ə). Housed within the collagen fibers and ground substance of this layer are mucin-secreting olfactory glands (or Bowman glands) and many blood vessels and nerves. Secretions from both supporting cells and olfactory glands form the mucus that covers the exposed surface of the olfactory epithelium.
Olfactory Receptor Cells

Olfactory receptor cells are bipolar neurons that have undergone extensive differentiation and modification, and serve as the primary neuron in the sensory pathway for smell. Olfactory receptor cells have both a single dendrite and an unmyelinated axon. Projecting from the dendrites are numerous thin, nonmotile cilia called olfactory hairs, which extend into the layer of mucus. Olfactory hairs contain chemoreceptors within their plasma membrane that detect one specific odorant molecule. There are approximately 400 types of scent receptors. Depending upon which olfactory receptor cells are stimulated, different smells will be perceived. Axons of olfactory receptor cells form bundles (fascicles) of the olfactory nerves (CN I) (see section 13.9). These fascicles project through foramina (holes) in the cribriform plate of the ethmoid bone to enter an olfactory bulb.

Olfactory Nerve Structures and Pathways

The olfactory bulbs are the terminal ends of olfactory tracts located inferior to the frontal lobes of the brain (see section 13.9). Axons of olfactory nerves synapse with both mitral cells and tufted cells (which are secondary neurons) within the olfactory bulbs. The resulting spherical structures are called olfactory glomeruli (glō-mär′yū-łī; sing., glomerulus; small ball). We have about 2000 glomeruli in our olfactory bulbs, and numerous olfactory receptor cells converge on each olfactory glomerulus. The convergence of signals within the glomerulus facilitates our ability to detect faint odors.

Axon bundles of the mitral and tufted cells form the paired olfactory tracts that project posteriorly along the inferior frontal lobe surface directly to the primary olfactory cortex in the temporal lobe (see table 13.5) and selected different regions of the brain, including the hypothalamus and amygdala. Unlike other sensory information, olfactory pathways do not project to the thalamus and therefore do not undergo any thalamic processing prior to reaching the cerebrum.

Detecting Smells

During normal, relaxed breathing, most inhaled air does not pass across the olfactory epithelium. To be sure to detect different smells, we must sniff repeatedly or breathe deeply, which causes the inhaled air to mix and swirl in the superior region of the nasal cavity, so that odor molecules diffuse into the mucus layer covering the olfactory receptor cells. Within the mucus, soluble proteins called odorant-binding proteins display an affinity for a variety of odorants.

Olfactory receptor cells are stimulated by contact of odorant-binding proteins with olfactory cell receptors. The olfactory pathway is so sensitive that only a few stimulating odorant-binding proteins with bound odorants are needed to bind to receptors and initiate olfactory sensation. Stimulation of olfactory receptor cells activates G proteins within these cells (see section 17.5b). In turn, activated G proteins stimulate adenylate cyclase enzymes, which convert ATP to cAMP (an intracellular second messenger). cAMP stimulates the opening of cation channels that allow the inflow of both Na\(^+\) and Ca\(^{2+}\). This net inflow of positive ions results in generation of local receptor potentials (a type of graded potential, which is described in section 12.8a) within the olfactory hairs of the olfactory receptor cells. These local potentials will initiate an action potential that is propagated along the axon of olfactory receptor cells, causing the release of neurotransmitter from the terminal ends of the axon. This results in stimulation of different patterns of the approximately 2000 glomeruli. Consider, for
example, that cooking a meal causes the release of numerous odorants, but the smell of the meal concoction has a unique “signature” recognized by the excitation pattern observed within the glomeruli.

Binding of neurotransmitter by secondary neurons results in propagation of nerve signals through the various olfactory pathways. Sensory information reaches different regions of the brain, including the (1) cerebral cortex, which allows us to consciously perceive and identify the smell; (2) hypothalamus, which controls visceral reactions to smell, such as salivation, sneezing, or gagging; and (3) amygdala, which is a center for recognition of odors and often associating those odors to a particular emotion.

Note that once the receptors are stimulated, changes to the ion channels alter the flow of ions. This results in interfering with the subsequent generation of local receptor potentials within olfactory receptor cells, and adaptation of smell occurs rapidly. Thus, an initially strong smell (such as rotting food in a trash can) may seem to dissipate as your olfactory receptor cells quickly adapt to the foul odor.

WHAT DID YOU LEARN?
7. What is the role of the mucus in detection of smells?
8. Why do some smells stimulate an emotional reaction?

16.3b Gustation: The Sense of Taste

LEARNING OBJECTIVES
11. Describe the structure and function of papillae of the tongue.
12. Discuss the structure and location of gustatory receptors, and describe the gustatory pathways that relay sensory input to the brain.
13. Describe the five types of tastes, and explain the association of smell with taste.

Our sense of taste, called **gustation** (gūs-ˈtāshən; gusto = to taste), occurs when we come in contact with the taste-producing molecules and ions of what we eat and drink (called **tastants**). Gustatory cells are chemoreceptors located within taste buds on the tongue and soft palate. The tongue and soft palate also house mechanoreceptors and thermoreceptors to provide us with information about the texture and temperature of our food, respectively.

**Papillae of the Tongue**

On the dorsal surface of the tongue are epithelial and connective tissue elevations called **papillae** (pă-pil′ē; papula = a small nipple), which are of four types: filiform, fungiform, foliate, and vallate (figure 16.6a, b):

**Filiform** (fil′i-fōrm; filum = thread) papillae are short and spiked; they are distributed on the anterior two-thirds of the tongue surface. These papillae do not house taste buds and...
Thus, have no role in gustation. Instead, their bristlelike structure serves a mechanical function; they assist in detecting texture and manipulating food.

**Fungiform** (fung’i-form; mushroom-shaped) papillae are blocklike projections primarily located on the tip and sides of the tongue. Each contains only a few taste buds.

**Foliate** (fo’le-át; leaflike) papillae are not well developed on the human tongue. They extend as ridges on the posterior lateral sides of the tongue and house only a few taste buds during infancy and early childhood.

**Vallate** (val’át; vallo = to surround) papillae, or **circumvallate papillae**, are the least numerous (about 10 to 12) yet are the largest papillae on the tongue. They are arranged in an inverted V shape on the posterior dorsal surface of the tongue. Each papilla is surrounded by a deep, narrow depression. Most of our taste buds are housed within the walls of these papillae along the side facing the depression.

### Taste Buds

Taste buds are cylindrical sensory receptor organs containing cells that have the appearance of an onion (figure 16.6c, d). Each taste bud is composed of three distinct cell types:

- **Gustatory cells** (also called gustatory receptors), which detect tastants (taste-producing molecules and ions) in our food
- **Supporting cells** that sustain the gustatory cells
- **Basal cells**, which function as neural stem cells to continually replace the relatively short-lived gustatory cells

Gustatory cells are regenerated every 7 to 9 days by basal cells within the taste bud. This process decreases with age, and our sensitivity to taste also decreases. Beginning at about age 50, our ability to distinguish between different tastes declines.

### Gustatory Cells

Gustatory cells within the taste buds are specialized neuroepithelial cells. The dendritic ending of each gustatory cell is formed by a slender **gustatory microvillus**, sometimes called a *taste hair*. Many gustatory microvilli extend through an opening in the taste bud, called the **taste pore**, to the surface of the tongue. This is the receptive portion of the cell. Within the oral cavity, saliva keeps the environment moist; the tastants in our food dissolve in the saliva, and then they are able to contact and stimulate gustatory cells.

### Gustatory Pathways

Dendritic endings of primary neurons (see section 14.4b) are associated with gustatory cells, with each neuron contacting several gustatory cells. These sensory neurons are primarily components of the facial nerve (CN VII), which innervates taste buds from the anterior two-thirds of the tongue and the glossopharyngeal nerve (CN IX), which innervates taste buds from the posterior one-third of the tongue (figure 16.7). Axons within these nerves project to the medulla oblongata (specifically, the nucleus solitarius) to synapse with secondary neurons. These secondary neurons project to the thalamus, and axons of tertiary neurons project to the primary gustatory cortex in the insula of the cerebrum.

### Gustatory Discrimination and Physiology of Taste

In contrast to the large number of olfactory receptors we have in our nose, our tongue detects just five basic **taste sensations**: sweet, salty, sour, bitter, and umami:

- **Sweet** tastes are produced by organic compounds such as sugar or other molecules (e.g., artificial sweeteners).
- **Salt** tastes are produced by metal ions, such as sodium ($\text{Na}^+$) and potassium ($\text{K}^+$).
- **Sour** tastes are associated with acids in the ingested material, such as hydrogen ions ($\text{H}^+$) in vinegar.
- **Bitter** tastes are produced primarily by alkaloids such as quinine, unsweetened chocolate, nicotine, and caffeine.
- **Umami** stimuli: *Umami* (u’ma-mé) is a Japanese word meaning “delicious flavor.” It is a taste related to amino acids, such as glutamate and aspartate, to produce a meaty flavor.
Recent research indicates there are also sensory receptors that specifically detect fatty acids, such as those found in fats and oil. In addition, scientists are examining whether there are receptors for other tastes, such as alkaline, metallic, and waterlike tastes.

Researchers previously thought certain tastes were best interpreted along specific regions of the tongue; however, research has found these “taste maps” to be incorrect and has shown that taste sensations are spread over broader regions of the tongue than previously thought.

The tastants in our food bind to specific receptor plasma membrane proteins of gustatory cells. The initial binding of a specific tastant molecule to its receptor causes depolarization of that specific receptor cell, but the manner in which cell depolarization occurs varies. In general, sweet, bitter, and umami stimuli (which are tastant molecules) bind to receptors on the taste bud surface, which activate a G protein (see figure 17.7). The G protein activation causes the formation of a secondary messenger, which results in cell depolarization (see section 12.8a). In contrast, salt and sour stimuli (which are tastant ions) do not use a G protein and depolarize the cell directly.

Depolarization of a receptor taste cell generates local receptor potentials (a type of graded potential, which is described in section 12.8a) that initiate nerve signals that cause the release of neurotransmitter at its basal side. The neurotransmitter stimulates a primary neuron, which is within the facial or glossopharyngeal nerves that relay nerve signals to the brain.

Sensory information first reaches the medulla oblongata (specifically, the nucleus solitarius) to trigger reflexes that increase salivation and release of stomach secretions in anticipation of the arrival of food. A gag or vomiting reflex may also occur in response to a nauseating substance. Sensory information is then relayed via secondary sensory neurons to the thalamus and then via tertiary sensory neurons to the primary gustatory cortex for the conscious perception of taste. This requires integrating taste sensations with those of temperature, texture, and smell.

**WHAT DO YOU THINK?**

1. When a person has a stuffy nose from a “cold” or hay fever, he or she typically can’t detect tastes as well. Why?

Note that our ability to taste what we eat relies heavily on our olfactory sense. Recall the last time you had a severe cold or sinus infection. The aroma of the food could not reach your olfactory receptors, so the food was bland and almost tasteless. Together, taste and smell give our food its flavor. We then perceive the taste of the food when the brain interprets sensory input from both gustatory receptors and from olfactory receptors.

**WHAT DID YOU LEARN?**

2. Which papillae of the tongue have taste buds, and what is the basic composition of a taste bud?

3. What are the five basic taste sensations, and what is the specific stimulus detected by each?

---

**16.4 Visual Receptors**

The sense of vision uses photoreceptors within the eyes to detect light, color, and movement to perceive detailed visual images of objects in our environment. We first describe the accessory structures of the eye before discussing the details of the anatomy of the eye and how it functions in vision.

**16.4a Accessory Structures of the Eye**

**LEARNING OBJECTIVE**

14. Describe the accessory structures of the eye, and list their functions.

The accessory structures of the eye are located either attached to the eye or around the eye (figure 16.8). These structures include the extrinsic eye muscles, eyebrows, eyelids, eyelashes, conjunctiva, and lacrimal glands.

The extrinsic eye muscles include six skeletal muscles that are attached externally to each eye and function in eye movement. These muscles are described in detail in section 11.3b.

**Eyebrows and Eyelids**

The eyebrows are slightly curved rows of thick, short hairs at the superior edge of the orbit along the supraorbital ridge. They function in both nonverbal communication associated with facial expressions and prevention of sweat from dripping into the eyes.

The eyelids, also called the palpebrae (pal-pe’brē; sing., palpebra), form the protective covering over the surface of the eye. Each eyelid is formed primarily by a fibrous core (the tarsal plate), the orbicularis oculi muscle (which closes the eyelid), and a thin covering of skin. A muscle associated only with the upper eyelid is the levator palpebrae superioris muscle, which pulls the upper eyelid to “open the eye.” The space between the open eyelids is the palpebral (pal’pe-brāl) fissure (or eyelid). The eyelids are joined at the medial and lateral palpebral commissures, or canthi. At the medial commissure is a small, reddish body called the lacrimal caruncle (kar’ung-kl; caro = flesh).

Eyelashes extend from the free margins of the eyelids and help prevent particulate matter from entering the eye. Sensory receptors associated with the base of an eyelash trigger the blink reflex when the eyelash is touched.

Several glands are associated with the eyelids and eyelashes. Tarsal glands, which are sebaceous glands located within the tarsal plates of the eyelid, release an oily secretion at the edge of the eyelid. Both a sebaceous gland and a modified sweat gland are located at the base of each eyelash. These glands contribute to the gritty, particulate material often noticed around the eyelids after waking.

**CLINICAL VIEW 16.2 Eye Infections**

A chalazion (cyst within the eyelid) forms from an infection of a tarsal gland.

A stye (which appears as a reddened area beneath the eyelid) is an infection of either a sebaceous (oil) gland or a modified sweat gland. Conjunctivitis (kon-junk-ti’vı̅-tis) (or pink eye) is an inflammation of the conjunctiva caused by either infectious agents or irritants (e.g., pollen, contact lenses) and is the most common nontraumatic eye complaint seen by physicians.

**Conjunctiva**

A specialized stratified columnar epithelium termed the conjunctiva (kon-jūnk-tı̅’vă) forms a continuous, transparent lining over the anterior surface of the sclera (“white”) of the eye (the ocular conjunctiva) and the internal surface of the eyelid (the palpebral conjunctiva). The junction of the ocular conjunctiva and palpebral conjunctiva is called the conjunctival fornix (for’niks; vault or arch). (This junction is what prevents a contact lens from moving behind the eye.)
The conjunctiva contains numerous goblet cells, which secrete mucin to lubricate and moisten the eye. Additionally, the conjunctiva contains many blood vessels, which supply oxygen and nutrients to the avascular sclera, as well as abundant nerve endings that detect foreign objects as they contact the eye. The conjunctiva does not cover the surface of the cornea (the transparent center of the anterior eye), so no blood vessels interfere with passage of light into the eye.

**Lacrimal Apparatus**

A lacrimal (lak′ri-məl; lacrima = a tear) apparatus is associated with each eye; it produces, collects, and drains lacrimal fluid (figure 16.9). Lacrimal fluid contains water, sodium ions, antibodies (see section 22.8), and an antibacterial enzyme called lysozyme. This

**INTEGRATE**

**CONCEPT CONNECTION**

Five cranial nerves innervate the eye (see section 13.9). These include the optic nerve (CN II), which is a sensory nerve that relays input from the retina when it is stimulated by light, and the trigeminal nerve (CN V), which relays sensations from the cornea. Then there are three primarily motor nerves that relay motor output to the eye muscles. The oculomotor nerve (CN III) innervates four of the six extrinsic eye muscles (see figure 11.7) to control eye movement and the intrinsic eye muscles (i.e., the iris and ciliary muscles) (see figure 16.10); the trochlear nerve (CN IV) and abducens nerve (VI) each innervate an extrinsic eye muscle.
fluid lubricates the anterior surface of the eye to reduce friction from eyelid movement; continuously cleanses and moistens the eye surface; helps prevent bacterial infection; and provides oxygen and nutrients to the corneal epithelium (described in section 16.4b).

The production and movement of lacrimal fluid occurs as follows (figure 16.9):

1. A lacrimal gland, which is about the size and shape of an almond and located within the superolateral depression of each orbit, continuously produces lacrimal fluid that drains through short ducts to the eye surface.

2. Blinking, which occurs about 15 to 20 times per minute, but less frequently when we are focusing on something such as reading a book, “washes” the lacrimal fluid over the eyes. Gradually, the lacrimal fluid is transferred to the lacrimal caruncle at the medial surface of the eye.

3. The lacrimal fluid drains into the lacrimal puncta (pungk’tā; sing., punctum; to prick), which are two small openings on the superior and inferior side of the lacrimal caruncle. (If you examine the lacrimal caruncle within your own eye, each punctum appears as a “hole.”)

4. Each lacrimal punctum has a lacrimal canaliculus (kan-ā lik’yō-lūs; small canal) that drains lacrimal fluid into a rounded lacrimal sac.

5. The fluid drains from the lacrimal sac into a nasolacrimal duct. This duct drains lacrimal fluid into the nasal cavity, where it mixes with mucus and then moves into the pharynx (throat) and is swallowed. Excess production of lacrimal fluid produces tears.

**WHAT DID YOU LEARN?**

11. Where is the conjunctiva located, and what are its functions?

12. How is lacrimal fluid spread across the eye surface and removed from the orbital region?

### 16.4b Eye Structure

#### LEARNING OBJECTIVE

**15.** Describe the structures of the eye.

The eye is an almost spherical organ that measures about 2.5 centimeters (1 inch) in diameter. Most of the eye is receded into the orbit of the skull (figure 16.10), a space also occupied by the lacrimal gland, extrinsic eye muscles, numerous blood vessels, and the cranial nerves that innervate the eye and other structures in the orbit. Orbital fat cushions the posterior and lateral sides of the eye (see figure 16.8b), providing support and protection and facilitating oxygen and nutrient delivery by the blood through its associated blood vessels.

The interior of the eye consists of two fluid-filled cavities. These two cavities are separated by the lens, which is a transparent, biconvex structure enclosed in a fibrous capsule (figure 16.10). The posterior cavity, which lies behind the lens, contains a permanent fluid called vitreous humor. The anterior cavity, which is in front of the lens, contains a circulating fluid called aqueous humor. The anterior cavity is subdivided into two chambers (or rooms) by the iris (the colored part of the eye): the anterior chamber, which is located between the iris and cornea, and the posterior chamber, which is located between the iris and the lens. The lens, iris, and both fluids (vitreous humor and aqueous humor) are described in detail later in this section.

The wall of the eye is formed by three principal tunics (or layers): the fibrous tunic (external layer), the vascular tunic (middle layer), and the retina (inner layer).

#### Fibrous Tunic

The external layer of the eye wall is called the fibrous tunic, or external tunic. It is composed of the posterior sclera and the anterior cornea.

Most of the fibrous tunic (the posterior five-sixths) is the tough sclera (sklērā; skleros = hard), a part of the outer layer that is called the “white” of the eye. It is composed of dense irregular connective tissue containing numerous blood vessels and nerves. The sclera provides for eye shape, protects the eye’s delicate internal components, and serves as an attachment site for extrinsic eye muscles. Posteriorly, the sclera is continuous with the optic nerve sheath, which is an extension of dura mater that surrounds the optic nerve. (“Bloodshot” eyes occur with vasodilation of the scleral blood vessels, which become visible through the transparent conjunctiva.)

The cornea (kör’nē-ā) is a convex, transparent structure that forms the anterior one-sixth of the fibrous tunic; its convex shape refracts (bends) light rays coming into the eye. The cornea is composed of an inner simple squamous epithelium, a middle layer of collagen fibers, and an outer stratified squamous epithelium, called the corneal epithelium. (Think of the cornea as a collagen protein sandwich with epithelial layers as the bread.) The cornea contains no blood vessels. Nutrients and oxygen are supplied to the internal epithelium of the cornea by aqueous humor within the anterior cavity of the eye, whereas the surface corneal epithelium receives its oxygen and nutrients from lacrimal fluid.

The cornea merges with the sclera at its outer edge; this region is called the limbus (lim′būs), or the corneal scleral junction. The corneal epithelium forming the external portion of the cornea is continuous with the ocular conjunctiva that covers the sclera. Thus, the entire eye is covered with an epithelium.

#### Vascular Tunic

The middle layer of the eye wall is the vascular tunic, also called the uvea (ā’vē-ā; uvea = grape). The vascular tunic houses an extensive array of blood vessels, lymph vessels, and the intrinsic muscles of the eye. It is composed of three distinct regions; from posterior to anterior, they are the choroid, the ciliary body, and the iris.

The choroid (kör’oyd) is the most extensive and posterior region of the vascular tunic, and it is composed of areolar connective tissue that houses both an extensive network of capillaries and melanocytes (cells that produce melanin pigment). Two primary functions are associated with the choroid. Its vast network of blood vessels supplies oxygen and nutrients to the retina (inner adjacent layer of the eye, which contains photoreceptors), and melanin produced by its...
melanocytes absorbs extraneous light to prevent it from scattering within the eye.

The ciliary (sil’ē-ar-ē; cillum = eyelid) body is located immediately anterior to the choroid and is composed of both a ciliary muscle and ciliary processes. The ciliary muscle is a ring of smooth muscle. Extending from the ciliary muscle to the lens are suspensory ligaments, which anchor the lens. Relaxation and contraction of the ciliary muscles change the tension on the suspensory ligaments, thereby altering the shape of the lens. The ciliary processes contain capillaries that secrete aqueous humor (both functions of the ciliary body are discussed in detail in section 16.4b).

The most anterior region of the vascular tunic is the iris (ī’ris; rainbow), which is the colored portion of the eye. The iris is composed of two layers of smooth muscle fibers, melanocytes, and an array of vascular and nervous structures. In the center of the iris is an opening called the pupil (pī’phil), which allows light to enter the eye to reach the retina. The iris controls pupil size, or diameter—and thus the amount of light entering the eye—using its two smooth muscle layers (figure 16.11). The sphincter pupillae (spyt’ī-nil’ē) muscle (or pupillary constrictor) is arranged in a pattern that resembles concentric circles around the pupil. This muscle contracts (and the pupil becomes smaller) when stimulated by visceral motor

---

**Figure 16.10 Anatomy of the Internal Eye.** (a) A superior view of the skull and orbits shows the anatomic position of the eyes within the skull. Sagittal views depict, (b) the three tunics of the eye, and (c) internal eye structures.
Chapter Sixteen

Nervous System: Sense

Sphincter pupillae contracts (parasympathetic innervation)

Dilator pupillae contracts (sympathetic innervation)

Figure 16.11 Iris Control of Pupil Diameter. Pupillary constriction is caused by contraction of the sphincter pupillae muscle of the iris, which is controlled by the parasympathetic division of the ANS. This narrows the diameter of the pupil to decrease the amount of light entering the eye. Pupillary dilation is caused by contraction of the dilator pupillae muscle of the iris, which is controlled by the sympathetic division of the ANS. This widens the pupil diameter to increase light entering the eye.

neurons of the parasympathetic division of the ANS that are within the oculomotor nerve (CN III). In comparison, the dilator pupillae muscle (or pupillary dilator) is organized in a radial pattern extending peripherally through the iris. This muscle contracts (and the pupil becomes larger) when stimulated by neurons of the sympathetic division of the ANS (see section 15.7b). Only one set of these smooth muscle layers can contract at a time. The pupillary reflex is the ability of the iris to change the size of the pupil in response to varying amounts of light. When stimulated by bright light, the pupillary reflex involves the relaying of sensory input from the photoreceptors of the eye to the brain, which initiates nerve signals along the parasympathetic division fibers of the oculomotor nerve to stimulate the sphincter pupillae muscle to contract, which decreases pupil diameter. When stimulated by low light levels, the pupillary reflex ultimately involves initiating nerve signals along sympathetic division fibers to stimulate the dilator pupillae muscle to contract, which increases pupil diameter. This reflex is tested if brain trauma is suspected (e.g., from a car accident or drug overdose).

Retina

The internal layer of the eye wall, called the retina (ret′i-nä; rete = a net) also is known as the internal tunic or neural tunic. It is composed of two layers: an outer pigmented layer and an inner neural layer (figure 16.12). The pigmented layer is immediately internal to the choroid and attached to it. Two primary functions are associated with the pigmented layer. It provides vitamin A for the photoreceptor (light-detecting) cells of the neural layer and absorbs extraneous light to prevent it from scattering within the eye (a function it shares with the choroid). The inner neural layer (or neural retina) houses all of the photoreceptor cells and their associated neurons. This layer of the retina is responsible for vision by absorbing light rays and converting them into nerve signals that are transmitted to the brain.

The ora serrata (ōrə sä-rä′tä; serratus = sawtooth) is a jagged margin between the photosensitive posterior region of the retina and the nonphotosensitive anterior region of the retina. This nonphotosensitive portion continues anteriorly to cover the ciliary body and the posterior aspect of the iris (see figure 16.10c).

Figure 16.12 Structure and Organization of the Retina. The retina is composed of two distinct layers: the outer pigmented layer and the inner neural layer, also called the neural retina. (a) The optic nerve is composed of ganglionic cell axons that originate in the neural layer. (b, c) The neural layer of the retina is composed of three primary cellular layers (in bold): the outer photoreceptor cells (rods and cones), the middle bipolar cells, and the inner ganglion cells. AP® ©McGraw-Hill Education/Al Telser
Cells of the Neural Layer  Three distinct layers of neurons form the neural layer: photoreceptor cells, bipolar cells, and ganglion cells. The outermost layer of cells in the neural layer is composed of photoreceptor (phot = light) cells, which contain pigment molecules that react to light energy. The two types of photoreceptor cells are rods, which have a rod-shaped outer portion and function in dim light, and cones, which have a cone-shaped outer portion and function in high-intensity light and in color vision. These cells are described in more detail in section 16.4d.

Immediately internal to the photoreceptor cells is a layer of bipolar cells. Bipolar cells are located between photoreceptor cells and ganglion cells. The dendrites of the bipolar cells synapse with rods and cones. The axons of bipolar cells synapse with dendrites of ganglion cells.

Ganglion cells form the innermost layer in the neural layer and are adjacent to the posterior cavity. Axons of the ganglionic cells extend into and through the optic disc to form the optic nerve. Note that incoming light must pass through the ganglion cells and bipolar cells before reaching the photoreceptor cells. Electrical signals (which are initiated by transduction of light by photoreceptor cells) are then relayed to bipolar cells and then to ganglion cells.

Other cells that function in transmission of light stimuli include horizontal cells and amacrine cells. Horizontal cells are sandwiched between the photoreceptor and bipolar cells in a thin web. These horizontal cells regulate and integrate the electrical signals sent from the photoreceptor cells to the other cell layers. Amacrine (am′-krin) cells are positioned between the bipolar and ganglion cells and help process and integrate electrical signals between bipolar and ganglion cells. The electrical signals are either action potentials or graded potentials (see section 12.9a). Only the amacrine and ganglion cells in the retina produce action potentials; the other cells generate graded potentials.

Components of the Retina  The distribution of rods and cones, the two types of photoreceptor cells, is not uniform throughout the retina. Three specific regions are identified: the optic disc, macula lutea, and peripheral retina (figure 16.13). The optic disc contains no photoreceptors. This is where axons of the ganglion cells extend from the back of the eye as the optic nerve (figure 16.12a). It is commonly called the blind spot because it lacks photoreceptor cells, and no image forms there. The macula lutea (mak′-ô-lút′ē-a; macula = small spot, lutea = saffron-yellow) is a rounded, yellowish region just lateral to the optic disc (figure 16.13). Within the macula lutea is no overt cause. Individuals who are nearsighted, due to a more elliptical eyeball, are at increased risk for detachment because their retina is typically thinned or stretched more than that of a normal eye. There is also increased risk for retinal detachment in diabetics and older individuals. A detached retina results in deprivation of nutrients for cells in the inner neural layer because it is pulled away from the vascularized choroid layer. Degeneration and death of the neural layer of the retina occur if the blood supply is not restored.

Symptoms of a detached retina include a large number of floaters (small, particle-like objects) in the vision; the appearance of a “curtain” in the affected eye; flashes of light; and decreased, watery, or wavy vision. Pneumatic retinopexy is a treatment for upper retinal detachment. The physician inserts a needle into the anesthetized eye and injects a gas bubble into the vitreous humor. The gas bubble rises and pushes the neural layer back into its normal position. The gas bubble is absorbed and disappears over 1 to 2 weeks, and then a laser may be used to tack the two layers of the retina together. The scleral buckle is another treatment, which uses a silicone band to press inward on the sclera to hold the retina in place. A laser is then used to reattach the retina.

Figure 16.13  Internal View of the Retina Showing the Optic Disc (Blind Spot).  (a) An ophthalmoscope is used to view the retina through the pupil. Blood vessels accompany the optic nerve as it enters the eye at the optic disc. (b) Check your blind spot! Close your left eye. Hold this figure in front of your right eye, and stare at the black spot. Move the figure toward your open eye. At approximately 6 inches from your eye, the image of the plus sign is over the optic disc and the plus sign seems to disappear.

(a) ©Paul Whitten/Science Source
(b) ©Paul Whitten/Science Source
a depressed pit called the **fovea centralis** (fō’vē-ā sen’tra’lis; *fovea* = pit, *centralis* = central), which contains the highest proportion of cones and almost no rods. This pit is the area of sharpest vision; when you read the words in your text, they are precisely focused here. Although the other regions of the retina also receive and interpret light rays, no other region can focus as precisely as can the fovea centralis because of its high concentration of cones. The remaining most extensive region of the retina is called the **peripheral retina**, which contains primarily rods and functions most effectively in low light.

### Lens

The **lens** is a strong yet deformable, transparent structure. It is composed of precisely arranged layers of cells that have lost their organelles and are filled completely by a protein called **crystallin**, which are enclosed by a dense, fibrous, elastic capsule. The lens focuses incoming light onto the retina, and its shape determines the degree of light refraction.

The **suspensory (sūs-pen’sŏ-rē; *suspendo* = to hang up) ligaments** attach to the lens capsule at its periphery, where they transmit tension that enables the lens to change shape. The relative tension in the suspensory ligaments is altered by relaxation and contraction of the ciliary muscles in the ciliary body. When we view objects greater than 20 feet away, the ciliary muscles relax, the ciliary body moves away from the lens, and so the tension on the suspensory ligaments increases. This constant tension causes the lens to flatten (**figure 16.14a**). This flattened shape of the lens is the “resting” position of the lens.

---

**Figure 16.14** Lens Shape in Far Vision and Near Vision. *(a)* To focus a distant object on the retina, the ciliary muscles within the ciliary body relax, which tenses the suspensory ligaments and flattens the lens. *(b)* To focus a near object on the retina, the ciliary muscles contract, causing release of tension on the suspensory ligaments and the lens to thicken (become more spherical or “puffy”). This process is called accommodation. Note: All focused images are inverted on the retina.
In contrast, when we wish to view objects closer than 20 feet, the ciliary muscles contract, the ciliary body moves closer to the lens, and the tension on the suspensory ligaments decreases. This releases some of their pull on the lens so the lens can become more spherical, or curved. The process of making the lens more spherical to view close-up objects is called accommodation (ā-kōm’ō-dā’shūn; accommodo = to adapt) (figure 16.14b). Accommodation is controlled by autonomic motor neurons of the parasympathetic division that extend within the oculomotor nerve (CN III; see section 13.9).

**Vitreous Humor and Aqueous Humor**

**Vitreous humor** (vit’rē-ūs; vitrum = glassy), or vitreous body, is the transparent, gelatinous fluid that completely fills the posterior cavity. This permanent fluid is produced during embryonic development and helps to both maintain eye shape and support the retina to keep it flush against the back of the eye (see Clinical View 16.3: “Detached Retina”).

**Aqueous humor** (ak’wē-ūs hū’mer; watery fluid) is a transparent, watery fluid that circulates within the anterior cavity (figure 16.15). It is continuously produced by the ciliary processes. The circulation of aqueous humor provides nutrients and oxygen to both the avascular cornea (specifically, its inner epithelium) and the lens.

Blood plasma (see section 18.2) is filtered across the walls of capillaries of ciliary processes and enters the posterior chamber to form aqueous humor. (This process is similar to the formation of cerebrospinal fluid by the choroid plexuses within the ventricles of the brain; see section 13.2c.) The aqueous humor circulates from the posterior chamber through the pupil and into the anterior chamber. Aqueous fluid drains from the anterior chamber into a circular canal at the limbus called the **scleral venous sinus** (previously called the canal of Schlemm). This fluid then drains into nearby veins. Thus, as with cerebrospinal fluid, aqueous humor is produced from capillaries, circulates, and then enters the venous circulation. Normally, the rate of formation by the ciliary processes is equal to the drainage into the scleral venous sinus; thus, a normal intraocular pressure is maintained. **Glaucoma** results from the blockage of aqueous humor drainage (see Clinical View 16.6: “Glaucoma”).
Aqueous humor is secreted by the ciliary processes into the posterior chamber.

Aqueous humor moves from the posterior chamber, through the pupil, to the anterior chamber.

Excess aqueous humor is resorbed into the scleral venous sinus.

**Figure 16.15 Aqueous Humor: Secretion and Resorption.** Aqueous humor is a watery secretion that is continuously produced and circulated through the anterior cavity of the eye, to provide oxygen and nutrients to the inner portion of the cornea and the adjacent region of the lens.

**INTEGRATE CLINICAL VIEW 16.5 Cataracts**

Cataracts (katˈə-rakt) are small opacities within the lens that, over time, may coalesce to completely obscure the lens. Most cases occur as a result of aging, although other factors include diabetes, intraocular infections, excessive ultraviolet light exposure, and glaucoma. The resulting vision problems include difficulty focusing on close objects, reduced visual clarity due to clouding of the lens, “milky” vision, and reduced intensity of colors.

A cataract needs to be removed only when it interferes with normal daily activities. Newer surgical techniques include phacoemulsification (fəˈkō-ə-mlˈə-sə-fi-kāˈshən), a process by which the opacified center of the lens is fragmented using ultrasonic sound waves, thus making it easier to remove. The destroyed lens is then replaced with an artificial intraocular lens, which becomes a permanent part of the eye.
Chapter Sixteen

Nervous System: Sense

16.4c Physiology of Vision: Refraction and Focusing of Light

LEARNING OBJECTIVES


17. Discuss how light is focused on the retina.

The physiology of vision requires that light enters the eye and is transduced into electrical signals, which are then sent to the brain for integration and interpretation. The primary processes of vision include the refraction and focusing of light on the retina (which is discussed in this section) and phototransduction and relaying of sensory input along visual pathways (which are discussed in sections 16.4d and 16.4e).

Refraction of Light

Light rays are straight as they first enter the eye. However, the ability to see clearly requires refraction (or bending) of the light rays so that they hit on the retina—specifically, at the fovea centralis, the portion of the retina that is predominantly composed of cones and provides the sharpest vision (figure 16.14). Light rays are refracted when (1) they pass between two media of different densities and (2) these media meet at a curved surface. Each medium—such as air, water, and other clear fluids, and even clear solids such as glass—is assigned a refractive index, a number that represents its comparative density. The refraction of light rays is greater when there is a larger difference in the refractive index between adjacent media, such as between air and water (figure 16.16) and with increasing curvature of the media surface.

Before light can reach the photoreceptor cells, it must pass from the air through the cornea, aqueous humor, lens, and vitreous humor, as well as through the cells forming the inner layers of the retina. Both the cornea and lens play a significant role in refraction of light for vision—the cornea because of the relatively large refraction of light that occurs as light passes...

INTEGRATE

CLINICAL VIEW 16.6

Glaucoma

Glaucoma (glaw-kō’mā) is a disease that exists in three forms, all characterized by increased intraocular pressure: angle-closure glaucoma, open-angle glaucoma, and congenital or juvenile glaucoma. Angle-closure and open-angle glaucoma both involve the angle formed in the anterior chamber of the eye by the union of the choroid and the sclera (see figure 16.10c), or corneal-scleral junction (i.e., limbus). This angle is the important passageway for draining the aqueous humor. If it narrows, fluid and pressure build up within the anterior chamber. About one-third of all cases of glaucoma develop as a direct consequence of the narrowing of this angle, a condition called angle-closure glaucoma. Open-angle glaucoma accounts for about two-thirds of glaucoma cases. In this instance, although the drain angles are adequate, fluid transport out of the anterior chamber is impaired. Congenital glaucoma (or childhood glaucoma) occurs only rarely and is due to hereditary factors or intrauterine infection.

Regardless of the cause, fluid buildup in the anterior cavity causes a posterior dislocation of the lens and a substantial increase in pressure in the posterior cavity. Compression of the choroid layer may occur, constricting the blood vessels that nourish the retina. Retinal cell death and increased pressure may distort the axons of ganglionic cells that form the optic nerve, leading to impaired vision. Eventually, the patient may experience such symptoms as reduced field of vision, dim vision, and halos around lights. These symptoms are often unrecognized until it is too late and the damage is irreversible, so it is essential individuals get regular eye screenings where early stages may be detected by an optometrist or ophthalmologist.
from air into the cornea and the lens because of its ability to change shape. Recall that the curvature of the lens (and thus the refraction of light) can be altered through accommodation by relaxation and contraction of the ciliary muscles.

**Focusing of Light**

The processes that occur in the eye for us to see clearly are dependent upon how far away the object is that we are viewing. Let us first consider the three significant changes that occur when we view objects that are closer than 20 feet. These include convergence of the eyes, accommodation of the lens, and constriction of the pupil. These include convergence of the eyes, accommodation of the lens, and constriction of the pupil.

**Convergence of the Eyes**  
Convergence of the eyes is the voluntary contraction of the extrinsic eye muscles to move the eyes medially. (The extreme case of this is when your eyes are cross-eyed such as occurs when you try to focus on your finger a few inches from your eyes.) This positions the eyes so that the image of the object being viewed is directed onto the fovea centralis. Individuals with extrinsic eye muscles that are weaker in one eye than in the other may be unable to converge the eyes and as a result will have diplopia (di-plō’pé-ă) or double vision.

**Accommodation of the Lens**  
Recall from section 16.4b that accommodation involves stimulation of the ciliary muscles by the parasympathetic division of the ANS when viewing objects closer than 20 feet. In response, the ciliary muscles contract to reduce tension in the suspensory ligaments, so the lens becomes more spherical, or curved. Consequently, the light is refracted to a greater extent. Note that this change in

---

**Emmetropia** (em-ĕ-trō’ŏ-ă; emmetros = according to measure, ops = eye) is the condition of normal vision, in which parallel rays of light are focused exactly on the retina. Any variation in the curvature of either the cornea or the lens, or in the overall shape of the eye, causes entering light rays to form an abnormal focal point. Conditions that can result include hyperopia, myopia, and astigmatism.

**Hyperopia** (hi-per-ŏ’ŏ-ă) have trouble seeing close-up objects and so are called farsighted. In this optical condition, only convergent rays (those that come together from distant points) can be brought to focus on the retina. The cause of hyperopia is a short eyeball; parallel light rays from objects close to the eye focus posterior to the retina. By contrast, people with myopia (mi-ŏ’ŏ-ă; myo = to shut) have trouble seeing faraway objects and so are called nearsighted. In myopia, only rays relatively close to the eye focus on the retina. The cause of this condition is a long eyeball; parallel light rays from objects at some distance from the eye focus anterior to the retina within the vitreous body. Another variation is astigmatism (ă-stig’mă-tiz-m), which causes unequal focusing and blurred vision.

**Emmetropia**

- Normal vision
  - Focal plane
  - Corrected focal plane

**Hyperopia (farsightedness)**

- Eyeball is too short, so near objects are blurry.
  - Hyperopia (uncorrected)
  - Corrected focal plane
  - Convex corrective lens

**Myopia (nearsightedness)**

- Eyeball is too long, so far objects are blurry.
  - Myopia (uncorrected)
  - Corrected focal plane
  - Concave corrective lens
light refraction is necessary because as objects become increasingly closer, the light rays reflecting from these objects must be bent to a greater degree so that the light rays hit on the retina.

**Constriction of the Pupil**  The parasympathetic division also stimulates the sphincter pupillae muscle to contract to decrease the light rays passing through the edges of the lens (see section 15.7b). This is required when looking at objects closer than 20 feet because the lens must become more curved, but the edges of the lens are unable to curve to the extent that occurs at the center of the lens. Thus, light rays are not refracted at the edges of the lens to the same extent as the center of the lens. Consequently, light passing through the edges of the lens are not focused on the retina, and this portion of the object appears blurry. By constricting the pupil and allowing less light into the eye, light is passing only through the center of the lens. Collectively, these changes associated with focusing on objects that are closer than 20 feet is called the **near response**.

In comparison, when viewing objects at a distance greater than 20 feet away, the near response is not occurring. Instead, the following is noted:

- The eyes are facing forward and are not converging.
- The ciliary muscles are relaxed and the lens is flatter, so the light is refracted to a lesser extent (i.e., there is no accommodation).
- The pupil is relatively dilated to allow a greater amount of light into the eye for maximizing visual input regarding the environment. Note that when viewing objects at any distance, it is an inverted image that hits the retina (see figure 16.14).
INTEGRATE

CLINICAL VIEW 16.8

Color blindness is an inherited genetic trait (see section 29.9c) that occurs when an individual has an absence or a deficit in one type of cone cell. The most common form of color blindness is the X-linked recessive trait, which involves the red and green cone cells, resulting in red-green color blindness. For these individuals, red and green colors appear similar and are difficult to distinguish. For example, in the adjacent image, a person with color blindness cannot distinguish the green number 74 from the rest of the speckled red background. The image instead would appear as a bunch of different-sized dots without great differences in color. Color blindness is much more common in males (seen in about 8% of the male population) because it is an X-linked recessive trait.

16.4d Physiology of Vision: Phototransduction

LEARNING OBJECTIVES

18. Define phototransduction.
19. Compare and contrast the two general types of photoreceptors, including their photopigments.
20. Explain the bleaching reaction and how it relates to dark adaptation and light adaptation.

Phototransduction is the converting (or transducing) of light energy into an electrical signal. Photoreceptor cells (rods and cones) are the specific cells within the neural layer of the retina that engage in phototransduction. We first describe the anatomic details of photoreceptor cells (and other cells of the neural layer of the retina) and then discuss the process of phototransduction and the initiating of nerve signals that are sent to the brain.

Photoreceptors and Other Cells of the Neural Layer of the Retina

Both types of photoreceptor cells are composed of an outer segment, an inner segment, a cell body, and synaptic terminals. The outer segment extends into the pigmented layer of the retina (rod-shaped in rods and conical-shaped in cones) (figure 16.17). The outer segment is composed of hundreds of discs that are flattened, membranous sacs, which are constantly being replaced. New discs are added at the base of the outer segment and begin to move externally toward the tip, where old, worn-out discs are removed by phagocytic cells within the pigmented layer. Usually, it takes about 10 days for a disc to traverse this distance. The outer segment is connected to the inner segment, which contains the organelles for the cell, such as mitochondria. The inner segment connects to the cell body, which contains the nucleus. Synaptic terminals on the other side of the cell body house synaptic vesicles with glutamate neurotransmitter.

Rods and Cones

Rods are longer and narrower than cones. Each eye contains more than 100 million rods, and they are primarily located in the peripheral retina. Rods are activated by dim (low-intensity) light, such as when you are in an unlit room at night, and provide no color recognition. We describe how rods produce limited sharpness of vision in section 16.4d.

Cones occur at a density of less than 10 million per eye and are concentrated in the fovea centralis (the place of our most acute vision). Cones are activated by high-intensity light and provide color recognition and precise visual sharpness. Thus, when you notice the fine details in a colorful picture, the cones of your retina are responsible.

Why are there two types of photoreceptor cells (rods and cones)? One explanation is based upon both the arrangement of the three primary layers of neurons within the different regions of the retina and the varying degrees of sensitivity of rods and cones to light stimuli. In the peripheral retina, many rods converge on fewer bipolar cells, which synapse on one ganglion cell. In this arrangement, one ganglion cell is receiving input from many rods. In addition, recall that rods are more sensitive to light than are cones and can be stimulated by low light. There is both an advantage and a disadvantage to this anatomic arrangement and characteristic of rods. The advantage to this arrangement can be seen in conditions of low light. Rods are stimulated and spatial summation (see section 12.8b) occurs at both the bipolar cells and ganglion cells. The additive effect can cause sufficient neurotransmitter to be released from bipolar cells to stimulate ganglion cells to initiate an action potential that is propagated to the brain. However, because one ganglion is stimulated by numerous rods that cover a relatively wide area (1 mm²), the brain’s perception of this sensory input is of a slightly blurry image.

In comparison, in the fovea centralis there is a one-to-one relationship between each cone and a bipolar cell, and between a bipolar cell and each ganglion cell. However, recall that cones are less sensitive to light than are rods and require bright light to be stimulated. There is also both an advantage and a disadvantage to this anatomic arrangement and characteristic of cones. The advantage is having visual input from a very small area of the retina (about 1 μm²) that allows the brain to perceive a sharp image. However, cones are stimulated only in
Figure 16.17 Photoreceptors. (a) The outer segments of both rods and cones consist of stacks of discs embedded in the pigmented layer. (b) Membranes of the discs contain photopigments. Each photopigment is composed of an opsin and a retinal.

bright light, and sufficient light must be present for our cones to function. Thus, rods allow us to see in dim light but produce a blurry image, whereas cones produce a sharp image but require bright light.

Photopigments Photopigments are the specific molecules that absorb light and that are embedded within the plasma membrane of the outer segment of both rods and cones (figure 16.17b). A photopigment is composed of a protein called an opsin (opˈsin; ˈopsis = vision) and a light-absorbing molecule called a retinal (or a retineme), which is formed from vitamin A. There are several different types of photopigments that contain different opsins, and each type transduces different wavelengths of light. Thus, some photopigments may transduce light of longer wavelengths like reds, whereas other photopigments may transduce light of shorter wavelengths like blues. However, each photoreceptor cell expresses only one photopigment type.

The photopigment in rods is called rhodopsin (ró-dopˈsin; rhodon = a rose). Rhodopsin is involved in the transduction of dim light and is most sensitive to light at a 500-nm wavelength (figure 16.18). It is less sensitive to other light wavelengths.

The photopigment in cones is called photopsin (fō-topˈsin; phos = light). There are three different photopsin proteins, and each type of photopsin protein maximally absorbs different
wavelengths of light. Cones are categorized into three different types on the basis of the specific type of photopsin protein they contain and the wavelength to which it is most sensitive. **Blue cones** best detect wavelengths of light at about 420 nanometers (nm); **green cones** maximally absorb light at 531 nm; and **red cones** best detect light at 558 nm.

Thus, certain colors are best perceived by specific cones. But what about conditions where there is a mixture of colors (such as a greenish-blue hue)? In this case, we perceive intricate colors based on patterns of nerve signals arriving from a combination of these cones. Note in figure 16.18 that at about 470 nm, only the blue and green cones are stimulated; however, they are not stimulated at their peak. Instead, both types of cones are stimulated at about 50% capacity. When the blue and green cones initiate nerve signals, the brain interprets the color as a blue-green.

**Phototransduction**

Phototransduction occurs as light enters the eye and is transduced to an electrical signal by photoreceptor cells. We first discuss what happens with rods (figure 16.19). Prior to being activated by light, the retinal portion of the rhodopsin is in a bent, twisted shape called **cis-retinal**. Upon exposure to light, the retinal straightens out into a form called **trans-retinal**. **Trans-retinal** dissociates from the opsin and phototransduction occurs. This dissociation of rhodopsin into its two components (trans-retinal and opsin) is a process termed a **bleaching reaction** because the rhodopsin goes from a bluish-purple color to colorless. Bleaching reduces rhodopsin amounts in rods and temporarily affects our ability to see in dim light conditions.

Rhodopsin must be regenerated for the rod cell to continue to function. Its regeneration occurs as follows: The dissociated trans-retinal is transported from the rod within the neural layer to the pigment layer using ATP. Cis-retinal associates with opsin to re-form rhodopsin.
pigmented layer, where it is converted back to its bent cis-retinal form—a process that requires ATP. The cis-retinal is then transported back to the rod, where it associates with the opsin and re-forms the rhodopsin. This process is relatively slow; typically, only half of the bleached rhodopsin is regenerated after about 5 minutes. Light will interfere with this process, and rhodopsin will bleach as fast as it is re-formed when we are in high-intensity light. For this reason, rods are essentially nonfunctional in bright light situations; the bleaching reaction in the neural retina occurs more quickly than rhodopsin reformation in the pigmented layer.

A similar process occurs for the photopigments of cone cells. Cis-retinal transforms to trans-retinal, and a bleaching reaction occurs, but a more intense light is required. However, the regeneration of photopigments occurs much more quickly than the regeneration of rhodopsin; thus, cone cells are not as negatively affected by bright light as rods.

Recall a time when you went from bright light conditions outside on a sunny day into a darkened movie theater. You probably remember the slow return of your sensitivity to low light levels. This phenomenon, called dark adaptation, occurs because initially our cones become nonfunctional in the low light (because they require a more intense stimulus), but our rods are still bleached from the bright light conditions from outside. It may take 20 to 30 minutes for your rod to be regenerated sufficiently that you can see well in low-light conditions.

In comparison, light adaptation is the process by which your eyes adjust from low light to bright light conditions, such as when you wake up at night and turn on the bright light in the bathroom. Even though your pupils constrict to reduce the amount of light entering your eyes, you are temporarily blinded as the rods become inactive and the cones, which initially were overstimulated, gradually adjust to the brighter light. In about 5 to 10 minutes, the cones can produce sufficient visual acuity and color vision.

Initiating Nerve Signals
How does the splitting of photopigments within photoreceptor cells in the retina initiate nerve signals that are relayed to the brain? We first describe what is occurring in the rods, bipolar cells, and ganglion cells within the retina in the absence of light (figure 16.20a). In the dark, the outer segment of rods continuously produces cyclic GMP (cGMP) from guanosine triphosphate (GTP). This reaction is catalyzed by the enzyme guanylate cyclase. cGMP binds to cation channels in the plasma membrane of the outer segment, allowing an influx of both Na\(^+\) and Ca\(^{2+}\). This influx of cations (called the dark current) depolarizes the photoreceptor cells to about –40 mV. These local currents of ions diffuse from the outer segment, reaching voltage-gated Ca\(^{2+}\) channels at the synaptic terminals of the rods; this change in voltage triggers these channels to open. Calcium ions enter the synaptic terminals, triggering the continuous (tonic) release of glutamate neurotransmitter. Glutamate binds with receptors of the bipolar cells to cause hyperpolarization of the bipolar cells. This inhibits the bipolar cells and prevents them from releasing glutamate neurotransmitter from their synaptic terminals. Thus, no nerve signals are generated by ganglion cells.

When exposed to light (figure 16.20b), rhodopsin is split, and through a G protein second messenger pathway (see figure 4.21), the enzyme (phosphodiesterase) that breaks down cGMP is activated. Lower levels of cGMP result in the closing of the cation channels, preventing the influx of both Na\(^+\) and Ca\(^{2+}\). Thus, the dark current ceases, and the photoreceptor cells hyperpolarize. Voltage-gated Ca\(^{2+}\) channels at the synaptic terminals of the photoreceptor cells now close, and release of glutamate neurotransmitter ceases. Bipolar cells are no longer inhibited and now release glutamate neurotransmitter that binds to receptors of ganglion cells. If sufficient neurotransmitter is released from the bipolar cells and the threshold is reached in a ganglion cell, a nerve signal is propagated along the axon of the ganglion cell into the brain.

WHAT DID YOU LEARN?
17. What are the differences between rods and cones with respect to their anatomy, their photopigments, and the light they process?
18. How does dark adaptation differ from light adaptation?
19. What occurs during phototransduction of light?

16.4e Visual Pathways

LEARNING OBJECTIVES
21. Describe the visual pathway from the photoreceptors to the brain.
22. Explain how stereoscopic vision provides depth perception.

Figure 16.21 depicts the visual pathways. The visual pathways begin at the retina, where the photoreceptor cells transduce light stimuli to an electrical signal. The bipolar cells are the primary neurons, and the ganglion cells are the secondary neurons with the visual pathways (see sensory pathways from section 14.4b). The axons of the ganglion cells form the optic nerve, which exits the back of the eye at the optic disc (see figure 16.10). Optic nerves project from each eye and converge at the optic chiasm (kī'azm) (immediately anterior to the pituitary gland; see figure 13.1b). The optic chiasm is a flattened structure anterior to the infundibulum where many of the optic nerve axons decussate (cross) to the other side. The ganglionic axons originating from the medial region of each retina cross to the opposite side of the brain at the optic chiasm, whereas ganglionic axons originating from the lateral region of each retina remain on the same side of the brain and do not cross. Optic tracts extend laterally from the optic chiasm as a composite of ganglionic axons originating from the retina of each eye.

The majority of the optic tract axons extend to the thalamus, specifically to the lateral geniculate (je-nik’u-lāt; genu = knee, referring to its appearance) nucleus, where visual information is processed within each thalamic body (see section 13.4b). Tertiary neurons project axons (projection fibers) from the thalamus to the visual cortex of the occipital lobe for conscious interpretation of incoming visual stimuli.

Note that the left and right eyes have somewhat overlapping visual fields. For the brain to interpret these two distinct visual images, it must process or unite them into one. These overlapping images then provide us with stereoscopic vision, or depth perception, which is the ability to determine how close or far away an object is. Animals that don’t have overlapping visual fields (such as horses and deer) may have a greater visual range, but they cannot perceive visual depths.

In addition to the neural pathway that relays input to the visual cortex, a limited number of axons within each optic tract project to the midbrain as part of reflexes. Those that extend to the superior colliculi (ko-lik’yū-lī) of the midbrain coordinate the reflexive movements of the extrinsic eye muscles (see section 13.5a), whereas those that extend to the pretectal nuclei of the midbrain function as the control centers in both the pupillary reflex to regulate the amount of the light that enters the eye and the accommodation reflex for focusing the lens. (Input sent to the pretectal nucleus is initiated by specialized ganglion cells that respond directly to light through the visual pigment melanopsin, a light-sensitive retinal protein.)
In the dark

1. Cation channels are kept open by high levels of continuously produced cGMP. Glutamate neurotransmitter is released continuously in the dark.

2. Voltage-gated Ca\(^{2+}\) channels open, and the neurotransmitter glutamate is released from photoreceptor.

3. Binding of glutamate hyperpolarizes the bipolar cell, causing inhibition.

4. There is no release of glutamate neurotransmitter from the bipolar cells.

5. No nerve signal is generated by the ganglion cells.

In the light

1. Stimulation by light causes the photoreceptor cell to be hyperpolarized at ~70 mV because of decreased entry of Na\(^+\) and Ca\(^{2+}\).

2. Voltage-gated Ca\(^{2+}\) channels close, and no glutamate neurotransmitter is released.

3. The bipolar cell is no longer inhibited and thus it depolarizes.

4. Bipolar cell releases neurotransmitter (glutamate).

5. The glutamate neurotransmitter binds to receptors in the ganglion cell, and a nerve signal is initiated to the brain.

Figure 16.20 Phototransduction in Rod Photoreceptors. (a) Events associated with dim light that prevent initiation of nerve signals to the brain. (b) Events associated with bright light that initiate nerve signals to the brain.

**WHAT DO YOU THINK?**

Why would it be an advantage for a deer to have a wide visual field, as compared to overlapping, stereoscopic vision?

The physiology of vision, which involves the eyes, visual pathways, and brain is integrated in figure 16.22. Vision loss may result from either disease or disorders in any structures involved with vision, including the eye, optic nerve, optic tract, or brain.
Figure 16.21 Visual Pathways. Each optic nerve conducts visual stimuli information. At the optic chiasm, some axons from the optic nerve decussate. The optic tract on each side then contains axons from both eyes. Visual stimuli information is processed by the thalamus and then interpreted by visual association areas within the occipital lobe of the cerebrum. Visual sensory input involved in reflexes is relayed to nuclei within the midbrain (superior colliculi and pretectal nuclei). Note: In this image we have used the color red (previously used in other images for motor pathways) to distinguish between the two eye sensory pathways.

WHAT DID YOU LEARN?

What areas of the brain consciously perceive visual stimuli, and which areas respond reflexively (below the conscious level)?

What is the significance of some ganglionic axons crossing to the opposite side of the brain?

16.5 Hearing and Equilibrium Receptors

The ear is the organ that detects both sound and movements of the head. These stimuli are transduced into nerve signals that are transmitted by the vestibulocochlear nerve (CN VIII) (see section 13.9), resulting in the sensations of hearing and equilibrium.

16.5a Ear Structure

Describe the structures of the outer, middle, and inner ear.

Name the auditory ossicles, and explain how they function in hearing.

Compare and contrast the bony labyrinth and the membranous labyrinth.

The ear is partitioned into three distinct anatomic regions: external, middle, and inner (figure 16.23). The external ear is located mostly on the outside of the body, and both the middle ear and inner ear are housed within the petrous part of the temporal bone (see section 8.2b).
Light rays are refracted by the cornea as they enter the eye.

Pupils dilate for low light or constrict for bright light.

Light passes through the pupil and is refracted by the lens. The lens flattens for distant vision, whereas the lens becomes more curved as the eye accommodates for near vision.

Visual image is perceived by the brain.

Figure 16.22 How We See. (a) Light is refracted and then focused on the retina. (b) Light rays are transduced to nerve signals, and (c) these nerve signals are transmitted to the brain.

(a) Refraction and Focusing of Light
An inverted image is focused on the retina.

**Phototransduction**

Cones provide sharp color vision in the presence of bright light. Rods detect movement and work best in dim light.

Hyperpolarized photoreceptors no longer inhibit bipolar cells, allowing them to stimulate ganglion cells, which initiate nerve signals that are propagated along the optic nerve.

Nerve signals generated from each eye are transmitted by each optic nerve. Some axons from each eye cross at the optic chiasm. Each optic tract transmits nerve signals from both eyes, which are relayed to the thalamus. Most nerve signals are propagated from the thalamus to the left and right primary visual cortices. Each visual cortex receives visual information from both eyes. A smaller number of axons are projected to regions of the midbrain involved in visual reflexes.
External Ear

The most visible portion of the external ear is a skin-covered, elastic cartilage–supported structure called the auricle (aw′r-i-kl; auris = ear), or pinna (pī′nā; wing). The auricle is funnel-shaped, and it both protects the entry into the ear and directs sound waves into the bony tube called the external acoustic meatus (or external auditory meatus; see section 8.2b). This canal, which is about 2.5 centimeters (1 inch) in length and 7.5 millimeters (0.3 inch) in diameter, extends slightly superiorly from the lateral surface of the head to the tympanic membrane. The narrow external opening in the external acoustic meatus prevents large objects from entering and damaging the tympanic membrane. Near its entrance, fine hairs help guard the opening. Deep within the canal, ceruminous glands produce a waxlike secretion called cerumen (sē′rū-men; cera = wax), which combines with dead, sloughed skin cells to form earwax. This material may help reduce infection within the external acoustic meatus by impeding microorganism (e.g., bacteria) growth.

The tympanic (tim-pan′ık; tympanon = drum) membrane, or ear-drum, is a funnel-shaped membrane (approximately 1 centimeter in diameter) composed of fibrous connective tissue sandwiched between two epithelial sheets. It serves as the boundary between the external and middle ear. The tympanic membrane vibrates when sound waves hit it, and its vibrations provide the means for transmission of sound wave energy from the external ear to the middle ear. Pain associated with trauma to the tympanic membrane is transmitted to the brain along sensory neurons within both the vagus and trigeminal nerves (see section 13.9).

Middle Ear

The middle ear contains an air-filled tympanic cavity (figure 16.24). Medially, a bony wall separates the middle ear from the inner ear. Two membrane-covered openings are located within this wall: the oval window and round window (discussed in detail in section 16.5b). Inferiorly, the auditory tube (also called the pharyngotympanic tube or Eustachian tube), which is approximately 3.5 centimeters (1.5 inches) in length, serves as a passageway that extends from the middle ear into the nasopharynx (portion of upper throat posterior to the nasal cavity; see figure 23.5). This tube is normally closed. Air movement through this tube occurs as a result of chewing, yawning, and swallowing, which equalize pressure on either side of the tympanic membrane—allowing the tympanic membrane to vibrate freely. The tympanic cavity, auditory tube, and nasopharynx are lined with a continuous mucous membrane. Middle ear infections result when infectious agents (e.g., a cold virus) move from the nasopharynx through the auditory tube into the middle ear (see Clinical View 16.9: “Otitis Media”).

**Figure 16.23 Anatomic Regions of the Right Ear.** The ear is divided into external, middle, and inner regions.

**WHAT DO YOU THINK?**

1. When an airplane descends to a lower altitude, you may feel greater pressure in your ears, followed by a popping sensation—then more normal pressure resumes. What do you think has happened?

The tympanic cavity of each middle ear houses the three smallest bones of the body, the auditory ossicles (os′i-kl) (see section 8.3). These three bones, which are positioned between the tympanic membrane and...
Chapter Sixteen

Nervous System: Sense

643

Temporal bone (petrous part)

Tympanic membrane

Malleus

Incus

Tensor tympani (cut)

Stapes

Stapedius

Auditory ossicles

Oval window

Stapedius

Tensor tympani (cut)

Round window

Auditory tube

Malleus

Normal tympanic membrane

Otitis media

Myringotomy

Middle ear views as seen with an otoscope.

©ISM/Medical Images

CLINICAL VIEW 16.9

Otitis Media

Otitis (ō-tī’tis; ēs = inflammation) media (mē’dē-ā; medius = middle) is an infection of the middle ear. It is most often experienced by young children, whose auditory tubes are horizontal, relatively short, and underdeveloped. If a young child has a respiratory infection, the causative agent may spread from the pharynx (throat) through the auditory tube. Fluid then accumulates in the middle ear cavity, resulting in pressure, pain, and sometimes impaired hearing.

Classic symptoms of otitis media include fever (sometimes over 104°F), pulling on or holding the affected ear, and general irritability. An otoscope (ō-tō-skōp; oto = ear, skopeo = to view) is an instrument used to examine the tympanic membrane, which normally appears white and pearly but in cases of severe otitis media is red (due to inflammation and sometimes bleeding) and may even bulge due to fluid pressure in the middle ear.

Repeated ear infections, or a chronic ear infection that does not respond to antibiotic treatment, usually requires a surgical procedure called a myringotomy (mir-ing-got’ō-mē; myringa = membrane), whereby a ventilation tube is inserted into the tympanic membrane. This procedure allows the infection to heal and the pus and mucus to drain from the middle ear into the external acoustic meatus and offers immediate relief from the pressure. Eventually, the inserted tube is sloughed, and the tympanic membrane heals.

When a child is about 5 years old, the auditory tube has become larger, more vertically angled, and better able to drain fluid and prevent infection from reaching the middle ear. Thus, the occurrence rate for ear infections drops dramatically at this time.

The middle ear contains the auditory ossicles and associated structures within the tympanic cavity of the temporal bone.
sensory receptors from blasts of sounds, as occurs with a gunshot. For this reason, loud blasts of sound are especially damaging to the sensory receptors within the inner ear.

**Inner Ear**

The inner ear is located within the petrous part of the temporal bone, where there are spaces, or cavities, called the **bony labyrinth** (lab′i-rinth; an intricate, mazelike passageway) (figure 16.25). Within the bony labyrinth are membranous, fluid-filled tubes and sacs called the **membranous labyrinth**. Receptors for both hearing and equilibrium are within the membranous labyrinth.

The space between the outer walls of the bony labyrinth and the membranous labyrinth is filled with a fluid called **perilymph** (per′i-limf) that is similar in composition to interstitial fluid. The perilymph suspends, supports, and protects the membranous labyrinth from the wall of the bony labyrinth. The space within the membranous labyrinth contains a fluid called **endolymph** (en′dō-limf), which is an unusual extracellular fluid because it is similar in composition to intracellular fluid with relatively high levels of K⁺ (see section 4.4a).

The bony labyrinth is structurally and functionally partitioned into three distinct regions, including the cochlea, vestibule, and semicircular canals:

- The **cochlea** (kok′lē-ä; snail shell) houses a membranous labyrinth structure called the **cochlear duct** (or scala media).
- The **vestibule** (ves′ti-bül; vestibulum = entrance court) contains two saclike, membranous labyrinth structures—the **utricle** (u′trī-kl; uter = leather bag) and the **saccule** (sa-kwel; saccus = sack).
- The **semicircular canals** each contain a membranous labyrinth structure called the **semicircular duct**.
The structures of the membranous labyrinth are continuous. The cochlear duct is continuous with the sacculle, which is connected through a narrow passageway to the utricle, and the utricle is continuous with the semicircular ducts.

**WHAT DID YOU LEARN?**

22. What is the function of the external acoustic meatus?
23. Where are the auditory ossicles located, and what is their function?
24. What are the membranous labyrinth structures, and what is the specific bony labyrinth structure in which each resides?

### 16.5b Hearing

**LEARNING OBJECTIVES**

26. Explain the components of the cochlea and how they function in the sense of hearing.
27. Trace the path of a sound wave from outside the ear to stimulation of the vestibulocochlear nerve (CN VIII).
28. Distinguish between frequency and intensity of sound.

Hearing is the ability to detect and perceive sound. Here we follow the progression of how sound from the environment enters the ear and is transduced in the inner ear into electrical signals that are relayed to the brain. First, we consider the structures in the inner ear that are related to sound detection.

**Structures for Hearing**

Hearing organs are housed within the cochlea in both inner ears. View both figure 16.26, which is a cross section of the cochlea, and figure 16.27, which is a longitudinal section of a cochlea (partially “unrolled” so the structure can be viewed more easily), as you read through this section.

**Cochlea** The cochlea is a snail-shaped, spiral chamber within the bone of the inner ear. Figure 16.26a depicts how this chamber “wraps” approximately 2.5 times around a spongy bone axis called the modiolus (mō-dē′lō-ūs; hub of a wheel), giving the cochlea its snail-shaped appearance. The membranous labyrinth called the cochlear duct is housed within the cochlea. The roof of the cochlear duct is formed by the vestibular membrane, and the floor is formed by the basilar membrane (figures 16.26b and 16.27). These membranes partition the bony labyrinth of the cochlea into two smaller chambers on either side of the cochlear duct; both are filled with perilymph. The chamber adjacent to the vestibular membrane is the scala vestibuli (vestibular duct), and the chamber adjacent to the basilar membrane is the scala tympani (tympanic duct). The scala vestibuli and scala tympani merge at the helicotrema (hel′i-kō-trē′mā; helix = spiral, trema = hole) at the apex of the cochlea (see figure 16.27).

**Spiral Organ** Protected within the membranous cochlear duct is the spiral organ (formerly called the organ of Corti), which is the sensory structure for hearing (figures 16.26c, d and 16.27). The cochlear duct contains endolymph. The spiral organ is a thick sensory epithelium, consisting of both hair cells and supporting cells, that rests on the basilar membrane. Two categories of hair cells rest on the basilar membrane, including a single row of inner hair cells (which function as the sensory receptors for hearing) and three rows of outer hair cells (which alter the response of the spiral organ to sound). The apical surface of each hair cell has a covering of numerous (more than 50) long, stiff microvilli that are called stereocilia (ster′ē-ō-sil′ē-ā; stereos = solid) and one long cilium, called a kinocilium (kī-nō-sil′ē-ām; kino = movement). The stereocilia and kinocilium are embedded in an overlying gelatinous structure called the tectorial (tek-tōr′ē-āl; tectus = to cover) membrane. Extending from the base of these hair cells are primary sensory neurons (about 90% from the inner hair cells and about 10% from the outer hair cells). The cell bodies of these sensory neurons are housed within the spiral ganglia in the modiolus, which is located medial to the cochlear duct (figure 16.26a, b).

**Pathway from Sound Wave to Nerve Signal**

How we detect sound waves, transduce sound energy to an electrical signal, and then transmit a nerve signal along the vestibulocochlear nerve to the brain is described here. See figure 16.27 as you read through this section.

Sound waves are collected and funneled by the auricle of the external ear to enter the external acoustic meatus, which make the tympanic membrane vibrate. The vibration of the tympanic membrane causes movement of the auditory ossicles (malleus, incus, and stapes), which makes...
Figure 16.26 Structure of the Cochlea and Spiral Organ. The cochlea exhibits a snail-like, spiral shape and is composed of three fluid-filled ducts. (a) A section through the cochlea details the relationship among the three ducts: the cochlear duct, scala vestibuli, and scala tympani. (b) A magnified view of the cochlea. (c) Hair cells rest on the basilar membrane of the spiral organ within the cochlear duct. (d) Light micrograph of the spiral organ.
Figure 16.27 Sound Wave Pathways Through the Ear. Sound waves enter the external ear and vibrate the tympanic membrane to move the ossicles of the middle ear, which ultimately causes movement of a specific region of the spiral organ within the inner ear.
Cochlear branch of the vestibulocochlear nerve (CN VIII, see section 13.9). Simultaneously, the pressure wave vibrations within the cochlear duct are transmitted to the perilymph within the scala tympani, and are absorbed at the round window, as the window bulges slightly.

Cochlear Hair Cell Stimulation

Recall that inner hair cells, which function in converting sound energy into an electrical signal, are components of the spiral organ within the cochlea. These cells reside on the basilar membrane, and the tips of their stereocilia and kinocilium are embedded within the gelatinous tectorial membrane (figures 16.26 and 16.27). The details of the inner hair cells are shown in figure 16.28. Note that stereocilia of the inner hair cells are aligned, with each stereocilium progressively taller. Also notice that the tips of each stereocilium contain an ion channel, and that each ion channel is connected to the tip of the adjacent taller stereocilium by a filamentous protein appropriately called a tip link. This arrangement of inner hair cells is bathed in endolymph. The endolymph is a fluid high in potassium ion ($K^+$), contributing to the endolymph's electrical potential of $+80$ mV. In comparison, the cytosol of the inner hair cell has an electrical potential of $-40$ mV. This electrical difference between the endolymph and cytosol of the inner hair cells that exists when the inner hair cells are at rest represents potential energy (similar to the potential energy in resting neurons; see section 12.7b).

How does this arrangement result in the production of an electrical signal? Motion of the endolymph repeatedly moves the basilar membrane upward and downward. When the basilar membrane moves upward, the inner hair cells are pushed into the tectorial membrane, causing each stereocilium to tilt toward its taller neighboring stereocilium. This pulls on the tip link, and the movement of each tip link opens an ion channel on its shorter neighboring stereocilium. Potassium ion (primarily) diffuses from the endolymph through the open ion channels into the inner hair cell. This movement of $K^+$ causes depolarization (becoming more positive) of the inner hair cell, which triggers the release of neurotransmitter from the base of the inner hair cell. Neurotransmitter binds to dendrites of the primary neuron, causing graded potentials to be established, which move toward the axon. When the threshold is reached, an action potential is initiated along the axon of the primary neuron to the brain. In comparison, the downward movement of the basilar membrane pulls the inner hair cells away from the tectorial membrane, causing the inner cells to straighten. The pull by the tip links decreases, and the ion channels close. The inner hair cells temporarily hyperpolarize (become more negative), and neurotransmitter is no longer released. Amazingly, this upward and downward movement of the basilar membrane can occur at a rate of up to 20,000 times per second.

**Figure 16.28 Inner Hair Cells.** (a) The inner hair cells contain ion channels at the tips of their stereocilia. (b) The ion channel is attached to its taller neighboring stereocilium by a tip link protein. (c) Open ion channels allow $K^+$ to move into the inner hair cell.
Perception of Sound

**Sound** is the perception of pressure waves that are established by a vibrating object (e.g., a drum, guitar string, vocal cord). These waves of pressure move through any medium, including air, liquid, or a solid. The vibrating object pushes molecules within the medium. Those molecules push adjacent molecules, which in turn push adjacent molecules. However, no one molecule moves very far—it simply transfers the energy of its movement to other molecules. (This would be similar to a line of individuals, with each person pushing the next.)

Two properties of sound that we perceive are pitch and loudness. **Pitch** refers to the perception of a sound as high or low. Pitch is ultimately dependent upon the frequency of the vibrating object. **Frequency** is the rate of back-and-forth motion of the vibrating object, and is measured in cycles per second and expressed in **Hertz (Hz)**. The spiral organ of the human ear can perceive sounds with frequencies that range from about 20 Hz to 20,000 Hz, but we are most sensitive to sounds with frequencies between 1500 and 4000 Hz. We are able to perceive variations in pitch because there is a continuous difference in relative “stiffness” of the basilar membrane, as it extends from being thick and short at the oval window to thin and long at the cochlear apex. Different regions of the basilar membrane move in response to the frequency of the sound waves. High-frequency sounds cause movement of the basilar membrane near the oval window (where the basilar membrane is relatively stiff), whereas low-frequency sounds move the basilar membrane far away from the oval window (where the basilar membrane is relatively flexible) (figure 16.29). (This is analogous to the difference in pitch of piano strings from one side of the piano to the other.) We cannot perceive frequencies either lower or higher than this because the basilar membrane does not move in response to these rates of vibration.

**Loudness** (or intensity of sound) is dependent upon the amount of back-and-forth motion of the vibrating object that establishes the degree of compression of the molecules (or the amplitude of the sound waves). Soft sounds cause relatively small movements of the basilar membrane in a relatively smaller area of the spiral organ, whereas loud sounds cause relatively larger movement of the basilar membrane in a wider area of the spiral organ. The greater movement of the basilar membrane associated with louder sounds increases both the rate of nerve signals that are initiated by the inner hair cells and the number of hair cells that are stimulated. The auditory cortex within the temporal lobe of the brain interprets this change in sensory input as a louder sound. The loudness of a sound is measured in decibels (dB). Zero decibels is the minimum sound (or threshold) that is heard by humans. Consider that the energy associated with sound increases ten times with every 10-decibel increase. This would mean that a sound of 20 dB has 10 times the energy of a sound with 10 dB, and a sound of 30 dB has 100 times the energy of a sound of 10 dB. A normal conversation usually occurs at about 60 dB, and prolonged
exposure to sounds of 90 dB or greater has sufficient energy to damage the sensory receptors that detect sound within the inner ear.

**WHAT DID YOU LEARN?**

25. What are the steps for detecting sounds?
26. Compare the difference in how we perceive pitch versus how we perceive loudness.

### 16.5c Auditory Pathways

**LEARNING OBJECTIVE**

29. Describe the auditory pathway from stimulation of the vestibulocochlear nerve (CN VIII) to the brain.

We discussed how sound waves travel through the inner ear and how an electrical signal is initiated by the inner hair cells within the cochlear duct in the previous section. But what is the nerve pathway on which the initiated nerve signals are transmitted to the brain? This auditory pathway, which is composed of a sequence of four sensory neurons instead of the normal two or three, is shown in [Figure 16.30](#) and described here:

1. When the basilar membrane moves, the stereocilia of the spiral organ hair cells distort because they are anchored by the tectorial membrane. This distortion initiates nerve signals that are transmitted through the cochlear branch of the vestibulocochlear nerve (the primary neurons in this sensory pathway) to the cochlear nucleus within the medulla oblongata.
2. After integration and processing of the incoming information within the cochlear nucleus, nerve signals are transmitted along secondary neurons to the inferior colliculus in the midbrain (see section 13.5a). These nerve signals are relayed either (a) directly to the inferior colliculus or (b) first to the superior olivary nucleus in the pons before transmission to the inferior colliculus. Nerve signals arriving at the inferior colliculus are involved in a reflex to loud sounds; here nerve signals are relayed along motor neurons to skeletal muscles of the body that cause us to jump and turn our head in response to loud sounds. Nerve signals arriving at the superior olivary nucleus function to (a) localize the sound and (b) respond reflexively to loud sounds by initiating nerve signals to the tensor tympani and stapedius to contract, which decreases the vibration of the ossicles.
Movement of the basilar membrane produces nerve signals that are propagated along the cochlear branch of CN VIII to the cochlear nucleus within the medulla oblongata.

Some secondary neurons relay nerve signals directly to the inferior colliculus of the midbrain.

Some secondary neurons relay nerve signals to the superior olivary nucleus within the pons, which are then relayed to the inferior colliculus of the midbrain.

Nerve signals are relayed from the inferior colliculus to the thalamus (medial geniculate nucleus).

Nerve signals are then relayed from the thalamus to the primary auditory cortex of the temporal lobe of the cerebrum for sound perception.

**Figure 16.30 Central Nervous System Pathways for Hearing.** Nerve signals are propagated along the cochlear branch of CN VIII to the brainstem, then relayed to the thalamus before being transmitted to the primary auditory cortex. Note: Although not shown in the figure, some of the axons decussate to the other side of the brain.

**INTEGRATE**

**CLINICAL VIEW 16.11 Deafness**

Deafness is defined as any hearing loss. Hearing loss is categorized as either conductive deafness or sensorineural deafness. **Conductive deafness** involves any interference with the transmission of sound waves from the auricle through the external acoustic meatus, tympanic membrane, and ossicles. Causes of conductive deafness include rupture of the tympanic membrane, fusion of the ossicles, and inflammation of the middle ear (otitis media). **Sensorineural deafness** involves malformation of or damage to either the structures of the inner ear or the cochlear nerve. Examples include damage to cilia of the inner ear from loud sounds (e.g., rock concerts, firing a weapon) and trauma to the cochlear nerve from a blow to the head.

3. Nerve signals are transmitted from the inferior colliculus to the **medial geniculate nucleus** of the thalamus (see section 13.4b) for initial processing and filtering of auditory sensory information.

4. Nerve signals are then relayed from the thalamus to the **primary auditory cortex** within the temporal lobe of the cerebrum, where nerve signals are consciously perceived as sounds.

To integrate what you’ve learned about how sounds are processed and interpreted by the brain, refer to **figure 16.31** to review the anatomy and physiology of hearing.

**WHAT DID YOU LEARN?**

What are the major brain structures involved in the auditory pathway, and what is the function of each?
Sound waves are directed to the external ear. The tympanic membrane vibration causes the auditory ossicles to vibrate, and they amplify the sound. The stapes moves the oval window, generating pressure waves in the perilymph of the scala vestibuli. The displacement of the basilar membrane causes the stereocilia on the hair cells to bend, and nerve signals are propagated along the cochlear branch of CN VIII.

Nerve signals are transmitted along the cochlear branch of CN VIII to the brainstem where nuclei that control reflexive responses to sound are located. Nerve signals are then relayed through the medial geniculate nucleus of the thalamus, and ultimately go to the primary auditory cortex of the temporal lobe, where they are perceived as sounds.

(a) Transmitting Sound Waves from External to Middle Ear

1. Sound waves are directed to the external ear.

2. Sound waves are funneled into the external acoustic meatus and vibrate the tympanic membrane.

(d) Auditory Pathway

8. Nerve signals are transmitted along the cochlear branch of CN VIII to the brainstem where nuclei that control reflexive responses to sound are located. Nerve signals are then relayed through the medial geniculate nucleus of the thalamus, and ultimately go to the primary auditory cortex of the temporal lobe, where they are perceived as sounds.
(b) Amplification and Transmission of Sound from Middle to Inner Ear

3. The tympanic membrane vibration causes the auditory ossicles to vibrate, and they amplify the sound.

4. The stapes moves the oval window, generating pressure waves in the perilymph of the scala vestibuli.

5. Pressure waves in the perilymph within the scala vestibuli cause vibration of the vestibular membrane and movement of endolymph within the cochlear duct.

(c) Transduction of Sound Energy to Nerve Signals

6. The pressure waves displace specific regions of the basilar membrane, depending upon the frequency of the sounds.

7. The displacement of the basilar membrane causes the stereocilia on the hair cells to bend, and nerve signals are propagated along the cochlear branch of CN VIII.

Chapter Sixteen  Nervous System: Sense
16.5d Equilibrium and Head Movement

LEARNING OBJECTIVES

30. Describe the structures of the inner ear involved in equilibrium.
31. Explain how the utricle and saccule detect static equilibrium and linear movements of the head, and explain how the semicircular ducts function to detect rotational movements of the head.
32. Summarize the nerve pathways involved in equilibrium.

The term equilibrium refers to our awareness and monitoring of head position. Sensory receptors in the utricle, saccule, and semicircular ducts, collectively called the vestibular apparatus, help monitor and adjust our equilibrium. Our brain receives this sensory input and, along with visual sensory input and input from our proprioceptors, integrates this information so we can keep our balance and make positional adjustments as necessary.

The utricle and saccule detect head position during static equilibrium—that is, when the head is stationary. For example, when you are standing in the anatomic position, the utricle and saccule inform your brain that your head is upright. The utricle and saccule also detect linear acceleration changes of the head. This occurs, for example, when you tilt your head downward to look at your shoes.

The semicircular ducts, in contrast, are responsible for detecting angular acceleration, or rotational movements of the head. The sensory receptors in the semicircular ducts are stimulated when you shake your head “no,” or when a figure skater does a spin on the ice.

Static Equilibrium and Linear Acceleration

Both static equilibrium and linear acceleration are detected by the sensory receptors housed within the vestibule of the inner ear. The sensory receptor, called a macula, is located along the internal wall of both the membranous utricle and saccule. Each macula is composed of a mixed layer of hair cells and supporting cells (figure 16.32). These hair cells not only have stereocilia, but each hair cell also has one long kinocilium on its apical surface. Stereocilia and kinocilia projecting from the hair cells embed within a gelatinous mass that completely covers the apical surface of the epithelium. This gelatinous layer is covered by a mass of small calcium carbonate crystals called otoliths (ō’to-lith; lithos = stone), or statoconia. Together,
Inhibition

Standard nerve signal frequency

Vestibular branch of CN VIII

Hair cell

Supporting cell

Otoliths

Gelatinous layer

Otolithic membrane

Kinocilium

Stereocilia

Stereocilia parallel to kinocilium

• Neurotransmitter released at regular interval

• Steady rate of nerve signals are transmitted along vestibular branch of CN VIII

Standard nerve signal frequency

(a) Macula in upright head position

Stereocilia of hair cells bend.

Otolithic membrane moves.

Stereocilia bent toward kinocilium

• Hair cells depolarize, increasing neurotransmitter release

• Increased nerve signal frequency along vestibular branch of CN VIII

(b) Macula in altered head position

Stereocilia bent away from kinocilium

• Hair cells hyperpolarize, inhibiting neurotransmitter release

• Decreased nerve signal frequency along vestibular branch of CN VIII

Excitation

Inhibition

Head tilted upward

Head tilted downward

Figure 16.33 How the Maculae Detect Head Position and Linear Acceleration of the Head. (a) When the head is in an upright position, hair cells and stereocilia are in parallel and supported by the otolithic membrane. (b) Tilting the head causes the otolithic membrane to move slightly, causing the stereocilia to bend and alter the frequency of propagated nerve signals, which reports the change in head position. When the stereocilia are bent toward the kinocilium, the hair cell depolarizes and thus nerve signal propagation increases in frequency. Conversely, when stereocilia are bent away from the kinocilium, the hair cell hyperpolarizes and thus nerve signal propagation decreases in frequency.

the gelatinous layer and the crystals form the otolithic membrane (or statoconic membrane). The otoliths push on the underlying gelatinous layer, thereby increasing the weight of the otolithic membrane covering the hair cells.

The position of the head influences the position of the otolithic membrane (Figure 16.33). When the head is held erect, the otolithic membrane applies pressure directly onto the hair cells, and minimal stimulation of the hair cells occurs. However, tilting the head causes the otolithic
membrane to shift its position on the macula surface, thus distorting the stereocilia. Bending of the stereocilia results in a change in the amount of neurotransmitter released from the hair cells and a simultaneous change in the stimulation of the sensory neurons of the vestibular branch of the vestibulocochlear nerve (CN VIII).

Bending of the stereocilia toward the kinocilium causes the hair cells to depolarize and increase their rate of neurotransmitter release (figure 16.33b). A greater frequency (rate) of nerve signals is generated in the vestibular branches of vestibulocochlear nerves (CN VIII) as a result. In contrast, bending of the stereocilia away from the kinocilium causes the hair cells to hyperpolarize and thus decrease their rate of neurotransmitter release. Ultimately, fewer and less frequent nerve signals are generated in the axons of the vestibular branch as time elapses. The brain interprets the change in nerve signals to determine the direction the head has tilted.

Angular Acceleration

Angular acceleration is detected by the sensory receptors housed within the semicircular ducts of the semicircular canals. At the base of each semicircular canal is an enlarged region called the ampulla (am-pul′lə; pl., ampullae, am-pulˈlē; bottle-shaped) (figure 16.34). The ampulla contains an elevated region, called the crista ampullaris (or ampullary crest), which is covered by an epithelium of hair cells and supporting cells. Both the stereocilia and kinocilia are embedded into an overlying gelatinous dome called the cupula (kūˈpə-lə).

The crista ampullaris in each semicircular duct detects rotational movements of the head (figure 16.35). When the head first rotates, inertia causes endolymph to lag behind. This endolymph pushes against the cupula, causing bending of the stereocilia. Stereocilia bending results in altered neurotransmitter release from the hair cells and simultaneous stimulation of the sensory neurons. As previously described for sensory receptors within the vestibule, bending of the stereocilia in the direction of the kinocilium results in depolarization of the hair cells and increased frequency of nerve signals, whereas bending in the opposite direction results in hyperpolarization of the hair cells and decreased frequency of nerve signals (see figure 16.33b). Interestingly, these sensory receptors respond primarily to changes in velocity—meaning they respond to rotational acceleration or deceleration. If the head is rotating at a constant speed, eventually the movement of the endolymph catches up with the ampulla, so the stereocilia on the hair cells are no longer bent and the hair cells are no longer stimulated.

You may have done the following as a child: You stood upright, closed your eyes, and then spun in a clockwise (or counterclockwise) direction for about 1 minute. Initially, you felt your head spinning, but after about 30 seconds that spinning sensation may have disappeared. The reason is that the endolymph movement caught up with the ampulla’s rotational movement. When you stopped spinning, your head may still have felt like it was moving even though you were standing still. When you came to a stop (and decelerated), the endolymph’s momentum resulted in endolymph movement after the body stopped.

**Figure 16.34 Ampulla.** A diagrammatic section through an ampulla in a semicircular duct details the relationships among the hair cells and supporting cells, the cupula, and the endolymph in detecting rotational movement of the head.

---

**INTEGRATE**

**CONCEPT CONNECTION**

Multiple systems are involved in maintaining balance and equilibrium of the entire body. The vestibular apparatus detects motion of the head, our eyes provide the brain with visual information about body position (see section 16.4e), and proprioceptors throughout the musculoskeletal system detect muscle and tendon tension (see section 14.6d).

**Equilibrium Pathways**

The nerve pathway that relays sensory input from the vestibular apparatus is shown in figure 16.36 and described here:

1. When the stereocilia of either the maculae (within the utricle and saccule housed within the vestibule) or the crista ampullaris (within the ampulla of a semicircular duct) distort, nerve signals are initiated through the vestibular branch of the vestibulocochlear nerve (CN VIII).
2. The sensory axons of the vestibular branch (the primary neurons in this sensory pathway) terminate at either the medulla oblongata (vestibular nuclei) or cerebellum. (a) The paired vestibular nuclei
Function of the Crista Ampullaris. Rotation of the head causes endolymph within the semicircular duct to push against the cupula covering the hair cells, resulting in bending of their stereocilia and an alteration in the frequency of nerve signal propagation.

Equilibrium Pathways. Information from the vestibular complex is sent to multiple parts of the brain, so posture and body movement may be adjusted accordingly. Sensory information pathways are shown in blue, and motor pathways are shown in red.

WHAT DID YOU LEARN?
28 What type of movement do the maculae detect, and how do they detect this movement?
29 What type of movement do the ampullae detect, and how do they detect this movement?
### Chapter Summary

- Sensory receptors provide us with information about our external and internal environments.

#### 16.1 Introduction to Sensory Receptors

**16.1a General Function of Sensory Receptors**
- Sensory receptors function as transducers to change stimulus energy to an electrical signal that is transmitted to the CNS.

**16.1b General Structure of Sensory Receptors**
- Sensory receptors range in complexity from the bare dendritic ending of a single sensory neuron to complex sense organs.

**16.1c Sensory Information Provided by Sensory Receptors**
- A sensation is a stimulus that is consciously perceived by the cerebral cortex. Most stimuli are not consciously perceived.
- A sensory receptor provides the CNS with several characteristics regarding a stimulus, including its modality, location, intensity, and duration.

**16.1d Sensory Receptor Classification**
- Sensory receptors are defined and characterized by receptor distribution (general senses and special senses); stimulus origin (exteroceptors, interoceptors, and proprioceptors); and modality of stimulus (chemoreceptors, thermoreceptors, photoreceptors, mechanoreceptors, and nociceptors).

#### 16.2 The General Senses

**16.2a Tactile Receptors**
- Tactile receptors are the most numerous type of sensory receptors and are organized into unencapsulated and encapsulated receptors.
- Unencapsulated receptors include free nerve endings, root hair plexuses, and tactile discs.
- Encapsulated receptors include end bulbs, lamellated corpuscles, bulbous corpuscles, and tactile corpuscles.

**16.2b Referred Pain**
- Referred pain is pain that is perceived as if it originates in the skin and skeletal muscle but actually is caused by sensory nerve signals originating from an internal organ.

#### 16.3 Olfaction and Gustation

**16.3a Olfaction: The Sense of Smell**
- The olfactory epithelium is the sensory receptor for the sense of smell and is located in the nasal cavity; it is composed of olfactory receptor cells, supporting cells, and basal cells.
- The sense of smell is transmitted by olfactory nerves to olfactory tracts, which project to the hypothalamus, amygdala, and directly to the olfactory cortex without first synapsing in the thalamus.

**16.3b Gustation: The Sense of Taste**
- Taste buds house the sensory receptors for the sense of taste, which are located primarily on the tongue; they are composed of gustatory cells, supporting cells, and basal cells.
- The five basic taste sensations are sweet, salt, sour, bitter, and umami.
- The sense of taste is transmitted by both the facial nerves (CN VII) and glossopharyngeal nerve (CN IX) through the gustatory pathway.

#### 16.4 Visual Receptors

- The eyes house photoreceptors that detect light, color, and movement.

**16.4a Accessory Structures of the Eye**
- Accessory structures include the extrinsic eye muscles, eyebrows, eyelashes, eyelids, conjunctiva, and lacrimal glands.
- The conjunctiva is a membrane that covers the anterior surface of the sclera of the eye (the ocular conjunctiva) and the internal surface of the eyelid (the palpebral conjunctiva); it does not cover the cornea.
- Each lacrimal apparatus includes a lacrimal gland that distributes lacrimal fluid to the eye surface. Lacrimal fluid is collected into the lacrimal puncta, which drain into the nasolacrimal duct and then the nasal cavity.

**16.4b Eye Structure**
- The eye is divided into two cavities by the lens: the posterior cavity, which contains the permanent, gelatinous vitreous humor, and the anterior cavity, which contains the circulating, watery aqueous humor.
- The fibrous tunic is composed of the sclera, which helps protect and maintain the shape of the eye, and the cornea, which helps focus light on the retina.
- The vascular tunic of the eye wall has three regions: the choroid, which contains blood vessels to nourish the retina; the ciliary body, which assists lens shape changes with the suspensory ligaments and secretes aqueous humor; and the iris, which controls pupil diameter.
- The neural tunic, or retina, is composed of an outer pigmented layer (that absorbs stray light rays) and an inner neural layer that houses all of the photoreceptors and their associated neurons.
- The retina has a posterior, yellowish region called the macula lutea. Vision is sharpest at a depression within the center of the macula lutea called the fovea centralis.
### 16.4c Physiology of Vision: Refraction and Focusing of Light
- Refraction is the bending of light rays—a process that occurs primarily at the cornea and lens so that light hits the retina.
- Focusing of light when viewing objects closer than 20 feet involves convergence of the eyes, accommodation of the lens, and constriction of the pupil.

### 16.4d Physiology of Vision: Phototransduction
- Phototransduction involves photoreceptor cells (rods and cones), which are located in the neural layer of the retina, converting light energy into an electrical signal.
- Rods, which are primarily located in the peripheral retina, are activated by dim light and provide no color recognition. The image produced has limited visual sharpness.
- Cones, which are primarily located within the fovea centralis, are activated by bright light and provide color recognition. The image produced has visual sharpness. There are three types of cones, and each type maximally absorbs at different wavelengths of light.

### 16.4e Visual Pathways
- The optic nerves are formed by ganglionic axons that project from each eye, converge at the optic chiasm, and extend into the brain as optic tracts.
- The optic tracts transmit nerve signals to the thalamus and superior colliculi. The thalamus then transmits visual information to the occipital lobe for conscious interpretation.

### 16.5 Hearing and Equilibrium Receptors
- Receptors in the ear provide for the senses of hearing and equilibrium.

#### 16.5a Ear Structure
- The external acoustic meatus funnels sound waves to the tympanic membrane, which then directs sound waves to the middle ear.
- The middle ear is an air-filled space occupied by three auditory ossicles. The auditory ossicles (malleus, incus, and stapes) transmit and amplify the sound waves from the tympanic membrane to the oval window.
- The inner ear houses the structures for hearing and equilibrium. Specialized receptors are housed in the membranous labyrinth, which lies within a cavernous space of the temporal bone called the bony labyrinth.

#### 16.5b Hearing
- The spiral organ (organ of hearing) is housed within the cochlea. Hair cells in the spiral organ of the cochlea rest on the basilar membrane and are anchored into the tectorial membrane.
- Sound is perceived when sound waves vibrate the tympanic membrane, resulting in auditory ossicle vibrations that lead to vibrations of the basilar membrane, which bend cilia to initiate nerve signals that are conducted along the cochlear branch of CN VIII.

#### 16.5c Auditory Pathways
- Secondary axons from the cochlear nuclei project directly to the inferior colliculus, or to the superior olivary nuclei and then the inferior colliculus. Axons then project to the thalamus, where thalamic axons project to the primary auditory cortex so sound is consciously perceived.

#### 16.5d Equilibrium and Head Movement
- The maculae within the saccule and utricle detect both the stationary position of the head and linear acceleration of the head.
- The semicircular canals are parts of the bony labyrinth that house the membranous semicircular ducts. Each semicircular duct has an expanded region called an ampulla that houses the crista ampullaris for detecting rotational movements of the head.
- Nerve signals from the vestibular apparatus (sensory receptors within the vestibule and semicircular canals) are transmitted via the vestibular branch of CN VIII either to the vestibular nuclei (in the medulla oblongata) or directly to the cerebellum. Nerve signals are then sent from the vestibular nuclei and cerebellum to the thalamus and eventually to the cerebral cortex for our conscious awareness of head position and movement.

