17

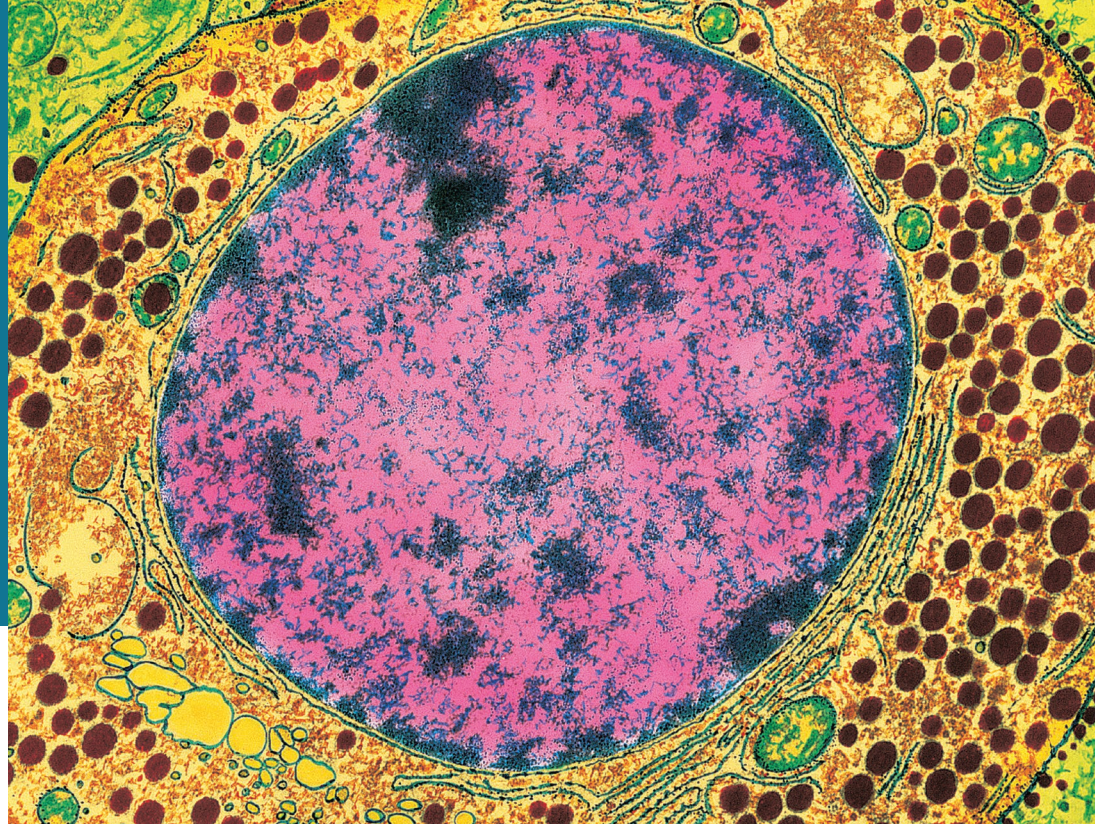


Photo: Colorized transmission electron micrograph of an endocrine cell from the anterior pituitary gland. The secretory vesicles (*brown*) contain hormones. ©Quest/Science Source

Learn to Predict

Liu Dan was one of the top wrestlers on his high school team, but he knew that his small size would make it difficult to compete at the college level. He had tried lifting weights, but that did not seem to be working. So Liu decided to try something he had never thought he would do—he began taking anabolic steroids. At first he was excited, because his muscles were larger and he felt stronger. After a few more weeks, though, he started noticing some troublesome changes: His pectoral muscles were getting larger, but they looked more feminine than masculine; his testes had shrunk; and he'd had some frightening episodes that could only be described as temper tantrums. **After reading this chapter, explain why anabolic steroids were able to alter muscle tissue growth and cause unintended changes in other tissues of the body.**

Functional Organization of the Endocrine System

If you search for the phrase "The Alton Giant" on the Internet, the image of Robert Wadlow will appear (see figure 18.8). Robert Wadlow was 8'11" when he died in 1940. His extraordinary growth was due to an overstimulation of human growth hormone (hGH; see chapter 6). Robert Wadlow's condition illustrates the powerful nature of these hormones. It also illustrates their critical role in homeostasis. Homeostasis is disrupted when hormone levels in the body are not tightly regulated. Growth hormone is one of hundreds of chemical messengers, called hormones, that circulate in the body. These chemical messengers have differences, but they all share the fundamental property of transmitting signals to target cells to regulate almost every aspect of homeostasis. This chapter focuses on one of the two major control systems in the body, the endocrine system. The other major control system is the nervous system. Here, we present the general principles of hormones; chapter 18 discusses specific hormones and their functions.

17.1 Principles of Chemical Communication

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Define *hormone* and *target tissue*.**
B. **Distinguish between endocrine and exocrine glands.**
C. **Compare and contrast the nervous system with the endocrine system.**
D. **Describe the four classes of chemical messengers.**

Characteristics of the Endocrine System

The **endocrine system** is composed of **endocrine glands** and specialized endocrine cells located throughout the body (figure 17.1). Endocrine glands secrete very small amounts of chemical messengers called **hormones** (hor′mōnz) into the interstitial fluid. The hormones diffuse into the blood to be transported to their target. Hormones circulate through the bloodstream to specific sites called **target tissues,** or *effectors*. At their target tissues, hormones stimulate a specific response. Thus, the term **endocrine** (en′dō-krin), derived from the Greek words *endo,* meaning "within," and *krino,* "to secrete," appropriately describes this system.

Endocrine glands are not to be confused with **exocrine glands.** Exocrine glands have ducts that carry their secretions to the outside of the body, or into a hollow organ, such as the stomach or intestines. Examples of exocrine secretions are saliva, sweat, breast milk, and digestive enzymes.

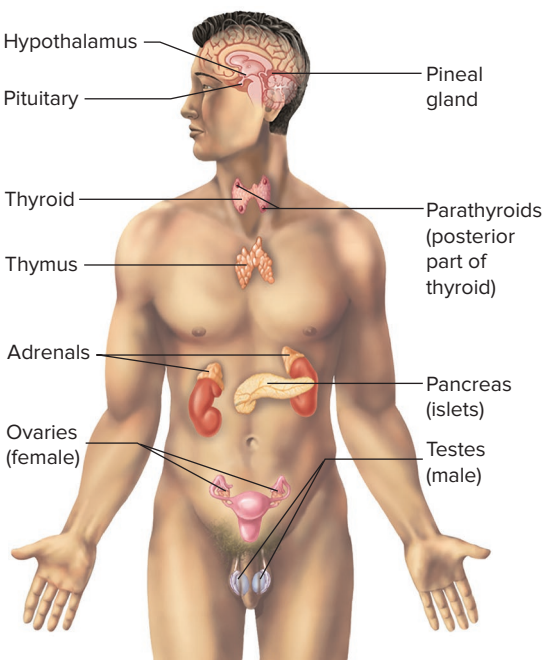


FIGURE 17.1 Major Endocrine Glands and Tissues
Glands that secrete chemical messengers that are transported to their targets by the blood are endocrine glands. AP|R

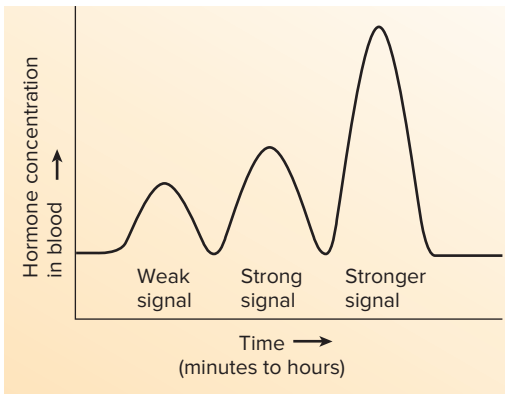
The study of the endocrine system, known as **endocrinology,** is the topic of this chapter as well as chapter 18. In this chapter, we present the general principles of hormones and, in chapter 18, we discuss specific hormones and their functions. Hormones have a role in most physiological processes in the body. However, the endocrine system does not work completely alone for every process it regulates. It works in conjunction with the body's other major regulatory system, the nervous system. Thus, before focusing on the endocrine system, it is important to understand its relationship to the nervous system.

Comparison of the Nervous and Endocrine Systems

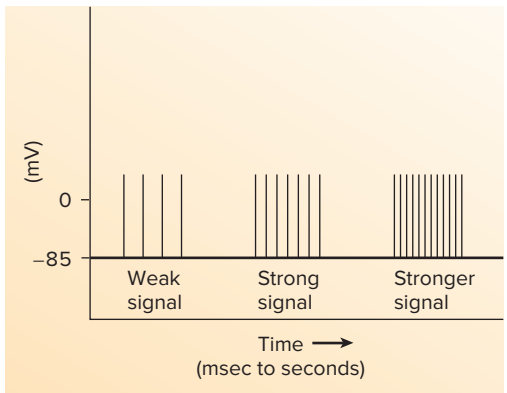
Together, the nervous system and the endocrine system regulate and coordinate the activities of essentially all body structures to achieve and maintain homeostasis. As you learned in chapter 11, the nervous system is a communication system. It transmits messages directly to its target cells through action potentials, which stimulate release of chemical messengers called neurotransmitters at synapses. Thus, the nervous system operates similarly to how you send a text to one or more people. In contrast, the endocrine system works more like Twitter. Your tweets are broadcast, so anyone can see them, but only those following you actually get them. But, instead of tweets, the endocrine system broadcasts information to the whole body through chemical messengers called hormones circulating in the bloodstream. Cells with receptors for those hormones respond to them, whereas cells lacking receptors do not.

Given that both the nervous system and the endocrine system control their targets with chemical messengers, what is the difference between the two systems? In fact, it is difficult to completely separate the two systems because they have many similarities:

1. Both systems use structures in the brain. In chapter 13, the hypothalamus is discussed as a critical area of the brain responsible for many functions, including nervous system functions and hormone production. An example of nervous function is when the hypothalamus detects changes in body temperature; it sends action potentials to either the sweat glands or skeletal muscle, depending on whether the body is too hot or too cold. On the other hand, an example of endocrine function is when the hypothalamus sends hormones to the pituitary gland that regulate the secretion of hormones from the pituitary. In addition, hypothalamic neurons synthesize two hormones, antidiuretic hormone and oxytocin, which are secreted directly into the bloodstream. Thus, the hypothalamus plays a role in both the nervous and endocrine systems.
2. In many cases, the nervous system may use certain molecules as neurotransmitters, whereas the endocrine system may use these molecules as hormones. For example, when a neuron secretes epinephrine into a synaptic cleft, it is a neurotransmitter. In contrast, when cells of the adrenal gland secrete epinephrine into the bloodstream, it is a hormone.
3. The two systems work together to regulate critical body processes. For example, epinephrine, the hormone, is important in stressful situations. However, the initial, immediate release of epinephrine, the neurotransmitter, in times of crisis



(a) **Amplitude-modulated system.** The concentration of the hormone determines the strength of the signal and the magnitude of the response. For most hormones, a small concentration of a hormone is a weak signal and produces a small response, whereas a larger concentration is a stronger signal and results in a greater response.



(b) **Frequency-modulated system.** The strength of the signal depends on the frequency, not the size, of the action potentials. All action potentials are the same size in a given tissue. A low frequency of action potentials is a weak stimulus, and a higher frequency is a stronger stimulus.

FIGURE 17.2 Regulatory Systems

(*a*) The endocrine system is based on changing the concentration of hormones. (*b*) The nervous system is based on changing the frequency of the messages.

is from the nervous system. Thus, the two systems work almost simultaneously.

4. Some neurons secrete hormones. In this case, the neuron's chemical messenger enters the bloodstream, where it functions as a hormone. As a strict part of their definition, recall that hormones circulate in the bloodstream. To help distinguish these chemical messengers from neurotransmitters and other hormones, they are often called **neuropeptides,** or *neurohormones*. An example of a neuropeptide is the labor-inducing hormone oxytocin.
5. Both neurotransmitters and hormones can affect their targets through receptors linked to G proteins (see chapter 3).

In addition to the similarities between the nervous and endocrine systems, there are some important differences:

1. *Mode of transport*. The endocrine system secretes hormones, which are transported in the bloodstream, whereas the nervous system secretes neurotransmitters, which are released directly onto their target cells.
2. *Speed of response*. In general, the nervous system responds faster than the endocrine system. However, it is not accurate to say the endocrine system responds slowly; rather, it responds *more slowly* than the nervous system. Neurotransmitters, such as acetylcholine, are delivered to their target cells in milliseconds, whereas some hormones are delivered to their target cells in seconds.
3. *Duration of response*. The nervous system typically activates its targets quickly and only for as long as action potentials are sent to the target. The target cells' response is terminated shortly after action potentials cease. In contrast, the endocrine system tends to have longer-lasting effects. Hormones remain in the bloodstream for minutes, days, or even weeks and activate their target tissues as long as they are present in the circulation. The target tissue products may remain active for a substantial length of time.

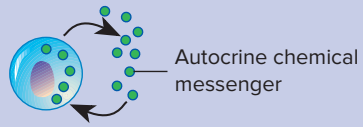
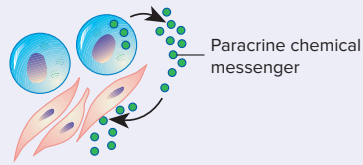
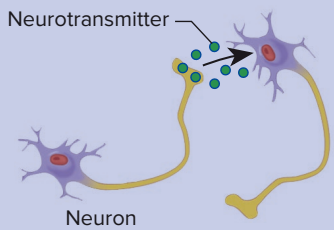
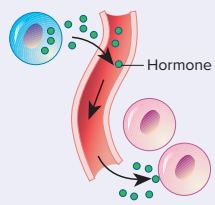
In summary, the hormones secreted by most endocrine glands can be described as **amplitude-modulated signals.** The term *amplitude* refers to the total amount of a signal that is produced. This type of signal consists of fluctuations in the *concentration* of hormones in the bloodstream (figure 17.2), over a period of time. This time period can range from minutes to hours. On the other hand, the all-or-none action potentials carried along axons can be described as **frequency-modulated signals.** The term *frequency* refers to how often a signal is sent in a certain period of time (figure 17.2). These types of signals vary in the number of signals sent but not in the amount of signal sent. A low frequency of action potentials is a weak stimulus, whereas a high frequency of action potentials is a strong stimulus. Thus, both the nervous system and the endocrine system work to maintain homeostasis using chemical messengers, but they differ from each other in the way their chemical messengers work to activate their target cells.

Classes of Chemical Messengers

The body has a remarkable capacity for maintaining homeostasis despite having to coordinate the activities of nearly 40 trillion cells. Chemical messengers from both the nervous system and the endocrine system are the primary regulators of this coordination. **Chemical messengers** allow cells to communicate with each other to regulate body activities.

Most chemical messengers are produced by a specific collection of cells or by a gland. Recall from chapter 4 that a gland is an organ consisting of epithelial cells. These cells specialize in **secretion**—the controlled release of chemicals from a cell. This text identifies four classes of chemical messengers based on the source of the chemical messenger and its mode of transport in the body (table 17.1). In this section, we describe chemical messengers in terms of how they function. But it is important to note that some chemical messengers fall into more than one functional category.

TABLE 17.1 Classes of Chemical Messengers

Chemical Messenger	Description	Example	
Autocrine	Secreted by cells in a local area; influences the activity of the same cell from which it was secreted	Eicosanoids (prostaglandins, thromboxanes, prostacyclins, leukotrienes)	
Paracrine	Produced by a wide variety of tissues and secreted into extracellular fluid; has a localized effect on nearby tissues	Somatostatin, histamine, eicosanoids	
Neurotransmitter	Produced by neurons; secreted into a synaptic cleft by presynaptic nerve terminals; travels short distances; influences postsynaptic cells	Acetylcholine, epinephrine	
Endocrine	Secreted into the blood by specialized cells; travels some distance to target tissues; results in coordinated regulation of cell function	Thyroid hormones, growth hormone, insulin, epinephrine, estrogen, progesterone, testosterone	

For example, the chemicals called prostaglandins are listed in multiple categories because they have several functions and cannot be restricted to just one class. Therefore, the study of the endocrine system includes several of the following categories:

1. *Autocrine chemical messengers*. An autocrine (*auto-*, self) chemical messenger stimulates the cell that originally secreted it. Good examples of autocrine chemical messengers are those secreted by white blood cells during an infection. Several types of white blood cells can stimulate their own replication, so that the total number of white blood cells increases rapidly (see chapter 22).
2. *Paracrine chemical messengers*. Paracrine chemical messengers act locally on neighboring cells. These chemical messengers are secreted by one cell type into the extracellular fluid and affect surrounding cells. An example of a paracrine chemical messenger is histamine, released by certain white blood cells during allergic reactions. Histamine stimulates vasodilation in nearby blood vessels.
3. *Neurotransmitters*. Neurotransmitters are chemical messengers secreted by neurons that activate an adjacent cell, whether it is another neuron, a muscle cell, or a glandular cell. Neurotransmitters are secreted into a synaptic cleft, rather than into the bloodstream (see chapter 11). Therefore, in the strictest sense neurotransmitters are paracrine agents, but for our purposes it is most appropriate to consider them as a separate category.
4. *Endocrine chemical messengers*. Endocrine chemical messengers are secreted into the bloodstream by certain glands and cells, which together make up the endocrine system. These chemical messengers travel through the general circulation to their target cells.

ASSESS YOUR PROGRESS

Answers to these questions are found in the section you have just completed. Re-read the section if you need help in answering these questions.

1. *How does an endocrine gland differ from an exocrine gland?*
2. *Describe the similarities between the nervous system and the endocrine system.*
3. *In what ways does the nervous system differ from the endocrine system?*
4. *Name and describe the four classes of chemical messengers.*

17.2 Hormones

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe the common characteristics of all hormones.**
B. **Define *binding protein*, *bound hormone*, and *free hormone* and discuss the effect of binding proteins on circulating hormone levels.**
C. **List and describe the two chemical categories of hormones.**
D. **Explain the influence of the chemical nature of a hormone on its transport in the blood, its removal from circulation, and its life span.**
E. **Describe the three main patterns of hormone secretion.**

The word *hormone* is derived from the Greek word *hormon,* which means "set into motion." Hormones are very powerful molecules, which all share general characteristics.

General Characteristics of Hormones

Hormones share several characteristics:

1. *Stability*. Hormone concentrations are stable in the bloodstream; however, some hormones are more stable than others. The life span of a given hormone varies with its chemical nature. Larger, more complex hormones are more stable, whereas smaller, simpler hormones are less stable. A hormone's life span can be expressed as its **half-life,** which is the amount of time it takes for 50% of the circulating hormone to be removed from the circulation and excreted. Some hormones have a short half-life, whereas others have a much longer half-life. For example, thyrotropin-releasing hormone (TRH) is a three-amino-acid hormone with a short half-life. Because of TRH's simple composition, it is quickly degraded in the circulation and can activate only the target cells it can reach within 2 minutes of being secreted. On the other hand, cortisol is a steroid hormone with a longer half-life, 90 minutes. Due to its lipid-soluble nature, it is not easily degraded and can activate target cells for more than an hour.
2. *Communication*. Hormones must be able to interact with their target tissue in a specific manner in order to activate a coordinated set of events. For example, the formation of reproductive organs in the fetus is activated by reproductive steroid hormones. This interaction occurs at a receptor on the target cells. Without proper functioning of the male reproductive steroid testosterone, a newborn will have the outward appearance of a female despite being genetically male. Hormones must be able to regulate specific cellular pathways once they arrive at their targets and bind to their receptors.
3. *Distribution*. Hormones are transported by the blood to many locations and therefore have the potential to activate any cell in the body, including those far away from where they were produced. However, the blood contains many hydrolytic enzymes, which break down substances. In addition, blood is an aqueous solution. These factors can present a challenge when transporting hormones to their targets. Small, water-soluble hormones are quickly digested by hydrolytic enzymes in the blood. With their small size, they become inactive with very little alteration in their structure. In addition, water-soluble hormones are easily filtered from the blood in the kidneys because they are so small. Still other hormones, such as lipid-soluble hormones, have low solubility in the blood plasma. The chemical nature of lipid-soluble hormones does not allow these hormones to easily dissolve in the plasma. Thus, some hormones require a chaperone, which binds to and protects hormones so that they arrive safely at their target. Hormones requiring a transport chaperone bind to blood proteins called **binding proteins.** Once hormones attach to a binding protein, they are then called **bound hormones.** For small hormones, the binding protein protects them from degradation by hydrolytic enzymes and from being filtered from the blood in the kidney. For lipid-soluble hormones that are insoluble in plasma, being bound to a binding protein causes them to become more water-soluble. Hormones bind only to selective binding proteins. For example, thyroid hormones bind to a specific binding protein, transthyretin; testosterone binds to a different type of binding protein, called testosterone-binding globulin; and progesterone binds to yet another type of binding protein, called progesterone-binding globulin.

The binding of hormones to binding proteins is reversible. Hormones dissociate (detach) from their binding proteins at their target tissues. Once the hormones detach from the binding protein, they are then called **free hormones.** It is important to note that some hormones always exist as free hormones because they do not have specific binding proteins to which they attach. Thus, some hormones are "always free," whereas other hormones are "sometimes free." The binding protein's affinity for its hormone determines the concentration of free hormones.

The reversible binding of hormones to their binding proteins is important because only free hormones are able to diffuse through capillary walls and bind to target tissues. When bound to a binding protein, a hormone is too large to pass through a capillary wall. The bound hormone thus serves as a reservoir for the hormone. If blood levels of the hormone begin to decline, some of the bound hormone is released from the binding proteins. Because of this reservoir function of the bound hormones, the circulating concentration of free hormones remains more stable than that of hormones that do not use binding proteins (figure 17.3). Consequently, hormones that attach to binding proteins tend to have longer half-lives than hormones that do not require binding proteins (figure 17.3).

Chemical Nature of Hormones

Hormones fit into two chemical categories: (1) lipid-soluble hormones and (2) water-soluble hormones, a distinction based on their chemical behavior. For example, recall from chapter 3 that the plasma membrane is a selectively permeable phospholipid bilayer that excludes water-soluble molecules but allows lipid-soluble molecules to pass through. Therefore, the entire basis of a hormone's interaction with its target is dependent on the hormone's chemical nature (table 17.2).

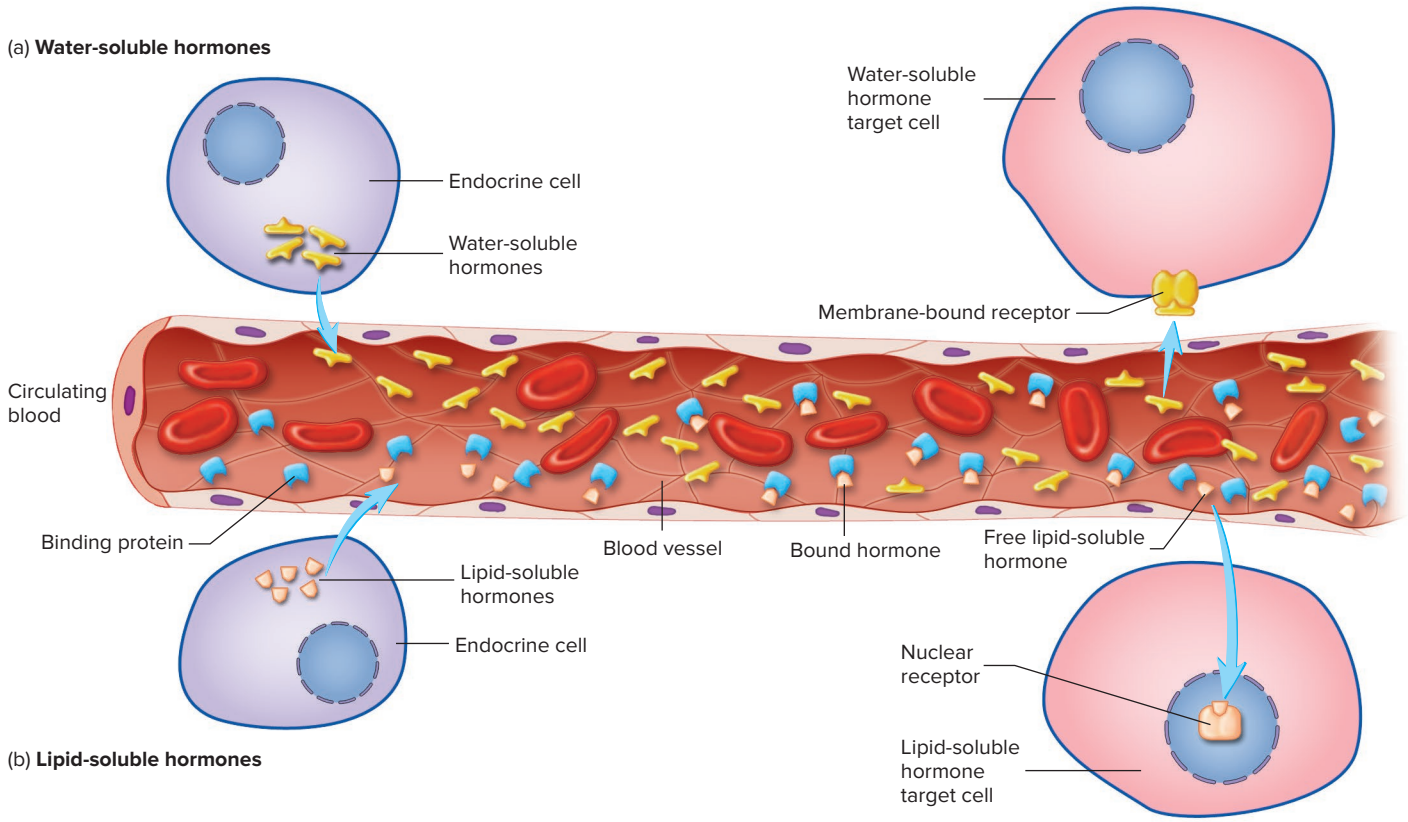


FIGURE 17.3 Effect of Binding Proteins

(*a*) Free hormones (those that circulate freely in the blood) immediately activate target cells once they are delivered from the blood. Thus, the blood levels of these hormones tend to fluctuate to a greater degree than the levels of hormones that attach to binding proteins; water-soluble hormones bind their receptors, which are membrane bound. (*b*) Hormones that are transported in the blood attached to binding proteins circulate in the blood as bound or free hormones. As the concentration of free hormones decreases, bound hormones are released from the binding proteins. This provides a chronic, stable supply of hormone and, thus, more consistent control of target cells. This is especially important for hormones that regulate basal metabolism. Lipid-soluble hormones bind their receptors in either the cytoplasm or the nucleus.

Within the two chemical categories, hormones can be subdivided into groups based on their chemical structures. Most hormones are categorized as amino acid derivatives, peptides, or proteins, including glycoproteins. However, there are two exceptions. Steroid hormones are derived from cholesterol, and thyroid hormones are derived from the amino acid tyrosine. Thyroid hormones are more like steroids in their chemical nature.

Lipid-Soluble Hormones

Lipid-soluble hormones are nonpolar and include steroid hormones, thyroid hormones, and fatty acid derivative hormones, such as certain eicosanoids.

Transport of Lipid-Soluble Hormones

Because of their small size and low solubility in aqueous fluids, lipid-soluble hormones travel in the bloodstream bound to binding proteins, proteins that chaperone the hormone. As a result, the rate at which lipid-soluble hormones are degraded or eliminated from the circulation is greatly reduced and their life spans range from a few days to as long as weeks.

Without the binding proteins, the lipid-soluble hormones would quickly diffuse out of capillaries and be degraded by enzymes of the liver and lungs or be filtered from the blood by the kidneys and would be unable to effectively regulate their targets. Circulating hydrolytic enzymes can also metabolize free lipid-soluble hormones. The breakdown products are then excreted in the urine or the bile.

In order to terminate a lipid-soluble hormone response, these hormones are removed from the circulation through a process called **conjugation** (kon-jŭ-gā′shŭn). Conjugation occurs when specific enzymes in the liver attach water-soluble molecules to the hormones. These water-soluble conjugation molecules are usually sulfate or glucuronic acid. Once the hormones are conjugated, the kidneys and liver can excrete them into the urine and bile at a greater rate.

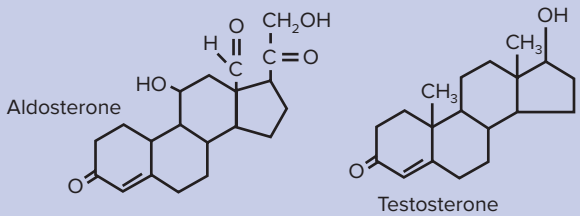
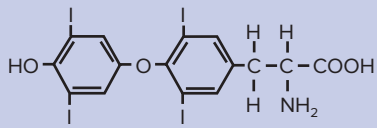
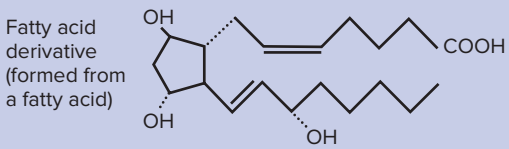
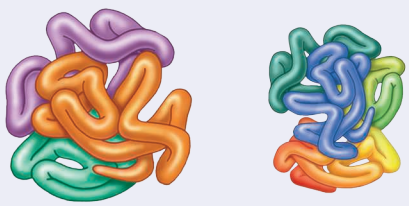
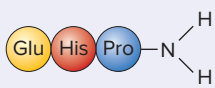
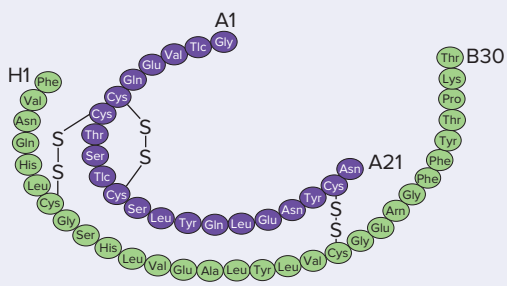
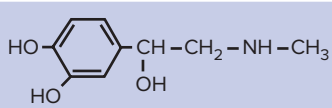
Water-Soluble Hormones

Water-soluble hormones are polar molecules; they include protein hormones, peptide hormones, and most amino acid derivative hormones.

Transport of Water-Soluble Hormones

Because water-soluble hormones can dissolve in the plasma of the blood, many circulate as free hormones, meaning that most of them dissolve directly into the plasma and are delivered to their target tissue without binding to a binding protein. Because many water-soluble hormones are quite large, they do not readily diffuse through the walls of all capillaries. Instead, they tend to diffuse from the blood into

TABLE 17.2 Chemical Nature of Hormones

Chemical Nature	Examples	Structures
Lipid-Soluble Hormones	Steroids (all cholesterol-based) Testosterone, aldosterone	
	Amino acid derivative (only one example of lipid-soluble) Thyroid hormone (thyroxine)	 Tetraiodothyronine or thyroxine (T_4)
	Fatty acid derivatives Prostaglandins	 Prostaglandin $F_{2\alpha}$($PGF_{2\alpha}$)
Water-Soluble Hormones	Proteins Thyroid-stimulating hormone, growth hormone	 Thyroid-stimulating hormone (a glycoprotein) Growth hormone
	Peptides Insulin, thyrotropin-releasing hormone	 Thyrotropin releasing hormone
		 Insulin
	Amino Acid Derivatives Epinephrine	Epinephrine 

tissue spaces more slowly. Thus, capillaries of organs that are regulated by protein hormones tend to be very porous, or *fenestrated* (see chapter 21). Some very small water-soluble hormones require being bound to a binding protein to avoid being filtered out of the blood.

All hormones are destroyed either in the circulation or at their target cells. The destruction and elimination of hormones limit the length of time they are active, and body processes change quickly when hormones are secreted and remain functional for only short periods.

The water-soluble hormones have relatively short half-lives because they are rapidly broken down by hydrolytic enzymes, called proteases, within the bloodstream. The kidneys then remove the hormone breakdown products from the blood. Target cells also destroy water-soluble hormones when the hormones are internalized via endocytosis. Once the hormones are inside the target cell, lysosomal enzymes degrade them. Often, the target cell recycles the amino acids of peptide and protein hormones and uses them to synthesize new proteins. Thus, hormones with short half-lives normally have concentrations that change rapidly within the blood and tend to regulate activities that have a rapid onset and short duration.

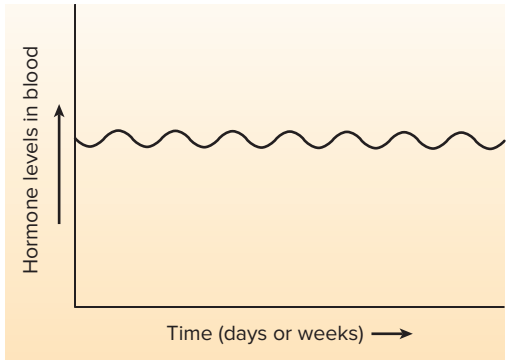
However, some water-soluble hormones are more stable in the circulation than others. There are many modifications made to hormone molecules that help protect them from being destroyed. Three important modifications include:

1. Having a carbohydrate attached to them. These hormones are then called glycoproteins.
2. Having a modified terminal end. These modifications protect them from protease activity to a greater extent than water-soluble hormones lacking such modifications (table 17.2).
3. Having binding proteins. Bound hormones circulate in the plasma longer than free water-soluble hormones do.

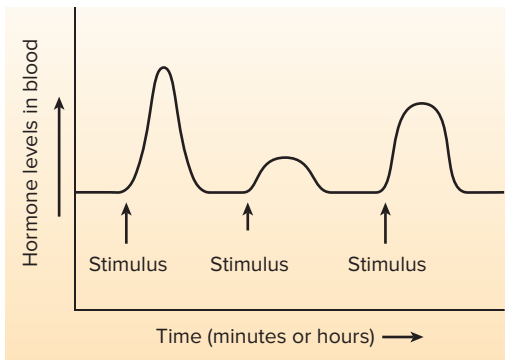
Patterns of Hormone Secretion

As a result of the variation in transport and removal of lipid-soluble hormones and water-soluble hormones, the blood levels of hormones differ. In addition, blood levels of hormones are further determined by the overall pattern of secretion. There are three main patterns of hormone secretion, however, individual hormones can be secreted in more than one pattern. These three main patterns are (1) chronic, (2) acute, and (3) episodic (figure 17.4):

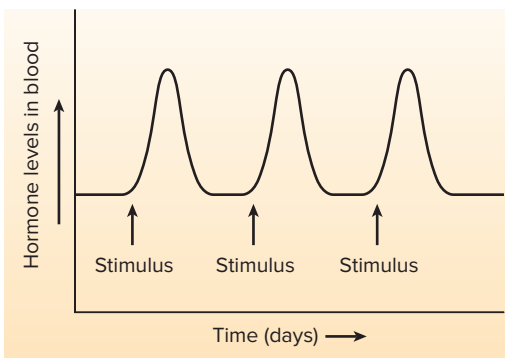
1. **Chronic hormone secretion** results in relatively constant blood levels of hormone over long periods of time. For example, thyroid hormones circulate in the blood within a small range of concentrations. Recall that thyroid hormones are lipid-soluble and thus bind to binding proteins, which also helps maintain them at chronic levels.
2. **Acute hormone secretion** occurs when the hormone's concentration changes suddenly and irregularly, and its circulating levels differ with each stimulus. For example, the amino acid derivative epinephrine is released in large amounts in response to stress or physical exercise. In addition, because epinephrine is small and usually circulates as a free hormone, it has a short half-life, which contributes to the fact that blood levels of epinephrine drop significantly within a few minutes of its secretion.



(a) **Chronic hormone secretion.** A relatively stable concentration of hormone is maintained in the circulating blood over a fairly long period, up to several weeks. This pattern is exemplified by the thyroid hormones.



(b) **Acute hormone secretion.** A hormone rapidly increases in the blood for a short time in response to a specific stimulus—for example, insulin (the blood sugar–regulating hormone) secretion following a meal. Note that the size of the stimulus arrow represents the stimulus strength. A smaller stimulus does not activate as much hormone secretion as a larger stimulus.



(c) **Episodic hormone secretion.** A hormone is stimulated so that it increases and decreases in the blood at a relatively consistent time and to roughly the same amount. Examples are the reproductive hormones regulating menstruation.

FIGURE 17.4 Patterns of Hormone Secretion

The overall pattern of hormone secretion is a result of the secretion, transport, and removal of the hormones, which is further dependent on the chemical nature of the hormones. (*a*) Chronic hormone secretion occurs over a relatively long period. (*b*) Acute hormone secretion occurs over a relatively short period. (*c*) Episodic hormone secretion occurs in relatively predictable bursts.

3. **Episodic hormone secretion** occurs when hormones are secreted at fairly predictable intervals and concentrations. An example of hormones secreted with this pattern are steroid reproductive hormones. Some reproductive steroid hormones fluctuate over a month in cyclic fashion during the human reproductive years. Additionally, because steroid hormones also often have binding proteins, they have longer half-lives than other hormones, which contributes to their relative stablity in the circulation.

In general, lipid-soluble hormones exhibit the two regular secretion patterns (chronic and episodic), whereas because of their short half-life, water-soluble hormones tend to exhibit the irregular (acute) secretion pattern, but there are a few exceptions. For instance, some protein reproductive hormones exhibit episodic secretion.

ASSESS YOUR PROGRESS

5. *What are the three general characteristics of hormones?*
6. *Explain how the half-life of a hormone relates to its stability.*
7. *Why do some hormones require a binding protein during transport in the blood?*
8. *What effect does a bound hormone have on the concentration of a free hormone in the blood?*
9. *What are the two chemical categories of hormones? Give examples of both types.*
10. *Describe how the chemical nature of a hormone affects its transport in the blood, its removal from circulation, and its half-life.*
11. *What happens to the half-life when a hormone binds to a binding protein? What kinds of hormones bind to binding proteins?*
12. *Why do organs regulated by protein hormones have fenestrated capillaries?*
13. *What kinds of activities are regulated by hormones with a short half-life? With a long half-life?*
14. *Describe chronic, acute, and episodic patterns of hormone secretion.*

17.3 Control of Hormone Secretion

LEARNING OUTCOMES

After reading this section, you should be able to

A. **List and describe the three stimulatory influences on hormone secretion and give examples of each.**
B. **List and describe the three inhibitory influences on hormone secretion and give examples of each.**
C. **Describe the major mechanisms that maintain blood hormone levels.**

Three types of stimuli regulate hormone release: (1) humoral, (2) neural, and (3) hormonal. No matter what stimulus releases the hormone, however, the blood level of most hormones fluctuates within a homeostatic range through negative-feedback mechanisms (see chapter 1). In a few instances, positive-feedback systems also regulate blood hormone levels.

Stimulation of Hormone Release

Control by Humoral Stimuli

Metabolites and other molecules in the bloodstream can directly stimulate the release of some hormones. These metabolites and molecules in the blood are referred to as **humoral stimuli.** The term *humoral* refers to body fluids, including blood. The cells that secrete these hormones have receptors for certain substances in the blood. For example, glucose, Ca^{2+}, and Na^{+} can stimulate hormone secretion. When the blood level of the particular substance changes, the hormone is released in response to the molecule's concentration (figure 17.5). For instance, if a runner has just finished a long race during hot weather, he may not produce urine for up to 12 hours after the race. This is because the elevated concentration of blood solutes stimulates the release of a water-conservation hormone called antidiuretic hormone (ADH). Similarly, elevated blood glucose levels directly stimulate insulin secretion by the pancreas, and elevated blood potassium levels directly stimulate aldosterone release by the adrenal cortex.

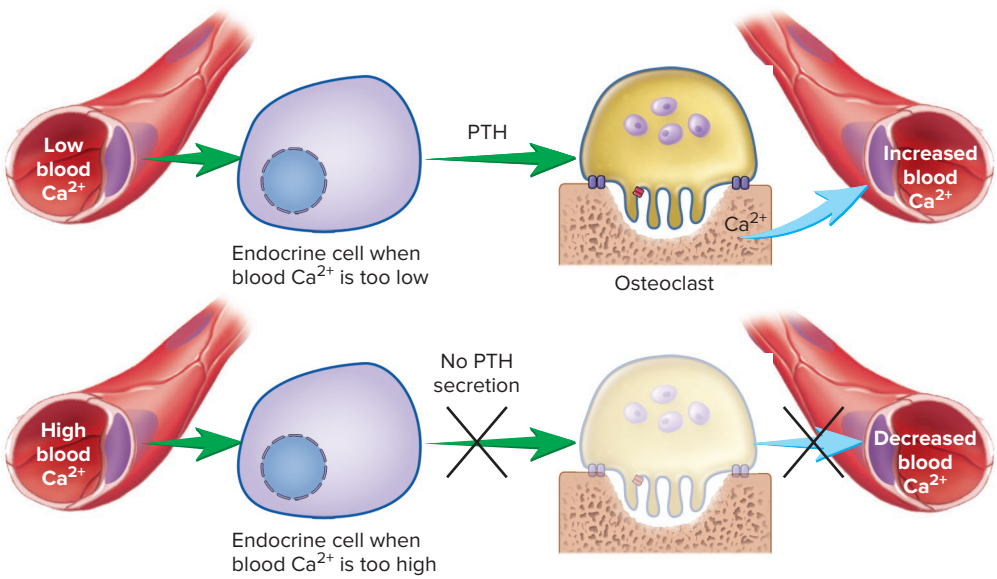
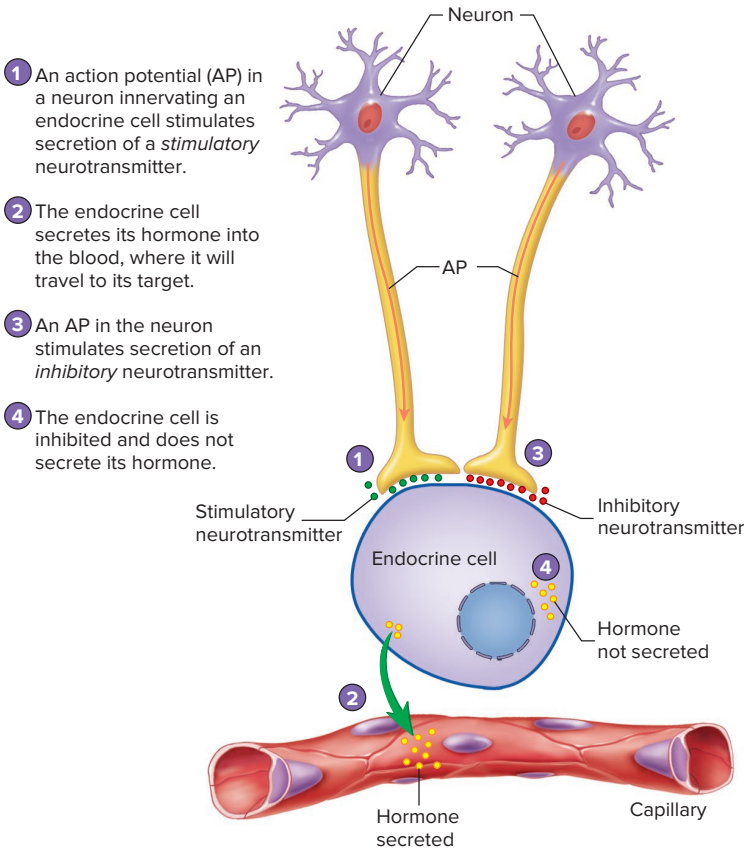


FIGURE 17.5 Humoral Regulation of Hormone Secretion
Some hormones are released when the blood levels of a certain chemical changes. For example, if blood Ca^{2+} levels decrease, PTH is secreted. If blood Ca^{2+} levels increase, PTH secretion slows.

Control by Neural Stimuli

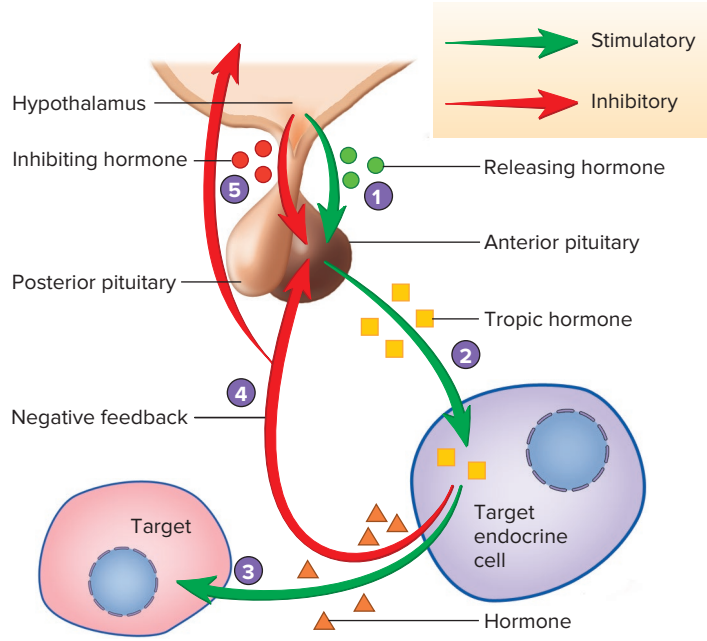
The second type of hormone regulation involves **neural stimuli** of endocrine glands. Following action potentials, neurons release a neurotransmitter into a synapse with hormone-producing cells. In these cases, the neurotransmitter stimulates the cells to secrete their hormone.



PROCESS FIGURE 17.6 Control of Hormone Secretion by Direct Neural Innervation

Some hormones are secreted in response to a neurotransmitter.

? *What cell membrane component must the endocrine cell have in order to respond to a neurotransmitter?*



1 Neurons in the hypothalamus release stimulatory hormones, called releasing hormones. Releasing hormones travel in the blood to the anterior pituitary gland.

2 Releasing hormones stimulate the release of tropic hormones from the anterior pituitary, which travel in the blood to their target endocrine cell.

3 The target endocrine cell secretes its hormone into the blood, where it travels to its target and produces a response.

4 The hormone from the target endocrine cell also inhibits the hypothalamus and anterior pituitary from secreting the releasing hormone and the tropic hormone. This is negative feedback.

5 In some instances, the hypothalamus can also secrete inhibiting hormones, which prevent the secretion of anterior pituitary tropic hormones.

PROCESS FIGURE 17.7 Hormonal Regulation of Hormone Secretion

Certain hormones are secreted in response to to another hormone.

? *What type of hormonal secretion mechanism is found in step 1?*

Figure 17.6 illustrates the neural control of hormone secretion from cells of an endocrine gland. For example, in response to stimuli, such as stress or exercise, neurons of the sympathetic division of the autonomic nervous system (see chapter 16) stimulate the adrenal gland to secrete epinephrine and norepinephrine into the bloodstream. Responses include an elevated heart rate and increased blood flow through the exercising muscles. When the stimulus is no longer present, the neural stimulation declines, and the secretion of epinephrine and norepinephrine decreases.

However, some neurons secrete their chemical messengers directly into the blood when they are stimulated, which makes these chemical messengers hormones. Hormones released by a neuron are neuropeptides. Some neuropeptides stimulate hormone secretion from other endocrine cells and are called **releasing hormones,** a term usually reserved for hormones from the hypothalamus. Thus, when a neuron releases a neurotransmitter at a synapse to stimulate a hormone's secretion, it is considered a neural stimulus. But, when a neuron releases a neuropeptide hormone into the blood, which stimulates another hormone's secretion, it is considered a hormonal stimulus.

Control by Hormonal Stimuli

The third type of regulation uses **hormonal stimuli.** It occurs when hormones stimulate the secretion of other hormones (figure 17.7). The most common examples are hormones from the anterior pituitary gland, called **tropic** (trō′pik) **hormones.** Many tropic hormones are part of a complex process in which a releasing hormone from the hypothalamus stimulates the release of a tropic hormone from the pituitary gland. The pituitary tropic hormone then travels to a separate endocrine gland and stimulates the release of a hormone from the endocrine gland (figure 17.7). For example, hormones from the hypothalamus and anterior pituitary regulate the secretion of thyroid hormones from the thyroid gland.

Inhibition of Hormone Release

Stimulating hormone secretion is important, but so is inhibiting hormone release. This process involves the same three types of stimuli: (1) humoral, (2) neural, and (3) hormonal.

Inhibition of Hormone Release by Humoral Stimuli

Often when a hormone's release is triggered by a particular humoral stimulus, there exists a companion hormone whose release is inhibited by the same humoral stimulus. Usually, the companion hormone's effects oppose those of the secreted hormone and counteract the secreted hormone's action. For example, to raise blood glucose (as influenced by low blood glucose levels), pancreatic islet cells secrete the hormone glucagon in response to low blood glucose. However, if blood glucose goes up (as influenced by high blood glucose levels), the pancreatic islet cells secrete the hormone insulin, which lowers blood glucose. Therefore, glucagon and insulin work together to maintain homeostasis of blood glucose.

Inhibition of Hormone Release by Neural Stimuli

Neurons inhibit targets just as often as they stimulate targets. If the neurotransmitter is inhibitory, the target endocrine gland does not secrete its hormone (figure 17.6).

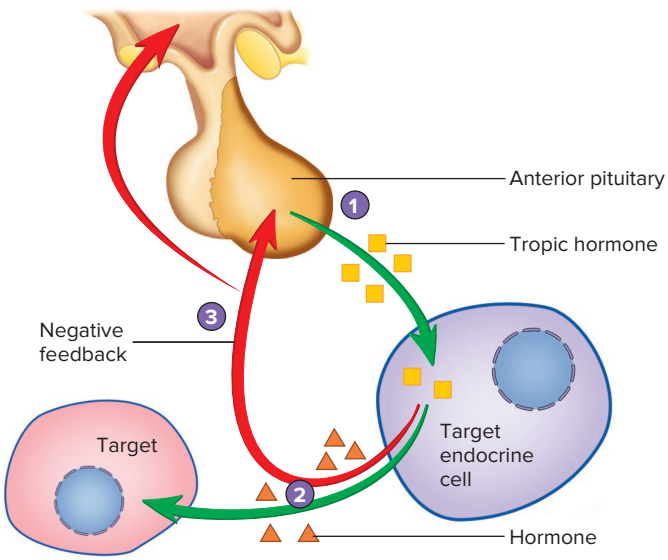
Inhibition of Hormone Release by Hormonal Stimuli

Some hormones prevent the secretion of other hormones. For example, hormones, called **inhibiting hormones,** from the hypothalamus prevent the secretion of tropic hormones from the pituitary gland (figure 17.7, *step 5*). Another example is that thyroid hormones can control their own blood levels by inhibiting their pituitary tropic hormone. Without the original stimulus, less thyroid hormone is released.

Regulation of Hormone Levels in the Blood

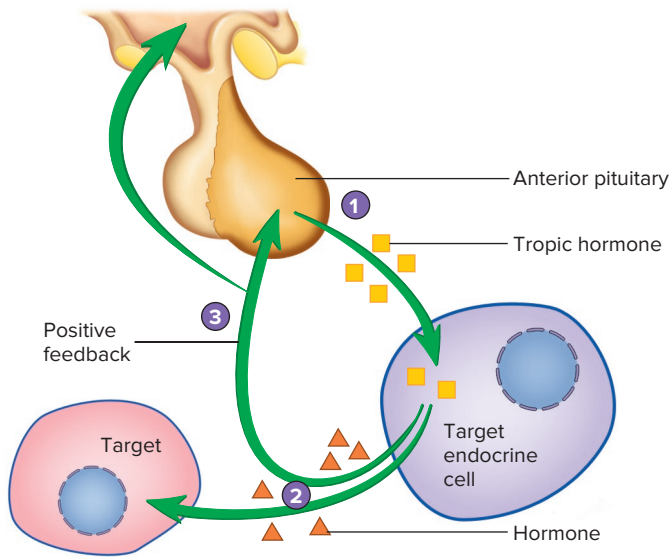
Two major mechanisms maintain hormone levels in the blood within a particular range of concentrations: (1) negative feedback and (2) positive feedback (see chapter 1).

1. *Negative feedback*. Most hormones are regulated by a negative-feedback mechanism, whereby the hormone's secretion is inhibited by the hormone itself once blood levels have reached a certain point and there is adequate hormone to activate the target cell. The hormone may inhibit the action of other, stimulatory hormones to prevent the secretion of the hormone in question. Thus, it is a self-limiting system (figure 17.8*a*). For example, thyroid hormones inhibit the secretion of TRH from the hypothalamus and TSH from the anterior pituitary.
2. *Positive feedback*. Some hormones, when stimulated by a tropic hormone, promote the further synthesis and secretion of the tropic hormone in addition to stimulating their target cell. In turn, this stimulates even more secretion of the original hormone. Thus, it is a self-propagating system (figure 17.8*b*).



(a) **Negative feedback by hormones**

1. The anterior pituitary gland secretes a tropic hormone, which travels in the blood to the target endocrine cell.
2. The hormone from the target endocrine cell travels to its target.
3. The hormone from the target endocrine cell also has a negative-feedback effect on the anterior pituitary and hypothalamus and decreases secretion of the tropic hormone.



(b) **Positive feedback by hormones**

1. The anterior pituitary gland secretes a tropic hormone, which travels in the blood to the target endocrine cell.
2. The hormone from the target endocrine cell travels to its target.
3. The hormone from the target endocrine cell also has a positive-feedback effect on the anterior pituitary and increases secretion of the tropic hormone.

PROCESS FIGURE 17.8 Negative and Positive Feedback

(*a*) Hormones whose blood levels are regulated by negative feedback are inhibited when they move outside a particular range. (*b*) Hormones whose levels are regulated by positive feedback are further stimulated by the original hormone in the pathway.

? *What is it that provides the negative feedback signal for a hormone that is regulated by a humoral stimulus? Explain.*

ASSESS YOUR PROGRESS

15. *Describe and give examples of the three major ways hormone secretion is stimulated and inhibited.*
16. *Is hormone secretion generally regulated by negative-feedback or positive-feedback mechanisms?*

17.4 Hormone Receptors and Mechanisms of Action

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe the general properties of a receptor and how a target cell may decrease or increase its sensitivity to a hormone.**
B. **Explain the mechanisms of action for the two types of receptor classes.**
C. **Define *amplification* and explain how, despite small hormone concentrations, water-soluble hormones can cause rapid responses.**

Hormones exert their actions by binding to target cell proteins called **receptors** (figure 17.9). A hormone can stimulate only the cells that have the receptor for that hormone. The specific portion of each receptor molecule where a hormone binds is called a **receptor site,** and the shape and chemical characteristics of each receptor site allow only a specific type of hormone to bind to it. The tendency for each type of hormone to bind to one type of receptor, and not to others, is called **specificity** (figure 17.10). For example, insulin binds to insulin receptors, but not to receptors for thyroid hormones. However, some hormones, such as epinephrine,

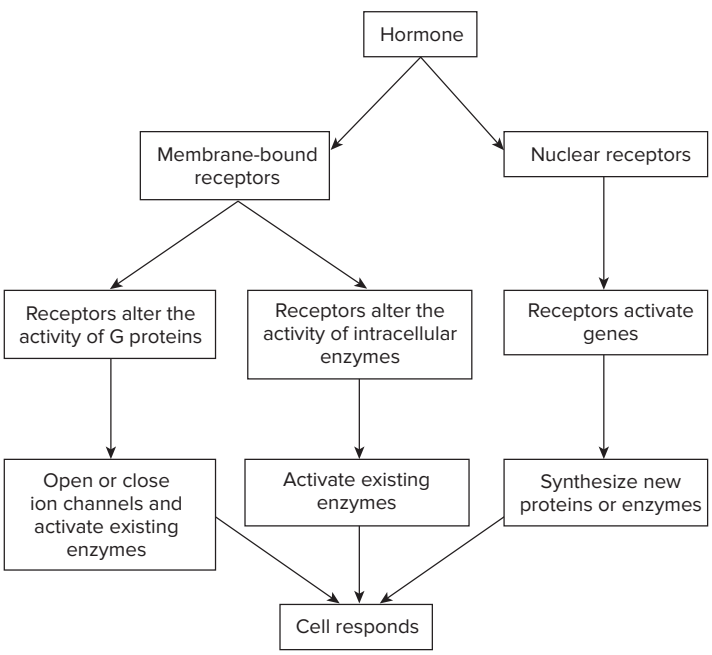


FIGURE 17.9 Overview of Responses to Hormones Binding to Their Receptors

FUNDAMENTAL Figure

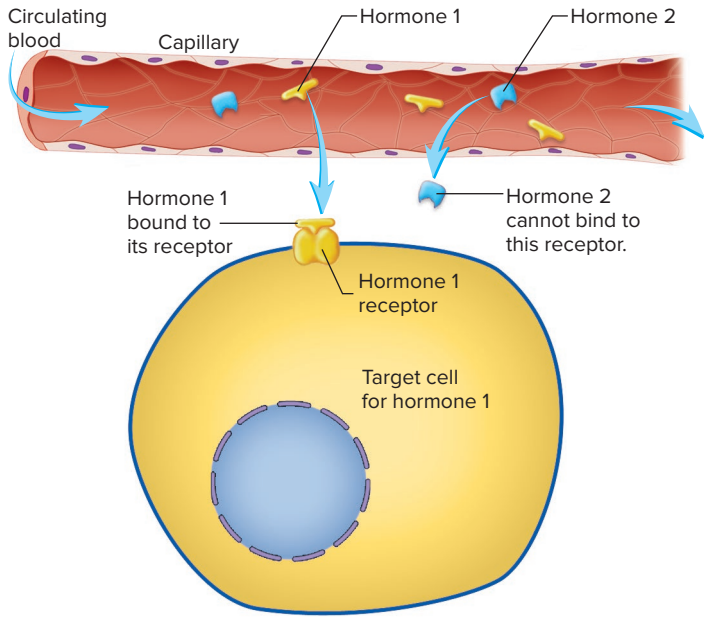


FIGURE 17.10 Target Tissue Specificity and Response
Hormones bind (physically attach) to receptor proteins. The shape and chemical nature of each receptor site allow only certain hormones to bind. This relationship is called specificity. In order for a target cell to respond to its hormone, the hormone must bind to its receptor.

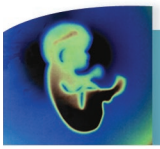
can bind to a "family" of receptors that are structurally similar. Because hormone receptors have a high affinity for the hormones that bind to them, they are very sensitive to low levels of the hormone. Thus, only a small concentration of a given hormone is needed to activate a significant number of its receptors.

Agonists and Antagonists

Drugs with structures similar to those of specific hormones will compete with those hormones for the same receptor (see chapter 3). A drug that binds to a hormone receptor and activates it is called an **agonist.** A drug that binds to a hormone receptor and inhibits its action is called an **antagonist.** For example, certain drugs mimic epinephrine and can bind to its receptors. Some of these drugs, called epinephrine agonists, activate epinephrine receptors. In fact, the drugs in asthma inhalers often work by mimicking epinephrine and causing the smooth muscle in lung bronchioles to relax. In contrast, some antistroke medications are epinephrine antagonists that prevent epinephrine-stimulated platelet aggregation and thus prevent the blockage of blood vessels.

Decrease in Receptor Number

Target tissues' sensitivity to hormone levels can change, for various reasons. Changing the receptor number at a target ensures an optimal target tissue response to a hormone. For example, the response of some target tissues rapidly decreases over time through desensitization. This happens because the cells' nutrient and energy



Clinical IMPACT 17.1

An Estrogen Receptor Antagonist Is Used to Treat and Prevent Breast Cancer

Breast cancer is the second-leading cause of cancer-related deaths in women in the United States. However, these numbers are significantly lower today than two decades ago, partly due to the development of effective **adjuvant therapies,** such as hormonal therapy. Adjuvant therapies are employed after primary treatments, such as surgery and chemotherapy, are completed. The most common adjuvant therapy for breast cancer is the use of an estrogen receptor antagonist. The particular antagonist prescribed depends on the stage and estrogen receptor status of each patient. Breast cancers are rated by many factors, but for simplicity, we will consider only estrogen receptor positive tumors. The primary estrogen receptor antagonist used for estrogen receptor positive tumors is **tamoxifen.** Tamoxifen was discovered in 1967 as part of a drug development program to find new contraceptive drugs. Originally, it was thought to be purely anti-estrogenic, an estrogen receptor antagonist. However, tamoxifen is now known to be one in the class of several drugs called selective estrogen receptor modulators (SERMs). SERMs can be antagonists or agonists depending on many factors, including the particular tissue type. In the case of breast tissue, tamoxifen is an estrogen receptor antagonist. It binds to the estrogen receptor and blocks the stimulatory actions of estrogen on breast epithelial cells. Tamoxifen is the only SERM approved as a hormonal agent for prevention of breast cancer. Among patients who use tamoxifen, risk of recurrence and death is reduced by 47% compared with patients who do not use tamoxifen.

supplies become depleted, causing the cells to lose the ability to respond to the hormone. Desensitization occurs when the number of receptors rapidly decreases after exposure to certain hormones, a phenomenon called **down-regulation** (figure 17.11*a*). Because most receptor molecules are degraded over time, a decrease in their synthesis rate reduces the total number of receptor molecules in a cell. Often, the target cells internalize the receptors and destroy them. For example, experimental exposure of anterior pituitary cells to the reproductive hormone gonadotropin-releasing hormone (GnRH) causes the number of receptor molecules for GnRH in the pituitary gland cells to decrease dramatically several hours after exposure to the hormone. This down-regulation causes the pituitary gland to become less sensitive to additional GnRH. Therefore, to ensure that the GnRH receptors are not down-regulated and that the pituitary gland remains responsive, the hypothalamus releases brief pulses of GnRH approximately once each hour. In this way, the reproductive system stays active and is less likely to stop working. From an organismal standpoint, because reproduction is one of the body's most protected functions, very tight regulation is necessary.

Increase in Receptor Number

In addition to down-regulation, a target tissue can also periodically increase sensitivity through up-regulation. **Up-regulation** results in an increase in the rate of receptor synthesis in the target cells, which increases the total number of receptor molecules in a cell (figure 17.11*b*). An example of up-regulation is a process that occurs to stimulate ovulation of the oocyte. During each menstrual cycle, there are an increased number of receptors for luteinizing hormone (LH) in ovary cells. Follicle-stimulating hormone (FSH) secreted by the pituitary gland increases the rate of LH receptor synthesis in ovary cells. This is important because a surge in LH will cause release of the oocyte. Thus, a tissue's exposure to one hormone can increase its sensitivity to a second hormone by causing the up-regulation of hormone receptors. This type of multilevel manipulation allows hormone levels to be very precisely controlled and enables the timing of certain processes to be tightly regulated.

Predict 1

Ovaries secrete the hormone estrogen in greater amounts after menstruation and a few days before ovulation. Among its many effects, estrogen causes the up-regulation of receptors in the uterus for another hormone secreted by the ovaries, called progesterone. Progesterone, which is secreted after ovulation, prepares the uterine wall for possible implantation of an embryo. Pregnancy cannot occur unless the embryo implants in the uterine wall. Predict the consequence of the ovaries' secreting too little estrogen.

Classes of Receptors

Lipid-soluble and water-soluble hormones each bind to their own unique class of receptors. Table 17.3 provides an overview of receptor type and mechanism of action.

1. *Lipid-soluble hormones bind to nuclear receptors*. Lipid-soluble hormones are relatively small and are nonpolar. Because of these properties, they easily diffuse through the plasma membrane and bind to **nuclear receptors** (figure 17.12*a*). Nuclear receptors are most often found in the nucleus of the cell, but they can also be located in the cytoplasm. These cytoplasmic receptors move to the nucleus when activated. When hormones bind to nuclear receptors, the hormone-receptor complex interacts with DNA in the nucleus or with cellular enzymes to regulate the transcription of particular genes in the target tissue. The lipid-soluble hormones include thyroid hormones and steroid hormones (testosterone, estrogen, progesterone, aldosterone, and cortisol). These hormones bind to nuclear receptors.

   In addition to modulating gene transcription, it is now recognized that lipid-soluble hormones have rapid effects (less than 1 minute) on target cells. These effects are most likely mediated through membrane-bound receptors.
2. *Water-soluble hormones bind to membrane-bound receptors*. Water-soluble hormones are large molecules and cannot pass through the plasma membrane. Instead, they interact with **membrane-bound receptors,** which are proteins that extend across the plasma membrane, with their hormone-binding sites exposed on the plasma membrane's outer surface (figure 17.12*b*). When a hormone binds to a receptor on the outside of the plasma membrane, the hormone-receptor complex initiates a response inside the cell. Hormones that bind to membrane-bound receptors include proteins, peptides, and some amino acid derivatives, such as epinephrine and norepinephrine.

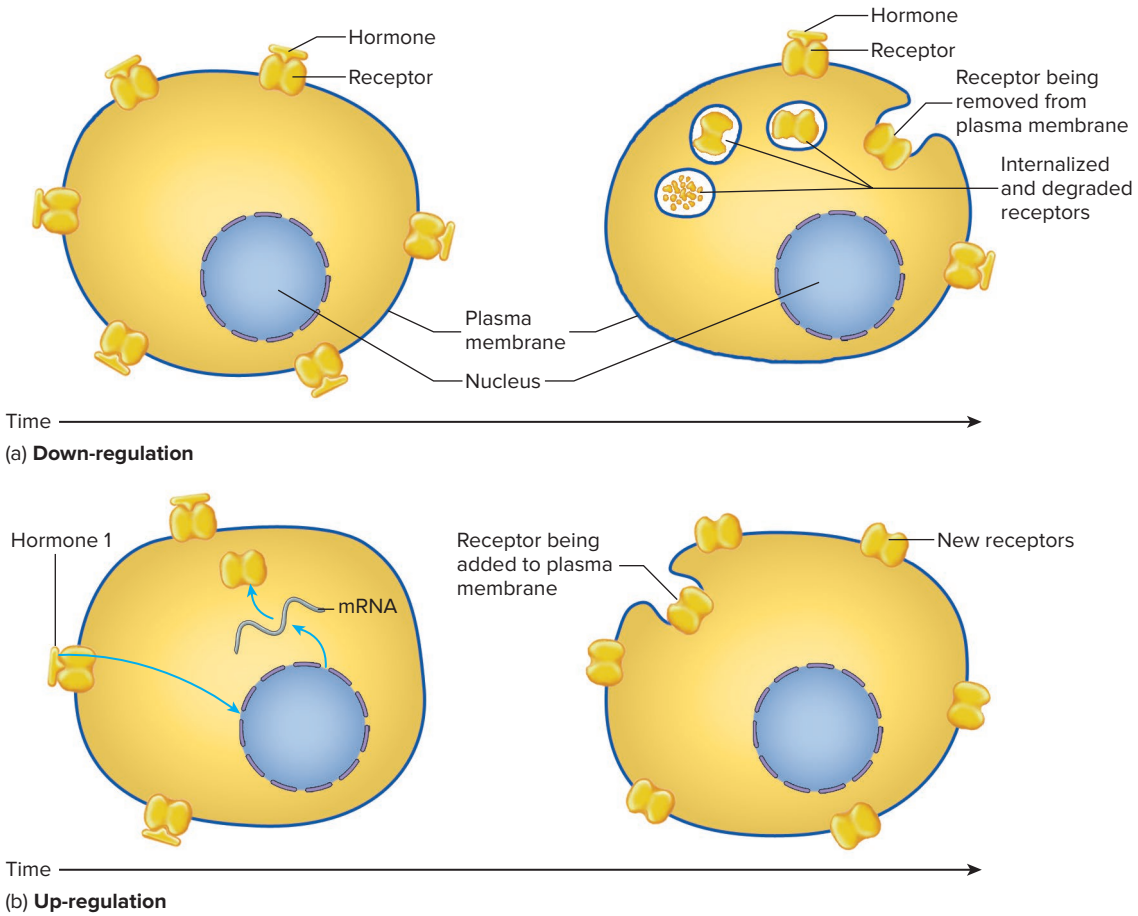


FIGURE 17.11 Down-Regulation and Up-Regulation of Target Cell Receptors

(*a*) Down-regulation occurs when the number of hormone receptors in a target cell decreases. Often, the target cells internalize the receptors and destroy them. (*b*) Up-regulation occurs when the number of receptors for a hormone in a target cell increases. Often, the hormone stimulates the synthesis of receptors in the target cells.

TABLE 17.3 Hormone Receptor Types and Mechanisms of Action

Hormone Category	Receptor Type	Hormone Examples	Mechanism of Action*
Lipid-soluble	Nuclear	Steroid hormones Testosterone Estrogen Progesterone Aldosterone Cortisol Thyroid hormone Vitamin D	Bind hormone to receptor within cell followed by hormone-receptor complex attachment to hormone response element on DNA; results in synthesis of mRNA specific to the particular hormone
Water-soluble	Membrane-bound	Luteinizing hormone Follicle-stimulating hormone Thyroid-stimulating hormone Adrenocorticotropic hormone Glucagon Oxytocin Antidiuretic hormone Calcitonin Parathyroid hormone	Activate G proteins Stimulate synthesis of cAMP
		Epinephrine	Open ion channels
		Insulin Growth hormone Prolactin	Phosphorylate intracellular proteins

*Hormones often exhibit more than one mechanism of action. For simplicity, hormones are listed in only one category.

FUNDAMENTAL **Figure**

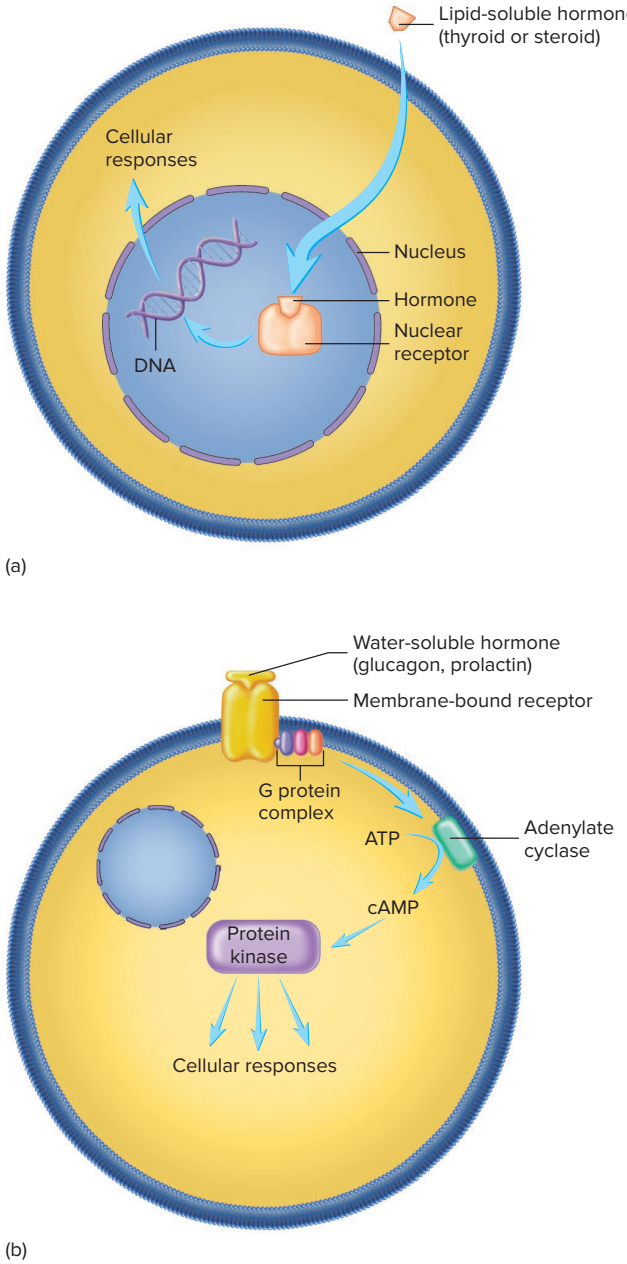


FIGURE 17.12 Overview of Nuclear and Membrane-Bound Receptors

(*a*) *Lipid-soluble* hormones diffuse through the plasma membrane of their target cell and bind to a cytoplasmic receptor or a nuclear receptor. In the nucleus, the combination of the hormone and the receptor initiates protein synthesis, described later in this chapter (see figure 17.13 for details). (*b*) *Water-soluble* hormones bind to the external portion of membrane-bound receptors, which are integral membrane proteins on their target cell (see figure 17.14 for details).

ASSESS YOUR PROGRESS

17. *What characteristics of a hormone receptor make it specific for one type of hormone?*
18. *What is down-regulation, and what may cause it to occur? Give an example of down-regulation in the body.*
19. *What is up-regulation, and what may cause it to occur? Give an example of up-regulation in the body.*
20. *What are the two classes of hormone receptors? How do they differ in the chemical category of hormones that will bind to them? Give examples of the types of hormones that bind to each type of receptor.*

Action of Nuclear Receptors

Lipid-soluble hormones primarily stimulate synthesis of new proteins. Recall from chapter 3 that protein synthesis relies on information stored in DNA. Therefore, after lipid-soluble hormones diffuse across the plasma membrane and bind to their receptors, the hormone-receptor complex binds to DNA to produce a response (figure 17.13). The receptors that bind to DNA have fingerlike projections that recognize and bind to specific nucleotide sequences in the DNA called **hormone-response elements.** The combination of the hormone and its receptor forms a **transcription factor,** because when the hormone-receptor complex binds to the hormone-response element, it activates the transcription of specific **messenger ribonucleic acid (mRNA)** molecules. The mRNA molecules then move to the cytoplasm to be translated into specific proteins at the ribosomes. The newly synthesized proteins produce the cell's response to the hormone. For example, testosterone stimulates the synthesis of the proteins that are responsible for male secondary sex characteristics, such as the formation of muscle mass and the typical male body structure. The steroid hormone aldosterone affects its target cells in the kidneys by stimulating the synthesis of proteins that increase the rate of Na^+ and K^+ transport. The result is a reduction in the amount of Na^+ and an increase in the amount of K^+ lost in the urine. Other hormones that produce responses through nuclear receptor mechanisms include thyroid hormones and vitamin D.

Target cells that synthesize new protein molecules in response to hormonal stimuli normally have a latent period of several hours between the time the hormones bind to their receptors and the time responses are observed. During this latent period, mRNA and new proteins are synthesized. Hormone-receptor complexes are eventually degraded within the cell, limiting the length of time hormones influence the cells' activities, and the cells slowly return to their previous functional states.

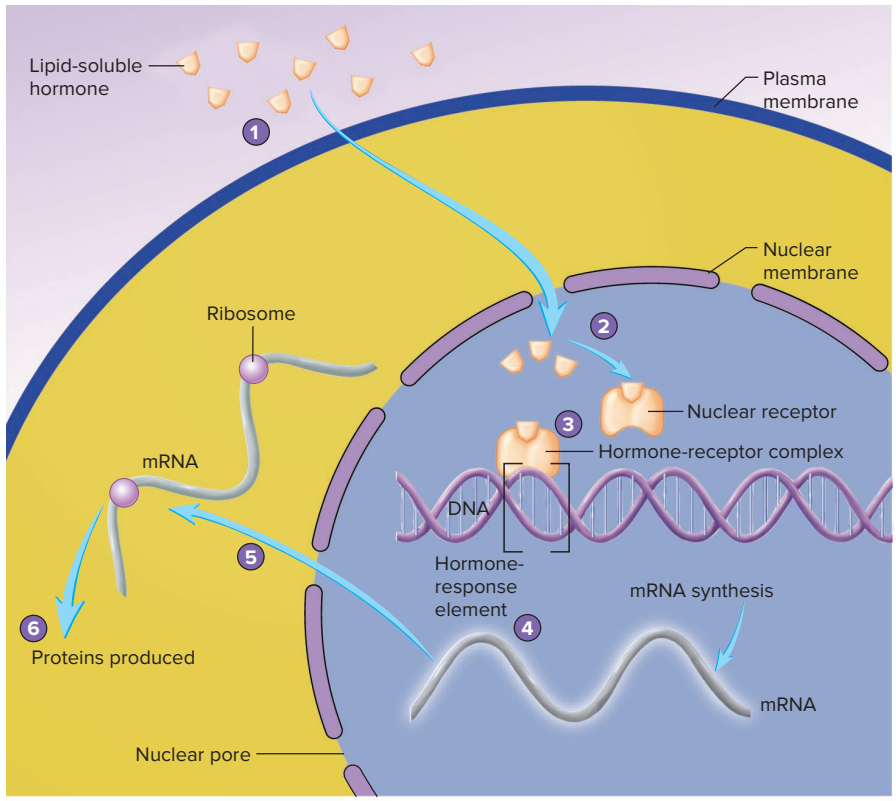
ASSESS YOUR PROGRESS

21. *Describe how a hormone that crosses the plasma membrane interacts with its receptor and how it affects protein synthesis.*
22. *Why is there normally a latent period between the time a hormone binds to its receptor and the time responses are observed?*
23. *What eventually limits the processes activated by the nuclear receptor mechanism?*

Membrane-Bound Receptors and Signal Amplification

Membrane-bound receptors are anchored in the phospholipid bilayer of the plasma membrane (see chapter 3). Membrane-bound receptors activate responses in two ways: (1) Some receptors alter the activity of G proteins at the inner surface of the plasma membrane. (2) Other receptors directly alter the activity of intracellular

1. Lipid-soluble hormones diffuse through the plasma membrane.
2. Lipid-soluble hormones bind to cytoplasmic receptors and travel to the nucleus or bind to nuclear receptors.
3. The hormone-receptor complex functions as a transcription factor by binding to a hormone response element on the DNA.
4. The binding of the hormone-receptor complex to DNA stimulates the synthesis of messenger RNA (mRNA), which codes for proteins.
5. The mRNA leaves the nucleus, passes into the cytoplasm of the cell, and binds to ribosomes, where it directs the synthesis of specific proteins.
6. The newly synthesized proteins produce the cell's response to the lipid-soluble hormones—for example, the secretion of a new protein.



PROCESS FIGURE 17.13 Nuclear Receptor Model

Lipid-soluble hormones bind to nuclear receptors, which activate synthesis of particular proteins. AP|R

? *Suppose you want to develop a drug that targets nuclear receptors. What chemical characteristic of the new drug would result in its binding to the nuclear receptor within the cytoplasm or nucleus of the target tissue cells?*

enzymes. These intracellular pathways elicit specific responses in cells, including the production of **intracellular mediators.** Some intracellular mediators are called *second messengers.* An intracellular mediator is a chemical produced inside a cell once a hormone or another chemical messenger binds to certain membrane-bound receptors (table 17.4). The intracellular mediator then activates specific cellular processes inside the cell in response to the hormone. In some cases, this coordinated set of events is referred to as a **second-messenger system.** For example, in chapter 3 we discussed that cyclic adenosine monophosphate (cAMP) is a common second messenger produced when a ligand binds to its receptor. Rather than the ligand entering the cell to activate a cellular process, cAMP stimulates the cellular process. This mechanism is usually employed by water-soluble hormones that are unable to cross the target cell's membrane.

Receptors That Activate G Proteins

Many membrane-bound receptors produce responses through the action of G proteins (see figures 3.9 and 17.12*b*). G proteins consist of three subunits; from largest to smallest, they are called alpha (α), beta (β), and gamma (γ; figure 17.14*a, step 1*). The G proteins are so named because one of the subunits binds to guanine nucleotides. In the inactive state, a guanine diphosphate (GDP) molecule is bound to the α subunit of each G protein. In the active state, guanine triphosphate (GTP) is bound to the α subunit.

After a hormone binds to the receptor on the outside of a cell, the receptor changes shape (figure 17.14*a, step 2*). As a result, the receptor binds to a G protein on the inner surface of the plasma membrane, and GDP is released from the α subunit. Guanine triphosphate (GTP) binds to the α subunit, thereby activating it (figure 17.14*a, step 3*). As a result, G proteins separate from the receptor, and the

TABLE 17.4 Common Intracellular Mediators

Intracellular Mediator	Example of Cell Type	Example of Response
Cyclic guanine monophosphate (cGMP)	Kidney cells	Increased Na^+ and water excretion by the kidneys
Cyclic adenosine monophosphate (cAMP)	Liver cells	Increased breakdown of glycogen and release of glucose into the circulatory system
Calcium ions (Ca^{2+})	Smooth muscle cells	Contraction of smooth muscle cells
Inositol triphosphate (IP_3)	Smooth muscle cells	Contraction of certain smooth muscle cells in response to epinephrine
Diacylglycerol (DAG)	Smooth muscle cells	Contraction of certain smooth muscle cells in response to epinephrine
Nitric oxide (NO)	Smooth muscle cells	Relaxation of smooth muscle cells of blood vessels, resulting in vasodilation

activated α subunit separates from the β and γ subunits. The activated α subunit can alter the activity of molecules within the plasma membrane or inside the cell, thus producing cellular responses. After a short time, the activated α subunit is turned off, because the G protein removes a phosphate group from GTP, which converts it to GDP (figure 17.14*a, step 4*). Thus, the α subunit is called a GTPase. The α subunit then recombines with the β and γ subunits.

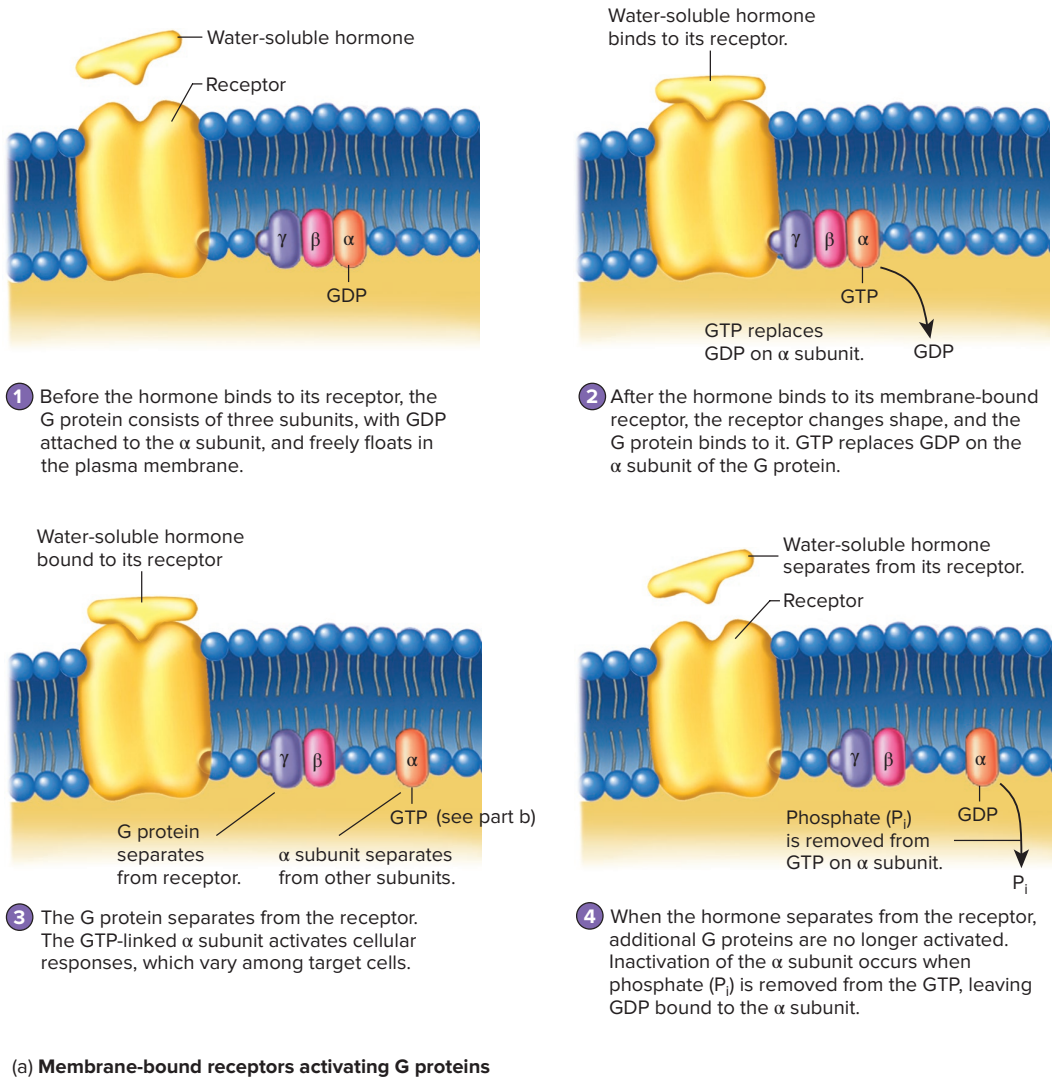
G Proteins That Interact with Adenylate Cyclase

Activated α subunits of G proteins can alter the activity of enzymes inside the cell membrane. For example, activated α subunits stimulate cAMP formation by activating the enzyme, **adenylate cyclase** (a-den′i-lāt sī′klās). Adenylate cyclase converts ATP to cAMP (figure 17.14*b*). Cyclic AMP functions as a second messenger, an intracellular mediator that carries out cellular metabolic processes in response to hormonal activation. For example, cAMP binds to protein kinases and activates them. **Protein kinases** are enzymes that regulate the activity of other enzymes. The protein kinases attach phosphates to other enzymes. Attachment of a phosphate to another molecule is called **phosphorylation.** Depending on the enzyme, phosphorylation increases or decreases the enzyme's activity. The amount of time cAMP is present to produce a response in a cell is limited. An enzyme in the cytoplasm, called **phosphodiesterase** (fos′fō-dī-es′ter-ās), breaks down cAMP to AMP. Once cAMP levels drop, the enzymes in the cell are no longer stimulated.

Cyclic AMP can elicit many different responses in the body, because each cell type possesses a unique set of enzymes. For example, the hormone glucagon increases blood glucose levels when it binds to receptors on the surface of liver cells. Binding to the receptor activates G proteins and causes an increase in cAMP synthesis. Cyclic AMP then stimulates the activity of enzymes that break down glycogen into glucose for release from liver cells (figure 17.14*b*).

G Proteins That Activate Other Intracellular Mediators

G proteins can also alter the concentration of intracellular mediators other than cAMP (table 17.4). For example, **diacylglycerol**



1 Before the hormone binds to its receptor, the G protein consists of three subunits, with GDP attached to the α subunit, and freely floats in the plasma membrane.

2 After the hormone binds to its membrane-bound receptor, the receptor changes shape, and the G protein binds to it. GTP replaces GDP on the α subunit of the G protein.

3 The G protein separates from the receptor. The GTP-linked α subunit activates cellular responses, which vary among target cells.

4 When the hormone separates from the receptor, additional G proteins are no longer activated. Inactivation of the α subunit occurs when phosphate (P_i) is removed from the GTP, leaving GDP bound to the α subunit.

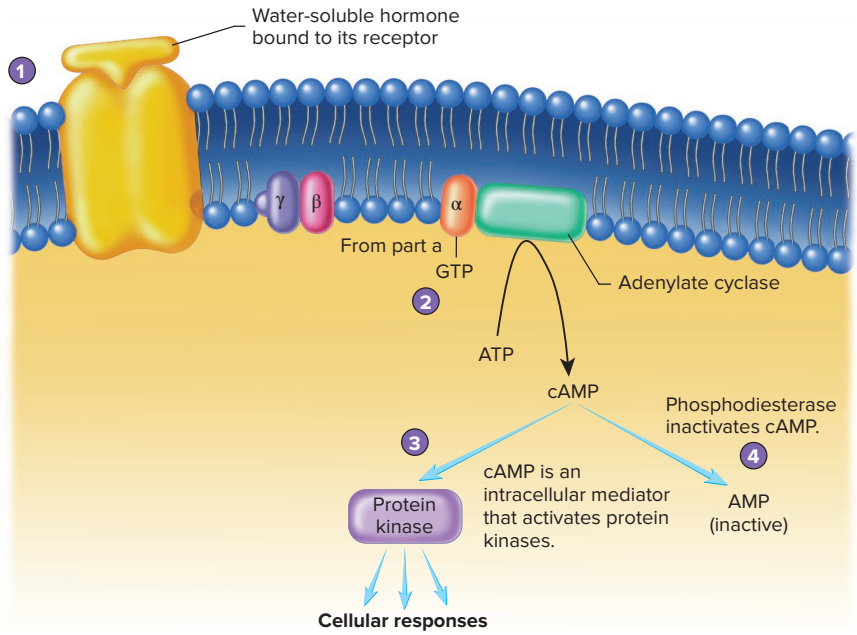
(a) **Membrane-bound receptors activating G proteins**

PROCESS FIGURE 17.14 Membrane-Bound Receptors Activating G Proteins and Interacting with Adenylate Cyclase

Water-soluble hormones must interact with the external portion of their receptor since they are unable to cross the plasma membrane. The cellular response is carried out through activation of a G protein and the second messenger, cAMP. (*a*) Binding of the ligand to its receptor activates the G protein. (*b*) The G protein activates the enzyme adenylate cyclase to produce the second messenger, cAMP. AP|R

? *Based on the information shown in this figure, is this type of receptor also a transport protein?*

1. After a water-soluble hormone binds to its receptor, the G protein is activated.
2. The activated α subunit, with GTP bound to it, binds to and activates an adenylate cyclase enzyme, so that it converts ATP to cAMP.
3. The cAMP can activate protein kinase enzymes, which phosphorylate specific enzymes activating them. The chemical reactions catalyzed by the activated enzymes produce the cell's response.
4. Phosphodiesterase enzymes inactivate cAMP by converting cAMP to AMP.

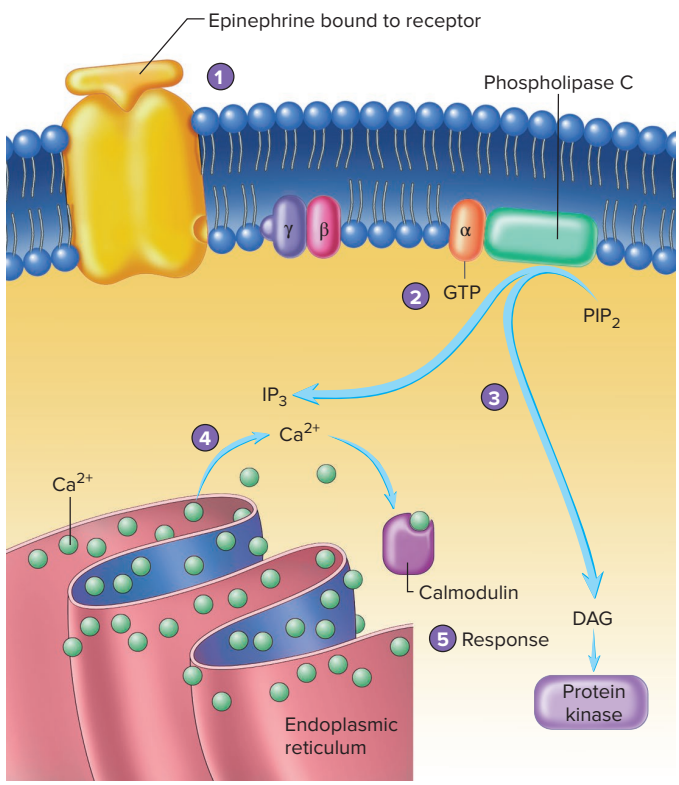


(b) **Membrane-bound receptors that interact with adenylate cyclase**

PROCESS FIGURE 17.14 (continued)

(dī-as-il-glis′er-ol; **DAG**) and **inositol** (in-ō′si-tōl, in-ō′si-tol) **triphosphate** (IP_3) are intracellular mediators that are influenced by G proteins (figure 17.15). Epinephrine binds to certain membrane-bound receptors in some types of smooth muscle. The combination activates a G protein mechanism, which in turn increases the activity of the enzyme phospholipase C. Phospholipase C converts phosphoinositol diphosphate (PIP_2), a constituent of the plasma membrane, to DAG and IP_3, which are released into the cytosol. DAG activates enzymes that synthesize prostaglandins, which increase smooth muscle

1. Epinephrine binds to its receptor in the smooth muscle plasma membrane.
2. The G protein is activated. The activated α subunit with GTP bound to it separates from the γ and β subunits.
3. The activated subunit then binds with phospholipase C, which acts on phosphoinositol diphosphate (PIP_2) and produces inositol triphosphate (IP_3) and diacylglycerol (DAG).
4. IP_3 releases Ca^{2+} from the endoplasmic reticulum or opens Ca^{2+} channels in the plasma membrane. Calcium ions then regulate enzyme activity.
5. DAG regulates enzymes such as protein kinases and those that synthesize prostaglandin. These responses increase smooth muscle contraction.



PROCESS FIGURE 17.15 Membrane-Bound Receptors Activating G Proteins to Increase the Synthesis of DAG and IP_3

Epinephrine receptors in some smooth muscle cells are associated with G proteins. AP|R

? *If DAG and IP_3 are second messengers, what function does Ca^{2+} serve? Would Ca^{2+} also be called a second messenger?*

contraction. IP_3 releases Ca^{2+} from the endoplasmic reticulum or opens Ca^{2+} channels in the plasma membrane, allowing the ions to enter the cytoplasm and increase the contraction of the smooth muscle cells.

Predict 2

As long as the smooth muscle cells in the airways of the lungs are relaxed, breathing is easy. However, during asthma attacks, these smooth muscle cells contract, and breathing becomes very difficult. Some of the drugs used to treat asthma increase cAMP in smooth muscle cells. Explain some of the different ways in which these drugs work.

G Proteins That Open Ion Channels

Some activated α subunits of G proteins can bind to ion channels, causing them to open or close (figure 17.16). For example, epinephrine activates α subunits to open Ca^{2+} channels in smooth muscle cells, allowing Ca^{2+} to move into those cells. The Ca^{2+} ions bind to calmodulin (kal-mod′ū-lin) proteins, and the calcium-calmodulin complexes activate enzymes that cause the smooth muscle cells to contract (figure 17.16, *steps 1 and 2;* see figure 9.26). After a short time, the activated α subunit is inactivated and muscle contraction ceases. The α subunit then recombines with the β and γ subunits (figure 17.16, *steps 3 and 4*).

Receptors That Directly Activate Intracellular Mediators

Cyclic guanine (gwahn′ēn) **monophosphate (cGMP),** an intracellular mediator, is synthesized in response to a hormone binding to a membrane-bound receptor (figure 17.17). The hormone binds to its receptor, and the combination activates an enzyme called **guanylate cyclase** (gwahn′i-lāt sī′klās) located at the inner surface of the plasma membrane. The guanylate cyclase converts guanine triphosphate (GTP) to cGMP and two inorganic phosphate groups. The cGMP molecules then interact with specific enzymes in the cytoplasm of the cell and activate them. In turn, the activated enzymes produce the cell's response to the hormone. For example, atrial natriuretic hormone, secreted by the heart atria, binds with its receptor in the plasma membrane of kidney cells. The result is an increase in the rate of cGMP synthesis at the inner surface of the plasma membrane (figure 17.17). Cyclic GMP influences the action of enzymes in the kidney cells, which increases the kidneys' rate of Na^+ and water excretion (see chapter 26). The cGMP is present in the cell for only a limited amount of time, because phosphodiesterase breaks down cGMP to GMP. Consequently, the length of time a hormone increases cGMP synthesis and has an effect on a cell is brief, once the hormone is no longer present.

Receptors That Phosphorylate Intracellular Proteins

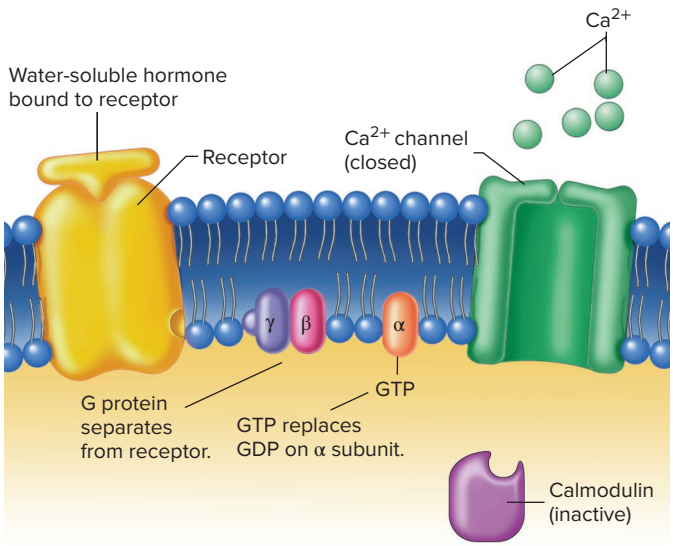
Some hormones bind to membrane-bound receptors, and the portion of the receptor on the inner surface of the plasma membrane acts as a kinase enzyme that phosphorylates several specific proteins (figure 17.18). Some of the phosphorylated proteins are part of the membrane-bound receptor; others are in the cytoplasm of the cell. The phosphorylated proteins influence the activity of other enzymes in the cytoplasm. For example, insulin binds to its membrane-bound receptor, resulting in the phosphorylation of parts of the receptor on the inner surface of the plasma membrane. The receptor then phosphorylates certain other important regulatory intracellular proteins. These intracellular proteins trigger the insertion of the glucose transporter protein into the plasma membrane of insulin target cells, allowing glucose to enter the cell. Sometimes, individuals, in particular, people with excess fat around their waist, develop a reduced ability to respond properly to insulin, called **insulin resistance.** In insulin resistance, certain target cells for insulin, such as skeletal muscle fibers and liver cells, do not take up as much glucose as normal and blood glucose levels become elevated. The mechanism for insulin resistance is not well defined, but it is likely that the insulin receptor has reduced phosphorylation activity, which results in fewer glucose transporters being inserted into the plasma membrane of insulin target cells. With fewer glucose transporters, glucose would not be taken up as readily and blood glucose levels would increase.

Case STUDY 17.1 Elevated Blood Glucose: Insufficient Receptor Response or Insufficient Hormone Secretion

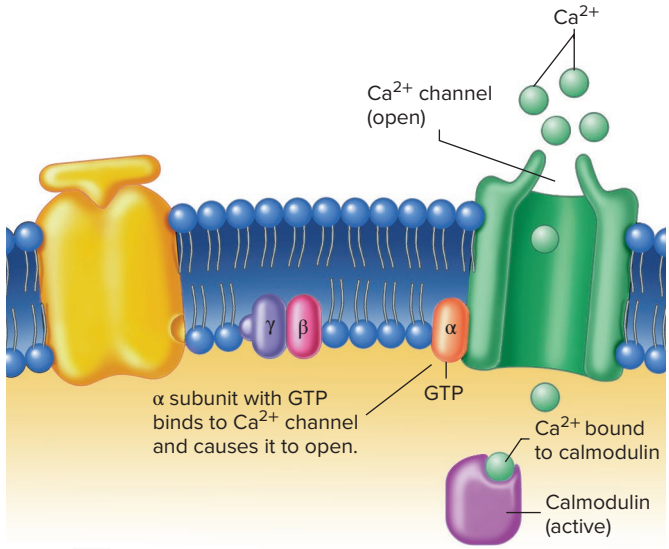
Sarah is a new mom. She gave birth to a beautiful baby boy after a challenging pregnancy. Sarah had been diagnosed with gestational diabetes, a temporary type of **diabetes mellitus** that occurs only during pregnancy. In diabetes mellitus including gestational diabetes, the hormone, insulin, does not properly regulate blood glucose levels. Despite trying to control her diet and exercising before the baby was born, she'd still gained 70 pounds during her pregnancy and her baby had weighed almost 10 pounds at birth. Since then, Sarah has not been sleeping nor has she started the exercise program her doctor had recommended for her. Lately, she's also noticed a dark ring on the skin around her neck. She made another appointment with her doctor because her mother had experienced some of these same symptoms prior to being diagnosed with diabetes mellitus. Sarah's doctor ordered a fasting plasma glucose test, which showed that Sarah's glucose levels were 122 mg/dL. The American Diabetes Association classifies this glucose level as being prediabetic. This means that Sarah is at a higher risk for developing diabetes mellitus if she continues with her current lifestyle.

