CHAPTER 16
ENDOCRINE SYSTEM

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KEY TERMS

| Adenohypophysis | Parathyroid |
| Hormone | Prostaglandin (PG) |
| Adrenal glands | Target cell |
| Endocrine | Thymus |
| Gonads | Thyroid |
| Hormone | Tropic hormone |

The endocrine systems and nervous system both function to achieve and maintain stability of the internal environment. Each system may work alone or in concert with others as a single neuroendocrine system, performing the same general functions within the body: communication, integration, and control.

Both the endocrine system and the nervous system perform their regulatory functions by means of chemical messengers sent to specific cells. In the nervous system, neurons secrete neurotransmitter molecules to signal nearby cells that have the appropriate receptor molecules. In the endocrine system, secreting cells send hormone (from the Greek hormaein, “to excite”) molecules by way of the bloodstream to signal specific target cells throughout the body. Tissues and organs that contain endocrine target cells are called target tissues and target organs, respectively. As with postsynaptic cells, endocrine target cells must have the appropriate receptor to be influenced by the signaling chemical. Many cells have receptors for neurotransmitters and hormones, so they can be influenced by both types of chemicals.

Whereas neurotransmitters are sent over very short distances across a synapse, hormones diffuse into the blood to
be carried to nearly every point in the body. The nervous system can directly control only muscles and glands that are innervated with efferent fibers, whereas the endocrine system can regulate most cells in the body. The effects of neurotransmitters are rapid and short-lived compared with the effects of hormones, which appear more slowly and last longer. Table 16-1 compares endocrine structure and function with nervous structure and function (Figure 16-1).

Endocrine glands secrete their products, hormones, directly into the blood. Because they do not have ducts, they are often called “ductless glands.” This characteristic distinguishes endocrine glands from exocrine glands, which secrete their products into ducts (see Chapter 5, p. 131). Many endocrine glands are made of glandular epithelium, whose cells manufacture and secrete hormones. However, a few endocrine glands are made of neurosecretory tissue. Neurosecretory cells are simply modified neurons that secrete chemical messengers that diffuse into the bloodstream rather than across a synapse. In such cases, the chemical messenger is called a hormone rather than a neurotransmitter. For example, when norepinephrine is released by neurons, diffuses across a synapse, and binds to an adrenergic receptor in a postsynaptic neuron, we call norepinephrine a neurotransmitter. On the other hand, we call norepinephrine a hormone when it diffuses into the blood (because there is no postsynaptic cell present), then binds to an adrenergic receptor in a distant target cell.

Glands of the endocrine system are widely scattered throughout the body. New discoveries in endocrinology continue to add to the long list of hormone-secreting tissues. However, even the most newly discovered endocrine tissues and their hormones operate according to some basic physiological principles. In this chapter, we will focus our discussion primarily on the major endocrine glands. Figure 16-2 and Table 16-2 summarize the names and locations of these major endocrine glands. After you are familiar with the basic principles of endocrinology and the major examples of glands and their hormones, you will be prepared for additional examples that you will encounter as you continue your study of the human body.

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**Table 16-1  Comparison of Features of the Endocrine System and Nervous System**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Endocrine System</th>
<th>Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Function</td>
<td>Regulation of effectors to maintain homeostasis</td>
<td>Regulation of effectors to maintain homeostasis</td>
</tr>
<tr>
<td>Control by regulatory feedback loops</td>
<td>Yes (endocrine reflexes)</td>
<td>Yes (nervous reflexes)</td>
</tr>
<tr>
<td>Effector tissues</td>
<td>Endocrine effectors: virtually all tissues</td>
<td>Nervous effectors: muscle and glandular tissue only</td>
</tr>
<tr>
<td>Effector cells</td>
<td>Target cells (throughout the body)</td>
<td>Postsynaptic cells (in muscle and glandular tissue only)</td>
</tr>
<tr>
<td>Chemical Messenger</td>
<td>Hormone</td>
<td>Neurotransmitter</td>
</tr>
<tr>
<td>Cells that secrete the chemical messenger</td>
<td>Glandular epithelial cells or neurosecretory cells (modified neurons)</td>
<td>Neurons</td>
</tr>
<tr>
<td>Distance traveled (and method of travel) by chemical messenger</td>
<td>Long (by way of circulating blood)</td>
<td>Short (across a microscopic synapse)</td>
</tr>
<tr>
<td>Location of receptor in effector cell</td>
<td>On the plasma membrane or within the cell</td>
<td>On the plasma membrane</td>
</tr>
<tr>
<td>Characteristics of regulatory effects</td>
<td>Slow to appear, long-lasting</td>
<td>Appear rapidly, short-lived</td>
</tr>
</tbody>
</table>

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1. What is meant by the term target cell?
2. Describe how the nervous system and the endocrine system differ in the way they control effectors.
HORMONES

CLASSIFICATION OF HORMONES
Hormone molecules can be classified in various useful ways. For example, when classified by general function, hormones can be identified as tropic hormones (hormones that target other endocrine glands and stimulate their growth and secretion), sex hormones (hormones that target reproductive tissues), anabolic hormones (hormones that stimulate anabolism in their target cells), and many other functional names. Another useful way to classify hormones is by their chemical structure. Because this method of classifying hormones is so widely used, we will briefly describe it in the following paragraphs.