---

### CHALLENGE YOURSELF

#### Do You Know the Basics?

1. Unencapsulated dendritic endings of sensory neurons are called
   a. lamellated corpuscles.
   b. free nerve endings.
   c. bulbous corpuscles.
   d. end bulbs.

2. Each of these sensory receptors is accurately matched with its function except
   a. chemoreceptor; detects specific molecules and ions dissolved in fluid
   b. nociceptor; detects pain
   c. proprioceptor; detects change in muscle tension
   d. thermoreceptor; detects change in pressure
3. All of the following are accurate about the conjunctiva except
   a. it contains blood vessels that nourish the sclera.
   b. it covers the cornea.
   c. it contains sensory neurons that detect foreign objects on the eye.
   d. it is composed of stratified columnar epithelium.

4. Lacrimal fluid performs all of the following functions except
   a. cleansing the eye surface.
   b. preventing bacterial infection.
   c. humidifying the orbit.
   d. moistening the eye surface.

5. The arrangement of tunics in the eye, from the innermost to outermost aspect of the eye, is
   a. retina, vascular, fibrous.
   b. vascular, retina, fibrous.
   c. vascular, fibrous, retina.
   d. retina, fibrous, vascular.

6. When viewing an object closer than 20 feet, all of the following processes occur except
   a. the eyes accommodate to focus on the close-up object.
   b. the ciliary body contracts, so the suspensory ligaments become less taut.
   c. the lens becomes more rounded to better refract light rays.
   d. the pupils dilate to let in more light for the retina.

7. Which ear structure is correctly matched with its function?
   a. round window; transmits sound waves into the inner ear
   b. external acoustic meatus; directs sound waves to the tympanic membrane
   c. auditory ossicles; dampen sound waves before they reach the inner ear
   d. vestibular membrane; bends the stereocilia on hair cells to produce a nerve signal

8. Which statement is accurate about the cochlear duct?
   a. It detects linear acceleration of the head when the otolithic membrane bends the hair cells.
   b. It is filled with perilymph.
   c. It contains hair cells that convert sound waves into nerve signals.
   d. It contains a spiral organ that rests on a vestibular membrane.

9. Which of the following is accurate about the maculae of the vestibular apparatus?
   a. They detect rotational movements of the head.
   b. They are located in the semicircular canal.
   c. Nerve signals are generated when the otolithic membrane bends the stereocilia of the hair cells.
   d. They are the organs of hearing.

10. The only sensation to reach the cerebral cortex without first processing through the synapses in the thalamus is
    a. olfaction.
    b. vision.
    c. proprioception.
    d. touch.

11. What are the five classifications of receptors according to modality of stimulus? Give an anatomic example of each.

12. How are visceral nociceptors different from somatic nociceptors, and how do they relate to the phenomenon known as referred pain?

13. What is the pathway by which taste sensations reach the brain?

14. Describe the pathway by which olfactory stimuli are transmitted from the nasal cavity to the brain.

15. What structure in the wall of the eye helps control the amount of light entering the eye?

16. How is the lens able to focus images from a book that you are reading, and then immediately also focus the image of children playing in your backyard?

17. Compare lacrimal fluid and aqueous humor in terms of their formation, circulation, and function.

18. Briefly describe the structural relationship between the membranous labyrinth and the bony labyrinth.

19. Describe the pathway by which sound waves enter the ear and how that sound is converted into a nerve signal.

20. Explain how the vestibule and semicircular canals detect equilibrium.

Can You Apply What You’ve Learned?

1. You are babysitting a 5-year-old child who does not want to eat his broccoli. He states that the broccoli tastes yucky. You tell him to hold his nose closed while he eats a piece of broccoli and see how it tastes. He says it doesn’t taste as yucky when he holds his nose (although he still doesn’t want to eat the broccoli). Why did the broccoli taste “less yucky” when the child held his nose?
   a. Cranial nerve IX was pinched when the child held his nose, so tastes could not be perceived as clearly.
   b. The activity of holding his nose took the child’s mind off of eating the broccoli.
   c. Olfaction is responsible for a large component of taste, so when the child cannot smell the broccoli, its taste is diminished.
   d. Holding the nose closed facilitated odiferous molecules to enter the mouth, thereby increasing the number of molecules that could be tasted by the taste buds.

2. Horner syndrome is a condition where sympathetic innervation to one side of the head and neck is damaged. What visual disturbances would you expect a person to have if she had Horner syndrome?
   a. inability to accommodate the eyes for near vision
   b. constricted pupil
   c. permanently flattened lens
   d. abduction of the affected eye

3. You may be familiar with cell phone “mosquito tones”—ringtones of a relatively high pitch that most children and teenagers can hear but most adults cannot. Why do you think adults cannot hear these tones as well?
   a. Hair cells close to the oval window of the inner ear become damaged as we age.
b. The tympanic membrane loses its flexibility as we age, so it is not as able to transmit sound waves to the middle ear.

c. Adults likely have damaged the spiral organ near the helicotrema, resulting in their inability to hear the tones.

d. As we age, there is a gradual accumulation of cerumen that blocks the external auditory meatus and makes hearing sounds more difficult.

4. Individuals with macular degeneration may experience loss of vision in their central vision area, but their peripheral vision either is not affected or is not as greatly affected. Why is this the case?

a. Macular degeneration damages the optic disc, making central vision impaired but leaving peripheral vision intact.

b. Only a single optic tract typically is damaged, so using your peripheral vision allows you to use the normal optic tract.

c. Only rods are damaged in macular degeneration, so peripheral vision (where there are fewer rods) is not as affected.

d. The central vision loss is due to damage to the fovea centralis; the peripheral retina is not greatly affected.

5. An elderly gentleman is taken to the emergency room. He is complaining of pain radiating down his left arm and has shortness of breath. The ER physician suspects the gentleman is suffering a heart attack. Why is the man experiencing pain down his left arm if the problem is with his heart?

a. Chemoreceptors in the blood vessels of the left arm have detected a change in oxygen levels in the blood and initiated the pain sensations.

b. The cerebral cortex has mistakenly located the source of the stimulus as being from skin and muscle in the arm instead of the heart.

c. The patient is experiencing phantom pain in the upper limb.

d. A heart attack stimulates baroceptors in the blood vessels of the upper limb.

⚠️ Can You Synthesize What You’ve Learned?

1. Savannah is an active 3-year-old who began to cough and snuffle. Then she experienced an earache and a marked decrease in hearing acuity. During a physical examination, her pediatrician noted the following signs: elevated temperature, a reddened tympanic membrane with a slight bulge, and some inflammation in the pharynx. What might the pediatrician call this condition, and how would it be treated? How does Savannah’s age relate to her illness?

2. After Alejandro quit smoking, he discovered that foods seemed much more flavorful than when he had smoked. How are smoking and taste perceptions linked?

3. George is unclear why nearsighted persons may need bifocal eyeglasses (which have two lenses—one for reading and one for nearsightedness) when they get older. He does not understand why the same set of glasses wouldn’t work for both reading and the nearsighted correction. Can you explain to George the difference between the two conditions, and why the treatment for both may appear to be similar?
Some days are just more hectic than others. We don’t have time for breakfast and then perhaps have a class that meets over the lunch hour, allowing us only enough time to grab something from the snack machine before heading off to work or other classes in the afternoon. Finally, upon returning home for the evening, we are so hungry we eat rapidly and have a second helping. Fortunately, our endocrine system has come to our rescue, maintaining blood glucose levels within normal homeostatic limits during this period of erratic food intake. Through the release of hormones, the endocrine system provides the means to regulate and control many diverse metabolic processes of the body, including regulating blood sugar.

This chapter has two primary purposes. The first is to provide an introduction and general discussion of the endocrine system’s central concepts, including endocrine glands, categories of hormones, hormone transport in the blood, and how hormones interact with body cells. The second is to present the general function of the major hormones of the body and the detailed processes by which selected representative hormones maintain body homeostasis. The final section of this chapter describes the effects of aging on the endocrine system. Please note that each major hormone described in this text can be quickly accessed in the summary tables provided in the reference section immediately after this chapter (designated R1–R10).
17.1 Introduction to the Endocrine System

The endocrine system serves as one of the two major control systems that regulate the human body; the other is the nervous system, which was described in the preceding chapters. Here we provide an overview of how this system of control functions, compare its means of controlling the body to that of the nervous system, and then preview the general functions of the endocrine system.

The endocrine system is composed of endocrine glands located throughout the body. These glands synthesize and secrete molecules called hormones (hormao = to rouse) that communicate with and control other body cells. This communication is possible because body cells display various receptors for specific types of hormones (e.g., skeletal muscle cells have receptors for testosterone, osteoblasts of bone have receptors for parathyroid hormone). Cells that have specific receptors for a hormone are called target cells. Each type of hormone differs in its target cells and thus, the cellular activities that it regulates.

How is it possible for endocrine glands to synthesize and secrete hormones that control cells, which are often located significant distances from the gland? The hormone molecules are transported from the endocrine gland to the target cells by the blood. This occurs as follows (figure 17.1):

- Endocrine glands lack ducts (unlike exocrine glands, which release their secretions into ducts (see section 5.1d). Hormone molecules are instead released from endocrine gland cells into the interstitial fluid and then enter the blood (figure 17.1a).
- These hormone molecules are transported within the blood from the endocrine gland’s associated capillaries by the cardiovascular system to all body tissues (figure 17.1b), a process that is relatively slow (in comparison to the nervous system).
- There the hormones randomly leave the blood from these capillaries and enter the interstitial fluid, which provides the hormone molecules access to potentially all body cells (figure 17.1c). Consequently, the response induced by each hormone can be widespread.
- The hormone binds to its target cells’ receptors, which may be either in the plasma membrane or within the cell. The binding of hormones to cellular receptors either initiates or inhibits selective metabolic activities within these cells (e.g., activate enzymes, open ion channels, stimulate protein synthesis or cellular division). These altered metabolic activities can have long-lasting effects and may continue after removal of the hormone.

Note that many types of hormones are continuously present within our blood at varying levels and are influencing our cells. Physicians and others are often provided critical information about an individual’s relative health or condition by having a patient’s blood hormone levels measured. For example, low levels of thyroid hormone indicate that a patient has hypothyroidism (see section 17.8b), and the presence of human chorionic gonadotropin (hCG) confirms that a woman is pregnant (see section 29.2c).

Figure 17.1 Nervous and Endocrine System Communication Methods. (a–c) In the endocrine system, hormones are secreted by endocrine cells. The hormones enter the blood and are transported throughout the body to reach their target cells. (d) In the nervous system, neurons release neurotransmitters into a synaptic cleft to stimulate their target cells.
17.1b Comparison of the Two Control Systems

Learning Objective

2. Compare and contrast the actions of the endocrine system and the nervous system to control body function.

The nervous system and endocrine system serve as the two complementary systems of control. The methods and effects of the two control systems differ, however. The nervous system exercises control between two specific locations in the body by way of neurons (figure 17.1d). Nerve signals trigger the release of neurotransmitter, which crosses the synaptic cleft and binds to another neuron, a muscle cell, or a gland cell to initiate a localized response of the target cell, such as muscle contraction or gland secretion. The neurotransmitter is quickly degraded or taken back into the neuron. The response induced by the nervous system is generally both rapid and short-lived. Notice, however, the two central features in common: (1) In response to stimuli, specialized cells of both systems release chemical substances called ligands (hormones or neurotransmitters) to communicate with particular target cells (see section 4.5b) and (2) the ligand binds to a cellular receptor in target cells to initiate a cellular change.

The general characteristics of these two complementary control systems are compared in table 17.1.

Table 17.1

<table>
<thead>
<tr>
<th>Features</th>
<th>Endocrine System</th>
<th>Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communication Method</td>
<td>Secretes hormones; hormones are transported within the blood and distributed to target cells throughout body</td>
<td>A nerve signal causes neurotransmitter release from a neuron into a synaptic cleft</td>
</tr>
<tr>
<td>Target of Stimulation</td>
<td>Any cell in the body with a receptor for the hormone</td>
<td>Other neurons, muscle cells, and gland cells</td>
</tr>
<tr>
<td>Response Time</td>
<td>Relatively slow reaction time: Seconds to minutes to hours</td>
<td>Rapid reaction time: Typically milliseconds to seconds</td>
</tr>
<tr>
<td>Range of Effect</td>
<td>Typically has widespread effects throughout the body</td>
<td>Typically has localized, specific effects in the body</td>
</tr>
<tr>
<td>Duration of Response</td>
<td>Long-lasting: Minutes to days to weeks; may continue after stimulus is removed</td>
<td>Short-term: Milliseconds; terminates with removal of stimulus</td>
</tr>
</tbody>
</table>

What Did You Learn?

2. How does the endocrine system differ from the nervous system with respect to their target cells?

17.1c General Functions of the Endocrine System

Learning Objective

3. Describe the general functions controlled by the endocrine system.

The endocrine system (through the release of hormones) can communicate with any body cell that has a receptor for that hormone. Consequently, its functions are very diverse. We have organized the functions of the endocrine system into the following four broad categories:

- Regulating development, growth, and metabolism. Hormones have regulatory roles in both cell division and cell differentiation, which occur during development and growth of the body. They also control our metabolic activities—both anabolic (synthesis) and catabolic (degradation) processes. For example, growth hormone controls growth and the thyroid hormone regulates cellular metabolism.
- Maintaining homeostasis of blood composition and volume. Hormones regulate the amount of specific substances dissolved within blood plasma, such as glucose, amino acids, and ions (e.g., Na⁺, Ca²⁺). Additionally, hormones also regulate other characteristics of blood, including its volume, its cellular concentration (erythrocytes and leukocytes), and number of platelets. Insulin, for example, regulates blood glucose levels (see section 17.10b).
- Controlling digestive processes. Several hormones influence both the secretory processes and the movement of materials through the gastrointestinal tract in our digestive system. An example is gastrin, which is released from the stomach and controls digestive processes by increasing stomach contractions and secretions (see section 26.2d).
- Controlling reproductive activities. Hormones affect both development and function of the reproductive system as well as expression of sexual behaviors. One example is prolactin. Prolactin, a hormone that influences reproductive activities, stimulates formation of breast milk by the mammary glands (see section 28.3f).

What Did You Learn?

3. Diabetes mellitus is noted by sustained high blood glucose levels. Which of the four functions listed is the most directly affected?

17.2 Endocrine Glands

This section and the following three sections provide a general overview of four central features of the endocrine system. These include a discussion of (1) the location of the major endocrine glands and how they are stimulated to release their hormones (see section 17.2); (2) the general categories of hormones and their chemical structures (see section 17.3); (3) how hormone molecules are transported within the blood (see section 17.4); and (4) how hormones interact with their target cells (see section 17.5). Here we describe the major endocrine glands.

17.2a Location of the Major Endocrine Glands

Learning Objective

4. Identify the major endocrine glands and their location within the body.

Endocrine glands are typically composed of a connective tissue framework, which houses and supports epithelial tissue that produces and releases hormones from their secretory cells. The secretory cells are organized in two general ways: either as a single organ with only an endocrine function, or as cells housed in small clusters within organs or tissues that have some other primary function (figure 17.2).

An endocrine organ is a single organ that is entirely endocrine in function. Endocrine organs include the pituitary gland, pineal gland, thyroid gland, parathyroid glands, and adrenal glands.

Some endocrine cells are housed in tissue clusters within specific organs or tissues. These cells secrete one or more hormones, but
the organs have some other primary function as well. These organs include the hypothalamus, skin, thymus, heart, liver, stomach, pancreas, small intestine, adipose connective tissue, kidneys, and gonads (testes and ovaries).

Note that the term endocrine gland will be used throughout the rest of this chapter when referring either to an endocrine organ or an organ or tissue containing endocrine cells. The major endocrine glands of the body are listed in table 17.2. This table includes the hormones produced by each gland, the primary target organs or tissue, and the primary function(s) of each hormone.

WHAT DID YOU LEARN?

What are the major endocrine organs in the human body? What are the organs (or tissues) that have another primary function and contain endocrine cells?

17.2b Stimulation of Hormone Synthesis and Release

LEARNING OBJECTIVE

5. Explain the three reflex mechanisms for regulating secretion of hormones.

The regulated secretion of a hormone from an endocrine gland is controlled through a reflex (see section 14.6a). Reflexes occur in both the nervous system and the endocrine system. Endocrine reflexes are initiated by one of three types of stimulation: hormonal stimulation, humoral stimulation, or nervous system stimulation (figure 17.3).

- **Hormonal stimulation.** The stimulus for the release of many hormones from an endocrine gland is the binding of another hormone. An example occurs when thyroid-stimulating hormone (which is released from the anterior pituitary) binds to the thyroid gland to cause release of thyroid hormone (figure 17.3a).

- **Humoral stimulation.** Some endocrine glands are stimulated to release their hormones in response to a changing level of nutrient molecules (e.g., glucose) or ions (e.g., Ca^{2+}) within the blood. (The term humoral is a historical term related to blood as one of the four “humors,” or fluids, of the body.) When either nutrient or ion levels decrease or increase within the blood, an endocrine gland is stimulated to release its hormone molecules. An example of humoral stimulation occurs when blood glucose increases and the pancreas releases insulin (figure 17.3b).

- **Nervous system stimulation.** A few endocrine glands are stimulated to release hormone(s) by direct stimulation from the nervous system. The classic example is the release of epinephrine and norepinephrine by the adrenal medulla in response to stimulation by the sympathetic division of the autonomic nervous system (figure 17.3c).
<table>
<thead>
<tr>
<th>Gland</th>
<th>Hormone(s) Produced</th>
<th>Primary Target Organ/Tissue</th>
<th>Primary Function(s) of the Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypothalamus</strong></td>
<td>Regulatory hormones</td>
<td>Anterior pituitary</td>
<td>Control release of hormones from anterior pituitary</td>
</tr>
<tr>
<td><strong>Antidiuretic hormone (ADH)</strong></td>
<td>Kidney; hypothalamus (thirst center); blood vessels</td>
<td>Stimulates the kidneys to decrease urine output and the thirst center to increase fluid intake when the body is dehydrated; in high doses, ADH is a vasoconstrictor (thus, it is also called vasopressin)</td>
<td></td>
</tr>
<tr>
<td><strong>Oxytocin</strong></td>
<td>Breast (mammary glands); brain</td>
<td>Contraction of smooth muscle of uterus; ejection of milk from mammary glands; increases feelings of emotional bonding between individuals</td>
<td></td>
</tr>
<tr>
<td><strong>Pituitary gland</strong></td>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>Thyroid gland</td>
<td>Stimulates thyroid gland to release thyroid hormone</td>
</tr>
<tr>
<td><strong>Prolactin (PRL)</strong></td>
<td>Breast (mammary glands)</td>
<td>Regulates mammary gland growth and breast milk production in females; function not fully known in males</td>
<td></td>
</tr>
<tr>
<td><strong>Follicle-stimulating hormone (FSH)</strong></td>
<td>Ovary; testis</td>
<td>Controls development of both oocyte and ovarian follicle (spherical structure that houses an oocyte) within ovaries; controls development of sperm within testes</td>
<td></td>
</tr>
<tr>
<td><strong>Luteinizing hormone (LH)</strong></td>
<td>Ovary; testis</td>
<td>Induces ovulation of secondary oocyte from the ovarian follicle; controls testosterone synthesis within testes</td>
<td></td>
</tr>
<tr>
<td><strong>Adrenocorticotropic hormone (ACTH)</strong></td>
<td>Adrenal cortex</td>
<td>Stimulates adrenal cortex to release corticosteroids (e.g., cortisol)</td>
<td></td>
</tr>
<tr>
<td><strong>Pineal gland</strong></td>
<td>Melatonin</td>
<td>Brain</td>
<td>Helps regulate the body’s circadian rhythms (biological clock); functions in sexual maturation</td>
</tr>
<tr>
<td><strong>Thyroid gland</strong></td>
<td>Thyroid hormones: T3 (triiodothyronine) and T4 (tetraiodothyronine or thyroxine)</td>
<td>All cells</td>
<td>Increase metabolic rate of all cells; increase heat production (calorigenic effect)</td>
</tr>
<tr>
<td><strong>Calcitonin</strong></td>
<td>Bone; kidney</td>
<td>Decreases blood calcium levels; most significant in children</td>
<td></td>
</tr>
<tr>
<td><strong>Parathyroid glands</strong></td>
<td>Parathyroid hormone (PTH)</td>
<td>Bone tissue; kidney</td>
<td>Increases blood calcium levels by stimulating both release of calcium from bone tissue and decrease loss of calcium in urine; causes formation of calcitriol hormone (a hormone that increases calcium absorption from small intestine)</td>
</tr>
<tr>
<td><strong>Thymus</strong></td>
<td>Thymosin, thymulin, thymopoietin</td>
<td>T-lymphocytes (a type of white blood cell)</td>
<td>Maturation of T-lymphocytes (a type of white blood cell, or leukocyte)</td>
</tr>
<tr>
<td><strong>Adrenal cortex</strong></td>
<td>Mineralocorticoids (e.g., aldosterone)</td>
<td>Kidney</td>
<td>Regulate blood Na⁺ and K⁺ levels by decreasing the Na⁺ and increasing the K⁺ excreted in urine</td>
</tr>
<tr>
<td><strong>Glucocorticoids (e.g., cortisol)</strong></td>
<td>Liver; adipose connective tissue; all cells</td>
<td>Participate in the stress response; increase nutrients (e.g., glucose) that are available in the blood</td>
<td></td>
</tr>
<tr>
<td><strong>Gonadocorticoids (e.g., dehydroepiandrosterone [DHEA])</strong></td>
<td>Various body cells</td>
<td>Stimulate maturation and functioning of reproductive system</td>
<td></td>
</tr>
<tr>
<td><strong>Adrenal medulla</strong></td>
<td>Epinephrine (EPI) and norepinephrine (NE)</td>
<td>Various body cells</td>
<td>Prolong effects of the sympathetic division of the autonomic nervous system</td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
<td>Insulin</td>
<td>Liver; adipose connective tissue; most body cells</td>
<td>Decreases blood glucose levels</td>
</tr>
<tr>
<td><strong>Glucagon</strong></td>
<td>Liver; adipose connective tissue</td>
<td>Increases blood glucose levels</td>
<td></td>
</tr>
<tr>
<td><strong>Testes (gonads)</strong></td>
<td>Testosterone</td>
<td>Reproductive organs; various body cells</td>
<td>Stimulates maturation and function of male reproductive system</td>
</tr>
<tr>
<td><strong>Inhibin</strong></td>
<td>Anterior pituitary</td>
<td>Inhibits release of follicle-stimulating hormone (FSH) from anterior pituitary</td>
<td></td>
</tr>
<tr>
<td><strong>Ovaries (gonads)</strong></td>
<td>Estrogen and progesterone</td>
<td>Reproductive organs; various body cells</td>
<td>Stimulate maturation and function of female reproductive system</td>
</tr>
<tr>
<td><strong>Inhibin</strong></td>
<td>Anterior pituitary</td>
<td>Inhibits release of follicle-stimulating hormone (FSH) from anterior pituitary</td>
<td></td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td>Atrial natriuretic peptide (ANP)</td>
<td>Kidneys; blood vessels</td>
<td>Functions primarily to decrease blood pressure by stimulating both the kidneys to increase urine output and the blood vessels to dilate</td>
</tr>
<tr>
<td><strong>Kidneys</strong></td>
<td>Erythropoietin (EPO)</td>
<td>Bone (red bone marrow)</td>
<td>Increases production of red blood cells (erythrocytes)</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td>Angiotensinogen</td>
<td>Blood vessels; kidney; hypothalamus (thirst center)</td>
<td>Converted by enzymes released from the kidney and within the inner lining of blood vessels to angiotensin II; increases blood pressure by causing vasoconstriction and decreasing urine output; stimulates thirst center</td>
</tr>
<tr>
<td><strong>Insulin-like growth factors (IGFs)</strong></td>
<td>Various body cells</td>
<td>Function synergistically with growth hormone to regulate growth</td>
<td></td>
</tr>
<tr>
<td><strong>Erythropoietin (EPO)</strong></td>
<td>Bone (red bone marrow)</td>
<td>Increases production of red blood cells (erythrocytes); note that kidneys are the major producers of EPO</td>
<td></td>
</tr>
</tbody>
</table>
Table 17.2  Endocrine Glands and Organs Containing Endocrine Cells (continued)

<table>
<thead>
<tr>
<th>Gland</th>
<th>Hormone(s) Produced</th>
<th>Primary Target Organ/Tissue</th>
<th>Primary Function(s) of the Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepcidin</strong></td>
<td>Small intestine and macrrophages of liver, spleen, and bone marrow</td>
<td>Regulates iron levels</td>
<td></td>
</tr>
<tr>
<td><strong>Stomach</strong></td>
<td>Gastrin</td>
<td>Stomach</td>
<td>Facilitates digestion within stomach</td>
</tr>
<tr>
<td><strong>Small intestine</strong></td>
<td>Secretin (CCK)</td>
<td>Digestive organs</td>
<td>Regulates digestion within small intestine by helping to maintain normal pH within small intestine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Regulates digestion within small intestine by facilitating digestion of proteins and fats within small intestine</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Vitamin D$_3$</td>
<td>Bone; kidney; small intestine</td>
<td>Converted by enzymes of liver and kidney to calcitriol; functions synergistically with PTH and increases calcium absorption from small intestine</td>
</tr>
<tr>
<td><strong>Adipose connective tissue</strong></td>
<td>Leptin</td>
<td>Brain</td>
<td>Helps regulate food intake</td>
</tr>
<tr>
<td><strong>Placenta</strong></td>
<td>Estrogen and progesterone</td>
<td>Reproductive organs</td>
<td>Stimulate development of fetus; stimulates physical changes within mother associated with pregnancy, including those in the uterus and mammary glands</td>
</tr>
</tbody>
</table>

1. These hormones are produced by the hypothalamus but stored and released in the posterior pituitary.

**Figure 17.3 Types of Endocrine Stimulation.** An endocrine gland can be stimulated to release its hormone in response to (a) hormonal stimulation, (b) humoral stimulation, or (c) nervous system stimulation.  

**WHAT DID YOU LEARN?**  
5. Adrenocorticotropic hormone (ACTH) stimulates the adrenal cortex to release cortisol hormone. This is an example of what type of stimulation: (a) hormonal, (b) humoral, or (c) nervous system?

### 17.3 Categories of Hormones

Hormones are organized (by some experts) into two broad categories based upon whether the hormone molecules are transported within the blood. **Circulating hormones** are transported within the blood (as described in section 17.1a), whereas **local hormones** are short-lived molecules that influence cells within the local tissue from which they are produced.

Circulating hormones are grouped according to their chemical structure into three general categories: steroids, biogenic amines, and proteins. These regulatory molecules are synthesized within endocrine cells from either (1) cholesterol, which is a type of lipid with a four-ring structure (see section 2.7b), or (2) amino acids,
which are the monomers that compose proteins (see section 2.7e). Cholesterol molecules are modified in the synthesis of steroid hormones. Amino acids are the building blocks for both biogenic amines and protein hormones. An example of each category is shown in figure 17.4. As you read about the chemical structure of these hormones, please note whether the molecules in each category are lipid-soluble or water-soluble. This difference in solubility influences both the transport of the hormone in the blood and how it interacts with its target cells.

Steroids

Steroids are lipid-soluble molecules synthesized from cholesterol (figure 17.4a). This category includes both the steroids produced within the gonads (e.g., estrogen and progesterone in the ovaries and testosterone in the testes) and the hormones synthesized by the adrenal cortex (e.g., corticosteroids such as cortisol, and mineralocorticoids such as aldosterone).

Calcitriol is the hormone produced from vitamin D (see section 7.6a), and it is sometimes classified as a steroid hormone. However, it is more accurately classified as a sterol hormone, a slightly different molecule but one that is also lipid-soluble.

Biogenic Amines

Biogenic amines are also called monoamines. They are modified amino acids (modification involves removal of a carboxyl functional group from an amino acid) (figure 17.4b). Biogenic amines include the catecholamines (e.g., epinephrine and norepinephrine) released from the adrenal medulla, thyroid hormone released from the thyroid gland, and melatonin from the pineal gland. Biogenic amines are water-soluble except for thyroid hormone. Thyroid hormone is lipid-soluble because it is produced from two tyrosine amino acids (see figure 17.16), which are amino acids that contain a nonpolar ring.

Proteins

Most hormones are proteins. These are molecules composed of small chains of amino acids and include small peptides, large polypeptides, and glycoproteins (figure 17.4c). All hormones in this category are water-soluble.

Figure 17.4 Hormone Types. (a) Steroids (which include hormones released from both the gonads and adrenal cortex) are lipid-soluble and formed from cholesterol. In comparison, (b) biogenic amines (which include hormones released from the adrenal medulla, thyroid hormone, and melatonin) and (c) proteins (which include most hormones) typically are water-soluble and formed from amino acids.

WHAT DID YOU LEARN?

6. Identify which of the following hormone categories are lipid-soluble: (a) reproductive hormones produced in the gonads, (b) adrenal cortex hormones, and (c) thyroid hormone.

7. What two events or processes associated with a hormone are influenced by whether a hormone is lipid-soluble or water-soluble?

17.3b Local Hormones

LEARNING OBJECTIVES

8. Describe the general structure, formation, and function of local hormones.

9. Compare autocrine and paracrine signaling that occurs through local hormones.

Local hormones are a large group of short-lived signaling molecules that do not circulate within the blood. Instead, cells synthesize and release these molecules, which then bind with either the same cell that produced them (autocrine stimulation) or neighboring cells (paracrine stimulation). These signaling molecules have properties similar to hormones because the released ligands (signaling molecules) initiate and regulate cellular changes. They just do so “in the tissue neighborhood.”

Eicosanoids (i̇kō-să-noydž; eicosa = twenty, eidos = formed), which were first introduced in section 2.7b (see table 2.4), are the primary type of local hormones. Eicosanoids include prostaglandins, thromboxanes, and leukotrienes (figure 17.5). These signaling
molecules are formed from *fatty acids*, which are cleaved from phospholipid molecules of a cell’s plasma membrane. Their production is not limited to one endocrine gland (as circulating hormones typically are) but instead are synthesized by cells composing many tissues located throughout the body. Thus, eicosanoid synthesis and release provides the means for all tissues to locally regulate cellular responses.

**Prostaglandins** are the most diverse category of eicosanoids (e.g., prostaglandin D, E, and F with various subtypes such as prostaglandin E2 [PGE2]), and their effects are wide-ranging, depending upon both the specific type of prostaglandin molecule and the specific type of cellular receptor to which it binds. Examples of prostaglandin activity include (1) stimulating the hypothalamus to raise body temperature to induce a fever, (2) inhibiting stomach acid secretion, (3) acting on mast cells to release molecules that increase inflammation, and (4) stimulating pain receptors.

Given the examples of prostaglandin activity just described, provide examples of why an individual might take aspirin, which blocks the synthesis of prostaglandins (see Clinical View 17.1: “Synthesis of Eicosanoids”).

**INTEGRATE**

**CONCEPT CONNECTION**

Prostaglandins, thromboxanes, and leukotrienes are local hormones that can act as local vasoactive substances (substances that change the size of blood vessels by narrowing blood vessels through vasoconstriction or widening blood vessels through vasodilation). The role of prostaglandins and thromboxanes as a vasoconstrictor to prevent blood loss is described in section 20.4c. In comparison, the role of prostaglandins and leukotrienes as vasodilators (as part of the inflammatory response) is discussed in section 22.3d.

**CLINICAL VIEW 17.1**

**Synthesis of Eicosanoids**

Eicosanoids are formed from phospholipid molecules within the plasma membrane of a cell (figure 17.5). The enzyme phospholipase A₂ releases a 20-carbon fatty acid called arachidonic acid. (This enzyme is inhibited by *steroid drugs* [e.g., hydrocortisone] to prevent formation of all eicosanoids.) Arachidonic acid is then acted upon by either (1) *cyclooxygenase*, which converts arachidonic acid to prostaglandins and thromboxanes (this enzyme is inhibited by *aspirin* to prevent formation of both of these eicosanoids) or (2) *lipoxygenase*, which converts arachidonic acid to leukotrienes (this enzyme is inhibited by *St. John’s wort* to prevent formation of leukotrienes).

**WHAT DID YOU THINK?**

1. Given the examples of prostaglandin activity just described, provide examples of why an individual might take aspirin, which blocks the synthesis of prostaglandins (see Clinical View 17.1: “Synthesis of Eicosanoids”).

**WHAT DID YOU LEARN?**

3. Leukotrienes from damaged tissue cause smooth muscle in local blood vessels to vasodilate (increase the diameter of the vessel lumen). Is this an example of (a) autocrine stimulation or (b) paracrine stimulation? Explain.

**17.4 Hormone Transport**

Hormone molecules are transported within the blood to target cells following their release from the endocrine gland that synthesized them (see figure 17.1). Here we consider how both lipid-soluble and water-soluble hormones are transported and the factors that influence the level of circulating hormone.

**17.4a Transport in the Blood**

**LEARNING OBJECTIVE**

10. Compare the transport of lipid-soluble hormones with that of water-soluble hormones.

Lipid-soluble hormones (e.g., steroids, calcitriol, thyroid hormone) do not dissolve readily within the aqueous environment of the blood (blood plasma), and so they require carrier molecules. These molecules are water-soluble proteins synthesized by the liver. Think of these proteins as boats that “ferry” the hormone molecules within the blood. Some hormone carrier proteins may be very selective, binding and transporting only one specific lipid-soluble molecule (e.g., thyroxine-binding globulin), whereas other carrier proteins are nonspecific (e.g., albumin), meaning they bind and transport numerous lipid-soluble molecules. A transport carrier protein has the added benefit of protecting the hormone molecule and helping to prevent its early destruction (or, for small hormones, their loss in the urine). Thus, the association of a hormone with a carrier protein often acts as a safeguard to help prolong the life of the hormone.

The binding between a lipid-soluble hormone and a carrier protein is temporary. Hormone molecules bind to the carrier molecule, detach from the carrier and float free within the blood, and then may later reattach to a different carrier molecule. Any hormone that is attached to a carrier is a *bound hormone*, whereas an unattached hormone is an *unbound (free) hormone*. Only unbound hormone, which represents a very small fraction of the hormone transported within the blood (0.1% to 10%), is generally able to exit the blood and bind to cellular receptors of target organs. It is the maintaining of a given homeostatic level (or steady state) of the physiologically active, unbound hormone that is required. The bound hormone simply serves as a readily available source within the blood.

Water-soluble hormones (i.e., most biogenic amines and proteins), in comparison, readily dissolve within the aqueous environment of the blood, and so these hormones do not generally require carrier proteins. Thus, water-soluble hormones are generally released directly into the blood and transported to target cells. Note that some water-soluble hormones (e.g., insulin-like growth factor) are transported by carrier proteins, which function to prolong the life of these hormones.

**WHAT DID YOU LEARN?**

9. Why are carrier proteins necessary for lipid-soluble hormones?

10. What is the added benefit of a carrier protein?

**17.4b Levels of Circulating Hormone**

**LEARNING OBJECTIVES**

11. Describe the two primary factors that affect the concentration level of a circulating hormone.

12. Explain what is meant by the half-life of a hormone.

Hormones exert their physiologic effects primarily as a result of their blood concentration. Consequently, the amount of each hormone
must be tightly regulated to prevent potential clinical consequences, such as organ or tissue malfunction and disease. For example, gigantism is due to high blood levels of growth hormone, whereas decreased metabolic rate is caused by low blood levels of thyroid hormone.

There are two primary factors that interact to influence hormone concentration—hormone release and hormone elimination:

- **Hormone release.** Hormone release from an endocrine gland and hormone concentration within the blood are positively correlated. An increase in release of the hormone results in a higher hormone concentration within the blood. In contrast, a decrease in release of the hormone results in a lower hormone concentration within the blood.

- **Hormone elimination.** Hormones are typically eliminated (1) through enzymatic degradation, which usually occurs in liver cells, (2) through removal of the hormone from the blood by its excretion from the kidneys as a component of urine, or (3) by uptake into target cells. Hormone elimination and hormone concentration in the blood are negatively correlated. The faster the rate of hormone elimination, the lower the hormone concentration within the blood, whereas the slower the rate of hormone elimination, the higher the hormone concentration within the blood.

To maintain homeostatic levels of each hormone, a balance is required between its rate of release by its endocrine gland and its elimination from the blood by the activities of the liver, kidney, and target cells. Note that hormone release is typically maintained through negative feedback (see section 1.6b) to maintain homeostatic blood levels of a hormone. For example, the release of insulin from the pancreas is increased in response to a rise in blood glucose level. However, as blood glucose level returns to normal (thus, removing the stimulus for insulin release), the pancreas releases less insulin. The release of some hormones from endocrine glands is regulated by positive feedback (see section 1.6c) in which progressively more of the hormone is released—for example, the release of oxytocin from the posterior pituitary during childbirth (see section 29.6c).

**WHAT DO YOU THINK?**

What effect would impaired function of the liver or kidneys potentially have on hormone concentration in the blood: increase, decrease, or no change? Explain.

**Half-Life**

The **half-life** of a hormone is the amount of time necessary to reduce the hormone concentration within the blood to one-half of what had been secreted originally (or measured previously). Generally, water-soluble hormones have a relatively short half-life, which amounts to a few minutes or less for small peptides and about an hour for larger proteins. Steroids generally have the longest half-life, since their carrier protein protects them from early destruction or loss. The half-life of testosterone, for example, is 12 days. Note that the shorter the half-life of a hormone, the more frequently it must be replaced to maintain its normal concentration in the blood.

**WHAT DID YOU LEARN?**

What is the relationship of hormone synthesis to the concentration of that hormone in the blood?

**17.5 Target Cells: Interactions with Hormones**

Hormones interact only with **target cells** (cells with receptors for those hormones) to initiate a specific cellular response. A specific hormone generally has different types of target cells. For example, the hormone insulin binds with muscle cells, hepatocytes (liver cells), and adipose connective tissue cells. The greater the number of different target cells, the wider the potential influence that may be exhibited by a given hormone.

The specific process of how hormones interact with cell receptors, and the cellular changes that are initiated, is significantly different for lipid-soluble hormones and water-soluble hormones.
17.5a Lipid-Soluble Hormones

**LEARNING OBJECTIVE**

13. Describe how lipid-soluble hormones reach their target cell receptors and the type of cellular change they initiate.

Lipid-soluble hormones (e.g., steroids, calcitriol) are relatively small, nonpolar molecules that are lipophilic (lip’o-fil’ik), or lipid-loving. Recall that the plasma membrane is not an effective barrier to small, nonpolar substances (see section 4.3a). Consequently, unbound lipid-soluble hormones such as steroids are able to diffuse across the plasma membrane. Upon entering the cell, the hormone binds to intracellular receptors located in either the cytosol or nucleus to form a hormone-receptor complex (figure 17.6).

The hormone-receptor complex formed within the target cell then binds to a particular DNA sequence in regions of chromatin called hormone-response elements (HREs). Binding to a specific DNA sequence results in transcription of messenger ribonucleic acid (mRNA). Subsequent translation of this mRNA by ribosomes synthesizes a specific protein (see section 4.8b). The change in protein synthesis pattern within the cell may result in either an alteration in cell structure (e.g., as occurs with a greater level of sex hormones during puberty) or a shift in the target cells’ metabolic activities if the newly synthesized proteins are enzymes. Consider, for example, that an increase in testosterone results in larger muscles due to formation of contractile proteins, a deeper voice from longer and thicker vocal cords, and facial hair growth. These effects induced by testosterone reflect a cellular increase in protein synthesis.

**WHAT DID YOU LEARN?**

12. Where are lipid-soluble hormone receptors located? What is the general cellular change that occurs with binding of a lipid-soluble hormone?

1. The unbound hormone diffuses readily through the plasma membrane and binds with an intracellular receptor, either within the cytosol or the nucleus to form a hormone-receptor complex.

2. The hormone-receptor complex binds with a specific DNA sequence called a hormone-response element (HRE).

3. Binding of the HRE stimulates mRNA synthesis.

4. mRNA exits the nucleus and is translated by a ribosome in the cytosol. A new protein is synthesized.

*Figure 17.6 Lipid-Soluble Hormones and Intracellular Receptors.* Lipid-soluble hormones enter a cell and ultimately cause the formation of new protein.
In the image, a figure illustrates the activation of a G protein in response to a water-soluble hormone binding to a plasma membrane receptor. The figure shows four stages:

1. **Hormone (first messenger) binds to receptor and induces shape change to activate the receptor.**
2. **G protein binds to activated receptor.**
3. **GDP is "bumped off" and GTP binds to G protein; G protein is then activated.**
4. **Activated G protein (with GTP) is released from the receptor and moves along the inside of the plasma membrane, which results in formation or availability of second messenger (see figure 17.8).**

**Figure 17.7 Activation of a G Protein.** An inactive G protein (a) is activated (b) in response to a water-soluble hormone binding to a plasma membrane receptor.

### 17.5b Water-Soluble Hormones

**LEARNING OBJECTIVE**

14. Describe how water-soluble hormones induce cellular change in their target cells.

**Water-soluble hormones** (e.g., proteins and biogenic amines, except thyroid hormone) are polar molecules and are unable to cross the plasma membrane. Denied entry into the cell, water-soluble hormones instead must use an alternative, slightly more complex way to stimulate a target cell. This stimulation is initiated when the hormone binds to a plasma membrane receptor.

The binding of water-soluble hormones to a plasma membrane receptor initiates a series of biochemical events across the membrane called a **signal transduction pathway**. In this pathway, the hormone is the signaling molecule, or **first messenger**. Its binding to the receptor results in the formation of a different molecule within the cell called the **second messenger**. The second messenger then modifies some cellular activity. The mechanisms of initiating cellular changes are described here for the two most common signal transduction pathways involving adenylate cyclase activity and phospholipase C activity.

### Adenylate Cyclase Activity

Activated G protein moves along the inside of the plasma membrane, where it binds to the plasma membrane protein **adenylate cyclase** (a-den’-it-lát) (**figure 17.8a**). Activated adenylate cyclase increases the formation of the second messenger, **cAMP** (3’,5’- cyclic adenosine monophosphate) from ATP. The cAMP then activates a **protein kinase** (protein kinase A), an enzyme that phosphorylates (adds phosphate to) other molecules (see section 3.3g). Phosphorylation results in activation or inhibition of these molecules. Examples of hormones that function through the activation of adenylate cyclase include glucagon and thyroid-stimulating hormone.

### Phospholipase C Activity

The second possibility as a result of G protein activation occurs when it binds with a different plasma membrane protein called **phospholipase C** (fos’-fo-lip’-ás) (**figure 17.8b**). Activation of phospholipase C results in the splitting of **PIP2** (phosphatidylinositol biphosphate), a phospholipid molecule within the plasma membrane. The splitting of PIP₂ results in the formation of two secondary messenger molecules: **DAG** (diacylglycerol; dí’a-sil’ glis’ér-ól) and **IP₃** (inositol; in-o’si-tol, -tol) **triphosphate**.
**Figure 17.8 Action of G Proteins.** Following its activation, G protein is an intracellular molecule that moves along the inside of the plasma membrane and can stimulate other molecules. Two of the most common are (a) adenylyl cyclase, which forms cyclic AMP second messenger, and (b) phospholipase C, which causes formation of DAG and IP₃ second messengers. Pathways involving G protein ultimately result in the activation kinase enzymes that activate or inhibit other enzymes through phosphorylation, change cell permeability, or both.

**Action of DAG** DAG is a second messenger that remains in the plasma membrane. It is similar in action to cAMP in that it activates a protein kinase (here, protein kinase C). This enzyme in turn phosphorylates other molecules.

**Action of IP₃** IP₃ is a second messenger that diffuses from the plasma membrane into the cytosol. It increases intracellular Ca²⁺ concentration by interacting either with the endoplasmic reticulum, causing the release of stored Ca²⁺, or with Ca²⁺ channels in the plasma membrane (not shown in figure), permitting Ca²⁺ entry from the interstitial fluid. Increased intracellular Ca²⁺ acts as a third messenger within the cytosol (1) to activate protein kinase enzymes directly, or by first binding with an intracellular protein called calmodulin, or (2) to alter plasma membrane permeability by binding to specific ion channels located within the plasma membrane and changing the flow of that specific ion either into or out of the cell. Examples of hormones that function through the activation of phospholipase C include oxytocin and antidiuretic hormone.

**Action of Water-Soluble Hormones**

The production of second messengers by cells that are stimulated by water-soluble hormones alters protein kinase activity, changes a cell’s permeability to ions, or both. Ultimately, the action may result in

- **Either activation or inhibition of enzymatic pathways** (e.g., insulin released from the pancreas stimulates glycogen formation from glucose within the liver by glycosynthesis; see section 17.10b)
- **Stimulation of growth through cellular division** (e.g., growth hormone released from the anterior pituitary and insulin-like growth factors [IGFs] released from the liver function synergistically to stimulate mitosis of chondrocytes within cartilage; see section 7.5c)
- **Release of cellular secretions** (e.g., testosterone released from the testes and other androgens such as dehydroepiandrosterone...
Changes in membrane permeability (e.g., epinephrine opens calcium channels in the pacemaker cells of the heart, which increases heart rate; see section 19.9b)

• Muscle contraction or relaxation (e.g., oxytocin stimulates contraction of smooth muscle of the uterus; see section 29.6c)

17.6 Target Cells: Degree of Cellular Response

A target cell’s response to a hormone is not an isolated event. This is because a single target cell (1) displays differing numbers of receptors for the same hormone and can bind varying amounts of the same hormone simultaneously and (2) may possess receptors for many different hormones, and thus it is able to respond to more than one type of hormone at the same time. Hepatocytes, for example, have changing numbers of receptors for both insulin and glucagon and respond to both of them. Consequently, the response of a given target cell is dependent upon the net effect of both its displayed receptors and the amounts and kinds of hormone that it binds.

Intracellular Enzyme Cascade and Amplification of Response

Recall that the water-soluble hormone molecule is not actually moved along a signaling pathway. The binding of the hormone to the receptor results in specific “information” being passed in a signal conduction pathway called an intracellular enzyme cascade. The cascade includes G protein, transmembrane enzyme (adenylate cyclase or phospholipase C), second messenger, and protein kinase enzymes. The activated protein kinase enzymes may either stimulate or inhibit enzymatic pathways within the cell, alter cell permeability to an ion, or both. Signaling pathways have two advantages:

• The signaling pathway amplifies the signal at each step to activate more molecules than were present in the previous step, which ultimately leads to a greater specific response. Consequently, the binding of a relatively small number of hormone molecules to their receptors in the plasma membrane of a target cell may result in the activation or inhibition of millions of molecules within that cell.

• Multistep signaling pathways provide more opportunities to regulate the pathway.

We have emphasized the amplification pathways in this discussion. However, metabolic cascade controls require precise regulation to be effective. Cells must have efficient mechanisms to quickly inactivate intermediates, including breakdown of second messenger molecules, and to terminate the activity of enzymes that had been activated during amplification (e.g., phosphodiesterase degrades cyclic AMP, limiting the response of those signaling pathways).

17.6a Number of Receptors on a Target Cell

LEARNING OBJECTIVES

15. Describe the conditions that influence the number of receptors available for a specific hormone.


The number of available receptors on a target cell fluctuates, and both the direction and degree to which it fluctuates are tightly regulated. This is necessary because the number of receptor molecules available for hormone binding directly influences the degree of cellular response. Target cells may increase the number of receptors, thereby increasing cell sensitivity to a hormone, a process called up-regulation. In contrast, a target cell may decrease its number of receptors and reduce the target cell’s sensitivity to a hormone through down-regulation.

Target cells alter the number of receptors available in response to changes in hormone concentration within the blood. A target cell may increase its number of receptors when there is a lower than normal hormone concentration level, or decrease its number of receptors in response to an elevated hormone level (figure 17.9a). The ability of a target cell to change the number of its available receptors helps to maintain a normal level of cellular response, preventing either under-stimulation or overstimulation of the target cell.

WHAT DO YOU THINK?

3 What cellular response (up-regulation or down-regulation) would you predict occurs in response to high doses of a drug that binds to a specific hormone receptor? Will more or less of the drug be required for the same response over time? Explain.

Changes in receptor number also occur as a consequence of developmental maturity, the target cell’s state of activity, and the different stages of the cell cycle. For example, when a secretory cell becomes a mature cell, it may become less responsive to growth hormone (GH) because it no longer needs to continue growing at an accelerated rate. Thereafter, the mature secretory cell develops the ability to respond to hormones that stimulate it to secrete its product. This response occurs because the secretory cell now produces and displays receptors for different hormones.

WHAT DID YOU LEARN?

13 What is the specific role of the protein kinase enzymes in the signal transduction pathway initiated by water-soluble hormones?

17.6b Hormone Interactions on a Target Cell

LEARNING OBJECTIVE

17. Compare and contrast the three types of hormone interactions.

A target cell can simultaneously bind different hormones. The cellular response to binding more than one type of hormone is often such that some integration occurs within their signaling pathways. There are three principal ways in which hormones interact: synergistically, permissively, or antagonistically (figure 17.9b).

Synergistic interaction occurs when the activity of one hormone reinforces the activity of another hormone. Synergy means “working together.” For example, female reproductive structures are more powerfully influenced by the presence of both estrogen and progesterone than by either hormone alone.

Permissive interaction takes place when the activity of one hormone requires a second hormone—as if one hormone “gives permission” for the first hormone to function. For example, prolactin is required to produce breast milk, and oxytocin is required for milk ejection from
the breast. Oxytocin is unable to cause milk ejection without the previous, or accompanying, prolactin release to produce the milk.

**Antagonistic** interaction occurs when the activity of one hormone opposes the effects of another hormone. An example is the opposing effects on blood glucose levels exhibited by insulin, which initiates cellular changes that decrease blood glucose levels and glucagon, which initiates cellular changes that increase blood glucose levels.

**Figure 17.10** provides a visual overview of the general concepts of the endocrine system, as previously discussed.

---

**WHAT DID YOU LEARN?**

What effects are seen when hormones act synergistically?

---

**CLINICAL VIEW 17.2 Hormone Analogs**

A hormone analog is a molecule that has a chemical structure that is similar to the chemical structure of a hormone. Specificity of receptors allows the pharmaceutical industry to produce hormone analogs for use as medicines to inhibit or activate particular cellular functions. The drugs may activate a receptor and mimic the effect of the native hormone. One potential consequence of long-term or high-dose hormone analog use is that a patient’s cells may down-regulate hormone receptors, an unintended effect. Consequently, following administration of the drug, the individual must be “weaned” from the medication (i.e., administered progressively smaller doses over several days). Weaning allows time for the body’s cells to up-regulate the specific receptor to the normal level. You may be familiar with weaning an individual from steroids following treatment for inflammation (e.g., inflammation associated with asthma, allergic reactions, or rheumatoid arthritis).

---

**17.7 The Hypothalamus and the Pituitary Gland**

Although some endocrine glands function primarily as independent structures (e.g., the parathyroid glands), many endocrine glands are under the influence or control of the hypothalamus. The hypothalamus has direct control over the release of hormones from the pituitary gland and, through its control of the pituitary gland, also influences the release of hormones from several other endocrine organs. Thus, the influence of the hypothalamus within the endocrine system is extensive. We first describe the anatomic relationship between the hypothalamus and pituitary gland.

---

**17.7a Anatomic Relationship of the Hypothalamus and the Pituitary Gland**

The pituitary gland is also called the hypophysis (hi-pof’i-sis; under-growth). It lies inferior to the hypothalamus and is connected to the hypothalamus by a very thin stalk, called either the infundibulum (in-fŭn’dĭb’ləm; a funnel) or the infundibular stalk (figure 17.11). This small, slightly oval gland, which is approximately the size of a large pea, is housed within the sella turcica of the sphenoid bone (see figure 8.8). The pituitary gland is partitioned both structurally and functionally into a posterior pituitary and an anterior pituitary and sometimes referred to as just the posterior lobe and anterior lobe, respectively. An important distinction between the two lobes of the pituitary gland is that they are composed of different types of cells: The posterior pituitary is composed of neurons, and the anterior pituitary is composed of hormone-producing cells.

**Posterior Pituitary**

The posterior pituitary makes up approximately one-quarter of the mass of the pituitary gland. It is the neural part of the pituitary...
(b) Hormones and Hormone Transport

- **Lipid-soluble hormones**: enter target cells, whereas water-soluble hormones bind to receptors within the plasma membrane to induce cellular changes.
- **Unbound hormone** binds to **carrier protein**.
- **Complex binds to DNA segment** and **mRNA transcribed**.
  - mRNA synthesis
  - Protein formation
  - Activation or inhibition of enzymatic pathways
  - Stimulation of growth through cellular division
  - Release of cellular secretions
  - Altered membrane ion permeability
  - Muscle contraction or relaxation

Possible results:
- **New protein is synthesized**.

When multiple hormones bind a target cell, their interactions can produce different effects.

- **Up-regulation**: cells increase receptors in response to reduced blood hormone level.
- **Down-regulation**: cells decrease receptors in response to elevated blood hormone level.

**Hormones** and **activation of kinase enzymes** and changes to ion permeability.

**Hormone binds to intracellular receptor** to form hormone-receptor complex.

**Unbound hormone**

**Carrier protein**

**Complex binds to DNA segment** and **mRNA transcribed**.

**Protein**
- Activation or inhibition of enzymatic pathways
- Stimulation of growth through cellular division
- Release of cellular secretions
- Altered membrane ion permeability
- Muscle contraction or relaxation

**Possible results**
- New protein is synthesized.
(a) Endocrine System

- Pituitary
- Adrenal
- Thyroid
- Kidneys
- Liver
- Ovary (female)
- Testis (male)
- Pineal
- Hypothalamus

B. Hormones and Hormone Transport

- Lipid-soluble hormones
  - Proteins
  - Biogenic amines (except TH)
  - Steroids
  - Calcitriol
  - Thyroid hormone (TH)

- Water-soluble hormones and activation of kinase enzymes and changes to ion permeability

  Hormone binds to intracellular receptor to form hormone-receptor complex.

  - Complex binds to DNA segment and mRNA transcribed.
  - mRNA synthesis
  - Proteins
    - Activation or inhibition of enzymatic pathways
    - Stimulation of growth through cellular division
    - Release of cellular secretions
    - Altered membrane ion permeability
    - Muscle contraction or relaxation

(d) Altering Number of Receptors

- Up-regulation: Cells up-regulate (increase) receptors in response to reduced blood hormone level.
- Down-regulation: Cells down-regulate (decrease) receptors in response to elevated blood hormone level.

(e) Hormone Interactions on a Target Cell

- Synergistic: Hormones work together to produce greater effect.
- Permissive: First hormone allows action of second hormone.
- Antagonistic: One hormone causes opposite effect of another hormone.

*Ca^2+* also binds with ion channels in plasma membrane to increase the cell’s ion permeability.
Endocrine System

Hypothalamic portal veins
Secondary plexus
Hypothalamo-hypophyseal portal system
Primary plexus
Anterior pituitary
Hypophyseal portal veins
Secondary plexus
Anterior pituitary

Figure 17.11 The Anatomic Relationship of the Hypothalamus and the Pituitary Gland. The hypothalamus is connected to the (a) posterior pituitary by the hypothalamo-hypophyseal tract, and the (b) anterior pituitary by the hypothalamo-hypophyseal portal system.

Hypothalamic nuclei:
- **Supraoptic nucleus** (produces oxytocin)
- **Paraventricular nucleus** (produces ADH)

Posterior pituitary:
- Antidiuretic hormone (ADH)
- Oxytocin

Anterior pituitary:
- Thyroid-stimulating hormone (TSH)
- Prolactin (PRL)
- Follicle-stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Adrenocorticotropic hormone (ACTH)
- Growth hormone (GH)

WHAT DID YOU LEARN?

1. What is the anatomic connection between the hypothalamus and the posterior pituitary?
The posterior pituitary stores two hormones—antidiuretic hormone and oxytocin (figure 17.11a). Both hormones are synthesized in the hypothalamus: The supraoptic nucleus primarily forms antidiuretic hormone, and the paraventricular nucleus primarily produces oxytocin. For this reason, these neurons in the hypothalamus are called neurosecretory (nūr′ō-se′k-rà-tér′-ē) cells. Following their synthesis in the hypothalamus, the hormones are packaged within secretory vesicles and transported by fast axonal transport (see section 12.2c) through the unmyelinated axons (of the hypothalamo-hypophyseal tract) to their synaptic knobs within the posterior pituitary. Note that the posterior pituitary does not produce hormones; it is simply a storage site for these two hormones synthesized in the hypothalamus.

Hormone is released from the posterior pituitary when a nerve signal is sent from the hypothalamus along the hypothalomo-hypophyseal tract. Specifically, nerve signals from the supraoptic nucleus primarily cause release of ADH, and those from the paraventricular nucleus primarily stimulate release of oxytocin. These molecules are considered hormones, and not neurotransmitters, because they enter the blood when released, even though they are released from synaptic knobs of neurons.

**Antidiuretic (an′tē-dr-yō-ret′-ik) hormone (ADH) (anti = against, oüresis = urination) functions to help maintain fluid balance, blood volume, and blood pressure. It is released when there is increased blood concentration, which indicates a state of dehydration. The hypothalamus detects this change in blood concentration as blood moves through this region of the brain and, in response, initiates nerve signals to the posterior pituitary to release ADH into the general circulation. Target cells of ADH include (1) the kidneys, which are stimulated to decrease urine output, and (2) the thirst center, which then relays nerve signals to the cerebral cortex for us to become conscious of being thirsty and our need to increase our fluid intake. ADH, in high doses, causes vasoconstriction (which is why ADH is also called vasopressin). The release of ADH is regulated by negative feedback (see section 1.6b). Following fluid intake, and as we become rehydrated and our blood concentration returns to normal, the hypothalamus relays fewer nerve signals to the posterior pituitary, resulting in a lower amount of ADH released. The details of the effect of ADH on the kidneys is presented in section 24.6d, and its role in helping to maintain blood pressure is covered in section 25.4b.

**Oxytocin (OT) (ok-sē-tō′sin; oektokes = swift birth) functions in both the delivery of a baby and the ejection of milk in females. During labor, OT is released in progressively higher amounts. Nerve signals are relayed from the uterus to the hypothalamus; in response, the hypothalamus initiates nerve signals to the posterior pituitary to release OT into the general circulation. Oxytocin stimulates the smooth muscle of the uterus to contract with increasing force until the baby is delivered (see figure 29.14). In addition, after a baby is born and when a baby suckles at the breast, nerve signals are initiated from the breast to the hypothalamus, and in response the hypothalamus initiates nerve signals to the posterior pituitary to release OT into the general circulation. Here, OT stimulates smooth muscle contractions within the breast to cause ejection of breast milk (see figure 29.16). (This release requires prolactin, which stimulates milk production, as described in section 17.6b). Oxytocin release, in both processes, is regulated by positive feedback (see section 1.6c).

Oxytocin facilitates the movement of sperm through the reproductive ducts in males (see section 28.4f). Additionally, research has shown that physical contact between individuals (e.g., hugging, holding hands) causes the release of OT, which improves our mood and alters our physiology (e.g., lowers our levels of stress hormones, reduces our blood pressure, increases our tolerance for pain). Oxytocin is even released when someone pets a dog—in both the individual and the dog.

The functional details of both ADH and oxytocin are summarized in the reference tables following this chapter (see tables R.7 and R.9, respectively).
Thyrotropin-releasing hormone (TRH) stimulates the anterior pituitary to release thyroid-stimulating hormone (TSH) (also called thyrotropin). TSH stimulates the thyroid gland to release thyroid hormone (TH), which regulates the metabolic rate. Thus, the general sequence of hormone release is TRH → TSH → TH (see section 17.9b).

Prolactin-releasing hormone (PRH) stimulates the anterior pituitary to release prolactin (pro-lak’tin; pro = milk) (PRL), which acts on mammary glands to influence gland growth and stimulate milk production. Prolactin release is inhibited by prolactin-inhibiting hormone (see section 29.8c).

Gonadotropin-releasing hormone (GnRH) stimulates the anterior pituitary to release both follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are collectively called gonadotropins. These hormones act on the gonads in both females and males to stimulate development of gametes (sperm and oocyte), and release hormones.

Corticotropin-releasing hormone (CRH) stimulates the adrenal cortex to produce and secrete glucocorticoids (e.g., cortisol), which raise blood levels of nutrient molecules (e.g., glucose). Thus, the general sequence of hormone release is CRH → ACTH → glucocorticoids (see section 17.10b).

Growth hormone–releasing hormone (GHRH) stimulates the anterior pituitary to release growth hormone (GH) (or somatotropin). GH stimulates the liver to release both insulin-like growth factor 1 and 2 (IGF-1 and IGF-2) (also called somatomedins) (si-ō-ma-tō-me’dins). GH and IGFs function synergistically to cause growth. Thus, the general sequence of hormone release is GHRH → GH → IGFs. Release of GH is inhibited by growth hormone–inhibiting hormone (GHIH).
Both are secreted by cells called gonadotropes. These hormones act on the gonads in both females and males. In the female, FSH and LH act on the ovaries to control (1) development of the oocyte and the follicle (the structural unit that encloses the oocyte), (2) ovulation, which is the release of oocyte from the follicle, and (3) the release of estrogen and progesterone (see section 28.3b). In the male, FSH and LH act on the testes to regulate the development of sperm and the release of testosterone (see section 28.4b).

- **Adrenocorticotropic** (ä-dré’nō-kör’ti-kō-trō’pik) hormone (ACTH) (also called corticotropin) is secreted by cells called corticotropes. ACTH stimulates the adrenal cortex to produce and secrete glucocorticoids (e.g., cortisol), which increase blood levels of nutrient molecules, including glucose, glyceral, fatty acids, and amino acids (see section 17.9b).

- **Growth hormone** (GH) (or somatotropin) is secreted by cells called somatotropes. GH stimulates the liver to release both insulin-like growth factor 1 and 2 (IGF-1 and IGF-2, also called somatomedins) (sō’mă-mē’din). Both GH and IGFs function synergistically to stimulate cell growth and cell division, particularly within the skeletal and muscular systems (see section 17.7d).

All of these hormones (except prolactin and growth hormone\(^1\)) are called **tropic** (trōp’ik) hormones, which are hormones that target another endocrine gland to secrete its hormone(s). Note: The anterior pituitary also secretes melanocyte-stimulating hormone (MSH), but because it normally has little effect in humans and secretion ceases prior to adulthood, it will not be discussed further in this text.

**Regulation of the Anterior Pituitary by the Hypothalamus**

The hormones released from the hypothalamus into the hypothalamo-hypophyseal portal system, which control specific cells of the anterior pituitary to release their hormones into the general circulation, are shown in figure 17.12. Take a moment to read the descriptions at the bottom of figure 17.12, which explain the functional relationship between the hypothalamus and each of the specific hormones released from the anterior pituitary. Each hormone released from the hypothalamus is color-coded with the specific hormone(s) that it triggers to release from the anterior pituitary.

1. Some experts consider growth hormone to be a tropic hormone because it stimulates the liver to release IGFs (in addition to GH stimulating bone and cartilage growth).

It is interesting to note that the pituitary gland is often dubbed the **master gland** because of controlling many other endocrine organs, including the thyroid, gonads (testes, ovaries), and adrenal cortex. As we have observed, however, the release of hormones from both the posterior pituitary and the anterior pituitary is regulated by the hypothalamus. Thus, the “master gland” does not function independently.

**WHAT DID YOU LEARN?**

What are the six primary hormones released from the anterior pituitary? How is the release of each of these hormones regulated by the hypothalamus?

**LEARNING STRATEGY**

Remember the primary anterior pituitary hormones with the **TP-FLAG** mnemonic:

- **T** = Thyroid-stimulating hormone
- **P** = Prolactin
- **L** = Luteinizing hormone
- **A** = Adrenocorticotropic hormone
- **G** = Growth hormone

**17.7d Growth Hormone: Its Regulation and Effects**

**LEARNING OBJECTIVES**

23. Describe how the release of growth hormone is regulated.

24. Describe the effects of growth hormone on its primary target organs.

**Regulation of Growth Hormone Release**

This section provides a detailed examination of the homeostatic system involving growth hormone to integrate many of the concepts that have been discussed in this chapter and in previous chapters. We describe its regulated release by the hypothalamus and its effects (as a water-soluble hormone) on its target cells. An overview of the homeostatic system involving growth hormone is presented in figure 17.13.

The release of GH from the anterior pituitary is controlled through hormonal stimulation (see section 17.2b) by the release of growth hormone–releasing hormone (GHRH) from the hypothalamus. GHRH enters the hypothalamo-hypophyseal portal system and is transported by the blood directly to the anterior pituitary (see section 17.7c). GHRH binds to receptors in specific cells of the anterior pituitary (somatotropic cells) and stimulates the release of GH into the general circulation to be transported throughout the body (see figure 17.1). The release of both GHRH from the hypothalamus and GH from the anterior pituitary (steps 3 and 4 in figure 17.13) is regulated by negative feedback (step 8 in figure 7.13). In response to increased levels of either GH or IGFs, the hypothalamus is stimulated to release growth hormone-inhibiting hormone (GHIH), which inhibits the release of GH from the anterior pituitary. GH also directly inhibits its own release from the anterior pituitary.

The amount of GHRH released from the hypothalamus (step 3 in figure 17.13) occurs in response to a number of other factors (as measured by growth hormone levels in the blood) (figure 17.14):

- **A person’s age.** Growth hormone levels fluctuate with age. Notice in figure 17.14a that children and adolescents experience the highest amounts of GH, with progressive...
Increased amino acid uptake, which results in protein synthesis

Figure 17.13 Regulation and Action of Growth Hormone. The hypothalamus responds to particular stimuli by releasing growth hormone–releasing hormone (GHRH), which stimulates the anterior pituitary to release growth hormone (GH). GH stimulates the release of insulin-like growth factor (IGFs) from the liver. Together, GH and IGFs stimulate growth and alter the availability of nutrient molecules within the blood to provide additional energy for growth. (Direction of arrows between the blood and effectors indicates the net movement of the nutrients.)
Variables That Influence Growth Hormone Levels. Release of growth hormone is influenced by (a) an individual’s age, with highest levels in childhood and declining with increasing age and (b) the time of day, with peak levels in the late evening before going to sleep.

- **Time of day.** At any age, there are daily fluctuations in the release of GH. Observe in figure 17.14b that in a normal sleep-wake cycle, peak GH levels correspond to the early stages of the normal sleep cycle, allowing the most growth to occur while we are sleeping. Nocturnal (nighy) peaks account for the majority of the GH released daily.

- **Nutrient levels.** Blood levels of nutrients influence GH release. GH levels increase in response to either an *increase* in amino acid levels (e.g., following a high-protein meal) or a *decrease* in glucose levels (e.g., when experiencing hypoglycemia).

- **Stress and exercise.** Emotional, physical, and chemical stress (including surgery, trauma, or exercise) increases GH release (although severe emotional stress can cause a decrease in its release in children).

### Effects of Growth Hormone

One of the primary target organs of GH is the liver (figure 17.13). Hepatocytes release the insulin-like growth factors (IGFs) into the general circulation when stimulated by GH. GH and IGFs have overlapping synergistic interactions (see section 17.6b), but IGFs are responsible for the greater response from the target cells. This results from the difference in their individual half-lives: GH (a protein hormone) has a half-life of 6 to 20 minutes, and IGFs (also protein hormones) have a half-life of approximately 20 hours because they are transported in the blood by carrier proteins that help protect IGFs from destruction (see section 17.4a).

All cells of the body have receptors for GH, IGFs, or both. Binding of the hormones activates second messengers within the target cells (see section 17.5b), altering enzymatic pathways (see section 3.3g) to increase protein synthesis (see section 4.8b), cellular division (see section 4.9b), cell differentiation (see Clinical View 5.4: “Stem Cells”), or a combination of these. Cartilage, bone, and muscle tissue, in particular, are affected by these hormones. Cartilage growth results from hyperplasia (increase in number) of chondrocytes and formation of extracellular matrix within cartilage (see section 7.3). Linear growth of bone occurs due to cartilage growth within the epiphyseal plate of bones. Appositional growth (growth in diameter) of bone is also stimulated (see sections 7.5a and c). In muscle fibers, uptake of amino acids increases, which stimulates the synthesis of contractile proteins composing myofibrils (see figure 10.3), resulting in skeletal muscle hypertrophy. Some athletes have been known to illegally use growth hormone—in an attempt to increase muscle size and strength. Sometimes GH is used in conjunction with anabolic steroids (see Clinical View 10.8: “Anabolic Steroids as Performance-Enhancing Compounds”).

In addition, nutrient release from storage is stimulated (e.g., glycogen from the liver and triglycerides from adipose connective tissue). These nutrient molecules are used as the fuel molecules in cellular respiration (see section 3.4), which provides ATP for the energy-consuming processes of growth. Hepatocytes are stimulated by GH to increase both glycogenolysis (breakdown of glycogen into glucose molecules) and gluconeogenesis (formation of glucose from noncarbohydrate sources); at the same time, the glycolysis (formation of glycogen from glucose molecules) pathway is inhibited (see section 2.7c). Glucose is released from the liver into the blood; as a result, blood glucose levels rise. This increase in blood glucose is referred to as a *diabetogenic* (di-a-bet-ō-ju-nik) effect due to the similarity to elevated blood glucose levels in individuals with diabetes mellitus (see Clinical View 17.8: “Conditions Resulting in Abnormal Blood Glucose Levels”).

Adipose connective tissue cells are stimulated by GH and IGFs to increase lipolysis (breakdown of triglycerides into glycerol and fatty acids) and decrease lipogenesis (formation of triglycerides from glycerol and fatty acids; see section 2.7b). Glycerol and fatty acids are released from adipocytes, causing an increase in the level of glycerol and fatty acids in the blood. Additional responses to the release of GH are listed in the summary table in the reference section, which directly follows this chapter (see table R.3).

**WHAT DO YOU THINK?**

You may have heard someone describe a teenager going through puberty as having “thinned out.” Which cellular process, stimulated by GH, directly accounts for the loss of fat tissue: glycogenolysis, lipolysis, or protein anabolism?

**WHAT DID YOU LEARN?**

19. How do GHRH, GH, and IGFs function together to regulate growth?

20. What are the primary target organs/tissues of GH and IGFs? Describe the effect on each.
Chapter Seventeen
Endocrine System

17.8 Thyroid Gland

The largest structure in the body entirely devoted to endocrine activities is the thyroid gland, which releases both thyroid hormone and calcitonin. We first describe thyroid gland anatomy, then discuss the regulation of both thyroid hormone and calcitonin release from the thyroid gland and the effect of each on its target organs.

17.8a Anatomy of the Thyroid Gland

LEARNING OBJECTIVES

25. Describe thyroid gland location and anatomy.

26. Identify the two specific types of endocrine cells within the thyroid and the specific hormone produced by each.

The thyroid gland (figure 17.15) is a butterfly-shaped gland located immediately inferior to the thyroid cartilage of the larynx and anterior to the trachea. This gland is composed of left and right lobes, which are connected at the anterior midline by a narrow isthmus (is’mūs). Both lobes of the thyroid gland are highly vascularized, giving the gland an intense reddish coloration. The entire gland is enclosed within a connective tissue capsule.

The thyroid gland at the histologic level is composed primarily of numerous microscopic, spherical structures called thyroid follicles (figure 17.15b). The wall of each follicle is formed by simple cuboidal epithelial cells (see table 5.2), called follicular cells, which surround a central lumen. The lumen (internal space) of each thyroid follicle houses a viscous, protein-rich fluid termed colloid (kol’oyd). (Think of thyroid follicles as microscopic, gelatin-filled balls.)

The follicular cells produce and later release thyroid hormone (TH) by first synthesizing a glycoprotein called thyroglobulin (TGB) and secreting it by exocytosis into the colloid-filled lumen. In brief, iodine molecules must be combined with the thyroglobulin in the colloid to produce hormone precursors, which are TGB molecules that contain immature thyroid hormone within their structure. The precursors are stored in the colloid until the secretion of thyroid hormone is needed. When the thyroid gland is stimulated to secrete thyroid hormone, some of the colloid with thyroid hormone precursors is internalized by endocytosis into a follicular cell. It is transported to a lysosome, where an

CLINICAL VIEW 17.4
Disorders of Growth Hormone Secretion

Growth hormone deficiency, also known as pituitary dwarfism, is a condition that exists at birth as a result of inadequate growth hormone production due to a hypothyroid or pituitary problem. Growth retardation is typically not evident until a child reaches 1 year of age, because the influence of growth hormone (GH) is minimal during the first 6 to 12 months of life. In addition to short stature, children with pituitary dwarfism often have periodic low blood sugar (hypoglycemia). Injections of growth hormone over a period of many years can bring about improvement, but not a normal state.

Oversecretion of growth hormone in childhood causes pituitary gigantism. Beyond extraordinary height (sometimes up to 8 feet), these affected individuals have enormous internal organs, a large and protruding tongue, and significant problems with blood glucose management. If untreated, a pituitary giant dies at a comparatively early age, often from complications of diabetes or heart failure.

Excessive growth hormone production in an adult results in acromegaly (ak’rō-meg’a-lī) instead of gigantism because the epiphyseal plate is closed in an adult. The individual does not grow in height, but the bones of the face, hands, and feet enlarge and widen (appositional growth), along with growth in cartilage. An increase in mandible size leads to a protruding jaw (prognathism). Internal organs, especially the liver, increase in size, and increased release of glucose leads to the development of diabetes in all individuals with acromegaly. Acromegaly may result from loss of feedback control of growth hormone at either the hypothalamic or pituitary level, or it may develop because of a GH-secreting tumor of the pituitary. Current treatment includes using a growth-inhibiting hormone analog, which acts to inhibit the release of growth hormone from the anterior pituitary.

Photos of a female with acromegaly in her 20s (a) and in her 40s (b) (c) Pituitary dwarfism (d) Pituitary gigantism

(a, b) Source: Atlas of Clinical Medicine/The U.S. National Library of Medicine; (c) ©CNImaging/Newscom; (d) ©Imaginechina/AP Photo

(a) Woman with acromegaly (age 20)
(b) Woman with acromegaly (age 40)
(c) Pituitary dwarfism
(d) Pituitary gigantism

684 Chapter Seventeen Endocrine System
Chapter Seventeen
Endocrine System

685

Figure 17.15 The Thyroid Gland. (a) A drawing and cadaver photo illustrate that the thyroid gland is located anterior to the thyroid cartilage of the larynx (voice box) and has a rich blood supply. (b) A diagram and micrograph reveal the histology of thyroid follicles, illustrating the simple cuboidal epithelium of the follicular cells, colloid within the follicle lumen, and the relationship of parafollicular cells to a follicle. Thyroid follicles produce thyroid hormone, and parafollicular cells produce the hormone calcitonin. ©McGraw-Hill Education/Christine Eckel; ©McGraw-Hill Education/Al Telser

enzyme releases the immature thyroid hormone molecules from the precursor in preparation for its secretion from the follicular cells. The details of thyroid hormone synthesis, storage, and release are covered in figure 17.16. Parafollicular (par‘ā’fo‘lik’yāl’tār; para = alongside, near) cells—which are the other, less numerous endocrine cells of the thyroid—are located around the follicular cells. These cells synthesize and release calcitonin, which is discussed in section 17.8c.

WHAT DO YOU THINK?
6 Have you ever noticed that the salt you buy in the grocery store is “iodized”? What is the function of iodine added to our salt?

WHAT DID YOU LEARN?
21 Describe the anatomic relationship of follicular and parafollicular cells, and identify the specific hormone released by each.

17.8b Thyroid Hormone: Its Regulation and Effects

LEARNING OBJECTIVE
27. Explain the homeostatic system involving thyroid hormone.

This section provides a detailed examination of the homeostatic system involving thyroid hormone. We describe its regulated release by the anterior pituitary and its effects (as a lipid-soluble hormone) on its target cells. An overview of the homeostatic system involving thyroid hormone is presented in figure 17.17.

Regulation of Thyroid Hormone Release
Thyroid hormone is released from the thyroid gland as a result of the integrated activities of the hypothalamus and anterior pituitary. This physiologic relationship is referred to as the hypothalamic-pituitary-thyroid axis, and was first described in section 17.7c.

The hypothalamus releases thyrotropin-releasing hormone (TRH), which enters the hypothalamo-hypophyseal portal system. TRH binds to receptors in cells of the anterior pituitary (thyrotropic cells) and stimulates the anterior pituitary to release thyroid-stimulating hormone (TSH) into the general circulation. TSH binds to receptors of the follicular cells of the thyroid gland and stimulates the release of thyroid hormone (TH). TH has two forms—triiodothyronine (T₃) and tetraiodothyronine (T₄) (thyroxine)—which are released into the circulation.

T₃ and T₄ are transported within the blood bound by carrier molecules (e.g., thyroxine-binding globulin [TBG], albumin). At any given time, a small percentage of T₃ and T₄ becomes unbound from the carrier proteins and can then exit from the blood.

The amount of TRH released from the hypothalamus and TSH from the anterior pituitary (steps 3 and 4 in figure 17.17) is regulated by negative feedback (step 8 in figure 17.17). Increased thyroid hormone inhibits both the release of TRH from the hypothalamus and the
release of TSH from the anterior pituitary. Other stimuli that may cause increased release of TRH include cold weather, pregnancy, high altitude, hypoglycemia, and, in children, decreased body temperature.

**Effects of Thyroid Hormone**

A cellular transport system (carrier-mediated endocytosis) moves TH into target cells, where it binds to intracellular receptors. T₃ is the most active form of TH. Most cells, however, have an enzyme to remove one iodine to convert T₄ to T₃. This increases a cell’s response to thyroid hormone because a much greater amount of T₃ (~90%) than T₄ (~10%) is produced and released from the thyroid gland.

TH is a lipid-soluble hormone that ultimately increases protein synthesis in all cells, especially neurons. TH specifically stimulates protein synthesis in all cells, especially neurons. TH specifically stimulates the synthesis of sodium-potassium (Na⁺/K⁺) pumps in neurons, and the action of these additional ion pumps generates heat. The rise in temperature is referred to as the calorigenic (kæ-lōr′i-jen′ik; calor = heat).
**Figure 17.17 Regulation and Action of Thyroid Hormone.** The hypothalamus responds to particular stimuli by releasing thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary to release thyroid-stimulating hormone (TSH). TSH stimulates the thyroid gland to release thyroid hormone (TH). This physiologic relationship is referred to as the hypothalamic-pituitary-thyroid axis. TH increases the body’s metabolic rate and alters the availability of nutrient molecules within the blood to provide additional energy for the higher metabolic rate. (Direction of arrows between the blood and effectors indicates the net movement of the nutrients.)
Disorders of Thyroid Hormone Secretion

Thyroid hormone (TH) release is very tightly controlled in the healthy state, but should the amount vary by even a little, a person could become either hyperactive and heat-intolerant or sluggish and overweight. Disorders of thyroid activity are among the most common metabolic problems clinicians see.

Hyperthyroidism results from excessive production of TH and is characterized by increased metabolic rate, weight loss, hyperactivity, and heat intolerance. Although there are a number of causes of hyperthyroidism, the more common ones are (1) ingestion of T₄ (weight control clinics sometimes use TH to increase metabolic activity); (2) excessive stimulation of the thyroid by the pituitary gland; and (3) loss of feedback control by the thyroid. This last condition, called Graves disease, is an autoimmune disorder involving the formation of autoantibodies that mimic TSH hormone. The autoantibodies bind to TSH receptors on the follicular cells of the thyroid, causing an abnormally high level of TH release. Graves disease includes all the symptoms of hyperthyroidism plus a peculiar change in the eyes known as exophthalmos (protruding and bulging eyeballs). Hyperthyroidism is treated by removing the thyroid gland, either by surgery or by intravenous injections of radioactive iodine (I-131). In the procedure for treating hyperthyroidism, the thyroid literally “cooks itself” as it sequesters the I-131, but other organs are not damaged because they do not store iodine as does the thyroid. Patients whose thyroid glands have been removed or destroyed must take daily hormone supplements.

Hypothyroidism results from decreased production of TH. It is characterized by low metabolic rate, lethargy, a feeling of being cold, weight gain (in some patients), and photophobia (the disdain and avoidance of light). Hypothyroidism may be caused by decreased iodine intake, loss of pituitary stimulation of the thyroid, post-therapeutic hypothyroidism (resulting from either surgical removal or radioactive iodine treatments), or destruction of the thyroid by the person’s own immune system (Hashimoto thyroiditis). Oral replacement of TH may be needed for most of these cases of hypothyroidism.

A goiter is the enlargement of the thyroid, typically due to an insufficient amount of dietary iodine. Although the pituitary releases more TSH in an effort to stimulate the thyroid, the lack of dietary iodine prevents the thyroid from producing the needed TH. The long-term consequence of the excessive TSH stimulation is overgrowth of the thyroid follicles and the thyroid itself. Goiter was a relatively common deformity in the United States until food processors began adding iodine to table salt. It still occurs in parts of the world where iodine is lacking in the diet and, as such, is referred to as endemic goiter. Unfortunately, goiters do not readily regress once iodine is restored to the diet, and surgical removal of the thyroid gland is often required.

WHAT DO YOU THINK?

Predict the signs/symptoms that a person with hyperthyroidism would exhibit in each of the following circumstances: (a) high temperature or low temperature, (b) elevated pulse or decreased pulse, (c) elevated breathing or decreased breathing, and (d) plump or thin body.

WHAT DID YOU LEARN?

What is the relationship of TRH, TSH, and TH in regulating metabolism?

What are the primary target organs/tissues of TH? Describe the effect on each.
17.8c Calcitonin: Its Regulation and Effects

**LEARNING OBJECTIVE**

**28.** Explain the role of calcitonin in regulating blood calcium.

Calcitonin is synthesized and released from the less numerous cells of the thyroid gland called the parafollicular cells. These cells are located around the follicular cells that produce thyroid hormone (see figure 17.15). The stimulus for calcitonin release from parafollicular cells is a high blood calcium level; it is also secreted in response to stress from exercise. Calcitonin primarily inhibits osteoclast activity within bone tissue (which decreases the breakdown of bone tissue) and stimulates the kidneys to increase the loss of calcium in the urine. The net effect of calcitonin is a reduction in blood calcium levels. The relationship of calcitonin to parathyroid hormone and calcitriol in regulating blood calcium is discussed in section 7.6c.

**WHAT DID YOU LEARN?**

**24.** Does calcitonin decrease or increase blood calcium? Explain.

17.9 Adrenal Glands

The adrenal glands, like the hypothalamus and pituitary gland, are composed of both nervous tissue and hormone-producing cells. The inner portion of each gland, called the adrenal medulla, is composed of nervous tissue. The outer portion, called the adrenal cortex, is composed of hormone-producing cells. Numerous types of hormones are released from this gland. We first describe adrenal gland anatomy and its associated hormones.

17.9a Anatomy of the Adrenal Glands

**LEARNING OBJECTIVES**

**29.** Describe the structure and location of the adrenal glands.

**30.** Name the three zones of the adrenal cortex and the hormones produced in each zone.

The **adrenal (á-dré’ náld; ad = to, ren = kidney) glands**, or **suprarenal glands**, are paired, pyramid-shaped endocrine glands anchored on the superior surface of each kidney (figure 17.18). These glands (like the kidney that each is superior to) are retroperitoneal, which is posterior to the parietal peritoneum (see section 24.2a). Each adrenal gland is embedded within fat and fascia to minimize their movement. Two regions constitute an adrenal gland: the adrenal medulla and the adrenal cortex (figure 17.18b).

**Adrenal Medulla**

The **adrenal medulla** forms the inner core of each adrenal gland. It has a pronounced reddish-brown color due to its extensive vascularization. It releases the catecholamines epinephrine and norepinephrine (which are biogenic amines; see section 17.3a). The stimulus for their release is activation by the sympathetic division (see figure 17.3c). Approximately 80% of the hormone released is epinephrine and about 20% is norepinephrine. Both hormones circulate within the blood and help prolong the fight-or-flight response, which is caused by the activation of the sympathetic division (see section 15.4).

**Adrenal Cortex**

The **adrenal cortex** exhibits a distinctive yellow color as a consequence of the stored lipids within its cells. These cells synthesize more than 25 different lipid-soluble corticosteroids (see section 17.3a). The adrenal cortex is partitioned into three separate regions: the outer zona glomerulosa, the middle zona fasciculata, and the inner zona reticularis (figure 17.18c). Different functional categories of steroids are synthesized and secreted in the separate zones.

**Hormones of the Adrenal Cortex**

The **zona glomerulosa** (zō’ná glo-mér-ū-loss’a; glomerulus = ball of yarn) is the thin, outer cortical layer composed of dense, spherical clusters of cells. These cells synthesize **mineralocorticoids** (min’er-al-ō-kör’ti-koyd), a group of hormones that help regulate the
Figure 17.18 Adrenal Glands. Each adrenal gland is a two-part gland that secretes stress-related hormones. The adrenal medulla produces epinephrine and norepinephrine, and the adrenal cortex produces mineralocorticoids (e.g., aldosterone), glucocorticoids (e.g., cortisol), and gonadocorticoids (e.g., androgens) from its different zones. (a) A cadaver photo shows the relationships of the kidneys and adrenal glands. (b) A sectioned adrenal gland shows the inner medulla and outer cortex. (c) A diagram and a micrograph illustrate the three zones of the adrenal cortex, as well as the relationship of the cortex to the external capsule and the internal medulla. 

(a) © McGraw-Hill Education/Christine Eckel; (c) © McGraw-Hill Education/Al Telser

690 Chapter Seventeen Endocrine System
composition and concentration of electrolytes (ions) in body fluids. The principal mineralocorticoid is **aldosterone** (al-dos’ter-ôn), which regulates the ratio of Na⁺ and K⁺ in our blood and body fluids by altering the amounts excreted by the kidney into the urine. Aldosterone stimulates Na⁺ retention and K⁺ secretion. Severe imbalances in this ratio can result in death. The functional details of aldosterone are described in sections 24.6d and 25.4c and summarized in the reference tables following this chapter (see table R.7).

The **zona fasciculata** (fâ-sik’û-la-ta; *fascicle* = bundle of parallel sticks) is the middle layer and largest region of the adrenal cortex. It is composed of parallel cords of lipid-rich cells that have a bubbly, almost pale appearance. The primary glucocorticoids (glû’kô-kör-tik’ôidz) synthesized in this region are cortisol and corticosterone, which are released in response to ACTH. Details of cortisol regulation and function are described in section 17.9b.

The innermost region of the cortex, the **zona reticularis** (rê-tik’û-lâr’âs; *reticulum* = network), is a narrow band of small, branching cells. They are capable of secreting minor amounts of sex hormones called **gonadocorticoids**. The primary gonadocorticoids secreted are male sex hormones called **androgens**, thus serving as a secondary site for androgens in males and the primary site in females. Gonadocorticoids include dehydroepiandrosterone (DHEA), DHEA-sulfate, and androstenedione. The amount of androgen secreted by the adrenal cortex is small compared to that secreted by the gonads; however, adrenal gland tumors in a female can result in elevated levels of testosterone and varying degrees of masculinization.

### 17.9b Cortisol: Its Regulation and Effects

#### LEARNING OBJECTIVE

31. Describe the homeostatic system involving cortisol.

This section provides a detailed examination of the homeostatic system involving cortisol. We describe its regulated release by the anterior pituitary and its effects (as a lipid-soluble hormone) on its target cells. An overview of the homeostatic system involving cortisol is presented in figure 17.19.

### Regulation of Cortisol Release

The release of **cortisol** (kôr’ti-sol) and **corticosterone** (kôr’ti-kos’ter-ôn) from the adrenal cortex occurs through hypothalamic regulation by means of corticotropin-releasing hormone (CRH) and the subsequent release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. This physiologic relationship is referred to as the **hypothalamic-pituitary-adrenal axis** (figure 17.19). This relationship is first described in section 17.7c.

The hypothalamus releases CRH, which is transported through the hypothalamo-hypophyseal portal system to the anterior pituitary, where it binds to receptors of the anterior pituitary (corticotrophic cells) and stimulates the release of adrenocorticotropic hormone (ACTH) into general circulation (figure 17.19). ACTH then binds to receptors within adrenal cortex cells (zona fasciculata) and stimulates the release of cortisol and corticosterone. Cortisol accounts for 95% of the glucocorticoid activity. Cortisol is transported within the blood by carrier proteins (corticosteroid-binding globulin [or CBG, also called transcortin] or albumin). Cortisol circulates in the blood, and small amounts become unbound from their carrier protein and exit from the blood.

The release of both CRH from the hypothalamus and ACTH from the anterior pituitary (steps 3 and 4 in figure 17.19) is regulated by negative feedback (step 8 in figure 17.19). Increasing levels of cortisol inhibit the release of CRH from the hypothalamus and ACTH from the anterior pituitary. Other factors influence the amount CRH released from the hypothalamus (as measured by cortisol hormone levels in the blood) (figure 17.20):

- **Time of Day.** There are daily fluctuations in the release of cortisol. Notice in figure 17.20a that in a normal sleep-wake cycle, peak levels of cortisol correspond to the late stages of a normal sleep cycle. About half of all cortisol release occurs when you are asleep, with cortisol levels peaking right before waking in the morning. This rhythm of release is regulated by light and dark cycles detected by the retina as nerve signals are relayed to the hypothalamus. (Among individuals, there is significant variation in normal levels.)
Increased glycogenolysis and gluconeogenesis
Decreased glycogenesis
Increased lipolysis
Decreased lipogenesis

Glucose
Amino acids
Glycerol fatty acids

Hypothalamus
Cortisol
ACTH
CRH

Amino acids
Glucose
Glycerol fatty acids
Amino acids
Blood vessel

Liver
Adipose connective tissue
All cells

Increased glycoenerolysis and gluconeogenesis
Decreased glycogenesis

Increased lipolysis
Decreased lipogenesis

Stimulation of protein catabolism (occurs in all cells except hepatocytes)
Decreased glucose uptake

Net Effect
Increase of all nutrient molecules in the blood occurs.

Effectors: Effectors respond to cortisol in the following ways:
- Liver
  - Increased glycogenolysis and gluconeogenesis
  - Decreased glycogenesis
- Adipose connective tissue
  - Increased lipolysis
  - Decreased lipogenesis
- All cells
  - Stimulation of protein catabolism (occurs in all cells except hepatocytes)
  - Decreased glucose uptake

High doses of cortisol:
- Increase retention of Na⁺, H₂O
- Decrease inflammation
- Supress the immune system
- Inhibit connective tissue repair

Figure 17.19 Regulation and Action of Cortisol Hormone. The hypothalamus responds to particular stimuli by releasing corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH). ACTH stimulates the adrenal cortex to release cortisol. Cortisol increases the availability of nutrient molecules to support the response to stress. (Direction of arrows between the blood and effectors indicates the net movement of the nutrients.)

- Stress. Both emotional stress (e.g., anxiety, anger, fear) and physical stress (e.g., fever, trauma, intense exercise) increase the release of cortisol (figure 17.20b). The influence of chronic stress in triggering increased cortisol levels in the blood is the reason that cortisol has been given the nickname “the stress hormone” (see Clinical View 17.7: “The Stress Response”).

Effects of Cortisol
Cortisol and corticosterone increase nutrient levels in the blood (glucose, fatty acids, and amino acids), especially in an attempt to resist stress and help repair injured or damaged tissues. Other physiologic changes are stimulated by glucocorticoids and become most evident when present in high doses.
Cortisol level is increased by stress. (a) Cortisol release fluctuates based on the time of day (circadian rhythm).

<table>
<thead>
<tr>
<th>Hours</th>
<th>Percent deviation from the mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-100</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>16</td>
<td>150</td>
</tr>
<tr>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>24</td>
<td>16</td>
</tr>
</tbody>
</table>

Sleep 24 hours

(b) Figure 17.20 Variables That Influence Blood Levels of Cortisol. Blood levels of cortisol (a) fluctuate throughout the day and (b) rise with increased stress, which is why cortisol is sometimes called the “stress hormone.”

Cortisol readily passes through the plasma membrane and binds to intracellular receptors to form a hormone-receptor complex. This complex binds to DNA and stimulates cellular changes through the activation of genes. The cellular changes depend upon the tissue being stimulated. For example, hepatocytes are stimulated by cortisol to increase glycogenolysis and gluconeogenesis (see section 2.7c). At the same time, they are inhibited from using the glycogenesis pathway, so blood glucose levels rise. Some cortisol is converted to cortisone in the liver.

INTEGRATE

CLINICAL VIEW 17.6 Disorders in Adrenal Cortex Hormone Secretion

Three abnormal patterns of adrenal cortical function are Cushing syndrome, Addison disease, and androgenital syndrome.

**Cushing syndrome** results from the chronic exposure of the body’s tissues to excessive levels of glucocorticoid hormones. This complex of symptoms is seen most frequently in people taking corticosteroids as therapy for autoimmune diseases such as rheumatoid arthritis, although some cases result when the adrenal gland produces too much of its own glucocorticoid hormones. Corticosteroids are powerful immunosuppressant drugs, but they have serious side effects, such as osteoporosis, muscle weakness, redistribution of body fat, and salt retention (resulting in overall swelling of the tissues). Cushing syndrome is characterized by body obesity, especially in the face (called moon face) and back (buffalo hump). Other symptoms include hypertension, excess hair growth, kidney stones, and menstrual irregularities.

**Addison disease** (previously termed Addison’s disease) involves insufficient production of steroids (usually glucocorticoids and perhaps mineralocorticoids) from the adrenal cortex. Addison disease can result from (1) adrenal glands that were malformed during development, (2) impaired enzymatic pathways for steroid synthesis, and (3) destruction of the adrenal gland (typically by an autoimmune disorder that forms autoantibodies against the adrenal gland that results in its destruction). The symptoms include weight loss, general fatigue and weakness, hypotension, and darkening of the skin. Perhaps the best-known person with Addison disease was John Fitzgerald Kennedy (JFK), 35th president of the United States.