Predict 3

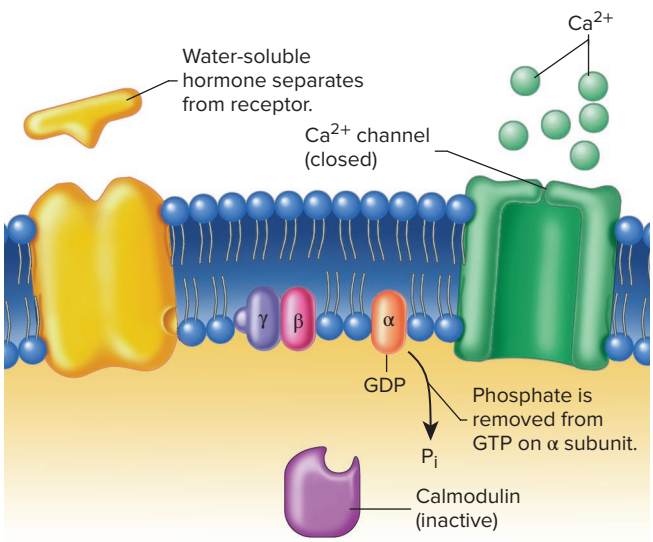
a. What is a likely mechanism for Sarah's elevated glucose levels?
b. What is the most important measure Sarah could take to reverse her condition?



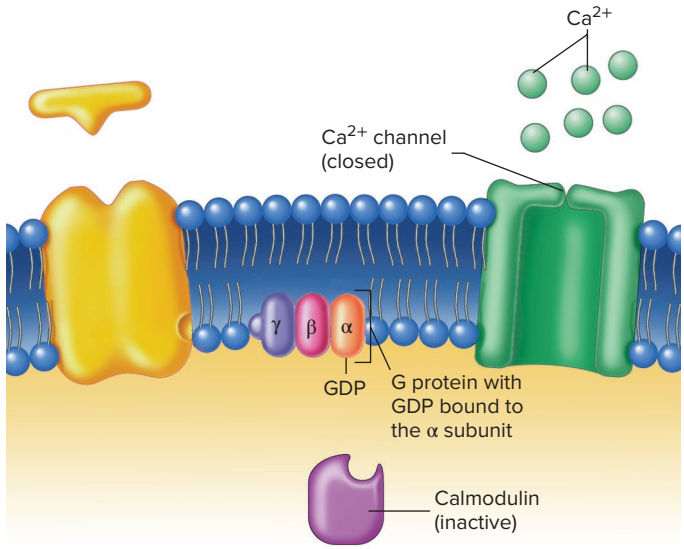
1 After a hormone binds to its receptor, the G protein is activated. The activated α subunit with GTP bound to it separates from the γ and β subunits.



2 The α subunit, with GTP bound to it, binds to the Ca^{2+} channel, and the combination causes the Ca^{2+} channel to open. The Ca^{2+} diffuses into the cell and combines with calmodulin. The combination of Ca^{2+} with calmodulin produces the cell's response to the hormone.



3 Phosphate is removed from the GTP bound to the α subunit, leaving GDP bound to the α subunit. The α subunit can no longer stimulate a cellular response; it separates from the Ca^{2+} channel, and the channel closes.



4 The α subunit recombines with the γ and β subunits.

PROCESS FIGURE 17.16 G Proteins Opening Ion Channels

Sometimes, the target cell of a hormone is an electrically excitable cell. When the hormone binds to its receptor, the target cell can be either hyperpolarized or depolarized depending on the ions that enter.

? *Recall from chapter 11 that diffusion of a positively charged ion into an electrically excitable cell is stimulatory to that cell. Predict the response in the cell if the GTP protein α subunit caused a Cl^- channel to open. Chloride ions are in higher concentration in the extracellular fluid.*

Receptors That Directly Alter the Activity of Intracellular Enzymes

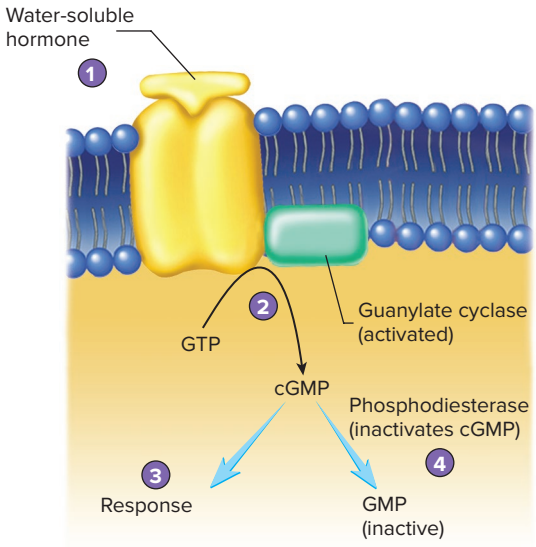
Some hormones bind to membrane-bound receptors and directly change the activity of an intracellular enzyme. The altered enzyme activity regulates the synthesis of intracellular mediators or results in the phosphorylation of intracellular proteins. The intracellular mediators or phosphorylated proteins activate processes that produce the cells' response to the chemical signals. Intracellular enzymes controlled by membrane-bound receptors can be part of the receptor, or they can be separate molecules. The intracellular mediators act as chemical

1 The water-soluble hormone binds to its receptor.

2 At the inner surface of the plasma membrane, guanylate cyclase is activated to produce cGMP from GTP.

3 Cyclic GMP is an intracellular mediator that alters the activity of other intracellular enzymes to produce the response of the cell.

4 Phosphodiesterase is an enzyme that converts cGMP to inactive GMP.



PROCESS FIGURE 17.17 Membrane-Bound Receptor Directly Activating an Intracellular Mediator

Some second messengers are produced when the hormone binds to its receptor, which activates the second messenger–producing enzyme.

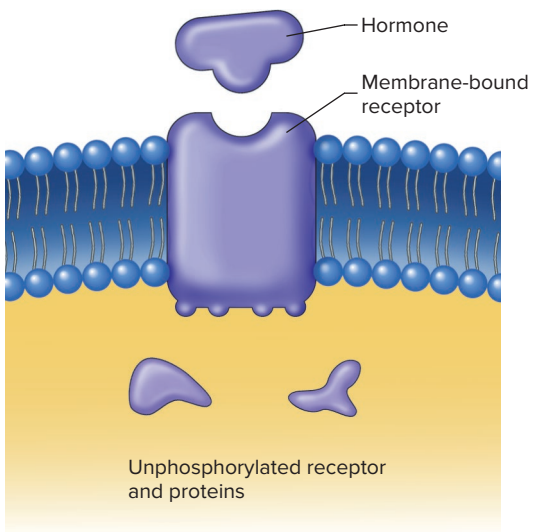
? *Because cGMP is produced when the hormone is bound to the receptor, predict the response of the cell if the hormone were to stay bound to the receptor longer than normal.*

signals that move from the enzymes that produce them into the cytoplasm of the cell, where they activate the processes that produce the cell's response. For example, the hormone glucagon activates enzymes that release glucose into the circulation from cells within the liver.

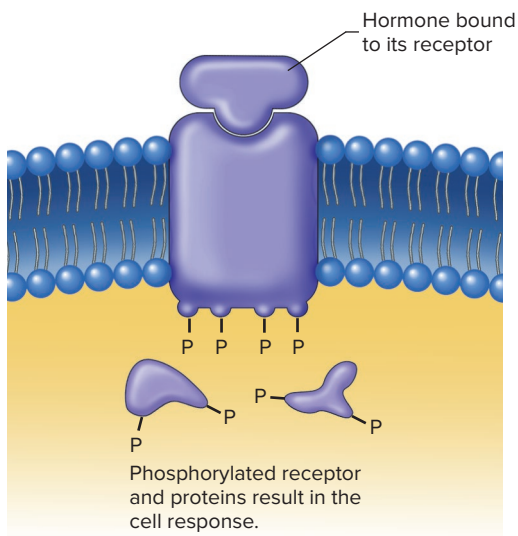
Signal Amplification

The rate and magnitude at which a hormone's response is elicited are determined by its mechanism of action at the receptor. Nuclear receptors work by activating protein synthesis, which for some hormones can take several hours. However, hormones that stimulate the synthesis of second messengers can produce an almost instantaneous response, because the second messenger influences existing enzymes. In other words, the response proteins are already present. Additionally, each receptor produces thousands of second messengers, leading to a cascade effect and ultimately **amplification** of the hormonal signal. With amplification, a single hormone activates many second messengers, each of which activates enzymes that produce an enormous amount of final product (figure 17.19). The efficiency of this second-messenger amplification is virtually unparalleled in the body and can be thought of as an "army of molecules" launching an offensive. In a war, the general gives the signal to attack, and thousands of soldiers carry out the order. The general alone could not neutralize thousands of enemies. Likewise, one hormone could not single-handedly produce millions of final products within a few seconds. However, with amplification, one hormone has an army of molecules working simultaneously to produce the final products.

Both nuclear receptor and membrane-bound receptor hormone systems are effective, but each is more suited to one type of



1 The membrane-bound receptor and other proteins have sites that can be phosphorylated at the inner surface of the plasma membrane. When the receptor is not bound to a hormone, these sites remain unphosphorylated.



2 The hormone binds to its receptor site on the outside of the plasma membrane. The receptor acts as an enzyme that phosphorylates the sites on the receptor and associated proteins. These phosphorylated proteins produce a response inside the cell.

PROCESS FIGURE 17.18 Membrane-Bound Receptors That Phosphorylate Intracellular Proteins

Some receptors serve as enzymes that phosphorylate intracellular molecules to activate them.

? *Given that most enzymes are proteins, why does it make sense that receptors can be both a receptor and an enzyme?*

FUNDAMENTAL **Figure**

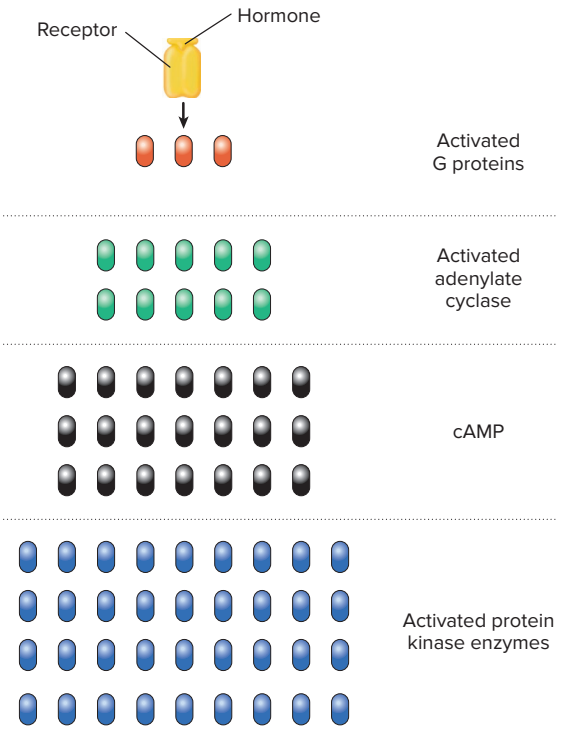


FIGURE 17.19 Amplification
The combination of a hormone with a membrane-bound receptor initiates a cascade effect that activates several G proteins. The G proteins, in turn, activate many inactive adenylate cyclase enzymes, which cause the synthesis of a large number of cAMP molecules. The large number of cAMP molecules, in turn, activate many inactive protein kinase enzymes, which produce a rapid and amplified response.

response than another. For example, the reason epinephrine, which binds to membrane-bound receptors, is effective in a fight-or-flight situation is that it can turn on the target cell responses within a few seconds. If running away from an immediate threat depended on producing new proteins, which usually involves nuclear receptors, a process that can take several hours, many of us would have already perished. On the other hand, pregnancy maintenance is mediated by steroids, which also bind to nuclear receptors, long-acting hormones, which is reflected by the fact that pregnancy is a long-term process. Thus, it is important for our bodies to have hormones that can function over differing time scales.

Predict 4

Of membrane-bound receptors and nuclear receptors, which is better adapted for mediating a response that lasts a considerable length of time, and which is better for mediating a response with a rapid onset and short duration? Explain why.

ASSESS YOUR PROGRESS

24. *What two ways can a membrane-bound receptor use to activate cellular response?*

25. *Explain how the hormone-receptor complex can alter the G proteins on the inner surface of the plasma membrane. Which subunit of the G protein alters the activity of molecules inside the plasma membrane or inside the cell?*

26. *List four intracellular mediators affected by G proteins.*

27. *Describe how G proteins can alter the permeability of the plasma membrane and how they can alter the synthesis of an intracellular mediator, such as cAMP. Give examples.*

28. *Describe how a hormone can bind to a membrane-bound receptor, directly change enzyme activity inside the cell, and increase phosphorylation of intracellular proteins. Give examples.*

29. *What limits the activity of intracellular mediators, such as cGMP, and phosphorylated proteins?*

30. *Explain the cascade effect for the second-messenger model of hormone action. Does the second-messenger amplification produce a slow or rapid response?*

Answer

Learn to Predict

After using anabolic steroids, Liu Dan's muscles increased in size, but he also experienced some unintended changes, including slight breast development, reduced testes size, and mood swings. We learned in this chapter that steroid hormones are all derived from cholesterol, a type of lipid, and are thus lipid-soluble. We also know that hormones, chemical messengers produced by the endocrine system, travel through the body via the bloodstream until they arrive at their target tissues. The cells of target tissues possess specific receptors that the hormones bind to and initiate changes in cellular metabolism or cell growth. Steroid hormones, because they are lipid-soluble, bind to intracellular receptors in the cell's cytoplasm or nucleus. Once the steroid hormone has bound to its receptor, the hormone-receptor complex stimulates increased gene expression and therefore increased protein production. In muscle cells, this leads to the increased muscle mass that Liu Dan experienced.

However, other tissues of the body contain receptors that can also bind the anabolic steroids, so using anabolic steroids can cause some unintended effects. The anabolic steroids Liu Dan used also led to the abnormal breast tissue growth, decreased testes size, and behavioral changes. Thus, although it may be tempting to take anabolic steroids to increase muscle mass, the risk for side effects is simply too great.

Answers to the odd-numbered Predict questions from this chapter appear in appendix E.

Summary

17.1 Principles of Chemical Communication

Characteristics of the Endocrine System

1. The endocrine system includes glands and specialized endocrine cells that secrete hormones into the bloodstream.
2. A hormone is a chemical messenger that is secreted into the blood, travels to a distant target tissue, and binds to specific receptors to produce a coordinated set of events in that target tissue.

Comparison of the Nervous and Endocrine Systems

1. The endocrine system and the nervous system are closely related.
   - They share anatomical structures in the brain.
   - They share molecules that are both neurotransmitters and hormones.
   - They cooperate to regulate important processes.
   - They both have chemical messengers that bind to the same receptor type.
2. The endocrine system and the nervous system have important differences.
   - Neurotransmitters deliver their chemical messengers directly to their target, whereas hormones travel in the bloodstream.
   - The endocrine system is slower than the nervous system.
   - The endocrine system has longer-lasting effects than the nervous system.

Classes of Chemical Messengers

1. The four classes of chemical messengers are autocrine, paracrine, neurotransmitter, and endocrine.
2. Endocrine chemical messengers are called hormones.

17.2 Hormones

General Characteristics of Hormones

1. Hormones have several characteristics in common: stability, communication, and distribution.
   - The length of time a hormone is active in the circulation is termed its half-life.
   - The half-life of some hormones is prolonged because they circulate in the blood bound to binding proteins.
2. Hormones not bound to binding proteins are called free hormones, and they can interact with their receptor.

Chemical Nature of Hormones

1. There are two chemical categories of hormones: lipid-soluble and water-soluble.
2. Lipid-soluble hormones include steroids, thyroid hormones, and some fatty acid derivatives.
   - Most lipid-soluble hormones are transported bound to binding proteins. Thus, their half-life extends from minutes to weeks.
   - Lipid-soluble hormones are removed from the circulation by conjugation to sulfate or glucuronic acid, which then allows them to be excreted in the bile.
3. Water-soluble hormones include proteins, peptides, and amino acid derivatives.
   - Water-soluble hormones circulate freely in the blood.
   - Proteases degrade protein and peptide hormones in the circulation; the breakdown products are then excreted in the urine. However, some water-soluble hormones have chemical modifications, such as the addition of a carbohydrate group, which prolongs their half-life.

Patterns of Hormone Secretion

The three main patterns of hormone secretions are chronic, acute, and episodic.

1. Chronic hormone secretion results in hormones whose circulating levels are relatively constant.
2. Acute hormone secretion results in hormone levels that can vary dramatically.
3. Episodic hormone secretion results in a cyclic pattern of hormone release.

17.3 Control of Hormone Secretion

Stimulation of Hormone Release

Three types of stimuli result in hormone secretion: humoral, neural, and hormonal.

1. Humoral stimulation is exhibited by hormones that are sensitive to circulating blood levels of certain molecules, such as glucose or calcium.
2. Neural stimuli cause hormone secretion in direct response to action potentials in neurons, as occurs during stress or exercise. Hormones from the hypothalamus that cause the release of other hormones are called releasing hormones.
3. Hormonal stimulation of other hormone secretion is common in the endocrine system. Hormones from the anterior pituitary that stimulate hormones from other endocrine glands are called tropic hormones.

Inhibition of Hormone Release

Although the stimulus of hormone secretion is important, inhibition is equally important.

1. Humoral substances can inhibit the secretion of hormones.
2. Neural stimuli can prevent hormone secretion.
3. Inhibiting hormones prevent hormone release.

Regulation of Hormone Levels in the Blood

Two processes regulate the overall blood levels of hormones: negative feedback and positive feedback.

1. Negative feedback prevents further hormone secretion once a set point is achieved.
2. Positive feedback is a self-promoting system whereby the stimulation of hormone secretion increases over time.

17.4 Hormone Receptors and Mechanisms of Action

Agonists and Antagonists

1. Agonists mimic the actions of a natural hormone.
2. Antagonists block the actions of a natural hormone.

Decrease in Receptor Number

1. Hormones stimulate their targets by binding to proteins in the target cell called receptors.
2. A target cell may decrease its sensitivity to a hormone through desensitization, which can occur through a decrease in receptor number, a process called down-regulation.

Increase in Receptor Number

A target cell may increase its sensitivity to a hormone through sensitization, which can occur through an increase in receptor number, a process called up-regulation.

Classes of Receptors

The two groups of hormones each have their own class of receptors.

1. Lipid-soluble hormones bind to nuclear receptors located inside the nucleus of the target cell.
2. Water-soluble hormones bind to membrane-bound receptors, which are integral membrane proteins.

Action of Nuclear Receptors

1. Nuclear receptors have portions that allow them to bind to the DNA in the nucleus once the hormone is bound.
   - The hormone-receptor complex activates genes, which in turn activate the DNA to produce mRNA.
   - The mRNA increases the synthesis of certain proteins that produce the target cell's response.
2. Nuclear receptors cannot respond immediately, because it takes time to produce the mRNA and the protein.

Membrane-Bound Receptors and Signal Amplification

1. Membrane-bound receptors activate a cascade of events once the hormone binds.
2. Some membrane-bound receptors are associated with membrane proteins called G proteins.
   - Hormone binds to a membrane-bound receptor, and G proteins are activated.
   - The α subunit of the G protein binds to ion channels and causes them to open or change the rate of synthesis of intracellular mediators, such as cAMP, cGMP, IP_3, and DAG.
3. Intracellular enzymes can be activated directly, which in turn causes the synthesis of intracellular mediators, such as cGMP, or adds a phosphate group to intracellular enzymes, which alters their activity.
4. Second-messenger systems act rapidly, because they act on already existing enzymes to amplify the signal.

REVIEW AND COMPREHENSION

1. When comparing the endocrine system and the nervous system, the endocrine system generally
   a. is faster-acting than the nervous system.
   b. produces effects that are of shorter duration.
   c. uses blood-borne chemical messengers.
   d. produces more localized effects.
   e. relies less on chemical messengers.
2. Given this list of molecule types:
   (1) nucleic acid derivatives
   (2) fatty acid derivatives
   (3) peptides
   (4) proteins
   (5) phospholipids

   Which could be hormone molecules?
   a. 1,2,3 c. 1,2,3,4 e. 1,2,3,4,5
   b. 2,3,4 d. 2,3,4,5
3. Which of these can regulate the secretion of a hormone from an endocrine tissue?
   a. other hormones
   b. negative-feedback mechanisms
   c. humoral substances in the blood
   d. the nervous system
   e. All of these are correct.
4. Hormones are released into the blood
   a. at relatively constant levels.
   b. in large amounts in response to a stimulus.
   c. in an episodic fashion.
   d. All of these are correct.
5. Lipid-soluble hormones readily diffuse through capillary walls, whereas water-soluble hormones, such as proteins, must
   a. pass through capillary cells.
   b. pass through pores in the capillary endothelium.
   c. be moved out of the capillary by active transport.
   d. remain in the blood.
   e. be broken down to amino acids before leaving the blood.
6. Concerning the half-life of hormones,
   a. lipid-soluble hormones generally have a longer half-life.
   b. hormones with a shorter half-life regulate activities with a slow onset and long duration.
   c. hormones with a shorter half-life are maintained at more constant levels in the blood.
   d. lipid-soluble hormones are degraded rapidly by enzymes in the circulatory system.
   e. water-soluble hormones usually bind to plasma proteins.
7. Given these observations:
   (1) A hormone affects only a specific tissue (not all tissues).
   (2) A tissue can respond to more than one hormone.
   (3) Some tissues respond rapidly to a hormone, whereas others take many hours to respond.

   Which of these observations can be explained by the characteristics of hormone receptors?
   a. 1 c. 2,3 e. 1,2,3
   b. 1,2 d. 1,3
8. Which of these is *not* a means by which hormones are eliminated from the circulatory system?
   a. excreted into urine or bile
   b. bound to binding proteins
   c. enzymatically degraded in the blood (metabolism)
   d. actively transported into cells
   e. conjugated with sulfate or glucuronic acid
9. Down-regulation
   a. produces a decrease in the number of receptors in the target cells.
   b. produces an increase in target cells' sensitivity to a hormone.
   c. is found in target cells that respond to hormones that are maintained at constant levels.
   d. occurs partly because of an increase in receptor synthesis by the target cell.
   e. All of these are correct.

10. Activated G proteins can
    a. cause ion channels to open or close.
    b. activate adenylate cyclase.
    c. inhibit the synthesis of cAMP.
    d. alter the activity of IP_3.
    e. All of these are correct.

11. Given these events:
    (1) GTP is converted to GDP.
    (2) The subunit separates from the β and γ units.
    (3) GDP is released from the α subunit.

    List the order in which the events occur after a hormone binds to a membrane-bound receptor.
    a. 1,2,3 c. 2,3,1 e. 3,1,2
    b. 1,3,2 d. 3,2,1

12. Which of these can limit a cell's response to a hormone?
    a. phosphodiesterase
    b. converting GTP to GDP
    c. decreasing the number of receptors
    d. blocking binding sites
    e. All of these are correct.

13. Given these events:
    (1) The α subunit of a G protein interacts with Ca^{2+} channels.
    (2) Calcium ions diffuse into the cell.
    (3) The α subunit of a G protein is activated.

    Choose the arrangement that lists the events in the order they occur after a hormone binds to a receptor on a smooth muscle cell.
    a. 1,2,3 c. 2,1,3 e. 3,2,1
    b. 1,3,2 d. 3,1,2

14. Given these events:
    (1) cAMP is synthesized.
    (2) The α subunit of G protein is activated.
    (3) Phosphodiesterase breaks down cAMP.

    Choose the arrangement that lists the events in the order they occur after a hormone binds to a receptor.
    a. 1,2,3 c. 2,1,3 e. 3,2,1
    b. 1,3,2 d. 2,3,1

15. When a hormone binds to a nuclear receptor
    a. DNA produces mRNA.
    b. G proteins are activated.
    c. the hormone-receptor complex causes ion channels to open or close.
    d. the cell's response is faster than when a hormone binds to a membrane-bound receptor.
    e. the hormone is usually a large, water-soluble molecule.

16. Given these events:
    (1) activation of cAMP
    (2) activation of genes
    (3) alteration of enzyme activity

    Which of these events can occur when a hormone binds to a nuclear hormone receptor?
    a. 1 b. 1,2 c. 2,3 d. 1,2,3

Answers appear in appendix F.

CRITICAL THINKING

1. Consider a hormone that is secreted in large amounts at a given interval, modified chemically by the liver, and excreted by the kidneys at a rapid rate, thus making the half-life of the hormone in the circulatory system very short. The hormone therefore rapidly increases in the blood and then decreases rapidly. Suppose that a patient has both liver and kidney disease. Predict the consequences on the blood levels of that hormone.
2. Consider a hormone that increases the concentration of a substance in the circulatory system. If a tumor begins to produce that substance in large amounts in an uncontrolled fashion, predict the effect on the hormone's secretion rate.
3. How could you determine whether a hormone-mediated response has resulted from the intracellular mediator mechanism or the nuclear receptor mechanism?
4. If a hormone affects a target tissue through a membrane-bound receptor that has a G protein associated with it, predict the consequences if a genetic disease causes the α subunit of the G protein to have a structure that prevents it from binding to GTP.
5. For a hormone that binds to a membrane-bound receptor and has cAMP as the intracellular mediator, predict and explain the consequences if a patient takes a drug that strongly inhibits phosphodiesterase.
6. When an individual is confronted with a potentially harmful situation, the adrenal glands release epinephrine (adrenaline). Epinephrine prepares the body for action by increasing the heart rate and blood glucose levels. Explain the advantages or disadvantages associated with a shorter half-life for epinephrine, such as when it is released as a neurotransmitter, and those associated with a longer half-life, such as when it is secreted as a hormone.
7. Thyroid hormones are important in regulating the body's basal metabolic rate. Thyroid hormones are lipid-soluble and have a long half-life. What are the advantages and disadvantages of a long half-life for thyroid hormones, compared with a short half-life?
8. Predict the effect on LH and FSH secretion if a small tumor in the hypothalamus continuously secretes large concentrations of GnRH. Given that LH and FSH regulate the function of the male and female reproductive systems, state whether the condition will increase or decrease the activity of these systems.
9. Predict some consequences of trying to use a skin patch to administer insulin, a protein hormone, to a person who has diabetes mellitus.

Answers to odd-numbered questions appear in appendix G.

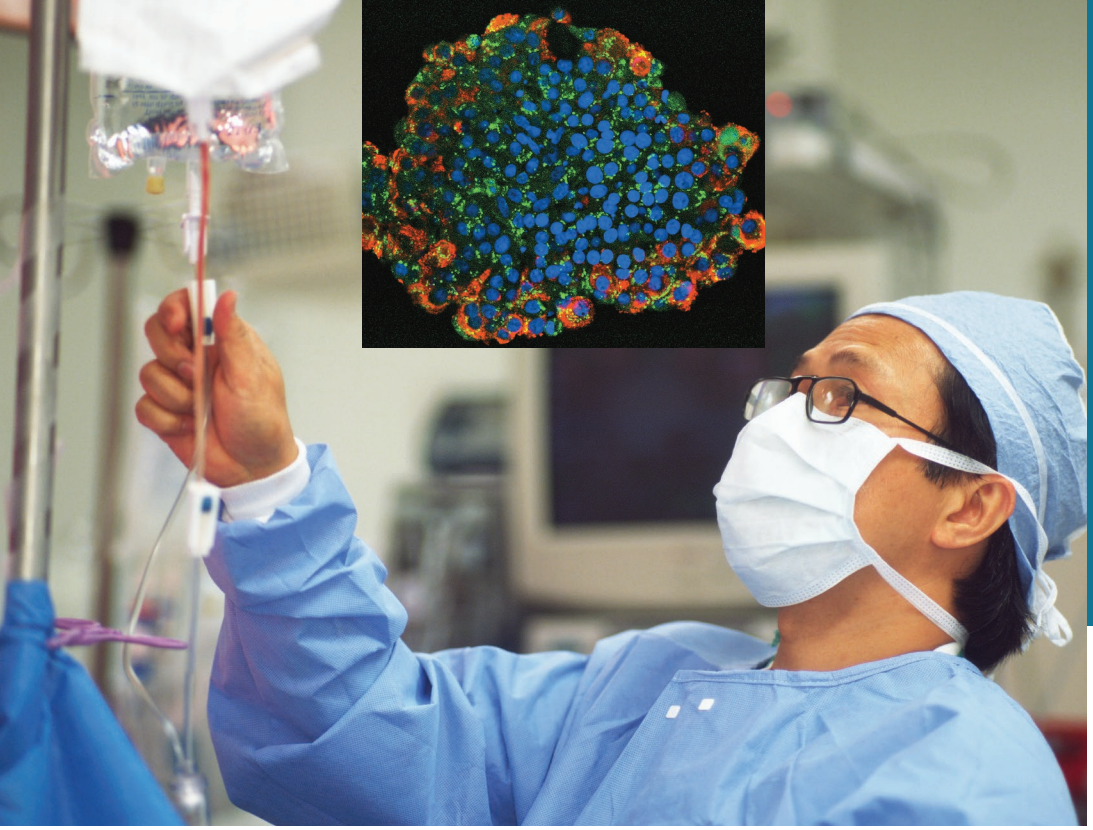


Photo: The surgeon in this photo is transfusing donor islet cells into a diabetic patient. The islet cells may take residence in the body and secrete insulin for the patient. Note the new islet cells in the photo inset. They are now functioning normally. The patient may never again need to inject insulin. (Bottom) ©ERproductions Ltd/ Blend Images LLC; (Top) Courtesy of Dr. Elizabeth Fenjves

18

Endocrine Glands

This chapter examines each of the organs of the endocrine system, describes the hormones they secrete, and explains how hormone secretion is regulated so that homeostasis is maintained. The endocrine system works with the nervous system to regulate and coordinate the activities of nearly all the other body structures. When either system fails to function properly, conditions can rapidly deviate from homeostasis, and disease may result. One of the most common endocrine system disorders is insulin-dependent diabetes mellitus. You may know someone who has this condition, but, as recently as the early 1900s, people who developed the disease died because no effective treatment was available. As physiologists learned more about the function of endocrine glands and the nature of their hormones, successful treatments were developed for diabetes mellitus, as well as for many other endocrine disorders.

Learn to Predict

Dylan, a 10-year-old boy, was constantly hungry and was losing weight rapidly in spite of his unusually large food intake. Dylan was also constantly thirsty and urinated frequently. In addition, he felt weak and lethargic, and his breath occasionally had a distinctive sweet, or acetone, odor. Dylan's parents tried to make sure he ate a healthy diet, but Dylan was sneaking candy and soft drinks when his parents were not around. **After reading this chapter and learning about the body's hormones, what type of hormonal imbalance do you think is responsible for Dylan's symptoms? What effect would eating candy and drinking sugary soda have on Dylan's health?**

18.1 Overview of the Endocrine System

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Explain the types of information that are necessary to understand endocrine function.**

B. **Describe the 10 regulatory functions of the endocrine system.**

The endocrine system is one of the two important control systems of the body. The nervous system is the body's other important control system. Recall from chapter 17 that the endocrine system is composed of glands and cells that secrete the chemical signals called hormones into the plasma of the blood (see figure 17.1). The hormones are secreted in response to humoral, neural, or hormonal stimuli and then travel in the blood plasma to target cells, where they regulate homeostasis. In order to understand completely how the endocrine system regulates body functions, you need to know the various endocrine glands, their hormones, and their mechanisms of action. In addition, many disorders of the body are caused by either hypersecretion or hyposecretion of hormones.

The main regulatory functions of the endocrine system are the following:

1. *Regulation of metabolism*. The endocrine system controls the rate of nutrient utilization and energy production.
2. *Control of food intake and digestion*. The endocrine system regulates the level of satiation (fullness) and the breakdown of food into individual nutrients.
3. *Modulation of tissue development*. The endocrine system influences the development of tissues, such as those of the nervous system.
4. *Regulation of ion levels*. The endocrine system helps monitor blood pH, as well as Na^+, K^+, and Ca^{2+} concentrations in the blood.
5. *Control of water balance*. The endocrine system regulates water balance by controlling the solute concentration of the blood.
6. *Changes in heart rate and blood pressure*. The endocrine system helps regulate the heart rate and blood pressure and prepare the body for physical activity.
7. *Control of blood glucose and other nutrients*. The endocrine system regulates the levels of glucose and other nutrients in the blood.
8. *Control of reproductive functions*. The endocrine system controls the development and functions of the reproductive systems in males and females.
9. *Stimulation of uterine contractions and milk release*. The endocrine system regulates uterine contractions during delivery and stimulates milk release from the breasts in lactating females.
10. *Modulation of immune system function*. The endocrine system helps control the production of immune cells.

ASSESS YOUR PROGRESS

Answers to these questions are found in the section you have just completed. Re-read the section if you need help in answering these questions.

1. *What pieces of information are needed to understand how the endocrine system regulates body functions?*
2. *List 10 regulatory functions of the endocrine system.*

18.2 Pituitary Gland and Hypothalamus

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe the location and structure of the pituitary gland.**

B. **Explain the physical, neural, and vascular connections between the hypothalamus and the pituitary gland.**

C. **Describe how the hypothalamus regulates hormone secretion from the pituitary gland.**

D. **List the hormones produced by the hypothalamus and state their structural type, target tissues, and actions.**

E. **List the hormones produced by the anterior pituitary gland and state their structural type, target tissues, and actions.**

F. **Explain the nature of a tropic hormone.**

G. **Describe the conditions that result from over- and undersecretion of pituitary hormones.**

As you learned in chapter 17, the endocrine system works closely with the nervous system to regulate and maintain homeostasis. Two important structures for integrating the nervous system and the endocrine system are the **pituitary** (pi-too′i-tār-rē) **gland,** or *hypophysis* (hī-pof′i-sis; an undergrowth), and the **hypothalamus** (hī′pō-thal′ă-mŭs; figure 18.1). The pituitary gland secretes nine major hormones that regulate numerous body functions and the secretory activity of several other endocrine glands. The hypothalamus regulates the secretory activity of the pituitary gland in response to other hormones, sensory information, and emotions.

Structure of the Pituitary Gland

The pituitary gland is connected to the base of the brain, just inferior to the hypothalamus. A stalk of tissue called the **infundibulum** (in-fŭn-dib′u-lŭm) connects the pituitary gland to the hypothalamus. The pituitary gland rests in the sella turcica of the sphenoid bone and is 1 cm in diameter and weighs 0.5–1.0 g, which is roughly the size of a pea (figure 18.1*a*).

The pituitary gland is divided into two lobes: (1) the **posterior pituitary gland,** or *neurohypophysis* (noor′ō-hī-pof′i-sis), and (2) the **anterior pituitary gland,** or *adenohypophysis* (ad′ĕ-nō-hī-pof′i-sis; *adeno,* gland).

Posterior Pituitary

The posterior pituitary is called the neurohypophysis because it is continuous with the hypothalamus in the brain (*neuro-* refers

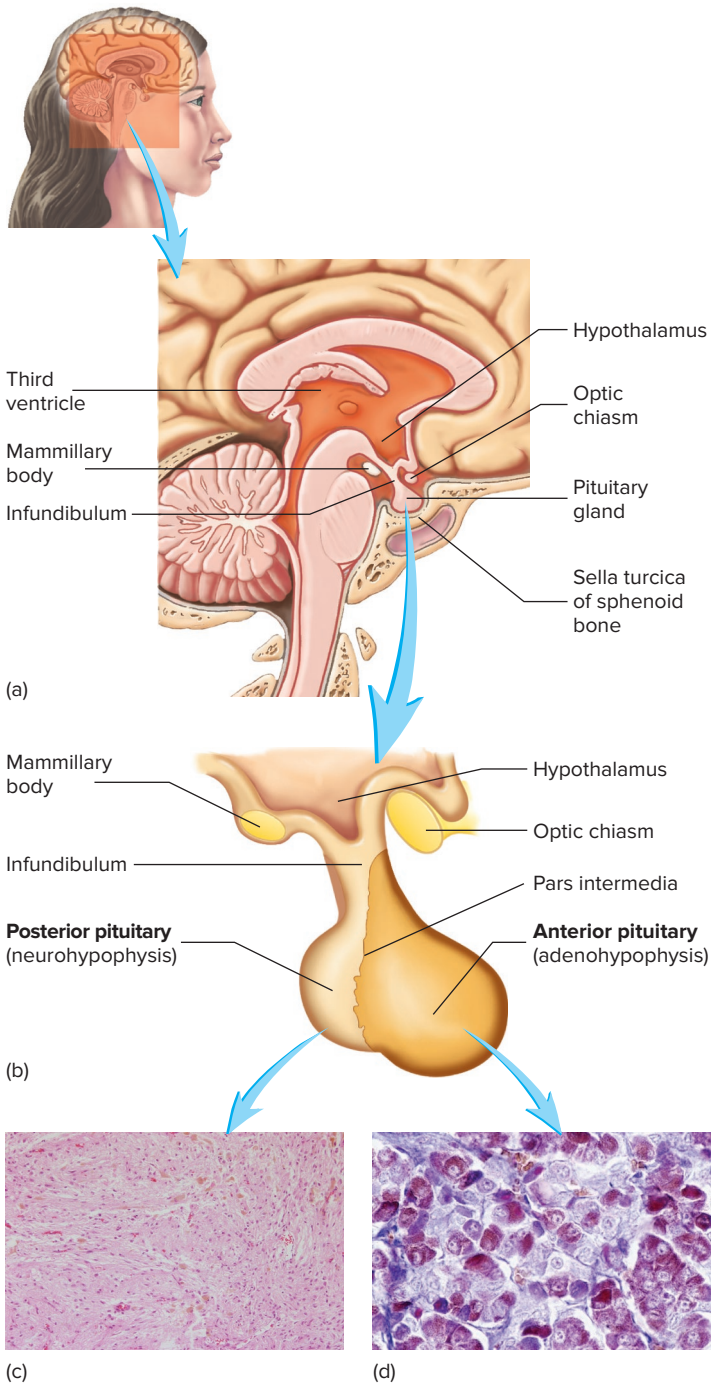


FIGURE 18.1 Subdivisions of the Pituitary Gland

(*a*) A midsagittal section of the head through the pituitary gland, showing the location of the hypothalamus of the brain and the pituitary gland. The pituitary gland is in a depression called the sella turcica in the floor of the skull. It is connected to the hypothalamus by the infundibulum. (*b*) The pituitary gland is divided into the anterior pituitary gland and the posterior pituitary gland. The posterior pituitary consists of the enlarged distal end of the infundibulum, which connects the posterior pituitary to the hypothalamus. (*c*,*d*) Histology of the pituitary gland: (c) The posterior pituitary consists of axon terminals, whereas (*d*) the anterior pituitary consists of groups of secretory cells. (c) ©Lutz Slomianka; (d) ©Victor P. Eroschenko AP|R

to the nervous system). During embryonic development, the posterior pituitary forms from an outgrowth of the hypothalamus region of the brain (see chapter 29). The outgrowth of the brain forms the infundibulum, and the distal end of the infundibulum enlarges to form the posterior pituitary (figure 18.1*b*). Because the posterior pituitary is a part of the nervous system, its hormones are called **neurohormones** (noor-ō-hōr′mōnz) or **neuropeptides**.

Anterior Pituitary

The anterior pituitary develops as an outpocketing of the roof of the embryonic oral cavity called the pituitary diverticulum, or Rathke pouch. The pituitary diverticulum continues growing toward the posterior pituitary. As it nears the posterior pituitary, the pituitary diverticulum loses its connection with the oral cavity and becomes the anterior pituitary. The anterior pituitary includes a thin band of tissue called the pars intermedia at its border with the posterior pituitary. The pars intermedia is not functional in adult humans (figure 18.2). Because the anterior pituitary is derived from epithelial tissue of the embryonic oral cavity, not from neural tissue, the hormones secreted from the anterior pituitary are traditional hormones, not neurohormones.

Relationship of the Pituitary Gland to the Brain: The Hypothalamus

The pituitary is regulated by a small region of the brain just superior to the pituitary called the hypothalamus. The hypothalamus differentially regulates the anterior and posterior pituitary. The hypothalamus regulates the anterior pituitary through a specialized set of blood vessels, whereas the hypothalamus regulates the posterior pituitary through a specialized neural pathway.

Hypothalamic Control of the Posterior Pituitary

Secretion of hormones by the posterior pituitary is very different from that of the anterior pituitary. There is no portal system to carry hypothalamic neuropeptides to the posterior pituitary. The posterior pituitary is simply a storage location for two neurohormones. The neurohormones released from the posterior pituitary are produced by neurosecretory neurons whose cell bodies are in the hypothalamus. The axons of these neurons extend from the hypothalamus through the infundibulum into the posterior pituitary and form a tract called the **hypothalamohypophysial tract** (figure 18.3). Neurohormones produced in the hypothalamus pass down these axons in tiny vesicles and are stored in secretory vesicles in the ends of the axons. Action potentials originating in the neuron cell bodies in the hypothalamus are propagated along the axons to the axon terminals in the posterior pituitary. The action potentials cause the release of neurohormones from the axon terminals, and they enter the general circulation. Neurohormones of the posterior pituitary gland are described later in this section.

Hypothalamic Control of the Anterior Pituitary

The specialized set of blood vessels connecting the hypothalamus and anterior pituitary is called the **hypothalamohypophysial**

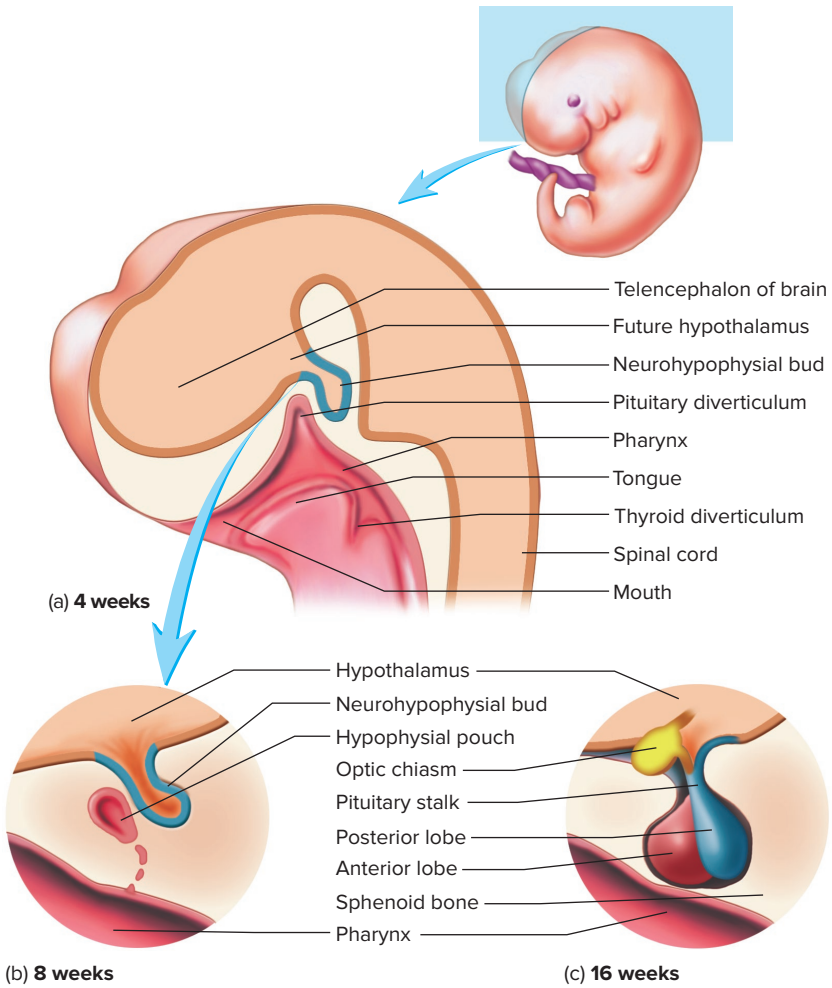


FIGURE 18.2 Development of the Pituitary Gland
The posterior pituitary develops as a downward growth of the hypothalamus. The anterior pituitary develops as an outpocketing of the embryonic gut called the pituitary diverticulum; the pars intermedia is not shown in this figure.

(hī′pō-thal′ă-mō-hī′pō-fiz′ē-ăl) **portal system** (figure 18.4). A portal system consists of two capillary networks directly connected by portal system vessels. The portal system connecting the hypothalamus and anterior pituitary is one of the major portal systems in the body. The others include the hepatic portal system and the renal nephron systems (see chapters 21 and 26).

It is through this portal system that the hypothalamus exerts direct control over hormone secretion from the anterior pituitary. The primary capillary network is located in the hypothalamus. There, hypothalamic neurons secrete their neurohormones into the portal system capillaries of the hypothalamus. The neurohormones are then transported directly to the second capillary network in the anterior pituitary. In the anterior pituitary, the hypothalamic neurohormones exit the portal system to regulate secretion from anterior pituitary cells.

Most hypothalamic neurohormones can be separated into two categories: (1) releasing hormones and (2) inhibiting hormones. **Releasing hormones** from the hypothalamus stimulate anterior pituitary hormone secretion. Once the anterior pituitary secretes a particular hormone, that hormone enters the general circulation for transport to its target tissues (figure 18.4). **Inhibiting hormones** from the hypothalamus decrease secretion of particular anterior pituitary hormones. Thus, the hypothalamohypophysial portal system provides the means by which the hypothalamus regulates the secretory activity of the anterior pituitary.

Many releasing and inhibiting hormones are produced and secreted by hypothalamic neurons (table 18.1). **Growth hormone–releasing hormone (GHRH)** is a small peptide that stimulates the secretion of growth hormone from the anterior pituitary gland, and growth hormone–inhibiting hormone (GHIH), which is more commonly called **somatostatin** (sō′mă-tō-stat′in), is a small peptide that inhibits growth hormone secretion. **Thyrotropin-releasing hormone (TRH)** is a small peptide that stimulates the secretion of thyroid-stimulating hormone from the anterior pituitary gland. **Corticotropin-releasing hormone (CRH)** is a peptide that stimulates the secretion of adrenocorticotropic hormone from the anterior pituitary gland. **Gonadotropin-releasing hormone (GnRH)** is a small peptide that stimulates the secretion of both luteinizing hormone and follicle-stimulating hormone from the anterior pituitary gland. Prolactin-inhibiting hormone (PIH), more commonly called **dopamine,** inhibits the secretion of prolactin from the anterior pituitary gland. However, identifying or even confirming the existence of a prolactin-releasing hormone has been elusive and is not known at this time. Secretions of the anterior pituitary gland are described later in this section.

Predict 1

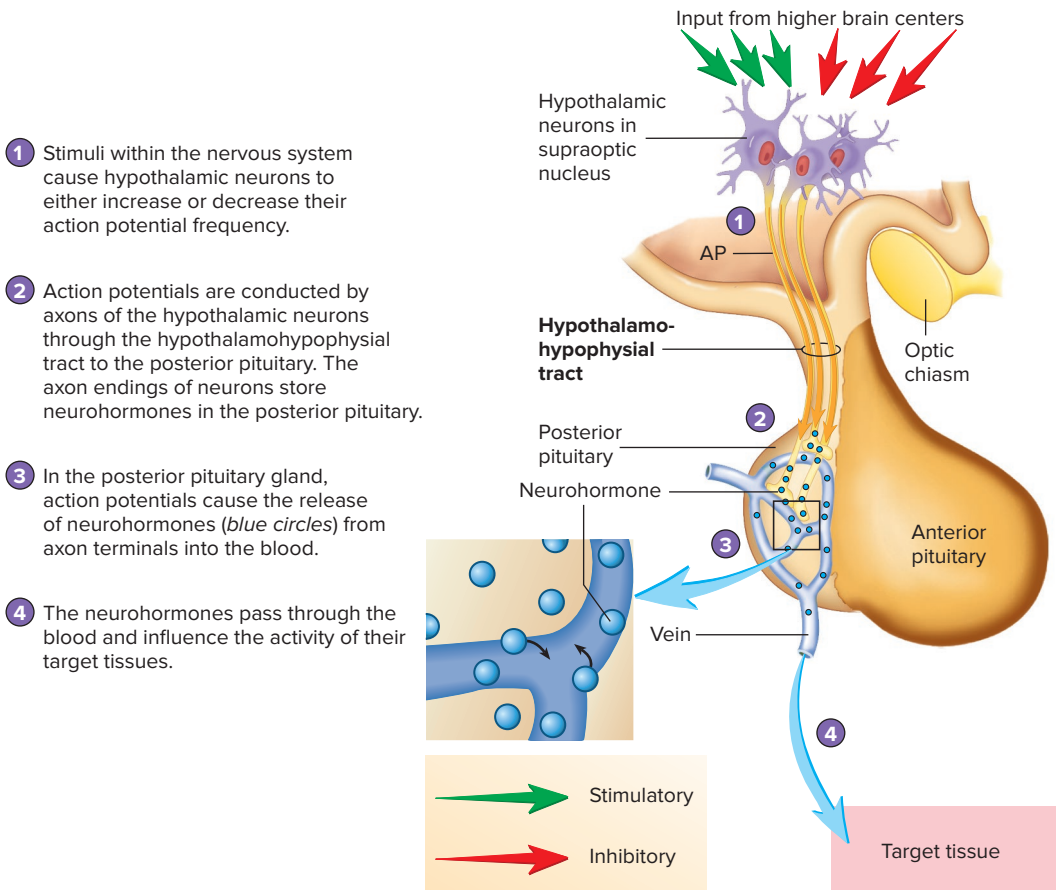
Surgical removal of the posterior pituitary in experimental animals results in clear symptoms of a hormone shortage, but they can be temporary. Surgical removal of the anterior pituitary, in contrast, results in many manifestations and a permanent shortage of several hormones. Explain these results.

ASSESS YOUR PROGRESS

3. *Where is the pituitary gland located? Contrast the embryonic origins of the anterior pituitary and the posterior pituitary.*
4. *What is a portal system? Describe the hypothalamohypophysial portal system.*
5. *How does the hypothalamus regulate the secretion of anterior pituitary hormones?*
6. *List the releasing and inhibiting hormones that are produced and released from hypothalamic neurons.*
7. *Describe the hypothalamohypophysial tract, including the production of neurohormones in the hypothalamus and their subsequent release from the posterior pituitary gland.*

Hormones of the Pituitary Gland

The hormones secreted from the pituitary gland are separated into two categories: (1) posterior pituitary hormones and (2) anterior



PROCESS FIGURE 18.3 Secretion of Posterior Pituitary Hormones

Posterior pituitary hormone secretion is regulated by neural input.

? *Are the posterior pituitary hormones water-soluble or lipid-soluble hormones? How do you know based solely on their mode of storage?*

pituitary hormones (table 18.2). Hormones from the pituitary gland have many, varied effects on the body and exert these effects in several ways. In addition, there are major consequences of abnormal pituitary hormone secretion on the body.

Posterior Pituitary Hormones

The posterior pituitary, composed of neural tissue, stores and secretes two neurohormones: (1) antidiuretic hormone and (2) oxytocin. A separate population of neurons secretes each neurohormone.

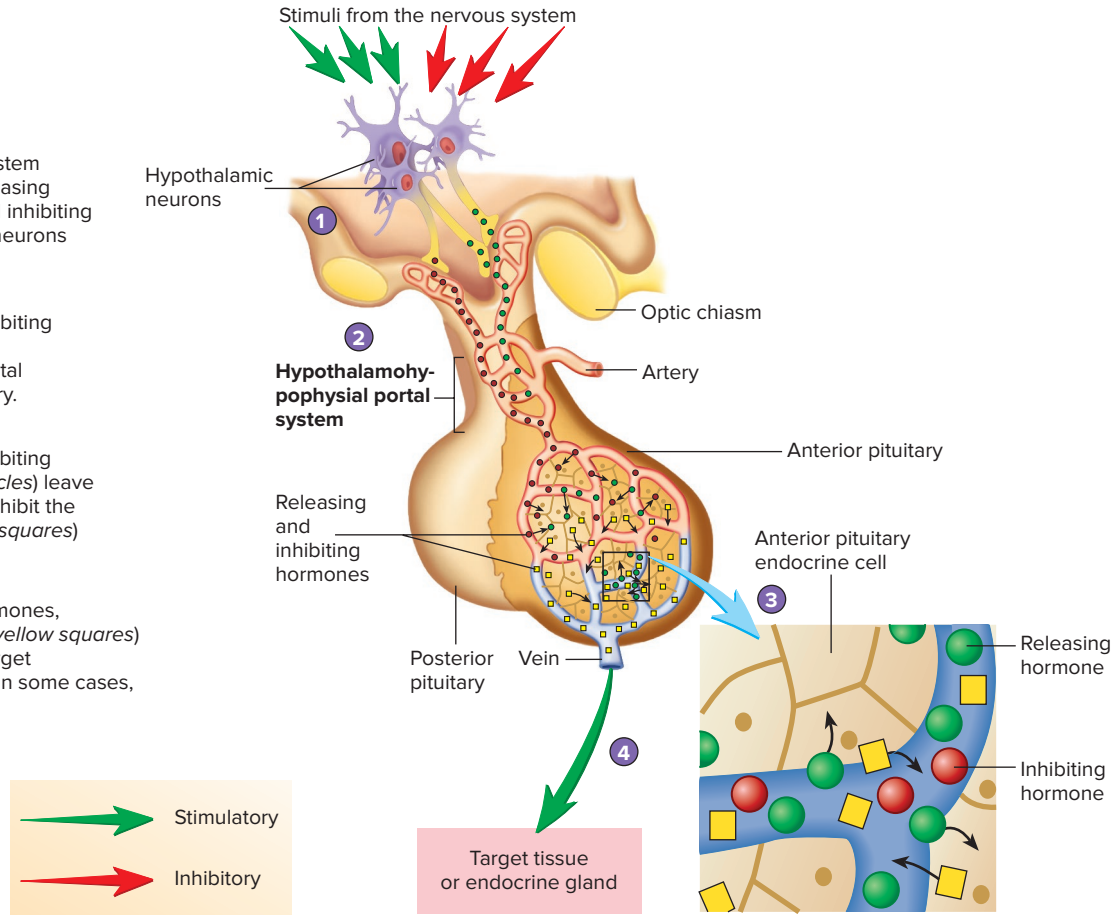
Antidiuretic Hormone

Antidiuretic (an′tē-dī-ū-ret′ik) **hormone (ADH)** is a water-conservation hormone. ADH prevents (*anti-*) the output of large amounts of urine (*diuresis*). An alternate name for ADH is **vasopressin** (vā-sō-pres′in, vas-ō-pres′in) because it also constricts blood vessels and raises blood pressure when large amounts are released. ADH molecules are synthesized predominantly by neurosecretory neuron cell bodies in the supraoptic nuclei of the hypothalamus. ADH is then transported to the posterior pituitary for storage. Action potentials in the supraoptic nuclei neurons stimulate the release of ADH into the blood. ADH acts on kidney tubules, the sites of urine production. ADH promotes the reabsorption of water from kidney tubules, which reduces urine volume (see chapter 26).

The secretion rate for ADH changes in response to alterations in blood osmolality and blood volume (figure 18.5). The **osmolality** of a solution increases as the concentration of solutes in the solution increases. Specialized neurons, called **osmoreceptors** (os′mō-rē-sep′terz), synapse with the ADH neurosecretory neurons in the hypothalamus. Osmoreceptors are sensitive to changes in blood osmolality. When blood osmolality increases, the frequency of action potentials in the osmoreceptors increases, resulting in a greater frequency of action potentials in the axons of ADH neurosecretory neurons. As a consequence, ADH secretion increases. ADH stimulates the kidney tubules to retain water, which reduces blood osmolality and resists any further increase in the osmolality of body fluids.

As the osmolality of the blood decreases, the action potential frequency in the osmoreceptors and the neurosecretory neurons

1. Stimuli within the nervous system regulate the secretion of releasing hormones (*green circles*) and inhibiting hormones (*red circles*) from neurons of the hypothalamus.
2. Releasing hormones and inhibiting hormones pass through the hypothalamohypophysial portal system to the anterior pituitary.
3. Releasing hormones and inhibiting hormones (*green and red circles*) leave capillaries and stimulate or inhibit the release of hormones (*yellow squares*) from anterior pituitary cells.
4. In response to releasing hormones, anterior pituitary hormones (*yellow squares*) travel in the blood to their target tissues (*green arrow*), which in some cases, are other endocrine glands.



PROCESS FIGURE 18.4 Hypothalamic Control of the Anterior Pituitary

Neurohormones from the hypothalamus travel to the anterior pituitary through a portal system. The neurohormones can be releasing hormones, which stimulate secretion of anterior pituitary hormones. The hypothalamic neurohormones also can be inhibiting hormones, which prevent secretion of anterior pituitary hormones.

? *Given that the anterior pituitary releases multiple hormones, how is it that a particular hypothalamus releasing hormone stimulates the secretion of a specific anterior pituitary hormone?*

TABLE 18.1 Hormones of the Hypothalamus

Hormones	Structure	Target Tissue	Response
Growth hormone–releasing hormone (GHRH)	Peptide	Anterior pituitary cells that secrete growth hormone	Increased growth hormone secretion
Growth hormone–inhibiting hormone (GHIH), or somatostatin	Small peptide	Anterior pituitary cells that secrete growth hormone	Decreased growth hormone secretion
Thyrotropin-releasing hormone (TRH)	Small peptide	Anterior pituitary cells that secrete thyroid-stimulating hormone	Increased thyroid-stimulating hormone secretion
Corticotropin-releasing hormone (CRH)	Peptide	Anterior pituitary cells that secrete adrenocorticotropic hormone	Increased adrenocorticotropic hormone secretion
Gonadotropin-releasing hormone (GnRH)	Small peptide	Anterior pituitary cells that secrete luteinizing hormone and follicle-stimulating hormone	Increased secretion of luteinizing hormone and follicle-stimulating hormone
Prolactin-releasing hormone (PRH)	Unknown		
Dopamine (Prolactin-inhibiting hormone, PIH)	Amino acid derivative The amino acid derivative, dopamine	Anterior pituitary cells that secrete prolactin	Decreased prolactin secretion

TABLE 18.2 **Hormones of the Pituitary Gland**

Hormones	Structure	Target Tissue	Response
Posterior Pituitary (Neurohypophysis)			
Antidiuretic hormone (ADH)	Small peptide	Kidneys	Increased water reabsorption (less water is lost in the form of urine)
Oxytocin	Small peptide	Uterus; mammary glands	Increased uterine contractions; increased milk expulsion from mammary glands; unclear function in males
Anterior Pituitary (Adenohypophysis)			
Growth hormone (GH), or somatotropin	Protein	Most tissues	Increased growth in tissues; increased amino acid uptake and protein synthesis; increased breakdown of lipids and release of fatty acids from cells; increased glycogen synthesis and increased blood glucose levels; increased somatomedin production
Thyroid-stimulating hormone (TSH)	Glycoprotein	Thyroid gland	Increased thyroid hormone secretion
Adrenocorticotropic hormone (ACTH)	Peptide	Adrenal cortex	Increased glucocorticoid hormone secretion
Lipotropins	Peptides	Adipose tissues	Increased lipid breakdown
β endorphins	Peptides	Brain, but not all target tissues are known	Analgesia in the brain; inhibition of gonadotropin-releasing hormone secretion
Melanocyte-stimulating hormone (MSH)	Peptide	Melanocytes in the skin	Increased melanin production in melanocytes to make the skin darker in color
Luteinizing hormone (LH)	Glycoprotein	Ovaries in females; testes in males	Ovulation and progesterone production in ovaries; testosterone synthesis and support for sperm cell production in testes
Follicle-stimulating hormone (FSH)	Glycoprotein	Follicles in ovaries in females; seminiferous tubules in males	Follicle maturation and estrogen secretion in ovaries; sperm cell production in testes
Prolactin	Protein	Ovaries and mammary glands in females	Milk production in lactating women; increased response of follicle to LH and FSH; unclear reproductive function in males; has been implicated in many other homeostatic functions, such as ion balance and immune regulation

decreases. Thus, less ADH is secreted from the posterior pituitary gland, and the decreased ADH secretion causes an increased volume of water to be eliminated in the form of urine.

Urine volume increases within minutes to a few hours in response to the consumption of a large volume of water. In contrast, urine volume decreases and urine concentration increases within hours if little water is consumed. ADH regulates these changes in urine formation by controlling the permeability of kidney tubules to water. Its effect is to maintain the osmolality and the volume of the extracellular fluid within a normal range of values.

Because ADH regulates blood volume, its secretion is also controlled by blood pressure changes. Sensory receptors that detect changes in blood pressure send action potentials through sensory nerve fibers of the vagus nerve that eventually communicate these changes to the ADH neurosecretory neurons. A decrease in blood pressure, which normally accompanies a decrease in blood volume, causes an increased action potential frequency in the neurosecretory neurons and increased ADH secretion, which stimulates the kidneys to retain water. Because the water in urine is derived from blood as it passes through the kidneys, ADH slows any further reduction in blood volume.

An increase in blood pressure decreases the action potential frequency in the ADH neurosecretory neurons. This leads to the secretion of less ADH from the posterior pituitary. As a result, the volume of urine produced by the kidneys increases (figure 18.5). Even small changes in blood osmolality influence ADH secretion. Larger changes in blood pressure are required to influence ADH secretion. The effect of ADH on the kidney and its role in regulating extracellular osmolality and volume are described in greater detail in chapters 26 and 27.

Predict 2

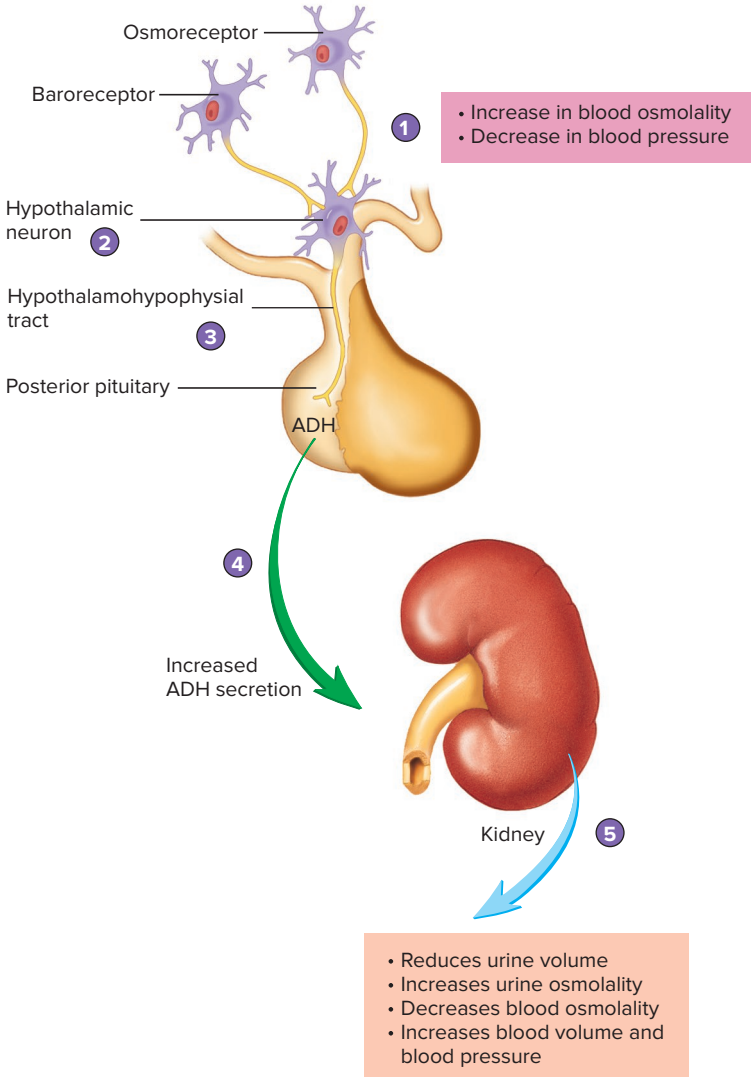
After his school's football team won the division championship, Luke went to a local bar with some friends and drank too much beer. Fortunately, one of his friends served as a designated driver. The next morning, Luke wondered why he was thirsty and felt somewhat dehydrated. His roommate, an anatomy and physiology student, pointed out that alcohol inhibits ADH secretion from the posterior pituitary. The roommate then explained why Luke was thirsty and dehydrated. What was the explanation?

Oxytocin

Oxytocin (ok-sē-tō′sin) is an important reproductive hormone, synthesized by the hypothalamic neurosecretory neuron cell bodies in the paraventricular nuclei. Oxytocin is transported to the posterior pituitary for storage.

Oxytocin stimulates labor in pregnant mammals. It does this by stimulating smooth muscle contraction in the uterus. It also causes contraction of uterine smooth muscle in nonpregnant

1. Osmoreceptors in the hypothalamus detect changes in blood osmolality, and baroreceptors detect changes in blood pressure and change the frequency of action potentials in axons of the vagus nerve to the hypothalamus.
2. An increase in osmolality and a decrease in blood pressure increase action potentials in ADH-secreting neurons.
3. Action potentials are carried by axons of ADH-secreting neurons through the hypothalamohypophysial tract to the posterior pituitary.
4. In the posterior pituitary, action potentials cause the release of ADH from the axon terminals into the blood.
5. Increasing ADH acts on the kidney tubules to increase water reabsorption, resulting in reduced urine volume, increased urine osmolality, and decreased blood osmolality. This helps maintain blood osmolality and volume.



PROCESS FIGURE 18.5 Control of Antidiuretic Hormone (ADH) Secretion

Small changes in blood osmolality are important in regulating ADH secretion. Larger changes in blood pressure are required to influence ADH secretion.

? *How would an inability to produce ADH affect urine volume?*

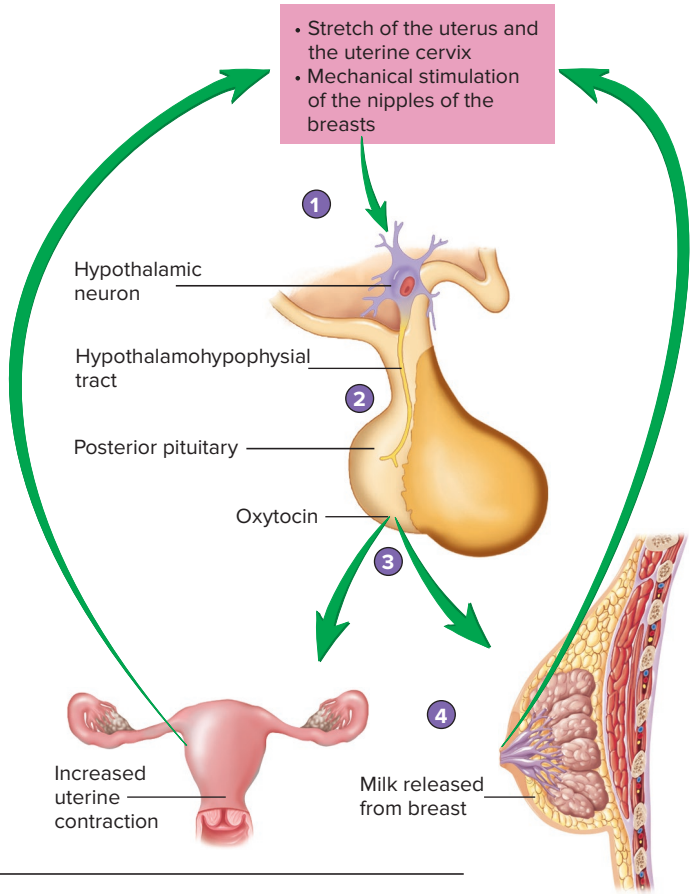
women, primarily during menstruation and sexual intercourse. The uterine contractions help rid the uterus of its lining along with small amounts of blood during menstruation. Oxytocin can also facilitate the movement of sperm cells through the uterus after sexual intercourse. Oxytocin is responsible for milk letdown in breastfeeding women and other lactating mammals. It promotes the contraction of smooth-muscle-like cells surrounding the milk ducts in the mammary glands. In addition, oxytocin is associated with maternal nurturing and bonding (see chapter 29). Although little is known about the specific effects of oxytocin in males, evidence suggests that it promotes sperm movement during ejaculation and pair bonding.

Stretch of the uterus, mechanical stimulation of the cervix, and stimulation of the nipples of the breast when a baby nurses activate nervous reflexes that stimulate oxytocin release. Action potentials are carried by sensory neurons from the uterus and from the nipples to the spinal cord. Action potentials then travel up the spinal cord to the hypothalamus, where they stimulate an increase in the action potential frequency in the axons of oxytocin-secreting neurons. The action potentials pass along the axons in the hypothalamohypophysial tract to the posterior pituitary, where they cause the axon terminals to secrete oxytocin (figure 18.6). The role of oxytocin in the reproductive system is described in greater detail in chapter 29.

ASSESS YOUR PROGRESS

8. *Where is ADH produced, from where is it secreted, and what is its target tissue?*
9. *When ADH levels increase, how are urine volume, blood osmolarity, and blood volume affected?*
10. *What two factors will cause changes in ADH secretion rates? Name the types of sensory cells that respond to alterations in those factors.*

1. Stretch of the uterus and the uterine cervix or stimulation of the breasts' nipples increases action potentials in axons of oxytocin-secreting neurons.
2. Action potentials are conducted by sensory neurons from the uterus and breast to the spinal cord and up ascending tracts to the hypothalamus.
3. Action potentials are conducted by axons of oxytocin-secreting neurons in the hypothalamohypophysial tract to the posterior pituitary, where they increase oxytocin secretion.
4. Oxytocin enters the circulation, increasing contractions of the uterus and milk letdown from the lactating breast.



PROCESS FIGURE 18.6 Control of Oxytocin Secretion
Oxytocin secretion is stimulated by neural input from the nipples and the uterus.

? *What outcome might you expect if a pregnant woman were to be given an oxytocin agonist?*

11. *Where is oxytocin produced, from where is it secreted, and what are its target tissues?*

12. *What effects does oxytocin have on its target tissues? What factors stimulate the secretion of oxytocin?*

Anterior Pituitary Hormones

The anterior pituitary is regulated differently than the posterior pituitary because its hormones are synthesized by cells in the anterior pituitary. Secretion of the anterior pituitary hormones is regulated by hypothalamic releasing and inhibiting hormones (figure 18.3).

The hormones secreted from the anterior pituitary are proteins, glycoproteins, or polypeptides. They are transported in the blood, have a half-life measured in minutes, and bind to membrane-bound receptor molecules on their target cells. For the most part, each hormone is secreted by a separate cell type. Adrenocorticotropic hormone and lipotropin are exceptions because these hormones are derived from the same precursor protein.

Many hormones from the anterior pituitary gland are **tropic** (trō′pik) **hormones,** which stimulate the secretion of other hormones from the target tissues. Tropic hormones also control the growth of target tissues. The anterior pituitary hormones include (1) the protein hormones, growth hormone, and prolactin; (2) the peptide hormone adrenocorticotropic hormone and related substances; and (3) the glycoprotein hormones, luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone.

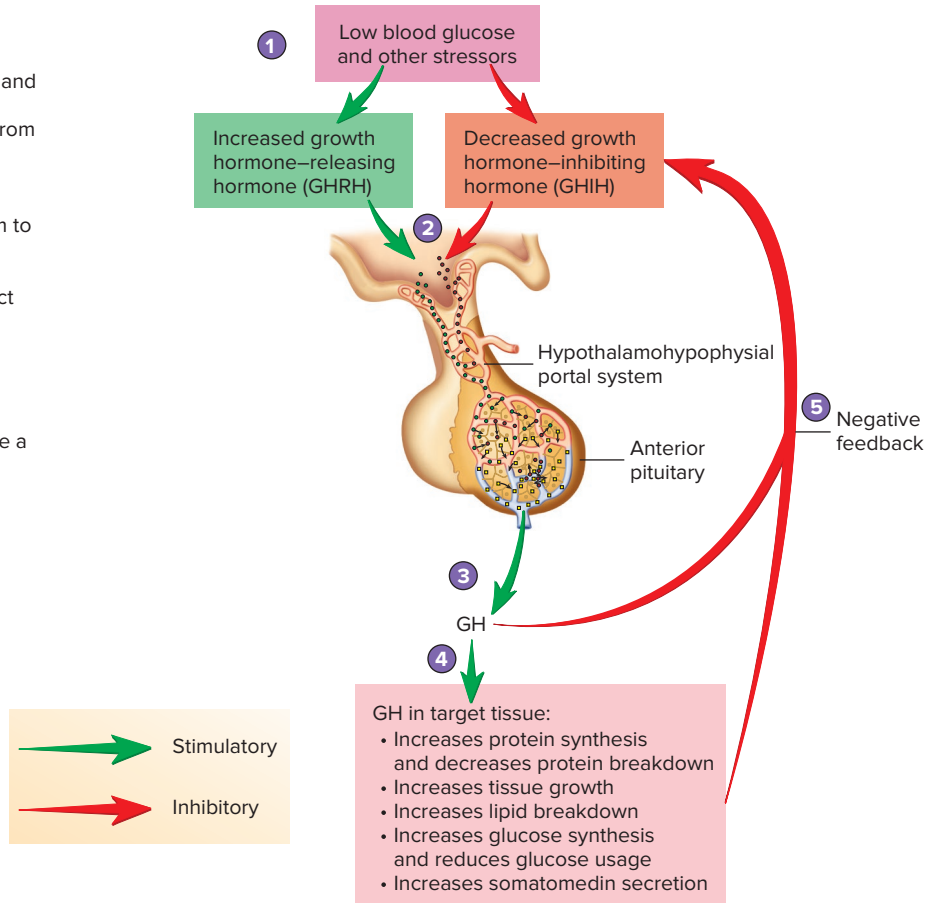
Growth Hormone

Growth hormone (GH), or *somatotropin,* stimulates growth in most tissues and plays an important role in determining how tall a person becomes. It also regulates metabolism. GH plays an important role in regulating blood nutrient levels after a meal and during periods of fasting. GH increases the movement of amino acids into cells, favors their incorporation into proteins, and slows protein breakdown. GH increases lipolysis (lipid breakdown) and the release of fatty acids from adipocytes into the blood. Fatty acids then can be used as energy sources to drive chemical reactions, including anabolic reactions, by other cells. GH also increases glucose synthesis by the liver, which releases glucose into the blood. The increased use of lipids as an energy source accompanies a decrease in glucose usage. Overall, GH activates the use of lipids to promote growth and protein synthesis.

GH binds directly to membrane-bound receptors on target cells (see chapter 17), such as adipocytes, to produce responses. These responses are called the direct effects of GH and include the increased breakdown of lipids and the decreased use of glucose as an energy source.

GH also has indirect effects on some tissues. It increases the production of a number of polypeptides, primarily by the liver but also by skeletal muscle and other tissues. These polypeptides are called **somatomedins** (sō′mă-tō-mē′dinz). The best-known somatomedins are **insulin-like growth factors (IGFs).** They are so named because of their structural

1. Stress and decreased blood glucose levels increase the release of growth hormone–releasing hormone (GHRH), and decrease the release of growth hormone–inhibiting hormone (GHIH), from the hypothalamus.
2. GHRH and GHIH travel through the hypothalamohypophysial portal system to the anterior pituitary.
3. Increased GHRH and reduced GHIH act on the anterior pituitary and result in increased GH secretion.
4. GH acts on target tissues.
5. Increasing GH and somatomedins have a negative-feedback effect on the hypothalamus, resulting in decreased GHRH and increased GHIH release.



PROCESS FIGURE 18.7 Control of Growth Hormone (GH) Secretion

Secretion of GH is controlled by two neurohormones released from the hypothalamus: growth hormone–releasing hormone (GHRH), which stimulates GH secretion, and growth hormone–inhibiting hormone (GHIH), which inhibits GH secretion. Stress increases GHRH secretion and inhibits GHIH secretion. High levels of GH have a negative-feedback effect on the production of GHRH by the hypothalamus.

? *Predict the effect of severing the infundibulum of the pituitary on GH secretion.*

resemblance to insulin and because the receptor molecules function through a mechanism similar to that of the insulin receptors. IGFs have paracrine effects and circulate in the blood until they bind to receptors on target tissues. IGFs stimulate growth in cartilage and bone and increase the synthesis of protein in skeletal muscles. Like IGFs, growth hormone and growth factors bind to membrane-bound receptors that phosphorylate intracellular proteins (see chapter 17).

Two neurohormones released from the hypothalamus regulate the secretion of GH (figure 18.7). One hormone, growth hormone–releasing hormone (GHRH), stimulates the secretion of GH, and the other, growth hormone–inhibiting hormone (GHIH), inhibits the secretion of GH. Stimuli that influence GH secretion act on the hypothalamus to increase or decrease the secretion of the releasing and inhibiting hormones. Low blood glucose levels and other stressors stimulate the secretion of GH, and high blood glucose levels inhibit the secretion of GH. Rising blood levels of certain amino acids also increase GH secretion.

In most people, a rhythm of GH secretion occurs. Daily peak levels of GH are correlated with deep sleep. Surprisingly, rapidly growing children do not have chronically elevated blood GH levels. However, their levels tend to be higher than those of adults. In addition to GH, factors such as genetics, nutrition, and sex hormones influence growth.

Several pathological conditions are associated with abnormal GH secretion. In general, hypersecretion or hyposecretion of GH is caused by tumors in the hypothalamus or pituitary, the synthesis of structurally abnormal GH, the liver's inability to produce somatomedins, or the lack of functional receptors in target tissues. The consequences of hypersecretion and hyposecretion of GH are described in Clinical Impact 18.1.

Predict 3

Zach has a son who wants to be a basketball player almost as much as Zach wants him to be one. Zach knows a little bit about growth hormone and asks his son's doctor if she would prescribe some for his son, so that he can grow tall. What do you think the doctor tells Zach?

Prolactin

Prolactin (**PRL;** prō-lak′tin) plays an important role in milk production by the mammary glands of lactating females. It binds to a membrane-bound receptor, which is linked to a kinase that phosphorylates intracellular proteins. The phosphorylated proteins produce the response in the cell. Prolactin also can enhance

Clinical IMPACT 18.1 Growth Hormone and Growth Disorders

Disruptions in GH secretion from the anterior pituitary interfere with normal growth patterns. There are two possible disruptions in GH secretion: (1) hyposecretion of GH leading to reduced growth and (2) hypersecretion of GH leading to excessive growth. Chronic hyposecretion, or insufficient secretion, of GH in infants and children leads to a condition called **pituitary dwarfism** (dwōrf′izm). Insufficient amounts of GH delay bone growth, resulting in short stature. However, the bones usually have a normal shape, and people with this condition exhibit normal intelligence, in contrast to those who have reduced growth caused by hyposecretion of thyroid hormones. Other symptoms resulting from the lack of GH include mild obesity and delayed development of adult reproductive functions.

There are two types of pituitary dwarfism: (1) hyposecretion of GH and other anterior pituitary hormones and (2) hyposecretion of GH alone. In approximately two-thirds of the cases, GH and other anterior pituitary hormones are secreted in reduced amounts. The decrease in other anterior pituitary hormones can result in additional disorders caused by reduced secretion of thyroid hormones, adrenal cortex hormones, and reproductive hormones. In the remaining approximately one-third of cases, GH secretion is reduced, and the secretion of other anterior pituitary hormones is closer to normal. Therefore, these individuals do not experience additional hormone-related disorders, and normal reproduction is possible for them. In adults, no obvious pathology is associated with hyposecretion of GH, although some evidence suggests that lack of GH can lead to reduced bone mineral content in adults.

The gene responsible for determining the structure of GH has been transferred successfully from human cells to bacterial cells, which can produce GH that is identical to human GH. GH produced in this fashion is available to treat patients who suffer from reduced GH secretion, especially children.

Chronic hypersecretion, or excessive secretion, of GH also leads to disorder, depending on whether the hypersecretion occurs before or after complete ossification of the epiphyseal plates in the skeletal system. Chronic hypersecretion of GH before the epiphyseal plates have ossified causes exaggerated and prolonged growth in long bones, a condition called **gigantism** (jī′gan-tizm). Some individuals thus affected have grown to be 8 feet tall or more (see figure 18.8*a*).

In adults, chronically elevated GH levels result in **acromegaly** (ak-rō-meg′ă-lē). No height increase occurs because the epiphyseal plates have ossified. But the condition does result in an increased diameter of the fingers, toes, hands, and feet; the deposition of heavy bony ridges above the eyes; and a prominent jaw (figure 18.8*b*). The influence of GH on soft tissues results in a bulbous or broad nose, an enlarged tongue, thickened skin, and sparse subcutaneous adipose tissue. Nerves are frequently compressed as a result of the proliferation of connective tissue. Because GH spares glucose usage, chronic hyperglycemia results, frequently leading to diabetes mellitus and severe atherosclerosis. Treatment for chronic hypersecretion of GH often involves the surgical removal or irradiation of a GH-producing tumor.

(a) (b)

FIGURE 18.8 (a) Robert Wadlow, standing next to his father, was affected by GH hypersecretion (see chapter 17 introduction). (b) The woman in these photographs was affected by acromegaly. Here you can see the progression of her condition over time from left to right.
(a) ©Toronto Star Archives/Getty Images; (b) Source: U.S. National Library of Medicine/NIH

progesterone secretion by the ovaries after ovulation. No role for this hormone has been clearly established in males. Several hypothalamic neuropeptides can be involved in the complex regulation of prolactin secretion, but the principal control is exerted by prolactin-inhibiting hormone (PIH), which is more commonly called dopamine. Dopamine tonically inhibits PRL secretion. To release PRL, dopamine levels decrease and PRL is secreted. PRL is now thought to be involved in multiple homeostatic roles,

including regulation of the ion composition of blood and immune function. The regulation of gonadotropin and prolactin secretion and their specific reproductive effects are explained more fully in chapter 28.

Thyroid-Stimulating Hormone

Thyroid-stimulating hormone (TSH), also called *thyrotropin* (thī-rot′rō-pin, thī-rō-trō′pin), stimulates the synthesis and secretion of thyroid hormones from the thyroid gland. TSH is a glycoprotein dimer consisting of two subunits, α and β, which bind to membrane-bound receptors of the thyroid gland. The α subunit is common among the glyoprotein hormones, TSH, luteinizing hormone, and follicle-stimulating hormone. It is the β subunit that dictates the specificity of each of the glycoprotein hormones. Thyroid hormone receptors respond through a G protein mechanism that increases intracellular cAMP levels. cAMP then initiates a series of actions in the target tissue (see chapter 17).

TSH secretion is controlled by two mechanisms: (1) TRH from the hypothalamus and (2) negative feedback by thyroid hormones. The hypothalamic-releasing hormone, TRH, stimulates TSH secretion. Thyroid hormones inhibit TSH secretion. Once thyroid hormone levels return to their set point, they inhibit both TRH and TSH levels. Although TSH is secreted in an episodic fashion and its blood levels are highest at night, thyroid hormone levels are maintained within a narrow range of values. This tight regulation of hormone levels is possible because thyroid hormone levels are regulated by negative feedback (see section 18.3).

Adrenocorticotropic Hormone and Related Substances

Adrenocorticotropic (ă-drē′nō-kōr′ti-kō-trō′pik) **hormone (ACTH)** from the anterior pituitary stimulates secretion of the hormone cortisol from the adrenal cortex (see section 18.5). ACTH is one of four smaller molecules derived from a large precursor protein called **proopiomelanocortin** (prō-ō′pē-ō-mel′ă-nō-kōr′tin; **POMC**). POMC is synthesized in the anterior pituitary and is subsequently broken down into multiple, smaller peptides. Many of these peptides are also hormones, including ACTH, lipotropins, β endorphins, and melanocyte-stimulating hormone.

Environmental stress is a key stimulus for ACTH secretion. Once ACTH arrives at its target tissues, it activates a G protein-mediated cAMP mechanism. The primary action of ACTH is release of the principal hormone that regulates chronic stress. This hormone is cortisol from the adrenal cortex. In pathological conditions such as chronic adrenocortical insufficiency (Addison disease), the adrenal cortex degenerates, usually due to an autoimmune condition (see chapter 22). Blood levels of ACTH and related hormones are chronically elevated, and the skin becomes markedly darker. This is because ACTH and melanocyte-stimulating hormone bind to melanocytes in the skin and increase skin pigmentation (see chapter 5). Regulation of ACTH secretion and the effects of the hypersecretion and hyposecretion of ACTH are described in section 18.5.

The **lipotropins** (li-pō-trō′pinz) secreted from the anterior pituitary bind to membrane-bound receptor molecules on adipocytes. They cause lipid breakdown and the release of fatty acids into the blood.

The **β endorphins** (en′dōr-finz) have the same effects as opiate drugs, such as morphine, and they can play a role in analgesia (pain relief) in response to stress and exercise. Other functions have been proposed for the β endorphins, including the regulation of body temperature, food intake, and water balance. Both ACTH and β endorphin secretions increase in response to stress and exercise.

Melanocyte-stimulating hormone (MSH) binds to membrane-bound receptors on skin melanocytes and stimulates increased melanin deposition in the skin. The regulation of MSH secretion and its function in humans are not well understood, although studies have shown that MSH is also important in regulating appetite and sexual behavior.

Luteinizing Hormone and Follicle-Stimulating Hormone

Gonadotropins (gō′nad-ō-trō′pinz) are glycoprotein hormones capable of promoting the growth and function of the **gonads,** the ovaries and testes. The two major gonadotropins secreted from the anterior pituitary are (1) **luteinizing** (loo′tē-i-nīz-ing) **hormone (LH)** and (2) **follicle-stimulating hormone (FSH).** LH and FSH play important roles in regulating reproduction.

LH and FSH secreted into the blood bind to membrane-bound receptors, increase the intracellular synthesis of cAMP through G protein mechanisms, and stimulate the production of **gametes** (gam′ēts)—sperm cells in the testes and oocytes in the ovaries. LH and FSH also control the production of reproductive hormones—estrogens and progesterone in the ovaries and testosterone in the testes.

LH and FSH are released from anterior pituitary cells under the influence of the hypothalamic-releasing hormone gonadotropin-releasing hormone (GnRH). Gonadal steroid hormones are also critical regulators of the gonadotropins and exhibit a complex cycle of hormone interactions, which are further described in chapter 28.

ASSESS YOUR PROGRESS

13. *Structurally, what kinds of hormones are released from the anterior pituitary gland? Do these hormones bind to plasma proteins? How long is their half-life, and how do they activate their target tissues?*
14. *What effects do stress, blood amino acid levels, and blood glucose levels have on GH secretion?*
15. *Describe the effects of GH on its target tissues.*
16. *What stimulates the release of somatomedins? Where are they produced, and what are their effects?*
17. *What pathological conditions are the result of hypersecretion of GH? Describe their symptoms.*
18. *What pathological conditions are the result of hyposecretion of GH? Describe their symptoms.*
19. *For each of the following hormones secreted by the anterior pituitary gland, name the target tissue and the hormone's effect on its target tissue: GH, prolactin, ACTH, LH, and FSH.*
20. *How are ACTH, lipotropins, β endorphins, and MSH related? What are the functions of these hormones?*
21. *What is a gonadotropin? Name two gonadotropins produced by the anterior pituitary gland, and explain their functions.*

18.3 Thyroid Gland

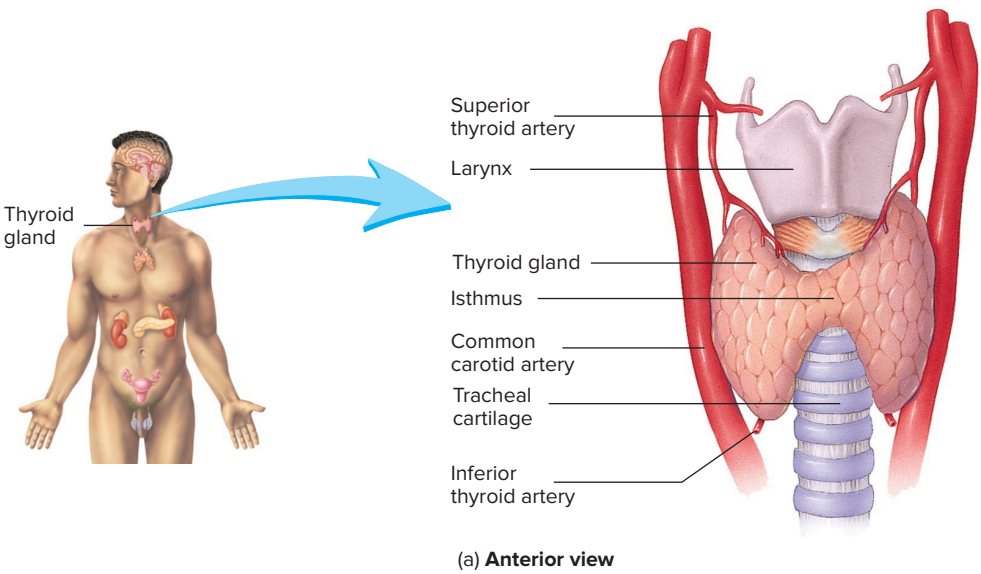
LEARNING OUTCOMES

After reading this section, you should be able to

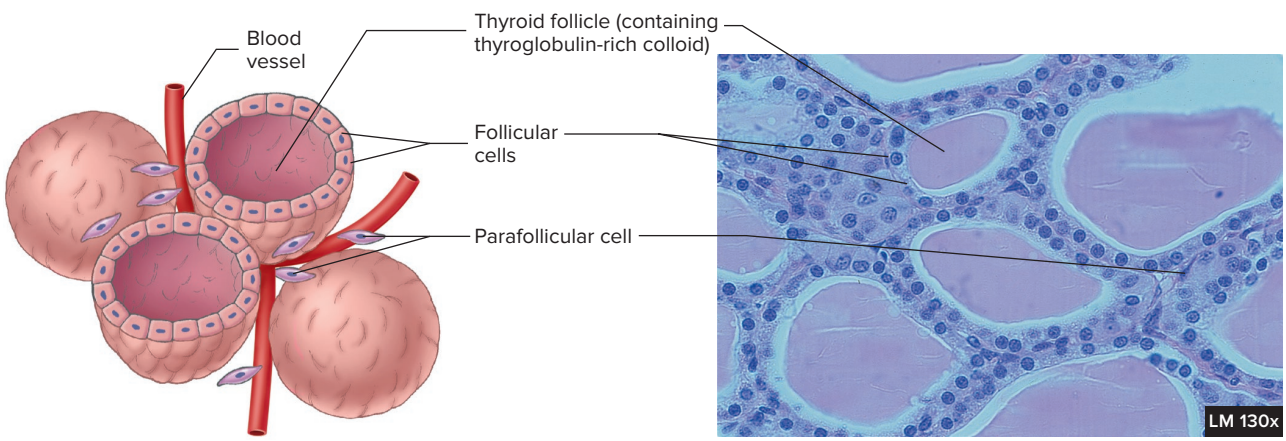
A. **Describe the structure of the thyroid gland.**
B. **Explain the processes for the synthesis, secretion, and blood transport of T_3 and T_4.**
C. **Describe the mechanism of action and the effects of T_3 and T_4 in the body.**
D. **Relate how thyroid hormone secretion is regulated.**
E. **Describe the effects of hyposecretion and hypersecretion of thyroid hormones and the pathological conditions that cause the abnormalities.**
F. **Describe the role of calcitonin in the maintenance of blood calcium levels and in bone health.**

The **thyroid gland** synthesizes and secretes three hormones: (1) triiodothyronine, (2) tetraiodothyronine, and (3) calcitonin. It is composed of two lobes connected by a narrow band of thyroid tissue called the **isthmus.** The lobes are lateral to the upper portion of the trachea just inferior to the larynx, and the isthmus extends across the anterior aspect of the trachea (figure 18.9*a*). The thyroid gland is one of the largest endocrine glands, with a weight of approximately 20 g. Because it is highly vascular, it is a darker red than surrounding tissues.

The thyroid gland contains numerous **follicles,** which are small spheres whose walls are composed of a single layer of cuboidal epithelial cells (figure 18.9*b,c*). The center of each thyroid follicle is filled with a gelatinous material called colloid. Colloid is composed of a high concentration of a protein called **thyroglobulin** (thī-rō-glob′ū-lin). Thyroglobulin is synthesized and secreted by cells of the thyroid follicle. Thyroglobulin is the precursor to thyroid hormones. It is a large collection of individual



(a) **Anterior view**



(b) (c)

FIGURE 18.9 Anatomy and Histology of the Thyroid Gland

(*a*) Anterior view of the thyroid gland. (*b*) Histology of the thyroid gland. The gland is made up of many spheric thyroid follicles containing thyroglobulin-rich colloid. Parafollicular cells are in the tissue between the thyroid follicles. (*c*) Low-power photomicrograph of thyroid follicles. (c) ©Victor P. Eroschenko AP|R

thyroid hormone molecules. Thus, thyroglobulin stores a huge amount of thyroid hormones. Storage of such a large amount of hormone is unique to the thyroid gland.

Between the follicles, a delicate network of loose connective tissue contains numerous capillaries. Scattered between the follicles and the cells that make up the walls of the follicle are **parafollicular** (par-ă-fo-lik′ū-lăr) **cells**. The parafollicular cells secrete **calcitonin** (kal-si-tō′nin), which plays a role in reducing the concentration of calcium in the body fluids when calcium levels become elevated.

Thyroid Hormones

The thyroid gland secretes a total of three hormones, including calcitonin. Although calcitonin is secreted by the parafollicular cells of the thyroid gland, it constitutes only about 10% of the secretions from the thyroid gland. Because the remaining two hormones are secreted from the thyroid follicles, they are considered to be the thyroid hormones. The thyroid hormones include **triiodothyronine** (trī-ī′ō-dō-thī′rō-nēn), commonly called **T_3,** and **tetraiodothyronine** (tet′ră-ī′ō-dō-thī′rō-nēn). A more common name for tetraiodothyronine is **thyroxine** (thī-rok′sēn; thī-rok′sin), or even more commonly **T_4.** T_4 is the precursor for T_3, and accounts for 80% of the secretions from the thyroid gland. T_3 accounts for the remaining 10% of thyroid gland secretions (table 18.3).

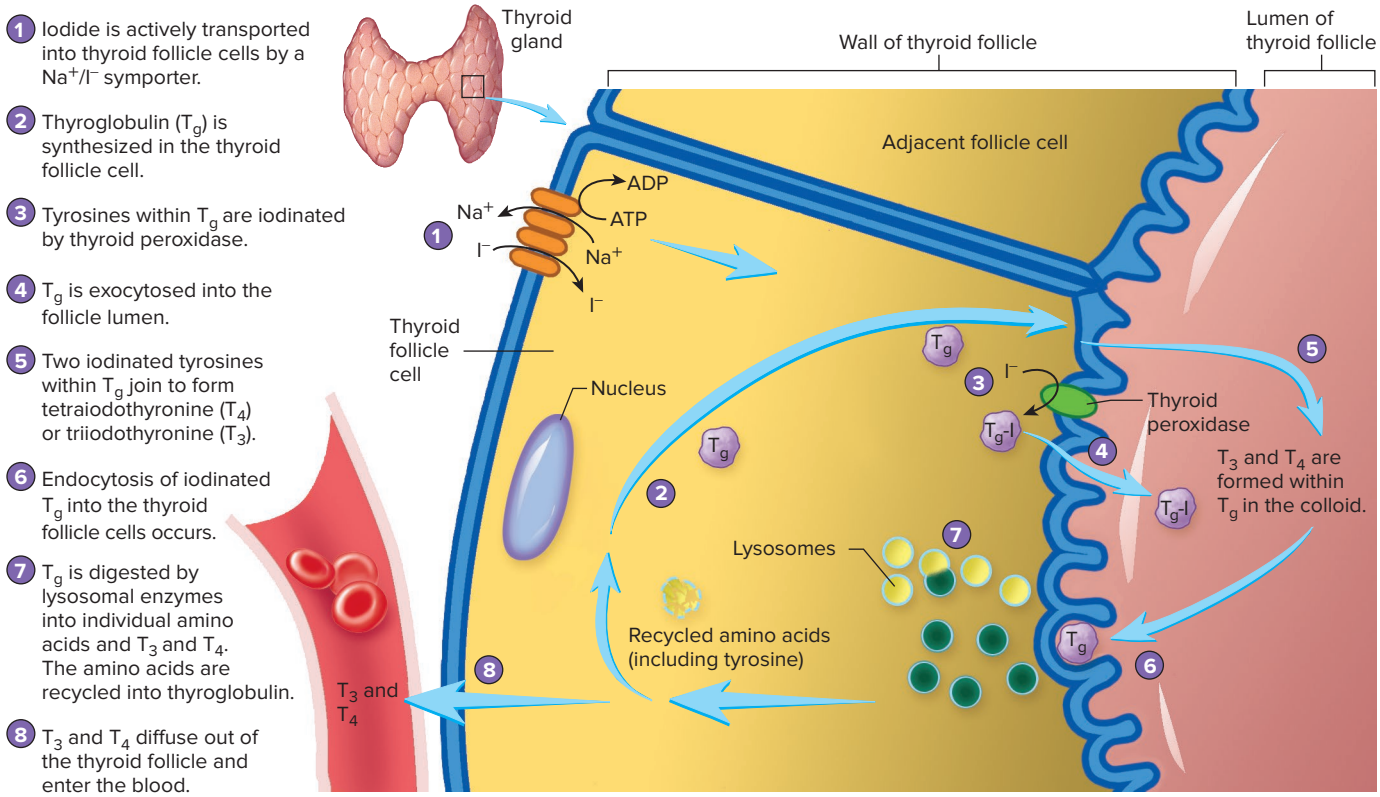
T_3 and T_4 Synthesis

Thyroid-stimulating hormone (TSH) from the anterior pituitary stimulates thyroid hormone synthesis and secretion. TSH causes an increase in the synthesis of T_3 and T_4, which are then stored inside the thyroid follicles as part of a large protein called thyroglobulin. TSH also causes T_3 and T_4 to be released from thyroglobulin and enter the plasma of the blood. Because iodine is an integral component of the T_3 and T_4 molecules, humans must consume an adequate amount of iodine in the diet to support thyroid hormone synthesis. In the United States, most of this dietary iodine is derived from iodized salt. The following events in the thyroid follicles result in T_3 and T_4 synthesis and secretion (figure 18.10):

1. Iodide ions (I^-) are taken up by thyroid follicle cells via secondary active transport by a sodium-iodide symporter. The active transport of the I^- is against a concentration gradient of approximately 30-fold in healthy individuals.
2. Thyroglobulins, which contain numerous tyrosine molecules, are synthesized within the cells of the follicles.
3. Nearly simultaneously, the I^- are oxidized to form iodine (I), and either one or two iodine atoms are bound to some of the tyrosine molecules of thyroglobulin by the enzyme thyroid peroxidase.
4. This occurs close to the time the thyroglobulin molecules are secreted by exocytosis into the lumen of the follicle. As a result, the secreted thyroglobulin contains iodinated tyrosine amino acids. If there is one iodine atom attached to the tyrosine amino acid, it is called a monoiodotyrosine. If there are two iodine atoms attached to the tyrosine, it is called a diiodotyrosine.
5. Thyroid hormones are synthesized within the colloid in the lumen of the follicle. If two diiodotyrosine molecules of thyroglobulin combine, tetraiodothyronine (T_4) is formed. If one monoiodotyrosine and one diiodotyrosine molecule combine, triiodothyronine (T_3) is formed. Large amounts of T_3 and T_4 are stored within the thyroid follicles as part of thyroglobulin. A reserve sufficient to supply thyroid hormones for approximately 2–4 months is stored in this form.
6. Thyroglobulin is taken into the thyroid follicle cells by endocytosis.
7. Lysosomes fuse with the endocytotic vesicles. Proteolytic enzymes break down thyroglobulin to release T_3 and T_4. The remaining amino acids of thyroglobulin are recycled to synthesize more thyroglobulin.
8. T_3 and T_4 either diffuse through the plasma membranes or are carried by specific transporters of the follicular cells into the interstitial spaces and finally into the capillaries of the thyroid gland.