Steroid Hormones
All of the many hormones secreted by endocrine tissues can be classified simply as steroid or nonsteroid (Figure 16-3). Steroid hormone molecules are manufactured by endocrine cells from cholesterol, an important type of lipid in the human body (see Chapter 2, p. 57). As Figure 16-4 shows, because all steroid hormones are derived from a common molecule, cholesterol, they have a characteristic chemical group at the core of each molecule. Because steroids are lipid-soluble, they can easily pass through the phospholipid plasma membrane of target cells. Examples of steroid hormones include cortisol, aldosterone, estrogen, progesterone, and testosterone (Figures 16-3 and 16-4).

Nonsteroid Hormones
Nonsteroid hormones are synthesized primarily from amino acids rather than from cholesterol (Figure 16-5). Some nonsteroid hormones are protein hormones. These hormones are long, folded chains of amino acids, a structure typical of protein molecules of any sort (see Chapter 2, p. 51). Included among the protein hormones are insulin, parathyroid hormone, and others listed in Figure 16-3. Protein hormones that have carbohydrate groups attached to their amino acid chains are often classified separately as glycoprotein hormones.

Another major category of nonsteroid hormones consists of the peptide hormones. Peptide hormones such as oxytocin and antidiuretic hormone are smaller than the protein hormones. They are each made of a short chain of amino acids
Steroid
- Cortisol (hydrocortisone)
- Aldosterone
- Estrogen
- Progesterone
- Testosterone

Nonsteroid
- Peptides
  - Growth hormone (GH)
  - Prolactin (PRL)
  - Parathyroid hormone (PTH)
  - Calcitonin
  - Adrenocorticotropic hormone (ACTH)
  - Insulin
  - Glucagon
- Glycoproteins
  - Follicle-stimulating hormone (FSH)
  - Luteinizing hormone (LH)
  - Thyroid-stimulating hormone (TSH)
  - Chorionic gonadotropin (CG)

Proteins
- Amines
  - Norepinephrine
  - Epinephrine
  - Melatonin
- Iodinated amino acids
  - Thyroxine (T₄)
  - Triiodothyronine (T₃)
- Antidiuretic hormone (ADH)
- Oxytocin
- Melanocyte-stimulating hormone (MSH)
- Somatostatin
- Thyrotropin-releasing hormone (TRH)
- Gonadotropin-releasing hormone (GnRH)
- Atrial natriuretic hormone (ANH)

Figure 16-3 Chemical classification of hormones.
acids, as Figure 16-5, B, shows. Examples of peptide hormones are listed in Figure 16-3.

Yet another category of nonsteroid hormones consists of the amino acid derivative hormones. Each of these hormones is derived from only a single amino acid molecule. There are two major subgroups within this category. One subgroup, the amine hormones, is synthesized by modifying a single molecule of the amino acid, tyrosine. Amine hormones such as epinephrine and norepinephrine are produced by neurosecretory cells (where they are secreted as hormones) and by neurons (where they are secreted as neurotransmitters). Another subgroup of amino acid derivatives produced by the thyroid gland are all synthesized by adding iodine (I) atoms to a tyrosine molecule (Figure 16-5, C). Examples of hormones derived from single amino acids are listed in Figure 16-3.

**HOW HORMONES WORK**

**General Principles of Hormone Action**

As previously stated, hormones signal a cell by binding to specific receptors on or in the cell. In a “lock-and-key” mechanism, hormones will bind only to receptor molecules that “fit” them exactly. Any cell with one or more receptors for a particular hormone is said to be a target of that hormone (Figure 16-6). Cells usually have many different types of receptors; therefore, they are target cells of many different hormones.

Each different hormone-receptor interaction produces different regulatory changes within the target cell. These cellular changes are usually accomplished by altering the chemical reactions within the target cell. For example, some hormone-receptor interactions initiate synthesis of new proteins. Other hormone-receptor interactions trigger...
the activation or inactivation of certain enzymes and thus affect the metabolic reactions regulated by those enzymes. Still other hormone-receptor interactions regulate cells by opening or closing specific ion channels in the plasma membrane. Specific mechanisms of hormone-receptor interactions are outlined in the next section.