**Adrenogenital syndrome,** or congenital adrenal hyperplasia, first manifests in the embryo and fetus. It is characterized by the inability to synthesize corticosteroids. The anterior pituitary, sensing the deficiency of corticosteroids, releases massive amounts of ACTH in an unsuccessful effort to bring the glucocorticoid content of the blood up to a healthy level. This large amount of ACTH produces hyperplasia (increased size) of the adrenal cortex and causes the release of intermediary hormones that have a testosterone-like effect. The result is virilization (masculinization) in a newborn. Virilization in girls means the clitoris is enlarged, sometimes to the size of a male penis. The effect may be so profound that the sex of a newborn female is questioned or even mistaken. A virilized male may have an enlarged penis and exhibit signs of premature puberty as early as age 6 or 7. (See Clinical View: 28.12: “Intersex Conditions” for additional details.)

---

**Photo prior to onset of Cushing syndrome.** Courtesy of the Cushing’s Support and Research Foundation, www.CSRF.net and Kathy Carbone

**Symptoms resulting from the excessive glucocorticoid secretion in Cushing syndrome include moon face.** Courtesy of the Cushing’s Support and Research Foundation, www.CSRF.net and Kathy Carbone
Stressors may fall under the category of either emotional stress (e.g., anxiety, anger, fear, excitement) or physical stress (e.g., fever, trauma, hemorrhage, surgery, malnutrition). Stressors elicit the stress response (or general adaptation syndrome), which was defined by Hans Selye (a pioneer in the endocrinology of stress) as “the nonspecific response of the body to any demand made upon it.” The body’s response to stress is initiated by the hypothalamus and involves both the nervous system and the endocrine system. In 1936, Hans Selye described the response to stressors in three stages: the alarm reaction, the stage of resistance, and the stage of exhaustion.

The Alarm Reaction
The alarm reaction is the initial reaction to stress and is regulated primarily by the sympathetic division of the autonomic nervous system (see section 15.4a). The hypothalamus activates the sympathetic division with subsequent stimulation of the adrenal medulla to release epinephrine and norepinephrine into the blood. The following changes occur to the body (see table 15.6):

- Pupils dilate.
- Bronchioles dilate.
- Respiration rate increases.
- Blood pressure increases as:
  - Cardiac output increases
  - Blood vessels vasoconstrict
  - Blood volume increases (with sodium and water retention)
- Potassium and hydrogen ions are excreted.
- Both glucose and lipid levels in the blood increase.
- Sweating increases.
- Both digestion and urine production activities decrease.

The Stage of Resistance
The stage of resistance occurs after a few hours as glycogen stores in the liver are depleted. This stage is regulated primarily by the endocrine system. The major changes are induced by the release of glucocorticoids (e.g., cortisol). The principal function of this stage is to provide glucose to meet the increased energy demands. Glucose is especially important for nervous tissue because it is the main nutrient molecule for cell respiration that these tissues can use. To meet the increased demands for energy, gluconeogenesis is increased in the liver, and glucose is released into the blood. Glycerol and fatty acids increase in the blood due to increased lipolysis in adipose connective tissue cells. Amino acids increase as a result of increased protein catabolism (and decreased protein synthesis) in most cells. Glycogen and amino acids provide the liver with alternative nutrients for gluconeogenesis. Additionally, glucose uptake is inhibited in most cells. The net result is elevated blood glucose levels.

The Stage of Exhaustion
The stage of exhaustion occurs after weeks or months, as fat stores in adipose connective tissue are depleted. With fat stores depleted, and as structural proteins of the body’s cells continue to be broken down for gluconeogenesis, the body becomes progressively weaker. Additionally, elevated levels of aldosterone may cause fluid, electrolyte, and pH imbalances. The combination of body weakness, electrolyte imbalances, and other factors may ultimately cause organ failure and death.

Adipose connective tissue cells are stimulated by cortisol to increase lipolysis and decrease lipogenesis (see section 2.7b), resulting in the release of glycerol and fatty acids into blood. This provides alternative nutrients for gluconeogenesis.

Most cells, including muscle cells, lymphatic tissue cells, skin cells, and bone cells, increase protein catabolism (breakdown of protein into amino acids) in response to cortisol. An exception to this occurs in hepatocytes. In liver cells, additional amino acid released into the blood provides alternative nutrient molecules for gluconeogenesis. Cortisol additionally stimulates most cells to decrease glucose uptake. This is the glucose-sparing effect, which saves blood glucose for use in the brain. The details for cortisol are listed in the summary table, in the reference section, on regulating the stress response, which directly follows this chapter (see table R.5).

Therapeutic Doses of Corticosterone
Corticosterone often is used as a treatment for chronic inflammation and selected allergic reactions (e.g., hives, eczema). The side effects of corticosterone, especially when administered in high doses, include retention of Na⁺ and water; inhibited release of inflammatory agents (the anti-inflammatory effect); suppression of the immune system; and inhibited connective tissue repair. Note that suppression of the immune system increases an individual’s susceptibility to infection and risk of cancer.

**WHAT DID YOU LEARN?**

26 What is the relationship of CRH, ACTH, and cortisol?
27 What are the primary target organs/tissues of cortisol? Describe the effect on each.
17.10 The Pancreas

The pancreas releases both insulin and glucagon. We first describe the anatomy of the pancreas and then discuss the regulation of insulin and glucagon and the effects of each hormone on its target organs.

17.10a Anatomy of the Pancreas

**LEARNING OBJECTIVES**

32. Describe the gross anatomy and cellular structure of the pancreas.

33. Identify the primary types of pancreatic islet cells and the hormones they produce.

The pancreas (pan’krē-as; pan = all, kreas = flesh) is an elongated organ situated posterior to the stomach (figure 17.21). The vast majority of the cells of the pancreas (about 99%) serve an exocrine gland function. These cells, specifically called acinar cells, are modified simple cuboidal epithelial cells arranged in saclike acini (sing., acinus; grape). Each is specifically called a pancreatic acinus. The pancreatic acini serve as an exocrine gland by producing digestive enzymes, which are released into the pancreatic ducts and ultimately into the duodenum region of the small intestine (see section 26.3c).

The endocrine cells of the pancreas are located within small clusters called pancreatic islets (‘let), also known as islets of Langerhans. These endocrine cell clusters form only about 1% of the total pancreatic volume. A pancreatic islet is composed of two primary types of cells: alpha cells, which secrete glucagon (glū’kă-gon), and beta cells, which secrete insulin (in′sū-lin; insula = island). Minor cells within the pancreatic islets include delta cells, which secrete somatostatin (also described as growth hormone–inhibiting hormone), and F cells, which secrete pancreatic polypeptide. These minor cells and their hormones will not be addressed.

**INTEGRATE CONCEPT CONNECTION**

The pancreas is unusual in that it functions as both an endocrine gland and an exocrine gland (see section 5.1d). Endocrine glands release their secretions (hormones) into the blood. The pancreas releases both insulin and glucagon into the blood. In contrast, exocrine glands release their secretions into ducts. The pancreas also releases pancreatic juice containing digestive enzymes into ducts that empty into the small intestine (duodenum), as described in section 26.3c.

**WHAT DID YOU LEARN?**

28 Why is the pancreas considered both an exocrine gland and an endocrine gland?

![Figure 17.21 Pancreas.](image)
### LEARNING OBJECTIVES

34. Describe the action of insulin in lowering blood glucose concentration.

35. Explain the action of glucagon in raising blood glucose concentration.

The primary endocrine function of the pancreas is to maintain the concentration of glucose in the blood within a normal range of 70 to 110 milligrams of glucose per deciliter (mg/dL; a deciliter is an amount equivalent to 100 milliliters). Chronically high blood glucose levels can be very damaging to blood vessels and the kidneys, so this excess glucose must be transported into other body cells that can use or store this resource. Conversely, low blood glucose levels result in lethargy, impairment of mental and physical function, and death if glucose levels drop too low. Thus, blood glucose levels must be closely regulated. The homeostatic mechanisms for insulin and glucagon are described next and are summarized in the reference section table, which directly follows this chapter (see table R.1).

### Lowering High Blood Glucose Levels with Insulin

Insulin is generally released from the pancreas following food intake (Figure 17.22). Chemoreceptors in the beta cells of the pancreas detect an increase in blood glucose (readings greater than the normal 70–110 mg/dL) and are stimulated to release insulin (a protein hormone). Insulin circulates in the blood and randomly exits from the blood into the interstitial fluid as it passes through capillaries (see figure 17.1). Target cells bind insulin, which activates second messengers within the target cell. (Additionally, recent evidence suggests that insulin may also enter the cell and directly bind to intracellular receptors.) Insulin's effects on altering specific enzymatic pathways are as follows:

- **Glycogenesis** (see section 2.7c) in hepatocytes is stimulated, and both glycogenolysis and gluconeogenesis are inhibited, resulting in glucose molecules being removed from the blood and stored as glycogen within liver cells.

- **Lipogenesis** (see section 2.7b) in adipose connective tissue cells is stimulated, and lipolysis is inhibited. Fatty acid levels in the blood decrease, and the storage of fat is increased as a result.

---

**Figure 17.22 Regulation and Action of Insulin.** Insulin is released from beta cells within pancreatic islets in response to high blood glucose. Insulin decreases the level of all nutrient molecules (glucose, fatty acids, and amino acids) within the blood. The uptake of fatty acids and amino acids from the blood limits their availability, making it more likely that cells will use glucose available within the blood as their nutrient molecule for cell respiration. Thus, blood glucose more quickly returns to within normal homeostatic levels.
Conditions Resulting in Abnormal Blood Glucose Levels

Diabetes Mellitus

Diabetes mellitus (di-á-bēˈtez = a siphon, me-riˈtōs = sweetened with honey) is a metabolic condition marked by inadequate uptake of glucose from the blood. The name is derived from the phrase sweet urine because some of the excess glucose may be filtered into the urine, a condition called glycosuria. Chronically elevated blood glucose levels damage blood vessels, especially the smaller arterioles. Because of its damaging effects on the vascular system, diabetes is the leading cause of retinal blindness, kidney failure, and nontraumatic leg amputations in the United States. Diabetes is also associated with increased incidence of heart disease and stroke. In fact, heart disease or stroke is the cause of death in approximately 65% of individuals with diabetes.

Measuring the amount of glucose attached to hemoglobin molecules within erythrocytes (hemoglobin A1C test) is an accurate means for determining the degree of risk for an individual. The greater the amount of attached glucose, the higher the risk of diabetes. The three classic signs of diabetes are (1) increased hunger (polyphagia) because the cells are unable to normally absorb the glucose from the blood into their cells and the cells lack sufficient energy, (2) increased urination (polyuria) because glucose lost in the urine acts to pull fluid into the urine by osmosis, and (3) increased thirst (polydipsia) because of the abnormal loss of fluid in the urine and the body is dehydrated. Three categories of diabetes mellitus are type 1 diabetes, type 2 diabetes, and gestational diabetes.

Type 1 diabetes is also referred to as insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes. It is characterized by absent or diminished production and release of insulin by the beta cells of the pancreatic islets. This type tends to occur in children and younger individuals, and is not directly associated with obesity. Type 1 diabetes may develop in a person who harbors a genetic predisposition, although some kind of triggering event is required to start the process. Often, the trigger is a viral infection leading to an autoimmune condition in which the beta cells of the pancreatic islets are destroyed. Treatment of type 1 diabetes requires daily injections of insulin. The recent use of stem cells shows promise as an effective means in treating type 1 diabetes.

Type 2 diabetes, also known as insulin-independent diabetes mellitus (IDDM), results from either decreased insulin release from the beta cells of the pancreatic islets or decreased insulin effectiveness at peripheral tissues. This type of diabetes was previously referred to as adult-onset diabetes because it tended to occur in people over the age of 30. However, type 2 diabetes is now often found in adolescents and young adults. Obesity plays a major role in the development of type 2 diabetes, and more young people are considered overweight than ever before. Most patients with type 2 diabetes can be successfully treated with a combination of diet, exercise, and medications that enhance insulin release or increase sensitivity to insulin at the tissue level. A person with type 2 diabetes must take insulin injections in more severe cases.

Gestational diabetes is seen in some pregnant women, typically in the latter half of the pregnancy. If untreated, gestational diabetes can pose a risk to the fetus as well as increase delivery complications. For further information, see Clinical View 29.3: “Gestational Diabetes.”

Hypoglycemia

Hypoglycemia occurs when blood glucose levels drop below 60 mg/dL. Hypoglycemia is not a disease; however, it may be a nonspecific indicator of some underlying homeostatic imbalance. The causes of hypoglycemia are numerous and include insulin overdose, prolonged and intense exercise, alcohol consumption on an empty stomach, liver or kidney dysfunction, deficiency of either glucocorticoids or growth hormone, and certain genetic conditions. Symptoms may include hunger, dizziness, nervousness, confusion, feeling anxious or weak, sweating, sleepiness, or any combination of these. Symptoms are thought to occur from insufficient glucose to the brain or from the activation of the sympathetic nervous system in response to low blood glucose levels.

If an individual is unable to eat or drink safely, such as if unconscious, unresponsive, or having convulsions, glucagon can be administered by injection. This provides a safe means to offset the low blood glucose level.

WHAT DO YOU THINK?

Bodybuilders have been known to inject insulin to increase muscle bulk. Explain their reasoning. What is the risk of an insulin overdose?

Raising Low Blood Glucose Levels with Glucagon

All nervous tissue depends almost exclusively upon glucose for cellular respiration. To prevent impairment of mental function, lethargy, and possibly death, blood glucose levels must be prevented from dropping too low. Glucagon is one of the important hormones released in response to low blood glucose levels (Figure 17.23).

Chemoreceptors in the alpha cells of the pancreas detect decreased blood glucose levels and subsequently release glucagon (a polypeptide hormone) into the blood. Nutrients are stored in various body tissues, and glucagon facilitates the breakdown of these nutrients and their release into the blood. Glucagon binds to plasma membrane receptors to activate second messengers (cAMP) (see section 17.5b) that cause the following:

- Glycogenolysis and gluconeogenesis (see section 2.7c) in hepatocytes are stimulated, and glycogen is inhibited; glucose is released into the blood, thereby increasing blood glucose levels. (Glucose within muscle cells is not released but remains within muscle cells and is oxidized in cellular respiration.)
Lipolysis (see section 2.7b) in adipose connective tissue cells is stimulated, and lipogenesis is inhibited. Fatty acids and glycerol are released from fat storage and are increased within the blood.

In summary, the release of glucagon results in an increase in glucose, glycerol, and fatty acids in the blood and in a decrease in the storage form of these molecules within body tissues. An increase in blood glucose levels results in a decrease in glucagon release by negative feedback.

Note that glucagon has no effect on the structural and functional protein components of the body. The physiologic significance of this lack of effect is that the ongoing, and regular, release of this hormone (e.g., during periods between meals) does not tear down the muscles and other protein components of the body to maintain blood glucose levels in “nonemergency” situations.

Interestingly, paramedics may administer glucagon subcutaneously under certain conditions when low blood glucose is detected. This may be done if the individual is unconscious and is unable to be given sugar orally to directly raise blood glucose.

**WHAT DID YOU LEARN?**

30 What are the stimulus, receptor, control center, and effector response to the release of insulin? Indicate what happens to nutrient levels in the blood.

31 Which of these hormones causes release of glucose into the blood: growth hormone, thyroid hormone, cortisol, insulin, or glucagon?

### Other Endocrine Glands

Here we describe other endocrine glands and the functions of the hormones that are released by each.

#### 17.11a Pineal Gland

**LEARNING OBJECTIVE**

36. Describe the general structure, location, and function of the pineal gland.

The pineal (pin′ē-āl) gland (or pineal body) is a small, cone-shaped structure forming the posterior region of the epithalamus within the diencephalon (see figure 17.2 and section 13.4a). The pineal gland secretes melatonin (mel-ă-ton′īn; melas = dark hue, ton as = contraction), which makes us drowsy. Melatonin production tends to be cyclic; it increases at night, decreases during the day, and has the lowest...
levels around lunchtime. Melatonin helps regulate the circadian rhythm (24-hour body clock). Studies have linked low melatonin levels with mood (affective) disorders, such as seasonal affective disorder (SAD), a condition that may be treated with light therapy.

Melatonin also appears to affect the synthesis of gonadotropin-releasing hormone (GnRH) from the hypothalamus. This hormone is responsible for regulating the synthesis of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary, which in turn regulate the reproductive system. The role of melatonin in sexual maturation is not well understood. However, excessive melatonin secretion is known to delay puberty in humans.

**WHAT DID YOU LEARN?**

32. How do melatonin levels change throughout the day?

### 17.11b Parathyroid Glands

#### LEARNING OBJECTIVE

37. Describe the general structure, location, and function of the parathyroid glands.

The small, brownish-red parathyroid (par-á-thi’royd) glands are located on the posterior surface of the thyroid gland (see figure 17.2). These glands are usually four small nodules, but some individuals may have as few as two or as many as six of these glands. There are two different types of cells in the parathyroid glands: chief cells and oxyphil cells.

The more common chief cells, or principal cells, are the source of parathyroid hormone (PTH), which is released from the parathyroid gland in response to a decrease in blood calcium levels. Parathyroid hormone functions to increase blood calcium levels. It stimulates release of calcium from bone tissue, decreases loss of calcium in urine, and causes the kidney to release an enzyme to convert the inactive calcidiol hormone to the active calcitriol hormone (see section 17.11c). The functional details of PTH and calcitriol are described in section 7.6b and summarized in the reference tables following this chapter (see table R.7). (See Clinical View 7.6: “Rickets” and Clinical View 7.7: “Osteoporosis.”)

The role of oxyphil cells is not known, although these cells are associated with a rare form of cancer called oxyphil cell adenoma.

**WHAT DID YOU LEARN?**

33. What is the primary hormone released from the parathyroid gland? What is its general function?

### 17.11c Structures with an Endocrine Function

#### LEARNING OBJECTIVE

38. Identify and provide a description of the general function of the hormone(s) released from each of the organs discussed in this section.

**Thymus**

The thymus (thî´müs) is a bilobed organ that is located anterior to the heart on its superior aspect (see figure 17.2). The thymus is relatively large in infants, continues to grow until puberty, and then begins to regress (decrease in size) after puberty. A connective tissue framework houses both epithelial cells and maturing T-lymphocytes (a specific type of white blood cell). The T-lymphocytes migrate to the thymus following their formation in the bone marrow, and epithelial cells there secrete thymic hormones (i.e., thymosin, thymulin, and thymopoietin), which participate in the maturation of T-lymphocytes (see sections 21.3b and 22.5).
Skin

Ultraviolet light penetrates into surface skin cells (keratinocytes) to convert modified cholesterol molecules to vitamin D₃ (cholecalciferol), which is then released into the blood. Vitamin D₃ is converted to calcidiol by an enzyme within the liver and then by an enzyme within the kidney to calcitriol, the active hormone (which is a lipid-soluble sterol hormone). Calcitriol is similar to parathyroid hormone because it increases blood calcium by stimulating release of calcium from bone tissue and decreases calcium loss in the urine. Additionally, calcitriol enhances the absorption of calcium from the contents of our digested food within the lumen of the small intestine. Calcitriol stimulates epithelial cells lining the small intestine to increase the number of plasma membrane Ca²⁺ transport proteins (e.g., calbindin). Without calcitriol, much of the calcium we ingest is not absorbed; it continues through the digestive tract and is lost in the feces. The functional details of calcitriol are described in sections 6.1d and 7.6b and summarized in the reference tables following this chapter (see table R.2).

Adipose Connective Tissue

Adipose connective tissue is located throughout the body, and it releases the hormone leptin. This hormone helps to regulate food intake by binding to the neurons within the hypothalamus that control appetite (see section 13.4c). Leptin stimulates down-regulation (see section 17.6a) of other receptors that are involved in increasing appetite. Lower percentage of body fat is associated with lower blood levels of leptin, which stimulates the appetite. Thus, one of the functions of leptin is to regulate energy balance within the body. Clinicians and researchers have become more aware of other endocrine functions of adipose connective tissue by observing the outcomes of either excess or deficiency of this tissue. Excess adipose connective tissue has been linked with various types of cancers (e.g., colon, breast) and delay puberty in males, whereas abnormally low body fat can both delay the onset of puberty and interfere with a normal menstrual cycle in females.

Summary Tables

The details of the major hormones discussed in this chapter (and throughout the text) are summarized in tables that are located directly following this chapter. They are organized based on their function (e.g., regulate blood glucose, regulate blood calcium). Each table includes the chemical structure of the hormone, the endocrine gland that produces it, the primary stimulus for its release, its primary target organs, and the cellular changes that it induces. In addition, the net result of the hormone action, an example of a related disease or condition, and the section(s) in the text where it is described in detail are also included.

WHAT DID YOU LEARN?

34. What is the function of the kidney in regulating erythrocyte concentration within the blood?
35. What organ releases angiotensinogen, and what is the function of angiotensinogen following its activation?

17.12 Aging and the Endocrine System

LEARNING OBJECTIVE

39. Describe how endocrine activity changes as people age.

The secretory activity of endocrine glands typically wanes as we age. Aging reduces the efficiency of endocrine system functions, and often normal levels of hormones decrease. Many conditions experienced after middle age, such as abdominal weight gain or muscle loss, are directly related to diminishing or reduced endocrine gland function.

One example is that the secretion of growth hormone (GH) often decreases. Reduction in GH levels leads to loss of weight and body mass in the elderly, although continued exercise reduces this effect.

In addition, testosterone and estrogen levels decline as males and females age. A decrease in estrogen level after menopause contributes to osteoporosis (see Clinical View 7.7 “Osteoporosis”). Hormone replacement therapy attempts to supplement sex hormone levels that have naturally diminished with age. The benefits and side effects of hormone replacement therapy are discussed in greater detail in section 28.5f.

WHAT DID YOU LEARN?

36. What general changes occur to the ability of endocrine glands to produce hormones as we age?
### CHAPTER SUMMARY

**17.1 Introduction to the Endocrine System**
- The two control systems of the body include the endocrine system and nervous system.

**17.1a Overview of the Endocrine System**
- The endocrine system is composed of endocrine glands, which release hormones into the blood to control target cells.

**17.1b Comparison of the Two Control Systems**
- The endocrine and nervous systems complement each other to maintain homeostasis.

**17.1c General Functions of the Endocrine System**
- The primary processes controlled by hormones include regulating development, growth, and metabolism; maintaining homeostasis of blood composition and volume; controlling digestive processes; and controlling reproductive activities.

**17.2 Endocrine Glands**
- Endocrine glands are located throughout the body and are regulated to secrete their hormones into the blood.

**17.2a Location of the Major Endocrine Glands**
- Endocrine organs include the pituitary gland, pineal gland, thyroid gland, parathyroid glands, and adrenal glands.

**17.2b Stimulation of Hormone Synthesis and Release**
- Release of hormones from endocrine cells is controlled through reflexes. There are three ways to stimulate these cells: (1) hormonal stimulation, (2) humoral stimulation by something in the blood other than another hormone, and (3) nervous system stimulation.

**17.3 Categories of Hormones**
- Hormones are categorized as circulating hormones or local hormones.

**17.3a Circulating Hormones**
- Circulating hormones are either lipid-soluble (these include steroids that are synthesized from cholesterol) or water-soluble (these include most biogenic amines and protein hormones that are synthesized from amino acids).

**17.3b Local Hormones**
- Eicosanoids are local hormones; they are synthesized from a fatty acid (arachidonic acid); following their formation, eicosanoids stimulate the cell that produced them (autocrine stimulation) or neighboring cells (paracrine stimulation).

**17.4 Hormone Transport**
- The mechanism of hormone transport is dependent upon whether the hormone is lipid-soluble or water-soluble.

**17.4a Transport in the Blood**
- Lipid-soluble hormones must attach to a carrier protein molecule to be transported within the blood.
- Water-soluble hormones readily dissolve in the aqueous environment of the blood and do not require a carrier protein.

**17.5 Target Cells: Interactions with Hormones**
- Hormones bind with receptors of target cells; how this occurs is significantly different for lipid-soluble and water-soluble hormones.

**17.5a Lipid-Soluble Hormones**
- Hormones that are lipid-soluble (steroids, calcitriol, and thyroid hormone) stimulate cellular activity by binding to intracellular receptors: The hormone-receptor complex activates a region of DNA, resulting in the production of new proteins.

**17.5b Water-Soluble Hormones**
- Hormones that are water-soluble (proteins and biogenic amines, except thyroid hormone) bind with plasma membrane receptors; the hormone is the first messenger, and it causes the activation of G protein and the formation of a second messenger through an intracellular enzyme cascade.
- The cellular response may include activation or inhibition of enzymatic pathways, stimulation of growth through cellular division, stimulation of cellular secretions, change in plasma membrane permeability, and muscle contraction or relaxation.

**17.6 Target Cells: Degree of Cellular Response**
- The degree of cellular response is a function of both its displayed receptors and the amounts and kinds of hormones that it binds.

**17.6a Number of Receptors on a Target Cell**
- Up-regulation is the increase in the number of receptors, and down-regulation is a decrease in the number of receptors. Being able to change receptor number allows a target cell to modify its responsiveness to a hormone.

**17.6b Hormone Interactions on a Target Cell**
- A single target cell may possess receptors for many different hormones.
- Multiple hormones may interact with target cells to have one of three effects: synergistic, permissive, or antagonist.

(continued on next page)
17.7 The Hypothalamus and the Pituitary Gland

- The hypothalamus directly controls the release of hormones from the pituitary gland and, through its control of the anterior pituitary, regulates the release of hormones from other endocrine glands.

17.7a Anatomic Relationship of the Hypothalamus and the Pituitary Gland

- The pituitary gland is inferior to the hypothalamus and connected to it by the infundibulum.
- The hypothalamus communicates with the posterior pituitary via the hypothalamo-hypophyseal tract, which contains axons from two nuclei in the hypothalamus: the supraoptic nucleus and the paraventricular nucleus.
- The hypothalamus communicates with the anterior pituitary via the hypothalamo-hypophyseal portal system, a vessel network that transports hormones from the hypothalamus to the anterior pituitary.

17.7b Interactions Between the Hypothalamus and the Posterior Pituitary Gland

- In response to nerve signals, the posterior pituitary releases antidiuretic hormone (ADH) or oxytocin (OT), which are hormones previously synthesized by the hypothalamus and stored in the posterior pituitary.

17.7c Interactions Between the Hypothalamus and the Anterior Pituitary Gland

- The regulatory hormones released from the hypothalamus include both “releasing” and “inhibiting” hormones.
- Releasing hormones stimulate the release of specific hormones from the anterior pituitary, and inhibiting hormones decrease the release of hormones from the anterior pituitary.
- The hormones synthesized and released from the anterior pituitary include thyroid-stimulating hormone (TSH), prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), and growth hormone (GH).

17.8 Thyroid Gland

17.8a Anatomy of the Thyroid Gland

- The thyroid gland is a butterfly-shaped gland anterior to the trachea and inferior to the larynx with follicles that produce thyroid hormone.

17.8b Thyroid Hormone: Its Regulation and Effects

- Decreased levels of thyroid hormone and certain stimuli cause the hypothalamus to secrete thyrotropin-releasing hormone (TRH), which causes release of thyroid-stimulating hormone (TSH) from the anterior pituitary. TSH reaches the thyroid gland and causes release of thyroid hormone (TH) from a stored precursor.
- Thyroid hormone increases metabolism with a subsequent increase in body temperature.

17.8c Calcitonin: Its Regulation and Effects

- Parafollicular cells of the thyroid gland release calcitonin, which functions to decrease blood calcium level.

17.9 Adrenal Glands

17.9a Anatomy of Adrenal Glands

- The adrenal glands have both an inner medulla (which releases epinephrine and norepinephrine) and an outer cortex.
- The adrenal cortex has three zones that produce mineralocorticoids, glucocorticoids (primarily cortisol), and gonadocorticoids.

17.9b Cortisol: Its Regulation and Effects

- Upon receiving certain stimulation, the hypothalamus secretes corticotropin-releasing hormone (CRH), which causes release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH brings about release of cortisol by the adrenal cortex.
- The net effect of cortisol is an increase in all nutrient molecules in the blood.

17.10 The Pancreas

17.10a Anatomy of the Pancreas

- The pancreas releases both insulin and glucagon, which regulate nutrient blood levels.

17.10b Pancreatic Hormones

- The release of insulin into the blood from beta cells results in a decrease in all nutrients in the blood (including glucose) and an increase in the storage of these molecules within body tissues.
- The release of glucagon from alpha cells results in an increase in glucose, glycerol, and fatty acids in the blood; it has no effect on structural and functional protein components of the body.

17.11 Other Endocrine Glands

17.11a Pineal Gland

- The pineal gland is a cone-shaped structure within the diencephalon that produces melatonin, which regulates circadian rhythms.

17.11b Parathyroid Glands

- The parathyroid glands produce parathyroid hormone, which increases blood calcium.

17.11c Structures with an Endocrine Function

- Structures with an endocrine function include the thymus, heart, kidneys, liver, stomach and small intestine, skin, and adipose connective tissue.

17.12 Aging and the Endocrine System

- The secretory activity of endocrine glands usually decreases with age, especially in regard to the production and activities of GH, testosterone, and estrogen.
1. Which of the following is not a general process controlled by the endocrine system?
   a. development, growth, and metabolism
   b. control of reproductive activities
   c. maintenance of homeostasis of blood composition
   d. programmed cell death/destruction of aged cells

2. This hormone’s primary function is to regulate metabolism.
   a. calcitonin
   b. thyroid hormone (TH)
   c. growth hormone (GH)
   d. glucagon

3. Which of the following are components of intracellular enzyme cascades initiated by water-soluble hormones?
   a. G proteins
   b. cAMP molecules
   c. protein kinase enzymes
   d. All of these are correct.

4. A hormone released from the anterior pituitary is
   a. glucagon.
   b. growth hormone (GH).
   c. melatonin.
   d. epinephrine.

5. The actions of lipid-soluble hormones include
   a. activation or inhibition of enzymatic pathways.
   b. binding with a hormone-responsive element.
   c. muscle contraction or relaxation.
   d. stimulation of cellular secretions.

6. Insulin increases _____________ within hepatocytes to decrease blood glucose.
   a. glycogenolysis
   b. gluconeogenesis
   c. glycogenesis
   d. lipogenesis

7. Glucagon has a(n) _____________ effect to insulin on target cells.
   a. antagonistic
   b. synergistic
   c. permissive
   d. both permissive and synergistic

8. Glucocorticoids (e.g., cortisol) are produced in the adrenal cortex to help regulate
   a. Na⁺ and K⁺ levels in body fluids.
   b. blood pressure.
   c. calcium levels in the blood.
   d. glucose levels in the blood.

9. Thyroid-stimulating hormone stimulates which of the following?
   a. anterior pituitary to release its hormones.
   b. hypothalamus to release its hormones.
   c. thyroid gland to release its hormones.
   d. All of these are correct.

10. All of the following hormones are released from the hypothalamus to control the anterior pituitary gland except
    a. growth-releasing hormone (GRH).
    b. antidiuretic hormone (ADH).
    c. prolactin-releasing hormone (PRH).
    d. corticotropin-releasing hormone (CRH).

11. Describe similarities and differences between the endocrine system and the nervous system in their method of operation and effects.

12. List the four primary functions of the endocrine system.

13. Explain the three mechanisms used to stimulate hormone release from a target cell to initiate an endocrine reflex.

14. Identify the three chemical classes of hormones, and give an example of each. Most hormones belong to which class?

15. Describe how local hormones differ from circulating hormones.

16. Explain the function of carrier proteins in transporting lipid-soluble hormones in the blood and how these hormones interact with cells.

17. Describe how water-soluble hormones interact with cells.

18. Explain how the hypothalamus oversees and controls endocrine system function of the posterior pituitary.

19. Explain how the hypothalamus oversees and controls endocrine system function of the anterior pituitary.

20. Discuss the homeostatic system involving insulin.

Can You Apply What You’ve Learned?

1. George is a 43-year-old construction worker who has developed a swelling in his neck that is painful and continues to grow. He visited the doctor and confided to his clinician that he has also lost weight and has become very hyperactive. What gland does the clinician suspect is functioning abnormally?
   a. pituitary
   b. thyroid
   c. adrenal
   d. pancreas

2. What is the best diagnostic test to determine if the gland described in question 1 is not functioning normally?
   a. measuring the amount of radioactive iodine taken up by the thyroid
   b. doing body temperature scans every morning and evening at the same time
   c. watching weight fluctuation over a 1-month time period
   d. taking a blood sample to measure the amount of thyroid hormone (T₃ and T₄) present
3. Jelena is late for work and is rushing to get out the door. Her commute to work is slow due to rush-hour traffic, and she begins to become anxious and upset. As she is attempting to park, someone hits her car and she becomes angry. What specific hormones are released during this “emergency”?
   a. insulin/glucagon
   b. epinephrine/cortisol
   c. insulin/thyroid hormone
   d. melatonin/epinephrine

4. Blood samples from a young woman named Michelle indicate an elevated blood glucose level. This homeostatic imbalance is most likely caused by an insufficient amount of, or decreased sensitivity to, which hormone?
   a. growth hormone
   b. glucagon
   c. insulin
   d. cortisol

5. Stephen is taking a new weight-loss supplement that is known to not only decrease the amount of adipose connective tissue (as advertised) but also decrease glycogen stores in the liver and cause breakdown of muscle protein (protein catabolism). What substance in this weight-loss supplement is responsible for these changes?
   a. growth hormone
   b. glucagon
   c. insulin
   d. cortisol

Can You Synthesize What You’ve Learned?

1. After seeing a physician for a sudden weight loss, 19-year-old Harold is diagnosed with type 1 diabetes, which is a condition in which the beta cells of the pancreas are producing insufficient amounts of insulin or target cells are not responding to insulin. Explain to Harold why results from his blood lab report indicate that he has an elevated blood glucose level.

2. Susan is a 35-year-old mother of two who works as an admissions officer at the university. She was recently diagnosed with a pituitary tumor. Discuss the challenges she may experience, and list the hormones released by both the posterior pituitary and anterior pituitary.

3. Henry is a well-informed patient who is interested in understanding how thyroid hormone is controlled by thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH). Briefly explain to him the hypothalamic-pituitary-thyroid axis.

The following study aids may be accessed through Connect.

**Clinical Case Study:** A Giant of a Man Is Defeated by a Young and Observant Boy

**Interactive Questions:** This chapter’s content is served up in a number of multimedia question formats for student study

**SmartBook:** Topics and terminology include introduction to the endocrine system; endocrine glands; hormones; nutrient metabolism; the hypothalamus and the pituitary gland; representative hormones regulated by the hypothalamus; pancreatic hormones; aging and the endocrine system

**Anatomy & Physiology Revealed:** Topics include pancreas; hypothalamus and pituitary glands; hormonal communication; intracellular receptor model; receptors and G proteins; thyroid; suprarenal (adrenal) glands

**Animations:** Topics include mechanism of lipid-soluble messengers; mechanism of thyroxine action
Major Regulatory Hormones of the Human Body

These tables provide a succinct reference for the major regulatory hormones of the human body. They are organized by the general variable or process regulated by each hormone or group of hormones. Each table includes the name of the hormone(s), its chemical structure (steroid, biogenic amine, or protein), the source of the hormone(s), primary stimulus for its release, its primary target organs and the cellular responses that it initiates, the net result or summary of its effect, an example of a related disease or condition, and the section reference(s) in the text where the hormone is discussed in detail.

### Table R.1
Regulating Blood Glucose with Pancreatic Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Insulin</th>
<th>Glucagon</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical structure</strong></td>
<td>Protein (51 amino acids); water-soluble</td>
<td>Protein (29 amino acids); water-soluble</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Pancreas (beta cells)</td>
<td>Pancreas (alpha cells)</td>
</tr>
<tr>
<td><strong>Primary stimulus for release</strong></td>
<td>Increased blood glucose levels</td>
<td>Decreased blood glucose levels</td>
</tr>
<tr>
<td><strong>Primary target organs and cellular changes</strong></td>
<td>Liver: Increased glycogen storage caused by increased glycogenesis (glycogen synthesized from glucose molecules, which are obtained from the blood) Adipose connective tissue: Increased triglyceride storage (triglycerides synthesized from glycerol and fatty acid, caused by increased lipogenesis; glycerol and fatty acids are obtained from the blood) Skeletal muscle cells: Increased glycogen storage caused by increased glycogenesis (glycogen synthesized from glucose molecules, which are obtained from the blood); increased uptake of K⁺ All target cells: Increased protein synthesis that results from increased uptake of amino acids from the blood; increased glucose uptake</td>
<td>Liver: Decreased glycogen storage results from increased glycogenolysis (glycogen digested to glucose molecules); increased gluconeogenesis (glucose synthesis from noncarbohydrate sources—e.g., amino acids, lactate); glucose molecules are released into the blood Adipose connective tissue: Decreased triglyceride storage (triglycerides digested into glycerol and fatty acids, caused by increased lipolysis; glycerol and fatty acids are released into the blood) Skeletal muscle cells: Decreased glycogen storage (glycogen digested to glucose molecules, which are oxidized in cellular respiration to produce ATP within the muscle cells)</td>
</tr>
<tr>
<td><strong>Net result</strong></td>
<td>Increased synthesis/storage of fuel molecules (glycogen, triglycerides, and protein) Decreased blood levels of fuel molecules (glycose, glycerol, fatty acids, and amino acids)</td>
<td>Increased blood levels of glucose, glycerol, and fatty acids; decreased storage of glycogen and triglyceride molecules</td>
</tr>
<tr>
<td><strong>Related diseases or conditions</strong></td>
<td>Diabetes mellitus</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td><strong>Text reference</strong></td>
<td>Section 17.10b</td>
<td>Section 17.10b</td>
</tr>
</tbody>
</table>
### Table R.2  Regulating Blood Calcium with Parathyroid Hormone and Calcitonin

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Parathyroid Hormone (PTH)</th>
<th>Calcitonin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical structure</strong></td>
<td>Protein (84 amino acids); water-soluble</td>
<td>Protein (32 amino acids); water-soluble</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Parathyroid gland</td>
<td>Thyroid gland (parafollicular cells)</td>
</tr>
<tr>
<td><strong>Primary stimulus for release</strong></td>
<td>Decreased blood calcium levels</td>
<td>Increased blood calcium levels</td>
</tr>
<tr>
<td><strong>Primary target organs and cellular changes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone: Increased osteoclast activity (Ca(^{2+}) released into the blood)</td>
<td>Bone: Primarily decreased activity of osteoclasts, especially in children (decreased release of Ca(^{2+}) into the blood)</td>
<td></td>
</tr>
<tr>
<td>Kidney: Decreased loss of Ca(^{2+}) and increased loss of phosphate (PO(_4)(^{3-})) in urine</td>
<td>Kidney: Increased loss of Ca(^{2+}) in urine</td>
<td></td>
</tr>
<tr>
<td>Increased number of enzymes that convert calcidiol (inactive hormone in blood formed from vitamin D) to calcitriol, a hormone that functions synergistically with PTH and increases absorption of Ca(^{2+}) from small intestine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Net result</strong></td>
<td>Increased blood calcium levels</td>
<td>Decreased blood calcium levels</td>
</tr>
<tr>
<td><strong>Related diseases or conditions</strong></td>
<td>Hyperparathyroidism; hypoparathyroidism</td>
<td>Hyperthyroidism; hypothyroidism</td>
</tr>
<tr>
<td><strong>Text reference</strong></td>
<td>Section 7.6b</td>
<td>Section 7.6c</td>
</tr>
</tbody>
</table>

### Table R.3  Regulating Growth with Growth Hormone and Insulin-like Growth Factor

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Growth Hormone (GH)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical structure</strong></td>
<td>Protein (191 amino acids); water-soluble</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Anterior pituitary</td>
</tr>
<tr>
<td><strong>Primary stimulus for release</strong></td>
<td>Growth hormone–releasing hormone (GHRH) is released from the hypothalamus and is transported in the hypophyseal portal veins to the anterior pituitary to stimulate the anterior pituitary to release growth hormone (GH). GH stimulates the release of insulin-like growth factors (IGFs) from the liver.</td>
</tr>
<tr>
<td><strong>Primary target organs and cellular changes(^1)</strong></td>
<td>Together, growth hormone and IGFs interact with the following:</td>
</tr>
<tr>
<td></td>
<td>• All cells, especially cartilage, bone, and muscle: Increased protein synthesis, cellular division, and cell differentiation</td>
</tr>
<tr>
<td></td>
<td>• Liver: Decreased glycogen storage results from increased glycogenolysis (glycogen digested to glucose molecules); increased gluconeogenesis (glucose synthesis from noncarbohydrate molecules [e.g., amino acids, lactate]); glucose molecules are released into the blood</td>
</tr>
<tr>
<td></td>
<td>• Adipose connective tissue: Decreased triglyceride storage results from increased lipolysis (triglycerides digested into glycerol and fatty acids), glycerol and fatty acid molecules are released into the blood</td>
</tr>
<tr>
<td><strong>Net result</strong></td>
<td>Cellular growth and protein synthesis; release of glucose, glycerol, and fatty acids into the blood provides necessary fuel molecules needed for growth</td>
</tr>
<tr>
<td><strong>Related diseases or conditions</strong></td>
<td>Pituitary dwarfism (in children); gigantism (in children); acromegaly (in adults)</td>
</tr>
<tr>
<td><strong>Text reference</strong></td>
<td>Section 17.7d</td>
</tr>
</tbody>
</table>

---

\(^1\) Other effects of growth hormone include increased hunger; skin development, including nails and hair; development of skeletal, muscular, and nervous system; increased metabolic rate in mother and fetus during pregnancy; enhanced development of mammary glands during pregnancy; insulin antagonist; increased reabsorption of sodium ions (Na\(^{+}\)), potassium ions (K\(^{+}\)), and chlorine ions (Cl\(^{-}\)) by the kidneys; increased absorption of Ca\(^{2+}\) by the small intestine; and increased uptake of sulfur for synthesis of chondroitin sulfate by chondrocytes.
Table R.4  
Regulating Metabolism with Thyroid Hormone

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Thyroid Hormone (TH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical structure</td>
<td>Biogenic amine (monoamine); water-insoluble (lipid-soluble)</td>
</tr>
<tr>
<td>Source</td>
<td>Thyroid gland</td>
</tr>
<tr>
<td>Primary stimulus for release</td>
<td>Thyrotropin-releasing hormone (TRH) is released from the hypothalamus and is transported in the hypophyseal portal veins to the anterior pituitary to stimulate the anterior pituitary to release thyroid-stimulating hormone (TSH) into the general circulation. TSH binds to cellular receptors of the thyroid gland, stimulating the release of thyroid hormone (TH)—triiodothyronine (T3) and tetraiodothyronine (T4).</td>
</tr>
</tbody>
</table>
| Primary target organs and cellular changes 1 | All cells, especially neurons: Increased metabolic rate; increased amino acid uptake and protein synthesis; increased glucose uptake  
Liver: Decreased glycogen storage through increased glycogenolysis (glycogen digested to glucose molecules); increased gluconeogenesis (glucose synthesis from noncarbohydrate sources—e.g., amino acids, lactate); glucose molecules are released into the blood  
Adipose connective tissue: Decreased triglyceride storage results from increased lipolysis (triglycerides digested into glycerol and fatty acids); glycerol and fatty acid molecules are released into the blood  
Heart: Increased heart rate and force of contraction, which increases cardiac output |
| Net result | Increased metabolism (results in increased production of ATP, increased body temperature [calorigenic effect], increased blood PCO2, which stimulates respiratory center to increase resting breathing rate); increased oxygen consumption; increased release of glucose, glycerol, and fatty acids into the blood (provides necessary fuel molecules needed for increased metabolic rate) |
| Related diseases or conditions | Hyperthyroidism; hypothyroidism |
| Text reference | Section 17.8b |

1. Other effects of thyroid hormone include increased appetite; increased alertness; bone growth and remodeling; skin development, including nails and hair; skeletal, muscular, and nervous system development; increased metabolic rate in mother and fetus during pregnancy; insulin antagonist; and release of GH from the anterior pituitary.

Table R.5  
Regulating the Stress Response with Catecholamines and Glucocorticoids

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Catecholamines: Epinephrine and Norepinephrine</th>
<th>Glucocorticoids: Cortisol and Corticosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical structure</td>
<td>Biogenic amine (monoamine); water-soluble</td>
<td>Steroid hormones; water-insoluble (lipid-soluble)</td>
</tr>
<tr>
<td>Source</td>
<td>Adrenal medulla</td>
<td>Adrenal cortex (zona fasciculata)</td>
</tr>
<tr>
<td>Primary stimulus for release</td>
<td>Sympathetic division stimulation causes release of epinephrine (80%) and norepinephrine (20%)</td>
<td>Corticotropin-releasing hormone (CRH) is released from the hypothalamus and is transported in the hypophyseal portal veins to the anterior pituitary to release adrenocorticotropic hormone (ACTH) into the general circulation. ACTH binds to cellular receptors of the adrenal cortex, stimulating the release of glucocorticoids (e.g., cortisol and corticosterone).</td>
</tr>
</tbody>
</table>
| Primary target organs and cellular changes 1 | Increases all effects of the sympathetic division of the autonomic nervous system (see table 15.6) | Adipose connective tissue: Decreased triglyceride storage caused by increased lipolysis (triglycerides digested into glycerol and fatty acids); glycerol and fatty acid molecules are released into the blood  
All cells, except liver cells: Increased protein catabolism (proteins are digested into amino acids); amino acids released into the blood  
Liver cells: Increased gluconeogenesis (glucose synthesis from noncarbohydrate sources—e.g., amino acids, lactate); increased breakdown of glycogen into glucose caused by increased glycogenolysis and glucose molecules are released into the blood  
Immune system: Anti-inflammatory effect |
| Net result | Increased level of response and increased duration of response (about 30 minutes) that is initiated by the sympathetic division of the autonomic nervous system | Increased available fuel molecules in blood, especially glucose (decreased storage of fuel molecules); anti-inflammatory |
| Related diseases or conditions | Chronic stress | Cushing syndrome, Addison disease |
| Text reference | Section 15.4 | Section 17.9b |

1. Other effects of glucocorticoids include impaired connective tissue repair (decreased fibroblasts and decreased protein synthesis of connective tissue matrix formation); atrophy of muscle, atrophy of skin, decrease in bone tissue; decreased lymphatic tissue (thymus, lymph nodes, spleen), decreased white blood cells (eosinophils, lymphocytes, and macrophages); decreased production of antibodies; decreased response by cell-mediated immunity and blocked production of fever; increased Na+ and water retention; permissive effects for epinephrine and norepinephrine (catecholamines) that enhance vasoconstriction and increase cardiac output; increased gastric secretion; and inhibited release of lungicinizing hormone, estrogen, and possibly testosterone. Cortisol-like drugs are administered as treatment for inflammatory diseases (e.g., rheumatoid arthritis, eczema, asthma). High doses can result in side effects that include edema, muscle weakness, osteoporosis, thin skin, suppressed immune response, and infertility.
### Table R.6
#### Regulating Erythrocyte Concentration in the Blood

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Erythropoietin (EPO)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical structure</strong></td>
<td>Glycoprotein; water-soluble</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Kidney (primarily) and liver</td>
</tr>
<tr>
<td><strong>Primary stimulus for release</strong></td>
<td>Decreased blood O2; testosterone</td>
</tr>
<tr>
<td><strong>Primary target organs and cellular changes</strong></td>
<td>Red bone marrow: Increases rate of production of erythrocytes, cells that transport oxygen</td>
</tr>
<tr>
<td><strong>Net result</strong></td>
<td>Increased O2-carrying capacity of blood</td>
</tr>
<tr>
<td><strong>Related diseases or conditions</strong></td>
<td>Anemia; polycythemia</td>
</tr>
<tr>
<td><strong>Text reference</strong></td>
<td>Section 18.3b</td>
</tr>
</tbody>
</table>

### Table R.7
#### Regulating Fluid Balance, Blood Volume, and Blood Pressure

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Angiotensin II (Ang II)</th>
<th>Antidiuretic Hormone (ADH)</th>
<th>Aldosterone (ALDO)</th>
<th>Atrial Natriuretic Peptide (ANP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical structure</strong></td>
<td>Protein (8 amino acids); water-soluble</td>
<td>Protein (9 amino acids); water-soluble</td>
<td>Steroid hormone; water-insoluble (lipid-soluble)</td>
<td>Protein (28 amino acids); water-soluble</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Liver (produces and releases angiotensinogen into the blood); activated in the blood in the presence of renin (released from kidney when stimulated) and angiotensin-converting enzymes (ACE) (endothelial layer of blood vessels, especially those in the lungs)</td>
<td>Produced by the hypothalamus and stored in the posterior pituitary (release is controlled by hypothalamus)</td>
<td>Adrenal cortex (zona glomerulosa)</td>
<td>Atrial chambers of the heart</td>
</tr>
</tbody>
</table>
| **Primary stimulus for release** | Release of renin from juxtaglomerular apparatus of kidney stimulated by the following:  
- Decreased blood pressure  
- Sympathetic division stimulation | Hypothalamus sends a nerve signal along the hypothalamo-hypophyseal tract to the posterior pituitary in response to the following:  
- Angiotensin II  
- Increased blood osmolarity  
- Decreased nerve signals initiated by baroreceptors in atria, aorta, and carotid arteries in response to decrease in stretch | Angiotensin II  
Increased blood K+  
Decreased blood Na+ | Increased stretch of atrial wall (reflects increase in blood volume and blood pressure) |
| **Primary target organs and cellular changes** | Blood vessels: Potent vasoconstrictor, increases vascular resistance  
Kidney: Decreases urine output by decreasing glomerular filtration rate (GFR) to maintain blood volume  
Thirst center within the hypothalamus: Stimulation  
Hypothalamus: Releases ADH from posterior pituitary  
Adrenal cortex: Releases aldosterone | Kidney: Decreases H2O excreted in urine  
Thirst center within the hypothalamus: Stimulation  
Blood vessels: Vasoconstrictor in high doses (why it is also called vasopressin) | Kidney: Decreases Na+ and H2O excreted in urine; increases K+ excretion (except under conditions of low pH when H+ is excreted instead) | Kidney: Increases GFR; increases Na+ and H2O excreted in urine; inhibits release of renin  
Blood vessels: Vasodilation, decreases vascular resistance  
Hypothalamus: Inhibits release of ADH from posterior pituitary  
Adrenal cortex: Inhibits release of aldosterone |
| **Net result**   | Increased vascular resistance, increased blood pressure; maintaining blood volume and blood pressure | Increased retention of water; maintaining blood volume and blood pressure | Maintenance of blood Na+ and blood K+ levels; maintaining blood volume and pressure by decreasing urine output | Increased urine output; decreased resistance, decreased blood volume and blood pressure |
| **Related diseases or conditions** | Blood pressure homeostasis | Diabetes insipidus | Hyperaldosteronism | Blood pressure homeostasis |
| **Text reference** | Sections 20.6b, 24.5e, and 25.4a | Sections 24.6d and 25.4b | Sections 24.6d and 25.4c | Sections 24.5c, 24.6d, and 25.4d |

1. Other names include atrial natriuretic factor (ANF), atrial natriuretic hormone (ANH), and atriopeptin.
<table>
<thead>
<tr>
<th>Hormone</th>
<th>Gastrin</th>
<th>Secretin</th>
<th>Cholecystokinin (CCK)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical structure</strong></td>
<td>Three forms of proteins (34, 17, 14 amino acids); water-soluble</td>
<td>Protein (27 amino acids); water-soluble</td>
<td>Protein (varying numbers of amino acids); water-soluble</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Stomach (enteroendocrine G cells)</td>
<td>Duodenal enteroendocrine cells</td>
<td>Duodenal enteroendocrine cells</td>
</tr>
<tr>
<td><strong>Primary stimulus for release</strong></td>
<td>Thought, smell, sight of food; parasympathetic division (vagal) stimulation; presence of partially digested protein in stomach; stretch of stomach wall, caffeine, increase in stomach pH</td>
<td>Acidic chyme entering small intestine (specifically, the duodenum)</td>
<td>Chyme high in lipids and protein entering small intestine (duodenum)</td>
</tr>
<tr>
<td><strong>Primary target organs and cellular changes</strong></td>
<td>Stomach: Parietal cells release HCl and intrinsic factor, chief cells release pepsinogen; increased motility Gallbladder: Contraction causing release of bile into small intestine Pancreas: Secretion of pancreatic juice Small intestine: Contraction of wall Large intestine: Mass movements Pyloric sphincter: Relaxes Ileocecal valve: Relaxes</td>
<td>Stomach: Decreased secretions and motility Liver and pancreas: Increased secretion of bicarbonate ion (weak base) in bile and pancreatic juice</td>
<td>Stomach: Decreased secretions and motility Pancreas: Secretion of pancreatic juice containing pancreatic digestive enzymes Liver: Secretion of bile Gallbladder: Contraction causing release of bile into small intestine Hepatopancreatic sphincter: Relaxes</td>
</tr>
<tr>
<td><strong>Net result</strong></td>
<td>Increased secretions and motility of stomach; preparation of small intestine for arrival of chyme by relaxing pyloric sphincter and stimulating accessory gland secretions; movement of contents through the large intestine</td>
<td>Inhibited stomach activity; buffering of acidic chyme entering duodenum</td>
<td>Most important in increasing ability of small intestine to digest triglycerides by decreasing stomach motility, and increasing secretions from accessory glands (liver, gallbladder, and pancreas) into small intestine</td>
</tr>
<tr>
<td><strong>Related diseases or conditions</strong></td>
<td>Zollinger-Ellison syndrome (a rare condition in which tumors called gastrinomas form in the pancreas or duodenum; resulting in overproduction of gastrin and an increase in stomach acid production, which can lead to peptic ulcers)</td>
<td>Low levels are associated with Helicobacter pylori infection</td>
<td>Altered levels of CCK are rarely associated with disease</td>
</tr>
<tr>
<td><strong>Text reference</strong></td>
<td>Section 26.2d</td>
<td>Sections 26.2d and 26.3c</td>
<td>Sections 26.2d and 26.3c</td>
</tr>
</tbody>
</table>
1. In both males and females, dehydroepiandrosterone (DHEA) is produced from adrenal cortex and is converted to testosterone (this is the only source of testosterone in females).

### Table R.9

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Estrogen</th>
<th>Progesterone</th>
<th>Prolactin</th>
<th>Oxytocin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical structure</strong></td>
<td>Steroid hormone; water-insoluble (lipid-soluble)</td>
<td>Steroid hormone; water-insoluble (lipid-soluble)</td>
<td>Protein (198 amino acids); water-soluble</td>
<td>Protein (9 amino acids); water-soluble</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Ovary (developing follicle)</td>
<td>Ovary (corpus luteum)</td>
<td>Anterior pituitary</td>
<td>Posterior pituitary</td>
</tr>
<tr>
<td><strong>Primary stimulus for release</strong></td>
<td>Gonadotropin-releasing hormone (GnRH) is released from the hypothalamus and is transported in the hypophyseal portal veins to stimulate the release of follicle-stimulating hormone (FSH) from the anterior pituitary into general circulation; FSH stimulates the development of follicles (in the ovary) and developing follicles produce estrogen</td>
<td>Gonadotropin-releasing hormone (GnRH) is released from the hypothalamus and is transported in the hypophyseal portal veins to stimulate the release of luteinizing hormone (LH) from the anterior pituitary into general circulation; LH triggers ovulation and the production of the corpus luteum; the corpus luteum produces progesterone</td>
<td>Prolactin-releasing hormone (PRH) is released from the hypothalamus and is transported in the hypophyseal portal veins to stimulate the release of prolactin (PRL) from the anterior pituitary into general circulation; Prolactin release is normally inhibited by the release of prolactin-inhibiting hormone [PIH] from the hypothalamus</td>
<td>Hypothalamus sends nerve signals along the hypothalamic-hypophysyal tract to the posterior pituitary in response to sensory nerve signals from contractions of uterus or suckling of breast, to stimulate release of oxytocin</td>
</tr>
<tr>
<td><strong>Primary target organs and cellular changes</strong></td>
<td>Uterus: Builds endometrial lining</td>
<td>Uterus: Builds and maintains endometrial lining</td>
<td>Breast: Development of mammary ducts and glands</td>
<td>Uterus: Stimulates uterine contraction during delivery (and after delivery to expel the placenta, and continues to cause contractions to firm up the uterus)</td>
</tr>
<tr>
<td></td>
<td>Hypothalamus: Moderate levels inhibit release of GnRH and FSH; high levels stimulate release of GnRH and FSH</td>
<td>Mammary glands: Prepares for secretion of milk</td>
<td>Breast: Stimulates uterine contraction during delivery (and after delivery to expel the placenta, and continues to cause contractions to firm up the uterus)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breast: Stimulates development of mammary gland</td>
<td>Kidney: Decreases retention of Na(^+) and water</td>
<td>Brain: Increases ejection of milk from mammary glands</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kidney: Retention of Na(^+) and water</td>
<td>All cells: Increases protein anabolism</td>
<td>Brain: Increases ejection of milk from mammary glands</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All cells: Increases protein anabolism</td>
<td>Regulates second half of uterine cycle</td>
<td>Regulates contraction of smooth muscle of uterus and breast; emotional bonding</td>
<td></td>
</tr>
<tr>
<td><strong>Net result</strong></td>
<td>Assists in ovarian follicle (and oocyte) development, regulation of female cycle; anabolic hormone; development of female characteristics; retention of Na(^+) and water</td>
<td>Prepares mammary glands for milk production; eliminates Na(^+) and water</td>
<td>Stimulates development of mammary ducts and glands within the breast for milk production</td>
<td></td>
</tr>
<tr>
<td><strong>Related diseases or conditions</strong></td>
<td>Infertility</td>
<td>Infertility</td>
<td>Prolactinomas</td>
<td>Severe cases of autism may be associated with low levels of oxytocin</td>
</tr>
<tr>
<td><strong>Text reference</strong></td>
<td>Sections 28.3 and 29.8</td>
<td>Sections 28.3 and 29.8</td>
<td>Sections 28.3 and 29.8</td>
<td>Sections 28.3, 29.6, and 29.8</td>
</tr>
</tbody>
</table>

### Table R.10

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical structure</strong></td>
<td>Steroid hormone; water-insoluble (lipid-soluble)</td>
</tr>
<tr>
<td><strong>Source</strong></td>
<td>Testes (interstitial cells)</td>
</tr>
<tr>
<td><strong>Primary stimulus for release</strong></td>
<td>Gonadotropin-releasing hormone (GnRH) is released from hypothalamus into the hypophyseal portal veins to stimulate the anterior pituitary to release both luteinizing hormone (LH) and follicle-stimulating hormone (FSH); LH stimulates testes (interstitial cells) to release testosterone; FSH stimulates release of androgen-binding protein (ABP) and release of inhibit from sustentacular cells</td>
</tr>
<tr>
<td><strong>Primary target organs and cellular changes</strong></td>
<td>Testes: With ABP, testosterone stimulates sperm production</td>
</tr>
<tr>
<td></td>
<td>Hypothalamus: Inhibits GnRH release</td>
</tr>
<tr>
<td></td>
<td>All cells with testosterone receptors: Increases protein anabolism</td>
</tr>
<tr>
<td></td>
<td>Bone: Stimulates osteoblasts</td>
</tr>
<tr>
<td><strong>Net result</strong></td>
<td>Assists in sperm production, regulation of male cycle; anabolic hormone; increases erythrocytes; development of male characteristics</td>
</tr>
<tr>
<td><strong>Related diseases or conditions</strong></td>
<td>Androgen insensitivity, infertility</td>
</tr>
<tr>
<td><strong>Text reference</strong></td>
<td>Sections 18.3b and 28.4b</td>
</tr>
</tbody>
</table>
Within our bodies is a connective tissue so valuable that donating a portion of it to someone else can save that person's life. This tissue is regenerated continuously and is responsible for transporting the gases, nutrients, and hormones our bodies need for proper functioning. Losing too much of this tissue can be fatal and yet blood is something we frequently take for granted.

This valuable connective tissue is blood. Blood is considered a fluid connective tissue because it contains formed elements (red blood cells, white blood cells, platelets) and dissolved proteins in a liquid ground substance called plasma. Four to six liters of this warm, alkaline, viscous fluid is continuously pumped through our blood vessels. It may help to think of the circulation of blood as a “fluid conveyor belt” where cells, ions, and molecules are both continuously added to it and dropped off from it. As a result, the composition of blood is ever changing as it is pumped by our heart and makes its continuous journey through our vessels. Because of its intimate contact with the cells of the body, various blood tests can be performed, providing a physician with important information for an accurate diagnosis in assessing the state of our health.

In this chapter, we describe the function of blood and the various blood components. Then we examine how these components are formed and function, and discuss hemostasis. Finally, we discuss the development and aging of blood.
18.1 Functions and General Composition of Blood

Blood is the specialized fluid that is transported through the cardiovascular system, which is composed of the heart and blood vessels. Blood vessels form a circuit away from the heart and back to the heart that includes the arteries, capillaries, and veins. Arteries transport blood away from the heart, whereas veins transport blood toward the heart. Capillaries are permeable, microscopic vessels between arteries and veins. Capillaries serve as the sites of exchange between the blood and body tissues; it is at our capillaries that oxygen and nutrients exit the blood, and carbon dioxide and cellular wastes enter the blood.

Blood is composed of formed elements (erythrocytes, leukocytes, and platelets) and plasma. Erythrocytes, also known as red blood cells, function to transport respiratory gases in the blood. Leukocytes, also known as white blood cells, contribute to defending the body against pathogens, and platelets help clot the blood and prevent blood loss from damaged vessels. Plasma is the fluid portion of blood containing plasma proteins and dissolved solutes.

18.1a Functions of Blood

LEARNING OBJECTIVE

1. Describe the general functions of blood.

Blood carries out a variety of important functions as it circulates throughout the body; these functions can be grouped as transportation, regulation, and protection.

Transportation

Blood transports formed elements and dissolved molecules and ions throughout the body. Consider that as blood is transported through the blood vessels it transports oxygen from and carbon dioxide to the lungs for gas exchange (see section 23.1a), nutrients absorbed from the gastrointestinal (GI) tract (see section 26.1a), hormones released by endocrine glands (see section 17.1a), and heat and waste products from the systemic cells. Even when you take a medication, it is the blood that delivers it to the cells of your body. Thus, the blood serves as the “delivery system” for the body.

Regulation

Blood participates in the regulation of body temperature, body pH, and fluid balance:

- **Body temperature.** Blood helps regulate body temperature. This is possible because blood absorbs heat from body cells, especially skeletal muscle, as it passes through blood vessels of body tissues. Heat is then released from blood at the body surface as blood is transported through blood vessels of the skin (see section 1.6b).
- **Body pH.** Blood, because it absorbs acid and base from body cells, helps maintain the pH of cells. Blood contains chemical buffers (e.g., proteins, bicarbonate) that bind and release hydrogen ions (H⁺) to maintain blood pH until the excess is eliminated from the body (see section 25.6a).
- **Fluid balance.** Water is added to the blood from the GI tract and lost in numerous ways (including in urine, sweat, and respired air). In addition, there is a constant exchange of fluid between the blood plasma in the capillaries and the interstitial fluid surrounding the cells of the body’s tissues. Blood contains proteins and ions that exert osmotic pressure to pull fluid back into the capillaries to help maintain normal fluid balance (see section 20.3b).

Protection

Blood contains leukocytes, plasma proteins, and various molecules that help protect the body against potentially harmful substances. These substances are part of the immune system, which is described in detail in chapter 22. Components of blood, including platelets and plasma proteins, also protect the body against blood loss, as described in section 18.4.

18.1b Physical Characteristics of Blood

LEARNING OBJECTIVE

2. Name six characteristics that describe blood, and explain the significance of each to health and homeostasis.

Blood is a type of connective tissue (see section 5.2d) that can be described based on its physical characteristics, including color, volume, viscosity, plasma concentration, temperature, and pH:

- **Color.** The color of blood depends upon whether it is oxygen-rich or oxygen-poor. Oxygen-rich blood is bright red or almost scarlet. Contrary to popular belief, oxygen-poor blood is not blue; rather, oxygen-poor blood is dark red. The bluish appearance of our veins can be attributed to both (1) the fact that we can see the blood moving through the superficial veins in the skin and (2) how light is reflected back to the eye from different colors. Lower-energy light wavelengths, like red, are absorbed by the skin and not reflected back to the eye, but higher-energy wavelengths, like blue, are reflected back to the eye, so the eyes can perceive only the blue coloration from the veins.
WHAT DO YOU THINK?

If a woman has 5 L of blood and she donates 1 pint (about 0.5 L), what approximate percentage is she donating: 1%, 5%, 10%, or 15%? Why do you think individuals below a certain weight (i.e., less than 110 pounds) are not allowed to give blood?

WHAT DID YOU LEARN?

3. Will blood be able to properly carry out its functions if blood pH is significantly altered? Why or why not?

18.1c Components of Blood

LEARNING OBJECTIVES

3. List the three components of a centrifuged blood sample.
4. Define hematocrit, and explain how the medical definition differs from the clinical usage.
5. Name the three formed elements of the blood, and compare their relative abundance.

Centrifuged Blood

Whole blood, which is both plasma and formed elements, can be separated into its liquid and cellular components by using a centrifuge, a device that spins the sample of blood in a tube so that heavier components collect at the bottom. Figure 18.1 shows the resulting three components separated in the test tube. From bottom to top, these components are as follows:

- Erythrocytes form the lower layer of the centrifuged blood. They typically make up about 44% of a blood sample.
- A thin buffy coat makes up the middle layer. This slightly gray-white layer is composed of both leukocytes and platelets. The buffy coat forms less than 1% of a blood sample.
- Plasma is a pale yellowish liquid that rises to the top in the test tube; it generally makes up about 55% of blood.

CONCEPT CONNECTION

Recall from section 2.5b that an acid increases the concentration of H⁺ by releasing it into the solution. Examples include hydrochloric acid (HCl) and carbonic acid (H₂CO₃). In contrast, a base decreases the concentration of H⁺ in the solution. Examples include bicarbonate ions (HCO₃⁻) and hydroxide ions (OH⁻). The pH is a measure of the relative amounts of H⁺ in solution. A buffer helps prevent pH changes by binding or releasing excess H⁺ to maintain the normal H⁺ concentration in a solution.

The percentage of the volume of all formed elements (erythrocytes, leukocytes, and platelets) in the blood is called the hematocrit (he´m-ô-krit, hem´-ôt-krif; hemato = blood, krino = to separate). This medical dictionary definition of the true hematocrit differs slightly from the clinical hematocrit definition, which equates the hematocrit to the percentage of only erythrocytes. (In practice, the true hematocrit and the clinical hematocrit are considered the same.)

Hematocrit values vary somewhat and are dependent upon the age and sex of the individual. A very young child’s hematocrit may vary from 30% to 60%, and that range will narrow to 35% to 50% as

Table 18.1 Physical Characteristics of Blood

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Scarlet (oxygen-rich) to dark red (oxygen-poor)</td>
</tr>
<tr>
<td>Volume</td>
<td>4–5 L (females) 5–6 L (males)</td>
</tr>
<tr>
<td>Viscosity (relative to water)</td>
<td>4.5–5.5 × (whole blood)</td>
</tr>
<tr>
<td>Plasma concentration</td>
<td>0.09%</td>
</tr>
<tr>
<td>Temperature</td>
<td>38°C (100.4°F)</td>
</tr>
<tr>
<td>pH</td>
<td>7.35–7.45</td>
</tr>
</tbody>
</table>
Withdraw blood into a syringe and place it into a glass centrifuge tube.

Place the tube into a centrifuge and spin for about 10 minutes.

Components of blood separate during centrifugation to reveal plasma, buffy coat, and erythrocytes.

Figure 18.1 Whole Blood Separation and Composition. Whole blood contains plasma (average is about 55%) and formed elements (average is about 45%). The percentages presented in this figure are average percentages of cells, and the values for components of the buffy coat represent average ranges. A cubic millimeter (mm³) of blood is equivalent to a microliter (μL).

INTEGRATE
CONCEPT CONNECTION
Not only does the blood contain buffers to help maintain the body’s pH, but the urinary system and respiratory system also help to maintain this pH (see sections 25.5b and c). An increase in breathing rate can decrease blood carbon dioxide levels and H⁺ levels, thus increasing blood pH, whereas a decrease in breathing rate can cause an increase in carbon dioxide levels and H⁺ levels, thus decreasing blood pH. The urinary system helps maintain a normal blood pH either by producing HCO₃⁻ and eliminating H⁺ in the urine to increase blood pH or by eliminating HCO₃⁻ and retaining H⁺ to decrease blood pH.

the child becomes older. Adult males tend to have a hematocrit ranging between 42% and 56%, whereas adult females’ hematocrits range from 38% to 46%. Males typically have a higher hematocrit because testosterone stimulates the kidneys to produce the hormone erythropoietin (EPO), which promotes erythrocyte production (see section 18.3b). An elevated hematocrit may indicate that the patient is either dehydrated or participating in blood doping, whereas a lowered hematocrit often suggests the patient is suffering from anemia.

Blood Smear
All of the components of the formed elements can be viewed by preparing a blood smear. A blood smear and the steps to produce a smear are shown in figure 18.2. Note the following:

- Erythrocytes are the most numerous of the formed elements. These are anucleate cells and appear as pink or pale purple, biconcave discs.
- Leukocytes are larger than erythrocytes. The nucleus is very noticeable in leukocytes. Several leukocytes (a lymphocyte, neutrophil, and two monocytes) are shown in figure 18.2.
- Platelets are cellular fragments and are much smaller than either erythrocytes or leukocytes.

WHAT DID YOU LEARN?
4. What are the three components visible in a centrifuged blood sample?
5. How does hematocrit vary among adult men and women, and how may dehydration affect hematocrit?
18.2 Composition of Blood Plasma

Plasma is composed primarily of water (about 92% of its volume), plasma proteins, and other solutes, including electrolytes (e.g., Na⁺), nutrients (e.g., glucose), respiratory gases (e.g., CO₂), and wastes (e.g., urea) (table 18.2). Plasma is classified as an extracellular fluid (ECF) because it is fluid found outside of cells. However, plasma is similar in composition to interstitial fluid, in that both have similar concentrations of electrolytes, nutrients, and waste products. Yet one of the most significant differences is that protein concentration is higher in plasma than in the interstitial fluid (see section 25.1b). We first describe plasma proteins and then the specific substances transported in the plasma.
### Table 18.2
The Composition of Blood Plasma

<table>
<thead>
<tr>
<th>Plasma Component (Percentage of Plasma)</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (≈92% of plasma)</td>
<td>The solvent in which formed elements are suspended and proteins and solutes are dissolved</td>
</tr>
<tr>
<td>PLASMA PROTEINS (~7% OF PLASMA): All proteins buffer against pH changes.</td>
<td></td>
</tr>
</tbody>
</table>
| Albumin (~58% of plasma proteins)      | Exerts osmotic force to retain fluid within the blood  
Contributes to blood’s viscosity  
Responsible for transport of some ions, lipids (e.g., fatty acids), and hormones |
| Globulins (~37% of plasma proteins)    | Alpha-globulins transport lipids and some metal ions (e.g., copper)  
Beta-globulins transport iron ions and lipids in blood  
Gamma-globulins are antibodies that immobilize pathogens |
| Fibrinogen (~4% of plasma proteins)    | Participates in blood coagulation (clotting) |
| Regulatory proteins (<1% of plasma proteins) | Consists of enzymes and hormones |
| OTHER SOLUTES (~1% OF BLOOD PLASMA)    | Help establish, maintain, and change membrane potentials, maintain pH balance, and regulate osmosis  
Energy source; precursor for synthesizing other molecules  
Oxygen is needed for aerobic cellular respiration; carbon dioxide is a waste product produced by cells during this process  
Waste products serve no function in the blood plasma; rather, they merely are being transported to the liver and kidneys, where they can be removed from the blood |

### 18.2a Plasma Proteins

<table>
<thead>
<tr>
<th>LEARNING OBJECTIVES</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Define colloid osmotic pressure.</td>
</tr>
<tr>
<td>7. Identify the various types of plasma proteins, and explain the general function of each.</td>
</tr>
</tbody>
</table>

Blood is considered a colloid (see section 2.6a) because it contains proteins in the plasma. Plasma proteins include albumin, globulins, fibrinogen and other clotting proteins, as well as regulatory proteins such as enzymes and some hormones. Most of these proteins are produced in the liver, including albumin, alpha- and beta-globulins, and both fibrinogen and other proteins involved with clotting. Some plasma proteins, such as gamma-globulins and regulatory proteins, are produced by leukocytes and other organs, respectively.

Collectively, these plasma proteins exert osmotic pressure and prevent the loss of fluid from the blood as it moves through the capillaries. Osmotic pressure exerted by plasma proteins is called colloid osmotic pressure. This osmotic force is responsible for drawing fluids into the blood and preventing excess fluid loss from blood capillaries into the interstitial fluid (see section 20.3b), thus helping to maintain blood volume and consequently blood pressure. If plasma protein levels decrease, as might occur due to liver disease (resulting in decreased production of plasma proteins) or kidney damage (resulting in increased elimination of plasma proteins), colloid osmotic pressure also decreases. This decrease results in fluid loss from the blood and fluid retention in the interstitial space (i.e., edema; see section 25.2b).

**Albumins** (al-bú’min; albumen = white of egg) are the smallest and most abundant of the plasma proteins, making up approximately 58% of all plasma proteins. Because albumin is the most abundant type of plasma protein, it exerts the greatest colloid osmotic pressure to maintain blood volume and blood pressure. Secondarily, albumins act as transport proteins that carry ions, hormones, and some lipids in the blood.

**Globulins** (glob’û-lin; globules = globule) are the second largest group of plasma proteins, forming about 37% of all plasma proteins. The smaller **alpha-globulins** and the larger **beta-globulins** primarily bind and transport certain water-insoluble molecules and hormones, some metals, and ions. Gamma-globulins are also called immunoglobulins, or antibodies, which play a part in the body’s defenses (see section 22.8).

**Fibrinogen** (fi’brin-ô-jen; fibra = fiber) makes up about 4% of all plasma proteins. Fibrinogen as well as other clotting proteins are responsible for blood clot formation. Following trauma to
the walls of blood vessels, fibrinogen is converted into long, insoluble strands of fibrin, which help form a blood clot. When the clotting proteins are removed from plasma, the remaining fluid is termed serum (ser’um; whey). Blood clotting is described in more detail in section 18.4.

Regulatory proteins form a very minor class of plasma proteins (less than 1% of total plasma proteins). This group of proteins includes both enzymes to accelerate chemical reactions in the blood (see section 3.3a) and hormones being transported throughout the body to target cells (see section 17.3a).

### WHAT DID YOU LEARN?
6. How are plasma protein levels related to colloid osmotic pressure?
7. What is the most abundant type of plasma protein, and what are its two primary functions?

### Table 18.3  Common Electrolytes in Arterial Plasma

<table>
<thead>
<tr>
<th>Electrolytes (Ions)</th>
<th>Normal Ranges (Values)</th>
<th>Function(s)</th>
<th>Substances and Structures That Regulate Electrolyte Blood Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (Na⁺)</td>
<td>135–145 milliequivalents per liter (mEq/L)</td>
<td>Neuron and muscle function; fluid balance; cotransporter</td>
<td>Aldosterone, atrial natriuretic peptide (ANP), estrogen, progesterone, glucocorticoids</td>
</tr>
<tr>
<td>Potassium (K⁺)</td>
<td>3.5–5.0 mEq/L</td>
<td>Neuron and muscle function</td>
<td>Aldosterone, ANP</td>
</tr>
<tr>
<td>Calcium (Ca²⁺)</td>
<td>8.4–10.2 milligrams per deciliter (mg/dL)</td>
<td>Hardens bone; release of neurotransmitter; muscle contraction; blood clotting; second messenger</td>
<td>Parathyroid hormone, calcitriol, calcitonin</td>
</tr>
<tr>
<td>Hydrogen (H⁺)</td>
<td>pH 7.35–7.45</td>
<td>pH balance</td>
<td>Buffering systems—chemicals in blood, kidney, respiratory system</td>
</tr>
</tbody>
</table>

### Table 18.4  Common Molecules Found in Blood Plasma

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Normal Ranges (Values)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Fasting: 70–100 mg/dL; 2 hours after a meal: &lt;145 mg/dL</td>
<td>Fuel molecule for cellular respiration (primary energy source for nervous tissue); tightly regulated by a number of hormones, including insulin and glucagon</td>
</tr>
<tr>
<td>Amino acids</td>
<td>Varies, based on specific amino acid being measured</td>
<td>Monomers for synthesizing protein; also regulated by some of the same hormones as glucose</td>
</tr>
<tr>
<td>Lactate</td>
<td>4.5–14.4 mg/dL</td>
<td>By-product of glycolysis</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
<td>Molecules that generally do not dissolve in water</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>100–200 mg/dL</td>
<td>Plasma membrane component; synthesis of steroid hormones; bile salts</td>
</tr>
<tr>
<td>HDL</td>
<td>40–80 mg/dL</td>
<td>Transports lipids to the liver</td>
</tr>
<tr>
<td>VLDL/LDL</td>
<td>10–100 mg/dL</td>
<td>Transport lipids from the liver</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>30–149 mg/dL</td>
<td>Fuel molecules</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>6–12 mg/dL</td>
<td>Molecules that form plasma membrane bilayer</td>
</tr>
</tbody>
</table>

### 18.2b Other Solutes

LEARNING OBJECTIVE
8. List dissolved substances in plasma by category.

Blood is also considered a solution because it contains dissolved ions as well as organic and inorganic molecules. These substances include electrolytes, nutrients, respiratory gases, some hormones, and waste products. Recall from sections 2.3c and 17.4 that polar or charged substances (e.g., glucose, salts) dissolve readily in the blood, and nonpolar molecules (e.g., cholesterol, triglycerides, and fatty acids) do not readily dissolve in blood and require a carrier protein. Tables 18.3 and 18.4 list the normal ranges and functions of common solutes transported in blood plasma.

### WHAT DID YOU LEARN?
8. What are the main dissolved substances found in plasma?
Table 18.5: Characteristics of the Formed Elements

<table>
<thead>
<tr>
<th>Formed Element</th>
<th>Size (Diameter)</th>
<th>Function</th>
<th>Life Span</th>
<th>Density (Average Number per mm³ of Blood = μL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytes</td>
<td>7.5 μm</td>
<td>Transport oxygen and carbon dioxide</td>
<td>~120 days</td>
<td>Females: ~4.8 million; Males: ~5.4 million</td>
</tr>
<tr>
<td>Leukocytes (e.g., neutrophils, eosinophils, basophils, monocytes, and lymphocytes)</td>
<td>1.5 to 3 times larger than an erythrocyte; 11.25–22.5 μm</td>
<td>Initiate immune response; defend against potentially harmful substances</td>
<td>Varies from 12 hours (neutrophils) to years (lymphocytes)</td>
<td>4500–11,000</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt;¼ the size of an erythrocyte; ~2 μm</td>
<td>Participate in hemostasis</td>
<td>~8–10 days</td>
<td>150,000–400,000</td>
</tr>
</tbody>
</table>

Table 18.6: Substances That Influence Hemopoiesis

<table>
<thead>
<tr>
<th>Substance</th>
<th>Growth Factor or Hormone</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-colony-stimulating factor (multi-CSF)</td>
<td>Growth factor</td>
<td>Increases the formation of erythrocytes, granulocytes, monocytes, and platelets from myeloid stem cells</td>
</tr>
<tr>
<td>Granulocyte-macrophage colony-stimulating factor (GM-CSF)</td>
<td>Growth factor</td>
<td>Accelerates the formation of all granulocytes and monocytes from their progenitor cells</td>
</tr>
<tr>
<td>Granulocyte colony-stimulating factor (G-CSF)</td>
<td>Growth factor</td>
<td>Stimulates the formation of granulocytes from myeloblast cells</td>
</tr>
<tr>
<td>Macrophage colony-stimulating factor (M-CSF)</td>
<td>Growth factor</td>
<td>Stimulates the production of monocytes from monoblasts</td>
</tr>
<tr>
<td>Thrombopoietin</td>
<td>Growth factor</td>
<td>Stimulates both the production of megakaryocytes in the bone marrow and the subsequent formation of platelets</td>
</tr>
<tr>
<td>Erythropoietin (EPO)</td>
<td>Hormone (produced primarily by the kidneys)</td>
<td>Increases the rate of production and maturation of erythrocyte progenitor and erythroblast cells</td>
</tr>
</tbody>
</table>
except lymphocytes (this would include granulocytes and monocytes), and megakaryocytes (cells that produce platelets). (2) The lymphoid (lim′foyd) line forms only lymphocytes.

The maturation and division of hemopoietic stem cells are influenced by colony-stimulating factors (CSFs), or colony-forming units (CFUs). These molecules are all growth factors, except for erythropoietin, which is a hormone. These substances are described in table 18.6 and shown in figure 18.3.
Erythropoiesis

Erythrocytes make up more than 99% of formed elements, with a concentration between 4.2 and 6.2 million per cubic millimeter. The process of erythrocyte production is called erythropoiesis (é-rith’rō-poy-ē’sis). Normally, erythrocytes are produced at the rate of about 3 million per second. The hormone erythropoietin (EPO) controls this rate by increasing the rate of erythrocyte formation (described in section 18.3b). Dietary requirements for normal erythropoiesis include iron, B vitamins (e.g., folic acid, riboflavin), and amino acids (to build proteins).

The process of erythropoiesis begins with a myeloid stem cell, which under the influence of multi-CSF forms a progenitor cell. The progenitor cell forms a proerythroblast, which is a large, nucleated cell. It then becomes an erythroblast, which is a slightly smaller cell that is producing hemoglobin in its cytosol. The next stage, called a normoblast, is a still smaller cell with more hemoglobin in the cytosol; its nucleus has been ejected. A cell called a reticulocyte (re-tik’ō-lō-sit) eventually is formed. The reticulocyte has lost all organelles except some ribosomes, so it can continue to produce hemoglobin (through protein synthesis). The transformation from myeloid stem cell to reticulocyte takes about 5 days.

Some reticulocytes finish maturation while circulating in blood vessels (and in normal circumstances, make up 0.5–2.0% of the circulating blood). One to two days after entering the circulation, the ribosomes in the reticulocyte degenerate, and the reticulocyte becomes a mature erythrocyte. Without a nucleus and cellular organelles, the mature erythrocyte is essentially a plasma membrane “bag” containing hemoglobin.

Leukopoiesis

Leukocytes make up less than 0.01% of formed elements, with a concentration between 4500 and 11,000 per cubic millimeter. The production of leukocytes is called leukopoiesis (lēk’ō-poy-ē’sis). Leukopoiesis involves three different types of maturation processes: granulocyte maturation, monocyte maturation, and lymphocyte maturation.

All three types of granulocytes (neutrophils, basophils, and eosinophils) are derived from a myeloid stem cell. This stem cell is stimulated by multi-CSF and GM-CSF to form a progenitor cell. The granulocyte line develops when the progenitor cell forms a myeloblast (mi’ē-lō-blast) under the influence of G-CSF. The myeloblast ultimately differentiates into one of the three types of granulocytes.

Like granulocytes, monocytes are also derived from a myeloid stem cell. The myeloid stem cell differentiates into a progenitor cell, and under the influence of M-CSF this cell forms a monoblast. This is the monocyte line. Eventually, the monoblast forms a promonocyte that differentiates and matures into a monocyte.

Lymphocytes are derived from a lymphoid stem cell through the lymphoid line. The lymphoid stem cell differentiates into B-lymphoblasts and T-lymphoblasts. B-lymphoblasts mature into B-lymphocytes, whereas T-lymphoblasts mature into T-lymphocytes. Some lymphoid stem cells differentiate directly into NK (natural killer) cells. Lymphocyte development and maturation are further described in section 22.5.

Thrombopoiesis

Platelets (or thrombocytes) make up less than 1% of formed elements, with a production of around 150,000 and 400,000 per cubic millimeter. The production of platelets is called thrombopoiesis (throm-bō-poy-ē’sis; thrombus = clot). From the myeloid stem cell, a committed cell called a megakaryoblast (meg-ā-kar’ē-ō-blast; mega = big) is produced. It matures under the influence of thrombopoietin to form a megakaryocyte (meg-ā-kar’ē-ō-sit) (figure 18.4). Megakaryocytes are easily distinguished both by their large size (about 100 micrometers [μm] in diameter) and by their dense, multilobed nucleus. Each megakaryocyte then produces thousands of platelets.

Megakaryocytes produce platelets by forming long extensions from themselves called proplatelets. While still attached to the megakaryocyte, these proplatelets extend through the blood vessel wall (between the endothelial cells) in the red bone marrow. The force from the blood flow “slices” these proplatelets into the fragments we know as platelets.

Researchers previously thought that most, if not all, megakaryocytes were located within red bone marrow. However, research on mice published in 2017 demonstrated that megakaryocytes circulate through the lung vasculature and that while in the lungs, these cells release platelets. This mouse model indicates that the lungs may be the site of up to 50% of platelet production. Research is ongoing to determine if this finding exists in humans.

WHAT DID YOU LEARN?

9. Describe the process of erythropoiesis, beginning with the stem cell and then placing the precursor cells in order until a mature erythrocyte is produced.

10. What are the two main types of precursor cells for formed element development, and what mature formed elements are derived from each?

Figure 18.4 Platelet Formation. Platelets are derived from megakaryocytes. (a) Photomicrograph of megakaryocytes in red bone marrow. (b) Megakaryocytes extend long processes (called proplatelets) through the blood vessel wall. These proplatelets are spilled (by the force of the blood flow) into platelets, which then circulate in the blood.
18.3b Erythrocytes

LEARNING OBJECTIVES

13. Describe the structure of erythrocytes.
14. List the events by which erythrocyte production is stimulated.
15. Explain the process by which erythrocyte components are recycled.
16. Compare and contrast the different blood types and their importance when transfusing blood.

Erythrocytes are very small, flexible cells, with a diameter of approximately 7.5 μm (figure 18.5). Although erythrocytes are commonly referred to as red blood cells, or RBCs, the term red blood cell is a misnomer because a mature erythrocyte lacks a nucleus and cellular organelles. As a result, it is more appropriate to refer to an erythrocyte as a formed element. An erythrocyte has a unique biconcave disc structure (at its narrowest point about 0.75 μm and at its widest point about 2.6 μm). It is composed of a plasma membrane within which are housed about 280 million hemoglobin molecules.

Erythrocytes transport oxygen and carbon dioxide between the tissues and the lungs. The fact that erythrocytes lack a nucleus and organelles enables them to carry respiratory gases more efficiently. The biconcave shape and flexibility of erythrocytes allow them to stack and line up in single file. This single file of erythrocytes is termed a rouleau (rû-lô’; pl., rouleaux; cylinder), as they pass through capillaries. A latticework of spectrin protein supports the plasma membrane of the erythrocyte on its internal surface and provides flexibility to the erythrocyte as it moves through the capillaries.

WHAT DO YOU THINK?

What does an erythrocyte gain by the loss of its nucleus and organelles? What three cellular processes can it no longer engage in due to the loss of its (a) nucleus and (b) mitochondria?

Hemoglobin

Hemoglobin (hē’mō-glō-bin) is a red-pigmented protein that transports oxygen and carbon dioxide. When blood is maximally loaded with oxygen, it is termed oxygenated (and appears bright red). Conversely, when some oxygen is lost and carbon dioxide is gained during systemic cellular gas exchange, blood is called deoxygenated (and appears dark red).

Each hemoglobin molecule consists of four protein molecules called globins. Two of these globins are called alpha (α) chains, and the other two, which are slightly different, are called beta (β) chains (figure 18.6). All globin chains contain a heme group, which is composed of a porphyrin (organic compound) ring, with an iron ion (Fe²⁺) in its center. Oxygen binds to the Fe²⁺ in heme groups for transport in the blood.

INTEGRATE

Blood Doping

To enhance their performance in endurance events, some athletes may try to boost their bodies’ ability to deliver oxygen to the muscles by increasing the number of erythrocytes in their blood. One way the number of erythrocytes can be increased naturally is by living and training at high altitude. The body compensates for the decreased oxygen concentration in the atmosphere by increasing the rate of erythrocyte production, thus increasing the number of erythrocytes per unit volume of blood.

An illegal procedure used by some athletes is called blood doping. There are two different methods for blood doping. In the first (and older) method, the athlete essentially donates erythrocytes to himself or herself. Prior to competition, the athlete has a unit of blood removed and stored. As the kidneys detect the decreased blood oxygen, the hormone erythropoietin (EPO) is released and the bone marrow responds by increasing production of erythrocytes. This causes the body to increase erythrocyte production to make up for the ones just removed. A few days before the competition, the erythrocytes from the donated unit are transfused back into the athlete’s body. The increased number of erythrocytes increases the amount of oxygen transported in the blood and is thought to favorably affect muscle performance, thereby improving athletic performance. The second method of blood doping has occurred with the development of pharmaceutical EPO, which is used to treat anemia.

In this method of blood doping, an athlete is injected with pharmaceutical EPO to further increase erythrocyte levels. Potentially deadly dangers are inherent in blood doping. By increasing the number of erythrocytes per measured volume of blood, blood doping also increases the viscosity of the blood. Thus, the heart must work harder to pump this more viscous blood. Eventually, temporary athletic success may be overshadowed by permanent cardiovascular damage that can even lead to death, as has occurred with some athletes. Thus, blood doping has now been banned by athletic competition governing bodies.
Figure 18.6 Molecular Structure of Hemoglobin. A single molecule of hemoglobin is composed of four protein subunits, called globins, each containing a lipid heme group that holds a single iron ion \( \text{Fe}^{2+} \) in its center. Each hemoglobin molecule transports four oxygen molecules that are weakly attracted to the \( \text{Fe}^{2+} \).

Because each molecule of hemoglobin has four heme groups, it has four \( \text{Fe}^{2+} \) and is capable of binding four molecules of oxygen. The oxygen binding is fairly weak; this allows rapid attachment of oxygen with hemoglobin when erythrocytes pass through the blood capillaries of the lungs, and rapid detachment when erythrocytes pass through the systemic capillaries of body tissues.

Carbon dioxide and the globin molecule (not the \( \text{Fe}^{2+} \)) have a similar weak attachment relationship for the transport of carbon dioxide molecules. Carbon dioxide binds to the globin protein molecule as blood moves through systemic capillaries and is released as blood moves through the capillaries of the lungs.

The Role of EPO in Erythropoiesis

Erythropoiesis is controlled by the hormone erythropoietin (EPO). The kidneys are the primary producers of EPO, although the liver also secretes a small amount of EPO (see Table 17.2). The process by which EPO release is stimulated is shown in Figure 18.7. The initial stimulus for EPO release is a decrease in blood oxygen levels. This decrease may be caused by the continuous removal of aged erythrocytes, blood loss, or exposure to high altitudes (where atmospheric oxygen levels are lower). Chemoreceptors within the kidneys detect low blood oxygen levels as the blood is transported through blood vessels within the kidneys. As a result, certain cells in the kidneys release the hormone EPO into the blood. EPO is transported through the blood and reaches the red bone marrow. There, EPO stimulates myeloid cells in the red bone marrow to increase the rate of erythrocyte production. Additional erythrocytes are released into circulation (a process that takes a few days), so more oxygen can be transported from the lungs and delivered to the cells. Blood oxygen levels increase as a result. Increased blood oxygen levels inhibit release of EPO from kidney cells through negative feedback.

The adrenal gland secretes small amounts of gonadocorticoids (including testosterone) in both sexes (see section 17.8c), and the testes secrete large amounts of testosterone in males.
Figure 18.7 How Erythropoietin (EPO) Regulates Erythrocyte Production. Low blood oxygen levels are detected by kidney chemoreceptors, which triggers the release of erythropoietin (EPO) into the blood. EPO stimulates the red bone marrow to produce more erythrocytes. EPO release is then inhibited when blood oxygen levels rise.
Erythrocyte Destruction

The absence of both a nucleus and cellular organelles comes at a cost to the erythrocyte and affects its longevity. A mature erythrocyte cannot synthesize proteins either to repair itself or to replace damaged membrane regions. Aging and the wear-and-tear of circulation through blood vessels cause erythrocytes to become more fragile and less flexible. Therefore, the erythrocyte has a finite maximum life span of about 120 days. Every day, about 1% of the oldest circulating erythrocytes are removed from circulation. These old erythrocytes are phagocytized in both the spleen and liver by cells called macrophages.

Three molecular components must be accounted for in the destruction of hemoglobin: the globin protein, the iron ion, and the heme group. Two of the components are processed for recycling; the other component is metabolically altered and then excreted from the body, as shown in figure 18.8.

Globin proteins are broken down into free amino acids, most of which are used by the body for protein synthesis to make new erythrocytes or other body proteins.

The iron ion (Fe\(^{2+}\)) component in hemoglobin is removed and transported by a globulin protein called transferrin (trans-fer’i-n; trans = across, ferrum = iron) to the liver or spleen, where the Fe\(^{2+}\) then is bound to storage proteins called ferritin (fer’i-tin) and hemosiderin (hē’mō-sid’ər-in). Ferritin is a large, water-soluble protein that serves as the primary storage mechanism for iron. Iron is stored mainly in the liver and spleen, and it is transported by transferrin to the red bone marrow as needed for erythrocyte production. However, small amounts of iron, approximately 0.9 mg, are lost daily in sweat, urine, and feces. In females, additional iron is lost in those who have a monthly menstrual flow.

The heme group (minus the Fe\(^{2+}\)) released from hemoglobin is converted within macrophages first into a green pigment called biliverdin (bil-i-ver′din; bilis = bile, verd = green). Biliverdin is eventually converted into a yellowish pigment called bilirubin (bil-i-rū’bin; rubin = reddish) within the macrophages. Bilirubin is then released into the blood and is transported by albumin to the liver. Bilirubin is a component of a digestive system secretion called bile, which is produced by the liver and released into the small intestine (see section 26.3c).