TABLE 18.3 Hormones of the Thyroid and Parathyroid Glands

Hormones	Structure	Target Tissue	Response
Thyroid Gland			
Thyroid hormones (T_3 and T_4) Secreted by thyroid follicles	Amino acid derivative	Most cells of the body	Increased metabolic rate; increased protein synthesis; essential for normal growth and maturation
Calcitonin Secreted by parafollicular cells	Peptide	Bone	Decreased rate of breakdown of bone by osteoclasts; prevention of a large increase in blood Ca^{2+} levels
Parathyroid Gland			
Parathyroid hormone (PTH)	Peptide	Bone, kidneys, small intestine	Increased rate of breakdown of bone by osteoclasts; increased reabsorption of Ca^{2+} in kidneys; increased absorption of Ca^{2+} from the small intestine; increased vitamin D synthesis; increased blood Ca^{2+} levels



PROCESS FIGURE 18.10 Biosynthesis of Thyroid Hormones

Thyroid hormones are synthesized in follicle cells of the thyroid gland. The hormones are stored as a component of a larger protein within a material called colloid, located in the center of each follicle.

? *If a person were injected with radioactive iodine, where would the highest concentration of radioactivity be located within the thyroid gland?*

Transport in the Blood

T_3 and T_4 are transported in combination with plasma proteins in the blood. Approximately 75% of the circulating T_3 and T_4 are bound to **thyroxine-binding globulin (TBG),** which is synthesized by the liver, and 20–30% are bound to other plasma proteins, including albumin. T_3 and T_4, bound to these plasma proteins, form a large reservoir of circulating thyroid hormones, and the half-life of these hormones is greatly increased because of this binding. After thyroid gland removal in experimental animals, it takes approximately 1 week for T_3 and T_4 levels in the blood to decrease by 50%. As free T_3 and T_4 levels decrease in the interstitial spaces, additional T_3 and T_4 dissociate from the plasma proteins to maintain the levels in the tissue spaces. When sudden secretion of T_3 and T_4 occurs, the excess binds to the plasma proteins. As a consequence, the concentration of thyroid hormones in the tissue spaces fluctuates very little.

Approximately 40% of the T_4 is converted to T_3 in the body tissues. This conversion is important for the action of thyroid hormones on their target tissues. T_3 is the major hormone that interacts with thyroid hormone target cells. T_3 is several times more potent than T_4 due to its higher affinity for the thyroid hormone receptor.

Much of the circulating T_4 is eliminated from the body by being converted to tetraiodothyroacetic acid, or by being modified, and then excreted in the urine or bile. In addition, a large amount is converted to an inactive form of T_3, rapidly metabolized, and excreted.

Mechanism of Action of T_3 and T_4

Because T_3 and T_4 are lipid-soluble hormones, they can bind to nuclear receptors in their target tissues (see section 17.4). Thyroid hormones diffuse through the plasma membrane into the cytoplasm of target cells, migrate to the nucleus, and bind to their receptors. When thyroid hormones are bound to their receptors, they interact with DNA in the nucleus to influence genes and generally stimulate protein synthesis. The newly synthesized proteins within the target cells mediate the cells' response to thyroid hormones.

Effects of T_3 and T_4

T_3 and T_4 affect nearly every tissue in the body, but not all tissues respond identically. Metabolism is primarily affected in some tissues, and growth and maturation are influenced in others.

The normal rate of metabolism for an individual depends on an adequate supply of thyroid hormone, which increases the rate at which glucose, lipids, and protein are metabolized. The metabolic rate can increase 60–100% when blood T_3 and T_4 are elevated, whereas low levels of T_3 and T_4 lead to the opposite effect. Because the increased rate of metabolism produces heat, normal body temperature is partly due to adequate thyroid hormones. Thyroid hormones increase the activity of Na^+–K^+ pumps, which give off heat as a "by-product." T_3 and T_4 also alter the number and activity of mitochondria, resulting in greater ATP synthesis and thus heat production.

In addition to metabolism, T_3 and T_4 regulate the normal growth and maturation of organs. For example, the growth of bone, hair, teeth, connective tissue, and nervous tissue requires thyroid hormone. One reason tissues require thyroid hormones for normal growth is that T_3 and T_4 play a permissive role for GH, which means that GH does not have its normal effect on target tissues if T_3 and T_4 are not present.

Failure to maintain homeostatic amounts of thyroid hormone dramatically affects the body's functions. Hypersecretion of T_3 and T_4 increases the rate of metabolism. High body temperature, weight loss, increased appetite, rapid heart rate, and an enlarged thyroid gland are major symptoms.

Hyposecretion of T_3 and T_4 decreases the rate of metabolism. Low body temperature, weight gain, reduced appetite, reduced heart rate, reduced blood pressure, weak skeletal muscles, and apathy are major symptoms. Hyposecretion of T_3 and T_4 that occurs during development causes a decreased metabolic rate, abnormal nervous system development, abnormal growth, and abnormal maturation of tissues. The consequence is neonatal hypothyroidism characterized by developmental delay, short stature, and specific physical deformities.

The specific effects of the hyposecretion and hypersecretion of thyroid hormones are outlined in table 18.4.

Regulation of Thyroid Hormone Secretion

Thyrotropin-releasing hormone (TRH) from the hypothalamus and TSH from the anterior pituitary function together to increase T_3 and T_4 secretion from the thyroid gland (figure 18.11). Stress and exposure to cold cause increased TRH secretion, and prolonged fasting decreases TRH secretion. TRH stimulates the secretion of TSH from the anterior pituitary. TSH travels to the thyroid gland, where it stimulates the synthesis and secretion of T_3 and T_4. TSH also causes hypertrophy (increased cell size) and hyperplasia (increased cell number) of the thyroid gland. Decreased blood levels of TSH lead to decreased T_3 and T_4 secretion and to thyroid gland atrophy. T_3 and T_4 have a negative-feedback effect on the hypothalamus and anterior pituitary gland. As T_3 and T_4 levels increase in the blood, they inhibit TRH and TSH secretion. If the thyroid gland is removed or if T_3 and T_4 secretion declines, TSH levels in the blood increase dramatically. Conditions in which TSH is elevated can often be charaterized by the abnormal thyroid gland overgrowth called goiter (table 18.5).

Hypothyroidism, or reduced secretion of thyroid hormones, can result from having an iodine deficiency, taking certain drugs, or being exposed to chemicals that inhibit T_3 and T_4 synthesis. It can also be caused by inadequate secretion of TSH, by an autoimmune disease that depresses thyroid hormone function, or by surgical removal of the thyroid gland. Hypersecretion of T_3 and T_4 can result from the synthesis of an immunoglobulin that stimulates TSH receptors and acts like TSH, from TSH-secreting tumors of the pituitary gland, and from thyroid tumors (see Systems Pathology 18.1).

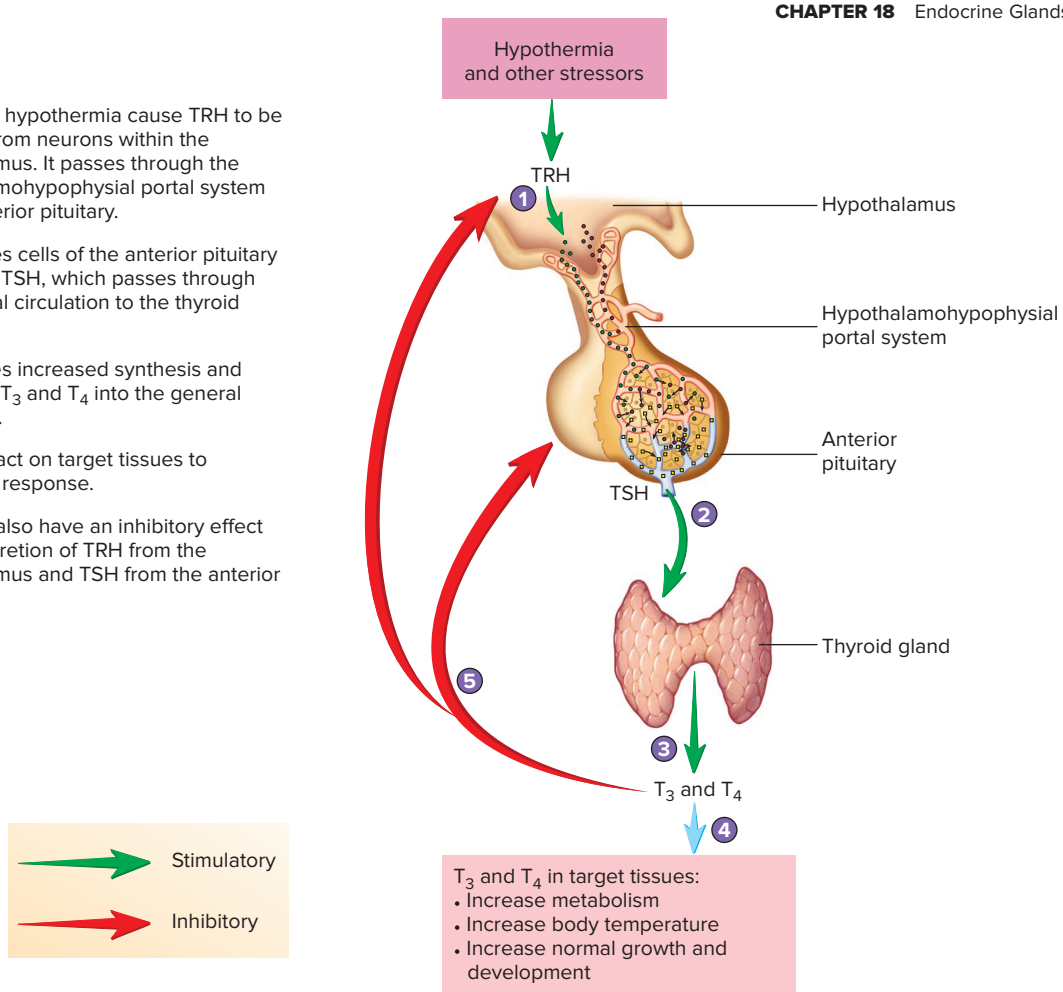
Predict 4

Becky has lost 30 pounds over the past several months, even though her appetite has been good and she has been eating more than usual. She complains to her physician that she is nervous and restless, has a short attention span, becomes fatigued easily but cannot sleep well, moves compulsively, and sweats excessively. Her physician notes that she also exhibits tachycardia. Suspecting hyperthyroidism, he orders a blood test, which indicates elevated levels of T_3 and T_4 and low levels of TSH. Becky also has a TSH-like immunoglobulin in her plasma. Explain these results.

TABLE 18.4 Effects of Hyposecretion and Hypersecretion of Thyroid Hormones

Hypothyroidism	Hyperthyroidism
Decreased metabolic rate, low body temperature, cold intolerance	Increased metabolic rate, high body temperature, heat intolerance
Weight gain, reduced appetite	Weight loss, increased appetite
Reduced activity of sweat and sebaceous glands; dry, cold skin	Copious sweating; warm, flushed skin
Reduced heart rate, reduced blood pressure, dilated and enlarged heart	Rapid heart rate, elevated blood pressure, abnormal electrocardiogram
Weak, untoned skeletal muscles; sluggish movements	Weak skeletal muscles that exhibit tremors, quick movements with exaggerated reflexes
Constipation	Bouts of diarrhea
Myxedema (swelling of the face and body) as a result of subcutaneous mucoprotein deposits	Exophthalmos (protruding eyes) as a result of connective tissue proliferation and other deposits behind the eye
Apathy, somnolence	Hyperactivity, insomnia, restlessness, irritability, short attention span
Coarse hair; rough, dry skin	Soft, smooth hair and skin
Decreased iodide uptake	Increased iodide uptake
Possible goiter (enlargement of the thyroid gland) due to loss of negative feedback	Almost always a goiter

1. Stress and hypothermia cause TRH to be released from neurons within the hypothalamus. It passes through the hypothalamohypophysial portal system to the anterior pituitary.
2. TRH causes cells of the anterior pituitary to secrete TSH, which passes through the general circulation to the thyroid gland.
3. TSH causes increased synthesis and release of T_3 and T_4 into the general circulation.
4. T_3 and T_4 act on target tissues to produce a response.
5. T_3 and T_4 also have an inhibitory effect on the secretion of TRH from the hypothalamus and TSH from the anterior pituitary.



PROCESS FIGURE 18.11 Regulation of Thyroid Hormone (T_3 and T_4) Secretion

Thyroid hormones are regulated by the hypothalamus and pituitary.

? *What is the general description for the role of TSH in stimulating T_3 and T_4 secretion?*

TABLE 18.5 Abnormal Thyroid Conditions

Cause	Description
Hypothyroidism	
Iodine deficiency	Causes inadequate T_3 and T_4 synthesis, which results in elevated thyroid-stimulating hormone (TSH) secretion; thyroid gland enlarges (goiter) as a result of TSH stimulation; T_3 and T_4 frequently remain in the low to normal range
Goitrogenic (goiter-causing) substances	Inhibit T_3 and T_4 synthesis; found in certain drugs and in small amounts in certain plants, such as cabbage
Neonatal hypothyroidism	Caused by maternal iodine deficiency or congenital errors in thyroid hormone synthesis; results in developmental delay and a short, malformed appearance
Pituitary insufficiency	Results from lack of TSH secretion; often associated with inadequate secretion of other anterior pituitary hormones
Hashimoto disease	Autoimmune disease in which thyroid hormone secretion can be normal or depressed
Lack of thyroid gland	Partial or complete surgical removal or drug-induced destruction of the thyroid gland as a treatment for Graves disease (hyperthyroidism)
Hyperthyroidism	
Graves disease	Characterized by goiter and exophthalmos; apparently an autoimmune disease; most patients have a TSH-like immunoglobulin, called thyroid-stimulating immunoglobulin (TSI), in their plasma
Tumors—benign adenoma or cancer	Result in either normal secretion or hypersecretion of thyroid hormones (rarely hyposecretion)
Thyroiditis—a viral infection	Produces painful swelling of the thyroid gland with normal or slightly increased T_3 and T_4 production
Elevated TSH levels	Result from a pituitary tumor
Thyroid storm	Sudden release of large amounts of T_3 and T_4; caused by surgery, stress, infections, or other, unknown factors

Calcitonin

Parafollicular cells, or C cells, secrete the hormone calcitonin in response to increased calcium levels in the blood. These cells are dispersed between the thyroid follicles throughout the thyroid gland.

The primary target tissue for calcitonin is bone (see chapter 6). Calcitonin binds to membrane-bound receptors, decreases osteoclast activity, and lengthens the life span of osteoblasts. The resulting bone deposition leads to decreases in blood calcium and phosphate levels.

Calcitonin's importance in regulating blood Ca^{2+} levels is unclear; it may be most important in juveniles in promoting bone growth. The rate of calcitonin secretion increases in response to elevated blood Ca^{2+} levels, and calcitonin may prevent large increases in blood Ca^{2+} levels following a meal. Blood levels of calcitonin decrease with age to a greater extent in females than in males.

Interestingly, complete thyroidectomy does not result in high blood Ca^{2+} levels, possibly because the regulation of blood Ca^{2+} levels by vitamin D and other hormones, such as parathyroid hormone (if the parathyroid glands are retained in the body), compensates for the loss of calcitonin in individuals who have undergone a thyroidectomy. No pathological condition is directly associated with a lack of calcitonin secretion. Some evidence suggests that calcitonin may play a role in regulating food intake by decreasing appetite. Clinically, calcitonin nasal sprays have been effective in the management of postmenopausal osteoporosis.

ASSESS YOUR PROGRESS

22. *Where is the thyroid gland located? Describe the follicles and the parafollicular cells within the thyroid. What hormones do they produce?*
23. *Starting with the uptake of iodide by the follicles, describe the production and secretion of thyroid hormones (T_3 and T_4).*
24. *How are the thyroid hormones transported in the blood? What effect does this transport have on their half-life?*
25. *What are the target tissues of thyroid hormones? By what mechanism do thyroid hormones alter the activities of their target tissues? What effects are produced?*
26. *Starting in the hypothalamus, explain how chronic exposure to cold, food deprivation, or stress can affect thyroid hormone production.*
27. *Diagram two negative-feedback mechanisms involving hormones that regulate the production of thyroid hormones.*
28. *What is a goiter? What can cause one to develop?*
29. *What conditions cause hypothyroidism? Describe the effects of hyposecretion of thyroid hormones.*
30. *What conditions cause hyperthyroidism? Describe the effects of hypersecretion of thyroid hormones.*
31. *What effect does calcitonin have on osteoclasts, osteoblasts, and blood calcium levels? What stimulus can cause an increase in calcitonin secretion?*

Case STUDY 18.1 Hypothyroidism

Josie owns a business and works hard to manage her employees and make time for her family. Over several months, she frequently felt weak, was often unable to concentrate, and felt cold when others did not. In addition, she began to gain weight, even though she had a small appetite. Finally, after noticing a large lump in her neck inferior and lateral to her larynx, Josie decided to see her physician. A blood sample was taken, and the results indicated low levels of thyroid hormones (hypothyroidism), high levels of TSH, and low levels of iodine.

The doctor concluded that Josie had developed a goiter, or an enlarged thyroid gland. Historically, iodine-deficiency goiters were common in people inhabiting areas where the soil was depleted of iodine, called "goiter belts." Consequently, plants grown in these areas had little iodine in them and caused iodine-deficient diets. In the United States, iodized salt has nearly eliminated iodine-deficiency goiters. However, iodine-deficiency diseases are still common throughout the world. The World Health Organization has called them the most common preventable cause of mental defects, and hypothyroidism may be the most common endemic disease on the planet.

Josie's doctor explained that her goiter had probably formed because her dietary intake of iodine was too low over a prolonged time. Without iodine, Josie's thyroid gland was unable to synthesize thyroid hormones. Thus, in response to low thyroid hormone levels, the anterior pituitary gland continued to secrete the tropic hormone TSH, which caused the thyroid gland to keep getting bigger and bigger. In addition, the hypothalamus continued to stimulate the anterior pituitary in the absence of thyroid hormones.

Josie was treated with radioactive iodine (^{131}I) atoms, which were actively transported into her thyroid cells, where the radiation helped shrink her thyroid gland back to normal size. Subsequently, Josie had to take dietary iodine supplements and thyroid hormone supplements until her thyroid gland was able to produce thyroid hormones on its own again.

Predict 5

a. Name and explain the mechanism controlling TSH in Josie's blood. Why were TSH levels high and the levels of thyroid hormones low prior to treatment?

b. Explain why the doctor could tell that Josie's condition was not the result of a tumor in the thyroid gland.

c. What role did a lack of iodine play in Josie's condition?

d. After treatment with iodine, predict how Josie's blood levels of thyroid hormones, as well as TSH, changed.

e. Explain why Josie had to take thyroid hormone supplements. Will Josie have to do this for the rest of her life?

18.4 Parathyroid Glands

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe the location and structure of the parathyroid glands.**

B. **Explain the mechanism of parathyroid hormone action and its effects.**

C. **Describe the causes and symptoms of hypoparathyroidism and hyperparathyroidism.**

The **parathyroid** (par-ă-thīʹroyd) **glands** are usually embedded in the posterior part of each lobe of the thyroid gland and are made up of two cell types: chief cells and oxyphils. The chief cells secrete parathyroid hormone, but, despite their relative abundance, the function of the oxyphils is unknown. Usually, four parathyroid glands are present, with their cells organized in densely packed masses, or cords, rather than in follicles (figure 18.12). In some cases, one or more of the parathyroid glands do not become embedded in the thyroid gland and remain in the nearby connective tissue.

Parathyroid hormone (PTH) is important in regulating calcium levels in body fluids (see table 18.3 and section 6.9). The major target tissues for PTH are (1) bone, (2) the kidneys, and (3) the small intestine. However, PTH targets the small intestine indirectly by stimulating vitamin D activation. Vitamin D acts directly on cells of the small intestine. PTH binds to membrane-bound receptors and activates a G protein mechanism that increases intracellular cAMP levels in target tissues. Without functional parathyroid glands, the ability to adequately regulate blood calcium levels is lost.

PTH stimulates osteoclast activity in bone and can cause the number of osteoclasts to increase. The increased osteoclast activity results in bone reabsorption and the release of calcium and phosphate, causing an increase in blood calcium levels. Osteoclasts have no PTH receptors, but osteoblasts and red bone marrow stem cells do. PTH binds to receptors on osteoblasts, which then promote an increase in osteoclast activity (see chapter 6).

PTH causes calcium reabsorption within the kidneys, so that less calcium leaves the body in urine. It also increases the enzymatic formation of active vitamin D in the kidneys. Calcium is actively absorbed by the epithelial cells of the small intestine, and the synthesis of transport proteins in the intestinal cells requires active vitamin D. PTH increases the rate of active vitamin D synthesis, which in turn increases the rate of calcium and phosphate absorption in the intestine, thereby elevating blood levels of calcium.

Although PTH increases the release of phosphate ions (PO_4^{3-}) from bone and indirectly stimulates PO_4^{3-} absorption in the small intestine, it increases PO_4^{3-} excretion in the kidney. The overall effect of PTH is to decrease blood phosphate levels. A simultaneous increase in both Ca^{2+} and PO_4^{3-} is undesirable because it allows calcium phosphate to precipitate in the body's soft tissues, where they cause irritation and inflammation.

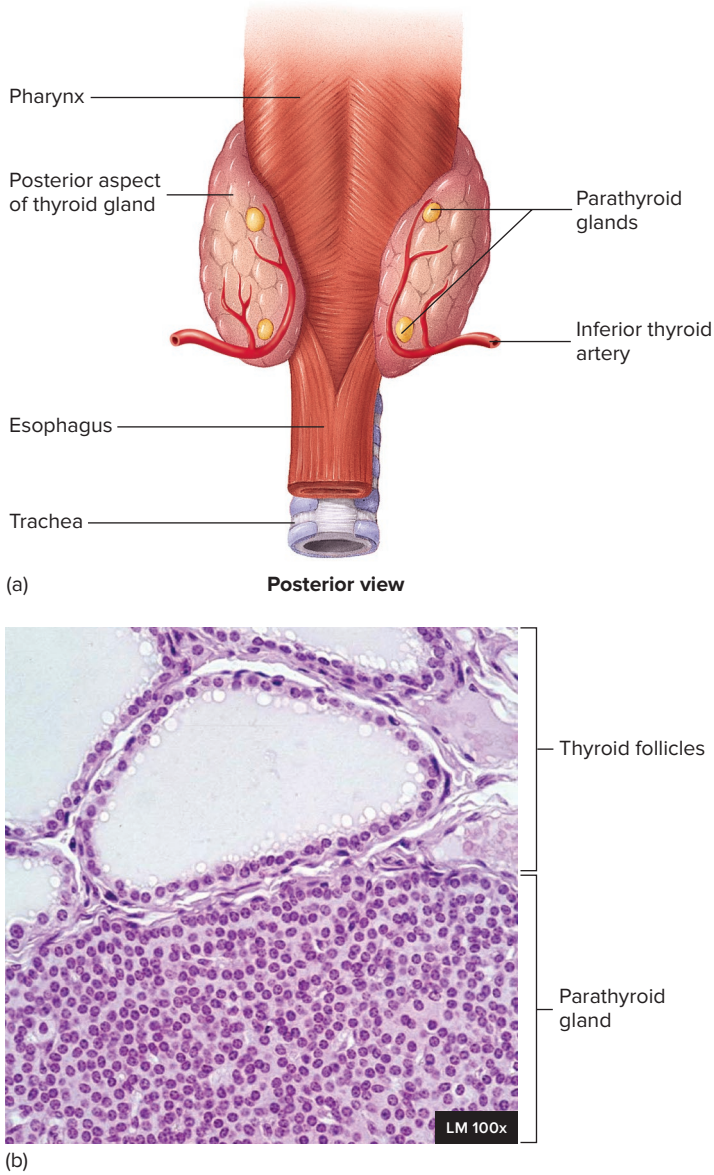
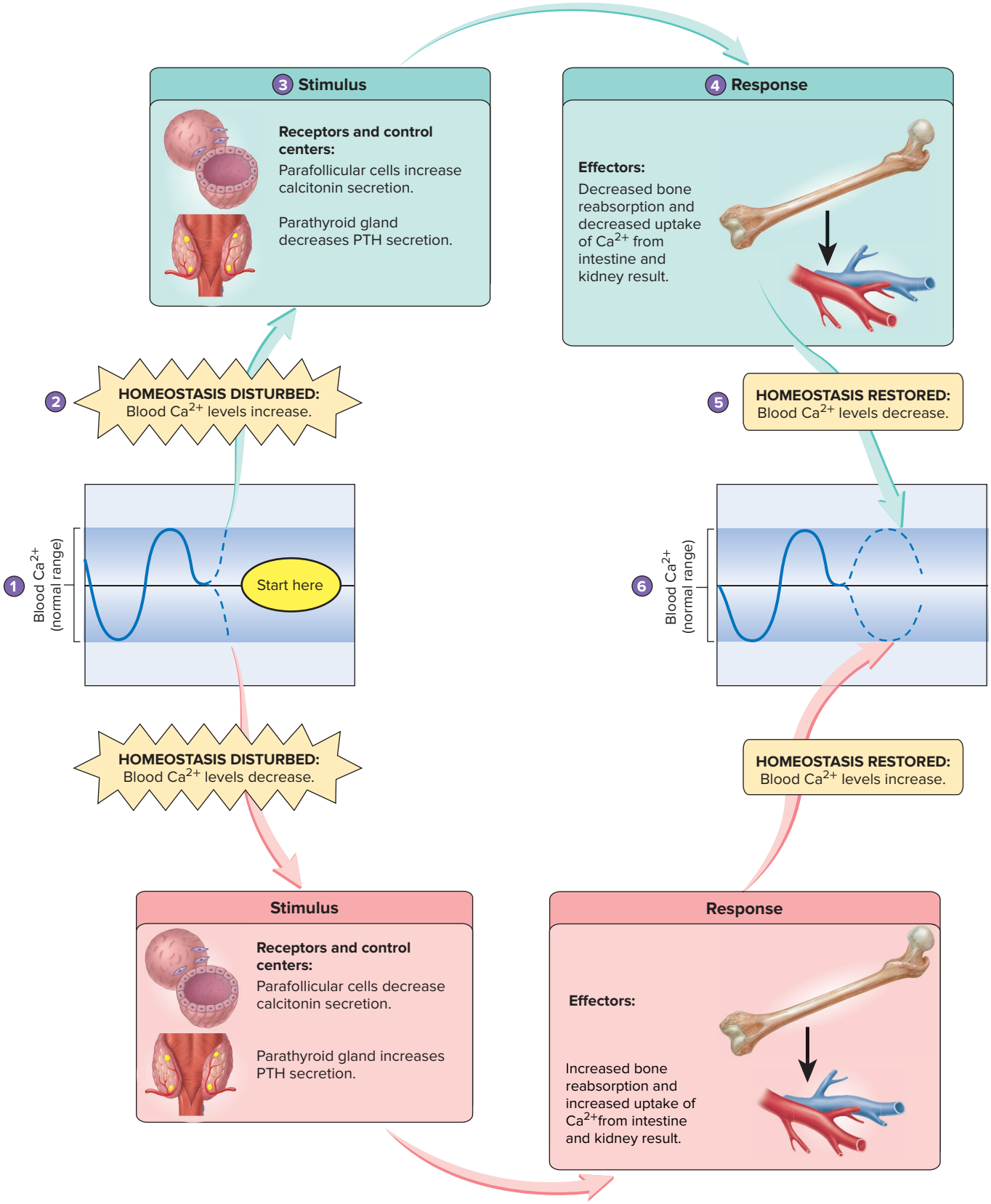


FIGURE 18.12 Anatomy and Histology of the Parathyroid Glands

(*a*) The parathyroid glands are embedded in the posterior part of the thyroid gland. (*b*) The parathyroid glands are composed of densely packed cords of cells. (b) ©Victor P. Eroschenko AP|R

The regulation of PTH secretion and the role of PTH and calcitonin in regulating blood Ca^{2+} levels are outlined in figure 18.13. The primary stimulus for the secretion of PTH is a decrease in blood Ca^{2+} levels, whereas elevated blood Ca^{2+} levels inhibit PTH secretion. This regulation keeps blood Ca^{2+} levels fluctuating within a normal range of values. Both hypersecretion and hyposecretion of PTH cause serious symptoms (table 18.6). The regulation of blood Ca^{2+} levels is discussed more thoroughly in chapter 27.

Inactive parathyroid glands result in **hypocalcemia,** abnormally low levels of calcium in the blood. Reduced extracellular calcium levels cause voltage-gated Na^+ channels in plasma membranes to



HOMEOSTASIS FIGURE 18.13 Regulation of Blood Levels of Calcium Ions

(1) Blood Ca^{2+} is within its normal range. (2) Blood Ca^{2+} level increases outside the normal range. (3) The parafollicular cells and the parathyroid gland cells detect elevated blood Ca^{2+}. The parafollicular cells secrete calcitonin; the parathyroid gland cells decrease PTH secretion. (4) There is less bone reabsorption and less uptake of Ca^{2+} from both the kidney and the intestine. (5) Blood Ca^{2+} level drops back to its normal range. (6) Homeostasis is restored. Observe the response to a drop in blood Ca^{2+} by following the *red arrows*.

TABLE 18.6 Causes and Symptoms of Hyposecretion and Hypersecretion of Parathyroid Hormone

	Cause	Symptoms
Hypoparathyroidism	Accidental removal during thyroidectomy	Hypocalcemia Increased neuromuscular excitability; possible tetany, laryngospasm, and death from asphyxiation Flaccid heart muscle; possible cardiac arrhythmia Diarrhea
Hyperparathyroidism	Primary hyperparathyroidism: a result of abnormal parathyroid function—adenomas of the parathyroid gland (90%), idiopathic (unknown cause) hyperplasia of parathyroid cells (9%), or carcinomas (1%) Secondary hyperparathyroidism: caused by conditions that reduce blood Ca^{2+} levels, such as inadequate Ca^{2+} in the diet, inadequate levels of vitamin D, pregnancy, or lactation	Hypercalcemia or normal blood Ca^{2+} levels; calcium carbonate salts may be deposited throughout the body, especially in the renal tubules (kidney stones), lungs, blood vessels, and gastric mucosa Bones weakened as a result of reabsorption; some cases are first diagnosed when a radiograph is taken of a broken bone Neuromuscular system less excitable; possible muscular weakness Increased force of contraction of cardiac muscle; at very high blood Ca^{2+} levels, possible cardiac arrest during contraction, constipation

open, which increases the permeability of plasma membranes to Na^+. As a consequence, Na^+ diffuses into cells and causes depolarization (see chapter 11). Symptoms of hypocalcemia are nervousness, muscle spasms, cardiac arrhythmia, and convulsions. Extreme cases may lead to tetany of skeletal muscles, including the respiratory muscles, which can cause death.

Predict 6

A patient with a malignant tumor had his thyroid gland removed. What effect does this removal have on blood levels of Ca^{2+}? If the parathyroid glands are inadvertently removed along with the thyroid gland, death can result because the muscles of respiration undergo sustained contractions. Explain.

ASSESS YOUR PROGRESS

32. *Where are the parathyroid glands located, and what hormone do they produce?*

33. *What are the major target tissues for parathyroid hormone?*

34. *What effect does PTH have on osteoclasts, osteoblasts, the kidneys, the small intestine, and bone?*

35. *How are blood calcium and phosphate levels regulated by PTH?*

36. *What can cause hypoparathyroidism? Describe the symptoms.*

37. *What can cause hyperparathyroidism? Describe the symptoms.*

18.5 Adrenal Glands

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Relate the location of the adrenal glands and explain the embryological origins of the two parts of the glands.**

B. **Describe the mechanisms and actions of the hormones secreted by the adrenal medulla.**

C. **Name the layers of the adrenal cortex, the type of product secreted by each layer, and the predominant hormone of each layer.**

D. **Describe the individual target tissues and their responses to the hormones of the adrenal cortex.**

E. **Explain the role of ACTH in the regulation of the adrenal cortex hormones.**

F. **Discuss the causes and symptoms of hyposecretion and hypersecretion of adrenal cortex hormones.**

The **adrenal** (ă-drē′năl) **glands** produce a diverse set of hormones. The adrenal glands, also called the *suprarenal* (soo′pră-rē′năl) *glands,* are near the superior poles of the kidneys. Like the kidneys, the adrenal glands lie behind the peritoneum, and they are surrounded by abundant adipose tissue. The adrenal glands are enclosed by a connective tissue capsule and have a well-developed blood supply (figure 18.14*a*).

The adrenal glands are composed of an inner **medulla** and an outer **cortex,** which are derived from two separate embryonic tissues. The adrenal medulla arises from neural crest cells, which also give rise to postganglionic neurons of the sympathetic division of the autonomic nervous system (see chapters 16 and 29). Unlike most glands of the body, which develop from invaginations of epithelial tissue, the adrenal cortex is derived from mesoderm.

Trabeculae of the connective tissue capsule penetrate the adrenal gland in several locations, and numerous small blood vessels course within the trabeculae to supply the gland. The adrenal medulla consists of closely packed polyhedral cells centrally located in the gland (figure 18.14*b*). The adrenal cortex is composed of smaller cells and forms three indistinct layers: (1) the **zona glomerulosa** (glō-mār′ū-lōs-ă), (2) the **zona fasciculata** (fa-sik′ū-lă-tă), and (3) the **zona reticularis** (re-tik′ū-lăr′is). These three layers are functionally and structurally specialized. The zona glomerulosa, located immediately beneath the capsule, is composed of small clusters of cells and secretes aldosterone. Beneath the zona glomerulosa is the thickest part of the adrenal cortex, the zona

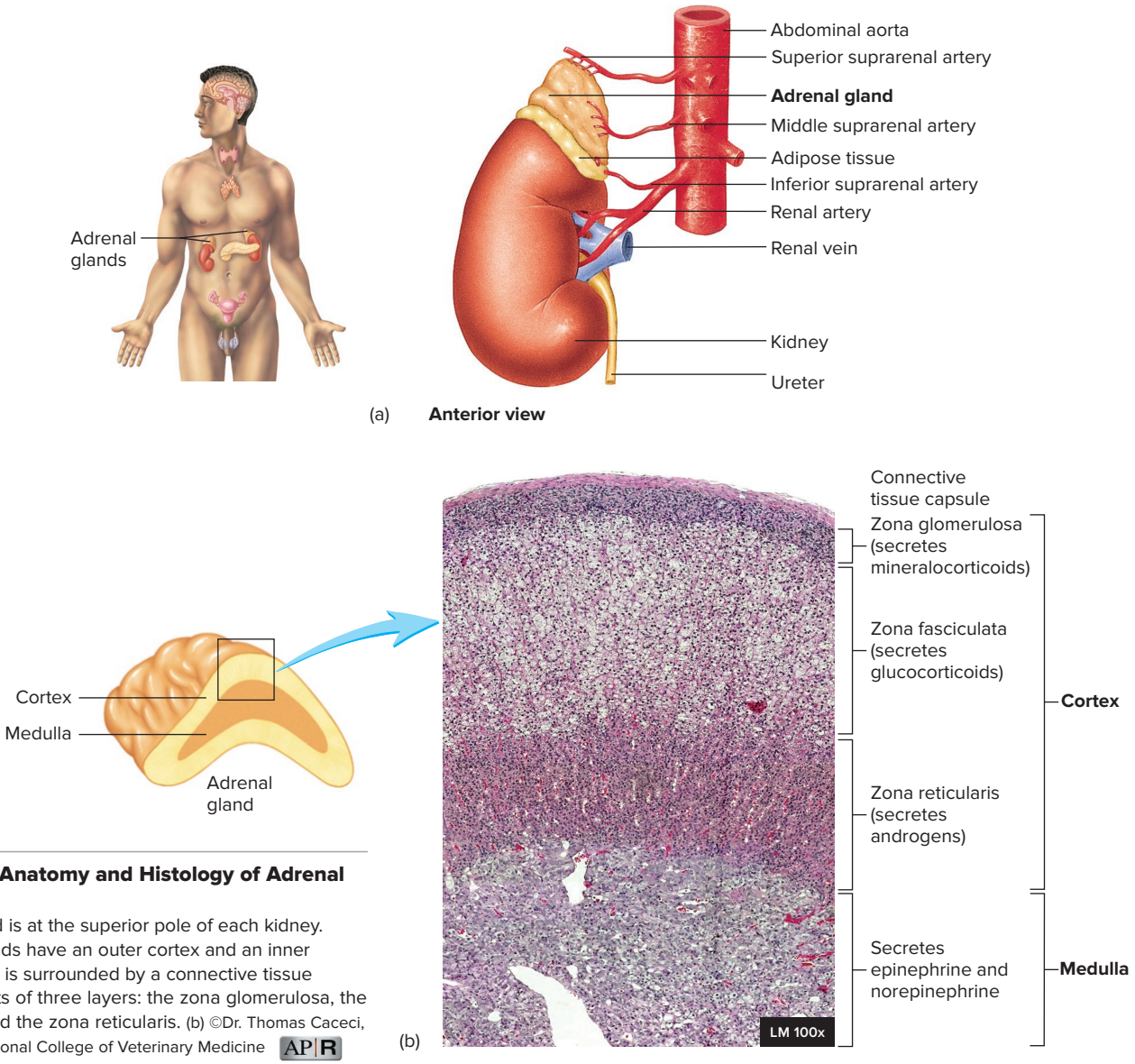


FIGURE 18.14 Anatomy and Histology of Adrenal Glands

(*a*) An adrenal gland is at the superior pole of each kidney. (*b*) The adrenal glands have an outer cortex and an inner medulla. The cortex is surrounded by a connective tissue capsule and consists of three layers: the zona glomerulosa, the zona fasciculata, and the zona reticularis. (b) ©Dr. Thomas Caceci, Virginia-Maryland Regional College of Veterinary Medicine AP|R

fasciculata, which secretes cortisol. In this layer, the cells form long columns, or fascicles, that extend from the surface toward the medulla of the gland. The deepest layer of the adrenal cortex, the zona reticularis, secretes androgens and is a thin layer of irregularly arranged cords of cells.

Hormones of the Adrenal Medulla

The adrenal medulla is a modified sympathetic nervous system ganglion. It secretes two major hormones: **epinephrine** (ep´i-nef´rin; *adrenaline;* ă-dren′ă-lin), which accounts for 80% of adrenal medulla hormones, and **norepinephrine** (nōr′ep-i-nef′rin; *noradrenaline;* nor-ă-dren′ă-lin), which accounts for 20% (table 18.7). Epinephrine and norepinephrine are closely related. In fact, norepinephrine is a precursor to the formation of epinephrine.

Epinephrine and norepinephrine combine with adrenergic receptors, which are membrane-bound receptors in target cells. They are classified as either α-adrenergic or β-adrenergic receptors, and each of these categories has subcategories that affect target tissues differently. All of the adrenergic receptors function through G protein mechanisms. In general, the α-adrenergic receptors cause Ca^{2+} channels to open, cause the release of Ca^{2+} from the endoplasmic reticulum by activating phospholipase enzymes, open K^+ channels, decrease cAMP synthesis, or stimulate the synthesis of eicosanoid molecules, such as prostaglandins. The β-adrenergic receptors all increase cAMP synthesis. A complete description of epinephrine and norepinephrine is not included in this chapter; rather, the effects of these hormones are described in the context of the body systems (see chapters 16, 20, 21, 24, and 26).

Secretion of adrenal medullary hormones prepares the individual for physical activity and is a major component of the fight-or-flight response (see chapter 16). This response results in reduced activity in organs not essential for physical activity, as well as increased blood flow and metabolic activity in organs that participate in physical activity. Epinephrine and norepinephrine increase

TABLE 18.7 Hormones of the Adrenal Gland

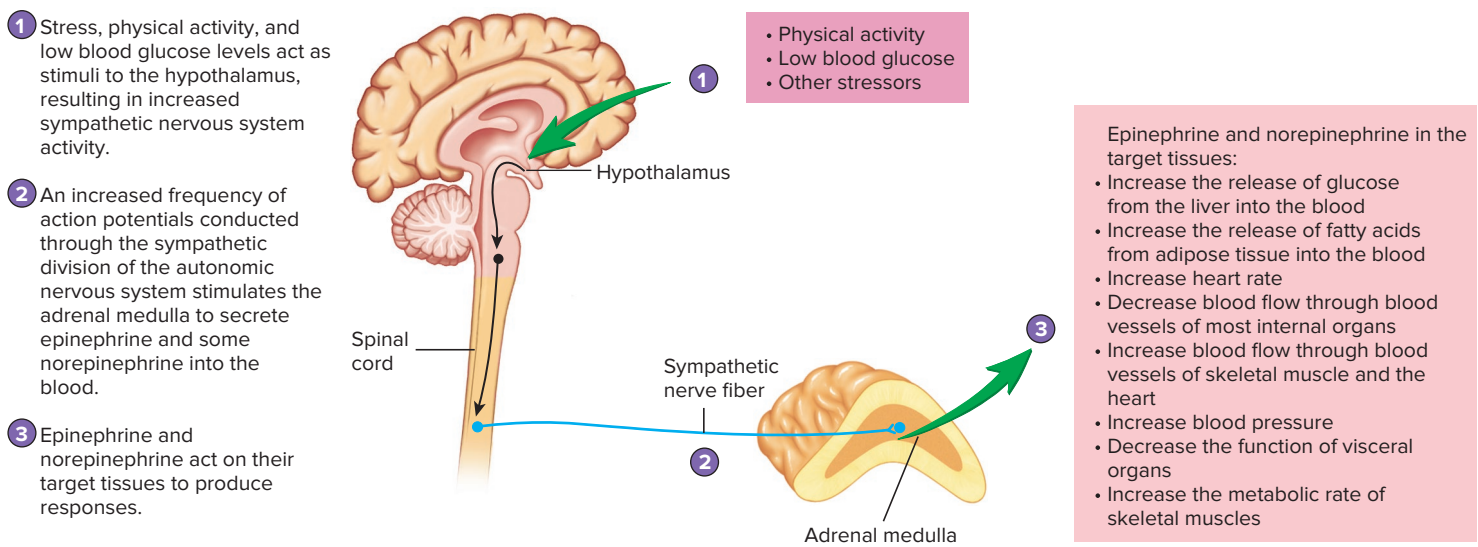
Hormones	Structure	Target Tissue	Response
Adrenal Medulla			
Epinephrine primarily; norepinephrine	Amino acid derivatives	Heart, blood vessels, liver, adipose cells	Increased cardiac output; increased blood flow to skeletal muscles and to the heart (see chapter 20); vasoconstriction of blood vessels, especially in the viscera and skin; increased release of glucose and fatty acids into the blood; in general, preparation for physical activity
Adrenal Cortex			
Mineralocorticoids (aldosterone)	Steroids	Kidney	Increased Na^+ reabsorption and K^+ and H^+ excretion; enhanced water reabsorption
Glucocorticoids (cortisol)	Steroids	Most tissues	Increased protein and lipid breakdown; increased glucose production; inhibition of immune response and decreased inflammation
Androgens	Steroids	Many tissues	Of minor importance in males; in females, development of some secondary sex characteristics, such as axillary and pubic hair

the heart's rate and force of contraction and cause blood vessels to constrict in the skin, kidneys, gastrointestinal tract, and other viscera. Also, epinephrine causes dilation of blood vessels in skeletal muscles and cardiac muscle. In addition, epinephrine mobilizes nutrients that can be used to sustain physical exercise. The specific actions of epinephrine that mobilize nutrients include the following:

1. Epinephrine increases blood glucose levels. It binds to membrane-bound receptors in liver cells. Cyclic AMP, in turn, activates enzymes that catalyze the breakdown of glycogen to glucose and the release of glucose from the liver cells into the blood.
2. Epinephrine also increases the breakdown of glycogen in muscle cells, but muscle cells do not release glucose into the blood because glucose is utilized in muscle cells.
3. Epinephrine increases lipid breakdown in adipose tissue, releasing fatty acids into the blood. The fatty acids can be taken up and metabolized by tissues such as skeletal and cardiac muscle.

The effects of epinephrine and norepinephrine are short-lived because they are rapidly metabolized, excreted, or taken up by tissues. Their half-life in the blood is measured in minutes.

The adrenal medulla is a specialized part of the autonomic nervous system. Thus, the release of adrenal medullary hormones primarily occurs in response to stimulation by sympathetic neurons. Several conditions, including emotional excitement, injury, stress, exercise, and low blood glucose levels, promote the release of adrenal medullary neuropeptides (figure 18.15).



PROCESS FIGURE 18.15 Regulation of Adrenal Medulla Secretions

Stress, physical exercise, and low blood glucose levels cause increased activity of the sympathetic nervous system, which increases epinephrine and norepinephrine secretion from the adrenal medulla.

? *How do epinephrine and norepinephrine from the adrenal medulla differ from epinephrine and norepinephrine released by neurons of the sympathetic nervous system?*

ASSESS YOUR PROGRESS

38. *Where are the adrenal glands located? Describe the embryonic origins of the adrenal medulla and the adrenal cortex.*
39. *Name two hormones secreted by the adrenal medulla, and list the effects of these hormones.*
40. *List several conditions that can stimulate the production of adrenal medullary hormones. What role does the nervous system play in the release of these hormones? How does this role relate to the embryonic origin of the adrenal medulla?*

Hormones of the Adrenal Cortex

The adrenal cortex secretes three types of steroid hormone: (1) **mineralocorticoids** (min′er-al-ō-kōr′ti-koydz), (2) **glucocorticoids** (gloo-kō-kōr′ti-koydz), and (3) **adrenal androgens** (an′drō-jenz; table 18.7). All adrenal cortex hormones have a similar structure in that they are steroids, which are highly specialized lipids derived from cholesterol. Because these hormones are lipid-soluble, they are not stored in the adrenal gland cells but diffuse from the cells as they are synthesized. Adrenal cortical hormones are transported in the blood bound to specific plasma proteins; they are metabolized in the liver and excreted in the bile and urine. The hormones of the adrenal cortex bind to nuclear receptors and stimulate the synthesis of specific proteins responsible for producing the target cell's responses.

Mineralocorticoids

As their name suggests, the mineralocorticoids regulate ion balance in the blood. The mineralocorticoids are the major secretory products of the zona glomerulosa of the adrenal cortex. **Aldosterone** (al-dos′ter-ōn) is produced in the greatest amounts, although other, closely related mineralocorticoids are also secreted. Aldosterone is secreted under low blood pressure conditions. It returns blood pressure to its normal range through modulation of kidney function. Aldosterone increases the rate of sodium reabsorption by the kidneys, which increases blood levels of sodium. The higher blood sodium levels enhance water reabsorption through osmosis. Recall from chapter 3 that osmosis is the diffusion of water toward higher solute areas. This reabsorption of water increases blood volume and thereby increases blood pressure. Aldosterone also stimulates K^+ excretion into the urine by the kidneys, which lowers blood levels of K^+. In addition, aldosterone increases the rate of H^+ excretion into the urine. When aldosterone is secreted in high concentrations, reduced blood K^+ levels and alkalosis (elevated pH of body fluids) may result. The specific effects of aldosterone and the mechanisms controlling aldosterone secretion are discussed along with kidney functions in chapters 26 and 27 and with cardiovascular system functions in chapter 21.

Glucocorticoids

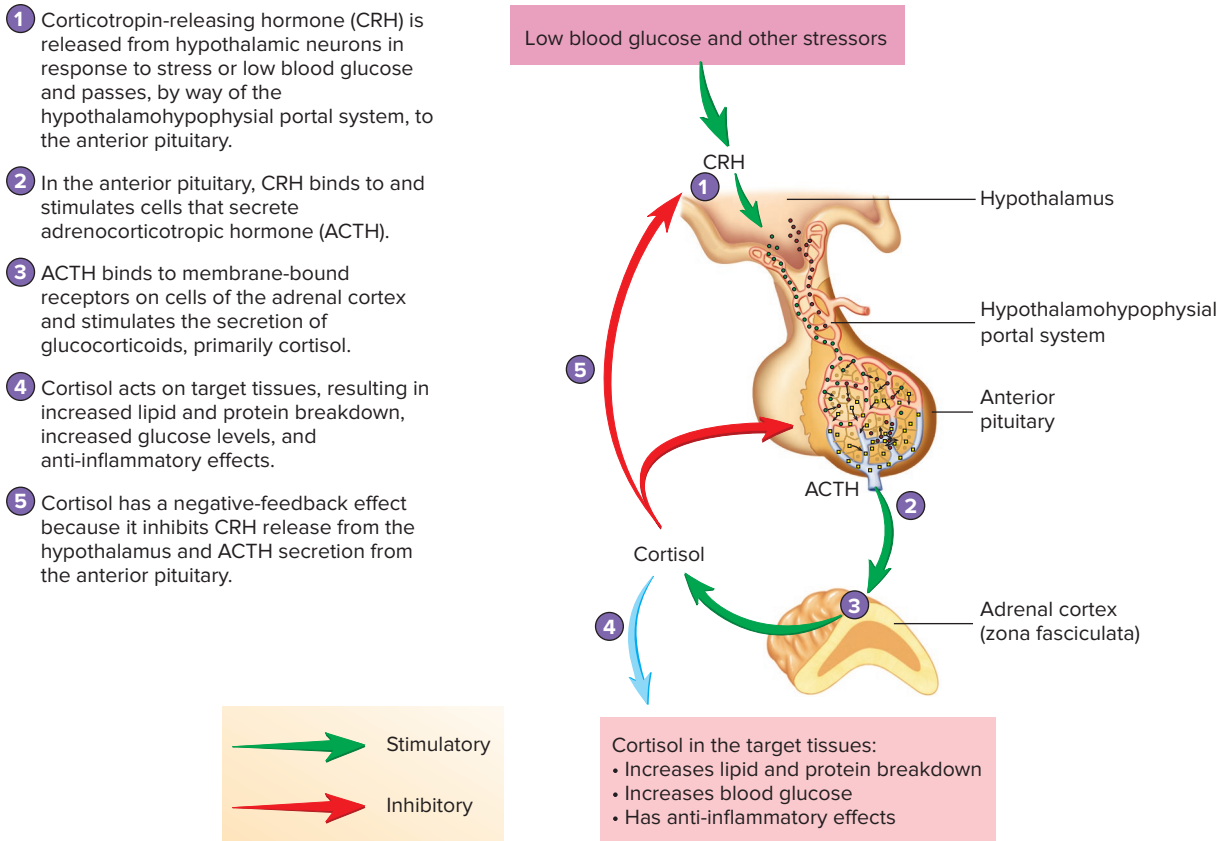
Glucocorticoids help to provide energy for cells by stimulating the increased use of lipids and proteins. It is the zona fasciculata of the adrenal cortex that secretes the **glucocorticoid hormones,** primarily **cortisol** (kōr′ti-sol). The numerous target tissues and responses to the glucocorticoids are listed in table 18.8. The responses are classified as metabolic, developmental, or anti-inflammatory. Glucocorticoids cause lipid breakdown, reduce glucose and amino acid uptake in skeletal muscle, stimulate **gluconeogenesis** (gloo′kō-nē-ō-jen′ĕ-sis; the synthesis of new glucose from precursor molecules, such as amino acids in the liver), and increase protein degradation. Glucocorticoids also increase blood glucose levels and glycogen deposits in cells. The glucose and glycogen are a reservoir of molecules that can be metabolized rapidly.

Glucocorticoids are also required for the maturation of tissues, such as fetal lungs, and for the development of receptor molecules in target tissues for epinephrine and norepinephrine. In addition, glucocorticoids decrease the intensity of the inflammatory and immune responses by decreasing both the number of white blood cells and the secretion of inflammatory chemicals from tissues. This anti-inflammatory effect is important under conditions of stress, when the rate of glucocorticoid secretion is relatively high. Synthetic glucocorticoids are often used to suppress the immune response in people suffering from autoimmune conditions and in transplant recipients (see chapter 22).

ACTH is necessary to maintain the secretory activity of the adrenal cortex, which rapidly atrophies without this hormone. Corticotropin-releasing hormone (CRH) released from the hypothalamus stimulates the anterior pituitary to secrete ACTH. The zona fasciculata is very sensitive to ACTH, and it responds by increasing cortisol secretion. The regulation of ACTH and cortisol secretion is outlined in figure 18.16. Both ACTH and cortisol inhibit CRH secretion from the hypothalamus by negative feedback. In addition,

TABLE 18.8 Target Tissues and Their Responses to Glucocorticoid Hormones

Target Tissues	Responses
Peripheral tissues, such as skeletal muscle, liver, and adipose tissue	Inhibit glucose use; stimulate the formation of glucose from amino acids and, to some degree, from lipids (gluconeogenesis) in the liver, which results in elevated blood glucose levels; stimulate glycogen synthesis in cells; mobilize lipids by increasing lipolysis, which results in the release of fatty acids into the blood and an increased rate of fatty acid metabolism; increase protein breakdown and decrease protein synthesis
Immune tissues	Anti-inflammatory; depress antibody production, white blood cell production, and the release of inflammatory components in response to injury; suppress the immune system
Target cells for epinephrine	Receptor molecules for epinephrine and norepinephrine decrease without adequate amounts of glucocorticoid hormone



PROCESS FIGURE 18.16 Regulation of Cortisol Secretion

Cortisol secretion is regulated by the hypothalamic hormone, CRH, and the anterior pituitary hormone, ACTH.

? *Explain why the drug cortisone (kor′ti sōn), a steroid closely related to cortisol, is prescribed to treat joint injuries, allergies, or asthma.*

high concentrations of cortisol in the blood inhibit ACTH secretion from the anterior pituitary, and low concentrations stimulate it. This negative-feedback loop is important in maintaining blood cortisol levels within a controlled range of concentration. Stress and hypoglycemia (low levels of glucose in the blood) trigger a large increase in CRH release from the hypothalamus by causing a rapid increase in blood levels of cortisol. In addition, CRH levels vary significantly throughout the day. Table 18.9 outlines several abnormalities associated with the hyposecretion or hypersecretion of adrenal hormones.

Predict 7

Cortisone, a drug similar to cortisol, is sometimes given to people who have severe allergies or extensive inflammation or to those who suffer from autoimmune diseases. Taking this substance chronically can damage the adrenal cortex. Explain how this damage can occur.

Adrenal Androgens

Some adrenal steroids function as weak androgens. *Androgen* is a generic term for steroid hormones that cause the development of male secondary sex characteristics (see chapter 28). Most androgens are secreted by the reproductive system (see chapter 28). However, there are adrenal androgens secreted by the zona reticularis. Some adrenal androgens are converted by peripheral tissues to the potent androgen testosterone, while other adrenal androgens are weak androgens such as androstenedione (an-drō-stēn′dī-ōn). Adrenal androgens stimulate pubic and axillary hair growth and sex drive in females. However, the effects of adrenal androgens in males are negligible, in comparison with testosterone secreted by the testes.

ASSESS YOUR PROGRESS

41. *Describe the three layers of the adrenal cortex, and name the hormones produced by each layer.*

42. *Name the target tissue of aldosterone, and list the effects of an increase in aldosterone secretion on the concentration of ions in the blood.*

43. *Describe the effects produced by an increase in cortisol secretion. Starting with the hypothalamus, describe how stress or low blood glucose levels can stimulate cortisol release.*

44. *List the possible causes of hyposecretion of adrenal cortex hormones, and describe the symptoms.*

45. *List the possible causes of hypersecretion of adrenal cortex hormones, and describe the symptoms.*

46. *What effects do adrenal androgens have on males and on females?*

TABLE 18.9 Symptoms of Hyposecretion and Hypersecretion of Adrenal Cortex Hormones

	Cause	Symptoms
Hyposecretion		
Mineralocorticoids (aldosterone)	Removal of gland or loss of function or Addison disease (low levels of aldosterone *and* cortisol)	Hyponatremia (low blood levels of sodium) Hyperkalemia (high blood levels of potassium) Acidosis Low blood pressure Tremors and tetany of skeletal muscles Polyuria
Glucocorticoids (cortisol)	Removal of gland or loss of function	Hypoglycemia (low blood glucose levels) Depressed immune system Unused proteins and lipids from diet, resulting in weight loss Loss of appetite, nausea, vomiting Bronzing of skin due to increased pigmentation (if ACTH levels are elevated)
Adrenal Androgens		In women, reduction of pubic and axillary hair
Hypersecretion		
Mineralocorticoids (aldosterone)	Tumor in gland or aldosteronism	Slight hypernatremia (high blood levels of sodium) Hypokalemia (low blood levels of potassium) Alkalosis High blood pressure Weakness of skeletal muscles Acidic urine
Glucocorticoids (cortisol)	Tumor in gland or Cushing syndrome (high cortisol *and* androgens)	Hyperglycemia (high blood glucose levels; adrenal diabetes; leads to diabetes mellitus) Depressed immune system Destruction of tissue proteins, causing muscle atrophy and weakness, osteoporosis, weak capillaries (easy bruising), thin skin, and impaired wound healing; mobilization and redistribution of lipids, causing depletion of adipose tissue from limbs and deposition in face (moon face), neck (buffalo hump), and abdomen (Cushing syndrome) Emotional effects, including euphoria and depression
Androgens	Tumor in gland or adrenogenital syndrome	In women, hirsutism (excessive facial and body hair), acne, increased sex drive, regression of breast tissue, and loss of regular menstruation

Case STUDY 18.2 Cushing Syndrome

Ethan noticed that he had gained a substantial amount of weight over the past few months and that he was feeling weak. His physician observed that the adipose tissue distribution was mainly in his trunk, face, and neck (figure 18.17). There was also evidence of decreased muscle mass, and Ethan had several bruises on his upper and lower limbs. Results of a routine blood test showed elevated blood glucose levels and low blood K^+ levels. There was no observable evidence that Ethan had cancer. His physician suspected that he was suffering from Cushing syndrome.

A second blood sample was taken. Ethan's blood cortisol levels were very high, and his blood ACTH levels were very low. Based on these data, Ethan's physician explained that he was probably suffering from an adrenal gland tumor, which was secreting large amounts of cortisol, and that the tumor was not responding to the negative-feedback mechanisms that normally control cortisol secretion. Subsequently, imaging techniques revealed a tumor in Ethan's left adrenal gland. After his left adrenal gland was surgically removed, Ethan's symptoms decreased dramatically over the next few weeks.

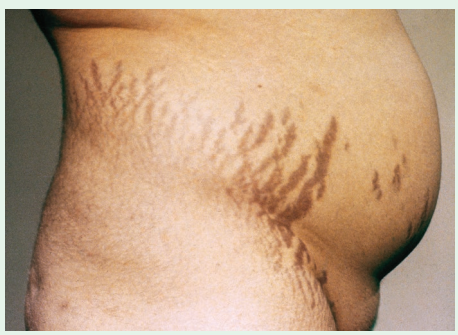


FIGURE 18.17 Cushing Syndrome
Rapid deposition of adipose tissue in the trunk can cause the skin to stretch, which can be seen as stretch marks in this photograph.

Predict 8

a. Why did the physician suspect Cushing syndrome?
b. Explain why Ethan's physician concluded that a hormone-secreting tumor in one of Ethan's adrenal glands was responsible for his symptoms.
c. After surgical removal of his left adrenal gland, how did Ethan's blood cortisol and ACTH levels change?
d. How would the data from the second blood sample have been different if Ethan's condition had been due to a hormone-secreting tumor in his anterior pituitary gland?

18.6 Pancreas

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe the location and structure of the pancreas.**
B. **Name the hormones secreted by the pancreatic islets and describe their effects on their target tissues.**
C. **Explain how pancreatic hormones are regulated.**
D. **Compare and contrast the causes and symptoms of type 1 and type 2 diabetes mellitus.**

The **pancreas** (pan′krē-us) is both an exocrine gland and an endocrine gland. The exocrine portion consists of acini (as′i-nī), which produce pancreatic juice, and a duct system, which carries the pancreatic juice to the small intestine (see chapter 24). The endocrine part, consisting of pancreatic islets (islets of Langerhans; figure 18.18), secretes hormones that enter the plasma of the blood. The pancreas lies behind the peritoneum between the greater curvature of the stomach and the duodenum. It is an elongated structure approximately 15 cm long, weighing approximately 85–100 g. The head of the pancreas lies near the duodenum, and its body and tail extend toward the spleen.

Between 500,000 and 1 million pancreatic islets are dispersed among the ducts and acini of the pancreas. Each islet is composed of (1) **alpha (α) cells** (20%), which secrete **glucagon,** a peptide hormone; (2) **beta (β) cells** (75%), which secrete **insulin,** a peptide hormone consisting of two peptide chains bound together; and (3) **delta (δ) cells,** which secrete somatostatin, also a peptide hormone. Nerves from both divisions of the autonomic nervous system innervate the pancreatic islets, and a well-developed capillary network surrounds each islet.

Effect of Insulin and Glucagon on Their Target Tissues

The pancreatic hormones play an important role in regulating the concentration of critical nutrients in the blood, especially glucose and amino acids (table 18.10). The major target tissues of insulin are the (1) liver, (2) adipose tissue, (3) skeletal muscles, and (4) satiety center within the hypothalamus of the brain. The **satiety** (sa′tī-ĕ-tē) **center** is a collection of neurons in the hypothalamus that controls appetite. However, insulin

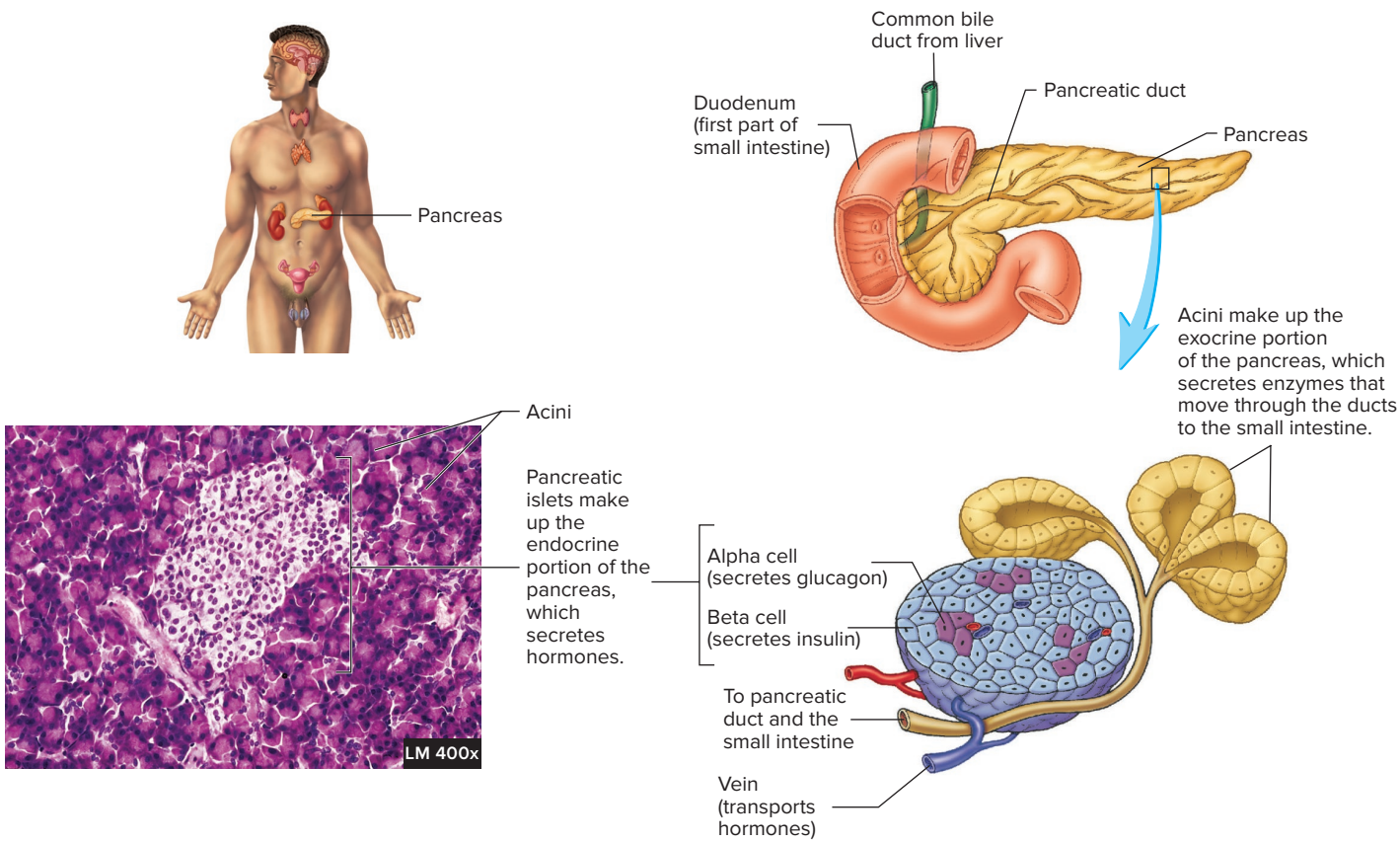


FIGURE 18.18 Histology of the Pancreatic Islets

A pancreatic islet consists of clusters of specialized cells among the acini of the exocrine portion of the pancreas. The stain used for this slide does not distinguish between alpha and beta cells. ©Biophoto Associates/Science Source AP|R

does not directly affect most other areas of the nervous system. The specific effects of insulin on these target tissues are listed in table 18.10.

Insulin

Insulin's primary function is to lower blood glucose levels by stimulating glucose transport into body cells. Insulin is secreted when blood glucose is elevated, such as after a meal. Insulin binds to membrane-bound receptors on target cells. Once insulin binds to its receptor, the receptor causes specific proteins in the membrane to become phosphorylated. Part of the cells' response to insulin is to increase the number of transport proteins in the plasma membrane for glucose and amino acids. Finally, insulin and its receptor enter the cell by endocytosis. The insulin is released from the insulin receptor and broken down within the cell, and the insulin receptor returns to the plasma membrane.

In general, the target tissue responds to insulin by increasing its ability to take up and use glucose and amino acids. Glucose molecules that are not needed immediately as an energy source to maintain cell metabolism are stored as glycogen in skeletal muscle, the liver, and other tissues and are converted to lipids in adipose tissue. Amino acids can be broken down and used as an energy source, or they can be converted to protein. Without insulin, the ability of these tissues to take up and use glucose and amino acids is minimal.

The normal regulation of blood glucose levels requires insulin. Blood glucose levels can increase dramatically when too little insulin is secreted or when insulin receptors do not respond to it (see Clinical Impact 18.2). In the absence of insulin, the movement of glucose and amino acids into cells declines dramatically, even though blood levels of these molecules may increase to very high levels. The hypothalamic satiety center requires insulin in order to take up glucose. In the absence of insulin, the satiety center cannot detect the presence of glucose in the extracellular fluid, even when glucose levels are high. The result is an intense sensation of hunger in spite of high blood glucose levels, a condition called *polyphagia* (pol-ē-fā′jē-ă). High blood glucose levels also cause increased urine volume (*polyuria;* pol-ē-ū′rē-ă) and loss of water in the urine. Glucose is filtered from the blood into the kidney tubules. There, the glucose creates an osmotic gradient favoring the movement of water into the tubules and its subsequent loss in urine (see chapter 26). Elevated blood glucose levels also increase blood osmolality, resulting in an increased sensation of thirst (*polydipsia;* pol-ē-dip′sē-ă; see chapter 27).

When too much insulin is secreted, blood glucose levels can fall very low because too much insulin causes target tissues to rapidly take up glucose from the blood. Although the nervous system, except for cells of the satiety center, is not a target tissue for insulin, the nervous system depends primarily on blood glucose as an energy source. Consequently, low blood glucose levels cause changes in the function of the CNS, including dizziness, loss of cognitive function, and in extreme cases, loss of consciousness.

Glucagon

Glucagon is the companion hormone to insulin (see chapter 17). Its secretion is stimulated when blood glucose levels decline. Glucagon promotes the release of glucose from intracellular stores. For example, glucagon primarily influences the liver, although it has some effect on skeletal muscle and adipose tissue (table 18.11). Glucagon binds to membrane-bound receptors, activates G proteins, and increases cAMP synthesis. In general, glucagon causes the breakdown of glycogen and increases glucose synthesis in the liver. It also increases the breakdown of lipids. The amount of glucose released from the liver into the blood increases dramatically after glucagon secretion increases.

Regulation of Pancreatic Hormone Secretion

Regulation of Insulin Secretion

Pancreatic secretion is partially under humoral control. The hormone-secreting cells can directly respond to low blood glucose levels. In addition, blood levels of other nutrients, neural stimulation, and other hormones control the secretion of insulin (figure 18.19).

The following factors increase insulin secretion:

1. *Hyperglycemia,* or elevated blood levels of glucose, directly stimulates insulin secretion from pancreatic β cells.
2. Certain amino acids also stimulate insulin secretion by acting directly on pancreatic β cells.

TABLE 18.10 Hormones of the Pancreas

Cells in Islets	Hormone	Structure	Target Tissue	Response
Alpha (α)	Glucagon	Peptide	Primarily liver	Increased breakdown of glycogen for release of glucose into the blood; increased production of new glucose
Beta (β)	Insulin	Peptide	Especially liver, skeletal muscle, adipose tissue	Increased uptake and use of glucose and amino acids
Delta (δ)	Somatostatin	Peptide	Alpha and beta cells (some somatostatin is produced in the hypothalamus)	Inhibition of insulin and glucagon secretion

TABLE 18.11 **Effect of Insulin and Glucagon on Target Tissues**

Target Tissue	Response to Insulin	Response to Glucagon
Skeletal muscle, cardiac muscle, cartilage, bone, fibroblasts, leukocytes, and mammary glands	Increased glucose uptake and glycogen synthesis; increased uptake of certain amino acids	Little effect
Liver	Increased glycogen synthesis; increased use of glucose for energy (glycolysis)	Rapid increase in the breakdown of glycogen to glucose (glycogenolysis) and release of glucose into the blood; increased formation of glucose (gluconeogenesis) from amino acids and, to some degree, from lipids; increased metabolism of fatty acids, resulting in more ketones in the blood
Adipose cells	Increased glucose uptake, glycogen synthesis, lipid synthesis, and fatty acid uptake; increased glycolysis	High concentrations cause breakdown of lipids (lipolysis); probably unimportant under most conditions
Nervous system	Little effect, except increased glucose uptake in the satiety center	No effect

3. Parasympathetic stimulation associated with food intake acts with elevated blood glucose levels to increase insulin secretion.
4. Gastrointestinal hormones involved with regulating digestion, such as gastrin, secretin, and cholecystokinin (see chapter 24), increase insulin secretion.

Thus, insulin secretion tends to increase after a meal, when glucose and amino acid levels in the blood are their highest.

Insulin secretion decreases under a different set of conditions, which tends to be when glucose and amino acid levels in the blood are their lowest.

The following factors decrease insulin secretion:

1. *Hypoglycemia,* or low blood levels of glucose, directly slows insulin secretion.
2. Activation of the sympathetic nervous system is inhibitory to insulin secretion. This helps prevent a rapid fall in blood glucose levels. Because most tissues, except nervous tissue, require insulin to take up glucose, sympathetic stimulation maintains blood glucose levels in a normal range during periods of physical activity or excitement. This response is important for supplying a constant level of glucose to the brain for normal nervous system function.
3. Somatostatin inhibits both insulin and glucagon secretion, but the factors that regulate somatostatin secretion are not clear. It can be released in response to food intake, in which case somatostatin may prevent the oversecretion of insulin.
4. During periods of fasting, when blood glucose levels are low, the rate of insulin secretion declines.

Predict 9

Explain why the increase in insulin secretion in response to parasympathetic stimulation and gastrointestinal hormones is consistent with the maintenance of blood glucose levels in the blood.

Regulation of Glucagon Secretion

Low blood glucose levels stimulate glucagon secretion, and high blood glucose levels inhibit it. Certain amino acids and sympathetic stimulation also increase glucagon secretion. After a high-protein meal, amino acids increase both insulin and glucagon secretion. Insulin causes target tissue uptake of amino acids for protein synthesis, and glucagon increases the process of glucose synthesis from amino acids in the liver (gluconeogenesis). Both protein synthesis and the use of amino acids to maintain blood glucose levels result from the low, but simultaneous, secretion of insulin and glucagon induced by meals high in protein.

Predict 10

Compare the regulation of glucagon and insulin secretion after a meal high in carbohydrates, after a meal low in carbohydrates but high in proteins, and during physical exercise.

ASSESS YOUR PROGRESS

47. *Where is the pancreas located? Describe the exocrine and endocrine parts of this gland and the secretions produced by each portion.*

48. *Name the target tissues for insulin and glucagon, and list their effects on the target tissues.*

49. *How does insulin affect the satiety center of the hypothalamus?*

50. *What effect do blood glucose levels, blood amino acid levels, the autonomic nervous system, and somatostatin have on insulin and glucagon secretion?*

51. *Describe the causes and symptoms of type 1 diabetes mellitus and type 2 diabetes mellitus.*

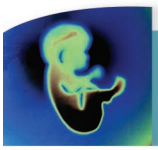
Clinical GENETICS 18.1 Type 2 Diabetes Mellitus

Most people with diabetes mellitus have type 2. Type 2 diabetes mellitus has a genetic basis, and it appears that several genes can make people more susceptible to developing the condition. For example, individuals whose close relatives have type 2 diabetes mellitus have an increased risk of developing it. In addition, type 2 diabetes mellitus is more prevalent among certain populations. For example, it is more common in Native Americans than in whites, African-Americans, and Latinos.

The pathways activated by the insulin receptor are complex, and genes on 10 different chromosomes that code for proteins in those pathways have been associated with the development of type 2 diabetes mellitus. Antibodies that bind to insulin receptors and make them nonfunctional or reduced numbers of functional insulin receptors can cause type 2 diabetes mellitus. In most cases, however, the insulin receptor is normal, but mutations in the genes that code for enzymes activated by the combination of insulin and its receptors result in a reduced response to insulin.

Type 2 diabetes mellitus involves a gradual failure of cells to respond to insulin and to take up glucose. Therefore, people who inherit genes that make them susceptible to type 2 diabetes mellitus are likely to develop the condition later in life. Also, symptoms are more likely to develop in people with an unhealthy lifestyle, which includes a diet high in calories and simple sugars and a sedentary tendency. A high percentage of people who have type 2 diabetes mellitus are obese. The severity of the condition may decrease in response to weight loss. An unhealthy lifestyle is also associated with a recent trend toward the development of diabetes mellitus in younger people.

The "thrifty genotype" hypothesis suggests that type 2 diabetes mellitus may be more common today because the genes that make people susceptible to the condition were once beneficial. For example, during periods of famine, the ability to store adipose tissue and to have altered glucose metabolism may have been advantageous, but today, when food is abundant, having these genes increases the likelihood of developing type 2 diabetes mellitus.



Clinical IMPACT 18.2 Diabetes Mellitus

Diabetes mellitus results primarily from the inadequate secretion of insulin or the inability of tissues to respond to insulin. **Type 1 diabetes mellitus,** also called *insulin-dependent diabetes mellitus (IDDM),* affects approximately 5–10% of people with diabetes mellitus and results from diminished insulin secretion. It develops as a result of autoimmune destruction of the pancreatic islets, and symptoms appear after approximately 90% of the islets have been destroyed. Type 1 diabetes mellitus most commonly develops in young people. Heredity may play a role in the condition, although the initiation of pancreatic islet destruction may involve a viral infection of the pancreas.

Type 2 diabetes mellitus, also called *noninsulin-dependent diabetes mellitus (NIDDM),* results from the inability of tissues to respond to insulin. Type 2 diabetes mellitus usually develops in people older than 40–45 years of age, although it is being observed more frequently in much younger patients.

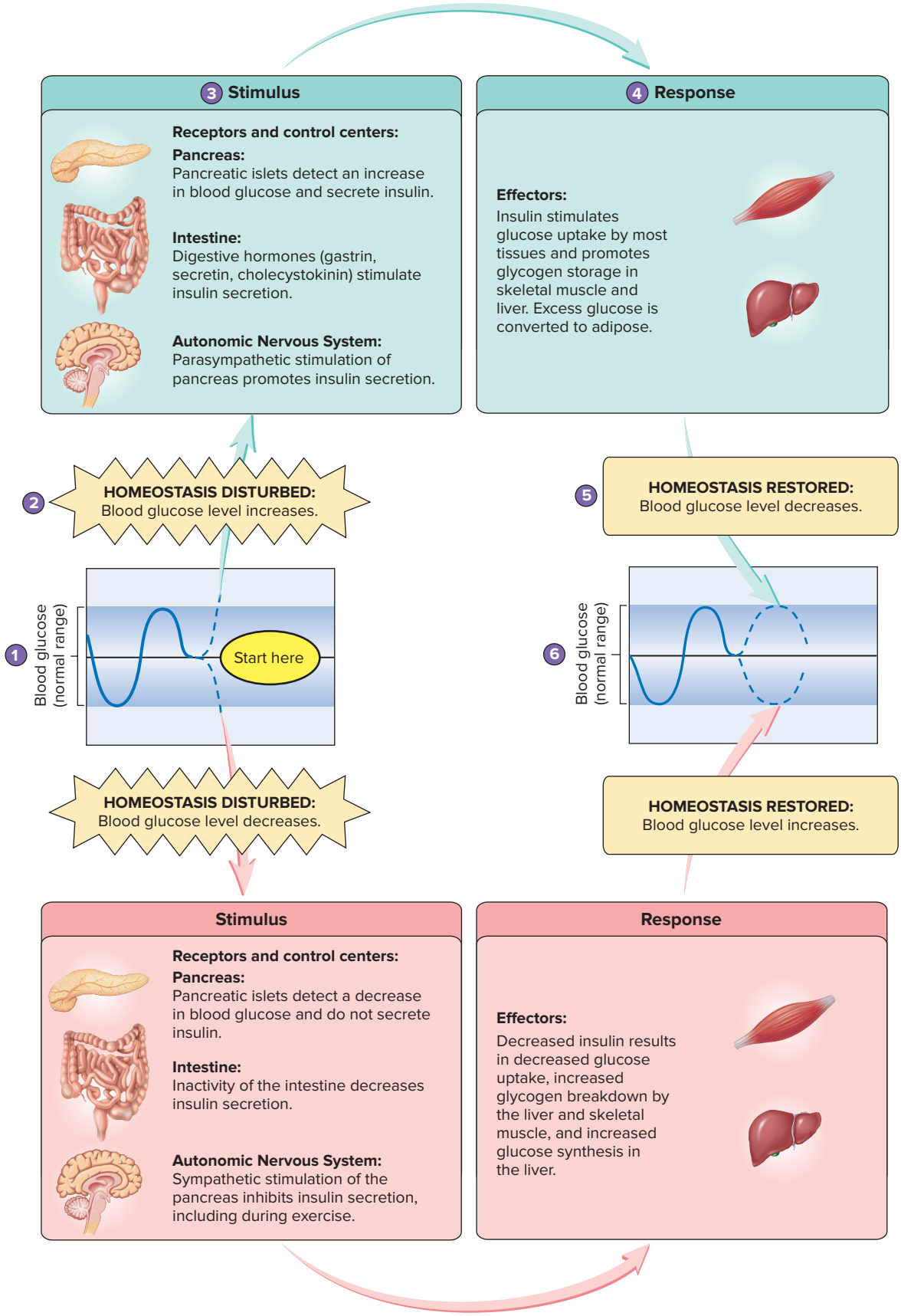
Type 2 diabetes mellitus is more common than type 1 diabetes mellitus. Approximately 90–95% of people who have diabetes mellitus have type 2. People with type 2 diabetes mellitus have a reduced number of functional receptors for insulin, or one or more of the enzymes activated by the insulin receptor are defective. Thus, glucose uptake by cells is very slow, which results in elevated blood glucose after a meal. Obesity is common, although not universal, in patients with type 2 diabetes mellitus. Elevated blood glucose levels cause adipose cells to convert glucose to lipid, even though the rate at which adipose cells take up glucose is impaired. Increased blood glucose and increased urine production lead to hyperosmolality of blood and dehydration of cells. The poor use of nutrients and dehydration of cells lead to lethargy, fatigue, and periods of irritability. Elevated blood glucose levels affect the endothelial tissue of blood vessels, as well as the nervous system's ability to respond to tactile sensation. The combination of these effects results in recurrent injury and infection, especially in distal tissues, such as the feet.

Patients with type 2 diabetes mellitus do not experience sudden, large increases in blood glucose and severe tissue wasting, as occurs with type 1 diabetes mellitus, because a slow rate of glucose uptake does occur, even though the insulin receptors are defective. In some people with type 2 diabetes mellitus, insulin production eventually decreases because pancreatic islet cells atrophy; then type 1 diabetes mellitus develops. Approximately 25–30% of patients with type 2 diabetes mellitus take insulin, 50% take oral medication to increase insulin secretion and improve the efficiency of glucose utilization, and the remainder control blood glucose levels with exercise and diet alone.

Glucose tolerance tests are used to diagnose diabetes mellitus. In general, the test involves feeding the patient a large amount of glucose after a period of fasting and then collecting blood samples for a few hours afterward. A sustained increase in blood glucose levels strongly indicates that the person has diabetes mellitus.

Too much insulin relative to the amount of glucose ingested leads to insulin shock. The high levels of insulin cause target tissues to take up glucose at a very high rate. As a result, the concentration of blood glucose rapidly falls to a low level. Because the nervous system depends on glucose as its major source of energy, neurons malfunction, leading to nervous system responses, such as disorientation, confusion, and convulsions. Too much insulin, too little food intake after an insulin injection, or increased metabolism of glucose due to excess physical exercise can cause insulin shock in a diabetic patient.

Keeping blood glucose within normal levels at all times can prevent damage to blood vessels and reduced nerve function in patients with either type of diabetes mellitus. However, doing so requires increased attention to diet and frequent blood glucose testing to ensure that blood glucose levels do not fall too low and lead to insulin shock.



HOMEOSTASIS FIGURE 18.19 Regulation of Insulin Secretion

(1) Blood glucose is within its normal range. (2) Blood glucose level increases outside the normal range. (3) Pancreatic islets secrete insulin in direct response to elevated blood glucose. Digestive hormones and parasympathetic activity also stimulate insulin secretion. (4) Most tissues take up glucose when insulin binds to its receptors on the tissue. Liver and skeletal muscle cells convert glucose to glycogen. (5) Blood glucose level drops back to the normal range. (6) Homeostasis is restored. Observe the response to a drop in blood glucose by following the *red arrows*.

18.7 Hormonal Regulation of Nutrient Utilization

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Explain the interactions of insulin, glucagon, cortisol, GH, and epinephrine immediately after a meal and 1–2 hours after a meal.**

B. **Describe the nervous and hormonal interactions during exercise that will provide enough energy to cells.**

Several hormones function together to regulate blood nutrient levels. The interactions of these hormones is illustrated in two situations—after a meal and during exercise. After a meal and under resting conditions, secretion of glucagon, cortisol, GH, and epinephrine is reduced (figure 18.20). Both increasing blood glucose levels and parasympathetic stimulation elevate insulin secretion to increase the uptake of glucose, amino acids, and lipids by target tissues. Substances not immediately used for cell metabolism are stored. Glucose is converted to glycogen in skeletal muscle and the liver, and it is used for lipid synthesis in adipose tissue and the liver. The rapid uptake and storage of glucose prevent too large an increase in blood glucose levels. Amino acids are incorporated into proteins, and lipids that were ingested as part of the meal are stored in adipose tissue and the liver. If the meal is high in protein, a small amount of glucagon is secreted, thereby increasing the rate at which the liver uses amino acids to form glucose.

Within 1–2 hours after the meal, absorption of digested materials from the digestive tract decreases, and blood glucose levels decline. To help maintain adequate levels of glucose for normal brain function, secretion of glucagon, GH, cortisol, and epinephrine increases soon after a meal. As blood glucose declines, insulin secretion decreases, and the rate of glucose entry into insulin target tissues slows. Glycogen, stored in cells, is converted back to glucose and used as an energy source. The liver releases glucose into the blood. Cells that use less glucose start using more lipids and proteins. Adipose tissue releases fatty acids, and the liver releases triglycerides (in lipoproteins) and ketones into the blood. Tissues take up these substances from the blood and use them for energy. Lipid molecules are a major source of energy for most tissues when blood glucose levels are low.

The interactions of insulin, GH, glucagon, epinephrine, and cortisol are excellent examples of negative-feedback mechanisms. When blood glucose levels are high, these hormones cause the rapid uptake and storage of glucose, amino acids, and lipids. When blood glucose levels are low, they cause the release of glucose and a switch to lipid and protein metabolism as a source of energy for most tissues.

During exercise, skeletal muscles require energy to support the contraction process (see chapter 9). Although metabolism of intracellular nutrients can sustain muscle contraction for a short time, additional energy sources are required during prolonged activity. Sympathetic nervous system activity, which increases during exercise, stimulates the release of epinephrine from the adrenal medulla and the release of glucagon from the pancreas (figure 18.21). These hormones induce the conversion of glycogen to glucose in the liver and the release of glucose into the blood, thus providing skeletal muscles with a source of energy. Because epinephrine and glucagon have short half-lives, they can rapidly adjust blood glucose levels for varying conditions of activity.

During sustained activity, glucose released from the liver and other tissues is not adequate to support muscle activity, and the danger exists that blood glucose levels will become too low to support brain function. A decrease in insulin prevents the uptake of glucose by most tissues, thus conserving glucose for the brain. In addition to other functions, epinephrine, glucagon, cortisol, and GH cause an increase in fatty acids, triglycerides, and ketones in the blood. Because GH increases protein synthesis and slows the breakdown of proteins, muscle proteins are not used as an energy source. Consequently, glucose metabolism decreases, and lipid metabolism in skeletal muscles increases. At the end of a long race, for example, muscles rely to a large extent on lipid metabolism for energy.

Predict 11

Explain why long-distance runners may not have much of a "kick" left when they try to sprint to the finish line.

ASSESS YOUR PROGRESS

52. *Describe the hormonal effects that occur immediately after a meal to cause nutrients to move into cells and be stored.*

53. *What occurs hormonally 1–2 hours after a meal that causes stored materials to be released and used for energy?*

54. *During exercise, how does sympathetic nervous system activity regulate blood glucose levels? Name five hormones that interact to ensure that the brain and the muscles have adequate energy sources during exercise, and explain the role of each.*

18.8 Hormones of the Reproductive System

LEARNING OUTCOMES

After reading this section, you should be able to

A. **List and describe the functions of the hormones secreted by the testes and ovaries.**

B. **Explain how the anterior pituitary regulates secretion by the testes and ovaries.**

C. **Explain how the placenta acts as a temporary endocrine gland.**

All aspects of reproduction, including puberty, menstruation, gamete formation, and pregnancy, are under the control of reproductive hormones. Reproductive hormones are secreted primarily from the ovaries, testes, placenta, and pituitary gland (table 18.12). These hormones are discussed in chapter 28. The main endocrine

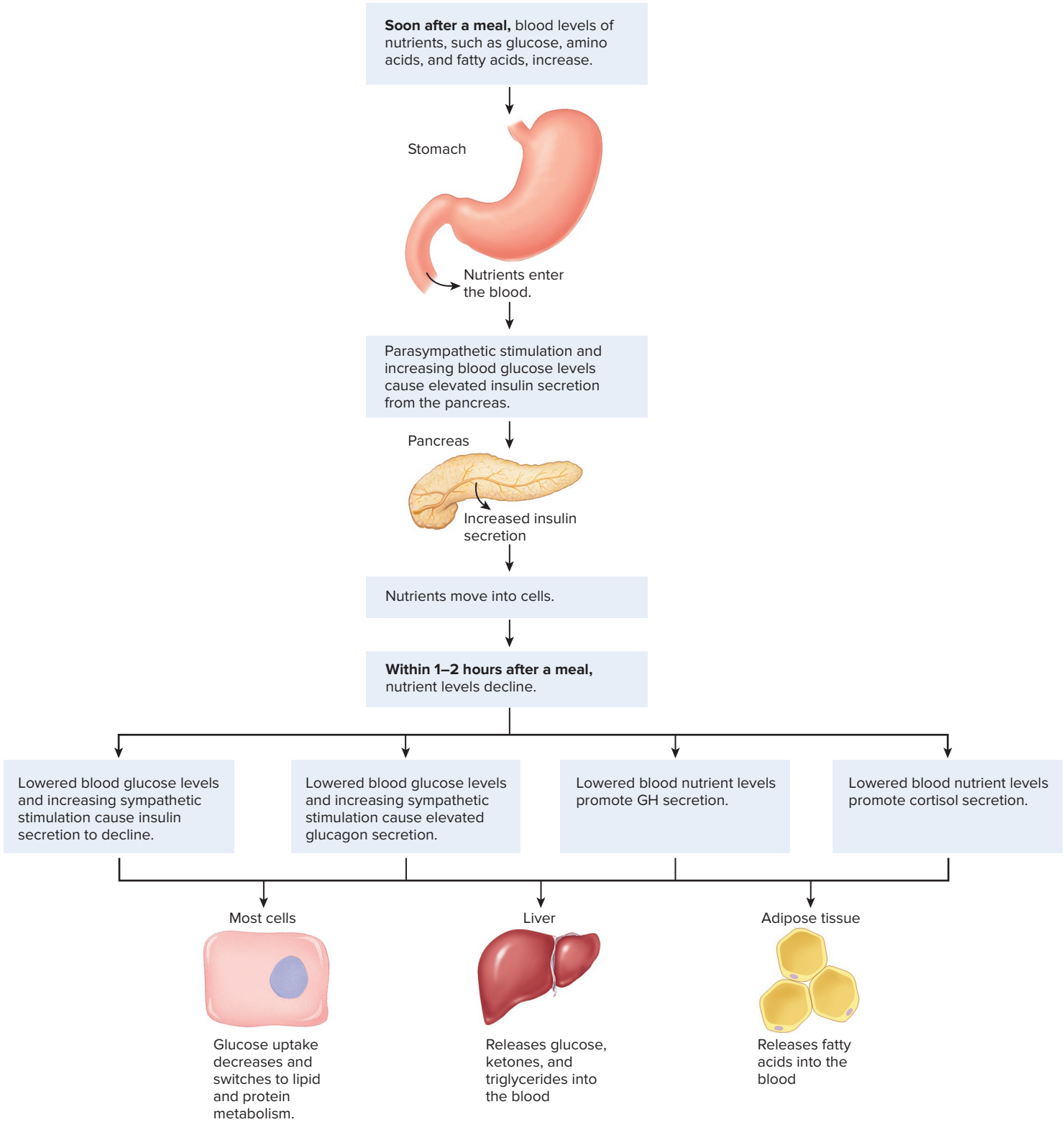


FIGURE 18.20 Regulation of Blood Nutrient Levels After a Meal
Blood nutrient levels are maintained immediately after a meal and for several hours afterward.

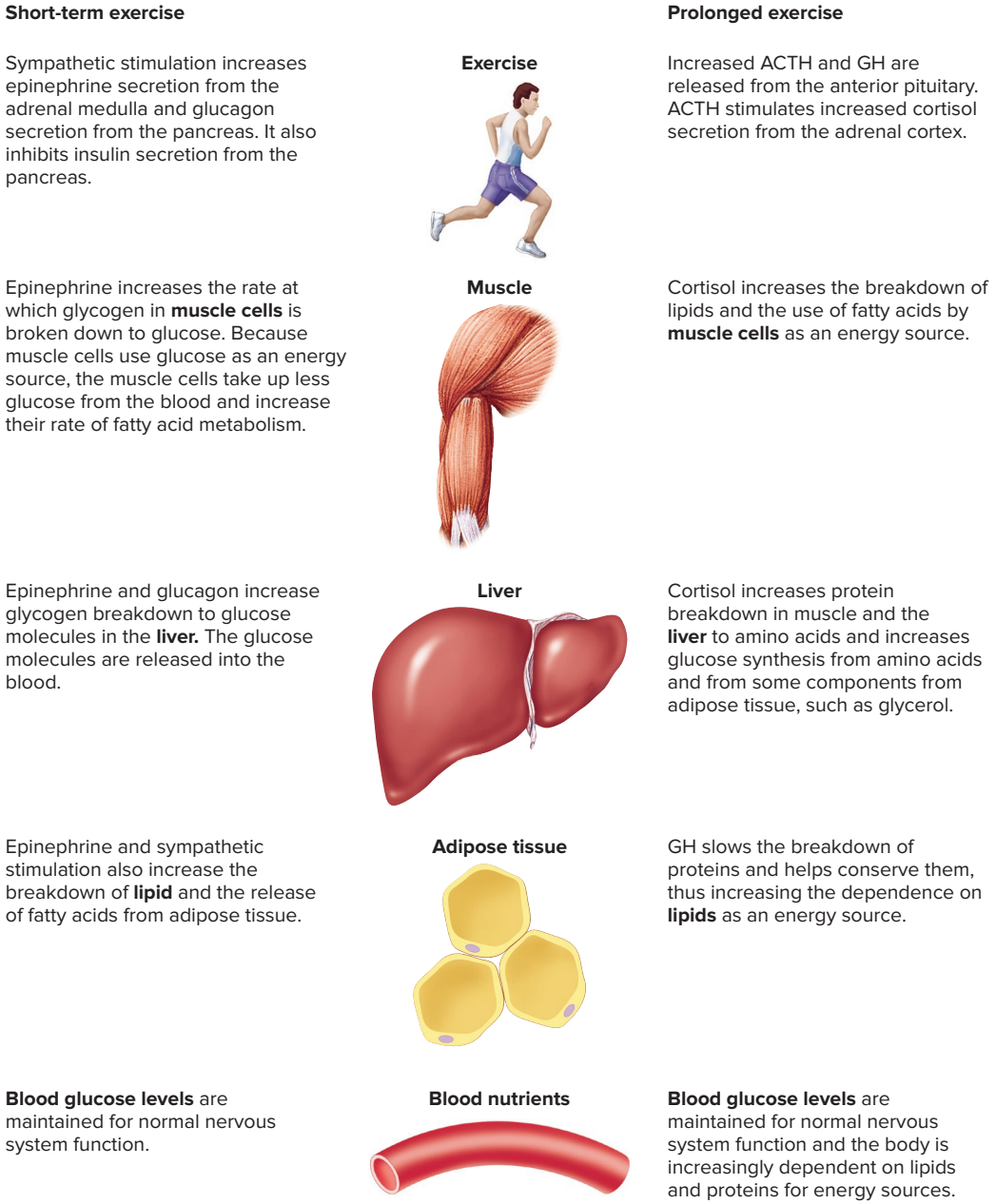


FIGURE 18.21 Regulation of Blood Nutrient Levels During Exercise
Short-term exercise blood nutrient levels are regulated primarily by epinephrine. Prolonged exercise blood nutrient levels are regulated primarily by cortisol and GH.

glands of the male reproductive system are the testes. The functions of the testes depend on the secretion of FSH and LH from the anterior pituitary gland. The main hormone secreted by the testes is testosterone, an androgen. **Testosterone** regulates the production of sperm cells by the testes and the development and maintenance of male reproductive organs and secondary sexual characteristics. The testes secrete another hormone, called **inhibin,** which inhibits the secretion of FSH from the anterior pituitary gland.

The main endocrine glands of the female reproductive system are the ovaries. Like the testes, the functions of the ovaries depend on the secretion of FSH and LH from the anterior pituitary gland. The main hormones secreted by the ovaries are **estrogen** and **progesterone.** These hormones, along with FSH and LH, control the female reproductive cycle, prepare the mammary glands for lactation, and maintain pregnancy. Estrogen and progesterone are also responsible for the development of the female reproductive organs and female secondary sexual characteristics. Like the testes, the ovaries secrete inhibin, which inhibits FSH secretion.

During the first one-third of pregnancy, the placenta secretes an LH-like substance that is necessary to maintain pregnancy (see chapter 28). Throughout most of pregnancy, the ovaries and placenta secrete increasing amounts of estrogen and progesterone, which are also necessary to maintain pregnancy. In addition, the ovaries secrete **relaxin,** which increases the flexibility of the connective tissue of the symphysis pubis and helps dilate the cervix of the uterus. This facilitates delivery by making the birth canal larger.