Bilirubin is converted to urobinogen (yur-ō-bi-lin’ō-jen, ouron = urine) within the small intestine. Urobinogen can either (1) continue through the large intestine and eventually be converted by the intestinal bacteria to stercobilin, a brown pigment that is expelled from the body as a component of feces; or (2) be absorbed back into the blood. In this latter case, it is converted to urobin, a yellow pigment that is excreted by the kidneys.

**INTEGRATE**

**CLINICAL VIEW 18.2**

**Anemia** (ā-nē′m-ə; an = without, haima = blood) is any condition in which either the percentage of erythrocytes is lower than normal or the oxygen-carrying capacity of the blood is reduced (as may occur if the amount of hemoglobin within erythrocytes is abnormal). In either case, there is decreased oxygen delivery to body tissues—and consequently, the heart must work harder to supply oxygen to the body. Symptoms of anemia include lethargy, shortness of breath, pallor of the skin and mucous membranes, fatigue, and heart palpitations. The types of anemia include the following:

- **Aplastic anemia** is characterized by significantly decreased formation of both erythrocytes and hemoglobin. This condition results from defective red bone marrow, perhaps as a result of poisons, toxins, or radiation exposure.

- **Congenital hemolytic anemia** occurs when destruction of erythrocytes is more rapid than normal. It is usually due to a genetic defect, which results in the production of abnormal membrane proteins that make the erythrocyte plasma membrane very fragile.

- **Erythroblastic anemia** is characterized by the presence of large numbers of immature, nucleated cells (called erythroblasts and normoblasts) in the circulating blood. An accelerated pace of cell maturation causes immature cells to be present in the blood. These cells cannot function normally and thus anemia results.

- **Hemorrhagic anemia** results from heavy blood loss. The hemorrhage may be caused, for example, by chronic ulcers or by heavy or prolonged menstrual flow.

- **Pernicious anemia** is a chronic, progressive anemia of adults caused by failure of the body to absorb vitamin B\(_2\). This vitamin is found in fish and meat, so most individuals receive enough B\(_2\) in their diets, unless they are vegans or strict vegetarians. (Thus, it is recommended that all vegetarians take a B\(_2\) vitamin supplement.) A defect in the production of intrinsic factor, a glycoprotein secreted by stomach lining cells to protect B\(_2\) in the stomach and enhance B\(_2\) absorption in the small intestine (see section 26.2d), leads to pernicious anemia. Individuals who have pernicious anemia due to defective intrinsic factor production must receive B\(_2\) intramuscular or subcutaneous injections, since they are unable to absorb oral B\(_2\) supplements.

- **Sickle-cell disease** is an autosomal recessive anemia that occurs when a person inherits two copies of the sickle-cell gene (see section 29.9b). Erythrocytes become sickle-shaped at lower blood oxygen concentrations, making them unable to flow efficiently through the blood vessels to body tissues and more prone to destruction (a process called hemolysis).

Most anemias are treated by letting the patient’s own red bone marrow replace the erythrocytes. This process may be facilitated through the use of pharmaceutical EPO. However, anemia is often a symptom of another disease or problem. For example, although many anemias are due to iron deficiency, the iron deficiency often is not because of diet, but rather the result of chronic blood loss, a process that depletes the body of its iron stores over months or years. The three most common causes of such chronic blood loss are excessive menstrual bleeding, undiagnosed stomach ulcer, and colon cancer. So, while restoring the patient’s erythrocyte count, a physician should also look for any underlying cause of the anemia.
Iron ion \( \text{Fe}^{2+} \) is converted to Globin. Small amounts of iron are lost in sweat, urine, and feces daily; iron is also lost via injury and menstruation. Iron is stored in the liver attached to ferritin. Iron is transported by transferrin to the red bone marrow as needed for erythrocyte production.

Globin proteins are broken down into amino acids and enter the blood. Some of these amino acids may be used to make new erythrocytes. Liver

Aged erythrocytes are phagocytized by macrophages in the liver and spleen. The three components of hemoglobin are separated.

Figure 18.8 Recycling and Elimination of Erythrocyte Components. Erythrocytes circulate in the blood for about 120 days, after which they are phagocytized in the liver and spleen. Various components are recycled; other components are altered and expelled as waste.

Each of the separated components of heme (globin, iron ion, and heme) has a different fate.

Bilirubin is transported to the liver by albumin and then released as a component of bile in the small intestine.

Bilirubin is converted to urobilinogen within the small intestine.

Some urobilinogen is absorbed back into the blood and converted to uroblin and excreted in the urine.

Most urobilinogen continues to the large intestine and is converted to stercobilin and expelled in feces.
This group consists of two surface antigens

Type A
Type B blood has anti-A antibodies within its plasma.

Type AB
Type O blood has
Type A blood has anti-B antibodies within its plasma.

Type B
11/11/17   6:54 pm
Type AB

INTEGRATE

Because of these differences, the FDA does not require plasma donations

elements of whole blood would be damaged if subjected to a similar process.

processed to help kill any pathogens they contain, whereas the formed

and test new therapies. Plasma and its protein components may be

centers, which use the plasma or specific proteins to manufacture drugs

centers, which use the plasma or specific proteins to manufacture drugs

INTEGRATE

Whole Blood Versus Plasma Donations: What’s the Difference?

A whole blood donation is a donation of all the components of blood (i.e.,

formed elements and plasma) in a single donation visit. In most cases, nonprofit

organizations (e.g., the American Red Cross) are responsible for holding blood
drives to collect whole blood donations. Donations almost always are voluntary,

and no cash compensation is given to donors. Whole blood donation is

regulated by the Food and Drug Administration (FDA), which requires that any

blood collected in a for-profit situation (i.e., someone is paid money to donate

whole blood) must be labeled as such. Although it is not illegal to pay someone

for a whole blood donation, the FDA and blood donation centers view the

practice as unethical, because an individual may lie about his or her medical

history (in order to receive the money for the donation) and, in so doing, taint

the nation’s blood supply.

In contrast, in a plasma donation, only the plasma (and the proteins within

the plasma) of someone’s whole blood is donated. The whole blood first is

removed as one unit, the plasma is extracted, and then the nonplasma

components of the blood are injected back into the donor’s circulation. Plasma

volume may be replaced by the body within days as a person hydrates, so

plasma donations may be made much more frequently than whole blood
donations.

Whereas whole blood donations typically are used to treat patients, most

plasma donations are sent to pharmaceutical companies and research

centers, which use the plasma or specific proteins to manufacture drugs

and test new therapies. Plasma and its protein components may be

processed to help kill any pathogens they contain, whereas the formed

elements of whole blood would be damaged if subjected to a similar process.

Because of these differences, the FDA does not require plasma donations
to be labeled if the donors have been paid for their donations. There is a
great demand for plasma and its components, resulting in a variety of for-

profit plasma donation centers.

Blood Types

The plasma membrane of an erythrocyte has numerous molecules
called surface antigens (or agglutinogens), which project from the

surface. These antigens have significant implications for blood trans-
fusion and, in some cases, pregnancy. There are two groups of surface

antigens that determine a person’s blood type: the ABO blood group

and the Rh protein.

ABO Blood Group  The best-known antigens are those that form

the ABO blood group. This group consists of two surface antigens

(which are glycoproteins) called A and B. The presence or absence of

the A antigen, the B antigen, or both is the criterion that determines

your ABO blood type, as shown in figure 18.9 and listed here:

- Type A blood has erythrocytes with surface antigen A only.
- Type B blood has erythrocytes with surface antigen B only.
- Type AB blood has erythrocytes having both surface antigens
  A and B.
- Type O blood has erythrocytes with neither surface antigen A
  nor B.

The ABO surface antigens on erythrocytes are accompanied by spe-
cific antibodies (or agglutinins; see table 2.6) within the blood plasma.

In general, an antibody is a Y-shaped protein that binds to a specific

antigen that is perceived as foreign to the body (see section 22.4a). The

ABO blood group has both anti-A and anti-B antibodies that react

with the surface antigen A and the surface antigen B, respectively. You
do not have antibodies in your blood plasma that bind to the surface

antigens on your erythrocytes. Within the ABO blood group, the fol-

lowing blood types and antibodies are normally associated as follows:

- Type A blood has anti-B antibodies within its plasma.
- Type B blood has anti-A antibodies within its plasma.
- Type AB blood has neither anti-A nor anti-B antibodies
  within its plasma.
- Type O blood has both anti-A and anti-B antibodies within its
  blood plasma.

Rh Factor  Another common surface antigen on erythrocyte plas-

ma membranes determines the Rh blood type. The Rh blood type

is determined by the presence or absence of the Rh surface antigen,
oc-
<table>
<thead>
<tr>
<th>ABO Blood Types</th>
<th>Type A</th>
<th>Type B</th>
<th>Type AB</th>
<th>Type O</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythrocytes</strong></td>
<td>Surface antigen A</td>
<td>Surface antigen B</td>
<td>Surface antigens A and B</td>
<td>Neither surface antigen A nor B</td>
</tr>
<tr>
<td><strong>Plasma</strong></td>
<td>Anti-B antibodies</td>
<td>Anti-A antibodies</td>
<td>Neither anti-A nor anti-B antibodies</td>
<td>Both anti-A and anti-B antibodies</td>
</tr>
</tbody>
</table>

(a) Rh Blood Types

<table>
<thead>
<tr>
<th>Blood type</th>
<th>Rh positive</th>
<th>Rh negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythrocytes</strong></td>
<td>Surface antigen D</td>
<td>No surface antigen D</td>
</tr>
<tr>
<td><strong>Plasma</strong></td>
<td>No anti-D antibodies</td>
<td>No anti-D antibodies unless exposed to Rh positive blood</td>
</tr>
</tbody>
</table>

(b) Rh Blood Types

Figure 18.9  ABO and Rh Blood Types. The blood type of an individual is determined by the specific antigens (agglutinogens) exposed on the surface of the erythrocyte membrane. Likewise, plasma contains antibodies (agglutinins) that react with antigens from outside the body. (a) ABO blood types. (Note that the antibodies are shown here with the antibodies already bound to the antigen, to clarify the differences between the different antibodies.) (b) Rh blood types.

INTEGRATE

CLINICAL VIEW 18.5

Fetal Hemoglobin and Physiologic Jaundice

A different type of hemoglobin molecule, called fetal hemoglobin, is found in the erythrocytes of unborn babies. Fetal hemoglobin has a greater affinity for binding oxygen than adult hemoglobin, ensuring a net movement of oxygen from the mother’s blood to the blood of the fetus. After the infant is born, the erythrocytes with fetal hemoglobin are replaced with erythrocytes containing adult hemoglobin. The infant may exhibit physiologic jaundice—a yellowish tinge to the skin due to elevated levels of bilirubin—as the fetal hemoglobin breaks down. This condition lasts about a week, sometimes 2 weeks in premature infants. To facilitate and accelerate the breakdown of bilirubin, an infant with jaundice may be treated with phototherapy (i.e., using blue or white lights that break down the bilirubin). Specific phototherapy devices include the Bili-lite (which shines down on an infant) or a BiliBlanket (which is partially wrapped around the infant).

INTEGRATE

LEARNING STRATEGY

To remember which ABO blood type is associated with which specific antibody, keep in mind that each blood type has an antibody of a different letter:

- Type A blood does not have anti-A antibodies (because anti-A antibodies and type A blood start with the same letter); it has only anti-B antibodies.
- Type B blood has a letter “B” in its name, so it has no anti-B antibodies, only anti-A antibodies.
- Type AB blood has both “A” and “B” in its name, so it has neither anti-A nor anti-B antibodies.
- Type O blood has neither an “A” nor a “B” in its name, so it has both anti-A and anti-B antibodies.
The ABO and Rh blood types are usually reported together. For example, types AB and Rh⁺ together are reported as AB⁺. However, remember that ABO and Rh blood types are independent of each other, and neither of them interacts with or influences the presence or activities of the other group.

Clinical Considerations About Blood Types

Blood types become clinically important when a patient needs a blood transfusion. Compatibility between donor and recipient must be ascertained prior to blood transfusions. If a person is transfused with blood of an incompatible type, antibodies in the plasma bind to surface antigens of the transfused erythrocytes, and clumps of erythrocytes bind together in a process termed **agglutination** (ə-glit-ə-nā’shən; *ad* = to, *gluten* = glue). Clumped erythrocytes can block blood vessels and prevent the normal circulation of blood (figure 18.10). Eventually, some or all of the clumped erythrocytes may rupture, a process called **hemolysis** (hē-məl’ ī-sis; *lysis* = destruction). The release of erythrocyte contents and fragments into the blood often causes further hemolytic reactions and ultimately may damage organs. Therefore, compatibility between donor and recipient must be determined prior to blood donations and transfusions using an agglutination test.

<table>
<thead>
<tr>
<th>Donor blood type</th>
<th>Recipient blood type</th>
<th>Agglutination reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Type A blood of donor" /> (has surface antigen A)</td>
<td><img src="image2.png" alt="Type A blood of recipient" /> (contains anti-B antibodies)</td>
<td><img src="image3.png" alt="No clumping seen. Successful blood type match." /></td>
</tr>
<tr>
<td><img src="image1.png" alt="Type A blood of donor" /> (has surface antigen A)</td>
<td><img src="image4.png" alt="Type B blood of recipient" /> (contains anti-A antibodies)</td>
<td><img src="image5.png" alt="Clumping seen. Hemolysis occurs. Unsuccessful blood type match." /></td>
</tr>
</tbody>
</table>

**Figure 18.10 Agglutination Reaction.** (a) If a person receives mismatched blood, antibodies in the blood plasma bind to their respective surface antigens within the erythrocyte plasma membranes; erythrocytes agglutinate (clump) and may block small blood vessels. (b) In a test between plasma and erythrocyte samples, a successful match (no clumping) is compared to an unsuccessful match (clumping). (b) (Top, Bottom) ©Jean Claude Revy/ISM/Medical Images

**WHAT DO YOU THINK?**

3. Why is an individual with type O− blood called a *universal donor*? Likewise, why is an individual with type AB⁺ blood called a *universal recipient*?

**WHAT DID YOU LEARN?**

11. What is the main function of an erythrocyte, and in what ways is an erythrocyte designed to efficiently carry out its function?
12. How do transferrin and ferritin participate in recycling erythrocyte components?
13. What are the structural and molecular differences between type A⁺ blood and type B− blood?
Leukocytes help defend the body against pathogens. Leukocytes differ from erythrocytes in that they are about 1.5 to 3 times larger in diameter, contain a nucleus and cellular organelles, and do not contain hemoglobin. The number of leukocytes in the blood normally ranges between 4500 and 11,000 per cubic millimeter (or microliter) of blood.

Leukocytes are motile (capable of movement within interstitial fluid) and remarkably flexible. In fact, most leukocytes are found within body tissues, as opposed to the blood. Leukocytes enter the tissues from blood vessels by a process called diapedesis (dī-ā-pē-de’sis; dia = through, pedesis = a leaping), whereby they squeeze between the endothelial cells of the blood vessel walls. Chemotaxis (kē-mō-tak’sis) is a process in which leukocytes are attracted to a site of infection by the presence of molecules released by damaged cells, dead cells, or invading pathogens (see figure 22.6). These processes are part of the inflammatory response discussed in depth in section 22.3d.

The five types of leukocytes are divided into two distinguishable classes—granulocytes and agranulocytes—based upon the visible presence or absence of secretory vesicles in the cytosol termed specific granules. The leukocytes are summarized in table 18.7.

**Clinical View 18.6 Rh Incompatibility and Pregnancy**

The potential presence of anti-D antibodies is especially important in pregnant women who are Rh negative and have an Rh positive fetus. An Rh incompatibility may result during pregnancy if the mother has been previously exposed to Rh positive blood (as can occur with a previously carried Rh positive fetus, typically at the time of childbirth). As a result of the prior exposure, the mother has anti-D antibodies that may cross the placenta and destroy the fetal erythrocytes, resulting in severe illness or death. The illness that occurs in the newborn is called hemolytic disease of the newborn (HDN), or erythroblastosis fetalis. The newborn typically presents with anemia and hyperbilirubinemia (increased bilirubin in the blood) due to erythrocyte destruction. In severe cases, the infant may develop heart failure and must be given a blood transfusion to survive.

Giving a pregnant Rh negative woman special immunoglobulins (e.g., RhoGAM) between weeks 28 to 32 of her pregnancy and at birth prevents the mother from developing anti-D antibodies. Specifically, these immunoglobulins bind to fetal erythrocyte surface antigens—and in so doing, prevent the mother’s immune system from recognizing Rh antigens and being stimulated to produce anti-D antibodies.

**Table 18.7**

<table>
<thead>
<tr>
<th>Mother Rh Blood Types</th>
<th>Fetus Rh Blood Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood type</td>
<td>Rh negative</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td>No antigen D</td>
</tr>
<tr>
<td>Plasma</td>
<td>No anti-D antibodies</td>
</tr>
<tr>
<td></td>
<td>(due to prior exposure)</td>
</tr>
</tbody>
</table>

**Hemolytic disease of the newborn.**

Leukocytes are motile (capable of movement within interstitial fluid) and remarkably flexible. In fact, most leukocytes are found within body tissues, as opposed to in the blood. Leukocytes enter the tissues from blood vessels by a process called diapedesis (dī-ā-pē-de’sis; dia = through, pedesis = a leaping), whereby they squeeze between the endothelial cells of the blood vessel walls. Chemotaxis (kē-mō-tak’sis) is a process in which leukocytes are attracted to a site of infection by the presence of molecules released by damaged cells, dead cells, or invading pathogens (see figure 22.6). These processes are part of the inflammatory response discussed in depth in section 22.3d.

The five types of leukocytes are divided into two distinguishable classes—granulocytes and agranulocytes—based upon the visible presence or absence of secretory vesicles in the cytosol termed specific granules. The leukocytes are summarized in table 18.7.
### Leukocytes

#### GRANULOCYTES

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
<th>Functions</th>
<th>Approximate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>Nucleus is multilobed (as many as 5 lobes)</td>
<td>Phagocytize pathogens, especially bacteria</td>
<td>50–70% of total leukocytes (1800–7800 cells per microliter)</td>
</tr>
<tr>
<td></td>
<td>Cytosol contains neutral, or pale, specific granules (when stained)</td>
<td>Release enzymes that target pathogens</td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Nucleus is bilobed</td>
<td>Phagocytize antigen-antibody complexes and allergens</td>
<td>1–4% of total leukocytes (100–400 cells per microliter)</td>
</tr>
<tr>
<td></td>
<td>Cytosol contains reddish or pink-orange specific granules (when stained)</td>
<td>Release chemical mediators to destroy parasitic worms</td>
<td></td>
</tr>
<tr>
<td>Basophils</td>
<td>Nucleus is bilobed</td>
<td>Release histamine (vasodilator and increases capillary permeability) and heparin (anticoagulant) during inflammatory reactions</td>
<td>0.5–1% of total leukocytes (20–50 cells per microliter)</td>
</tr>
<tr>
<td></td>
<td>Cytosol contains deep blue-violet specific granules (when stained)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### AGRANULOCYTES

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
<th>Functions</th>
<th>Approximate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>Round or slightly indented nucleus (fills the cell in smaller lymphocytes)</td>
<td>Coordinate immune cell activity Attack pathogens and abnormal and infected cells Produce antibodies</td>
<td>20–40% of total leukocytes (1000–4800 cells per microliter)</td>
</tr>
<tr>
<td></td>
<td>Nucleus is usually darkly stained</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thin rim of cytosol surrounds nucleus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>Kidney-shaped or C-shaped nucleus</td>
<td>Exit blood vessels and become macrophages Phagocytize pathogens (e.g., bacteria, viruses), cellular fragments, dead cells, debris</td>
<td>2–8% of total leukocytes (100–700 cells per microliter)</td>
</tr>
<tr>
<td></td>
<td>Nucleus is generally pale staining</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abundant cytosol around nucleus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Granulocytes
Granulocytes (gran’u-lō-sī) have specific granules in their cytosol that are clearly visible when viewed with a microscope. When a blood smear is stained to provide contrast, three types of granulocytes can be distinguished: neutrophils, eosinophils, and basophils. Their names refer to the granules’ affinities for certain stains.

Neutrophils
The most numerous leukocyte in the blood is the neutrophil (nət-rō-fīl; neuter = neither, philos = fond), constituting about 50–70% of the total number of leukocytes. The neutrophil is named for its neutral or pale-colored granules within a light lilac-colored cytosol. A neutrophil is about 1.5 times larger in diameter than an erythrocyte. Neutrophils exhibit a multilobed nucleus; as many as five lobes are interconnected by thin strands. For this reason, neutrophils also may be called polymorphonuclear (PMN) leukocytes because of the number of lobes and various shapes of their nuclei.

Neutrophils usually remain in circulation for about 10 to 12 hours before they exit the blood vessels and enter the tissue spaces, where they phagocytize infectious pathogens, especially bacteria. The mechanisms that help destroy bacteria are described in section 22.3b. The number of neutrophils in a person’s blood rises dramatically in the presence of an acute bacterial infection, as more neutrophils are produced that target the bacteria.

Eosinophils
Eosinophils (ē-os′in-ō-fīl; eos = dawn) have reddish or pink-orange granules in their cytosol. Typically, eosinophils constitute about 1–4% of the total number of leukocytes. Their nucleus is bilobed, and the two lobes are connected by a thin strand. An eosinophil is about 1.5 times larger in diameter than an erythrocyte. Eosinophils phagocytize numerous antigen-antibody complexes or allergens (antigens that initiate a hypersensitive or allergic reaction). If the body is infected by parasitic worms, the eosinophils release chemical mediators that attack the worms.

Basophils
Basophils (ba-sō′fil; basis = base) are usually about 1.5 times larger than erythrocytes. They are the least numerous of the granulocytes; typically, basophils constitute about 0.5–1% of the total number of leukocytes. Basophils exhibit a bilobed nucleus and abundant deep blue-violet granules in the cytosol. The primary components of basophil granules are histamine and heparin. When histamine is released from these granules, it causes both an increase in the diameter of blood vessels (called vasodilation) and increased capillary permeability. The classic allergic symptoms of swollen nasal membranes, itchy and runny nose, and watery eyes are partially attributed to the release of histamine. The release of heparin from basophils inhibits blood clotting (a process called anticoagulation).

Agranulocytes
Agranulocytes are leukocytes that have such small specific granules in their cytosol that they are not clearly visible under the light microscope—hence the name agranulocyte (a = without). Agranulocytes include both lymphocytes and monocytes.

Lymphocytes
As their name implies, most lymphocytes (lim’fō-sī) reside in lymphatic organs and structures (e.g., lymph nodes, spleen). Usually, lymphocytes constitute about 20–40% of the total number of leukocytes in the blood. Their dark-staining nucleus is typically rounded, and smaller lymphocytes exhibit only a thin rim of blue-gray cytosol around the nucleus. A lymphocyte usually is about the same size as or slightly larger than an erythrocyte. When activated, lymphocytes grow larger and have proportionally more cytosol. Thus, some of the smaller, nonactivated lymphocytes have a diameter less than that of an erythrocyte, whereas activated lymphocytes may be two times the diameter of an erythrocyte.

There are three categories of lymphocytes. T-lymphocytes (T-cells) manage and direct an immune response; some directly attack foreign cells and virus-infected cells. B-lymphocytes (B-cells) are stimulated to become plasma cells and produce antibodies. NK (natural killer) cells attack abnormal and infected tissue cells. Lymphocytes are examined in detail in section 22.4b.

Monocytes
A monocyte (mon′ō-sī) can be up to three times the diameter of an erythrocyte. Monocytes usually constitute about 2–8% of all leukocytes. The nucleus of a monocyte is kidney-shaped or C-shaped. After approximately 3 days in circulation, monocytes exit blood vessels and take up residence within the tissues, where they transform into large, phagocytic cells called macrophages (mak′rō-fā’j); macros = large, phago = to eat). Macrophages phagocytize bacteria, viruses, cell fragments, dead cells, and debris.

Differential Count and Changes in Leukocyte Profiles
Abnormal numbers of leukocytes result from various pathologic conditions. For example, a reduced number of leukocytes causes a serious disorder called leukopenia (lū-kō-pē′nē-ā; penia = poverty). This decreased number of leukocytes may increase the risk of a person developing an infection or decrease the ability to fight infection effectively. Conversely, leukocytosis (lū-kō-sī-tōs′is) results from a slightly elevated leukocyte count and may be caused by a variety of factors, such as a recent infection or stress.

A differential count, or white blood cell differential count, measures the amount of each type of leukocyte in your blood and determines whether any of the circulating leukocytes are immature. Infection, tissue necrosis, bone marrow failure, cancers, or some other stresses to the body can affect the total ranges or percentages of a specific type of leukocyte, so differential counts are useful for diagnosing ailments.

Acute bacterial infecions, acute stress, and tissue necrosis typically are associated with an increase in neutrophils, called neutrophilia. Their numbers will be in the tens of thousands, and some ailments may cause neutrophil counts of up to 50,000. In addition, as the body tries to produce more and more neutrophils, some immature neutrophils (called band neutrophils, or band cells) enter the circulation and are detected by the differential count. Increased presence of these immature neutrophils is referred to as a left-shifted differential. This phrase reflects that historically a lab printout listed numbers of cells according to maturity from left to right, so an increased number of immature neutrophils was listed on the left. Decreased neutrophil count, called neutropenia, may occur with certain anemias, drug or radiation therapy, and other causes.

INTEGRATE
LEARNING STRATEGY
The mnemonic “Never let monkeys eat bananas” is a simple way to recall the leukocytes in order of their relative abundance:

- Never = Neutrophil (most abundant)
- Let = Lymphocyte
- Monkeys = Monocyte
- Eat = Eosinophil
- Bananas = Basophil (least abundant)
INTEGRATE

CLINICAL VIEW 18.7

Leukemia

Leukemia ([lu-ke’me-a]) is a malignancy (cancer) in the leukocyte-forming cells. There are several categories of leukemia, but all are marked by abnormal development and proliferation of leukocytes, both in the red bone marrow and in the circulating blood. Leukemias represent a malignant transformation of a leukocyte cell line, and as abnormal leukocytes increase in number, the erythrocytic and megakaryocytic lines typically decrease in numbers because the proliferating malignant cells overtake the red bone marrow and leave no room for the normal formed elements (e.g., erythrocytes, mature leukocytes, plateletes). This decrease in erythrocyte and platelet production results in both anemia and bleeding, which are often the first signs of leukemia. Leukemias are classified based on their duration as either acute or chronic.

Acute leukemia progresses rapidly, and death typically occurs within a few months after the onset of symptoms (severe anemia, hemorrhages, and recurrent infections). Acute leukemias tend to occur in children and young adults. Chronic leukemia progresses more slowly; survival usually exceeds 1 year from the onset of symptoms. Symptoms include anemia and a tendency to bleed. Chronic leukemias usually occur in middle-aged and older individuals.

Eosinophil numbers can increase in response to allergic reactions, parasitic infections, or some autoimmune diseases. Monocyte numbers may increase with chronic inflammatory disorders or tuberculosis and may decrease due to prolonged prednisone (steroid) drug therapy. Finally, basophil counts can increase due to myeloproliferative disorders (which result from an overproduction of some formed elements in the bone marrow) and can decrease due to acute allergic and stress reactions.

Viral infections, such as mumps, rubella, or mononucleosis, typically produce an increased number of lymphocytes. Lymphocyte values can increase to 20,000 cells per microliter in extreme cases. Additionally, the lymphocytes develop morphologic changes, in which their cytosol appears watery. Other conditions that can cause lymphocytosis include chronic bacterial infections, some leukemias, and multiple myeloma (a cancer of plasma cells, which are derived from B-lymphocytes). Decreased lymphocyte counts may increase with chronic inflammatory disorders or tuberculosis, parasitic infections, or some autoimmune diseases. Monocyte numbers may increase with chronic inflammatory disorders or tuberculosis and may decrease due to prolonged prednisone (steroid) drug therapy. Finally, basophil counts can increase due to myeloproliferative disorders (which result from an overproduction of some formed elements in the bone marrow) and can decrease due to acute allergic and stress reactions.

18.4 Hemostasis

When your blood vessels are healthy and functioning well, blood flows through them freely and does not clot unnecessarily. But if there is damage to a blood vessel, hemostasis is initiated. Hemostasis (he’mō-stā’sis; hemo = blood, stasis = stability) is a stoppage of bleeding. It consists of three sequential phases, although there is some overlap between phases: vascular spasm, platelet plug formation, and the coagulation phase (figure 18.12).

18.4a Vascular Spasm

LEARNING OBJECTIVES

21. Describe vascular spasm, the first phase of hemostasis.
22. Name conditions that bring about vascular spasm.

When a blood vessel is injured, the first phase in hemostasis to occur, which begins immediately, is a vascular spasm, whereby damage to smooth muscle within the vessel wall causes smooth muscle contraction. This contraction results in vasoconstriction (i.e., the blood vessel lumen narrows) and thus limits the amount of blood that can leak from this damaged vessel. The spasm continues during the next phase, as both platelets and the endothelial cells of the blood vessel wall release an array of chemicals to further stimulate the vascular spasms.

The vascular spasm phase usually lasts from a few to many minutes. The more extensive the vessel and tissue damage, the greater the degree of vasoconstriction.


**WHAT DID YOU LEARN?**

17. What occurs during a vascular spasm, and how long does this phase last?

18.4b Platelet Plug Formation

**LEARNING OBJECTIVE**

23. Describe what happens when platelets encounter damage in a blood vessel.

The next phase in hemostasis is the formation of a platelet plug. Normally, the endothelial wall (inner lining of a blood vessel) is smooth and is coated with an eicosanoid (see section 17.3b) called prostacyclin, which activates a pathway in both platelets and endothelial cells that involves production of cAMP to ultimately inhibit platelet activation. (The prostacyclin is produced by the endothelial cells in the vessel wall.) The end result is that prostacyclin serves as a platelet repellent. However, once a blood vessel is damaged, the collagen fibers within the connective tissue internal to the endothelial cells in the vessel wall become exposed. Platelets begin to stick to the exposed collagen fibers. Platelets adhere to the collagen fibers with the assistance of a plasma protein called von Willebrand factor, which serves as a bridge between platelets and collagen fibers.

Platelets start to stick to the vessel wall and their morphology changes dramatically; they develop long processes that further adhere them to the blood vessel wall. As more and more platelets aggregate to the site, a platelet plug develops to close off the injury. The timing of this entire phase typically is less than a few minutes for a small- to medium-sized injury. Again, this is a temporary measure to block the flow of blood through the vessel wall where it is damaged.

Platelets undergo this morphologic change and become activated: Their cytosol degranulates, releasing chemicals to assist with hemostasis. The following processes occur in response to these different chemicals:

- **Prolonged vascular spasms** (due to smooth muscle contractions) with the release of serotonin and thromboxane A2 (an eicosanoid)
- **Attraction of other platelets** with the release of adenosine diphosphate (ADP) and thromboxane A2, which facilitates the degranulation and release of these chemicals in other platelets
- **Stimulation of coagulation** with the release of procoagulants that enhance blood clotting (the third phase)
- **Repair of the blood vessel** as platelets secrete substances to stimulate epithelial tissue, smooth muscle, and fibroblasts (cells of connective tissue) to replicate

**WHAT DO YOU THINK?**

4. Is the formation of the platelet plug an example of negative feedback or positive feedback?

Note that platelets not only are involved in the second phase of platelet plug formation but also increase events of the first and third phases, vascular spasm and coagulation phase, respectively. Thus, through the release of specific substances, platelets increase all three processes of hemostasis. (Thus, decreased hemostasis becomes a concern in individuals with a low platelet count, known as thrombocytopenia.)

The formation of the platelet plug is an example of positive feedback and typically is formed within 1 minute. But what is to prevent a platelet plug from becoming too big and growing out of control? As just mentioned, endothelial cells normally release prostacyclin. The healthy endothelial cells near the site of injury are still releasing their prostacyclin, so the plug does not grow larger than what is needed. The next phase, the coagulation phase, is beginning.

**WHAT DID YOU LEARN?**

18. What prevents platelets from forming plugs in healthy blood vessels?

19. How do platelets serve a central function in all three phases of hemostasis?
18.4c Coagulation Phase

**LEARNING OBJECTIVES**

24. Compare and contrast the intrinsic pathway and the extrinsic pathway for activating blood clotting.
25. Describe events in the common pathway.
26. Discuss the survival response that occurs when blood loss exceeds 10%.

Perhaps the most important and most complex component of hemostasis is **coagulation**, or blood clotting. A blood clot has an insoluble protein network composed of fibrin, which is derived from soluble fibrinogen. This meshwork of protein traps other elements of the blood, including erythrocytes, leukocytes, platelets, and plasma proteins, to form the clot (figure 18.11).

**Substances Involved in Coagulation**

Blood coagulation is a process that requires numerous substances, including calcium, clotting factors, platelets, and vitamin K. The specific clotting factors, including their numerical designation, name, function, and pathway and the disorders associated with the factor, are listed in [table 18.8](#). Note that the clotting factor numbers are in order of their discovery, and not their position in the clotting pathway.

Most clotting factors are inactive enzymes, and most of these are produced by the liver. Vitamin K is a fat-soluble vitamin that is required for the synthesis of clotting factors II, VII, IX, and X; it acts as a coenzyme (see section 3.3c). Proteases (i.e., enzymes that break peptide bonds within a protein) such as factor VII and IX, when activated, act as scissors to convert another separate factor from its inactive to its active form. This active factor acts as scissors to convert yet

<table>
<thead>
<tr>
<th>Table 18.8 Clotting Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor Designator</strong></td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>V</td>
</tr>
<tr>
<td>VI</td>
</tr>
<tr>
<td>VII</td>
</tr>
<tr>
<td>VIII</td>
</tr>
<tr>
<td>IX</td>
</tr>
<tr>
<td>X</td>
</tr>
<tr>
<td>XI</td>
</tr>
<tr>
<td>XII</td>
</tr>
<tr>
<td>XIII</td>
</tr>
</tbody>
</table>

1. All proteins produced by the liver except tissue factor (thromboplastin; factor III) formed by perivascular tissue; fibrin-stabilizing factor (factor XIII) produced by platelets and plasma; and factor IV, which is simply Ca\(^{2+}\) (not a protein). Hageman factor is produced by both the liver and platelets. Additional factors released from platelets: platelet factors 1, 2, 3, and 4.
2. This item is a hypercoagulation problem and not due to deficient clotting factor.
3. Named for the first person diagnosed with the disease.
CLINICAL VIEW 18.8

Bleeding and Blood Clotting Disorders

If hemostasis fails to occur when needed, uncontrolled bleeding and death could result. On the other hand, if hypercoagulation develops, then unwanted blood clots could form in the blood and lead to the risk of deep vein thrombosis (blood clot in the leg), pulmonary embolism (blood clot in the lung), stroke (blood clot in the brain), or heart attack. Here we discuss several blood clotting disorders.

Bleeding Disorders

Bleeding disorders can be caused by several different conditions, including hemophilia, a vitamin K deficiency, thrombocytopenia, or intake of various drugs.

Hemophilia is a group of bleeding disorders caused by specific genetic mutations. The two most common types of hemophilia are hemophilia A and hemophilia B, both of which are inherited in an X-linked recessive pattern. Females typically are carriers of the gene but may not experience symptoms because they have two X chromosomes, and one of the two X chromosomes may be normal. In contrast, males typically exhibit the full-blown disease because they have only one X chromosome.

Hemophilia A, also known as classic hemophilia, represents the vast majority of all hemophilias. It results in a deficiency or complete lack of normal factor VIII protein in the clotting cascade; the protein is abnormal and typically cannot participate in the proper clotting of the blood. This hemophilia occurs in approximately 1 in 5000 males in the United States. Hemophilia B is a deficiency of factor IX. It occurs in approximately 1 in 25,000 males in the United States.

Hemophilia C is a relatively rare autosomal dominant deficiency of factor XI. It occurs in approximately 1 in 25,000 males in the United States. Hemophilia A, B, and C are the three most common of which is the classic hemophilia, a vitamin K deficiency, thrombocytopenia, or intake of various drugs [NSAIDs], and warfarin (Coumadin), and some herbal supplements (e.g., ginkgo biloba, garlic supplements) interfere with blood clotting and may cause bleeding if taken at sufficiently high doses. Physicians always should be monitoring their patients for bleeding disorders if they are taking any of these medications regularly. Additionally, they should ask their patients what herbal supplements they may be taking, so as to avoid any herbal supplement–drug interactions.

Hypercoagulation Problems

The term hypercoagulation refers to an increased tendency for blood to clot. Hypercoagulation can lead to a thrombus (thrombūs; thrombos = clot), which is a clot within a blood vessel. If the thrombus dislodges and is transported within the blood, it is called an embolus (em-bō′lūs; embolus = wedge or stopper). An embolus is particularly dangerous because it can wedge within an artery and obstruct blood flow. A pulmonary embolism occurs in the pulmonary circulation of the lungs and can lead to breathing problems and perhaps death if not treated, whereas an embolus that is transported to the blood vessels of the brain can cause a stroke. Treatment for a thrombus or an embolus typically is with blood thinning medication (e.g., warfarin, heparin, low-molecular-weight heparin).

Hypercoagulation can also have drug-related, environmental, and genetic causes. Certain medications such as birth control pills or hormone replacement therapy are associated with an increased risk of developing blood clots. Smoking greatly increases your risk, as nicotine is a vasoconstrictor, and it appears smoking increases levels of blood components related to clotting. Environmental causes include prolonged bedrest, surgery, pregnancy, or sitting in an airplane seat for a long time. In all of these cases, blood may pool in veins that are not being worked by exercise, and clotting can occur.

Genetic causes of hypercoagulation can be due to mutations of several genes, the most common of which is the Leiden mutation, which is a mutation of the gene for the synthesis of factor V. This mutation is present in 3% of the population and 3–15% of all Caucasians, and it accounts for 20–40% of all venous thromboses. Individuals with this mutation are unable to inactivate factor V in the clotting cascade, causing hypercoagulation and increased risk of thrombus formation. Young (under age 50), active individuals who present with a thrombus or an embolus, and who don’t have other significant risk factors for clotting, may need to be screened for these genetic mutations.

Initiation of the Coagulation Cascade

The initiation of blood clotting can occur by two separate mechanisms: the intrinsic pathway (also known as the contact activation pathway) or the extrinsic pathway (or tissue factor pathway) (figure 18.13). Both pathways converge, through a series of complicated steps, to the common pathway.

The intrinsic pathway is triggered by damage to the inside of the vessel wall and is initiated by platelets. This pathway typically takes approximately 3 to 6 minutes:

1. Platelets adhering to a damaged vessel wall release factor XII.
2. Factor XII converts the inactive factor XI to the active factor XI.
3. Factor XI converts inactive factor IX to active factor IX.
4. Factor IX binds with Ca²⁺ and platelet factor 3 to form a complex that converts inactive factor VIII to active factor VIII.
5. Factor VIII converts inactive factor X to active factor X.

In contrast, the extrinsic pathway is initiated by damage to the tissue that is outside the vessel, and this pathway usually takes approximately 15 seconds. This pathway occurs more quickly because there are fewer steps required. The steps include the following:

1. Tissue factor (thromboplastin; factor III) released from damaged tissues combines with factor VII and Ca²⁺ to form a complex.
2. This complex converts inactive factor X to active factor X.

In both the intrinsic and extrinsic processes of clotting initiation, the final result is the production of factor X (factor 10). Use these tips to remember the sequence of factors:

- In the intrinsic pathway, a series of steps takes you to X by counting backward from 12 to 8—factors XII, XI, IX, and VIII (simply skip 10 because that is “the goal”).
- The extrinsic pathway involves the coming together of factors VII and III, and if you add 7 and 3, the result is 10 (X).
Figure 18.13 Coagulation Pathways. The process of coagulation typically involves both an intrinsic and an extrinsic pathway. Both pathways “merge” into a common pathway that ultimately converts fibrinogen (factor I) into fibrin.
Factor X, activated by either the intrinsic or extrinsic pathway, is the first step in the common pathway:

1. Active factor X combines with factors II and V, Ca$^{2+}$, and platelet factor 3 (PF3) to form prothrombin activator.
2. Prothrombin activator activates prothrombin to thrombin.
3. Thrombin converts soluble fibrinogen into insoluble fibrin.
4. In the presence of Ca$^{2+}$, factor XIII is activated. Factor XIII cross-links and stabilizes the fibrin monomers into a fibrin polymer that serves as the framework of the clot.

Other components of blood become trapped in this spiderweb-like protein mesh. Like platelet plug formation, the clotting cascade is regulated by positive feedback (see section 1.6c). Once initiated by the intrinsic or extrinsic pathway, the events of the clotting cascade continue until a clot is formed (the climactic event). The size of the clot is limited because thrombin is either trapped within the clot or quickly degraded by enzymes within the blood.

The Sympathetic Response to Blood Loss

In severe cases, when over 10% of the blood volume has been lost, a survival response is initiated.

As blood volume decreases, blood pressure decreases. If greater than 10% of the blood volume is lost from the blood vessels, the sympathetic division of the autonomic nervous system (ANS) is activated (see section 15.4), bringing about increased vasoconstriction of blood vessels, increased heart rate, and increased force of heart contraction in an attempt to maintain blood pressure. Blood flow is also redistributed to the heart and brain to keep these vital structures functioning. These processes are effective in maintaining blood pressure until approximately 40% of the blood is lost. Blood loss greater than 40% results in insufficient blood volume within the blood vessels, and blood pressure decreases to levels unable to support life.

A “balancing act” is occurring continually within your blood between clot formation processes and those processes that prevent clot formation. The balance can be tipped so that blood clotting is initiated. A damaged blood vessel, impaired blood flow, atherosclerosis, or inflammation of the blood vessels can initiate blood clotting. Additionally, certain nutrients and vitamins must be present and available for blood clotting to occur normally. For example, calcium is used during the clotting process, and vitamin K is required for the synthesis of certain plasma proteins by the liver. Problems with the balance can lead to either bleeding or blood clotting disorders.

**18.5 Development and Aging of Blood**

**LEARNING OBJECTIVES**

28. Describe when and how blood is formed in the embryo, fetus, childhood, and adulthood.
29. List some conditions that occur with the bone marrow and blood in the elderly.

The first primitive hemopoietic stem cells develop in the yolk sac wall of the embryo by the third week of development. The primitive hemopoietic stem cells go on to colonize other organs, such as the liver, spleen, and thymus. In these organs, these very primitive stem cells develop into the hemocytoblasts that produce all of the formed elements. Later in fetal development (perhaps beginning at 10 weeks), the hemocytoblasts begin to colonize red bone marrow, although the liver doesn’t completely cease its blood cell production until close to birth.

Recall from section 7.2d that hemopoiesis occurs in most bones in young children, but as an individual reaches adulthood, hemopoiesis is restricted to selected bones in the axial skeleton. More red bone marrow is replaced with fat as individuals continue to age. Thus, older individuals have relatively less red bone marrow and may be more prone to developing anemia, which is a decrease in the ability to deliver oxygen to body cells. This decreased ability may be due to either a decrease in the numbers of circulating erythrocytes or lower than normal amounts of hemoglobin. In addition, older red bone marrow may be less able to meet any demands for an increased number of leukocytes. The leukocytes in the elderly may be less efficient and active than those in younger individuals, and the elderly also may have decreased numbers of leukocytes. Certain types of leukemias also are more prevalent among the elderly, probably due to the immune system (and its leukocytes) being less efficient.

**WHAT DID YOU THINK?**

5. Predict why an individual confined to a wheelchair is more likely to develop unwanted clots.

**WHAT DID YOU LEARN?**

22. What is fibrinolysis, and what is its purpose?

23. Where does hemopoiesis occur in (a) a fetus, (b) a child, and (c) an adult?

24. What are some ways that red bone marrow changes in the elderly?
### CHAPTER SUMMARY

**18.1 Functions and General Composition of Blood**
- **18.1a Functions of Blood**
  - Blood transports nutrients, wastes, and respiratory gases; regulates body temperature, pH, and fluid levels; and protects the body against the activities of pathogens and the loss of blood.
- **18.1b Physical Characteristics of Blood**
  - The physical characteristics of blood include color, volume, viscosity, plasma concentration, temperature, and pH.
- **18.1c Components of Blood**
  - Centrifugation separates blood into three components: erythrocytes, a buffy coat composed of leukocytes and platelets, and plasma.
  - Hematocrit represents the percentage of formed elements in blood. Males typically have higher hematocrits than females.
  - Formed elements can be viewed in a blood smear.

**18.2 Composition of Blood Plasma**
- Blood plasma is a mixture of water, plasma proteins, and other solutes. It forms about 55% of whole blood.
- **18.2a Plasma Proteins**
  - Plasma is similar in composition to interstitial fluid, except the plasma contains proteins.
  - Plasma proteins include albumin, globulins, fibrinogen and other clotting proteins, and regulatory proteins.
- **18.2b Other Solutes**
  - Other solutes include electrolytes, nutrients, respiratory gases, and waste products.

**18.3 Formed Elements in the Blood**
- Formed elements include erythrocytes that transport respiratory gases, leukocytes that serve some roles in protecting the body from harmful substances, and platelets that participate in hemostasis.
- **18.3a Hemopoiesis**
  - Hemopoiesis is the process by which formed elements develop.
  - Formed elements develop in the red bone marrow from stem cells called hemocytoblasts.
- **18.3b Erythrocytes**
  - Erythrocytes exhibit a biconcave disc structure that facilitates the exchange of respiratory gases into and out of the erythrocytes.
  - Hemoglobin is a pigmented protein within mature erythrocytes; it transports oxygen and carbon dioxide.
  - Erythrocyte production is controlled by erythropoietin (and indirectly by testosterone).
  - Aged erythrocytes are broken down and their components recycled after about 120 days in the blood.
  - The ABO blood group consists of surface antigens (A or B) on the erythrocytes and plasma antibodies (anti-A or anti-B). Blood type is determined by the surface antigens on the erythrocytes (type O blood has no antigens). Individuals have plasma antibodies in their blood that are different from their surface antigens.
- **18.3c Leukocytes**
  - Leukocytes are white blood cells that defend against invading pathogens and remove damaged cells, debris, and antigen-antibody complexes.
  - The types of leukocytes are granulocytes (neutrophils, eosinphils, and basophils) and agranulocytes (lymphocytes and monocytes).
- **18.3d Platelets**
  - Platelets are cellular fragments derived from megakaryocytes and function in hemostasis.

**18.4 Hemostasis**
- Hemostasis is a process to halt bleeding. There are three phases of hemostasis: vascular spasm, platelet plug formation, and the coagulation phase.
- **18.4a Vascular Spasm**
  - When a blood vessel wall is damaged, the vessel undergoes vascular spasms and constricts as smooth muscle within the blood vessel wall contracts.
- **18.4b Platelet Plug Formation**
  - Platelets stick to the exposed collagen fibers within the damaged vessel wall, the platelets degranulate, and they release an array of chemicals to (1) attract more platelets to the site, (2) enhance the vascular spasm phase, (3) act as procoagulants, and (4) initiate healing of the blood vessel wall.
  - The platelets form a plug to close off the broken part of the blood vessel wall.
- **18.4c Coagulation Phase**
  - Coagulation is a clotting cascade involving the activation of numerous clotting factors that results in a network of fibrin strands that trap formed elements and plasma proteins.
  - The clotting cascade consists of an intrinsic pathway (which is initiated within a blood vessel by platelets), an extrinsic pathway (which is initiated by substances released outside the blood vessel), and a common pathway that produces fibrin.
- **18.4d Elimination of the Clot**
  - The blood clot is removed through clot contraction and fibrinolysis.

**18.5 Development and Aging of Blood**
- The first hemopoietic stem cells arise from the yolk sac wall in the embryo.
- In the fetus, hemopoiesis shifts to the liver, and then shifts to red bone marrow.
- Older individuals may have decreased production of formed elements.
1. Which individual is most likely to have the highest hematocrit level?
   a. a 10-year-old child
   b. a dehydrated adult male
   c. a healthy, nonmenstruating adult female
   d. a healthy, menstruating adult female

2. Which type of leukocyte increases during allergic reactions and parasitic worm infections?
   a. basophil
   b. eosinophil
   c. lymphocyte
   d. neutrophil

3. Which cell type forms platelets in the red bone marrow?
   a. lymphocyte
   b. megakaryocyte
   c. eosinophil
   d. reticulocyte

4. Which of the following is not a function of blood?
   a. prevention of fluid loss
   b. transport of nutrients and waste
   c. maintenance of constant pH levels
   d. production of hormones

5. A person with blood type A has
   a. anti-B antibodies in her blood plasma.
   b. anti-A antibodies in her blood plasma.
   c. both anti-A and anti-B antibodies in her blood plasma.
   d. no antibodies in her blood plasma.

6. The hematocrit is a measure of
   a. water concentration in the plasma.
   b. the percentage of formed elements in the blood.
   c. the number of platelets in the blood.
   d. antibody concentration in the plasma.

7. Oxygen attaches to a(n) _____ ion in hemoglobin.
   a. calcium
   b. sodium
   c. iron
   d. potassium

8. During the recycling of components following the normal destruction of erythrocytes, globin is broken down, and its components are
   a. used to synthesize new proteins.
   b. stored as iron in the liver.
   c. eliminated from the body in the bile.
   d. removed in the urine.

9. The extrinsic pathway of coagulation is initiated by
   a. platelets.
   b. fibrinogen.
   c. factor VIII.
   d. damage to tissue.

10. A clot is best described as
    a. an aggregation of platelets.
    b. a fibrin network with trapped formed elements.
    c. agglutination of erythrocytes.
    d. All of these contribute to the formation of a clot.

11. How does blood help regulate body temperature?

12. What are alpha- and beta-globulins? What do they do?

13. When blood is centrifuged, a thin, whitish-gray layer called the buffy coat covers the packed erythrocytes. What are the components of the buffy coat?

14. What is the shape of an erythrocyte, and why is this shape advantageous to its function?

15. How are respiratory gases (oxygen and carbon dioxide) transported by erythrocytes?

16. What are the anatomic characteristics of each type of leukocyte? How can you tell these leukocytes apart when you view a blood smear under the microscope?

17. How do the functions of basophils differ from those of lymphocytes?

18. Briefly describe the origin, structure, and functions of platelets.

19. Compare and contrast the formation of lymphocytes versus granulocytes and monocytes. What precursor cells form each? What specific formed elements are formed from each? What is the common stem cell from which all leukocytes originate?

20. Describe the three phases of hemostasis, and list the major events that occur in each phase.

---

Can You Apply What You’ve Learned?

Use the following paragraph to answer questions 1–5.

Taylor is an active 25-year-old woman. She was brought into the emergency room after being hit by a car. Taylor suffered extensive blood loss, and the physicians felt she might be in need of a transfusion. They began the procedure of typing her blood.

1. Taylor’s blood type was determined to be type A−. This meant she could be transfused with type
   a. A+.
   b. O+.
   c. AB−.
   d. O−.
2. Taylor was weak but conscious. The physicians asked her what medications, if any, she had taken. They asked her to list herbal supplements, pain relievers, and any multivitamins she took over the last few days. Her list included Advil (ibuprofen)—2 tablets that morning, 2 tablets that afternoon; a multivitamin—daily; a birth control pill—daily; and an iron supplement—daily. Which of these medications, if any, would exacerbate and prolong Taylor’s bleeding?
   a. Advil
   b. multivitamin
   c. birth control pill
   d. iron supplement

3. Which sequence or pathway best describes the process of hemostasis that must occur in Taylor to stop her bleeding?
   a. intrinsic pathway → common pathway → clotting
   b. common pathway → extrinsic pathway → clotting
   c. extrinsic pathway → common pathway → clotting
   d. intrinsic pathway → extrinsic pathway → clotting

4. Taylor was given the proper blood type and admitted into the hospital to recuperate from her injuries. The following evening, Taylor presented with a high fever, and the physicians suspected she had the complication of an acute bacterial infection. They sent her blood to the lab for a differential count. Assuming the physicians’ guess was correct, the lab results would be returned showing which of the following?
   a. increased number of eosinophils
   b. decreased number of basophils
   c. increased number of neutrophils
   d. increased number of lymphocytes

5. Taylor recovered from her injuries and left the hospital. Several months later, Taylor discovered that she was pregnant with her first child. Her OB/GYN told her she needed to take RhoGAM to ensure this pregnancy would culminate normally and there would be no problems for her child. If Taylor did not take RhoGAM, what complication could occur?
   a. The baby could develop anti-D antibodies to Taylor’s A− blood.
   b. The anti-D antibodies in Taylor’s blood could attack the erythrocytes of all subsequent babies that Taylor carried.
   c. The child could survive only if it also had an A+ blood type.
   d. The anti-D antibodies in the baby’s blood could attack Taylor’s erythrocytes.

Can You Synthesize What You’ve Learned?

1. While taking a clinical laboratory class, Marilyn prepared and examined blood smears from several donors. One of the smears had an increased percentage (about 10% of observed leukocytes) of cells containing reddish-orange granules. Discuss the type of cell described and the condition that may have caused this increase in the donor.

2. Abby is a nurse on duty in a hospital emergency room when a critically injured patient is brought in. The physician calls for an immediate blood transfusion, but the patient’s blood type is unknown. What blood type should the patient be given, and why?

3. Your roommate and you are watching the track and field events at the Olympics. One of the sportscasters mentions that a particular athlete has been banned from competing because he was found guilty of blood doping. Your roommate asks you what blood doping is and why an athlete would be banned for doping his blood. How would you answer your roommate?
When we think about staying healthy, many thoughts may come to mind: eating a diet that includes plenty of fruits and vegetables with limited amounts of fat and salt, participating in regular aerobic exercise, getting plenty of rest, and avoiding unhealthy behaviors such as smoking and heavy drinking. One significant reason for following this advice is to minimize our risk for developing cardiovascular disease. The importance of doing so becomes more obvious when we realize that cardiovascular disease—which is any disease that affects the heart or blood vessels—is the leading cause of death, both in the United States and worldwide.

We discuss the cardiovascular system in both this chapter on the heart and the next chapter on blood vessels. Our goal is to provide a clear and straightforward discussion on both a normal, healthy cardiovascular system and some of its more common malfunctions (e.g., myocardial infarction, heart murmurs, atherosclerosis, and circulatory shock). We hope to help you to develop both an understanding of and an appreciation for this system—a system so central to life that when it fails, the outcome often proves fatal.
19.1 Introduction to the Cardiovascular System

The cardiovascular (kar′dē-ō-vas′kū-lər; cardio = heart, vascular = vessels) system is composed of both the heart and the blood vessels (figure 19.1). Here we describe the general function of the cardiovascular system, provide an overview of its components, and then examine how these components are organized into two circuits: pulmonary circulation and systemic circulation.

19.1a General Function

LEARNING OBJECTIVE

1. Describe the general function of the cardiovascular system.

The general function of the cardiovascular system is to circulate blood throughout the body to meet the changing needs of body cells. To remain healthy, all cells require (1) a continuous delivery of oxygen and nutrients and (2) the removal of carbon dioxide and other waste products. Additionally, cells of each body system have their own specific needs that must be met. Examples of the different requirements of specific body systems are presented in the Concept Connection on this page.

Providing Adequate Perfusion

The cardiovascular system is effective in fulfilling its function if it provides adequate perfusion to maintain the health of all body cells. Perfusion (per-fyʊ′zhən; perfusio = pouring) is the delivery of blood per unit time per gram of tissue. It is typically expressed in milliliters per minute per gram (mL/min/g). Maintaining adequate perfusion requires both the continual pumping action of the heart...
and healthy, patent (open and unblocked) blood vessels. If the heart fails to pump sufficient volumes of blood, or the vessels become hardened or occluded (blocked), then an adequate amount of blood may not reach the body’s cells. Thus, tissues will be deprived of needed oxygen and nutrients, waste products accumulate, and cell death may occur.

**WHAT DID YOU LEARN?**

1. Define perfusion. Why would it be significant if the cardiovascular system failed to maintain adequate perfusion?

### 19.1b Overview of Components

#### LEARNING OBJECTIVES

2. Differentiate among the three primary types of blood vessels.
3. Describe the general structure and function of the heart.

Here we provide an overview of the components of the cardiovascular system: (1) the primary types of blood vessels, through which blood is transported, and (2) the heart, which pumps the blood.

## Blood Vessels

Blood vessels are the conduits, or “soft pipes,” of the cardiovascular system that transport blood throughout the body (figure 19.1). They are categorized into three primary types: Arteries (ar’ter-ēz) transport blood away from the heart; veins (vānz) transport blood toward the heart; and capillaries (kap’i-lār-ēz; relating to hair) serve as the sites of exchange, either between the blood and the alveoli (air sacs) of the lungs or between the blood and the systemic cells. (The details of blood vessel anatomy are described in section 20.1.)

A common error is to describe arteries as the vessels that always transport oxygenated (ok’si-jē-nēd) blood (blood high in O₂ and low in CO₂) and veins as the vessels that always transport deoxygenated blood (blood low in O₂ and high in CO₂). As you will see, this is not an accurate generalization; in some parts of the cardiovascular system, the reverse is true. The defining factor is whether the blood is moving away from the heart (as it does in arteries) or toward the heart (as it does in veins).

## The Heart

The heart is the center of the cardiovascular system. It is a hollow, four-chambered organ that pumps blood throughout the body. Three anatomic features are significant in the normal function of the heart: (1) the two sides of the heart, (2) the great vessels attached to the heart, and (3) the two sets of valves located within the heart (figure 19.2).

**Figure 19.2 Significant Anatomic Features of the Heart.** The heart is composed of the following features seen in an anterior view: (a) a right side and a left side, (b) great vessels that are directly attached to it, and (c) two sets of valves that permit one-way flow of blood.
First, the heart is composed of two sides: the right side and the left side (figure 19.2a). The two sides of the heart allow separation of circulating deoxygenated and oxygenated blood:

- The right side of the heart receives deoxygenated blood from the body and pumps it to the lungs. (The blue shading in figure 19.2 [and throughout this chapter] represents deoxygenated blood.)
- The left side of the heart receives oxygenated blood from the lungs and pumps it to the body. (The red shading in figure 19.2 [and throughout this chapter] represents oxygenated blood.)

Notice that each side of the heart must both receive blood and pump blood. These two tasks are the functions of different types of chambers present on each side of the heart. A smaller chamber called an atrium receives blood, and a larger chamber called a ventricle pumps blood. Thus, four chambers in the heart are identified. On the right side of the heart are the right atrium and right ventricle, and on the left side of the heart are the left atrium and left ventricle.

Second, blood is transported directly to and from the chambers of the heart by the great vessels that directly connect with specific chambers of the heart (figure 19.2b). These vessels include both arteries and veins. There are two large arteries (or arterial trunks) attached to the superior border of the ventricles: They transport blood from a ventricle away from the heart. The pulmonary trunk transports blood from the right ventricle, whereas the aorta (ā-ôr’tā) transports blood from the left ventricle. Large veins deliver blood to the heart into an atrium. These include the two venae cavae: the superior vena cava (SVC), which drains blood from the head, neck, upper limbs, and superior region of the trunk (essentially from areas above the heart), and the inferior vena cava (IVC), which drains blood from the lower limbs and inferior regions of the trunk (essentially from areas below the heart). Both venae cavae drain blood into the right atrium. In addition, the pulmonary veins drain blood from the lungs into the left atrium. Remember, ventricles pump blood into the arterial trunks, and atria receive blood from the veins.

**WHAT DID YOU THINK?**

1. What vessels attached to the heart contain oxygenated blood? Are they both arteries? Explain.

Third, two sets of valves are located within the heart (figure 19.2c). The atrioventricular (ā-trē-ō-ven-trik’ā-lər) (AV) valves are between the atrium and ventricle of each side of the heart. The right AV valve, also called the tricuspid valve, is located between the right atrium and the right ventricle. (Remember that the TRicuspid is on the RIght side.) The left AV valve, also called the bicuspid valve, or mitral valve, is located between the left atrium and left ventricle.

The other set of valves is the semilunar valves, which mark the boundary between a ventricle and its associated arterial trunk. (Note that each is named for its associated arterial trunk.) The pulmonary semilunar valve is between the right ventricle and the pulmonary trunk, and the aortic semilunar valve is between the left ventricle and the aorta. The valves open to allow blood to flow through the heart and then close to prevent its backflow. This ensures one-way, or unidirectional, flow of blood through the heart.

**WHAT DID YOU LEARN?**

1. What generalization can be made about all arteries? What generalization can be made about all veins?
2. Where does the right ventricle pump blood? Where does the left ventricle pump blood?
3. What great veins deliver blood to the right atrium? What great veins deliver blood to the left atrium?
4. Where are AV valves located within the heart? Where are semilunar valves located within the heart?

**19.1c Pulmonary and Systemic Circulation**

**LEARNING OBJECTIVE**

4. Compare and contrast pulmonary circulation and systemic circulation of the cardiovascular system. Trace blood flow through both circulations.

The two sides of the heart and the blood vessels are arranged in two circuits: the pulmonary circulation and systemic circulation. View figure 19.3 as you read through this section.

The pulmonary (pūl’mō-nār-ē; pulmo = lung) circulation (or pulmonary circuit) includes the movement of blood to and from the lungs for gas exchange. Deoxygenated blood is transported from (1) the right side of the heart through blood vessels to (2) the lungs. Exchange of respiratory gases occurs within the lungs as oxygen moves from the alveoli into the blood and
Figure 19.3 Cardiovascular System Circulations. The cardiovascular system is composed of the pulmonary circulation (steps 1, 2 and back to step 3) and the systemic circulation (steps 3, 4 and back to step 1).

Carbon dioxide moves from the blood into the alveoli. Oxygenated blood is then transported through blood vessels to (3) the left side of the heart. Thus, the pulmonary circulation is movement of blood from the right side of the heart, to the lungs, and back to the left side of the heart.

The systemic circulation (or systemic circuit) includes the movement of blood to and from the systemic cells. Oxygenated blood is transported from (3) the left side of the heart through blood vessels to (4) the systemic cells such as those of the liver, skin, muscle, and brain. Exchange of respiratory gases occurs at systemic cells as oxygen moves from the blood into systemic cells and carbon dioxide moves from systemic cells into the blood. Deoxygenated blood is then transported through blood vessels that return blood to the (1) right side of the heart. Thus, the systemic circulation is movement of blood from the left side of the heart, to the systemic cells of the body, and back to the right side of the heart. The overall pattern of blood flow as shown in the inset in figure 19.3 is (1) the right side of the heart → (2) the lungs → (3) the left side of the heart → (4) the systemic cells of the body → back to the right side. Notice that the right side of the heart pumps blood to the lungs and the left side of the heart pumps blood to the systemic cells. This has important clinical implications if one side of the heart fails (see Clinical View 19.1: “Congestive Heart Failure”).

The details of the blood flow pattern are summarized in figure 19.4. Consider spending some time reviewing this figure and becoming familiar with the details of both the pulmonary circulation and the systemic circulation. This will provide you with the “big picture” of the cardiovascular system to keep in mind as the details of the heart are covered in the remaining sections of this chapter and the details of blood vessels are covered in chapter 20.

**WHAT DID YOU LEARN?**

6. What path does blood follow through the heart and through the two circulations? Identify all structures that it passes through, including each chamber, valve, and great vessel. Begin at the right atrium (figure 19.4).

7. Which of the great vessels is an artery and transports deoxygenated blood? Which of the great vessels is a vein and transports oxygenated blood?
Figure 19.4 Blood Flow Through the Heart and Circulatory Routes. The two circulatory routes for blood flow are (a) the pulmonary circulation, which includes the pumping of blood by the right side of the heart to the lungs and the return of blood to the left side of the heart, and (b) the systemic circulation, which includes the pumping of blood by the left side of the heart to the systemic cells and the return of blood to the right side of the heart.

(a) Pulmonary Circulation

Transports blood from the right side of the heart to the alveoli of the lungs for gas exchange and back to the left side of the heart.

Blood flow through pulmonary circulation:
1. Deoxygenated blood enters the right atrium from the venae cavae (SVC and IVC) and coronary sinus (not shown). This blood then passes through the right AV valve (tricuspid valve).
2. enters the right ventricle,
3. passes through the pulmonary semilunar valve, and
4. enters the pulmonary trunk.
5. This blood continues through the right and left pulmonary arteries to both lungs, and
6. enters pulmonary capillaries of both lungs for gas exchange.
7. This blood, which is now oxygenated, enters right and left pulmonary veins, and is returned to
8. the left atrium of the heart.
**Blood flow through systemic circulation**

1. Oxygenated blood enters the **left atrium**, passes through the **left AV valve** (bicuspid or mitral valve), enters the **left ventricle**, passes through **aortic semilunar valve**, and enters the **aorta**.
2. This blood is distributed by the **systemic arteries**, and enters **systemic capillaries** for nutrient and gas exchange.
3. This blood, which is now deoxygenated, ultimately drains into the **SVC, IVC, and coronary sinus** (not shown), and enters the **right atrium**.
19.2 The Heart Within the Thoracic Cavity

The heart is the center of the cardiovascular system, and the remaining sections of this chapter discuss both the anatomic and physiologic details of the heart. The location and position of the heart, as well as the pericardium that encloses it, are described in this section. Here our emphasis is on the specific orientation of the heart and the anatomic features that protect and support it.

19.2a Location and Position of the Heart

LEARNING OBJECTIVE

5. Describe the location and position of the heart in the thoracic cavity.

The heart is located within the thoracic cavity, as shown in figure 19.5. Supporting the thoracic cavity is the thoracic cage, the protective bony framework that encloses both the heart and lungs (see section 8.6). The heart is positioned posterior to the sternum left of the body midline between the lungs within the mediastinum (me′dē-as-tī′nŭm; medius = middle). The orientation of the heart is slightly rotated such that its right side or right border is located more anteriorly, whereas its left side or left border is located more posteriorly. The postero-superior surface of the heart is called the base (not labeled on figure 19.5). The inferior, conical end of the heart is called the apex (ā′pek; tip). It projects slightly anteroinferiorly toward the left side of the body with the right ventricle lying on the diaphragm. You may find it helpful to think of the heart’s position as an upside down pyramid with the apex below the base.

WHAT DID YOU LEARN?

8. What is the bony structure that protects both the heart and the lungs?

9. Where is the heart positioned, and how is it oriented within the thoracic cavity?

19.2b The Pericardium

LEARNING OBJECTIVES

6. List the structural components of the pericardium.

7. Describe the function of the pericardium and the purpose of the serous fluid within the pericardial cavity.

The heart is enclosed in three layers, collectively called the pericardium (per-i-kar′dē-əm; peri = around, kardia = heart) (figure 19.6). These layers are (from outside to inside) as follows:

- The fibrous pericardium, which is composed of dense irregular connective tissue that encloses the heart but does not attach to it. Rather, this layer is attached inferiorly to the diaphragm and superiorly to the base of the great arterial trunks (pulmonary trunk and aorta).

Figure 19.5 Heart Position Within the Thoracic Cavity. (a) The heart is located within the mediastinum of the thoracic cavity between the lungs. (b) A cross-sectional view depicts the heart’s relationship to the other organs in the thoracic cavity.
• The **parietal layer of the serous pericardium**, which is composed of simple squamous epithelium and an underlying delicate layer of areolar connective tissue, adheres to the inner surface of the fibrous pericardium.

• The **visceral layer of the serous pericardium** (also called the epicardium) is also composed of a simple squamous epithelium and an underlying delicate layer of areolar connective tissue. This serosal layer adheres directly to the heart. The two serosal layers are continuous with one another (near the great vessels of the heart) and separated by a potential space called the **pericardial cavity**.

The fibrous pericardium and the parietal layer of the serous pericardium together compose the more loosely fitting “bag,” called the **pericardial sac**, that encloses the heart (see section 1.5e and figure 1.9).

The tough, fibrous pericardium of the pericardial sac both anchors the heart within the thoracic cavity and prevents the heart chambers from overfilling with blood. The two layers of the serous pericardium produce and release **serous fluid** into the pericardial cavity. This fluid has the consistency of an oily mixture, and it lubricates the serous membranes to minimize friction with every heartbeat (see section 1.5e).

### WHAT DID YOU LEARN?

Describe the three layers that cover the heart. Where is the pericardial cavity relative to these layers?

**LEARNING STRATEGY**

Imagine your heart as a fist that is placed into a balloon (as shown). The two layers of the balloon are serous membranes. The portion adhered to your hand is the visceral layer; the outer portion is the parietal layer, and the space between them is the pericardial cavity. Now imagine a sandwich bag placed around your hand and balloon; this represents the fibrous pericardium. Together, the outer layer of the balloon and the sandwich bag form the pericardial sac.

### CLINICAL VIEW 19.2

**Pericarditis**

**Pericarditis** (per′-kar-di′tis; **itis** = inflammation) is an inflammation of the pericardium typically caused by viruses, bacteria, or fungi. The inflammation is associated with an increase in permeability of capillaries within the pericardium, which become more “leaky,” resulting in excess fluid leaving the blood and accumulating within the pericardial cavity. At this point, the potential space of the pericardial cavity becomes an actual space as it fills with fluid. In severe cases, the excess fluid accumulation limits the heart’s movement and keeps the heart chambers from filling with an adequate amount of blood. The heart is unable to pump blood, leading to a medical emergency called **cardiac tamponade** (tam′-pō-nād′) and possibly resulting in heart failure and death.

A helpful physical finding in diagnosing pericarditis is **friction rub**. This is a crackling or scraping sound heard with a stethoscope that is caused by the movement of the inflamed pericardial layers against each other.

### 19.3 Heart Anatomy

When the pericardial sac is cut and reflected, the heart can be removed from the mediastinum and examined in greater detail. It is a relatively small, conical, muscular organ approximately the size of a person’s clenched fist. In the average normal adult, it weighs about 300 grams (0.7 pound), but certain diseases may cause heart size to increase dramatically. Here we examine the heart’s external and internal structures.

The superficial anatomic features of the heart are presented in **figure 19.7** from both an anterior and a posterior view in their normal position within the thoracic cavity. Both an illustration and a photo are included. The heart is rotated slightly within the thoracic cavity so that the right side of the heart is more visible from an anterior view (figure 19.7a) and the left side of the heart is more visible from a posterior view (figure 19.7b).

### 19.3a Superficial Features of the Heart

**LEARNING OBJECTIVE**

8. Compare the superficial features of the anterior and posterior aspects of the heart.

**Anterior View: Chambers and Great Vessels**

The right atrium and right ventricle are prominent when observing the heart from an anterior view (figure 19.7a). The portion of the right atrium that is most noticeable is its wrinkled, flaplike extension called the **right auricle** (aw′-ri-k; **auris** = ear). Portions of both the **left auricle** of the left atrium and the left ventricle are also visible. Also seen in this view are the positions of attachment for both the pulmonary trunk to the right ventricle and the aorta to the left ventricle. Note that the pulmonary trunk splits into the **right and left pulmonary arteries**, and that the aorta includes the **ascending aorta** (which extends superiorly from the heart), the curved **aortic arch**, and the **descending aorta** (which extends inferiorly through the trunk. (The three branches off the aortic arch are described in section 20.9a.)

**Posterior View: Chambers and Great Vessels**

The left atrium and left ventricle are prominent when observing the heart from a posterior view (figure 19.7b). The left atrium primarily forms the base on the posterosuperior surface of the heart. Also seen in this view are the point of attachment for the superior and inferior venae cavae to the right atrium and the pulmonary veins to the left atrium.

**Sulci of the Heart**

The atria are separated from the ventricles externally by a relatively deep groove called the **coronary** (kōr′-ō-nār′-ē; **corona** = crown) **sulcus** (or **atrioventricular sulcus**), which extends around the circumference of the heart. It can be viewed on both the anterior and posterior view. An **interventricular** (in-ter-ven-trik′-ū-lār; **inter** = between) **sulcus** is a groove between the ventricles that extends inferiorly from the coronary sulcus toward the heart apex, and delineates the superficial boundary between the right and left ventricles. The **anterior interventricular sulcus** is located on the anterior side of the heart, and the **posterior interventricular sulcus** is located on the posterior side of the heart. Located within all of these sulci are coronary vessels associated with supplying blood to the heart wall. Coronary vessels are described in detail in section 19.4.
Figure 19.7 External Anatomy and Features of the Heart. A drawing and a cadaver photo show the superficial features of the heart. (a) Anterior view. Note: Adipose connective tissue, which supports the coronary vessels within the heart sulci, was removed prior to the taking of these photos.
Figure 19.7 External Anatomy and Features of the Heart (continued). (b) Posterior view. ©McGraw-Hill Education/Christine Eckel
A coronal section provides a view of the internal structures of the heart (figure 19.8). First, observe the heart wall of the different heart chambers. Notice that the walls of the ventricles are thicker than the walls of the atria; this is because the ventricles are the “pumping chambers” and must exert force to move the blood from the heart through the cardiovascular circuits. Also note that the wall of the left ventricle is typically three times thicker than the right ventricular wall. This difference is because the left ventricle must generate enough pressure to force the blood through the entire systemic circulation, whereas the right ventricle merely has to pump blood to the nearby lungs as part of the pulmonary circulation. This difference in thickness can also be seen when a transverse section is made through the heart (figure 19.9).

Three distinctive layers compose the wall of each chamber: an external epicardium, a thick middle myocardium, and an internal endocardium (figure 19.8b).

The epicardium (ep-i-kar′dē-ŭm; epi = upon) is the outermost heart layer and is also called the visceral layer of serous pericardium. This layer, as previously described in section 19.2b, is composed of simple squamous epithelium and an underlying layer of areolar connective tissue. As we age, the epicardium thickens as it becomes more invested with adipose connective tissue.

The myocardium (my-ō-kar′dē-ŭm; mys = muscle) is the middle layer of the heart wall. It is composed of cardiac muscle tissue (see section 5.3) and is the thickest of the three heart wall layers. Contraction of cardiac muscle composing the myocardium generates the force necessary to pump blood. The ventricular myocardium may change in thickness as we age or if we participate in regular, rigorous exercise. For example, it hypertrophies in response to narrowing of systemic arteries because the heart must work harder to pump the blood. We consider the microscopic anatomy of cardiac muscle in section 19.3f.
through them.

of blood circulation and are described in the order that blood moves

(fos′ă fossa ovalis)

but it exhibits muscular ridges called

The internal wall of the right atrium is smooth on its posterior surface,

Right Atrium

Figure 19.8 also depicts the internal anatomy and structural organization

Figure 19.9 Comparison of Right and Left Ventricular

Wall Thickness. The wall of the left ventricle is typically three times

thicker than that of the right ventricle, because the left ventricle must

generate a force sufficient to push blood through the systemic circulation.

The internal surface of the heart and the external surfaces of the heart

valves are covered by endocardium (en-dō-kar′dē-ə; endon = within). The endocardium, like the epicardium, is composed of a simple squamous epithelium and an underlying layer of areolar connective tissue. The epithelial layer of the endocardium is continuous with the epithelial layer called the endothelium, which lines the blood vessels (see figure 20.1).

WHAT DID YOU LEARN?

14. What are the layers of the heart (in order) that a scalpel would pass through during dissection? What are the two names given to the outer layer of the heart wall?

19.3c Heart Chambers

LEARNING OBJECTIVE

10. Characterize the four chambers of the heart and their functions.

Each of the four chambers plays a role in the continuous process of blood circulation and are described in the order that blood moves through them.

Right Atrium

The internal wall of the right atrium is smooth on its posterior surface, but it exhibits muscular ridges called pectinate (pek′tı-nār; teeth of a comb) muscles on its anterior wall and within the auricle (figure 19.8a).

Inspection of the interatrial septum reveals an oval depression called the fossa ovalis (fos′ă; trench; ó-va′lis). It occupies the former location of the fetal foramen ovale (Ó-val′e), which shunted blood from the right atrium to the left atrium, bypassing the lungs during fetal life (fetal circulation is described in section 20.12). Immediately inferior to the fossa ovalis is the opening of the coronary sinus, which drains deoxygenated blood from the heart wall. Openings of the superior and inferior venae cavae are also visible. Thus, three veins drain deoxygenated blood into the right atrium: the coronary sinus, superior vena cava, and inferior vena cava. Separating the right atrium from the right ventricle is the right atrioventricular opening that contains the right AV valve. Deoxygenated blood flows from the right atrium, through the right atrioventricular opening when the valve is open, into the right ventricle.

Right Ventricle

The internal wall surface of the right ventricle displays characteristic large, smooth, irregular muscular ridges, called the trabeculae carneae (trā-bek′u-lē; trabs = beam; kar′nē-ə; carne = flesh). Extending from the internal wall of the right ventricle are typically three cone-shaped, muscular projections called papillary (pap′i-lār-ə; papilla = nipple) muscles. (The number of papillary muscles in the right ventricle can range from two to nine.) Papillary muscles anchor thin strands of collagen fibers called tendinous cords or chordae tendineae (kör′dē ten′di-nē-ə), which are attached to the free edge of the right atrioventricular valve. The superior portion of the right ventricle narrows into a smooth-walled region leading into the pulmonary trunk. The pulmonary semilunar valve is positioned between the right ventricle and pulmonary trunk. Deoxygenated blood is pumped from the right ventricle through the open pulmonary semilunar valve into the pulmonary trunk. This blood is delivered to the lungs for gas exchange and returned via pulmonary veins to the left atrium.

Left Atrium

The left atrium, like the right atrium, has pectinate muscles in its atrial opening. The position of the pulmonary veins are visible. (Two are seen in figure 19.8.) Separating the left atrium from the left ventricle is the left atrioventricular opening, which contains the left AV valve. Oxygenated blood flows from the left atrium, through the left atrioventricular opening when the valve is open, into the left ventricle.

Left Ventricle

The internal surface of the left ventricle also displays characteristic trabeculae carneae. It has two papillary muscles that are anchored by tendinous cords. The entrance into the aorta is located at the superior aspect of the left ventricle. The aortic semilunar valve is positioned at the boundary of the left ventricle and ascending aorta. Oxygenated blood is pumped from the left ventricle through the open aortic semilunar valve into the pulmonary trunk.

WHAT DID YOU LEARN?

15. What is the structure that separates the two ventricles? What is the superficial landmark that identifies the location of this structure?

16. How are the papillary muscles, tendinous cords, and atrioventricular valve positioned relative to one another?

19.3d Heart Valves

LEARNING OBJECTIVE

11. Compare and contrast the structure and function of the two types of heart valves.

Effective blood flow requires valves to control the flow of blood and ensure it is “one-way.” Recall that the two categories of heart valves are the atrioventricular (AV) valves and the semilunar valves. Each valve consists of endothelium-lined fibrous connective tissue flaps called cusps (figure 19.10).
Atrioventricular valve closed

Cusps of semilunar valve

Ve
ntricle

Arterial trunk (aorta or pulmonary trunk)

Blood flow

Cusp

Tendinous cords

Papillary muscle

Ventricle

Right atrioventricular valve

Left atrioventricular valve

Aortic semilunar valve

Pulmonary semilunar valve

(b) Atrioventricular (AV) valves

Coronal section

Transverse section

(a) Heart valves

Right atrioventricular valve

Aortic semilunar valve

Pulmonary semilunar valve

(c) Semilunar valves

Semilunar valve open

Semilunar valve closed

Figure 19.10 Heart Valves. (a) Location of heart valves as viewed in coronal section and transverse section. (b) Atrioventricular valves in open and closed positions. (c) Semilunar valves in open and closed positions.
Atrioventricular Valves

The right AV valve is located between the right atrium and the right ventricle, and it has three cusps (which is why it is also called the tricuspid valve). The left AV valve is located between the left atrium and left ventricle, but it has only two cusps (which is why it is also called the bicuspid valve; the name mitral is sometimes used for this valve because it resembles the headdress of bishops, which is called a mitre). The AV valves are shown in both the open and closed positions in figure 19.10. When open, the cusps of the valve extend into the ventricles. This allows blood to move from an atrium into the ventricle. When the ventricles contract, blood is forced superiorly as ventricular pressure rises. This causes the AV valves to close. The papillary muscles secure the tendinous cords that attach to the lower surface of each AV valve cusp. This prevents the valve from inverting into the atrium when the valve is closed. By being properly held in place, the cusps of the AV valves prevent backflow of blood into the atrium.

Semilunar Valves

The pulmonary semilunar valve is located between the right ventricle and the pulmonary trunk, and the aortic semilunar valve is located between the left ventricle and the ascending aorta. Each valve is composed of three pocketlike cusps, which have the shape of a half-moon (figure 19.10a, c). Neither papillary muscles nor tendinous cords are associated with these valves. The semilunar valves are shown in both the open and closed positions in figure 19.10b.

The semilunar valves open when the ventricles contract and the force of the blood pushes the semilunar valves open and blood enters the arterial trunks. The valves close when the ventricles relax and the pressure in the ventricle becomes less than the pressure in an arterial trunk. Blood in the arteries begins to move backward toward the ventricle and is caught in the cusps of the semilunar valves, and they close. The closure of the semilunar valves prevents backflow of blood into the ventricle.

Both flexibility and elasticity of connective tissue composing heart valves decrease with aging (or disease). This may cause the heart valves to become inflexible. As a result, blood flow through the heart may be altered, and a heart murmur may be detected (see Clinical View 19.4: “Heart Sounds and Heart Murmurs”).

WHAT DID YOU LEARN?

17 What are the functions of the tendinous cords and papillary muscles?
The sarcolemma (plasma membrane), which invaginates to form desmosomes. The sarcoplasmic reticulum surrounds bundles of myofilaments called myofibrils—thus, cardiac muscle cells are arranged in sarcomeres—thus, cardiac muscle bundles are arranged in spiral bundles around the heart chambers attached to the fibrous skeleton (figure 19.11b). The sarcolemma that permits adjoining membranes to interconnect, markedly increases exposed surface areas between neighboring cells (figure 19.12b). This can be demonstrated by interlocking your fingers. This increases structural stability of the myocardium and facilitates communication between cardiac muscle cells.

Unique structures called intercalated (in-ter′kă-lă-ted) discs are found at these cell-to-cell junctions. They link cardiac muscle cells together both mechanically and electrically and contain two distinctive structural features:

- **Desmosomes.** These are protein filaments that anchor into a protein plaque located on the internal surface of the sarcolemma (see section 4.6d). They act as mechanical junctions to prevent cardiac muscle cells from pulling apart.
Gap junctions. These are protein pores between the sarcolemma of adjacent cardiac muscle cells. They provide a low-resistance pathway for the flow of ions between the cardiac cells. Gap junctions allow an action potential to move continuously along the sarcolemma of cardiac muscle cells, resulting in essentially simultaneous stimulation of cardiac muscle cells within a chamber and, thus, synchronous contraction of that chamber. A chamber is called a functional syncytium (sin-sī’shē-ūm) because it functions as a single unit. (Note: A syncytium is defined as a multinucleated mass that is formed by the union of originally separate cells. Thus, to say that a heart chamber is a functional syncytium is to say that the chamber functions as if it were one cell.)

Metabolism of Cardiac Muscle
Cardiac muscle has features that support its great demand for energy, including an extensive blood supply, numerous mitochondria, and other structures such as myoglobin (which is a globular protein that binds oxygen when the muscle is at rest) and creatine kinase (which catalyzes the transfer of Pi from creatine phosphate to ADP, yielding ATP and creatine). Myoglobin was first described in section 10.2b, and creatine kinase in section 10.4a (see Clinical View 10.5: "Creatine Kinase Blood Levels as a Diagnostic Tool").

Cardiac muscle relies almost exclusively on aerobic cellular respiration (see section 3.4). Its cellular structures and metabolic processes support this. Cardiac muscle has a large number of mitochondria (comprising approximately 25% of its volume compared to about 2% of the volume in skeletal muscle). It is also versatile in being able to use different types of fuel molecules, including fatty acids, glucose, lactate, amino acids, and ketone bodies (see section 3.4h). The relative amounts of these molecules that cardiac muscle cells use fluctuate depending upon conditions. For example, during intense exercise when greater amounts of lactate are released into the blood by skeletal muscle, cardiac muscle will absorb the additional lactate from the blood and use this resource.
Yet, as a consequence of its reliance on aerobic cellular respiration, cardiac muscle is quite susceptible to failure if ischemic (low-oxygen) conditions prevail. Cardiac muscle has limited capability in using glycolysis (see section 3.4b) or accruing an oxygen debt (see section 10.4b) in its activities. Therefore, any change that interferes with blood flow to the heart muscle, such as narrowing of the coronary arteries, can cause damage or death of the cardiac muscle cells composing the myocardium (see Clinical View 19.5: “Coronary Heart Disease, Angina Pectoris, and Myocardial Infarction”).

**WHAT DID YOU LEARN?**

19. Which features of cardiac muscle support aerobic cellular respiration?

### 19.4 Coronary Vessels: Blood Supply Within the Heart Wall

Although the heart continuously pumps blood through its chambers, it cannot absorb the oxygen and nutrients it requires from this blood. The diffusion of oxygen and nutrients at the needed rates through the thick wall of the heart is not possible; instead, an intricate distribution system called the coronary circulation handles the task (figure 19.13).

The vessels that transport oxygenated blood to the wall of the heart are called coronary arteries, whereas coronary veins transport deoxygenated blood away from the heart wall. Vessels on the posterior aspect of the heart are shown shaded in figure 19.13a, b.

---

**Figure 19.13 Coronary Circulation.** Diagram of the anterior view of (a) coronary arteries that transport blood to cardiac muscle tissue and (b) coronary veins that transport blood from cardiac muscle tissue. (Vessels on the posterior aspect of the heart are shown shaded.) (c) Photo of polymer cast of coronary vessels. AP/Science Source
19.4a Coronary Arteries

LEARNING OBJECTIVES

16. Identify the coronary arteries, and describe the specific areas of the heart supplied by their major branches.
17. Explain the significance of coronary arteries as functional end arteries.
18. Describe blood flow through the coronary arteries.

Right and left coronary arteries are positioned within the coronary sulcus of the heart to supply the heart wall (figure 19.13a). These arteries are the first and only branches of the ascending aorta and originate immediately superior to the aortic semilunar valve.

The right coronary artery typically branches into the right marginal artery to supply the lateral wall of the right ventricle, and the posterior interventricular artery (or posterior descending artery) to supply the posterior wall of both the left and right ventricles. The left coronary artery typically branches into the circumflex (ser’kum-fleks; circum = around, flexus = to bend) artery to supply the lateral wall of the left ventricle, and the anterior interventricular artery (also called the left anterior descending artery, or LAD) to supply both the anterior wall of the left ventricle and most of the interventricular septum. However, this arterial pattern can vary greatly among individuals. Note that the anterior interventricular artery is nicknamed the widowmaker. This name reflects the fact that if this artery becomes occluded, there is a very high risk of a fatal heart attack, which makes a widow of the spouse. The coronary arteries and veins also are shown in figure 19.7a, b.

Functional End Arteries

Body tissues are generally served by one artery; it is called an end artery. In comparison, some body tissues are served by two or more arteries; this is referred to as an arterial anastomosis (see section 20.1e). An arterial anastomosis provides two means of effectively delivering blood to a given region. The left and right coronary arteries provide blood to the myocardium and are described by some as an arterial anastomosis. However, if one of these arteries becomes blocked, this anastomosis is too small to shunt sufficient blood from one artery to the other, as may happen with coronary artery disease. As a result, the coronary arteries are more accurately called functional end arteries.

Blood Flow

Coronary arterial blood flow to the heart wall is intermittent. This occurs because coronary vessels are patent (open) when the heart is relaxed and blood flow is possible. However, coronary vessels are compressed when the heart contracts, temporarily interrupting blood flow. Thus, blood flow to the heart wall is not a steady stream; it is impeded and then flows, as the heart rhythmically contracts and relaxes.

CLINICAL VIEW 19.5

Coronary Heart Disease, Angina Pectoris, and Myocardial Infarction

Coronary heart disease (which goes by many other names, including coronary artery disease, atherosclerosis, hardening of the arteries, and heart disease) is the buildup of a waxy substance, called plaque, within the coronary arteries. The lumen of coronary vessels becomes narrowed and occluded, which decreases blood flow through the coronary arteries that supply blood to the heart wall (see Clinical View 20.1: “Atherosclerosis,” which discusses etiology, risk factors, and treatment options). In contrast, some individuals may experience coronary spasm, which is sudden narrowing of the vessels caused by smooth muscle contraction. Either atherosclerosis or coronary spasm can lead to angina pectoris or the more severe myocardial infarction.

Angina (an’ji-n˘a, an-j˘ı-n˘a) pectoris is a poorly localized pain sensation in the left side of the chest, the left arm and shoulder, or sometimes the jaw and the back (although these symptoms may vary, especially in women). Generally, it results from strenuous activity, when workload demands on the heart exceed the ability of the narrowed coronary vessels to supply blood. The pain from angina is typically referred (referred pain; see section 16.2b) along the sympathetic pathways (T1–T5 spinal cord segments; see section 15.4), so an individual may experience pain in the chest region or down the left arm, where the T1 dermatome (see section 14.5a) is located. The pain diminishes shortly after the person stops the exertion, and normal blood flow to the heart is restored. Treatment may include medications that cause temporary vascular dilation, such as nitroglycerin. The prognosis and long-term therapy for angina depend upon the severity of the vascular narrowing or spasming.

The term infarction refers to the death of tissue due to lack of blood supply. Myocardial infarction (MI), commonly called a heart attack, is a potentially lethal condition resulting from sudden and complete occlusion of a coronary artery. A region of the myocardium is deprived of oxygen, and some of this tissue may die (undergo necrosis). Some people experiencing an MI report the sudden development of excruciating and crushing substernal chest pain that typically radiates into the left arm or left side of the neck. Women may not experience these symptoms, but instead be overcome with jaw pain, incredible fatigue, and flulike symptoms and thus may be misdiagnosed. Other immediate symptoms include weakness, shortness of breath, nausea, vomiting, anxiety, and marked sweating. Mature cardiac muscle cells have little or no capacity to regenerate (i.e., they cannot undergo cellular division), so when an MI results in cell death, scar tissue forms to fill the gap. If a large amount of tissue is lost, the person may die within a few hours or days because the heart has been profoundly and suddenly weakened.
19.4b Coronary Veins

LEARNING OBJECTIVE
19. Identify the coronary veins, and describe the specific areas of the heart drained by their major branches.

Transport of deoxygenated blood from the myocardium occurs through one of several cardiac veins (figure 19.13b). These include the great cardiac vein within the anterior interventricular sulcus, positioned alongside the anterior interventricular artery; the middle cardiac vein within the posterior interventricular sulcus, positioned alongside the posterior interventricular artery; and a small cardiac vein positioned alongside the right marginal artery. These cardiac veins all drain into the coronary sinus, a large vein that lies within the posterior aspect of the coronary sulcus. The coronary sinus then returns this deoxygenated blood directly into the right atrium of the heart.

WHAT DID YOU LEARN?
21. What is the function of the coronary sinus?

19.5 Anatomic Structures Controlling Heart Activity

The heart pumps blood continuously and depends upon rhythmic stimulation of cardiac muscle cells. Precise electrical events are orchestrated by the heart’s conduction system, beginning with stimulation by the sinoatrial node and then transmission of an action potential by specialized conduction fibers of the heart to ensure that the atria contract prior to the ventricles. These events are influenced by the activity of the autonomic nervous system.

19.5a The Heart’s Conduction System

LEARNING OBJECTIVE
20. Identify and locate the components of the heart’s conduction system.

Specialized cardiac muscle cells within the heart are located internal to the endocardium; they are collectively called the heart’s conduction system (figure 19.14a). These distinct cardiac cells do not contract, but rather they initiate and conduct electrical signals. The conduction system includes the following structures:

- The sinoatrial (sī’nō-ā’trē-āl) (SA) node is located in the posterior wall of the right atrium, adjacent to the entrance of the superior vena cava. The cells here initiate the heartbeat and are commonly referred to as the pacemaker of the heart.
- The atrioventricular (AV) node is located in the floor of the right atrium between the right AV valve and the opening for the coronary sinus.
- The atrioventricular (AV) bundle (bundle of His) extends from the AV node into and through the interventricular septum. It divides into left and right bundles.
- The Purkinje (pūr-kīn’jē) fibers extend from the left and right bundles beginning at the apex of the heart and then continue through the walls of the ventricles.

WHAT DID YOU LEARN?
22. Why is the SA node referred to as the pacemaker?

19.5b Innervation of the Heart

LEARNING OBJECTIVE
21. Compare and contrast parasympathetic and sympathetic innervation of the heart.

While the heartbeat is initiated by the SA node, both the heart rate and the strength of contraction are regulated by the autonomic nervous system—specifically by the cardiac center of the cardiovascular center within the medulla oblongata (see section 13.5c). Sensory input is relayed from receptors (baroreceptors and chemoreceptors within specific blood vessels and the right atrium) to the cardiac center. Parasympathetic and sympathetic neurons extend from the cardiac center to the heart. The cardiac center houses both the cardioinhibitory and cardioacceleratory centers (figure 19.14b). The innervation from this center does not initiate the heartbeat; it merely modifies cardiac activity, including both the heart rate and its force of contraction.
Sympathetic innervation
Cardioinhibitory center sends nerve signals along the vagus nerves (CN X), which result in a decrease in heart rate.

Parasympathetic innervation
Cardioacceleratory center sends nerve signals along cardiac nerves, which result in an increase in both heart rate and force of contraction.

(a) Conduction system
Sinoatrial (SA) node (pacemaker)
Atrioventricular (AV) node
Atrioventricular (AV) bundle
Right and left bundles
Purkinje fibers

(b) Innervation of the heart
Figure 19.14 Anatomic Structures Controlling Heart Activity. (a) The heart’s conduction system, composed of the sinoatrial (SA) node, atrioventricular (AV) node, right and left bundles, and Purkinje fibers, initiates and conducts the electrical activity to cause heart contraction. (b) Heart rate and force of contraction are modified by autonomic centers (cardioacceleratory and cardioinhibitory centers) in the medulla oblongata. Parasympathetic neurons extend from the cardioinhibitory center to both the SA node and AV node. Sympathetic neurons extend from the cardioacceleratory center to the SA node, AV node, myocardium, and coronary vessels.
Parasympathetic innervation comes from the cardioinhibitory center via the right and left vagus nerves (CN X; see table 13.5). As these nerves descend into the thoracic cavity, they give off branches that supply the heart (see section 15.3). Primarily, the right vagus nerve innervates the SA node, and the left vagus nerve innervates the AV node. Parasympathetic stimulation decreases heart rate but generally has no direct effect on the force of contraction (because the vagus nerve does not innervate the myocardium).