TABLE 18.12 Hormones of the Reproductive Organs

Hormones	Structure	Target Tissue	Response
Testes			
Testosterone	Steroid	Most cells	Aids in spermatogenesis, development of genitalia, maintenance of functional reproductive organs, secondary sexual characteristics, and sexual behavior
Inhibin	Polypeptide	Anterior pituitary gland	Inhibits FSH secretion
Ovaries			
Estrogen	Steroid	Most cells	Aids in uterine and mammary gland development and function, maturation of genitalia, secondary sex characteristics, sexual behavior, and menstrual cycle
Progesterone	Steroid	Most cells	Aids in uterine and mammary gland development and function, maturation of genitalia, secondary sex characteristics, and menstrual cycle
Inhibin	Polypeptide	Anterior pituitary gland	Inhibits FSH secretion
Relaxin	Polypeptide	Connective tissue cells	Increases the flexibility of connective tissue in the pelvic area, especially the symphysis pubis

ASSESS YOUR PROGRESS

55. *List the hormones secreted by the testes, and describe their functions.*

56. *List the hormones secreted by the ovaries, and describe their functions.*

57. *What hormones from the anterior pituitary gland regulate secretion by the testes and ovaries? Explain how these hormones function.*

58. *What hormones are secreted by the placenta to help maintain pregnancy and facilitate birth?*

MICROBES In Your Body 18.1 Hormonal Regulation of Nutrient Metabolism Is Influenced by Gut Microbes

Obesity has increased at an alarming rate over the last three decades. It is estimated that over 150 billion adults worldwide are overweight or obese. In the United States, one-third of adults are obese. As obesity rates have increased, so have the rates of obesity-related health conditions such as insulin resistance, diabetes, and cardiovascular disease. Why this dramatic increase? There are two main reasons for obesity: diet/lifestyle and gut bacteria; it seems these two may be related.

The most familiar cause of obesity is diet and lifestyle. The "typical" Western diet consists of frequent large meals high in refined grains, red meat, saturated fats, and sugary drinks. Combined with a reduction in physical activity and less sleep for many Americans, the Western diet and lifestyle can lead to obesity and poor health.

However, could humans' gut microbiota be just as responsible (or even more responsible) for obesity? Comparisons between the gut microbiota of lean versus obese individuals seem to suggest the possibility of an important link between gut microbiota and our weight. The gut in humans, like other animals, is densely populated with microbiota. The majority (90%) of human gut bacteria fall into two groups: *Firmicutes* and *Bacteroidetes*. Lean people have more *Bacteroidetes* than *Firmicutes,* while the opposite is true for obese people.

We now know that gut microbiota affect nutrient processing and absorption, hormonal regulation of nutrient use by body cells, and even our hunger level.

Changes in gut microbiota alter the hormonal regulation of nutrient use. Inflammation-promoting effects of an imbalanced gut microbiota is thought to induce obesity via promoting insulin resistance. Normal gut microbiota metabolism is critical for secretion of several antihunger hormones, and anti-depressive neurotransmitters and neurochemicals. Shifts in normal gut microbiota, as related to diet, may very well disrupt normal antihunger signals and gut permeability leading to overeating and inflammation related to obesity.

Can gut microbiota in obese people be manipulated to cause them to become lean? Several possibilities exist, including the distinct possibility that prescribing antibiotics against bacteria associated with obesity could shift the metabolism of an obese person to become leaner. Another possibility is the use of prebiotics—nondigestible sugars that enhance the growth of beneficial microbiota. Finally, probiotic use is another possible intervention for obesity. Probiotics are nonpathogenic live bacteria that confer a health benefit to the host. This is a rapidly expanding field that holds much promise, but it is still in its beginning stages of our understanding.

Predict 12

Using section 18.7 In this chapter and knowledge you galned about how levels of growth hormone (GH) and cortisol determine nutrient use and metabolic reactions, predict the following relationship. Predict whether GH and cortisol levels are higher or lower in a person whose gut microbiota population has more *Firmicutes* than *Bacteroidetes* bacteria. Would this person experience hunger more or less often than an individual with more *Bacteroidetes* bacteria in his or her gut?

18.9 Hormones of the Pineal Gland

LEARNING OUTCOMES

After reading this section, you should be able to

A. **List the hormones secreted by the pineal gland and describe their possible functions.**

B. **Explain the photoperiod and its relationship to pineal gland secretion.**

The **pineal** (pin′ē-ăl) **gland** in the epithalamus of the brain secretes hormones that act on the hypothalamus and the gonads to inhibit reproductive functions, such as by inhibiting the secretion of certain reproductive hormones. Two substances have been proposed as secretory products: (1) **melatonin** (mel-ă-tōn′in) and (2) **arginine vasotocin** (ar′ji-nēn vā-sō-tō′sin; table 18.13). Melatonin can decrease hypothalamic GnRH secretion. This mechanism may inhibit reproductive functions. It may also help regulate sleep cycles by increasing the tendency to sleep.

Arginine vasotocin works with melatonin to regulate the function of the reproductive system in some animals. Evidence for the role of melatonin is more extensive, however.

In some animals, pineal secretions are regulated by the **photoperiod,** the amount of daylight and darkness that occurs each day and changes with the seasons of the year (figure 18.22). For example, increased daylight initiates action potentials in the retina of the eye, which are propagated to the brain and cause a decrease in the action potentials sent first to the spinal cord and then through sympathetic neurons to the pineal gland, resulting in decreased secretions. In the dark, action potentials delivered by sympathetic neurons to the pineal gland increase, stimulating the secretion of pineal hormones. Thus, humans secrete larger amounts of melatonin at night than during the day. In animals that breed in the spring, the increasingly longer days as summer approaches reduce pineal secretions. Because pineal secretions inhibit reproductive functions in these species, they experience hypertrophy of the reproductive structures in the summer.

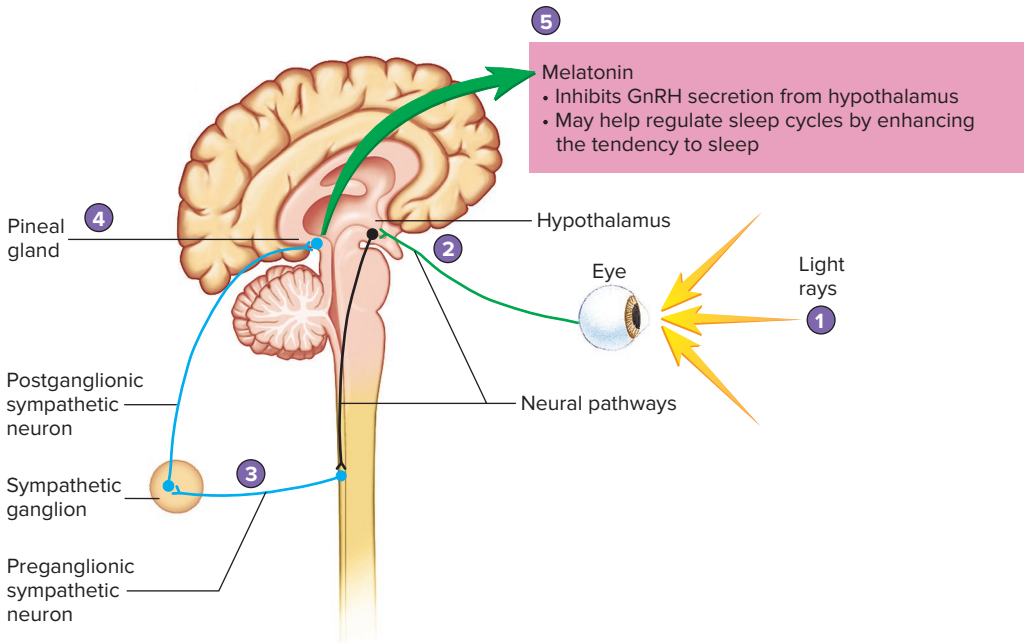
Melatonin's role in regulating reproductive functions in humans is not clear, but some researchers recommend its use to enhance sleep. However, because melatonin causes atrophy of reproductive structures in some species, undesirable side effects on the reproductive system may be possible for people who take supplemental melatonin.

The function of the pineal gland in humans is not clear, but tumors that destroy the pineal gland correlate with early sexual development, and tumors that result in pineal hormone secretion correlate with delayed development of the reproductive system. It is not clear, however, if the pineal gland controls the onset of puberty.

TABLE 18.13 **Other Hormones and Hormonelike Substances**

Chemical Messenger	Structure	Target Tissue	Response
Pineal Gland			
Melatonin	Amino acid derivative	At least the hypothalamus	Inhibition of gonadotropin-releasing hormone secretion, thereby inhibiting reproduction; significance is not clear in humans; may help regulate sleep-wake cycles
Arginine vasotocin	Peptide	Possibly the hypothalamus	Possible inhibition of gonadotropin-releasing hormone secretion
Thymus			
Thymosin	Peptide	Immune tissues	Development and function of the immune system
Several Tissues (autocrine and paracrine chemical messengers)			
Eicosanoids			
Prostaglandins	Modified fatty acid	Most tissues	Mediation of the inflammatory response; increased uterine contractions; involved in ovulation, possible inhibition of progesterone synthesis; blood coagulation; other functions
Thromboxanes	Modified fatty acid	Most tissues	Mediation of the inflammatory response; other functions, including blood clotting
Prostacyclins	Modified fatty acid	Most tissues	Mediation of the inflammatory response; other functions, including blood clotting
Leukotrienes	Modified fatty acid	Most tissues	Mediation of the inflammatory response; other functions, including blood clotting
Enkephalins and endorphins	Peptides	Nervous system	Reduction of pain sensation; other functions
Epidermal growth factor	Protein	Many tissues	Stimulation of division in many cell types; embryonic development
Fibroblast growth factor	Protein	Many tissues	Stimulation of cell division in many cell types; embryonic development
Interleukin-2	Protein	Certain immune-competent cells	Stimulation of cell division of T lymphocytes

1. Light entering the eye stimulates neurons in the retina to initiate action potentials.
2. Action potentials are transmitted to the hypothalamus.
3. Action potentials from the hypothalamus are transmitted through the sympathetic division to the pineal gland.
4. A *decrease* in light (an increase in darkness) results in increased sympathetic stimulation of the pineal gland and increased melatonin secretion. An *increase* in light results in decreased sympathetic stimulation of the pineal gland and decreased melatonin secretion.
5. Melatonin inhibits GnRH secretion from the hypothalamus and may help regulate sleep cycles.



PROCESS FIGURE 18.22 Regulation of Melatonin Secretion from the Pineal Gland

Light entering the eye inhibits the release of melatonin from the pineal gland, and dark stimulates the release of melatonin.

? *Joe works the night shift at the hospital and has had trouble sleeping. His doctor suggested taking prescription melatonin for 2–3 months to help regulate Joe's sleep cycle. What time of day did Joe's doctor suggest he take the melatonin? Explain.*

ASSESS YOUR PROGRESS

59. *Where is the pineal gland located? Name the hormones it produces and their possible effects.*

60. *Explain the relationship between the photoperiod and pineal gland secretion.*

18.10 Other Hormones and Chemical Messengers

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe the functions of the hormones secreted by the thymus, digestive system, heart, and kidneys.**

B. **Differentiate between autocrine and paracrine chemical messengers.**

C. **Give examples of both autocrine and paracrine chemical messengers and describe their functions.**

Hormones of the Thymus

The **thymus** (thī′mŭs) is important for immune function. It is in the neck and superior to the heart in the thorax. The thymus secretes the hormone **thymosin** (thī′mō-sin; table 18.13). Both the thymus and thymosin play a role in the development and maturation of the immune system (see chapter 22).

Hormones of the Digestive Tract

Several hormones are released from the digestive tract. They regulate digestive functions by influencing the activity of the stomach, intestines, liver, and pancreas (see chapter 24).

Hormonelike Chemicals

Recall from chapter 17 that some chemical messengers differ from hormones in that they are not secreted from discrete endocrine glands (see table 17.1). The effects of these chemicals are often local rather than systemic, or their functions are not understood adequately to explain their role in the body. **Autocrine chemical messengers** are released from cells that influence the same cell from which they are released. **Paracrine chemical messengers** are released from one cell type, diffuse short distances, and influence the activity of another cell type, which is the target tissue. Certain molecules sometimes function in an autocrine fashion and sometimes in a paracrine fashion. This distinction is similar to that for differentiating when a particular molecule is acting as a neurotransmitter and when it is acting as a hormone. The difference lies in the mode of transport (see chapter 17).

Systems PATHOLOGY | Graves Disease (Hyperthyroidism)

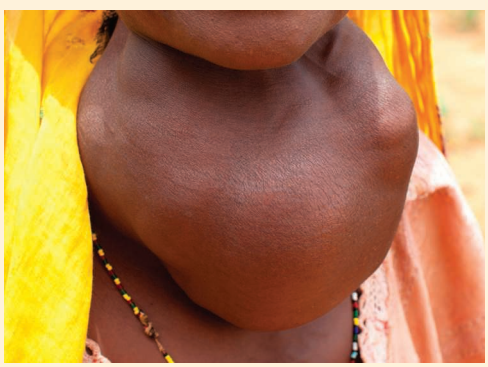
Background Information

Grace manages a business, has several employees, and works hard to make time for her husband and two children. Over several months, she slowly noticed that she was sweating excessively and appeared flushed. In addition, she often felt her heart pounding, was much more nervous than usual, and found it difficult to concentrate. Then Grace began to feel weak and lose weight, even though her appetite was greater than normal. Her family recognized some of these changes and noticed that her eyes seemed larger than usual. They encouraged her to see her physician. After an examination and some blood tests, Grace was diagnosed with Graves disease, a type of hyperthyroidism. Graves disease is caused by altered regulation of hormone secretion—specifically, the elevated secretion of thyroid hormones from the thyroid gland. In approximately 95% of Graves disease cases, the immune system produces an unusual antibody type, which binds to receptors on the cells of the thyroid follicle and stimulates them to secrete increased amounts of thyroid hormone. The secretion of the releasing hormone and thyroid-stimulating hormone is inhibited by elevated thyroid hormones. However, the antibody is produced in large amounts and is not inhibited by thyroid hormones. A very elevated rate of thyroid hormone secretion is therefore maintained. In addition, the size of the thyroid gland increases. Enlargement of the thyroid gland is called a goiter. Connective tissue components are deposited behind the eyes, causing them to bulge (figure 18.23).

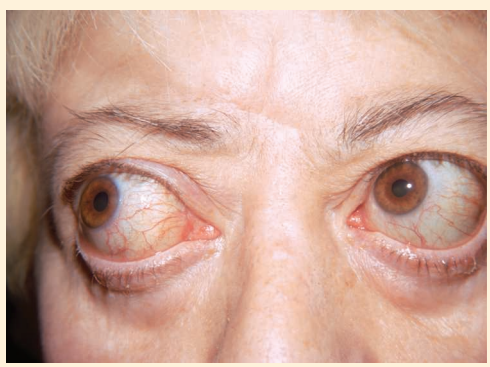
Grace was treated with radioactive iodine (^{131}I) atoms that were actively transported into thyroid cells, where they destroyed a substantial portion of the thyroid gland. Data indicate that this treatment has few side effects and is effective in treating most cases of Graves disease. Other options include (1) drugs that inhibit the synthesis and secretion of thyroid hormones and (2) surgery to remove part of the thyroid gland. Unfortunately, removal of the thyroid gland normally does not reverse exophthalmos. Figure 18.24 shows the effects Graves disease has on the other systems in the body. Table 18.14 lists some other representative endocrine diseases and disorders.

Predict 13

Explain why removal of part of the thyroid gland is an effective treatment for Graves disease.



(a)



(b)

FIGURE 18.23 Effects of Graves Disease

(*a*) A goiter and (*b*) protruding eyes are symptoms of hyperthyroidism. (a) ©Mike Goldwater/Alamy; (b) ©Ralph C. Eagle, Jr./Science Source

Examples of autocrine chemical messengers include chemical mediators of inflammation derived from the fatty acid arachidonic (ă-rak-i-don′ik) acid, such as eicosanoids and modified phospholipids. The eicosanoids include prostaglandins (pros′tă-glan-dinz), thromboxanes (throm′bok-zānz), prostacyclins (pros-tă-sī′klinz), and leukotrienes (loo′kō-trī′enz). An example of a modified phospholipid is platelet-activating factor (see chapter 19). Paracrine chemical messengers include substances that play a role in modulating the sensation of pain, such as **endorphins** (en′dōr-finz), **enkephalins** (en-kef′ă-linz), prostaglandins, and several peptide growth factors, such as **epidermal growth factor, fibroblast growth factor,** and **interleukin-2** (in-ter-loo′kin; table 18.13).

Prostaglandins, thromboxanes, prostacyclins, and leukotrienes are released from injured cells and are responsible for initiating some of the symptoms of inflammation (see chapter 22), in addition to being released from certain healthy cells. For example, prostaglandins are involved in the regulation of uterine contractions during menstruation and childbirth, the process of ovulation, the inhibition of progesterone synthesis by the corpus luteum, the regulation of coagulation, kidney function, and the modification of the effect of other hormones on their target tissues. Pain receptors are stimulated directly by prostaglandins and other inflammatory compounds, and prostaglandins cause vasodilation of blood vessels, which is

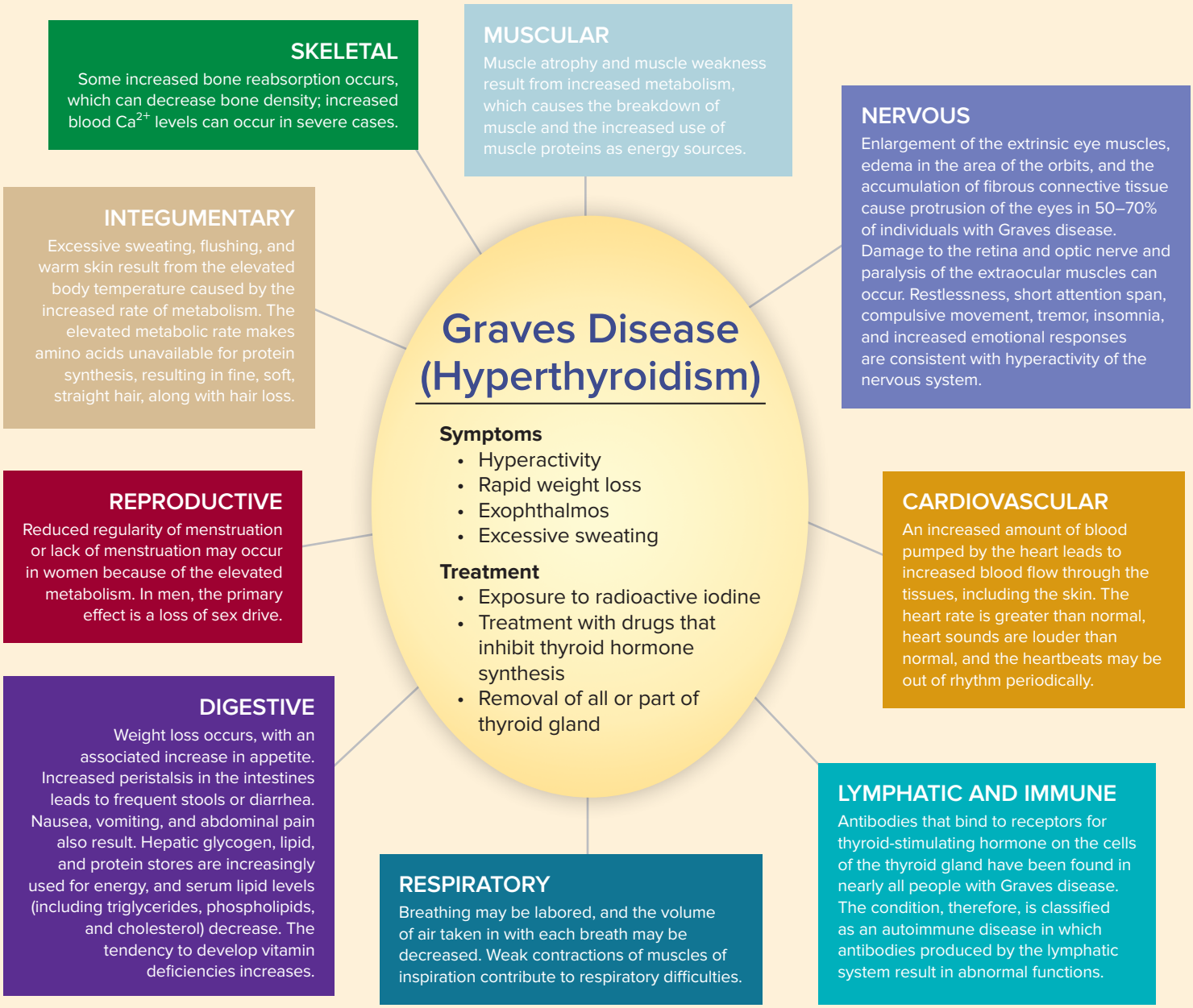


FIGURE 18.24 Interactions Between Graves Disease and Other Systems in the Body

Patients with Graves disease have higher-than-normal thyroid hormone levels, which increases the activity of most body systems.

associated with headaches. Anti-inflammatory drugs, such as aspirin, inhibit prostaglandin synthesis and, as a result, reduce inflammation and pain. These examples are paracrine chemical messengers because they are synthesized and secreted by the cells near their target cells. Once prostaglandins enter the blood, they are metabolized rapidly.

Three classes of peptide molecules, which are endogenously produced analgesics, bind to the same receptors as morphine. They include enkephalins, endorphins, and **dynorphins** (dī′nōr-finz). They are produced in several body sites, such as in parts of the brain, pituitary gland, spinal cord, and intestines. They act as neurotransmitters in some neurons of both the central and the peripheral nervous systems and as hormones or paracrine regulatory substances. In general, they moderate the sensation of pain (see chapter 14). Decreased sensitivity to painful stimuli during exercise and stress may result from the increased secretion of these substances.

Several proteins can be classified as growth factors. They generally function as paracrine chemical messengers because they are secreted near their target tissues. Epidermal growth factor stimulates cell divisions in a number of tissues and plays an important role in embryonic development. Interleukin-2 stimulates the proliferation of T lymphocytes and plays a very important role in immune responses (see chapter 22).

TABLE 18.14 Representative Diseases and Disorders of the Endocrine System

Condition	Description
Diabetes insipidus	Due to a lack of ADH from the posterior pituitary; results in excessive urination
Hashimoto thyroiditis	Autoimmune disease in which thyroid hormone secretion can be decreased; metabolic rate is decreased, weight gain is possible and activity levels are depressed
Primary hyperparathyroidism	90% of cases due to adenoma of the parathyroid gland; causes blood PTH levels to increase above normal; elevated blood Ca^{2+} levels, weakened bones, and possible muscular weakness
Addison disease	Low levels of aldosterone and cortisol from the adrenal cortex; low blood Na^{+} levels, low blood pressure, and excessive urination
Gestational diabetes	Develops in pregnant women due to actions of the placental hormone, human placental lactogen (HPL); in some women, HPL overly desensitizes the woman's insulin receptors; causes elevated blood glucose levels in the mother and, if left untreated, excessive fetal growth

The number of hormonelike substances in the body is large, and only a few of them have been mentioned here. Chemical communication among body cells is complex, well developed, and necessary to maintain homeostasis. Investigations into chemical regulation increase our knowledge of body functions—knowledge that can be used to develop new treatments for pathological conditions.

ASSESS YOUR PROGRESS

61. *What hormone is secreted by the thymus? What is its function?*

62. *What function do the hormones secreted by the stomach and small intestine perform?*

63. *What is the difference between an autocrine and a paracrine chemical messenger?*

64. *List eicosanoids and modified phospholipids that function as autocrine chemical messengers, and explain how they work.*

65. *List examples of paracrine chemical messengers that play a role in modulating pain or are peptide growth factors.*

66. *Describe the paracrine functions of prostaglandins and how anti-inflammatory drugs can reduce pain and inflammation.*

18.11 Effects of Aging on the Endocrine System

LEARNING OUTCOME

After reading this section, you should be able to

A. **Describe major age-related changes that occur in the endocrine system.**

Age-related changes in the endocrine system are not the same for all of the endocrine glands. Some, but not all, undergo a gradual decrease in secretory activity. In addition, some decreases in the secretory activity of endocrine glands appear to be secondary to a decrease in physical activity as people age.

GH secretion decreases as people grow older. The decrease is greater in people who do not exercise, but it may not occur at all in those who exercise regularly. Decreasing GH secretion may explain the gradual decrease in lean body mass. For example, bone mass and muscle mass decrease as GH levels decline. At the same time, the proportion of adipose tissue increases.

Melatonin secretion decreases in aging people. This decrease may influence age-related changes in sleep patterns and the secretory patterns of other hormones, such as GH and testosterone.

The secretion of thyroid hormones decreases slightly with increasing age, and the T_3:T_4 ratio decreases. However, this may be less of a decrease in the secretory activity of the thyroid gland than a compensation for the decreased lean body mass in aging people. Age-related damage to the thyroid gland by the immune system can occur and is more common in women than in men. As a result, approximately 10% of elderly women's thyroid glands do not produce enough T_3 and T_4.

Parathyroid hormone secretion does not appear to decrease with age. Blood levels of Ca^{2+} may decline slightly because of reduced dietary calcium intake and vitamin D levels. The greatest risk is loss of bone matrix as parathyroid hormone increases to maintain blood levels of Ca^{2+} within their normal range.

Reproductive hormone secretion gradually declines in elderly men, and women experience menopause, as described in chapter 28.

The ability to regulate blood glucose levels does not decline with age. However, there is an age-related probability of developing type 2 diabetes mellitus for those who have the familial tendency, and the incidence of the condition is correlated with age-related increases in body weight.

Secretion of thymosin from the thymus decreases with age. Fewer immature lymphocytes are able to mature and become functional, and the immune system becomes less effective in protecting the body. Thus, people's susceptibility to infection and to cancer increases.

ASSESS YOUR PROGRESS

67. *Describe age-related changes in the secretion of the following hormones and the consequences of each: GH, melatonin, thyroid hormones, reproductive hormones, and thymosin.*

68. *Which hormone does not appear to decrease with age?*

Answer

Learn to Predict

The first piece of information is that, although Dylan is always hungry and eating, he is losing weight. You learned in this chapter that two of the most important hormones for metabolism and blood glucose regulation are insulin and glucagon. The disease most often affiliated with disruptions in insulin regulation is diabetes mellitus. Normally, insulin allows for glucose to enter the body's cells for energy production, but in cases of diabetes mellitus, insufficient insulin causes excessive circulating blood glucose. When coupled with Dylan's other symptoms, chronic thirst and urination, there is a clear link to diabetes mellitus. Recall from chapter 3 that membrane transport proteins can be saturated by their transport molecule. The reason Dylan is always thirsty is that too much glucose is filtered out of his blood in his kidneys to be reabsorbed; the excess filtered glucose saturates its transport molecule. In the filtrate, the glucose has an osmotic effect and prevents the kidneys from conserving water. The sweet, or acetone, breath is derived from the fact that, when starved from glucose, cells begin to catalyze lipids, and the by-products of this metabolism are acetone and other molecules chemically related to acetone. Dylan was treated with injectable insulin and began to feel much better. However, if Dylan keeps eating candy and drinking sugary soda, elevated blood glucose levels will continue to dehydrate Dylan and his neurons can become dehydrated. This would cause him to feel irritable and unwell. Dylan may also experience a sudden weight gain because of sugar intake while injecting insulin. His cells will be able to use the extra glucose and may convert it to adipose tissue. Dylan should eat a healthy diet and avoid sugary foods.

Answers to the odd-numbered Predict questions from this chapter appear in appendix E.

Summary

18.1 Overview of the Endocrine System

The main regulatory functions of the endocrine system are metabolism, control of food intake and digestion, tissue maturation, ion regulation, water balance, heart rate and blood pressure regulation, control of blood glucose and other nutrients, control of reproductive functions, uterine contractions and milk letdown, and immune system regulation.

18.2 Pituitary Gland and Hypothalamus

1. The pituitary gland secretes at least nine hormones that regulate numerous body functions as well as other endocrine glands.
2. The hypothalamus regulates pituitary gland activity through neurohormones and action potentials.

Structure of the Pituitary Gland

1. The posterior pituitary develops from the floor of the brain and consists of the infundibulum and the neurohypophysis.
2. The anterior pituitary develops from the roof of the mouth.

Relationship of the Pituitary Gland to the Brain: The Hypothalamus

1. The hypothalamohypophysial tract connects the hypothalamus and the posterior pituitary.
   - Neurohormones are produced in hypothalamic neurons.
   - The neurohormones move down the axons of the tract and are secreted from the posterior pituitary.
2. The hypothalamohypophysial portal system connects the hypothalamus and the anterior pituitary.
   - Neurohormones are produced in hypothalamic neurons.
   - Through the portal system, the neurohormones inhibit or stimulate hormone production in the anterior pituitary.

Hormones of the Pituitary Gland

1. ADH promotes water retention by the kidneys.
2. Oxytocin promotes uterine contractions during delivery and causes milk letdown in lactating women.
3. GH is sometimes called somatotropin.
   - GH stimulates growth in most tissues and regulates metabolism.
   - GH stimulates the uptake of amino acids and their conversion into proteins and stimulates the breakdown of lipids and the synthesis of glucose.
   - GH stimulates the production of somatomedins; together, they promote bone and cartilage growth.
   - GH secretion increases in response to an increase in blood amino acids, low blood glucose, or stress.
   - GH is regulated by GHRH and somatostatin.
4. TSH, or thyrotropin, causes the release of thyroid hormones.
5. ACTH is derived from proopiomelanocortin; it stimulates cortisol secretion from the adrenal cortex and increases skin pigmentation.
6. Several hormones in addition to ACTH are derived from proopiomelanocortin.
   - Lipotropins cause lipid breakdown.
   - β endorphins play a role in analgesia.
   - MSH increases skin pigmentation.
7. LH and FSH are major gonadotropins.
   - Both hormones regulate the production of gametes and reproductive hormones (testosterone in males, estrogen and progesterone in females).
   - GnRH from the hypothalamus stimulates LH and FSH secretion.
8. Prolactin stimulates milk production in lactating females. Prolactin-releasing hormone (PRH) and prolactin-inhibiting hormone (PIH) from the hypothalamus affect prolactin secretion.

18.3 Thyroid Gland

1. The thyroid gland is just inferior to the larynx.
2. The thyroid gland is composed of small, hollow balls of cells called follicles, which contain thyroglobulin.
3. Parafollicular cells are scattered throughout the thyroid gland.

Thyroid Hormones

1. T_3 and T_4 synthesis occurs in thyroid follicles.
   - Iodide ions are taken into the follicles by active transport, oxidized, and bound to tyrosine molecules in thyroglobulin.
   - Thyroglobulin is secreted into the follicle lumen. Tyrosine molecules with iodine combine to form T_3 and T_4 thyroid hormones.
   - Thyroglobulin is taken into the follicular cells and broken down; T_3 and T_4 diffuse from the follicles to the blood.
2. T_3 and T_4 are transported in the blood.
   - T_3 and T_4 bind to thyroxine-binding globulin and other plasma proteins.
   - The plasma proteins prolong the half-life of T_3 and T_4 and regulate the levels of T_3 and T_4 in the blood.
   - Approximately one-third of the T_4 is converted into functional T_3.
3. T_3 and T_4 bind with nuclear receptor molecules and initiate new protein synthesis.
4. T_3 and T_4 affect nearly every tissue in the body.
   - T_3 and T_4 increase the rate of glucose, lipid, and protein metabolism in many tissues, thus increasing body temperature.
   - Normal growth of many tissues is dependent on T_3 and T_4.
5. TRH and TSH regulate T_3 and T_4 secretion.
   - Increased TSH from the anterior pituitary increases T_3 and T_4 secretion.
   - TRH from the hypothalamus increases TSH secretion. TRH increases as a result of chronic exposure to cold, food deprivation, and stress.
   - T_3 and T_4 inhibit TSH and TRH secretion.

Calcitonin

1. An increase in blood calcium levels stimulates calcitonin secretion by the parafollicular cells.
2. Calcitonin decreases blood calcium and phosphate levels by inhibiting osteoclasts.

18.4 Parathyroid Glands

1. The parathyroid glands are embedded in the thyroid gland.
2. PTH increases blood calcium levels.
   - PTH stimulates osteoclasts.
   - PTH promotes calcium reabsorption by the kidneys and the formation of active vitamin D by the kidneys.
   - Active vitamin D increases calcium absorption by the intestine.
3. A decrease in blood calcium stimulates PTH secretion.

18.5 Adrenal Glands

1. The adrenal glands are near the superior poles of the kidneys.
2. The adrenal medulla arises from neural crest cells and functions as part of the sympathetic nervous system. The adrenal cortex is derived from mesoderm.
3. The adrenal medulla is composed of closely packed cells.
4. The adrenal cortex is divided into three layers: the zona glomerulosa, the zona fasciculata, and the zona reticularis.

Hormones of the Adrenal Medulla

1. Epinephrine accounts for 80% and norepinephrine for 20% of the adrenal medulla hormones.
   - Epinephrine increases blood glucose levels, the use of glycogen and glucose by skeletal muscle, and heart rate and force of contraction. It also causes vasoconstriction in the skin and viscera and vasodilation in skeletal and cardiac muscle.
   - Norepinephrine and epinephrine stimulate cardiac muscle and cause the constriction of most peripheral blood vessels.
2. The adrenal medulla hormones prepare the body for physical activity.
3. Release of adrenal medulla hormones is mediated by the sympathetic nervous system in response to emotions, injury, stress, exercise, and low blood glucose.

Hormones of the Adrenal Cortex

1. The zona glomerulosa secretes the mineralocorticoids, especially aldosterone. Aldosterone acts on the kidneys to increase sodium and to decrease potassium and hydrogen levels in the blood.
2. The zona fasciculata secretes glucocorticoids, especially cortisol.
   - Cortisol increases lipid and protein breakdown, increases glucose synthesis from amino acids, decreases the inflammatory response, and is necessary for the development of some tissues.
   - ACTH from the anterior pituitary stimulates cortisol secretion. CRH from the hypothalamus stimulates ACTH release. Low blood glucose levels and stress stimulate CRH secretion.
3. The zona reticularis secretes androgens. In females, androgens stimulate axillary and pubic hair growth and sex drive.

18.6 Pancreas

1. The pancreas, located along the small intestine and the stomach, is both an exocrine and an endocrine gland.
2. The exocrine portion of the pancreas consists of a complex duct system, which ends in small sacs, called acini, that produce pancreatic digestive juices.
3. The endocrine portion consists of the pancreatic islets. Each islet is composed of alpha cells, which secrete glucagon; beta cells, which secrete insulin; and delta cells, which secrete somatostatin.

Effect of Insulin and Glucagon on Their Target Tissues

1. Insulin's target tissues are the liver, adipose tissue, muscle, and the satiety center in the hypothalamus. The nervous system is not a target tissue, but it does rely on blood glucose levels maintained by insulin.
2. Insulin increases the uptake of glucose and amino acids by cells. Glucose is used for energy or is stored as glycogen. Amino acids are used for energy or are converted to glucose or proteins.
3. Glucagon's target tissue is mainly the liver.
4. Glucagon causes the breakdown of glycogen and lipids for use as an energy source.

Regulation of Pancreatic Hormone Secretion

1. Insulin secretion increases because of elevated blood glucose levels, an increase in some amino acids, parasympathetic stimulation, and gastrointestinal hormones. Sympathetic stimulation decreases insulin secretion.

2. Glucagon secretion is stimulated by low blood glucose levels, certain amino acids, and sympathetic stimulation.
3. Somatostatin inhibits insulin and glucagon secretion.

18.7 Hormonal Regulation of Nutrient Utilization

1. After a meal, the following events take place:
   - High glucose levels inhibit glucagon, cortisol, GH, and epinephrine, which reduces the release of glucose from tissues.
   - Insulin secretion increases as a result of the high blood glucose levels, thereby increasing the uptake of glucose, amino acids, and lipids, which are used for energy or stored.
   - Sometime after the meal, blood glucose levels drop. Glucagon, GH, cortisol, and epinephrine levels increase, insulin levels decrease, and glucose is released from tissues.
   - Adipose tissue releases fatty acids, triglycerides, and ketones, which most tissues use for energy.
2. During exercise, the following events occur:
   - Sympathetic activity increases epinephrine and glucagon secretion, causing a release of glucose into the blood.
   - Low blood sugar levels, caused by the uptake of glucose by skeletal muscles, stimulate epinephrine, glucagon, GH, and cortisol secretion, causing an increase in fatty acids, triglycerides, and ketones in the blood, all of which are used for energy.

18.8 Hormones of the Reproductive System

The ovaries, testes, placenta, and pituitary gland secrete reproductive hormones.

18.9 Hormones of the Pineal Gland

The pineal gland produces melatonin and arginine vasotocin, which can inhibit reproductive maturation and may regulate sleep-wake cycles.

18.10 Other Hormones and Chemical Messengers

1. The thymus produces thymosin, which is involved in the development of the immune system.
2. The digestive tract produces several hormones that regulate digestive functions.
3. Autocrine and paracrine chemical messengers are produced by many cells of the body and usually have a local effect on body functions.
4. Eicosanoids, such as prostaglandins, prostacyclins, thromboxanes, and leukotrienes, are derived from fatty acids and mediate inflammation and other functions. Endorphins, enkephalins, and dynorphins are analgesic substances. Growth factors influence cell division and growth in many tissues, and interleukin-2 influences cell division in the T cells of the immune system.

18.11 Effects of Aging on the Endocrine System

A gradual decrease in the secretion rate occurs for most, but not all, hormones. Some of these decreases are related to gradual decreases in physical activity.

REVIEW AND COMPREHENSION

1. The pituitary gland
   a. develops from the floor of the brain.
   b. develops from the roof of the mouth.
   c. is stimulated by neurohormones produced in the midbrain.
   d. secretes only three major hormones.
   e. Both a and b are correct.
2. The hypothalamohypophysial portal system
   a. contains one capillary bed.
   b. carries hormones from the anterior pituitary to the body.
   c. carries hormones from the posterior pituitary to the body.
   d. carries hormones from the hypothalamus to the anterior pituitary.
   e. carries hormones from the hypothalamus to the posterior pituitary.
3. Which of these hormones is *not* secreted into the hypothalamohypophysial portal system?
   a. GHRH c. PIH e. ACTH
   b. TRH d. GnRH
4. Which of these stimulates the secretion of ADH?
   a. elevated blood osmolality
   b. decreased blood osmolality
   c. release of hormones from the hypothalamus
   d. ACTH
   e. increased blood pressure
5. Oxytocin is responsible for
   a. preventing milk letdown from the mammary glands.
   b. preventing goiter.
   c. causing contraction of the uterus.
   d. maintaining normal calcium levels.
   e. increasing the metabolic rate.
6. Growth hormone
   a. increases the usage of glucose.
   b. increases the breakdown of lipids.
   c. decreases the synthesis of proteins.
   d. decreases the synthesis of glycogen.
   e. All of these are correct.
7. Which of these hormones stimulates somatomedin secretion?
   a. FSH d. prolactin
   b. GH e. TSH
   c. LH
8. Hypersecretion of growth hormone
   a. results in gigantism if it occurs in children.
   b. causes acromegaly in adults.
   c. increases the probability that a person will develop diabetes.
   d. can lead to severe atherosclerosis.
   e. All of these are correct.

9. LH and FSH
   a. are produced in the hypothalamus.
   b. production is increased by TSH.
   c. promote the production of gametes and reproductive hormones.
   d. inhibit the production of prolactin.
   e. All of these are correct.

10. T_3 and T_4
   a. require iodine for their production.
   b. are made from the amino acid tyrosine.
   c. are transported in the blood bound to thyroxine-binding globulin.
   d. All of these are correct.

11. Which of these symptoms is associated with hyposecretion of thyroid hormones?
   a. hypertension
   b. nervousness
   c. diarrhea
   d. weight loss with either normal or increased food intake
   e. decreased metabolic rate

12. Choose the statement that most accurately predicts the long-term effect of exposure to a substance that prevents the active transport of iodide by the thyroid gland.
   a. Large amounts of T_3 and T_4 accumulate within the thyroid follicles, but little is released.
   b. The person exhibits hypothyroidism.
   c. The anterior pituitary secretes smaller amounts of TSH.
   d. The circulating levels of T_3 and T_4 increase.

13. Calcitonin
   a. is secreted by the parathyroid glands.
   b. levels increase when blood calcium levels decrease.
   c. causes blood calcium levels to decrease.
   d. insufficiency results in weak bones and tetany.

14. Parathyroid hormone secretion increases in response to
   a. a decrease in blood calcium levels.
   b. increased production of parathyroid-stimulating hormone from the anterior pituitary.
   c. increased secretion of parathyroid-releasing hormone from the hypothalamus.
   d. increased secretion of calcitonin.
   e. decreased secretion of ACTH.

15. If parathyroid hormone levels increase, which of these conditions is expected?
   a. Osteoclast activity increases.
   b. Calcium absorption from the small intestine is inhibited.
   c. Calcium reabsorption from the urine is inhibited.
   d. Less active vitamin D forms in the kidneys.
   e. All of these are correct.

16. The adrenal medulla
   a. produces steroids.
   b. secretes cortisol as its major product.
   c. decreases its secretions during exercise.
   d. forms from a modified portion of the sympathetic division of the ANS.
   e. All of these are correct.

17. In the condition in which a benign tumor results in hypersecretion of hormones from the adrenal medulla, expected symptoms include
   a. hypotension.
   b. bradycardia (slow heart rate).
   c. pallor (decreased blood flow to the skin).
   d. lethargy.
   e. hypoglycemia.

18. Which of these is *not* a hormone secreted by the adrenal cortex?
   a. aldosterone
   b. androgens
   c. cortisol
   d. epinephrine

19. If aldosterone secretions increase,
   a. blood potassium levels increase.
   b. blood hydrogen levels increase.
   c. acidosis results.
   d. blood sodium levels decrease.
   e. blood volume increases.

20. Glucocorticoids (cortisol)
   a. increase the breakdown of lipids.
   b. increase the breakdown of proteins.
   c. increase blood glucose levels.
   d. decrease inflammation.
   e. All of these are correct.

21. Which of these is (are) expected in Cushing syndrome (hypersecretion of adrenal cortex hormones)?
   a. loss of hair in women
   b. deposition of adipose tissue in the face, neck, and abdomen
   c. low blood glucose
   d. low blood pressure
   e. All of these are correct.

22. Within the pancreas, the pancreatic islets produce
   a. insulin.
   b. glucagon.
   c. digestive enzymes.
   d. Both a and b are correct.
   e. All of these are correct.

23. Insulin increases
   a. the uptake of glucose by its target tissues.
   b. the breakdown of protein.
   c. the breakdown of lipids.
   d. glycogen breakdown in the liver.
   e. All of these are correct.

24. Glucagon
   a. primarily affects the liver.
   b. causes glycogen to be stored.
   c. causes blood glucose levels to decrease.
   d. decreases lipid metabolism.
   e. performs all of these functions.

25. When blood glucose levels increase, the secretion of which of these hormones increases?
   a. glucagon
   b. insulin
   c. GH
   d. cortisol
   e. epinephrine

26. If a person who has diabetes mellitus has forgotten to take an insulin injection, the symptoms that may soon appear include
   a. acidosis.
   b. hyperglycemia.
   c. increased urine production.
   d. lethargy and fatigue.
   e. All of these are correct.

27. Which of the following is *not* a hormone produced by the ovaries?
    a. estrogen
    b. progesterone
    c. prolactin
    d. inhibin
    e. relaxin
28. Melatonin
    a. is produced by the posterior pituitary.
    b. production increases as day length increases.
    c. inhibits the development of the reproductive system.
    d. increases GnRH secretion from the hypothalamus.
    e. decreases the tendency to sleep.
29. Which of these substances, produced by many body tissues, can promote inflammation, pain, and vasodilation of blood vessels?
    a. endorphins
    b. enkephalins
    c. thymosin
    d. epidermal growth factor
    e. prostaglandins
30. Which of these secretions does *not* decrease with aging of the endocrine system?
    a. GH secretion
    b. melatonin secretion
    c. thyroid hormone secretion
    d. parathyroid hormone secretion

Answers appear in appendix F.

CRITICAL THINKING

1. The hypothalamohypophysial portal system connects the hypothalamus with the anterior pituitary. Why is such a special circulatory system advantageous?
2. A patient exhibits polydipsia (thirst), polyuria (excess urine production), and urine with a low specific gravity (contains few ions and no glucose). If you wanted to reverse the symptoms, would you administer insulin, glucagon, ADH, or aldosterone? Explain.
3. A patient complains of headaches and visual disturbances. A casual glance reveals enlarged finger bones, a heavy deposition of bone over the eyes, and a prominent jaw. The doctor determines that the headaches and visual disturbances result from increased pressure within the skull and that the presence of a pituitary tumor is affecting hormone secretion. Name the hormone causing the problem, and explain why increased pressure exists within the skull.
4. Most laboratories are able to determine blood levels of TSH, T_3, and T_4. Given that ability, design a method of determining whether hyperthyroidism in a patient results from a pituitary abnormality or from the production of a nonpituitary thyroid stimulatory substance.
5. Over the past year, Julie has gradually gained weight. The increase in adipose tissue is distributed over her trunk, face, and neck, and her muscle mass appears to be decreased. Julie also feels weak and bruises easily. Her physician suspects Cushing syndrome and orders a series of blood tests. The results reveal elevated blood levels of cortisol and ACTH. There is no evidence of an extrapituitary source of ACTH. Predict the cause of Julie's condition and the treatments that are likely to be recommended.
6. An anatomy and physiology instructor asks two students to predict a patient's response to chronic vitamin D deficiency. One student claims the person would suffer from hypocalcemia. The other student claims the calcium levels would remain within their normal range, although at the low end, and that bone reabsorption would occur to the point that advanced osteomalacia might occur. With whom do you agree, and why?
7. A patient arrives at the emergency room in an unconscious condition. A medical emergency bracelet reveals that he has diabetes. The patient is in either diabetic coma or insulin shock. How can you tell which, and what treatment do you recommend for each condition?
8. Predict some of the consequences of exposure to intense and prolonged stress.
9. Katie was getting nervous. At 16, she was the only one in her group of friends who had not started menstruating. Katie had always dreamed of having three beautiful children someday and she was worried. Her mother took her to see Dr. Josephine, who ordered several blood tests. When the results came back, Dr. Josephine gently explained to Katie and her mother that Katie would never be able to have children and would never menstruate. Dr. Josephine then asked Katie to wait in the outer room while she spoke privately to her mother. She explained to Katie's mom that Katie has androgen insensitivity syndrome. Though Katie is genetically male and her gonads produce more of the male reproductive hormone, testosterone, than the female reproductive hormone, estrogen, Katie did not reflect the tissue changes expected. What malfunction in Katie's body would cause this? Why does Katie's body look feminine if she is genetically male?

Answers to odd-numbered questions appear in appendix G.

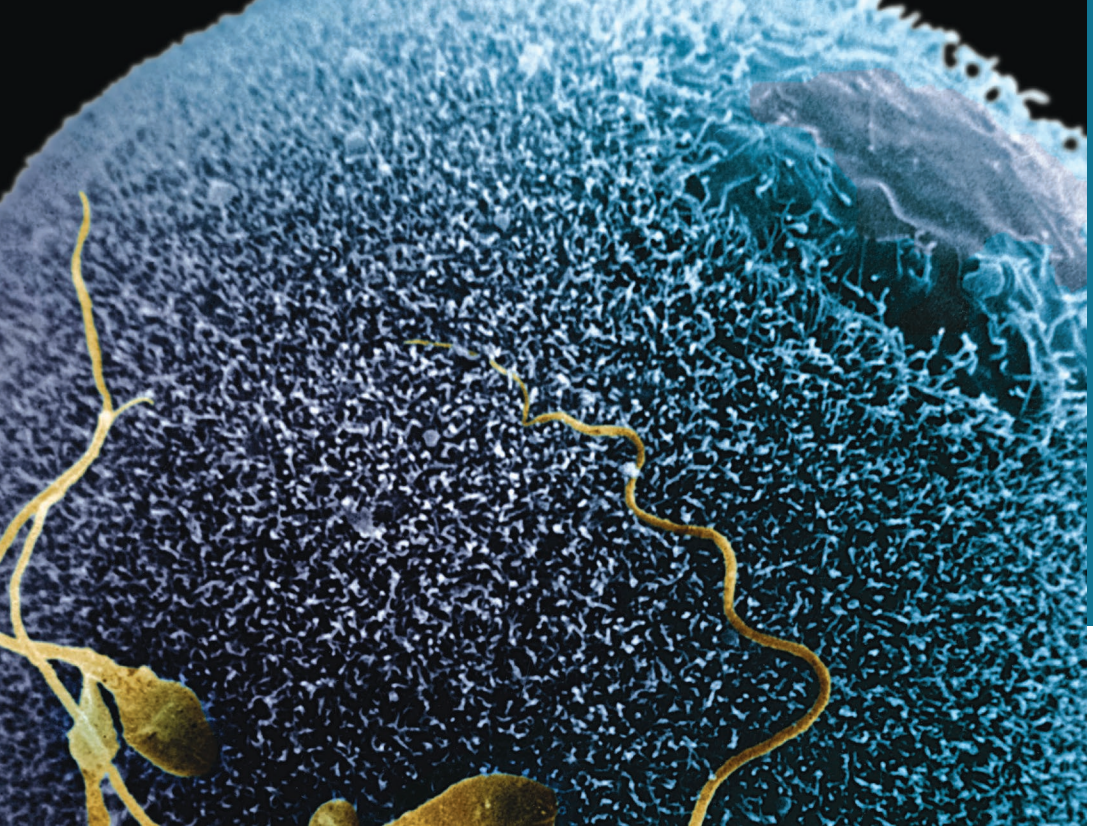


Photo: Color-enhanced scanning electron micrograph of a human oocyte and sperm cells. ©David M. Phillips/ Science Source

28

Reproductive System

Learn to Predict

Chase and Christina were studying for their last anatomy and physiology exam of the semester. After reviewing his notes on meiosis, Chase said, "Well, since gametogenesis is exactly the same in males and females, I don't need to study the notes from the female reproductive system lecture." Christina quickly pointed out that he was wrong and that if he reviewed his notes he would see that gametogenesis is very different in males and females. **After reading chapter 28, explain the major differences between gametogenesis in males and females.**

The reproductive system functions in **gametogenesis,** the process of gamete production, as well as the events involved in fertilization of these gametes. In addition, the female reproductive system ensures the product of fertilization, a new human, is protected and nourished. However, the reproductive systems also influence many other aspects of a person's life, anatomically, physiologically, as well as psychologically. In this chapter, the basic anatomical and physiological characteristics of the male and female reproductive systems will be discussed.

The male and female reproductive systems are obviously different, but these two systems also have numerous similarities. Many reproductive organs of males and females are derived from the same embryological structures (see chapter 29), and some of the same hormones function in both males and females, even though these hormones influence traits differently in males and females.

28.1 Functions of the Reproductive System

LEARNING OUTCOMES

After reading this section, you should be able to

A. **List the functions of the reproductive system.**
B. **Distinguish among the functions that occur in males, females, and both.**

Reproduction is an essential characteristic of living organisms, and functional male and female reproductive systems are necessary for humans to reproduce. In addition, even in individuals who do not reproduce, the reproductive system plays important roles. The reproductive system performs the following functions:

1. *Gametogenesis.* Gametogenesis is the production of gametes, which are reproductive cells that are produced in the gonads. The male gonads are the testes, which are the site of sperm cell production. The female gonads are the ovaries, which are the site of oocyte (egg) production.
2. *Fertilization.* The reproductive system enables fertilization of the oocyte by the sperm. The duct system in males nourishes sperm cells until they are mature and are deposited in the female reproductive tract by the penis. The female reproductive system receives the sperm cells from the male and provides a passageway for them to the fertilization site.
3. *Development and nourishment of a new individual*. The female reproductive system nurtures the developing fetus in the uterus until birth and provides nourishment (breast milk) after birth.
4. *Production of reproductive hormones*. Hormones produced by the reproductive system control its development and the development of the sex-specific body form (table 28.1). These hormones are also essential for the routine functions of the reproductive system and for reproductive behavior.

ASSESS YOUR PROGRESS

Answers to these questions are found in the section you have just completed. Re-read the section if you need help in answering these questions.

1. *What are the functions of the reproductive system?*
2. *What functions occur in both males and females, and what functions occur only in females?*

28.2 Meiosis

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe the process of meiosis, highlighting the change in chromosome number and structure after each division.**
B. **Explain why meiosis is necessary in sexually reproducing organisms.**
C. **Describe the different events in meiosis that result in genetic variation among gametes.**

Meiosis (mī-ō′sis) is a type of cell division specialized for sexual reproduction. During meiosis, one cell undergoes two consecutive divisions to produce four genetically different daughter cells. Each of these daughter cells contains half as many chromosomes as the parent cell (figure 28.1). In humans, meiosis occurs only in the testes and ovaries and produces sperm cells in males and oocytes in females.

In humans, the somatic cells normally have 46 chromosomes, called the **diploid** (dip′loyd) number (2*n*). Chromosomes exist in 23 **homologous** (hŏ-mol′ō-gŭs) **pairs**—22 autosomal pairs and 1 pair of sex chromosomes. One chromosome of each homologous pair is inherited from the male parent, and the other chromosome of each pair is inherited from the female parent. The chromosomes of each homologous pair are alike in size and shape and contain genes for the same traits, with the exception of the X chromosome and Y chromosome. The combination of sex chromosomes is known as the sexual karyotype. The female sexual karyotype is two X chromosomes; the male sexual karyotype includes one X chromosome and one Y chromosome. Though the X and Y chromosomes pair during meiosis, they are not the same size nor do they carry the same genetic information (see figure 29.25).

Sperm cells and oocytes contain the **haploid** (hap′loyd) number (***n***) of chromosomes, or 23. Each gamete contains one chromosome from each of the homologous pairs. Reduction in the number of chromosomes in sperm cells or oocytes to a haploid number is important. When a sperm cell and an oocyte fuse to form a fertilized egg, each provides a haploid number of chromosomes, which reestablishes a diploid number. If meiosis did not take place, the number of chromosomes in the fertilized oocyte would double each time fertilization occurred, and the extra chromosomal material would be lethal to the developing offspring.

Upon fertilization, the sex of the baby is determined by the sperm cell. The baby is male if the oocyte is fertilized by a Y-carrying sperm cell or female if it is fertilized by an X-carrying sperm cell. Though the sexual karyotype determines the development of the reproductive system (see section 29.1), other factors also influence the psychological development of an individual (see Clinical Impact 28.1).

The two divisions of meiosis are called **meiosis I** and **meiosis II.** The stages of meiosis have the same names as the stages of mitosis—that is, prophase, metaphase, anaphase, and telophase—but distinct differences exist between mitosis and meiosis. See section 3.10 for a review of mitosis.

Before meiosis begins, all the chromosomes are duplicated. At the beginning of meiosis, each of the 46 chromosomes consists of two sister **chromatids** (krō′mă-tids) connected by a **centromere** (sen′trō-mēr; figure 28.1, *step 1*). In prophase I, the chromosomes become visible, and the homologous pairs come together in a process called **synapsis** (si-nap′sis). Because each chromosome consists of two chromatids, the pairing of the homologous chromosomes brings two chromatids of each chromosome close together, an arrangement called a **tetrad** (figure 28.1, *step 2*). Occasionally, part of a chromatid of one homologous chromosome breaks off and is exchanged with part of another chromatid from the other homologous chromosome. This exchange of genetic material between maternal and paternal chromosomes is called

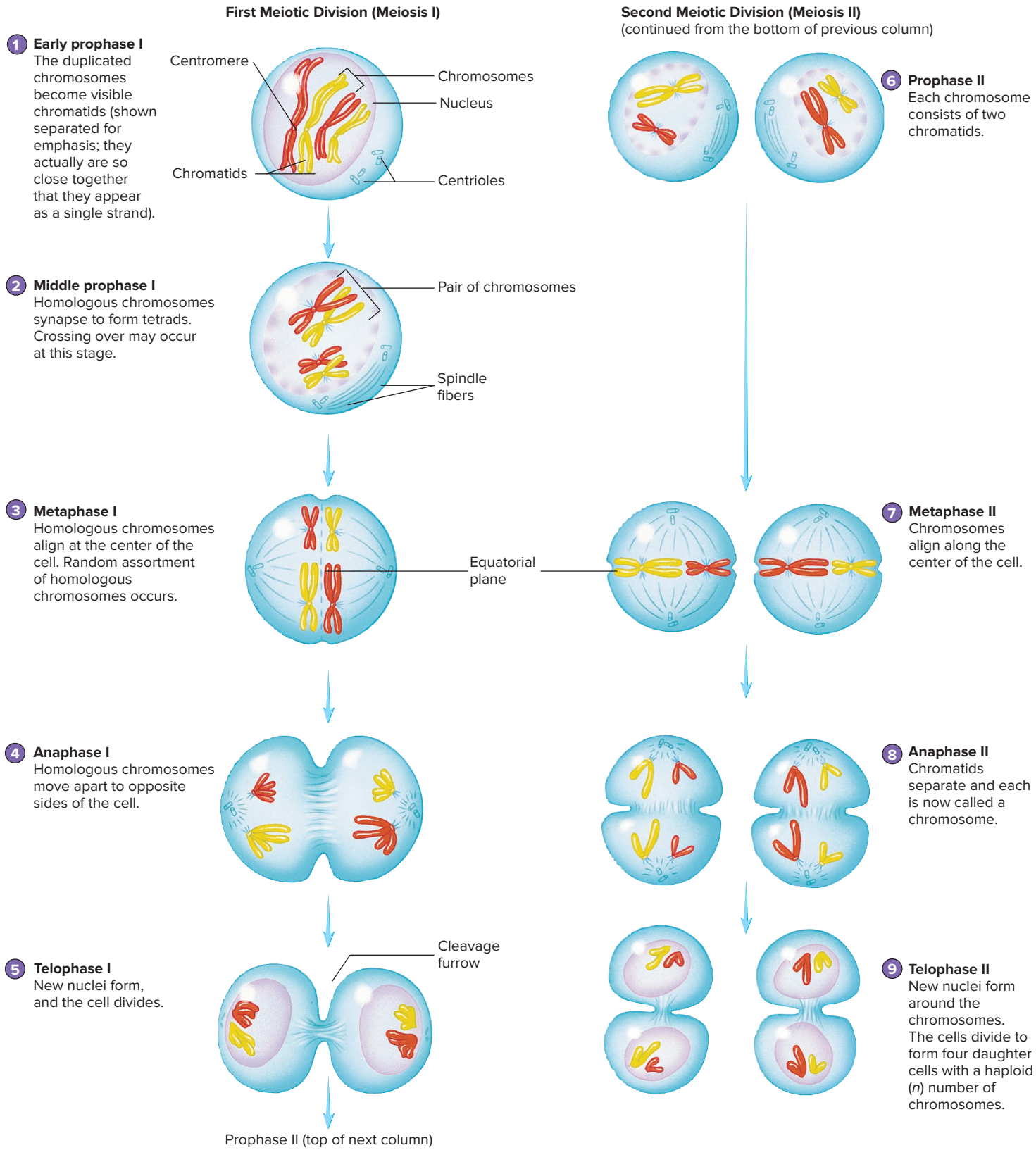
TABLE 28.1 **Major Reproductive Hormones and Their Effects**

Hormone	Source	Target Tissue	Response
Males			
Gonadotropin-releasing hormone (GnRH)	Hypothalamus	Anterior pituitary	Stimulates secretion of LH and FSH
Luteinizing hormone (LH) (also called interstitial cell–stimulating hormone [ICSH] in males)	Anterior pituitary	Interstitial cells in the testes	Stimulates synthesis and secretion of testosterone
Follicle-stimulating hormone (FSH)	Anterior pituitary	Seminiferous tubules (sustentacular cells)	Supports spermatogenesis
Testosterone	Interstitial cells in the testes	Testes and body tissues	Supports spermatogenesis; stimulates development and maintenance of reproductive organs; causes development of secondary sexual characteristics
		Anterior pituitary and hypothalamus	Inhibits GnRH, LH, and FSH secretion through negative feedback
Females			
Gonadotropin-releasing hormone (GnRH)	Hypothalamus	Anterior pituitary	Stimulates production of LH and FSH
Luteinizing hormone (LH)	Anterior pituitary	Ovaries	Causes follicles to complete maturation and undergo ovulation; causes ovulated follicle to become the corpus luteum
Follicle-stimulating hormone (FSH)	Anterior pituitary	Ovaries	Causes follicles to begin development
Prolactin	Anterior pituitary	Mammary glands	Stimulates milk secretion following childbirth
Estrogen	Follicles of ovaries	Uterus	Causes proliferation of endometrial cells
		Mammary glands	Causes development of mammary glands (especially duct systems)
		Anterior pituitary and hypothalamus	Has a positive-feedback effect before ovulation, resulting in increased LH and FSH secretion; has a negative-feedback effect, with progesterone, on the hypothalamus and anterior pituitary after ovulation, resulting in decreased LH and FSH secretion
		Other tissues	Causes development of secondary sexual characteristics
Progesterone	Corpus luteum of ovaries	Uterus	Causes hypertrophy of endometrial cells and secretion of fluid from uterine glands; helps maintain pregnancy
		Mammary glands	Causes development of mammary glands (especially alveoli)
		Anterior pituitary	Has a negative-feedback effect, with estrogen, on the hypothalamus and anterior pituitary after ovulation, resulting in decreased LH and FSH secretion
		Other tissues	Causes development of secondary sexual characteristics
Oxytocin*	Posterior pituitary	Uterus and mammary glands	Causes contraction of uterine smooth muscle during intercourse and childbirth; causes contraction of myoepithelial cells in the breast, resulting in milk letdown in lactating women
Human chorionic gonadotropin (hCG)	Placenta	Corpus luteum of ovaries	Maintains corpus luteum and increases its rate of progesterone secretion during the first one-third (first trimester) of pregnancy; increases testosterone production in testes of male fetuses

*Covered in chapter 29.

crossing over and may result in new gene combinations on the chromosomes.

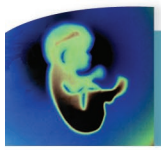
During metaphase I, homologous pairs of chromosomes line up near the center of the cell (figure 28.1, *step 3*). For each homologous pair, however, the orientation of the maternal and paternal chromosomes is random. The way the chromosomes align during synapsis results in the random assortment of maternal and paternal chromosomes in the daughter cells during meiosis. Crossing over and the random assortment of maternal and paternal chromosomes are responsible for the large degree of diversity in the



PROCESS FIGURE 28.1 Meiosis

During meiosis, the chromosome number is halved in preparation for sexual reproduction. AP|R

? *How many chromosomes would an oocyte contain if during anaphase II, the chromatids of one chromosome did not separate?*



Clinical IMPACT 28.1 Gender and Sex

At birth, people are assigned one of three biological sexes based solely on the anatomy of their external genitalia. Males have a penis, females have a vagina, and intersex people can have a wide variation in sexual characteristics. However, anatomy does not always dictate a person's gender identity. Gender identity is how people view and express themselves in the world. Biological sex also does not determine a person's sexual orientation. Sexual orientation is the interpersonal interactions people have with others with regard to physical, emotional, and romantic attraction. Sexual orientation also does not determine sexual preference. Sexual preference refers to the way a person wishes to receive and participate in physically intimate actions.

Until about the 1990s, the societal norm for humans in the United States consisted of a gender binary. The gender binary is the system of viewing gender as consisting of only two identities and two sexes: male and female. However, since the 1990s, it has been recognized that gender exists along a gender spectrum, sometimes referred to as nonbinary. The gender spectrum is a continuum of gender identity that includes male and female, but does not assert male and female as absolutes or as polar opposites. For parents of a gender-expansive child, one who goes against societal norms for gender identity, the first source of information is usually a medical professional. This means that physicians, nurses, and all medical professionals are put into a pivotal role of helping to provide understanding and resources to parents.

An immense set of terms exists to describe gender identity, sexual orientation, and sexual preference. Here, we provide a brief introduction to some of these terms:

1. Gender identity—how individuals view themselves; gender identity can be the same or different than the sex assigned to them at birth
2. Gender expression—how individuals present themselves in terms of appearance, behavior, clothing, haircut, etc.
3. Gender nonconforming—behaving in a way that does not conform to societal expectation of biological sex
4. Queer—a previously derogatory term used for certain sexual orientations, but now is used to express fluid identities and orientations; usually used by people who do not identify as straight (heterosexual)
5. Transgender—individuals whose gender identity and/or gender expression is not the same as societal expectations based on their assigned biological sex. Although this does not imply a particular sexual orientation, it can be described as an FtM (F2M), female to male, transition or an MtF (M2F), a male to female, transition when individuals begin to express the knowledge of their internal identity by their outward appearance.
6. Gender dysphoria—the term used to describe the long-term distress individuals experience when their assigned biological sex does not align with their gender identity
7. Gay—the sexual attraction and affectional orientation between members of the same gender (assigned or expressed); refers to males and females
8. Pansexual—not limited in attraction to an individual with regard to biological sex, gender, or gender identity
9. Lesbian—the sexual attraction and affectional orientation between two females (assigned or expressed)
10. Bisexual—being sexually, emotionally, and physically attracted to people of both the same gender and another gender

genetic composition of sperm cells and oocytes produced by each individual.

During anaphase I, the homologous pairs are separated to each side of the cell (figure 28.1, *step 4*). During telophase I, new nuclei form, and the cell completes division of the cytoplasm to form two cells (figure 28.1, *step 5*). As a consequence, when meiosis I is complete, each daughter cell has 1 chromosome from each homologous pair. Since the chromosome number is reduced from a diploid number (46 chromosomes, or 23 pairs) to a haploid number (23 chromosomes, or 1 from each homologous pair) during meiosis I, this division is often called a **reduction division.**

At the end of meiosis I, each of the 23 chromosomes in the daughter cells still consists of two chromatids. The separation of the chromatids of the duplicated chromosomes occurs in meiosis II. The second meiotic division is similar to mitosis (figure 28.1, *steps 6–9*). The duplicated chromosomes line up near the middle of the cell. Then the chromatids separate at the centromere, and each daughter cell receives one of the chromatids from each chromosome. When the centromere separates, each of the chromatids is called a chromosome. Consequently, each of the four daughter cells produced by meiosis contains 23 chromosomes.

ASSESS YOUR PROGRESS

3. *Describe the events of meiosis I and meiosis II. How are the cells produced by meiosis I different from the cells produced by meiosis II?*
4. *Why is meiosis important in sexually reproducing organisms?*
5. *Describe two mechanisms that occur during meiosis that produce genetic variation among gametes.*

28.3 Anatomy of the Male Reproductive System

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe the scrotum and its role in regulating the temperature of the testes.**
B. **Describe the structure of the testes, the specialized cells of the testes, and the process of spermatogenesis.**

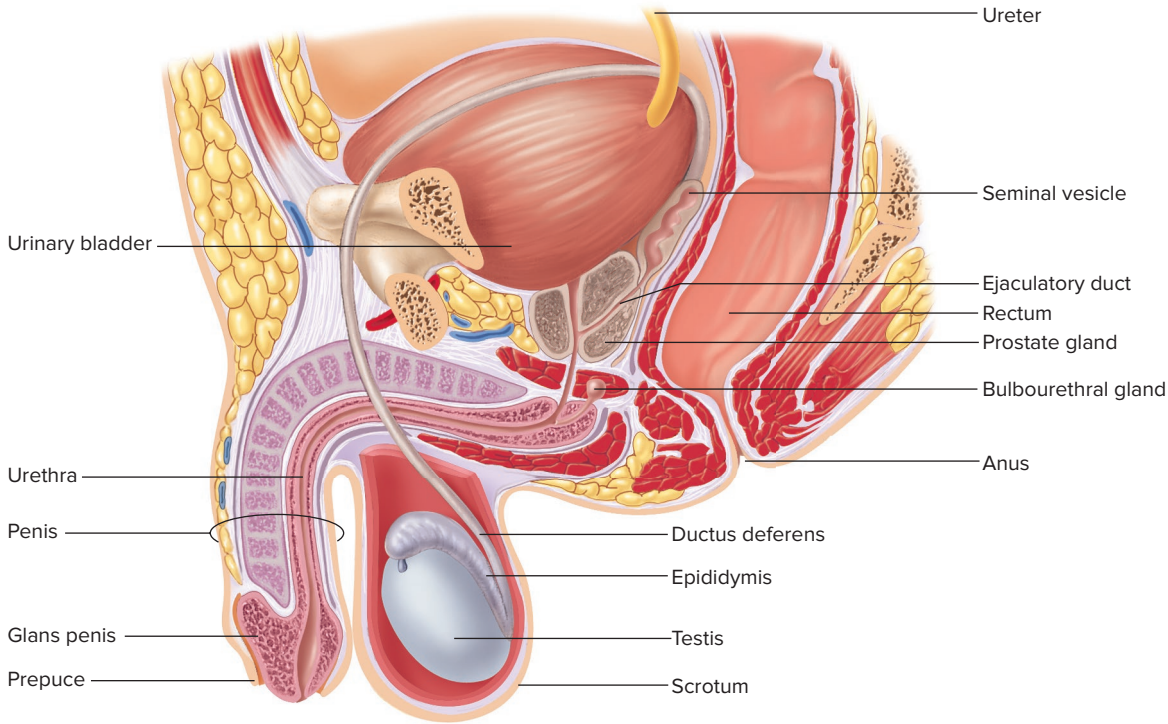


FIGURE 28.2 Male Reproductive System

Sagittal section of the male pelvis, showing the male reproductive structures. Some structures are drawn as a modified medial section to reveal the testis, epididymis, and seminal vesicles and to show the relationship of the ductus deferens to the ureter and urinary bladder. AP|R

C. **List the ducts of the male reproductive system and explain their functions.**

D. **Describe the structure of the penis, seminal vesicles, prostate gland, and bulbourethral glands and explain their functions.**

The male reproductive system consists of the testes (sing. testis), a series of ducts, accessory glands, and supporting structures. The ducts include the epididymides (sing. epididymis), the ducta deferentia (sing. ductus deferens; also vas deferens), and the urethra. Accessory glands include the seminal vesicles, the prostate gland, and the bulbourethral glands. Supporting structures include the scrotum and the penis (figure 28.2).

The testes and epididymides, in which the sperm cells develop, are located outside the body cavity in the scrotum. The ducta deferentia lead from the testes into the pelvis, where they join the ducts of the seminal vesicles to form the ampullae. Extensions of the ampullae, called the ejaculatory ducts, pass into the prostate and empty into the urethra within the prostate. The urethra, in turn, exits the pelvis and passes through the penis to the outside of the body.

Scrotum

The **scrotum** (skrō′tŭm) is a saclike structure that contains the testes. It is divided into two internal compartments by an incomplete connective tissue septum. Externally, the compartments of the scrotum are marked by a midline irregular ridge called the **raphe** (rā′fē; a seam). The raphe extends posteriorly to the anus and anteriorly onto the inferior surface of the penis.

The wall of the scrotum includes the skin, a layer of superficial fascia consisting of loose connective tissue, and a layer of smooth muscle called the **dartos** (dar′tōs) **muscle.** In cold temperatures, the dartos muscle contracts, causing the skin of the scrotum to become firm and wrinkled and reducing its overall size. At the same time, the **cremaster** (krē-mas′ter) **muscles** (see figure 28.7), which are extensions of abdominal skeletal muscles into the scrotum, contract and help pull the testes nearer the body. These changes in size and position of the scrotum help keep the testes warm. When temperature increases due to a warmer environment or as a result of exercise or fever, the dartos and cremaster muscles relax, and the skin of the scrotum becomes loose and thin, allowing the testes to descend away from the body and keep cool. The response of the dartos and cremaster muscles is important because sperm cells are very temperature-sensitive and do not develop normally if the testes become too warm or too cool.

Perineum

The **perineum** (per′i-nē′ŭm) is the area between the thighs that is bounded by the pubic symphysis anteriorly, the coccyx

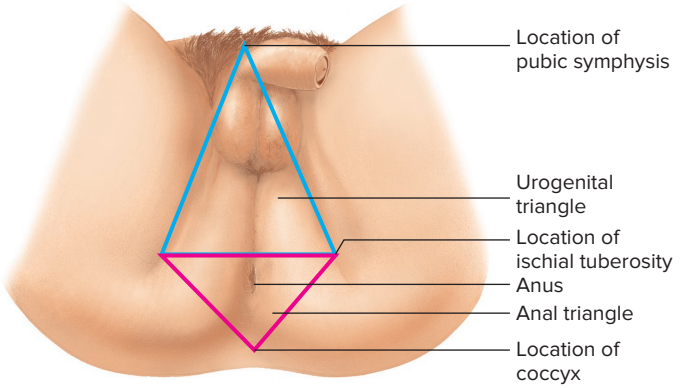


FIGURE 28.3 Male Perineum
Inferior view of the male perineum.

posteriorly, and the ischial tuberosities laterally. The perineum is divided into two triangles by the superficial transverse muscles and the deep transverse perineal muscles. These muscles run transversely between the two ischial tuberosities (see figure 10.19). The two triangles are the urogenital triangle and the anal triangle. In males, the **urogenital** (ū′rō-jen′i-tăl) **triangle,** or *anterior triangle,* contains the base of the penis and the scrotum, and the smaller **anal triangle,** or *posterior triangle,* contains the anal opening (figure 28.3). The female perineum is described later in the chapter (see section 28.5).

ASSESS YOUR PROGRESS

6. *List the structures of the male reproductive system.*
7. *Describe the structure of the scrotum.*
8. *Explain the role of the dartos and cremaster muscles in regulating the temperature of the testes.*
9. *Locate the boundaries of the perineum and the two triangles within it.*

Testes

Testicular Histology

The **testes** (tes′tēz) are small, oval-shaped organs, each about 4–5 cm long, within the scrotum (see figure 28.2). The testes function as both exocrine and endocrine glands. Their major exocrine secretion is sperm cells, and their major endocrine secretion is the hormone testosterone.

The outer part of each testis is a thick, white capsule consisting mostly of fibrous connective tissue called the **tunica albuginea** (al-bū-jin′ē-ă). Extensions of the tunica albuginea extend into the testis and form incomplete **septa** (sep′tă; figure 28.4*a*). The septa divide each testis into about 300–400 cone-shaped **lobules.** The lobules contain **seminiferous** (sem′i-nif′er-ŭs; seed carriers) **tubules,** in which sperm cells develop. Loose connective tissue surrounding the seminiferous tubules contains clusters of endocrine cells called **interstitial cells,** or *Leydig cells* (figure 28.4). The interstitial cells secrete testosterone.

The combined length of the seminiferous tubules in both testes is nearly half a mile. Considering that sperm cells are produced in the seminiferous tubules, it is not surprising that adult males are capable of producing such high numbers of gametes. The seminiferous tubules empty into a set of short, straight tubules called the **tubuli recti.** These in turn empty into a tubular network called the **rete** (rē′tē; net) **testis.** The rete testis empties into 15–20 tubules called **efferent ductules** (dŭk′tools) that pass through the tunica albuginea to exit the testis. The efferent ductules have a ciliated pseudostratified columnar epithelium, which helps move sperm cells out of the testis.

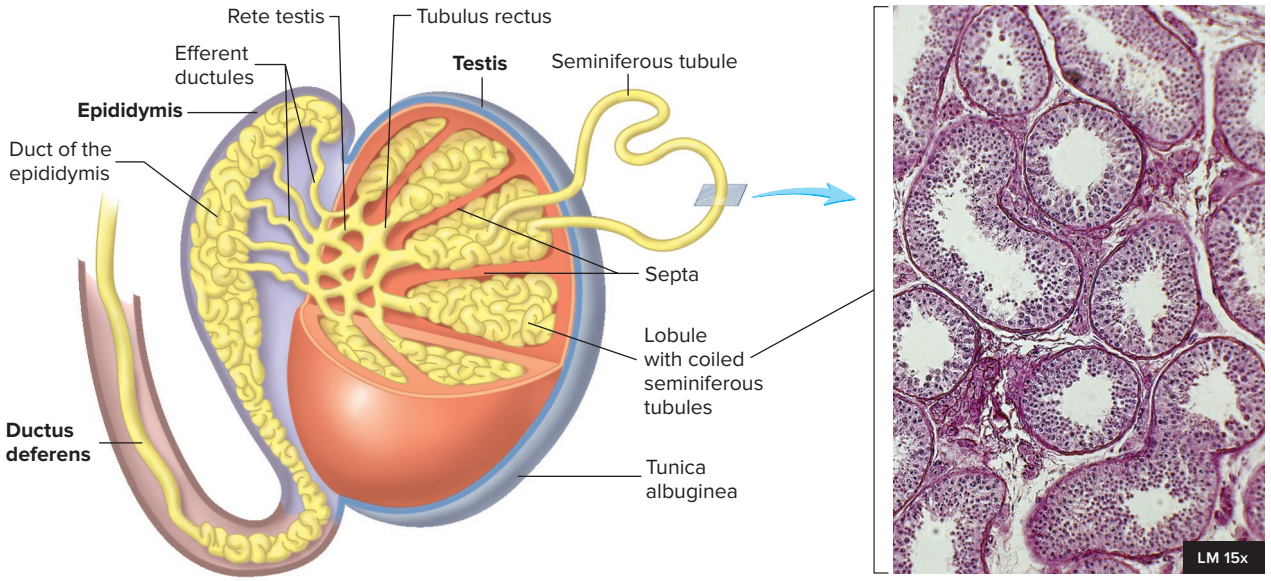
Descent of the Testes

By approximately 8 weeks following fertilization, the testes have developed as retroperitoneal organs. Initially, the testes are located high in the abdominopelvic cavity near the developing kidneys. Each testis is connected to a labioscrotal swelling by a **gubernaculum** (goo′ber-nak′ū-lŭm), a fibromuscular cord (figure 28.5, *step 1;* see chapter 29). The labioscrotal swelling becomes the scrotum. The testes descend toward the area where the **inguinal** (ing′gwi-năl) **canals** will form (figure 28.5, *step 2*). The gubernaculum extends through the inguinal canal, enlarging the canal. Between 7 and 9 months of development, the testes move through the inguinal canals into the scrotum (figure 28.5, *step 3*). As it moves into the scrotum, each testis is preceded by an outpocketing of the peritoneum called the **process vaginalis** (vaj′i-nă-lis). The superior part of each process vaginalis usually degenerates, and the inferior part remains as a small, closed sac called the **tunica** (too′ni-kă) **vaginalis** (figure 28.5, *step 4*). The tunica vaginalis is a serous membrane consisting of a layer of simple squamous epithelium resting on a basement membrane. The tunica vaginalis surrounds most of the testis in much the same way that the pericardium surrounds the heart. The tunica vaginalis secretes a small amount of fluid, which allows the testes to move in the scrotum, producing little friction.

The testes have descended into the scrotum in approximately 79% of male infants delivered prior to 28 weeks of development. In male infants delivered after 28 weeks, greater than 97% show normal testes descent. By 9 months of age, 98.2% of male infants show normal testes descent.

The inguinal canals are bilateral, oblique passageways in the anterior abdominal wall. They originate at the **deep inguinal rings,** which open through the aponeuroses of the transversus abdominis muscles. The canals extend inferiorly and obliquely and end at the **superficial inguinal rings,** openings in the aponeuroses of the external abdominal oblique muscles. In females, the inguinal canals develop, but they are much smaller than in males, and the ovaries do not normally descend through them.

Cryptorchidism (krip-tōr′ki-dizm) is the failure of one or both of the testes to descend into the scrotum. Because the higher temperature of the abdominal cavity prevents normal sperm cell development, sterility can result if both testes are involved (see chapter 29). In addition, approximately 10% of testicular cancer cases occur in men with a history of cryptorchidism.



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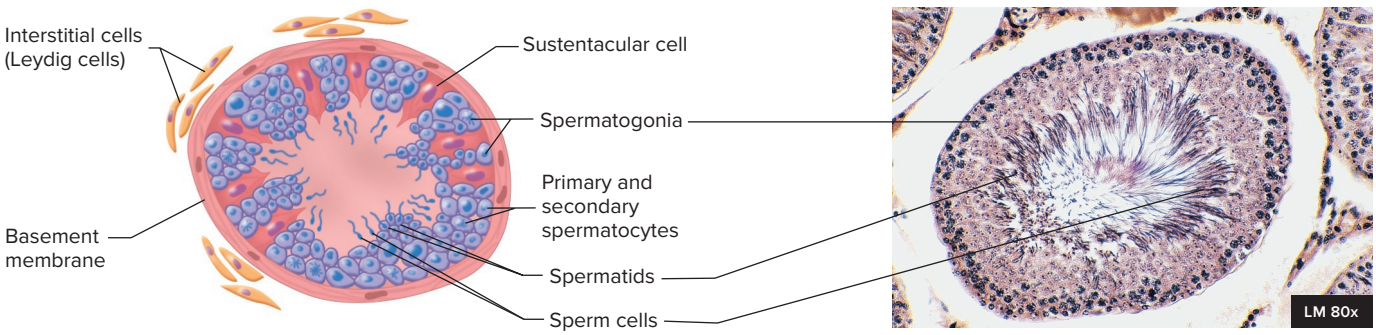

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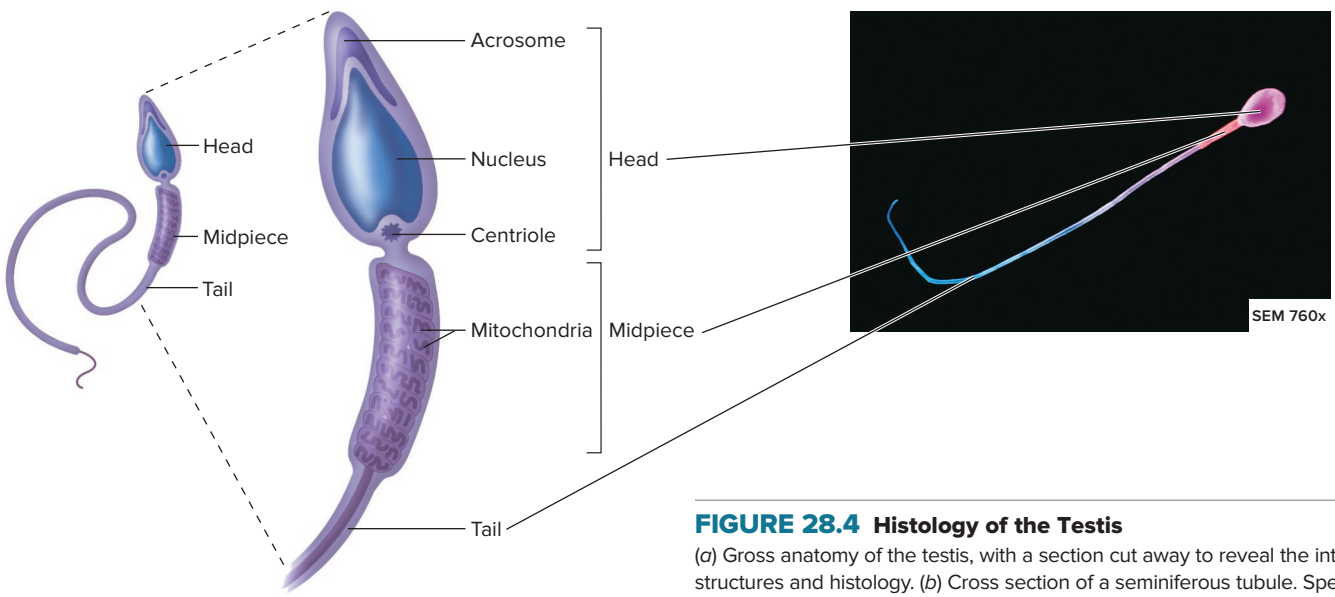
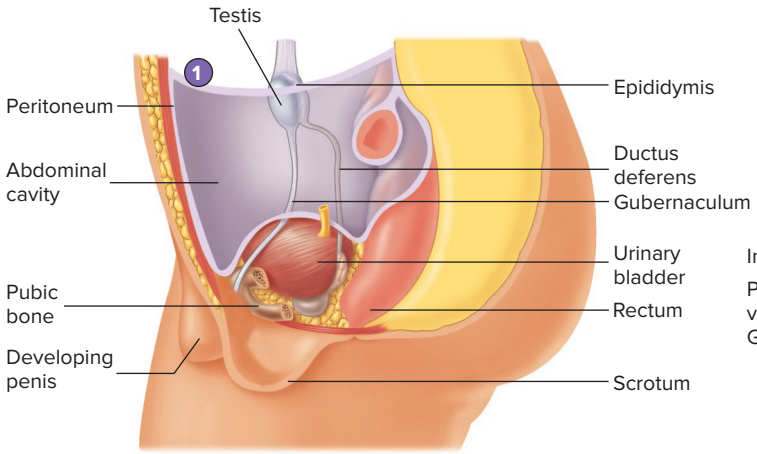


(c)

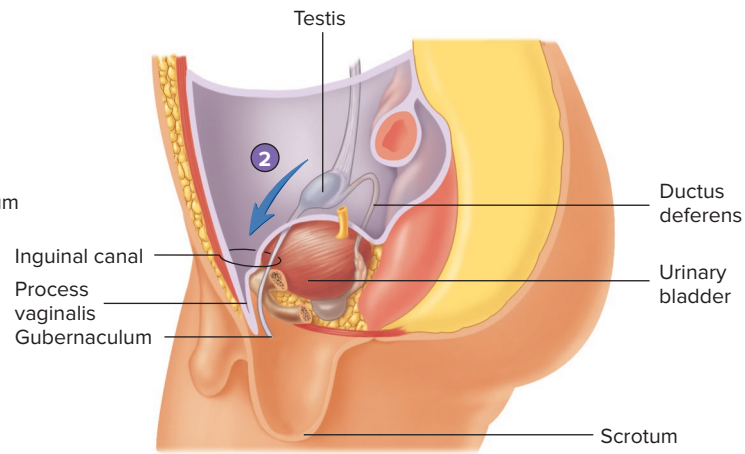
FIGURE 28.4 Histology of the Testis

(*a*) Gross anatomy of the testis, with a section cut away to reveal the internal structures and histology. (*b*) Cross section of a seminiferous tubule. Spermatogonia are near the periphery, and mature sperm cells are near the lumen of the seminiferous tubules. (*c*) The regions of a mature sperm cell include the head, midpiece, and tail. (a) ©De Agostini Picture Library/Science Source (b) ©Ken Wagner/Phototake; (c) ©Dennis Kunkel Microscopy, Inc./Phototake AP|R



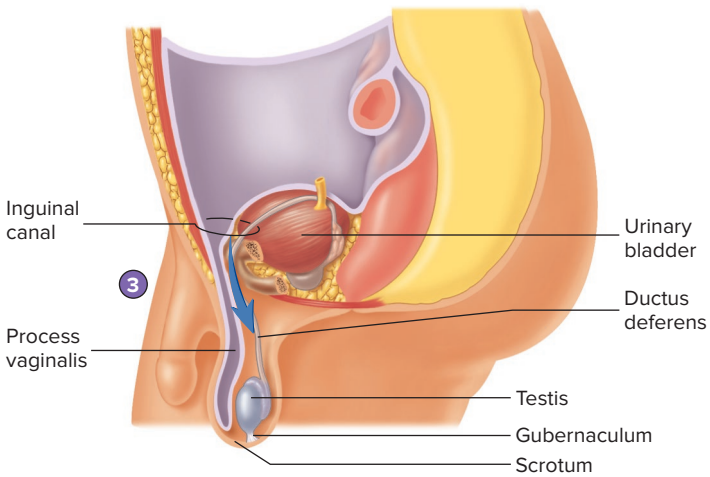
Approximately 8 weeks

1 Each testis forms as a retroperitoneal structure near the level of the kidney.



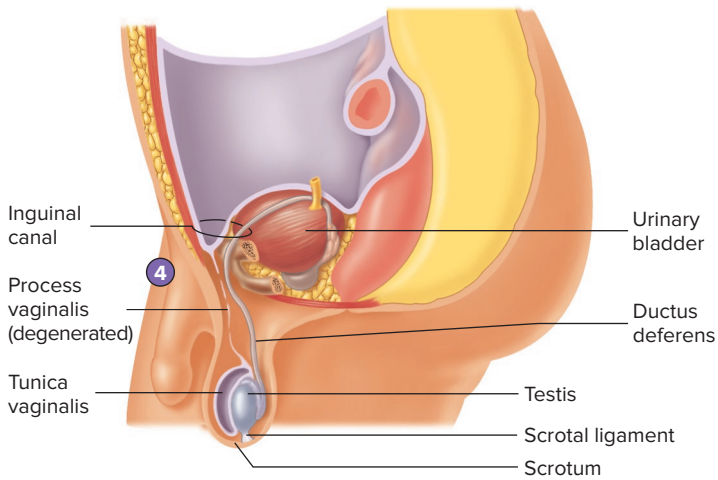
Approximately 12 weeks

2 The testis beneath the parietal peritoneum is descending toward the inguinal canal. The process vaginalis extends into the inguinal canal alongside the gubernaculum.



Between 7 and 9 months

3 The testis follows the process vaginalis and descends through the inguinal canal into the scrotum.



Adult

4 Between birth and adulthood, the superior portion of the process vaginalis degenerates and its inferior portion becomes the tunica vaginalis. The gubernaculum becomes the scrotal ligament.

PROCESS FIGURE 28.5 Descent of the Testes

The testes form within the abdominal cavity and descend into the scrotum by passing through the inquinal canal of the abdominal wall.

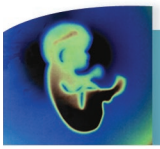
? *Propose an explanation of why males are more prone to inguinal hernias, abnormal openings in the abdominal wall, compared to females.*

ASSESS YOUR PROGRESS

10. *Describe the covering and connective tissue of the testis.*
11. *Where are the seminiferous tubules and interstitial cells located? What are their functions?*
12. *List the ducts that will move sperm from the seminiferous tubules out of the testis.*
13. *When and how do the testes descend into the scrotum?*
14. *What is the function of the tunica vaginalis?*

Spermatogenesis

Before puberty, the testes remain relatively simple and unchanged from the time of their initial development. The interstitial cells are not particularly prominent during this period, and the seminiferous tubules lack a lumen and are not yet functional. At 12–14 years of age, the interstitial cells increase in number and size, a lumen develops in each seminiferous tubule, and sperm cell production begins. It takes approximately 74 days for sperm cells to be produced. For about 50 of those days, the sperm cells are in the seminiferous tubules.



Clinical IMPACT 28.2

Inguinal Hernia

An **inguinal hernia** (her′nē-ă) is an abnormal opening in the abdominal wall in the inguinal region through which a structure, such as a portion of the small intestine, can protrude. Normally, the inguinal canals are closed, but they represent weak spots in the abdominal wall.

Inguinal hernias can be of two types—indirect or direct. If the deep inguinal ring remains open, or if it is weak and enlarges later in life, a loop of intestine can protrude into or even pass through the inguinal canal, resulting in an indirect inguinal hernia. A direct inguinal hernia results from a tear, or rupture, in a weakened area of the anterior abdominal wall near the inguinal canal, but not through the inguinal canal.

Inguinal hernias can be quite painful and even very dangerous, especially if a portion of the small intestine is compressed so that its blood supply is cut off. Fortunately, inguinal hernias can be repaired surgically. Because a male's inguinal canals are larger and weakened as a result of the testes passing through them on their way into the scrotum, males are much more prone to inguinal hernias than are females.

Spermatogenesis (sper′mă′-tō-jen′ĕ-sis), sperm cell development, occurs in the seminiferous tubules (figure 28.6*a;* see figure 28.4*b*). The seminiferous tubules contain two types of cells, germ cells and **sustentacular** (sŭs-ten-tak′ū-lăr) **cells,** or *Sertoli* (sēr-tō′lē) *cells* (also sometimes referred to as *nurse cells*).

The germ cells are the ones that divide and differentiate during spermatogenesis to form sperm cells. The sustentacular cells are large cells that extend from the periphery to the lumen of the seminiferous tubule (figure 28.6*b;* see figure 28.4*b*). The sustentacular cells nourish the germ cells and probably produce, together with the interstitial cells, a number of hormones, such as androgens, estrogens, and inhibins. In addition, tight junctions between the sustentacular cells form a **blood-testis barrier** between germ cells and sperm cells. The blood-testis barrier isolates the sperm cells from the immune system (figure 28.6*b*). This barrier is necessary because, as the sperm cells develop, they form surface antigens that could stimulate an immune response, resulting in their destruction.

Interstitial cells secrete testosterone, which passes into the sustentacular cells and binds to intracellular receptors. This binding enables the sustentacular cells to function normally. In addition, testosterone in the sustentacular cells is converted to two other steroids: (1) **dihydrotestosterone** (dī-hī′drō-testos′ter-ōn) and (2) **estradiol,** a specific type of estrogen. These are then secreted as hormones by the sustentacular cells. The sustentacular cells also secrete a protein called **androgen-binding** (an′drō-jen) **protein** into the seminiferous tubules. Testosterone and dihydrotestosterone bind to androgen-binding protein and are carried along with other secretions of the seminiferous tubules to the epididymis. Estradiol and dihydrotestosterone may be the active hormones that promote sperm cell formation.

Germ cells are partially embedded in the sustentacular cells (figure 28.6). The most peripheral cells, those adjacent to the basement membrane of the seminiferous tubules, are **spermatogonia** (sper′mă-tō-gō′nē-ă), which divide by mitosis (figure 28.6*a, step 1*). Some of the daughter cells produced from these mitotic divisions remain spermatogonia and continue to produce additional spermatogonia. Other daughter cells differentiate to form **primary spermatocytes** (sper′mă-tō-sītz), which divide by meiosis (figure 28.6*a, step 2;* see figure 28.1).

Spermatogenesis begins when the primary spermatocytes divide. Each primary spermatocyte passes through the first meiotic division to produce two **secondary spermatocytes** (figure 28.6*a, step 2*). Each secondary spermatocyte undergoes a second meiotic division to produce two even smaller cells called **spermatids** (sper′mă-tidz; figure 28.6*a, step 3*). Each spermatid contains one of each of the homologous pairs of chromosomes. Therefore, each sperm cell contains 23 chromosomes, 22 autosomes, and either an X or a Y chromosome. Each spermatid undergoes the last phase of spermatogenesis, called **spermiogenesis** (sper′mē-ō-jen′ĕ-sis), to form a mature **sperm cell,** or *spermatozoon* (sper′mă-tō-zō′on; pl. spermatozoa, sper′mă-tō-zō′ă; figure 28.6*a, step 4;* see figure 28.4*c,d*). During spermiogenesis, each spermatid develops a head, a midpiece, and a tail, or flagellum. The nucleus of the sperm is located in the head. Just anterior to the nucleus is a vesicle called the **acrosome** (ak′rō-sōm), which contains enzymes necessary for the sperm cell to penetrate the female oocyte (see figure 28.4*c*). The flagellum is similar to a cilium (see chapter 3), and microtubules within the flagellum move, propelling the sperm cell forward. The midpiece contains large numbers of mitochondria, which produce the ATP necessary for microtubule movement.

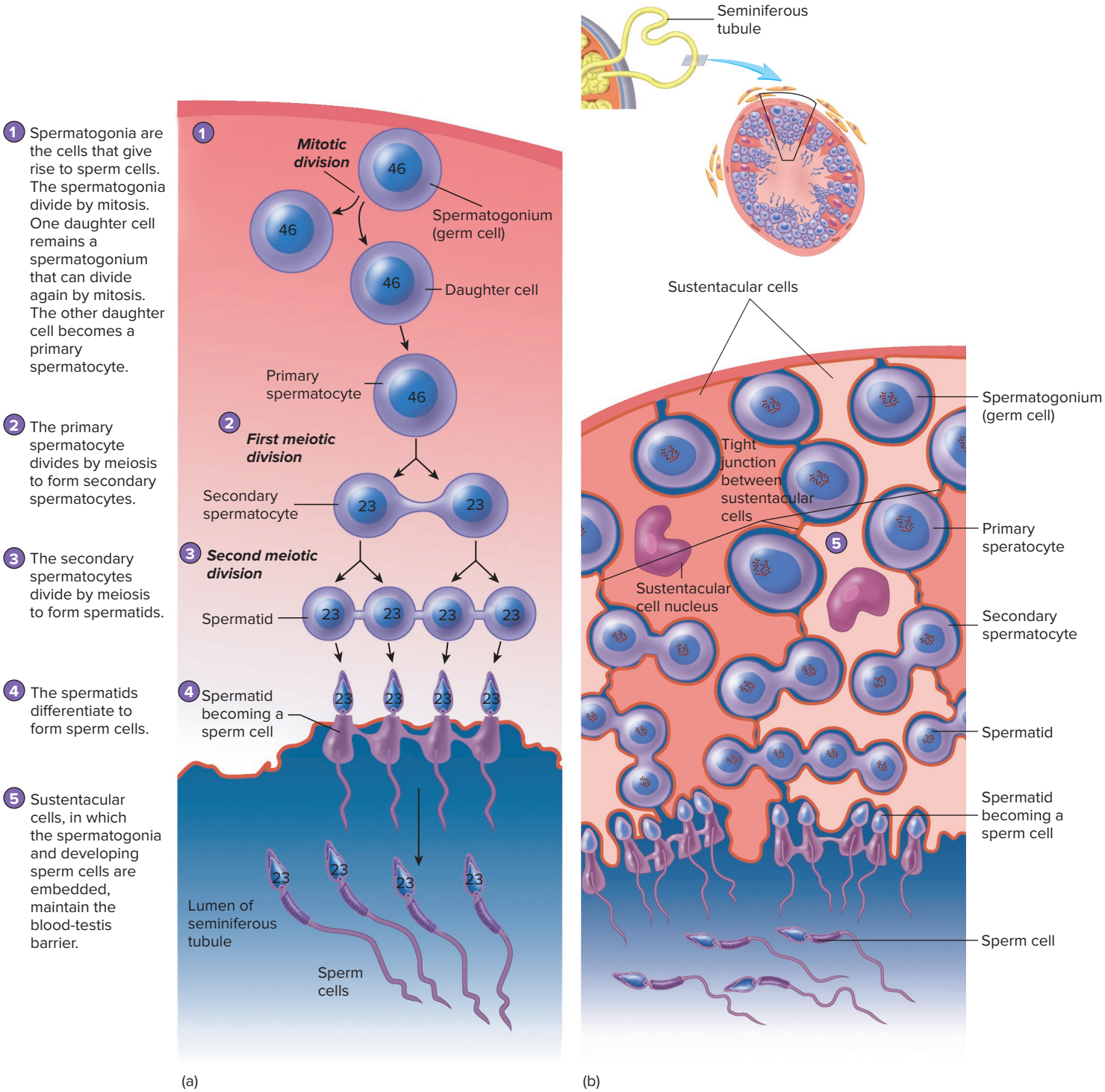
At the end of spermatogenesis, the developing sperm cells gather around the lumen of the seminiferous tubules, with their heads directed toward the surrounding sustentacular cells and their tails directed toward the center of the lumen (figure 28.6; see figure 28.4*b*). Finally, sperm cells are released into the lumen of the seminiferous tubules.