Sympathetic innervation arises from the cardioacceleratory center. Neurons within the T1–T5 segments of the spinal cord extend to the SA node, AV node, and the myocardium (see section 15.4). Stimulation by the sympathetic division increases both heart rate and the force of heart contraction. There is also sympathetic innervation to the coronary arteries, causing dilation of these vessels to support increased blood flow to the myocardium.

**19.6 Stimulation of the Heart**

The physiologic processes associated with heart contraction are organized into two major events (figure 19.15):

- **Conduction system.** Electrical activity is initiated at the SA node, and an action potential is then transmitted through the conduction system.
- **Cardiac muscle cells.** The action potential spreads across the sarcolemma of the cardiac muscle cells, causing sarcomeres within cardiac muscle cells to contract. These events occur twice in cardiac muscle cells during a heartbeat, first in the cells of the atria and then in the cells of the ventricles.

Here we discuss the events associated with the conduction system, including the physiologic conditions of nodal cells at rest and how they serve as the heart’s pacemaker. The processes associated with cardiac muscle cells are described in section 19.7.

**WHAT DID YOU LEARN?**

23. Which autonomic division is associated with the cardioacceleratory center in the brainstem, and how does it affect heart activity?

**CONCEPT CONNECTION**

A resting membrane potential (RMP) is the electrical charge difference at the plasma membrane when a cell is at rest (see section 4.4). The types of cells that exhibit an RMP include cardiac muscle cells, skeletal muscle fibers (see section 10.2d), neurons (see section 12.7b), and sensory receptor cells (see section 16.1a).

**19.6a Nodal Cells at Rest**

**LEARNING OBJECTIVE**

22. Describe a nodal cell at rest.

Nodal cells in the SA node are the pacemaker cells that initiate a heartbeat by spontaneously depolarizing to generate an action potential. These specialized cardiac cells exhibit several significant features. Refer to figure 19.16a as you read through this section.

One essential feature of nodal cells is the electrical charge difference across the plasma membrane; the intracellular fluid (cytosol) just inside the plasma membrane is relatively negative in comparison to the fluid outside the cell (interstitial fluid). This electrical charge difference when the nodal cell is at rest is called the resting membrane potential (RMP). Nodal cells have an RMP of about −60 millivolts (mV). An RMP, which is discussed in detail in section 4.4, is established and maintained by $K^+$ leak channels, $Na^+$ leak channels, and $Na^+/K^+$ pumps (not shown in figure 19.16a). The primary function of the $Na^+/K^+$ pumps is to maintain the concentration gradients for $Na^+$ (with more $Na^+$ outside the cell) and $K^+$ (with more $K^+$ inside the cell). Nodal cells also contain calcium ion ($Ca^{2+}$) pumps that establish a $Ca^{2+}$ concentration gradient with more $Ca^{2+}$ outside the cell than inside. It is important to note that nodal cells (unlike other cells) do not have a stable RMP, as described in section 19.6b.

Additionally, nodal cells contain specific voltage-gated channels, including slow voltage-gated $Na^+$ channels (which are open) and both fast voltage-gated $Ca^{2+}$ channels and voltage-gated $K^+$ channels (which are closed).

\[\text{Figure 19.15} \quad \text{Physiologic Processes Associated with Heart Contraction.} \quad \text{Both the conduction system and cardiac muscle cells have two significant physiologic processes that occur for heart contraction. (a) Initiation and spread of an action potential occurs in the conduction system. (b) Action potentials spread along the sarcolemma of cardiac muscle cells, triggering contraction of sarcomeres within these cardiac muscle cells. Events of cardiac muscle cells occur twice in one heartbeat: once in the cells of the atria and once in the cells of the ventricles.}\]
WHAT DID YOU LEARN?

What is the resting membrane potential (RMP) value of nodal cells?

19.6b Electrical Events at the SA Node: Initiation of the Action Potential

LEARNING OBJECTIVES

23. Define autorhythmicity.

24. Describe the steps for SA nodal cells to spontaneously depolarize and serve as the pacemaker cells.

SA nodal cells are unique in that they exhibit autorhythmicity (or automaticity), meaning that they are capable of depolarizing and initiating an action potential spontaneously without any external influence. The following series of events occur within SA nodal cells, as depicted in figure 19.16b:

1. Reaching threshold. Slow voltage-gated Na⁺ channels open (this is caused by repolarization from the previous cycle). The Na⁺ flows into the nodal cells, changing the resting membrane potential from −60 mV to −40 mV, which is the threshold value. Notice that the threshold is reached without outside stimulation.

2. Depolarization. Changing of the membrane potential to the threshold triggers the opening of fast voltage-gated Ca²⁺ channels, and Ca²⁺ entry into the nodal cell causes a change in the membrane potential from −40 mV to a slightly positive membrane potential (just above 0 mV). This reversal of polarity is called depolarization.

3. Repolarization. Calcium channels close and voltage-gated K⁺ channels open; K⁺ flows out to change the membrane potential from a positive value to −60 mV, which is the RMP. The process of reestablishing the RMP is called repolarization. Repolarization triggers the reopening of slow voltage-gated Na⁺ channels, and the process begins again. This process typically takes approximately 0.8 second, at rest; this results in a resting heart rate of 75 beats per minute. Note that the inherent rhythm at which SA nodal cells spontaneously depolarize is at a much faster rate of approximately 100 times per minute. (This inherent rhythm is determined when excised cardiac muscle cells are placed into cell culture, without autonomic nerve innervation.) The normal resting heart rate of 75 beats per minute is due to continuous parasympathetic stimulation of the SA node by the vagus nerve. This slowing of the heart rate is called vagal tone (see section 15.7a).

WHAT DO YOU THINK?

3 What specific type of channel is unique to cardiac nodal cells? What is the significance of this channel?

Pacemaker Potential of Nodal Cells

Nodal cells do not have a stable resting membrane potential. Instead, the RMP gradually increases to threshold when slow Na⁺ channels reopen. This ability to reach the threshold without stimulation is called a pacemaker potential. The pacemaker potential of nodal cells is responsible for initiating electrical signals, which will be propagated along the conduction system to stimulate the cardiac muscle cells of the heart to rhythmically contract. It is for this reason that initiation of heart contraction does not require stimulation by the autonomic nervous system.
Cardiac muscle stimulation requires that the action potential initiated by the SA node be spread through the conduction system. The sequence of events occurs as follows (figure 19.17):

1. **Action potential is distributed throughout both atria.** The action potential initiated in the SA node is propagated first along the sarcolemma of cardiac muscle cells within the atria and spread between atrial cardiac muscle cells by gap junctions. This allows for almost instantaneous excitation of all cardiac muscle cells in the atrial walls and for both atria to contract at the same time.

2. **The action potential is relayed to the AV node and delayed.** The action potential arrives at the AV node. AV nodal cells have both smaller fiber diameters and fewer numbers of gap junctions—thus, they exhibit characteristics that slow the conduction rate of the action potential by serving as “a bottleneck.” This is facilitated by the insulating characteristics of the fibrous skeleton, which only allow the action potential to move through the AV node. The delay in conduction (about 100 milliseconds, or 0.1 second) may seem very brief, but it is long enough to allow the atria to finish contracting and force blood into the ventricles to complete ventricular filling before the ventricles are stimulated to contract.

3. **The action potential travels from the AV node through the AV bundle to Purkinje fibers.** The action potential is propagated from the AV node along the AV bundle to the bundle branches to the Purkinje fibers.

4. **The action potential continues throughout both ventricles via gap junctions.** The action potential is then propagated along the sarcolemma of cardiac muscle cells within the ventricles and spread between ventricular cardiac muscle cells by gap junctions. This allows for the almost simultaneous stimulation of all the cardiac muscle cells in the ventricular walls and simultaneous contraction of both ventricles. Generally, these cells begin to contract within 120 to 200 milliseconds after the firing of the SA nodal cells.

**Figure 19.17 Initiation and Spread of an Action Potential Through the Cardiac Conduction System.** The initiation and spread of an action potential begins at the SA node and is propagated through the cardiac conduction system. The average rate at rest is one per 0.8 second. (The black arrows indicate the propagation of the action potential.)

**WHAT DID YOU LEARN?**

What is autorhythmicity? Describe how nodal cells function as autorhythmic cells to serve as the pacemaker of the heart.

**INTEGRATE CONCEPT CONNECTION**

Nodal cells are like neurons because they have an RMP. However, a significant difference between them is that neurons require stimulation (in the form of neurotransmitters or a modality; see section 12.6a), whereas nodal cells spontaneously depolarize. Another difference between neurons and nodal cells is that depolarization results from the entrance of Na+ into neurons, whereas it results from the entrance of Ca2+ into nodal cells.
19.7 Cardiac Muscle Cells

Two significant and interrelated events occur by cardiac muscle cells following their stimulation by the conduction system: propagation of an action potential at the sarcolemma and contraction of sarcomeres within the cardiac muscle cells. Remember that the events of cardiac muscle cells occur twice per heartbeat: first in the cardiac muscle cells of the atria (propagation of an action potential and contraction occur), and then in the cardiac muscle cells of the ventricles (propagation of an action potential and contraction occur).

19.7a Cardiac Muscle Cells at Rest

Describe the conditions at the sarcolemma of cardiac muscle cells at rest.

Cardiac muscle cells exhibit several significant features at their sarcolemma. Refer to figure 19.18a as you read through this section.

The sarcolemma of cardiac muscle cells, like nodal cells, has K⁺ leak channels, Na⁺ leak channels, and Na⁺/K⁺ pumps to establish and maintain a resting membrane potential with a greater concentration of Na⁺ outside the cardiac muscle cells and a greater concentration of K⁺ inside. The RMP value of cardiac muscle cells, however, is –90 millivolts (mV) (in comparison to –60 mV for nodal cells). Cardiac muscle cells also contain Ca²⁺ pumps that form a Ca²⁺ concentration gradient with more Ca²⁺ outside the cell than inside.

The sarcolemma of cardiac muscle cells has both fast voltage-gated Na⁺ channels that participate in depolarization at the membrane and voltage-gated K⁺ channels that participate in repolarization of the membrane. Additionally, cardiac muscle cells have slow voltage-gated Ca²⁺ channels within the sarcolemma. Slow voltage-gated Ca²⁺ channels, when open, allow Ca²⁺ into the cell. The movement of Ca²⁺ is significant in the normal function of cardiac muscle cells, as described in section 19.7b.

WHAT DID YOU LEARN?

INTEGRATE

Ectopic Pacemaker

A pacemaker other than the SA node is called an ectopic (ek-top′ik; ekto = outside, topo = place) pacemaker, or ectopic focus. Cells of the conduction system other than the SA node and cardiac muscle cells also have the ability to spontaneously depolarize and serve as the pacemaker. However, they depolarize at slower rates than the SA node. The AV node has an inherent rhythm of 40 to 50 beats per minute, and cardiac muscle cells have a rate of 20 to 40 beats per minute. If the SA node is not functioning, the AV node becomes the “default” pacemaker, and the AV node then establishes the rhythm of the heart rate. Survival is possible because a rhythm of 40 to 50 beats per minute pumps sufficient blood to sustain life. However, if both the SA node and the AV node are not functioning, cardiac muscle cells will attempt to establish the rhythm. The heart rate will be only 20 to 40 beats per minute, which is almost always too slow to support life. A mechanical pacemaker is a small device that is surgically implanted in a patient in order to deliver repeated electrical impulses to heart muscle. It sustains a required heart rate and rhythm for the patient.

WHAT DID YOU LEARN?

Specialized Features Associated with Ventricles

The efficient functioning of the ventricles requires a coordination of contraction that includes the following features:

- Purkinje fibers are relatively large in diameter, so action potential propagation is extremely rapid to the ventricular myocardium. Thus, the cardiac muscle cells of both ventricles contract at the same time.
- Papillary muscles within the ventricles are stimulated to contract immediately. These muscles anchor the tendinous cords to the AV valve cusps; they tighten the relaxed cords and cause them to start to pull on the AV valve cusps just prior to the increase in pressure within the ventricles. Thus, the valves are “braced” and better able to prevent backflow of blood into the atria.
- The stimulation of the ventricles begins at the apex of the heart. This feature ensures that blood is efficiently ejected superiority toward the arterial trunks.

19.7b Electrical and Mechanical Events of Cardiac Muscle Cells

List the electrical events of an action potential that occur at the sarcolemma.

Briefly summarize the mechanical events of muscle contraction.

We can distinguish certain electrical and mechanical events that occur as the heart contracts.

Electrical Events

Electrical events involving propagation of the action potential at the sarcolemma of cardiac muscle cells occur as follows (figure 19.18b):

1. Depolarization. An action potential transmitted through the conduction system (or via gap junctions) triggers the opening of fast voltage-gated Na⁺ channels in the sarcolemma of cardiac muscle cells. Sufficient Na⁺ enters the cardiac muscle cell to change the membrane potential from –90 mV to +30 mV. Voltage-gated Na⁺ channels close to the inactivated state. This change from a relatively negative membrane potential to a relatively positive membrane potential is depolarization (see section 12.6a).

2. Plateau. Depolarization triggers the opening of voltage-gated K⁺ channels, and K⁺ leaves the cardiac muscle cells. There is a slight change in the membrane potential. Almost immediately, slow voltage-gated Ca²⁺ channels in the sarcolemma also open, and Ca²⁺ enters from the interstitial fluid into the cardiac muscle cells. The entering of Ca²⁺ stimulates the sarcoplasmic reticulum (SR) to release more Ca²⁺ (greater than 80% of the Ca²⁺ is released from the SR). The exit of positively charged K⁺ from the sarcoplasm and the simultaneous entrance of positively charged Ca²⁺ into the sarcoplasm result in no electrical change at the sarcolemma. Thus, the sarcolemma of the cardiac muscle cell remains in a depolarized state. This “leveling off” is referred to as the plateau.

3. Repolarization. Voltage-gated Ca²⁺ channels then close, and K⁺ channels remain open to complete repolarization. Sufficient K⁺ exits the cardiac muscle cells to change the membrane...
Repolarization

- Voltage-gated K⁺ channels remain open.
- K⁺ moves out of the cardiac muscle cell.
- Voltage-gated Ca²⁺ channels close.
- Repolarization occurs (+30 mV to −90 mV).

**Figure 19.18 Electrical Events of Cardiac Muscle Cells.** (a) Cardiac muscle cells have a resting membrane potential of −90 mV. Voltage-gated channels in the sarcolemma are closed when the cardiac muscle cell is at rest. (b) Graph and accompanying diagrams of the sequential electrical events of an action potential at the sarcolemma of cardiac muscle cells. (Cytosol is the fluid portion of the sarcoplasm within the cardiac muscle cell.)

**Mechanical Events (Crossbridge Cycling)**

Cardiac muscle contraction is initiated with the entry of Ca²⁺ into the sarcoplasm from both the interstitial fluid and SR (as described in step 2). Calcium ions now bind to troponin to begin crossbridge cycling within a sarcomere, similar to the way in which skeletal muscle contracts (see section 10.3c).

A summary of the steps of muscle contraction involving sarcomeres is as follows (see figure 10.13):

- **Crossbridge formation:** Myosin heads attached to actin form a crossbridge between the thick and thin filaments.
- **Powerstroke:** The myosin head swivels (the powerstroke), which pulls the thin filament past the thick filament a short distance, which decreases the width of a sarcomere.
- **Release of myosin head:** ATP binds to the myosin head to release the myosin head from actin.
- **Reset of myosin head:** ATP is split by myosin ATPase, providing the energy to reset the myosin head.

Cardiac muscle relaxation is initiated with the closing of voltage-gated Ca²⁺ channels (as described in step 3). The continuous reuptake of Ca²⁺ from the sarcoplasm into the sarcoplasmic reticulum by Ca²⁺ pumps and the removal of Ca²⁺ from the cell by plasma membrane Ca²⁺ pumps decrease calcium levels within the sarcoplasm. Calcium is released from troponin with the subsequent decrease in crossbridges between the thin and thick filaments. Sarcomeres return to their resting length as the cardiac muscle cell now relaxes (see section 10.3d).
Cardiac muscle cells (unlike skeletal muscle fibers) cannot exhibit tetany, which is a sustained muscle contraction without relaxation (see section 10.6c). This distinction is critical for the heart to be able to function as a mechanical pump to move blood through the cardiovascular system. Here we compare the characteristics of skeletal muscle fibers to cardiac muscle cells to understand the reason for this difference. Refer to figure 19.19 as you read through this section.

Examine the graphs in figure 19.19, and notice the following in the graphs of both skeletal muscle fibers and cardiac muscle cells:

- **Muscle tension**, which is depicted as the red line on each graph, includes both muscle contraction and muscle relaxation. (These mechanical events are due to sarcomeres within these muscle cells first shortening during contraction and then lengthening during relaxation.)

---

**Figure 19.19** Comparison of Electrical and Mechanical Events in Skeletal Muscle Cells and Cardiac Muscle Cells.

The electrical changes associated with an action potential propagated along the sarcolemma and the mechanical changes associated with generating muscle tension when a muscle contracts are shown for (a) skeletal muscle with a single stimulation, (b) skeletal muscle with frequent stimulation, (c) cardiac muscle with a single stimulation, and (d) cardiac muscle with frequent stimulation. The extended refractory period in cardiac muscle cells (due to the plateau) allows time for cardiac muscle to contract and relax before being stimulated again. Thus, a sustained contraction (tetany) is prevented.
• An action potential, which is shown as a blue line on the graph in figure 19.19a, c, includes both depolarization and repolarization. (These electrical events are occurring at the sarcolemma of these muscle cells.)

• The refractory period, which is the shaded green region on each graph, represents the time when the muscle cannot be re-stimulated to contract. (The refractory period is dependent upon how quickly depolarization and repolarization occur at the sarcolemma; the faster that repolarization occurs, the shorter the refractory period.)

Now observe just the two graphs that represent what is occurring in skeletal muscle fibers (figure 19.19a, b). Figure 19.19a represents the events of a single stimulation of skeletal muscle. Notice that muscle contraction and relaxation associated with sarcomeres within skeletal muscle fibers occur over approximately 100 milliseconds. Observe also that repolarization at the sarcolemma occurs immediately following depolarization, which results in a refractory period that is relatively short (approximately 1 to 2 milliseconds). Consequently, while sarcomeres are still contracting within skeletal muscle fibers, the sarcolemma has already been repolarized to allow for a new stimulation.

Figure 19.19b represents the events of frequent stimulation of skeletal muscle. Notice that skeletal muscle, because it has a relatively short refractory period, can be restimulated at a frequency that does not allow the skeletal muscle sufficient time to relax completely. In fact, skeletal muscle can be stimulated at a rate that the muscle remains contracted (without any relaxation). Recall that this condition of sustained muscle contraction is called tetany.

Now refer to the two graphs that represent what is occurring in cardiac muscle cells (figure 19.19c, d). Figure 19.19c represents the events of a single stimulation of cardiac muscle. Notice that muscle contraction and relaxation associated with sarcomeres within cardiac muscle cells occur over approximately 250 milliseconds (a longer period than in skeletal muscle). Note also that repolarization at the sarcolemma does not occur immediately following depolarization, which results in a refractory period that is relatively long (almost 250 milliseconds). This relatively long refractory period is due to the plateau event at the sarcolemma, which delays repolarization. Consequently, while sarcomeres are still contracting and relaxing within cardiac muscle, the sarcolemma has not been repolarized to allow for a new stimulation.

Figure 19.19d represents the events of frequent stimulation of cardiac muscle. Notice that cardiac muscle, because it has a relatively long refractory period, has an extended period of time in which it cannot be restimulated. This delay in restimulation allows time for the sarcomeres of cardiac muscle cells within the heart chamber wall to fully contract and relax before being stimulated again. Thus, cardiac muscle cells composing the myocardium of the heart chamber walls do not exhibit tetany, but continue to both contract and relax following each stimulation—an essential feature for the heart to pump the blood. (Note that if tetany were possible in cardiac muscle, the chambers of the heart would experience a sustained contraction—this would be similar to a pump ceasing or “locking up.”)

**WHAT DID YOU LEARN?**

What is the significance of the extended refractory period in cardiac muscle?

### 19.7d The ECG Recording

**LEARNING OBJECTIVE**

31. Identify the components of an ECG recording.

Electrical changes within the heart can be detected during a routine physical examination using monitoring electrodes attached to the skin—usually at the wrists, the ankles, and six separate locations on the chest. The electrical signals are collected and charted as an electrocardiogram (ē-lek-trō-kar′dē-ō-gram; gramma = drawing), also called an ECG or EKG. When readings from the different electrodes are compared, they collectively provide an accurate, comprehensive assessment of the electrical changes of the heart.

**Waves and Segments**

An ECG provides a composite tracing of all cardiac action potentials generated by myocardial cells. A typical ECG tracing for one heart cycle has three principal deflections: a P wave above the baseline, a QRS complex that begins (Q) and ends (S) with small downward deflections from the baseline and has a large deflection (R) above the baseline, and a T wave above the baseline (figure 19.20). These waves indicate the electrical changes associated with depolarization and repolarization within specific heart regions:

1. The P wave reflects electrical changes of atrial depolarization that originates in the SA node. This event typically lasts 0.08 to 0.1 second.
2. The **QRS complex**, which usually lasts between 0.06 and 0.1 second, represents the electrical changes associated with **ventricular depolarization**. Note that the atria are simultaneously repolarizing; however, this repolarization signal is masked by the greater electrical activity of the ventricles.

3. The **T wave** is the electrical change associated with **ventricular repolarization**.

The two segments between the waves correspond with a plateau (where there is essentially no electrical change). During these time periods, the sarcomeres are shortening within the cardiac muscle cells. The **P-Q segment** is associated with the atrial plateau at the sarcolemma when the cardiac muscle cells within the atria are contracting, and the **S-T segment** is the ventricular plateau when the cardiac muscle cells within the ventricles are contracting.

Figure 19.20b shows two of the graphs of the electrical changes associated with the atria and ventricles (see figure 19.18b) superimposed on the ECG. Notice how the waves of an ECG reflect electrical changes—either depolarization or repolarization—and how the flat or level portions in the segments correspond to a plateau when there is no electrical change. The flat line between cycles represents when the heart is resting between beats.

**Intervals**

Additional characteristics of an ECG include two intervals: the **P-R interval** and the **Q-T interval** (figure 19.20a). Changes in length of an interval may reflect abnormal changes to the heart.

The **P-R interval** represents the period of time from the beginning of the P wave (atrial depolarization) to the beginning of the QRS deflection (ventricular depolarization). This interval of time normally ranges from 0.12 to 0.20 second. It is the time required to transmit an action potential through the entire conduction system (i.e., from the SA nodal cells to the Purkinje fibers, which stimulate the ventricles). P-R intervals that extend longer than 0.20 second generally indicate an impaired conduction, often indicating a **heart block**. (See Clinical View 19.7: “Cardiac Arrhythmia.”)

The **Q-T interval** represents the time from the beginning of the QRS (ventricular depolarization) to the end of the T wave (ventricular repolarization). This is the time required for the action potential to occur within the ventricles. This interval ranges from 0.2 to 0.4 second. A chronically longer Q-T interval may indicate a risk for a fast, irregular heart rate, which is called **tachyarrhythmia** (tak′ē-a’ril’thē-mē-ā; tachys = quick).
Cardiac arrhythmia (ă-rith’mē-ă), also called dysrhythmia, is any abnormality in the electrical activity of the heart.

Heart blocks refer to an impairment within the heart’s conducting system so the normal electrical activity is “blocked” or slowed in its progression through the conduction system. Heart blocks may result in a feeling of light-headedness, fainting, irregular heartbeat, and chest palpitations. The three different types of heart blocks differ in the extent to which electrical signals are not transmitted through the conduction system.

First-degree AV block is also called PR prolongation because of a lengthened PR interval. The action potentials are slowed between the atria and ventricles. This type of block is generally asymptomatic.

Second-degree AV block is the failure of some atrial action potentials to be conducted to the ventricles. The PR interval may be either normal or prolonged.

Third-degree AV block is a complete heart block and is the failure of all action potentials to be conducted to the ventricles. This condition is life-threatening and requires medical intervention.

**WHAT DID YOU LEARN?**

31. What events in the heart are indicated by each of the following: P wave, QRS complex, and T wave? Identify the two segments of an ECG that reflect the plateau.

**19.8 The Cardiac Cycle**

A cardiac cycle is the inclusive changes within the heart from the initiation of one heartbeat to the start of the next. One heartbeat involves the contraction and relaxation of the heart chambers. Note that the term systole (sis’tō-lē) refers to contraction of a heart chamber, whereas diastole (dī-as’tō-lē; dilation) refers to relaxation of a heart chamber.

**Premature ventricular contractions (PVCs)** involve single or rapid bursts of abnormal action potentials initiated within the AV node or the ventricular conduction system instead of the SA node. PVCs often result from stress, stimulants such as caffeine, or sleep deprivation. They are not detrimental unless they occur in great numbers. Most PVCs go unnoticed, although occasionally one is perceived as the heart “skipping a beat” and then “jumping” in the chest.

**Atrial fibrillation** (ā-bri-lā’shūn) involves chaotic action potentials within the atria. The ventricles respond by increasing and decreasing contraction activities, which may lead to serious disturbances in cardiac rhythm.

**Ventricular fibrillation** is chaotic electrical activity within the ventricles. Muscle contraction of the cardiac muscle cells within the ventricles is uncoordinated, and the heart does not pump blood. Blood circulation stops (cardiac arrest), which leads to death of cardiac muscle (myocardial infarction), commonly called a “heart attack.” To restore normal heart contractions, medical personnel apply a strong electrical shock to the chest using paddle electrodes in an attempt to synchronize the electrical events of cardiac muscle cells.

An automated external defibrillator (AED) can also be used to save an individual who is in sudden cardiac arrest (see Clinical View 19.4: “Coronary Heart Disease, Angina Pectoris, and Myocardial Infarction”). The most likely cause of a sudden cardiac arrest is ventricular fibrillation. An AED can be used to potentially restore a normal heart rhythm in ventricular fibrillation. An AED is typically available in public places where there are large numbers of people—for example, at airports, shopping malls, schools, hotels, and businesses.

**19.8a Overview of the Cardiac Cycle**

**LEARNING OBJECTIVES**

32. Identify the two processes within the heart that occur due to pressure changes associated with the cardiac cycle.

33. List the five phases of the cardiac cycle.

The alternating contraction and relaxation of both the atria and ventricles cause pressure changes within their chambers. Pressure increases during contraction and decreases during relaxation. These alternating pressure changes are responsible for two significant physiologic processes:

- Unidirectional movement of blood through the heart chambers, as blood moves along a pressure gradient (i.e., from an area of greater pressure to an area of lesser pressure).
- Opening and closing of heart valves to ensure that blood continues to move in a “forward” direction without backflow.

Keep in mind that contraction and relaxation of the ventricles are the most important driving force to continually move blood...
through the heart and to open and close heart valves during the cardiac cycle:

- **Ventricular contraction.** Ventricles contract and ventricular pressure rises. The one-way flow of blood occurs as the AV valves are closed, preventing backflow of blood into each atrium, and then the semilunar valves are opened, allowing ejection of blood from a ventricle into an arterial trunk (into the pulmonary trunk from the right ventricle and into the aorta from the left ventricle).

- **Ventricular relaxation.** Ventricles relax and ventricular pressure decreases. Now, the semilunar valves close, preventing backflow of blood into each ventricle, and then the AV valves open, allowing blood to again flow from each atrium into the right or left ventricle.

Here we organize the cardiac cycle into five phases: atrial contraction and ventricular filling, isovolumetric contraction, ventricular ejection, isovolumetric relaxation, and atrial relaxation and ventricular filling. These events are summarized in figure 19.21. Consider the following as you read through the description of each of the phases of the cardiac cycle: (1) whether the atria and ventricles are contracted or relaxed, (2) whether the pressure in the ventricles is higher or lower than the arterial trunk pressure.

**INTEGRATE**

**LEARNING STRATEGY**

The action of heart valves is similar to the saying about doors (which originated from Alexander Graham Bell): “When one door closes, another opens.” More specifically, as the ventricles contract, the AV valves close and the semilunar valves open. Then they reverse their position as the ventricles relax: The semilunar valves close and the AV valves open.

**Figure 19.21 Phases of the Cardiac Cycle.** Contraction and relaxation of heart chambers, changes in ventricular pressure, and opening and closing of heart valves occur during the phases of the cardiac cycle.
Pressure in the atria and higher or lower than the pressure in the arterial trunks (aorta and pulmonary trunk), and (3) if the AV valves and semilunar valves are opened or closed.

**WHAT DID YOU LEARN?**

Pressure changes that occur during the cardiac cycle are responsible for what two physiologic processes within the heart?

19.8b Events of the Cardiac Cycle

**LEARNING OBJECTIVES**

34. List and describe what occurs during the five phases of the cardiac cycle.

35. Explain the significance of ventricular balance.

Because this is a cycle, we could start at any point and describe the events. However, for orientation and convenience we begin when all chambers are at rest and the atria are just initiating the contraction phase.

**As the Cardiac Cycle Begins**

We can note the following characteristics of the heart prior to atrial contraction as a new round of the cardiac cycle begins.

- All four chambers are at rest.
- Blood continues to return to the right atrium through the superior vena cava, inferior vena cava, and the coronary sinus, and to the left atrium through the pulmonary veins.
- Passive filling of the ventricles is under way. No contraction of the atria is needed at this time to assist with the continual ventricular filling.
- The AV valves are open because the pressure exerted by the blood filling the atria is greater than the pressure exerted by the blood in the resting ventricles.
- The semilunar valves are closed because the pressure exerted by the blood in the filling ventricles is lower than the pressure exerted by the blood in the arterial trunks.

**Atrial Contraction and Ventricular Filling**

This phase is distinguished from the resting conditions of the heart just described by two events: atrial contraction and completion of ventricular filling (phase 1 in figure 19.21). Atrial contraction is initiated by the SA node stimulating cardiac muscle cells of the atrial wall. Ventricular filling is complete upon termination of atrial contraction, and the ventricles now hold their maximum blood volume. This is appropriately called the end-diastolic volume (EDV) because it is the volume of blood within the ventricle at the end of diastole (or rest). EDV is labeled in phase 2 in figure 19.21. In a resting adult, the value of EDV is approximately 130 milliliters (mL) of blood.

Note that during atrial contraction, both the inflow of additional blood from the supplying veins into the atria (i.e., blood flow from the superior vena cava, inferior vena cava, and coronary sinus into the right atrium and blood flow from the pulmonary veins into the left atrium) and the backflow of blood from the atria into these veins are prevented because contraction of the atria compresses the openings for the great veins.

You will find it helpful to remember that at the end of this phase, the atria relax and will remain relaxed until the beginning of the next cardiac cycle, as shown in phases 2 through 5 in figure 19.21. These four phases (2 through 5) involve the changes associated with contraction and relaxation of the ventricles.

**Isovolumetric Contraction**

Isovolumetric (i’sō-vol’yū-met’rik; *iso* = same) contraction involves no change in ventricular blood volume when the ventricles are contracting. Two distinctive changes occur in this phase: ventricular contraction and closure of the AV valves (phase 2 in figure 19.21). Ventricular contraction is initiated by the Purkinje fibers of the conduction system stimulating the cardiac muscle cells of the ventricular wall. As the ventricles begin to contract, the pressure within the ventricles increases and exceeds the pressure within the atria. Consequently, the AV valves are forced closed. Recall that these valves are braced by tendinous cords to the papillary muscles. The closure of these valves prevents backflow of blood from the ventricles.
into the atria. The semilunar valves remain closed because the pressure within the ventricle is still less than the pressure within the attached arterial trunk.

Note that all heart valves are closed at this time. Thus, although the ventricular cardiac muscles are contracting during this phase, no blood is entering or leaving the ventricle and the volume within the ventricular chambers remains the same.

**Ventricular Ejection**

**Ventricular ejection**, which is the movement of blood from the ventricles into the arterial trunks, occurs during this phase as ventricular contraction continues and the semilunar valves are forced open (phase 3 in figure 19.21). As the ventricles continue to contract, the pressure within the ventricles increases and exceeds the pressure within the arterial trunk. Consequently, the semilunar valves open, which allows blood to be ejected from the ventricles into their associated arterial trunk (i.e., blood is ejected from the left ventricle into the aorta and blood is ejected from the right ventricle into the pulmonary trunk). The AV valves remain closed because the pressure within the ventricles remains greater than the pressure within the atria. The amount of blood pumped out during ventricular contraction is termed the **stroke volume (SV)**. Generally, this volume is approximately 70 mL of blood.

Not all of the blood in either ventricle is ejected. The blood remaining in a ventricle at the end of systole is appropriately called the **end-systolic volume (ESV)** because it is the volume of blood in the ventricle at the end of systole (or contraction). ESV is labeled in phase 4 in figure 19.21. ESV is determined by subtracting SV from EDV (EDV – SV = ESV): 130 mL – 70 mL = 60 mL.

**Isovolumetric Relaxation**

**Isovolumetric relaxation** involves no change in ventricular blood volume when the ventricles are relaxing. Two distinctive changes occur in this phase: ventricular relaxation and closure of the semilunar valves (phase 4 in figure 19.21). As the ventricles start to relax and the ventricular chamber expands back to its resting size, pressure within the ventricles decreases below the pressure within the attached arterial trunks. Blood initially flows backward slightly within the arterial trunks but is caught in the semilunar valves, causing them to close. This closure of the semilunar valves prevents blood backflow from the arterial trunks into the ventricles. The AV valves remain closed because the pressure within the ventricles is still greater than the pressure within the atria.

Note that all heart valves are again closed simultaneously. Thus, although the ventricular cardiac muscles are relaxing during this phase, no blood is entering or leaving the ventricle and the volume within the ventricular chambers remains the same.

**Atrial Relaxation and Ventricular Filling**

The final phase of the cardiac cycle is distinguished by the continued relaxation of the ventricles and the opening of the AV valves (phase 5 in figure 19.21). As the ventricles continue to relax, the pressure within the ventricles decreases below the pressure within the atria, and the AV valves open. The opening of these valves allows blood to once again move from the atria into the ventricles for ventricular filling. The semilunar valves remain closed because the pressure within the ventricles remains lower than the pressure with the arterial trunks. Amazingly, these events of the cardiac cycle, as organized and described in these five phases, are repeated with each heartbeat!

Figure 19.22 shows all of the principal events of one heartbeat, including the electrical events that control heart contraction, as depicted on an ECG; the contraction and relaxation of the heart chambers and position of the heart valves that occur during a cardiac cycle; the relative pressure within the left atrium, left ventricle, and aorta; and the changes in blood volume within the left ventricle.

**Ventricular Balance**

It is important to realize that *equal* amounts of blood are normally pumped by the two ventricles through the two circulations, a condition called **ventricular balance**. However, the right ventricle has to pump the blood only to the adjacent lungs (a relatively short circuit), whereas the left ventricle has to pump the blood through the systemic circulation throughout the body (a relatively long circuit). Thus, the left ventricle must be larger and stronger than the right ventricle to pump the blood farther—but it is the same amount of blood pumped from both sides of the heart. Sustained pumping of unequal amounts of blood may result in **edema** (e-dé’mä; aoidema = swelling), which is excess fluid in the interstitial space or within cells. (See Clinical View 19.1: “Congestive Heart Failure.”)
Figure 19.22 Changes Associated with a Cardiac Cycle. A cardiac cycle is the inclusive changes within the heart from the initiation of one heartbeat to the start of the next. The cardiac cycle is organized here into five phases and includes (a) an ECG; (b) heart diagrams of the five phases; (c) a graph of the relative pressure within the aorta, left atrium, and left ventricle, which is the driving force for both opening and closing the heart valves and moving blood through the heart (for the left side of the heart); and (d) a graph showing the changes in left ventricular blood volume.

(a) ECG (electrocardiogram)

(b) Stages

1. Atrial contraction and ventricular filling
   - Semilunar valve
   - AV valve
   - Atrial depolarization (P wave in ECG) triggers atrial contraction; ventricles are relaxed to receive the blood; AV valves are opened and the semilunar valves are closed.
   - Ventricular pressure (blue line) < both atrial pressure (green line) and pressure in aorta (red line).
   - Ventricular blood volume increases slightly.

2. Isovolumetric contraction
   - Ventricular depolarization (QRS wave in ECG) triggers ventricular contraction; atria are relaxed; both the AV valves and semilunar valves are closed.
   - Ventricular pressure (blue line) > atrial pressure (green line), < pressure in aorta (red line).

3. Ventricular ejection
   - Pressure in aorta rises and exceeds ventricular pressure (blue line);
     - Dicrotic notch:
       - A temporary drop in pressure in the aorta that occurs when the aortic semilunar valve closes.
     - Stroke volume (SV) leaves the ventricle.
     - End-systolic volume (ESV) remains the same.

4. Isovolumetric relaxation
   - No electrical activity.
   - Ventricles relax; both atrial pressure and pressure in aorta (red line) are < ventricular pressure (blue line).
   - Ventricular blood volume remains the same.

5. Atrial relaxation and ventricular filling
   - Atrial relaxation (atrial depolarization) occurs; ventricular pressure remains < both atrial pressure and pressure in aorta.
   - Ventricular blood volume increases (as blood flows from the atrium).

INTEGRATE CONCEPT OVERVIEW

Events of a cardiac cycle

- End-diastolic volume (EDV)
- End-systolic volume (ESV)
- Stroke volume (SV)
- Atrial depolarization
- Ventricular depolarization
- Atrial repolarization
- Ventricular repolarization
- Atrial contraction
- Ventricular contraction
19.9 Cardiac Output

The function of the cardiovascular system is to move blood throughout the body to transport respiratory gases, nutrients, and other substances to provide adequate perfusion of all body tissues (see section 19.1a). Cardiac output is a measure of how effective the cardiovascular system is in fulfilling its function. In a healthy individual, cardiac output increases during strenuous effort or exercise to meet the additional cellular demands for oxygen and nutrients and eliminating waste products. In contrast, individuals with impaired heart function may not experience an increase in cardiac output, thus limiting their ability to engage in physically demanding activities. Here we first define cardiac output and then discuss the variables that influence it.

19.9a Introduction to Cardiac Output

LEARNING OBJECTIVES

36. Define cardiac output.
37. Explain what is meant by cardiac reserve.

Cardiac output (CO) is defined as the amount of blood that is pumped by a single ventricle (left or right) in 1 minute and is typically expressed as liters per minute. As just described, both ventricles eject equal amounts of blood (i.e., balanced ventricular output), so either the left or right ventricle can be used.

Cardiac output is determined by heart rate and stroke volume. Heart rate (HR) is the number of beats per minute (bpm). Stroke volume (SV) is the volume of blood ejected during one beat and is expressed as milliliters per beat. Cardiac output is determined as follows:

\[
\text{HR} \times \text{SV} = \text{CO}
\]

Beats per minute \( \text{mL ejected per beat} \) \( \text{mL ejected per minute} \)

For example, when a person is at rest and the HR is 75 beats per minute and SV is 70 mL per beat, the CO is 5250 milliliters per minute (5250 mL/min), or 5.25 liters per minute (5.25 L/min). Note that 1000 mL = 1 liter.

The total volume of blood in the body is approximately 5 L (see section 18.1b). Thus, with a cardiac output of approximately 5 L per minute, the total blood volume is pumped through both the pulmonary circulation and systemic circulation every minute. This is equivalent to moving over 7000 L of blood daily!

Maintaining Resting Cardiac Output

The ability to maintain normal resting cardiac output is a function of both heart rate and stroke volume, and the value of one influences the value of the other. For example, individuals with smaller hearts produce a smaller stroke volume. Consequently, their resting heart rates must be higher to maintain normal resting cardiac output. This accounts for women’s typically faster resting heart rate compared to men, and it explains why infants and young children, with their relatively small hearts, have a faster resting heart rate than adults. Newborns, for example, typically have a resting heart rate between 120 and 160 beats per minute.

In comparison, highly trained athletes tend to have larger and stronger hearts. This is because the cardiac muscle cells of the heart wall hypertrophy in response to the additional cardiovascular demands made during consistent strenuous effort. The larger heart generates a greater stroke volume. Thus, an athlete’s normal resting cardiac output is maintained with a larger stroke volume and a lower heart rate. Well-conditioned elite athletes, for example, may have resting heart rates below 40 beats per minute.
Cardiac Reserve

An increase in both heart rate and stroke volume results in an increase in cardiac output. During physical exertion, heart rate can be accelerated to more than 170 beats per minute. Likewise, stroke volume can be increased to more than 100 mL. Cardiac reserve is an increase in cardiac output above its level at rest. It can be determined by subtracting cardiac output at rest from the cardiac output during exercise.

Cardiac reserve is a measure of the level and duration of physical effort in which an individual can engage. Cardiac output may be increased by about four-fold in a healthy, nonathletic individual (to approximately 20 L/min), and up to seven-fold in a highly trained athlete (to approximately 35 L/min). In comparison, individuals with a weakened heart may have little cardiac reserve and thus experience limitations in exerting themselves.

WHAT DID YOU LEARN?

16. What are the two factors that determine cardiac output?

27. What is the cardiac output at rest and during exercise, and the cardiac reserve, if (a) the heart rate is 75 beats per minute and stroke volume is 70 mL at rest, and (b) if the heart rate is 150 beats per minute and stroke volume is 100 mL during exercise?

19.9b Variables That Influence Heart Rate

LEARNING OBJECTIVES

38. Define chronotropic agents, and describe how they affect heart rate.

39. Discuss how autonomic reflexes alter heart rate.

Cardiac output is directly influenced by both heart rate and stroke volume. Both heart rate and stroke volume, in turn, have variables that influence each of them. Here we describe the variables that influence heart rate and then in section 19.9c discuss the variables that influence stroke volume.

The heart rate can be altered by external factors that act on the SA node (the pacemaker) and the AV node. The primary external factors to increase and decrease heart rate come from autonomic nervous system innervation (both the sympathetic division and the parasympathetic division) and varying levels of some hormones. These factors that change heart rate are called chronotropic (kron’ō-trop’ik; chronos = time, tropos = change) agents and are classified as either positive chronotropic agents or negative chronotropic agents.

Positive chronotropic agents cause an increase in heart rate and include sympathetic nerve stimulation and certain types of hormonal stimulation. Review figure 19.23 as you read through this section. Sympathetic axons release the neurotransmitter norepinephrine (NE) to act directly on the SA nodal cells (see section 15.6b). The sympathetic division also causes release of both epinephrine (EPI) and NE from the adrenal medulla into the blood (step 1). Both NE and EPI bind to β1-adrenergic receptors of the heart (step 2). This binding initiates an intracellular pathway involving G protein that results in the activation of adenylate cyclase enzyme with the accompanying production of the second messenger, cAMP (see section 17.5b). Ultimately, protein kinase enzymes phosphorylate Ca2+ channels, causing them to open. Positively charged Ca2+ enters the nodal cells, and nodal cells reach threshold more quickly, increasing the firing rate of the SA node (step 3). (Recall that an influx of Ca2+ is responsible for depolarization of nodal cells; see section 19.6b). Sympathetic stimulation of the AV node also increases calcium influx into these cells (not shown in figure 19.23). The delay in the AV node is decreased, and the conduction rate is increased. Thus, heart rate increases.

Thyroid hormone (see section 17.8b) is also a positive chronotropic agent because it makes nodal cells more responsive to NE and EPI by increasing the number of β1-adrenergic receptors (at step 2). Additionally, several drugs act on this pathway to increase heart rate. Nicotine and cocaine both increase the amount of NE present in the synaptic cleft (at step 1). Nicotine functions by increasing the release of NE, and cocaine functions by inhibiting the reuptake of NE. Caffeine, in comparison, inhibits the breakdown of cAMP (at step 3). (Very high intake of caffeine in some “energy drinks” has resulted in several fatal heart attacks.)

In contrast, negative chronotropic agents decrease heart rate. Parasympathetic innervation is one of the most important of these agents. Parasympathetic axons release acetylcholine that binds to M2 muscarinic receptors (see section 15.6b), which are K+ channels (see figure 19.16). These channels open, and K+ moves down its concentration gradient to exit the cells. This loss of positive ion causes hyperpolarization (membrane potential becomes more negative) of nodal cells, and it takes a longer period of time for these cells to reach threshold—thus, the heart rate is slower. Beta-blocker drugs (which
interfere with binding of norepinephrine and epinephrine to beta receptors) are another type of negative chronotropic agent and are used to treat high blood pressure.

### Autonomic Reflexes

The ability of the autonomic nervous system to influence heart rate through the sympathetic and parasympathetic divisions is controlled through **autonomic reflexes** (see section 15.8). The cardiac center receives sensory input from baroreceptors (regarding stretch of blood vessels) and chemoreceptors (concerning blood carbon dioxide and hydrogen ion [H\(^+\)] levels). The cardiac center reflexively responds to this input by altering nerve signals relayed through sympathetic and parasympathetic neurons that innervate the heart to adjust heart rate and stroke volume as needed to maintain homeostasis (see figure 19.14).

One specific autonomic reflex is the **atrial reflex**, also called the **Bainbridge reflex**, which protects the heart from overfilling. It is initiated when baroreceptors in the atrial walls are stimulated by an increase in venous return. Nerve signals are increased along sensory neurons to the cardioacceleratory center, resulting in an increase in nerve signals relayed along sympathetic neurons to the heart. Heart rate increases so blood moves more quickly through the heart, thus decreasing atrial stretch. Arterial reflexes associated with regulating systemic blood pressure that are initiated by baroreceptors and chemoreceptors in the aorta and carotid are described in section 20.6a.

### WHAT DID YOU LEARN?

39. Describe the atrial reflex, which involves baroreceptors within the atria, the cardiac center, and the heart.

### 19.9c Variables That Influence Stroke Volume

#### LEARNING OBJECTIVES

40. List the three variables that may influence stroke volume.

41. Define each of the three variables, and describe the factors that influence each variable and how each variable affects stroke volume.

**Stroke volume (SV)** is the volume of blood pumped from a ventricle during a ventricular contraction (i.e., the amount of blood ejected per heartbeat) (figure 19.24). Recall from section 19.8b that stroke volume is dependent upon the volume of blood that enters the heart at the end of heart relaxation (called the **end-diastolic volume (EDV)**). The typical EDV in a resting adult is approximately 130 mL. However, not all blood in either ventricle is normally ejected from the heart during ventricular contraction. The blood remaining in a ventricle at the end of ventricular contraction is called the **end-systolic volume (ESV)**. The typical ESV in an adult is 60 mL. Thus, stroke volume is the difference between EDV and ESV:

$$\text{EDV} - \text{ESV} = \text{SV}$$

$$130 \text{ mL} - 60 \text{ mL} = 70 \text{ mL}$$

These values for ESV, EDV, and SV are typical values for an adult. The specific volume of blood ejected as stroke volume varies and is influenced by several variables. These include (1) venous return, which is the amount of blood returned to the heart; (2) inotropic agents, which are external factors that alter the force of contraction of the myocardium; and (3) afterload, which is the resistance in the arteries to the ejection of blood from the heart.

### Venous Return

**Venous return** is the volume of blood returned to the heart via the great veins and is directly related to stroke volume. Venous return determines the amount of blood in the ventricle at the end of rest immediately prior to contraction (i.e., end-diastolic volume, or EDV). This volume of blood, in turn, determines the preload on the heart. **Preload** is stretch of the heart wall due to the load to which a cardiac muscle is subjected before shortening. In other words, preload is the heart muscle wall stretch just prior to contraction.

The direct relationship of venous return and stroke volume can be explained by the **Frank-Starling law** of the heart (or simply Starling’s law). This law essentially states that as the volume of blood entering the heart increases, there is greater stretch of the heart wall (or preload). This results in greater overlap of the thick and thin filaments in the sarcomeres of the cardiac muscle cells composing the myocardium, allowing formation of greater numbers of crossbridges. (Recall that cardiac muscle does not exhibit maximum overlap of thin and thick filaments at rest; see section 19.3f.) Consequently, a more forceful ventricular contraction is generated, and stroke volume increases.

As venous return decreases, there is less stretch of the heart wall (smaller preload), and this results in less overlap of the thick and thin filaments and fewer crossbridges form. Consequently, a less forceful ventricular contraction is generated, and stroke volume decreases.
What causes venous return, and thus preload, to either increase or decrease? Venous return is increased by either an increase in venous pressure or an increase in time to fill, and venous return may be decreased by a decrease in either of these two factors. You might find the analogy of filling a balloon helpful. The water pressure and the time to fill the balloon will determine how much water you can add to the balloon in a given period of time.

Venous return increases during exercise, for example, because of greater venous pressure. Veins are “squeezed” by skeletal muscles, which helps return blood to the heart (see section 20.5a). Greater muscular movement increases the action of the skeletal muscle pump. During exercise, venous return can approximately double in comparison to its rate at rest. Venous return also increases with a slower heart rate. The slower heart rate allows a greater amount of time for blood to enter the heart. This is most noticeable in highly trained athletes who have a very low resting heart rate.

In comparison, low blood volume (e.g., due to hemorrhage) or an abnormally high heart rate decreases venous return. The result is a smaller end-diastolic volume and preload, and a smaller stroke volume.

Balanced ventricular output is primarily a function of the inherent ability of the heart to contract more forcefully in response to increased venous return. Consider, for example, that when you first start to exercise, venous return from the body into the right side of the heart increases, causing it to contract more forcefully and increasing stroke volume. Increased amount of blood then moves through the pulmonary circulation and returns to the left ventricle. The left ventricle, in turn, will experience greater stretch of its chamber wall and will contract more forcefully.

**Inotropic Agents**

Stroke volume is similar to heart rate in that it is altered by external factors. The primary external factors to increase and decrease heart rate come from autonomic innervation and varying levels of some hormones. These factors that change stroke volume are called inotropic (in′ō-trop′ik; ino = fiber) agents. Inotropic agents alter contractility, which is the force of contraction at a given stretch of the cardiac muscle cells. An increase or a decrease in the force of contraction is generally due to a change in the available Ca$^{2+}$ in the sarcoplasm. Changes in Ca$^{2+}$ concentration alter the number of crossbridges formed and thus the force of contraction generated.

A positive inotropic agent increases Ca$^{2+}$ concentration, which results in formation of additional crossbridges. Positive inotropic agents include norepinephrine that is released from sympathetic neurons and epinephrine and norepinephrine from the adrenal medulla. These ligands bind to β₁-adrenergic receptors to cause an increase in Ca$^{2+}$ levels within cardiac muscle cells. Thyroid hormone is also a positive inotropic agent because it increases the number of β₁-adrenergic receptors in the cardiac muscle cells. Certain drugs (e.g., digitalis) are positive inotropic agents used to treat abnormally low cardiac output that accompanies some heart conditions (e.g., congestive heart failure).

In comparison, a negative inotropic agent decreases contractility by decreasing available Ca$^{2+}$ and fewer numbers of crossbridges are formed. Electrolyte imbalances (see table 25.1 and sections 25.3b and 25.6), including an increase in either K$^+$ or H$^+$, act as negative inotropic agents. Certain drugs (e.g., nifedipine, a Ca$^{2+}$ channel–blocking drug) are negative inotropic agents and are given to decrease cardiac output, typically in an effort to treat high blood pressure.

**Afterload**

Afterload is the resistance in arteries to the ejection of blood by the ventricles, and it represents the pressure that must be exceeded before blood is ejected from the chamber. Afterload generally becomes a consideration only in older individuals. Arteries typically develop atherosclerosis as we age. (However, because of the increased rate of obesity in teenagers and young adults, the prevalence of atherosclerosis is increasing in these age groups.) It is a condition in which plaque accumulates on the inner linings of a blood vessel. The smaller arterial lumen exerts greater resistance to the movement of blood into the arterial trunks, and stroke volume decreases. The relationship of these variables that influence stroke volume is integrated in figure 19.25.

**WHAT DID YOU LEARN?**

Which of the following increases stroke volume: (a) increased venous return, (b) increased Ca$^{2+}$ in sarcoplasm, or (c) afterload? Explain.
19.9d Variables That Influence Cardiac Output

**LEARNING OBJECTIVE**

42. Summarize the variables that influence cardiac output.

The factors that influence heart rate and stroke volume, and ultimately cardiac output, are integrated in a flowchart in [Figure 19.26](#). Note the following:

- **Heart rate.** An increase or a decrease in heart rate is dependent upon chronotropic agents that influence the conduction system. These agents stimulate the SA node to change its firing rate or the AV node to alter the amount of delay.

- **Stroke volume.** An increase or a decrease in stroke volume is generally due to changes in the myocardium. Venous return (which alters the stretch of the heart) and inotropic agents (which change the Ca²⁺ level in the sarcoplasm) influence the number of crossbridges, which alters the force of contraction. The only exception is afterload, which reflects increased resistance in arteries, making it more difficult for the heart to pump blood. Afterload is generally a factor only as we age.

- **Cardiac output.** Both heart rate and stroke volume are directly related to cardiac output. When both heart rate and stroke volume increase, cardiac output increases. In contrast, when both heart rate and stroke volume decrease, cardiac output decreases. It is not

---

**CLINICAL VIEW 19.8**

**Bradycardia and Tachycardia**

A persistently low resting heart rate below 60 beats per minute in adults is called **bradycardia**. Bradycardia is considered a normal change in highly trained athletes who engage in a sustained aerobic exercise program. Abnormal conditions that cause bradycardia include hypothyroidism (see Clinical View 17.5: “Disorders of Thyroid Hormone Secretion”), electrolyte imbalances (see section 25.3b), and congestive heart failure (see Clinical View 19.1: “Congestive Heart Failure”). In comparison, a persistently high resting heart rate above 100 beats per minute in adults is called **tachycardia**. Tachycardia is caused by abnormal conditions such as heart disease, fever, or anxiety.
possible to predict the net effect on cardiac output (i.e., whether it will increase or decrease) if heart rate and stroke volume change in opposite directions (e.g., stroke volume decreases from blood loss, and heart rate increases in an attempt to maintain cardiac output). The net effect will be determined by the relative change to both heart rate and stroke volume.

WHAT DID YOU LEARN?

If both heart rate and stroke volume increase, does cardiac output (a) stay the same, (b) increase, or (c) decrease? Thus, is the relationship between these two variables and cardiac output direct or inverse?

19.10 Development of the Heart

LEARNING OBJECTIVES

43. Explain how postnatal heart structures develop from the primitive heart tube.

44. Describe septal defects that may occur during development.

Development of the heart commences in the third week, when the embryo becomes too large to receive its nutrients through diffusion alone. The steps involved in heart development are complex, because the heart must begin working before its development is complete (figure 19.27).

By day 19 (middle of week 3), two heart tubes (endocardial tubes) form from mesoderm in the embryo. By day 21, these paired tubes fuse, forming a single primitive heart tube (figure 19.27a). By day 22, the heart begins to beat, and later in the fourth week, this single heart tube bends and folds upon itself to begin to form the external heart shape (figure 19.27b). This tube develops the following named expansions that give rise to postnatal heart structures (listed from inferior to superior): sinus venosus, primitive atrium, primitive ventricle, and bulbus cordis (būl’būs kör’dis). The sinus venosus and primitive atrium form parts of the left and right atria. The primitive ventricle forms most of the left ventricle. The bulbus cordis may be further subdivided into a trabeculated part of the right ventricle, which forms most of the right ventricle; the conus cordis, which forms the outflow tracts for the ventricles; and the truncus arteriosus, which forms the ascending aorta and pulmonary trunk (figure 19.27c).

The next major steps in heart development occur during weeks 5–8, when the single heart tube becomes partitioned into four chambers (two atria and two ventricles), and the great vessels form. This partitioning is complex, and errors in development lead to many of the more common congenital heart malformations.

The common atrium is subdivided into a left and right atrium by an interatrial septum, which consists of two parts (septum primum and septum secundum) that partially overlap (figure 19.27d). An opening in the septum secundum (which is covered by the septum primum) is called the foramen ovale. Because the embryonic lungs are not functional, much of the blood is shunted from the right atrium to the left atrium by moving through the foramen ovale and pushing the septum primum into the left atrium. When the baby is born and the lungs are fully functional, the blood from the left atrium pushes the septum primum and septum secundum together, closing the interatrial septum. The only remnant of the embryonic opening is an oval-shaped depression in the interatrial septum called the fossa ovalis.
Left and right ventricles are partitioned by an **interventricular septum** that grows superiorly from the floor of the ventricles. The AV valves, papillary muscles, and tendinous cords all form from portions of the ventricular walls as well.

Many congenital heart malformations result from incomplete or faulty development during the early weeks of development. For example, in an **atrial septal defect**, the postnatal heart still has an opening between the left and right atria. Thus, blood from the left atrium (the higher-pressure system) is shunted to the right atrium (the lower-pressure system). This can lead to enlargement of the right side of the heart.

**Ventricular septal defects** can occur if the interventricular septum is incompletely formed. A common malformation called **tetralogy of Fallot** occurs when the aortico pulmonary septum divides the truncus arteriosus unevenly. As a result, the patient has a ventricular septal defect, a very narrow pulmonary trunk (pulmonary stenosis), an aorta that overlaps both the left and right ventricles, and an enlargement of the right ventricle (right ventricular hypertrophy).

**WHAT DID YOU LEARN?**

What would be the path of blood flow through the heart if the foramen ovale did not close shortly after birth?
### 19.1 Introduction to the Cardiovascular System
- The cardiovascular system is composed of the heart and blood vessels organized into the pulmonary circulation and systemic circulation.

#### 19.1a General Function
- The function of the cardiovascular system is to transport substances throughout the body and provide adequate perfusion to all tissues.

#### 19.1b Overview of Components
- The primary types of blood vessels include arteries, capillaries, and veins.
- The heart acts as two “side-by-side” pumps with the right side composed of a right atrium and right ventricle and the left side composed of a left atrium and left ventricle. Valves within the heart help ensure a one-way flow of blood.

#### 19.1c Pulmonary and Systemic Circulation
- The circulation routes include the pulmonary circulation to the lungs and the systemic circulation to the body.

### 19.2 The Heart Within the Thoracic Cavity
- The heart is located in the thoracic cavity and enclosed within a fibroserous sac.

#### 19.2a Location and Position of the Heart
- The heart is located left of the body midline, posterior to the sternum in the mediastinum with its apex projecting inferiorly.

#### 19.2b The Pericardium
- The pericardium that encloses the heart includes the pericardial sac, which has an outer fibrous pericardium and an inner parietal layer of serous pericardium, and a visceral layer of serous pericardium (epicardium) that forms the outer layer of the heart wall.
- The pericardial cavity is a potential space between the layers of the serous pericardium that contain serous fluid, which is produced by the serous membranes and lubricates the surfaces to reduce friction.

### 19.3 Heart Anatomy
- The heart is a relatively small, conical-shaped organ, which is approximately the size of a human fist.

#### 19.3a Superficial Features of the Heart
- The right side of the heart is more visible from the anterior view, and the left side of the heart is more visible from the posterior view.
- The coronary sulcus and interventricular sulci are visible from the external surface of the heart. These grooves house coronary vessels.

#### 19.3b Layers of the Heart Wall
- The heart wall has an epicardium (visceral layer of serous pericardium), a myocardium, and an endocardium.

#### 19.3c Heart Chambers
- Atria are separated by an interatrial septum, and ventricles are separated by an interventricular septum.
- The four heart chambers include the right atrium, right ventricle, left atrium, and left ventricle.

#### 19.3d Heart Valves
- The atrioventricular valves are located between an atrium and a ventricle, and the semilunar valves are between a ventricle and an arterial trunk (pulmonary trunk or aorta).

#### 19.3e Fibrous Skeleton of the Heart
- The fibrous skeleton provides an attachment site for heart valves and cardiac muscle, and prevents action potentials from spreading between the atria and ventricles except through the AV node.

#### 19.3f Microscopic Structures of Cardiac Muscle
- Cardiac muscle cells are small, have one or two centrally located nuclei, and are branched.
- Intercalated discs, which are composed of desmosomes and gap junctions, tightly link the cardiac muscle cells together and permit the passage of action potentials, respectively.
- Cardiac muscle cells rely almost exclusively on aerobic cellular respiration for supplying ATP, which makes them susceptible to failure if the oxygen supply is inadequate.

### 19.4 Coronary Vessels: Blood Supply Within the Heart Wall
- The coronary circulation is the circulation of blood to and from the heart wall.

#### 19.4a Coronary Arteries
- Coronary arteries supply blood to the heart wall and include the left and right coronary arteries that branch off the ascending aorta.

#### 19.4b Coronary Veins
- Venous return is through the cardiac veins into the coronary sinus, which drains into the right atrium of the heart.

### 19.5 Anatomic Structures Controlling Heart Activity
- Heart activity is initiated by the conduction system and altered by the autonomic nervous system.

#### 19.5a The Heart’s Conduction System
- Stimulation of the heart involves initiation of an action potential at the SA node and its transmission through the conduction system.
- The conducting system includes sinoatrial (SA) node, atrioventricular (AV) node, AV bundle, bundle branches, and Purkinje fibers, which are composed of specialized cardiac cells that initiate and conduct action potentials, resulting in a heartbeat.

#### 19.5b Innervation of the Heart
- Parasympathetic innervation comes from the cardioinhibitory center to decrease the heart rate. Sympathetic innervation comes from the cardioacceleratory center to increase both the heart rate and the force of contraction.
<table>
<thead>
<tr>
<th>Section</th>
<th>Textual Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.6 Stimulation of the Heart</td>
<td>- Heart contraction involves two events, which are the initiation and spread of an action potential through the conduction system and the spread of the action potential at the sarcolemma of cardiac muscle and cardiac muscle contraction.</td>
</tr>
<tr>
<td>19.6a Nodal Cells at Rest</td>
<td>- The pumps and channels associated with neurons are also in the plasma membrane of nodal cells. A type of channel unique to nodal cells is the slow voltage-gated Na⁺ channel that allows the nodal cells to spontaneously depolarize.</td>
</tr>
<tr>
<td>19.6b Electrical Events at the SA Node: Initiation of the Action Potential</td>
<td>- The three events of SA nodal cells are (1) reaching the threshold as Na⁺ enters the nodal cells through open voltage-gated Na⁺ channels, (2) depolarization as Ca²⁺ enters the nodal cells through open voltage-gated Ca²⁺ channels, and (3) repolarization as K⁺ exits the nodal cells through open voltage-gated K⁺ channels. - At rest, the parasympathetic nervous system decreases the inherent rhythm of nodal cells from a firing rate of 100 per minute to approximately 75 per minute.</td>
</tr>
<tr>
<td>19.6c Conduction System of the Heart: Spread of the Action Potential</td>
<td>- The action potential travels through the conduction system as follows: (1) SA node, (2) AV node, (3) AV bundle, (4) bundle branches, and (5) Purkinje fibers.</td>
</tr>
<tr>
<td>19.7 Cardiac Muscle Cells</td>
<td>- Following stimulation by the conduction system, there is a propagation of the action potential at the sarcolemma and contraction of sarcomeres within the cardiac muscle cells.</td>
</tr>
<tr>
<td>19.7a Cardiac Muscle Cells at Rest</td>
<td>- The pumps and channels associated with skeletal muscle fibers are also in the plasma membrane of cardiac muscle cells. A type of channel unique to the function of cardiac muscle cells in transmitting an action potential is the voltage-gated Ca²⁺ channel.</td>
</tr>
<tr>
<td>19.7b Electrical and Mechanical Events of Cardiac Muscle Cells</td>
<td>- The electrical events of cardiac muscle include depolarization, plateau, and repolarization at the sarcolemma. - The mechanical events are similar to those of skeletal muscle fibers and involve crossbridge cycling and the shortening of sarcomeres within cardiac muscle cells.</td>
</tr>
<tr>
<td>19.7c Repolarization and the Refractory Period</td>
<td>- Cardiac muscle exhibits a longer refractory period than skeletal muscle fibers to allow time for contraction and relaxation of the muscle cells before they are stimulated again—a necessary requirement for the pumping action of the heart.</td>
</tr>
<tr>
<td>19.7d The ECG Recording</td>
<td>- An electrocardiogram (ECG) is a graphic recording of the electrical changes in the heart and is used in the diagnosis and treatment of abnormal heart function.</td>
</tr>
<tr>
<td>19.8 The Cardiac Cycle</td>
<td>- A cardiac cycle is the inclusive period of time from initiation of one heartbeat to the start of the next.</td>
</tr>
<tr>
<td>19.8a Overview of the Cardiac Cycle</td>
<td>- The cardiac cycle involves contraction and relaxation of heart chambers and associated pressure changes within the chambers, which result in the opening and closing of heart valves to allow for the one-way flow of blood through the heart.</td>
</tr>
<tr>
<td>19.8b Events of the Cardiac Cycle</td>
<td>- The cardiac cycle involves five phases: atrial contraction and ventricular filling, isovolumetric contraction, ventricular ejection, isovolumetric relaxation, and atrial relaxation and ventricular filling.</td>
</tr>
<tr>
<td>19.9 Cardiac Output</td>
<td>- Cardiac output is a measure of how effective the cardiovascular system is in transporting substances through the body.</td>
</tr>
<tr>
<td>19.9a Introduction to Cardiac Output</td>
<td>- Cardiac output (CO) is defined as the amount of blood pumped by a single ventricle in 1 minute. - Cardiac output is the heart rate multiplied by the stroke volume. - Cardiac reserve is a measure of the ability of the heart to increase pumping capacity beyond the normal resting CO.</td>
</tr>
<tr>
<td>19.9b Variables That Influence Heart Rate</td>
<td>- Heart rate is altered through chronotropic agents, which change SA node and AV node activity. Positive chronotropic agents increase the heart rate, and negative chronotropic agents decrease the heart rate.</td>
</tr>
<tr>
<td>19.9c Variables That Influence Stroke Volume</td>
<td>- Stroke volume is influenced by venous return, inotropic agents, and afterload. Venous return is directly correlated with stroke volume. Positive inotropic agents increase stroke volume, negative inotropic agents decrease stroke volume, and afterload is inversely correlated with stroke volume.</td>
</tr>
<tr>
<td>19.9d Variables That Influence Cardiac Output</td>
<td>- Heart rate is altered by stimulating the conducting system, and stroke volume is altered by changes in the myocardium. - Both heart rate and stroke volume are directly related to cardiac output.</td>
</tr>
<tr>
<td>19.10 Development of the Heart</td>
<td>- Development of the heart commences in the third week. - Mesodermal cells in the cardiogenic region of the embryo form two heart tubes, which fuse by day 21, forming a single primitive heart tube. - The foramen ovale connects the two atria, allowing most of the blood to bypass the pulmonary circulation. This foramen closes shortly after birth.</td>
</tr>
</tbody>
</table>
5. Calcium channels in the nodal cells function to
   a. cause depolarization and initiate the cardiac action potential.
   b. assure excess calcium can leave the cell.
   c. bring the cell quickly to its resting membrane potential.
   d. sustain contraction of the cell.

6. Action potentials are spread rapidly between cardiac muscle cells by
   a. sarcomeres.
   b. intercalated discs.
   c. chemical neurotransmitters.
   d. the fibrous skeleton.

7. Why is it necessary to stimulate papillary muscles in the ventricle slightly earlier than the rest of the ventricular wall myocardium?
   a. to assure rapid conduction speed of the action potential
   b. to pull on AV valve cusps to prevent backflow
   c. to assure blood will surge toward the semilunar valves
   d. to assure coordinated contraction of the ventricular myocardium

8. Preload is a measure of
   a. stretch of the heart chamber prior to contraction.
   b. contraction rate in cardiac muscle.
   c. reduced filling during exercise.
   d. autonomic nervous system stimulation of the heart.

9. All of the following occur when the ventricles contract except
   a. the AV valves close.
   b. blood is ejected into the aorta.
   c. the semilunar valves open.
   d. blood from the pulmonary trunk enters the atria.

10. What occurs during the atrial reflex?
    a. Atria slow their filling rate.
    b. There is a decrease in heart rate due to an increase in blood pressure.
    c. The SA node rhythm decreases.
    d. An increase in heart rate occurs in response to an increase in blood volume within the atria.

11. Describe and compare the differences between the pulmonary and systemic circulations.

12. Compare the structure, location, and function of the parietal and visceral layers of the serous pericardium.

13. Why are the tendinous cords required for the proper functioning of the AV valves?

14. Explain why the walls of the atria are thinner than those of the ventricles, and why the wall of the right ventricle is relatively thin when compared to the wall of the left ventricle.

15. Describe the structure and function of intercalated discs in cardiac muscle tissue.

16. Explain the general location and function of coronary vessels.

17. Describe the functional differences in the effects of the sympathetic and parasympathetic divisions of the autonomic nervous system on the activity of the heart.

18. Provide an overview of the two events for cardiac muscle contraction that include the conduction system and cardiac muscle cells.

19. List the five events of the cardiac cycle, and indicate for each if the atria are contracted or relaxed, if the ventricles are contracted or relaxed, if the AV valves are open or closed, and if the semilunar valves are open or closed.

20. Define cardiac output, and explain how it is influenced by both heart rate and stroke volume.

Can You Apply What You’ve Learned?

Use the following paragraph to answer questions 1 and 2.

A young man was doing some vigorous exercise when suddenly he felt chest pains just before he passed out. Upon being revived, he was taken to the hospital for examination. The medical personnel ran standard tests and ECG tracings, then said it would be fine for him to resume his normal activities and workouts.
1. Why might the increase in heart rate associated with a vigorous exercise program be the cause of his becoming unconscious?
   a. increase in blood pressure throughout the body
   b. failure of the conduction system
   c. increase in return volume of blood to the heart
   d. coronary blood flow reduction due to tachycardia

2. Which of the following tests would not be used to rule out that a myocardial infarction had occurred?
   a. doing an ECG
   b. performing constant blood pressure monitoring
   c. measuring blood levels of creatine kinase released from damaged heart muscle
   d. measuring blood levels of troponin released from damaged heart muscle

3. Calcium channel blockers are drugs that are given to cause
   a. an increase in the volume of blood being pumped.
   b. the afterload to be increased.
   c. contractility to decrease.
   d. preload to decrease.

4. A patient has been in a serious car accident and is hemorrhaging. Which of the following changes would be seen in this patient?
   a. a decrease in stroke volume
   b. an increase in heart rate
   c. a possible decrease in cardiac output
   d. All of these are correct.

5. During surgery, the right vagus nerve was accidentally cut. Explain the effect on the heart rate.
   a. There is no change to the heart rate because the vagus nerve does not innervate the heart.
   b. The heart rate increases to the inherent rhythm of SA nodal cells.
   c. The heart stops beating, and the heart rate becomes zero.
   d. The heart rate decreases to the inherent rhythm of SA nodal cells.

Can You Synthesize What You’ve Learned?

1. A young couple that you are friends with gave birth to a new baby. They were told by their physician that the foramen ovale did not close between the right atrium and left atrium (i.e., that their baby has “a hole in her heart”). They know that you are a nurse and have come to you to help them understand what is going on. Explain both the normal flow of blood through the heart and the flow with the foramen ovale still open. Include in your description the concept of oxygenated and deoxygenated blood.

2. Josephine is a 55-year-old overweight woman who has a poor diet and does not exercise. One day while walking briskly, she experienced pain in her chest and down her left arm. Her doctor told her that she was experiencing angina due to heart problems. Josephine asks you to explain what causes angina and why she was feeling pain in her arm even though the problem was with her heart. What do you tell her?

3. Your grandfather was told that his SA node (pacemaker) has stopped functioning. Explain how his heart is still beating at a rate of 40 to 50 times per minute. Are the atria stimulated to contract? Explain.
Most adults are aware that high blood pressure (hypertension) is not healthy. Hypertension can damage blood vessels and lead to cardiovascular disease. But a minimal amount of blood pressure is needed to effectively pump blood (and the nutrients and respiratory gases it transports) throughout the body and deliver these materials to the body tissues. If blood pressure drops too low, the body will be deprived of nutrients and death may occur. Multiple body systems (including the endocrine, nervous, and urinary systems) participate in maintaining sufficient blood pressure to ensure that all tissues are adequately perfused (supplied with blood).

We begin this chapter by describing the general structure and function of blood vessels, blood flow velocity, processes of capillary exchange, and factors that influence both blood flow and blood pressure in vessels. Pulmonary circulation and the major arteries and veins of systemic circulation are then described for each body region, and we conclude with a comparison of fetal versus adult circulation.
20.1 Structure and Function of Blood Vessels

Blood vessels are classified into three primary types based on function. Arteries (ar′ter-ē) transport blood away from the heart to the capillaries. Capillaries (kap′i-lar-ē; capillaris = relating to hair) are microscopic, relatively porous blood vessels for the exchange of substances between blood and tissues. Veins (vān) drain blood from the capillaries, transporting it back to the heart.

**20.1a General Structure of Vessels**

**LEARNING OBJECTIVES**

1. Describe the three tunics common to most vessels.
2. Explain the distinguishing features of the tunics found in arteries, capillaries, and veins.

Vessel walls are composed of layers called tunics (tū′nik; tunica = coat). The tunics surround the lumen (lū′men), or inside space, of the vessel through which blood flows. The three tunics are the tunica intima, tunica media, and tunica externa (Figure 20.1). Arteries, capillaries, and veins differ in both the specific composition of their tunics and their functions.

**Tunics**

The innermost layer of a blood vessel wall is the tunica intima (tū′ni-kā in′tim-mā; intimus = inmost), or tunica interna. It is composed of an endothelium (a simple squamous epithelium; see section 5.1c) that is adjacent to the blood vessel lumen and a thin subendothelial layer of areolar connective tissue. The endothelium both provides a smooth surface as the blood moves through the lumen of the blood vessel and releases substances (e.g., nitric oxide, endothelin) to regulate contraction and relaxation of smooth muscle.
within the tunica media. Recall that the endothelium is continuous with the endocardium, which is the inner lining of the heart (see section 19.3b).

The tunica media (me’dē-ə; medius = middle) is the middle layer of the vessel wall. It is composed predominantly of circularly arranged layers of smooth muscle cells that are supported by elastic fibers. Contraction of smooth muscle in the tunica media results in vasoconstriction (vā’sō-kon-strīk′shŭn), or narrowing of the blood vessel lumen; relaxation of the smooth muscle causes vasodilation (vāsó-di-lā′shŭn), or widening of the blood vessel lumen.

The tunica externa (eks-ter′nă; externe = outside), or tunica adventitia, is the outermost layer of the blood vessel wall. It is composed of areolar connective tissue that contains elastic and collagen fibers. The tunica externa helps anchor the vessel to other structures. Very large blood vessels require their own blood supply to the tunica externa in the form of a network of small arteries called the vasa vasorum (vāsā vā-sŏr′əm; vessels of vessels). The vasa vasorum extends through the tunica externa.

Comparison of the Different Vessel Types
Arteries and veins that supply the same body region and tend to lie next to one another are called companion vessels. Figure 20.2 is a histologic image of a companion artery and vein. Compared to their venous companions, arteries have a thicker tunica media, a narrower lumen, and more elastic and collagen fibers. These differences mean that arterial walls can spring back to shape and are more resilient and resistant to changes in blood pressure than are veins. In addition, an artery remains patent (open) even without blood in it.

In contrast, veins have a thicker tunica externa, a wider lumen, and less elastic and collagen fibers than a companion artery. The wall of a vein is typically collapsed if no blood is in the vessel. The characteristics of arteries and veins are summarized in table 20.1.

Capillaries are unique in that they contain only the tunica intima composed of an endothelium and its underlying basement membrane; there is no subendothelial layer. Having this thin barrier allows for rapid gas and nutrient exchange between the blood in capillaries and the tissues.

### WHAT DID YOU LEARN?
1. What are three differences in anatomic structure between arteries and veins?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Artery</th>
<th>Vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen Diameter</td>
<td>Narrower than vein lumen</td>
<td>Wider than artery lumen</td>
</tr>
<tr>
<td>General Wall Thickness</td>
<td>Thicker than vein</td>
<td>Thinner than artery</td>
</tr>
<tr>
<td>Cross-Sectional Shape</td>
<td>Cross-sectional shape retained; even without blood in vessel</td>
<td>Cross-sectional shape tends to flatten out (collapse) without blood in vessel</td>
</tr>
<tr>
<td>Thickest Tunic</td>
<td>Tunica media</td>
<td>Tunica externa</td>
</tr>
<tr>
<td>Elastic and Collagen Fibers in Tunics</td>
<td>More than in vein</td>
<td>Less than in artery</td>
</tr>
<tr>
<td>Valves</td>
<td>None</td>
<td>Present in most veins</td>
</tr>
<tr>
<td>Blood Pressure Range</td>
<td>Higher than in veins (100 mm Hg in larger arteries to 40 mm Hg in smaller arterioles)</td>
<td>Lower than in arteries (20 mm Hg in venules to 0 mm Hg in the inferior vena cava)</td>
</tr>
<tr>
<td>Blood Flow</td>
<td>Transports blood away from heart to the body</td>
<td>Transports blood from the body toward the heart</td>
</tr>
<tr>
<td>Blood Oxygen Levels</td>
<td>Systemic arteries transport blood high in O$_2$ Pulmonary arteries transport blood low in O$_2$</td>
<td>Systemic veins transport blood low in O$_2$ Pulmonary veins transport blood high in O$_2$</td>
</tr>
</tbody>
</table>
20.1b Arteries

LEARNING OBJECTIVE

3. Distinguish among elastic arteries, muscular arteries, and arterioles.

Arteries progressively branch into smaller vessels as they extend from the heart to the capillaries. There is both a corresponding decrease in lumen diameter and a change in the composition of the tunic wall that includes both a decrease in the relative amount of elastic fibers and an increase in the relative amount of smooth muscle. Arteries may be classified into three basic types: elastic arteries, muscular arteries, and arterioles (figures 20.3 and 20.4).

Elastic Arteries

Elastic arteries are the largest arteries, with diameters ranging from 2.5 to 1 centimeters. They are also called conducting arteries because they conduct blood—from the heart to the smaller muscular arteries. As their name suggests, these arteries have a large proportion of

---

**Figure 20.3** Comparison of Companion Vessels. The thickness of the tunics in companion arteries and veins differs, depending upon the size of the vessels. Capillaries are microscopic vessels and function as sites of exchange between the body tissues.
Muscular arteries have a proportionately thicker tunica media, with multiple layers of smooth muscle cells. Unlike in elastic arteries, the elastic fibers in muscular arteries are confined to two circumscribed sheets: The internal elastic lamina (lam′i-nă) separates the tunica media from the tunica intima, and the external elastic lamina separates the tunica media from the tunica externa. The relatively greater amount of muscle and lesser amount of elastic tissue result in a better ability to vasoconstrict and vasodilate, although with a lessened ability to stretch in comparison to elastic arteries.

Most named arteries (e.g., the brachial, anterior tibial, coronary, and inferior mesenteric arteries) are examples of muscular arteries (see figure 20.19a). Muscular arteries branch into arterioles.

Muscular Arteries

Muscular arteries typically have diameters ranging from 1 centimeter to 0.3 millimeter. These medium-sized arteries are also called distributing arteries because they distribute blood to specific body regions and organs.

Elastic fibers; these are present throughout all three tunics, especially in the tunica media. The abundant elastic fibers allow the artery to stretch and accommodate the blood when a heart ventricle ejects blood into it during ventricular systole (contraction) and then recoil, which helps propel the blood through the arteries during ventricular diastole (relaxation).

The largest arteries close to the heart (e.g., aorta, pulmonary trunk, brachiocephalic, common carotid, subclavian) and the common iliac arteries are examples of elastic arteries (see figure 20.19a). Elastic arteries branch into muscular arteries.

**Muscular Arteries**

Muscular arteries typically have diameters ranging from 1 centimeter to 0.3 millimeter. These medium-sized arteries are also called distributing arteries because they distribute blood to specific body regions and organs.

---

**INTEGRATE**

**CLINICAL VIEW 20.1**

**Atherosclerosis**

Atherosclerosis (ath′er-ŏ-skler-ŏ-sis; athere = gruel, sclerosis = hardening) is a progressive disease of the elastic and muscular arteries. It is characterized by the presence of an atheroma (ath′er-ŏ-ma; oma = tumor) or atheromatous plaque, which leads to thickening of the tunica intima and narrowing of the arterial lumen.

**Etiology**

Although the etiology (cause) of atherosclerosis is not completely understood, the response-to-injury hypothesis is the most widely accepted. This proposal states that injury to the endothelium of an arterial wall, especially repeated injury caused by infection, trauma, or hypertension (high blood pressure), results in an inflammatory reaction, eventually leading to the development of an atheroma. The injured endothelium becomes more permeable, which encourages leukocytes and platelets to adhere to the lesion and initiate an inflammatory response.

Muscular arteries have a proportionately thicker tunica media, with multiple layers of smooth muscle cells. Unlike in elastic arteries, the elastic fibers in muscular arteries are confined to two circumscribed sheets: The internal elastic lamina (lam′i-nă) separates the tunica media from the tunica intima, and the external elastic lamina separates the tunica media from the tunica externa. The relatively greater amount of muscle and lesser amount of elastic tissue result in a better ability to vasoconstrict and vasodilate, although with a lessened ability to stretch in comparison to elastic arteries.

Most named arteries (e.g., the brachial, anterior tibial, coronary, and inferior mesenteric arteries) are examples of muscular arteries (see figure 20.19a). Muscular arteries branch into arterioles.

**Arterioles**

Arterioles are the smallest arteries, with diameters ranging from 0.3 millimeters to 10 micrometers; these vessels are not named. In general, arterioles have fewer than six layers of smooth muscle in their tunica media. Larger arterioles have all three tunics, whereas the smallest arterioles may have a tunica intima surrounded by a single layer of smooth muscle cells. Smooth muscle in the arterioles is slightly contracted (just as your skeletal muscles often are in a partial state of contraction; see section 10.7a). This contracted state is called vasomotor tone and is regulated by the vasomotor center in the brainstem (see section 13.5c). Sympathetic motor tone results in vasoconstriction, which allows for varying degrees of change from this slightly contracted state (see section 15.7a). Blood vessels can be
Chapter Twenty
Cardiovascular System: Vessels and Circulation

either vasoconstricted to a greater degree to decrease blood flow or vasodilated to allow more blood into an area. Arterioles have a significant role in regulating systemic blood pressure and blood flow to the different areas of the body.

Atherosclerosis is a progressive disease. The plaques typically begin to develop in early adulthood and grow and enlarge as we age. People are unaware of the plaques until they become large enough to restrict blood flow in an artery and cause vascular complications.

Risk Factors
Some individuals are genetically prone to atherosclerosis. Hypercholesterolemia (an increased amount of cholesterol in the blood; see Clinical View 27.4: “Blood Cholesterol Levels”), which also tends to run in families, has been positively associated with the rate of development and severity of atherosclerosis. Additionally, males tend to be affected more than females, and symptomatic atherosclerosis increases with age. Finally, smoking and hypertension cause vascular injury, which increases the risk.

Treatment Options
If an artery is occluded (blocked) in one or just a few areas, one form of treatment is an angioplasty (anˈjē-ə-plas-tē; angeion = vessel, plastos = formed). A physician inserts a balloon-tip catheter into an artery and positions it at the site where the lumen is narrowed. Then the balloon is inflated, forcibly expanding the narrowed area, and a stent is placed in the vessel. A stent is a piece of wire-mesh that springs open to keep the vessel lumen open. For occluded coronary arteries, sometimes a much more invasive treatment known as coronary bypass surgery may be needed. A vein (e.g., the great saphenous vein) or artery (e.g., the internal thoracic artery) is detached from its original location and grafted from the aorta to the coronary artery system, thus bypassing the area(s) of atherosclerotic narrowing.

WHAT DID YOU LEARN?

2. What changes are seen in the composition of the tunic wall of arteries as they branch into smaller and smaller vessels?

20.1c Capillaries

LEARNING OBJECTIVES

4. Describe the general anatomic structure and function of capillaries.
5. Compare the anatomic structure, function, and location of continuous capillaries, fenestrated capillaries, and sinusoids.
6. Trace the movement of blood through a capillary bed.
Capillaries are the smallest blood vessels. They connect arterioles to venules (the smallest veins). The average capillary is approximately 1 mm in length with a diameter of 8 to 10 micrometers, just slightly larger than the diameter of a single erythrocyte. The narrow vessel diameter means erythrocytes must move in single file (termed rouleau) through each capillary (see section 18.3b). Capillaries consist solely of an endothelial layer (of simple squamous cells) resting on a basement membrane. The narrow vessel diameter and the thin wall are optimal for exchange of substances between blood and body tissues.

Types of Capillaries

Capillaries are differentiated based on their relative degree of permeability and include continuous capillaries, fenestrated capillaries, and sinusoids (Table 20.2).

**Continuous capillaries** are the most common type of capillary. The endothelial cells form a complete, continuous lining around the lumen that rests on a complete basement membrane. Tight junctions (see section 4.6d) secure endothelial cells to one another; however, they do not form a complete “seal.” The gaps between the endothelial cells are called intercellular clefts. Materials can move into or out of the blood either through endothelial cells by membrane transport processes (e.g., diffusion, pinocytosis; see section 4.3) or between endothelial cells through intercellular clefts by diffusion and bulk flow (see section 20.3).

The size of intercellular clefts prevents the movement of large substances, including formed elements and plasma proteins, while allowing the movement of fluid containing small substances (smaller than about 5 nanometers), such as glucose, amino acids, and ions. Continuous capillaries are found, for example, in muscle, the skin, the thymus, the lungs, and the central nervous system.

**Fenestrated** (fen’ĕs-trä’ted; fenestra = window) capillaries are also composed of a complete, continuous lining of endothelial cells and a complete basement membrane. However, small regions of the endothelial cells (typically 10 to 100 nanometers in diameter) are extremely thin; these thin areas are called fenestrations (or pores). Fenestrations are small enough to prevent formed elements from passing through the wall yet large enough to allow the movement of some smaller plasma proteins. Fenestrated

### Table 20.2 Types of Capillaries

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>(a) Continuous Capillary</th>
<th>(b) Fenestrated Capillary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td><img src="image" alt="Diagram of Continuous Capillary" /></td>
<td><img src="image" alt="Diagram of Fenestrated Capillary" /></td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Lining of endothelial cells is complete around lumen; basement membrane is complete; intercellular clefts between endothelial cells</td>
<td>Same as continuous capillary, except also contains fenestrations</td>
</tr>
<tr>
<td><strong>Materials That Pass Through Vessel Wall</strong></td>
<td>Plasma and its contents (except most proteins); some leukocytes</td>
<td>Large amounts of materials are filtered, released, or absorbed; some smaller proteins</td>
</tr>
<tr>
<td><strong>Locations</strong></td>
<td>Most capillaries (e.g., capillaries within muscles, skin, thymus, lungs, and central nervous system [CNS])</td>
<td>Small intestine; for absorbing nutrients Ciliary process; to produce aqueous humor in the eye Choroid plexus; to produce cerebrospinal fluid (CSF) in the brain Most endocrine glands; for release of hormones into the blood Kidneys; for filtering blood</td>
</tr>
</tbody>
</table>
capillaries are seen where a great deal of fluid transport between the blood and interstitial tissue occurs. Examples of structures that contain fenestrated capillaries include the small intestine for the absorption of nutrients (see section 26.3b), the ciliary process of the eye in the production of aqueous humor (see section 16.4b), the choroid plexus of the brain in the production of cerebrospinal fluid (see section 13.2c), most of the endocrine glands to facilitate the absorption of hormones into the blood (see section 17.1a), and the kidneys for the filtering of blood (see section 25.5c).

**Sinusoids** (si’nū-soid; sinus = cavity, eidos = appearance), or *discontinuous capillaries*, have an incomplete lining of the endothelial cells with large openings, or gaps, and the basement membrane is either discontinuous or absent. These openings allow for transport of large substances (formed elements, large plasma proteins), as well as plasma between the blood and tissues. Sinusoids are found in red bone marrow for the entrance of formed elements into the blood (see section 18.3a), the liver (see section 26.3c) and spleen (see section 21.4b) for the removal of aged erythrocytes from the cardiovascular circulation, and some endocrine glands (e.g., anterior pituitary, adrenal, and parathyroid) for the movement of hormone molecules into the blood. A common feature of structures with sinusoids is their reddish color.

### Table 20.2 Types of Capillaries

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Materials That Pass Through</th>
<th>Locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Continuous Capillary</td>
<td>Lining of endothelial cells is complete around lumen; basement membrane is complete; intercellular clefts between endothelial cells</td>
<td>Plasma and its contents (except most proteins); some leukocytes</td>
<td>Most capillaries (e.g., capillaries within muscles, skin, thymus, lungs, and central nervous system [CNS])</td>
</tr>
<tr>
<td>(b) Fenestrated Capillary</td>
<td>Same as continuous capillary, except also contains fenestrations</td>
<td>Large amounts of materials are filtered, released, or absorbed; some smaller proteins</td>
<td>Small intestine; for absorbing nutrients Ciliary process; to produce aqueous humor in the eye Choroid plexus; to produce cerebrospinal fluid (CSF) in the brain Most endocrine glands; for release of hormones into the blood Kidneys; for filtering blood</td>
</tr>
<tr>
<td>(c) Sinusoid</td>
<td>Lining of endothelial cells is incomplete around lumen; basement membrane is incomplete or absent</td>
<td>Large substances (formed elements, large plasma proteins) and plasma</td>
<td>Red bone marrow; for formed elements to enter the blood Liver and spleen; for removal of old erythrocytes from the cardiovascular circulation Some endocrine glands (anterior pituitary, adrenal, and parathyroid); for release of hormones into the blood</td>
</tr>
</tbody>
</table>

**INTEGRATE CONCEPT CONNECTION**

The blood-brain barrier (BBB) (see section 13.2d) is formed by modified continuous capillaries that have thickened basement membranes and no intercellular clefts. Substances can pass through endothelial cells only by regulated membrane transport processes (e.g., facilitated diffusion, active transport). However, movement of nonpolar substances is not regulated by cells (see section 4.3a) and so these nonpolar substances (e.g., nicotine, alcohol) may pass through the cells by simple diffusion and enter the brain cells.
Capillary Beds

Capillaries do not function independently; rather, a group of capillaries (10 to 100) function together and form a **capillary bed** (figure 20.5). A capillary bed is fed by a **metarteriole** (met′ar-te′rē-ōl; meta = between), which is a branch of an arteriole. The proximal part of the metarteriole is encircled by scattered smooth muscle cells, whereas the distal part of the metarteriole (called the **thoroughfare channel**) has no smooth muscle cells. The thoroughfare channel connects to a **postcapillary venule** (ven′ūl, vē′nūl), which drains the capillary bed.

Vessels called **true capillaries** branch from the metarteriole and make up the bulk of the capillary bed. At the origin of each true capillary, a smooth muscle ring called the **precapillary sphincter** controls blood flow into the true capillaries. Sphincter relaxation permits blood to flow into the true capillaries, whereas sphincter contraction causes blood to flow directly from the metarteriole and thoroughfare channel into the postcapillary venule with blood bypassing the capillary bed. The precapillary sphincters go through cycles of contracting and relaxing at a rate of about 5 to 10 cycles per minute. This cyclical process is referred to as **vasomotion**.

At any given time, only about one-quarter of the capillary beds are open, because there are over 60,000 miles of capillaries and only about 250 to 300 milliliters (mL) of blood (about 5% of the total blood volume) moving through the capillaries. There is simply not enough blood available to fill all capillaries at the same time. The specific amount of blood entering capillaries per unit time per gram of tissue is called **perfusion**, typically expressed in milliliters per minute per gram (mL/min/g) (see section 19.1a).

**WHAT DID YOU LEARN?**

3. What type of capillary is the most permeable, and where in the body are these capillaries found?

---

**Figure 20.5 Capillary Bed Structure and Perfusion Through the Bed.** A capillary bed originates from a metarteriole. The metarteriole continues as a thoroughfare channel that merges with the postcapillary venule. True capillaries branch from the metarteriole, and blood flow into these true capillaries is regulated by the precapillary sphincters. (a) A well-perfused capillary bed, with all of the precapillary sphincters relaxed, and (b) a capillary bed where most blood bypasses the capillary bed due to contracted precapillary sphincters.
20.1d Veins

**LEARNING OBJECTIVES**

7. Describe the structure and general function of veins.

8. Explain how veins serve as a blood reservoir for the cardiovascular system.

Veins merge into larger and larger vessels with a corresponding increase in lumen diameter as they extend from the capillaries to the heart (see figure 20.3).

**Venules**

Venules are the smallest veins, measuring from 8 to 100 micrometers in diameter. Venules are companion vessels with arterioles. The smallest venules, called postcapillary venules, drain capillaries (figure 20.5). Smaller venules merge to form larger venules. The largest venules have all three tunics. Venules merge to form veins (see figure 20.3).

**Small, Medium-Sized, and Large Veins**

A venule becomes a vein when its diameter is greater than 100 micrometers. Small and medium-sized veins are companion vessels with muscular arteries, whereas the largest veins are positioned alongside elastic arteries. Most veins contain numerous valves, so as to prevent blood from pooling in the limbs. The valves are formed primarily of tunica intima and strengthened by elastic and collagen fibers. Valves have an anatomic structure similar to semilunar valves of the heart (see section 19.3d).

**Systemic Veins as Blood Reservoirs**

The percentage of the total blood that is moving through each of the different components of the cardiovascular system while at rest is illustrated in figure 20.6. Relatively small amounts of blood are within the pulmonary circulation (about 18%) and the heart (about 12%). The largest percentage of blood is within the systemic circulation (about 70%), with the greatest amount (about 55%) within the body’s systemic veins. The relatively large amount of blood within veins allows veins to function as blood reservoirs. Blood may be shifted from venous reservoirs into circulation through vasoconstriction of veins, when more blood is needed with increased physical exertion—and shifted back into venous reservoirs through vasodilation of veins, when less blood is needed at rest.

Figure 20.7 integrates how each blood vessel structure is adapted for the specific functions of that vessel.

**20.1e Pathways of Blood Vessels**

**LEARNING OBJECTIVE**

9. Compare and contrast the simple and alternative pathways of blood vessels.

Blood vessels are arranged in either simple or alternative pathways (figure 20.8). Each pathway is described here in detail.