ASSESS YOUR PROGRESS

15. *Describe the role of germ cells, sustentacular cells, and the blood-testis barrier in the structure of the seminiferous tubules.*
16. *Describe the conversion of testosterone to other hormones in the sustentacular cells.*
17. *Where, specifically, are sperm cells produced in the testis?*
18. *Describe the role of meiosis in sperm cell formation.*
19. *List the parts of a mature sperm. What are their functions? Explain the events of spermiogenesis.*

Ducts

After being released into the seminiferous tubules, the sperm cells pass through a series of ducts from the interior of the testes until they



PROCESS FIGURE 28.6 **Spermatogenesis**

(*a*) Meiosis during spermatogenesis. A section of a seminiferous tubule illustrating the process of meiosis and sperm cell formation. (*b*) The sustentacular cells extend from the periphery to the lumen of the seminiferous tubules shown in alternating dark and light shades for emphasis. The tight junctions that form between adjacent sustentacular cells form the blood-testis barrier. Spermatogonia are peripheral to the blood-testis barrier, and spermatocytes are central to it. AP|R

? *Given that each secondary spermatocyte has 23 chromosomes, how is it possible that at the end of meiosis II, each of the four spermatids also has 23 chromosomes?*

potentially exit the body through the urethra. Specifically, sperm cells in the seminiferous tubules move through the tubuli recti to the rete testis. From the rete testis, they pass through the efferent ductules, which leave the testis and enter the epididymis. The sperm cells then leave the epididymis, passing through the ductus deferens, ejaculatory duct, and urethra to the exterior of the body.

Epididymis

The efferent ductules from each testis become extremely convoluted and form a comma-shaped structure on the posterior side of the testis called the **epididymis** (ep-i-did′i-mis; pl. epididymides, ep-i-di-dim′i-dēz). Each epididymis consists of a head, a body, and a long tail (figure 28.7). The head contains the convoluted efferent ductules, which empty into the **duct of the epididymis,** a single convoluted tube located primarily within the body of the epididymis (see figure 28.4*a*). This duct alone, if unraveled, would extend for several meters. The duct of the epididymis has a pseudostratified columnar epithelium with elongated microvilli called **stereocilia** (ster′ē-ō-sil′ē-ă). The stereocilia increase the surface area of epithelial cells that absorb fluid from the lumen of the duct of the epididymis. The duct of the epididymis ends at the tail of the epididymis, which is located at the inferior border of the testis.

The final maturation of the sperm cells occurs within the epididymis. It takes 12–16 days for sperm to travel through the epididymis and appear in the ejaculate. Several structural and functional changes occur in sperm cells as they pass through the epididymis. Structural changes include a further reduction in

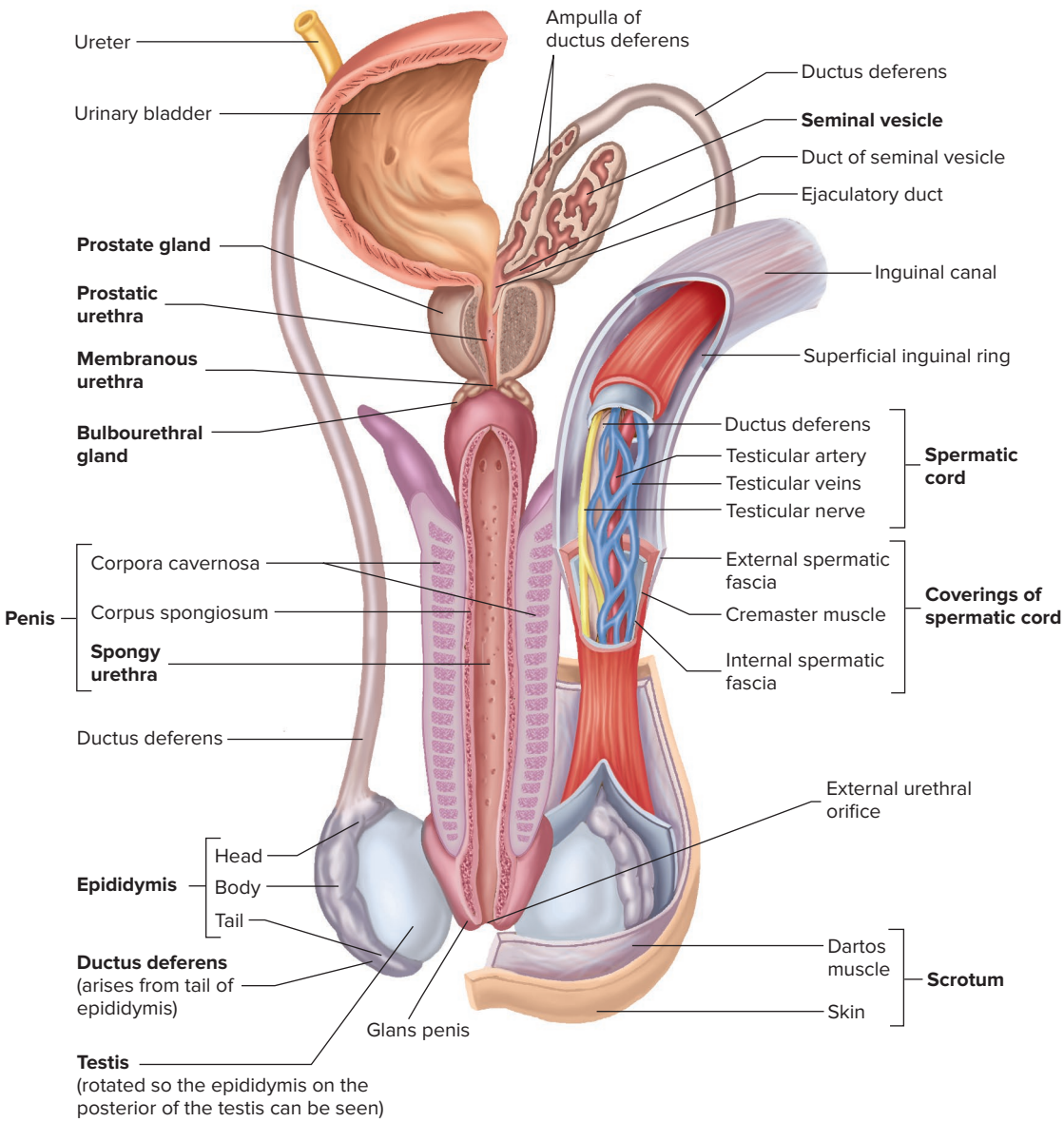


FIGURE 28.7 Male Reproductive Structures

Testes, epididymis, ductus deferens, and glands of the male reproductive system. The urethra is cut open along its dorsal side. AP|R

cytoplasm and maturation of the acrosome. Functionally, the sperm cells develop the ability to bind to the zona pellucida of the secondary oocyte during fertilization (see section 28.5). Sperm cells taken from the head of the epididymis are unable to fertilize secondary oocytes, and they are not yet able to become motile; however, sperm cells taken from the tail of the epididymis are able to perform both functions.

Ductus Deferens and Ejaculatory Duct

The **ductus deferens** (pl. ducta deferentia), or *vas deferens,* emerges from the tail of the epididymis and ascends along the posterior side of the testis medial to the epididymis, where it associates with the blood vessels and nerves that supply the testis to form the **spermatic cord** (figure 28.7; see figures 28.2 and 28.4*a*). The spermatic cord consists of (1) the ductus deferens, (2) the testicular artery and venous plexus, (3) lymphatic vessels, (4) nerves, and (5) fibrous remnants of the process vaginalis. The coverings of the spermatic cord include (1) the **external spermatic fascia** (fash′ē-ă); (2) the cremaster muscle, an extension of the muscle fibers of the internal abdominal oblique muscle of the abdomen; and (3) the **internal spermatic fascia** (figure 28.7).

The ductus deferens and the rest of the spermatic cord structures ascend and pass through the inguinal canal to enter the pelvic cavity (figure 28.7; see figure 28.2). The ductus deferens crosses the lateral and posterior walls of the pelvic cavity, travels over the ureter, and loops over the posterior surface of the urinary bladder to approach the prostate gland. Near the prostate gland, the end of the ductus deferens enlarges to form an **ampulla** (am-pul′lă). The lumen of the ductus deferens is lined with pseudostratified columnar epithelium, which is surrounded by smooth muscle. Peristaltic contractions of the smooth muscle help propel sperm cells through the ductus deferens.

Adjacent to the ampulla of each ductus deferens is a sac-shaped gland called the seminal vesicle. A short duct from each seminal vesicle joins the ampulla of the ductus deferens to form the **ejaculatory** (ē-jak′ū-lă-tōr-ē) **duct.** Each ejaculatory duct is approximately 2.5 cm long. These ducts extend into the prostate gland and open into the urethra (figure 28.7; see figure 28.2).

Urethra

The male **urethra** (ū-rē′thră) is about 20 cm long and extends from the urinary bladder to the distal end of the penis (figure 28.8; see figures 28.2 and 28.7). The urethra is a passageway for both urine and male reproductive fluids. The urethra is divided into three parts: (1) the prostatic urethra, (2) the membranous urethra, and (3) the spongy urethra. The **prostatic** (pros-tat′ik) **urethra** is connected to the bladder and passes through the prostate gland. Fifteen to 30 small ducts from the prostate gland and the two ejaculatory ducts empty into the prostatic urethra. The **membranous urethra** is the shortest part of the urethra, extending from the prostate gland through the perineum. The **spongy urethra,** also called the *penile* (pē′nīl) *urethra,* is the longest part of the urethra; it extends from the membranous urethra through the length of the penis, where it opens to the exterior at the **external urethral orifice** (figure 28.8). In rare cases, the penis does not develop normally, and the urethra may open to the exterior along the inferior surface of the penis (see chapter 29). Stratified columnar epithelium lines most of the urethra, but transitional epithelium is in the prostatic urethra near the bladder, and stratified squamous epithelium is near the external urethral orifice of the spongy urethra. Several minute, mucus-secreting **urethral glands** empty into the urethra.

Penis

The **penis** is the male organ of copulation, through which sperm cells are transferred from the male to the female. The penis contains three columns of erectile tissue. Erectile tissue is composed of a network of connective tissue and smooth muscle tissue with many sinusoids, or spaces, that can fill with blood (figure 28.8). This condition is referred to as engorgement. Engorgement of this erectile tissue causes the penis to enlarge and become firm, a process called **erection** (ē-rek′shŭn). The **corpora cavernosa** (kōr′pōr-ă kav-er-nos′ă) are the erectile columns that form the dorsum and sides of the penis. The third column, the **corpus spongiosum** (kōr′pŭs spŭn′jē-ō′sŭm), forms the ventral portion of the penis. The corpus spongiosum expands to form a cap, the **glans penis,** over the distal end of the penis. The spongy urethra passes through the corpus spongiosum, penetrates the glans penis, and opens as the external urethral orifice.

At the base of the penis, the corpus spongiosum expands to form the **bulb of the penis.** Each corpus cavernosum expands to form the **crus** (kroos; pl. crura, kroo′ră) **of the penis,** which attaches the penis to the pelvic bones. Together, the bulb of the penis and the crura of the penis constitute the **root of the penis.**

Skin is loosely attached to the connective tissue that surrounds the erectile columns in the shaft of the penis. The skin is firmly attached at the base of the glans penis, and a thinner layer of skin tightly covers the glans penis. The skin of the penis, especially the glans penis, is well supplied with sensory receptors. A loose fold of skin called the **prepuce** (prē′poos), or *foreskin,* covers the glans penis (see figure 28.2).

In many cultures, the prepuce is surgically removed shortly after birth, a procedure called **circumcision** (ser-kŭm-sizh′ŭn). There are no compelling medical reasons for circumcision. Uncircumcised males have a higher incidence of penile cancer, but the underlying causes seem related to chronic infections and poor hygiene. In the few cases in which the prepuce is "too tight" to be moved over the glans penis, circumcision may be necessary to avoid chronic infections and maintain normal circulation.

The primary nerves, arteries, and veins of the penis pass along its dorsal surface (figure 28.8*b*). Dorsal arteries, with dorsal nerves lateral to them, exist on each side of a single, midline dorsal vein. Additional deep arteries lie within the corpora cavernosa.

ASSESS YOUR PROGRESS

20. *Describe the structure and functions of the epididymis.*

21. *How do sperm move from the epididymis, and what changes occur in sperm cells while in the epididymis?*

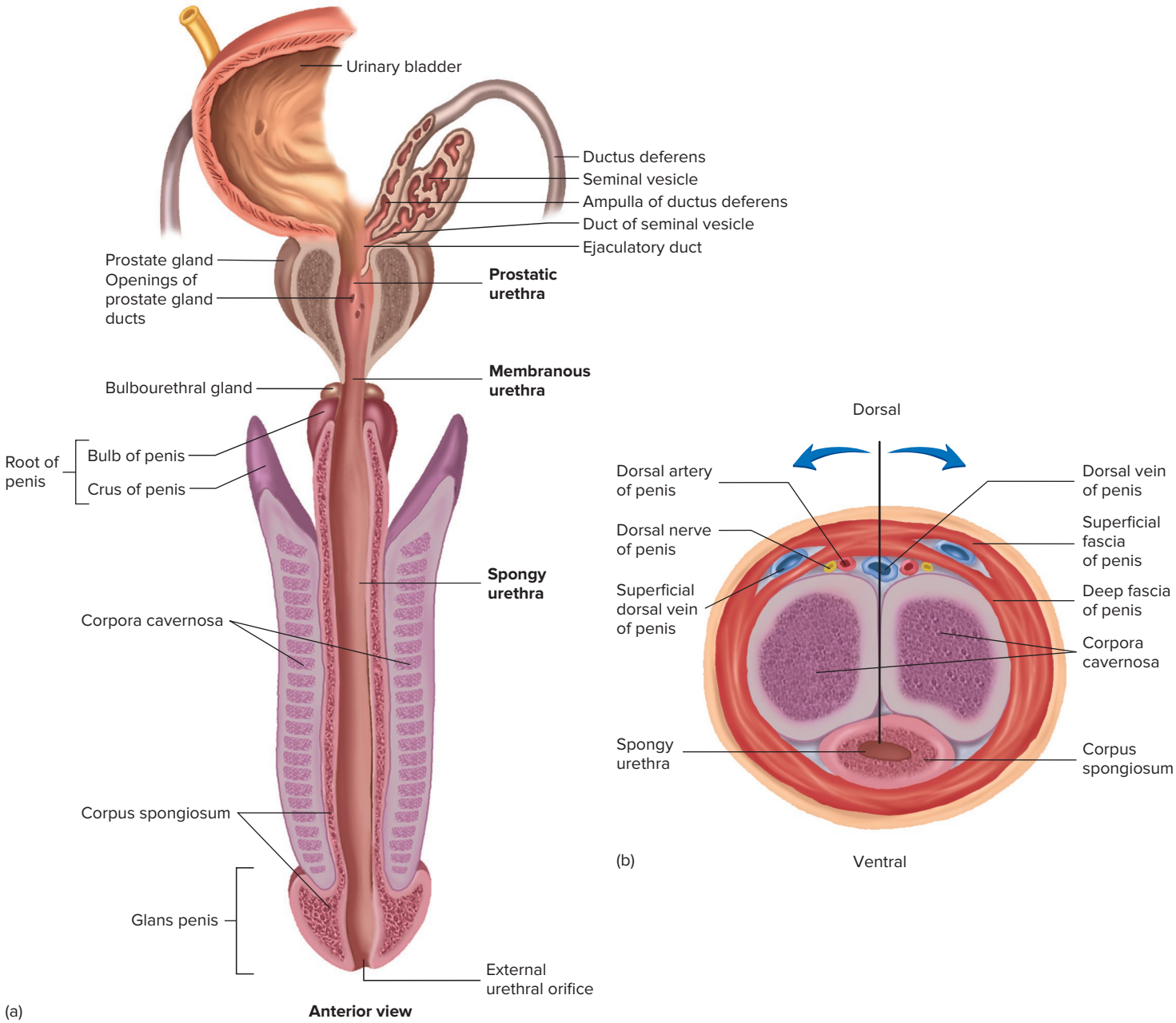


FIGURE 28.8 Penis

(*a*) Section through the spongy, or penile, urethra laid open and viewed from above. The prostate is also cut open to show the prostatic urethra. (*b*) Cross section of the penis, showing principal nerves, arteries, and veins along the dorsum of the penis. The *black line* and *blue arrows* depict the manner in which (*a*) is cut and laid open.

22. *Describe the structure and functions of the ductus deferens.*
23. *List the components and coverings of the spermatic cord.*
24. *Relate the route by which the ductus deferens extends from the testis to the prostate gland.*
25. *What is the ejaculatory duct?*
26. *Distinguish among the three parts of the male urethra.*
27. *Describe the erectile tissue of the penis.*
28. *Describe the structures and locations of the glans penis, crus, bulb, and prepuce.*

Accessory Glands

The male reproductive system also includes three accessory glands that are important for normal reproductive function. The accessory glands are exocrine glands that secrete material into the ducts of the male reproductive tract. These glands are (1) the seminal vesicles, (2) the prostate gland, and (3) the bulbourethral glands.

Seminal Vesicles

The **seminal vesicles** (sem′i-năl ves′i-klz) are sac-shaped glands located next to the ampullae of the ducta deferentia (see

Case STUDY 28.1 Prostate Cancer

Vern is a 65-year-old African-American male who has a family history of prostate cancer. Vern is very health conscious and has a physical examination every year. Due to his family history, Vern has elected to have his **prostate specific antigen (PSA)** levels evaluated every two years since he turned 55. His most recent test indicated that his PSA levels were elevated compared with his previous tests. His physician performed a digital examination and reported moderate enlargement of the prostate gland and two obvious tumorlike structures. Because of the increased PSA levels and the results of the digital examination, needle biopsies of Vern's prostate gland were taken through his rectum. Suspicious cells consistent with prostate cancer were detected in one of the six biopsy samples. The physician explained that, since the cancer had been discovered before it had metastasized, Vern's chances of surviving were high. Vern could choose to do nothing, have his prostate gland surgically removed, or treat the cancer with radiation therapy, hormonal therapy, or chemotherapy. Vern's physician indicated that doing nothing is a reasonable option for men who are significantly older than Vern because older men diagnosed with prostate cancer often die of other conditions before they succumb to prostate cancer.

Vern elected to have radiation therapy, which focuses radiation on the prostate gland to kill the cancer cells. Statistics indicate that surgery and radiation therapy have similar success rates for small, localized tumors like Vern's. The trauma of surgery and the higher probability of erectile dysfunction following surgery convinced Vern that radiation therapy was preferable. The physician explained that approximately 85% of patients like Vern are cancer-free 5 years after radiation treatments. Prostate cancer represents 29% of cancers in males in the United States and 14% of the deaths due to cancer. Only lung cancer causes more cancer deaths in men.

Predict 1

Explain why cancer cells were present in only one of the six needle biopsy samples.

figure 28.7). Each gland is about 5 cm long and tapers into a short excretory duct that joins the ampulla of the ductus deferens to form the ejaculatory duct. The seminal vesicles have a capsule containing fibrous connective tissue and smooth muscle cells.

Prostate Gland

The **prostate** (pros′tāt; one standing before) **gland** consists of both glandular and muscular tissue. It resembles a walnut in shape and size and is approximately 4 cm long and 2 cm wide. It is dorsal to the pubic symphysis at the base of the urinary bladder, where it surrounds the prostatic urethra and the two ejaculatory ducts (see figure 28.2). The prostate gland is composed of a fibrous connective tissue capsule containing distinct smooth muscle cells and numerous fibrous partitions, also containing smooth muscle, that radiate inward toward the urethra. Covering these muscular partitions is a layer of columnar epithelial cells that form saccular dilations. The columnar cells secrete prostatic fluid into the saccular dilations. Fifteen to 30 small prostatic ducts carry these secretions into the prostatic urethra.

Bulbourethral Glands

The **bulbourethral** (bŭl′bō-ū-rē′thrăl) **glands,** or *Cowper glands,* are a pair of small glands located near the membranous urethra (see figures 28.2 and 28.7). In young males, each gland is about the size of a pea, but they decrease in size with age and are almost impossible to detect in older men. Each bulbourethral gland is a compound mucous gland (see chapter 4). The small ducts of each gland unite to form a single duct, which empties into the spongy urethra at the base of the penis.

Semen

Collectively, the sperm cells and secretions from the accessory glands are called **semen** (sē′men). The seminal vesicles produce about 60% of the fluid, the prostate gland contributes about 30%, the testes contribute 5%, and the bulbourethral glands contribute 5%. **Emission** (ē-mish′ŭn) is the discharge of all these secretions from the ducta deferentia into the urethra. **Ejaculation** (ē-jak-ū-lā′shŭn) is the forceful expulsion of semen from the urethra caused by contraction of the urethra, the skeletal muscles in the pelvic floor, and the muscles at the base of the penis.

The major component of the testicular secretions is sperm cells. In addition to the sperm cells, the testes also secrete a small amount of fluid necessary for moving the sperm cells through the reproductive tract. Metabolic by-products are also included in this fluid, as sperm cells carry out basic cellular processes.

The bulbourethral glands and urethral mucous glands produce a mucous secretion just before ejaculation. This alkaline mucous secretion lubricates the urethra, neutralizes the contents of the normally acidic spongy urethra, provides a small amount of lubrication during intercourse, and helps reduce vaginal acidity.

The thick, mucuslike secretions of the seminal vesicles contain large amounts of fructose, citric acid, and other nutrients that nourish the sperm cells. The seminal vesicle secretions also contain fibrinogen, which is involved in a weak coagulation reaction of the semen immediately after ejaculation. In addition, seminal vesicle secretions contain prostaglandins that can cause uterine contractions, which help transport sperm cells through the female reproductive tract to the site of fertilization.

The prostate produces a thin, milky, alkaline secretion. In combination with secretions of the seminal vesicles, bulbourethral glands, and urethral mucous glands, the prostatic secretions help neutralize the acidic urethra. The secretions of the prostate and seminal vesicles also help neutralize the acidic secretions of the testes and the vagina. In addition, the prostatic secretions are important in the transient coagulation of semen because they contain clotting factors that convert fibrinogen from the seminal vesicles to fibrin, resulting in coagulation. The coagulated material keeps the semen a sticky

mass for a few minutes after ejaculation, and then fibrinolysin, also secreted by the prostate, causes the mass to dissolve. This releases the sperm cells to make their way up the female reproductive tract.

Predict 2

Explain a possible function of the coagulation reaction.

Before ejaculation, the ductus deferens begins to contract rhythmically to propel sperm cells and testicular and epididymal secretions from the tail of the epididymis to the ampulla of the ductus deferens. Contractions of the ampullae, seminal vesicles, and ejaculatory ducts cause the sperm cells, along with testicular and epididymal secretions, to move into the prostatic urethra with the prostatic secretions. Secretions of the seminal vesicles then enter the prostatic urethra, where they mix with the other secretions.

Normal sperm cell counts in the semen range from 75 to 400 million sperm cells per milliliter of semen, and a normal ejaculation usually consists of about 2–5 mL of semen. The semen with the highest sperm count is expelled from the penis first because it contains the greater percentage of sperm-containing fluid from the epididymis. Sperm cells become motile after ejaculation once they are mixed with secretions of the male accessory glands and the female reproductive tract. The alkaline pH (an average of 7.5), nutrients, and removal of inhibitory substances from the surface of sperm cells appear to increase sperm cell motility. Enzymes carried in the acrosomal cap of each sperm cell help digest a path through the mucoid fluids of the female reproductive tract and through materials surrounding the oocyte. Once the acrosomal fluid is depleted from a sperm cell, the sperm cell is no longer capable of fertilization. As a result, most of the sperm cells (millions) are expended in moving the general group of sperm cells through the female reproductive tract.

ASSESS YOUR PROGRESS

29. *State where the seminal vesicles, prostate gland, and bulbourethral glands empty into the male reproductive duct system.*
30. *Define* emission *and* ejaculation.
31. *Describe the contributions to semen from the accessory glands.*
32. *What is the function of the secretions of each of the accessory glands?*

28.4 Physiology of Male Reproduction

LEARNING OUTCOMES

After reading this section, you should be able to

A. **List the hormones that influence the male reproductive system and describe their functions.**
B. **Demonstrate an understanding of the changes that occur in males during puberty.**
C. **Explain the events that occur during the male sexual act.**

The male reproductive system is under hormonal and nervous control. Hormones are primarily responsible for the development of reproductive structures and the maintenance of their functional capacities, the development of secondary sexual characteristics, and the control of sperm cell formation. Hormones also influence sexual behavior. Neural mechanisms are primarily involved in sexual behavior and control of the sexual act.

Regulation of Reproductive Hormone Secretion

Hormonal mechanisms that influence the male reproductive system involve the hypothalamus, the pituitary gland, and the testes (figure 28.9). A small peptide hormone called **gonadotropin-releasing hormone (GnRH)** is released from neurons in the hypothalamus. GnRH passes through the hypothalamohypophysial portal system to the anterior pituitary gland (see chapter 18). In response to GnRH, cells within the anterior pituitary gland secrete two hormones, referred to as **gonadotropins** (gō′nad-ō-trō′pinz, gon′ă-dō-trō′pinz) because they influence the function of the **gonads** (gō′nadz; testes or ovaries).

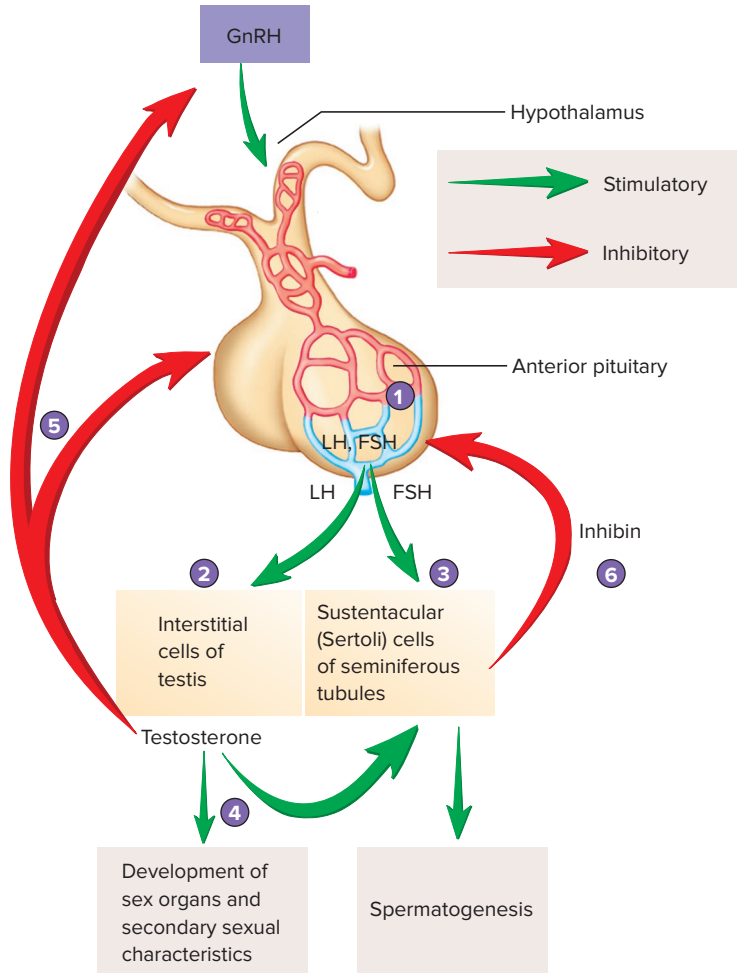
The two gonadotropins are **luteinizing hormone (LH)** and **follicle-stimulating hormone (FSH).** They are named for their functions in females, but they also have important functions in males. When discussing the male reproductive system, LH is sometimes called **interstitial cell–stimulating hormone (ICSH).** LH binds to the interstitial cells in the testes and causes them to increase their rate of testosterone synthesis and secretion. FSH binds primarily to sustentacular cells in the seminiferous tubules and promotes sperm cell development. Both gonadotropins bind to specific receptor molecules on the membranes of the cells they influence, and cyclic adenosine monophosphate (cAMP) is an important intracellular mediator in those cells.

For GnRH to stimulate the secretion of large quantities of LH and FSH and thereby influence sperm cell production, the anterior pituitary must be exposed to a series of pulses, or brief increases and decreases in GnRH. Interestingly, GnRH can be produced synthetically; if administered in small amounts in frequent pulses or surges, it can be useful in treating male infertility. However, chronically elevated GnRH levels in the blood cause the anterior pituitary cells to become insensitive to stimulation by GnRH molecules, and little LH or FSH is secreted. Long-term administration of synthetic GnRH, therefore, can reduce sperm cell production, causing infertility.

Testosterone is the major male hormone secreted by the testes. It is classified as an **androgen** (Gr. *andros,* male human) because it stimulates the development of male reproductive structures (see chapter 29) and male secondary sexual characteristics. The testes secrete other androgens, but they are produced in smaller concentrations and are less potent than testosterone. In addition, the testes secrete small amounts of estrogen and progesterone.

Testosterone has a major influence on many tissues. It plays an essential role in the embryonic development of reproductive structures, their further development during puberty, the development of secondary sexual characteristics during puberty, the maintenance of sperm cell production, and the regulation of gonadotropin secretion. It also influences behavior.

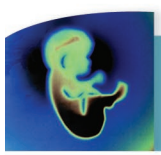
1. GnRH from the hypothalamus stimulates the secretion of LH and FSH from the anterior pituitary.
2. LH stimulates testosterone secretion from the interstitial cells.
3. FSH stimulates sustentacular cells of the seminiferous tubules to increase spermatogenesis and to secrete inhibin.
4. Testosterone has a stimulatory effect on the sustentacular cells of the seminiferous tubules, as well as on the development of sex organs and secondary sexual characteristics.
5. Testosterone has a negative-feedback effect on the hypothalamus and pituitary to reduce LH and FSH secretion.
6. Inhibin has a negative-feedback effect on the anterior pituitary to reduce FSH secretion.



PROCESS FIGURE 28.9 Regulation of Reproductive Hormone Secretion in Males

Male reproductive hormones are produced by the hypothalamus, the anterior pituitary, and the testes.

? *Suppose an adult male developed a tumor in one of his testes that resulted in abnormally high levels of testosterone. What would happen to his levels of GnRH, FSH, and LH?*



Clinical IMPACT 28.3 Male Infertility

Infertility (in-fer-til′i-tē) is the inability or the reduced ability to produce offspring. The most common cause of infertility in males is a low sperm cell count. A count of less than 20 million sperm cells per milliliter usually indicates infertility.

The sperm cell count can decrease because of damage to the testes as a result of trauma, radiation, cryptorchidism, or an infection, such as mumps. **Varicocele** (var′i-kō-sēl) is an abnormal dilation of a spermatic vein that results from incompetent or absent valves in spermatic veins, from thrombi, or from tumors. As a result, both testicular blood flow and spermatogenesis decrease. Reduced sperm cell counts can also result from inadequate secretion of LH and FSH, which can be caused by hypothyroidism, trauma to the hypothalamus, infarctions of the hypothalamus or anterior pituitary gland, or tumors. Decreased testosterone secretion reduces the sperm cell count as well. Some reports suggest that the average sperm cell count has decreased substantially since the end of World War II (1945), although there is some controversy about the accuracy of these reports. Researchers speculate that certain synthetic chemicals are responsible.

Even when the sperm cell count is normal, fertility can be reduced if sperm cell structure is abnormal, as occurs due to chromosomal abnormalities or other genetic factors. Reduced sperm cell motility also results in infertility. A major cause of reduced sperm cell motility is the presence of antisperm antibodies, which are produced by the immune system and bind to sperm cells.

In cases of infertility due to low sperm count or reduced motility, fertility can sometimes be achieved by collecting several ejaculations and concentrating the sperm cells before inserting them into the female reproductive tract, a process called **artificial insemination** (in-sem-i-nā′shŭn).

Inside some target tissue cells, such as cells of the scrotum and penis, an enzyme converts testosterone to dihydrotestosterone, which is the active hormone for these cells. If the enzyme is not active, these structures do not fully develop normally. In other target tissue cells, an enzyme converts testosterone to estrogen, and estrogen becomes the active hormone. Some brain cells convert testosterone to estrogen. In these cells, estrogen may be the active hormone responsible for certain aspects of male sexual behavior.

The sustentacular cells of the testes secrete a polypeptide hormone called **inhibin** (in-hib′in), which inhibits FSH secretion from the anterior pituitary.

Puberty in Males

Before birth, a gonadotropin-like hormone called **human chorionic** (kō-rē-on′ik) **gonadotropin (hCG),** secreted by the placenta, stimulates the synthesis and secretion of testosterone by the fetal testes. After birth, however, no source of stimulation is present, and the testes of the newborn baby atrophy slightly and secrete only small amounts of testosterone until puberty, which normally begins when a boy is 12–14 years old.

Puberty (pū′ber-tē) is the age at which individuals become capable of sexual reproduction. Before puberty, GnRH release from the hypothalamus is inhibited by small amounts of testosterone and other androgens. At puberty, the hypothalamus becomes much less sensitive to the inhibitory effect of these androgens, and the rate of GnRH secretion increases. This causes an increase in LH and FSH secretion from the anterior pituitary gland. Elevated FSH levels promote sperm cell formation, and elevated LH levels cause the interstitial cells to secrete larger amounts of testosterone. Testosterone still has a negative-feedback effect on GnRH secretion after puberty but is not capable of completely suppressing it.

Effects of Testosterone

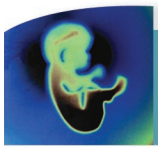
Testosterone is by far the major androgen in males. Nearly all the androgens, including testosterone, are produced by the interstitial cells, with small amounts produced by the adrenal cortex and possibly by the sustentacular cells. Testosterone causes the enlargement and differentiation of the male genitals and reproductive duct system and is necessary for sperm cell formation. Testosterone also stimulates growth of thicker, coarser, pigmented hair in the pubic area and extending up the linea alba, as well as on the legs, chest, axillary region, face, and back. Testosterone causes existing vellus hair to be converted to terminal hair, which is coarser and more pigmented.

Testosterone also affects the appearance of the skin. Specifically, it causes the texture of the skin to become rougher or coarser. The quantity of melanin in the skin also increases, making the skin darker. In addition, testosterone increases the rate of secretion from the sebaceous glands, especially on the face. Near puberty, the increased testosterone level and increased sebaceous gland secretion frequently cause acne (see chapter 5).

Testosterone also causes hypertrophy of the larynx and reduced tension on the vocal folds, beginning near puberty. At first, the structural changes can make the voice difficult to control, but ultimately its normal masculine quality is achieved.

Testosterone stimulates metabolism so that males have a slightly higher metabolic rate than females. The red blood cell count increases by nearly 20% as a result of testosterone's effect on erythropoietin production. Testosterone also has a minor mineralocorticoid-like effect, causing Na^+ to be retained in the body and, consequently, an increased volume of body fluids. Testosterone promotes protein synthesis in most tissues; as a result, skeletal muscle mass increases at puberty. The average percentage of the body weight composed of skeletal muscle is greater for males than for females because of the effect of androgens.

Testosterone, historically, was believed to be the major hormone influencing bone growth in males. Recent studies though have found that testosterone is converted to estrogen, which affects bone growth. At puberty, the increase in sex hormone production, both testosterone and the subsequent production of estrogen, causes rapid bone growth and increases the deposition of Ca^{2+} in bone, resulting in increased height. However, the growth in height is limited because these sex hormones also stimulate ossification of the epiphyseal plates of long bones (see chapter 6). Males who mature sexually at an earlier age grow rapidly but reach their maximum height earlier. Males who mature sexually at a later age do not exhibit a rapid period of growth, but they grow for a longer period and can become taller than those who mature sexually at an earlier age.



Clinical IMPACT 28.4

Anabolic Steroids

In an attempt to improve their performance, some athletes, especially those who depend on muscle strength, may either ingest or inject synthetic androgens, commonly called **anabolic steroids,** or simply *steroids*. These hormones have testosterone-like effects, such as stimulating the development of male secondary sexual characteristics, but many anabolic steroids are structurally different from testosterone, and their effect on muscle is greater than their effect on the reproductive organs. However, when taken in large amounts, they can influence the reproductive system. Large doses of anabolic steroids have a negative-feedback effect on the hypothalamus and anterior pituitary, reducing GnRH, LH, and FSH levels. As a result, the testes can atrophy and sterility can develop. Other side effects of large doses of anabolic steroids include kidney and liver damage, heart attack, and stroke. In addition, anabolic steroids cause abrupt mood swings, usually toward intense anger and rage. Taking anabolic steroids is highly discouraged by medical professionals, violates the rules of most athletic organizations, and is illegal without a prescription.

Male Sexual Behavior and the Male Sexual Act

Testosterone is required to initiate and maintain male sexual behavior. Testosterone enters cells within the hypothalamus and the surrounding areas of the brain and influences their function, resulting in sexual behavior. However, male sexual behavior may depend, in part, on the conversion of testosterone to other steroids, such as estrogen, in cells of the brain.

The blood levels of testosterone remain relatively constant in a male from puberty until about 40 years of age. Thereafter, the levels slowly decline to about 20% of this value by 80 years of age, causing a slow decrease in sex drive and fertility.

The male sexual act is a complex series of reflexes that result in erection of the penis, secretion of mucus into the urethra, emission, and ejaculation. Sensations that are normally interpreted as pleasurable occur during the male sexual act and result in a climactic sensation, called **orgasm** (ōr′gazm), associated with ejaculation. After ejaculation, a phase called **resolution** occurs. Resolution is characterized by a flaccid penis, an overall feeling of satisfaction, and the inability to achieve erection and a second ejaculation for a period that can range from many minutes to many hours or longer.

Sensory Action Potentials and Integration

Male sexual reflexes are initiated by a variety of sensory stimuli. Action potentials are conducted by sensory neurons from the genitals through the pudendal nerve to the sacral region of the spinal cord, where reflexes that result in the male sexual act are integrated. Action potentials travel from the spinal cord to the cerebrum to produce conscious sexual sensations.

Rhythmic massage of the penis, especially the glans penis, produces extremely important sensory action potentials that initiate erection and ejaculation. In addition, sensory action potentials produced in surrounding tissues, such as the scrotum and the anal, perineal, and pubic regions, reinforce sexual sensations. Engorgement of the prostate and seminal vesicles with their secretions also causes sexual sensations. In some cases, mild irritation of the urethra, as may result from an infection, can cause sexual sensations.

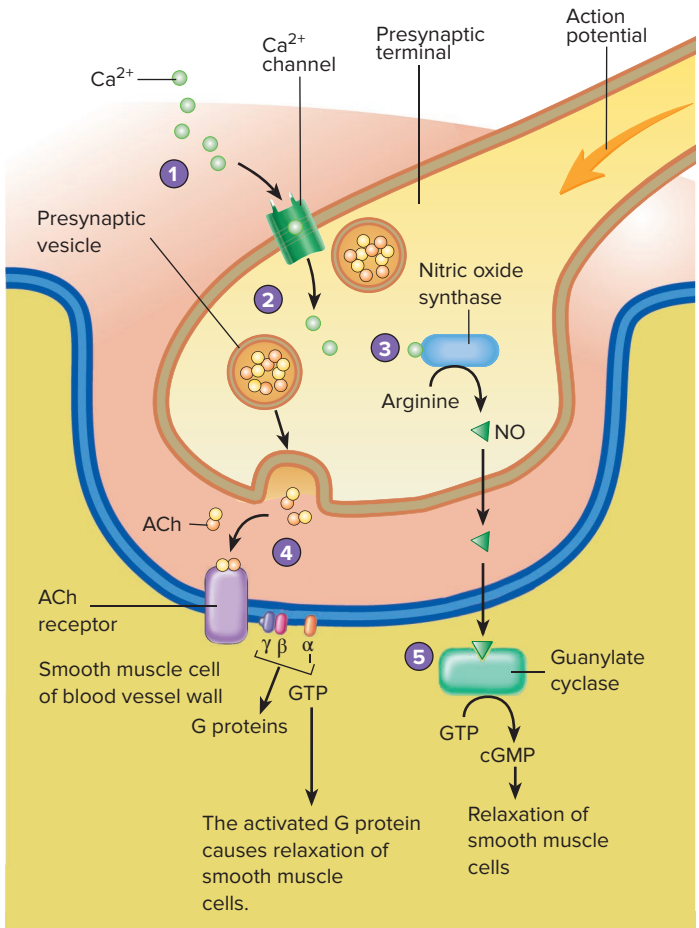
Psychic stimuli, including sight, sound, odor, and thoughts, have a major effect on sexual reflexes. Thinking sexual thoughts or dreaming about erotic events tends to reinforce stimuli that trigger sexual reflexes, such as erection and ejaculation. Ejaculation while sleeping is a relatively common event in young males and is thought to be triggered by psychic stimuli associated with dreaming. Psychic stimuli can also inhibit the sexual act, and thoughts that are not sexual tend to decrease the effectiveness of the male sexual act.

Action potentials from the cerebrum that reinforce the sacral reflexes are not absolutely required for the culmination of the male sexual act. The sexual act can be performed by males who have suffered spinal cord injuries superior to the sacral region.

Erection, Emission, and Ejaculation

When erection occurs, the penis becomes enlarged and rigid. Erection is the first major component of the male sexual act. Figure 28.10 illustrates the neural events that lead to an erection. First, action potentials travel from the spinal cord through the pudendal nerve to the arteries that supply blood to the erectile tissues. The release of acetylcholine and nitric oxide (NO) causes smooth muscle cells to relax and blood vessels to dilate (figure 28.10). At the same time, other arteries of the penis constrict to shunt blood to the erectile tissues. As a consequence, blood fills the sinusoids of the erectile tissue and compresses the veins. Because venous outflow is partially occluded, the blood pressure in the sinusoids causes inflation and rigidity of the erectile tissue. Nerve action potentials that result in erection come from parasympathetic centers (S2–S4) or sympathetic centers (T2–L1) in the spinal cord. Normally, the parasympathetic centers are more important for erection; however, in cases of damage to the sacral region of the spinal cord, erection can occur through the sympathetic system.

Parasympathetic action potentials also cause the mucous glands within the penile urethra and the bulbourethral glands at the base of the penis to secrete mucus.

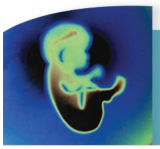


1. Action potentials in parasympathetic neurons cause voltage-gated Ca^{2+} channels to open, and Ca^{2+} diffuses into the presynaptic terminals.
2. Calcium ions initiate the release of acetylcholine (ACh) from presynaptic vesicles.
3. Calcium ions also activate nitric oxide synthase, which promotes the synthesis of nitric oxide (NO) from arginine.
4. ACh binds to ACh receptors on the smooth muscle cells and activates a G protein mechanism. The activated G protein causes the relaxation of smooth muscle cells and erection of the penis.
5. NO binds to guanylate cyclase enzymes and activates them. The activated enzymes convert GTP to cGMP, which causes relaxation of the smooth muscle cells and erection of the penis.

PROCESS FIGURE 28.10 Nervous Control of Erection

Parasymphathetic neurons release acetylcholine and nitric oxide, which bind to receptors on the smooth muscle cells in erectile tissue. As a result of neurotransmitter binding, smooth muscle cells relax, increasing blood flow into the erectile tissue.

? *What effect would an acetylcholine competitor have on erection of the penis? Explain your answer.*



Clinical IMPACT 28.5

Erectile Dysfunction

Failure to achieve erection, or **erectile dysfunction (ED),** sometimes called *impotence,* can be a major source of frustration for some men. ED can be due to reduced testosterone secretion resulting from hypothalamic, pituitary, or testicular complications. In other cases, ED is due to defective stimulation of the erectile tissue by nerve fibers or reduced response of the blood vessels to neural stimulation.

Some men can achieve erections by taking oral medication, such as sildenafil (Viagra), tadafil (Cialis), or vardenafil (Levitra). Sildenafil is a drug that blocks the activity of the enzyme that converts cGMP to GMP. Consequently, it allows cGMP to accumulate in smooth muscle cells in the arteries of erectile tissues. This response is effective in enhancing erection in males. Sildenafil's action is not specific to the erectile tissue of the penis, however. It causes vasodilation in other tissues and can increase the workload of the heart.

As mentioned in section 28.3, emission is the accumulation of sperm cells and secretions of the accessory glands in the urethra. Sympathetic centers in the spinal cord (T12–L1), which are stimulated as the level of sexual tension increases, control emission. Sympathetic action potentials cause peristaltic contractions of the reproductive ducts and stimulate the seminal vesicles and the prostate gland to release their secretions. Consequently, semen accumulates in the prostatic urethra and produces sensory action potentials that pass through the pudendal nerves to the spinal cord. Integration of these action potentials results in both sympathetic and somatic motor output. Sympathetic action potentials cause the internal sphincter of the urinary bladder to constrict, so that semen and urine are not mixed. Somatic motor action potentials travel to the skeletal muscles of the urogenital diaphragm and the base of the penis, causing ejaculation by several rhythmic contractions that force the semen out of the urethra. Muscle tension increases throughout the body as well.

Predict 3

Mr. Grover suffers from the periodic inability to achieve an erection. His doctor could find no structural or physiological abnormalities, so he prescribed sildenafil. After taking the pills, Mr. Grover could sometimes, but not always, achieve an erection. Assuming no pathology affected Mr. Grover, explain his experiences.

ASSESS YOUR PROGRESS

33. *Where are GnRH, LH, FSH, and inhibin produced? What effects do they have on the male reproductive system?*
34. *Where is testosterone produced?*
35. *Explain the regulation of testosterone secretion.*
36. *What changes in hormone production occur at puberty?*
37. *Describe the effects of testosterone on the male body.*
38. *What effects do psychic, tactile, parasympathetic, and sympathetic stimulation have on the male sex act?*
39. *Describe the processes of erection, emission, ejaculation, orgasm, and resolution.*

28.5 Anatomy of the Female Reproductive System

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Name the organs of the female reproductive system and describe their functions.**
B. **Describe the anatomy and histology of the ovaries.**
C. **Discuss the development of the oocyte and the follicle and describe ovulation and fertilization.**
D. **Describe the structure of the uterine tubes, uterus, vagina, external genitalia, and mammary glands.**

The female reproductive organs are the ovaries, the uterine tubes, the uterus, the vagina, the external genital organs, and the mammary glands. The internal reproductive organs are within the pelvis between the urinary bladder and the rectum (figure 28.11). The uterus and the vagina are in the midline, with the ovaries to each side of the uterus. A group of ligaments holds the internal reproductive organs in place. The most conspicuous of these ligaments is the **broad ligament,** an extension of the peritoneum that spreads out on both sides of the uterus and attaches to the ovaries and uterine tubes (figure 28.12).

Ovaries

The two **ovaries** (ō′var-ēz), the female gonads, are small organs about 2–3.5 cm long and 1–1.5 cm wide (figure 28.12). A peritoneal fold called the **mesovarium** (mez′ō-vā′rē-ŭm; mesentery of the ovary) attaches each ovary to the posterior surface of the broad ligament. Two other ligaments are associated with the ovary: (1) the **suspensory ligament,** which extends from the mesovarium to the body wall, and (2) the **ovarian ligament,** which attaches the ovary to the superior margin of the uterus. The ovarian arteries, veins, and nerves traverse the suspensory ligament and enter the ovary through the mesovarium.

Ovarian Histology

The ovary is covered by a portion of the visceral peritoneum, made up of simple cuboidal epithelium, called the **ovarian epithelium,** or *germinal epithelium.* Immediately below the ovarian epithelium is a capsule of dense fibrous connective tissue called the **tunica albuginea** (al-bū-jin′ē-ă). The tissue of the ovary is divided into two areas: the cortex and the medulla. The **cortex** is the denser, outer part of the ovary, and the **medulla** is the looser, inner part of the ovary (figure 28.13). The connective tissue of the ovary is called the **stroma.** Numerous **ovarian follicles,** each of which contains an **oocyte** (ō′ō-sīt), are distributed throughout the stroma of the cortex. Blood vessels, lymphatic vessels, and nerves from the mesovarium enter the medulla.

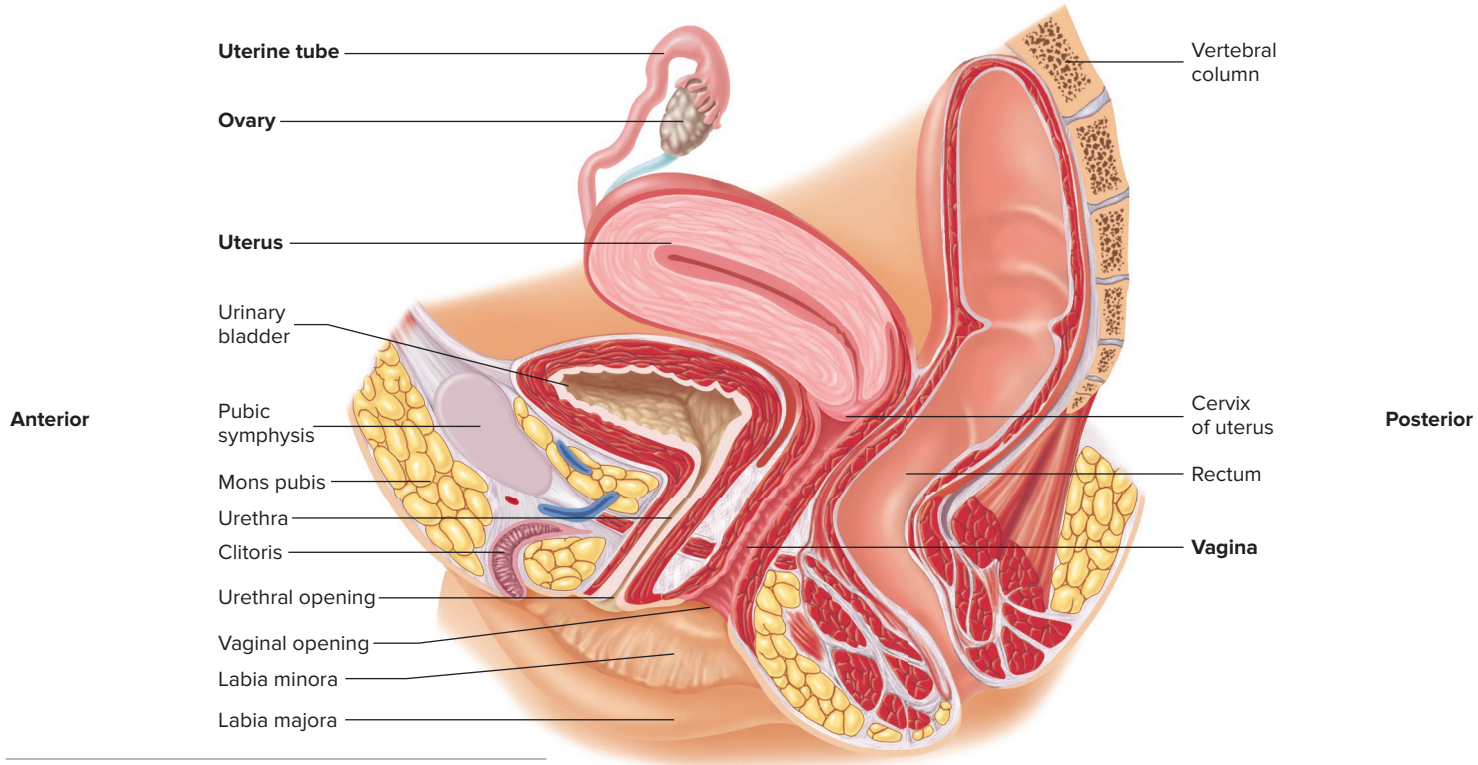


FIGURE 28.11 Female Reproductive Structures
The structures are depicted in sagittal section.

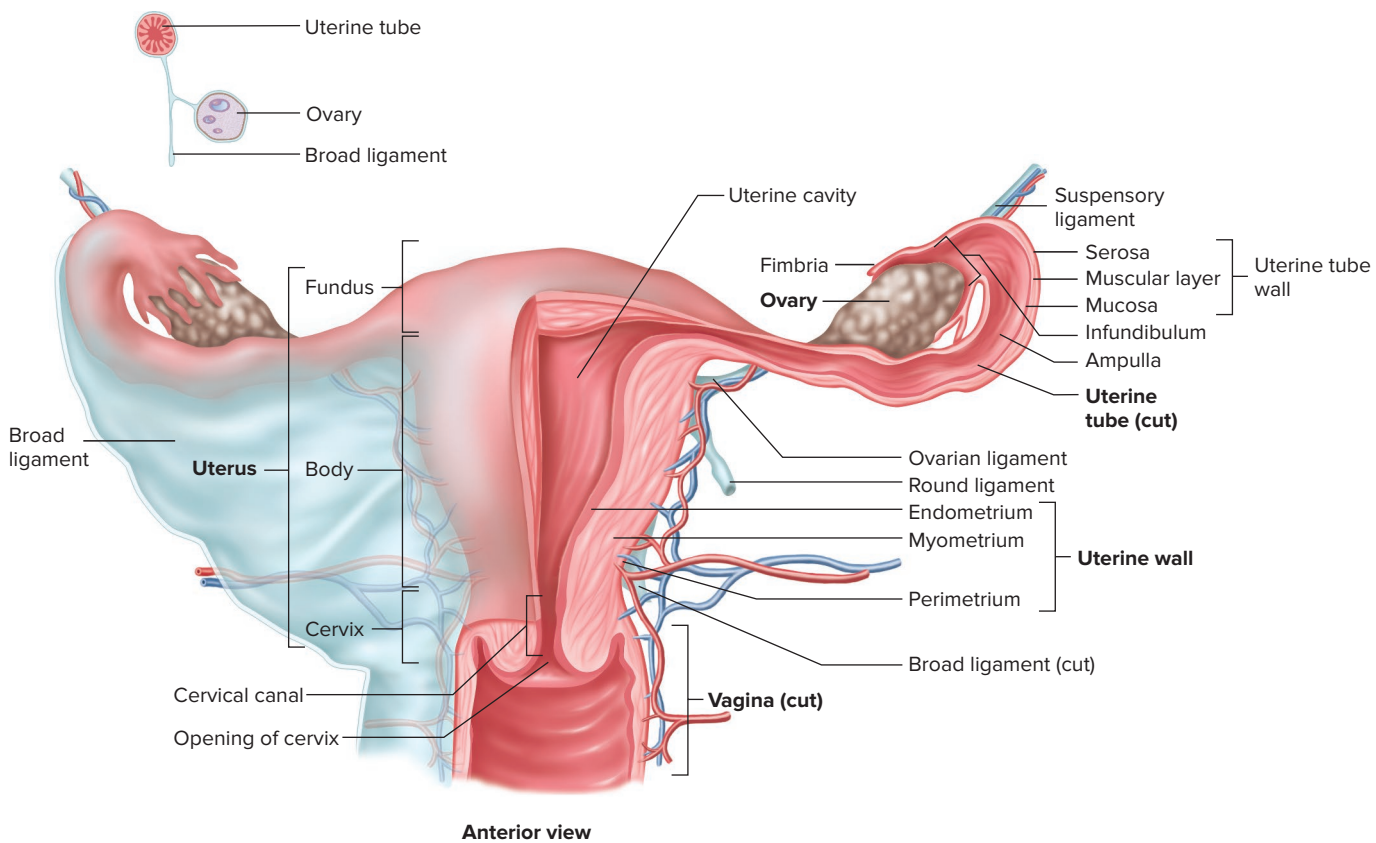


FIGURE 28.12 Uterus, Vagina, Uterine Tubes, Ovaries, and Supporting Ligaments
The uterus and uterine tubes are cut in section (on the left side), and the vagina is cut to show the internal anatomy. The inset (top, left) shows the relationships among the ovary, the uterine tube, and the ligaments that suspend them in the pelvic cavity.

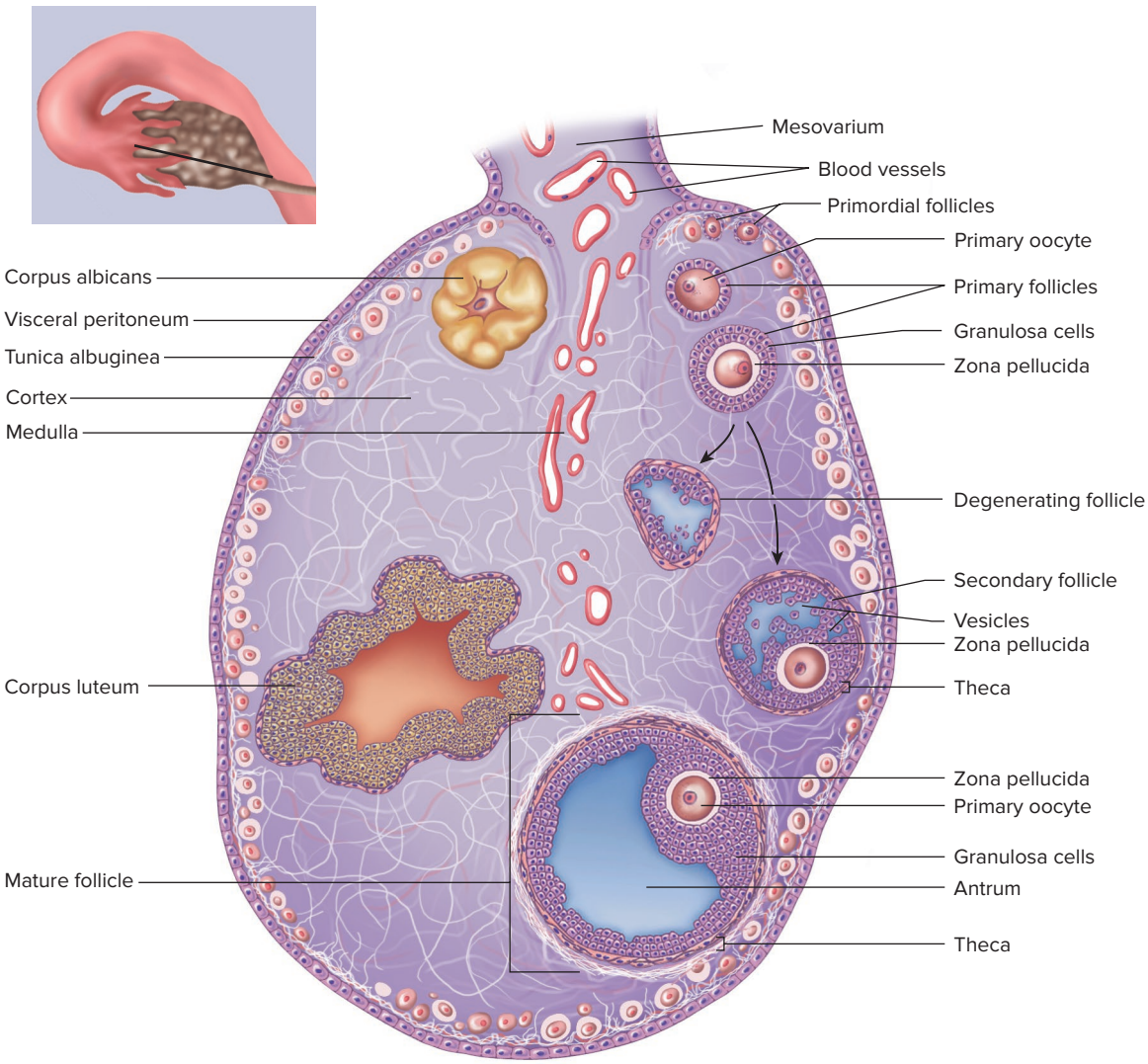


FIGURE 28.13 Histology of the Ovary

The ovary is sectioned to illustrate its internal structure (the inset shows plane of section). Ovarian follicles from each major stage of development are shown. AP|R

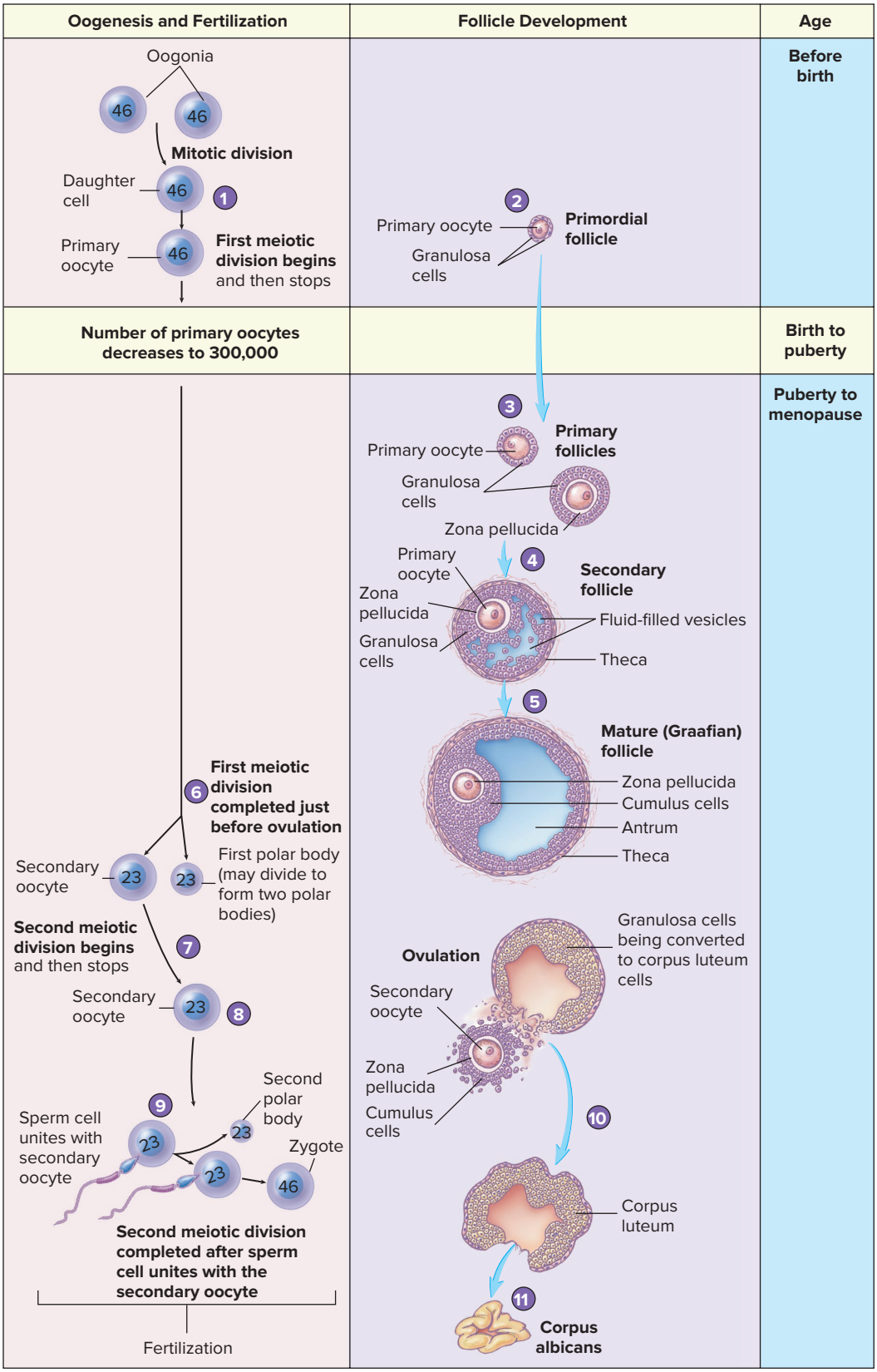
Oogenesis and Fertilization

The process of gamete production in females is called **oogenesis.** This process begins before a female is born. By the fourth month of development, the ovaries contain 5 million **oogonia** (ō-ō-gō′nē-ă; *oon,* egg + *gone,* generation), the cells from which oocytes develop (figure 28.14, *step 1*). By the time of birth, many of the oogonia have degenerated, and the remaining ones have begun meiosis. Oogonia can form after birth from stem cells, but the extent to which this occurs, and how long it occurs, is not clear. Meiosis stops, however, during the first meiotic division at prophase I (see figure 28.1). The cell at this stage is called a **primary oocyte.** At birth a female possesses about 2 million primary oocytes. From birth to puberty, the number of primary oocytes decreases to around 300,000–400,000. On average, about 400 primary oocytes will actually complete development and give rise to the secondary oocytes that are eventually released from the ovaries.

Ovulation (ov′ū-lā′shŭn, ō′vū-lā′shŭn) is the release of a **secondary oocyte** from an ovary. Just before ovulation, the primary oocyte completes the first meiotic division to produce a secondary oocyte and a **first polar body** (figure 28.14, *steps 6–8*). Unlike meiosis in males, cytoplasm is not split evenly between the two cells. Most of the cytoplasm of the primary oocyte remains with the secondary oocyte. As a result, the secondary oocyte is much larger than the first polar body. The cytoplasm contains organelles, such as mitochondria, and nutrients that increase the viability of the secondary oocyte. The first polar body, which has less cytoplasm and therefore fewer organelles and nutrients, either degenerates or divides to form two second polar bodies. Eventually, the polar bodies degenerate. The secondary oocyte begins the second meiotic division, but it stops in metaphase II.

After ovulation, the secondary oocyte may be fertilized by a sperm cell (figure 28.14, *step 9*). **Fertilization** (fer′til-i-zā-shŭn) begins when a sperm cell binds to the plasma membrane and

1. Oogonia give rise to primary oocytes. Before birth, oogonia multiply by mitosis. During development of the fetus, many oogonia begin meiosis, but stop in prophase I and are now called primary oocytes. They remain in this state until puberty.
2. Before birth, the primary oocytes become surrounded by a single layer of granulosa cells, creating a primordial follicle. These are present until puberty.
3. After puberty, primordial follicles develop into primary follicles when the granulosa cells enlarge and increase in number.
4. Secondary follicles form when fluid-filled vesicles develop and thecal cells arise on the outside of the follicle.
5. Mature follicles form when the vesicles create a single antrum.
6. Just before ovulation, the primary oocyte completes meiosis I, creating a secondary oocyte and a first polar body.
7. The secondary oocyte begins meiosis II, but stops at metaphase II.
8. During ovulation, the secondary oocyte is released from the ovary.
9. The secondary oocyte only completes meiosis II if it is fertilized by a sperm cell. The completion of meiosis II forms an oocyte and a second polar body. Fertilization is complete when the oocyte nucleus and the sperm cell nucleus unite, creating a zygote.
10. Following ovulation, the granulosa cells divide rapidly and enlarge to form the corpus luteum.
11. The corpus luteum degenerates to form a scar, or corpus albicans.



PROCESS FIGURE 28.14 Oogenesis and Follicle Development

The events of oogenesis and follicle development are closely linked. Once these structures are mature, fertilization can result. The numbers written in the cells are total numbers of chromosomes.

? *If fertilization does not occur, what happens to the secondary oocyte after ovulation?*

penetrates the plasma membrane of a secondary oocyte. Subsequently, the secondary oocyte completes the second meiotic division to form two cells, each containing 23 chromosomes. One of these cells has very little cytoplasm and is called the second polar body, which degenerates. In the other, larger cell, the 23 chromosomes from the sperm cell nucleus join with the 23 chromosomes from the oocyte to form a **zygote** (zī′gōt), completing fertilization. The zygote has 23 pairs of chromosomes (a total of 46 chromosomes). All cells of the human body contain 23 pairs of chromosomes, except for the male and female gametes. The zygote divides by mitosis to form two cells, which divide to form four cells, and so on. Seven days after ovulation, the mass of cells may implant in or attach to the uterine wall. The implanted mass of cells continues to develop for approximately 9 months to form a new individual (see chapter 29).

Follicle Development

Within the cortex of the ovary are specialized structures called ovarian follicles. These follicles contain the developing primary oocytes. As the primary oocytes progress through meiosis I, the ovarian follicle undergoes development, changing in size and structure (figure 28.14). The **ovarian cycle** refers to the reoccurring events that occur in the ovaries of sexually mature, nonpregnant females, particularly the changes in the ovarian follicles. The ovarian cycle is hormonally regulated. A more detailed description of hormonal regulation is presented in section 28.6. In this section, we will focus primarily on the anatomical changes in the ovarian follicle.

As discussed earlier, oogenesis begins when a female is in her mother's uterus. The primary oocytes present at birth are located in primordial follicles. A **primordial follicle** is a primary oocyte surrounded by a single layer of flat cells, called **granulosa cells** (figure 28.14, *step 2;* see figure 28.13). Once puberty begins, some of the primordial follicles become **primary follicles.** This transition to a primary follicle occurs as the oocyte enlarges and the single layer of granulosa cells becomes thicker and the cells become cuboidal in shape (figure 28.14, *step 3*). Subsequently, several layers of granulosa cells form, and a layer of clear material called the **zona pellucida** (zō′nă pel-lū′sid-dă; girdle + *pellucidus,* passage of light) is deposited around the primary oocyte.

Approximately every 28 days, hormonal changes stimulate some of the primary follicles to continue to develop. The primary follicle becomes a **secondary follicle** as fluid-filled spaces called **vesicles** form among the granulosa cells, and a capsule called the **theca** (thē′kă; a box) forms around the follicle (figure 28.14, *step 4;* see figure 28.13). Cells of the **theca interna** surround the granulosa cells, where they participate in the synthesis of ovarian hormones. The **theca externa** is primarily connective tissue that merges with the stroma of the ovary.

The secondary follicle continues to enlarge. When the fluid-filled vesicles fuse to form a single, fluid-filled chamber called the **antrum** (an′trŭm), the follicle is called a **mature follicle,** or *Graafian* (graf′ē-ăn) *follicle.* In the mature follicle, the oocyte is pushed off to one side and lies in a mass of granulosa cells called the **cumulus cells,** or *cumulus oophorus* (kū′mū-lŭs ō-of′ōr-ŭs; figure 28.14, *step 5*).

The mature follicle forms a lump on the surface of the ovary. During ovulation, the mature follicle ruptures, releasing a small amount of blood, follicular fluid, and the oocyte, surrounded by the cumulus cells, into the peritoneal cavity (figure 28.14, *step 8*). The cumulus cells resemble a crown radiating from the oocyte and are thus called the **corona radiata.**

Usually, only one mature follicle reaches the most advanced stages of development and is ovulated. The other follicles that were undergoing this maturation process degenerate, a process called **atresia.**

Fate of the Follicle

After ovulation, the ruptured mature follicle still has an important function. It is transformed into an endocrine structure called the **corpus luteum** (kōr′pŭs loo′tē-ŭm; yellow body). The corpus luteum has a convoluted appearance as a result of its collapse after ovulation (figure 28.14 , *step 10;* see figure 28.13). The granulosa cells and the theca interna, now called **luteal cells,** enlarge and begin to secrete hormones—progesterone and smaller amounts of estrogen.

If pregnancy occurs, the corpus luteum enlarges and remains active, particularly through the first trimester, as the **corpus luteum of pregnancy.** If pregnancy does not occur, the corpus luteum remains functional for about 10–12 days and then begins to degenerate. As the corpus luteum degenerates, progesterone and estrogen secretion decreases. Within the corpus luteum, connective tissue cells become enlarged and clear, giving the whole structure a whitish color. The structure is then called the **corpus albicans** (al′bī-kanz; white body; figure 28.14, *step 11*). The corpus albicans continues to shrink and eventually disappears after several months or even years.

ASSESS YOUR PROGRESS

40. *List the organs of the female reproductive system.*
41. *Name and describe the ligaments that hold the ovaries in place.*
42. *Discuss the coverings and structure of the ovary.*
43. *Starting with oogonia, describe the formation of secondary oocytes by meiosis. What are polar bodies?*
44. *Describe the formation of a zygote. How many pairs of chromosomes are in a zygote, and where do the chromosomes within a pair come from?*
45. *Distinguish among primordial, primary, secondary, and mature follicles.*
46. *Describe the process of ovulation.*
47. *What is the corpus luteum? What happens to it if fertilization occurs? If fertilization does not occur?*

Uterine Tubes

A **uterine tube,** also called a *fallopian* (fa-lō′pē-an) *tube* or *oviduct* (ō′vi-dŭkt), is associated with each ovary. It extends from the area of the ovary to the uterus (see figure 28.12). Each uterine tube is located along the superior margin of the broad ligament. The part of the broad ligament most directly associated with the uterine tube is called the **mesosalpinx** (mez′ō-sal′pinks).

The uterine tube opens directly into the peritoneal cavity to receive the secondary oocyte released from the ovary during ovulation. Near the ovary, the uterine tube expands to form the

infundibulum (in-fŭn-dib′ū-lŭm; funnel). Long, thin processes called **fimbriae** (fim′brē-ē; fringe) surround the opening of the infundibulum. The inner surfaces of the fimbriae consist of a ciliated mucous membrane. Movement of the cilia sweeps the secondary oocyte into the uterine tube.

The part of the uterine tube that is nearest the infundibulum is called the **ampulla.** It is the widest and longest part of the tube and accounts for about 7.5–8 cm of the total 10 cm length of the tube. Fertilization usually occurs in the ampulla. The part of the uterine tube nearest the uterus is the **isthmus.** It is much narrower and has thicker walls than the ampulla. The **uterine part,** or *intramural part,* of the uterine tube passes through the uterine wall and ends in a very small uterine opening.

The wall of each uterine tube consists of three layers: (1) the serosa, (2) the muscular layer, and (3) the mucosa (see figure 28.12). The outer **serosa** is formed by the visceral peritoneum, the middle **muscular layer** consists of longitudinal and circular smooth muscle cells, and the inner **mucosa** consists of a mucous membrane of simple ciliated columnar epithelium. The mucosa is arranged into numerous longitudinal folds.

The mucosa of the uterine tubes provides nutrients for the oocyte or, if fertilization has occurred, for the developing embryo as it passes through the uterine tube. The ciliated epithelium helps move the small amount of fluid and the oocyte, or the developing embryo, through the uterine tube.

Uterus

The **uterus** (ū′ter-ŭs) is the size and shape of a medium-sized pear—about 7.5 cm long and 5 cm wide (see figures 28.11 and 28.12). It is slightly flattened anteroposteriorly and is oriented in the pelvic cavity with the larger, rounded part, the **fundus** (fŭn′dŭs), directed superiorly and the narrower part, the **cervix** (ser′viks), directed inferiorly. The main part of the uterus, the **body,** is the region between the fundus and the cervix. A slight constriction called the **isthmus**

MICROBES In Your Body 28.1 Human Papillomavirus and Cancer

In the majority of the "Microbes in Your Body" features, we have focused on bacteria. However, recall from chapter 1 that the human microbiota also includes viruses, protists, and fungi. Human papillomaviruses (HPV) belong to a family of DNA viruses that are naturally found on the skin soon after birth. Over 100 types of HPV have been identified, and most are not harmful. However, more than 13 types have been shown to be oncogenic, or cancer-causing, with two types, HPV 16 and HPV 18, being linked to 70% of all cervical cancer cases. In addition, the number of cases of mouth and throat cancers caused by HPV is on the rise, especially in males. HPV has also been linked to cancers of the anus, vulva, vagina, and penis. It is the most common viral infection of the reproductive tract and is easily transferred from one person to another. Viral transfer only requires direct contact of genital skin. Infection with noncancer-causing forms of HPV, such as types 6 and 11, can result in development of genital warts or respiratory papillomatosis (tumors in the air passages).

Viruses take over their host cell's machinery to replicate and form thousands of new individual viruses. In the case of HPV, the virus targets undifferentiated cells in the stratified squamous epithelium of the outer body skin, as well as the stratified squamous epithelium of the mucosal lining of the reproductive tract or pharynx (see chapter 4). Once the virus is inside the host cell nucleus, its DNA is replicated at the same time the host cell DNA is replicated. HPV induces uncontrolled division in its host's cells. The continued division causes an accumulation of mutations, and eventually the cell becomes cancerous. New HPV are released through normal shedding of cells. Fortunately, full-blown metastasizing cancer from an HPV infection takes 15–20 years in females with normal immune systems and 5–10 years in females with weakened immune systems to develop, which gives enough time for screening, identification, and treatment.

Because HPV is present for years with no clinical symptoms, the most effective way to avoid the oncogenic forms is to be vaccinated against them. Acquisition of HPV is usually through sexual transmission, but the virus can also be passed from mother to child or from very close contact with an infected individual, such as providing personal hygienic care. Naturally acquired HPV does not usually elicit a strong immune response, which prevents development of a memory immune response. Immune memory protects against potential future exposures. Thus, the vaccine Gardasil® was developed to vaccinate against HPV types 16 and 18. There is now the Gardasil-9® vaccine that provides protection against 9 types of HPV. Additional HPV vaccines also protect against several other types of HPV. Vaccination for all male and female preteens and previously unvaccinated males and females through age 26 is recommended by the Centers for Disease Control and Prevention.

For males, genital warts caused by HPV are usually readily visible. However, there is not an approved HPV-related cancer test for males. For females, there are two types of HPV-related cancer screenings available. The first is the traditional Pap test for women. It is recommended that women ages 21–65 be screened with a Pap test every 3 years. The Pap test involves collecting cells from the surface of the cervix for examination under a microscope. If the cells are abnormally shaped, as precancerous or cancerous cells would be, it is indicative that further testing should be done. However, the Pap test can be negative for abnormal cells even if the female has HPV. If that is the case, the HPV test is recommended to test if HPV is present. The HPV test is also recommended for females over 30 years of age even if the female has been vaccinated for HPV, since the vaccine does not target all oncogenic forms of HPV. HPV testing is not recommended for females under age 30 nor for females who have had a hysterectomy. Eventually, with continued vaccination, the oncogenic types may become less relevant to human health.

Predict 4

The identity of the cell surface receptors used by HPV to enter their host cell has not been completely identified but will most likely be known within the next several years. Propose a future mechanism that could use the cell surface receptor protein to prevent HPV uptake and the subsequent development of cancer-inducing uncontrolled cell division.

marks the junction of the cervix and the body. Internally, the uterine cavity continues as the **cervical canal,** which opens through the **ostium** into the vagina.

The uterus is supported by (1) the broad ligament, (2) the **round ligaments** (see figure 28.12), and (3) the **uterosacral ligaments.** The broad ligament is a peritoneal fold extending from the lateral margins of the uterus to the wall of the pelvis on either side. It also surrounds and supports the ovaries and the uterine tubes. The round ligaments extend from the uterus through the inguinal canals to the labia majora of the external genitalia, and the uterosacral ligaments attach the lateral wall of the uterus to the sacrum. Normally, the uterus is *anteverted,* meaning that the body of the uterus is tipped slightly anteriorly. However, in some women, the uterus is retroverted, or tipped posteriorly.

In addition to the ligaments, skeletal muscles of the pelvic floor support the uterus inferiorly. If these muscles are weakened (e.g., in childbirth), the uterus can extend inferiorly into the vagina, a condition called a **prolapsed uterus.**

The uterine wall is composed of three layers: (1) the perimetrium, (2) the myometrium, and (3) the endometrium (see figure 28.12). The **perimetrium** (per-i-mē′trē-ŭm), or *serous layer,* is the visceral peritoneum that covers the uterus. The next layer, just deep to the perimetrium, is the **myometrium** (mī′ō-mē′trē-ŭm), or *muscular layer,* composed of a thick layer of smooth muscle. The myometrium accounts for the bulk of the uterine wall and is the thickest layer of smooth muscle in the body, although the structure is not the same in all areas of the uterus. In the cervix, the muscular layer contains less muscle and more dense connective tissue. The cervix is therefore more rigid and less contractile than the rest of the uterus. The innermost layer of the uterus is the **endometrium** (en′dō-mē′trē-ŭm). The endometrium is a mucous membrane that consists of a simple columnar epithelial lining and a connective tissue layer called the lamina propria. Simple tubular glands, called spiral glands, are scattered about the lamina propria and open through the epithelium into the uterine cavity. The endometrium consists of two layers: (1) the basal layer and (2) the functional layer. The thin, deep **basal layer** is the deepest part of the lamina propria and is continuous with the myometrium. The thicker, superficial **functional layer** consists of most of the lamina propria and the endothelium and lines the uterine cavity itself. The functional layer is so named because it undergoes changes and sloughing during the uterine cycle (see section 28.6). Small **spiral arteries** of the lamina propria supply blood to the functional layer of the endometrium. These blood vessels play an important role in the cyclic changes of the endometrium.

Columnar epithelial cells line the cervical canal, which contains **cervical mucous glands.** The mucus fills the cervical canal and acts as a barrier to substances that could pass from the vagina into the uterus. Near ovulation, the consistency of the mucus changes, easing the passage of sperm cells from the vagina into the uterus.

ASSESS YOUR PROGRESS

48. *Describe the structure of the uterine tube.*

49. *How are the uterine tubes involved in moving the oocyte or the zygote?*

50. *Name the parts of the uterus.*

51. *Describe the major ligaments holding the uterus in place.*

52. *Describe the layers of the uterine wall.*

Vagina

The **vagina** (vă-jī′nă) is the female organ of copulation, receiving the penis during intercourse. It also allows menstrual flow and childbirth. The vagina is a tube about 10 cm long that extends from the uterus to the outside of the body (see figure 28.12). Longitudinal ridges called **columns** extend the length of the anterior and posterior vaginal walls, and several transverse ridges called **rugae** (roo′gē) extend between the anterior and posterior columns. The superior, domed part of the vagina, the **fornix** (fōr′niks), is attached to the sides of the cervix, so that a part of the cervix extends into the vagina.

The wall of the vagina consists of an outer muscular layer and an inner mucous membrane. The muscular layer is smooth muscle that allows the vagina to increase in size to accommodate the penis during intercourse and to stretch greatly during childbirth. The mucous membrane is moist, stratified squamous epithelium that forms a protective surface layer. Lubricating fluid passes through the epithelium into the vagina. During intercourse, increased lubrication is provided by increased fluid released from the vaginal wall as well a secretions from the cervix and glands of the external genitalia.

The **hymen** (hī′men) is a thin mucous membrane that covers the **vaginal opening,** or *orifice.* Sometimes, the hymen completely closes the vaginal opening (a condition called imperforate hymen), and it must be removed to allow menstrual flow. More commonly, the hymen is perforated by one or several holes. The openings in the hymen are usually greatly enlarged during the first sexual intercourse. In addition, the hymen can be perforated earlier in a young woman's life, such as during strenuous physical exercise. Thus, the absence of an intact hymen does not necessarily indicate that a woman has had sexual intercourse, as was once thought.

ASSESS YOUR PROGRESS

53. *What are the functions of the vagina?*

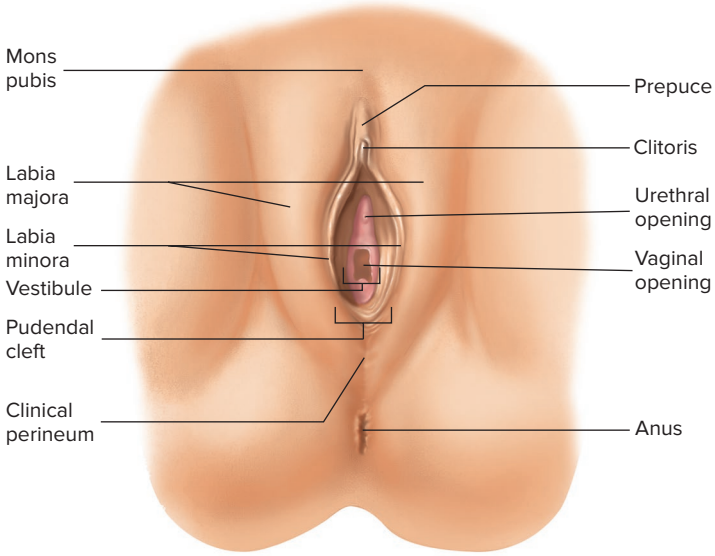
54. *Describe the layers of the vaginal wall. What are rugae and columns?*

55. *What is the hymen?*

Female External Genitalia

The female external genitalia are called the **vulva** (vŭl′vă), or *pudendum* (pū-den′dŭm). It consists of the vestibule and its surrounding structures (figure 28.15). The **vestibule** (ves′ti-bool) is the space into which the vagina opens posteriorly and the urethra opens anteriorly. A pair of thin, longitudinal skin folds called the **labia** (lā′bē-ă; lips) **minora** (sing. labium minus) form a border on each side of the vestibule. A small, erectile structure called the **clitoris** (klit′ō-ris) is located in the anterior margin of the vestibule. Anteriorly, the two labia minora unite over the clitoris to form a fold of skin called the **prepuce.**

The clitoris is usually less than 2 cm in length and consists of a shaft and a distal glans. Well supplied with sensory receptors, it



PROCESS FIGURE 28.15 Female External Genitalia
The female external genitalia are called the vulva. It consists of the vestibule, labia majora, labia minora, and clitoris.

initiates and intensifies levels of sexual sensation. The clitoris contains two erectile structures, the **corpora cavernosa,** each of which expands at the base end of the clitoris to form the **crus of the clitoris** and attaches the clitoris to the pelvic bones. The corpora cavernosa of the clitoris are comparable to the corpora cavernosa of the penis, and they become engorged with blood as a result of sexual excitement. In most women, this engorgement results in an increase in the diameter, but not the length, of the clitoris. With increased diameter, the clitoris makes better contact with the prepuce and surrounding tissues and is more easily stimulated.

Erectile tissue that corresponds to the corpus spongiosum of the male lies deep to and on the lateral margins of the vestibular floor on each side of the vaginal orifice. Each erectile body is called a **bulb of the vestibule.** Like other erectile tissue, it becomes engorged with blood and is more sensitive during sexual arousal. Expansion of the bulbs causes narrowing of the vaginal orifice and allows better contact of the vagina with the penis during intercourse.

Glands associated with the vestibule secrete a lubricating fluid that prevents drying of the vestibule. The ducts of the greater vestibular glands open on each side of the vestibule, between the vaginal opening and the labia minora. Additional small mucous glands, the **lesser vestibular glands,** or *paraurethral glands,* are located near the clitoris and urethral opening.

Lateral to the labia minora are two prominent, rounded folds of skin called the **labia majora** (sing. labium majus). Subcutaneous adipose tissue is primarily responsible for the prominence of the labia majora. The two labia majora unite anteriorly in an elevation over the pubic symphysis called the **mons pubis** (monz pū′bis). The lateral surfaces of the labia majora and the surface of the mons pubis are covered with coarse hair. The medial surfaces are covered with numerous sebaceous and sweat glands. The space between the labia majora is called the **pudendal cleft.** Most of the time, the labia majora are in contact with each other across the midline, closing the pudendal cleft and concealing the deeper structures within the vestibule.

Perineum

Similar to the male perineum, the female **perineum** is divided into two triangles by the superficial and deep transverse perineal muscles (figure 28.16; see figure 28.2). The anterior urogenital triangle contains the external genitalia, and the posterior anal triangle contains the anal opening. The region between the vagina and the anus is the **clinical perineum.** The skin and muscle of this region can tear during childbirth. Allowing the perineum to stretch slowly during delivery may prevent tearing. Alternatively, an incision called an **episiotomy** (e-piz-ē-ot′ō-mē, e-pis-ē-ot′ō-mē) is sometimes made in the clinical perineum. This clean, straight incision is easier to repair than a tear would be. The use of episiotomy has decreased since the 1970s, because research indicated that the procedure did not benefit the mother or the child in most cases.

ASSESS YOUR PROGRESS

56. *What are the vulva and vestibule?*
57. *What erectile tissue is in the clitoris and bulb of the vestibule?*
58. *What is the function of the clitoris and bulb of the vestibule?*

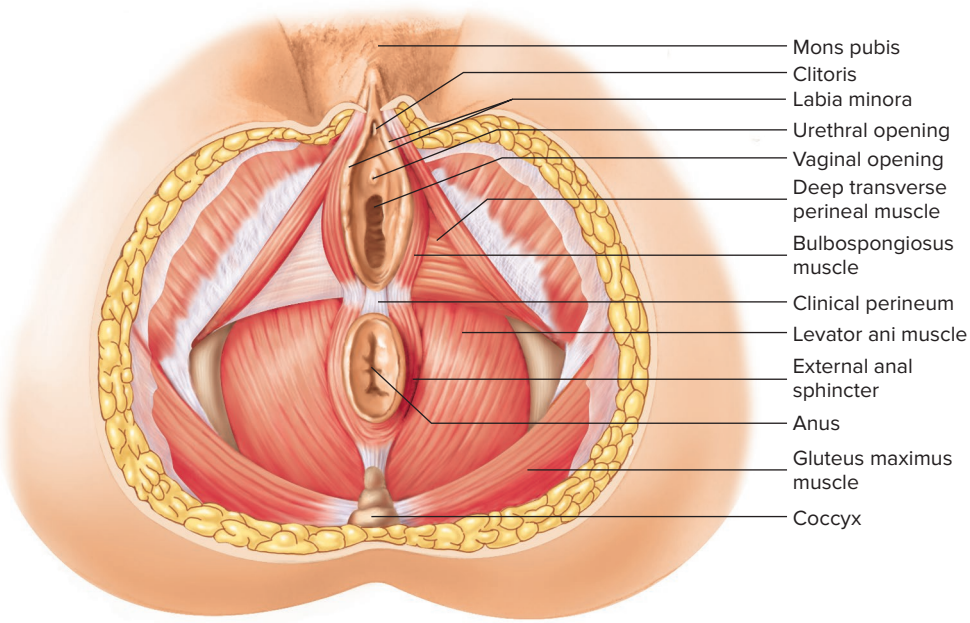


FIGURE 28.16 Inferior View of the Female Perineum
The perineum is divided into two regions by the superficial and deep transverse perineal muscles.

59. *Describe the labia minora, the prepuce, the labia majora, the pudendal cleft, and the mons pubis.*
60. *Where are the greater and lesser vestibular glands located? What is their function?*
61. *Describe the perineum.*
62. *What is the clinical perineum?*

Mammary Glands

The **mammary glands** are the organs of milk production and they are located within the **breasts** (figure 28.17). The mammary glands are modified sweat glands. Externally, the breasts of both males and females have a raised **nipple** surrounded by a circular, pigmented region called the **areola** (ă-rē′ō-lă). The areolae normally have a slightly bumpy surface caused by **areolar glands** just below the surface. The areolar glands are actually rudimentary mammary glands. Secretions from these glands lubricate and protect the nipple and the areola from chafing during nursing.

Before puberty, the general structure of the breasts is similar in both males and females. The breasts possess a rudimentary glandular system, which consists mainly of ducts with sparse alveoli. The female breasts begin to enlarge during puberty, primarily under the influence of estrogen and progesterone. Increased sensitivity or pain in the breasts often accompanies this enlargement. Males often experience the same sensations during early puberty, and their breasts can even develop slight swellings; however, these symptoms usually disappear fairly quickly. On rare occasions, the breasts of a male become enlarged, a condition called **gynecomastia** (gī′ne-kō-mas′tē-ă).

Each adult female mammary gland usually consists of 15–20 glandular **lobes** covered by a considerable amount of adipose tissue. It is primarily this superficial adipose tissue that gives the breast its form. The lobes of each mammary gland form a conical mass, with the nipple located at the apex. Each lobe has a single **lactiferous** (lak-tif′er-ŭs; milk-producing) **duct,** which opens independently of other lactiferous ducts on the surface of the nipple. Just deep to the surface, each lactiferous duct enlarges to form a small, spindle-shaped **lactiferous sinus.** In lactating females, milk accumulates in the lactiferous sinuses during milk letdown. The lactiferous duct supplying a lobe subdivides to form smaller ducts, each of which supplies a **lobule.** Within a lobule, the ducts branch and become even smaller. In milk-producing, or lactating,

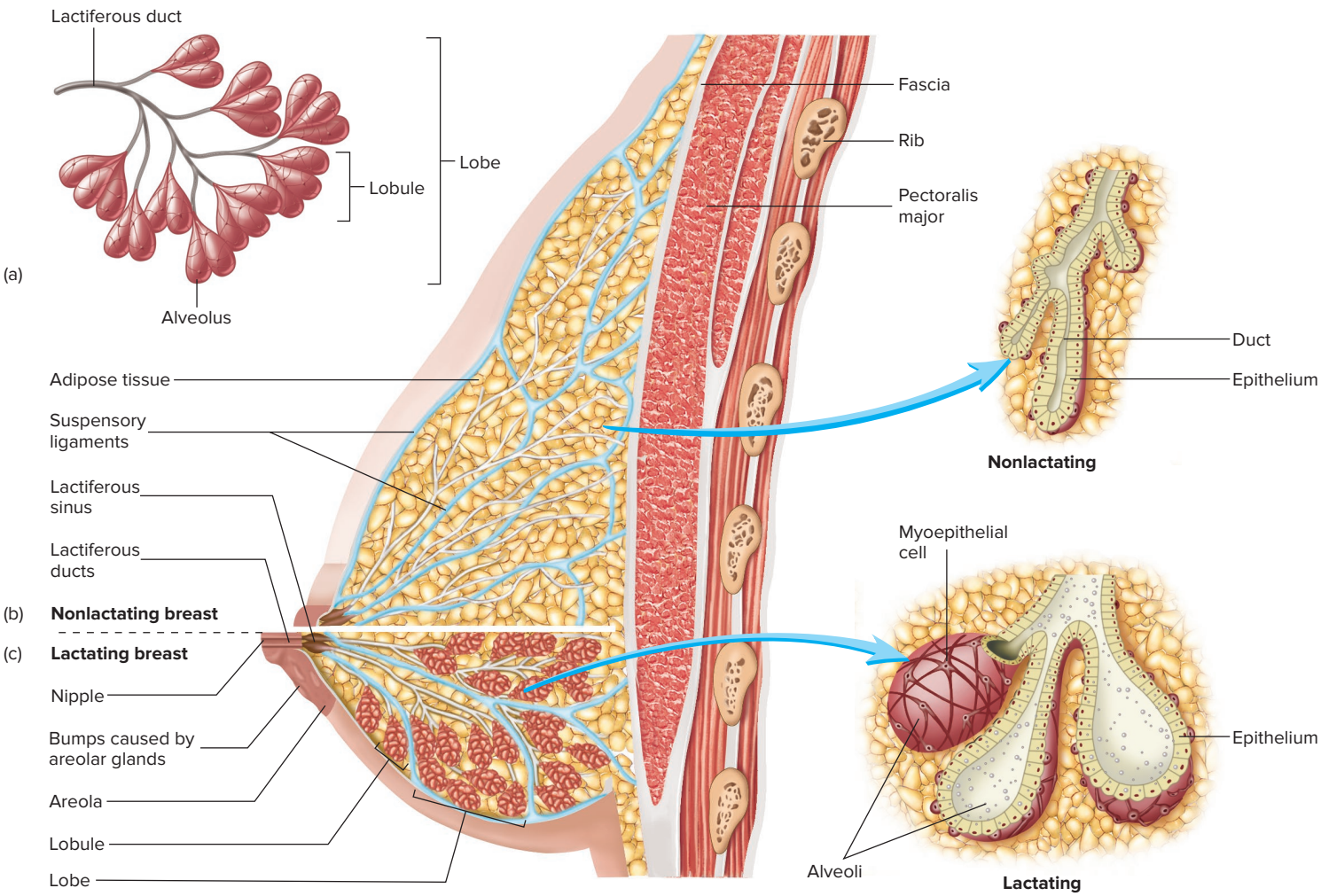


FIGURE 28.17 Anatomy of the Breast

(*a*) Lactiferous ducts divide to supply lobules, which form lobes. (*b*) In the nonlactating breast, only the duct system is present. (*c*) In the lactating breast, the ends of the mammary gland ducts have secretory sacs, called alveoli, that produce milk. Surrounding the alveoli are myoepithelial cells, which can contract, causing the milk to move out of the alveoli. AP|R

mammary glands, the ends of these small ducts expand to form secretory sacs called **alveoli. Myoepithelial cells** surround the alveoli and contract to expel milk (see chapter 29). In non-lactating mammary glands, only the duct system is present.

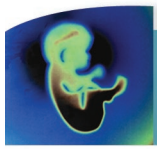
A group of **suspensory ligaments,** or *Cooper ligaments,* support and hold the breasts in place. These ligaments extend from the fascia over the pectoralis major muscles to the skin over the mammary glands and prevent the breasts from excessive sagging.

The nipples are very sensitive to tactile stimulation and contain smooth muscle cells that contract, causing the nipple to become erect in response to stimulation. These smooth muscle cells respond to stimuli such as touch, cold, and sexual arousal.

ASSESS YOUR PROGRESS

63. *Describe the anatomy of the mammary glands.*

64. *Trace the route taken by a drop of milk from its site of production to the outside of the body.*



Clinical IMPACT 28.6

Fibrocystic Changes in the Breast

Fibrocystic changes in the breast are benign and include the formation of fluid-filled cysts, hyperplasia (accelerated growth) of the duct system of the breast, and the deposition of fibrous connective tissue. Breast pain sometimes occurs, especially during the luteal phase of the menstrual cycle and continuing until menstruation. These changes occur in approximately 10% of women who are less than 21 years of age, 25% of women in their reproductive years, and 50% of women who are postmenopausal. The cause of the condition is not known.

Some evidence suggests that women with certain types of duct hyperplasia, along with a family history of breast cancer, have an increased likelihood of developing breast cancer.

Clinical GENETICS 28.1 Breast Cancer

Breast cancer is a serious, often fatal disease that most often occurs in women. It is the most common cancer in North American women. Greater than 75% of the breast cancer cases occur in women older than 50 years of age, and 85% involve cancer of the epithelium of the mammary gland ducts (ductal carcinoma).

The risk for breast cancer appears to be lower if a woman has had a child. Women who have never given birth are at a greater risk than those who have given birth. The younger a woman is when her first child is born, the lower her risk of developing breast cancer. However, the risk for breast cancer is not lowered in young women who become pregnant but do not carry to full term. It appears that differentiation of the breast epithelium caused by the first pregnancy decreases the risk for cancer by reducing the amount of undifferentiated epithelium in the breast.

Breast cancer development correlates with long-term exposure to high levels of estrogen. Since pregnancy delays the menstrual cycle and decreases estrogen secretion, this may explain its effect on breast cancer risk. In addition, early menopause or removal of the ovaries also correlate with a reduced cancer risk. In both cases there is a decreased exposure of breast tissue to estrogen. Unfortunately, hormone replacement therapy for postmenopausal women correlates with an increased incidence of cancer; however, breast cancer incidence decreases with the use of drugs that block the effect of estrogen receptors.

A number of environmental factors have been associated with the development of breast cancer. Exposure to ionizing radiation, especially during adolescence and during pregnancy when epithelial cells are dividing more rapidly, is correlated with breast cancer. High dietary fat intake and obesity are also linked to breast cancer, although the fish oil–derived omega-3 fatty acids may help prevent cancer. Breast cancer rates are low in Japanese women; however, Japanese women who immigrate to the United States and adopt a Western diet have breast cancer rates close to those of women in the United States. A number of environmental factors that mimic estrogen, such as components of plastics, fuels, pharmaceuticals, and chlorine-based chemicals (such as DDT, PCBs, and chlorofluorocarbons), may increase the incidence of breast cancer.