**Simple Pathway**

In the simple pathway, one major artery delivers blood to the organ or body region and then branches into smaller and smaller arteries to become arterioles. Each arteriole feeds into a single capillary bed. A venule drains blood from the capillaries and merges with other venules to form one major vein that drains blood from the organ or body region. Thus, the simple pathway includes one artery, a capillary bed, and one vein associated with an organ or a body region.

Blood transported to and from the spleen is an example of a simple blood flow pathway. A single splenic artery delivers oxygenated blood to the spleen with the exchange made in a capillary bed of the spleen, and a single splenic vein drains deoxygenated blood from the spleen (see figure 21.7a). Arteries that provide only one pathway through which blood can reach an organ are referred to as end arteries (see section 19.4a).

**Alternative Pathways**

Several alternative circulatory pathways are possible, and these include various types of anastomoses and the portal systems. They differ from the simple pathway in the number of arteries, capillary beds, or veins that serve an organ or a body region.
**Figure 20.7 How Blood Vessel Form Influences Function.** The structure and function of (a) arteries, (b) capillaries, and (c) veins are compared.

### (a) Arteries
Systemic arteries transport oxygenated blood away from the heart. (Remember that pulmonary arteries transport deoxygenated blood to the lungs.) Larger arteries branch into progressively smaller arteries that lead into arterioles.

- **Elastic arteries** stretch to accommodate the pulses of blood ejected from the heart and recoil to propel blood through the arteries.
- **Muscular arteries** regulate distribution of blood through vasoconstriction and vasodilation.

### (b) Capillaries
Capillaries receive blood from arterioles and allow for exchange of substances between the blood and cells.

### (c) Veins
Systemic veins transport deoxygenated blood toward the heart. (Remember that pulmonary veins transport oxygenated blood from the lungs.)

- **Large veins** serve as a blood reservoir (at rest ~ 55% total blood).
- **Small/medium veins** receive blood from venules; blood drains into small/medium veins and then into large veins.
- **Valves** prevent backflow of blood.

**Blood flow**

- **Continuous capillary**
  - Least permeable

- **Fenestrated capillary**
  - Varying degrees of permeability determine the size and amount of substances exchanged across capillary walls.

- **Sinusoid**
  - Most permeable
Three of the alternative pathways are designated as anastomoses. An anastomosis (a-nas′tə-mō′sēs; pl., anastomoses) is the joining together of blood vessels. An arterial anastomosis includes two or more arteries converging to supply the same body region. (For example, figure 20.22a shows anastomoses among the superior and inferior epigastric arteries that serve the abdominal wall.) Other vessels, such as the coronary arteries, may have anastomoses that are so tiny that the function of the arteries may almost be considered end arteries; these arteries are called functional end arteries (see section 19.4a).

A venous anastomosis includes two or more veins draining the same body region. Veins tend to form many more anastomoses than do arteries. Veins that drain the upper limb including the basilic, brachial, and cephalic veins provide an example of a venous anastomosis (see figure 20.19b).

An arteriovenous anastomosis, or shunt, transports blood from an artery directly into a vein, bypassing the capillary bed. These shunts are present in the fingers, toes, palms, and ears, and they allow these areas to be bypassed if the body is becoming hypothermic (cold). It is the bypassing of these body structures, as blood is shunted through an arteriovenous anastomosis, that makes them particularly vulnerable to frostbite (see Clinical View 27.6: “Hyperthermia, Frostbite, and Dry Gangrene”).

A different type of blood vessel arrangement is a portal system. Blood flows through two capillary beds, with the two capillary beds separated by a portal vein. A portal vein delivers blood to another organ first, before the blood is sent back to the heart. Thus, the sequence of blood vessels is as follows: artery, capillary bed, portal vein, capillary bed, and vein. One example is the hypothalamic-hypophyseal portal system that extends between the hypothalamus and the anterior pituitary (see section 17.7a). This portal system provides a more direct means of delivering hypothalamic regulatory hormones to the anterior pituitary. Another portal system is the hepatic portal system, which is described in section 20.10d.

**LEARNING OBJECTIVES**

10. Describe the relationship of the total cross-sectional area and velocity of blood flow.

11. Predict the significance of slow blood flow in the capillaries.

The cross-sectional area of a vessel is the diameter of the vessel’s lumen. The total cross-sectional area is estimated as the aggregate lumen diameter across the total number of a given type of vessel (artery, capillary, or vein) if they were all positioned side by side. You may be surprised to learn that, although the cross-sectional area of an individual artery is relatively large, the total cross-sectional area of arteries is relatively small. This observation is also accurate for veins, which have a relatively small total cross-sectional area. See the blue line on the graph in figure 20.9. In comparison, an individual.
capillary has a very small cross-sectional area; however, the total cross-sectional area of capillaries—of which there are approximately 60,000 miles—is the largest with a value of approximately 4500 square centimeters (cm²). The total cross-sectional area is physiologically significant because of its influence on blood flow velocity.

**Blood flow velocity** is the rate of blood transported per unit time and typically measured in centimeters per second. Observe the graph in figure 20.9 and notice that there is an inverse relationship between the total cross-sectional area and blood flow velocity (red line on the graph). Blood flow velocity in both arteries and veins, with their relatively small total cross-sectional area, is relatively fast. In comparison, blood flow velocity in capillaries, with their relatively large total cross-sectional area, is relatively slow. Thus, blood flow velocity changes as it moves through the different types of vessels: Velocity of blood flow is relatively fast in the arteries, slowest in the capillaries, and relatively fast again through the veins. Consider the analogous phenomenon of water flow in a river. In regions where the river is narrow, the river moves more quickly, and where the river is wider, the river moves more slowly. Of course, the amount of water flow is the same in these different regions and always moves toward the ocean. Likewise, blood flow velocity is altered as it moves through the different portions of the vasculature, but it always moves along a blood pressure gradient (described in section 20.5a) as it is transported through the vasculature of the cardiovascular system.

What is the significance of the much slower rate of blood flow through the capillaries? The slower blood flow rate allows sufficient time for efficient capillary exchange of respiratory gases, nutrients, wastes, and hormones between the body tissues and the blood (see section 20.3).

### WHAT DID YOU LEARN?
In which type of vessel is blood flow the slowest? Explain the anatomic structure that accounts for this and the physiologic significance.

#### 20.3 Capillary Exchange
The function of capillaries is to allow for the exchange of substances (e.g., respiratory gases, nutrients, wastes, and hormones) between the blood and the surrounding tissues. Exchange processes include diffusion, vesicular transport, and bulk flow.

#### 20.3a Diffusion and Vesicular Transport

**LEARNING OBJECTIVE**

12. Explain the process of diffusion and vesicular transport between capillaries and tissues.

Within systemic capillaries, substances such as oxygen, hormones, and nutrients move by diffusion (see section 4.3a) from their relatively high concentration in the blood into the interstitial fluid and then into the tissue cells, where the concentration of these materials is lower. Conversely, carbon dioxide and waste products diffuse from the higher concentration in the tissue cells to the lower concentration in the interstitial fluid and then to the blood. Very small solutes (e.g., O₂, CO₂, glucose, ions) and fluids may diffuse via the endothelial cells or intercellular clefts, whereas larger solutes, such as small proteins, must pass through the fenestrations in fenestrated capillaries or gaps in sinusoids.

Vesicular transport occurs when endothelial cells use pinocytosis (see section 4.3c) to form fluid-filled vesicles, which are then transported to the other side of the cell and released by exocytosis. Substances can be moved either from the blood into the interstitial fluid or from the interstitial fluid into the blood. Solutes that are relatively large (e.g., insulin) are transported across the endothelial cells by this method.

### WHAT DID YOU LEARN?

What substances are transported by diffusion through the capillaries? Which substances leave the capillaries by vesicular transport?

#### 20.3b Bulk Flow

**LEARNING OBJECTIVES**

13. Explain the processes of bulk flow, filtration, and reabsorption.

14. Compare and contrast hydrostatic pressure and colloid osmotic pressure in the capillaries.

**Bulk flow** refers to the movement of large amounts of fluids and their dissolved substances in one direction down a pressure gradient. **Filtration**, a process that occurs on the arterial end of a capillary, is the movement of fluid by bulk flow out of the blood through the openings in the capillaries (e.g., intercellular clefts, fenestrations). During this process, fluids and small, dissolved solutes flow through easily, whereas large solutes are generally blocked. In contrast, reabsorption occurs on the venous end of a capillary. **Reabsorption** is the movement of fluid by bulk flow in the opposite direction, back into the blood (figure 20.10).

How is it possible to have filtration on the arterial end, and reabsorption on the venous end, of a capillary? The direction of movement is dependent upon the net pressure of two opposing forces at the capillary level—hydrostatic pressure and colloid osmotic pressure; both are measured in millimeters of mercury (mm Hg).

**Hydrostatic Pressure**

Hydrostatic pressure (HP) is the physical force exerted by a fluid on a structure. For example, **blood hydrostatic pressure** (HP₅) is the force exerted per unit area by the blood as it presses against the internal surface of the vessel wall. Blood hydrostatic pressure promotes filtration from the capillary.

The interstitial fluid also has its own hydrostatic pressure, called **interstitial fluid hydrostatic pressure** (HPᵢₙ), which is the force of the interstitial fluid on the external surface of the blood vessel. For most tissues, the interstitial fluid hydrostatic pressure is very small and for simplicity’s sake is assumed to be close to zero. Thus, for our discussion, the main hydrostatic pressure is the blood hydrostatic pressure, which pushes materials out of the capillary.

**Colloid Osmotic Pressure**

The other main force regulating filtration and reabsorption is osmotic pressure, which refers to the “pull” of water into an area by osmosis due to the higher relative concentration of solutes. **Colloid osmotic pressure** (COP) refers to the pull of water back into a tissue by the tissue’s concentration of proteins (colloid). There are two specific types of colloid osmotic pressure: blood colloid osmotic pressure and interstitial fluid colloid osmotic pressure.

The **blood colloid osmotic pressure** (COP₅) is the force that draws fluid back into the blood due to the proteins in blood, such as albumin. Blood colloid osmotic pressure opposes hydrostatic pressure, and thus promotes reabsorption. Clinicians also use the term oncotic (onkosis = swelling) pressure to describe the blood colloid osmotic pressure.

An **interstitial fluid colloid osmotic pressure** (COPᵢₙ) also exists, but its value is relatively low because few proteins are present.
in the interstitial fluid. COP_d may range from 0 to 5 mm Hg. By knowing the specific values for the hydrostatic and osmotic pressures, the direction of bulk flow can be determined through the calculation of net filtration pressure.

**WHAT DID YOU LEARN?**

What is the difference between hydrostatic pressure and osmotic pressure?

### 20.3c Net Filtration Pressure

#### LEARNING OBJECTIVES

15. Define net filtration pressure (NFP).

16. Calculate net filtration pressure for both the arterial end and the venous end of a capillary.

Net filtration pressure (NFP) is the difference between the net hydrostatic pressure (difference between the blood and interstitial fluid hydrostatic pressures) and the net colloid osmotic pressure (difference between the blood and the interstitial fluid colloid osmotic pressures) and is shown in figure 20.10. The net filtration pressure may be determined by the following equation:

\[
NFP = (HP_b - HP_d) - (COP_b - COP_d)
\]

where HP_b = the hydrostatic pressure of blood, HP_d = the hydrostatic pressure of the interstitial fluid, COP_b = the colloid osmotic pressure of blood, and COP_d = the colloid osmotic pressure of the interstitial fluid. This equation is a variation of Starling’s law, developed by the physiologist Ernest Starling (see section 19.9c). Starling was among the first to discover that hydrostatic and osmotic forces work against one another to drive the filtration and reabsorption of materials across a capillary wall.

Net filtration pressure changes as the blood moves from the arterial end of the capillary to the venous end of the capillary. On the arterial end of a capillary, HP_b is typically around 35 mm Hg, HP_d is assumed to be 0 mm Hg, COP_b is around 26 mm Hg, and COP_d is around 5 mm Hg. The net filtration pressure is calculated as follows:

\[
(35 \text{ mm Hg} - 0 \text{ mm Hg}) - (26 \text{ mm Hg} - 5 \text{ mm Hg}) = 14 \text{ mm Hg}
\]

Notice that NFP has a positive value of 14 mm Hg at the arterial end. A positive value indicates that the hydrostatic pressure pushing fluids out of the blood is greater than the net colloid osmotic pressure pulling the fluid back into the capillary. Consequently, filtration, or the net movement of fluid out of the blood vessel into the surrounding tissue, occurs on the arterial end of a capillary.

Now consider the events on the venous end of a capillary. Blood hydrostatic pressure decreases continuously as it moves through the capillary to reach the venule end, because there is a net movement of fluids out of the capillary as blood moves through the length of the capillary. This smaller amount of blood means the blood hydrostatic pressure at the venous end of a capillary is lower—usually around 16 to 20 mm Hg.

In contrast, both blood colloid osmotic pressure and interstitial fluid osmotic pressure remain relatively constant throughout the capillary and have values similar to those on the arterial end of the capillary: COP_b is around 26 mm Hg and COP_d is around 5 mm Hg.
Again, $H_P$ is assumed to be 0 mm Hg. Net filtration pressure (NFP) is calculated on the venous end as follows:

\[
(16 \text{ mm Hg} - 0 \text{ mm Hg}) - (26 \text{ mm Hg} - 5 \text{ mm Hg}) = \text{NFP}
\]

\[
16 \text{ mm Hg} - 21 \text{ mm Hg} = -5 \text{ mm Hg}
\]

Notice that in this case, NFP has a negative value (-5 mm Hg). A negative value for NFP occurs because blood hydrostatic pressure is less than net osmotic pressure. Consequently, reabsorption occurs on the venous end of the capillary with a net movement of fluid back into the blood vessel from the surrounding tissue.

Keep in mind that the numbers for the pressures used to calculate net filtration pressure are examples only. The specific values depend upon the part of the body, the amount of blood entering a specific capillary bed, and the general health of the individual.

**WHAT DO YOU THINK?**

1. Is it possible for blood pressure to decrease to such a degree that capillary exchange ceases? Explain.

**WHAT DID YOU LEARN?**

9. How does the hydrostatic pressure change from the arterial end of a capillary to the venous end of a capillary? Do you see similar changes in colloid osmotic pressure?

10. Which two pressures have the largest values? Explain how each of these specifically influences filtration and reabsorption.

### 20.3d Role of the Lymphatic System

**LEARNING OBJECTIVE**

17. Explain the lymphatic system’s role at the capillary bed.

Although net filtration occurs at the arterial end of a capillary and net reabsorption at its venous end, not all of the fluid is reabsorbed at the venous end of the capillary. The capillary typically reabsorbs only about 85% of the fluid that has passed into the interstitial fluid. What happens to the excess 15% of fluid that is not reabsorbed?

Another body system, the **lymphatic system**, is responsible for picking up this excess fluid and returning it to the blood. Lymph vessels reabsorb this excess fluid, filter it, and return it to the venous circulation (see section 21.1). The lymphatic system is described in detail in chapter 21.

**WHAT DID YOU LEARN?**

11. If these lymph vessels were nonfunctional, what would happen to the amount of interstitial fluid around the capillary bed?

### 20.4 Local Blood Flow

Recall that there is simply not enough blood in the body to fill all capillaries at the same time. Blood must therefore be directed to organs and tissues where it is most needed and away from areas where it is not. **Local blood flow** is the blood delivered locally to the capillaries of a specific tissue and is measured in milliliters per minute. Recall that the specific amount of blood entering capillaries per unit time per gram of tissue is called perfusion. The ultimate function of the cardiovascular system is **adequate perfusion of all tissues** (see section 19.1a).

The amount of blood delivered to a specific organ or tissue is dependent upon several factors, including (1) the degree of vascularization of the tissue, (2) the myogenic response, (3) local regulatory factors that alter blood flow, and (4) total blood flow.

### 20.4a Degree of Vascularization and Angiogenesis

**LEARNING OBJECTIVES**

18. Describe what is meant by degree of vascularization.

19. Explain the process of angiogenesis and how it aids perfusion.

The **degree of vascularization**, or the extent of blood vessel distribution within a tissue, determines the potential ability of blood delivery. Organs that are very active metabolically, such as the brain, skeletal muscle, the heart, and the liver, generally are highly vascularized. In comparison,
some structures, such as tendons and ligaments, have little vascularization; blood delivery to these tissues is limited. Additionally, some structures contain no capillaries (are avascular); these include epithelial tissue, cartilage, and the cornea and lens of the eye.

The amount of vascularization in a given tissue may change over time through the process of angiogenesis. **Angiogenesis** (an′jē-ə-jen′ē-sis; angio = vessel, genesis = production) is the formation of new blood vessels in tissues that require them. This process helps provide adequate perfusion through long-term anatomic changes that occur over several weeks to months. For example, angiogenesis is stimulated in skeletal muscle in response to aerobic training; in adipose tissue, angiogenesis occurs in adipose connective tissue when an individual gains weight in the form of fat deposits. Angiogenesis also occurs in response to a slow, gradual occlusion (blockage) of coronary vessels, thus potentially providing alternative routes to deliver blood to the heart wall.

**Regression** (or return to previous state) of vessels is also possible. For example, some skeletal muscle blood vessels regress when an individual who was physically active becomes sedentary, or blood vessels in adipose tissue regress when the amount of adipose tissue is decreased through restriction of food and increased physical activity.

### WHAT DID YOU LEARN?

12. In what ways is angiogenesis stimulated in skeletal muscle? In adipose tissue?

### 20.4b Myogenic Response

**LEARNING OBJECTIVE**

20. Describe the myogenic response that maintains normal blood flow through a tissue.

Systemic blood pressure, which is the driving force to move blood through blood vessels, changes under different conditions (e.g., when we get excited or become relaxed). However, blood flow into a tissue may remain relatively constant because of the **myogenic** (mi′-ō-jen′ık; mys = muscle) response, which is contraction and relaxation of smooth muscle within blood vessels in response to changes in stretch of the blood vessel wall (see section 10.10d).

An increase in systemic blood pressure causes an additional volume of blood to enter the blood vessel, which stretches the smooth muscle cells within the blood vessel wall. This stimulates the smooth muscle cells to contract, resulting in vasoconstriction. Thus, although systemic blood pressure is higher, which would drive additional blood into the blood vessel, the resulting vasoconstriction decreases the size of the blood vessel lumen offsetting the change, and blood flow into a tissue remains constant. In contrast, a decrease in systemic blood pressure causes a lower volume of blood to enter the blood vessel, with decreased stretch of the smooth muscle cells within the blood vessel wall. This stimulates the smooth muscle cells to relax, resulting in vasodilation. Thus, although systemic blood pressure is lower, which would drive less blood into the blood vessel, the resulting vasodilation increases the size of the blood vessel lumen offsetting the change, and blood flow into a tissue remains constant.

### WHAT DID YOU LEARN?

13. Explain the myogenic response to an increase in systemic blood pressure.

### 20.4c Local, Short-Term Regulation

**LEARNING OBJECTIVES**

21. Compare and contrast a vasodilator and a vasoconstrictor.

22. Explain how a tissue autoregulates local blood flow based on metabolic needs.

23. Describe how local blood flow is altered by tissue damage and as part of the body’s defense.

Local regulation of blood flow occurs on a continual basis in response to changes in metabolic activity of tissues. Local blood flow is also altered in response to tissue damage or as part of the body’s defense systems. The stimulus is changing concentrations of certain chemicals, collectively called **vasoactive chemicals**. They are classified according to their action as either vasodilators or vasoconstrictors. **Vasodilators** are substances that cause smooth muscle relaxation, which results in both vasodilation of arterioles and opening of precapillary sphincters. Consequently, blood flow increases into a capillary bed. **Vasoconstrictors** are substances that cause smooth muscle contraction, which results in both arterioles vasoconstricting and precapillary sphincters closing. Thus, blood flow decreases into a capillary bed (see figure 20.5).
Autoregulation and Changing Metabolic Activity

**Autoregulation** is the process by which a tissue itself regulates or controls its local blood flow in response to its changing metabolic needs. The initial stimulus for autoregulation typically is inadequate perfusion due to increased metabolic activity of the tissue. If the tissue is not adequately perfused, then the oxygen and nutrient levels decline, while there is an increase in carbon dioxide, lactate, hydrogen ion (H^+), and potassium ion (K^+) levels. These altered levels act as local vasodilators, and as a result additional blood enters the capillaries serving the tissue. As perfusion increases in the tissue and these levels adjust back to homeostatic values, the vessels constrict. Thus, there is a negative feedback loop between elevated levels of these molecules and the degree of vasodilation.

Autoregulation is most noticeable when blood supply is temporarily disrupted and then restored. When the blood flow is temporarily disrupted, the tissue is deprived of needed oxygen and nutrients, and metabolic wastes accumulate. When the local blood flow is restored, there is a marked increase in blood flow to the affected tissue—a condition called **reactive hyperemia**. The additional blood is required to resupply the oxygen and nutrients and eliminate the accumulated wastes.

An example of reactive hyperemia occurs when you enter a warm room after being outside in the cold, and your cheeks turn bright red. When you were outside in the cold, the blood vessels in the dermis constricted, forcing more blood away from the dermis through an arteriovenous shunt to conserve heat (see sections 1.6b, 6.1d and 27.8b). When you leave the cold, the reddish color of your cheeks is due to increased blood flow in the dermis. After a short period of time, the reddish color subsides, as normal blood flow in the skin resumes.

**Short-Term Regulation Due to Damaged Tissue or as Part of the Body’s Defense System**

Local blood flow is also regulated when vasoactive chemicals are released from damaged tissue, leukocytes, and platelets in response to tissue damage or as part of the body’s defense. This process is referred to as **inflammation** and is discussed in detail in section 22.3d. For example, histamine and bradykinin are inflammatory mediators, which are released in response to a trauma, an allergic reaction, an infection, or even exercise. These chemicals cause vasodilation by either directly stimulating arterioles or indirectly by stimulating endothelial cells of the vessel to release nitric oxide. **Nitric oxide** is a very powerful, but short-lived, vasodilator.

Other vasoactive substances, such as prostaglandins and thromboxanes, are local hormones released with tissue injury that can cause vasoconstriction (see description of local hormones in section 17.3b). Recall from section 18.4a that if endothelial cells are damaged, they release an array of chemicals (including endothelin) that are powerful vasoconstrictors to help prevent blood loss from the damaged vessel. Systemic hormones also alter blood flow, and their effects are described in section 20.6b. See table 20.3 for a list of vasodilators and vasoconstrictors.

---

**WHAT DID YOU LEARN?**

14. What relationship exists between metabolic activity and local blood flow?

**20.4d Relationship of Local and Total Blood Flow**

**LEARNING OBJECTIVE**

24. Explain the general relationship of total blood flow to local blood flow.

Maintaining sufficient local blood flow throughout the body (to ensure adequate perfusion of all tissues) ultimately depends upon total blood flow. **Total blood flow** is the amount of blood transported throughout the entire vasculature in a given period of time (usually expressed in liters per minute). Total blood flow equals cardiac output. The average cardiac output at rest is 5.25 liters per minute (L/min), and may increase substantially during exercise (see section 19.9). If cardiac output increases, total blood flow increases, and additional blood is available to body tissues. If cardiac output decreases, total blood flow decreases, and less blood is available to the tissues. The factors that regulate total blood flow are dependent upon the two components of the cardiovascular system (both the heart and blood vessels), as well the blood that is transported through them. These factors are described in detail in section 20.5.

---

**WHAT DID YOU LEARN?**

15. How is local blood flow dependent on total blood flow?
20.5 Blood Pressure, Resistance, and Total Blood Flow

Here we integrate concepts on the heart, blood vessels, and blood to describe, first, blood pressure and how the pumping action of the heart establishes a pressure gradient to drive the blood through the vasculature; second, how blood experiences resistance as it is transported through blood vessels; and, third, how together blood pressure and resistance determine total blood flow.

20.5a Blood Pressure

LEARNING OBJECTIVES

25. Define blood pressure and blood pressure gradient.

26. Compare and contrast blood pressure and blood pressure gradients in the arteries, capillaries, and veins.

27. Calculate pulse pressure and mean arterial pressure (MAP) in the arteries.

28. Explain the mechanisms that help overcome the small pressure gradient in veins to return blood to the heart.

Blood pressure is the force per unit area that blood exerts against the inside wall of a vessel (as described earlier in section 20.3b). A blood pressure gradient is the change in blood pressure from one end of a blood vessel to its other end. A blood pressure gradient exists in the vasculature because blood pressure is highest in the arteries as the heart rhythmically contracts, and it is lowest in the veins. Blood pressure gradients are both clinically and physiologically significant because they are the driving force that propels blood through the vessels. Please refer to figure 20.11 as you read through this section.

Arterial Blood Pressure

Blood flow is pulsing, or pulsatile, in arteries as a consequence of the ventricles contracting and relaxing. The highest blood pressure generated in arteries is during ventricular systole.

Table 20.3 Substances and Systems That Affect Blood Pressure and Flow

<table>
<thead>
<tr>
<th>Effect</th>
<th>Local Substances</th>
<th>Hormones and Neurotransmitters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilators</td>
<td>Decreased oxygen levels</td>
<td>Atrial natriuretic peptide (ANP)</td>
</tr>
<tr>
<td></td>
<td>Decreased nutrient levels</td>
<td>Epinephrine (bound to β2 receptors within coronary and skeletal muscle blood vessels)</td>
</tr>
<tr>
<td></td>
<td>Increased CO2, H+, K+, lactate levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histamine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bradykinin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nitric oxide</td>
<td></td>
</tr>
<tr>
<td>Vasoconstrictors</td>
<td>Increased oxygen levels</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td></td>
<td>Increased nutrient levels</td>
<td>Aldosterone</td>
</tr>
<tr>
<td></td>
<td>Decreased CO2, H+, K+, lactate levels</td>
<td>Antidiuretic hormone (ADH)</td>
</tr>
<tr>
<td></td>
<td>Endothelins</td>
<td>Norepinephrine and to a lesser extent epinephrine (bound to α1 receptors of most blood vessels, including the skin and abdominal organs)</td>
</tr>
<tr>
<td></td>
<td>Prostaglandins</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thromboxanes</td>
<td></td>
</tr>
</tbody>
</table>

1. A decrease in sympathetic stimulation will result in a decrease in the listed effect, much like taking the foot off the gas pedal will slow down a car.
when the artery is maximally stretched; this value is recorded as the **systolic pressure**. The lowest pressure is during ventricular diastole when the artery recoils no further; this value is recorded as the **diastolic pressure**. Arterial blood pressure is expressed as a ratio, in which the numerator (upper number) is the systolic pressure and the denominator (lower number) is the diastolic pressure. The average adult has an arterial systemic blood pressure of 120/80 mm Hg, but blood pressure can vary greatly among individuals. Two values can be calculated from systolic pressure and diastolic pressure: pulse pressure and mean arterial pressure (see Clinical View 20.9: “Measuring Blood Pressure”).

**Pulse Pressure**  
**Pulse pressure** is the additional pressure placed on the arteries from when the heart is resting (diastolic blood pressure) to when the heart is contracting (systolic blood pressure). Pulse pressure can be calculated by taking the difference between the systolic and the diastolic blood pressure. So, for an individual with a blood pressure of 120/80 mm Hg, the pulse pressure would be 40 mm Hg (120 mm Hg − 80 mm Hg = 40 mm Hg).

Pulse pressure is significant because it is a measure of the elasticity and recoil of arteries. Healthy elastic arteries expand and recoil easily, assisting in the movement of blood through the cardiovascular system. However, as vessels age or become diseased (e.g., with atherosclerosis; see Clinical View 20.1: “Atherosclerosis”), arteries lose their elasticity and expand and recoil less readily, making it more difficult for the heart to pump blood. Thus, although temporary changes in pulse pressure are associated with increased cardiac output, as would occur during exercise, permanent changes in pulse pressure may be an indication of unhealthy arteries.
The rhythmic throbbing sensations associated with pulse pressure are palpated in superficial elastic and muscular arteries to determine one’s “pulse” (see Clinical View 20.4: “Detecting a Pulse Point”).

**Mean Arterial Pressure**

Mean arterial pressure (MAP) is the average (or mean) measure of the blood pressure forces on the arteries. Because diastolic pressure usually lasts slightly longer than systolic pressure, MAP is not simply an average of these two pressures. Rather, MAP may be estimated as follows:

\[
\text{MAP} = \text{Diastolic pressure} + \frac{1}{3} \times \text{Pulse pressure}
\]

So for a person with average blood pressure of 120/80 mm Hg, his or her MAP would be approximately 93 mm Hg \((80 + 40/3 = 93)\).

Mean arterial pressure is clinically significant because it provides a numeric value for how well body tissues and organs are perfused. A MAP of 70 to 110 mm Hg typically indicates good perfusion. A MAP lower than 60 mm Hg may indicate insufficient blood flow, and a very high MAP could indicate the delivery of too large of blood flow to body tissues with the possibility of causing edema (swelling) in the tissues (see Clinical View 20.5: “Cerebral Edema”). High blood pressure is also a risk factor for

---

**Table 20.4**

<table>
<thead>
<tr>
<th>Artery</th>
<th>Best Location to Detect Pulse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial temporal</td>
<td>Anterior to the ear superior to the root (origin) of the zygomatic process of the temporal bone</td>
</tr>
<tr>
<td>Facial</td>
<td>Immediately anterior to the angle of the mandible and the masseter muscle</td>
</tr>
<tr>
<td>Common carotid</td>
<td>Anterior to the sternocleidomastoid muscle and lateral to the larynx and trachea</td>
</tr>
<tr>
<td>Brachial</td>
<td>Along the medial surface of the arm, midway between the axilla and antecubital regions</td>
</tr>
<tr>
<td>Radial</td>
<td>Radial (lateral) side of the wrist, between the brachioradialis and flexor carpi radialis tendons</td>
</tr>
<tr>
<td>Femoral</td>
<td>Immediately inferior to the inguinal ligament (groin), approximately halfway between the pubis and the anterior superior iliac spine</td>
</tr>
<tr>
<td>Popliteal</td>
<td>Popliteal fossa, with the knee flexed slightly</td>
</tr>
<tr>
<td>Posterior tibial</td>
<td>Posteroinferior to the medial malleolus of the tibia</td>
</tr>
<tr>
<td>Dorsalis pedis</td>
<td>Either over the navicular tarsal (on the dorsal medial side of the foot) or between the dorsal interspace between the first and second toes</td>
</tr>
</tbody>
</table>

**Clinical View 20.4**

**Detecting a Pulse Point**

A pulse is the rhythmic throbbing of an arterial wall as blood is being pumped through the vessel. A pulse reflects the pulse pressure. Measuring the pulse is clinically significant for the following reasons:

1. It allows us to indirectly determine the rate of our heartbeat.
2. The force of the pulse can inform us about blood pressure, as high blood pressure will produce a more forceful pulse and low blood pressure will produce a weaker pulse.

Pulse points can be found throughout the body and typically are located where an artery may be compressed against a bone or other solid structure (e.g., a muscle). Two fingers are used to palpate the pulse, but the thumb is typically not used because it has a weak pulse of its own, which may interfere with pulse detection. Some common pulse locations are shown and listed in Table 20.4. See if you can palpate these pulse points on yourself.
INTEGRATE

**CLINICAL VIEW 20.5**

**Cerebral Edema**

Maintaining a normal mean arterial pressure (MAP) to the brain is critical. A possible consequence of an elevated MAP is **cerebral edema**, which is excess interstitial fluid in the brain. It can occur if MAP is greater than 160 mm Hg, a pressure that is reached, for example, with a blood pressure reading of 240/140 mm Hg. The high MAP substantially increases filtration in the capillaries of the brain (see section 20.3c).

the development of atherosclerosis (see Clinical View 20.1: “Atherosclerosis”).

Pulse pressure and mean arterial pressure are highest in the arteries closest to the heart, such as the aorta. As the arteries branch into smaller vessels and are greater distances from the ventricles, both of these pressures decrease. The pressure gradient in arteries is relatively steep and facilitates the movement of blood through the arteries (figure 20.11b).

**Capillary Blood Pressure**

By the time the blood reaches the capillaries, fluctuations between systolic and diastolic blood pressure disappear, so the pulse pressure disappears. Blood flow is smooth and even as it enters the capillaries.

Capillary blood pressure must be sufficient for exchange of substances between the blood and surrounding tissue, but not so high that it would damage the relatively fragile capillaries. Blood pressure on the arterial end of the capillary is about 40 mm Hg and drops quickly (along the approximately 1-millimeter length of a capillary) to below 20 mm Hg on the venous end of the capillary. These blood pressure values are used to determine net filtration pressure for capillary exchange, as previously described in section 20.3c. Recall that the relatively high blood pressure on the arteriolar end of the capillary accounts for filtration and the relatively low blood pressure on the venous end allows for reabsorption as colloid osmotic pressure pulls fluids back into the blood.

**INTEGRATE**

**CLINICAL VIEW 20.6**

**Deep Vein Thrombosis**

Deep vein thrombosis (throm-bo’sis; a clotting) (DVT) refers to a **thrombus** (blood clot) in a vein. The most common site for the thrombus is a vein in the sural region (calf). DVT typically occurs in individuals with heart disease or those who are inactive or immobile for a long period of time, such as bedridden patients. Even healthy individuals who have been on a long airline trip may develop DVT.

Initial signs of DVT include fever, tenderness and redness in the affected area, severe pain and swelling in the areas drained by the affected vein, and rapid heartbeat. The most serious complication of DVT is a **pulmonary embolus** (em-bō-lūs; a plug), in which a blood clot breaks free and is transported to the lung, eventually blocking a branch of the pulmonary artery and potentially causing respiratory failure and death. If a DVT is diagnosed, the patient is given anticoagulation medication, such as low-molecular-weight heparin, to help prevent further clotting and break up the existing clot.

Venous Blood Pressure

The movement of blood from the capillaries back to the heart via the veins is called **venous return**. Blood pressure in the venules and veins is not pulsatile because the blood is far removed from the pumping action of the heart. Therefore, veins also have no demonstrable pulse pressure. Blood pressure is 20 mm Hg in the venules and almost 0 mm Hg by the time blood is transported through the inferior vena cava to the right atrium of the heart. Thus, the pressure gradient in the veins is only 20 mm Hg. This relatively small blood pressure gradient is generally insufficient to move blood through the veins under given conditions without assistance, as when an individual is standing. Thus, venous return must be facilitated by valves within veins and two “pumps”—the skeletal muscle pump and the respiratory pump (figure 20.12).

The **skeletal muscle pump** assists the movement of blood primarily within the limbs. As skeletal muscles contract, veins are squeezed to help propel the blood toward the heart, and valves prevent blood backflow. When skeletal muscles are more active—for example, when a person is walking—blood is circulated more quickly and efficiently toward the heart by the skeletal muscle pump. Conversely, extended inactivity leads to blood pooling in the leg veins, which increases an individual’s risk for development of deep vein thrombosis (see Clinical View 20.6: “Deep Vein Thrombosis”).

The **respiratory pump** assists the movement of blood within the thoracic cavity (see section 23.5b). The diaphragm contracts and flattens as we inspire (inhale). Intra-abdominal pressure increases and places pressure on the vessels within the abdominal cavity. Conversely, thoracic cavity volume increases and intrathoracic pressure decreases. Blood is propelled from the vessels in the abdominopelvic cavity into the vessels in the thoracic cavity. When we expire (exhale), the diaphragm relaxes and returns to its dome shape.

**INTEGRATE**

**CLINICAL VIEW 20.7**

**Varicose Veins**

Varicose (var’ık-ös; varix = dilated vein) veins are dilated and tortuous (having many curves or twists). The valves in these veins have become nonfunctional, causing blood to pool in one area and the vein to swell and bulge. Varicose veins are most common in the superficial veins of the lower limbs. They may be a result of genetic predisposition, aging, or some form of stress that inhibits venous return (such as standing for long periods of time, obesity, or pregnancy). Varicose veins in the anorectal region are called **hemorrhoids** (hem’ô-rōydz). Hemorrhoids occur due to increased intra-abdominal pressure, as when a person strains to have a bowel movement or when a woman is in labor during childbirth.
**CLINICAL VIEW 20.8**

**Circulatory Shock**

Circulatory shock is any state in which there is insufficient blood flow for adequate perfusion of the body’s tissues. This is typically due either to impaired pumping of the heart (e.g., caused by congestive heart failure [see Clinical View 19.1: “Congestive Heart Failure”] or a malfunctioning pacemaker [SA node; see Clinical View 19.6: “Ectopic Pacemaker”]) or to low venous return. Circulatory shock associated with low venous return can result from the following (see figure 25.5):

- Decreased blood volume due to hemorrhage, dehydration, or systemic release of histamine in an allergic reaction that increases capillary permeability
- An obstructed vein
- Venous pooling caused by extended immobility or by extensive vasodilation (resulting from certain bacterial toxins or from brainstem trauma that results in loss of vasomotor tone)

**Blood Pressure Gradient in the Systemic Circulation**

We now know the normal range of blood pressure values in various portions of the vasculature. We can use the average blood pressure in the arteries close to the heart and the blood pressure in the inferior vena cava to calculate the total blood pressure gradient in the systemic circulation. This can be determined by viewing figure 20.11. The average, or mean, arterial blood pressure (MAP) in the arteries is 93 mm Hg. The blood pressure in the inferior vena cava is 0 mm Hg. Thus, the blood pressure gradient established by the pumping action of the heart is 93 mm Hg.

Most importantly, this blood pressure gradient is the driving force to move blood through the vasculature. Changes in the blood pressure gradient are directly correlated with changes in total blood flow. An increase in the blood pressure gradient increases total blood flow, whereas a decrease in the blood pressure gradient decreases total blood flow.

**INTEGRATE**

LEARNING STRATEGY

A blood pressure gradient is established by the heart when it pumps blood through the vessels, much as a pressure gradient is created by a water pump to force water through pipes. In both cases, the stronger the pump, the greater the pressure gradient that can be established, and the greater the flow that is possible.

**Figure 20.12 Factors That Influence Venous Return.** To help overcome the small blood pressure gradient within veins, blood return to the heart via veins is facilitated by both (a) a skeletal muscle pump within the limbs and (b) the respiratory pump within the torso.
How is it possible to change the steepness of the pressure gradient? The blood pressure gradient is altered by changes in cardiac output. An increase in cardiac output will increase the pressure gradient. Conversely, a decrease in cardiac output will decrease the pressure gradient (see section 19.9).

### WHAT DID YOU LEARN?

1. A 55-year-old female has an arterial blood pressure reading of 155/95 mm Hg. What are her pulse pressure and mean arterial pressure?
2. What is the physiologic significance of capillary blood pressure?
3. How is the small pressure gradient in veins overcome?
4. How is the pressure gradient to move blood through the systemic circulation calculated? What is the significance of this pressure gradient?

### 20.5b Resistance

#### LEARNING OBJECTIVE

29. Define resistance, and explain how it is influenced by blood viscosity, vessel length, and vessel radius.

Resistance also influences total blood flow. Resistance is defined as the amount of friction the blood experiences as it is transported through the blood vessels. Blood flow is always opposed by resistance. This friction is due to the contact between blood and the blood vessel wall. The term peripheral resistance is typically used when discussing the resistance of blood in the blood vessels (as opposed to the resistance of blood in the heart). Several factors affect peripheral resistance, including blood viscosity, blood vessel length, and the size of the lumen of blood vessels (as indicated by vessel radius).

### Blood Viscosity

**Viscosity** refers to the resistance of a fluid to its flow. More generally, it is the “thickness” of a fluid. The thicker the fluid, the more viscous it is, and the greater its resistance to flow. The thickness is dependent upon the relative percentage of particles in the fluid and their interactions with one another. Because blood contains formed elements (erythrocytes, leukocytes, platelets) and plasma proteins, it is approximately 4.5 to 5.5 times more viscous than water. As a result, blood exhibits greater resistance to flow than water.

A change in blood’s viscosity causes a change in resistance of blood flow through a vessel. For example, if someone is anemic (and has a lower than normal number of erythrocytes), then that person’s blood viscosity is lower, and the blood has less resistance to flow. Conversely, if someone has a greater than normal concentration of erythrocytes, blood viscosity is higher, and the blood is more viscous and has greater resistance to flow.

### Vessel Length

Increasing vessel length increases resistance, because longer vessels result in greater friction, which the fluid experiences as it is transported through the vessel. In contrast, shorter vessels offer less resistance than longer vessels with comparable diameters. Normally, vessel length remains relatively constant. However, if a person gains a large amount of weight, the body must produce miles of additional vessel length by angiogenesis for blood to be transported through the extra fat. Thus, vessel resistance increases if one gains weight, and decreases if someone loses a lot of weight (because those vessels are no longer needed and regress).

### Vessel Radius

Blood viscosity and vessel length remain relatively constant in a typical healthy individual. The major way resistance may be regulated is by altering vessel lumen radius (and thus changing the vessel diameter).

How specifically does vessel radius influence resistance? Blood tends to flow fastest in the center of the vessel lumen, whereas blood near the sides of the vessels slows, because it encounters resistance from the nearby vessel wall. This difference in flow rate within a blood vessel (or in any conduit) is called **laminar flow**. You can see evidence of laminar flow by studying a river: The water flow near the banks, or edges, of the river is a bit slower or sluggish, whereas the water flow near the center of the river is quite fast in comparison. So, if vessel diameter increases, relatively less blood flows near the edges and overall blood flow increases. In contrast, if vessel radius decreases, then relatively more blood flows near the edges and overall blood flow decreases.

The relationship between blood flow and the radius of blood vessel lumen may be stated as follows (where the symbol $\propto$ means “is proportional to”):

$$ F \propto r^4 $$

where $F = \text{flow}$ and $r = \text{radius of the lumen of a vessel}$ (The radius is 1/2 the diameter of the lumen.). This mathematical expression reflects that flow is directly proportional to the fourth power of a radius. If a vessel vasodilates and its radius increases from 1 millimeter (mm) to 2 mm, the overall change in flow is 16 times greater: If $r = 1$ mm, then $r^4 = 1$, and $F = 1$ mm per second; and when $r = 2$ mm, then $r^4 = 16$, and $F = 16$ mm per second. In contrast, if a vessel vasoconstricts and its radius decreases from 2 mm to 1 mm, the overall change in flow is 16 times less.

Any vessel may vasoconstrict or vasodilate; however, resistance usually is regulated specifically by vasoconstriction and vasodilation of muscular arteries and arterioles, a change systemically controlled by the vasomotor center of the medulla oblongata (see sections 13.5e and 20.6a). Thus, because there are so many muscular arteries and arterioles (and the overall length of all these vessels is so great), even

---

**LEARNING STRATEGY**

Drinking through a straw provides an easy way to demonstrate the variables that influence resistance:

- **Viscosity**. Water or soda moves through a straw more easily than does a thick vanilla milkshake.
- **Vessel length**. It is easier to drink through a relatively short straw compared with a very long, twisty straw.
- **Vessel radius**. Water can be sipped through a normal-sized straw more easily than through a hollow coffee stirrer with its smaller diameter.

Greater resistance is experienced when drinking thick liquids, using a longer straw, or using a more narrow straw. In the same way, an increase in resistance is exhibited with more viscous blood, increased total length of blood vessels, and vasoconstriction of blood vessels.
small changes in vessel radius significantly change resistance, and therefore can have dramatic effects on blood flow.

Note that atherosclerosis is a disease process where a plaque narrows the lumen of blood vessels. Thus, in individuals with atherosclerosis, the blood experiences greater resistance as it moves through the atherosclerotic blood vessels.

**WHAT DID YOU LEARN?**

20. How is resistance defined?
21. What are the three factors that alter resistance? How does each affect blood flow in vessels?

### 20.5c Relationship of Blood Flow to Blood Pressure Gradients and Resistance

#### LEARNING OBJECTIVES

30. Explain the relationship of both the blood pressure gradient and resistance to total blood flow.
31. Discuss why blood pressure increases with increased resistance in the systemic circulation.

Total blood flow is the amount of blood that moves through the cardiovascular system per unit time and is influenced by both blood pressure gradients and resistance, as previously described. This relationship is expressed mathematically as follows:

\[ F \propto \frac{\Delta P}{R} \]

where \( F \) = blood flow, \( \Delta P \) = pressure gradient \((P_1 - P_2)\), and \( R \) = resistance.

#### Systemic Blood Pressure Gradient

The preceding formula demonstrates that blood flow is directly related to the pressure gradient. Thus, as the blood pressure gradient increases, total blood flow is greater, and as the blood pressure gradient decreases, total blood flow lessens (assuming resistance remains the same). Recall that an increase in cardiac output will increase the pressure gradient, whereas a decrease in cardiac output will decrease the pressure gradient. Consequently, increasing blood flow is possible with a steeper blood pressure gradient—however, it is a change exhibited only with greater effort exerted by the heart.

#### Resistance

The preceding mathematical expression also demonstrates that blood flow is inversely related to resistance. If resistance increases, blood flow lessens, whereas if resistance decreases, blood flow increases (assuming the pressure gradient remains the same).

Recall that resistance is increased with (1) an increase in blood viscosity (e.g., as occurs with greater concentration of erythrocytes); (2) an increase in blood vessel length (e.g., a change that accompanies weight gain); and (3) a decrease in vessel lumen diameter (e.g., a change that occurs with a net increase in vasoconstriction and in individuals with atherosclerosis).

#### Relationship of Systemic Blood Pressure and Resistance

Individuals with sustained increased resistance (e.g., that accompanies significant weight gain or atherosclerosis) generally exhibit elevated arterial blood pressure readings. This condition is clinically significant; it occurs because a greater pressure gradient must be produced to overcome the higher resistance and ensure normal blood flow and adequate perfusion of all tissues. The relationship of blood flow, blood pressure gradients, and resistance is summarized in figure 20.13.

#### WHAT DID YOU LEARN? 

22. In general, would you predict a higher blood pressure, lower blood pressure, or normal blood pressure in individuals with sustained increased resistance? Explain.
20.6 Regulation of Blood Pressure and Blood Flow

Blood pressure must be high enough to propel blood through the cardiovascular system to maintain adequate perfusion of all tissues, yet not so high that it causes damage to the blood vessels. Blood pressure is dependent upon three primary variables: cardiac output, resistance, and blood volume. Regulation of these variables is critical in maintaining homeostasis and occurs through short-term mechanisms of the nervous system, long-term mechanisms of the endocrine system, or both.

20.6a Neural Regulation of Blood Pressure

LEARNING OBJECTIVES

32. Describe the anatomic components associated with regulating blood pressure through short-term mechanisms.

33. Explain the autonomic reflexes that alter blood pressure.

Short-term regulation of blood pressure occurs through autonomic reflexes involving nuclei within the medulla oblongata. These reflexes adjust blood pressure quickly, as occurs when you arise from a sitting to a standing position, by altering cardiac output, resistance, or both. We first describe the anatomic structures involved in the autonomic reflexes and then discuss how they function to maintain a normal blood pressure. Please refer to figure 20.14 as you read through this section.

Cardiovascular Center

Two distinct groups of autonomic nuclei in the medulla oblongata participate in the regulation of blood pressure, specifically the cardiac center and the vasomotor center (see section 13.5c). Collectively, these two centers are called the cardiovascular center. The cardiac center regulates heart activity (and thus cardiac output), and the vasomotor center controls the degree of vasoconstriction and vasodilation of blood vessels (and, thus, regulates resistance).

Cardiac Center

Recall that two regulatory nuclei are housed within the cardiac center: the cardioacceleratory center and the cardioinhibitory center (see section 19.5b). Sympathetic division pathways extend from the cardioacceleratory center to both the sinoatrial (SA) node and the atrioventricular (AV) node. Nerve signals relayed along these sympathetic pathways cause release of norepinephrine from their ganglionic neurons, which both (1) increases the firing rate of the SA node and (2) shortens the delay of nerve signals at the AV node as they are relayed along the heart’s conduction pathway. Thus, sympathetic stimulation increases heart rate. In addition, sympathetic division pathways extend to the myocardium; when stimulated, these sympathetic pathways cause a more forceful contraction of the heart. Thus, sympathetic stimulation also increases stroke volume. The resulting increase in both heart rate and stroke volume produces a greater cardiac output.

Figure 20.14 Cardiovascular Center. The cardiovascular center regulates blood pressure via a negative feedback loop. It receives sensory input from baroreceptors and chemoreceptors within the carotid arteries and aortic arch. This center then regulates blood pressure (through motor output along sympathetic nerves and vagus nerves) by adjusting cardiac output and peripheral resistance experienced by blood in blood vessels.
Parasympathetic division pathways extend from the cardioinhibitory center to also innervate both the SA node and AV node. Nerve signals relayed along these parasympathetic pathways cause release of acetylcholine from their ganglionic neurons, which both decreases the firing rate of the SA node and lengthens the delay of nerve signals at the AV node as they are relayed along the heart’s conduction pathway. Thus, parasympathetic stimulation decreases heart rate. The resulting decrease in heart rate produces a smaller cardiac output. (Note that parasympathetic pathways do not extend to the myocardium and, so, do not alter the force of contraction and stroke volume.)

**Vasomotor Center** The vasomotor center, in comparison, regulates the degree of vasoconstriction and vasodilation of blood vessels. Blood vessels, unlike the heart, do not have dual innervation (see section 15.7b). Instead, they are typically innervated by only the sympathetic division with no innervation by the parasympathetic division. Thus, only sympathetic division pathways extend from the vasomotor center to most blood vessels; the neurotransmitter norepinephrine is also released from these ganglionic neurons.

**Blood Vessels** Variations in response of blood vessels (vasoconstriction and vasodilation) is dependent upon the subtypes of receptors in the smooth muscle cells within the tunica media of the blood vessel wall. The receptor subtype is specific to the location of the blood vessels within the different vascularized tissues of the body (e.g., skeletal muscle, skin). These smooth muscle cells typically contain one of several receptor subtypes that bind different neurotransmitters and hormones. Two of the most common subtypes are alpha-1 (α1) receptors and beta-2 (β2) receptors (see section 15.6c). Smooth muscle cells that contain α1 receptors contract in response to primarily norepinephrine, which causes vasoconstriction of these blood vessels (e.g., most blood vessels in the body). In contrast, smooth muscle cells that contain β2 receptors relax in response to epinephrine, which causes vasodilation of these blood vessels (e.g., coronary arteries and arteries supplying skeletal muscle). Note that the source of epinephrine hormone (and some norepinephrine) is the adrenal medulla, which releases both of these hormones in response to stimulation by the sympathetic division; see section 15.4b.

Activation of the sympathetic division and subsequent stimulation of the adrenal medulla cause the following:

- **Increased peripheral resistance.** More blood vessels are stimulated to vasoconstrict than vasodilate because there are more blood vessels that house smooth muscle with α1 receptors than β2 receptors; consequently, peripheral resistance is increased, raising blood pressure.

- **Larger circulating blood volume.** Vasoconstriction of veins shifts blood from venous reservoirs (see section 20.1d) and circulating blood volume increases, thus increasing blood pressure.

- **Redistribution of blood flow.** More blood flow reaches skeletal muscles and the heart, and less blood flow goes to most other structures. Thus, organs requiring additional nutrients and oxygen have adequate perfusion.

Inhibition of the sympathetic division reverses these changes: Peripheral resistance decreases, blood shifts to venous reservoirs, and blood flow distribution returns toward its previous levels.

**Baroreceptors**

Baroreceptors are specialized sensory nerve endings that respond to stretch (see section 16.1d). Here the baroreceptors detect stretch of the blood vessel wall that occurs as the blood volume within them changes. The two main baroreceptors for the cardiovascular system are those located within the aortic arch and carotid sinuses, specifically within the tunica externa.

The aortic arch baroreceptors transmit nerve signals to the cardiovascular center through the vagus nerve (CN X; see table 13.5). The aortic arch baroreceptors are important in regulating systemic blood pressure.

The carotid sinus baroreceptors are located within each internal carotid artery, near the artery’s initial bifurcation (branching) from the common carotid artery. They transmit nerve signals to the cardiovascular center through the glossopharyngeal nerve (CN IX; see table 13.5). These baroreceptors within the carotid sinuses monitor blood pressure changes in the head and neck—thus, they are important in monitoring blood pressure affecting the brain. Baroreceptors in the carotid sinuses are more sensitive to blood pressure changes than baroreceptors in the aortic arch—a condition that is not surprising, given the importance of delivering sufficient blood to the brain.

Baroreceptors continuously transmit nerve signals along sensory neurons within the vagus nerves and glossopharyngeal nerves to the cardiovascular center at a particular rate. Their firing rate changes when the stretch in the blood vessel wall changes.

**Autonomic Reflexes**

Baroreceptors are activated in response to changes in stretch of the blood vessel wall to initiate autonomic reflexes (see section 15.8) that help regulate blood pressure. These reflexes are appropriately called baroreceptor reflexes. These reflexes are initiated by either a decrease or an increase in blood pressure.

**If blood pressure decreases:**

1. **Decreased stretch in the blood vessel wall (reflecting a decrease in blood pressure, as might occur when you arise from bed in the morning) is detected by baroreceptors in the aortic arch, carotid sinuses, or both.**

2. The baroreceptors *decrease* the frequency of nerve signals relayed along sensory neurons within the vagus and glossopharyngeal nerves to both the cardiac center and vasomotor center.

3. In response, the cardiovascular center within the cardiac center *increases* nerve signals relayed along sympathetic pathways extending to the heart, including the SA node, AV node, and myocardium. Concomitantly, the cardioinhibitory center of the cardiac center *decreases* nerve signals relayed along parasympathetic pathways that extend to the SA node and AV node. Consequently, both heart rate and stroke volume increase, resulting in a greater cardiac output. (This would be analogous to both putting your foot on the gas and taking your foot off the brake when driving a car.)

4. Simultaneously, the vasomotor center *increases* nerve signals along sympathetic pathways that extend to blood vessels, resulting in net vasoconstriction and an increase in peripheral resistance, along with shifting of blood from venous reservoirs. The resulting increase in cardiac output, increase in resistance, and larger circulating blood volume quickly elevate blood pressure to maintain sufficient blood pressure to move blood through the vasculature.

**If blood pressure increases:**

1. Increased stretch in the blood vessel wall (reflecting an increase in blood pressure) is detected by baroreceptors in the aortic arch, carotid sinuses, or both.

2. The baroreceptors *increase* the frequency of nerve signals relayed along sensory neurons within the vagus nerve (CN X) and glossopharyngeal nerve (CN IX) to both the cardiac center and vasomotor center of the medulla oblongata.
3. In response, the cardioacceleratory center within the cardiac center decreases nerve signals relayed along sympathetic pathways extending to the heart, including the SA node, AV node, and myocardium. Concomitantly, the cardioinhibitory center of the cardiac center increases nerve signals relayed along parasympathetic pathways that extend to the SA node and AV node. Consequently, both heart rate and stroke volume decrease, resulting in a smaller cardiac output. (This would be analogous to both taking your foot off the gas and putting your foot on the brake when driving a car.)

4. Simultaneously, the vasomotor center decreases nerve signals along sympathetic pathways to blood vessels, resulting in net vasodilation and a decrease in resistance, along with shifting of blood to venous reservoirs. The resulting decrease in cardiac output, decrease in resistance, and smaller circulating blood volume lower blood pressure, and blood flow returns to its resting levels.

Baroreceptors respond best to sudden, short-term changes in blood pressure, but they are not effective long-term or chronic blood pressure regulators. If someone has chronically high blood pressure, eventually the baroreceptors will adapt to the change in blood pressure and thus adjust their normal “set point” (see section 1.6b).

Chemoreceptor Reflexes

Chemoreceptors are most important in regulating respiration but are also secondarily involved in regulating blood pressure. When chemoreceptors are stimulated, they initiate chemoreceptor reflexes, which are negative feedback loops that ultimately bring blood chemistry levels back to normal.

The two main peripheral chemoreceptors are the aortic bodies and carotid body. The aortic bodies are located in the arch of the aorta, whereas a carotid body is located at the bifurcation of each common carotid as it splits into an external carotid and an internal carotid artery. Both aortic and carotid bodies send sensory input to the cardiovascular center; the aortic bodies send nerve signals via the vagus nerve, and the carotid body along the glossopharyngeal nerve. High carbon dioxide levels, low pH, and very low oxygen levels stimulate the chemoreceptors, and their increased firing primarily stimulates the vasomotor center. The vasomotor center responds by increasing nerve signals along sympathetic pathways to blood vessels, which increases resistance and shifts blood from venous reservoirs to increase venous return. The changes raise blood pressure and increase blood flow, including blood flow to the lungs, which allows for an accompanying change in respiratory gas exchange. As a result, blood gas levels return to normal. (The reason high carbon dioxide, low blood pH, and very low oxygen levels function in stimulating chemoreceptors is discussed in detail in section 23.5c.)

Higher Brain Centers

Blood pressure is also influenced by higher brain centers. For example, increases in body temperature, or experiencing the fight-or-flight response associated with exercise or an emergency, result in the hypothalamus increasing cardiac output and resistance. Even anxiety over a new or dangerous experience, such as skydiving, can increase blood pressure. In addition, the limbic system alters blood pressure in response to emotions or emotional memories (see section 13.8f).

**WHAT DID YOU LEARN?**

23. When are the short-term mechanisms for regulation of blood pressure important?

24. What is the initial change to blood pressure when you arise in the morning? Describe the autonomic reflex to maintain your blood pressure when you arise.

**20.6b Hormonal Regulation of Blood Pressure**

**LEARNING OBJECTIVES**

34. Describe the hormones that regulate blood pressure.

35. Explain the renin-angiotensin system and its influence on blood pressure.

36. Contrast the effects of angiotensin II, aldosterone, and antidiuretic hormone on blood pressure with those of atrial natriuretic peptide.

Several hormones, in addition to epinephrine and norepinephrine, participate in regulating blood pressure. These include angiotensin II, aldosterone, antidiuretic hormone, and atrial natriuretic peptide. These typically regulate blood pressure by altering resistance, blood volume, or both. Blood volume is regulated by stimulating fluid intake (assuming fluid intake occurs) or altering urine output. A general description of each hormone is presented next. A more detailed discussion of these hormones is included in chapters 24 and 25.

**Renin-Angiotensin System**

The renin-angiotensin system “straddles” short-term neural regulation and long-term hormonal regulation because the synthesis of the angiotensin II is initiated by the nervous system (short-term mechanisms), and angiotensin II causes the release of other hormones (long-term mechanisms).

The liver produces a plasma protein called angiotensinogen (an inactive hormone) and continuously releases it into the blood (see section 17.11c). The kidney releases the enzyme renin into the blood in response to either low blood pressure or stimulation by the sympathetic division (figure 20.15). Within the blood, renin converts angiotensinogen into angiotensin I. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme (ACE), an enzyme associated with the capillary endothelium. ACE is found in very high concentrations on the pulmonary capillary endothelium, so most (but not all) angiotensin I conversion to angiotensin II occurs in the lungs.

Having most of the ACE enzyme in pulmonary capillary endothelium helps ensure that sufficient angiotensin I is converted to angiotensin II. This is because all blood moves through the pulmonary circulation to be oxygenated, so contact between angiotensin I and ACE is maximized.

Angiotensin II has several important effects: It is a powerful vasoconstrictor—much more powerful than comparable hormones, such as norepinephrine—and thus it increases peripheral resistance and raises blood pressure to a greater extent. Angiotensin II stimulates the thirst center; fluid intake increases blood volume, which increases blood pressure. Angiotensin II also regulates blood volume by direct action in the kidneys to decrease urine formation, and by
indirect action through stimulating the release of other hormones (aldosterone and antidiuretic hormone). A decrease in urine formation results in less fluid lost from the blood; this helps maintain blood volume and thus blood pressure. Angiotensin II is discussed in detail in section 25.4a.

**WHAT DO YOU THINK?**

Do you think an ACE inhibitor drug would be used to treat hypertension or hypotension? Explain.

**Aldosterone and Antidiuretic Hormone**

Aldosterone is released from the adrenal cortex in response to several stimuli, including angiotensin II. Aldosterone increases the absorption of sodium ion (Na⁺) and water in the kidney, decreasing their loss in the urine; this helps maintain blood volume and blood pressure. Aldosterone is discussed in sections 17.9a and 25.4c.

Antidiuretic hormone (ADH) is released from the posterior pituitary in response to nerve signals from the hypothalamus (see section 17.7b). The hypothalamus stimulates the posterior pituitary following either detection of increased concentration of blood (typically correlated with low blood volume) or stimulation of the hypothalamus by angiotensin II. ADH increases the absorption of water in the kidney, decreasing its loss in the urine; this helps maintain blood volume and blood pressure. ADH also stimulates the thirst center so that there is fluid intake, and blood volume increases. During extreme cases of low blood volume, as might occur with hemorrhaging, extensive release of ADH occurs, which causes vasoconstriction. This vasoconstriction increases peripheral resistance and blood pressure. This is why ADH is also referred to as vasopressin. Antidiuretic hormone is discussed in detail in section 25.4b.

In summary, angiotensin II, aldosterone, and ADH decrease urine output to help maintain blood volume and blood pressure. Angiotensin II and ADH (in high doses) increase peripheral resistance and blood pressure, and they further increase blood pressure if there is fluid intake.

**Atrial Natriuretic Peptide**

Atrial natriuretic peptide (ANP) is released from the atrium of the heart in response to an increase in stretch of the atrial walls due to increased blood volume and increased venous return. ANP both (1) stimulates vasodilation, which decreases peripheral resistance, and (2) increases urine output, which decreases blood volume. The net effect is a decrease in blood pressure. Atrial natriuretic peptide is described in detail in section 25.4d. Table R.7 lists the details for these four hormones regarding their regulation of fluid balance, blood volume, and blood pressure.

**Integration of Variables That Influence Blood Pressure**

Homeostatic mechanisms to maintain a normal blood pressure are dependent on three primary variables: cardiac output, resistance, and blood volume. All three of these variables are directly related to blood pressure. An increase in any of the three increases blood pressure, and a decrease in any of the three decreases blood pressure. The relationship of these primary variables is summarized in figure 20.16.

**WHAT DID YOU LEARN?**

25 How is angiotensinogen activated to become angiotensin II? How does angiotensin II influence blood pressure?

26 Which hormone decreases blood pressure?
**INTEGRATE CONCEPT OVERVIEW**

**Figure 20.16 Factors That Regulate Blood Pressure.** Three primary factors influence blood pressure: (a) cardiac output, (b) peripheral resistance, and (c) blood volume.

**INTEGRATE**

**CLINICAL VIEW 20.9 Measuring Blood Pressure**

Arterial blood pressure is measured indirectly using a sphygmomanometer (sfig’mə-mə-nəm’-ə-ter; sphygmos = pulse, metron = measure). A cuff is wrapped around the arm, and a stethoscope is placed just distal to the compressed artery, allowing a practitioner to listen for pulse sounds. The cuff is inflated until the brachial artery is completely compressed, temporarily stopping blood flow. The pressure in the cuff is then decreased as air is gradually released. Two values are recorded (e.g., 120/80), and the unit of measurement is millimeters of mercury (mm Hg).

**Cardiac Output (CO)**

Cardiac output is the volume of blood pumped per minute. CO is a function of heart rate (HR) and stroke volume (SV): $CO = HR \times SV$.

<table>
<thead>
<tr>
<th>Heart rate (HR)</th>
<th>Stroke volume (SV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased heart rate increases cardiac output and blood pressure.</td>
<td>Increased stroke volume increases cardiac output and blood pressure.</td>
</tr>
<tr>
<td>Decreased heart rate decreases cardiac output and blood pressure.</td>
<td>Decreased stroke volume decreases cardiac output and blood pressure.</td>
</tr>
</tbody>
</table>

**Systolic pressure**
- Top number of a blood pressure reading
- Pressure in the arteries when the ventricles contract
- Recorded when the first pulsating sound is heard (when pressure in the brachial artery is sufficient to overcome pressure in the cuff, reestablishing blood flow)

**Diastolic pressure**
- Bottom number of a blood pressure reading
- Pressure in the arteries when the ventricles relax
- Recorded when sounds are no longer heard (because pressure in the cuff is no longer compressing the artery)
INTEGRATE

**CLINICAL VIEW 20.10**

**Hypertension and Hypotension**

**Hypertension** is chronically elevated blood pressure, defined as a systolic pressure greater than 140 mm Hg or a diastolic pressure greater than 90 mm Hg. Hypertension may damage blood vessel walls, making arteries more likely to develop **atherosclerosis**, or the arteriole walls may become stiff or harden, a condition called **arteriolosclerosis** (or **hardening of the arteries**). Hypertension also places an extra workload on the heart that may lead to **congestive heart failure** (see Clinical View 19.1: “Congestive Heart Failure”).

In contrast, **hypotension** is a chronically low blood pressure that results in symptoms such as fatigue, dizziness, and fainting. Some physicians define hypotension as a systolic pressure below 90 mm Hg or a diastolic pressure below 60 mm Hg, whereas other physicians state that “normal” low blood pressure for one individual may be hypotensive for another.

**Orthostatic hypotension**, or **postural hypotension**, is a drop in blood pressure when an individual suddenly changes position, as when a person stands up after lying down. As a result, the person may experience dizziness, light-headedness, and fainting after this positional change. Essentially, orthostatic hypotension occurs when the nervous system responses that help regulate blood pressure do not function quickly enough, and MAP temporarily decreases below 60 mm Hg. Thus, the blood remains pooled in the veins, and not enough reaches the cerebral vasculature within the brain, resulting in the symptoms of hypotension.

---

**Peripheral resistance** is the opposition to flow of blood in vessels, and is a function of vessel radius, vessel length, and blood viscosity.

<table>
<thead>
<tr>
<th>Vessel radius</th>
<th>Vessel length</th>
<th>Blood viscosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasoconstriction narrows vessel and forces blood through a narrower lumen, increasing peripheral resistance and blood pressure.</td>
<td>Longer vessels increase peripheral resistance, which raises blood pressure.</td>
<td>Decreased blood viscosity decreases peripheral resistance and blood pressure.</td>
</tr>
<tr>
<td>Vasodilation widens vessel, decreasing peripheral resistance and blood pressure.</td>
<td>Shorter vessels decrease peripheral resistance, which lowers blood pressure.</td>
<td>Increased blood viscosity increases peripheral resistance and blood pressure.</td>
</tr>
</tbody>
</table>

**Blood volume** is the volume of blood in the body, and is a function of fluid intake and fluid output.

<table>
<thead>
<tr>
<th>Fluid intake (~2500 mL/day)</th>
<th>Fluid output (~2500 mL/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food and drink</td>
<td>Metabolic water</td>
</tr>
<tr>
<td>Sweat and transpiration</td>
<td>Urine</td>
</tr>
<tr>
<td>Feces</td>
<td>Moisture in expired air</td>
</tr>
</tbody>
</table>
During exercise, there is an increase in total blood flow due to a faster and stronger heartbeat and because blood is removed from the “reservoirs” of the veins to the active circulation. There is also a redistribution of blood. Both of these changes help ensure that the most metabolically active tissues are receiving adequate blood flow to meet the needs of the tissue cells.

Figure 20.17 provides an example in which blood flow changes from 5.25 L/min (5250 mL/min) at rest to 17.5 L/min (17,500 mL/min) during exercise. The following increases in blood flow to specific regions or organs can be noted:

- Blood flow to the coronary arteries of the heart increases approximately three-fold (from 250 mL/min to 750 mL/min), a change that helps to ensure that sufficient oxygen reaches the cardiac muscle within the heart wall (see section 19.4a).
- Skeletal muscle blood flow increases an amazing 11-fold (from 1100 mL/min to 12,500 mL/min)—which is approximately 70% of the total cardiac output—a change needed to meet the high metabolic demands experienced by skeletal muscle during exercise (see section 10.4a).
- The percentage of blood flow to the skin increases to almost five times its resting level (from 400 mL/min to 1900 mL/min) to dissipate heat (see sections 1.6b and 6.1d).

In contrast, relatively less total blood flow is distributed to the abdominal organs, slowing digestive processes; less is transported to the kidneys, which decreases urine output to maintain blood volume and blood pressure. Smaller amounts reach other structures that are not as metabolically active during exercise.

**WHAT DID YOU LEARN?**

27. Which organs have an increased proportion of cardiac output during exercise? Which receive a decreased proportion of cardiac output during exercise?

**20.8 Pulmonary Circulation**

The pulmonary circulation is responsible for transporting deoxygenated blood from the right side of the heart to the lungs and then returning the newly oxygenated blood to the left side of the heart.

**20.8a Blood Flow Through the Pulmonary Circulation**

In the pulmonary circulation, deoxygenated blood is pumped out of the right ventricle into the pulmonary trunk (figure 20.18). This vessel bifurcates into a left and right pulmonary artery that go to the corresponding lungs. The pulmonary arteries divide into smaller arteries that continue to subdivide to form arterioles. These arterioles finally branch into pulmonary capillaries, where gas exchange occurs. Carbon dioxide diffuses from the blood and enters the alveoli.
(air sacs) of the lungs, while oxygen moves in the opposite direction, from the alveoli into the blood.

The capillaries merge to form venules and then the **pulmonary veins**. Typically, two left and two right pulmonary veins transport the newly oxygenated blood to the left atrium of the heart.

**WHAT DID YOU LEARN?**

What is the percentage of blood returning to the right side of the heart that is then pumped to the lungs?

### 20.8b Characteristics of the Pulmonary Circulation

**LEARNING OBJECTIVE**

39. Identify features of the pulmonary circulation that distinguish it from systemic circulation.

Pulmonary arteries have less elastic connective tissue and wider lumens than systemic arteries. Compared to the systemic circulation, pulmonary vessels are relatively short, because the lungs are close to the heart. As a result, blood pressure is lower throughout the pulmonary circulation in comparison to the systemic circulation. The pressure changes associated with the pulmonary circulation are as follows:

- Blood leaves the right ventricle with a systolic pressure of about 15 to 25 mm Hg, depending upon whether the body is resting or active.
- Blood pressure drops as the blood passes through the pulmonary trunk and right and left pulmonary arteries, reaching an overall pressure of about 10 mm Hg in the pulmonary capillaries of the alveoli. This lower pressure means that the blood moves more slowly in pulmonary capillaries than in systemic capillaries, facilitating gas exchange within the lungs.
- Blood exits the pulmonary capillaries into progressively larger veins that become the pulmonary veins; blood pressure is almost 0 mm Hg as these veins empty into the left atrium.

**WHAT DID YOU LEARN?**

29. How does blood pressure in the pulmonary circulation compare to the pressure in the systemic circulation?

---

**Figure 20.18** **Pulmonary Circulation and Blood Flow Through the Heart.** The pulmonary circulation transports blood to and from the gas exchange surfaces (respiratory membrane) within the lungs. Blood circulation through the heart is indicated by colored arrows: deoxygenated blood (blue arrows), oxygenated blood (red arrows). [APR]
20.9 Systemic Circulation: Vessels from and to the Heart

We discuss the vessels from and to the heart and then look at the circulatory routes for each body region: the head and trunk and the upper and lower limbs. As you read these descriptions, refer to figure 20.19, which shows the locations of the major arteries and veins.

20.9a General Arterial Flow Out of the Heart

**LEARNING OBJECTIVE**

40. List the arteries that transport blood away from the left ventricle of the heart to the major areas of the body.

Oxygenated blood is pumped out of the left ventricle of the heart and enters the ascending aorta. The left and right coronary arteries emerge immediately from the wall of the ascending aorta and supply the heart wall (figure 20.19 inset; also see figure 19.13a).

**Figure 20.19 General Vascular Distribution.** Arteries in the systemic circulation transport blood from the heart to systemic capillary beds; systemic veins return this blood to the heart. (a) Anterior view of the systemic arteries, with an inset of the heart and aorta.
The ascending aorta curves toward the left side of the body and becomes the aortic arch (also called the arch of the aorta). Recall from section 20.6a that the aortic bodies for regulating blood pressure are within the tunica externa of the aortic arch. Three main arterial branches emerge from the aortic arch:

1. The **brachiocephalic** (brā-kē-o-se-fal′ik) trunk, which bifurcates into the **right common carotid** (ka-rot′id) artery, supplying arterial blood to right side of the head and neck, and the **right subclavian** (sūb-klā′vē-an; sub = beneath) artery, supplying the right upper limb and some thoracic structures
2. The **left common carotid artery**, supplying the left side of the head and neck
3. The **left subclavian artery**, supplying the left upper limb and some thoracic structures

The aortic arch curves posterior to the heart and projects inferiorly as the **descending thoracic aorta**, several branches of which supply the...
As this artery extends inferiorly through the aortic opening (hiatus) in the diaphragm, it is renamed the **descending abdominal aorta**, where it supplies the abdominal wall and internal organs.

At the level of the fourth lumbar vertebra, the descending abdominal aorta bifurcates into **left** and **right common iliac** (i'lē-ak; *ileum* = groin) **arteries**. Each of these arteries further divides into an **internal iliac artery** (to supply pelvic and perineal structures) and an **external iliac artery** (to supply the lower limb).

### WHAT DID YOU LEARN?

30. What are the three main branches off of the aortic arch? What areas in general do these branches serve?

---

**20.9b General Venous Return to the Heart**

#### LEARNING OBJECTIVE

41. Name the veins that return blood from the systemic circulation to the right atrium of the heart.

Blood is returned to the right atrium of the heart by three vessels: the superior vena cava, the inferior vena cava, and the coronary sinus (figure 20.19b). The veins that drain the head, neck, upper limbs, and thoracic and abdominal walls from each side of the body merge to form the **left** and **right brachiocephalic veins**. The two brachiocephalic veins merge to form the **superior vena cava**. The veins that drain blood inferior to the diaphragm merge to collectively form the **inferior vena cava**. The inferior vena cava is responsible for transporting venous blood toward the heart from the lower limbs, pelvis and perineum, and abdominal structures. It lies to the right side of the descending abdominal aorta and extends through an opening (caval opening) in the diaphragm. Recall from section 19.4b that the **coronary sinus** also drains into the right atrium, delivering deoxygenated blood from the heart myocardium (see figure 19.13b).

### WHAT DID YOU LEARN?

31. Which body regions are drained by (a) the superior vena cava and (b) the inferior vena cava?

---

**20.10 Systemic Circulation: Head and Trunk**

Blood flow to the head and to the thoracic and abdominal organs is critical to survival, so it is not surprising that these regions receive blood flow soon after it leaves the heart.

---

**20.10a Head and Neck**

#### LEARNING OBJECTIVES

42. Name the arteries and veins associated with the head and neck structures.

43. Diagram and explain the cerebral arterial circle and its function.

44. Describe the general structure and function of dural venous sinuses.

Arterial supply to the head and neck comes from the branches of the aortic arch. Venous drainage of the head and neck is through the jugular veins, which then drain into the brachiocephalic veins. We discuss the arterial supply first.

#### Arterial Supply

Most of the blood to the head and neck is supplied by the **common carotid arteries** (figure 20.20a). The common carotid arteries are positioned parallel immediately lateral to either side of the trachea. At the superior border of the thyroid cartilage of the larynx, each artery divides into an **external carotid artery**, which supplies structures external to the skull, and an **internal carotid artery**, which supplies internal skull structures. Recall that the carotid sinus, a receptor that helps regulate blood pressure, is within the internal carotid artery near its bifurcation from the common carotid artery (see sections 19.5b and 20.6a).
Figure 20.20 Arterial Blood Flow to the Head and Neck. (a) Right lateral view shows the branches that supply blood to the head and neck. (b) An inferior view of the brain shows the branches of the internal carotid and vertebral arteries that supply the brain. An inset shows an enlarged view of the cerebral arterial circle, which is an anastomosis of blood vessels that surrounds the hypophyseal fossa of the sphenoid bone, which houses the pituitary gland.
Additional blood to the head and neck comes from the vertebral artery, thyrocervical (thyˈrō-serˈvi-kal) trunk, and costocervical (kosˈtō-serˈvi-kal) trunk. These are all branches of the subclavian artery.

**External Carotid** The external carotid artery supplies blood to several branches that include the superior thyroid artery, ascending pharyngeal (āsˈkən-ding fäˈrīn-je-əl; pharynx = throat) artery, lingual (linˈgwāl) artery, facial artery, occipital artery, and posterior auricular artery. Thereafter, the external carotid artery divides into the maxillary artery and the superficial temporal artery. The specific regions supplied by these arteries are listed in figure 20.20.

**Internal Carotid** The internal carotid artery branches only after it enters the skull through the carotid canal. Once inside the skull, it forms multiple branches, including the anterior and middle cerebral arteries, which supply the brain, and the ophthalmic (op-thalˈmik; ophthalmos = eye) arteries, which supply the eyes and some of the surrounding structures (figure 20.20b).

**Vertebral Arteries** The vertebral arteries emerge from the subclavian arteries and extend through the transverse foramina of the cervical vertebrae before entering the skull through the foramen magnum, where they merge to form the basilar (basˈi-lər; basis = base) artery. The basilar artery is located immediately anterior to the pons and extends many branches prior to subdividing into the posterior cerebral arteries.

**Cerebral Arterial Circle** The cerebral arterial circle (circle of Willis) is an important arterial anastomosis (figure 20.20b, inset). This anastomosis is located around the hypophyseal fossa of the sphenoid bone (see section 8.2b), which houses the pituitary gland (see section 17.7). The circle is formed from posterior cerebral arteries, posterior communicating arteries (branches of the posterior cerebral arteries), internal carotid arteries, anterior cerebral arteries, and an anterior communicating artery (which connects the two anterior cerebral arteries). This arterial circle equalizes blood pressure in the brain and can provide collateral channels, should one vessel become blocked.

**Venous Drainage**

Three primary pairs of veins drain the neck and head (figure 20.21a). On each side of the head is a vertebral vein and an external jugular vein, both of which empty into the subclavian vein. The third vein is an internal jugular vein, which joins with the subclavian vein to form the brachiocephalic vein. The external jugular primarily drains superficial head and neck structures, while the internal jugular drains blood from the cranial cavity. The right and left brachiocephalic veins join to form the superior vena cava (see figure 20.19).

**Cranial Cavity** Some cranial venous blood is drained by the vertebral veins that extend through the transverse foramina of the cervical vertebrae and drain into the brachiocephalic veins. However, most of the venous blood of the cranium drains through several large veins collectively known as the dural (dūˈrāl) venous sinuses (figure 20.21b). Recall that these large, modified veins are formed between the two layers of dura mater and receive excess cerebrospinal fluid (see section 13.2a). Blood from the dural venous sinus system is drained primarily into the internal jugular vein.

---

**WHAT DID YOU LEARN?**

32 What major arteries supply the head and neck? What primary veins drain these regions?

33 What is the function of the dural venous sinuses?
Figure 20.21 Venous Blood Flow from the Head and Neck. (a) Right lateral view shows the major veins and their tributaries that drain blood from the head and neck. (b) Venous drainage of the cranium from a superior anterolateral view. The dural venous sinuses are labeled in bold.
20.10b Thoracic and Abdominal Walls

**LEARNING OBJECTIVES**

45. Describe the pairs of arteries that supply the thoracic wall.
46. Discuss the arteries that supply the abdominal wall.
47. List veins that drain the thoracic and abdominal walls and delineate their pathways.

The systemic circulation to the walls of the trunk region is primarily via paired vessels that have extensive anastomoses. The venous drainage is more complex than the arterial supply.

**Arterial Supply**

The thoracic and abdominal walls are both supplied by several pairs of arteries (figure 20.22a). A left and right internal thoracic artery emerge from each subclavian artery to supply the anterior thoracic wall and mammary gland. Each internal thoracic artery is located lateral to the sternum and has the following branches: the first six anterior intercostal arteries and a musculophrenic (mūs′kū-lō-fren′ık; phren = diaphragm) artery that divides into anterior intercostal arteries 7–9. The intercostal arteries supply the contents of the intercostal spaces. The internal thoracic artery then becomes the superior epigastric (ep-i-gas′trik; epi = upon, gastric = stomach) artery, which transports blood to the superior abdominal wall.

The inferior epigastric artery, a branch of the external iliac artery, supplies the inferior abdominal wall. This artery anastomoses extensively with the superior epigastric artery.

The supreme intercostal artery is a branch of the costocervical trunk; it branches into the first and second posterior intercostal arteries. Posterior intercostal arteries 3–11 are branches of the descending thoracic aorta. The posterior and anterior intercostal artery emerge from each subclavian artery to supply the anterior thoracic wall and mammary gland. Each internal thoracic artery is located lateral to the sternum and has the following branches: the first six anterior intercostal arteries and a musculophrenic (mūs′kū-lō-fren′ık; phren = diaphragm) artery that divides into anterior intercostal arteries 7–9. The intercostal arteries supply the contents of the intercostal spaces. The internal thoracic artery then becomes the superior epigastric (ep-i-gas′trik; epi = upon, gastric = stomach) artery, which transports blood to the superior abdominal wall.

The inferior epigastric artery, a branch of the external iliac artery, supplies the inferior abdominal wall. This artery anastomoses extensively with the superior epigastric artery.

The supreme intercostal artery is a branch of the costocervical trunk; it branches into the first and second posterior intercostal arteries. Posterior intercostal arteries 3–11 are branches of the descending thoracic aorta. The posterior and anterior intercostal...
arteries anastomose, and each pair forms a horizontal vessel arc that spans a segment of the thoracic wall.

Finally, five pairs of **lumbar arteries** branch from the descending abdominal aorta to supply the posterolateral abdominal wall. In addition, a single **median sacral artery** arises at the bifurcation of the aorta in the pelvic region to supply the sacrum and coccyx.

**Venous Drainage**
Venous drainage of the thoracic and abdominal walls is a bit more complex than the arterial pathways (figure 20.22b). **Anterior intercostal veins**, a musculophrenic vein, and the **superior epigastric vein** all merge into the **internal thoracic vein**, which drains into the brachiocephalic vein.

The **inferior epigastric vein** merges with the **external iliac vein**. The first, second and third **posterior intercostal veins** merge with the **supreme intercostal vein** that drains into the brachiocephalic vein.

The **lumbar veins** and the remaining **posterior intercostal veins** drain into the azygos system of veins along the posterior thoracic wall. The **hemiazygos (hem′-az′-ī-gos)** and **accessory hemiazygos veins** on the left side of the vertebrae drain the left-side veins. The **azygos vein** drains the right-side veins and receives blood from the hemiazygos veins. The azygos vein drains into the superior vena cava. A schematic for venous return can be viewed in figure 20.22c.

***WHAT DID YOU LEARN?***

Does the azygos system, which receives venous blood from the thoracic and abdominal walls, drain into the superior vena cava or the inferior vena cava?
LEARNING OBJECTIVE

48. Describe the vessels that supply and drain the lungs, esophagus, and diaphragm.

The main thoracic organs include the heart, lungs, esophagus, and diaphragm. The vessels supplying the heart wall (coronary arteries) and draining the heart wall (cardiac veins and coronary sinus) were described in section 19.4. The vessels of the other thoracic organs are discussed here (figure 20.23).

Lungs

The bronchi and bronchioles (airways of the lung) and connective tissue of the lungs are supplied by three or four small bronchial arteries that emerge as tiny branches from the anterior wall of the descending thoracic aorta. Left and right bronchial veins (not shown) drain into the azygos system of veins and the pulmonary veins (see figure 23.27). The rest of the lung receives its oxygen via diffusion directly from the alveoli (air sacs) of the lungs.

Esophagus

Several small esophageal (ě-sof′ə-jē′əl, ě′sō-faj′ē-əl) arteries (figure 20.23) emerge from the anterior wall of the descending thoracic aorta and supply the esophagus. Additionally, the left gastric artery forms several esophageal branches that supply the abdominal portion of the esophagus. Esophageal veins drain the esophageal wall and may take either of two routes: into the azygos vein or into the left gastric vein (not shown). The latter merges with the hepatic portal vein (described in section 20.10d).

Diaphragm

Arterial blood is supplied to the diaphragm by paired vessels. Superior phrenic (fren′ik; phren = diaphragm) arteries emerge from the descending thoracic aorta (figure 20.23);
**Figure 20.23 Arterial Blood Supply of Organs of the Thoracic Cavity and Diaphragm.** The blood vessels to the bronchi (airways), esophagus, and diaphragm are shown. The ribs and superficial vessels have been removed from the left side of the body so as to see the deeper vessels.

**WHAT DID YOU LEARN?**

35. What are the systemic arteries that supply oxygenated blood to the lungs? What specific structures of the lung receive the blood?

---

**20.10d Gastrointestinal Tract**

**LEARNING OBJECTIVES**

49. Name the three major arteries that branch from the descending aorta to supply the gastrointestinal tract, and list their major branches.

50. Explain the function of the hepatic portal system.

51. Trace the route of blood from the gastrointestinal tract to the inferior vena cava.

The gastrointestinal (GI) tract receives arterial blood from unpaired arteries that arise from the abdominal aorta. Venous blood is transported through a hepatic portal system before draining into the inferior vena cava.
Arterial Supply to the Abdomen

Three unpaired arteries emerge from the anterior wall of the descending abdominal aorta to supply the GI tract. From superior to inferior, these arteries are the celiac trunk, superior mesenteric artery, and inferior mesenteric artery (figure 20.24). The specific regions that each arterial branch supplies blood to are included in figure 20.24b.

**Celiac Trunk** The **celiac** (sē′lē-ak; koilía = belly) **trunk** is located immediately inferior to the aortic opening (hiatus) of the diaphragm. Three branches emerge from this arterial trunk: (1) the **left gastric artery**, (2) the **splenic artery**, and (3) the **common hepatic artery**. The common hepatic artery divides into the **hepatic artery proper** and the **gastroduodenal** (gas′trō-du′ō-de′nāl) **artery**.

**Figure 20.24 Arterial Supply to the Gastrointestinal Tract and Abdominal Organs.** The celiac trunk, superior mesenteric artery, and inferior mesenteric artery supply most of the abdominal organs. (a) Branches of the celiac trunk supply part of the esophagus, stomach, spleen, pancreas, liver, and gallbladder. (b) Branches of the superior mesenteric and inferior mesenteric arteries primarily supply the intestines.
**Superior Mesenteric Artery** The superior mesenteric (mez-en-ter′ık; mesos = middle, enteron = intestine) artery is located immediately inferior to the celiac trunk. Its branches include 18–20 intestinal arteries, the middle colic artery, the right colic artery, and the ileocolic (il′é-o-kol-ık) artery.

**Inferior Mesenteric Artery** The inferior mesenteric artery emerges approximately 5 centimeters superior to bifurcation of the aorta at about the level of the L₃ vertebral. Its branches include the left colic artery, the sigmoid arteries, and the superior rectal (rek′tal; rectus = straight) artery.

**Venous Return from the Abdomen and the Hepatic Portal System**

Blood that has passed through the capillaries of digestive organs and the spleen, and is then drained by its respective veins, is not directly returned to the inferior vena cava and returned to the heart (figure 20.25). Instead, the blood is transported from the veins of the digestive organs and spleen into a hepatic portal system that drains the blood into the liver before this blood drains to the inferior vena cava.

The hepatic portal system provides the means for the liver to process blood that has passed through the blood vessels of the digestive organs before it is returned to the heart and redistributed throughout the body. This blood is nutrient-rich, is deoxygenated, and may contain harmful substances (e.g., alcohol, toxins) that were absorbed from the digestive organs. The hepatic portal system allows for the most efficient route for handling these absorbed substances. The hepatic portal system also receives products of erythrocyte destruction (see section 18.3b) from the spleen, so that the liver can recycle some of these components.

Within the hepatic portal system, blood from the digestive organs drains into three main venous branches:

1. The splenic vein, a horizontally positioned vein
2. The inferior mesenteric vein, a vertically positioned vein
3. The superior mesenteric vein, another vertically positioned vein located more to the right side of the body

Blood from all three of these veins drains into the hepatic portal vein, which drains blood to the liver (at its inferior portion). Some small veins, such as the left and right gastric veins, drain directly into the hepatic portal vein. The venous blood in the hepatic portal vein flows through the sinusoids of the liver. In these sinusoids, the venous blood mixes with arterial oxygenated blood entering the liver via the hepatic arteries. Thus, deoxygenated but high-nutrient-filled blood from digestive organs and oxygenated blood from the hepatic artery merge and flow within the liver sinusoids (see section 26.3c).

Blood leaves the liver (from its superior portion) through hepatic veins that merge with the inferior vena cava.

**WHAT DID YOU LEARN?**

36. What are the three branches off of the celiac trunk, and which organs do these vessels supply?

37. What are the three primary veins that drain into the hepatic portal vein of the hepatic portal system? What is the function of the hepatic portal system?

**Figure 20.25 Hepatic Portal System.** The hepatic portal system is a network of veins that transports venous blood from the digestive organs and spleen to the liver for processing. Black arrows indicate the direction of blood flow. ©Victor P. Eroschenko
20.10e Posterior Abdominal Organs, Pelvis, and Perineum

LEARNING OBJECTIVES

52. Describe the arteries and veins that supply and drain the adrenal glands, kidneys, and gonads.

53. Name the main vessels associated with the pelvis and perineum.

Branches from the descending abdominal aorta and the internal iliac arteries supply the posterior abdominal organs and pelvis, and veins having the same names drain them (figure 20.26). Several paired arterial branches emerge from the sides of the descending abdominal aorta in addition to the arteries, as described in section 20.10d.

Posterior Abdominal Organs

Each middle suprarenal artery supplies an adrenal gland; each renal artery supplies a kidney; and each gonadal artery supplies a gonad. Subsequently, these organs are drained by veins having the same names as the arteries (figure 20.26a).

Pelvis and Perineum

The aorta divides at its inferior end into the right and left common iliacs. Each common iliac further divides into an internal iliac artery and an external iliac artery. The internal iliac artery is the primary arterial supply to the pelvis and perineum (figure 20.26b). Some branches of the internal iliac artery include the superior and inferior gluteal arteries, the superior vesical artery, the middle rectal artery, the vaginal artery and uterine artery (in females), the internal pudendal artery (pu-den’dāl; pudeo = to feel ashamed) artery, and the obturator (ob’tō-ra-tōr) artery. Remnant vessels of fetal circulation are the medial umbilical ligaments—previously, umbilical arteries that transported blood from the fetus to the placenta (see section 20.12).

The pelvis and perineum are drained by veins with the same names as the supplying arteries (see figure 20.22b). The veins merge with the internal iliac vein that merges with the common iliac vein, which subsequently drains into the inferior vena cava.

WHAT DID YOU LEARN?

38 What arteries supply the kidneys? The adrenal glands? The female uterus?
Figure 20.26 Arterial Supply to the Abdominal Organs, Pelvis, and Perineum. (a) Unpaired arteries directly off the descending abdominal aorta supply blood as illustrated in figure 20.24 (except median sacral). Paired arteries directly off the descending abdominal aorta supply blood to the adrenal glands, kidneys, gonads, and pelvis. (b) Branches of the right internal iliac artery distribute blood to the pelvic organs on the right side of the body. Shown is a female pelvis; a male pelvis would have no uterine artery and, instead of a vaginal artery, would have an inferior vesical artery (not all internal iliac artery branches are labeled).
**20.11 Systemic Circulation: Upper and Lower Limbs**

Blood flow through the upper limbs mirrors blood flow through the lower limbs. Both the upper and lower limbs (1) are supplied by a main arterial vessel: the subclavian artery for the upper limb, the external iliac artery for the lower limb; (2) have their main artery bifurcating at either the elbow or the knee; (3) have arterial and venous arches; and (4) have superficial and deep networks of veins.

**20.11a Upper Limb**

**LEARNING OBJECTIVES**

54. Trace the arteries of the upper limb from the subclavian artery to the fingers.

55. Compare and contrast the superficial venous drainage and the deep venous drainage of the upper limb.

Each upper limb is supplied by a subclavian artery and drained by a subclavian vein. The venous system includes both deep and superficial drainage.

**Arterial Flow to the Upper Limb**

A subclavian artery supplies blood to each upper limb. The left subclavian artery emerges directly from the aortic arch, while the right subclavian artery is a division of the brachiocephalic trunk (see figure 20.22a).

Before extending into the arm, the subclavian artery extends multiple branches to supply parts of the body’s upper region: the vertebral artery, the thyrocervical trunks, the costocervical trunk, and the internal thoracic artery, as described in section 20.10a.

After the subclavian artery passes over the lateral border of the first rib, it is renamed the axillary (ak’sil-är-e) artery (figure 20.27). The axillary artery extends many branches to the shoulder and thoracic region. When the axillary artery passes the inferior border of the teres major muscle, it is renamed the brachial (brā’kē-āl) artery. One of its branches is the deep brachial artery, which supplies blood to most brachial (arm) muscles. In the antecubital region, the brachial artery divides into a radial artery and an ulnar artery. Both arteries supply the forearm and wrist before they anastomose and form two arterial arches in the palm: the deep palmar arch (formed primarily from the radial artery) and the superficial palmar arch (formed primarily from the ulnar artery). Digital arteries emerge from the arches to supply the fingers.

**WHAT DO YOU THINK?**

If the left ulnar artery were cut, would any blood be able to reach the left hand and fingers? Why or why not?

**Venous Drainage of the Upper Limb**

Venous drainage of the upper limb, which converges on the axillary vein and into the subclavian vein, is accomplished through two groups of veins: superficial and deep.

**Superficial Venous Drainage** On the dorsum of the hand, a dorsal venous network (or arch) of veins drains into both the medially located basilic (ba-sil’ik) vein and the laterally located cephalic (se-fal’ik) vein. These veins drain into the axillary vein, and they also have perforating branches that allow them to connect to the deeper veins.

In the cubital region, an obliquely positioned median cubital vein connects the cephalic and basilic veins. The median cubital vein is a common site for venipuncture, in which a vein is punctured with a hollow needle to draw blood or inject fluids and medications. All of these superficial veins are highly variable among individuals and have multiple superficial tributaries draining into them.

**Deep Venous Drainage** The digital veins and deep and superficial palmar venous arches drain into pairs of radial veins and ulnar veins that run parallel to arteries of the same name. At the level of the antecubital region, the radial and ulnar veins merge to form a pair of brachial veins that are positioned alongside the brachial artery. Brachial veins and the basilic vein merge to form the axillary vein.
Superior to the lateral border of the first rib, the axillary vein is renamed the subclavian vein. When the subclavian vein and internal jugular veins of the neck merge, they form the brachiocephalic vein. As we have seen, the left and right brachiocephalic veins form the superior vena cava (see figure 20.19b).

**WHAT DID YOU LEARN?**

39 What is the sequence of vessels from the subclavian artery to the digital artery of the thumb?

40 What are the primary superficial veins of the upper limb?


20.11b Lower Limb

LEARNING OBJECTIVES

56. Trace the arteries of the lower limb from the external iliac artery to the toes.
57. Compare and contrast the superficial venous drainage and the deep venous drainage of the lower limb.

The arterial and venous blood flow of the lower limb is very similar to that of the upper limb. As we discuss lower limb blood flow, compare it with that of the upper limb.

Arterial Flow to the Lower Limb

The main arterial supply for the lower limb is the external iliac artery, which is a branch of the common iliac artery (figure 20.28a). The external iliac artery is located inferior to the inguinal ligament, where it is renamed the femoral (fem′o-rāl) artery. The deep femoral artery (or deep artery of the thigh) emerges from the femoral artery to supply the hip joint (via medial and lateral femoral circumflex arteries) and many of the thigh muscles, before traversing posteromedially along the thigh. When the femoral artery enters the popliteal fossa, it is renamed the popliteal (pop-lit′ē-āl, pop-li-tē′ēl) artery. The popliteal artery supplies the knee joint and muscles in this region.

The popliteal artery divides into an anterior tibial artery, which supplies the anterior compartment of the leg, and a posterior tibial artery, which supplies the posterior compartment of the leg. The posterior tibial artery extends a branch called the fibular artery, which supplies the lateral compartment leg muscles.

The posterior tibial artery continues to the plantar side of the foot, where it branches into medial and lateral plantar arteries. The anterior tibial artery crosses over the anterior surface of the ankle, where it is renamed the dorsalis pedis artery (dorsal artery of the foot). The dorsalis pedis artery and a branch of the lateral plantar artery unite to form the plantar arterial arch of the foot. Digital arteries extend from the plantar arch and supply the toes.

Venous Drainage of the Lower Limb

Venous drainage of the lower limb is similar to that of the upper limb in that there are both superficial and deep veins that drain the lower limb (figure 20.28b).

Superficial Venous Drainage On the dorsum of the foot, a dorsal venous arch drains into the great saphenous (sāf′ē-nūs, sā-fē′nūs) vein and the small saphenous vein. The great saphenous vein originates in the medial ankle and extends adjacent to the medial surface of the entire lower limb before it drains into the femoral vein. The small saphenous vein extends adjacent to the lateral ankle and then extends within the posterior calf, before draining into the popliteal vein. These superficial veins have perforating branches that connect to the deeper veins. If the valves in these veins (or the perforating branches) become incompetent, varicose veins develop. (See Clinical View 20.7: “Varicose Veins”).

Deep Venous Drainage The digital veins and deep veins of the foot drain into pairs of medial and lateral plantar veins. These veins and a pair of fibular veins drain into a pair of posterior tibial veins. On the dorsum of the foot and ankle, deep veins drain into a pair of anterior tibial veins, which traverse alongside the anterior tibial artery. The anterior and posterior tibial veins merge to form a popliteal vein that curves to the anterior portion of the thigh and is renamed the femoral vein. Once this vein passes superiorly to the inguinal ligament, it is renamed the external iliac vein. The external and internal iliac veins merge in the pelvis, forming the common iliac vein. Left and right common iliac veins then merge to form the inferior vena cava.

WHAT DID YOU LEARN?

41 Can you trace one pathway that blood may be transported through from the external iliac artery to the digital arteries?
42 How do the great saphenous vein and small saphenous vein compare in terms of their anatomic position and length?
**Figure 20.28 Vascular Supply to the Lower Limb.** The external iliac artery transports oxygenated blood to the lower limb; veins merge to return deoxygenated blood to the heart. (a) Anterior and posterior views of arteries distributed throughout the lower limb. (continued on next page)
Figure 20.28 Vascular Supply to the Lower Limb (continued). (b) Anterior and posterior views of the superficial and deep veins that return blood from the lower limb.
20.12 Comparison of Fetal and Postnatal Circulation

The cardiovascular system of the fetus is structurally and functionally different from that of the newborn. Whereas the fetus receives oxygen and nutrients directly from the mother through the placenta, the newborn’s postnatal cardiovascular system must be independent. Additionally, because the fetal lungs are not functional, the blood pressure in the pulmonary arteries and right side of the heart is greater than the pressure in the left side of the heart. Finally, several fetal vessels help shunt blood directly to the organs in need and away from the organs that are not yet functional. As a result, the fetal cardiovascular system has some structures that are modified or that cease to function once the baby is born.

20.12a Fetal Circulation

LEARNING OBJECTIVE

58. Trace the pathway of blood circulation in the fetus.

The fetal circulatory route is listed here and shown in figure 20.29:

1. Oxygenated blood from the placenta enters the body of the fetus through the **umbilical vein**.
2. The blood from the umbilical vein is shunted away from the liver and directly toward the inferior vena cava through the **ductus venosus** (dŭk′tŭs vē-nō’sŭs).
3. Oxygenated blood in the ductus venosus mixes with deoxygenated blood in the inferior vena cava.
4. Blood from the superior and inferior venae cavae empties into the right atrium.
5. Because pressure is greater on the right side of the heart than on the left side, most of the blood is shunted from the right atrium to the left atrium via the **foramen ovale**. This blood flows into the left ventricle and then is pumped out through the aorta.
6. A small amount of blood enters the right ventricle and then the pulmonary trunk, but much of this blood is shunted from the pulmonary trunk to the aorta through a vessel detour called the **ductus arteriosus** (ar-tĕr′ē-ŏ’sŭs).
7. Blood is transported to the rest of the body, and the deoxygenated blood returns to the placenta through a pair of **umbilical arteries**.
8. Nutrient and gas exchange occurs at the **placenta** (see section 29.2e), and the cycle repeats.

At birth, the fetal circulation begins to change into the postnatal pattern. When the baby takes its first breath, pulmonary resistance drops, and the pulmonary arteries dilate. As a result, pressure on the right side of the heart decreases so that the pressure is greater on the left side of the heart, which handles the systemic circulation.

WHAT DID YOU LEARN?

43. List the five structures of fetal circulation, and identify the function of each.

20.12b Postnatal Changes

LEARNING OBJECTIVE

59. Describe the changes that occur after the baby is born and must utilize the pulmonary circulation.

The postnatal changes occur as follows:

- The umbilical vein and umbilical arteries constrict and become nonfunctional. They turn into the **round ligament of the liver** (or ligamentum teres) (see figure 26.19b) and the **medial umbilical ligaments** (see figure 20.16), respectively.
- The ductus venosus ceases to be functional and constricts, becoming the **ligamentum venosum** (see figure 26.19b).
### CHAPTER SUMMARY

| 20.1 Structure and Function of Blood Vessels | • Arteries take blood away from the heart, capillaries are responsible for gas and nutrient exchange, and veins take blood toward the heart. |
| 20.1a General Structure of Vessels | • Arteries and veins have a tunica intima (innermost layer), a tunica media (middle layer), and a tunica externa (outermost layer). • Capillaries have a tunica intima, composed of an endothelial layer and a basement membrane only. |
| 20.1b Arteries | • Arteries progressively branch into elastic arteries, muscular arteries, and arterioles. |
| 20.1c Capillaries | • Capillaries, the smallest blood vessels, connect arterioles with venules. Gas and nutrient exchange occurs in the capillaries. • The three types of capillaries are continuous capillaries, fenestrated capillaries, and sinusoids, which have different degrees of permeability and are arranged in capillary beds. |
| 20.1d Veins | • Venules are small veins that merge into larger veins. One-way valves prevent blood backflow in veins. • Blood pressure is low in the veins, which act as reservoirs and hold about 55% of the body’s blood at rest. |
| 20.1e Pathways of Blood Vessels | • Blood vessels may be arranged in simple pathways (artery → capillary bed → veins → heart) or in alternative pathways, which include anastomoses and portal venous systems. |
| 20.2 Total Cross-Sectional Area and Blood Flow Velocity | • The velocity of blood flow is inversely related to the total cross-sectional area of the blood vessels. • Blood flows slowest in the capillaries, increasing efficiency of nutrient and gas exchange. |
| 20.3 Capillary Exchange | • Materials may pass through the capillary walls via diffusion, vesicular transport, and bulk flow. |
| 20.3a Diffusion and Vesicular Transport | • Small solutes (e.g., oxygen, carbon dioxide, glucose, ions) move between blood and interstitial fluid via diffusion. • Certain solutes that are relatively large (e.g., insulin) are transported via vesicular transport. |
| 20.3b Bulk Flow | • Bulk flow is the net filtration and reabsorption that occur at the capillary level due to hydrostatic pressure and osmotic pressure. |
| 20.3c Net Filtration Pressure | • The net filtration pressure is the difference between the net hydrostatic pressure and the net colloid osmotic pressure. • The net filtration pressure is positive at the arterial end of the capillary, resulting in filtration, and is negative at the venous end of the capillary, resulting in reabsorption. |
| 20.3d Role of the Lymphatic System | • Lymph vessels reabsorb interstitial fluid that is not picked up at the venous end of the blood capillaries. Lymph vessels eventually return this fluid back to the venous circulation. |
| 20.4 Local Blood Flow | • Perfusion is the specific amount of blood per time per gram of tissue. • Local blood flow is dependent upon the degree of vascularization of the tissue, the myogenic response, local regulatory factors, and total blood flow. |
| 20.4a Degree of Vascularization and Angiogenesis | • The degree of vascularization is tissue dependent, but the amount of vascularization may increase over a time through angiogenesis (the formation of new blood vessels) or decrease through regression. |
Veins from the head, neck, upper limbs, and thoracic and abdominal walls merge to form the superior vena cava. The descending aorta (divided into the thoracic and abdominal aorta) bifurcates into the left and right common iliac arteries. Three branches of the aortic arch are the brachiocephalic trunk, the left common carotid, and the left subclavian. Oxygenated blood is pumped from the left ventricle through the ascending aorta; the coronary arteries branch from the ascending aorta.

The pulmonary circulation is a smaller circuit and has lower blood pressure than the systemic circulation. Blood is pumped from the right ventricle to the lungs and back to the left side of the heart. Both total blood flow and distribution of blood change during exercise. Atrial natriuretic peptide (ANP) increases urine output, which decreases blood volume and causes vasodilation to lower blood pressure. Both antidiuretic hormone and aldosterone decrease urine output to maintain blood volume and blood pressure. The renin-angiotensin system involves the activation of angiotensinogen to angiotensin II by the enzymes renin and angiotensin-activating enzyme (ACE). Angiotensin II increases resistance and blood volume both directly and through the release of aldosterone and antidiuretic hormone (ADH).

Both antidiuretic hormone and aldosterone decrease urine output to maintain blood volume and blood pressure. Atrial natriuretic peptide (ANP) increases urine output, which decreases blood volume and causes vasodilation to lower blood pressure.

Mean arterial pressure (MAP) is the average pressure that pushes the blood from the heart to the tissues, and it is measured as the diastolic pressure plus one-third of the pulse pressure. Blood pressure in the capillaries is approximately 40 mm Hg on the arterial end and about 20 mm Hg on the venule end. Venous blood return is facilitated by valves, the skeletal muscle pump, and the respiratory pump.

Blood pressure is dependent upon cardiac output, peripheral resistance, and blood volume, which are regulated by the short-term mechanisms of the nervous system, long-term mechanisms of the endocrine system, or both.

Neural regulation of blood pressure involves baroreceptors located in the aorta and carotid arteries that detect changes in stretch of blood vessel walls. In response, nerve signals relayed along sensory neurons to the cardiovascular center are altered. Subsequently, motor output to both the heart and blood vessels is changed. Chemoreceptor reflexes regulate blood pressure in response to changing blood chemistry levels.

The myogenic response involves both contraction of smooth muscle in blood vessel walls in response to an increase in stretch and relaxation of smooth muscle in blood vessel walls in response to a decrease in stretch to maintain a constant blood flow. Local, short-term regulation of blood flow is altered by autoregulation (which is the process of regulating local blood flow into a tissue by the tissue itself in response to vasoactive molecules or ions produced due to its changing metabolic needs) or in response to molecules released from either damaged tissue or as part of the body’s defense system.

Total blood flow is relatively constant at rest, is the same as cardiac output (about 5.25 L/min), and may increase substantially during exercise to make additional blood available to tissues.

Blood flow is directly related to blood pressure and inversely related to resistance. Resistance is defined as the amount of friction the blood experiences as it is transported through the blood vessels. Increased blood viscosity and increased vessel length both cause an increase in peripheral resistance. Vasoconstriction causes an increase in peripheral resistance; vasodilation causes a decrease in peripheral resistance.

Blood flow (F) is proportional to the blood pressure gradient (∆P) divided by the resistance (R) in the blood vessels: 

\[ F \propto \frac{\Delta P}{R} \]

A greater blood flow occurs with a steeper pressure gradient or lower peripheral resistance; a lesser blood flow occurs with a smaller pressure gradient or greater resistance.

Blood flow is directly related to blood pressure and inversely related to resistance. Resistance is defined as the amount of friction the blood experiences as it is transported through the blood vessels. Increased blood viscosity and increased vessel length both cause an increase in peripheral resistance. Vasoconstriction causes an increase in peripheral resistance; vasodilation causes a decrease in peripheral resistance.

Blood pressure is dependent upon cardiac output, peripheral resistance, and blood volume, which are regulated by the short-term mechanisms of the nervous system, long-term mechanisms of the endocrine system, or both.
### 20.10a Head and Neck
- The common carotid artery supplies most of the blood to the head and neck and divides into the external carotid artery and internal carotid artery.
- The external carotid artery supplies superficial regions of the head and organs of the neck, whereas the internal carotid artery supplies the brain and orbits.
- Blood from the cranium drains via the vertebral veins and the dural venous sinuses, which primarily drain into the internal jugular veins. Venous return is via the internal and external jugular veins.

### 20.10b Thoracic and Abdominal Walls
- Two internal thoracic arteries, as well as other arteries, supply the thoracic and abdominal walls.
- Venous return from the thoracic and abdominal walls is complex and involves the azygos system of veins.

### 20.10c Thoracic Organs
- The lungs are supplied by bronchial arteries branching from the descending thoracic aorta; they are drained by bronchial veins.
- The esophagus receives blood from the esophageal arteries that branch from the aorta and from the esophageal branches of the left gastric artery; it is drained via the esophageal veins.
- The diaphragm is supplied by phrenic arteries and drained by the phrenic veins.

### 20.10d Gastrointestinal Tract
- The three major unpaired arteries from the descending abdominal aorta that supply the abdominal organs are the celiac trunk, the superior mesenteric artery, and the inferior mesenteric artery.
- The hepatic portal vein receives oxygen-poor but nutrient-rich blood from the gastrointestinal (GI) organs and spleen; this vessel takes this blood to the liver for processing. Blood leaves the liver via the hepatic veins.

### 20.11 Systemic Circulation: Upper and Lower Limbs
- The upper and lower limbs are each supplied by a single artery that branches into multiple vessels. Both deep and superficial veins drain the limbs.

#### 20.11a Upper Limb
- The upper limb is supplied by the subclavian artery and its branches and is drained into the subclavian vein.

#### 20.11b Lower Limb
- The lower limb is supplied by the external iliac artery and is drained by the external iliac vein.

### 20.12 Comparison of Fetal and Postnatal Circulation
- In the fetus, oxygenated blood is supplied by the umbilical vein from the placenta, and deoxygenated blood leaves through a pair of umbilical arteries.
- The fetal cardiovascular system bypasses the liver via the ductus venosus and bypasses the pulmonary circulation via the foramen ovale and ductus arteriosus.

### 20.12b Postnatal Changes
- In the newborn, the umbilical vein and arteries degenerate, and the ductus venosus, foramen ovale, and ductus arteriosus close.
4. Which of the following decreases perfusion of a tissue?
   a. decreased total blood flow
   b. vasodilator
   c. angiogenesis
   d. increased carbon dioxide, decreased pH (increased H⁺), and low O₂

5. A(n) ________ is a type of vessel with the smallest pressure gradient that must be overcome by contraction of skeletal muscles and breathing.
   a. artery
   b. vein
   c. capillary
   d. sinusoid

6. An increase in ________ will result in an increase in blood flow to an area.
   a. vessel length
   b. vessel diameter
   c. blood viscosity
   d. the number of formed elements

7. Which of the following is accurate?
   a. Total blood flow increases with a steeper pressure gradient (assuming resistance stays the same).
   b. Total blood flow decreases with increased resistance (assuming cardiac output stays the same).
   c. Total blood flow is significant in maintaining adequate perfusion of all tissues.
   d. All of these are correct.

8. Velocity of blood flow is the slowest in
   a. muscular arteries.
   b. capillaries.
   c. veins.
   d. elastic arteries.

9. Blood pressure is regulated by the
   a. cardiac center.
   b. vasomotor center.
   c. hormones.
   d. All of these are correct.

10. Choose the correct pathway that blood flows through in the upper limb arteries.
    a. subclavian → axillary → ulnar → radial → brachial
    b. subclavian → axillary → brachial → cephalic → basilic
    c. subclavian → ulnar → brachial → radial
    d. subclavian → axillary → brachial → radial and ulnar

11. List and describe the three tunics found in most blood vessels.

12. Compare and contrast arteries and veins with respect to function, tunic size, lumen size, and blood pressure.

13. Explain the difference between hydrostatic and osmotic pressures. How do these pressures change from the arteriole end of a capillary to the venule end of a capillary?

14. Write the formula for determining net filtration pressure in the capillaries.

15. Describe the relationship of vessel radius, vessel length, blood viscosity, and blood pressure to blood flow.

16. Explain how it is possible for the sympathetic division to cause vasoconstriction in most blood vessels but vasodilation in coronary and skeletal muscle blood vessels.

17. Briefly explain how changes in cardiac output, resistance, and blood volume influence blood pressure.

18. Compare how the cardiac center and vasomotor center regulate blood pressure and blood flow.

19. Compare the systemic circulation and pulmonary circulation. Discuss the function of arteries and veins in each system.

20. What postnatal changes occur in the heart and blood vessels? Why do these occur?

---

**Can You Apply What You’ve Learned?**

1. If a patient has cirrhosis of the liver and is unable to produce sufficient albumin and other plasma proteins, then what variable is changed in capillary exchange, and what is the effect?
   a. There is no change in the capillary exchange process.
   b. Hydrostatic pressure in the blood decreases, and fluid remains in the blood.
   c. Colloid osmotic pressure in the capillary increases, and blood volume increases in the blood vessels.
   d. Colloid osmotic pressure in the capillary decreases, and fluid remains in the interstitial fluid, potentially causing edema.

2. Arlene heads to the gym and initiates a vigorous exercise regimen. Which hormone will not be released?
   a. epinephrine
   b. atrial natriuretic peptide
   c. angiotensin II
   d. norepinephrine

3. After her workout, Arlene lies down on a mat to stretch out her leg muscles. She stands up suddenly after stretching and feels a bit light-headed. However, the light-headed feeling passes quickly. What physiologic process occurred that resulted in the passing of her light-headed feeling?
   a. The aortic bodies detected an increase in blood pressure in the head and initiated a chemoreceptor reflex that decreased blood pressure.
   b. The carotid bodies detected low CO₂ and high O₂ levels from exercising and stimulated the vasomotor center to vasoconstrict the vessels of the head and neck.
   c. Only α receptors in the head and neck initially were being stimulated, resulting in the light-headed feeling.
   d. The baroreceptors within the carotid detected decreased stretch in the carotid vessel wall and initiated an autonomic reflex to increase blood flow to the head and neck.

4. Over a period of 6 months, Harold loses 40 pounds. When Harold next visits his doctor, he discovers that his blood...
pressure levels have fallen too. Which of the following best explains why Harold’s blood pressure has dropped?

a. When fat is lost, the extra length in blood vessels supplying the adipose connective tissue is lost too. Decreased blood vessel length has resulted in decreased blood pressure.

b. Most of the fat that Harold lost was around his thoracic organs, which compressed these organs. By losing the weight, he removed this compressive force.

c. The resistance in the blood vessels increased due to the fat loss, resulting in decreased blood pressure.

d. The fat previously constricted the blood vessels. When Harold lost the fat, the blood vessels were allowed to dilate, and thus blood pressure was reduced.

5. Alejandro was hit by a car, which resulted in massive injury and bleeding to his right foot. You realize that you have to compress a lower limb artery so that Alejandro will not lose too much blood. Which vessel, if compressed, will completely stop the flow of blood to the foot?

a. anterior tibial artery

b. posterior tibial artery

c. deep femoral artery

d. popliteal artery

Can You Synthesize What You’ve Learned?

1. Your patient is Thomas, a 50-year-old man who rarely exercises, is overweight, and only occasionally eats healthy meals, which put him at risk for atherosclerosis. Explain to him the relationship between atherosclerosis and high blood pressure.

2. Arteries tend to have a lot of vascular anastomoses around body joints, such as the elbow and knee. Can you think of a reason this would be beneficial?

3. Explain why an overweight individual with high blood pressure is advised to lose weight. Include in your response the relationship of blood vessel length, resistance, and blood pressure.
It is not uncommon for young children to develop tonsillitis—a condition in which the tonsils become inflamed and enlarged. Often, the lymph nodes in the neck also are swollen, and the spleen may become enlarged. You might initially be curious about why the lymph nodes and the spleen are also affected when a child has tonsillitis. All of these structures—the tonsils, lymph nodes, and spleen—are components of the lymphatic system, and these structures function in helping the immune system defend the body against potentially harmful agents. The inflammation and enlargement that occur in lymphatic structures are signs that these organs are actively engaged in defending the body against potentially harmful substances.

The lymphatic system has two significant functions, and both provide support to other body systems: (1) The lymphatic system transports and houses lymphocytes and other immune cells that help the immune system defend against potentially harmful substances, and (2) the lymphatic system aids the cardiovascular system by returning excess fluid to venous blood to maintain fluid balance, blood volume, and blood pressure. Interestingly, the lymphatic system has no unique function of its own.

Here, we describe lymph vessels and the absorption of excess fluid from the interstitial space and then discuss lymphatic organs, including lymph nodes and the spleen. Integrated within the chapter are brief descriptions of some of the common malfunctions of the lymphatic system. The details of the immune system are described in chapter 22.
Figure 21.1 Lymphatic System. The lymphatic system is composed of both lymph vessels and lymphatic tissue and organs. Lymphatic tissue and organs are organized into primary and secondary lymphatic structures.
21.1 Lymph and Lymph Vessels

The lymphatic (lim-fat’ık) system is composed of (1) lymph vessels and (2) lymphatic tissues and organs (figure 21.1). Lymph is the fluid transported within lymph vessels. We begin by describing the formation and characteristics of lymph. We then discuss its transport through progressively larger lymph vessels until the lymph is returned to the cardiovascular system. Note that the term lymph vessel is used to indicate any type of vessel of the lymphatic system (e.g., lymphatic capillary, lymphatic vessel, lymphatic trunk), whereas the term lymphatic vessels is used when referring specifically to the vessels between the lymphatic capillaries and lymphatic trunks.

21.1a Lymph and Lymphatic Capillaries

LEARNING OBJECTIVES

1. Describe lymph and its contents.
2. Discuss the location and anatomic structure of lymphatic capillaries.
3. Explain how fluid enters lymphatic capillaries.

Lymph originates as interstitial fluid surrounding tissue cells; it moves passively into the lymphatic capillaries due to a hydrostatic pressure gradient. Lymphatic capillaries merge to form larger lymph vessels.

Characteristics of Lymph

Approximately 15% of the fluid that enters the interstitial space surrounding the cells is not reabsorbed back into the blood capillaries during capillary exchange (see section 20.3d). This interstitial fluid amounts to about 3 liters daily and is normally absorbed into lymphatic capillaries.

Once inside the lymph vessels, the interstitial fluid is called lymph (limf; lympha = clear spring water). The components of lymph include water, dissolved solutes (e.g., ions), a small amount of protein (approximately 100 to 200 grams that leaked into the interstitial space during capillary exchange), sometimes foreign material that includes both cell debris and pathogens, and perhaps metastasized cancer cells (see Clinical View 21.1: “Metastasis”).

Lymphatic Capillaries

The lymph vessel network begins with lymphatic capillaries, which are the smallest lymph vessels (figure 21.2). Lymphatic capillaries are microscopic, closed-ended vessels that absorb interstitial fluid. They are interspersed throughout areolar connective tissue among capillary networks, except those within the red bone marrow and avascular tissues (such as epithelia). In addition, recent research has found lymph vessels associated with the dural venous sinuses that drain blood away from the brain.

A lymphatic capillary resembles the anatomic structure of a blood capillary in that its wall is composed of an endothelium (figure 21.2b). However, lymphatic capillaries are typically larger in diameter than blood capillaries, lack a basement membrane, and have overlapping endothelial cells. These overlapping endothelial cells act as one-way flaps to allow fluid to enter the lymphatic capillary but
The gastrointestinal (GI) tract, called lymphatic capillaries located within the gastrointestinal (GI) tract, called lacteals (lak′tē-āl; lactis = milk), allow for the absorption of lipid-soluble substances from the GI tract, a concept detailed in section 26.4c.

Movement of Lymph into Lymphatic Capillaries

The driving force to move fluid into the lymphatic capillaries is an increase in hydrostatic pressure (see section 4.3b) within the interstitial space. Interstitial hydrostatic pressure rises as additional fluid is filtered from the blood capillaries (see section 20.3b). This pressure exerted by interstitial fluid at the margins of the lymphatic capillary endothelial cells “pushes” interstitial fluid into the lymphatic capillary lumen when the interstitial fluid hydrostatic pressure becomes greater than the lymph hydrostatic pressure. The higher the interstitial fluid pressure, the greater the amount of fluid that enters the lymphatic capillary. The anchoring filaments extending between lymphatic capillary cells and the surrounding tissue prevent the collapse of the lymphatic capillaries as pressure exerted by the interstitial fluid increases.

The pressure exerted by lymph after it enters the lymphatic capillary forces the endothelial cells of these vessels to close. Thus, lymph becomes “trapped” within the lymphatic capillary and cannot be released back into the interstitial space. Lymph is then transported through a network of increasingly larger vessels that include (in order) lymphatic capillaries, lymphatic vessels, lymphatic trunks, and lymphatic ducts.

**WHAT DID YOU LEARN?**

1. What substances typically are absorbed from the interstitial space into lymphatic capillaries?
2. How does fluid enter and become “trapped” in the lymphatic capillaries?

**LEARNING STRATEGY**

Fluid entry into a lymphatic capillary is analogous to the movement of the entryway door to your house or apartment. Imagine that the door is unlocked and the knob is turned. Putting pressure on the outside of the door (like the pressure of interstitial fluid on the outside of the lymphatic capillary wall) causes it to open to the inside so you can enter. Once inside, pressure applied to the inside surface of the door (or fluid pressure against the inside of the lymphatic capillary surface) causes it to close.

**21.1b Lymphatic Vessels, Trunks, and Ducts**

**LEARNING OBJECTIVES**

4. Explain the mechanisms that move lymph through lymphatic vessels, trunks, and ducts.
5. Name the five types of lymphatic trunks and the regions of the body from which they drain lymph.
6. Describe the regions that are drained by the right lymphatic duct and by the thoracic duct.

After lymph enters the lymphatic capillaries, it continues to flow into increasingly larger lymphatic vessels, trunks, and ducts. Ultimately, the lymph empties into the venous circulation.

**Lymphatic Vessels**

Lymphatic capillaries merge to form larger structures that are called lymphatic vessels (figure 21.1). Superficial lymphatic vessels are generally positioned adjacent to the superficial veins of the body; in contrast, deep lymphatic vessels are next to deep arteries and veins. Lymphatic vessels resemble small veins because both contain all three vessel tunics (intima, media, and externa) and have valves within their lumen. Valves are required to prevent lymph from pooling in these vessels and help prevent lymph backflow because the lymphatic vessel network is a low-pressure system. These valves are especially important in areas where lymph flow is against the direction of gravity, such as in the lower limbs.

The lymphatic system lacks a pump and, thus, relies on other mechanisms to move lymph through its vessels. These include (1) contraction of nearby skeletal muscles in the limbs (skeletal muscle pump) and the respiratory pump in the torso, which is similar to how blood movement is assisted through the venous circulation (see section 20.5a), (2) rhythmic contraction of smooth muscle within the walls of larger lymph vessels (trunks and ducts), which narrows the lumen and squeezes the lymph within the lymph vessel, and (3) pulsatile movement of blood in nearby arteries. All of these mechanisms are dependent upon valves within lymph vessels, which prevent the backflow of lymph, causing the lymph to move in one direction to be returned to venous blood circulation.

Some lymphatic vessels connect directly to lymphatic organs called lymph nodes. Foreign or pathogenic material is filtered as lymph passes through lymph nodes. They are arranged in a series along lymph vessels and are described in more detail in section 21.4a.

**Lymphatic Trunks**

Lymphatic vessels drain into lymphatic trunks on both the right and left sides of the body (figure 21.3). Each lymphatic trunk removes lymph from a specific major body region:

- **Jugular trunks** drain lymph from both the head and neck.
- **Subclavian trunks** remove lymph from the upper limbs, breasts, and superficial thoracic wall.
- **Bronchomediastinal trunks** drain lymph from deep thoracic structures.
- A single **intestinal trunk** drains lymph from most abdominal structures.
- **Lumbar trunks** drain lymph from the lower limbs, abdominopelvic wall, and pelvic organs.
Lymphatic System

Chapter Twenty-One

Figure 21.3 Lymphatic Trunks and Ducts. Lymph drains from lymphatic trunks into two lymphatic ducts (right lymphatic duct and thoracic duct) that empty into the junctions of the right jugular and right subclavian veins and left jugular and left subclavian veins, respectively. (a) An anterior view of the posterior thoracic wall illustrates the major lymphatic trunks and ducts and the site of lymph drainage into the venous circulation of the cardiovascular system. (b) Areas of lymph drainage into the right lymphatic duct and the thoracic duct.

WHAT DO YOU THINK?
1. Predict what may occur with respect to lymphatic drainage if a group of lymph nodes and their associated lymph vessels are surgically removed, as might occur when breast cancer has metastasized.

Lymphatic Ducts

Lymphatic trunks drain into the largest lymph vessels called lymphatic ducts. There are two lymphatic ducts: the right lymphatic duct and the thoracic duct. Both of these convey lymph back into the venous blood circulation.

Right Lymphatic Duct    The right lymphatic duct is located near the right clavicle. It receives lymph from the lymphatic trunks that drain the following areas: (1) the right side of the head and neck, (2) the right upper limb, and (3) the right side of the thorax. It returns the lymph into the junction of the right subclavian vein and the right internal jugular vein. Thus, the right lymphatic duct drains lymph from the upper right quadrant of the body (figure 26.3b).

Thoracic Duct    The larger of the two lymphatic ducts is the thoracic duct. It has a length of about 37.5 to 45 centimeters (15 to 18 inches) and extends from the diaphragm to the junction of the left subclavian and left jugular veins. The thoracic duct drains lymph from the remaining areas of the body (left side of the head and neck, left upper limb, left thorax, all of the abdomen, and both lower limbs).

At the base of the thoracic duct and anterior to the L₁ vertebra is a rounded, saclike structure called the cisterna chyli (sis-ter′n kī′lī). The cisterna chyli gets its name from the milky, lipid-rich lymph called chyle (kīl; chylōs = juice), which it receives from vessels that drain the small intestine of the gastrointestinal (GI) tract (see section 26.4c). Both the intestinal trunk and the left and right lumbar trunks drain into the cisterna chyli. The thoracic duct extends superiorly from the cisterna chyli and lies directly anterior to the vertebral bodies. It passes through the aortic opening of the diaphragm, then ascends to the left of the vertebral body midline.

WHAT DID YOU LEARN?
3. What mechanisms are used to assist lymph movement through lymph vessels?
4. Which major body regions drain lymph to the right lymphatic duct?
The lymphatic system is made up of specialized lymphatic tissue and organs. These tissues and organs include red bone marrow, the thymus, lymph nodes, the spleen, tonsils, lymphatic nodules, and MALT (mucosa-associated lymphatic tissue) (see figure 21.1; diffuse lymphatic nodules not shown).

Lymphatic system tissues and organs are categorized as either primary or secondary lymphatic structures:

- **Primary lymphatic structures** are involved in the formation and maturation of lymphocytes. Both the red bone marrow and thymus are considered primary lymphatic structures.
- **Secondary lymphatic structures** are not involved in lymphocyte formation; instead, they house both lymphocytes and other immune cells following their formation. Secondary lymphatic structures are the sites where an immune response is initiated (see section 22.6). The major secondary lymphatic structures include the lymph nodes, spleen, tonsils, lymphatic nodules, and MALT.

Table 21.1 provides details on the function and location of each component of the lymphatic system:

<table>
<thead>
<tr>
<th>Component</th>
<th>Primary or Secondary Lymphatic Structures</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red bone marrow</td>
<td>Primary</td>
<td>Spongy bone of selected bones</td>
<td>Formation of all formed elements; site of B-lymphocyte maturation</td>
</tr>
<tr>
<td>Thymus</td>
<td>Primary</td>
<td>Superior mediastinum (in adults); anterior and superior mediastinum (in children)</td>
<td>Site of T-lymphocyte maturation and differentiation</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>Secondary</td>
<td>Along length of lymphatic vessels; clusters in axillary, inguinal, and cervical regions</td>
<td>Filter lymph; where immune response is initiated against a substance in the lymph</td>
</tr>
<tr>
<td>Spleen</td>
<td>Secondary</td>
<td>Left upper quadrant of abdomen, near 9th–11th ribs, “wraps” partially around stomach</td>
<td>Filters blood; where immune response is initiated against a substance in the blood; removes aged erythrocytes and platelets; serves as erythrocyte and platelet reservoir</td>
</tr>
<tr>
<td>Tonsils</td>
<td>Secondary</td>
<td>Oral cavity and pharynx (throat)</td>
<td>Protect against inhaled and ingested substances</td>
</tr>
<tr>
<td>Lymphatic nodules</td>
<td>Secondary</td>
<td>Every body organ and wall of appendix</td>
<td>Protect body organs</td>
</tr>
<tr>
<td>MALT (mucosa-associated lymphatic tissue)</td>
<td>Secondary</td>
<td>Clusters of lymphatic nodules within walls of gastrointestinal (GI), respiratory, urinary, and reproductive tracts</td>
<td>Protects mucosal membranes against foreign substances</td>
</tr>
</tbody>
</table>
21.3 Primary Lymphatic Structures

The general structure and function of the primary lymphatic structures are described in this section. These include the red bone marrow and the thymus.

21.3a Red Bone Marrow

LEARNING OBJECTIVES

8. Describe the location and general function of red bone marrow.
9. Identify the two major types of lymphocytes.

Red bone marrow is located within trabeculae in portions of spongy bone within the skeleton. In adults, these include the flat bones of the skull, the vertebrae, the ribs, the sternum, the ossa coxae, and proximal epiphyses of each humerus and femur (see section 7.2d).

Red bone marrow is responsible for hemopoiesis (or hematopoiesis), which is the production of formed elements. Hemopoiesis is described in detail in section 18.3a. Recall that the formed elements include erythrocytes, platelets, granulocytes (neutrophils, eosinophils, and basophils), and agranulocytes (monocytes and lymphocytes) (figure 21.4). Two of the major types of lymphocytes are B-lymphocytes (also called B-cells) and T-lymphocytes (also called T-cells). Most formed elements move directly from the red bone marrow into the blood following hemopoiesis. Unlike the other formed elements, T-lymphocytes must migrate to the thymus to complete their maturation. The functions of both B-lymphocytes and T-lymphocytes are described in detail in chapter 22. The “T” in the name T-lymphocytes originates from the requirement of these cells to complete their maturation in the thymus.

WHAT DID YOU LEARN?

6. Why is red bone marrow considered a primary lymphatic structure?

LEARNING STRATEGY

Lymphocytes can be identified according to the tissue or organ where they mature. T-lymphocytes mature in the thymus. B-lymphocytes mature in the bone marrow. However, the “B” in the name B-lymphocytes did not originate because B-lymphocytes develop in the bone marrow. Rather, these cells were first discovered in chickens and were named for where they develop in chickens—in the bursa of fabricius (a lymphatic structure in birds). Humans lack the bursa of fabricius, and B-lymphocytes complete their maturation in the bone marrow.

21.3b Thymus

LEARNING OBJECTIVE

10. Describe the structure and general function of the thymus.

The thymus (thî′mûs) is a bilobed organ that is located in the superior mediastinum and functions in T-lymphocyte maturation (figure 21.5). In infants and young children, the thymus is quite large and extends into the anterior mediastinum as well. The thymus continues to grow until puberty, when it reaches a maximum weight of 30 to 50 grams (approximately 1/10 of a pound). Cells within the thymus begin to regress after it reaches this size. Thereafter, much of the thymic tissue is replaced by adipose connective tissue (figure 21.5c).
**Figure 21.5 Thymus.** (a) The thymus is a bilobed lymphatic organ that is most prominent in children. (b) A micrograph of a child’s thymus reveals the arrangement of the outer cortex and the central medulla within a lobule. (c) A micrograph of an adult’s thymus showing loss of thymic tissue and gain of adipose connective tissue.  

The thymus in a child consists of two fused thymic lobes, each surrounded by a connective tissue capsule (figure 21.5b). Fibrous extensions of the capsule, called trabeculae (trā-bek’ē-ə-lē), or septa, subdivide the thymic lobes into lobules. Each lobule is arranged into an outer cortex and inner medulla. Both parts are composed primarily of epithelial tissue infiltrated with T-lymphocytes in varying stages of maturation. The cortex contains immature T-lymphocytes, and the medulla contains mature T-lymphocytes. The epithelial cells secrete thymic hormones (e.g., thymulin) that participate in the maturation of T-lymphocytes (see section 17.11c). Because the thymus contains both lymphatic cells and epithelial tissue, it is described as a lymphoepithelial organ. The details of T-lymphocyte maturation are described in section 22.5.

Secondary lymphatic structures are organized into both lymphatic organs and aggregates of lymphatic nodules. They are differentiated by the presence or absence of a capsule composed of dense irregular connective tissue that encloses the lymphatic structure. A complete capsule is present in lymphatic organs, which include lymph nodes and the spleen. A capsule is either incomplete or absent in other lymphatic structures, which include tonsils, diffuse lymphatic nodules, and MALT.

### 21.4 Secondary Lymphatic Structures

Structures that house both lymphocytes and other immune cells are called secondary lymphatic structures. These structures are composed of lymphatic cells that are enmeshed within a reticular connective tissue matrix.

### 21.4a Lymph Nodes

#### LEARNING OBJECTIVES

11. Describe the structure of lymph nodes.

12. Explain the function of lymph nodes.

Lymph nodes are small, round or oval, encapsulated structures located along the pathways of lymphatic vessels, where they serve as the main lymphatic organ. Lymph nodes function in the filtering of lymph and removal of unwanted substances.

Lymph nodes vary in both their size (from 1 to 25 millimeters) and their number (estimated between 500 and 700 throughout the entire body). Lymph nodes are located both superficially and deep within the body and typically occur in clusters that receive lymph from selected body regions. Some examples of clustered lymph nodes
include the *cervical lymph nodes* that receive lymph from the head and neck; the *axillary lymph nodes* in the armpit that receive lymph from the breast, axilla, and upper limb; and *inguinal lymph nodes* in the groin that receive lymph from the lower limb and pelvis (see figure 21.1). In addition to clusters, lymph nodes are individually distributed throughout the body.

Numerous **afferent lymphatic vessels** bring lymph into a lymph node (figure 21.6). There is typically only one **efferent lymphatic vessel**, which originates at the involuted portion of the lymph node called the **hilum** (hi’lŭm), or hilus. Lymph is drained via the efferent lymphatic vessel from this region of the lymph node.

The capsule of a lymph node is composed of dense irregular connective tissue that encapsulates the node. The capsule also has numerous internal extensions called **trabeculae**, which both subdivide the node into compartments and provide support for blood vessels and nerves that are within the lymph node.

The lymph node regions internal to the capsule are subdivided into an outer **cortex** and an inner **medulla**. The cortex is composed in part of multiple **lymphatic nodules**. Each lymphatic nodule within the lymph node is composed of reticular fibers, which support an inner **germinall center** that houses both proliferating B-lymphocytes and some macrophages. The germinal center is surrounded by an outer region called a **mantle zone**, which contains T-lymphocytes, macrophages, and dendritic cells (described in section 22.2a). The medulla differs because it has strands of connective tissue fibers that support B-lymphocytes, T-lymphocytes, and macrophages. These structures are called **medullary cords**.

Both the cortex and medulla of a lymph node also contain tiny, open channels called lymphatic sinuses (cortical sinuses and medullary sinuses, respectively). These spaces are lined with macrophages.

**Lymph Flow Through Lymph Nodes**

Lymph enters a lymph node through numerous afferent lymphatic vessels, then flows through the lymph node sinuses, before typically draining through one efferent lymphatic vessel. Numerous afferent lymphatic vessels and generally one efferent lymphatic vessel are significant in the normal function of a lymph node. Consider that in this anatomic arrangement the collective diameter of the “inflow pipes” (i.e., afferent lymphatic vessels) is larger than the diameter of the “outflow pipe” (i.e., efferent lymphatic vessel). This creates a higher fluid pressure in the intervening structures (i.e., the lymph node sinuses), which helps to force the lymph through the lymph node.

Lymph is continuously monitored for the presence of foreign or pathogenic material as it passes through nodes. Macrophages residing in the lymph node remove foreign debris from the lymph by phagocytosis (see section 22.3b). Lymph then exits the lymph node through an efferent lymphatic vessel. Recall that lymph nodes are often found in clusters, so after one lymph node receives and filters lymph, the lymph is then transported to another lymph node in the cluster, then to another, and so on. Thus, lymph is repeatedly screened for unwanted substances.
A lymphoma (lim-fō’mā; oma = tumor) is a malignant neoplasm (cancer) that develops within lymphatic structures. These tumors develop most often from abnormal B-lymphocytes, and less commonly from abnormal T-lymphocytes. Usually (but not always), a lymphoma presents as a nontender, enlarged lymph node, often in the neck or axillary region. Some patients have no further symptoms, whereas others may experience night sweats, fever, and unexplained weight loss in addition to the nodal enlargement. Lymphomas are grouped into two categories: Hodgkin lymphoma and non-Hodgkin lymphoma.

Hodgkin lymphoma (or Hodgkin disease) is characterized by the presence of the Reed-Sternberg cell, a large cell whose two nuclei resemble owl eyes, surrounded by lymphocytes within the affected lymph node. Hodgkin lymphoma affects young adults (ages 16–35) and people over 60. It arises in a lymph node and then spreads to other nearby lymph nodes. If caught early, Hodgkin lymphoma can be treated and cured by excision of the tumor, followed by radiation, chemotherpay, or both.

Non-Hodgkin lymphomas are much more common than Hodgkin lymphomas. Some kinds of non-Hodgkin lymphoma are aggressive and often fatal, whereas others are slow-growing and more responsive to treatment. Treatment depends upon the type of non-Hodgkin lymphoma, the extent of its spread at the time of discovery, and the rate of progression of the malignancy.

Lymphocytes housed within the lymph node also come into contact with foreign substances. An immune response may be initiated after this contact, during which lymphocytes undergo cellular division, especially in the germinal centers. Some of these new lymphocytes remain within the lymph node, whereas others are transported within the lymph and then enter the blood, to ultimately reach areas of infections (see section 22.6).

When a person has an infection, often some lymph nodes are swollen and tender to the touch. This is a condition erroneously termed swollen glands. These enlarged nodes are a sign that lymphocytes are proliferating and attempting to fight an infection. Swollen superficial lymph nodes, such as those in the neck and axilla, can generally be palpated (felt).

The spleen is the largest lymphatic organ in the human body. It is located in the left upper quadrant of the abdomen, inferior to the diaphragm and adjacent to ribs 9–11 (figure 21.7a). This deep red organ lies lateral to the left kidney and posterolateral to the stomach. The spleen can vary considerably in size and weight, but typically is about 12 centimeters (5 inches) long and 7 centimeters (3 inches) wide.

The spleen’s posterolateral aspect (called the diaphragmatic surface) is convex and rounded; the concave anteromedial border (the visceral surface) contains the hilum (or hilus), where blood vessels and nerves connect to the spleen. The splenic (splen’ik) artery delivers blood to the spleen, whereas blood is drained by the splenic vein.

The spleen is surrounded by a connective tissue capsule from which trabeculae extend into the organ. The spleen lacks a cortex and medulla. Rather, the trabeculae subdivide the spleen into regions of white pulp and red pulp. White pulp consists of spherical clusters of T-lymphocytes, B-lymphocytes, and macrophages, which surround a central artery.

The remaining splenic tissue, called red pulp, contains erythrocytes, platelets, macrophages, and B-lymphocytes. The cells in red pulp are housed in reticular connective tissue and form structures called splenic cords (cords of Bilroth). Splenic sinusoids are associated with red pulp. (Recall from section 20.1c that sinusoids are very permeable capillaries that have a discontinuous basal lamina [a component of the basement membrane], so blood cells can easily enter and exit across the vessel wall.) The sinusoids drain into small venules that ultimately lead into the splenic vein.

Red pulp of the spleen serves as a blood reservoir, including a storage site for both erythrocytes and platelets (about 30% of all platelets are stored in the spleen). In situations where more erythrocytes and platelets are needed, such as during hemorrhage, these stored formed elements reenter the blood (see section 18.3d).
Monitor Blood as It Flows Through the Spleen

The spleen functions to filter blood (not lymph). As blood enters the spleen and flows through the central arteries, the white pulp monitors the blood for foreign materials, bacteria, and other potentially harmful substances.

After passing through a central artery, blood is transported through sinusoids of red pulp. As blood moves through the sinusoids, macrophages lining the sinusoids phagocytize bacteria and foreign debris from the blood, as well as both old and defective erythrocytes and platelets. Thus, the general flow of blood through the spleen is the splenic artery, the central artery (of white pulp), the splenic sinusoid (of red pulp), venules (that drain sinusoids), and ultimately the splenic vein (figure 21.7c).

In summary, the spleen serves several functions, including (1) phagocytosis of bacteria and other foreign materials in the blood as part of the body’s defense (red and white pulp); (2) phagocytosis of old, defective erythrocytes and platelets from circulating blood (red pulp); and (3) a role as a blood reservoir and storage site for both erythrocytes and platelets (red pulp).

During fetal development through the fifth month, the spleen also engages in the formation of blood cells, a function performed after birth by the bone marrow. This function remains latent in the spleen and may be reactivated under certain conditions (e.g., some hematologic disorders). This process of reactivation is called extramedullary hematopoiesis (or hemopoiesis).
21.4c Tonsils

LEARNING OBJECTIVE
16. Identify the main groups of tonsils and their location and function.

Tonsils (tonˈsɪlz; tonsilla = a stake) are secondary lymphatic structures that are not completely surrounded by a connective tissue capsule. They are found in the pharynx (throat) and oral cavity. The pharyngeal tonsil is found in the posterior wall of the nasopharynx; when this tonsil becomes enlarged, it is called adenoids (adˈə-noidz; aden = gland). Palatine tonsils are in the postero-lateral region of the oral cavity, and lingual tonsils are along the posterior one-third of the tongue (Figure 21.8). Tonsils help protect against foreign substances that may be either inhaled or ingested.

Invaginated outer edges called tonsillar crypts increase the tonsil’s surface area to help trap material. Lymphatic nodules, some containing germinal centers, are housed with the tonsils.

WHAT DID YOU LEARN?
11. What are the three main groups of tonsils and their function?

21.4d Lymphatic Nodules and MALT

LEARNING OBJECTIVES
17. Describe the composition of individual lymphatic nodules.
18. Compare the locations of MALT and Peyer patches.

Lymphatic nodules and MALT make up the last category of secondary lymphatic structures. These relatively small masses of lymphatic tissue are located throughout the body.

Lymphatic Nodules

Lymphatic nodules (nodˈilz), or lymphatic follicles, are small, oval clusters of lymphatic cells (e.g., B-lymphocytes, T-lymphocytes, macrophages) with some extracellular matrix that are not completely surrounded by a connective tissue capsule. Scattered lymphatic nodules are referred to as diffuse lymphatic tissue. This tissue can be found in every body organ and within the wall of the appendix, where it helps to defend against infections in these structures. However, in some areas of the body, many lymphatic nodules group together to form larger structures, such as MALT.

WHAT DID YOU LEARN?
12. What is the function of MALT in the mucosal linings of the gastrointestinal, respiratory, urinary, and reproductive tracts?
Figure 21.9 Relationship of the Lymphatic System to Both the Cardiovascular System and Immune System. The lymphatic system assists both (a) the cardiovascular system by returning fluid from the interstitial space back into the blood to help maintain fluid balance, blood volume, and blood pressure and (b) the immune system in the body’s defense.

(a) Lymphatic Structures That Assist the Cardiovascular System
- **Lymphatic trunks and ducts**: Receive lymph from lymphatic vessels. Lymphatic trunks drain into lymphatic ducts. Lymphatic ducts drain lymph into the venous circulation.
- **Lymphatic vessels**: Transport lymph and drain lymph into lymph nodes (which filter the lymph).
- **Lacteals**: Lymphatic capillaries in the small intestine absorb lipid-soluble substances from gastrointestinal (GI) tract.
- **Capillaries**: Absorb interstitial fluid that is renamed lymph when it enters the lymphatic capillaries.

(b) Lymphatic Structures That Assist the Immune System
- **PRIMARY LYMPHATIC STRUCTURES** (Formation and maturation of lymphocytes)
  - **Red bone marrow**: Produces formed elements, including lymphocytes; site of B-lymphocyte maturation.
  - **Thymus**: Site of T-lymphocyte maturation and differentiation.
- **SECONDARY LYMPHATIC STRUCTURES** (House both lymphocytes and other immune cells to protect against potentially harmful substances)
  - **Lymph nodes**: Monitor lymph for foreign materials.
  - **Spleen: White pulp**: Monitors blood for foreign materials.
  - **Spleen: Red pulp**: Phagocytizes old or defective erythrocytes and platelets from circulating blood; serves as a blood reservoir and storage site for both erythrocytes and platelets.
  - **Tonsils**: Provide defense against pathogens in air and ingested food.
  - **Lymphatic nodules/MALT**: Protect body organs (lymphatic nodules) and mucosal linings (MALT) against potentially harmful substances.
## Chapter Summary

- The lymphatic system, which is composed of lymph vessels and lymphatic tissues and organs, supports the functions of the cardiovascular and immune system.

### 21.1 Lymph and Lymph Vessels
- Lymph is transported in lymph vessels.

#### 21.1a Lymph and Lymphatic Capillaries
- Lymph is interstitial fluid containing solutes and sometimes foreign material that is absorbed into lymphatic capillaries, transported through lymph vessels, and returned to the blood.
- Lymphatic capillaries are endothelium-lined vessels with overlapping endothelial cells where interstitial fluid enters lymph vessels to become lymph.

#### 21.1b Lymphatic Vessels, Trunks, and Ducts
- Lymph is transported through a network of increasing larger vessels that include lymphatic capillaries, lymphatic vessels, lymphatic trunks, and lymphatic ducts.
- Movement of lymph through lymph vessels is assisted by the presence of valves within the larger lymphatic vessels and trunks and several mechanisms that help propel the lymph.

### 21.2 Overview of Lymphatic Tissue and Organs
- Primary lymphatic structures are involved in the formation and maturation of lymphocytes.
- Secondary lymphatic structures house lymphocytes and other immune cells, serving as sites to initiate the immune response.

### 21.3 Primary Lymphatic Structures
#### 21.3a Red Bone Marrow
- Red bone marrow produces all formed elements, including lymphocytes.

#### 21.3b Thymus
- The thymus is a bilobed organ found in the mediastinum. It is most active in childhood until puberty, and then it declines in size and function.
- The thymus is the site of T-lymphocyte maturation, which occurs in the presence of thymic hormones.

### 21.4 Secondary Lymphatic Structures
- Secondary lymphatic structures may be organized into lymphatic organs, which are enclosed within a complete capsule, and lymphatic nodules, which have an incomplete or absent capsule.
- Both lymphatic organs and lymphatic nodules are composed of a reticular connective tissue matrix that houses lymphatic cells (e.g., B-lymphocytes).

#### 21.4a Lymph Nodes
- Lymph nodes are numerous, small, encapsulated lymphatic organs that filter lymph.
- Each lymph node is organized into an outer cortex and inner medulla that house lymphatic cells (e.g., B-lymphocytes).

#### 21.4b Spleen
- The spleen is the largest lymphatic organ. It is partitioned into white pulp and red pulp that filters blood.
- The spleen functions in the removal of bacteria and other foreign material from blood, the removal of old erythrocytes and platelets, and as a blood reservoir and storage site for both erythrocytes and platelets.

#### 21.4c Tonsils
- Tonsils are large clusters of partially encapsulated lymphatic cells located in the pharynx and oral cavity to protect against potentially harmful substances that may be either inhaled or ingested.
- Tonsils are named based on their specific location and include the pharyngeal tonsil, palatine tonsils, and lingual tonsils.

#### 21.4d Lymphatic Nodules and MALT
- Lymphatic nodules can be found in every organ throughout the body.
- MALT (mucosa-associated lymphatic tissue) is composed of large groups of lymphatic nodules housed in the mucosal-lined walls of the gastrointestinal tract, respiratory tract, urinary tract, and reproductive tract.

### Challenge Yourself

#### Do You Know the Basics?

1. What body systems are supported by the lymphatic system?
   - a. cardiovascular and urinary
   - b. cardiovascular and immune
   - c. respiratory and cardiovascular
   - d. respiratory and urinary

2. Lymph is drained into the thoracic duct from which of the following body regions?
   - a. right lower limb
   - b. right upper limb
   - c. right side of the head
   - d. right side of the thorax
3. The spleen is a secondary lymphatic structure located
   a. in the oral cavity.
   b. along lymphatic vessels.
   c. attached to the gastrointestinal tract.
   d. inferior to the diaphragm adjacent to the stomach.
4. What is the function of the thymus?
   a. It is the site of T-lymphocyte maturation.
   b. It filters lymph.
   c. It filters blood.
   d. It produces the formed elements of the blood.
5. Which type of lymph vessel consists solely of an endothelium
   and has one-way flaps that allow interstitial fluid to enter but
   not exit?
   a. lymphatic vessel
   b. lymphatic capillary
   c. lymphatic duct
   d. lymphatic trunk
6. Which statement is accurate about lymph nodes?
   a. Lymph nodes do not become swollen and tender.
   b. Lymph nodes filter blood.
   c. Lymph enters the lymph node through afferent lymphatic
      vessels.
   d. Lymphatic sinuses are located in the cortex of a lymph
      node only.
7. In a *Streptococcus* infection of the throat, all of the following
   structures may swell except the
   a. pharyngeal tonsil.
   b. spleen.
   c. cervical lymph node.
   d. palatine tonsil.
8. The lymphatic trunk that drains lymph from the upper limb,
   breasts, and superficial thoracic wall is the
   a. lumbar trunk.
   b. jugular trunk.
   c. subclavian trunk.
   d. bronchomediastinal trunk.
9. Aged erythrocytes are removed from circulation by the
   a. mucosa-associated lymphatic tissue.
   b. lymph nodes.
   c. thymus.
   d. spleen.
10. Interstitial fluid that is absorbed into lymph vessels will be
    monitored by the ________________ before the fluid is
    dumped into venous blood.
    a. mucosa-associated lymphatic tissue (MALT)
    b. spleen
    c. thymus
    d. lymph nodes
11. List the anatomic structures of the lymphatic system,
    including lymph vessels, primary lymphatic structures, and
    secondary lymphatic structures.
12. Explain what distinguishes a primary lymphatic structure
    from a secondary lymphatic structure.
13. Describe what lymph is, and draw a flowchart that illustrates
    what structures the lymph is transported through to return to
    the blood.
14. Which body regions have their lymph drained to the thoracic duct?
15. Describe how the thymus’s anatomy changes as we age.
16. Describe the basic anatomy of a lymph node, how lymph
    enters and leaves the node, and the functions of this organ.
17. Compare and contrast the red and white pulp of the spleen
    with respect to the anatomy and functions of each.
18. Describe the specific locations of the tonsils.
19. Describe the location and function of diffuse lymphatic
    nodules and mucosa-associated lymphatic tissue (MALT).
20. Explain how the lymphatic system supports the functions
    of both the cardiovascular system and the immune system.

**Can You Apply What You’ve Learned?**

1. A tick has embedded itself in the scalp of a young boy. His
   mother is most likely to find which lymph nodes to be swollen?
   a. cervical
   b. inguinal
   c. axillary
   d. femoral
2. A child born without his thymus would not have mature
   a. macrophages.
   b. B-lymphocytes.
   c. dendritic cells.
   d. T-lymphocytes.
3. A young woman was in a car accident and had to have her
   spleen removed as a consequence of its rupture during the
   accident. She now has a greater risk of
   a. an overactive immune response.
   b. bacterial infections.
   c. low blood pressure.
   d. a pathogen surviving in her lymph.
4. One of the postoperative complications from the removal
   of lymph nodes during a mastectomy would be
   a. edema in the upper limb.
   b. regrowth of the lymph nodes.
   c. an overactive immune system.
   d. tender and swollen lymph nodes in other regions of the body.
5. All of the following can result in lymphedema (the
   accumulation of interstitial fluid due to interference with
   lymphatic drainage) except
   a. surgical removal of a group of lymph nodes.
   b. obstruction of lymph vessels that drain a lymph node, as
      might occur with a tumor or an infection.
   c. radiation therapy, which may cause scar formation of
      lymph vessels.
   d. exercise that increases the flow of lymph in the lymph vessels.
Can You Synthesize What You’ve Learned?

1. Arianna was diagnosed with mononucleosis, an infectious disease that targets B-lymphocytes. The doctor palpated her left side, just below the rib cage, and told Arianna she was checking to see if a certain organ was enlarged, a complication that can occur with mononucleosis. What lymphatic organ was the doctor checking, and why would it become enlarged? Include some explanation of the anatomy and histology of this organ in your answer.

2. Jordan has an enlarged lymph node along the side of his neck, and he is worried that the structure may be a lymphoma. Explain how malignant cells may have reached the lymph node.

3. Mark has come to the emergency care facility complaining of a sore throat. Upon examination, his tonsils appear swollen. When questioned further, he reports that although he has no history of his tonsils being swollen, his throat has been sore for almost a week. He is concerned that he will need to go to the hospital to have his tonsils removed. Explain the conditions that would generally require a tonsillectomy.

INTEGRATE

The following study aids may be accessed through Connect.

Clinical Case Study: A Young Woman with a Neck Mass
Interactive Questions: This chapter’s content is served up in a number of multimedia question formats for student study
SmartBook: Topics and terminology include lymph and lymph vessels; overview of lymphatic tissue and organs; primary lymphatic structures; secondary lymphatic structures
Anatomy & Physiology Revealed: Topics include lymphatic system overview; thoracic duct; thymus; lymph node; spleen; tonsils
Animations: Topics include lymphatic system overview

There are children born without an immune system—a condition called severe combined immune deficiency syndrome (SCIDS). The most famous of these children was a boy named David Vetter, born in 1971. He was dubbed by the media as “The Boy in the Bubble” because without an immune system, David literally had to live in a sterile plastic bubble. At the age of 12, David received a bone marrow transplant from his sister with the hope of his being able to live outside the bubble. This new bone marrow would have the ability to produce the immune cells that David’s bone marrow was unable to form. Sadly, residing in his sister’s bone marrow was a dormant (not active) virus called Epstein-Barr. This virus is generally kept under control by a healthy immune system. However, because David did not have a functioning immune system, the bone marrow with the Epstein-Barr virus induced formation of cancerous tumors throughout his body, and he died several months later.

Most of us may take for granted that we have a functioning immune system. While each of us may catch a cold or the flu on occasion, our immune system is—without our typically being aware of it—protecting us from infectious agents and other harmful substances. This system is unique because, unlike all other body systems, the immune system is not made up of organs. Rather, it is composed of numerous cellular and molecular structures located throughout the body that function together in the body’s defense to provide us with immunity.

Our coverage of the immune system in this chapter is not comprehensive. Rather, our discussion is tailored to provide a general overview of how the immune system functions, as well as a description of some of the more common immune system malfunctions (e.g., hypersensitivities). We hope to help you to develop both an understanding of, and an appreciation for, this system that so diligently functions to protect us. We first provide a brief overview of the different infectious agents. This is a necessary preliminary step because immune system function is often dependent upon the specific type of infectious agent against which it must defend.
22.1 Overview of Diseases Caused by Infectious Agents

LEARNING OBJECTIVES

1. Compare and contrast the five major classes of infectious agents.
2. Describe prions, and name a disease they cause.

Infectious agents are organisms that cause damage, or possibly death, to the host organism that they invade. Infectious agents that cause harm to the host are said to be pathogenic (path’-ō-jen’-ik; pathos = disease, genesis = production). The five major categories of infectious agents that cause disease in humans are bacteria, viruses, fungi, protozoans, and multicellular parasites. These categories, including examples of each, are summarized and compared in table 22.1 and described here:

- **Bacteria** are microscopic, single-celled organisms composed of prokaryotic cells. These cells are fundamentally different from the cells of humans and other living organisms. Prokaryotic cells are smaller in size, averaging between 1 and 2 micrometers (µm), which is approximately the size of a mitochondrion (see figure 4.2). Prokaryotic cells lack a nuclear envelope, and their cytoplasm and DNA are enclosed by both a plasma membrane and a cell wall (formed by complex carbohydrates cross-linked with peptides). Some bacteria also have an external, sticky polysaccharide capsule, which increases their virulence (vir’-ū-lens)—the ability to cause serious illness. Pathogenic bacteria may also have pili (pi’-li), which are hairlike structures that act like Velcro for attaching to body structures (e.g., *E. coli* that cause urinary tract infections). Additionally, some pathogenic bacteria cause disease by releasing enzymes or toxins that interfere with the function of cells; an example is the bacterium *Clostridium tetani* (see Clinical View 10.3: “Muscular Paralysis and Neurotoxins”). (Note: The cells of humans and other living organisms are composed of eukaryotic cells (cells with a nucleus and organelles), and their structure is discussed in detail in chapter 4.)

- **Viruses** are not cells. Viruses are much smaller than a bacterial cell at about one-hundredth of a micrometer (see figure 4.2), and they are composed of DNA or RNA within a viral capsid, or shell. The protein capsid of some viruses may also be enclosed within a membrane. Viruses are obligate intracellular parasites; that is, they must enter a cell to replicate. The process of viral reproduction includes directing the infected cell to synthesize copies of both the viral DNA or RNA molecule and its capsid protein. New viral particles are then formed within the infected cells and released from them to enter surrounding cells. A virus, or the immune system’s response to it, ultimately kills the cells it invades. Viruses cause different diseases depending upon the type of cell they infect. Examples of viral diseases include the common cold, chicken pox, ebola, and HIV.

- **Fungi** (fun’-ji) are composed of eukaryotic cells that have a cell wall external to the plasma membrane. This group includes molds, yeasts, and multicellular fungi that produce spores. Proteolytic (protein-digesting) enzymes released from fungi induce inflammation (see section 22.3d) that causes redness and swelling of the infected area.

Fungal diseases (mycoses) in healthy individuals in the United States are usually limited to superficial infections of the skin, scalp, and nails (e.g., ringworm, “athlete’s foot”). Other fungal diseases involve infections of mucosal linings (e.g., vaginal yeast infections) or may cause internal fungal infections (e.g., histoplasmosis, which affects the respiratory system).

- **Protozoans** are microscopic, unicellular eukaryotic organisms that lack a cell wall. One example of a disease-causing protozoan is plasmodium, which causes malaria. This infectious agent is spread by mosquitoes and enters the blood, where it then infects erythrocytes, causing their destruction.

- **Multicellular parasites** are nonmicroscopic organisms (larger than a centimeter in size) that reside within a host from which they take nourishment. Parasitic worms such as tapeworms, for example, infect the intestinal tract of humans.

Prions (prī’on) are small fragments of infectious proteins that cause disease in nervous tissue. Variant Creutzfeldt-Jakob disease (also known as bovine spongiform encephalopathy, or “mad cow disease”) is an example. This prion disease can be spread from cows to humans by consuming infected meat because nerves within the muscle are contaminated with prions. Prions are neither cells nor viruses, and research into how they cause disease is ongoing.

WHAT DID YOU LEARN?

1. Which pathogen must enter a cell to replicate? Which type of pathogen is composed of prokaryotic cells?

<table>
<thead>
<tr>
<th>Table 22.1</th>
<th>Major Categories of Infectious Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristic</strong></td>
<td><strong>Bacteria</strong></td>
</tr>
<tr>
<td>Cellular</td>
<td>Prokaryotic</td>
</tr>
<tr>
<td>Significant Features</td>
<td>Intracellular and extracellular microbes—some have a sticky polysaccharide capsule and/or hairlike pili; some produce enzymes and/or toxins</td>
</tr>
<tr>
<td>Selected Diseases Caused by the Agent</td>
<td>Streptococcal infections (e.g., strep throat), staphylococcal infections, tuberculosis, syphilis, diphtheria, tetanus, Lyme disease, salmonella, and anthrax</td>
</tr>
</tbody>
</table>
22.2 Overview of the Immune System

Eleven organ systems are introduced in section 1.4c—and the immune system is not one of them. This is because, unlike those 11 body systems, the immune system does not have organs (e.g., lungs of the respiratory system). Instead, numerous types of cells (including specialized cells called immune cells), secreted molecules (including cytokines), and plasma proteins (e.g., antibodies) are functionally integrated to form our immune system. The function of this system is to protect our body from infectious agents and other potentially harmful substances to provide us with immunity (i-myū′ni-tē).

Here we provide a brief introduction to the location of the specialized immune cells and the secreted cytokine molecules that regulate them. We then give an overview of how the immune system is organized into two overlapping and complementary components: the innate immune system and the adaptive immune system.

22.2a Immune Cells and Their Locations

**LEARNING OBJECTIVE**

3. List the types of leukocytes of the immune system, and describe where they may be found.

**Leukocytes** (white blood cells) are the specialized cells of our immune system. They were first described in section 18.3c as the cells that help defend the body against pathogens. They are formed in the red bone marrow prior to circulating in the blood. Recall that leukocytes include (1) the three types of granulocytes (neutrophils, eosinophils, and basophils); (2) monocytes that become macrophages or dendritic cells when they exit blood vessels and take up residence in the tissues; and (3) the three types of lymphocytes, which include T-lymphocytes (or T-cells), B-lymphocytes (or B-cells), and NK (natural killer) cells.

**Structures That House Immune System Cells**

Most leukocytes are found in body tissues. The primary locations that house immune cells include secondary lymphatic structures, select organs, epithelial layers of the skin and mucosal membranes, and connective tissues of the body (figure 22.1). The housing of the specific types of immune cells varies by the location:

- **Secondary lymphatic structures.** T-lymphocytes and B-lymphocytes are housed in secondary lymphatic structures of lymph nodes, the spleen, tonsils, lymphatic nodules, and MALT (mucosa-associated lymphatic tissue) (see section 21.4). The presence of lymphocytes accounts for the collective name (lymphatic structures). Other immune cells, including macrophages, dendritic cells, and NK cells, are also present.

---

**Table 22.1** Major Categories of Infectious Agents

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Fungi</th>
<th>Protozoans</th>
<th>Multicellular Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="bacteria" alt="Photo" /> Dr. William A. Clark/CDC; <img src="viruses" alt="Photo" /> Centers for Disease Control; <img src="fungi" alt="Photo" /> Centers for Disease Control; <img src="protozoans" alt="Photo" /> Janice Haney Carr/CDC; ![Photo](multicellular parasites) CDC</td>
<td><img src="fungi" alt="Photo" /> Centers for Disease Control; <img src="protozoans" alt="Photo" /> Janice Haney Carr/CDC; ![Photo](multicellular parasites) CDC</td>
<td><img src="protozoans" alt="Photo" /></td>
<td>![Photo](multicellular parasites) CDC</td>
</tr>
<tr>
<td>Structure</td>
<td>Characteristic</td>
<td>Significant Features</td>
<td>Selected Diseases Caused by the Agent</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Prokaryotic Not a cell; DNA or RNA within a capsid protein</td>
<td>Eukaryotic Eukaryotic Eukaryotic</td>
<td>Intracellular and extracellular microbes—some have a sticky polysaccharide capsule and/or hairlike pili; some produce enzymes and/or toxins</td>
<td>Streptococcal infections (e.g., strep throat), staphylococcal infections, tuberculosis, syphilis, diphtheria, tetanus, Lyme disease, salmonella, and anthrax</td>
</tr>
<tr>
<td>Obligate intracellular parasites; must enter cell to replicate</td>
<td>Produce spores; release proteolytic enzymes</td>
<td>Intracellular and extracellular parasites that interfere with normal cellular functions</td>
<td>Common cold, influenza, polio, mumps, measles, hepatitis, rubella, chicken pox, ebola, herpes, and HIV (which leads to AIDS)</td>
</tr>
<tr>
<td>Obligate intracellular parasites; must enter cell to replicate</td>
<td>Produce spores; release proteolytic enzymes</td>
<td>Intracellular and extracellular parasites that interfere with normal cellular functions</td>
<td>Ringworm, diaper rash, jock itch, athlete’s foot, yeast infections, and histoplasmosis</td>
</tr>
<tr>
<td>Obligate intracellular parasites; must enter cell to replicate</td>
<td>Produce spores; release proteolytic enzymes</td>
<td>Intracellular and extracellular parasites that interfere with normal cellular functions</td>
<td>Malaria, toxoplasmosis, giardiasis, amoebiasis, leishmaniasis, trichomoniasis, and African sleeping sickness</td>
</tr>
<tr>
<td>Obligate intracellular parasites; must enter cell to replicate</td>
<td>Produce spores; release proteolytic enzymes</td>
<td>Intracellular and extracellular parasites that interfere with normal cellular functions</td>
<td>Parasitic infection from tapeworms, lung flukes, liver flukes, blood flukes, hookworms, Trichinella, Ascaris, whipworms, and pinworms</td>
</tr>
</tbody>
</table>

**INTEGRATE**

**LEARNING STRATEGY**

You might find it helpful to consider that developing an understanding of the immune system is like putting together a puzzle. You will first need to become familiar with the numerous “pieces” of the immune system, many of which at first seem unrelated. It is only when these pieces are integrated into a whole that you are able to see the relationships between them.

---

*Photos used: (bacteria) Dr. William A. Clark/CDC; (viruses) Centers for Disease Control; (fungi) Centers for Disease Control; (protozoans) Janice Haney Carr/CDC; (multicellular parasites) CDC*
Select organs. Macrophages, which are derived from monocytes that have exited the blood, are also housed in select organs (see section 18.3c). Some of these cells are specifically named based on their location, such as alveolar macrophages of the lungs (see section 23.3d) and microglia of the brain (see section 12.4b). Macrophages may be permanent residents, referred to as fixed macrophages, or migrate through tissues and are called wandering macrophages.

Epithelial layers of the skin and mucosal membranes. Dendritic cells are also located in the skin and mucosal membranes, and they are typically derived from monocytes. These cells in the epidermis of the skin are more specifically called epidermal dendritic cells (see sections 6.1a and 6.1d). Dendritic cells engulf pathogens in the skin and mucosal membranes and subsequently migrate to a lymph node through lymph vessels that drain the tissue (see section 21.4a).

Connective tissue. Mast cells (cells similar to basophils within the blood) are located within the connective tissue throughout the body, typically in close proximity to small blood vessels (see section 5.2a). They are especially abundant in the dermis of the skin and the mucosal linings of the respiratory, gastrointestinal, urinary, and reproductive tracts. However, they are also housed in connective tissue of organs, such as the endomysium that ensheathes muscle fibers (see section 10.2a).

WHAT DID YOU LEARN?
1. Identify the specific type of immune cell(s) within each of these structures: (a) connective tissue, (b) skin, (c) organs, and (d) secondary lymphatic organs.

22.2b Cytokines

Learning Objectives
4. Define cytokines, and describe their similarities to hormones.
5. List the general categories of cytokines.

Cytokines (sīˈto-kīn; cyto = cell, kinesis = movement) are small, soluble proteins produced by cells of both the innate and adaptive immune system to regulate and facilitate immune system activity. These soluble proteins (1) serve as a means of communication between the cells; (2) control the development and behavior of immune cells; (3) regulate the inflammatory response of the innate immune system; and (4) function as weapons to destroy cells. Cytokines have also recently been shown to influence other, non-immune cells such as those of the nervous system.

A cytokine is released from one cell and binds to a specific receptor of a target cell, where its action is similar to that of a hormone. Cytokines can act on the cell that released it (autocrine stimulation), local neighboring cells (paracrine stimulation; see...
Chapter Twenty-Two
Immune System and the Body’s Defense

22.2 Comparison of Innate Immunity and Adaptive Immunity

**LEARNING OBJECTIVE**

6. Compare and contrast the primary features of innate and adaptive immunity.

The means of protecting the body through the cells, cytokines, and physiologic processes of the immune system are organized into two categories based on the type of immunity that is provided. The two categories are *innate immunity* and *adaptive immunity* (figure 22.2). Although both work to protect us from potentially harmful agents, the two differ in several respects, including the participating cells that are involved, the specificity with which the cells respond, the mechanisms involved in eliminating harmful substances, and the amount of time required for a response.

### Innate Immunity

Some defense mechanisms of the immune system protect us against numerous different substances, and because we are born with these defenses, this type of immunity is referred to as *innate immunity* (or *nonspecific immunity*). The components that provide innate immunity collectively form the *innate immune system*. These include the barriers of the skin and mucosal membranes that prevent entry, as well as

---

**Table 22.2 Major Categories of Cytokines**

<table>
<thead>
<tr>
<th>Category</th>
<th>Primary Function</th>
<th>Source</th>
<th>Designation</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin (IL)</td>
<td>Regulates immune cells</td>
<td>T-lymphocytes, macrophages, endothelial cells, and other various cells</td>
<td>IL followed by number</td>
<td>IL-1, IL-2</td>
</tr>
<tr>
<td>Tumor necrosis factor (TNF)</td>
<td>Destroys tumor cells; may have other functions as well</td>
<td>T-lymphocytes, macrophages, mast cells, dendritic cells</td>
<td>TNF followed by Greek letter</td>
<td>TNF-α</td>
</tr>
<tr>
<td>Colony-stimulating factor (CSF)</td>
<td>Stimulates leukopoiesis in bone marrow to increase synthesis of a specific type (colony) of leukocytes (see table 18.6 in section 18.3a)</td>
<td>T-lymphocytes, monocytes</td>
<td>First letter of cell(s) it is regulating, followed by CSF</td>
<td>G-CSF (granulocyte CSF) GM-CSF (granulocyte-macrophage CSF)</td>
</tr>
<tr>
<td>Interferon (IFN)</td>
<td>Three classes: IFN-α and IFN-β are antiviral agents, and IFN-γ is a pro-inflammatory agent</td>
<td>Virus-infected cells, NK cells, T-lymphocytes</td>
<td>IFN followed by Greek letter</td>
<td>IFN-α, IFN-β, IFN-γ</td>
</tr>
</tbody>
</table>

section 17.3b), or circulate in the blood to cause systemic effects (endocrine stimulation; see section 17.1a). To prevent continuous stimulation, cytokines have a short half-life (see section 17.4b).

Although the terminology of cytokines continues to evolve within the discipline of immunology, a current method of organizing cytokines identifies these different categories: interleukin (IL), tumor necrosis factor (TNF), colony-stimulating factor (CSF), and interferon (IFN). Table 22.2 summarizes the cytokine categories.

**WHAT DID YOU LEARN?**

3. What is the definition of a cytokine? How are cytokines similar to hormones?

---

**INTEGRATE**

**LEARNING STRATEGY**

A military analogy can help describe how the cells of the immune system function in the body’s defense. The cells are the “troops,” the pathogen is the “opposition,” and cytokines serve as both a means of communication and weapons available to the troops to fight infection.

---

**Figure 22.2 Overview of the Immune System.**

The immune system is composed of two overlapping and complementary components: the innate immune system, which is initiated by many different components against a wide array of substances, and the adaptive immune system, which involves the response of lymphocytes to a specific antigen.
Pathogenic organisms may enter the body through a number of different routes to cause disease (table 22.3). The body has many anatomic structures, various secretions, and specific physiologic processes that are typically effective in either preventing the entry of these organisms or eliminating them from the body (table 22.3).

The skin forms a physical, chemical, and biological barrier that plays a significant role in preventing entry of pathogens at the body’s surface if the skin is intact. The stratified squamous epithelium of the epidermis (see section 6.1a) and the dense irregular connective tissue and areolar connective tissue of the dermis (see section 6.1b) provide a formidable barrier to prevent entry of most microbes. One specific substance within the areolar connective tissue of the dermis is a gel-like mucopolysaccharide (hyaluronic acid) that slows the migration of microbes that have penetrated the epidermis—much as a sticky fly paper traps flies. Secretions of exocrine glands of the skin help inhibit microbial growth (see section 6.2c). These secretions include those of sweat glands (which contain antimicrobial lysozyme, defensins, and dermicidin) and sebaceous glands (which contain lactate and fatty acids that contribute to a low skin pH). The importance of skin in protecting us from pathogens can be appreciated when we consider that when the skin is compromised by a serious burn, one of the major causes of death is a fatal infection (see Clinical View 6.6: “Burns”).

The mucous membranes also form a physical, chemical, and biological barrier, but these membranes function to prevent entry at the openings of the body. The epithelium and underlying connective tissue of mucous membranes (see section 5.5b) help to block microbes from entering the body through our respiratory, gastrointestinal (GI), urinary, and reproductive tracts. These membranes produce mucin (protein) that when released and hydrated forms mucus, a viscous fluid that also contains antimicrobial substances (e.g., lysozyme, defensins, IgA). Additionally, each tract has specific physiologic mechanisms that help to protect it.

The respiratory tract has cilia that sweep mucus with trapped microbes upward from the lungs to be expectorated (spit out) or swallowed (see section 23.1c) and the coughing and sneezing reflexes, which remove microbes with blasts of exhaled air (see section 23.3a). Secretions associated with the GI tract also function to protect us from microbes: The viscous saliva (with lysozyme and IgA) within the mouth traps microbes, acid within the stomach creates a very low pH that destroys most microbes and toxins, and defecation and vomiting eliminate microbes before they can enter the body from the GI tract. Urine “flushes” microbes from the urinary tract and acidic secretions inhibit microbial growth within the vagina of the female reproductive tract.

Commensal microflora (or normal microflora) are microorganisms that reside on body surfaces (e.g., the skin, GI tract). These non-pathogenic microorganisms interfere with the attachment and growth of other, potentially more virulent types. The significant role of the normal flora in a healthy GI tract is just beginning to be understood.

Other structures have secretions that protect them. Lacrimal fluid (which contains lysozyme and IgA) washes microbes from the surface of the eye (see section 16.4a) and cerumen (i.e., earwax) is thought to impede microbial growth within the external acoustic meatus (see section 16.5a).

The various mechanisms used by the skin, mucosal membranes, and other structures to help prevent entry are summarized in table 22.3. These mechanisms generally are very successful. However, if microbes are present in sufficient numbers, or the barrier is compromised, as occurs with a puncture or burns, microbes may be able to penetrate into the underlying connective tissue and establish an infection. Microbes typically enter through the moist mucous membranes of one of the tracts (e.g., respiratory tract) and only enter through the skin when it is penetrated (e.g., by a mosquito, tick, or wound). Subsequent to their entry into the body, the internal processes that provide both innate immunity (the second line of defense) and adaptive immunity (the third line of defense) are set in motion to eliminate the infectious agent.
### Table 22.3  
**First Line of Defense: Preventing Entry of Pathogens**

<table>
<thead>
<tr>
<th>Structure, Substance, or Process</th>
<th>Description</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SKIN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidermis and dermis</td>
<td>Stratified squamous epithelium forms epidermis; areolar and dense irregular connective tissue forms dermis</td>
<td>Provide a physical, chemical, and biological barrier for body surface</td>
</tr>
<tr>
<td>Normal flora</td>
<td>Commensal microflora, including nonpathogenic bacteria</td>
<td>Help prevent growth of pathogenic microbes</td>
</tr>
<tr>
<td>Exfoliation</td>
<td>Sloughing off of epidermal cells</td>
<td>Removes potential pathogens from skin surface</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Mucopolysaccharide with a gel-like consistency that is located in areolar tissue of the dermis</td>
<td>Slows migration of microbes that have penetrated the epidermis</td>
</tr>
<tr>
<td>Sebaceous (oil) gland secretions</td>
<td>Secretions called sebum that contain lactate and fatty acids</td>
<td>Create a low pH (3–5) that interferes with the growth of microbes</td>
</tr>
<tr>
<td>Sweat gland secretions</td>
<td>Secretions that contain lysozyme, defensins, and dermicidin</td>
<td>Help wash away microbes; contain antibacterial and antifungal substances</td>
</tr>
<tr>
<td><strong>MUCOUS MEMBRANES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelial and connective tissue</td>
<td>Lining of respiratory, gastrointestinal, urinary, and reproductive tracts; contain hyaluronic acid</td>
<td>Provide a physical, chemical, and biological barrier of body structures exposed to the external environment</td>
</tr>
<tr>
<td>Normal flora</td>
<td>Commensal microflora, including nonpathogenic bacteria</td>
<td>Help prevent growth of pathogenic microbes</td>
</tr>
<tr>
<td>Mucus</td>
<td>Formed from hydrated mucin; contains lysozyme, defensins, and IgA</td>
<td>Thick secretion that helps trap microbes; contains antimicrobial substances</td>
</tr>
<tr>
<td><strong>RESPIRATORY TRACT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal secretions</td>
<td>Secretions that contain lysozyme, defensins, and IgA</td>
<td>Contain antimicrobial substances</td>
</tr>
<tr>
<td>Vibrissae</td>
<td>Hairs in nasal cavity</td>
<td>Trap microbes in the nose</td>
</tr>
<tr>
<td>Cilia</td>
<td>Extensions of plasma membranes</td>
<td>Sweep mucus in the respiratory tract so that it can be expectorated or swallowed</td>
</tr>
<tr>
<td>Coughing and sneezing</td>
<td>Blasts of expired air</td>
<td>Mechanical elimination of microbes or other foreign substances from the respiratory tract</td>
</tr>
<tr>
<td><strong>GASTROINTESTINAL TRACT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saliva</td>
<td>Secretions released into the mouth from the salivary glands; contains lysozyme and IgA</td>
<td>Helps wash away microbes; contains antimicrobial substances</td>
</tr>
<tr>
<td>Hydrochloric acid (HCl)</td>
<td>Strong acid produced within the stomach</td>
<td>Creates very low pH (pH ~2) that destroys many bacteria, bacterial toxins, and other microbes that enter the stomach</td>
</tr>
<tr>
<td>Defecation and vomiting</td>
<td>Removal of waste from the gastrointestinal tract</td>
<td>Eliminate microbes before they can be absorbed into the blood</td>
</tr>
<tr>
<td><strong>UROGENITAL TRACT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>Urine formed in kidneys is transported out of the body through the urinary tract</td>
<td>Flow of urine flushes microbes from urinary tract</td>
</tr>
<tr>
<td>Lactate</td>
<td>Weak acid</td>
<td>Produced by the vagina; creates a low pH that slows or prevents the growth of microbes</td>
</tr>
<tr>
<td><strong>SECRETIONS PRODUCED BY THE SKIN AND MUCOUS MEMBRANES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lysozyme</td>
<td>Antibacterial enzyme</td>
<td>Attacks the cell wall of some bacteria (gram positive bacteria)</td>
</tr>
<tr>
<td>Defensins</td>
<td>Small proteins</td>
<td>Form pores in the plasma membrane of microbes, compromising their structural integrity</td>
</tr>
<tr>
<td>Dermicidin</td>
<td>Small proteins produced by the skin</td>
<td>Antibacterial agent against both gram positive and gram negative bacteria; antifungal agent</td>
</tr>
<tr>
<td>Immunoglobulin A (IgA)</td>
<td>Specific type of antibody present in areas exposed to the environment</td>
<td>Binds with a specific foreign substance (antigen)</td>
</tr>
<tr>
<td><strong>OTHER SECRETIONS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lacrimal fluid</td>
<td>Fluid produced by lacrimal glands; contains lysozyme and IgA</td>
<td>Washes microbes away from surface of eyes; contains antimicrobial agents</td>
</tr>
<tr>
<td>Cerumen</td>
<td>Waxy secretions within external auditory meatus</td>
<td>Waterproofs external auditory meatus; may trap microbes in external ear</td>
</tr>
</tbody>
</table>
**22.3b Nonspecific Internal Defenses: Cells**

**LEARNING OBJECTIVE**

8. Describe the cells that function as part of the nonspecific internal defenses in providing innate immunity.

**Nonspecific internal defenses** of the innate immune system include (1) activities of various types of cells; (2) chemicals such as interferon and complement; and (3) physiologic processes that include the inflammatory response and development of a fever (figure 22.2). The structure and function of the innate immune cells are organized and described here by their function. Refer to figure 22.3 as you read through this section.

**Phagocytic Cells**

Phagocytic cells include **neutrophils**, **macrophages**, and **dendritic cells**, which engulf unwanted substances such as infectious agents and cellular debris through phagocytosis (figure 22.3a) (see sections 6.1a and 18.3c). The vesicle formed during phagocytosis that contains the unwanted substance (a **phagosome**) merges with a lysosome to form a **phagolysosome**. Within the phagolysosome, digestive enzymes contributed from the lysosome chemically digest the unwanted substances. Destruction of bacteria and viruses within neutrophils and macrophages is facilitated by the production of reactive oxygen-containing molecules (e.g., nitric oxide, hydrogen peroxide, superoxide); the release of these molecules is called a **respiratory burst** (or **oxidative burst**). Degraded residues of the engulfed substance are then released from the cell by exocytosis. Phagocytosis and the subsequent destruction of microbes are highly effective in protecting us. In fact, most microbes that enter the body are engulfed and destroyed by phagocytic cells. Participation in phagocytosis however, is fatal for neutrophils, which die soon after engulfing microbes. Dead neutrophils become the major component of the pus that is produced during some infections (see Clinical View 22.1: “Pus and Abscesses”).

Macrophages and dendritic cells, in comparison, continue to function following phagocytosis. They serve an additional role, which is to present fragments of the microbe on their cell surface to T-lymphocytes. This process, called **antigen presentation**, is necessary for initiating adaptive immunity and is described in detail in section 22.4c.

**Proinflammatory Chemical-Secreting Cells**

Chemical-secreting cells that enhance inflammation (which is described in section 22.3d) include both **basophils** and **mast cells** (figure 22.3b). Recall from section 18.3c that basophils circulate in the blood and mast cells reside in connective tissue of the skin, mucosal linings, and various internal organs. Substances secreted by basophils and mast cells increase fluid movement from the blood to an injured tissue. They also serve as **chemotactic chemicals**, which are molecules that attract immune cells as part of the inflammatory response.

Basophils and mast cells release granules during the inflammatory response. These granules contain various substances, including **histamine**, which increases both vasodilation and capillary permeability, and **heparin**, an anticoagulant. They also release **eicosanoids** (T’kō-sā′noydz) from their plasma membrane (see section 17.3b), which increase inflammation.

**Apoptosis-Initiating Cells**

**NK (natural killer) cells**, which are located within secondary lymphatic structures, destroy a wide variety of unhealthy or unwanted cells through apoptosis (see section 4.10). The types of cells eliminated by NK cells include virus-infected cells, bacteria-infected cells, tumor cells, and cells of transplanted tissue (figure 22.3c).

**Figure 22.3 Cells of the Innate Immune System.** The cells of the innate immune system use multiple tactics to combat pathogens, including (a) phagocytosis (example shown is a macrophage), (b) chemical secretion that increases inflammation (example shown is a basophil), (c) chemical secretion by NK cells that destroys unhealthy cells by inducing apoptosis, and (d) chemical secretion by eosinophils that helps eliminate parasites.
NK cells patrol the body in an effort to detect unhealthy cells, a process referred to as immune surveillance. NK cells make physical contact with unhealthy cells and destroy them by release of cytotoxic chemicals. These cytotoxic chemicals include perforin, which forms a transmembrane pore in the unwanted cells, and granzymes, which then enter the cell through the transmembrane pore initiating apoptosis. Apoptosis is a form of cellular death in which the cell does not lyse (i.e., rupture), but rather "shrivels"; this helps limit the spread of the infectious agent.

**Eosinophils**

Eosinophils (é’-sin’-ō-fil) target multicellular parasites, attacking the organisms’ surfaces (figure 22.3d). Mechanisms of destruction include degranulation and release of enzymes and other substances (e.g., reactive oxygen-containing compounds, neurotoxins) from the eosinophils that are lethal to the parasite (see section 18.3c). Like NK cells, eosinophils can release proteins that form a transmembrane pore to destroy cells of the multicellular organism.

Eosinophils also participate in the immune response associated with allergy and asthma (see Clinical View 22.8: “Hypersensitivities”) and engage in phagocytosis of antigen-antibody complexes (see section 22.8b).

Each of the innate immune cells is able to “see” many different types of microbes as foreign. How is this possible? Microbes (e.g., bacteria, viruses) possess molecular structures (or motifs) that they have in common. These molecular structures may be on the microbe’s surface (e.g., bacterial cell wall) or within the microbe (e.g., viral RNA). These patterned molecular structures serve as “hazard signs” to the innate immune cells. Our innate immune cells possess pattern recognition receptors (e.g., toll-like receptors, or TLRs) on their cell surface, which allows them to make physical contact with these common molecular motifs, like two pieces of a puzzle fitting together. This binding of the immune cell to the microbe activates each type of the innate immune cells to function as just described.

**Complement System**

Complement is a diverse array of proteins (at least 30) produced by our liver and released into the blood. Individual complement proteins

<table>
<thead>
<tr>
<th>Figure 22.4 Effects of Interferon. Interferon (IFN) is one category of cytokines released from a variety of cells. A virus-infected cell releases IFN-α and IFN-β, which stimulate antiviral changes to neighboring cells to prevent their infection and induce NK cells to both destroy virus-infected cells and release IFN-γ to activate macrophages to destroy virus-infected cells.</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: A body cell is first infected with a virus (see section 22.1).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 2: In response, the virus-infected cell releases both IFN-α and IFN-β.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 3a: IFN-α and IFN-β bind to receptors of neighboring body cells. This triggers these cells to synthesize enzymes that both destroy viral RNA or DNA and inhibit synthesis of viral proteins. Thus, these cells are protected from becoming infected with the virus.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 3b: IFN-α and IFN-β also stimulate NK cells to destroy the virus-infected cells by apoptosis (see section 22.3b).</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Step 4: NK cells release IFN-γ to stimulate macrophages to aid in destroying the virus-infected cells through phagocytosis.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Interferons**

Recall from section 22.2b that interferons (IFNs) are a category of cytokines (table 22.2). Here we describe the process of how IFNs serve as a nonspecific defense mechanism against the spread of any viral infection (figure 22.4).

- **Step 1**: A body cell is first infected with a virus (see section 22.1).
- **Step 2**: In response, the virus-infected cell releases both IFN-α and IFN-β.
- **Step 3a**: IFN-α and IFN-β bind to receptors of neighboring body cells. This triggers these cells to synthesize enzymes that both destroy viral RNA or DNA and inhibit synthesis of viral proteins. Thus, these cells are protected from becoming infected with the virus.
- **Step 3b**: IFN-α and IFN-β also stimulate NK cells to destroy the virus-infected cells by apoptosis (see section 22.3b).
- **Step 4**: NK cells release IFN-γ to stimulate macrophages to aid in destroying the virus-infected cells through phagocytosis.

**Antimicrobial Proteins**

Antimicrobial proteins are specific types of molecules of the innate immune system that function against microbes. Two of those, interferons and complement, are described in this section.

**WHAT DID YOU LEARN?**

1. What distinguishes neutrophils from dendritic cells? How do basophils differ from mast cells?
2. How do NK cells accomplish the task of eliminating unwanted cells?
3. Explain the general function of interferons.
4. Define the complement system, and describe how it is activated.
5. Describe the four major means by which complement participates in providing innate immunity.

**LEARNING OBJECTIVES**

9. Explain the general function of interferons.
10. Define the complement system, and describe how it is activated.
11. Describe the four major means by which complement participates in providing innate immunity.

**CONCEPT CONNECTION**

In section 18.3c, we discussed the differential count of white blood cells, a process that measures the amount of each type of leukocyte in your blood. Differential counts are useful in diagnosing different types of infections. For example:

- An increase in neutrophils is associated with an acute bacterial infection.
- Monocytes may increase with chronic inflammatory disorders or tuberculosis.
- An increase in eosinophils occurs in response to a parasitic infection.
- An elevated number of lymphocytes generally is associated with viral infections or with chronic bacterial infections.

In contrast, decreased lymphocyte counts can occur with HIV infection and sepsis (presence of a large number of pathogens in the blood).
are generally identified with the letter “C” followed by a number (e.g., C1, C2). These proteins are very abundant and make up approximately 10% of the blood serum proteins. The collective name for these proteins is derived from how they complement, or work along with, antibodies (proteins produced by differentiated B-lymphocytes, which are described in section 22.8).

The liver continuously synthesizes and releases inactive complement proteins into the blood. Once in the blood, inactive complement proteins are activated by an enzyme cascade. (Recall from section 18.4c that a similar process of an enzyme cascade of inactive proteins produced by the liver is also involved in blood clotting.)

Activation of complement occurs following entry of a pathogen into the body. Two of the major means of activation include the classical pathway, in which a complement protein binds to an antibody that has previously attached to a foreign substance (i.e., an antigen), and the alternative pathway, in which surface polysaccharides of certain bacterial and fungal cell walls (see section 22.1) bind directly with a complement protein. Note that antibody is required for activation by the classical pathway, but not for activation by the alternative pathway.