Between 5% and 10% of breast cancers are hereditary. Women who have inherited specific gene mutations have an increased risk for breast cancer. Therefore, a history of breast cancer in a close relative, such as a mother or sister, makes breast cancer more likely, and the risk increases further if more than one close relative has had breast cancer, especially if the cancer affected both breasts and if it occurred before menopause. Genetic tests can identify breast cancer genes. However, the presence of breast cancer genes does not mean that cancer will develop. Some women who are known to be at high risk because of their genetic makeup have frequent breast examinations, whereas others elect to have their breasts surgically removed before cancer develops.

Mutations in the *BRCA1* and *BRCA2* genes are responsible for about 30–40% of inherited breast cancers. The *BRCA* genes are tumor suppressor genes, which normally suppress cell division. A person who has two mutated *BRCA* alleles is much more likely to develop breast cancer. Although a person with one normal and one mutated *BRCA* allele may have sufficient tumor suppressor activity, she has a greater risk of developing cancer because only one mutation in the remaining normal *BRCA* allele is necessary to eliminate tumor suppressor activity. Consequently, a person who has inherited two normal alleles is much less likely to develop breast cancer than a person who has inherited one or two mutated alleles.

Another tumor suppressor gene is called *p53*. The cells of almost 50% of all cancers have a mutated *p53* gene, and these cancers are more aggressive and more often fatal than cancers without a mutated *p53* gene. Approximately 20–40% of individuals with hereditary breast cancer have a mutated *p53* gene. *P53* is a regulatory gene that has been called the "guardian of the genome," since *p53* is activated when DNA is damaged. Once activated, *p53* arrests the cell cycle and initiates the repair of damaged DNA before the cell cycle continues. If the DNA damage is too extensive, *p53* causes cell death. Thus, the *p53* gene normally helps repair or eliminate cells that may become cancer cells. When *p53* is mutated, this protection against aberrant cell proliferation is reduced and there is a greatly increased risk for tumor formation.

28.6 Physiology of Female Reproduction

LEARNING OUTCOMES

After reading this section, you should be able to

A. **Describe the changes that occur in females during puberty.**
B. **Explain the changes in the ovary and uterus during the ovarian and uterine cycles.**
C. **List the hormones of the female reproductive system and explain their functions and how their secretion is regulated.**
D. **Explain the events that occur during the female sexual act.**
E. **Describe the events that occur following fertilization of the oocyte and the process of implantation of the embryo.**
F. **Discuss menopause, including the changes that result from it.**

Female reproduction is under hormonal and nervous control. The development of the female reproductive organs and their normal function depend on a number of hormones. Estrogen and progesterone are the female reproductive hormones. The term *estrogen* actually refers to several hormones, including estradiol, estrone, and estriol. Estradiol is the primary estrogen in humans and the most prevalent in the blood.

Puberty in Females

The initial change that results in puberty is most likely maturation of the hypothalamus. In girls, puberty, which typically begins between ages 11 and 13 and is largely completed by age 16, is marked by the first episode of menstrual bleeding, which is called **menarche** (me-nar′kē; *mēn,* month + *archē,* beginning). During puberty, the vagina, uterus, uterine tubes, and external genitalia begin to enlarge. Adipose tissue is deposited in the breasts and around the hips, causing them to enlarge and assume an adult form. In addition, pubic and axillary hair grows. The development of sexual drive is also associated with puberty.

The changes associated with puberty primarily result from the increasing rate of estrogen and progesterone secretion by the ovaries. Before puberty, estrogen and progesterone are secreted in very small amounts. At puberty, the cyclical adult pattern of hormone secretion is gradually established.

Before puberty, the rate of GnRH secretion from the hypothalamus and the rate of LH and FSH secretion from the anterior pituitary are very low. Estrogen and progesterone from the ovaries have a strong negative-feedback effect on the hypothalamus and pituitary. After the onset of puberty, the hypothalamus and anterior pituitary secrete larger amounts of GnRH, LH, and FSH. Estrogen and progesterone have less of a negative-feedback effect on the hypothalamus and pituitary, and a sustained increase in estrogen concentration has a positive-feedback effect. The normal cyclical pattern of reproductive hormone secretion that occurs during the menstrual cycle becomes established.

ASSESS YOUR PROGRESS

65. *Define* menarche. *Describe other physical changes that occur during female puberty.*

66. *What changes occur in LH, FSH, estrogen, and progesterone secretion during puberty?*

Menstrual Cycle

The term **menstrual** (men′stroo-ăl) **cycle** technically refers to the cyclic changes in sexually mature, nonpregnant females. Although the term *menstrual cycle* typically refers to the changes in the uterus, the term is often used to refer to all the cyclic events in the female reproductive system, including alterations in hormone secretion and changes in the ovaries (table 28.2).

In discussing the *menstrual cycle,* we normally describe it as 28 days long, although it can be as short as 18 days in some women and as long as 40 days in others (figure 28.18). Variation in duration of the menstrual cycle occurs among females, but can also occur from month to month in the same female, depending on many factors including nutrition, stress, and level of activity.

So that it is easier to discuss the processes occurring in different components of the female reproductive system, the menstrual cycle is divided into the ovarian cycle and the uterine cycle. The *ovarian cycle* describes the changes that are associated specifically with the ovaries, and the *uterine cycle* describes the changes that are associated specifically with the uterus.

Ovarian Cycle

The term **ovarian cycle** refers to the regular events that occur in the ovaries of sexually mature, nonpregnant women during the menstrual cycle. This cycle can be divided into the follicular phase, which occurs before ovulation, and the luteal phase, which occurs after ovulation. During the follicular phase, a primordial follicle develops into a mature follicle as the primary oocyte within undergoes the first meiotic division (see figure 28.14). Given the idealized 28-day cycle, the follicular phase occurs between days 1 and 14. On day 14, the mature follicle ruptures, releasing the newly formed secondary oocyte. Following ovulation, the follicle forms the endocrine structure, the corpus luteum. Ovulation marks the transition to the luteal phase (days 15–28). The corpus luteum secretes progesterone and a small amount of estrogen. If fertilization of the secondary oocyte occurs, the corpus luteum continues to secrete progesterone to maintain pregnancy, particularly in the first trimester; after which, the placenta becomes the primary source for progesterone. If fertilization does not occur, the corpus luteum degenerates to form the corpus albicans (see figure 28.14).

The hypothalamus and anterior pituitary release hormones that control the events of the ovarian cycle. FSH from the anterior pituitary is primarily responsible for initiating the development of primary follicles, and as many as 25 follicles begin to mature during each ovarian cycle. However, normally only 1 is ovulated. The follicles that start to develop in response to FSH may not ovulate during the same ovarian cycle in which they begin to mature, but they may ovulate one or two cycles later. The remaining follicles degenerate. Larger, more mature follicles appear to secrete estrogen and other substances that have an inhibitory effect on other, less mature follicles.

TABLE 28.2 Hormone Secretion During the Menstrual Cycle

Ovarian Cycle: Follicular Phase		Ovulation	Luteal Phase
Uterine Cycle: Menses	**Proliferative Phase**		**Secretory Phase**
Pituitary Hormones			
LH levels are low and remain low; FSH increases somewhat.	Near the end of the proliferative phase, LH and FSH levels begin to increase rapidly in response to increases in estrogen.	Increasing levels of LH trigger ovulation. Ovulation generally occurs after LH levels have reached their peak. FSH reaches a peak about the time of ovulation and initiates the development of follicles that may complete maturation during a later cycle.	LH and FSH levels decline to low levels following ovulation and remain low during the secretory phase in response to increases in estrogen and progesterone.
Developing Follicles			
FSH secreted during menses causes several follicles to begin to enlarge.	As several follicles continue to enlarge, they begin to secrete estrogen. In addition, many follicles degenerate. By the end of the proliferative phase, only one of the follicles has become a mature follicle that is capable of ovulation.	Normally, a single follicle reaches maturity and ovulates in response to LH. The oocyte and some cumulus cells are released during ovulation.	Following ovulation, the granulosa cells of the ovulated follicle change to luteal cells and begin secreting large amounts of progesterone and some estrogen.
Estrogen			
The ovarian follicles secrete very little estrogen.	Near the end of the proliferative phase, the enlarging follicles begin to secrete increasing amounts of estrogen. The estrogen causes the pituitary gland to secrete increasing quantities of LH and smaller quantities of FSH. The positive-feedback relationship between estrogen and LH results in rapidly increasing LH and estrogen levels several days prior to ovulation. The rapid increase in LH triggers ovulation.	Estrogen, secreted by developing follicles, reaches a peak at ovulation.	Following ovulation, estrogen levels decline. After the luteal cells have been established, smaller amounts of estrogen are secreted by the corpus luteum.
Progesterone			
The ovarian follicles secrete very little progesterone.	Progesterone levels are low during the proliferative phase.	Progesterone levels are low.	Following ovulation, progesterone levels increase due to progesterone secretion by the corpus luteum. Progesterone levels remain high throughout the secretory phase and fall rapidly just before menses unless pregnancy occurs.
Uterine Endometrium			
The endometrium of the uterus undergoes necrosis and is eliminated during menses. The necrosis is a result of decreasing progesterone concentrations near the end of the proliferative phase.	In response to estrogen, endometrial cells of the uterus undergo rapid cell division and proliferate rapidly. In addition, the number of progesterone receptors in the endometrial cells increases in response to estrogen.	Ovulation occurs over a short time. It signals the end of the proliferative phase, as estrogen levels decline, and the onset of the secretory phase, as progesterone levels begin to increase.	Progesterone causes the endometrial cells to enlarge and secrete a small amount of fluid. The endometrium continues to thicken throughout the secretory phase. Near the end of the secretory phase, declining progesterone levels allow the spiral arteries of the endometrium to constrict, causing ischemia, and the endometrium becomes necrotic unless pregnancy occurs.

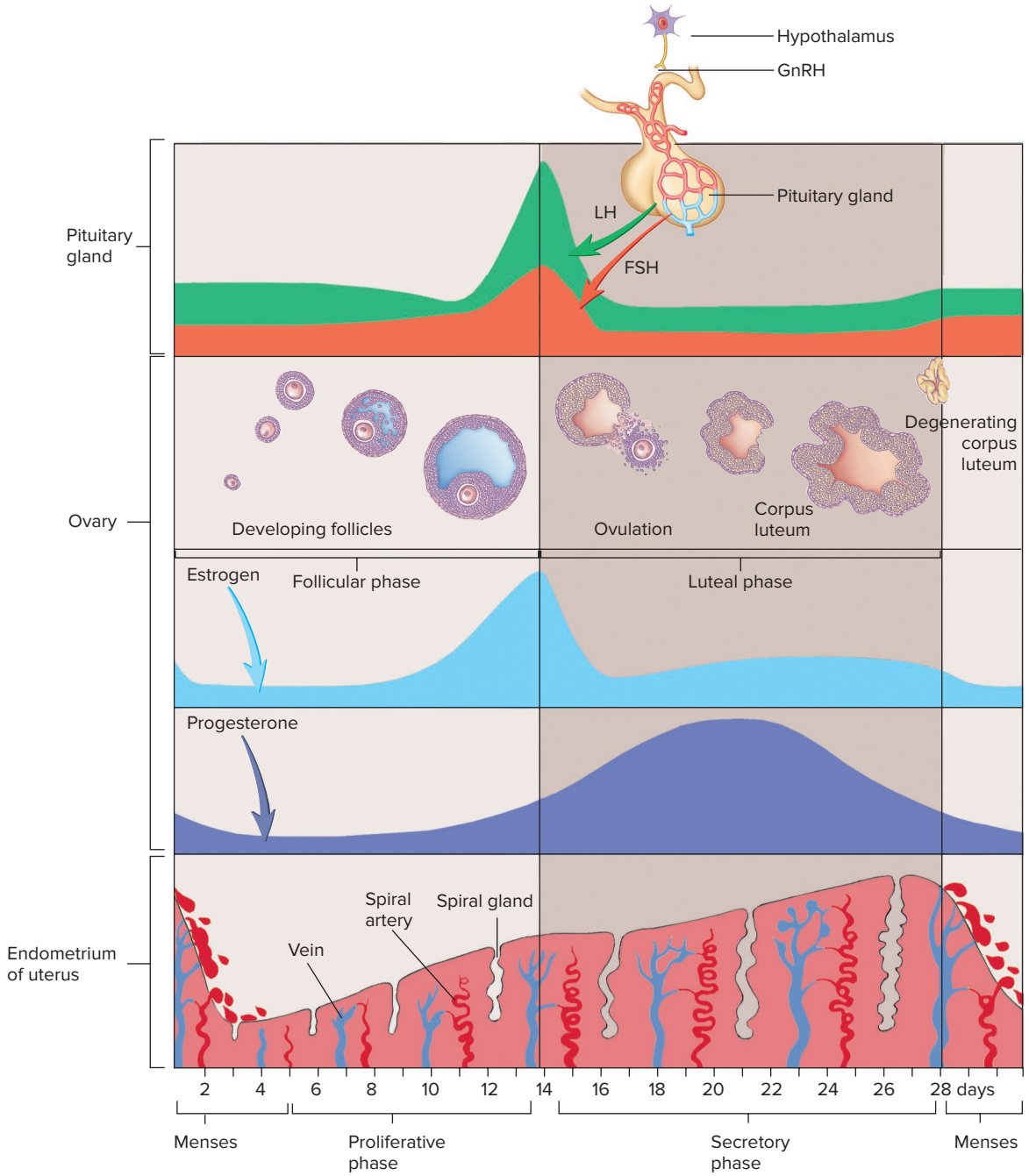


FIGURE 28.18 Menstrual Cycle
This graph depicts the changes that occur in blood hormone levels, follicles, and the endometrium during the menstrual cycle.

Early in the ovarian cycle, the release of GnRH from the hypothalamus increases, as does the sensitivity of the anterior pituitary to GnRH. These changes stimulate the anterior pituitary to produce and release small amounts of FSH and LH (figure 28.18). FSH and LH stimulate follicular growth and maturation. They also cause an increase in estrogen secretion by the developing follicles. FSH exerts its main effect on the granulosa cells, whereas LH exerts its initial effect on the theca interna cells and later on the granulosa cells.

Hormone production by granulosa cells of the follicle involve a complex interplay among the gonadotropins (LH and FSH), granulosa cells of the follicle, and theca interna cells of the ovary. LH stimulates the theca interna cells to produce androgens, which diffuse from these cells to the granulosa cells. FSH stimulates the granulosa cells to convert androgens to estrogen. In addition, FSH gradually increases LH receptors in the granulosa cells. Estrogen produced by the granulosa cells increases LH receptors in the theca interna cells. Estrogen, in turn, increases receptors for LH in both theca interna cells and granulosa cells.

After LH receptors in the granulosa cells have increased, LH stimulates the granulosa cells to produce progesterone, which diffuses

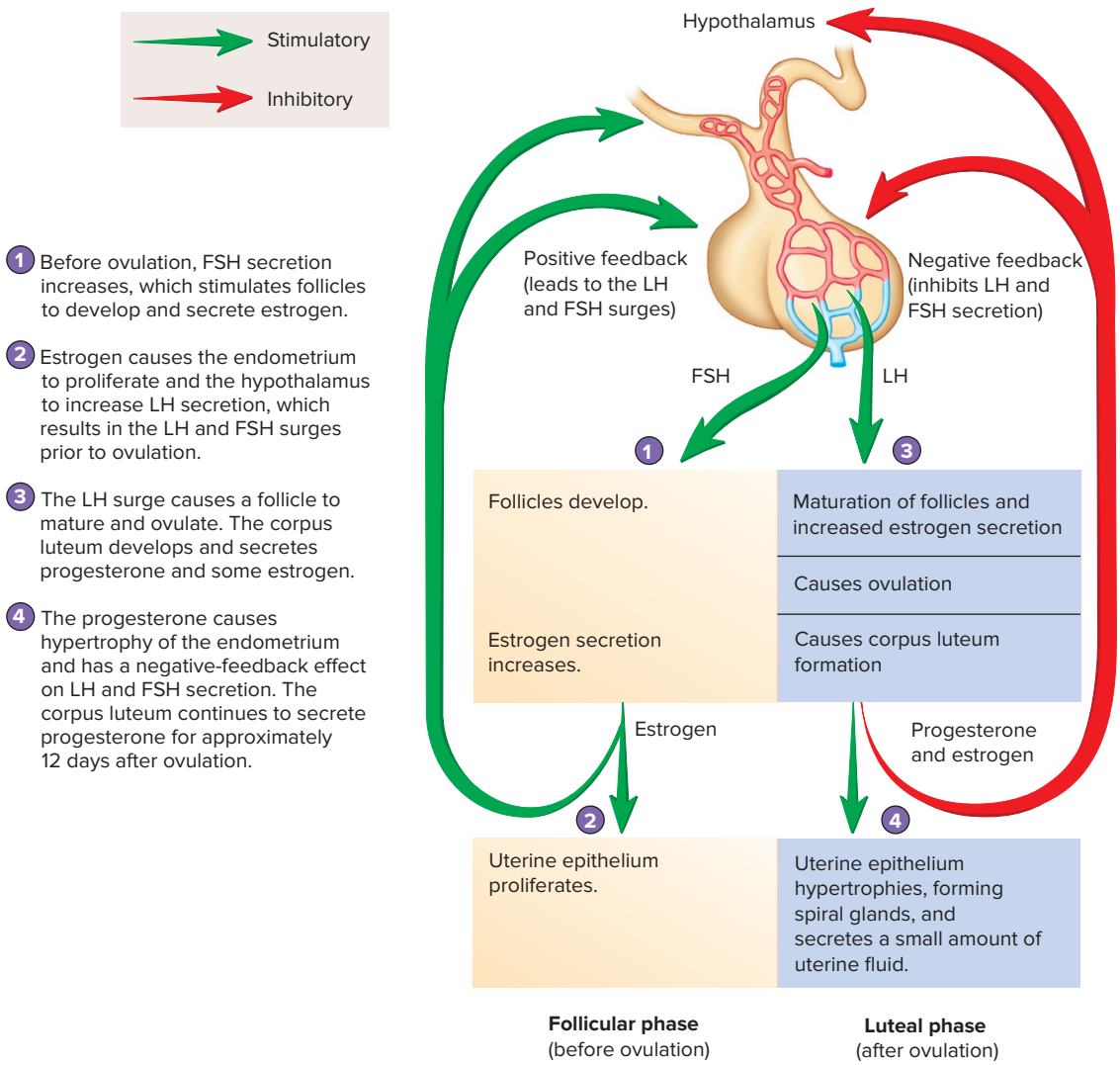
from the granulosa cells to the theca interna cells, where it is converted to androgens. These androgens are also converted to estrogen by the granulosa cells. Thus, the production of androgens by the theca interna cells increases, resulting in a gradual increase in estrogen secretion by granulosa cells throughout the follicular phase, even though only a small increase in LH secretion occurs. FSH levels actually decrease during the follicular phase because developing follicles produce inhibin, which has a negative-feedback effect on FSH secretion (see figure 28.18).

The gradual increase in estrogen levels, especially late in the follicular phase, begins to have a positive-feedback effect on LH and FSH release from the anterior pituitary. Consequently, as the estrogen level in the blood increases, it stimulates greater LH and FSH secretion. The sustained increase in estrogen is necessary for this positive-feedback effect. In response, LH and FSH secretion increases rapidly and in large amounts just before ovulation (figure 28.19). The increase in blood levels of both LH and FSH is called the **LH surge,** and the increase in FSH is called the **FSH surge.** The LH surge occurs several hours earlier and to a greater degree than the FSH surge, and the LH surge can last up to 24 hours.

Ovulation is intiatied by the LH surge and causes the ovulated follicle to become the corpus luteum. FSH can make the follicle more sensitive to the influence of LH by stimulating the synthesis of additional LH receptors in the follicles and by stimulating the development of follicles that may ovulate during later ovarian cycles.

The LH surge causes the primary oocyte to complete the first meiotic division just before or during the process of ovulation. Also, the LH surge triggers several events that are very much like inflammation in a mature follicle. These events result in ovulation. The follicle enlarges due to edema. Proteolytic enzymes break down the ovarian tissue around the follicle, causing the follicle to rupture, and the oocyte and some surrounding follicle cells are slowly released from the ovary.

Shortly after ovulation, the follicle's production of estrogen decreases. The remaining granulosa cells of the ovulated follicle are converted to corpus luteum cells and begin to secrete progesterone. After the corpus luteum forms, progesterone levels become



PROCESS FIGURE 28.19 Regulation of Hormone Secretion During the Ovarian Cycle

Hormone secretion is regulated from the anterior pituitary and the ovary before and after ovulation.

? *Explain how this process can involve positive feedback and negative feedback.*

much higher than before ovulation, and some estrogen is produced. The increased progesterone and estrogen have a negative-feedback effect on GnRH release from the hypothalamus. As a result, LH and FSH release from the anterior pituitary decreases. Estrogen and progesterone also cause the down-regulation of GnRH receptors in the anterior pituitary, and the anterior pituitary cells become less sensitive to GnRH. Because of the decreased secretion of GnRH and decreased sensitivity of the anterior pituitary to GnRH, the rate of LH and FSH secretion declines to very low levels after ovulation (figure 28.19; see figure 28.18).

If the ovulated oocyte is fertilized, the developing embryo secretes the LH-like substance **human chorionic gonadotropin (hCG),** which keeps the corpus luteum from degenerating. As a result, blood levels of estrogen and progesterone do not decrease, and menses does not occur. If fertilization does not occur, hCG is not produced. The cells of the corpus luteum begin to atrophy after day 25 or 26, and the blood levels of estrogen and progesterone decrease rapidly, resulting in menses.

Predict 5

Predict the effect on the ovarian cycle of administering a relatively large amount of estrogen and progesterone just before the preovulatory LH surge. Also predict the consequences of continually administering high concentrations of GnRH.

Uterine Cycle

The term **uterine cycle** refers to changes that occur primarily in the endometrium of the uterus during the menstrual cycle (figure 28.20; see figure 28.18). Other, more subtle changes also take place in the vagina and other structures during the menstrual cycle. Cyclic secretions of estrogen and progesterone are the primary cause of these changes.

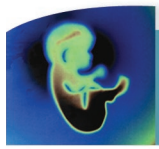
The uterine cycle can be divided into three phases: (1) menses, (2) the proliferative phase, and (3) the secretory phase (figure 28.20).

Menses (men′sēz) is a period of mild hemorhage that occurs approximately once each month, during which the functional layer of the endometrium is sloughed and expelled from the uterus (figure 28.20; *step 1*). **Menstruation** is the discharge of the sloughed endometrial tissue and blood.

The time between the ending of menses and ovulation is called the **proliferative phase** (figure 28.20, *step 2*). During the proliferative phase, the endometrium of the uterus begins to regenerate. The remaining epithelial cells rapidly divide and replace the cells of the functional layer that were sloughed during the last menses. A relatively uniform layer of low cuboidal endometrial cells is produced. The cells later become columnar, and the layer of cells folds to form tubular **spiral glands.** Blood vessels called **spiral arteries** project through the delicate connective tissue that separates the individual spiral glands to supply nutrients to the endometrial cells.

The period after ovulation and before the next menses is called the **secretory phase,** because of the maturation of and secretion by spiral glands (figure 28.20, *step 3*). During the secretory phase, the endometrium becomes thicker, and the spiral glands develop to a greater extent and begin to secrete small amounts of a fluid rich in glycogen. Approximately 7 days after ovulation, or about day 21 of the menstrual cycle, the endometrium is prepared to receive a developing embryonic mass, if fertilization has occurred. If the developing embryonic mass arrives in the uterus too early or too late, the endometrium does not provide a suitable environment for it.

The first day of menses is considered day 1 of the uterine cycle, and menses typically lasts 4–5 days. Recall that ovulation occurs on about day 14 of a 28-day menstrual cycle; however, the timing of ovulation varies from individual to individual and even within a single individual from one menstrual cycle to the next. The time between ovulation (day 14) and the next menses is typically 14 days. The time between the first day of menses and the day of ovulation is more variable than the time between ovulation and the next menses.



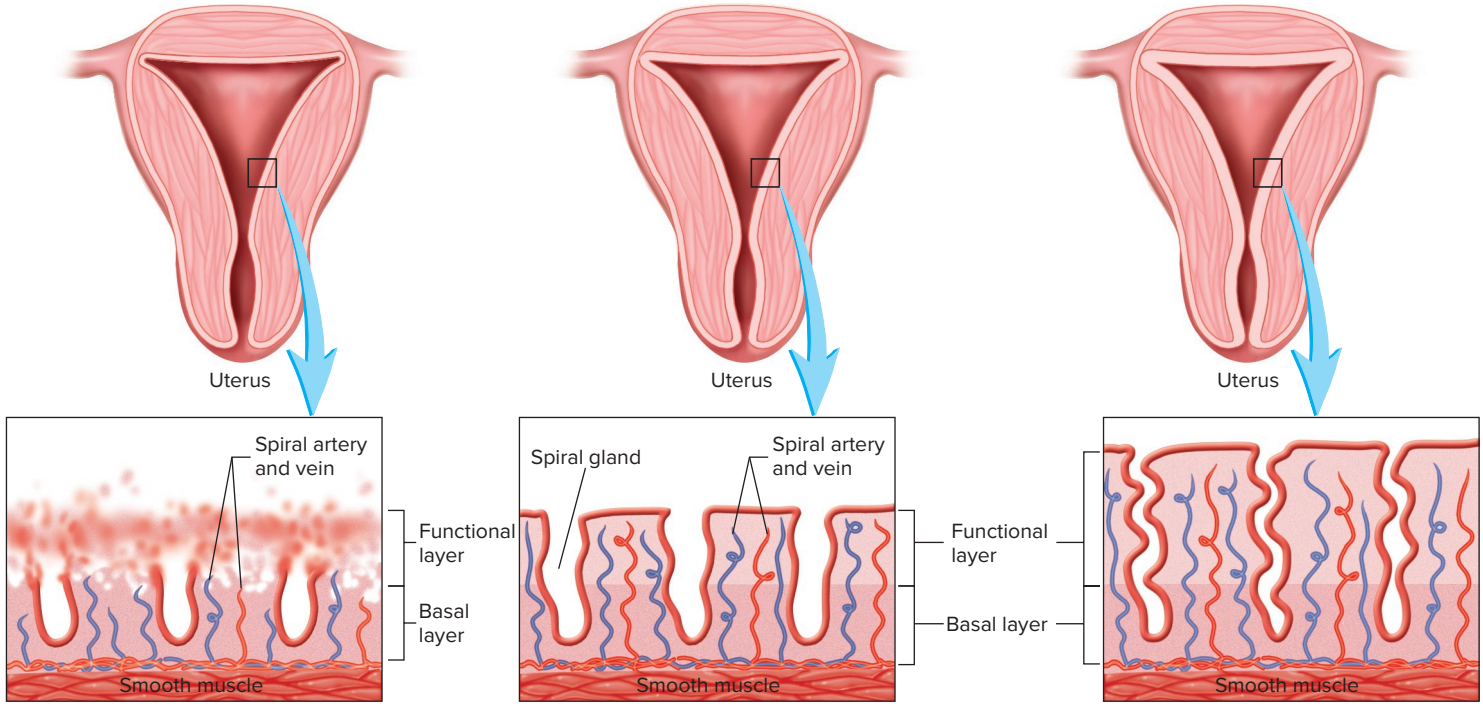
Clinical IMPACT 28.7

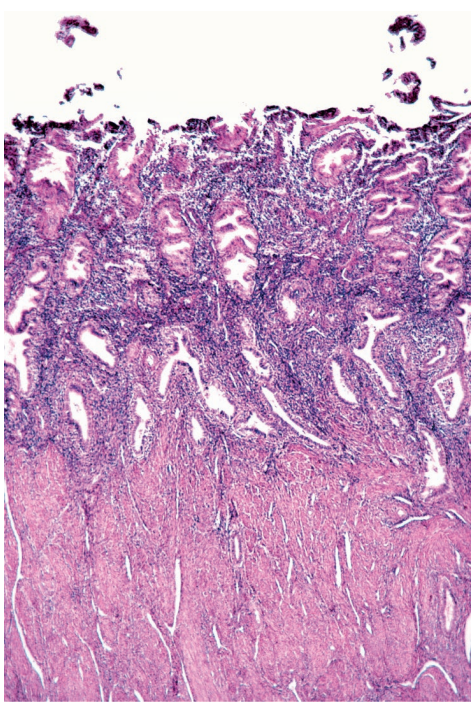
Menstrual Cramps and Amenorrhea

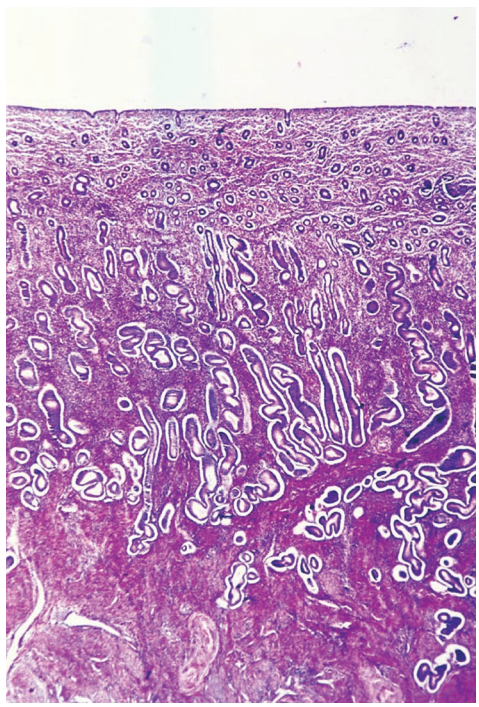
Menstrual cramps are the result of strong myometrial contractions that occur before and during menstruation. The cramps can result from excessive prostaglandin secretion. As the endometrium of the uterus sloughs off, it becomes inflamed, and prostaglandins are produced as part of the inflammatory process. Sloughing of the endometrium and uterine contractions are inhibited by progesterone but stimulated by estrogen. Many women can alleviate painful cramps by taking nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen, which inhibit prostaglandin biosynthesis, just before the onset of menstruation. These medications, however, are not effective in treating all painful menstruation, especially when the pain is not due to inflammation but to other conditions, such as tumors of the myometrium or obstruction of the cervical canal.

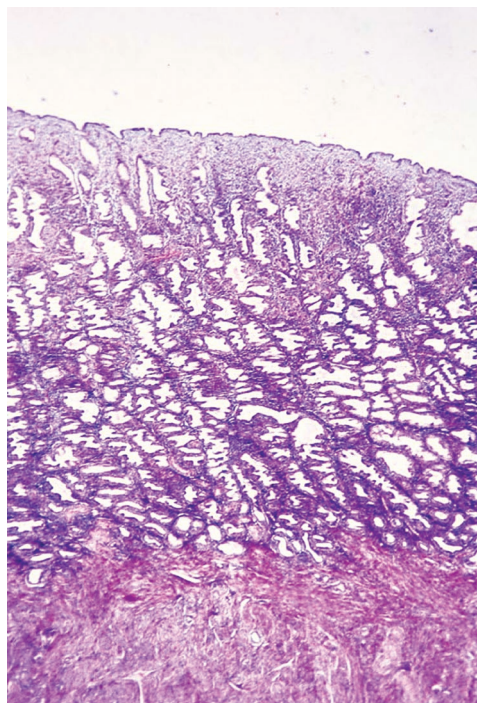
The absence of a menstrual cycle is called **amenorrhea** (ă-men-ō-rē′ă). If the pituitary gland does not function properly because of abnormal development, a female does not begin to menstruate at puberty. This condition is called **primary amenorrhea.** In contrast, if a female has had normal menstrual cycles and later stops menstruating, the condition is called **secondary amenorrhea.** One cause of secondary amenorrhea is anorexia, in which lack of food causes the hypothalamus to decrease GnRH secretion to levels so low that the menstrual cycle cannot occur. Many female athletes and ballet dancers who pursue rigorous training schedules have secondary amenorrhea. Physical stress coupled with inadequate food intake also result in very low GnRH secretion. Increased food intake, for anorexic women, and reduced training, for women who exercise intensely, generally restore normal hormone secretion and normal menstrual cycles.

Secondary amenorrhea can also result from a pituitary tumor that decreases FSH and LH secretion or from a lack of GnRH secretion from the hypothalamus due to head trauma or a tumor. In addition, secondary amenorrhea can occur due to a lack of normal hormone secretion from the ovaries, which can be caused by autoimmune diseases that attack the ovary or by polycystic ovarian disease, in which cysts in the ovary produce large amounts of androgens that are converted to estrogens by other body tissues. The increased estrogen prevents the normal cycle of FSH and LH secretion required for ovulation. Other hormone-secreting tumors of the ovary can also disrupt the normal menstrual cycle and result in amenorrhea.









1 Menses
The apical portion of the endometrium is the functional layer. It sloughs off as the spiral arteries remain in a constricted state in response to low levels of progesterone, depriving the functional layer of an adequate blood supply. Functional layer tissue and some blood make up most of the menstrual fluid. The basal layer of the endometrium remains intact.

2 Proliferative phase
Epithelial cells of the basal layer of the endometrium proliferate in response to estrogen. As a result, the epithelial cells and loose connective tissue on which they rest form the tubular, spiral glands. The spiral arteries found in the loose connective tissue between the spiral glands nourish the functional layer.

3 Secretory phase
Epithelial cells of the basal and functional layers undergo hypertrophy in response to progesterone. As a result, the spiral glands become more elongated and more spiral. Consequently, the endometrial layer reaches its greatest thickness. The spiral arteries can be seen in the loose connective tissue between the spiral glands. The spiral arteries remain dilated due to the presence of progesterone.

PROCESS FIGURE 28.20 Uterine Cycle

The uterine cycle is divided into three phases: (1) menses, (2) the proliferative phase, and (3) the secretory phase.

? *What events are occurring in the ovary during menses? At what point in the uterine cycle would a secondary oocyte form at the ovary?* (a) ©Educational Images Ltd./Custom Medical Stock Photo; (b, c) ©Biophoto Associates/Science Source AP|R

Estrogen causes the endometrial cells and, to a lesser degree, the myometrial cells to divide during the proliferative phase. It also makes the uterine tissue more sensitive to progesterone by stimulating the synthesis of progesterone receptor molecules within the uterine cells. After ovulation, during the secretory phase, progesterone from the corpus luteum binds to the progesterone receptors, resulting in cellular hypertrophy in the endometrium and myometrium and causing the endometrial cells to become secretory. Estrogen increases the tendency of the smooth muscle cells of the uterus to contract in response to stimuli, but progesterone inhibits smooth muscle contractions. When progesterone levels increase while estrogen levels are low, contractions of the uterine smooth muscle are reduced.

In uterine cycles in which pregnancy does not occur, progesterone and estrogen levels decline to low levels as the corpus luteum degenerates. The drop in these hormones initiates the beginning of the next uterine cycle, beginning with the next menses. As a consequence of low progesterone and estrogen levels, the uterine lining begins to degenerate. The spiral arteries constrict in a rhythmic pattern for longer and longer periods as progesterone levels fall. As a result, all but the basal parts of the spiral glands become ischemic and then necrotic. As the cells become necrotic, they slough into the uterine lumen. The necrotic endometrium, mucous secretions, and a small amount of blood released from the spiral arteries make up the menstrual fluid. Decreases in progesterone levels and increases in inflammatory substances that stimulate myometrial smooth muscle cells cause uterine contractions, which expel the menstrual fluid from the uterus through the cervix and into the vagina.

Predict 6

Predict the effect on the endometrium of maintaining high progesterone levels in the blood, including periods of time during which estrogen normally increases following menstruation.

ASSESS YOUR PROGRESS

67. *What are the major phases of the ovarian cycle? What happens during these phases?*

68. *On which day does ovulation occur?*

69. *What roles do FSH and LH play in the ovarian cycle?*

70. *Describe how the cyclic increase and decrease in FSH and LH is produced.*

71. *What is the importance of the LH surge and the FSH surge?*

72. *Where is hCG produced, and what effect does it have on the ovary?*

73. *What are the phases of the uterine cycle?*

74. *What is the length of a typical menstrual cycle? What event marks the beginning of a cycle?*

75. *What are the effects of estrogen and progesterone on the uterus?*

Female Sexual Behavior and the Female Sexual Act

The female sex drive, like the sex drive in males, depends on hormones. The adrenal gland and other tissues, such as the liver, convert steroids, such as progesterone, to androgens. Androgens and possibly estrogens affect cells in the brain, especially in the hypothalamus, to influence sexual behavior. However, androgens and estrogen alone do not control sex drive. In other words, sex drive cannot be predictably increased simply by injecting these hormones into healthy individuals. Psychological factors also affect sexual behavior. For example, after removal of the ovaries or after menopause, many females report an increased sex drive because they no longer are concerned with the probability of pregnancy.

The neural pathways, both sensory and motor, involved in controlling sexual responses are the same for females and males. Sensory action potentials are conducted from the genitals to the sacral region of the spinal cord, where reflexes that govern sexual responses are integrated. Ascending pathways, primarily the spinothalamic tracts (see chapter 14), conduct sensory information through the spinal cord to the brain, and descending pathways conduct action potentials back to the sacral region of the spinal cord. As a result, cerebral influences modulate the sacral reflexes. Motor action potentials are conducted from the spinal cord to the reproductive organs by both parasympathetic and sympathetic nerve fibers and to skeletal muscles by the somatic motor nerve fibers.

During sexual excitement, as a result of parasympathetic stimulation, erectile tissue within the clitoris and around the vaginal opening becomes engorged with blood. The nipples of the breast often become erect as well. The mucous glands within the vestibule, especially the vestibular glands, secrete small amounts of mucus. Large amounts of mucuslike fluid are also extruded into the vagina through its wall, although no well-developed mucous glands are within the vaginal wall. These secretions provide lubrication that allows for easy entry of the penis into the vagina and easy movement of the penis during intercourse. Tactile stimulation of the female's genitals that occurs during sexual intercourse, along with psychological stimuli, normally triggers an orgasm. The vaginal, uterine, and perineal muscles contract rhythmically, and muscle tension increases throughout much of the body. After the sexual act, a period of resolution characterized by an overall sense of satisfaction and relaxation occurs. In contrast to males, females can be receptive to further stimulation and can experience successive orgasms. Although orgasm is a pleasurable component of sexual intercourse, it is not necessary for females to experience an orgasm for fertilization to occur.

Female Fertility and Pregnancy

After sperm cells are ejaculated into the vagina during sexual intercourse, they are transported through the cervix, the body of the uterus, and the uterine tubes to the ampulla (figure 28.21). The forces responsible for moving sperm cells through the female reproductive tract include the swimming ability of the sperm cells and possibly the muscular contractions of the uterus and the uterine tubes. During sexual intercourse, oxytocin is released from the posterior pituitary of the female, and the semen introduced into the vagina contains prostaglandins. Both of these substances stimulate smooth muscle contractions in the uterus and uterine tubes, which may also enhance the movement of sperm cells through the female reproductive tract.

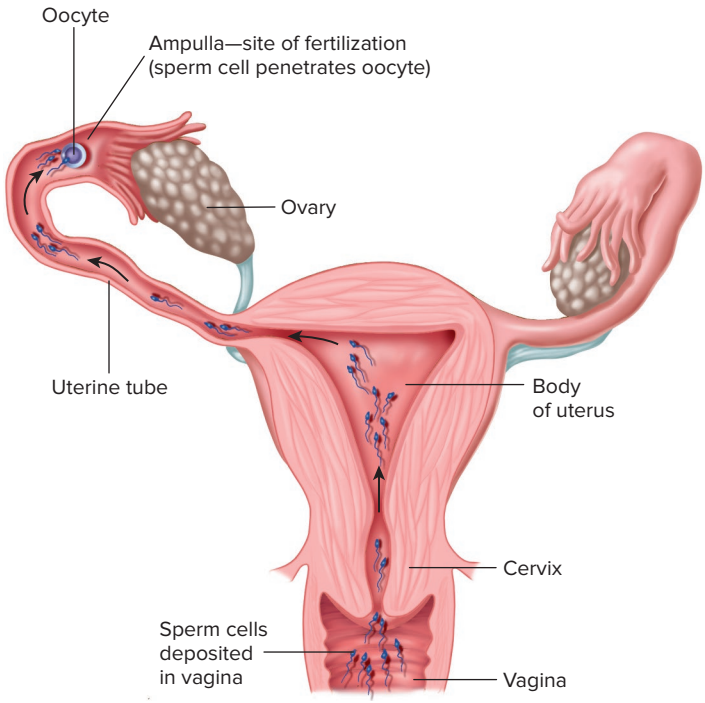


FIGURE 28.21 Sperm Cell Movement
Sperm cells are deposited into the vagina as part of the semen when the male ejaculates. Sperm cells pass through the cervix, the body of the uterus, and the uterine tube. Fertilization normally occurs when the oocyte is in the upper one-third of the uterine tube (the ampulla).

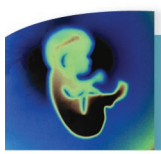
While passing through the vagina, uterus, and uterine tubes, the sperm cells undergo **capacitation** (kă-pas′i-tā′shŭn), which involves the removal of proteins and the modification of glycoproteins of the sperm cell plasma membranes. Following capacitation, as the sperm cells move through the female reproductive tract, some of them release acrosomal enzymes. These enzymes help the sperm cells penetrate the cervical mucus, cumulus mass, zona pellucida, and oocyte plasma membrane.

One sperm cell enters the secondary oocyte, and fertilization occurs (see chapter 29). The oocyte can be fertilized for up to 24 hours after ovulation, and some sperm cells remain viable in the female reproductive tract for up to 6 days, although most of them have degenerated after 24 hours. For fertilization to occur successfully, sexual intercourse must occur between 5 days before and 1 day after ovulation.

For the next several days following fertilization, a sequence of cell divisions occurs while the developing embryo passes through the uterine tube to the uterus. By 7 or 8 days after ovulation, which is day 21 or 22 of the average menstrual cycle, the endometrium of the uterus has been prepared for implantation. Estrogen and progesterone have caused it to reach its maximum thickness and secretory activity, and the developing embryo begins to implant. The outer layer of the developing embryo, the **trophoblast** (trof′ō-blast, trō′fō-blast), secretes proteolytic enzymes that digest the cells of the thickened endometrium (see chapter 29), and the developing embryo digests its way into the endometrium.

The trophoblast secretes hCG, which is transported in the blood to the ovary and causes the corpus luteum to remain functional. As a consequence, both estrogen and progesterone levels continue to increase rather than decrease. The secretion of hCG increases rapidly and reaches a peak about 8–9 weeks after fertilization (figure 28. 22). Subsequently, hCG levels in the circulatory system have declined to a lower level by 16 weeks and remain at a relatively constant level throughout the remainder of pregnancy. The detection of hCG in the urine is the basis for some pregnancy tests.

The progesterone and estrogen secreted by the corpus luteum are essential for the maintenance of pregnancy. After the **placenta** (plă-sen′tă) forms from the trophoblast and uterine tissue, however, it also begins to secrete progesterone and estrogen. After the first 3 months of pregnancy, the corpus luteum is no longer needed to maintain pregnancy. Instead, the placenta, in addition to its function of nutrient and waste exchange between the fetus and the mother, functions as an endocrine gland that secretes sufficient quantities of progesterone and estrogen to maintain pregnancy. Progesterone and estrogen levels increase in the woman's blood throughout pregnancy (figure 28.22).



Clinical IMPACT 28.8

Ectopic Pregnancy

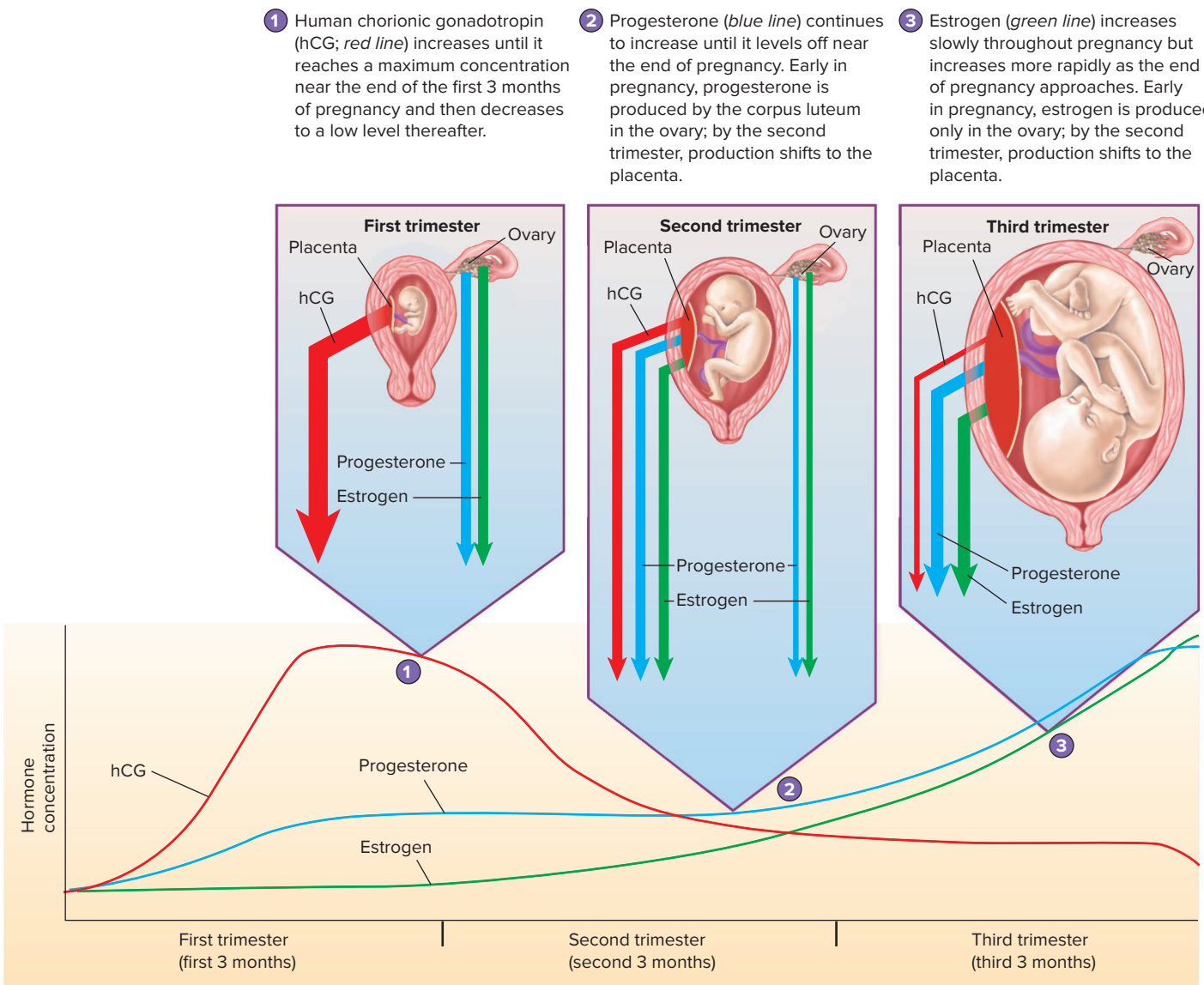
If implantation occurs anywhere other than in the uterine cavity, an ectopic pregnancy results. The most common site of ectopic pregnancy is the uterine tube. Implantation in the uterine tube is eventually fatal to the fetus and can cause the tube to rupture. The possibility of hemorrhage makes ectopic pregnancy dangerous to the mother as well.

In rare cases, implantation occurs in the mesenteries of the abdominal cavity. Although the fetus may develop normally, the pregnancy is considered extremely high-risk due to the serious threat to the mother's life and that of the fetus. Severe hemorrhaging at or near the time of delivery is the most serious concern. Delivery by cesarean section, with special precautions to prevent uncontrolled bleeding, can result in a successful outcome for this type of ectopic pregnancy. However, maternal mortality rates for abdominal pregnancies are significantly higher than for uterine tube ectopic pregnancies.

Menopause

When a female is 40–50 years old, menstrual cycles become less regular, and ovulation often does not occur consistently. Eventually, menstrual cycles stop completely. The cessation of menstrual cycles is called **menopause** (men′ō-pawz). The time from the onset of irregular cycles to the complete cessation, which is often 3 to 5 years, is called **perimenopause,** or the *female climacteric* (klī-mak′ter-ik, klī-mak-ter′ik).

Menopause is associated with changes in the ovaries. The number of follicles remaining in the ovaries of menopausal women is small. In addition, the follicles that remain become less sensitive to stimulation by LH and FSH; therefore, fewer mature follicles and corpora lutea are produced.



PROCESS FIGURE 28.22 Changes in Hormone Concentration and Changes in Hormone Secretion During Pregnancy

During pregnancy, hCG, progesterone, and estrogen are secreted. The placenta secretes hCG. Early in the pregnancy, the ovaries are responsible for progesterone and estrogen secretion; however, by midpregnancy, there is a shift to placental secretion of these two hormones.

? *Why is hCG secretion important during the first trimester?*

Older females experience gradual changes in response to the reduced amount of estrogen and progesterone produced by the ovaries (table 28.3). For example, some females experience sudden episodes of uncomfortable sweating (hot flashes), fatigue, anxiety, temporary decreases in sex drive, and occasionally severe emotional disturbances. Many of these symptoms can be treated successfully with hormone replacement therapy (HRT). HRT usually involves administering small amounts of estrogen, or estrogen in combination with progesterone, and then gradually decreasing the treatment over time. It appears that administering estrogen following menopause also helps prevent osteoporosis and may reduce colorectal cancer. However, although estrogen therapy has been successful, it prolongs the symptoms associated with menopause, in many females and some potential side effects are of concern, including an increased risk for breast, ovarian, and uterine cancer. In addition, HRT does not reduce the risk for heart disease for the first few years after the beginning of menopause. Some data indicate that the risk for heart attacks, strokes, and blood clots is also increased.

ASSESS YOUR PROGRESS

76. *Compare the female sexual act with the male sexual act.*

77. *Is an orgasm required for fertilization to occur?*

78. *Describe the transport of sperm cells through the female reproductive system.*

79. *What is capacitation of sperm cells?*

80. *Describe the events that follow fertilization.*

TABLE 28.3 Possible Changes Caused by Decreased Ovarian Hormone Secretion in Postmenopausal Females

Affected Structures and Functions	Changes
Menstrual cycle	Five to 7 years before menopause, the cycle becomes less regular; finally, the number of cycles in which ovulation occurs decreases, and corpora lutea do not develop.
Uterine tubes	Little change occurs.
Uterus	Irregular menstruation is gradually followed by no menstruation; the chance of cystic glandular hypertrophy of the endometrium increases; the endometrium finally atrophies, and the uterus becomes smaller.
Vagina and external genitalia	The dermis and epithelial lining become thinner; the vulva becomes thinner and less elastic; the labia majora become smaller; pubic hair decreases; the vaginal epithelium produces less glycogen; vaginal pH increases; reduced secretion leads to dryness; the vagina is more easily inflamed and infected.
Skin	The epidermis becomes thinner; melanin synthesis increases.
Cardiovascular system	Hypertension and atherosclerosis occur more frequently.
Vasomotor instability	Hot flashes and increased sweating are correlated with the vasodilation of cutaneous blood vessels; hot flashes are not caused by abnormal FSH and LH secretion but are related to decreased estrogen levels.
Sex drive	Temporary changes, such as either decreases or increases in sex drive, are often associated with the onset of menopause.
Fertility	Fertility begins to decline approximately 10 years before the onset of menopause; by age 50, almost all oocytes and follicles have been lost; the loss is gradual, and no increased follicular degeneration is associated with the onset of menopause.

81. *Describe implantation of the embryo and formation of the placenta.*

82. *Differentiate between menopause and the female climacteric.*

83. *What causes the changes that lead to menopause?*

28.7 Effects of Aging on the Reproductive System

LEARNING OUTCOME

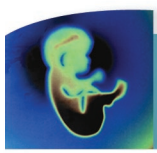
After reading this section, you should be able to

A. **Describe the major age-related changes in the male and female reproductive systems.**

Age-Related Changes in Males

Several age-related changes occur in the male reproductive system. In some but not all males, the size and weight of the testes decrease. In addition, there is an associated decrease in the number of interstitial cells and a thinning of the wall of the seminiferous tubules. These changes may be secondary to a decrease in blood flow to the testes or to a gradual decrease in reproductive hormone production. In addition, the rate of sperm cell production is reduced, and the number of abnormal sperm cells produced increases. However, sperm cell production does not stop, and it remains adequate for fertility for most males.

Age-related changes become obvious in the prostate gland by age 40. By age 60, there is a clear decrease in blood flow to the prostate gland, an increased thickness in the epithelial cell lining of the prostate gland, and a decrease in the number of functional smooth muscle cells in the wall of the prostate. The changes in the prostate gland do not decrease fertility, but the incidence of benign prostatic hypertrophy (enlargement of the prostate) increases substantially and can lead to difficulty in urination due to compression of the prostatic urethra. A significant number (approximately



Clinical IMPACT 28.9

Causes of Female Infertility

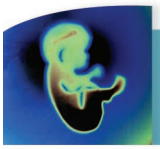
The causes of infertility in females include malfunctions of the uterine tubes, reduced hormone secretion from the pituitary gland or the ovaries, and interruption of implantation.

Uterine tube malfunction can occur when infections result in pelvic inflammatory disease (PID), which causes adhesions to form in one or both uterine tubes.

Inadequate secretion of LH and FSH can result in reduced ovulation. The insufficient amount of hormones may be caused by hypothyroidism, trauma to the hypothalamus, infarctions of the hypothalamus or anterior pituitary gland, or tumors.

Interruption of implantation may result from uterine tumors or conditions causing abnormal ovarian hormone secretion.

Endometriosis (en′dō-mē-trē-ō′sis), in which endometrial tissue is present in abnormal locations, also reduces fertility. Generally, endometriosis is thought to result when some endometrial cells pass from the uterus through the uterine tubes into the pelvic cavity, where they invade the peritoneum. Because the endometrium is sensitive to estrogen and progesterone, the areas where the endometrial cells have invaded periodically become inflamed. Endometriosis is one possible cause of abdominal pain associated with menstruation.



Clinical IMPACT 28.10 Birth Control Methods

Birth control methods, also called *contraception methods,* are procedures or devices used to prevent pregnancy (table 28.4). In addition, protection from sexually transmitted infections (STIs, table 28.5) can be achieved with some birth control methods. There are six main types of birth control. They are listed in order from the most effective methods to the least effective methods: (1) long-acting reversible contraception, (2) sterilization, (3) hormonal methods, (4) barrier methods, (5) fertility awareness, and (6) emergency contraception. For each of these methods, there are measures of effectiveness for perfect use each time compared with typical use. We express the effectiveness of a particular birth control method as the number out of every 100 females who could become unintentionally pregnant with typical use within the first year of beginning a particular method. We present a few examples of each type of birth control rather than an exhaustive list of all birth control methods that are available.

Long-Acting Reversible Contraception

This type of birth control provides the highest rates of effectiveness with typical use. In addition, these methods do not require daily action or action with each incidence of sexual intercourse. However, none of these listed methods reduce the risk of STIs.

1. *Intrauterine devices*
   An **intrauterine device (IUD)** is a medical device that is placed in a female's uterus through the cervix by a medical caregiver. There are two main types of IUDs: (1) a copper IUD and (2) a synthetic progesterone-coated or levonorgestrel-releasing (LNG-IUD). Copper IUDs are effective for up to 10 years, while the LNG-IUDs are effective for approximately 5 years. Both types of IUDs work primarily by preventing fertilization through thickening of cervical mucus. The thicker mucus prevents sperm cells from entering the uterus. In addition, the copper from the copper IUDs damages sperm cells. Both types of IUDs result in less than 1 unintended pregnancy/100 females.
2. *Birth control implant*
   The **implant** is a small capsule containing etonogestrel, or synthetic progesterone, that a female's medical caregiver places under the skin of the upper arm. It slowly releases hormone for a period of 3–5 years. The hormone acts to thicken the cervical mucus, which prevents sperm cells from entering the uterus; the hormone also prevents ovulation. The implant results in less than 1 unintended pregnancy/100 females.

Permanent Methods of Birth Control

A male or female may choose a surgical sterilization method as a form of permanent birth control. None of these listed methods reduce the risk of STIs.

1. *Female sterilization*
   In females, the most common permanent birth control is **tubal ligation** where the uterine tubes are blocked or cut. The cutting or blocking of the uterine tubes prevents the oocyte and sperm cell from meeting, and thus prevents fertilization. Tubal ligations result in less than 1 unintended pregnancy/100 females.
2. *Male sterilization*
   The permanent form of birth control in males is a **vasectomy** where the ductus (vas) deferens is cut or blocked. A vasectomy prevents sperm cells from being ejaculated as part of the semen. Thus, no sperm cells enter the vagina. Three months after surgery, a vasectomy results in less than 1 unintended pregnancy/100 females.

Hormonal Methods of Birth Control

The principal mechanism of hormonal birth control methods is prevention of ovulation. Development of male hormonal birth control to inhibit sperm cell production is under investigation and is not widely available. Some of these methods require daily attention and none of these reduce the risk of STIs.

1. *Injectables*
   These hormonal methods must be injected under the skin every 2–3 months for progesterone-only injectables and into the muscle every month for combined injectable contraceptives. The progesterone-only injectable acts to thicken cervical mucus to prevent sperm cell entry into the uterus as well as preventing ovulation. The combined injectables prevent ovulation. Injectables result in about 6 unintended pregnancies/100 females. The challenge with injectables is being sure to receive repeat injections within the proper time frame.
2. *Pills*
   Oral contraceptives are taken almost exclusively by females since male oral contraceptives are not currently available. One form, referred to as "the pill," is a combination of estrogen and progestogen (synthetic progesterone) and works to prevent ovulation. Another form, "the minipill," contains only progestogen and works to thicken cervical mucus. Each of these pills results in about 9 unintended pregnancies/100 females. The challenge with the pills is remembering to take a pill each day.
3. *Patch and vaginal ring*
   Each of these methods continuously releases progestogen and estrogen for 3 weeks and then a new one is put into place. The transdermal contraceptive patch, also simply called the patch, is applied directly to the skin every 3 weeks. The vaginal ring is inserted into the vagina and remains in place for 3 weeks and is then removed. A new ring is inserted after 1 week. Each of these methods prevents ovulation and results in about 9 unintended pregnancies/100 females. The challenge is to remember to change the patch or ring on the appropriate schedule.

Barrier Methods of Birth Control

A barrier method is a device that physically prevents the sperm cells and oocyte from meeting. The major advantage of certain barrier methods is that these are the only contraceptive methods that also reduce the risk of STI transmission. To reduce the risk of STIs, the Centers for Disease Control and Prevention (CDC) recommend that condoms should always be used.

1. *Female condom*
   A female condom is made of thin, soft plastic, which fits inside the female's vagina. The condom traps any sperm cells released into the vagina and prevents them from reaching the oocyte. It also protects against HIV and other STIs. Use of the female condom results in about 21 unintended pregnancies/100 females. The challenge with the female condom is that it must be inserted before each incidence of sexual intercourse.
2. *Male condom*
   A male condom is a covering that is placed over a male's erect penis. Condoms can be made of several different materials, including natural latex, Vytex©, which has been treated to remove 90% of proteins responsible for latex allergies, or synthetic latex,

called polyisoprene. There are also completely nonlatex condoms made of polyurethane, and "lambskin" condoms, which are made of sheep intestine. However, the latter have not been shown to reduce the risk of STIs. All other condoms reduce the risk of HIV transmission and many other STIs. Use of male condoms results in approximately 18 unintended pregnancies/100 females. The challenge is to use them correctly with every instance of intercourse.

3. *Diaphragm*
   A diaphragm is a flexible latex dome that a female inserts into her vagina along with a spermicide before each instance of sexual intercourse. The diaphragm will unfold and fit over the cervix to block sperm cells from entering the uterus. However, unlike the other barrier methods, such as the male and female condoms, a diaphragm does not prevent transmission of STIs. In addition, a diaphragm must be refitted in the event of a significant (20%) weight gain or loss. A diaphragm results in about 12 unintended pregnancies/100 females.

Fertility-Awareness–Based Methods of Birth Control

With fertility-awareness–based methods, a female determines and tracks the days when she is most fertile. In each menstrual cycle, there is approximately a 6–8 day window during which a female has the greatest chance of becoming pregnant if she has unprotected intercourse. This window is due to the fact that both the oocyte and sperm cell are viable for a period of time inside the female reproductive tract. Sperm cells are able to survive up to 5 days inside the female. The oocyte is viable for up to 24 hours after ovulation. Thus, fertility-awareness–based methods require focused attention. It is estimated that only 25–30% of females know when their most fertile period occurs.

1. *Standard days method*
   A female tracks her fertile period using a tracking tool such as cycle beads, or an app for her smartphone. This method is effective for females whose cycles are 26–32 days long. Using this method, around 12 in 100 females experienced an unintended pregnancy.
2. *Two-day method*
   Females monitor their cervical mucus traits such as color and consistency. Around 14 in 100 females become unintentionally pregnant using this method. When cervical mucus monitoring is combined with body temperature tracking, this method is called the symptothermal method and results in only 2 in 100 females becoming unintentionally pregnant.

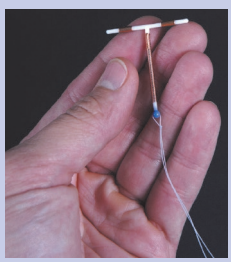
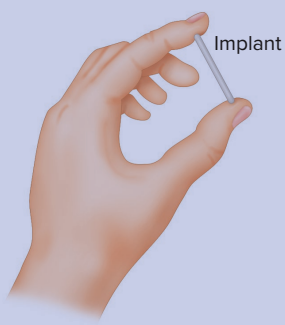
Emergency Contraception

If unprotected intercourse occurs, ingestion of emergency contraceptive pills or insertion of a copper IUD significantly lowers the possibility of an unintended pregnancy. Both methods must be utilized within 5 days after unprotected intercourse. Emergency contraceptive pills such as Plan B (the morning-after pill) or Ella (the week-after pill) disrupt or delay ovulation. The copper IUD works to immobilize sperm cells preventing them from reaching the oocyte. It also causes thinning of the endometrium and potentially inhibits the ability of oocytes to be fertilized. These methods result in only 1 in 100 unintended pregnancies.

Traditional Methods of Birth Control

Some traditional birth control methods are still in use; however, only abstinence is 100% effective in prevention of unintended pregnancies. Other traditional methods include the withdrawal method where the male ejaculates outside the female's body, and the calendar method, or rhythm method, where fertile days are estimated. Each of these traditional methods results in approximately 15–17 in 100 females becoming unintentionally pregnant.

TABLE 28.4 Methods of Birth Control

Birth Control Method		Effectiveness (number of females in 100 who became unintentionally pregnant with typical use)
Long-acting reversible contraception		
IUD		<1
Birth control implant		<1

(continued)

TABLE 28.4 Methods of Birth Control

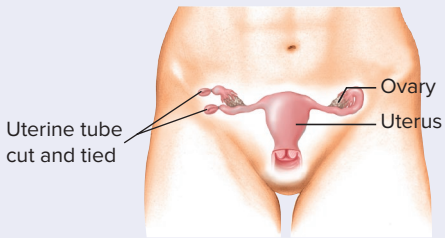
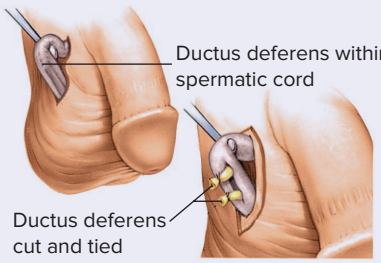
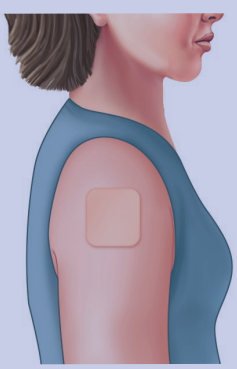
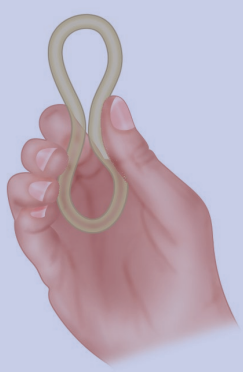
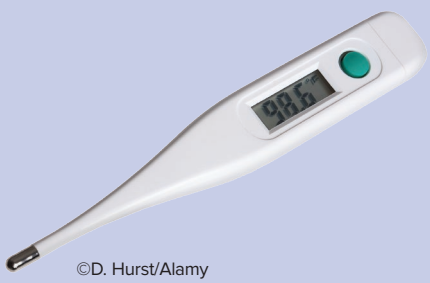
Birth Control Method		Effectiveness (number of females in 100 who became unintentionally pregnant with typical use)
Permanent Methods		
Female		<1
Male		<1
Hormonal Methods		
Injectables	 Injectable	6
Pills	 ©Martin Shields/Alamy	9
Patch and vaginal ring	 Patch  Ring	9

TABLE 28.4 Methods of Birth Control

Birth Control Method	Effectiveness (number of females in 100 who became unintentionally pregnant with typical use)
Barrier Methods	
Female condom	21
 Female condom	
Male condom	18
 Male condom	
Diaphragm	12
 ©McGraw-Hill Education/Jill Braaten, photographer	
Fertility-Aawareness–Based Methods	
Standard and 2-day method	12-14
 ©Alexey Boldin/Shutterstock	
Symptothermal	2
 ©D. Hurst/Alamy	

Systems PATHOLOGY

Benign Uterine Tumors

Background Information

Molly is 43 years old and has four children. She noticed that menstruation was becoming gradually more severe and lasting up to several days longer each time. After menstruating almost continuously for 2 months, Molly made an appointment with her physician.

Palpation of the uterus indicated the presence of enlarged masses in Molly's uterus. The doctor performed a D&C, which is dilation of the cervix and scraping (curettage) of the endometrium to remove growths or other abnormal tissues. The results of the D&C indicated that Molly had developed leiomyomas.

Leiomyomas (lī′-ō-mī-ō′măs; figure 28.23) are also called fibroid tumors of the uterus. They are one of the most common disorders of the uterus and are the most frequent tumor in women, affecting one of every four. However, three-fourths of the women with this condition experience no symptoms. The enlarged masses that originate from smooth muscle tissue compress the uterine lining (endometrium), resulting in ischemia and inflammation. The increased inflammation, which shares some characteristics with menstruation, results in frequent and severe menses, with associated abdominal cramping due to strong uterine contractions. Constant menstruation is a frequent manifestation of these tumors, and consequently, other systems of the body are affected (figure 28.24). The presence of these tumors and the constant menstruation are the most common reasons women elect to have the uterus removed, a procedure called a **hysterectomy** (his-ter-ek′tō-mē).

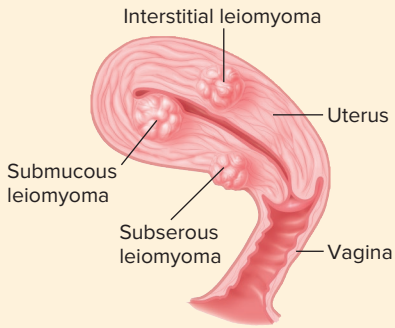


FIGURE 28.23 Leiomyomas

Leiomyomas, or fibroid tumors, are enlarged masses of smooth muscle. They can be located near the mucosa (submucous), within the myometrium (interstitial), or near the serosa (subserous).

Predict 7

When discussing her condition with her mother, Molly discovered that her mother had experienced frequent menses that were irregular and prolonged when she was in her late forties. Molly's mother did not have a hysterectomy, and in a few years the frequency of menstruation gradually began to subside. Explain.

15%) of males older than 60 require medical treatment for benign prostatic hypertrophy; by age 80, this number is 50%. Before age 50, prostate cancer is rare. After 55, it is the third-leading cause of death from cancer in males.

Erectile dysfunction increases in males with age. By age 60, approximately 15% of males have ED; by 80, 50% do. In addition, the amount of fibrous connective tissue in the erectile tissue of the penis increases, which generally decreases the speed of erection by age 60.

Although there is great variation among males, many exhibit decreases in the frequency of sexual activity and in sexual performance. Psychological changes, age-related changes in the nervous system, and decreased blood flow explain some of the decline. The side effects of medications taken for other conditions are responsible for decreased sexual activity in many older males.

Age-Related Changes in Females

The most significant age-related change in females is menopause. By age 50, few viable follicles remain in the ovaries. As a result, the amount of estrogen and progesterone produced by the ovaries has decreased.

The uterus decreases in size, and the endometrium decreases in thickness. The time between menses becomes irregular and longer. Finally, menstruations stop. As the uterus decreases in size, it tips posteriorly and assumes a lower position in the pelvic cavity. Occasionally, uterine prolapse, in which the ligaments of the uterus allow it to descend and protrude into the vagina, occurs. Within 15 years after menopause, the uterus is 50% of its original size.

The vaginal wall becomes thinner and less elastic. There is less lubrication of the vagina, and the epithelial lining is more

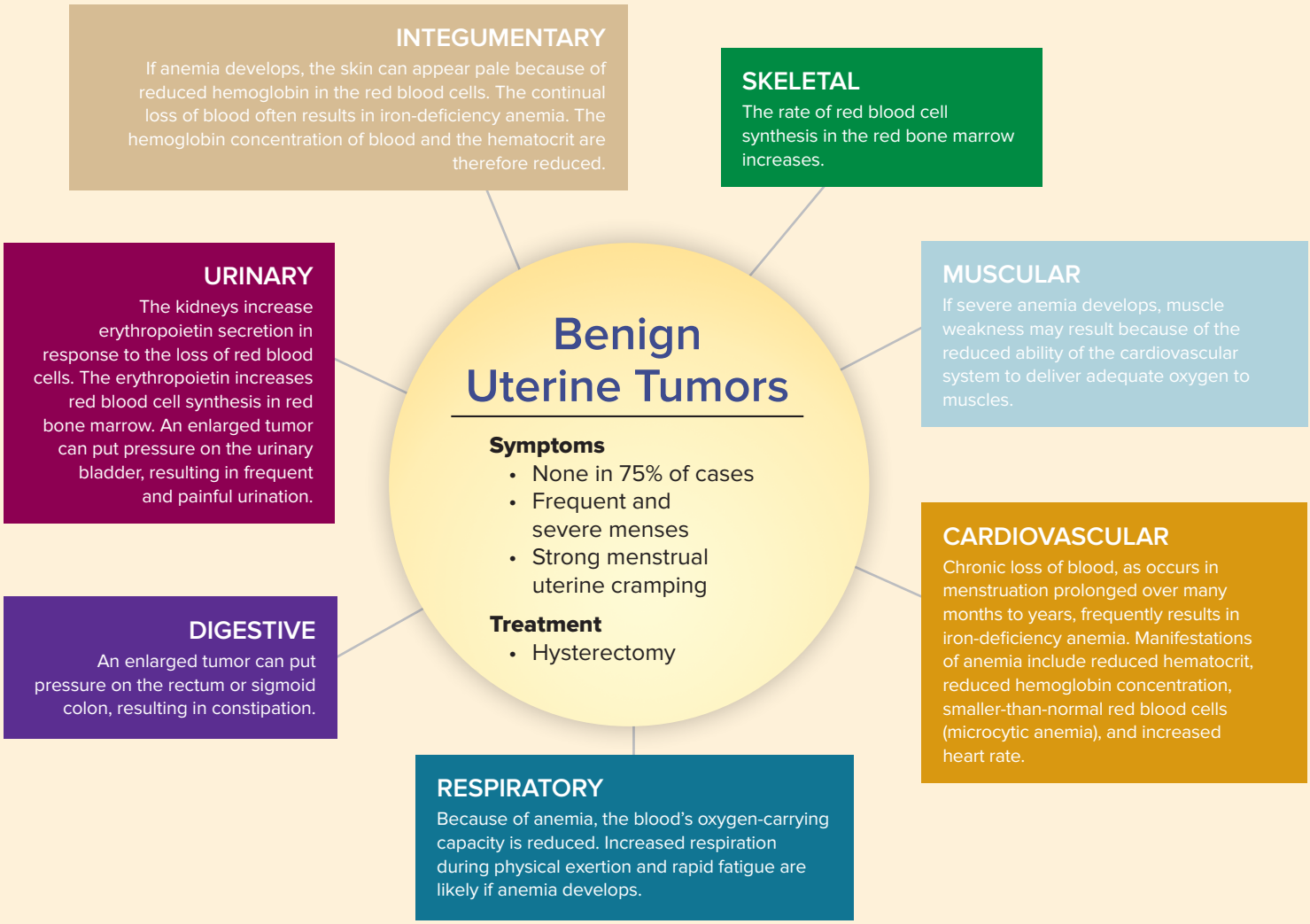


FIGURE 28.24 **Effects of Benign Uterine Tumors on the Body's Organ Systems**

fragile, resulting in an increased tendency for vaginal infections. Vaginal contractions during intercourse decrease, and the vagina narrows with age. In healthy females, sexual excitement requires greater time to develop, the peak levels of sexual activity are lower, and return to the resting state occurs more quickly.

The incidence of breast cancer is greatest between 45 and 65 years of age and is greater for females who have a family history of breast cancer. Approximately 10% of all females will develop breast cancer. The most important measure to guard against death from breast cancer is early detection through breast self-exams and annual mammograms after age 45. The incidences of uterine cancer and cervical cancer increase between 50 and 65 years of age. Ovarian cancer increases in frequency in older females, and it is the second most common cancer of the reproductive system in older females. Regular medical checkups, including Pap smears, are important for early detection and treatment of these cancers.

ASSESS YOUR PROGRESS

84. *List the major age-related changes that occur in the male reproductive system.*

85. *What are the age-related changes in the prostate gland?*

86. *List the major age-related changes that occur in the female reproductive system.*

87. *What are some of the long-term consequences of menopause?*

TABLE 28.5 **Representative Diseases and Disorders of the Reproductive System**

Condition	Description
Infectious Diseases	
Pelvic inflammatory disease (PID)	Bacterial infection of the female pelvic organs; commonly caused by vaginal or uterine infection by the bacteria that cause gonorrhea or chlamydia; early symptoms include increased vaginal discharge and pelvic pain; antibiotics are effective; if untreated, can lead to sterility or be life-threatening
Sexually Transmitted Diseases	Commonly known as STDs; spread by intimate sexual contact
Nongonococcal urethritis (non-gon´ō-kok´ăl u-rē-thrī´tis)	Inflammation of the urethra that is not caused by gonorrhea; can be caused by trauma, insertion of a nonsterile catheter, or sexual contact; usually due to infection with the bacterium *Chlamydia trachomatis* (kla-mid´ē-ă tra-kō´mă-tis); may go unnoticed and result in pelvic inflammatory disease or sterility; antibiotics are effective treatment
Trichomoniasis (trik-ō-mō-nī´ă-sis)	Caused by *Trichomonas* (trik´ō-mō´nas), a protozoan commonly found in the vagina of women and in the urethra of men; results in a greenish-yellow discharge with a foul odor; more common in women than in men
Gonorrhea (gon-ō-rē´ă)	Caused by the bacterium *Neisseria gonorrhoeae* (nī-sē´rē-ă gon-ō-rē´ă), which attaches to the epithelial cells of the vagina or male urethra and causes pus to form; pain and discharge from the penis occur in men; asymptomatic in women in the early stages; can lead to sterility in men and pelvic inflammatory disease in women
Genital herpes (her´pēz)	Caused by herpes simplex 2 virus; characterized by lesions on the genitals that progress into blisterlike areas, making urination, sitting, and walking painful; antiviral drugs can be effective
Genital warts	Caused by a viral infection; very contagious; warts vary from separate, small growths to large, cauliflower-like clusters; lesions are not painful, but sexual intercourse with lesions is; treatments include topical medicines and surgery to remove the lesions
Syphilis (sif´i-lis)	Caused by the bacterium *Treponema pallidum* (trep-ō-nē´mă pal´i-dŭm); can be spread by sexual contact; multiple disease stages occur; children born to infected mothers may be developmentally delayed; antibiotics are effective
Acquired immunodeficiency syndrome (AIDS)	Caused by the human immunodeficiency virus (HIV), which ultimately destroys the immune system (see chapter 22); transmitted through intimate sexual contact or by allowing infected body fluids into the interior of another person

Answer

Learn to Predict

In this chapter, we learned that gametogenesis involves meiosis, cell division that produces haploid cells. When comparing gametogenesis in males and females, we find that the processes differ in several ways: the stage in an individual's life when gametogenesis begins, the types of cells produced, the number of functional cells produced with each cell division, and the stage of life when gametogenesis ceases to occur.

In males, gametogenesis begins at puberty in the seminiferous tubules. Spermatogonia give rise to primary spermatocytes, which will undergo the process of meiosis. During this process, each primary spermatocyte eventually gives rise to four mature sperm cells. Males continue to produce sperm until death.

Gametogenesis in females is more complex. The process actually begins before a female is born. During fetal development, many of the oogonia in the ovaries degenerate. The remaining oogonia actually begin meiosis I and are called primary oocytes. At birth, the existing primary oocytes stop meiosis. After puberty and just before the ovulation of each oocyte, the primary oocyte that is ovulated completes the first meiotic division to produce one secondary oocyte and one polar body. The secondary oocyte begins the second meiotic division but will complete the process only if fertilized by a sperm cell. In the case of fertilization, the secondary oocyte divides to form two cells. One cell is another polar body and degenerates. In the other cell, the haploid sperm nucleus combines with the haploid oocyte nucleus to form a zygote. Thus, in females, each primary oocyte produces only one functional cell. For females, the process of gametogenesis stops at menopause.

Answers to odd-numbered Predict questions from this chapter appear in appendix E.

Summary

28.1 Functions of the Reproductive System

The reproductive systems produce male and female gametes, enhance fertilization of an oocyte by a sperm cell, and produce reproductive hormones. In addition, the female reproductive system nurtures the new individual until birth.

28.2 Meiosis

The reproductive organs in males and females produce gametes by meiosis.

1. Two consecutive cell divisions halve the chromosome number from 46 total chromosomes to 23 total chromosomes.
2. Meiosis ensures that the diploid number (46, in humans) is maintained in each generation.
3. Crossing over and random sorting of chromosomes during meiosis I produce genetic variation in gametes.

28.3 Anatomy of the Male Reproductive System

The male reproductive system includes the testes, ducts, accessory glands, and supporting structures.

Scrotum

1. The scrotum is a two-chambered sac that contains the testes.
2. The dartos and cremaster muscles help regulate testicular temperature.

Perineum

The perineum, the diamond-shaped area between the thighs, consists of a urogenital triangle and an anal triangle.

Testes

1. The tunica albuginea is the outer connective tissue capsule of the testes.
2. The testes are divided by septa into lobules that contain the seminiferous tubules and the interstitial cells.
3. The seminiferous tubules straighten to form the tubuli recti, which lead to the rete testis. The rete testis opens into the efferent ductules of the epididymis.
4. During development, the testes pass from the abdominal cavity through the inguinal canal to the scrotum.
5. Spermatogenesis begins in the seminiferous tubules at the time of puberty.
6. Spermatogonia divide (mitosis) to form primary spermatocytes.
7. Primary spermatocytes divide (first division of meiosis) to form secondary spermatocytes, which divide (second division of meiosis) to form spermatids.
8. Spermatids develop an acrosome and a flagellum to become sperm cells.
9. Sustentacular cells nourish the sperm cells, form a blood-testis barrier, and produce hormones.

Ducts

1. Efferent ductules extend from the testes to the head of the epididymis.
2. The epididymis, a coiled tube system, is located on the testis and is the site of sperm cell maturation. It consists of a head, a body, and a tail.
3. The ductus deferens passes from the epididymis into the abdominal cavity.
4. The end of the ductus deferens, called the ampulla, and the seminal vesicle join to form the ejaculatory duct.
5. The prostatic urethra extends from the urinary bladder and joins with the ejaculatory ducts to form the membranous urethra.
6. The membranous urethra extends through the urogenital diaphragm and becomes the spongy urethra, which continues through the penis.
7. The spermatic cord consists of the ductus deferens, blood and lymphatic vessels, nerves, and remnants of the process vaginalis. Coverings of the spermatic cord consist of the external spermatic fascia, cremaster muscle, and internal spermatic fascia.
8. The spermatic cord passes through the inguinal canal into the abdominal cavity.

Penis

1. The penis consists of erectile tissue.
   - The two corpora cavernosa form the dorsum and the sides of the penis.
   - The corpus spongiosum forms the ventral part and the glans penis.
2. The bulb of the penis and the crura form the root of the penis, and the crura attaches the penis to the pelvic bones.
3. The prepuce covers the glans penis.

Accessory Glands

1. The seminal vesicles empty into the ejaculatory ducts.
2. The prostate gland consists of glandular and muscular tissue and empties into the prostatic urethra.
3. The bulbourethral glands are compound mucous glands that empty into the spongy urethra.

Semen

1. Semen is a mixture of sperm cells and glandular secretions.
2. The bulbourethral glands and the urethral mucous glands produce mucus, which neutralizes the acidic pH of the urethra.
3. The testicular secretions contain sperm cells.
4. The seminal vesicle fluid contains fructose and fibrinogen.
5. The prostate secretions make the seminal fluid more pH-neutral. Clotting factors activate fibrinogen, and fibrinolysin breaks down fibrin.

28.4 Physiology of Male Reproduction

Normal function of the male reproductive system depends on hormonal and neural mechanisms.

Regulation of Reproductive Hormone Secretion

1. GnRH is produced in the hypothalamus and released in surges.
2. GnRH stimulates LH and FSH release from the anterior pituitary.
   - LH stimulates the interstitial cells to produce testosterone.
   - FSH stimulates sperm cell formation.
3. Inhibin, produced by sustentacular cells, inhibits FSH secretion.

Puberty in Males

1. Before puberty, small amounts of testosterone inhibit GnRH release.
2. During puberty, testosterone does not completely suppress GnRH release, resulting in increased production of FSH, LH, and testosterone.

Effects of Testosterone

1. Interstitial cells, the adrenal cortex, and possibly the sustentacular cells produce testosterone.
2. Testosterone causes the development of male sex organs in the embryo and stimulates the descent of the testes.
3. Testosterone causes enlargement of the genitals and is necessary for sperm cell formation.
4. Other effects of testosterone
   - Hair growth stimulation (pubic area, axilla, and beard) and inhibition (male pattern baldness)
   - Enlargement of the larynx and deepening of the voice
   - Increased skin thickness and melanin and sebum production
   - Increased protein synthesis (muscle), bone growth as mediated by estrogen, blood cell synthesis, and blood volume
   - Increased metabolic rate

Male Sexual Behavior and the Male Sexual Act

1. Testosterone is required for normal sex drive.
2. Stimulation of the sexual act can be tactile or psychological.
3. Afferent action potentials pass through the pudendal nerve to the sacral region of the spinal cord.
4. Parasympathetic stimulation
   - Erection is due to vasodilation of the blood vessels that supply the erectile tissue.
   - The glands of the urethra and the bulbourethral glands produce mucus.
5. Sympathetic stimulation causes erection, emission, and ejaculation.

28.5 Anatomy of the Female Reproductive System

The female reproductive system includes the ovaries, uterine tubes, uterus, vagina, external genitals, and mammary glands.

Ovaries

1. The broad ligament, the mesovarium, the suspensory ligaments, and the ovarian ligaments hold the ovaries in place.
2. The peritoneum (ovarian epithelium) covers the surface of the ovaries.
3. The ovary has an outer capsule called the tunica albuginea and is divided internally into a cortex, which contains follicles, and a medulla, which receives blood and lymphatic vessels and nerves.
4. Oocyte development and fertilization
   - Oogonia proliferate and become primary oocytes that are in prophase I of meiosis.
   - Ovulation is the release of an oocyte from an ovary.
   - Prior to ovulation, a primary oocyte continues meiosis I and produces a secondary oocyte, which begins meiosis II, and a polar body, which either degenerates or divides to form two polar bodies.
   - Fertilization is the joining of a sperm cell and a secondary oocyte to form a zygote. A sperm cell enters a secondary oocyte, which then completes the second meiotic division and produces a polar body. A zygote is formed when the nuclei of the sperm cell and the oocyte fuse to form a diploid nucleus.
5. Follicle development
   - Primordial follicles are surrounded by a single layer of flat granulosa cells.
   - Primary follicles are primary oocytes surrounded by cuboidal granulosa cells.
   - The primary follicles become secondary follicles as granulosa cells increase in number and fluid begins to accumulate in the vesicles. The granulosa cells increase in number, and a theca forms around the secondary follicles.
   - Mature follicles are enlarged secondary follicles at the surface of the ovary.
6. Ovulation occurs when the follicle swells and ruptures and the secondary oocyte is released from the ovary.
7. Fate of the follicle
   - The mature follicle becomes the corpus luteum.
   - If pregnancy occurs, the corpus luteum persists. If no pregnancy occurs, it becomes the corpus albicans.

Uterine Tubes

1. The mesosalpinx holds the uterine tubes.
2. The uterine tubes transport the oocyte or zygote from the ovary to the uterus.
3. Structures
   - The ovarian end of the uterine tube is expanded as the infundibulum. The opening of the infundibulum is the ostium, which is surrounded by fimbriae.
   - The infundibulum connects to the ampulla, which narrows to become the isthmus. The isthmus is the part of the uterine tube nearest the uterus.
4. The uterine tube consists of an outer serosa, a middle muscular layer, and an inner mucosa composed of simple ciliated columnar epithelium.
5. Movement of the oocyte
   - Cilia move the oocyte over the fimbriae surface into the infundibulum.
   - Peristaltic contractions and cilia move the oocyte within the uterine tube.
   - Fertilization occurs in the ampulla, where the zygote remains for several days.

Uterus

1. The uterus consists of the body, the isthmus, and the cervix. The uterine cavity and the cervical canal are the spaces formed by the uterus.
2. The uterus is held in place by the broad, round, and uterosacral ligaments.
3. The wall of the uterus consists of the perimetrium (serous membrane), the myometrium (smooth muscle), and the endometrium (mucous membrane).

Vagina

1. The vagina connects the uterus (cervix) to the outside of the body.
2. The vagina consists of a layer of smooth muscle and an inner lining of moist, stratified squamous epithelium.
3. The vagina is folded into rugae and longitudinal folds.
4. The hymen covers the opening of the vagina.

External Genitalia

1. The vulva, or pudendum, comprises the external genitalia.
2. The vestibule is the space into which the vagina and the urethra open.
3. Erectile tissue
   - The two corpora cavernosa form the clitoris.
   - The corpora spongiosa form the bulbs of the vestibule.
4. The labia minora are folds that cover the vestibule and form the prepuce.
5. The greater and lesser vestibular glands produce a mucous fluid.
6. When closed, the labia majora cover the labia minora.
   - The pudendal cleft is a space between the labia majora.
   - The mons pubis is an elevated fat deposit superior to the labia majora.

Perineum

The clinical perineum is the region between the vagina and the anus.

Mammary Glands

1. The mammary glands are modified sweat glands located in the breasts.
   - The mammary glands consist of glandular lobes and adipose tissue.
   - The lobes consist of lobules that are divided into alveoli.
   - The lobes connect to the nipple through the lactiferous ducts.
   - The areola surrounds the nipple.
2. Suspensory ligaments support the breasts.

28.6 Physiology of Female Reproduction

Puberty in Females

1. The first menstrual bleeding (menarche) occurs during puberty.
2. Puberty begins when GnRH levels increase.

Menstrual Cycle

1. Ovarian cycle
   - FSH initiates the development of the primary follicles.
   - The follicles secrete a substance that inhibits the development of other follicles.
   - LH stimulates ovulation and completion of the first meiotic division by the primary oocyte.
   - The LH surge stimulates the formation of the corpus luteum. If fertilization occurs, hCG stimulates the corpus luteum to persist. If fertilization does not occur, the corpus luteum becomes the corpus albicans.
2. A positive-feedback mechanism causes FSH and LH levels to increase near the time of ovulation.
   - Estrogen produced by the theca cells of the follicle stimulates GnRH secretion.
   - GnRH stimulates the production and release of FSH and LH, which stimulate more estrogen secretion, and so on.
   - Inhibition of GnRH levels causes FSH and LH levels to decrease after ovulation. Inhibition is due to the high levels of estrogen and progesterone produced by the corpus luteum.
3. Uterine cycle
   - Menses (from day 1 to day 4 or 5). The spiral arteries constrict, and endometrial cells die. The menstrual fluid is composed of sloughed cells, secretions, and blood.
   - Proliferative phase (from day 5 to day 14). Epithelial cells multiply and form glands, and the spiral arteries supply the glands.
   - Secretory phase (from day 15 to day 28). The endometrium becomes thicker, and the endometrial glands secrete.
   - Estrogen stimulates proliferation of the endometrium and synthesis of progesterone receptors.
   - Increased progesterone levels cause hypertrophy of the endometrium, stimulate gland secretion, and inhibit uterine contractions. Decreased progesterone levels cause the spiral arteries to constrict and start menses.

Female Sexual Behavior and the Female Sexual Act

1. Female sex drive is partially influenced by androgens (produced by the adrenal gland) and other steroids (produced by the ovaries).
2. Parasympathetic effects
   - The erectile tissue of the clitoris and the bulbs of the vestibule become filled with blood.
   - The vestibular glands secrete mucus, and the vagina extrudes a mucuslike substance.

Female Fertility and Pregnancy

1. If fertilization is to occur, intercourse must take place between 5 days before and 1 day after ovulation.
2. Sperm cell transport to the ampulla depends on the ability of the sperm cells to swim and possibly on contractions of the uterus and the uterine tubes.
3. Implantation of the developing embryo into the uterine wall occurs when the uterus is most receptive.
4. Estrogen and progesterone, secreted first by the corpus luteum and later by the placenta, are essential for the maintenance of pregnancy.

Menopause

The female climacteric begins with irregular menstrual cycles and ends with menopause, the cessation of the menstrual cycle.

28.7 Effects of Aging on the Reproductive System

Several age-related changes occur in the male and female reproductive systems.

Age-Related Changes in Males

1. Decreases occur in the size and weight of the testes, the number of interstitial cells, and the number of sperm produced, but sperm cell production is still adequate for fertilization. The wall of the seminiferous tubule becomes thin.
2. The prostate gland enlarges, and the incidence of prostate cancer increases.
3. Erectile dysfunction becomes more common, and sexual activity gradually decreases.

Age-Related Changes in Females

1. The most significant age-related change in females is menopause.
2. The uterus decreases in size, and the vaginal wall thins.
3. The incidence of breast, uterine, and ovarian cancer increases.

REVIEW AND COMPREHENSION

1. During meiosis I
   a. homologous chromosomes synapse.
   b. crossing over between homologous chromosomes occurs.
   c. the chromosomal number is reduced by half.
   d. two haploid cells are produced.
   e. All of these are correct.
2. Testosterone is produced in the
   a. interstitial cells.
   b. seminiferous tubules of the testes.
   c. anterior lobe of the pituitary gland.
   d. sperm cells.

3. Early in development (4 months after fertilization), the testes
   a. are found in the abdominal cavity.
   b. move through the inguinal canal.
   c. produce a membrane that becomes the scrotum.
   d. produce sperm cells.
   e. All of these are correct.

4. The site of spermatogenesis in the male is the
   a. ductus deferens.
   b. seminiferous tubules.
   c. epididymis.
   d. rete testis.
   e. efferent ductule.

5. The site of final maturation and storage of sperm cells before their ejaculation is the
   a. seminal vesicles.
   b. seminiferous tubules.
   c. glans penis.
   d. epididymis.
   e. sperm bank.

6. Given these structures:
   (1) ductus deferens
   (2) efferent ductule
   (3) epididymis
   (4) ejaculatory duct
   (5) rete testis

   Choose the arrangement that lists the structures in the order a sperm cell passes through them from the seminiferous tubules to the urethra.
   a. 2,3,5,4,1
   b. 2,5,3,4,1
   c. 3,2,4,1,5
   d. 3,4,2,1,5
   e. 5,2,3,1,4

7. Concerning the penis,
   a. the membranous urethra passes through the corpora cavernosa.
   b. the glans penis is formed by the corpus spongiosum.
   c. the penis contains four columns of erectile tissue.
   d. the crus of the penis is part of the corpus spongiosum.
   e. the bulb of the penis is covered by the prepuce.

8. Which of these glands is correctly matched with the function of its secretions?
   a. bulbourethral gland—neutralizes acidic contents of the urethra
   b. seminal vesicles—contain large amounts of fructose, which nourishes the sperm cells
   c. prostate gland—contains clotting factors that cause coagulation of the semen
   d. All of these are correct.

9. LH in the male stimulates
   a. the development of the seminiferous tubules.
   b. spermatogenesis.
   c. testosterone production.
   d. Both a and b are correct.
   e. All of these are correct.

10. Which of these factors causes a decrease in GnRH release?
    a. decreased inhibin
    b. increased testosterone
    d. decreased FSH
    e. decreased LH

11. In the male, before puberty
    a. FSH levels are higher than after puberty.
    b. LH levels are higher than after puberty.
    c. GnRH release is inhibited by testosterone.
    d. All of these are correct.

12. Testosterone
    a. stimulates the development of terminal hairs.
    b. decreases red blood cell count.
    c. prevents closure of the epiphyseal plate.
    d. decreases blood volume.
    e. All of these are correct.

13. Which of these events is consistent with erection of the penis?
    a. parasympathetic stimulation
    b. dilation of arterioles
    c. engorgement of sinusoids with blood
    d. occlusion of veins
    e. All of these are correct.

14. After ovulation, the mature follicle collapses, taking on a yellowish appearance to become the
    a. degenerating follicle.
    b. corpus luteum.
    c. corpus albicans.
    d. tunica albuginea.
    e. cumulus mass.

15. The ampulla of the uterine tube
    a. is the opening of the uterine tube into the uterus.
    b. has long, thin projections called the ostium.
    c. is connected to the isthmus of the uterine tube.
    d. is lined with simple cuboidal epithelium.

16. The layer of the uterus that undergoes the greatest change during the menstrual cycle is the
    a. perimetrium.
    b. hymen.
    c. endometrium.
    d. myometrium.
    e. broad ligament.

17. The vagina
    a. consists of skeletal muscle.
    b. has ridges called rugae.
    c. is lined with simple squamous epithelium.
    d. All of these are correct.

18. During sexual excitement, which of these structures fills with blood and causes the vaginal opening to narrow?
    a. bulbs of the vestibule
    b. clitoris
    c. mons pubis
    d. labia majora
    e. prepuceligament.

19. Concerning the breasts,
    a. lactiferous ducts open on the areola.
    b. each lactiferous duct supplies an alveolus.
    c. they are attached to the pectoralis major muscles by suspensory ligaments.
    d. even before puberty, the female breast is quite different from the male breast.

20. The major secretory product of the mature follicle is
    a. estrogen.
    b. progesterone.
    c. LH.
    d. relaxin.
    e. FSH.

21. In the average adult female, ovulation occurs at day _____ of the menstrual cycle.
    a. 1 b. 7 c. 14 d. 21 e. 28

22. Which of these processes or phases in the monthly reproductive cycle of the human female occur at the same time?
    a. maximal LH secretion and menstruation
    b. early follicular development and the secretory phase of the uterus
    c. regression of the corpus luteum and an increase in ovarian progesterone secretion
    d. ovulation and menstruation
    e. proliferative stage of the uterus and increased estrogen production

23. During the proliferative phase of the uterine cycle, one would normally expect
    a. the highest levels of estrogen that occur during the menstrual cycle.
    b. the mature follicle to be present in the ovary.
    c. an increase in the thickness of the endometrium.
    d. Both a and b are correct.
    e. All of these are correct.

24. The cause of menses in the uterine cycle appears to be
    a. increased progesterone secretion from the ovary, which produces blood clotting.
    b. increased estrogen secretion from the ovary, which stimulates the muscles of the uterus to contract.
    c. decreased progesterone secretion by the ovary.
    d. decreased production of oxytocin, causing the muscles of the uterus to relax.
25. After fertilization, the successful development of a mature, full-term fetus depends on
    a. the release of human chorionic gonadotropin (hCG) by the developing placenta.
    b. the production of estrogen and progesterone by the placental tissues.
    c. maintenance of the corpus luteum for all 9 months.
    d. Both a and b are correct.
    e. All of these are correct.
26. A female with a 28-day menstrual cycle is most likely to become pregnant as a result of intercourse on days
    a. 1–3.
    b. 5–8.
    c. 9–14.
    d. 15–20.
    e. 21–28.
27. Menopause
    a. develops when follicles become less responsive to FSH and LH.
    b. results from elevated estrogen levels in 40- to 50-year-old females.
    c. occurs because too many follicles develop during each cycle.
    d. results when follicles develop but contain no oocytes.
    e. occurs because FSH and LH levels decline.

Answers appear in appendix F.

CRITICAL THINKING

1. If an adult male were castrated (testes were removed), what would happen to the levels of GnRH, FSH, LH, and testosterone in his blood? What effect would these hormonal changes have on his sexual characteristics and sexual behavior?
2. If a 9-year-old male were castrated, what would happen to the levels of GnRH, FSH, LH, and testosterone in his blood? What effect would these hormonal changes have on his sexual characteristics and sexual behavior as an adult?
3. Suppose you want to produce a male birth control pill. On the basis of what you know about the male hormone system, what process should the pill affect? Discuss any possible side effects of the pill.
4. If the ovaries are removed from a postmenopausal female, what happens to the levels of GnRH, FSH, LH, estrogen, and progesterone in her blood? What symptoms would you expect to observe?
5. If the ovaries are removed from a 20-year-old female, what happens to the levels of GnRH, FSH, LH, estrogen, and progesterone in her blood? What side effects would these hormonal changes have on her sexual characteristics and sexual behavior?
6. A study divides healthy females into two groups (A and B). Both groups are composed of those who have been sexually active for at least 2 years and are not pregnant at the beginning of the experiment. The subjects weigh about the same amount, and none smoke cigarettes, although some drink alcohol occasionally. Group A individuals receive a placebo in the form of a sugar pill each morning of their menstrual cycles. Group B individuals receive a pill containing estrogen and progesterone each morning of their menstrual cycles. Then plasma LH levels are measured before, during, and after ovulation. The results are as follows:

Group	4 Days Before Ovulation	Day of Ovulation	4 Days After Ovulation
A	18 mg/100 mL	300 mg/100 mL	17 mg/100 mL
B	21 mg/100 mL	157 mg/100 mL	15 mg/100 mL

   The number of pregnancies in group A is 37/100 females/year. The number of pregnancies in group B is 1.5/100 females/year. What conclusion can you reach on the basis of these data? Explain the mechanism involved.
7. A female who is taking birth control pills that consist of only progesterone experiences the hot flashes of menopause. Explain why.
8. GnRH can be used to treat some females who want to have children but have not been able to get pregnant. Explain why it is critical to administer the correct concentration of GnRH at the right time during the menstrual cycle.
9. Dr. Smith has two patients, one of whom has elevated blood PSA. A digital exam reveals that both patient 1 and patient 2 have enlarged prostate glands. Patient 1's enlarged prostate has the same shape as a smaller prostate, except that it is larger than normal, with a smooth contour. Patient 2's prostate is enlarged and asymmetrical, with a rough contour. In what way are these patients' lives probably being affected by their enlarged prostates? Explain how the doctor was able to conclude that one of the patients is likely to have prostate cancer.
10. The left testis of a newborn baby failed to descend into his scrotal sac. For some reason, the condition was not treated, and the testis remained in that position until after puberty. Select the observation consistent with the fate of the left testis after puberty.
    (1) normal testosterone secretion
    (2) no interstitial cells in the testis
    (3) no sustentacular cells in the testis
    (4) no spermatogonia in the testis
    (5) increased number of interstitial cells
    (6) normal LH secretion
    a. 1 b. 1,2,3,4 c. 1,2,3,6 d. 1,4,6 e. 4,6
11. Norman had a stroke that decreased blood flow to his anterior pituitary gland. The condition had a sudden onset, and the manifestations lasted for about a week before collateral circulation developed and the manifestations disappeared. Which of the following are most consistent with this temporary interruption of anterior pituitary function?
    (1) increased testosterone levels in the blood
    (2) reduced sperm counts during the week Norman was in the hospital
    (3) decreased testosterone levels in the blood
    (4) normal sperm counts during the week Norman was in the hospital
    (5) increased LH secretion
    (6) decreased LH secretion
    a. 1,5 b. 3,5 c. 2,3,6 d. 3,4,6 e. 1,4,5

Answers to odd-numbered questions appear in appendix G.

Appendix F

ANSWERS TO REVIEW AND COMPREHENSION QUESTIONS

Chapter One

1. a; 2. b; 3. a; 4. c; 5. e; 6. a; 7. b; 8. c; 9. d; 10. c; 11. d; 12. a; 13. b; 14. b; 15. a; 16. c; 17. b; 18. a; 19. e

Chapter Two

1. e; 2. b; 3. b; 4. a; 5. d; 6. b; 7. e; 8. c; 9. e; 10. c; 11. d; 12. b; 13. c; 14. c; 15. d; 16. c; 17. d; 18. e; 19. b; 20. d; 21. b; 22. c; 23. d; 24. a; 25. e

Chapter Three

1. a; 2. e; 3. c; 4. e; 5. c; 6. e; 7. c; 8. a; 9. a; 10. d; 11. d; 12. b; 13. b; 14. c; 15. c; 16. c; 17. b; 18. e; 19. c; 20. a; 21. d; 22. c; 23. d

Chapter Four

1. e; 2. c; 3. a; 4. b; 5. d; 6. c; 7. d; 8. b; 9. a; 10. b; 11. e; 12. a; 13. d; 14. b; 15. b; 16. d; 17. d; 18. a; 19. e; 20. b; 21. c; 22. c; 23. b; 24. c; 25. b; 26. d

Chapter Five

1. d; 2. e; 3. b; 4. a; 5. c; 6. d; 7. c; 8. d; 9. b; 10. a; 11. b; 12. b; 13. c; 14. c; 15. d; 16. b; 17. c; 18. b; 19. a; 20. b; 21. d; 22. c; 23. d; 24. c

Chapter Six

1. e; 2. d; 3. a; 4. b; 5. d; 6. c; 7. a; 8. b; 9. e; 10. c; 11. d; 12. d; 13. c; 14. b; 15. c; 16. e; 17. d; 18. a; 19. b; 20. c; 21. a; 22. e; 23. c; 24. e; 25. d

Chapter Seven

1. c; 2. c; 3. c; 4. d; 5. c; 6. a; 7. d; 8. a; 9. b; 10. a; 11. c; 12. a; 13. a; 14. d; 15. e; 16. b; 17. a; 18. c; 19. b; 20. c; 21. a

Chapter Eight

1. d; 2. d; 3. c; 4. d; 5. b; 6. e; 7. d; 8. c; 9. d; 10. e; 11. a; 12. b; 13. c; 14. d; 15. b; 16. b; 17. a; 18. c; 19. c

Chapter Nine

1. c; 2. e; 3. d; 4. c; 5. e; 6. b; 7. a; 8. b; 9. d; 10. b; 11. d; 12. c; 13. e; 14. d; 15. c; 16. c; 17. a; 18. b; 19. d; 20. a; 21. d; 22. c; 23. c; 24. c; 25. a

Chapter Ten

1. d; 2. b; 3. b; 4. c; 5. c; 6. d; 7. b; 8. c; 9. a; 10. a; 11. d; 12. a; 13. b; 14. d; 15. b; 16. d; 17. a; 18. c; 19. a; 20. e; 21. c; 22. b; 23. b; 24. d

Chapter Eleven

1. b; 2. c; 3. c; 4. b; 5. c; 6. a; 7. b; 8. d; 9. a; 10. c; 11. b; 12. a; 13. a; 14. b; 15. d; 16. c; 17. e; 18. b; 19. d; 20. d; 21. b; 22. b; 23. e; 24. e; 25. e; 26. a

Chapter Twelve

1. d; 2. c; 3. c; 4. b; 5. b; 6. d; 7. c; 8. c; 9. c; 10. d; 11. d; 12. c; 13. e; 14. c; 15. d

Chapter Thirteen

1. a; 2. c; 3. b; 4. e; 5. d; 6. b; 7. b; 8. b; 9. a; 10. e; 11. d; 12. d; 13. a; 14. c; 15. d; 16. b; 17. b; 18. a; 19. d; 20. b; 21. b; 22. e; 23. b; 24. c; 25. c; 26. b

Chapter Fourteen

1. c; 2. d; 3. e; 4. c; 5. a; 6. d; 7. b; 8. e; 9. a; 10. b; 11. b; 12. e; 13. c; 14. c; 15. b; 16. d; 17. a; 18. b; 19. b; 20. d; 21. b; 22. b; 23. d; 24. e; 25. d; 26. b; 27. b; 28. d; 29. e; 30. c

Chapter Fifteen

1. e; 2. c; 3. a; 4. b; 5. b; 6. a; 7. c; 8. d; 9. c; 10. d; 11. c; 12. c; 13. a; 14. d; 15. c; 16. d; 17. a; 18. d; 19. c; 20. a; 21. a; 22. b; 23. d; 24. a; 25. c

Chapter Sixteen

1. e; 2. d; 3. a; 4. e; 5. b; 6. d; 7. e; 8. d; 9. d; 10. d; 11. c; 12. a; 13. c; 14. e; 15. d; 16. c; 17. e

Chapter Seventeen

1. c; 2. b; 3. e; 4. d; 5. b; 6. a; 7. e; 8. b; 9. a; 10. e; 11. e; 12. e; 13. d; 14. c; 15. a; 16. c

Chapter Eighteen

1. e; 2. d; 3. e; 4. a; 5. c; 6. b; 7. b; 8. e; 9. c; 10. d; 11. e; 12. b; 13. c; 14. a; 15. a; 16. d; 17. c; 18. d; 19. e; 20. e; 21. b; 22. d; 23. a; 24. a; 25. b; 26. e; 27. c; 28. c; 29. e; 30. d

Chapter Nineteen

1. e; 2. c; 3. a; 4. d; 5. a; 6. d; 7. c; 8. d; 9. b; 10. a; 11. c; 12. b; 13. e; 14. e; 15. b; 16. a; 17. a; 18. d; 19. d; 20. c; 21. c

Chapter Twenty

1. e; 2. c; 3. a; 4. b; 5. c; 6. e; 7. a; 8. c; 9. d; 10. a; 11. b; 12. a; 13. a; 14. e; 15. b; 16. c; 17. d; 18. a; 19. a; 20. d; 21. c; 22. c; 23. c; 24. e; 25. c

Chapter Twenty-One

1. b; 2. a; 3. a; 4. d; 5. d; 6. c; 7. d; 8. a; 9. a; 10. d; 11. e; 12. c; 13. a; 14. b; 15. b; 16. a; 17. e; 18. d; 19. b; 20. b; 21. d; 22. d; 23. c; 24. b; 25. e

Chapter Twenty-Two

1. d; 2. b; 3. e; 4. e; 5. d; 6. b; 7. e; 8. b; 9. a; 10. d; 11. d; 12. d; 13. b; 14. e; 15. e; 16. a; 17. d; 18. c; 19. a; 20. b; 21. c; 22. a; 23. d; 24. d; 25. d

Chapter Twenty-Three

1. a; 2. e; 3. d; 4. c; 5. d; 6. b; 7. c; 8. b; 9. d; 10. a; 11. d; 12. c; 13. c; 14. c; 15. d; 16. b; 17. c; 18. b; 19. c; 20. a; 21. c

Chapter Twenty-Four

1. a; 2. d; 3. d; 4. a; 5. b; 6. a; 7. b; 8. a; 9. c; 10. d; 11. c; 12. e; 13. d; 14. d; 15. e; 16. b; 17. b; 18. a; 19. e; 20. e; 21. e; 22. a; 23. c; 24. a

Chapter Twenty-Five

1. d; 2. a; 3. e; 4. b; 5. d; 6. e; 7. e; 8. b; 9. d; 10. d; 11. a; 12. e; 13. c; 14. a; 15. b; 16. c

Chapter Twenty-Six

1. d; 2. b; 3. c; 4. e; 5. b; 6. b; 7. e; 8. a; 9. b; 10. b; 11. a; 12. a; 13. a; 14. c; 15. d; 16. c; 17. b; 18. e; 19. d; 20. a; 21. d; 22. e; 23. d; 24. c; 25. c; 26. d

Chapter Twenty-Seven

1. a; 2. b; 3. c; 4. d; 5. a; 6. a; 7. b; 8. a; 9. b; 10. d; 11. b; 12. a; 13. a; 14. c; 15. c; 16. d

Chapter Twenty-Eight

1. e; 2. a; 3. a; 4. b; 5. d; 6. e; 7. b; 8. d; 9. c; 10. b; 11. c; 12. a; 13. e; 14. b; 15. c; 16. c; 17. b; 18. a; 19. c; 20. a; 21. c; 22. e; 23. e; 24. c; 25. d; 26. c; 27. a

Chapter Twenty-Nine

1. b; 2. e; 3. a; 4. a; 5. d; 6. a; 7. c; 8. b; 9. c; 10. a; 11. a; 12. e; 13. d; 14. c; 15. c; 16. e; 17. a; 18. b; 19. a; 20. c; 21. d; 22. c; 23. b; 24. c; 25. c

Appendix D

ANSWERS TO PROCESS FIGURE QUESTIONS

Process Figure 1.1

First, consider the definition of an organ: An organ is a structure that is composed of at least two types of tissue. Because the skin consists of both epithelial and connective tissues, it fits the definition of an organ. The integumentary system is composed of the skin and other small organs, such as sweat glands and sebaceous glands. The combination of these organs constitutes an organ system: a group of organs with a common function.

Process Figure 1.4

All homeostatic mechanisms are regulated by feedback. All three components of a homeostatic mechanism are necessary to keep body variables within their normal range. There are multiple points at which the mechanism may break down.

1. If the receptors are not functioning, then the stimulus cannot be detected and no response will be initiated. In this example, if the body temperature receptors have become insensitive to high temperatures, then they wouldn't send a signal to the control center and the temperature would rise.
2. If the control center does not receive the receptors' signal, or is insensitive to the receptors' input, then it will not send a message to the effector. If the control center allows the body temperature to rise much higher than normal without stimulating the sweat glands, then a person would not sweat when they became too hot.
3. If the effector does not work properly, it cannot carry out the response that will return the body to the set point. If the sweat glands are not functioning and do not secrete sweat, the body is not capable of cooling down as effectively as when sweat is produced and they could suffer a heat stroke.

Process Figure 2.7

First, recall that covalent bonds are formed when atoms share electrons, while ionic bonds are formed when atoms transfer electrons. Now with that in mind, since the question stated that electrons were shared, you know that it must be a covalent bond, not an ionic bond. The next point to remember is that an atom with higher electronegativity will attract electrons more strongly than an atom with weak electronegativity so that there will be unequal sharing of electrons. This tells you that the covalent bond must be a polar bond since equal sharing of electrons results in a nonpolar covalent bond.

Process Figure 2.15

Addition of a basic solution to the beaker of water will cause a large increase in pH. Addition of a basic solution to the beaker with buffer will cause only a small increase in pH because the buffer acts as a conjugate acid to release H^+. Recall that because buffers act as both an acid and a base, the buffer can both bind and donate protons.

Process Figure 2.28

Recall that complementary base pairs are held together by hydrogen bonds. Guanine and cytosine have 3 hydrogen bonds between them, while adenine and thymine only have 2 hydrogen bonds. Therefore, G-C base pairs are stronger and more difficult to break apart when the strands unwind during cellular processes discussed in chapter 3.

Process Figure 3.5

A competitor molecule with a similar concentration difference across the membrane would increase the time to saturation because few transport proteins would be available for the original molecule.

Process Figure 3.7

The area that would be most impacted by a change in structure would be the binding site for the transported material. If the structure of this area was altered, the specificity of the carrier protein would be altered; therefore, it would not be able to transport the appropriate substance. Structural changes in other areas may also be problematic. For example, if a structural change interfered with how the protein was incorporated into the lipid bilayer, the function of the protein would be lost.

Process Figure 3.8

The protein is an integral membrane protein, meaning that it is embedded in the lipid bilayer and spans the width of the membrane. This allows for a complete passageway across the membrane for the specific substance transported.

Process Figure 3.9

The toxin is demonstrating competition. By blocking the binding site of acetylcholine, the toxin must have a similar shape and be able to bind to the site that is specific for acetylcholine.

Process Figure 3.10

It is the fluid nature of the plasma membrane that allows for the movement of the G protein complex. Proteins float within the lipid bilayer similar to ice cubes floating in water.

Process Figure 3.11

Temperature is a measure of the amount of heat energy in a system. As heat increases, movement of atoms and molecules increases and as heat decreases, movement of atoms and molecules decreases. Recall that diffusion is the result of the random motion of atoms and molecules; therefore, if temperature decreases, the rate of diffusion would also decrease.

Process Figure 3.12

Recall from chapter 2 that nonpolar refers to molecules that have nonpolar covalent bonds. Also, nonpolar molecules are considered neutral compared polar molecules that have slight charge differences across the molecule. Polar molecules are said to be hydrophilic because they readily associate with water, which is also a polar molecule. Nonpolar molecules are hydrophobic, because they do not readily associate with water. Polar molecules can also be referred to as non–lipid soluble, whereas nonpolar molecules are referred to as lipid soluble. So in conclusion, polar molecules are both hydrophilic *and* non–lipid soluble; nonpolar molecules are both hydrophobic *and* lipid soluble.

Process Figure 3.13

If the tube were shorter, the fluid would spill out of the top of the tube. The solution would continue to rise into and out of the tube because the weight of the smaller volume of fluid would not be enough to oppose the osmosis of water into

the tube. This would not continue because, as the fluid spills out and into the beaker, the solute concentrations in the tube and now in the beaker would be altered, and this would change the rate of osmosis.

Process Figure 3.15

The carrier protein is moving the substance with the concentration gradient. The figure represents facilitated diffusion; diffusion is defined as a substance moving from an area of higher concentration to an area of lower concentration.

Process Figure 3.16

Recall that one ATP molecule is spent to transport 3 Na^+, so it would require 4 ATP to transport 12 Na^+ (12/3 = 4). Each cycle of the Na^+–K^+ pump transports 2 K^+ and requires 1 ATP. So, during the four cycles needed to transport 12 Na^+, 8 K^+ were also transported across the plasma membrane of the cell.

Process Figure 3.17

The cell is "paying" the energy cost through the use of ATP. Recall that the sodium-potassium pump is an active transport mechanism that requires ATP to move Na^+ and K^+ across the membrane. As such, the cell's energy cost is "paid" during the first step of the figure.

Process Figure 3.20

Receptor-mediated endocytosis is similar to facilitated diffusion in that the receptor proteins functioning in receptor-mediated endocytosis have many of the same characteristics as the carrier proteins involved in facilitated diffusion. These characteristics include specificity, competition, and saturation. These two processes differ in the number of molecules that can be transported in one "cycle." Facilitated diffusion transports individual molecules across the membrane per cycle. Receptor-mediated endocytosis moves many copies of the substance across the membrane with the formation of a single vesicle.

Process Figure 3.21

Exocytosis involves the release of substances from a cell, not the uptake of substances into the cell. Of the choices, secretion of newly synthesized proteins involves the release of material from the cell into the extracellular space, so this activity is most likely to involve exocytosis. The other two choices, ingestion of a bacterium and absorption of lipid-soluble material, both involve uptake of something into the cell, either by phagocytosis in the case of the ingestion of a bacterium or by simple diffusion in the case of absorption of lipid-soluble material.

Process Figure 3.25

From the figure we can see that ribosomal subunits are composed of ribosomal RNA (rRNA) and ribosomal proteins. Recall from chapter 2 that RNA is composed of nucleotides and proteins that are composed of amino acids.

Process Figure 3.28

Recall that the rough ER is rough because of the presence of ribosomes; therefore, we would expect protein synthesis to occur there and the transport vesicles sent to the Golgi apparatus to contain proteins. Transport vesicles sent by the smooth ER to the Golgi apparatus are likely to contain lipids because the smooth ER is involved in lipid synthesis.

Process Figure 3.29

The digestive enzymes are isolated in the lysosomes to prevent the digestion of the normal parts of the cell.

Process Figure 3.35

As shown in the figure, transcription occurs in the nucleus and translation occurs in the cytoplasm, in association with ribosomes. Recall that our cells have membrane-bound nuclei and the nuclear envelope separates the contents of the nucleus from the cytoplasm. As a result, transcription must be completed before the mRNA molecule can exit the nucleus and enter the cytoplasm. Only then can the mRNA interact with the ribosome to complete the translation process. Bacterial cells do not have membrane-bound nuclei, so the ribosomes can associate with the mRNA as it is being synthesized before the process of transcription is completed.

Process Figure 3.36

Recall that each nucleotide of nucleic acids is composed of a sugar, a base, and a phosphate group. RNA nucleotides have ribose sugar, thus the name ribonucleic acid. DNA nucleotides have deoxyribose sugar, thus the name deoxyribonucleic acids.

Process Figure 3.37

The DNA gene sequence would be longer than the mRNA. The pre-mRNA has the same number of nucleotides as the coding section of the DNA gene sequence. The mRNA is shortened as introns are removed.

Process Figure 3.39

We learned that each codon specifies a single amino acid. That would mean that 50 codons specified the 50 amino acids in the polypeptide chain. Each codon is composed of 3 nucleotides, so the answer to the second question would be 150 (50 × 3) nucleotides specified the polypeptide chain.

Process Figure 3.41

The two processes are similar in that the DNA sequence is used to produce new RNA molecules during transcription and new DNA molecules during replication. The process of transcription produces RNA molecules; replication produces DNA molecules. Also, remember that transcription only involves specific genes, which are portions of a DNA molecule, but replication involves the entire DNA molecule.

Process Figure 3.42

Each mitotic chromosome is a replicated chromosome, consisting of two identical chromatids. Each chromatid is a DNA molecule and associated proteins. Each mitotic chromosome, therefore, consists of 2 DNA molecules. Recall that each DNA molecule is composed of 2 strands of DNA nucleotides; therefore, each mitotic chromosome consists of 4 DNA nucleotide strands.

Process Figure 3.43

We know that the process of mitosis produces daughter cells with the exact DNA as the parent and therefore the exact diploid number. The information provided suggests that one cell is lacking a chromosome (45) and one cell has an extra chromosome (47). It appears that the chromatids of a chromosome did not separate correctly and both moved into one new cell. Since the separation of chromatids occurs during anaphase, we can conclude that this is where the error occurred.

Process Figure 4.7

The characteristics of inflammation (redness, swelling, etc.) are due to increased blood flow to the site of injury. While it is very important to bring more blood to the injury site to provide more oxygen to the different cells as well as to increase the number of white blood cells, sometimes the inflammation response can become detrimental. RICE helps control the amount of blood arriving at the injured location. Rest reduces activity of the tissues so less oxygen is needed. Ice causes vasoconstriction, which reduces blood flow, and compression aids in moving excess fluid away from the area. Finally, elevation uses the force of gravity to aid in drawing fluid from the area. This is useful in recovery because excess swelling can actually prevent oxygen and nutrient delivery and can cause more damage than the original injury.

Process Figure 4.8

Recall from chapter 3 that the cellular division process called mitosis creates new cells. In preparation for mitosis, existing cells copy their DNA and then during mitosis each cell separates into two new, identical cells. This increases the total number of cells in an area. Mitosis creates cells to fill in the gap in the epidermis created by an injury.

Process Figure 5.3

A paper cut usually penetrates only the epidermal layer of the skin. The epidermis, like all epithelial tissues, is avascular, meaning it lacks blood vessels. If a "paper cut" does result in bleeding, we know that it has penetrated to the dermis of the skin.

Process Figure 5.4

DNA is primarily located in the nucleus. But recall that mitochondria also contain DNA. We can therefore assume that the melanosomes would congregate around the structures that contain DNA, the nucleus, and possibly the mitochondria.

Process Figure 5.10

Blood flows through the skin to release heat but also to ensure that the temperature of the skin is maintained at a homeostatic level. As the skin temperature drops due to the placement of the ice pack, blood vessels in that area will dilate to increase blood flow and therefore heat at the site.

Process Figure 6.11

Recall from chapter 3 and section 6.3 that cellular material is released in bulk by exocytosis. Thus, osteoblasts release the materials for bone matrix production by exocytosis.

Process Figure 6.13

You learned that regardless of starting material, bone ossification proceeds with osteoblasts secreting bony matrix until surrounded, at which point they are called osteocytes. In addition, you learned that bone is formed as woven bone first followed by lamellar bone formation. Because osteoblasts produce bone matrix for each ossification type and osteoclasts remodel the new matrix, the basic process is the same. The primary difference is the starting material in the fetus.

Process Figure 6.14

Looking at figure 6.14, we can see that the mechanism promoting long bone growth is division of chondrocytes. This cell division increases the amount of hyaline cartilage in the epiphyseal plate, which makes the overall bone length greater. Therefore, the major effect of GH is to stimulate chondrocyte cell division.

Process Figure 6.16

Because this bone growth in width resulted in a new osteon, the tunnel is now the central canal. Remember, an osteon consists of 4–20 concentric lamellae surrounding a central canal containing blood vessels and, often, nerves.

Process Figure 6.21

To answer this question, first recall stimuli for bone remodeling. One of the major promoters of bone remodeling and increased bone thickness is mechanical stress on the bone. Astronauts in very low gravity do not experience as much stress on their bones as do people living on Earth with its gravitational pull. Because there is less mechanical stimulation of osteoblasts, you would expect bones to heal more slowly in astronauts living in the international space station without the normal pull of gravity.

Process Figure 9.8

You learned that the charge on the inside of the membrane of an electrically excitable cell is negative (below zero). You also learned that K^+ is in higher concentration inside the cell membrane and constantly diffuses out of the cell through K^+ leak channels. Negatively charged proteins inside the cell cannot diffuse through the cell membrane. Thus, if the cell has a greater number of K^+ leak channels, the permeability of the membrane to K^+ is greater. Thus, more K^+ than normal will diffuse out of the cell. The negatively charged proteins left behind will cause the charge inside the cell to become even more negative. With the inside more negative, the resting membrane potential will be further from zero.

Process Figure 9.10

This is facilitated diffusion. Recall from chapter 3 that movement of a molecule or ion down its concentration gradient is a type of passive transport, specifically diffusion if the molecule or ion is a solute. However, diffusion of ions cannot occur directly through the phospholipid bilayer. Thus, a transport protein is required to "help" along the diffusion of the molecule or ion.

Process Figure 9.11

The action potential would be propagated in both directions, away from the point of stimulus. This is because an action potential is self-propagating. This means that it is the very Na^+ entering the cell causing the action potential that generates the action potential in the next section of the cell membrane. The Na^+ depolarizes the membrane, which stimulates voltage-gated Na^+ channels to open letting more Na^+ into the cell.

Process Figure 9.12

To answer this question, recall that the neuromuscular junction is the structure where skeletal muscle contractions are stimulated. The neurotransmitter acetylcholine binds to acetylcholine receptors on the sarcolemma. Without acetylcholine receptors, no signal for contraction will be transmitted to the muscle fiber and skeletal muscles would remain flaccid (not contracted). Giving the patient an acetylcholinesterase inhibitor is effective because it prevents degradation of acetylcholine in the synaptic cleft. By keeping the concentration of acetylcholine elevated, the limited number of receptors will be stimulated to a greater degree.

Process Figure 9.14

Given that the primary symptom of malignant hyperthermia is uncontrolled muscle contraction and you learned that Ca^{2+} release into the sarcoplasm triggers contraction, a likely culprit is higher than normal levels of Ca^{2+} in the sarcoplasm. Indeed, malignant hyperthermia patients have a mutated Ca^{2+} channel in the terminal cisternae of the sarcoplasmic reticulum that is prevented from closing, which allows excess Ca^{2+} to diffuse into the sarcoplasm. At this time, the primary treatment's mechanism of action is uncertain, but in theory, inhibiting the Ca^{2+} channels in the sarcoplasmic reticulum to reduce the total Ca^{2+} released from the sarcoplasmic reticulum would minimize the excessive muscle contraction. Fewer muscle contractions would also, most likely, prevent the spike in body temperature since skeletal muscle contraction is a major source of our body heat. In addition, fewer muscle contractions would also avoid fatigue and damage to the muscle tissue and muscle tissue would be preserved instead of breaking down.

Process Figure 9.15

The question tells you that Ca^{2+} diffuses out of the sarcoplasmic reticulum after a person dies. Because the myosin heads are in their resting position in a relaxed muscle, the presence of Ca^{2+} will cause the myosin heads to automatically engage the actin myofilaments and the muscle will contract. However, ATP production ceases upon the death of a person. You learned that ATP is required for two steps in the cross-bridge cycle: (1) detachment of the myosin head and (2) returning the myosin head to its resting position. Thus, the absence of ATP in a corpse prevents the release of already formed cross-bridges and the muscles stay rigid. Rigor mortis does not

happen in a living person because during life ATP does not get completely depleted. However, it can be significantly reduced when muscles have been overworked. In the case of severely overworked muscles, there is still enough ATP to allow a few cross-bridges to form, resulting in a weak contraction. However, there are not enough cross-bridges formed to allow a person to stand or walk.

Process Figure 9.16

Because the sarcoplasmic reticulum stores a high level of Ca^{2+} for rapid diffusion upon activation of a muscle contraction, during relaxation, Ca^{2+} must be pumped against its concentration gradient. Movement of molecules or ions against their concentration gradient is called active transport.

Process Figure 9.26

ATP binds to myosin heads to detach them from the active sites in skeletal muscle. In smooth muscle, however, myosin phosphatase cleaves a phosphate from the myosin heads.

Process Figure 11.8

Ions are charged atoms or molecules. The charge of ions will affect the direction of movement because opposite charges are attracted to each other and same charges are repelled from each other. We learned that the inside surface of the cell membrane is slightly negative. Since Cl^- are also negative, we can conclude that the negative charge inside the cell repels Cl^- thereby reducing the number that enter the cell.

Process Figure 11.12

The process is active. In figure 11.12, we learned that the pump functions to maintain the differential levels of Na^+ and K^+ across the cell membrane. This membrane protein is an active-transport mechanism, requiring ATP to transport the ions from one side of the membrane to the other.

Process Figure 11.14

We learned that action potential propagation is unidirectional toward the axon terminal due to the refractory period. The region of the membrane that reached threshold is not flanked by areas, just an action potential. The action potential could propagate in both directions.

Process Figure 11.16

Recall that local currents are due to the movement of ions, specifically Na^+. In the area of the membrane that is experiencing the action potential, Na^+ is flowing into the cell. The Na^+ that is positioned around the adjacent areas of the membrane will also move due to the normal tendency to diffuse to areas of lower concentration. This leads to the local currents described along the adjacent areas of the membrane.

Process Figure 11.17

Looking at figure 11.17, imagine removing the regions of the axon that are myelinated. The nodes of Ranvier are the only areas that experience the action potential. The combined length of just the nodes of Ranvier of the myelinated axons is much shorter than the overall length of the axon.

Process Figure 11.18

The region of the cell membrane where Na^+ diffuses through the gap junction is at resting membrane potential. Because ions diffuse in all directions away from their point of entry, any region of the membrane that reaches threshold will fire an action potential.

Process Figure 11.19

The ion channel depicted is a ligand-gated channel. Opening of these channels leads to graded potentials. If enough Na^+ enters through the ligand-gated channels, the cell will reach threshold and trigger the opening of voltage-gated Na^+ channels. Action potentials result from the opening of voltage-gated Na^+ channels.

Process Figure 11.20

MAO is the enzyme that degrades norepinephrine. If the enzyme is prevented from working properly, it cannot break down norepinephrine and levels increase within the synaptic cleft. With higher levels of norepinephrine, the target can be stimulated to a greater degree and thus relieve anxiety.

Process Figure 12.5

Recall that the motor division of the PNS is divided into the somatic nervous system, which controls skeletal muscle tissue, and the autonomic nervous system, which controls cardiac and smooth muscle and glands. The reflex example in this figure is a somatic reflex because the effector is skeletal muscle.

Process Figure 12.6

The result we want for this particular reflex is for the upper limb to bend or flex. To determine this, we just need to identify the flexor muscles of the upper limb. By reviewing the muscles described in table 10.16, we can see that the biceps brachii and the brachialis are the flexor muscles; therefore, these are the muscles that must be stretched to initiate the reflex to flex or bend the arm.

Process Figure 12.7

First, recall that sensory nerves conduct signals from the Golgi tendon organs within the tendon near the muscle-tendon junction. These signals initiate the Golgi tendon reflex, which activates inhibitory interneurons in the spinal cord. These interneurons inhibit the motor neurons, leading to muscle relaxation and reduced tension on the tendons. In the absence of this reflex, the force may become so great that tendons, and even muscles, may be torn.

Process Figure 12.8

The key to understanding the difference between these two reflexes is the type of interneuron that is activated in the spinal cord. The withdrawal reflex activates an excitatory interneuron, while the Golgi tendon reflex activates an inhibitory interneuron. Thus, the withdrawal reflex activates the alpha motor neuron to cause contraction, while the Golgi tendon reflex inhibits the alpha motor neuron to cause relaxation.

Process Figure 12.9

Remember that stretching of a muscle stimulates the stretch reflex. During the withdrawal reflex, as the flexor muscles contract, the extensor muscles are stretching. The inhibition overrides the normal response of these muscles to contract and allows for the coordinated movement of the limb.

Process Figure 12.10

This hypothetical situation is meant to illustrate the importance of both the reciprocal innervation that inhibits the extensor muscle in the same limb and the crossed extensor reflex that stimulates the extensor muscle in the opposite limb. In this situation, the collateral branches of sensory neurons would have activated excitatory interneurons that do not cross to the opposite side of the spinal cord. As a result, there would be activation of the extensor muscles in the same leg, which would counteract the flexor muscles. This is the opposite of reciprocal innervation, which would normally have inhibited the extensor muscles. Likewise, the lack of a crossed extensor reflex would reduce the shifting of weight to the opposite, unaffected limb. Hence, the person would most likely have difficulty removing the limb from the source of pain and would likely fall in the effort.

Process Figure 13.2

The neural crest cells that migrate from the cephalic portion of the neural tube give rise to all the craniofacial bones and cartilage. Consequently, the cephalic neural crest is responsible for normal development of facial structures and altered cephalic neural crest development leads to craniofacial defects in newborns.

Process Figure 13.14

If production levels of CSF are normal, accumulation of CSF would result from problems with the movement and drainage of CSF into the venous system. We can conclude that either flow of CSF within the brain is blocked or that the veins that drain CSF from the brain tissue are abnormal.

Process Figure 14.6

A primary sensory receptor can be activated only by stimulation of the type of receptor on its axon, for example, a Pacinian corpuscle. In contrast, a secondary sensory receptor is activated by neurotransmitters released by primary receptor cells. Consequently, the secondary neuron can be activated by multiple receptor cells responding to multiple stimuli. In addition, recall from section 11.7 that convergence of signals, such as occurs between multiple receptor cells and a sensory neuron, allows summation of signals. In this way, signals from multiple secondary receptor cells could contribute to activation of the sensory neuron.

Process Figure 14.19

The athletic trainer's conclusion is sensible considering the function of the cerebellum. Recall that the cerebellum ensures smooth and coordinated muscle contractions. The jerky, exaggerated movements exhibited by the kicker may be an indication of cerebellar damage. A thorough exam by a trained physician is needed to verify this diagnosis so the athletic trainer was right to insist that the player be transported to a hospital.

Process Figure 14.24

Recall that long-term potentiation involves both presynaptic and postsynaptic mechanisms. And, importantly, both mechanisms involve the neurotransmitter glutamate. Hence, inhibition of glutamate signaling activity would blunt both presynaptic and postsynaptic mechanisms.

Process Figure 15.2

The cholinergic synapse described in chapter 11 depended on neurotransmitters binding to receptor sites on the extracellular surface of the actual ion channel to open it, leading to depolarization. In the ion channels depicted in this figure, the ion channels open due to changes in the intracellular activity. Odorants do not directly interact with the ion channels but rather lead to opening of the ion channels through a G protein interaction.

Process Figure 15.3

The olfactory neuronal pathway from the olfactory bulb to the olfactory cortex areas represents a diverging pathway. Recall from section 11.7 that divergent pathways involve fewer presynaptic cells than postsynaptic cells. Essentially, presynaptic axons have collateral branches allowing them to communicate with more than one postsynaptic cell. We see this pattern as axons from the olfactory bulb synapse with multiple areas within the cerebrum.

Process Figure 15.7

Damage to the tractus solitarius would affect the sense of taste more because signals from all three cranial nerve pairs monitoring the taste buds synapse within the tractus solitarius. Damage to the glossopharyngeal nerve would only affect taste sensations from the posterior one-third of the tongue, the vallate papillae, and the superior pharynx.

Process Figure 15.10

If the lacrimal ducts are blocked, tears would not be released on to the surface of the eyeball. This could lead to irritation and damage of the eyeball due to the lack of lubrication and the protective enzyme lysozyme. Blocking the lacrimal canaliculi would result in "crying" as tears would not be able to drain from the surface of the eye and would eventually spill over the lower eyelid.

Process Figure 15.20

Recall from chapter 3 that mitochondria are the primary location for ATP production in the cell. In step 5 of this figure, we can see that ATP is needed for the recombination of rhodopsin molecules, which are necessary for the normal function of photoreceptors. We can hypothesize that mitochondrial diseases reduce normal ATP levels and therefore reduce the recycling of rhodopsin molecules in the photoreceptors.

Process Figure 15.21

The level of glutamate release from rods would be lower in the students sitting under the light. Recall that glutamate release is higher under dark conditions compared to bright conditions.

Process Figure 15.26

The superior colliculi of the midbrain are involved in reflexive movements of the head and body to visual and auditory stimuli. Essentially, we look in the directions of noises and movement in our periphery. Receiving visual stimuli is imperative for this reflex activity.

Process Figure 15.34

The basilar membrane is flexible. This flexibility is important for the physiology of hearing because movement of the basilar membrane moves the hair cells against the tectorial membrane, thus bending the stereocilia and affecting the membrane potential of the receptors. As we age, tissues become less flexible, including the basilar membrane. As a result, a person can experience hearing loss as the basilar membrane becomes less flexible.

Process Figure 15.36

Remember that the middle ear is normally an air-filled space. If fluid accumulated in the middle ear, the auditory ossicles would not be able to move as easily. The auditory ossicles transmit vibrations of the tympanic membrane to the oval window, and therefore into the inner ear. If they cannot not move as easily, the vibrations would not be conducted as accurately to the inner ear, resulting in less stimulation of the hair cells. Essentially, the accumulated fluid reduces the transmission of sound waves toward the inner ear.

Process Figure 15.38

Cochlear implants function by detecting sounds and stimulating the cochlear nerve. This type of device works well for individuals who suffer from conduction deafness. If a person has sensorineural hearing loss due to damage of the cochlear nerve, stimulating it artificially most likely will not alleviate the hearing loss.

Process Figure 15.43

Recall from chapter 13 that our conscious awareness of sensory input is only detected through the cerebrum. We, therefore, are aware of action potentials associated with our balance pathways conducted to the vestibular area of the cerebral cortex. We are not consciously aware of action potentials conducted to other areas of the brain.

Process Figure 17.6

The cell must have membrane receptors for the neurotransmitter. Recall from chapter 3 that the cell membrane contains embedded membrane proteins that act as receptors for chemicals, such as neurotransmitters. Once the neurotransmitter

binds to its receptor, the receptor triggers a specific sequence of events in the cell.

Process Figure 17.7

You learned that there are three ways to regulate hormone secretion by endocrine cells: humoral stimuli, neural stimuli, and hormonal stimuli. Process figure 17.7 shows hormonal stimuli for hormone secretion. In step 1, a hormone from the hypothalamus binds to receptors on particular endocrine cells of the anterior pituitary. The hypothalamic hormone then stimulates the anterior pituitary cell to secrete a specific hormone.

Process Figure 17.8

First, define humoral stimulus. A humoral stimulus is when a blood-borne chemical, such as glucose or Ca^{2+}, stimulates secretion of a hormone. Levels of the chemical in the blood regulate the hormone's secretion. For example, high blood levels of glucose stimulate insulin secretion. Insulin stimulates cells to take up glucose, lowering blood levels back to the normal range. The lower levels of blood glucose inhibit further insulin secretion. In other words, blood levels of glucose provide a negative feedback signal for reduced insulin secretion.

Process Figure 17.13

To answer this question, you need to relate the chemical characteristics of a molecule to the ability of that molecule to cross plasma membranes. You learned that lipid-soluble hormones can easily cross plasma membranes. Once these hormones are inside the cell, they bind to nuclear receptors either in the cell's cytoplasm or nucleus and stimulate a response. Thus, a newly developed drug that would modulate a nuclear receptor upon binding to it would need to be a lipid-soluble molecule in order to enter the cell with the targeted nuclear receptor.

Process Figure 17.14

First, define transport protein. You learned in chapters 3 and 9 that polar molecules cannot enter the cell by diffusing directly through the phospholipid bilayer. Instead, a transport protein, such as an ion channel, serves as a tunnel or pore through which a molecule or ion can move into or out of the cell. As shown in the figure, membrane-bound hormone receptors are simply "docking stations" for the hormones. The water-soluble hormone does not enter the cell through the receptor because the receptor is not a channel or transport protein. The binding of the hormone to the membrane-bound receptor triggers a sequence of events inside the cell to carry out the hormone's effect.

Process Figure 17.15

Yes, Ca^{2+} is an important second messenger. As this figure illustrates, in second messenger systems, binding of the hormone to its receptor activates second messengers inside the cell to stimulate the response of the target cell to the hormone. In the phospholipase C second messenger system, IP_3 stimulates Ca^{2+} release, which in turn plays a crucial role in intracellular signaling.

Process Figure 17.16

Because Cl^- has a negative charge, its entry into a cell causes the cell to become hyperpolarized, which is inhibitory to the cell. In chapter 11 you learned that a hyperpolarization takes the membrane potential further from threshold and the cell is less likely to generate an action potential.

Process Figure 17.17

The cell would continuously produce cGMP and would become overstimulated. This is the mechanism of certain stimulants, such as an epinephrine agonist like albuterol, when given as a medication for asthma. The stimulant molecules act as agonists and bind many times longer than the natural hormone to receptors of stimulatory hormones or neurotransmitters and the target cell responds to a much greater degree and for a longer time period than normal.

Process Figure 17.18

Receptor molecules are proteins. It is common for large proteins to serve a dual purpose. For example, remember from chapters 9 and 11 that ligand-gated ion channels act in two capacities: (1) they are receptors and (2) they are membrane channels to allow passage of ions across the plasma membrane. Thus, certain receptors also have enzymatic activities in addition to being a binding site for a hormone.

Process Figure 18.3

You learned that a certain hormone is synthesized by a specific cell type and that each hormone must bind to a specific receptor in order to generate its response. In order to respond independently to hypothalamic hormones, each cell type of the anterior pituitary possesses a unique receptor for its specific hypothalamic releasing hormone.

Process Figure 18.4

To answer this question, first recall that the two posterior pituitary hormones are synthesized by neurons whose cell bodies are in the hypothalamus. The hormones are stored in membrane-bound vesicles in the axon terminals, which are located in the posterior pituitary. Because the posterior pituitary hormones are stored in vesicles, they must be water-soluble hormones since lipid-soluble hormones would simply diffuse out of the vesicles.

Process Figure 18.5

Because ADH is a water-conserving hormone, its secretion reduces the amount of urine produced by the kidneys. If the body could not produce ADH, the kidneys would produce significantly more urine than normal. Individuals who have primary diabetes insipidus cannot produce ADH and must consume water on a regular basis and sometimes must take medications to help balance the ion composition of the blood.

Process Figure 18.6

Recall that an agonist is a molecule that binds to a receptor and mimics the action of the normal ligand. Because oxytocin stimulates uterine contractions and is involved in initiation of labor, a standard approach to induce labor is to give Pitocin, an oxytocin agonist. Pitocin is also sometimes given to women whose labor contractions have slowed after labor has been initiated to increase the strength and frequency of contractions.

Process Figure 18.7

The infundibulum is the stalk of tissue connecting the pituitary to the brain. It is also the location of the hypothalamohypophysial portal system. It is these portal system vessels through which GHRH and somatostatin GHIH travel to arrive at the anterior pituitary. Without either of these hormones, GH secretion would be inhibited. It is tempting to think that without somatostatin, GH secretion would increase; however, GH is not secreted without GHRH and so there would be little to no circulating GH in the event of a severed infundibulum.

Process Figure 18.10

The thyroid gland is the only gland in the body that utilizes iodine for synthesis of biological molecules. Additionally, thyroid hormones are synthesized as part of a larger protein, which is stored in the colloid of each follicle. Therefore, the colloid of each follicle would have the highest radioactive iodine concentration. The iodine is integrated into the protein thyroglobulin and would be stored within the colloid.

Process Figure 18.11

Hormones from the anterior pituitary function as tropic hormones. A tropic hormone stimulates

the secretion of another hormone and is the term used for the anterior pituitary hormones. Thus, TSH is a tropic hormone.

Process Figure 18.15

The chemical composition of epinephrine and norepinephrine from the adrenal medulla and sympathetic neurons is the same. The difference is simply the way the chemicals arrive at their target. When secreted by the adrenal medulla, epinephrine and norepinephrine are called hormones because they travel in the blood to their targets. Epinephrine and norepinephrine secreted by sympathetic neurons are called neurotransmitters because they are secreted into a synapse directly onto their targets.

Process Figure 18.16

Because cortisol suppresses the immune system, prescription of the related cortisone or other similar drugs is useful to reduce the inflammatory and immune responses. These drugs are often given to reduce inflammation caused by joint injuries. Cortisone can also reduce the immune and inflammatory responses that result from allergic reactions or abnormal immune responses, such as rheumatoid arthritis or asthma.

Process Figure 18.22

Darkness is a key stimulus for melatonin secretion, which, in turn, signals the brain to help with sleep cycles. Therefore, because Joe is trying to sleep during the day, he should take melatonin in the daytime, a few hours before his next sleep cycle. However, it is important to note that most physicians recommend that melatonin be taken for only a few months, that the only form of melatonin should be a prescription form, and that only adults should take melatonin. There are still many unanswered questions regarding the full role of melatonin in our body's overall function.

Process Figure 19.7

One of the products of hemoglobin breakdown is bilirubin. Bilirubin is secreted into the small intestine as part of bile and eventually excreted as part of feces. Bilirubin derivatives contribute to the color of feces. A person who is suffering from anemia due to fewer, smaller red blood cells would excrete less bilirubin; therefore, the color of the feces would be affected.

Process Figure 19.10

In step 2 we see that thromboxane is one of the chemical signals that activate platelets. Without platelet activation, platelet plug formation will not occur.

Process Figure 19.12

The name *antithrombin* suggests that it counters or interrupts thrombin activity. If that is the case, antithrombin would prevent the conversion of fibrinogen to fibrin and the clot formation.

Process Figure 19.15

In this case, the fetus would be capable of producing the anti-Rh antibodies. Remember that the fetal blood and maternal blood are in separate circulations and the mixing of blood usually occurs later in the pregnancy. The production of anti-Rh antibodies in the fetus would not pose a threat to the fetus and would not be sufficient to pose a threat to the mother at this point in the pregnancy.

Process Figure 20.9

The left ventricle will need to generate more pressure to overcome the higher pressure in the aorta to force open the aortic semilunar valve. This increased pressure actually leads to hypertrophy (thickening) of the left ventricle wall and negatively affects heart function.

Process Figure 20.10

The first question refers only to the pulmonary circulation. Remember that the right side of the heart pumps blood into the pulmonary circulation. Starting in the right atrium, a red blood cell will pass through the tricuspid valve into the right ventricle and then through the pulmonary semilunar valve into the pulmonary trunk. From the pulmonary trunk, blood flows to the lungs. So, for the first question, the answer is 2 (tricuspid and pulmonary semilunar valves).

The second question refers to the systemic circulation. The left side of the heart pumps blood to the systemic circulation, but remember, we are starting in the right atrium in this scenario as well. Blood returning from the lungs passes from the left atrium through the bicuspid into the left ventricle and then through the aortic semilunar valve into the aorta. Blood is then distributed to the different systems including the brain. So we include the tricuspid and pulmonary semilunar valves from the right side as well as the bicuspid and aortic semilunar valves from the left side for a total of 4.

Process Figure 20.12

Blood flows from the ventricles to the great vessels, which are located superiorly, at the base of the heart. Contraction of the ventricles from the apex to the base moves the blood toward the great vessels. Similar to squeezing a toothpaste tube from the crimped end toward the opening, contraction of the ventricles from the apex toward the base empties the ventricles more effectively.

Process Figure 20.15

During pacemaker potentials, as with action potentials in skeletal muscle fibers and contractile cardiac cells, Na^+ and Ca^{2+} move into the cell and K^+ primarily moves out of the cell.

Process Figure 20.18

From the figure we can see that ventricular systole includes steps 3 and 4. Also, the question states that isovolumetric means "same volume." In step 3, the ventricles are contracting but the AV valves and semilunar valves are closed. During this time of ventricular contraction, blood is not moving so the volume in the ventricles remains the same. We can conclude that the isovolumetric phase occurs at the beginning of ventricular systole when all valves are closed. In step 4, the semilunar valves are forced open and blood flows into the pulmonary trunk and aorta. This would be the ventricular ejection phase given that blood is forced or ejected from the ventricles.

Process Figure 20.22

As you can see from this figure, the sympathetic and parasympathetic divisions influence the heart rate by increasing or decreasing it, respectively, from the rate established by the SA node. Meditation is a method that helps to reduce emotional excitement and stress, thereby reducing sympathetic stimulation of the heart.

Process Figure 21.32

Recall that the brachial artery branches at the elbow forming the radial and ulnar arteries. When blood flow is blocked through the brachial artery, then blood flow will also be blocked in these two arteries as well.

Process Figure 21.36

An obstruction in the capillary would most likely cause an increase in capillary hydrostatic pressure (CHP) as the blood moves into the vessel faster than it can move out. This would increase net filtration pressure increasing the movement of fluid into the surrounding tissue.

Process Figure 21.37

When you are sleeping, skeletal muscle activity is low and therefore the buildup of metabolic by-products and the tissues need for O_2 and nutrients would be low. Based on these points, we can conclude that condition 2, when precapillary sphincters are contracted and blood flow is reduced, would exist in skeletal muscle of a sleeping individual.

Process Figure 21.39

Consistent with the vagal name, step 3 is most important to a vasovagal response. Parasympathetic stimulation via the vagus nerve decreases heart rate and therefore blood pressure. The sudden drop in blood pressure leads to lack of blood flow to the brain and fainting can occur. In addition to its major effect on parasympathetic stimulation, the vasovagal response also decreases sympathetic stimulation (shown in steps 4 and 5), which further influences a drop in blood pressure.

Process Figure 21.42

Theoretically, holding your breath leads to an increase in blood CO_2 and a decrease in pH. These chemical changes would lead to increased sympathetic stimulation that would increase heart rate, stroke volume, and vasoconstriction, all leading to an increase in blood pressure. This increases blood flow to the lungs where CO_2 can exit the blood.

Process Figure 21.44

The answer to this question is simply osmosis. Remember that water moves from areas of low solute concentration to areas of higher solute concentration. As more Na^+ is reabsorbed at the kidneys, water will follow the solute and be reabsorbed as well.

Process Figure 22.9

It seems simple, but this is a point that may be easy to overlook. The lymph nodes and spleen differ as to which body fluid is filtered. The lymph nodes filter debris and pathogens from lymph before it is returned to the blood. The spleen filters debris, worn-out red blood cells, and pathogens from blood.

Process Figure 22.10

Promotion of inflammation and chemotaxis will increase the number of white blood cells arriving at the site of infection. Promotion of phagocytosis eliminates the pathogen, preventing tissue damage.

Process Figure 22.15

The MHC class I molecules will most likely display the abnormal protein. Recall that MHC class I molecules display antigens produced inside the cell, such as abnormal proteins. MHC class II molecules display antigens that have been phagocytized by antigen-presenting cells.

Process Figure 22.17

In table 17.1 we can see that autocrine communication involves the release of chemical messengers that bind to receptors on the secreting cell. In this figure, that type of communication occurs at step 4 as the helper T cell releases interleukin-2 that then binds to interleukin-2 receptors on the same helper T cell.

Process Figure 22.18

Recall that proteins are produced at ribosomes. Also, these proteins will be released from the cell, which requires that they be packaged in vesicles for secretion. In this case, we can assume that plasma cells will have ample rough endoplasmic reticulum, as this is the site of protein synthesis for secreted proteins, as well as the Golgi apparatus for packaging the antibodies into secretory vesicles.

Process Figure 22.21

Memory cells are the key to secondary responses. Memory cells allow for a *faster* and *greater* response to a specific antigen. The presence of memory cells allows for a faster response because these cells do not have to go through the same number of steps (interacting with helper T cells) to produce plasma cells. Also, the presence of memory cells increases the actual number of cells specific to the antigen. Therefore, there are more immune cells responding to the antigen in the secondary response compared to the primary response.

Process Figure 22.22

There are several differences that can be identified when comparing the events in this figure to the events in figure 22.17. First, cytotoxic T cells respond to antigens on individual target cells, meaning those that are infected or mutated. Helper T cells respond to antigen displayed by antigen-presenting cells, which are other immune cells that have encountered the antigen. Next, cytotoxic T cells interact with MHC class I molecules on the target cell. This type of MHC molecules is present on most nucleated cells. Helper T cells interact with MHC class II molecules, which are associated with antigen-presenting cells. Finally, costimulation of cytotoxic T cells involves CD8 markers; whereas helper T cell costimulation involves CD4 markers.

Process Figure 23.14

Airflow into the lungs is achieved by pressure differences. As step 2 indicates, inspiration occurs when the diaphragm contracts and the thoracic wall expands. These two events increase the volume in the thoracic cavity, which lowers the pressure there. If atmospheric pressure is higher than alveolar pressure, air flows into the lungs. At higher altitudes, the atmospheric pressure is lower than at sea level. Thus, when a person inhales while at higher altitude, less air flows into the lungs. The reduced airflow per breath is what causes people to feel that the air is "thinner" at higher altitudes.

Process Figure 23.15

The barometric pressure on the graph would not change. Barometric pressure is always set to zero. The difference would be that there is a greater difference between barometric pressure and intra-alveolar pressure. This means that there is less resistance on the flow of air into the lungs, which is the benefit of a patient being in a hyperbaric chamber. Blood is more readily oxygenated due to the larger pressure gradient into the lungs.

Process Figure 23.16

At the alveoli, CO_2 diffuses from the blood into the alveoli because the partial pressure of CO_2 is higher in the blood than in the alveoli. If a person breathed into and out of a paper bag, the PCO_2 in the bag would increase and less CO_2 would diffuse out of the blood due to a less steep partial pressure gradient. Eventually, CO_2 levels in the blood would increase and the brain would adjust the breathing rate. This is why breathing into a paper bag is one way to control hyperventilation due to anxiety. Hyperventilation actually causes CO_2 levels to drop, so taking 6–12 normal breaths into and out of a paper bag helps return CO_2 levels to normal, which relieves hyperventilation.

Process Figure 23.18

The concentration of H^+ is the determinant of pH. Recall from chapter 2 that acidic pH is due to a high concentration of H^+. The pH of the red blood cell cytoplasm is maintained within the normal range in part by hemoglobin binding to H^+. If red blood cells had fewer hemoglobin molecules, as is the case with some forms of anemia, the concentration of H^+ not bound to hemoglobin would increase and the pH would become acidic. Hemoglobin serves as a pH buffer in the red blood cell cytoplasm.

Process Figure 24.2

If materials move through the digestive tract too quickly, there isn't enough time to absorb sufficient water from the chyme and it stays too liquid. Liquid feces is called diarrhea.

Process Figure 24.3

Because segmental contractions mix and disperse the chyme throughout the small intestine, there is more surface area of the food exposed to digestive enzymes and the digested food is exposed to transport proteins on the intestinal

epithelium. Without the segmental contractions, digestion and absorption would be reduced and malnourishment could eventually result.

Process Figure 24.10

It is impossible to talk or breathe during the pharyngeal phase because of closure of the nasopharynx and the larynx. Recall that, during this phase, the soft palate is elevated, which closes off the nasopharynx connection to the nasal passages. Further down, the vestibular and vocal folds close the passage through the larynx in to the trachea and lungs. In addition, the epiglottis is flipped down like a lid to further close off the opening to the larynx.

Process Figure 24.12

The pH of the blood would increase (become more alkaline) as acid is lost upon vomiting. The cells continue to produce HCl to replace the lost contents and as a result, HCO_3^- would continue to be secreted into the blood. This pathological condition is an exaggeration of the same process that normally generates a smaller alkaline tide after eating a meal.

Process Figure 24.13

Stomach emptying takes 4–6 hours after a full meal. If the entire stomach contents were to enter the duodenum all at once, the enzymes and epithelial cells lining the small intestine would be overwhelmed. Not all of the nutrients would be processed nor absorbed.

Process Figure 24.14

The longer stomach acid is in the stomach, the more likely it is to be forced back into the esophagus through the weakened gastroesophageal opening. Since it is the introduction of stomach acid to the esophagus that causes the symptoms of heartburn, a medication that slows stomach emptying could worsen heartburn symptoms. The medication may increase the chance that instead of the stomach acid entering the small intestine, it would be forced back into the esophagus. If untreated, prolonged exposure of the esophagus to stomach acid could cause esophageal ulcers or other disorders.

Process Figure 24.18

If the gallstones become too large, they block the cystic duct preventing bile from leaving the gallbladder. This can be very painful. Sometimes, smaller gallstones migrate to the duodenal papilla and become lodged there, which also blocks pancreatic secretions from entering the duodenum. In each example, blocking secretions of the gallbladder or pancreas interferes with the digestion process. For example, stomach acids are not diluted and neutralized to as great an extent as if bile were present. Lipids are not emulsified by the bile, which results in decreased lipid digestion and absorption. Excretory products, such as the bile pigments, cholesterol, and lipids, are not as readily removed from the body.

Process Figure 24.20

Unlike most other organs, the liver receives not only oxygenated blood via an artery, but it also receives a second supply of blood via a vein. This second supply is from the hepatic portal vein, which has nutrient-rich, but oxygen-poor, blood from the small intestine. Both the hepatic artery and hepatic portal vein are flowing in the same direction in the portal triad since they are both bringing essential oxygen and nutrients to the liver. The liver is the first stop for the portal blood before it is reoxygenated since the liver is a metabolic center designed to store and process nutrients, as well as scan the blood for pathogens. Blood does leave the liver, but it does so via the central veins, then into hepatic veins.

Process Figure 24.21

The principal function of cholecystokinin is to stimulate contractions of the gallbladder. Contractions of the gallbladder send a burst of bile into the duodenum. If the gallbladder is absent, this cannot happen. Doctors often recommend a low-fat diet to patients whose gallbladder has been removed.

Process Figure 24.23

Both processes require the enzyme carbonic anhydrase and the exchange of $HCO3^-$ and Cl^-.

Process Figure 24.24

Because the secretion of cholecystokinin and secretin is regulated by nutrients in the duodenum and parasympathetic nerves, a blockage to the pancreatic duct would not have an effect on cholecystokinin and secretin blood levels.

Process Figure 24.27

First, recall that the spinal cord is required for a normal defecation reflex and for voluntary control of the external anal sphincter. Spinal cord injuries that occur above the conus medullaris, where the defecation reflex center is located, will initially cause a temporary loss of the reflex, but with time the reflex usually returns. However, voluntary control of defecation will likely be permanently damaged due to lack of control of the external anal sphincter.

Process Figure 24.29

Movement of glucose into the intestinal epithelial cells is driven by Na^+ movement down its concentration gradient into the epithelial cell. Without the Na^+-K^+ pump continually moving Na^+ out of the intestinal cells to keep the concentration low, Na^+ levels would build up inside the cell. This would destroy the necessary concentration gradient. Consequently, glucose absorption would be greatly reduced.

Process Figure 24.30

The lipids become surrounded with hydrophilic proteins inside the intestinal epithelial cells to form chylomicrons. Chylomicrons cannot move through the hydrophobic cell membrane by simple diffusion and are too large to move through a membrane transport protein. Consequently, they are packaged into vesicles for exocytosis across the plasma membrane and into lacteals.

Process Figure 24.32

The levels of LDL cholesterol in the blood would increase. The inability of the receptor to undergo endocytosis would prevent the uptake of LDL cholesterol. When less LDL cholesterol is transported into cells, blood LDL cholesterol rises for two reasons: (1) The normal removal of LDL cholesterol does not occur, and (2) there is less inhibition of cholesterol synthesis. This would be similar to the effect of mutations in the LDL receptor that cause familial hypercholesterolemia (see Clinical Genetics 24.1).

Process Figure 24.33

Both mechanisms involve symport of either an amino acid or a sugar with Na^+ across the intestinal epithelium. In both cases, the transport is driven by a Na^+ gradient produced by the Na^+-K^+ pump.

Process Figure 25.3

Anabolic reactions result in the synthesis of molecules such as proteins. In table 3.1, we can see that the site of protein synthesis is ribosomes as well as the rough endoplasmic reticulum.

Process Figure 25.5

Recall that for each glucose molecule metabolized in glycolysis, a net yield of 2 ATP is gained. If 10 glucose molecules undergo glycolysis, a net yield of 20 ATP would be gained ($10 \times 2 = 20$).

Process Figure 25.6

Remember that a single glucose molecule is a 6-carbon molecule. The products of anaerobic respiration are lactic acid, NADH, and ATP.

During the breakdown of glucose, only H atoms and electrons are transferred to ATP or NADH; therefore, the 6 carbons of glucose are distributed evenly into the lactic acid molecules. As a result, each lactic acid molecule has 3 carbon atoms.

Process Figure 25.7

The CO_2 produced during aerobic respiration leaves cells and enters the blood. In the blood, much of the CO_2 moves into red blood cells and is converted to bicarbonate ions, which then move into the plasma of the blood. Bicarbonate ion and CO_2 participate in the carbonic acid/bicarbonate ion buffer system to help maintain blood pH.

Process Figure 25.8

The molecule oxaloacetic acid is needed to initiate the citric acid cycle. Acetyl-coA combines with oxaloacetic acid to form citric acid. At the end of the citric acid cycle, oxaloacetic acid is formed and used for another "turn" of the cycle.

Process Figure 25.9

The electronegativity of the components of the electron transport chain increases from the beginning to the end, so that electrons "flow" down the chain. If the electronegativity were reversed, the electrons would not move along the chain, and therefore, H^+ would not be pumped into the intermembrane space, eliminating the energy source for ATP production.

Process Figure 26.8

Osmosis is the driving force for water reabsorption. An increase in osmotic pressure would increase the rate of water movement into the blood from the kidney tubules. This would increase the total water reabsorbed.

Process Figure 26.9

You learned that there are three forces responsible for filtration: one outward force and two inward forces. If the inward forces were to exceed the outward force, no filtrate could be formed. If a person were to eat a high protein diet, levels of nitrogen-based breakdown products in the blood would increase. The higher solute levels in the blood would increase one of the inward forces, the colloid osmotic pressure. With a higher colloid osmotic pressure, water in the Bowman capsule would be drawn back into the blood. Less filtrate would be formed, which would decrease the urine volume.

Process Figure 26.14

Because the descending limb of the loop of Henle is permeable to water, water moves out of the filtrate into the more concentrated interstitial fluid. The longer the loop of Henle, the more surface area there is to allow a greater degree of water conservation. Because water is not readily available to desert animals, being able to conserve the majority of water filtered out of the blood in the kidney is critical for their survival.

Process Figure 26.16

By producing an excessive amount of filtrate, the blood is rapidly and repetitively filtered over the course of a day, which improves the efficiency of cleansing the blood and allows rapid removal of toxins. Reabsorption of nearly all of this filtered material is essential or else we would soon be dehydrated.

Process Figure 26.17

Because aldosterone is active under low blood pressure conditions and increases Na^+ and water reabsorption, too little aldosterone could result in blood pressure that is too low. In addition, blood K^+ levels would increase because its secretion is linked to Na^+ reabsorption. Thus, if there's less Na^+ reabsorption, there is less K^+ secretion.

Process Figure 26.18

ADH increases water reabsorption from the filtrate, which enters the blood and increases blood volume. Increased blood volume causes increased blood pressure. If an individual had excess ADH, their blood pressure would be abnormally elevated due to excess water reabsorption.

Process Figure 26.23

Damage to sacral spinal nerves can result in either an overactive urinary bladder or an underactive urinary bladder, depending on the specific details of the injury to the sacral spinal cord nerves. It is still unclear why injury in this region of the spinal cord results in more than one type of response by the urinary bladder. An overactive urinary bladder causes frequent urination urges regardless of the urinary bladder fullness. In addition, urine may only dribble out of the urethra when urinating. An underactive urinary bladder causes a lack of urge to urinate even if the urinary bladder is completely full. In extreme cases, the urinary bladder may become so full that it bursts.

Process Figure 27.2

Because blood loss results in decreased blood volume and thus decreased blood pressure, we know that the mechanism being activated is the baroreceptor mechanism. Stimulation of thirst encourages water intake, which would help return blood volume to its normal level. As a result, blood pressure would return to its normal range as well.

Process Figure 27.7

Potassium is not the only intracellular solute; proteins constitute a significant portion of the intracellular solutes. Proteins tend to have a net negative charge and K^+ ions tend to diffuse out of the cell, down their concentration gradient. These factors are the principal reasons the charge on the inside of the plasma membrane is negative compared to the outside of the plasma membrane. See chapters 9 and 11 for a more detailed discussion on the electrical charge difference across the plasma membrane.

Process Figure 27.13

You learned that elevated CO_2 levels in the blood cause the pH of the blood to decrease. Increasing the rate and depth of breathing helps to counter this by increasing the amount of CO_2 that is expired. If blood pressure and heart rate also increase, then a greater volume of blood is directed to the lungs and even more CO_2 is expired. Thus, chemoreceptors activated by low pH also stimulate an increase in blood pressure and heart rate.

Process Figure 27.14

Because the Na^+/HCO_3^- symporter moves both Na^+ and HCO_3^- out of kidney tubule cells and into the blood, the level of HCO_3^- in the blood would increase. This increase would allow more H^+ to react with HCO_3^-, thereby lowering the levels of free H^+ and raising the pH of the blood.

Process Figure 27.15

The buffering ability of the filtrate would increase and the pH of the urine would become more alkaline. When a person's digestive tract eliminates wastes very quickly, such as occurs with diarrhea, there is a greater amount of HCO_3^- that is reabsorbed from the digestive tract to enter the blood. This is because the digestive tract loses H^+ very quickly and attempts to reestablish homeostasis by increasing the synthesis of stomach acid. Recall that the production of stomach acid involves the carbonic acid/bicarbonate ion reaction. When carbonic acid dissociates into free H^+ and HCO_3^-, the HCO_3^- is moved by an antiporter from the digestive tract into the blood. Therefore, in the kidneys, there will be more HCO_3^- that ends up in the filtrate. This is due to an increased level of HCO_3^- that gets filtered out of the blood. The increased

HCO_3^- in the filtrate will bind to any free H^+, which causes the pH of the filtrate to become alkaline and therefore, the pH of the urine becomes alkaline.

Process Figure 28.1

Normally, each of the two cells undergoing anaphase II has 23 chromosomes. Each of the 23 chromosomes is present in two copies, or chromatids. If the chromatids don't separate during anaphase II, but instead migrate together, one cell will have one extra chromosome, or 24. The other cell will have one less chromosome, or 22.

Process Figure 28.5

During the descent of the testes, the inguinal canal openings are stretched. This process does not happen in females. This leads to a weakened area of the abdominal wall, increasing the likelihood of herniation.

Process Figure 28.6

The key to this question lies in the definition of a chromosome and how many copies of each chromosome exist during meiosis. Recall that prior to beginning meiosis, each chromosome is replicated such that a chromosome consists of two copies, called chromatids. Thus, although it states that each secondary spermatocyte has 23 chromosomes, each one exists in two copies. During meiosis II, it is the *chromatids* that separate. Thus, each spermatid has 23 chromosomes, each with only one copy.

Process Figure 28.9

You learned that testosterone has a negative-feedback effect on GnRH, LH, and FSH. If testosterone levels are higher than normal, we would expect the levels of GnRH, LH, and FSH to be lower than normal.

Process Figure 28.10

As indicated in step 4 of the figure, acetylcholine is important for relaxation of smooth muscle in the erectile tissue of the penis. If a competitor blocked the activity of acetylcholine, smooth muscle relaxation would be reduced and engorgement of the erectile tissue would be decreased, leading to the inability to achieve an erection.

Process Figure 28.14

A secondary oocyte does not complete meiosis unless united with a sperm in fertilization. Thus, without sperm in the female reproductive tract, the secondary oocyte will exit the body during menstruation and will still contain chromosomes that have two chromatids.

Process Figure 28.19

Reviewing the figure, it is apparent that the two feedback mechanisms occur at different times and involve different hormonal interactions. The positive feedback mechanism occurs during the follicular phase of the ovarian cycle and FSH stimulates follicle development, which increases estrogen secretion by the ovary. Estrogen stimulates more FSH secretion as well as LH secretion, resulting in the positive feedback. Increased LH stimulates ovulation and the development of the corpus luteum. At this point, the luteal phase begins as the corpus luteum secretes progesterone. It is progesterone that initiates the negative feedback mechanism by decreasing LH and FSH secretion.

Process Figure 28.20

Recall that menses occurs during days 1–5 of the menstrual cycle. During this time, the primary follicle is developing and the primary oocyte is progressing through the first meiotic division. A secondary oocyte forms just prior to ovulation, so this would coincide with the end of the proliferative phase of the uterine cycle.

Process Figure 28.22

The secretion of hCG by the chorion ensures that the corpus luteum remains functional. Remember from section 28.5 that the corpus luteum, if not stimulated by endocrine signals from the embryo, degenerates. The secretion of progesterone and estrogen by the corpus luteum is important in the early stages of pregnancy to maintain the endometrial lining of the uterus. Without those signals, menses of the next menstrual cycle would begin and the embryo would be lost with the functional zone of the endometrium.

Process Figure 29.1

Recall that each human sperm cell has 23 chromosomes. A human zygote normally has 46 chromosomes, 23 received from the sperm cell and 23 received from the oocyte. If two sperm cells fertilized the same secondary oocyte, the resulting zygote would have 69 chromosomes, 23 from the first sperm cell, 23 from the second sperm cell, and 23 from the oocyte (following the second meiotic division). Such a zygote would almost always be nonviable.

Process Figure 29.3

The antibodies would pass from the maternal blood in the lacuna through the syncytiotrophoblast tissue, cytotrophoblast, mesodermal tissue, and the walls of the forming embryonic vessels.

Process Figure 29.6

Though the embryonic disk changes from a two-layer structure to a three-layer structure, do not make the mistake of assuming that only one new layer of tissue develops. As you can see in steps 2 and 3 of this figure, the three embryonic layers (endoderm, mesoderm, and ectoderm) all are derived from the original ectoderm as a result of gastrulation. The hypoblast becomes part of the membranes around the developing embryo.

Process Figure 29.7

The notochord is a cordlike structure that forms from specialized cells of the primitive streak and delineates the central axis of the body. The neural tube is derived from ectoderm and gives rise to parts of the nervous system.

Process Figure 29.10

We can see from this figure that the lower jaw and lower lip are formed from the mandibular processes, so we can assume that any defect in the lower lip is due to issues with the mandible. Similarly, we can see that the cheeks of the face are primarily formed by the maxillary processes, so any defect in the development of the cheeks would involve the maxillary processes.

Process Figure 29.12

During the development of the interatrial septum, a hole called the foramen ovale normally exists that should close at birth. The interventricular septum, on the other hand, forms as a solid structure. Given that a hole is already present in the interatrial septum, it would be more likely that this existing hole does not close properly. When the foramen ovale does close properly, the location remains visible in the adult heart as the fossa ovalis.

Process Figure 29.13

Remember that the number of lobes differs between the right and left lung. The right lung is composed of three lobes and the left lung is composed of two lobes. The number of branches in the embryonic tissue, therefore, would be higher in the right lung.

Process Figure 29.16

The male homologous structure for the clitoris is the glans penis. The female homologous structures for the scrotum are the labia majora.

Process Figure 29.20

Synthetic oxytocin, called Pitocin, is often administered to women to increase uterine contractions.

Process Figure 29.21

Progesterone has an inhibitory effect on the uterus, which affects the spiral arteries. Estrogen, prostaglandins, and oxytocin all have stimulatory effects on the uterus that affect growth and smooth muscle contraction.

Process Figure 29.22

Before birth, the umbilical veins carry oxygenated blood from the placenta to the fetus's circulation. Umbilical arteries carry deoxygenated blood from the fetus to the placenta. This is opposite of normal blood oxygenation levels after birth. Most arteries carry oxygenated blood and most veins carry deoxygenated blood. The exception to this pattern is in the pulmonary circulation where pulmonary arteries carry deoxygenated blood from the heart to the lungs and pulmonary veins carry oxygenated blood from the lungs to the heart.

Process Figure 29.23

Recall that milk production occurs in mammary glands, specifically at the alveoli. Prolactin targets the secretory cells of the alveoli, stimulating increased milk production. The milk accumulates in the alveoli. Oxytocin stimulates smooth muscle cell contraction to expel the milk from the alveoli as well as smooth muscle cell contraction to move the milk through the lactiferous ducts of the mammary glands. Both hormones are needed so that milk production occurs (under the influence of prolactin) and so that the milk is released from the glands (under the influence of oxytocin).

Process Figure 29.29

Recall that the cells that undergo the second meiotic division are initially haploid, so in humans, they have 23 chromosomes. These chromosomes were duplicated prior to meiosis, so that each chromosome at the beginning of the second meiotic division consists of two chromatids. Normally, the chromatids then separate, resulting in gametes with 23 chromosomes. If a secondary spermatocyte undergoes the second meiotic division and the chromatids of one chromosome fail to separate, the resulting gametes would both be abnormal. One would have 22 chromosomes and one would have 24 chromosomes.

Appendix E

ANSWERS TO ODD-NUMBERED PREDICT QUESTIONS

Chapter 1

1. Although you may not know the specific mechanisms of antibiotics, you learned that bacteria in our body have been found to be very important for our overall health. Any disruption in our body's microbial population could disturb homeostasis. In addition, you learned that the gut microbial population is particularly important. Therefore, ingestion of an antibiotic could disturb the gut's microbiome. You also learned in chapter 1 that sometimes a negative feedback mechanism may be insufficient to restore homeostasis and medical intervention is necessary. In this case, as you will learn more about in chapter 24, transplanting microbes from one person to another may restore the gut's microbiota and homeostasis.
3. To answer this question, we must first recognize the components of the feedback systems that maintain homeostasis in the body: receptor, control center, and effector. Recall that any disruption in normal function (such as fainting) is a disruption in homeostasis.
   a. Normally, homeostasis of blood pressure is maintained in this kind of situation when receptors near the heart are stimulated by lower blood pressure upon standing (blood falls away from the brain due to gravity). These receptors send a signal to the brain control center, which stimulates the effector, the heart, to beat faster. The increased heart rate causes blood pressure to go back to normal, thus maintaining homeostasis.
   b. Because Molly's blood pressure dropped when she stood, the feedback system described in (a) was initiated and her heart rate increased. However, the elevated heart rate was not sufficient to prevent Molly from fainting. Too little blood was delivered to her brain, and she lost consciousness.
   c. When Molly fell to the floor, she returned to a lying-down position. This eliminated the pooling effect of the blood in the veins below the heart because of gravity. Therefore, blood return to the heart increased, blood pressure increased, blood flow to the brain increased, homeostasis of brain tissue was restored, and she regained consciousness.
5. Initially, we might think that Ashley's increased respiratory rate is indicative of positive feedback. However, we must first look at the underlying reason for her elevated breathing rate. If you have ever run a race, you know that, eventually, your breathing rate goes back to normal once you stop running. However, during the race your body needs more oxygen to be able to keep running. Because running requires oxygen, oxygen levels in the blood go down. The lowered oxygen level is detected by receptors, which communicate with the control center. The control center stimulates the effector, the diaphragm, to increase breathing rate. Once oxygen levels are returned to the set point, the breathing rate returns to normal. This is the essence of negative feedback: The response is stopped when the variable returns to the normal range.
7. In order to recognize which term to use here, we must first realize that directional terms are relative to the body. Therefore, it does not matter what position our body is in compared with the earth; body parts always have the same relationship to each other. Thus, the kneecap is always both proximal (closer to point of attachment to the body) and superior (closer to head) to the heel. It is also anterior to the heel because it is on the anterior side of the lower limb, whereas the heel is on the posterior side.

Chapter 2

1. The question asks us to differentiate between mass and weight. First, consider the definitions. Weight, in particular, is dependent on the force of gravity. Therefore, if an astronaut is in outer space, where the force of gravity from Earth is nearly nonexistent, the astronaut is "weightless." However, the definition of mass is the amount of matter present in the object itself. Thus, no matter the location of an object, the mass remains constant.
3. To answer this question, we must recall the relationship among CO_2, H_2O, and H^+ in solution. Carbon dioxide readily combines with water resulting in the production of free H^+. Therefore, as the amount of CO_2 decreases, the reversible reaction will shift in the other direction to form CO_2. Similar to the trough of water example, if CO_2 levels decrease, it is like raising the right side of the trough, causing water to flow to the left. The reaction "flows" to the left: $CO_2 + H_2O \rightarrow H^+ + HCO_3^-$. In order for this to happen, free H^+ combines with HCO_3^-, decreasing its level in the blood. Section 2.3 explains that this decrease in H^+ levels changes the pH of the blood so that it becomes more basic.
5. During exercise, our body is doing work by muscular contractions. Work involves converting one form of energy into another, and as we read in the previous section, this conversion is not 100% efficient. As a result, heat energy is released. When contracting our muscles, potential energy is converted to kinetic energy and heat energy. Thus, more heat is produced when exercising than when at rest, and our body temperature increases.

Chapter 3

1. Recall that a substance that binds to a protein receptor must be specific to the binding site. The drug is able to bind to the receptor as well, presumably, because it is structural similar to the normal ligand. Similar to transport proteins, substances with similar structures compete for binding sites on the membrane. We can conclude that the lower dosage (250 mg) was not high enough to overwhelm the binding of the normal ligand. Increasing the dosage (750 mg) allowed the drug to outcompete and bind more often to the receptor, thereby blocking the normal activity.
3. If the membrane is freely permeable, there is no barrier to the movement of solutes or water. The solutes and water would each move down their concentration gradients. Since the solute concentration is higher in the tube, the solutes diffuse from the tube to the beaker until equal amounts of solutes

exist inside the tube and beaker (i.e., equilibrium). In a similar fashion, water, which is at a higher concentration in the beaker compared with the tube, will diffuse into the tube until equal amounts of water are inside the tube and beaker. As a result of the diffusion of the water and solutes, the solution concentrations inside the tube and beaker will be the same because they both contain the same amounts of solutes and water.

5. a. We have learned that Na^+, as with other ions, must be transported across plasma membranes by transport proteins. We can therefore assume that aldosterone plays some role in stimulating Na^+ conservation at the kidneys through some type of membrane transport mechanism. We can also assume that since Na^+ is lost in the absence of aldosterone, the presence of aldosterone is involved in some type of active transport of Na^+ increasing the number of the ions that remain in the body as opposed to being lost as part of urine.
   b. Recall that osmosis, the diffusion of water, occurs when water moves from areas of low solute concentration to areas of higher solute concentration. Since the lack of aldosterone leads to an increase in the loss of Na^+ and water, we can conclude that water is diffusing to areas of higher Na^+ levels. As more water is lost in urine, blood volume will decrease. A decrease in blood volume leads to a decrease in blood pressure.
7. The first piece of relevant information is that viruses aren't cells. Antibiotics are drugs that attack features of cells. Bacteria are cells—independent, free-living organisms with their own, specific molecules and cellular mechanisms. Bacteria can synthesize their own proteins and reproduce on their own. Conversely, viruses occupy human cells and use human molecules for survival. In order to medically attack a virus, attack of human cells and human-specific molecules is often necessary. In general, antibiotics attack bacteria-specific molecules and processes.

Chapter 4

1. a. The question asks about the relationship between form and function of tissues. First, consider the name of the tissue type: nonkeratinized, stratified epithelium. The term *stratified* means more than one layer of cells, whereas the term *simple* means a single layer of cells. In the digestive tract, a principal function is absorption, a process that would be hindered by the many layers of stratified epithelium. Stratified epithelium is more suited to areas where the layers would protect underlying tissues from abrasion. Cuboidal cells are specialized for secretion and absorption. These cells contain a large number of organelles that produce the secretions and transporters needed to support absorption.
   b. In this scenario, both tissue types are stratified, but one type lacks keratin. The protein keratin provides a tough layer that retards water movement. If keratin were absent from the epidermis, the body could not retain water effectively and would be more prone to damage from abrasion.
   c. In the mouth, because whole foods are sometimes very coarse, the tissue needs to be thick and tough like stratified squamous. If the mouth were lined with simple columnar, it would be severely damaged during chewing.
3. The question asks how the structure of a tissue's components contributes to its function. When the vertebrae flex, elastic ligaments attached to the vertebrae help them return to their normal, upright position. When a muscle contracts, the pull it exerts is transmitted along the length of its tendons. The tendons need to be very strong in that direction but not as strong in others. The collagen fibers, which are like microscopic ropes, are therefore all arranged in the same direction to maximize their strength. If tendons were elastic, muscle contraction tension would not move the bone effectively. Imagine trying to connect train cars end to end with rubber bands, rather than steel couplings. Movement of the train would be ineffective, as the engine would be able to move quite a distance before the next car would move, and so on.
5. First, consider the characteristics of hyaline cartilage that make it an effective tissue for ease of joint mobility. Hyaline cartilage provides a smooth surface, so that bones in joints can move easily. In contrast, dense irregular collagenous connective tissue is a fibrous meshwork that is noted for its strength and ability to withstand stretching—for example, in the dermis layer of the skin. When the smooth surface provided by hyaline cartilage is replaced by fibrous connective tissue, the smooth surface is replaced by a less smooth surface, and the movement of bones in joints is much more difficult. The increased friction helps increase the inflammation and pain that occur in the joints of people who have rheumatoid arthritis.

Chapter 5

1. In the description of the epidermis, the superficial layer of the skin, we learned that the keratinized cells are coated with lipids to prevent fluid loss. Recall from chapter 3 that substances that are lipid-soluble easily diffuse through lipid layers but water-soluble substances do not. By applying the same principles of diffusion across cell membranes to diffusion across the skin, we can predict that lipid-soluble substances diffuse easily but water-soluble substances do not.
3. From the description of the injury, we know that the hammer struck Bob's nail bed. It is apparent that the hit was hard enough to rupture small blood vessels deep to the nail matrix. Blood accumulated between the nail and the nail bed, causing the dark area. In chapter 4 we learned that inflammation is the response that occurs when tissues are damaged and a normal inflammatory event is edema, or swelling at the injury site. The accumulation of blood and edema increased the pressure deep to the nail body, which stimulated pain receptors. When a hole was drilled through the nail, the accumulated bloody fluid drained, reducing the pressure and, consequently, the pain. Since the nail matrix, which is proximal to the injury site, was not injured, the nail continued to grow over the next 2 months, until the injured area was pushed distally to the free edge of the nail.
5. We learned that one of the functions of the skin is to reduce water loss. Sam's burns resulted in severe damage to his skin, which most likely led to increased water loss at the injury site, causing dehydration and reduced urine production. We learned that Sam was administered large volumes of fluid to counteract his increased fluid loss. But how much fluid should be given? The amount of fluid given should match the amount that is lost, plus enough to keep the kidneys functioning properly. An adult receiving intravenous fluids should produce 30 to 50 mL of urine per hour, and children should produce 1 mL/kg of body weight per hour. By monitoring Sam's urine output, the nurse can determine if he is getting enough fluids. If his urine output is too low, more fluids can be given.

Chapter 6

1. First, let's consider the structure of cartilage. The book tells us that the perichondrium, which surrounds the cartilage, contains blood vessels, but the blood vessels do not enter the cartilage. The book also states that nutrients must diffuse through the matrix before reaching the chondrocytes. Logically, cells that aid in tissue repair would also

enter cartilage more slowly than if blood vessels penetrated the cartilage. The question next asks whether the lack of perichondrium, blood vessels, and nerves would be advantageous for articular cartilage. When considering the function of articular cartilage, the absence of such structures makes sense. Articular cartilage provides a smooth, low-friction surface for two bones to move past each other easily. If there were solid structures within the joint, the effect of smooth movement would be lost. Imagine trying to ice skate on a rink whose ice had garden hoses frozen just under and along the surface. We would spend more time trying to get back to our feet than skating.

3. This question requires knowledge of cartilage histology, bone formation, and bone histology. Recall that, to acquire O_2 and nutrients, cartilage relies on diffusion though the matrix. As osteoclasts migrate into the developing bone structure and start to remove the cartilage, the cartilage becomes calcified, no more diffusion is possible, and the chondrocytes die. However, when we examine bone histology, we see that adjacent osteocytes are connected via cell processes. As the matrix is laid down, the area where the cell processes meet does not become covered in ossified matrix, forming canaliculi. Therefore, osteocytes continue receiving oxygen and nutrients through the canaliculi or from one osteocyte to another through cell processes.
5. It is likely that Jill is still growing. Consequently, the epiphyseal plates in her long bones have not yet been converted to epiphyseal lines. If a break occurs in an epiphyseal plate, it can slow bone growth and interfere with bone elongation. As a result, the femur, and therefore her left leg, will be shorter than her right leg. Recovery is difficult because cartilage repairs slowly due to the fact that cartilage is much less vascular than bone.
7. The question tells us that Nellie's blood levels of estrogen are much higher than normal for a 12-year-old girl. The text explained that important growth stimulators are reproductive hormones, which usually promote a burst of growth at puberty (approximately 12 years for girls). Because Nellie's estrogen levels are higher than normal, she will most likely grow at a faster rate than she normally would have over the next 6 months. However, if the estrogen levels are not lowered back to normal, Nellie will probably be shorter at 18 than expected. Recall that, in addition, to stimulating a burst of growth at puberty, estrogen causes a closure of the epiphyseal plate and growth in bone length stops. Also, estrogen is more effective at this than testosterone, so Nellie may stop growing years before she would have with normal estrogen levels.
9. a. Henry's bone density is less than normal for a man his age. Less dense bone is more likely to break.
   b. Henry's eating habits have resulted in insufficient dietary intake of Ca^{2+} and vitamin D. Therefore, the absorption of Ca^{2+} from his intestine into his blood has been inadequate.
   c. We might expect Henry's blood Ca^{2+} to be low because of his diet. However, low blood Ca^{2+} levels stimulate increased PTH secretion. An increase in PTH maintains normal blood Ca^{2+} by increasing the number of osteoclasts, which break down bone and release Ca^{2+} into the blood. Thus, Henry's blood Ca^{2+} levels are maintained at the expense of his bones, which become less dense as more matrix than usual is broken down. Increased PTH levels also promote more Ca^{2+} reabsorption from the urine.
   d. Normally, exposure to sunlight activates a precursor molecule in the skin that eventually becomes activated vitamin D in the kidneys (see chapter 5). Henry produces few, if any, precursor molecules because of his nocturnal lifestyle. Therefore, Henry has low vitamin D levels and, so, has reduced absorption of Ca^{2+} from his small intestine.
   e. Exercise is a major source of mechanical stress on bones, which increases osteoblast activity. Because Henry does not exercise, his osteoblasts have not been as active as they might have otherwise been, which has allowed the osteoclasts to dissolve his bone to a greater degree than normal. The overactivity of the osteoclasts partially accounts for Henry's lower bone density.

Chapter 7

1. After reading section 7.2, you probably realize that common structures, such as the "arm," the "hand," and the "nose," are actually a combination of multiple bones. Therefore, a "broken nose" could involve the nasal bones, the ethmoid bones, the vomer bone, the maxillae bones, or the inferior nasal conchae.
3. In this scenario, Dr. Smart is able to diagnose a broken clavicle without x-rays. To determine how this is possible, we first need to know the normal position of the arm and the clavicle's role in attaining this. The text explains that the clavicle's job is to hold the upper limb away from the body. In addition, if we look at figure 7.27, it shows that the clavicle supports the scapula anteriorly. Therefore, when Sarah arrived at the emergency room, Dr. Smart probably saw that her shoulder was more inferior and anterior than normal and that her arm was resting against the side of her body and not being held away from the body, as it normally is.
5. The top of modern ski boots is placed high up the leg to make the weakest point of the fibula less susceptible to great strain during a fall. Modern ski boots are also designed to reduce ankle mobility, which increases comfort and performance.
7. The question addresses the form and function of the femur, especially in older people. Recall from chapter 6 that as people age bone density declines because the reproductive hormones decline. We learned that estrogen in women and testosterone in men help bones grow and stay dense. However, because older women's estrogen levels tend to be lower than older men's testosterone levels, their bones are even more fragile than men's. Additionally, the femoral neck is commonly injured in elderly people because it is the smallest portion of the femur, which supports the weight of the body. It also forms an angle between the pelvis and the shaft of the femur, so the downward force of gravity on the body places enormous pressure on this part of the femur. That pressure is usually resisted in younger people with strong bones, but not as much in the elderly.

Chapter 8

1. First, we must define a suture and its location. A suture is a seam between two skull bones. Second, we need to define a synostosis: an ossified joint, such that two bones have become one solid bone. Next, the question asks about the effect of skull bones fusing prematurely on a child's brain development. To address this, recall that, in a normal newborn, the sutures are more extensive than in an adult skull and are called fontanels (soft spots). The fontanels allow for expansion of the skull to accommodate brain growth. If a newborn's skull were completely solid, the brain's growth would be impeded, and developmental problems would arise in the child.
3. To begin, it is required to know what anatomical position is involved. Recall that, when a person is standing, the face is forward, the arms are to the sides, and the palms of the hands are facing forward. Next, it is necessary to know the different terms used to describe movements of limbs and body parts relative to others. Now,

picture yourself in this anatomical position: Your right arm would move laterally out to the side (abduction) and then your hand would move closer to your head, bending at the elbow (flexion). Flexion at the shoulder and elbow also works.

5. This question requires you to apply your knowledge of the knee ligaments to a clinical situation involving two tests of ligament integrity (anterior and posterior drawer tests). For Ford, the normal anterior drawer test result indicates that the anterior cruciate ligament was not injured. However, the increased movement in the posterior direction indicates that his posterior cruciate ligament (PCL) was torn. The PCL connects the femur to the tibia at the back of the knee to limit the backward or posterior motion of the tibia. A PCL tear occurs most commonly when there is a strong direct blow to the front of the knee. The sudden force backwards can tear the PCL, especially if the knee is flexed (bent) close to a 90-degree angle. Common incidents that cause PCL damage are car accidents when the knee hits the dashboard and contact sports such as when a football player is tackled from the front below the knee.

Chapter 9

1. The first step to answering this question is to define the resting membrane potential and the distribution of ions across the cell membrane in a resting, electrically excitable cell. At rest, the concentration of K^+ is higher inside the cell than outside the cell. This means that a concentration gradient exists for K^+ from inside the plasma membrane to outside the plasma membrane. Therefore, if K^+ ion channels were opened, regardless of the stimulus that caused them to open, K^+ would diffuse out of the cell. Because K^+ is a positively charged ion and other, negatively charged particles, such as proteins, remain in the cell, the resting membrane potential would decrease or would become more negative.
3. To answer this question, we first need to understand what a motor unit is and how it works. In chapter 9 we learned that a motor unit is a motor neuron and all the muscle fibers it innervates. The pattern is that motor units with few muscle fibers perform more precise, delicate tasks (e.g., the motor units in our fingers), whereas motor units with a greater number of muscle fibers perform more gross movement tasks (e.g., the motor units in the gastrocnemius [calf] muscle). Therefore, upon recovery from poliomyelitis, muscle control decreases when reinnervation of muscle fibers occurs because the number of motor units in the muscle is decreased. The greater the number of motor units in a muscle, the greater the potential for fine gradations of muscle contraction as motor units are recruited. A smaller number of motor units means that gradations of muscle contraction are not as fine.
5. As a weight is lifted, the muscle contractions are concentric contractions. When a weight lifter lifts a heavy weight above the head, most of the muscle groups contract with a force while the muscle is shortening. Concentric contractions are a category of isotonic contractions in which tension in the muscle increases or remains about the same while the muscle shortens. While the weight is held above the head, the contractions are isometric contractions, because the length of the muscles does not change. While the weight is lowered, unless the weight lifter simply drops the weight, the length of the muscles increases as the weight is lowered for most of the muscle groups. Eccentric contractions are contractions in which tension is maintained in a muscle while the muscle increases in length. The major muscle groups are therefore contracting eccentrically while the weight is lowered. So Mary explained to the two students that they were each correct, since the weight lifter used all three types of contractions.
7. The first step to answer this question is to define *glycogen* and its role in exercise in the nondisease state. Glycogen is the stored form of glucose. Free, immediately usable glucose is in limited supply, and the body quickly relies on glycogen for sustained exercise. Without the ability to break down glycogen to glucose molecules, muscle depends on the uptake of glucose from outside the cells (e.g., from the blood) or from the metabolism of fatty acids. Consequently, a person's ability to carry out vigorous exercise, including anaerobic exercise, is reduced. Fatigue and lower exercise tolerance are characteristic of the condition, but exercise can be maintained at a slow pace.
9. To answer this question, the first step is to refer to figure 9.26. We learned that a ligand is a chemical that, upon binding to its receptor, will stimulate a response. In figure 9.26, a smooth muscle cell is depicted, which shows that the ligand receptors are G protein–linked receptors. Binding of the ligand results in the opening of Ca^{2+} channels. Calcium ions diffuse into the cell and bind to calmodulin, which activates the enzyme myosin kinase to phosphorylate myosin heads and start the cross-bridge cycle. As long as intracellular Ca^{2+} levels are elevated, the cross-bridge cycle will take place. Because the cross-bridges release slowly, the contraction is sustained: Once a myosin head has been phosphorylated, it can form cross-bridges, move the actin, detach, and re-form cross-bridges again and again without breaking down new ATP molecules for each cycle.

Chapter 10

1. The question is asking about which muscles of the tongue allow people to "stick their tongue out," or protrude it. Refer to table 10.6, where the actions of tongue muscles are described. There, we find it is the extrinsic muscle genioglossus that works to protrude the tongue. Further, the question tells us that Rachel's left mandible was broken and nerves were damaged. Recall from chapter 9 that skeletal muscles require a nerve impulse in order to contract. Therefore, we can conclude that the left genioglossus is unable to contract and the right is able to contract. So, when Rachel protrudes her tongue, it will only go to the left because it is only getting pushed out on the right side.
3. The first step is to remember what we learned in chapter 8: the definition of abduction is movement away from the body's midline. Next, it is necessary to know the location of the supraspinatus muscle to answer the question. The supraspinatus rests in the supraspinous fossa of the scapula. Then refer to table 10.14, where the function of the supraspinatus is summarized. Also recall that the supraspinatus is a member of the rotator cuff muscles. In extreme abduction the supraspinatus would be compressed against the acromion process of the scapula.

Chapter 11

1. First, consider the basic function of the axon. At this point in the reading, we know that axons are a cellular projection from the neuron, sometimes called nerve fibers. We also know that the cell body is the site of protein synthesis for the entire cell. Therefore, if the distal portion of an axon is severed from the rest of the cell, it will die. There is no way for the distal axon to replenish the enzymes and other proteins essential for survival. On the other hand, any remaining portion of axon still attached to the cell body survives and, in many cases, grows to replace the severed portion.
3. The first step to answer this question is to define the basis for the resting membrane potential. Recall that the inside of the plasma membrane is more negative than the outside of the plasma membrane due to a higher concentration of negatively charged proteins

inside the cell. The K^+ is also in higher concentration inside the cell and tends to "offset" the negative charge of the proteins. However, the K^+ leak channels allow K^+ to diffuse out of the cell, down the concentration gradient. Removal of K^+ removes positive charge inside the cell, and the membrane potential becomes more negative. Therefore, because tissue A has more K^+ leak channels, more K^+ can leak out of tissue A cells than in tissue B cells, and the inside of tissue A cells becomes more negative. The resting membrane potential is larger for tissue A than for tissue B; it is further from threshold.

5. To answer this question, let us first describe the Na^+ concentration and its role in a normal excitable cell. We learned that, in a normal cell, the concentration of Na^+ is much higher outside the cell than inside the cell. As a result, when Na^+ channels open, Na^+ diffuses into the cell quickly, causing the changes in the membrane potential that result in an action potential. The movement of Na^+ into the cell is the result of its steep concentration gradient. Remember, also, that enough Na^+ must enter a cell for the membrane potential to reach threshold, opening the voltage-regulated Na^+ channels and causing an action potential. If the extracellular concentration of Na^+ were reduced, then the concentration gradient would also be reduced. The effect would be that, if the cell were stimulated, less Na^+ would enter the cell. The cell would not reach threshold, and an action potential would not occur.
7. First, what is the absolute refractory period? Recall that it is the time during which a neuron cannot fire an action potential no matter how strong the stimulus. This is due to all the voltage-gated Na^+ channels already being open. Thus, if the axon is nonresponsive for 1 ms, action potentials can be generated no faster than every millisecond. Because there are 1000 ms in 1 second, the maximal frequency is 1000 action potentials/second.
9. The key piece of information in the question is the fact that neuron B releases both a neurotransmitter and a neuromodulator, which is excitatory (produces EPSPs). EPSPs depolarize neuron C and bring it closer to threshold than it is when stimulated by only neuron A. Neuron C does not require as much time for temporal summation to reach threshold to fire an action potential when stimulated by neuron B vs. neuron A. Therefore, neuron C fires more action potentials with stimulation by neuron B alone than with temporal summation of neuron A alone. In other words, the neurotransmitter from neuron B is more effective when released with the neuromodulator from neuron B than it is when released alone from neuron A.

Chapter 12

1. In chapter 11, we learned that a ganglion is a cluster of neuron cell bodies. Similarly, in this chapter we learned that the dorsal root ganglia are clusters of sensory cell bodies and the dorsal roots are bundles of sensory axons. The ganglia are larger in diameter than the roots because of the size difference between the cell bodies and axons. To answer the second question, refer to figure 12.4 to see the direction of action potential propagation in sensory axons and motor axons. Sensory axons carry action potentials from peripheral tissues to the central nervous system (CNS), which includes the brain and spinal cord. Motor axons carry action potentials from the CNS to peripheral tissues. Now, identify the types of axons in each structure listed. Recall that spinal nerves have both sensory and motor axons, so action potentials are propagated both to the spinal cord and away from the spinal cord. Dorsal roots contain only sensory axons, so action potentials are conducted to the spinal cord only. Finally, ventral roots contain only motor axons, so action potentials are conducted away from the spinal cord.
3. Recall that the phrenic nerve innervates the diaphragm, allowing for the contraction necessary for breathing. If the right phrenic nerve were damaged, then we would expect lack of muscle contraction in the right half of the diaphragm, affecting breathing. To answer the second part of the question, we need to consider the location of spinal cord injury to predict the effect it would have on the diaphragm. Remember that the phrenic nerve is part of the cervical plexus, which includes spinal nerves C1–C4. If the spinal cord were severed at the level of C2, the phrenic nerve would be damaged, and the contractions of the diaphragm would not occur, eliminating the person's ability to breathe. Death would likely occur if medical assistance were not administered quickly. On the other hand, if the spinal cord were completely severed at the level of C6, the phrenic nerve would not be damaged, and the diaphragm would not be affected.
5. Figure 12.25 indicates that the femoral nerve innervates several muscles involved in hip flexion and knee extension, both activities that were difficult for Carl. This indicates that the femoral nerve is involved. The sources of nerve fibers in the femoral nerve are L2, L3, and L4; therefore, the intervertebral disk involved compresses L2, L3, or L4 on the left side of the vertebral column. Recall that figure 12.14 includes a dermatomal map. We can see from the map that L3 innervates the dermatome of the medial thigh and is the most likely spinal nerve involved. Carl's motor movements were affected because the reduced control of action potentials from the femoral nerve to the muscles of the thigh caused muscle weakness. The referred pain results from compression of the spinal nerve that innervates the medial thigh and the knee. The compression stimulates action potentials in the nerves, and the pain is referred to the site of the sensory receptors for that nerve.

Chapter 13

1. We learned in this chapter that reflexes that maintain blood pressure are integrated by the medulla oblongata. In response to blood loss, the reflexes increase the heart rate. Similarly, the reflexes cause the constriction of blood vessels in the skin and viscera to increase blood volume and therefore blood pressure. The lack of blood flow through the skin results in pallor. Recall that respiratory reflexes are integrated in the medulla oblongata and the pons.
3. To answer this question, let us first review the functions of the oculomotor, trochlear, and abducens nerves, listed in table 13.5. Besides innervating the levator palpebrae superioris muscle, the oculomotor nerve innervates the four eye muscles that move the eyeball so that the gaze is directed superiorly, inferiorly, medially, or superolaterally. If the patient can move the eyes in these directions, the oculomotor nerve is not damaged. Similarly, the abducens nerve directs the gaze laterally, and the trochlear nerve directs the gaze inferolaterally. If the patient can move the eyes in these directions, the associated nerves are intact.