Following its activation, the complement system mediates several important defense mechanisms, and it is especially potent against bacterial infections (figure 22.5).

- **Opsonization** (op’sō-nā-shūn) is the binding of a protein (in this case, complement) to a portion of bacteria or other cell type that enhances phagocytosis. The binding protein is called an opsonin (op’sō-nin). The binding of complement makes it more likely that a substance is identified and engulfed by a phagocytic cell (e.g., macrophage). An opsonin functions as a red flag to indicate the tagged microbe.

- **Inflammation.** Complement increases the inflammatory response through the activation of mast cells and basophils and by attracting neutrophils and macrophages (see section 22.3d).

- **Cytolysis.** Various complement components (e.g., C5–C9) trigger direct killing of a target by forming a protein channel in the plasma membrane of a target cell called a membrane attack complex (MAC). The MAC protein channel compromises the cell’s integrity, allowing an influx of fluid that causes lysis of the cell.

- **Elimination of immune complexes.** Complement links immune (antigen-antibody) complexes to erythrocytes so they may be transported to the liver and spleen. Erythrocytes are stripped of these complexes by macrophages within these organs, and the erythrocytes then continue circulating in the blood.

**LEARNING STRATEGY**

You can remember the various actions of complement with the acronym O-ICE: Opsonization, Inflammation, Cytolysis, and Elimination of immune complexes.

**WHAT DID YOU LEARN?**

1. How is the complement system defined? What are the four major means by which complement participates in providing innate immunity?

**22.3d Nonspecific Internal Defenses: Inflammation**

**LEARNING OBJECTIVES**

12. Define inflammation, and discuss the basic steps involved, including the formation of exudate and its role in removing harmful substances.

13. Describe the benefits of inflammation.

14. List the cardinal signs of inflammation, and explain why each occurs.

**Inflammation,** or the **inflammatory response,** is an immediate, local, nonspecific event that occurs in vascularized tissue against a great variety of injury-causing stimuli. Inflammation occurs, for example, in response to a scratch of your skin, a bee sting, overuse of a body structure (e.g., pitching arm), or proteolytic enzymes released by fungi. This physiologic process is the major effector response of the innate immune system and is successful in helping to eliminate most infectious agents and other unwanted substances from the body!

**Events of Inflammation**

Inflammation involves several steps (figure 22.6). The first step is the release of various chemicals. Damaged cells of injured tissue, macrophages, dendritic cells, basophils, mast cells, and infectious organisms release numerous chemicals that promote inflammation (e.g., histamine, leukotrienes, prostaglandins, interleukins, TNFs, and chemotactic factors). Table 22.4 lists various chemicals of inflammation, describes their function, and identifies their source.

The second step encompasses vascular changes. Released chemicals cause a variety of responses in local blood vessels, including vasodilation of arterioles, increase in capillary permeability, and

---

**Figure 22.5 Complement System.** Upon activation, complement (C) proteins protect the body through various mechanisms, including opsonization, increasing inflammation, cytolysis of target cells, and elimination of immune complexes.
stimulation of the capillary endothelium to provide molecules for leukocyte adhesion (cell-adhesion molecules, or CAMs).

The third step involves the recruitment of leukocytes. Leukocytes make their way from the blood to the infected tissue through the following processes:

- **Margination** is the process by which CAMs on leukocytes adhere to CAMs on the endothelial cells of capillaries within the injured tissue. The result is similar to “cellular Velcro.” Neutrophils are generally the first to arrive and are short-lived, followed later by the longer-lived macrophages.

- **Diapedesis** (dī′ə-pē-dē-sis) is the process by which cells exit the blood by “squeezing out” between vessel wall cells, usually in the postcapillary venules, and then migrate to the site of infection (see section 18.3c).

- **Chemotaxis** is migration of cells along a chemical gradient (see section 18.3c). Chemicals released from damaged cells, dead cells, or invading pathogens diffuse outward and form a chemical gradient that attracts immune cells. Recruited cells also participate in the inflammatory response through the release of specific cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), that stimulate leukopoiesis within red bone marrow (see section 18.3a). This helps account for the increase in leukocyte count that occurs during an active infection. Macrophages may also release pyrogens, such as interleukin 1 (IL-1), that induce a fever (see section 22.3e).

**Delivery of plasma proteins** also occurs, as shown in the fourth step. Selective plasma proteins are brought into the injured or infected site, including immunoglobulins (described in section 22.8), complement (just described), clotting proteins, and kinins. Clotting proteins lead to formation of a clot that walls off microbes and prevents them from spreading into blood and other tissues (see section 18.4c). However, some bacterial species can dissolve clots. Kinins (kīˈnīnz) are produced from kininogens, which are inactive plasma proteins produced by the liver (and released into and transported by the blood) and locally by numerous other cells. Kinins, including bradykinin, are activated by tissue injury and have similar effects to histamine; they increase capillary permeability and the production of CAMs by the capillary endothelium. Kinins also stimulate sensory pain receptors and are the most significant stimulus for causing the pain associated with inflammation.

**Effects of Inflammation**

One of the most important consequences produced by the inflammatory response is a net movement of additional fluid from the blood through the infected or injured area and then into the lymph. Increased fluid, immune cells, and protein leave the capillaries and then enter the
interstitial space of the tissue; this fluid and cellular/protein mix collectively is referred to as **exudate** (eks′-ú-dát). Exudate delivers immune cells and substances needed to eliminate the injurious agent and promote healing.

This increase in fluid movement is due to several factors, including the following:

- **Vasodilation**, which allows more blood into the infected area
- **Increased capillary permeability** as endothelial cells lining the blood vessel wall contract, which causes larger openings between the endothelial cells and allows more fluid to move from the blood into the interstitial fluid

- **Loss of plasma protein**, which decreases capillary osmotic pressure, resulting in less fluid being retained in the blood and reabsorbed back into the blood during capillary exchange (see section 20.3b)

Increased hydrostatic pressure exerted by the interstitial fluid causes additional fluid uptake by lymphatic capillaries (see section 21.1a). The newly formed lymph carries with it unwanted substances that include infectious agents, dead cells, and cellular debris. The contents of lymph can then be monitored as it passes through a series of lymph nodes. You may find it helpful to think of the inflammatory response as “washing” the infected or injured area.

The inflammatory response typically slows down and tissue healing begins within 3 days. Monocytes exit the blood and become macrophages to begin the cleanup of the affected area. Bacteria, damaged host cells, and dying neutrophils are engulfed and destroyed by macrophages. Tissue repair begins as fibroblasts multiply and synthesize collagen, forming new connective tissue. (Connective tissue formation may lead to the formation of scar tissue in the case of an extensive injury.)

Several benefits are associated with the inflammatory response, including helping to eliminate pathogens by limiting their spread; destroying infectious agents and removing cellular debris; and producing the conditions for tissue repair and healing.

### Table 22.4  
**Chemicals of Inflammation**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Function in Inflammation</th>
<th>Source of the Chemical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Vasodilation; increased permeability of capillaries; conversion of an inactive protein</td>
<td>Mast cells, basophils, platelets</td>
</tr>
<tr>
<td>(kininogen)</td>
<td>released early in inflammation</td>
<td></td>
</tr>
<tr>
<td>Kinins (e.g., bradykinin)</td>
<td>Vasodilation and increased permeability of capillaries; increase production of CAMs;</td>
<td>Plasma protein produced by the liver and other cells as</td>
</tr>
<tr>
<td></td>
<td>stimulate sensory pain receptors</td>
<td>kininogen; activated by tissue injury</td>
</tr>
<tr>
<td>Leukotrienes (slow-reacting</td>
<td>Effects similar to histamine; released later in the inflammatory response</td>
<td>Eicosanoids produced from arachidonic acid molecules</td>
</tr>
<tr>
<td>substance of anaphylaxis</td>
<td>than histamine and longer lasting</td>
<td>of mast cell and basophil plasma membranes</td>
</tr>
<tr>
<td>(SRS-A))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Vasodilation, fever, stimulate sensory pain receptors</td>
<td>Eicosanoids produced from arachidonic acid molecules</td>
</tr>
<tr>
<td></td>
<td>(categories include E, D, A, F, and B)</td>
<td>of mast cell and basophil plasma membranes</td>
</tr>
<tr>
<td>Chemotactic factor</td>
<td>Attracts immune cells; release of specific chemotactic factors attract a specific type</td>
<td>Mast cells and basophils</td>
</tr>
<tr>
<td></td>
<td>of cell (e.g., neutrophil chemotactic factor attracts neutrophils early in the inflammatory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>response; with a parasitic infection, eosinophil chemotactic factor attracts eosinophils)</td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>Effects similar to histamine</td>
<td>Platelets</td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Vasodilation; may inhibit mast cells and platelets</td>
<td>Endothelium of blood vessels</td>
</tr>
<tr>
<td>Alpha-1 antitrypsin</td>
<td>Inhibits damage to connective tissue by enzymes released from destroyed phagocytes</td>
<td>Plasma protein formed by the liver</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>Activates complement by binding to polysaccharides on bacteria surface</td>
<td>Liver</td>
</tr>
<tr>
<td>IL-1 and TNF-α</td>
<td>Increase cell-adhesion molecules (CAMs) to cause margination; cause endothelial cell</td>
<td>Dendritic cells, macrophages</td>
</tr>
<tr>
<td></td>
<td>contraction to facilitate diapedesis</td>
<td></td>
</tr>
</tbody>
</table>

### INTEGRATE

#### CLINICAL VIEW 22.1

**Pus and Abscesses**

**Pus** may form in severe infections, most typically from severe bacterial infections. Pus is exudate (i.e., excess fluid, protein, and immune cells that leave the capillaries and then enter the interstitial space of the tissue) that contains destroyed pathogens, dead neutrophils, macrophages, and cellular debris. Pus may be removed by the lymphatic system or through the skin (for surface injuries). If the pus is not completely cleared, an **abscess** may form in the area, whereby the pus is walled off with collagen fibers. If an abscess forms, it usually requires surgical intervention to remove.

### INTEGRATE

#### CLINICAL VIEW 22.2

**Applying Ice for Acute Inflammation**

The advice typically given for acute inflammation is to apply ice. Ice vasoconstricts blood vessels (decreasing the inflammatory response) and numbs the area so that it seems less painful.

### WHAT DO YOU THINK?

**1** How can you tell by looking at an injured area of the skin that inflammation has occurred?

#### Cardinal Signs of Inflammation

Inflammation is accompanied by certain **cardinal signs** (i.e., major representative characteristics) that may include the following:

- **Redness**, due to increased blood flow
- **Heat**, due to increased blood flow and increased metabolic activity within the area
- **Swelling**, resulting from increase in fluid loss from capillaries into the interstitial space
• Pain, which is caused by stimulation of pain receptors from compression due to accumulation of interstitial fluid, and chemical irritation by kinins, prostaglandins, and substances released by microbes
• Loss of function (which may occur in more severe cases of inflammation due to pain and swelling)

The inflammatory response typically lasts no longer than 8 to 10 days under normal conditions. The ending of the normal acute inflammatory response (the process just described) is necessary to prevent the unwanted detrimental effects of chronic inflammation (see Clinical View 22.3; “Chronic Inflammation”).

WHAT DID YOU LEARN?
9. What is inflammation, and what are the basic steps involved in the inflammatory response?
10. In what ways does exudate assist in the body’s defense?

22.3e Nonspecific Internal Defenses: Fever

LEARNING OBJECTIVES
15. Define a fever, and describe how it occurs.
16. List the benefits and risks of a fever.

A fever is defined as an abnormal elevation of body temperature (pyrexia) of at least 1°C (1.8°F) from the typically accepted core body temperature of 37°C (98.6°F). It results from release of fever-inducing molecules called pyrogens (e.g., IL-1, IL-6, TNF-α) that are released from either infectious agents (e.g., bacteria) or immune cells in response to infection, trauma, drug reactions, and brain tumors. A fever is a physiologic process of the innate immune system and may accompany the inflammatory response.

Events of Fever

Pyrogens are released from various types of cells and circulate in the blood; they target the hypothalamus (see section 13.4c) and cause release of prostaglandin E2 (PGE2) (a local hormone). It raises the temperature set point of the hypothalamus from the normal 37°C. The following stages of a fever occur in response: onset, stadium, and defervescence. (Keep in mind that these stages can be cyclical until the pathogen is eliminated or at least brought under control.)

During the onset of a fever, the hypothalamus stimulates blood vessels in the dermis of the skin to vasoconstrict to decrease heat loss through the skin, and a person shivers to increase heat production through muscle contraction (see section 1.6b). Consequently, body temperature rises. The person may experience chills during this stage, which leads to the shivering.

The period of time when the elevated temperature is maintained is referred to as stadium. The metabolic rate increases to promote physiologic processes of the innate and adaptive immune systems that are involved in eliminating the harmful substance. The liver and spleen bind zinc and iron (minerals needed by microbes) to slow microbial reproduction.

Defervescence (def′er-ves′ents) occurs when the temperature returns to its normal set point. This happens when the hypothalamus is no longer stimulated by pyrogens, prostaglandin release decreases, and the temperature set point reverts to its normal value. The hypothalamus then stimulates the mechanisms to release heat from the body, including vasodilation of blood vessels in the skin and sweating. The person may appear flushed and the skin warm to the touch. An increase in fluid intake should occur during a fever to prevent dehydration caused by an increased loss of body fluid.

Benefits of Fever

Fever actually has numerous benefits. A fever inhibits replication of bacteria and viruses, promotes interferon activity, increases activity of lymphocytes, and accelerates tissue repair. Most recently, it has been demonstrated that a fever also increases CAMs on the endothelium of capillaries in the lymph nodes, resulting in additional immune cells migrating out of the blood and into the lymphatic tissue. Thus, it is not necessary (and may be detrimental) to treat a mild fever. Most physicians recommend letting a fever “run its course” and give fever-reducing medication only if the fever becomes very high or if the patient is in significant discomfort from the fever.

Risks of a High Fever

A fever is considered high (i.e., clinically significant) when it is above 100°F. High fevers (103°F in children, and slightly lower in an adult) are potentially dangerous because of the changes in metabolic pathways and denaturation of body proteins (see section 2.8b). Seizures may occur at sustained body temperature above 102°F (although generally they occur at much higher temperatures), irreversible brain damage may occur at body temperatures that are sustained at greater than 106°F, and death is likely when body temperature reaches 109°F.

Figure 22.7 is a visual summary of the means of providing innate immunity. Both the structures and processes that prevent entry (first line of defense) and the nonspecific internal defenses, including cells, antimicrobial proteins, and physiologic processes of inflammation and fever (second line of defense), are included. Remember that the processes of nonspecific internal defenses are generally effective in eliminating most pathogens.

WHAT DID YOU LEARN?
11. What is a fever, and what are the three stages of a fever?
12. What are the benefits and risks of a fever?

INTEGRATE

CLINICAL VIEW 22.3

Chronic Inflammation

Chronic inflammation is the condition in which inflammation continues for longer than 2 weeks. Chronic inflammation elicits all the discomfort of the inflammatory response without necessarily ridding the body of the foreign substance. Whereas the acute inflammatory response is generally characterized by neutrophils, chronic inflammation is generally characterized by the presence of cells that arrive later in the inflammatory response, such as macrophages and lymphocytes.

One primary cause of chronic inflammation is overuse injuries, which occur as a result of repetitive, minute trauma to a given area of the body. These include tennis elbow, swimmer’s shoulder, and shin splints.

Some forms of chronic inflammation occur when the processes of acute inflammation do not eliminate the pathogen or injurious agent, as with tuberculosis, allergens, a splinter that is not removed, injury to a blood vessel, or an autoimmune disorder (e.g., rheumatoid arthritis, shown in the image). Unfortunately, chronic inflammation can lead to tissue destruction and formation of scar tissue (fibrosis).
Phagocytic cells that engulf and destroy infectious agents: Neutrophils, macrophages, and dendritic cells.

Skin and mucosal membranes provide a physical, chemical, and biological barrier.

Sebaceous (oil) gland secretions called sebum are low in pH; interfere with microbial growth.

Skin: Covers body surface
- Normal flora help prevent growth of pathogenic organisms.
- Epidermis exfoliates, which removes potential pathogens.
- Dermis contains gel-like hyaluronic acid; limits spread of microbes.
- Sebaceous (oil) gland secretions are low in pH; interfere with microbial growth.
- Sweat gland secretions help wash away microbes; contain lysozyme, defensins, and dermicidin, which inhibit microbial growth.

Mucosal membranes: Line organ system tracts
- Normal flora
- Mucus traps microbes, and contains lysozyme, defensins, and IgA to defend against potential pathogens.
- Cilia sweep material along some tracts.
- Epithelium provides a physical barrier.
- Connective tissue contains hyaluronic acid; limits spread of infection.

Lacrimal gland secretions contain lysozyme, IgA.

Hairs in nasal cavity.

Saliva contains lysozyme, IgA.

Nasal secretions contain lysozyme, defensins, and IgA.

Defecation eliminates microbes.

Vomiting eliminates microbes.

HCl (low pH) destroys most microbes and microbial toxins.

Urine flushes potential pathogens from urinary tract.

Hairs in nasal cavity.

Coughing and sneezing eliminate microbes.

Sweat gland secretions help wash away microbes; contain lysozyme, defensins, and dermicidin, which inhibit microbial growth.

Normal flora help prevent growth of pathogenic organisms.

Skin: Covers body surface
- Normal flora
- Epidermis exfoliates, which removes potential pathogens.
- Dermis contains gel-like hyaluronic acid; limits spread of microbes.
- Sebaceous (oil) gland secretions are low in pH; interfere with microbial growth.
- Sweat gland secretions help wash away microbes; contain lysozyme, defensins, and dermicidin, which inhibit microbial growth.

Mucosal membranes: Line organ system tracts
- Normal flora
- Mucus traps microbes, and contains lysozyme, defensins, and IgA to defend against potential pathogens.
- Cilia sweep material along some tracts.
- Epithelium provides a physical barrier.
- Connective tissue contains hyaluronic acid; limits spread of infection.

Dermis contains gel-like hyaluronic acid; limits spread of microbes.

Normal flora

Cilia sweep material along some tracts.

Epithelium provides a physical barrier.

Connective tissue contains hyaluronic acid; limits spread of infection.

INTEGRATE CONCEPT OVERVIEW

Figure 22.7 Innate Immunity.
Innate immunity is provided by the innate immune system. This system includes the (a) first line of defense (cellular and molecular structures that help prevent entry) and (b) second line of defense (all internal, nonspecific means of eliminating a foreign substance).
**CELLULAR DEFENSES**

- Phagocytic cells that engulf and destroy infectious agents: Neutrophils, macrophages, and dendritic cells.

- Release chemicals that initiate and enhance inflammation: Basophils and mast cells.
  - Heparin is an anticoagulant.
  - Histamine increases capillary permeability.
  - Eicosanoids (e.g., leukotrienes) enhance inflammation.

- Destroy abnormal cells by release of cytotoxic chemicals: NK cells.
  - Perforin
  - Granzymes

- Destroy parasites by release of cytotoxic chemicals: Eosinophils.

**ANTIMICROBIAL PROTEINS AND CHEMICALS**

- Interferons (IFN): Antiviral substances that help prevent spread of virus.

- Complement system: Cascade of plasma proteins that is especially effective against bacteria.
  - Complement increases inflammation through activation of basophils, mast cells, and attraction of macrophages and neutrophils.
  - Complement promotes opsonization by binding to pathogens to increase phagocytosis by immune cells.
  - Complement eliminates immune complexes by attaching immune (antigen-antibody) complexes to erythrocytes.
  - Complement induces cytolysis through formation of a MAC transmembrane protein.
22.4 Adaptive Immunity: An Introduction

Recall that adaptive immunity is provided by the adaptive immune system and involves T-lymphocytes and B-lymphocytes exclusively (see figure 22.2). The lymphocytes formed and the products they secrete in the body’s defense are collectively referred to as the immune response. The adaptive immune response is initiated upon entry of a foreign substance (or antigen); however, it takes longer to effectively develop than the responses of the innate immune system. Lymphocytes must make contact with an antigen, which causes a lymphocyte to proliferate and differentiate to form a specialized clone, or “army,” of lymphocytes against that antigen. At least several days are generally required to develop an immune response upon the first exposure to the antigen, and it is for this reason that providing adaptive immunity is considered the third line of defense.

Adaptive immunity may be more specifically divided into two parts: cell-mediated immunity and humoral immunity. **Cell-mediated immunity** (or cellular immunity) is the immune response specifically involving T-lymphocytes, which differentiate into helper T-lymphocytes and cytotoxic T-lymphocytes. In comparison, **humoral immunity** (or antibody-mediated immunity) is the immune response involving B-lymphocytes that develop into plasma cells to synthesize and release antibodies. A general overview of the two branches of adaptive immunity is shown in **figure 22.8**.

In this section, we first introduce several central concepts related to developing adaptive immunity, including a description of antigens, the general structure of lymphocytes, antigen-presenting cells and MHC molecules (structures that interact with T-lymphocytes for their activation), and an overview of the critical events in the life cycle of a lymphocyte.

### 22.4a Antigens

**LEARNING OBJECTIVES**

17. Describe the features of an antigen, and explain what is meant by antigenic determinant.
18. Explain immunogenicity, and list attributes that affect it.
19. Discuss how haptens stimulate immune responses.

Pathogenic organisms and other foreign substances are detected by T-lymphocytes and B-lymphocytes because they contain antigens. An **antigen** (an’ti-gen; anti[body] + gen = producing) is a substance that binds to a component of the adaptive immune system (T-lymphocyte or an antibody). Antigens are unique to each infectious agent and are usually proteins or large polysaccharide molecules (see section 2.7). Examples of antigens include parts of infectious agents such as the protein capsid of viruses, cell wall of bacteria or fungi, and bacterial toxins (see section 22.1). Tumor cells also contain antigens. In the case of cancerous cells, mutations occur that generally result in the production of unique (abnormal) proteins designated as tumor antigens.

**Foreign antigens**, or nonself-antigens, bind with the body’s immune components because they are different enough in structure from the human body’s molecules. In contrast, the body’s molecules (structures called self-antigens) typically do not bind with the body’s immune components. Lymphocytes are generally very effective in distinguishing a self-antigen from foreign antigen. One malfunction of the adaptive immune system, however, involves the lymphocytes reacting to self-antigens as if they were foreign. These conditions are collectively called **autoimmune disorders** (see Clinical View 22.4: “Autoimmune Disorders”). (Note that plastic and some metals are generally not antigens and are “ignored” by the immune system. This accounts for why plastics and metals, including titanium, stainless steel, and cobalt chrome, are used in artificial implants such as for a hip replacement.)
Lymphocytes normally have contact with only a portion of the antigen. The specific site on the antigen molecule that is recognized by lymphocytes (and antibodies) is referred to as the **antigenic determinant**, or epitope. Each type of antigenic determinant has a different shape, and a pathogenic organism can have numerous different antigenic determinants. Figure 22.9 shows an antigen and several antigenic determinants.

An antigen that induces an immune response is more specifically called an **immunogen**, and its ability to cause an immune response is termed its **immunogenicity**. Important attributes that affect an antigen’s immunogenicity include degree of foreignness, size, complexity, and quantity of the antigen. An increase in one or more of these attributes increases the antigen’s ability to elicit an immune response, and thus its immunogenicity.

Some substances are too small to function as an antigen alone but, when attached to a carrier molecule in the host, become antigenic and trigger an immune response; these small molecules are called **haptens** (hap’ten; hapt = to grasp). An example is the lipid toxin in poison ivy, which penetrates the skin and combines with a body protein forming a molecular complex, which triggers an immune response. Hapten-stimulating immune responses account for hypersensitivity reactions to drugs, such as penicillin, and to chemicals in the environment, such as pollen, animal dander, mold, and snake or bee venom (see Clinical View 22.8: “Hypersensitivities”).

**WHAT DID YOU LEARN?**

1. How is an antigenic determinant related to an antigen?
2. What distinguishes a hapten from an antigen?

### 22.4b General Structure of Lymphocytes

**LEARNING OBJECTIVE**

- Describe receptors of both T-lymphocytes and B-lymphocytes.

T-lymphocytes and B-lymphocytes differ from other immune cells because each lymphocyte has a unique **receptor complex**, which are composed of several different and separate proteins. There are typically about 100,000 receptor complexes per cell. A receptor complex will bind one specific antigen. The antigen receptor (which is a portion of a receptor complex) of a T-lymphocyte is referred to as the **TCR** (or **T-cell receptor**), and the antigen receptor of a B-lymphocyte is called a **BCR** (or **B-cell receptor**) (figure 22.10).

**WHAT DO YOU THINK?**

2. If an antigen mutates, will the same lymphocytes recognize it?

The initial contact made between a TCR or BCR of a lymphocyte and the antigen it recognizes is different in T-lymphocytes and B-lymphocytes. T-lymphocytes must first have the antigen processed and presented in the plasma membrane of another type of cell. T-lymphocytes simply are not able to recognize the antigen without this preliminary step. In contrast, B-lymphocytes can make direct contact with an antigen.

---

**INTEGRATE**

**CLINICAL VIEW 22.4**

**Autoimmune Disorders**

**Autoimmune disorders** occur when the immune system does not have tolerance for a specific self-antigen and subsequently initiates an immune response to these self-antigens as if they were foreign. Lack of tolerance and the development of autoimmune disorders can result from cross reactivity, from altered self-antigens, or when immune cells enter an area of immune privilege.

**Cross-reactivity** occurs when a foreign antigen is similar in structure to a self-antigen and the immune system is unable to distinguish between the two. For example, antigens of *Streptococcus* bacteria are similar to certain heart proteins, and immune cells damage the bicuspid (mitral) and aortic valves, resulting in **rheumatic heart disease**.

**Altered self-antigens** occur when a microbe induces changes in a specific protein in the body (self-antigen) and the immune cells now respond to it as if it were foreign. Examples of diseases include the following:

- **Type 1 (insulin-dependent) diabetes**, which is thought to result from a microbe’s inducing changes in the proteins of the beta cells of the pancreatic islets in the pancreas; the immune system then destroys these cells (see Clinical View 17.8: “Conditions Resulting in Abnormal Blood Glucose Levels”).
- **Multiple sclerosis**, which results from the destruction of the myelin sheath formed by oligodendrocytes; this destruction is caused by T-lymphocytes (see Clinical View 12.3: “Nervous System Disorders Affecting Myelin”).

**Areas of immune privilege** are structures within the body that prevent or limit access of immune cells (e.g., the brain, eye, testes, ovaries, placenta). Previously, it was thought that these areas were protected passively by the blood-tissue barrier and lack of lymphatic drainage. However, recent studies have shown that these areas actively participate in maintaining immune privilege by producing various molecules, including specific immunosuppressive cytokines and special plasma proteins that actively destroy T-lymphocytes that infiltrate the area. If large numbers of immune cells enter an immune privileged area, they can destroy structures that are “perceived” as foreign. For example, if a male takes a forceful blow to the scrotum that destroys the blood-testis barrier, immune cells may destroy developing sperm cells and cause sterility.
T-lymphocytes have additional receptor molecules (called coreceptors) that facilitate T-lymphocyte physical interaction with a cell presenting antigen. One significant category of coreceptors is the CD molecules. In fact, the two major types of T-lymphocytes—helper T-lymphocytes and cytotoxic T-lymphocytes—can be distinguished based on the specific CD protein associated with the TCR (figure 22.10a). The plasma membranes of helper T-lymphocytes contain the CD4 protein, and the plasma membranes of cytotoxic T-lymphocytes contain the CD8 protein.

Note that the terminology associated with T-lymphocytes can be confusing because they may have several designations. Keep in mind that their names reflect either the lymphocyte’s function or the type of membrane protein receptor associated with the TCR:

- **Helper T-lymphocytes** (T\(\text{H}\)) function to coordinate the immune response—helping to initiate both cell-mediated immunity and humoral immunity, as well as enhancing certain aspects of innate immunity (e.g., activate NK cells); it is for this reason they are called “helper” T-lymphocytes. Structurally, helper T-lymphocytes contain the CD4 plasma membrane protein and are classified as CD4 (or CD4\(^+\)) cells.

- **Cytotoxic T-lymphocytes** (T\(\text{C}\)) release chemicals that are toxic to cells, resulting in their destruction. Because cytotoxic T-lymphocytes contain the CD8 plasma membrane protein, they are also classified as CD8 (or CD8\(^+\)) cells.

Various other types of T-lymphocytes are also formed, including (1) memory T-lymphocytes (both T\(\text{C}\) and T\(\text{H}\)), which cause a more rapid response to an antigen when future encounters of the same antigen occur, and (2) regulatory T-lymphocytes (Tregs), which function in suppressing the immune response. (The specific role of each is described later in the chapter.)

### Figure 22.10 T-Lymphocytes and B-Lymphocytes

The receptors of T-lymphocytes and B-lymphocytes are plasma membrane molecules. (a) Helper T-lymphocytes contain TCRs (T-cell receptors) and CD4 proteins, whereas cytotoxic T-lymphocytes contain TCRs and CD8 protein. (b) B-lymphocytes contain BCRs (B-cell receptors). Note: There are many other receptors embedded within both T-lymphocytes and B-lymphocytes. This figure depicts only the TCR, CD4, or CD8 receptors of T-lymphocytes and the BCR of B-lymphocytes.

### 22.4c Antigen-Presenting Cells and MHC Molecules

#### LEARNING OBJECTIVES

22. Describe antigen-presenting cells, and list cells that serve this function.
23. Explain the process of formation of MHC class I molecules in nucleated cells and MHC class II molecules in professional antigen-presenting cells.
24. Diagram the interaction of TCR and CD receptors of a T-lymphocyte with antigen associated with the MHC molecules of other cells.

**Antigen presentation** is the display of antigen on a cell’s plasma membrane surface. This is a necessary process performed by other cells so that T-lymphocytes can recognize an antigen. Generally, two categories of cells present antigen to T-lymphocytes: all nucleated cells of the body (i.e., all cells except erythrocytes) and a category of cells called antigen-presenting cells. The term **antigen-presenting cell (APC)** is used to describe any immune cell that functions specifically to communicate the presence of antigen to both helper T-lymphocytes and cytotoxic T-lymphocytes. Dendritic cells and macrophages (see section 22.3b), as well as B-lymphocytes, function as APCs.

Antigen presentation requires the physical attachment of antigen to a specialized transmembrane protein called **MHC**. MHC is an abbreviation for **major histocompatibility** (his’tö-kom-pat’i-bil’i-tē; histō = tissue) **complex**. This name refers to the group of genes that code for MHC molecules embedded within plasma membranes. There are two primary categories of MHC molecules: MHC class I molecules and MHC class II molecules. All nucleated cells present antigen with MHC class I molecules, whereas APCs display antigen with both MHC class I molecules and MHC class II molecules (a molecule displayed only by APCs).

#### Synthesis and Display of MHC Class I Molecules on Nucleated Cells

**MHC class I molecules** are glycoproteins; they are genetically determined and are unique to each individual (see Clinical View 22.5: “Organ Transplants and MHC Molecules”).

### WHAT DID YOU LEARN?

What features distinguish the receptors of helper T-lymphocytes, cytotoxic T-lymphocytes, and B-lymphocytes?
MHC class I molecules are continuously synthesized by the rough endoplasmic reticulum (RER), inserted into the ER, shipped within and modified by the endomembrane system (see section 4.6a), and then embedded within the plasma membrane for the purposes of displaying peptide fragments of endogenous proteins (proteins within the cell). This process is referred to as the endogenous pathway (figure 22.11a).

A significant event occurs during the synthesis and transport of MHC class I molecules to the cell surface involving the endogenous pathway: Peptide fragments in the cell randomly bind with the MHC class I molecules. This occurs within the RER. These peptide fragments in uninfected, healthy cells are simply partially degraded proteins of the cell and are considered “self.” Consequently, in uninfected,
healthy cells, MHC class I molecules are displaying only self-antigens on their surface. These self-antigens are ignored or tolerated by the T-lymphocytes.

However, if the cell is infected, the antigens presented are foreign antigens (figure 22.11b). Proteins of an intracellular infectious agent (e.g., viral particle) are cleaved by a proteasome into peptide fragments of 3 to 15 amino acids (see section 4.6b); these degraded peptide fragments of the infectious agent are considered “nonself.” The peptide fragments of the infectious agent that are in the cytosol are shipped into the RER, where the peptide fragments combine with MHC class I molecules within the RER. Through the endomembrane system, the MHC class I molecules with bound foreign antigen are shipped to the plasma membrane, where they are displayed at the cell surface. We will see that the display of foreign antigens with an MHC class I molecule provides the means of communicating specifically with cytotoxic T-lymphocytes and will result in the destruction of these infected cells.

Synthesis and Display of MHC Class II Molecules on Professional Antigen-Presenting Cells

Recall that APCs display both MHC class I and MHC class II molecules. MHC class I molecules are synthesized in an APC in a manner similar to other nucleated cells. Here we describe the synthesis and display of MHC class II molecules.

The MHC class II molecule, like the MHC class I molecule, is a glycoprotein continuously synthesized by the rough endoplasmic reticulum (RER), modified by the endomembrane system, and then embedded within the plasma membrane (figure 22.12). However, antigens are presented with MHC molecules only after an APC (e.g., macrophage, dendritic cell) first engulfs exogenous antigens (pathogens, cellular debris, or other potentially harmful substances located outside of cells). The process involving proteins that are engulfed from outside a cell is referred to as the exogenous pathway. (Recall from section 22.3b that innate immune cells, including dendritic cells and macrophages, recognize microbes through pattern recognition receptors, such as toll-like receptors, that are displayed on their cell surface, which bind with molecular motifs of a microbe.)

Figure 22.12 Formation and “Docking” of MHC Class II Molecules in Antigen-Presenting Cells. Antigen-presenting cells (APCs), which include dendritic cells, macrophages, and B-lymphocytes, display both MHC class I and MHC class II molecules. Here we see the engulfment of exogenous antigen (Ag) (antigen from outside a cell) and its presentation with MHC class II molecules in the plasma membrane.
A phagosome (vesicle) is formed as the APC engulfs the microbe through phagocytosis. The phagosome containing foreign antigen merges with a lysosome to form a phagolysosome, where the substance is digested into peptide fragments. The vesicle containing peptide fragments (antigens) then merges with vesicles containing newly synthesized MHC class II molecules. The peptide fragments are then “loaded” into the MHC class II molecules. These vesicles in turn then merge with the plasma membrane of the APC, with exogenous antigen now displayed bound to MHC class II molecules. This display of foreign antigen with an MHC class II molecule provides the means of communicating specifically with helper T-lymphocytes. A similar process occurs by APCs to display antigen with MHC class I molecules. However, this display of foreign antigen with an MHC class I molecule provides the means of communicating specifically with cytotoxic T-lymphocytes. In either case, the communication between the APCs and T-lymphocyte will trigger their activation (as described in detail in section 22.6).

Figure 22.13 illustrates how the receptors of a helper T-lymphocyte (TCR and CD4) interact with an MHC class II molecule that contains antigen on the surface of an APC (figure 22.13b), and how the receptors of a cytotoxic T-lymphocyte (TCR and CD8) interact with an MHC class I molecule that contains antigen on the surface of an APC (figure 22.13c). Details of these interactions are described in section 22.6.

WHAT DID YOU LEARN?

Which type of MHC-class molecule is found on all nucleated cells and is used to communicate with cytotoxic T-lymphocytes? Which classes are displayed on APCs, and which class is used specifically to communicate with (a) helper T-lymphocytes and (b) cytotoxic T-lymphocytes?

INTEGRATE

CLINICAL VIEW 22.5

Organ Transplants and MHC Molecules

An organ transplant involves the transfer of an organ from one individual to another (see Clinical View 5.6: “Tissue Transplants”). Examples of transplanted organs include the kidney, liver, heart, and lungs. Prior to the transplant, the donor and recipient are tested for the major histocompatibility complex (MHC) molecules and the ABO blood group antigens. No two individuals (except identical twins) have exactly the same MHC molecules.

Organ transplants are risky because the MHC molecules of the cells of the transplanted tissue or organ may be detected by the immune system as foreign. Consequently, components of the innate and adaptive immune systems attempt to destroy it. Thus, the recipient’s immune system is suppressed with drugs that make it less likely that it will detect the foreign antigens and cause rejection. However, these immunosuppressive drugs increase the risk that infectious disease and tumor cells will go undetected.

An important exception to these required precautions involves corneal transplants. The cornea of the eye is in an area of immune privilege (i.e., an area where immune cells are generally prevented from entering) (see Clinical View 22.4: “Autoimmune Disorders”). Thus, a cornea can be transplanted from one individual to another without the need for matching the tissue or administering immunosuppressive drugs.
Chapter Twenty-Two
Immune System and the Body’s Defense

(a) Formation of lymphocytes

(b) Activation of lymphocytes

(c) Effector response

Figure 22.14 Overview of Life Events of Lymphocytes.  
(a) Lymphocyte formation occurs in primary lymphatic structures (bone marrow and thymus), and mature (immunocompetent) cells migrate to secondary lymphatic structures.  
(b) Activation occurs in secondary lymphatic structures.  
(c) The effector response occurs at the site of infection.
22.4d Overview of Life Events of Lymphocytes

LEARNING OBJECTIVE

25. Identify the three significant events that occur in the lifetime of a lymphocyte.

Participation of lymphocytes in the body’s defense involves three significant events (figure 22.14):

- **Formation of lymphocytes.** The formation and maturation of lymphocytes occur within primary lymphatic structures (red bone marrow and the thymus; see section 21.3). Here T-lymphocytes and B-lymphocytes become able to recognize only one specific foreign antigen.

- **Activation of lymphocytes.** Following their formation, lymphocytes then migrate to secondary lymphatic structures (e.g., lymph nodes, the spleen, tonsils, MALT) where they are housed (see section 21.4). Typically, these locations are where lymphocytes have their first exposure to the antigen that they bind, and thus become activated. In response to activation, lymphocytes replicate to form many identical lymphocytes.

- **Effector response.** The effector response is the specific action of the T-lymphocytes and B-lymphocytes to help eliminate the antigen at the site of infection. T-lymphocytes leave the secondary lymphatic structures, migrating to the site of infection. B-lymphocytes (as differentiated plasma cells) primarily remain within the secondary lymphatic structures, synthesizing and releasing large quantities of antibodies against the antigen. The antibodies enter the blood and lymph and are transported to the site of infection.

Please note that these processes are sequential but generally differ in where they take place in the body: lymphocyte development in primary lymphatic structures, activation of lymphocytes in secondary lymphatic structures, and effector response at the site of infection.

**WHAT DID YOU LEARN?**

17. Where does a lymphocyte typically encounter an antigen for the first time: primary lymphatic structure, secondary lymphatic structure, or site of infection?

22.5 Formation and Selection of T-Lymphocytes in Primary Lymphatic Structures

Lymphocytes originate in red bone marrow (see section 18.3a). Following their formation, lymphocytes are “tested” to see whether they are able to bind antigen and respond to it—that is, whether they are immunocompetent. This process occurs primarily during development and shortly after birth in primary lymphatic structures (bone marrow and thymus). We describe how this occurs in T-lymphocytes.

22.5a Formation of T-Lymphocytes

LEARNING OBJECTIVE


T-lymphocytes originate in red bone marrow and then migrate to the thymus to complete their maturation. (The “T” of T-lymphocytes reflects the role of the thymus in its maturation.) Millions of pre-T-lymphocytes, which are called thymocytes, migrate from the red bone marrow to the thymus; they possess a unique TCR receptor and initially neither the CD4 nor the CD8 proteins (called “double negative”). Within the thymus, these cells will synthesize and display both CD4 and CD8 proteins (referred to as “double positive”). Thymocytes are immature T-lymphocytes with a TCR that was produced randomly through “gene shuffling,” a concept beyond the scope of this text. Keep in mind that each lymphocyte has a unique TCR.

Each T-lymphocyte must have its TCR tested to determine not only whether it is able to bind to the MHC molecule with presented antigen but also whether it binds only to antigen that is foreign, or “nonself.” This testing results in T-lymphocyte selection.

**WHAT DID YOU LEARN?**

18. Where does the maturation of T-lymphocytes take place?
22.5b Selection and Differentiation of T-Lymphocytes

LEARNING OBJECTIVE

27. Compare and contrast positive and negative selection of T-lymphocytes and what is meant by central tolerance.

Thymocytes go through two selection processes in the thymus to become T-lymphocytes, collectively called thymic selection (see figure 22.15 as you read through this section):

1. **Positive selection.** Positive selection occurs within the outer cortex of the thymus. The TCR embedded in the plasma membrane of a T-lymphocyte must be able to recognize and bind an MHC molecule. This is tested by having thymocytes (pre-T-lymphocytes) bind with thymic epithelial cells that have MHC molecules. Those thymocytes that can bind an MHC molecule survive, and those that cannot are eliminated. Thus, those cells that perform this function are selected for, a process referred to as positive selection (figure 22.15, step 1). Thymocytes migrate into the medulla for negative selection.

2. **Negative selection.** These cells must also not bind to any self-antigens that are presented within an MHC molecule. This is tested by thymic dendritic cells presenting self-antigens with MHC class I and II molecules. If the thymocyte does bind to the self-antigen, then it is destroyed. Thus, those cells that perform this function are selected against, a process referred to as negative selection (figure 22.15, step 2). This is the process by which cells generally learn to “ignore” molecules of the body or self-antigens, a state referred to as self-tolerance. This process, which occurs in the primary lymphatic structures, is more specifically called central tolerance.

Consequently, thymocytes that survive both positive and negative selection can bind an MHC molecule and recognize foreign antigen. Only approximately 2% of the originally formed thymocytes survive both selection processes; the remaining 98% are eliminated in the thymus by apoptosis (see section 4.10).

3. The final step in T-lymphocyte selection is the differentiation of each thymocyte into either a helper T-lymphocyte (CD4+ cell) by the selective loss of the CD8 protein, or a cytotoxic T-lymphocyte (CD8+ cell) by the selective loss of CD4 protein (figure 22.15, step 3). Consequently, two primary types of T-lymphocytes leave the thymus: helper T-lymphocytes (that are CD4+) and cytotoxic T-lymphocytes (that are CD8+).

WHAT DID YOU LEARN?

What would happen if a thymocyte that failed the negative selection test was not destroyed and instead entered the blood to circulate as a T-lymphocyte?

22.5c Migration of T-Lymphocytes

LEARNING OBJECTIVES

28. Explain why T-lymphocytes leaving the thymus are called both immunocompetent and naïve.

29. Describe the formation and function of T-lymphocytes (Tregs) in peripheral tolerance.

The T-lymphocytes that leave the thymus are immunocompetent cells (able to bind antigen and respond to it). However, each of these T-lymphocytes is also classified as a naïve T-lymphocyte. (Here the term naïve refers to T-lymphocytes that lack experience because they have not yet encountered the antigen that they recognize.) Naïve immunocompetent helper T-lymphocytes and naïve immunocompetent...
cytotoxic T-lymphocytes migrate from the thymus to secondary lymphatic structures, where they are housed (figure 22.14b).

It should be noted, however, that a subclass of CD4 cells, called regulatory T-lymphocytes (Tregs), is also formed. (These cells were previously called suppressor T-lymphocytes.) Tregs are formed from T-lymphocytes that bind self-antigens to a moderate extent compared to other CD4+ cells. Tregs migrate to the periphery (body structures outside the primary lymphatic structures), where they release inhibitory chemicals that turn off both the cell-mediated immune response and the humoral immune response. Tregs function in self-tolerance outside the primary lymphatic structures—a process that is more specifically called peripheral tolerance. Current studies have focused extensively on the role of Tregs in disease (e.g., microbial infections, autoimmune disorders, allergies, tumors; see Clinical View 22.6: “Regulatory T-Lymphocytes and Tumors”).

A similar process to form and select B-lymphocytes occurs in the bone marrow. (However, MHC is not involved in selection of B-lymphocytes.) Naive immunocompetent B-lymphocytes also then migrate to secondary lymphatic structures where they are housed and come in contact with foreign antigen that stimulates them to proliferate and differentiate. New T- and B-lymphocytes continue to form throughout one’s lifetime, and these cells participate in the immune response when exposed to a particular foreign antigen.

### 22.6 Activation and Clonal Selection of Lymphocytes

Lymphocyte activation involves physical contact between a lymphocyte and the antigen it recognizes and the subsequent proliferation and differentiation of lymphocytes into a clone of identical cells that have the same TCR or BCR that matches that specific antigen. This process of forming a clone in response to a specific antigen is called clonal selection.

The first encounter between an antigen and a lymphocyte is called an antigen challenge. It typically occurs in secondary lymphatic structures. The specific secondary lymphatic structure in the body in which the antigen challenge occurs generally depends upon the point of entry of the antigen. Antigen in the blood is taken to the spleen; antigen that penetrates the skin is engulfed and transported by epidermal dendritic cells to a lymph node; and antigen that enters through the mucosal membrane of the respiratory, gastrointestinal, urinary, or reproductive tract comes into contact with the tonsils or MALT (mucosa-associated lymphatic tissue).

### CLINICAL VIEW 22.6

**Regulatory T-Lymphocytes and Tumors**

Tumors have been shown to induce Tregs (specifically called tumor Tregs) to proliferate. The increased production of these cells results in greater than normal suppression of the immune system. Consequently, immune cells are less likely to detect the tumor cells, and the tumor continues to grow. Potential cancer treatments are in development that involve diminishing the inhibitory influences of tumor Tregs.

Both types of T-lymphocytes must undergo activation before they can carry out immune system functions. Activation of both types of T-lymphocytes requires two signals; however, the specific process differs between the two types.

### Activation of Helper T-Lymphocytes

The specifics of activation of helper T-lymphocytes is shown in figure 22.16b. The first signal is direct physical contact between the MHC class II molecule of an antigen-presenting cell (APC) and the TCR of a helper T-lymphocyte. Exogenous antigen previously engulfed by an APC is presented on its surface with MHC class II molecules (as described in section 22.4c). The APC either is housed in the secondary lymphatic structure (e.g., macrophage) or migrates there from the skin (e.g., dendritic cells) to make contact with the helper T-lymphocyte.

A helper T-lymphocyte binds to the APC to inspect the antigen: The specific TCR of a T-lymphocyte binds with the peptide fragment presented with an MHC class II molecule of the APC. This interaction is stabilized by the CD4 molecule of the helper T-lymphocyte binding to other regions of the MHC class II molecule. If the TCR does not recognize the presented antigen, it disengages from the APC. If it does recognize the antigen, contact between the two cells lasts several hours.

The second signal takes place when other receptors of the APC (e.g., B7) interact with receptors of the helper T-lymphocyte (e.g., CD28). Ultimately, helper T-lymphocytes are induced to synthesize and release the cytokine interleukin 2 (IL-2), which occurs within about 24 hours. IL-2 acts as an autocrine hormone (see section 17.3b) to further stimulate the helper T-lymphocyte from which it was released.

T-lymphocytes are activated and proliferate to form clones of helper T-lymphocytes (T-lymphocytes that possess TCRs that bind that specific antigen). Some of the cells produced are activated helper T-lymphocytes that continue to produce IL-2, and some are memory helper T-lymphocytes, cells available for subsequent encounters with the specific antigen. (Note that lack of a second signal is thought to result in helper T-lymphocytes becoming Tregs. Recall that Tregs can also be formed in the thymus when CD4 cells bind self-antigen with moderate affinity.)

### Activation of Cytotoxic T-Lymphocytes

The first signal for a cytotoxic T-lymphocyte is similar to the first stimulation for a naïve helper T-lymphocyte (figure 22.16a). However, direct physical contact is made between the TCR of a cytotoxic T-lymphocyte and a peptide fragment presented with an MHC class I molecule of either an APC or an infected cell. This interaction is stabilized by the CD8 of the cytotoxic T-lymphocyte binding to other regions of the MHC class I molecule. The second signal is the binding of IL-2 that is released from helper T-lymphocytes. IL-2 acts as a paracrine hormone (see section 17.3b) to stimulate the cytotoxic T-lymphocyte. IL-2 is required for cytotoxic T-lymphocytes to become fully activated. (Note that only APCs [e.g., dendritic cells] are able to activate naïve cytotoxic T-lymphocytes—that is, when cytotoxic T-lymphocytes are first exposed to the antigen they recognize.)

Upon activation, cytotoxic T-lymphocytes proliferate and differentiate into clones, some becoming activated cytotoxic T-lymphocytes, and others developing into memory cytotoxic T-lymphocytes that are activated upon reexposure to the same antigen.
Activation of lymphocytes occurs in secondary lymphatic structures, usually the lymph nodes or spleen. Activation results in lymphocyte proliferation and differentiation to form a clone of identical cells that includes memory cells. Two signals (costimulation) are required to activate each type of lymphocyte: (a) cytotoxic T-lymphocyte, (b) helper T-lymphocyte, and (c) B-lymphocyte.

22.6b Activation of B-Lymphocytes

LEARNING OBJECTIVE

31. Compare the activation of B-lymphocytes with that of T-lymphocytes.

Immunocompetent but naive B-lymphocytes are also activated by a specific antigen in secondary lymphatic structures. As with T-lymphocytes, two signals are required. However, B-lymphocytes do not require antigen to be presented by other nonlymphocyte cells. B-lymphocytes recognize and respond to antigens outside of cells, such as antigens of viral particles, bacterial toxins, or yeast spores.

The first signal occurs when antigen binds to the BCR, and the antigen cross-links BCRs (figure 22.16c). The stimulated B-lymphocyte engulfs, processes, and presents the antigen to the helper T-lymphocyte that recognizes that antigen. (This is similar to the action of other APCs; see section 22.4c.) The second signal occurs when an activated helper T-lymphocyte releases IL-4 to stimulate the B-lymphocyte.

Activation of B-lymphocytes causes the B-lymphocytes to proliferate and differentiate. Most of the activated B-lymphocytes differentiate into plasma cells that produce antibodies, and the remainder become memory B-lymphocytes that are activated upon reexposure of the same antigen. Memory B-lymphocytes differ from plasma cells in some respects: (1) The memory B-lymphocytes retain their BCRs, and (2) memory B-lymphocytes have a much longer life span (months to years) than plasma cells (typically 5 to 7 days). Note that B-lymphocytes can be stimulated by antigen without direct contact between a B-lymphocyte and helper T-lymphocyte under certain conditions. However, the production of memory B-lymphocytes and the various forms of antibodies (described in section 22.8) requires helper T-lymphocyte participation during B-lymphocyte activation. Observe figure 22.16 and notice the central role that helper T-lymphocytes play in activating both cytotoxic T-lymphocytes (cell-mediated branch of immunity) and B-lymphocytes (humoral branch of immunity).

WHAT DID YOU LEARN?

23. Is a separate APC required for B-lymphocyte activation, or is a B-lymphocyte able to serve the role of an APC?

24. Explain the role of cytokines that are released from helper T-lymphocytes in the activation of B-lymphocytes.

22.6c Lymphocyte Recirculation

LEARNING OBJECTIVE

32. Describe lymphocyte recirculation, and explain its general function.

One of the hurdles of developing adaptive immunity is the requirement of direct physical contact between antigen and the specific lymphocyte with the unique receptor that recognizes the antigen. It is estimated that only 1 in every 100,000 to 1 million T-lymphocytes or B-lymphocytes can bind with a specific antigen on the first exposure to that antigen—that is, during the antigen challenge. The “odds” for contact are increased because lymphocytes reside only temporarily in any given secondary lymphatic structure, and after a period of time they exit and then circulate through blood and lymph every several days. This process is referred to as
lymphocyte recirculation. Lymphocyte recirculation provides a means of delivering different lymphocytes to secondary lymphatic structures, making it more likely that a lymphocyte will encounter its antigen, if present.

WHAT DID YOU LEARN?

What advantage is provided by lymphocyte recirculation?

22.7 Effector Response at Infection Site

The effector response comprises the specific mechanisms that activated lymphocytes use to help eliminate the antigen. Each type of lymphocyte has a unique function. Helper T-lymphocytes release IL-2, IL-4, and other cytokines that regulate (or stimulate) cells of both the adaptive and innate immune systems. Cytotoxic T-lymphocytes destroy unhealthy cells by apoptosis. Plasma cells (differentiated B-lymphocytes) produce antibodies (see figure 22.8).

22.7a Effector Response of T-Lymphocytes

The "military" contribution of the different lymphocytes can be thought of as follows:

- **Helper T-lymphocytes** are generals of the army; they recruit and regulate other immune cells.
- **Cytotoxic T-lymphocytes** are highly trained soldiers; they engage in "cell-to-cell" combat against a specific foe.
- **B-lymphocytes** are the elite military forces that release "munitions" (antibodies) that are typically released from a distance.

Just as with activation, the effector response of helper T-lymphocytes and cytotoxic T-lymphocytes differs, as is reflected in their names.

**Effector Response of Helper T-lymphocytes**

Activated and memory helper T-lymphocytes leave the secondary lymphatic structure after several days of exposure to antigen. They migrate to the site of infection, where they continue to release the cytokines to regulate other immune cells (figure 22.17a).

Although helper T-lymphocytes were named based on their function in helping activate B-lymphocytes, their contributions are much more encompassing. Helper T-lymphocytes activate cytotoxic T-lymphocytes, as described in section 22.6a, through the release of cytokines (e.g., IL-2); they also enhance formation and activity of cells of the innate immune system, including macrophages and NK cells. Thus, healthy helper T-lymphocytes play a central role in a normally functioning immune system (see Clinical View 22.9: “HIV and AIDS”).

WHAT DO YOU THINK?

HIV (the virus that causes AIDS) specifically targets the helper T-lymphocytes, causing the destruction of these cells. Given the role of helper T-lymphocytes, why does this disease increase a person’s susceptibility to infectious diseases?
Chapter Twenty-Two

Immune System and the Body’s Defense

Effector Response of Cytotoxic T-Lymphocytes

Like helper T-lymphocytes, activated and memory cytotoxic T-lymphocytes also leave the secondary lymphatic structure after several days and migrate to the site of infection in the body’s tissue. Cytotoxic T-lymphocytes destroy unhealthy or infected cells that display the antigen (e.g., a virus-infected cell, bacteria-infected cell, tumor cell, foreign transplanted cell; figure 22.17b). The effector response of cytotoxic T-lymphocytes is initiated when physical contact is made between a cytotoxic T-lymphocyte and the specific foreign antigen displayed on an unhealthy or foreign cell.

If the cytotoxic T-lymphocyte recognizes the antigen presented by the infected cell (with MHC class I molecules), it destroys the cell by releasing granules containing the cytotoxic chemicals perforin and granzymes (the same substances released from NK cells described in section 22.3b). Perforin forms a channel in the target plasma membrane that increases the cell’s permeability; granzymes enter the cell through the perforin channels. Granzymes induce cell death by apoptosis, which helps to limit spread of the infectious agent. It is because the immune response of T-lymphocytes is effective against antigens associated with cells that it is referred to as cell-mediated immunity.

Antibodies circulate throughout the body in the lymph and blood, ultimately coming in contact with antigen at the site of infection. Plasma cells, over their life span of about 5 days, produce hundreds of millions of antibodies against the specific antigen. The circulating blood concentration of antibody against a specific antigen is referred to as the antibody titer. This can be a measure of immune response. The details of antibody structure and function are described next.

WHAT DID YOU LEARN?

26. Are cells of both the innate and adaptive immune systems regulated by cytokines released by helper T-lymphocytes?

27. Cell-mediated immunity is specifically effective against what type of target? Provide examples.

22.8 Immunoglobulins

An antibody is an immunoglobulin (imm′-nō-glob′-o-lin) (Ig) protein produced against a particular antigen (figure 22.18). The structure of antibodies (“bodies” against antigens) reflects their ability to target specific antigens that they may encounter. Antibodies do not destroy pathogens directly but facilitate the destruction by other immune cells.
You may find it helpful to think of the function of antibodies as “tagging” a specific antigen so that it can be eliminated. Here we consider both the structure of immunoglobulins and their actions.

### 22.8a Structure of Immunoglobulins

#### LEARNING OBJECTIVE

38. Describe the general structure of an immunoglobulin molecule, including its two functional regions.

An immunoglobulin molecule is a Y-shaped, soluble protein composed of four polypeptide chains: two identical heavy chains and two identical light chains, with flexibility at the hinge region of the two heavy chains. These four polypeptide chains are held together by covalent disulfide bonds (see section 2.8a) to form an antibody monomer (i.e., a single, Y-shaped protein). Two important functional regions of the antibody monomer are the variable regions and the constant region.

#### Variable Regions

The variable regions located at the ends of the “arms” of the antibody contain the antigen-binding site, which attach to a specific antigenic determinant of an antigen. The antigen-binding sites vary among antibodies that bind different antigens (figure 22.19). Most antibodies have two antigen-binding sites, which allow each antibody to bind to two antigenic determinants. The variable region binds the antigen through weak intermolecular forces, including hydrogen bonds, ionic bonds, and hydrophobic interactions (see section 2.3d).

#### Constant Region

The constant region contains the Fc region, which is the portion of the antibody that determines the biological functions of the antibody. The constant region is the same or nearly the same in structure for antibody molecules of a given class; there are five major classes of immunoglobulins: IgG, IgM, IgA, IgD, and IgE. These classes are described in greater detail in section 22.8c.

#### WHAT DID YOU LEARN?

29. What is the significance of the variable regions of an immunoglobulin molecule?

### 22.8b Actions of Antibodies

#### LEARNING OBJECTIVE

39. List the functions of the antigen-binding site and Fc region of antibodies, and briefly describe how each occurs.

Antibodies are effective against antigens through the use of either (1) the antigen-binding region within the variable region (at the ends of the two arms of the Y-shaped antibody) or (2) the Fc constant region (stem of the Y-shaped antibody). The antibodies immobilize specific antigens and ultimately cause their elimination by other immune cells.

The binding of the antigen-binding site with the antigen can cause neutralization, agglutination, and precipitation (Table 22.5). The three other functions first require the binding of antibody to an antigen; the Fc region of the antibody projects externally. The Fc region can then bind complement, bind to phagocytic cells to enhance phagocytosis, or bind to NK cells to trigger apoptosis.

Antibodies are especially effective in binding soluble antigens (e.g., viral particles, bacteria, toxins, yeast spores). It is because the immune response of B-lymphocytes is effective against soluble antigens (antigens dissolved in the body’s “humors”) that the action of antibodies produced by activated B-lymphocytes (i.e., plasma cells) is referred to as humoral immunity.

#### WHAT DID YOU LEARN?

30. What are the six major functions of antibodies? Which occur due to antigen-binding, and which depend on the Fc region?

### 22.8c Classes of Immunoglobulins

#### LEARNING OBJECTIVE

40. Describe the structure, location, and specific function of the five major classes of immunoglobulins.

The five classes of immunoglobulins are IgG, IgM, IgA, IgD, and IgE. These may be remembered with the acronym G-MADE. Each class of immunoglobulin is unique in a number of aspects. Table 22.6 summarizes the characteristics of the five immunoglobulin classes.

- **IgG** is a monomer (one Y-shaped protein) that is the major class of immunoglobulins. It makes up 75–85% of antibody in the blood and is the predominant antibody in the lymph, cerebrospinal fluid, serous fluid, and peritoneal fluid. IgG can participate in all of the functions previously listed for actions of antibodies, including the neutralization of toxins. Additionally, IgG antibodies cross the placenta and can be responsible for hemolytic disease of the newborn (see Clinical View 18.5: “Rh Incompatibility and Pregnancy”).

- **IgM** is normally a pentamer (composed of five monomers) found mostly in the blood. IgM is not as versatile in its biological functions as IgG. For example, IgM is not as efficient at virus neutralization. However, IgM is the most effective at causing agglutination of cells and binding complement. Additionally, naturally occurring IgM antibodies are responsible for rejection of mismatched blood transfusions (see Clinical View 18.3: “Transfusions”).

- **IgA** is typically a dimer (composed of two monomers) and is found in areas exposed to the environment, such as mucosal membranes and tonsils, and it is produced in various secretions, including mucus, saliva, tears, and breast milk (see table 22.3). IgA plays a significant role in protecting the respiratory and gastrointestinal tract. It helps to prevent pathogens (e.g., viruses, bacteria) from adhering to epithelial tissue and penetrating underlying tissue through the process of neutralization. IgA is especially effective at agglutination.

![Figure 22.19 Variable Regions of an Antibody.](image)
Neutralization. The antigen-binding site of an antibody physically covers an antigenic determinant of a pathogen to make it ineffective in establishing an infection or causing harm. For example, neutralization occurs when an antibody covers the region of a virus used to bind to a cell receptor, preventing entry of the virus into a cell (see section 22.1). A similar process neutralizes toxins (e.g., snake venom).

Agglutination. The antigen-binding site of an antibody cross-links antigens of foreign cells, causing them to agglutinate, or “clump.” This is especially effective against bacterial cells and mismatched erythrocytes in a blood transfusion (see section 18.3b).

Precipitation. The antigen-binding site of an antibody can cross-link soluble, circulating antigens such as viral particles (not whole cells) to form an antigen-antibody complex. These complexes become insoluble and precipitate out of (drop out of) body fluids. The precipitated complexes are then engulfed and eliminated by phagocytic cells such as macrophages.

**Table 22.5 Actions of Antibodies Following Antigen Binding**

**BINDING OF ANTIGEN-BINDING SITE OF AN ANTIBODY WITH ANTIGEN CAUSES**

<table>
<thead>
<tr>
<th>Neutralization</th>
<th>Agglutination</th>
<th>Precipitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody covers biologically active portion of microbe or toxin.</td>
<td>Antibody cross-links cells (e.g., bacteria), forming a “clump.”</td>
<td>Antibody cross-links circulating particles (e.g., toxins), forming an insoluble antigen-antibody complex.</td>
</tr>
</tbody>
</table>

**Complement fixation.** The Fc region of certain classes of antibodies (IgG and IgM) can bind specific complement proteins to cause activation of complement by the classical pathway. The functions of complement are described in section 22.3c and include opsonization, increasing inflammation, inducing cytotoxicity, and elimination of immune complexes.

**Opsonization.** The Fc region of certain classes of antibodies (e.g., IgG) can also cause opsonization (making it more likely that a target is “seen” by phagocytic cells). Phagocytic cells such as neutrophils and macrophages have receptors for the Fc region of certain antibody classes. The phagocytic receptors bind in a zipperlike fashion to the Fc region of the antibodies to engulf both the antigen and antibody.

**Activation of NK cells.** The Fc region of certain classes of antibodies (IgG) binds to specific receptors on NK cells (much like phagocytes). This induces NK cells to destroy abnormal cells by the release of cytotoxic chemicals that cause apoptosis of the cell. This process is called antibody-dependent cell-mediated cytotoxicity (ADCC).

**INTEGRATE LEARNING STRATEGY**

Generally, the role of antibodies as weapons is to “tie up the prisoner” until other help arrives. You can remember the six functions of an antibody with the acronyms NAP and CON: Neutralization, Agglutination, and Precipitation (NAP), as well as Complement, Opsonization, and NK cells (CON). Remember—a NAP can help you CONcentrate.
IgD is a monomer that (along with a monomer form of IgM) functions as the antigen-specific B-lymphocyte receptor. It also identifies when B-lymphocytes may be ready for activation to participate in providing adaptive immunity.

IgE is a monomer that has a very low rate of synthesis. It is generally formed in response to allergic reactions and to parasitic infections. IgE causes release of histamine and other mediators of inflammation from basophils and mast cells, and it attracts eosinophils. The formation of IgE and its response to allergens is described in section 22.9c (see Clinical View 22.8: “Hypersensitivities”).

**Class Switching**

Each plasma cell has the potential to produce different classes of antibodies. This process of changing the class of antibody produced from IgM to IgG, IgE, and IgA is called class switching. Direct contact between the helper T-lymphocytes (e.g., CD40 surface protein) and plasma cells (e.g., CD154) is required, along with the release of various cytokines from the helper T-lymphocytes. Specific cytokines determine the type of antibody class formed.

**Figure 22.20** is a visual summary of adaptive immunity. Adaptive immunity is considered the third line of defense because, although its response is initiated immediately, on the first exposure to an antigen there is a lag time that occurs from the time of exposure to the development of the immune response. This process may take several days.

**22.9 Immunologic Memory and Immunity**

One of the central features of adaptive immunity is the development of “memory” that provides immunity against a specific antigen. Here we discuss immunologic memory and how immunity is obtained through both active and passive means.

**22.9a Immunologic Memory**

**LEARNING OBJECTIVE**

41. Define immunologic memory, and explain how it occurs.

Activation of lymphocytes requires direct physical contact between a lymphocyte and an antigen. On the first exposure to an antigen (the antigen challenge), limited numbers of helper T-lymphocytes, cytotoxic T-lymphocytes, and B-lymphocytes recognize the antigen (about a 1 in 100,000 to 1 million chance of being the cell that recognizes a specific antigen). Generally, a lag time occurs between the body’s initial exposure to the antigen and the physical contact with lymphocytes required to develop an immune response.

The antigen challenge, however, causes the formation of memory cells in response to the activation of T-lymphocytes and B-lymphocytes, as described in sections 22.6a and 22.6b. These long-lived lymphocytes represent an “army” of thousands against specific antigens and are responsible for immunologic memory.

On subsequent exposures to an antigen, these vast number of memory cells make contact with the antigen more rapidly and produce a more powerful response, which is referred to as the...
Adaptive immunity is considered the third line of defense. It is the specific means by which lymphocytes defend the body against specific antigens. Development of adaptive immunity requires three events in the life of lymphocytes: (a) formation of lymphocytes within primary lymphatic structures, (b) activation and clonal selection of lymphocytes within secondary lymphatic structures, and (c) effector response of T-lymphocytes and antibodies at the site of infection.

(a) Formation of Lymphocytes

T-lymphocyte and B-lymphocyte formation and maturation into naive immunocompetent lymphocytes occur in primary lymphatic structures (red bone marrow and the thymus) primarily during development and shortly after birth, but they continue throughout one’s lifetime. These cells migrate to secondary lymphatic structures.
**Site of infection**

**CELL-MEDIATED IMMUNITY**

- Activated helper T-lymphocyte releases cytokines to stimulate activity of B-lymphocytes and cytotoxic T-lymphocytes, and regulates cells of the innate immune system.

- Activated cytotoxic T-lymphocytes release cytotoxic molecules (perforin and granzymes), causing apoptosis of foreign or abnormal cells.

**HUMORAL IMMUNITY**

- Variable region of antibody binds to antigen to cause several consequences, including neutralization of microbial cells (e.g., bacteria) and particles (e.g., virus, toxins), agglutination of cells, and precipitation of particles (e.g., toxins).

- Fc region of antibody serves as point of interaction with several structures, including complement to cause complement activation, binding of phagocytic cells to cause phagocytosis of an unwanted substance or cell, and binding of NK cells to induce apoptosis of an unwanted cell.

**Activation and Clonal Selection of Lymphocytes**

The first exposure to antigen (the antigen challenge) typically occurs in secondary lymphatic structures (e.g., lymph nodes, spleen, tonsils, MALT). Clones of activated and memory helper and cytotoxic T-lymphocytes, and plasma cells and memory B-lymphocytes, are formed.

**Effectors**

- Activated cytotoxic T-lymphocyte releases perforin and granzymes, causing apoptosis of foreign or abnormal cells.

- Activated helper T-lymphocyte releases cytokines to stimulate activity of B-lymphocytes and cytotoxic T-lymphocytes, and regulates cells of the innate immune system.

- Activated helper T-lymphocyte proliferates and differentiates to form a clone of activated and memory helper T-lymphocytes.

- Activated cytotoxic T-lymphocyte proliferates and differentiates to form a clone of activated and memory cytotoxic T-lymphocytes.

- Activated B-lymphocyte proliferates and differentiates to form a clone of plasma cells and memory B-lymphocytes.
secondary response, also known as the memory response or anamnestic (an’am-nes’tik; an = not, amnesia = forgetfulness) response. On each subsequent exposure to a specific pathogen, the pathogen is typically eliminated even before disease symptoms develop. For example, a person who develops measles will not develop measles again, even if reexposed to that virus. The virus is eliminated by activated memory T-lymphocytes, memory B-lymphocytes, and antibodies before it causes harm. This feature of immunologic memory makes adaptive immunity a highly potent means of protection. Vaccines are typically effective in developing memory, and a secondary response is seen on exposure to the substance vaccinated against (see Clinical View 22.7: “Vaccinations”).

WHAT DID YOU LEARN?
32 Briefly describe immunologic memory, and explain its significance.

22.9b Measure of Immunologic Memory

LEARNING OBJECTIVE
42. Discuss the difference between the primary response and the secondary response to antigen exposure.

Antibody titer (concentration of antibody) in blood serum is one measure of immunologic memory. The graphs shown in figure 22.21 reflect the changes in serum antibody titer (specifically, the amount of IgM and IgG in the blood) over time in response to both the initial exposure (the antigen challenge) and subsequent exposures to an antigen. The degree of protection is indicated by levels of circulating IgG.

Initial Exposure and the Primary Response
The initial exposure to a specific antigen can be in the form of an active infection or a vaccine. The measurable response of antibody production to the first exposure is called the primary response:
- Lag or latent phase. There is initially a period of no detectable antibody in the blood. This period may extend 3 to 6 days. Antigen detection, activation, proliferation, and

INTEGRATE

CLINICAL VIEW 22.7

Vaccinations

A vaccine is an attenuated (weakened) or dead microorganism, or some component of the microorganism (may be bioengineered), that is administered through one of several routes: oral, intradermal, intravenous (IV), intraperitoneal, or intranasal.

The function of a vaccine is to stimulate the immune system to develop memory B-lymphocytes (predominantly) while providing a relatively safe means for the initial exposure to a microorganism. The risk is relatively low because the microorganism (or its components) has no ability (or limited ability) to establish an infection. If an individual is later exposed to the same antigens, the secondary response is triggered and it will be swift and powerful; the individual is generally not even aware of contact with the microbe.

However, a vaccine is different from having an active infection in these ways:
- The immune response to a vaccine is predominantly from the humoral-mediated branch. The reason is that B-lymphocytes bind unattached microbes to induce humoral-mediated immunity, but few, if any, of the weakened or dead microbes in the vaccine can infect cells to induce T-lymphocytes to establish cell-mediated immunity. (The B-lymphocytes present the antigen to T-lymphocytes in some instances.)
- Depending upon the life span of the particular memory B-lymphocytes, the vaccine may provide lifelong immunity, or periodic booster shots may be needed to ensure continued protection against the antigen. For example, booster shots are needed every 10 years for protection against tetanus.
differentiation of lymphocytes, including development of memory lymphocytes, occur during the lag phase.

- **Production of antibody.** Within 1 to 2 weeks, plasma cells produce IgM and then IgG. Antibody titer levels peak and then generally decrease over time.

### Subsequent Exposures and the Secondary Response

Subsequent exposures to an antigen can occur after varying lengths of time following the initial exposure, and the measurable response to subsequent exposure is called the **secondary response:**

- **Lag or latent phase.** A much shorter lag phase occurs with subsequent exposures to the same antigen. This difference is due to the presence of memory lymphocytes.
- **Production of antibody.** Antibody levels rise more rapidly, with a greater proportion of the IgG class of antibodies. This higher level of IgG production may continue for longer periods, perhaps even years.

**WHAT DID YOU LEARN?**

33. How does the secondary response differ from the primary response? What is the advantage of the secondary response?

### 22.9c Active and Passive Immunity

**LEARNING OBJECTIVES**

43. Define active immunity and passive immunity.

44. Describe how both active and passive immunity can be acquired naturally and artificially.

Immunity can be active or passive (figure 22.22). **Active immunity** results from a direct encounter with a pathogen or foreign substance that results in the production of memory cells and can be obtained either naturally or artificially (e.g., clinically). **Naturally acquired active immunity occurs when an individual is directly exposed to the antigen of an infectious agent. Artificially acquired active immunity takes place when the exposure occurs through a vaccine. In both cases, memory cells against that specific antigen are formed.**

In contrast to active immunity, **passive immunity** is obtained from another individual or an animal, and it can be obtained naturally or artificially. Naturally acquired passive immunity occurs from the transfer of antibodies from the mother to the fetus across the placenta (IgG) or to the baby in the mother’s breast milk (IgA, IgM, and IgG). In contrast, when serum containing antibodies against a specific antigen is transferred from one individual to another, this process is referred to as artificially acquired passive immunity. For example, serum containing antibodies against the toxins associated with tetanus and botulism can be transferred to an individual who is at risk from one of these toxins. Antibodies to a poisonous snake venom (antivenom) can also be transferred to an individual who has been bitten by that species of snake. The antibodies neutralize the toxin or venom to prevent it from doing harm until the body is able to eliminate it.

In both types of passive immunity, the individual has not had an antigenic challenge and has not produced memory cells. Passive immunity lasts only as long as the antibody proteins are present in the individual. For example, the half-life of IgG in the blood is 23 days; IgM is 5 days (table 22.6).

**WHAT DID YOU LEARN?**

34. Which type of immunity—active or passive—results in the production of memory cells and generally provides lifelong protection from that antigen?
Hypersensitivity is an abnormal and exaggerated response of the immune system to an antigen. The various types of hypersensitivities are categorized based on the amount of time required for the immune response to occur following exposure to an antigen: **Acute hypersensitivities** occur within seconds; **subacute hypersensitivities** within 1 to 3 hours, and **delayed hypersensitivities** within 1 to 3 days. The difference in time of onset reflects the components of the immune system that are involved. Both acute and subacute hypersensitivity reactions involve humoral immunity. Immunoglobulin E (IgE) antibodies are involved in acute hypersensitivities, whereas subacute hypersensitivity reactions are triggered by immunoglobulin G (IgG) and immunoglobulin M (IgM). In contrast, delayed hypersensitivity reactions involve cell-mediated immunity. We limit our discussion to acute hypersensitivities.

**Acute Hypersensitivity (Allergies)**

An acute hypersensitivity is more commonly referred to as an **allergy** (or **type I hypersensitivity**), and it is an overreaction of the immune system to a noninfectious substance, or **allergen**. Examples of different allergens include pollen, latex, peanuts, and bee venom. Following exposure to the allergen, an allergic reaction occurs within seconds and continues for about a half hour.

There are three major phases associated with an allergic reaction:

1. **Sensitization phase.** An individual is exposed to an allergen. The allergen is engulfed by an antigen-presenting cell (APC) and presented to a helper T-lymphocyte (not shown in figure). The helper T-lymphocytes release cytokines that cause the B-lymphocytes to mature into plasma cells that produce IgE antibodies against the allergen. The IgE antibodies bind to basophils and mast cells (by the Fc region of the antibody) and may remain bound to these cells for several weeks or longer.

2. **Activation phase.** If the individual is reexposed to the same allergen, the allergen binds to the IgE antibodies that are bound to the basophils and mast cells, cross-linking the receptors.

3. **Effector phase.** The mast cells or basophils release chemicals (histamine, heparin, and eicosanoids) that cause an inflammatory response. The inflammatory response is responsible for the symptoms associated with allergies. The symptoms an individual experiences depend upon where the inflammatory response occurs in the body:

   - Contact with the mucous membranes of the nasal passage and conjunctiva of the eye result in a runny nose and watery eyes (**allergic rhinitis**, or **hay fever**). This is the most common site, with approximately 20% of the general population experiencing allergic rhinitis.

   - Exposure of the skin surface can result in red welts and itchy skin (**hives**).

   - Entrance into the respiratory passageway causes bronchoconstriction and increases secretion of mucus, causing labored breathing and coughing (**allergic asthma**).

   - Entrance into the gastrointestinal tract causes increased fluid secretions and peristalsis that may cause vomiting and diarrhea (not shown in figure).

   - Circulation in the blood through a bee sting or injection by needle causes systemic vasodilation and inflammation. In extreme cases, extensive loss of fluid from the blood into the interstitial space results in a marked decrease in blood volume and blood pressure. Consequently, the individual may have insufficient blood pressure to maintain adequate perfusion (**anaphylactic shock**).
INTEGRATE

CLINICAL VIEW 22.9

HIV and AIDS

AIDS (acquired immunodeficiency syndrome) is a life-threatening condition that is the result of the human immunodeficiency virus (HIV). An HIV infection targets the immune system—in particular, the helper T-lymphocyte (CD4 T-cell). HIV infects and destroys these helper T-lymphocytes over a period of time (months to years). Prolonged HIV infection leads to the devastating effects of AIDS.

Epidemiology

HIV resides in the body fluids of infected individuals, including their blood, semen, vaginal secretions, or even breast milk. HIV can be transmitted in the following ways: during unprotected sexual (vaginal or anal) intercourse, sharing hypodermic needles with other intravenous drug users, during delivery (because HIV crosses the placenta), or breastfeeding an infant. Current evidence indicates HIV is not spread by casual kissing, sharing eating utensils, using a public toilet, or casual physical contact. First seen in the United States among the homosexual male population, it is now a prominent disease among heterosexual populations. The United Nations Programme on AIDS (UNAIDS) estimates that 90% of all HIV infections are currently transmitted heterosexualy. Prior to 1985, before HIV and AIDS were well known, HIV could be transmitted through the donated blood supply. Individuals who received blood transfusions sometimes received HIV-infected blood, thereby infecting them as well. This discovery has led to more stringent screening of blood donors.

Since the early 1980s, over 78 million people have become infected with HIV, and over 39 million people have died. The incidence of AIDS is increasing throughout the world, but the disease is particularly rampant on the continents of Africa and Asia. The AIDS epidemic in Africa has led to massive numbers of deaths, and children are frequently orphaned as both parents succumb to the disease. Asian countries are seeing a surge of new HIV and AIDS cases, especially among sex workers and their clients.

Prevention

The key to limiting the spread of HIV infection is to refrain from behaviors that allow the virus’s transmission. Unprotected sexual intercourse (especially anal intercourse) can spread HIV, so individuals should either practice abstinence or protect themselves with the use of condoms. HIV can also be spread through oral sex. (Other contraceptives like birth control pills do not protect an individual from HIV infection.) Both partners in a monogamous relationship should be tested for the presence of the HIV virus (done via a simple blood test) before engaging in sexual intercourse. Intravenous drug users should not share needles. Health-care workers should wear gloves and be careful around patient bodily fluids. HIV-infected pregnant women need special prenatal care to help prevent the transmission of the virus to their fetus. In addition, HIV-infected mothers are discouraged from breastfeeding an infant, as the virus is present in breast milk. HIV cannot survive for long periods of time outside the human body. The virus can be eliminated from medical equipment or personal care items by cleaning them with a common disinfectant (such as bleach or hydrogen peroxide) or by heating them to temperatures above 135°F.

How HIV Causes Its Damage

Helper T-lymphocytes are destroyed by HIV infection. This destruction occurs in several ways. Some helper T-lymphocytes are programmed to produce HIV RNA at such a fast rate that the cell undergoes lysis, or bursts. Other helper T-lymphocytes are targeted and destroyed by other immune cells, such as macrophages or cytotoxic T-lymphocytes. Over a period of months to years, the helper T-lymphocyte population declines to a dangerously low level. Helper T-lymphocytes initiate and oversee the body’s immune response; therefore, a decrease in helper T-lymphocytes results in a loss of normal immune function.

Early Symptoms

Approximately several weeks to several months after initial HIV infection, many individuals will experience flu-like symptoms, including sore throat, fever, fatigue, headache, and swollen lymph nodes. Some people may also experience night sweats, whereas still others may be completely asymptomatic. Often, these symptoms disappear after a few weeks when the body’s other immune cells target and destroy HIV infected cells. Healthy helper T-lymphocytes divide to replace those cells that were destroyed. However, HIV continues to replicate at a faster rate than the immune system can rid itself of infected cells; in addition, the virus mutates to avoid detection. Over a period of years, the helper T-lymphocyte population drops to very low numbers, setting the stage for AIDS.

What Do HIV Blood Tests Look For?

HIV blood tests look for the evidence of HIV antibodies in the blood. These antibodies are produced by plasma cells about a month after initial infection. These antibodies indicate the body is responding to HIV infection. It can take up to 6 months for antibody levels in the blood to rise to a point where they can be detected by the blood test. Thus, individuals who have been exposed to HIV but get tested within the first 6 months may receive false negative results and are still at risk for infecting others.

When Does HIV Become AIDS?

HIV infection is diagnosed as AIDS when either a person’s helper T-lymphocyte count drops to below 200 cells per cubic millimeter (in comparison to 800 to 1200 cells per cubic millimeter for a healthy individual) or a person develops an opportunistic infection or illness.

Opportunistic infections are those that thrive due to the compromised immune system. Some examples of opportunistic illness include protozoan infections (e.g., toxoplasmosis and pneumonia caused by *Pneumocystis jiroveci*), fungal infections (e.g., candidiasis, histoplasmosis), some bacterial infections, and neoplasms (cancers such as Kaposi sarcoma, aggressive non-Hodgkin lymphoma, and cervical cancer). Opportunistic infections account for up to 80% of all AIDS-related deaths. Additionally, many AIDS patients have some form of central nervous system (CNS) complications, including meningitis, encephalitis, neurologic deficits, and neuropathies.

Treatment Options

There is no cure for HIV, so HIV infection is a lifelong illness. Current pharmaceutical treatments are “cocktails” of multiple drugs that alleviate symptoms or help prevent the spread of HIV in the body, but they cannot eradicate HIV from an infected individual. Most of these drugs also have unpleasant side effects.

Unfortunately, HIV drugs are expensive and not widely available in developing countries, where their need is greatest. One hopeful sign is that pharmaceutical companies are negotiating with these governments to make cheaper forms of the drugs available. In the meantime, education about preventing HIV infection continues throughout the world.
The immune system is a functional system composed of cells, plasma proteins, and other substances that protect the body from harmful agents.

The five major classes of infectious agents are bacteria, viruses, fungi, protozoans, and multicellular parasites. Bacteria are composed of prokaryotic cells; viruses are composed of either DNA or RNA in a protein capsid; and fungi, protozoans, and parasites are composed of eukaryotic cells.

The immune system is composed of immune cells and cytokines, and it is organized into the innate immune system and the adaptive immune system.

Immune cells circulate in the blood and are also located in body tissues, including lymphatic tissues, select organs, epithelial tissue of the skin and mucosal membranes, and connective tissue throughout the body.

Cytokines are small, soluble proteins produced by immune cells that function similarly to hormones; cytokines include interleukins, tumor-necrosis factors, colony-stimulating factors, and interferons.

Innate immunity is provided by the innate immune system. The innate immune system encompasses defenses we are born with and includes barriers to prevent entry and nonspecific internal defenses.

Adaptive immunity encompasses defenses developed by lymphocytes in response to exposure to specific antigens and includes both cell-mediated immunity (T-lymphocytes) and humoral immunity (B-lymphocytes).

The advantages of innate immunity include an immediate response against a wide array of potentially harmful substances; however, the responses do not result in memory.

The skin and mucous membranes provide a physical, chemical, and biological barrier that is usually successful in preventing entry of harmful substances. These are considered the body’s first line of defense.

Cells of the innate immune system include neutrophils, macrophages, dendritic cells, basophils and mast cells, NK (natural killer) cells, and eosinophils.

Antimicrobial proteins include interferon and the complement system.

Inflammation is an immediate, local, nonspecific response that occurs in vascularized tissue against a great variety of injury-causing stimuli. Inflammation is the major effector response of the innate immune system.

A fever is an abnormal elevation of body temperature of at least 1°C (1.8°F), and three phases associated with a fever are onset, stadium, and defervescence. Mild fevers are beneficial, whereas high fevers may be detrimental.

Adaptive immunity is initiated with stimulation of T-lymphocytes and B-lymphocytes by a specific antigen.

An antigen is a substance that binds to a component of the adaptive immune system (i.e., T-lymphocytes or antibodies).

Helper T-lymphocytes contain TCRs (T-cell receptors) and CD4 proteins, cytotoxic T-lymphocytes contain TCRs and CD8 proteins, and B-lymphocytes contain BCRs (B-cell receptors).

TCRs bind with presented antigen, and BCRs bind with free antigen (e.g., viral particles).

Major histocompatibility complex (MHC) molecules, which are plasma membrane proteins, display antigen on a cell’s surface so the antigen can be encountered by T-lymphocytes.

All nucleated cells present antigen with MHC class I molecules, and antigen-presenting cells (APCs) present antigen with both MHC class I and MHC class II molecules.

Three significant events occur in the lifetime of a lymphocyte: (a) formation, which occurs in primary lymphatic structures; (b) activation and clonal selection, which occurs within secondary lymphatic structures; and (c) participation in an effector response, which occurs at the site of infection.

Formation of T-lymphocytes begins in the red bone marrow and is completed in the thymus to produce immunocompetent but naive lymphocytes, a process that contributes to central self-tolerance.
### 22.5 Formation and Selection of T-Lymphocytes in Primary Lymphatic Structures (continued)

**22.5b Selection and Differentiation of T-Lymphocytes**
- T-lymphocytes undergo positive selection, in which their ability to recognize foreign antigen attached to an MHC molecule is determined, and negative selection, in which their tolerance for self-antigens attached to an MHC molecule is tested. Only those lymphocytes that successfully pass both types of selection are allowed to survive to become either helper T-lymphocytes or cytotoxic T-lymphocytes. (Tregs are formed from CD4 cells that moderately bind self-antigen.)

**22.5c Migration of T-Lymphocytes**
- Naive but immunocompetent T-lymphocytes migrate from the thymus to secondary lymphatic structures.
- A similar process of selection takes place in red bone marrow to produce B-lymphocytes.

### 22.6 Activation and Clonal Selection of Lymphocytes

**22.6a Activation of T-Lymphocytes**
- Activation of both helper T-lymphocytes and cytotoxic T-lymphocytes requires presentation of antigen by APCs and stimulation by interleukin 2 (IL-2).

**22.6b Activation of B-Lymphocytes**
- Activation of B-lymphocytes requires binding and engulfing antigen that is presented to a helper T-lymphocyte that recognizes the same antigen, and stimulation by IL-4 released by the helper T-lymphocyte.

**22.6c Lymphocyte Recirculation**
- The probability of an encounter occurring between a lymphocyte and the antigen it responds to is increased by lymphocyte recirculation, the circulation of lymphocyte through the blood and lymph every several days.

### 22.7 Effector Response at Infection Site

**22.7a Effector Response of T-Lymphocytes**
- Activated helper T-lymphocytes play a central role in the immune response by releasing cytokines that regulate the activation of other lymphocytes and the activity of cells of the innate immune system.
- Activated cytotoxic T-lymphocytes go to the site of infection and produce cytotoxic chemicals that kill the unwanted cells (infected cells, transplanted cells, or cancer cells) that contain antigen it recognizes.

**22.7b Effector Response of B-Lymphocytes**
- Plasma cells (differentiated B-lymphocytes) produce large amounts of antibody against a specific antigen.

### 22.8 Immunoglobulins

**22.8a Structure of Immunoglobulins**
- An antibody is an immunoglobulin that is produced against a specific antigen.
- An immunoglobulin is a Y-shaped protein. It has two identical variable regions in the arms that include the antigen-binding sites and an Fc region that determines the molecule’s biological activity.

**22.8b Actions of Antibodies**
- An antibody binds antigen and cause neutralization, agglutination, and precipitation of pathogens.
- Once antibody is bound with antigen, the Fc region of an antibody can bind complement, cause opsonization, and initiate destruction of a cell through NK cells.

**22.8c Classes of Immunoglobulins**
- There are five major classes of immunoglobulins: IgG, IgM, IgA, IgD, and IgE. Of these, IgG is the most prevalent in the blood and other body fluids.

### 22.9 Immunologic Memory and Immunity

**22.9a Immunologic Memory**
- Memory is a significant feature of acquired immunity that protects us from subsequent exposures to a given antigen.

**22.9b Measure of Immunologic Memory**
- The level of immune response can be gauged by measuring the antibody titer of a specific antibody. The first exposure results in the primary response, and subsequent exposures to the same antigen result in the secondary response.

**22.9c Active and Passive Immunity**
- Active immunity involves the production of memory cells and can be acquired through contact with an infectious agent (naturally acquired) or through a vaccine (artificially acquired).
- Passive immunity does not involve the production of memory cells because protection comes from another individual—from the mother across the placenta or in breast milk (naturally acquired) or from the serum of another individual (artificially acquired).
1. All of the following are phagocytic cells except
   a. neutrophils.
   b. T-lymphocytes.
   c. macrophages.
   d. dendritic cells.

2. This cell releases cytokines to activate B-lymphocytes, increases the activity of macrophages, and in general regulates the overall immune response.
   a. cytotoxic T-lymphocyte
   b. helper T-lymphocyte
   c. natural killer cell
   d. basophil

3. This cell is activated by binding antigen, and then engulfing and presenting the antigen with MHC class II molecules to helper T-lymphocytes. The helper T-lymphocytes release cytokines as the second form of stimulation.
   a. NK (natural killer) cell
   b. macrophage
   c. B-lymphocyte
   d. cytotoxic T-lymphocyte

4. These two cells destroy an infected cell by releasing chemicals that cause apoptosis.
   a. NK cell and cytotoxic T-lymphocyte
   b. macrophage and NK cell
   c. helper T-lymphocyte and cytotoxic T-lymphocyte
   d. B-lymphocyte and T-lymphocyte

5. All of the following are functions of antibodies except
   a. neutralization of pathogen.
   b. destruction of antigen.
   c. agglutination of antigen.
   d. opsonization.

6. The four characteristics of adaptive immunity include all of the following except
   a. activation by a specific antigen.
   b. memory.
   c. production of clones of cells that have the same TCR or BCR.
   d. effective against a wide array of pathogens.

7. During which process does additional fluid enter an injured or infected area from the blood and additional fluid is removed by the lymph vessels?
   a. fever
   b. clonal selection
   c. inflammation
   d. activation of helper T-lymphocytes

8. This chemical is released by virus-infected cells to decrease the spread of virus to nearby cells.
   a. interferon
   b. bradykinin
   c. perforin
   d. complement

9. The correct sequence of the major events in the life of a lymphocyte is
   a. effector response, formation, and activation.
   b. activation, formation, and effector response.
   c. activation, effector response, and formation.
   d. formation, activation, and effector response.

10. Two of the major actions of complement are
    a. increased inflammatory response and cytolysis.
    b. recognition and destruction of a specific antigen and cytolysis.
    c. production of antibody and increased inflammatory response.
    d. release of cytokines to increase the immune response and production of antibody.

11. Compare the general characteristics of innate immunity and adaptive immunity in terms of the cells involved, specificity, general mechanisms, and time required.

12. Define the inflammatory response, and explain its benefits.

13. Describe an antigen.

14. Describe class I and class II MHC molecules, and explain how they function in assisting T-lymphocytes in recognizing an antigen.

15. Explain positive and negative selection that occurs during the selection of T-lymphocytes.

16. Describe how helper T-lymphocytes play a pivotal role in a healthy, normally functioning immune system.

17. Explain the general function of cytotoxic T-lymphocytes.

18. Describe the functions of antibodies and complement in defending the body.

19. There are two branches of adaptive immunity: cell-mediated and humoral immunity. Distinguish the types of antigens they are each effective against.

20. Explain the difference between the primary and secondary immune response.
Can You Apply What You’ve Learned?

1. Maria, who is 3 years old, was stung by a bee. The area where the stinger entered the skin became red, warm, and swollen. This normal response to a foreign venom is called
   a. a fever.
   b. the complement cascade.
   c. an inflammatory response.
   d. an antigen challenge.

2. Jay, a young dad, takes his baby to the pediatrician several times in the first year of the child’s life. These visits will stimulate the baby to make memory cells against specific antigens. Why are these visits necessary?
   a. The baby is being vaccinated.
   b. The visits verify that the baby has a normal inflammatory response.
   c. The baby must have an unusual immune deficit that must be monitored.
   d. The baby’s blood is being filtered to remove foreign antigen.

3. A young woman has just been diagnosed with the human immunodeficiency virus (HIV). This virus is especially devastating because it infects the cells that regulate the immune response. The cells HIV infects are
   a. B-lymphocytes.
   b. helper T-lymphocytes.
   c. NK cells.
   d. cytotoxic T-lymphocytes.

4. One-year-old Matthew always seems to be sick. When his blood is tested, there are no antibodies. The physician concludes that the child is lacking
   a. the ability to develop an inflammatory response.
   b. helper T-lymphocytes.
   c. cytotoxic T-lymphocytes.
   d. B-lymphocytes.

5. Upon further testing, it is found that Matthew in question 4 does have normal cellular immunity. However, without antibodies Matthew will be less able to
   a. destroy cancer cells.
   b. destroy virus-infected cells.
   c. bind viral particles.
   d. destroy intracellular pathogens.

Can You Synthesize What You’ve Learned?

1. Dianne is an avid tennis player but has recently been complaining of tendonitis in her elbow. She knows that you work in health care and asks you to explain what caused this flare-up.

2. Stephanie is in her first year of college and has recently come down with a cold. She is running a slight fever of 100°F. Explain to her why a fever is beneficial.

3. Describe the events that occur in an individual who has an allergy to ragweed.
The respiratory system provides the means for gas exchange necessary for living cells. As cells engage in aerobic cellular respiration, they need both the uninterrupted supply of oxygen and the removal of carbon dioxide waste that is produced. This continuous exchange of oxygen and carbon dioxide between the atmosphere and body cells occurs through collective processes called respiration. Respiration requires both coordinated and integrated physiologic activities of a number of systems, including the respiratory, skeletal, muscular, nervous, and cardiovascular systems. The respiratory system is responsible for the exchange of gases between the atmosphere and the lungs. The skeletal and muscular systems alter the volume and pressure within the thoracic cavity to facilitate movement of air into and out of the lungs, whereas the nervous system stimulates and coordinates the contraction of skeletal muscles associated with breathing. The cardiovascular system transports oxygen and carbon dioxide between the lungs and the cells.

Our discussion begins by examining both the general functions and the anatomic structures of the respiratory system components. Next, we consider the processes involved in respiration, including (1) how the respiratory, skeletal, muscular, and nervous systems function together during breathing (pulmonary ventilation); (2) the exchange of respiratory gases between the lungs and blood (alveolar gas exchange) and between the blood and systemic cells (systemic gas exchange); and (3) gas transport by the cardiovascular system. We conclude by considering the influence of breathing rate on homeostasis.