Chapter 14

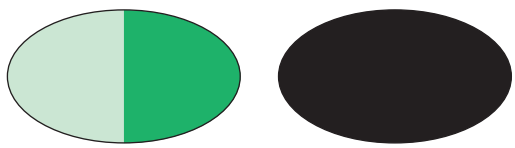
1. First, let us review the sensory information carried by the spinothalamic tract. From table 14.3 we can see that these include pain, temperature, light touch, pressure, tickle, and itch. Next, we can also see from table 14.3 and figure 14.8 that crossover of axons of the spinothalamic tract occurs in the spinal cord. From this we can conclude that a lesion on one side of the spinal cord that interrupts the spinothalamic tract would eliminate the specific sensations carried by that tract below the level of the lesion, but on the opposite side of the body. Not all sensations associated with the spinothalamic tract will be eliminated. Pain and temperature sensation from the opposite side of the body below the lesion would be eliminated. There would be few,

if any, clinical changes in detecting light touch because other tracts still carry this information.

3. Before answering this question, consider the activities carried out by the two sets of limbs. We use the lower limbs primarily for standing and walking, both of which are activities we do not focus our attention. We use our upper limbs for all kinds of activities, including writing, texting on our cellphones, or even playing video games. These activities require much more conscious effort compared with the activities of the lower limbs.
5. Recall that stimulating the reticular activating system (RAS) promotes consciousness. Also, remember that acoustic stimuli, such as a dripping faucet, stimulate the RAS. Luke could not sleep because his RAS was stimulated, promoting consciousness and preventing sleep.
7. The vagus nerve supplies the muscles of the larynx that aid in voice production; therefore, minor injury to this nerve in the neck can lead to hoarseness or changes in the voice. In our reading of "Motor Output and Reflexes Projecting Through the Brainstem," we also learned that the vagus nerve controls muscles of the pharynx, larynx, and soft palate associated with swallowing and speech. Damage to the vagus nerve could therefore affect these two activities.
9. The first clue to answering this is to understand that these microbial metabolites are chemicals in the same way that the body's signal molecules are also chemicals. Therefore, as you learned in chapter 11, neurotransmitters are chemical signals, produced by neurons that bind to receptors on their targets. Once the neurotransmitters have bound to the receptor, many different types of cell processes can be initiated. In addition, you learned in chapter 3 that other chemical signals also bind to receptors in the cell membrane. In the same way, if gut bacterial metabolites function in our body as chemical signals, upon arriving at their target, these bacterial metabolites could also bind to receptors in neuron cell membranes and stimulate cellular mechanisms to begin. Recall that lipid-soluble molecules can easily cross plasma membranes and because the short-chain fatty acids are lipid-based, they also easily cross the blood-brain barrier (see chapter 13). You will learn in the next chapter that our sense of smell and taste function in a similar fashion. Chemicals from the air or our food bind to receptors in neuron cell membranes in our nose and our taste buds. Thus, it is not out of the realm of possibilities that our body could utilize bacterial chemicals to regulate internal processes. In fact, this is a hallmark of a symbiotic relationship, such as what we have with our gut microbiota.

Chapter 15

1. Ernie's sensory neuropathy is the loss of taste sensation in the posterior one-third of the right half of his tongue. In reviewing "Neuronal Pathways for Taste" we learn that the glossopharyngeal nerves carry taste sensations from the posterior one-third of the tongue. Considering that only the right side of Ernie's tongue is affected, we can conclude that it is the right glossopharyngeal nerve that is damaged.
3. In this question, Max and his grandfather were looking at an object that was far away (the glacier) and an object that was close (the piece of ice). To answer this question, we need to consider three important factors for each scenario: accommodation, pupil constriction, and convergence. While Max and his grandfather were looking at the distant glacier, the ciliary muscles of their eyes were relaxed, and the suspensory ligaments of their ciliary bodies maintained elastic pressure on the lenses of the eyes, keeping the lenses relatively flat and allowing for distant vision. When they looked at the piece of ice that was close to them, accommodation occurred. The ciliary muscles contracted, pulling the choroids toward the lenses and reducing the tension on the suspensory ligaments. This allowed the lenses to assume a more spherical form because of their own elastic nature. More spherical lenses have more convex surfaces, causing greater refraction of light. Also, pupil constriction occurred when they were looking at the piece of ice. As the pupils constrict during close vision, the depth of focus is greater, and more light is required on the observed object. Convergence also occurs during close vision. As an object moves closer to the eye, the eyes must rotate medially so that the object is kept in focus on corresponding areas of each retina; otherwise, the object becomes blurry. The reason Max's grandfather had to reach for his glasses to view the piece of ice is because he suffers from presbyopia, which occurs because the lenses become sclerotic and less flexible as people age. Presbyopia is corrected by wearing reading glasses for close work and removing them when the person wants to see at a distance. Either bifocals or progressive lenses can also be used if a person also has myopia, or problems seeing distant objects clearly.
5. Before answering this question, let us review figure 15.25 to see the normal visual fields. We can see that each visual field is divided into temporal and nasal portions. The visual pathway is then color-coded to correlate with each portion for the right and left side. In the case of lesion *A*, we can see that the temporal part of the left visual field (light green) and the nasal part of the right visual field (dark blue) are affected. The black areas correlate with the same areas in the visual field. Using the same strategy, we can see that lesion *B* would affect both the temporal part (light blue) and the nasal part (dark blue) of the right visual field, so the entire right visual field would be affected, and an oval representing it would be black. The left visual field would be normal, with the temporal (light green) and nasal (dark green) parts indicated. Following is an illustration of the right and left visual fields.



7. Recall that the sound wave amplitude determines the volume of a sound, whereas wave frequency determines the pitch of the sound. Loud sounds have sound waves with greater amplitude. This greater amplitude causes the basilar membrane to vibrate more violently over a wider range. The spreading of the wave in the basilar membrane to some extent counteracts the reflex from the superior olivary nucleus that is responsible for enabling a person to hear subtle tone differences.

Chapter 16

1. This question is referring to the different types of cholinergic receptors: nicotinic receptors and muscarinic receptors. Remember that, even though these are cholinergic receptors to which acetylcholine normally binds, they were classified based on laboratory findings that nicotine binds to one type of cholinergic receptor and muscarine binds to the other type of cholinergic receptor. Also recall that all preganglionic neurons of the sympathetic and parasympathetic divisions and all postganglionic neurons of the parasympathetic division release acetylcholine. Also, the postganglionic neurons of the sympathetic division that innervate sweat glands also release acetylcholine. Figure 16.7 allows us to determine which of these synapses would be affected by nicotine and which of these synapses would be

affected by muscarine. Nicotinic receptors are located within the autonomic ganglia in the membranes of postganglionic neurons of both the sympathetic and parasympathetic divisions. Consumption of nicotine would result in stimulation of the postganglionic neurons, and consequently, the stimulation of the effectors of both the sympathetic and parasympathetic divisions. Again, figure 16.7 illustrates that muscarinic receptors are located on the effectors of the parasympathetic division. After the consumption of muscarine, only the effectors that respond to acetylcholine would be affected. This includes all the effectors innervated by the parasympathetic division and the sweat glands, which are innervated by the sympathetic division.

3. a. Dilation of the pupil is caused by the contraction of the dilator pupillae, which are the radial muscles of the iris.
   b. Recall from the discussion of the iris that the sympathetic division innervates and therefore controls the radial muscles (dilator pupillae). The parasympathetic division innervates and therefore controls the circular muscles (sphincter pupillae).
   c. A drug that mimics sympathetic stimulation, such as an adrenergic drug, could activate α1 receptor on the radial muscles of the iris and cause Sally's pupils to dilate. On the other hand, a drug that blocks parasympathetic stimulation, such as a muscarinic blocking agent, would prevent constriction of the pupil and therefore cause dilation.
   d. Remember from chapter 15 that the ciliary muscles constrict, changing the shape of the lenses when viewing close objects. Blurred vision indicates the eyedrops are inhibiting ciliary muscle contraction. From table 16.3 we can see that ciliary muscle contraction is a parasympathetic effect, so we would predict that the eyedrops contain a muscarinic blocking agent, one that would affect parasympathetic effectors.
   e. Notice that this scenario is essentially the opposite as that described in part c. Based on our answer for part c, we would expect that an adrenergic blocking agent that binds to α1 receptors and prevents sympathetic stimulation would cause the pupils to constrict. Similarly, a muscarinic agent could stimulate the circular muscles of the iris, causing the pupils to constrict.
   f. Recall that sympathetic stimulation of blood vessels normally keeps them in a state of partial contraction. An adrenergic blocking agent that inhibits sympathetic stimulation allows the blood vessels in the conjunctiva of the eye to dilate, causing the appearance of blood-shot eyes.
5. Recall that the primary function of the autonomic nervous system is to maintain homeostasis. In both of the scenarios, Sarah's blood pressure changes. In chapter 1 we learned that most homeostasis control mechanisms are negative-feedback mechanisms that reverse the change. Also, notice that both questions address sympathetic reflexes controlling blood vessels. Remember that blood vessels are only innervated by the sympathetic nervous system. When Sarah does a headstand, blood drains toward her head, and the blood pressure in the arteries of her chest and head increases. Sensory receptors detect the increase in blood pressure, so the frequency of action potentials in sensory neurons increases. The brain, in turn, activates sympathetic stimulation of the blood vessels, which causes them to dilate. Consequently, the blood pressure in the arteries of the neck and head does not increase dramatically. When Sarah stands quickly after crouching for a short time, blood tends to drain away from her head, and the blood pressure in the arteries of her chest and head decreases. Sensory receptors detect the decrease in blood pressure, so the frequency of action potentials in sensory neurons decreases. The brain, in turn, activates sympathetic reflexes that cause blood vessels to constrict. Consequently, the blood pressure in her neck and head does not fall dramatically.

Chapter 17

1. The question gives us two very important pieces of information: (1) Estrogen stimulates an increase in progesterone receptor number in the uterus and (2) progesterone action (binding to its receptors) is required for pregnancy. Thus, if too little estrogen is secreted, the up-regulation of receptors in the uterus for progesterone cannot occur. As a result, progesterone cannot prepare the uterus for the embryo to attach to its wall following ovulation, and pregnancy cannot occur. Because of the lack of up-regulation of progesterone receptors, the uterus cannot respond adequately to progesterone. If fewer than normal progesterone receptors are present, then a much larger-than-normal amount of progesterone is needed to produce its normal response.
3. Sarah's doctor explained to her that she is most likely experiencing insulin resistance. In order for a glucose transporter to allow glucose entry into a cell, the glucose transporter must be inserted into the cell's plasma membrane. Normal insulin action is to induce phosphorylation of intracellular regulatory proteins that control this insertion. Most instances of insulin resistance are due to the failure of the glucose transporter to be properly inserted into the plasma membrane, which has been linked to an impairment in the ability of the receptor to properly phosphorylate the intracellular regulatory proteins. Thus, Sarah's cells cannot receive adequate glucose because many of the glucose transporters never reach the plasma membrane of insulin target cells.

Chapter 18

1. Secretions from the posterior pituitary are sometimes called neurohormones because the posterior pituitary is continuous with the brain and an extension of the nervous system. The neurons that secrete these hormones have their cell bodies in the hypothalamus of the brain, and their axons extend into the posterior pituitary. If the posterior pituitary is removed, the distal ends of the axons of the neurons that have their cell bodies in the hypothalamus are removed. The neurons survive, and after a few days, the proximal ends of the axons become capable of secreting the neuropeptides that the neurons normally secrete. Cells located entirely within the gland secrete the hormones of the anterior pituitary. They are released in response to neurohormones that travel through the hypothalamo-hypophysial portal system from the hypothalamus to the anterior pituitary. Removal of the anterior pituitary removes the cells that synthesize and secrete anterior pituitary hormones. Consequently, there is a permanent decrease in anterior pituitary hormones.
3. Recall that growth hormone (GH) targets cartilage in the epiphyseal plate of long bones and stimulates cell division of the chondrocytes. Administering GH to young people before the growth of their long bones is complete causes their long bones to grow. While Zach's son is actively growing, GH administration would cause him to grow taller. To accomplish this, GH has to be administered over a considerable length of time. However, there could also be unwanted changes consistent with acromegaly (oversecretion of GH). Other side effects, such as abnormal joint formation and diabetes mellitus, are also possible. In addition to undesirable changes in the skeleton, nerves frequently are compressed as a result of the proliferation of connective

tissue. Because GH spares glucose usage, chronic hyperglycemia results, frequently leading to diabetes mellitus and severe atherosclerosis. Thus, Zach's doctor would not prescribe GH.

5. a. The major clue we are given is that Josie has low thyroid hormone levels, yet her TSH levels (the hormone that stimulates thyroid hormone release) are very high. Normally, thyroid hormone would negatively feedback at the anterior pituitary to inhibit TSH secretion once thyroid hormone levels had reached their set point. But since Josie's thyroid is unable to produce thyroid hormone, there has been a loss of negative feedback, and TSH never receives the signal to shut off, so the TSH levels rise above normal.
   b. Usually, tumors create more cells than normal that contribute to the higher hormone levels. Therefore, if Josie had more thyroid hormone–secreting cells than normal, as with cancer, her thyroid hormone levels would be much higher than normal, not lower than normal as the tests indicated.
   c. The thyroid gland requires iodine to produce thyroid hormones because iodine is an integral part of the hormone molecule. Thus, lack of iodine prevented the synthesis of thyroid hormones and the lack of negative feedback on the anterior pituitary gland. Thus, TSH levels increased, overstimulated the thyroid gland, and caused it to grow larger than normal.
   d. By providing the thyroid gland with iodine, it was able to resume normal production of thyroid hormone. Once thyroid hormone levels reached their set point, they would negatively feedback at the anterior pituitary to inhibit TSH release, and its levels would return to normal.
   e. Josie will probably need to continue taking thyroid hormone supplements for some time. After a large portion of the thyroid gland was destroyed by 131I, its ability to secrete T3 and T4 would fall below their normal range of values unless Josie took supplemental thyroid hormone. Theoretically, her doctor could slowly reduce her supplement, which could cause her thyroid to grow to compensate for the reduced intake levels.
7. To answer this question, you must first realize that, because cortisone mimics the normal adrenal cortex hormone, cortisol, it will also act by negative feedback at the anterior pituitary. Cortisone inhibits ACTH secretion from the anterior pituitary. Second, it is important to understand that ACTH is required to prevent atrophy of the adrenal cortex. In the absence of ACTH, the adrenal cortex shrinks and may never recover to produce its normal secretions, even if ACTH secretion increases again.
9. Recall from chapter 16 that the parasympathetic nervous system is the "rest-and-digest" portion of the autonomic nervous system. Therefore, an increase in insulin secretion in response to parasympathetic stimulation and gastrointestinal hormones is consistent with the maintenance of homeostasis because parasympathetic stimulation and increased gastrointestinal hormones result from conditions such as eating a meal. Insulin levels therefore increase just before large amounts of glucose and amino acids enter the blood. The elevated insulin levels prevent a large increase in blood glucose and the loss of glucose in the urine.
11. Recall from chapter 16 that the sympathetic nervous system is activated during intense exercise and inhibits insulin secretion. Blood glucose levels are not high because skeletal muscle tissue continues to take up some glucose and metabolize it. In chapter 9, we learned that skeletal muscles store glucose as glycogen, and muscle contraction depends on glucose and fatty acid metabolism. During a long run, muscle glycogen levels are depleted as the cells metabolize more and more glucose. The "kick" at the end of a race results from increased energy produced by anaerobic respiration, which uses glucose or glycogen as an energy source. However, because blood glucose levels and glycogen levels are low at the end of a long-distance race, the runners' source of energy is insufficient for the greatly increased muscle activity a sprint to the finish would require.
13. Removal of part of the thyroid gland reduces the amount of thyroid hormone secreted by the gland. Usually, enough thyroid tissue can be removed to reduce secretion of thyroid hormone to within the normal range. In addition, the remaining thyroid tissue normally does not enlarge enough to produce more thyroid hormone, although there are exceptions. The removal of the thyroid tissue does not remove the influence of the abnormal antibodies on the tissues behind the eyes. Thus, in many cases the condition's effect on the eyes is not improved.

Chapter 19

1. To develop the diagram, we must first determine the order we will use. Referring to table 19.1, column "Description", we can see the average size of the various formed elements. The smallest of the formed elements is platelets (2–4 mm). Based on the smallest number in a range, the second smallest would be lymphocyte (6–14 mm), followed by red blood cell (7 mm). Neutrophil and basophil have similar sizes (10–12 mm). Eosinophil is slightly larger (11–14 mm). The largest of the formed elements is the monocyte (12–20 mm). Using images from the table, you can create a visual representation of the formed elements in order of size from smallest to largest (platelet, lymphocyte, red blood cell, neutrophil and basophil, eosinophil, and monocyte).
3. We learned in this chapter that reticulocytes are immature red blood cells released from the red bone marrow into the circulation. Considering that, by donating a unit of blood, Juan's red blood cell count dropped below normal, we would expect his body to respond by producing more red blood cells. Erythropoietin secretion from the kidneys stimulates erythropoiesis, red blood cell production, in the red bone marrow to increase. As a result, we would expect Juan's reticulocyte count to increase during the week after he donated blood. This process continues at the increased rate until Juan's normal red blood cell count is reestablished.
5. Platelets are normally inactive; however, they become activated at sites of tissue injury. These are the areas where clot formation is needed to stop bleeding.
7. a. We learned that HDN is caused by an Rh incompatibility between a pregnant mother with Rh-negative blood and her Rh-positive child. If the mother is sensitized to the Rh antigen, she can produce anti-Rh antibodies that cross the placenta and cause agglutination and hemolysis of fetal red blood cells. A transfusion would replace the red blood cells lost by agglutination and hemolysis.
   b. Remember that erythropoietin stimulates red blood cell production. Even though new red blood cells were introduced during the exchange transfusion, administering erythropoietin will also increase Billy's red blood cell count.
   c. Erythropoietin levels increase as a result of low blood oxygen levels. This is directly related to the red blood cell count. Considering that Billy's red blood cell count was extremely low as a result of HDN, we would predict that his erythropoietin level would be higher than a fetus without HDN.
   d. A major physiological change that occurred after birth was that Billy was able to breathe on his own. The ability to oxygenate the blood using the lungs is greater than the ability to oxygenate the blood across the placenta. Billy's blood oxygen levels increased and his erythropoietin levels decreased. Thus, his production of red blood cells decreased and his anemia got worse.
   e. To treat HDN with an exchange transfusion, the donor's blood should be

Rh-negative, even though the newborn is Rh-positive. Rh-negative red blood cells do not have Rh antigens. Therefore, any anti-Rh antibodies in the newborn's blood do not react with the transfused Rh-negative red blood cells. Eventually, all of the Rh-negative red blood cells die, and only Rh-positive red blood cells are produced by the newborn.

f. Remember that blood types are genetically determined. Giving an Rh-postive newborn a transfusion of Rh-negative blood would not change the newborn's blood type. Even though Rh-negative blood is introduced to the body, over time all of the Rh-negative red blood cells die. The new red blood cells are produced from the bone marrow stem cells, which are genetically Rh-positive. Thus, only Rh-positive red blood cells are produced by the newborn.

Chapter 20

1. Pericarditis is an inflammation of the serous pericardium. In Tony's case, the pericarditis is a result of a viral infection. Pericarditis can lead to fluid accumulation in the pericardial sac. Tony's pain results from inflammation and distention of the pericardial membranes. His pulse was weak because the fluid in the pericardial sac compressed both the heart and the veins delivering blood to the heart; consequently, the heart could not fill with as much blood as normal. With less blood entering the heart, Tony's stroke volume, or volume of blood pumped from the heart, also decreased, causing a weak pulse and lower blood pressure. Recall from chapter 16 that increased sympathethic stimulation of the heart occurs when blood pressure begins to decrease, resulting in tachycardia. The increased heart rate helps maintain blood pressure. The jugular veins, which carry blood toward the heart, are distended because the accumulated fluid in the pericardial sac compresses the heart, preventing complete filling of the heart and reducing the flow of blood from the jugular veins toward the heart. Tony's physician used a needle to remove excess fluid from the pericardial space. Reviewing figure 20.2, we can see that the needle is most likely inserted in the fifth or sixth intercostal space near the sternum and penetrates the following body layers: the skin, the subcutaneous tissue, the intercostal muscles, the fibrous pericardium, and the parietal pericardium.
3. Before answering the question, we need to define tetanic contraction. Recall from chapter 9 that a tetanic contraction is a sustained contraction in which the frequency of stimulation of the muscle is so rapid that no relaxation occurs. The purpose of cardiac muscle contractions is to pump blood through the circulation by contracting and relaxing in a repeated cycle. Tetanic contractions in cardiac muscle would interrupt the pumping action produced by the cycle of contraction and relaxation, and the blood flow would cease. Tetanic skeletal muscle contractions are important to maintain posture or to hold a limb in a specific position.
5. In section 20.3, we learned that the left ventricle has the thicker wall. The pressure produced by the left ventricle is much higher than the pressure produced by the right ventricle. It is important for each ventricle to pump the same amount of blood because, with two connected circulation loops (pulmonary circuit and systemic circuit), the volume of blood flowing into one must equal the volume of blood flowing into the other, so that one does not become overfilled at the expense of the other. For example, if the right ventricle pumps less blood than the left ventricle, blood accumulates in the systemic blood vessels. If the left ventricle pumps less blood than the right ventricle, blood accumulates in the pulmonary blood vessels.
7. Figure 20.19 will be very useful in answering this question. From the figure we can see that ventricular diastole occurs between the second heart sound of one cardiac cycle and the first heart sound of the next cardiac cycle. The second heart sound is produced as the aortic semilunar valve closes. The aortic pressure decreases from 95 mm Hg to approximately 80 mm Hg when the left ventricle contracts again. This causes the bicuspid valve to close, producing the first heart sound of the next cardiac cycle. Now, let us consider the pressure changes in the left atrium and ventricle. When the aortic semilunar valve closes (second heart sound), the pressure in the left ventricle decreases rapidly to nearly 0 mm Hg. As soon as the pressure decreases below the pressure in the left atrium, the bicuspid valve opens, and blood flows into the left ventricle. Pressure remains low in the left atrium and the left ventricle, with pressure in the left atrium slightly greater than in the left ventricle. Finally, pressure increases a few mm Hg when the left atrium contracts, causing additional blood to flow from the left atrium into the left ventricle. When the left ventricle begins to contract, the pressure in the left ventricle increases but, as soon as the pressure is greater in the left ventricle than in the left atrium, the bicuspid valve closes, causing the first heart sound of the next cardiac cycle.
9. Rupture of the left ventricle can occur several days after a myocardial infarction. As the necrotic tissues are being removed by macrophages, the wall of the ventricle becomes thinner and may bulge during systole. If the wall of the ventricle becomes very thin before new connective tissue is deposited, it can rupture. If the left ventricle ruptures, blood flows from the left ventricle into the pericardial sac, resulting in cardiac tamponade. As blood fills the pericardial sac, it compresses the ventricle from the outside. As a consequence, the ventricle is not able to fill with blood, and its pumping ability is rapidly eliminated. Rupture of the left ventricular wall, therefore, quickly results in death.

Chapter 21

1. As stated in the question, atherosclerosis of vessels occurs when lipid deposits block the vessels, which results in reduced blood flow through the vessel. The tissues to which the blocked vessels supply blood will therefore have reduced O_2 and nutrients. Since the carotid artery supplies blood to the brain, we would expect atherosclerosis of these vessels to lead to reduced brain function, which may include confusion and loss of memory.
3. Vasoconstriction of Richard's cutaneous blood vessels would cause a substantial increase in his systemic blood pressure. From Laplace's law, we learned that, as the diameter of a vessel increases, the force applied to the vessel wall increases. An aneurysm is a bulge that forms in an arterial wall that has weakened. The increase in Richard's blood pressure due to the sudden vasoconstriction of his cutaneous blood vessels would apply more force on the aneurysm. Because this is a weakened area of the artery wall, the increase in force applied to the aneurysm is more likely to rupture the wall. The rupture of an arterial wall is life threatening.
5. a. The blocked vein in Harry's right leg caused edema and led to tissue ischemia. Edema developed inferior to the blocked vein. Blockage of the vein increased the capillary hydrostatic pressure in the capillary beds drained by the blocked vein. The increased capillary hydrostatic pressure increased the amount of fluid that flowed from the capillaries into the tissue spaces and reduced the amount of fluid that returned to the capillaries. Consequently, fluid accumulated in the tissue spaces and caused edema (see figure 21.36). The ischemia resulted in pain, much the way ischemia of the heart causes pain during myocardial infarctions (see chapter 20).

   b. Emboli that originated in the posterior tibial vein would pass through the following parts of the circulatory system before lodging in the pulmonary arteries of the lungs: posterior tibial vein, popliteal vein, femoral vein, external iliac

vein, common iliac vein, inferior vena cava, right atrium, right ventricle, pulmonary trunk, right or left pulmonary artery. Emboli lodge in branches of the pulmonary arteries and are most likely to lodge in the lungs because the pulmonary arteries branch many times before delivering blood to the pulmonary capillaries, and as they branch, their diameters decrease. Even small emboli eventually lodge in the smaller branches of the pulmonary arteries. The other parts of the circulatory system through which the emboli pass have much larger diameters, so emboli can pass readily through them.

c. When emboli are large enough or numerous enough to block blood flow through a significant part of the lungs, resistance to blood flow through the lungs increases. The increased resistance increases the pulmonary venous pressure, which increases the afterload for the right ventricle. If the right ventricle is unable to overcome the increased afterload, failure of the right side of the heart can occur, and blood flow through the lungs is reduced.

d. First let us address the effect of pulmonary emboli on blood oxygen levels. Pulmonary emboli large enough to significantly reduce blood flow through the lungs reduce the lungs' ability to carry out gas exchange with blood, and blood oxygen levels decrease. Next, let us address the affect of pulmonary emboli on the left ventricle's ability to pump blood. Pulmonary emboli block normal blood flow through the lungs, thereby reducing the blood volume returning to the left ventricle. This would also cause a reduction in cardiac output. Recall that cardiac output also affects blood pressure, so we would expect hypotension, or a reduction in blood pressure, to occur. As blood pressure falls, the homeostatic mechanisms described in figure 21.40 are activated to increase blood pressure to normal levels. Manifestations of hypotension, such as increased heart rate, weak pulse, and pallor, would be present.

e. Heparin and coumadin are anticoagulants, discussed in chapter 19. They are prescribed to slow down the rate of blood clot formation. Heparin must be administered intravenously, but coumadin can be taken orally, which makes home use possible. Harry's prothrombin time will be checked periodically to ensure that enough anticoagulant is administered to prevent enlargement of the thrombus in the deep vein of his leg and to prevent additional emboli from forming. Remember that enzymes naturally found in our blood break down coagulated blood. In Harry's case the clots are removed because the slower rate of coagulation allows the clots to be broken down faster than they can form.

7. During a headstand, gravity acts on the blood, causing it to settle in the vessels of the head and chest. Blood pressure in the area of the aortic arch and carotid sinus baroreceptors increases. Figure 21.40 illustrates how the baroreceptor reflexes regulate changes in blood pressure. The increased blood pressure activates the baroreceptor reflexes, increasing parasympathetic stimulation of the heart and decreasing sympathetic stimulation. Thus, the heart rate decreases. As blood from the periphery runs down to the heart, venous return increases, causing stroke volume to increase (Starling law of the heart). The activated baroreceptor reflexes also decrease vasomotor tone, and some peripheral vasodilation can occur.

Chapter 22

1. a. Cancer cells can break free from a tumor and spread, or metastasize, to other parts of the body by entering lymphatic or blood capillaries (see chapter 3). If the cancer cells enter the lymphatic capillaries, they are carried to the lymph nodes, which filter lymph. The first lymph nodes in which cancer cells are likely to become trapped are the sentinel lymph nodes.

   b. Test results showed that all of the sentinel lymph nodes contained cancer cells, indicating that cancer cells had spread into her lymphatic system. Cindy's cancerous tumor is in her left breast, and the axillary lymph nodes drain the superficial thorax and upper limb. Removal of these lymph nodes minimizes the risk of further metastasis.

   c. Recall from chapter 21 approximately one-tenth of the fluid entering tissues is normally removed by the lymphatic system. Removal of the lymph nodes and their attached lymphatic vessels disrupts the normal removal of fluid from tissues, resulting in lymphedema, the accumulation of fluid in the tissues.

   d. Remember that contraction of skeletal muscle and the thoracic pressure changes associated with breathing are both mechanisms for moving lymph through lymphatic vessels. Exercise increases skeletal muscle contractions and breathing. Consequently, more fluid can enter lymphatic capillaries, reducing edema.

   e. The external force applied to tissues by a compression bandage or garment reduces the movement of fluid from the circulation into tissues (see chapter 21), thereby reducing lymphedema.

   f. Recall that contraction of lymphatic vessels and the presence of valves along these vessels ensure that lymph moves through lymphatic vessels in one direction, from the peripheral tissues toward the venous system of the thorax. A compression pump mimics the normal contraction and relaxation of the lymphatic vessels, moving the lymph in a distal-to-proximal direction.

3. Remember that the combination of an MHC class I molecule and an antigen is necessary to activate T cells. MHC molecules are genetically determined. Thus, unless mouse B is essentially genetically identical to mouse A, the T cells from mouse A that are introduced to mouse B will not respond to the antigen. The T cells are MHC-restricted, meaning they must interact with the MHC proteins of mouse A as well as the antigen from virus X, to be activated and respond.

5. The first exposure to the disease-causing agent (antigen) evokes a primary immune response, which destroys the existing pathogens but also produces memory cells that can respond to future infections. As time passes, the antibodies produced during the primary immune response will degrade, and memory cells will die. If, before all of the memory cells are eliminated, a second exposure to the antigen occurs, a secondary response results, increasing the number of antibodies and memory cells again. The newly produced memory cells can provide immunity until the next exposure to the antigen.

7. First, recall that vaccines are a form of artificial active immunity caused by deliberately introducing an antigen into the body, stimulating a primary response by the immune system. The immune system responds to the vaccine by increasing the number of specific memory cells and antibodies for the particular disease. This provides long-lasting immunity without disease symptoms. The booster shot stimulates a memory (secondary) response, resulting in the formation of even more memory cells and antibodies. A booster shot improves the effectiveness of the immune system's ability to fight the types of infections for which a person is vaccinated.

Chapter 23

1. It could be that Jake was fibbing when he claimed to be unafraid, trying to impress

his girlfriend. But whether he was frightened or not, in order for his body to produce such a sound, certain muscles need to contract. The muscles of expiration cause airflow from the lungs to the exterior through the larynx. As air rushes past the vocal cords, they vibrate. If air is explosively pushed past the vocal cords, they vibrate to a greater degree than when air is pushed past them to a lesser degree, and they produce a louder sound. As for the high pitch of the scream, it is the position of the vocal cords that is important. More tension results in a higher frequency of vibration of the vocal cords, producing a higher-pitched sound. How does the tension increase? The arytenoid cartilages are rotated medially, which moves the vocal cords medially and posteriorly. Finally, the epiglottis-controlling muscles cause it to tip anteriorly so that air can flow past and out of the mouth. For Jake, the result was a high-pitched scream that either endeared him to his girlfriend or left him single.

3. To answer this question, knowledge you gained from chapter 22 about artificial active immunity is critical. Recall that a vaccination consists of isolated epitopes from the surface of a pathogen that are then injected into a person. In doing so, the vaccine serves to introduce the pathogen to the immune system. This exposure to the pathogen's isolated epitopes allows the immune system to activate specific cytotoxic T cells and B cells for that pathogen. The adaptive immune system will then create antibodies and memory cells for the pathogen, a central role of the immune system. By identifying and purifying the *B. pertussis* virulence factors that allow the bacterium to avoid the complement system, the vaccine would allow the immune system to create antibodies against both the virulence factors and *B. pertussis*'s epitopes. Binding of the antibodies to the complement avoidance virulence factors would neutralize these factors, thereby enabling complement to quickly attack and kill the bacteria. In addition, because complement and adaptive immunity work cooperatively, antibody production would occur more quickly. This provides protection against future exposures to *B. pertussis.*
5. The air the diver is breathing has a greater total pressure than atmospheric pressure at sea level. Consequently, the partial pressure of each gas in the air increases. According to Henry's law, as the partial pressure of a gas increases, the amount (concentration) of gas dissolved in the liquid (e.g., body fluids) with which the gas is in contact increases. When the diver suddenly ascends, the partial pressure of gases in the body returns toward sea level barometric pressure. As a result, the amount (concentration) of gas that can be dissolved in body fluids suddenly decreases. When the fluids can no longer hold all the gas, gas bubbles form.
7. When CO_2 moves from fetal blood into maternal blood, it increases CO_2 levels inside maternal red blood cells. As a result, pH inside maternal red blood cells decreases, the affinity of maternal hemoglobin for oxygen decreases, and more oxygen is released. In other words, the maternal oxygen-hemoglobin curve shifts to the right. Simultaneously, the movement of CO_2 from fetal blood into maternal blood decreases CO_2 levels inside fetal red blood cells and increases pH inside fetal red blood cells. This means that the affinity of fetal hemoglobin for oxygen increases, and more oxygen will bind to fetal hemoglobin. In other words, the fetal oxygen-hemoglobin dissociation curve shifts to the left. This shifting of the maternal and fetal oxygen-hemoglobin curves is called the double Bohr effect. The double Bohr effect increases the delivery of oxygen from maternal blood to fetal blood because maternal hemoglobin releases more oxygen and fetal hemoglobin is more effective at picking up that oxygen.
9. A person who cannot synthesize BPG has mild erythrocytosis because his or her hemoglobin releases less oxygen to tissues. Consequently, increased erythropoietin will probably be released from the kidneys, and increased red blood cell production will occur in red bone marrow.
11. To answer this question, we need to consider what types of stimuli affect the respiratory center. Look at figure 23.21. Notice that receptors for temperature (e.g., cold water), pain (e.g., very cold water), and touch (e.g., swatting on the buttocks) all stimulate the respiratory center. That is why we gasp when we jump into a cold swimming pool—it is involuntary—and babies were swatted on the buttocks—to stimulate their first breath of air.

Chapter 24

1. Four. Recall that the greater omentum is a localized mesentery, which consists of serous membranes. Each single layer of the mesentery has two layers of simple squamous epithelium. Since the greater omentum is folded back on itself, that results in four layers of simple squamous epithelium.
3. Alice's physician concluded that the inflammation of her larynx was due to the reflux of gastric fluid into her esophagus while she was sleeping. In general, reflux is more likely after eating a meal and while lying down. Gastric acid secretion increases after a meal mainly because of the cephalic and gastric phases of gastric secretion, and gravity normally helps keep gastric fluid in the stomach. During the night, the gastric fluid moved through the esophagus and entered her larynx. An antacid was prescribed to neutralize the low pH of the gastric secretions. Two classes of drugs decrease H^+ secretion. Both histamine receptor antagonists and proton pump inhibitors reduce the movement of H^+ into the lumen of the stomach, thereby increasing the pH of the gastric fluid secreted by the stomach mucosa. The histamine receptor antagonist binds to histamine receptors and blocks the action of histamine, and the proton pump inhibitor reduces the H^+–K^+ exchange pump. Either type could have been prescribed for Alice. The smaller volume of gastric acid secreted by the stomach mucosa and the higher pH of the stomach secretions reduce the acid reflux that cause inflammation of her larynx.
5. First, let us consider that acidic chyme in the small intestine is the stimulus. Stimuli are detected by receptors, and then control centers send a signal to initiate a response that will regulate homeostasis. In this case, the control center is the pancreas. In response to the acidic chyme, pancreatic secretin stimulates bicarbonate ion secretion from the pancreas (the effector), which neutralizes the acidic chyme. Thus, secretin prevents the acid levels in the chyme from becoming too high and keeps them in the normal range. The neutralization of the acidic chyme removes the stimulus for more secretin release, and bicarbonate ion is no longer secreted. Because the response was inhibited, this is an example of a negative-feedback system.
7. An enema is the introduction of fluid into the rectum, which causes it to distend. Recall that the defecation reflex is initiated by the movement of feces into the rectum and the subsequent stretch of the rectal wall. Therefore, because an enema stretches the rectal wall, it initiates the defecation reflex.

Chapter 25

1. Most of the vitamins, with the exception of A, D, and niacin, are essential vitamins, meaning they cannot be produced by the

body but must be obtained from the diet. Recall that, after a vitamin is destroyed, its function is lost. If the vitamins were broken down by digestion before being absorbed, they would not be functional, and vitamin deficiencies would occur.

3. The last step in the electron-transport chain is when the electrons are passed to oxygen to form water. If this step is blocked, the citric acid and electron-transport chain cannot function, so ATP will not be produced aerobically. Lactic acid fermentation alone cannot produce sufficient levels of ATP to maintain normal cellular activity, and death will occur.
5. Recall that catabolism of food releases energy that can be used by the body for normal biological work, such as muscle contraction. However, about 40% of the total energy released is actually used for biological work. The remaining energy is lost as heat. Exercise increases the amount of biological work and therefore requires more energy in the form of ATP. As more ATP is produced to fuel the exercise, more heat is also generated as lost energy, thereby increasing body temperature. Shivering consists of small, rapid muscle contractions that produce heat in an effort to prevent a decrease in body temperature in the cold.

Chapter 26

1. Even though hemoglobin is a smaller molecule than albumin, it does not normally enter the filtrate because hemoglobin is contained within red blood cells, and these cells cannot pass through the filtration membrane. However, if red blood cells rupture, by a process called hemolysis, the hemoglobin is released into the plasma, and large amounts of hemoglobin enter the filtrate. Conditions that cause red blood cells to rupture in the circulatory system allow large amounts of hemoglobin to enter the urine.
3. Inhibition of ADH secretion is one of alcohol's numerous effects on the body. Lack of ADH causes the distal convoluted tubules and the collecting ducts to be relatively impermeable to water. Therefore, the water cannot move by osmosis from the distal nephrons and collecting ducts but remains in the nephrons to become urine. In addition, because other fluids are normally consumed with the alcohol, the increased water intake also results in an increase in dilute urine.
5. During the race, Amanda's blood volume decreased because of increased water loss through breathing and sweating. Because of Amanda's severe dehydration, her body immediately initiated the mechanism that maintains blood pressure. The vasoconstriction and reduced blood volume explain her pallor. Increased sympathetic stimulation caused the more rapid heart rate. The renal arteries also became vasoconstricted. Subsequently, the GFR decreased, and urine production was reduced. In addition, Amanda's ADH levels increased, which increased water reabsorption from the distal convoluted tubules and collecting ducts.
7. The first piece of information you need to make this prediction is that the micturition reflex is initiated by stretch receptors in the bladder wall. However, when the volume of fluid in the bladder is below 300 mL, the urge to urinate can be repressed by centers in the pons and cerebrum. You also learned that a bacterial infection or another source of irritation could stimulate the urge to urinate, even if there is not much urine in the bladder. Purposeful infection of the bladder wall with tuberculosis bacteria during the BCG treatment causes irritation of the bladder wall and would stimulate an increased frequency of action potentials along the sensory neurons. The higher frequency of action potentials is interpreted as a greater urge to urinate. This is true for all bacterial infections in the bladder.

Chapter 27

1. The first step is to define hemorrhagic shock. Hemorrhagic shock is due to excessive internal or external bleeding, which lowers blood volume. During hemorrhagic shock, blood pressure decreases and visceral blood vessels constrict. As a consequence, blood flow to the kidneys and the blood pressure in the glomeruli decrease dramatically. The total filtration pressure decreases, as does the amount of filtrate formed each minute. The rate at which Na^+ enters the nephron therefore decreases. In addition, the kidneys secrete large amounts of renin, which causes the formation of angiotensin I from angiotensinogen. Angiotensin I is converted to angiotensin II, which stimulates aldosterone secretion. Aldosterone increases the rate at which Na^+ is reabsorbed from the filtrate in the distal convoluted tubules and collecting ducts.
3. Aldosterone hyposecretion results in acidosis. Aldosterone increases the rate at which Na^+ is reabsorbed from nephrons, but it also increases the rate at which K^+ and H^+ are secreted. Hyposecretion of aldosterone decreases the rate at which H^+ is secreted by the nephrons and therefore can result in acidosis.

Chapter 28

1. We can assume that the six biopsy samples were of different regions of Vern's prostate gland. It appears that the cancerous tumor is small and the needle biopsy only passed through the tumor two of the six times.
3. Erection is the result of neural stimulation of arteries that supply the erectile tissue. Erectile dysfunction (ED) is caused by either defective stimulation of the erectile tissue by nerve fibers or reduced response of the blood vessels to neural stimulation. Recall from Clinical Impact 28.5 that sildenafil does not stimulate erection, but instead increases the effectiveness of stimulation by enhancing the response of blood vessels to action potentials by slowly breaking down cGMP. As cGMP accumulates in the smooth muscle cells of the blood vessels, they relax, allowing blood to flow into the erectile tissue. Mr. Grover is sometimes able to achieve erections, especially after treatment, so it is reasonable to assume that he is unable to achieve erections at other times because of dysfunction in neural stimulation. There could be fewer action potentials reaching the erectile tissue due to nerve damage or decreased ability of the central nervous system to increase action potentials in the nerves. Another possibility is that Mr. Grover is unable to achieve minimal sexual excitement, which would decrease action potentials in the appropriate nerves.
5. The question addresses the time period in the menstrual cycle just before the LH surge, which promotes ovulation. Referring to figure 28.18, it is evident that estrogen and progesterone are normally at their lowest levels before the LH surge. In contrast, progesterone is at its highest level after ovulation and prevents further development of follicles. Therefore, administration of a large amount of progesterone and estrogen just before the preovulatory LH surge inhibits the release of GnRH, LH, and FSH. Consequently, ovulation does not occur. However, progesterone is the more potent hormone when it comes to inhibiting ovulation. Injections of a small amount of estrogen just before ovulation could stimulate GnRH, LH, and FSH secretion with little negative effect on ovulation. Continual administration of high concentrations of GnRH causes the anterior pituitary cells to become insensitive to GnRH. Thus, LH and FSH levels remain low and the ovarian cycle stops.
7. Molly's mother could have had leiomyomas also, although, without direct data of

medical examinations, one cannot be certain. If that was the cause of her irregular menstruations, they may have become less frequent as Molly's mother experienced menopause. During menopause, the uterus gradually becomes smaller, and eventually the cyclical changes in the endometrial lining cease. If the condition was relatively mild, the onset of menopause could explain the gradual disappearance of the irregular and prolonged menstruations. (Note: If the tumors are large, constant, and severe, menstruations are likely even if regular menstrual cycles stop due to menopause.)

Chapter 29

1. The primitive streak essentially forms the central axis of an embryo. If two primitive streaks formed in one embryonic disk, we would expect two different embryos, or essentially twins, to develop. If the two primitive streaks were touching each other, conjoined twins would develop. The degree to which the two primitive streaks were touching would determine the severity of the attachment.
3. Recall that clinical age is dependent on LMP (last menstrual period) of the mother and that developmental age begins at fertilization, which is assumed to occur on day 14 after LMP. Most of the times reported in the text are developmental age. To determine the clinical age, add 14 to the developmental age. The one exception is parturition, which is reported as clinical age. To determine the developmental age, subtract 14 from the clinical age. We can easily construct a table to compare the ages:

	Clinical Age	Developmental Age
Fertilization	14 days	0 days
Implantation	21 days	7 days
Beginning of fetal period	70 days	56 days
Parturition	280 days	266 days

5. Suckling causes a reflex release of oxytocin from the mother's posterior pituitary. Oxytocin causes expulsion of milk from the breast, but it also causes contraction of the uterus. Contraction of the uterus is responsible for the sensation of cramps in her abdomen.
7. When fertilization occurs, the two haploid gametes combine to form a new diploid zygote. If the gametes had the same number of chromosomes as somatic cells, the chromosome number would double with each generation.
9. Duchenne muscular dystrophy is an X-linked condition. Remember that a male child receives an X chromosome from his mother and a Y chromosome from his father. We can therefore assume that Wilma is a "carrier" for Duchenne muscular dystrophy, meaning she is heterozygous for the condition. As a male, Wally has only one X chromosome in his cells, and his X chromosome must have the normal allele because Wally does not have Duchenne muscular dystrophy. Because each of their children will receive an X chromosome from Wilma, they may receive either an X chromosome with the normal allele or an X chromosome with the Duchenne muscular dystrophy allele. Males who receive a chromosome with a normal allele from Wilma and a Y chromosome from Wally will be normal. Males who receive an X chromosome with the muscular dystrophy allele from Wilma and the Y chromosome from Wally will have Duchenne muscular dystrophy. Therefore, the probability that their next child will have the condition is 0 if the child is female and 0.5 (or 1/2) if the child is male. However, the probability that each female child will be a carrier for the condition is 0.5 (or 1/2).

Appendix G

ANSWERS TO ODD-NUMBERED CRITICAL THINKING QUESTIONS

Chapter 1

1. Student B is correct. Body temperature begins to rise as a result of exposure to the hot environment. Sweating eliminates heat from the body and lowers body temperature. Body temperature returning to its ideal normal value is an example of negative feedback. Student A probably thought it was positive feedback because sweating continued to increase. However, sweating is the response. The variable being regulated by sweating is body temperature.
3. When a boy is standing on his head, his nose is superior to his mouth. Directional terms refer to a person's body in the anatomical position, not to the body's current position.
5. After the pole passes through the abdominal wall, it pierces the parietal peritoneum. In passing through the stomach, it penetrates the visceral peritoneum, the stomach itself, and the visceral peritoneum on the other side of the stomach. Because the diaphragm is lined inferiorly by parietal peritoneum and superiorly by parietal pleura, these are the next two membranes pierced. The pole then passes through the pleural space and visceral pleura to enter the lung.

Chapter 2

1. An atom of iron has 26 protons (the atomic number), 30 neutrons (the mass number minus the atomic number), and 26 electrons (because the number of electrons is equal to the number of protons). If an atom of iron loses 3 electrons, it has 3 more protons (positive charges) than electrons (negative charges). Therefore, the iron ion has an overall charge of +3, which is represented symbolically as Fe^{3+}.
3. The slight amount of heat functions as activation energy and starts a chemical reaction. The reaction releases a large amount of heat, causing the solution to become hot.
5. Muscle contains proteins. To increase muscle mass, proteins must be synthesized from amino acids. The synthesis of molecules in living organisms requires the input of energy. That energy comes from the potential energy stored in the chemical bonds of food molecules, which is released during the decomposition of food molecules.
7. Rapid respiration before diving into the water causes blood levels of carbon dioxide to decrease. As a result, there is a slight increase in blood pH. Recall that carbon dioxide molecules react with water to produce carbonic acid, and some of the carbonic acid molecules dissociate to form hydrogen ions and bicarbonate ions. These reactions are reversible. As Ned hyperventilates, the blood carbon dioxide levels decrease, which causes some hydrogen ions to react with bicarbonate ions to produce carbonic acid. The carbonic acid then dissociates to form water and carbon dioxide, so there is a net loss of protons. While holding his breath under water, carbon dioxide levels increased in Ned's blood. The carbon dioxide molecules react with water to form carbonic acid, which then dissociates to form hydrogen ions and bicarbonate ions. As a result, there is a slight decrease in blood pH. However, the pH of the blood does not change dramatically, in part because of buffers in the blood.
9. Heating the substances might help because proteins can be denatured and can coagulate (as in frying an egg). Another possibility is to try dissolving the substances in water. Most lipids are insoluble in water, whereas many proteins either are soluble in water or form colloids with water.

Chapter 3

1. The cells within the wound swell with water and lyse when a hypotonic solution is introduced. This kills potentially metastatic cells that may still be present in the wound.
3. Answer *b* is correct. At point A on the graph, the extracellular concentration is equal to the intracellular concentration. If movement were by simple diffusion or by facilitated diffusion, at this point the rate of movement would be zero. Because it is not zero, it is reasonable to conclude that the mechanism involved is active transport.
5. It is obvious that the heart and leg muscles of people who are jogging require the formation of ATP as a source of energy. As the heart and leg muscles increase in size, more ATP is produced by a greater number of mitochondria. Mitochondria are the critical membrane-bound organelles that increased in number by dividing. The genetic information for some of the proteins in mitochondria comes from the DNA of the mitochondria, and the genetic information for other proteins comes from DNA from the nuclei of the muscle cells.

Chapter 4

1. The tissue is epithelial tissue because it is lining a free surface, and the epithelium is stratified because it consists of more than one layer. The types of stratified epithelium are stratified squamous, stratified cuboidal, stratified columnar, and transitional epithelium. The structure of the cells in the surface layers determines the tissue type. Flat cells in the surface layer indicate stratified squamous epithelium. Cuboidal cells in the surface layer indicate stratified cuboidal epithelium, and columnar cells in the surface layer point to stratified columnar epithelium. The surface cells of transitional epithelium are roughly cuboidal with cubelike or columnar cells beneath them. When transitional epithelium is stretched, the surface cells are still roughly cuboidal, but underlying layers can be somewhat flattened.
3. Pseudostratified squamous epithelium has goblet cells that secrete mucus. The cilia move the mucus over the surface of the epithelium toward the upper portion of the trachea. Stratified squamous epithelium does not secrete abundant mucus, and it does not have cilia. Consequently, mucus secreted by the area of the trachea that is still lined by pseudostratified columnar epithelium is not moved over the portion of the trachea lined by stratified squamous epithelium. The mucus accumulates below the area of the trachea lined by stratified squamous epithelium, causing Humphrey frequent cough.
5. The tissue described is dense, regularly arranged, collagenic connective tissue. Injury to this type of tissue affects structures made up of this type of connective tissue, which includes tendons. Damage to neck vertebrae

can be ruled out because they are connected by ligaments containing abundant dense, regularly arranged elastic connective tissue. A ruptured intervertebral disk is not indicated because it would consist of dense, irregularly arranged collagenic connective tissue.

Chapter 5

1. The stratum corneum, the outermost layer of the skin, consists of many rows of flat, dead epithelial cells. The many rows of cells, which are continuously shed and replaced, are responsible for the protective function of the integument. In infants, there are fewer rows of cells, resulting in skin that is more easily damaged than that of adults.
3. Alcohol is a solvent that dissolves lipids (see chapter 2). It removes the lipids from the skin, especially in the stratum corneum. The rate of water loss increases after soaking the hand in alcohol because of the removal of the lipids that normally prevent water loss.
5. Yes, the skin (dermis) can be overstretched due to obesity or rapid growth.
7. The hair follicle, but not the hair, is surrounded with nerve endings that can detect movement and pulling of the hair. The hair is dead, keratinized epithelium, so cutting the hair is not painful.
9. Rickets is a disease of children resulting from inadequate vitamin D intake. Inadequate vitamin D leads to insufficient absorption of calcium from the small intestine, resulting in soft bones. If adequate vitamin D is ingested, rickets is prevented, whether a person is dark- or fair-skinned. However, if dietary vitamin D is inadequate, when the skin is exposed to ultraviolet light, 7-dehydrocholesterol is converted into cholecalciferol, which can be converted to vitamin D. Dark-skinned children are more susceptible to rickets because the additional melanin in their skin screens out the ultraviolet light and they produce less vitamin D.

Chapter 6

1. Normally, bone matrix and bone trabeculae are organized to be strongest along lines of stress. Random organization of the collagen fibers of bone matrix results in weaker bones. In addition, the reduced amount of trabecular bone makes the bone weaker. Fractures can occur when the weakened bone is subjected to stress.
3. The loss of bone density results because the bones are not bearing weight in the weightless environment. Therefore, osteoblasts are not sufficiently stimulated and bone reabsorption exceeds bone building. Bone loss can be slowed by stressing the bones using exercises against resistance, such as cycling.
5. Blood vessels in central canals run parallel to the long axis of the bone, and perforating canals run at approximately a right angle to the central canals. Thus, perforating canals connect to central canals, which allows blood vessels in the perforating canals to connect with blood vessels in the central canals. After a fracture, blood flow through the central canals stops back to the point where the blood vessels in the central canals connect to the blood vessels in the perforating canals. The regions of bone on both sides of the fracture associated with this lack of blood delivery die.

Chapter 7

1. An infection in the nasal cavity could spread to adjacent cavities and fossae, including the paranasal sinuses: (1) frontal, (2) maxillary, (3) ethmoidal, and (4) sphenoidal; (5) the orbit (through the nasolacrimal duct); (6) the cranial cavity (through the cribriform plate); and (7) the throat (through the posterior opening of the nasal cavity).
3. Forceful rotation of the vertebral column is most likely to damage the articular processes, especially in the lumbar region, where the articular processes tend to prevent excessive rotation (the superior articular processes face medially and the inferior articular processes face laterally).
5. The ischial tuberosity is the bony protuberance.
7. The lateral malleolus extends farther distally than the medial malleolus does, thus making it more difficult to turn the foot laterally than to turn it medially. The styloid process of the radius extends farther distally than the styloid process of the ulna, thus making it more difficult to cock the wrist toward the thumb (laterally) than toward the little finger (medially).

Chapter 8

1. If the sternocostal synchondrosis were to ossify, becoming a synostosis, there would no longer be any stretch through the costal cartilage, the thorax could not expand, and respiration would be severely hampered.
3. a. flexion and supination
   b. flexion of the hip and extension of the knee
   c. abduction of the arm at the shoulder
   d. flexion of the knee and plantar flexion of the foot

Chapter 9

1. Botulism poisoning results from ingesting botulism toxin produced by the bacterium *Clostridium botulinum.* The toxin binds to presynaptic nerve terminals and prevents the release of acetylcholine. Thus, action potentials in nerves cannot produce action potentials in skeletal muscles, and skeletal muscles become paralyzed, which explains the difficulty in breathing and swallowing. Other reasonable explanations are that the toxin binds to and blocks the receptors for acetylcholine, that the toxin blocks the entry of Ca^{2+} into the presynaptic terminal and thus prevents acetylcholine release, and that the toxin specifically prevents the entry of ions through Na^{+} channels of skeletal muscle fibers.
3. Start with a subthreshold stimulus and increase the stimulus strength by very small increments. Apply the stimulus to the nerve of muscle A and muscle B. If the number of motor units is the same for both preparations, each time the stimulus strength is increased, the degree of tension produced by the muscles will also increase to the same degree in each muscle. If one muscle has more motor units than the other, the muscle with the greater number of motor units will exhibit a greater number of separate increases in tension, and the magnitude of the increases in tension will be smaller than those seen in the muscle with fewer motor units.
5. The shape of an active tension curve for skeletal muscle can be seen in figure 9.22. In contrast, an active tension curve is much flatter for smooth muscle. That is, for each increase in the length of a muscle fiber, there is little change in the active tension produced by the smooth muscle fiber. Smooth muscle has the ability to increase in length without much increase in tension.
7. During the 100-meter race, Seth depended on ATP produced by anaerobic respiration. That produced an oxygen deficit at the end of the run, which resulted in an elevated rate of respiration for a time. During the longer and slower run, most of the ATP for muscle contractions was produced by aerobic respiration, and very little oxygen deficit developed. Prolonged aerobic respiration is required to "pay back" the oxygen deficit. Therefore, Seth's rate of respiration was prolonged after the 100-meter race but not after the longer but slower run.
9. The muscles would contract. ATP would be available to bind to the myosin heads, thus allowing myosin molecules to be released from actin molecules. The cross-bridges would immediately re-form, and complete cross-bridge cycling would result in contraction of the muscle fibers. As long as Ca^{2+} were present at high concentrations in

the sarcoplasm, contraction of the muscles would occur. If the sarcoplasmic reticulum were intact, ATP would be available to drive the active transport of Ca^{2+} into the sarcoplasmic reticulum. As the Ca^{2+} decreased in the sarcoplasm, relaxation would result. If the sarcoplasmic reticulum were not intact, however, and could not transport Ca^{2+} into the sarcoplasmic reticulum as fast as they leaked out, the muscle would remain contracted until it fatigued.

11. In experiment A, the students used anaerobic respiration as they started to run in place, but aerobic respiration also increased to meet most of their energy needs. When they stopped, their respiration rate was increased over resting levels because of the repayment of the oxygen deficit due to anaerobic respiration. In experiment B, almost all of the students' respiration came from anaerobic respiration because the students held their breath while running in place. Consequently, the students had a much larger oxygen deficit. The students' respiratory rate and depth would be greater than in experiment A, or their respiration rates would be elevated for a longer period of time than in experiment A.

Chapter 10

1.

Muscle	Action	Synergist	Antagonist
Longus capitis	Flexes neck	Rectus capitis anterior, longus colli	Most of the posterior neck muscles
Erector spinae	Extends vertebral column	Interspinales, multifidus, semispinalis thoracis	Most of the anterior abdominal muscles
Coraco-brachialis	Adducts arm	Latissimus dorsi, pectoralis major, teres major, teres minor	Deltoid, supra-spinatus
	Flexes arm	Deltoid (anterior), pectoralis major, biceps, brachii	Deltoid (posterior), latissimus dorsi, teres major, teres minor, infra-spinatus, sub-scapularis, triceps brachii

3. The muscles that flex the head also oppose extension of the neck. In an accident causing hyperextension of the neck, these muscles can be stretched and torn. The muscles involved can include the sternocleidomastoid, longus capitis, rectus capitis anterior, and longus colli. Automobile headrests are designed so that, if adjusted correctly, the back of the head hits the headrest during a rear-end accident, thereby preventing hyperextension of the neck.
5. The genioglossus muscle protrudes the tongue. If it becomes relaxed, or paralyzed, the tongue may fall back and obstruct the airway. This can be prevented or reversed by pulling forward and down on the mandible, thus opening the mouth. The genioglossus originates on the genu of the mandible. As the mandible is pulled down and forward, the genioglossus is pulled forward with the mandible, thus pulling the tongue forward also.
7. Savannah has ruptured the calcaneal tendon, and the gastrocnemius and soleus muscles have retracted, causing the abnormal bulging of the calf muscles. Because the major plantar flexors are no longer connected to the calcaneus, the runner cannot plantar flex the foot, and the foot is abnormally dorsiflexed because the antagonists have been disconnected.

Chapter 11

1. Because the plasma membrane is much less permeable to Na^+ than to K^+, changes in the extracellular concentration of Na^+ affect the resting membrane potential less than do changes in the extracellular concentration of K^+. Therefore, increases in extracellular Na^+ have a minimal effect on the resting membrane potential. Because the membrane is much more permeable to Na^+ during the action potential, the elevated concentration of Na^+ in the extracellular fluid allows Na^+ to diffuse into the cell at a more rapid rate during the action potential, resulting in a greater degree of depolarization during the depolarization phase of the action potential.
3. Action potential conduction along a myelinated nerve fiber is more energy-efficient because the action potential is propagated by saltatory conduction, which produces action potentials at the nodes of Ranvier. Compared with an unmyelinated nerve fiber, only a small portion of the myelinated neuron's membrane has action potentials. Thus, less Na^+ flows into the neuron (depolarization) and less K^+ flows out of the neuron (repolarization). Consequently, the sodium-potassium pump has to move fewer ions in order to restore ion concentrations. Because the sodium-potassium pump requires ATP, myelinated axons use less ATP than unmyelinated axons.
5. With aging, the amount of myelin surrounding axons decreases, which decreases the speed of action potential propagation. Also, at synapses, action potentials in the presynaptic terminal take longer to cause the production of action potentials in the postsynaptic membrane. It is believed this results from a reduced release of neurotransmitter by the presynaptic terminal and a reduced number of receptors in the postsynaptic membrane.
7. If the motor neurons supplying skeletal muscle are innervated by both excitatory and inhibitory neurons, blocking the activity of the inhibitory neurons with strychnine results in overstimulation of the motor neurons by the excitatory neurons.
9. When the neurotoxin binds to ligand-gated Na^+ channels in the postsynaptic membrane of a skeletal muscle fiber, they open, and Na^+ enters the cell, producing graded potentials. When the graded potentials reach threshold, an action potential is produced, stimulating the muscle fiber to contract. However, the neurotoxin tends to remain bound to the ligand-gated Na^+ channels, which prevents ACh from binding. Thus, the nervous system's ability to stimulate the muscle fiber decreases as more and more neurotoxin binds to ligand-gated Na^+ channels. Because the ligand-gated Na^+ channels with bound neurotoxin remain open, Na^+ continues to enter the muscle fiber, causing its resting membrane potential to depolarize. Eventually, the membrane becomes so depolarized that it is unresponsive to stimulation. Death from a cobra bite usually occurs because of paralysis of respiratory muscles.

Chapter 12

1. If the neuron with its cell body in the cerebrum is an inhibitory neuron and if it synapses with the motor neuron of a reflex arc, stimulation of the cerebral neuron can inhibit the reflex.
3. Pulling on the upper limb when it is raised over the head can damage the lower brachial plexus—in this case, the origin of the ulnar nerve. The ulnar nerve innervates muscles that abduct/adduct the fingers and flex the wrist.
5. a. obturator nerve
   b. femoral nerve
   c. sciatic (tibial) nerve
   d. obturator nerve
   e. obturator nerve, some from femoral nerve
7. Lack of sensation in the lower limbs and inability to move them are consequences of complete transection (transverse cut) of the spinal cord. Because Cecil could still breathe on his own, the phrenic nerves,

which innervate the diaphragm, must still be intact. The phrenic nerves originate from C3, C4, and C5, so the transection must have occurred below C5. Also, Cecil was able to move his upper limbs, and the upper arms are controlled by nerve fibers that originate from C3, C4, and C5. However, the hands and fingers (whose movement was somewhat impaired) are primarily controlled by nerve fibers that originate from C6, C7, C8, and T1. Thus, the transection is probably between C5 and C6 or between C6 and C7.

Chapter 13

1. If CSF does not drain properly, the fluid accumulates and exerts pressure on the brain (hydrocephalus). In the developing fetus, the ventricles enlarge because of the excess fluid pressure. The head also enlarges because the skull bones have not fused. However, the expansion of the head is not sufficient to relieve all the pressure exerted on the developing brain by the expanding ventricles. As a result, the cerebral cortex becomes proportionately thinner as it is compressed between the ventricles and the skull. In many cases, fewer gyri form in the cerebral cortex. Brain damage may or may not result, depending on the amount of excess CSF, the ventricular pressure generated, and the areas of the brain damaged by the pressure.
3. Blood in the CSF taken through a spinal tap indicates the presence of blood in the subarachnoid space and suggests that the patient has a damaged blood vessel in the subarachnoid space.
5. The cerebellum, which is in charge of controlling coordinated muscle movement and maintaining muscle tone, was damaged in this patient.
7. The abducens nerves supply the lateral rectus muscles, which are responsible for moving the eyes laterally (abducting the eyes). Damage to the abducens nerve on the left side reduced or eliminated Stanley's ability to abduct his left eye. The inability to move the left eye in concert with the right eye results in double vision.
9. It is likely that Afton experienced facial palsy (Bell palsy), which can be temporary. This condition may result from a stroke or a tumor, or it can be triggered by inflammation of the parotid gland, anesthesia, or exposure of the superficial branches of the nerve to cold (which is probably the cause in Afton's case). The loss of motor tone in the face is due to decreased innervation of the muscles of facial expression. Also, some muscles of the pharynx are affected, but these are not related to drooping of the face.

Chapter 14

1. The first sensations the woman perceives when she picks up an apple and bites into it are visual (special), tactile (general), and proprioceptive (general). The woman holds the apple in her hand and looks at it. The tactile sensations from mechanoreceptors in the hand tell her the apple is firm and smooth. The proprioceptive sensations originating in the joints of the hand tell her the size and shape of the apple. Visual input also tells her the size and color of the apple and that it has a smooth surface. As the woman bites into the apple and begins to chew, proprioceptive sensations from the teeth and jaws provide information on how widely she must open her mouth to accommodate the apple and how hard to bite down. Tactile sensations originating in the tongue and cheeks tell her the location of the bite of apple and its texture as it is moved about in the mouth. In chapter 15 you will learn that taste sensations (special, chemoreceptor) from the tongue indicate that the apple has both sweet and sour characteristics. Olfactory sensations (special) provide more specific information that the "fruity taste" is that of an apple.
3. It is possible that the dorsal-column/medial-lemniscal system within the right side of the spinal cord was damaged. However, it is also possible that this system was damaged within the medulla oblongata, where neurons synapse and cross over to the left side of the brain, or within the tracts on the left side that ascend from the medulla oblongata to the thalamus. Another possibility is damage to the cerebral cortex on the left side. Additional information is needed to determine exactly where the injury is located.
5. The damaged tracts are the lateral corticospinal tract, controlling motor functions on the right side of the body, and the lateral spinothalamic tract for pain and temperature sensations from the left side of the body. Damage to these tracts in the right side of the spinal cord produces the observed symptoms because within the cord the lateral spinothalamic tract crosses over at the level of entry and is therefore located on the opposite side of the cord from its peripheral nerve endings, whereas the corticospinal tract lies on the same side of the cord as its target muscles.
7. Damage to the cerebellum can result in decreased muscle tone, balance impairment, a tendency to overshoot when reaching for or touching something, and an intention tremor. These symptoms are opposite those seen with basal ganglia dysfunction. Cerebellar dysfunction exhibits symptoms very similar to those seen in an inebriated person, and the same tests can be applied, such as having the person touch his or her nose or walk a straight line.
9. The subdural hematoma is likely to be over the medial portion of the left side of the cerebral hemisphere in the area of the premotor cortex and expanding to the area of the primary motor cortex. The premotor area must be intact for a person to carry out complex, skilled, or learned movements, especially those requiring manual dexterity. If blood is removed from the hematoma and if no more bleeding occurs, it is likely that Perry's motor movements will improve rapidly.

Chapter 15

1. The lens of the eye is biconvex and causes light rays to converge. If the lens is removed, the replacement lens should also cause light rays to converge. A biconvex lens or a lens with a single convex surface should work. Bifocals or trifocals can also be recommended to compensate for because of the loss of accommodation.
3. This phenomenon is called a negative afterimage. While the man is staring at the clock, the darkest portion of the image (the black clock) causes dark adaptation in part of the retina—that is, part of the retina becomes more sensitive to light. At the same time, the lightest part of the image (the white wall) causes light adaptation in the rest of the retina, and that part of the retina becomes less sensitive to light. When the man looks at a white wall, the dark-adapted portion of the retina, which is more sensitive to light, produces more action potentials than does the light-adapted part of the retina. Consequently, he perceives a light clock against a darker background.
5. Eyestrain, or eye fatigue, occurs primarily in the ciliary muscles. It occurs because close vision requires accommodation. Accommodation occurs as the ciliary muscles contract, releasing the tension of the suspensory ligaments and allowing the lens to become more rounded. Continued close vision requires the maintenance of accommodation, which requires that the ciliary muscles remain contracted for a long time, resulting in their fatigue.
7. Normally, as pressure changes, the auditory tubes open to allow equalization of pressure between the middle ear and the external environment. If this does not occur, the

built-up pressure in the middle ear can rupture the tympanic membrane, or the pressure can be transmitted to the inner ear and cause sensorineural damage.

Chapter 16

1. The sympathetic division of the ANS is responsible for dilation of the pupil. Preganglionic fibers from the upper thoracic region of the spinal cord pass through spinal nerves (T1 and T2), into the white rami communicantes, and into the sympathetic chain ganglia. The preganglionic fibers ascend the sympathetic chain and synapse with postganglionic neurons in the superior cervical sympathetic chain ganglia. The axons of the postganglionic neurons leave the sympathetic chain ganglia as small nerves that project to the iris of the eye.
3. a. pelvic splanchic nerves
   b. outflow of gray ramus
   c. vagus nerve
   d. oculomotor nerve
   e. pelvic splanchnic nerve
5. Epinephrine causes vasoconstriction and confines the drug to the site of administration. This increases the drug's duration of action locally and decreases its systemic effects. Vasoconstriction also reduces bleeding if a dry field (an area clear of blood on its surface) is required.
7. Because cutting the white rami of T1–T4 does not affect the drug's action, sympathetic preganglionic neurons in the spinal cord and sympathetic centers in the brain can be ruled out as a site of action. Because cutting the vagus nerves eliminates the drug's effect, the drug cannot be acting at the synapse between the preganglionic neurons and the postganglionic neurons, or between the synapse of the postganglionic neuron and the effector of either division of the ANS. The drug must therefore excite parasympathetic centers in the brainstem, resulting in decreased heart rate.

Chapter 17

1. Liver disease and kidney disease would increase the concentration of this hormone in the blood, and the concentration would remain high for a longer time. The liver modifies the hormone to cause it to be excreted by the kidneys more rapidly. In the case of liver disease, the hormone is not modified and excreted rapidly. Therefore, the concentration becomes higher than normal, and the high concentration remains for longer than normal. A similar result is seen if the kidneys are diseased and the hormone cannot be excreted rapidly.
3. Usually, intracellular mediator mechanisms respond quickly, and the hormone's effect is brief. Nuclear receptor mechanisms usually take a long time (several hours) to respond, and their effects last much longer. If the hormone is large and water-soluble, it is probably functioning through an intracellular mediator mechanism; if the hormone is lipid-soluble, it is probably a nuclear receptor mechanism. If you have the ability to monitor the concentration of a suspected intracellular mediator and it increases in response to the hormone, or if you can inhibit the synthesis of an intracellular mediator and it prevents the target cells' response to the hormone, it is an intracellular mediator mechanism. If you can inhibit the synthesis of mRNA and this inhibits the action of the hormone, or if you can measure an increase in mRNA synthesis in response to the hormone, then the mechanism is a nuclear receptor mechanism.
5. Phosphodiesterase causes the conversion of cAMP to AMP, thus reducing the concentration of cAMP. Therefore, a drug that inhibits phosphodiesterase increases the amount of cAMP in cells where cAMP is produced. Thus, an inhibitor of phosphodiesterase increases a tissue's response to a hormone that has cAMP as an intracellular mediator.
7. Because thyroid hormones are important in regulating the basal metabolic rate, their long half-life is an advantage. Thyroid hormones are secreted and have a prolonged effect without large fluctuations in the basal metabolic rate. If thyroid hormones had a short half-life, the basal metabolic rate could fluctuate with changes in the rate of secretion of thyroid hormones. Certainly, the rate of secretion of thyroid hormones would have to be controlled within narrow limits if it did have a short half-life.
9. Insulin levels normally change in order to maintain normal blood sugar levels, despite periodic fluctuations in sugar intake. A constant supply of insulin from a skin patch might result in insulin levels that are too low when blood sugar levels are high (after a meal) and might be too high when blood sugar levels are low (between meals). In addition, insulin is a protein hormone that would not readily diffuse through the lipid barrier of the skin (see chapter 5).

Chapter 18

1. The hypothalamohypophysial portal system allows neurohormones that function as releasing and inhibiting hormones, which are secreted by neurons in the hypothalamus, to be carried directly from the hypothalamus to the anterior pituitary gland. Consequently, the releasing and inhibiting hormones are not diluted or destroyed by the enzymes, which are abundant in the kidneys, liver, lungs, and general circulation, before they reach the anterior pituitary. Also, the time it takes for releasing and inhibiting hormones to reach the anterior pituitary is less than if they were secreted into the general circulation.
3. The symptoms are consistent with acromegaly, which is a consequence of elevated GH secretion after the epiphyses have closed. Increased GH causes enlarged finger bones, the growth of bony ridges over the eyes, and increased growth of the jaw. The anterior pituitary tumor increases pressure at the base of the brain near the optic nerves as it enlarges. The pituitary rests in the sella turcica of the sphenoid bone; as it enlarges, pressure increases because the pituitary is nearly surrounded by rigid bone, and the brain is located just superior to the pituitary. As the anterior pituitary enlarges because of a tumor, it pushes superiorly, and pressure is applied to the ventral portion of the brain. In addition, the GH causes bone deposition on the inner surface of skull bones, which also increases the pressure inside the skull.
5. It is likely that Julie's elevated ACTH levels are causing elevated blood levels of cortisol, which in turn are causing the observed symptoms. The elevated ACTH levels are probably due to a hormone-secreting tumor (adenoma) in the anterior pituitary gland. According to National Institutes of Health sources, pituitary adenomas cause 70% of Cushing syndrome cases, excluding those caused by glucocorticoid use. Most people with the disorder have a single adenoma. Cushing syndrome affects women five times more often than men. The most widely used treatment is surgical removal of the tumor, known as transsphenoidal adenomectomy. Using a special microscope and fine instruments, the surgeon approaches the pituitary gland through a nostril or an opening made below the upper lip. Because this procedure is extremely delicate, patients are often referred to centers specializing in this type of surgery. The success rate of this procedure is more than 80% when performed by a surgeon with extensive experience. If surgery fails or produces only a temporary cure, the surgery can be repeated, often with good results. Radiation of the pituitary gland is another possible treatment.
7. Because the person is diabetic and probably taking insulin, insulin shock is more

likely than diabetic coma. To confirm the condition, however, a blood sample should be taken. If the condition is due to diabetic coma, the blood glucose levels will be elevated. If the condition is due to insulin shock, the blood glucose levels will be below normal. In the case of insulin shock, glucose can be administered intravenously. In the case of diabetic coma, insulin should be administered. An isotonic solution containing insulin can be administered to reduce the osmolality of the extracellular fluid.

9. We learn that Katie has androgen insensitivity syndrome. The name suggests that her tissues are not sensitive to androgens (malelike hormones). We learned that a tissue responds to hormones on the presence of specific receptors. With androgen insensitivity syndrome, the endocrine malfunction is not the production of the hormone, as in insulin-dependent (type I) diabetes mellitus, but the presence of the receptor in the target cells. Even though her cells produce plenty of the hormone testosterone, the target cells do not respond because the testosterone receptor has malfunctioned and does not recognize testosterone. Katie's feminine appearance is a direct result of the lack of a normal male body because her tissues were resistant to testosterone, which is responsible for growth of the male genitalia and other sex characteristics (see table 18.12 and chapter 19). Therefore, externally Katie looked female when she was born. Without testosterone working in her body or her brain and without normal social cues to associate with other males, she had always identified herself as female and was devastated to learn she could not have children. Her doctor and mother decided to wait until she was older to explain the entire condition to her.

Chapter 19

1. Because of the rapid destruction of the red blood cells, we would expect erythropoiesis to increase in an attempt to replace the lost red blood cells. The reticulocyte count would therefore be above normal. Jaundice is a symptom of hereditary hemolytic anemia because the destroyed red blood cells release hemoglobin, which is converted into bilirubin. Removal of the spleen cures the disease because the spleen is the major site of red blood cell destruction.
3. The correct answer is *c*. Ben's red blood cells are of normal size. However, his reticulocyte level is low, which indicates a reduced rate of red blood cell synthesis. The low red blood cell count is also consistent with a reduced rate of red blood cell synthesis. Hemoglobin concentration and hematocrit are low, both of which are consistent with the reduced red blood cell count. The prothrombin time is longer than normal, the prothrombin count is low, and the platelet count is low. All these observations are consistent with aplastic anemia, in which the stem cells that produce blood cells in the red marrow are damaged. Chemicals such as benzene and chloramphenicol can also destroy red marrow cells and cause aplastic anemia.
5. Vitamin B_{12} and folic acid are necessary for blood cell division. Lack of these vitamins results in pernicious anemia. Iron is necessary for the production of hemoglobin. Lack of iron results in iron-deficiency anemia. Vitamin K is necessary for the production of many blood clotting factors. Lack of vitamin K can greatly increase blood clotting time, resulting in excessive bleeding.
7. The correct answer is *c*. As Pam went from a lower to a higher elevation, the barometric pressure decreased; therefore, the availability of oxygen in the air also decreased. Consequently, as Pam moved from sea level to a higher elevation, her kidneys secreted greater amounts of erythropoietin, and red blood cell synthesis increased. After about 4 days in Jackson Hole, Pam's blood should have increased numbers of reticulocytes and red blood cells. By day 6, Pam's red blood cell count had increased significantly and was still rising. Changes in oxygen levels should not affect platelet count.

Chapter 20

1. The walls of the ventricles are thicker than the walls of the atria because the ventricles must produce a greater pressure to pump blood into the arteries. Only a small pressure is required to pump blood from the atria into the ventricles during diastole. The wall of the left ventricle is thicker than the wall of the right ventricle because the left ventricle produces a much greater pressure to force blood through the aorta than the right ventricle produces to move blood through the pulmonary trunk and pulmonary arteries.
3. Contraction of the ventricles, beginning at the apex and moving toward the base of the heart, forces blood out of the ventricles and toward their outflow vessels—the aorta and pulmonary trunks. The aorta and pulmonary trunks are located at the base of the heart.
5. A drug that prolongs the plateau of cardiac muscle cell action potentials prolongs the time each action potential exists and increases the refractory period. Therefore, the drug slows the heart. A drug that shortens the plateau shortens the length of time each action potential exists and shortens the refractory period. Therefore, the drug can allow the heart rate to increase further.
7. The two heartbeats occurring closely together can be heard through the stethoscope because the heart valves open and close normally during each of the heartbeats even if they are close together. The second heartbeat, however, produces a greatly reduced stroke volume because there is not enough time for the ventricles to fill with blood between the first and second contractions. Thus, the preload is reduced. Because the preload is reduced, the second heartbeat has a greatly reduced stroke volume, which fails to produce a normal pulse. The pulse deficit results from the reduced stroke volume of the second of the two beats that are very close together.
9. An ECG measures the electrical activity of the heart and would not indicate a slight heart murmur. Heart murmurs are detected by listening to the heart sounds. The boy may have a heart murmur, but the mother does not understand the basis for making such a diagnosis.
11. Venous return declines markedly in hemorrhagic shock because of the loss of blood volume. With decreased venous return, stroke volume decreases (Starling law of the heart). The decreased stroke volume results in a decreased cardiac output, which produces decreased blood pressure. In response to the decreased blood pressure, the baroreceptor reflex causes an increase in heart rate in an attempt to restore normal blood pressure. However, with inadequate venous return, the increased heart rate is not able to restore normal blood pressure.

Chapter 21

1. a. aorta, left coronary artery, circumflex artery, posterior interventricular artery or aorta, right coronary artery, posterior interventricular artery
   b. aorta, brachiocephalic artery, right common carotid artery, right internal carotid artery or aorta, left common carotid artery, left internal carotid artery
   c. aorta, brachiocephalic artery, right subclavian artery, right vertebral artery, basilar artery or aorta, left subclavian artery, left vertebral artery, basilar artery
   d. aorta, left or right common carotid artery, left or right external carotid artery
   e. aorta, left subclavian artery, axillary artery, brachial artery, radial or ulnar artery, deep or superficial palmar arch, digital artery (on the right: the brachiocephalic artery would be included)

f. aorta, common iliac artery, external iliac artery, femoral artery, popliteal artery, anterior tibial artery
g. aorta, celiac artery, common hepatic artery
h. aorta, superior mesenteric artery, intestinal branches
i. aorta, left or right internal iliac artery

3. A superficial vessel is easiest, such as the right cephalic or basilic vein. The catheter is passed through the cephalic (or brachial) vein and the superior vena cava to the right atrium. Because the pulmonary veins are not readily accessible, dye is not normally placed directly into them. Instead, the dye is placed in the right atrium using the procedure just described. The dye passes from the right atrium into the right ventricle, the pulmonary arteries, the lungs, the pulmonary veins, and the left atrium. If the catheter has to be placed into the left atrium, it can be inserted through an artery, such as the femoral artery, and passed via the aorta to the left ventricle and then into the left atrium.
5. According to Laplace's law, as the diameter of a blood vessel increases, the force applied to the vessel wall increases, even if the pressure remains constant. The increased connective tissue in the walls of the large blood vessels makes the wall of those vessels stronger and more capable of resisting the force applied to the wall.
7. Decreased liver function includes a decrease in the synthesis of plasma proteins. Consequently, the concentration of plasma proteins decreases, and the colloid osmotic pressure of the blood decreases. Less water moves by osmosis into the capillaries at the venous ends, and edemas result.
9. Epinephrine is secreted from the adrenal medulla in response to stressful stimuli. The responses it stimulates are consistent with increased physical activity. Vasoconstriction of the blood vessels in the skin shunts blood away from the skin to skeletal muscles. Vasodilation occurs in blood vessels of exercising skeletal muscles. Blood flow through the exercising skeletal muscles increases. Because epinephrine causes vasodilation of the blood vessels of cardiac muscle, blood flow through the cardiac muscle increases. This response is consistent with the increased work performed by the heart under conditions of increased physical activity.
11. The answer is *e*. It is possible that Mr. Wilson had a stroke, which activated the CNS ischemic response. The fact that he was unconscious is consistent with a stroke, and his rapid heart rate and high blood pressure are consistent with activation of the CNS ischemic response. A heart attack would not necessarily cause Mr. Wilson to be unconscious and would be associated with decreased blood pressure rather than increased blood pressure, especially if it caused unconsciousness. Shock would also be associated with a decrease in blood pressure.

Chapter 22

1. Elevating the limb reduces blood pressure in the limb, resulting in less fluid movement from the blood into the tissues (see chapter 21). Thus, the edema is reduced as fluid moves out of the tissues faster than it enters them. Massage moves lymph through the lymphatic vessels in the same fashion as the contraction of skeletal muscle does. The periodic application of pressure to lymphatic vessels forces lymph to flow toward the trunk of the body, but valves prevent flow in the reverse direction. The removal of lymph from the tissue helps relieve edema.
3. That there is no immediate effect indicates a reservoir of T cells exists in the lymphatic tissue. As the reservoir is depleted over time, the number of lymphocytes decreases and cell-mediated immunity is depressed, the animal becomes more susceptible to infections, and the ability to reject grafts decreases. The ability to produce antibodies decreases because of the loss of helper T cells that are normally involved with the activation of B cells.
5. If the patient has already been vaccinated, the booster shot stimulates a memory (secondary) response and rapid production of antibodies against the toxin. If the patient has never been vaccinated, vaccinating now is not effective because there is not enough time for the patient to develop his or her own primary response. Therefore, antiserum is given to provide immediate, but temporary, protection. Sometimes both are given: The antiserum provides short-term protection, and the tetanus vaccine stimulates the patient's immune system to provide long-term protection. If the shots are given at the same location in the body, the antiserum (antibodies against the tetanus toxin) can cancel the effects of the tetanus vaccine (tetanus toxin is altered to be nonharmful).
7. (a) At the first location, an antibody-mediated response resulted in an immediate hypersensitivity reaction, which produced inflammation. Most likely, the response resulted from IgE antibodies. (b) At the second location, a cell-mediated response resulted in a delayed hypersensitivity reaction, which produced inflammation. This probably involved the release of cytokines and the lysis of cells. (c) At the other locations, neither an antibody-mediated nor a cell-mediated response occurred.
9. The correct answer is *b*. The immune response that occurred in the next several hours was primarily the innate immune response. Tissue was damaged, and mediators of inflammation were released. As a consequence, there were increases in capillary permeability, coagulation of blood, and chemotaxis of neutrophils; all are components of inflammation and the innate immune response. Increased mitosis of memory B cells is likely, but more than a few hours would be required, and it is most likely to occur in response to antigens. Bacteria and other antigens may enter the wound, and an adaptive immune response may result, but this, too, would take more than several hours to occur.

Chapter 23

1. We expect vital capacity to be greatest when standing because the abdominal organs move inferiorly, thereby allowing greater depression of the diaphragm and a greater inspiratory reserve volume.
3. The increase in atmospheric pressure increases the partial pressure of oxygen. According to Henry's law, as the partial pressure of oxygen increases, the amount of oxygen dissolved in the body fluids increases. The increase in dissolved oxygen is detrimental to the gangrene bacteria. Because hemoglobin is already saturated with oxygen, the HBO treatment does not increase hemoglobin's ability to pick up oxygen in the lungs.
5. The left side of the diaphragm moves superiorly. During inspiration, thoracic volume increases as the right side of the diaphragm moves inferiorly and the intercostal muscles move the ribs outward. Increased thoracic volume causes a decrease in pressure in the thoracic cavity. As a result, the pressure on the superior surface of the diaphragm is less than on the inferior surface. The paralyzed left side of the diaphragm moves superiorly because of this pressure difference.
7. All else being equal (i.e., the thickness of the respiratory membrane, the diffusion coefficient of the gas, and the surface area of the respiratory membrane), diffusion is a function of the partial pressure difference of the gas across the respiratory membrane. The greater the difference in partial pressure, the greater the rate of diffusion. The greatest rate of oxygen diffusion should therefore occur at the end of inspiration, when the partial pressure of oxygen in the alveoli is at its highest. The greatest rate of carbon

dioxide diffusion should occur at the end of inspiration, when the partial pressure of carbon dioxide in the alveoli is at its lowest.

9. (a) Cutting the vagus nerves would eliminate the Hering-Breuer reflex and result in greater-than-normal inspiration. This would increase tidal volume. (b) Cutting the phrenic nerves would eliminate contraction of the diaphragm. Tidal volume would decrease drastically, and death would probably result. (c) Cutting the intercostal nerves would eliminate raising of the ribs and sternum and decreased tidal volume, unless the diaphragm compensated.
11. When Stephanie is hyperventilating, the stimulus for the hyperventilation is anxiety, which is more important than the carbon dioxide in controlling respiratory movements. As the blood levels of carbon dioxide decrease during hyperventilation, vasodilation occurs in the periphery. As a result, the systemic blood pressure decreases. The systemic blood pressure can decrease enough that blood flow to the brain decreases. Decreased blood flow to the brain results in a reduced oxygen level in the brain tissue, causing dizziness. Breathing into a paper bag raised Stephanie's blood levels of carbon dioxide toward normal. Because the carbon dioxide did not rise above normal, it did not increase the urge to breathe. The more normal level of carbon dioxide prevented peripheral vasodilation. As Stephanie breathed into the paper bag, her anxiety likely subsided, allowing the normal regulation of respiration to resume.

Chapter 24

1. With the loss of the swallowing reflex, the vocal folds no longer occlude the glottis. Consequently, vomit can enter the larynx and block the respiratory tract.
3. Even though ulcers are usually caused by bacteria, overproduction of hydrochloric acid due to stress is a possible contributing factor. Reducing hydrochloric acid production is recommended. In addition to antibiotic therapy, commonly recommended treatments include relaxation, drugs that reduce stomach acid secretion, and antacids to neutralize the hydrochloric acid. Smaller meals are also advised because distension of the stomach stimulates acid production. In addition, proper diet is important, and patients are advised to avoid alcohol, caffeine, and large amounts of protein because they stimulate acid production. Stress also stimulates the sympathetic nervous system, which inhibits duodenal gland secretion. As a result, the duodenum has less mucous coating, making it more susceptible to gastric acid and enzymes. Relaxing after a meal helps decrease sympathetic activities and increase parasympathetic activities.
5. The patient is still able to defecate. Following a meal, the gastrocolic and duodenocolic reflexes initiate mass movement of the feces into the rectum. In the rectum, local reflexes and the defecation reflex (integrated in the sacral level of the spinal cord and not requiring connections to high brain centers) cause defecation. However, the patient loses awareness of the need to defecate (due to loss of sensory input to the brain) and the ability to prevent defecation voluntarily via the external anal sphincter.
7. Oral rehydration therapy relies on the principle of osmosis. Water follows solutes as they are absorbed across the intestinal epithelium. The combination of sodium and glucose is optimal, since the two molecules are cotransported by a symporter that is driven by a sodium gradient established by the Na^+–K^+ pump. Hence, the presence of sodium aids glucose absorption. Fructose is absorbed by a facilitated diffusion transporter that is not coupled to a sodium gradient.

Chapter 25

1. In figure 25.2, the Daily Value for saturated fat is listed as less than 20 g for a 2000 kcal/day diet. The % Daily Values appearing on food labels are based on a 2000 kcal/day diet. Therefore, the % Daily Value for saturated fat for one serving of this food would be 10% (2/20 = 0.10, or 10%).
3. The % Daily Value is the amount of the nutrient in one serving divided by its Daily Value. Therefore, the % Daily Value is 10% (10/100 = 0.10, or 10%).
5. Copper is necessary for the proper functioning of the electron-transport chain. Inadequate copper in the diet results in reduced ATP production—that is, not enough energy.
7. This approach will not work because he is not losing stored energy from adipose tissue. In the sauna, he gains heat, primarily by convection from the hot air and by radiation from the hot walls. The evaporating sweat is removing heat gained from the sauna. The loss of water will make him thirsty, and he will regain the lost weight from fluids he drinks and food he eats.
9. During a fever, the body produces heat by shivering. The body also conserves heat by the constriction of blood vessels in the skin (producing pale skin) and by reduction in sweat loss (producing dry skin). When the fever breaks—that is, "the crisis is over"—heat is lost from the body to lower body temperature to normal. This is accomplished by the dilation of blood vessels in the skin (producing flushed skin) and increased sweat loss (producing wet skin).

Chapter 26

1. The beer consumed composes a large volume of hyposmotic fluid, which increases blood volume and causes blood osmolality to decrease. The increased blood volume is detected by baroreceptors, and the decreased blood osmolality is detected by osmoreceptors in the hypothalamus. The response to these stimuli is inhibition of ADH secretion. The alcohol in the beer also inhibits ADH secretion. The increased volume inhibits the renin-angiotensin-aldosterone hormone mechanism, which in turn inhibits aldosterone secretion. The changes in aldosterone, however, take much longer to influence kidney function than changes in ADH. As a result of these changes, a large volume of dilute urine is produced until the blood osmolality and blood volume return to normal.
3. As aldosterone levels decrease, sodium reabsorption in the nephron decreases; consequently, plasma sodium levels decrease. The sodium is lost in the urine, and water follows the sodium by osmosis. Thus, a large amount of urine having a high concentration of sodium is produced. The loss of water reduces blood volume, which causes the low blood pressure. As aldosterone levels decrease, potassium secretion into the nephron also decreases, resulting in increased plasma potassium levels. The increased extracellular potassium causes the depolarization of nerve and muscle membranes, leading to tremors of skeletal muscles and cardiac arrhythmias, including fibrillation.
5. Assume that the ascending limb of the loop of Henle and the distal convoluted tubules are impermeable to sodium and other ions but actively pump out water. Other characteristics of the kidney are assumed to be unchanged. As the urine moves up the ascending limb, it becomes hyperosmotic, because sodium remains behind as water is pumped out. Assuming that the collecting ducts are impermeable to sodium, on reaching the collecting ducts the presence or absence of ADH determines the final concentration of the urine. If ADH is absent, little or no water is exchanged as the urine passes down the collecting ducts and a hyperosmotic urine is produced. On the other hand, if ADH is present, water moves from the interstitial fluid into the collecting ducts, thus diluting the urine and producing a hyposmotic urine.

7. A low-salt diet tends to reduce the osmolality of the blood. Consequently, ADH secretion is inhibited, producing dilute urine and thus eliminating water. This in turn reduces blood volume and blood pressure.
9. Answer *a* is correct. The respiratory system responds to below-normal pH by increasing the rate of respiration. However, Marvin's kidneys were not able to respond to the low pH because of the hypoxic injury. The hypoxic injury is responsible for the metabolic acidosis (lower-than-normal blood pH), and the damaged nephrons could not adequately increase HCO_3^- reabsorption or H^+ secretion.
11. Water that moves into the collecting duct cells would diffuse into the interstitial fluid at a reduced rate because of the reduced number of aquaporins. Urine volume would increase because of water retention in the distal convoluted tubule and collecting ducts. Urine concentration would decrease because of dilution by the water. ADH can cause an increase in the number of aquaporin-2 water channel proteins in the apical membrane of the distal convoluted tubules and collecting ducts, but not in aquaporin-3 or aquaporin-4 channels in the basal membranes. These channels determine the permeability of the basal membranes to water. Therefore, ADH would not be an effective treatment. The net effect would be polyuria, which is similar to nephrogenic diabetes insipidus caused by an abnormal aquaporin-2 water channel protein.

Chapter 27

1. When excess glucose is not reabsorbed, it osmotically obligates water to remain in the nephron. This results in the production of a large amount of urine, called polyuria, with a consequent loss of water, salts, and glucose. The loss of water can be compensated for by increasing fluid intake. The intense thirst that stimulates increased fluid intake is called polydipsia. The loss of salts can be compensated for by increasing the salt intake. The high glucose levels in the blood increase the blood osmolality, thus stimulating the secretion of ADH. This increases the permeability of the distal convoluted tubule and collecting duct to water. Normally, this allows reabsorption of water from the collecting ducts and thus conserves water. However, if glucose levels in the urine are high enough, water loss increases even with high levels of ADH.
3. Blocking H^+ secretion produces acidosis. Because H^+ is exchanged for Na^+, the Na^+ remains in the urine as sodium bicarbonate. This effectively prevents the reabsorption of HCO_3^- and produces an alkaline urine. The blood pH is reduced because H^+ is not being secreted as rapidly by the nephron. The respiratory rate increases because of the stimulatory effect of decreased blood pH on the respiratory center.
5. Answer *e* is correct. The rate of stomach secretion increased prior to the time Harry vomited. Gastric secretions include a high concentration of HC1. As the stomach secretes HC1, it secretes H^+ into the stomach and absorbs HCO_3^- into the blood. Also, after Harry took the antacid, which is mostly $NaHCO_3$, the HCO_3^- was absorbed and entered the circulatory system. A significant amount of HCO_3^- entering the circulatory system causes an increase in the blood pH. The increased pH affects the regulatory centers of the respiratory system and causes respiration to slow. Although the kidney's response is slower, by 24 hours later, the rate of H^+ secretion by the kidney slows, and HCO_3^- absorption slows in response to an increase in the blood pH. The slower rates of respiration, H^+ secretion, and HCO_3^- absorption by the kidneys help keep the blood pH from becoming higher than normal.

Chapter 28

1. Removing the testes would eliminate the major source of testosterone. Blood levels of testosterone would therefore decrease. Because testosterone has a negative-feedback effect on the hypothalamus and pituitary gland, GnRH, FSH, and LH secretion would increase, and the blood levels of these hormones would increase. An adult male's primary and secondary sex characteristics are already developed; however, removal of the testes would eliminate sperm production. Also, the lack of testosterone would cause a decrease in sex drive and muscular strength.
3. Ideally, the pill would inhibit spermatogenesis. Using the same approach as the birth control pill in females, the inhibition of FSH and LH secretion should work. Chronic administration of GnRH suppresses FSH and LH levels enough to cause infertility through down-regulation. However, lack of LH can also result in reduced testosterone levels and loss of sex drive. Some evidence indicates that administering testosterone in the proper amounts reduces FSH and LH secretion, thus leading to less sperm cell production while still maintaining normal sex drive. For a large percentage of males the technique results in a sperm concentration in the semen that is too low to allow fertilization. However, the technique is not sufficiently precise to be used as a standard birth control technique.
5. The removal of the ovaries from a 20-year-old female eliminates the major site of estrogen and progesterone production, thereby causing an increase in GnRH, FSH, and LH levels due to lack of negative feedback. We would expect to see the symptoms of menopause, such as cessation of menstruation and reduction in the size of the uterus, vagina, and breasts. A temporary reduction in sex drive may also occur.
7. The progesterone inhibits GnRH in the hypothalamus. Consequently, the anterior pituitary is not stimulated to produce LH and FSH. Lack of LH prevents ovulation, and lack of FSH prevents development of the follicles. LH is also required for the maturation of follicles prior to ovulation. Without follicle development, inadequate estrogen is produced, which causes the hot flashes.
9. Because of their enlarged prostates, the patients are likely to have difficulty urinating. An enlarged prostate gland compresses the prostatic urethra, slowing the emptying of the urinary bladder and enhancing the urgency to urinate. Dr. Smith conducted a digital exam by palpating the men's prostate glands through their rectums. The patient with the enlarged but smooth prostate is likely to have benign prostatic hypertrophy and low blood levels of PSA. Benign prostatic hypertrophy is general enlargement of the prostate without specific tumors. The patient with the enlarged but asymmetrical prostate gland is more likely to have elevated blood levels of PSA and prostate cancer. Lack of symmetry and a rough surface can be caused by tumors within the prostate gland.
11. The correct answer is *d*. Decreased blood flow to the anterior pituitary gland would result in decreased LH secretion, not increased LH secretion. The decreased secretion of LH from the anterior pituitary causes a decrease in the blood level of testosterone. Because it takes approximately 74 days to produce a sperm cell, the sperm count is likely to remain normal during the week when the blood LH and FSH levels are reduced.

Chapter 29

1. Triploidy can occur as a result of polyspermy, the fertilization of one oocyte with two sperm cells. Polyspermy is usually prevented by the fast and slow blocks to polyspermy, both of which depend on the depolarization of the oocyte membrane. If this depolarization does not occur, the zona pellucida does not degenerate, and other sperm cells can attach to the oocyte membrane, leading to polyspermy.

3. The fever occurred on days 21–31 of development, during the time of neural tube closure (days 18–25). If the fever prevented neural tube closure, the child could be born with anencephalus or spina bifida.
5. The Apgar score of 5 indicates appearance (A, 0) white or blue; pulse (P, 1) low; grimace (G, 1) slight; activity (A, 1) little movement and poor muscle tone; and respiration (R, 2) normal. The white or blue appearance (A, 0) is consistent with a poor circulation, as also indicated by reduced pulse (P, 1). The reduced heart rate, resulting in the low pulse, may indicate a circulatory system problem. The reduced reflexes and motor activity (G, 1; A, 1) can result from lack of oxygen in the muscles due to poor circulation. Because the infant has poor circulation despite normal respiration, clearing the airway (if obstructed) and administering oxygen are in order. This Apgar score can have several causes, and additional information would be necessary to determine the specific cause.
7. The woman most likely has an XY genotype. The spherical structures in the inguinal area are testes, but a genetic abnormality caused the androgen receptors to be defective or absent. Consequently, reproductive structures could not respond to androgens secreted by the testes. The embryonic testes secreted müllerian-inhibiting hormone, and therefore the müllerian duct system degenerated. This explains the lack of a uterus and a cervix. Female external genitalia developed because of the absence of androgen receptors. Normal breast development occurred because of the small amount of estrogen produced by the adrenal glands and because some testosterone is converted to estrogen in peripheral tissues.
9. It is not possible from this information alone. If tongue rolling is designated *T* and the inability to roll the tongue is designated *t,* then a *Tt* woman and a *tt* man have a 50% probability of having a *Tt* child and a 50% probability of having a *tt* child. Therefore, a man who cannot roll his tongue and a woman who can roll her tongue can have a child who can roll his or her tongue. This connection alone, however, is not sufficient to establish paternity.