Different hormones may work together to enhance each other’s influence on a target cell. In a phenomenon called synergism, combinations of hormones have a greater effect on a target cell than the sum of the effects that each would have if acting alone. Combined hormone actions may exhibit instead the phenomenon of permisiveness. Permissiveness occurs when a small amount of one hormone allows a second hormone to have its full effect on a target cell; the first hormone “permits” the full action of the second hormone. A common type of combined action of hormones is seen in the phenomenon of antagonism. In antagonism, one hormone produces the opposite effect of another hormone. Antagonism between hormones can be used to “fine tune” the activity of target cells with great accuracy, signaling the hormone produces the opposite effect of another hormone.

As previously stated, hormones travel to their target cells by way of the circulating bloodstream. This means that all hormones travel throughout the body. Because they only affect their target cells, however, the effects of a particular hormone may be limited to specific tissues in the body. Some hormone molecules are attached to plasma proteins while they are carried along the bloodstream. Such hormones must free themselves from the plasma protein to leave the blood and combine with their receptors. Because blood carries hormones nearly everywhere in the body, even where there are no target cells, endocrine glands produce more hormone molecules than actually hit their target. Unused hormones usually are quickly excreted by the kidneys or broken down by metabolic processes.

**Mechanism of Steroid Hormone Action**

Steroid hormones are lipids and thus are not very soluble in blood plasma, which is mostly water. Instead of traveling in the plasma as free molecules, they attach to soluble plasma proteins. As you can see in Figure 16-7, a steroid hormone molecule dissociates from its carrier before approaching the target cell. Because steroid hormones are lipid-soluble and thus can pass into cells easily, it is not surprising that their receptors are normally found inside the cell rather than on the surface of the plasma membrane. After a steroid hormone molecule has diffused into its target cell, it passes into the nucleus where it binds to a mobile receptor molecule to form a hormone-receptor complex. Some hormones must be activated by enzymes before they can bind to their receptors. Because steroid hormone receptors are not attached to the plasma membrane, but seem to move freely in the nucleoplasm, this model of hormone action has been called the mobile-receptor hypothesis.

Once formed, the hormone-receptor complex activates a certain gene sequence to begin transcription of messenger RNA (mRNA) molecules. The newly formed mRNA molecules then move out of the nucleus into the cytosol, where they associate with ribosomes and begin synthesizing protein molecules.

The new protein molecules synthesized by the target cell would not have been made if not for the arrival of the steroid hormone molecule. Steroid hormones regulate cells by regulating their production of certain critical proteins, such as enzymes that control intracellular reactions or membrane proteins that alter the permeability of a cell.

This mechanism of steroid hormone action implies several things about the effects of these hormones. For one thing, the more hormone-receptor complexes formed, the more mRNA molecules are transcribed, the more new protein molecules are formed, and thus the greater the magnitude of the regulatory effect. In short, the amount of steroid hormone present determines the magnitude of a target cell’s response. Also, because transcription and protein synthesis take some time, responses to steroid hormones are often slow—from 45 minutes to several days before the full effect is seen.

**Mechanisms of Nonsteroid Hormone Action**

The second messenger mechanism. Nonsteroid hormones typically operate according to a mechanism originally called the second messenger hypothesis. This concept of hormone action—first proposed several decades ago by Dr. Earl W. Sutherland—was a milestone in endocrinology for which he received the 1971 Nobel Prize in Medicine and Physiology. According to this concept, a nonsteroid hormone molecule acts as a “first messenger,” delivering its chemical message to fixed receptors in the target cell’s plasma membrane. The “message” is then passed into the cell where a “second messenger” triggers the appropriate cellular changes. This concept of nonsteroid hormone action is also called the fixed-membrane-receptor hypothesis.

In the example illustrated in Figure 16-8, formation of the hormone-receptor complex causes a membrane protein,
called the G protein, to bind to a nucleotide called guanosine triphosphate (GTP). This, in turn, activates another membrane protein, adenyl cyclase. Adenyl cyclase is an enzyme that promotes the removal of two phosphate groups from adenosine triphosphate (ATP) molecules in the cytosol. The product thus formed is cyclic adenosine monophosphate (cAMP). The cAMP molecule acts as a "second messenger" within the cell. cAMP activates protein kinases, a set of enzymes that activate other types of enzymes. It is this final set of specific enzymes, which are now activated, that catalyze the cellular reactions that characterize the target cell's response. In short, the hormone "first messenger" binds to a membrane receptor, triggering formation of an intracellular "second messenger," which activates a cascade of chemical reactions that produces the target cell's response.

Since the time Sutherland first began his pioneering work, other second messenger systems have been discovered. As a matter of fact, the study of second messenger mechanisms is still a very active area of research, with new discoveries continuing to be revealed in scientific journals around the world. Although most nonsteroid hormones seem to use cAMP as the second messenger, we now know that a few hormones use compounds such as inositol triphosphate (IP₃) and cyclic guanosine monophosphate (GMP) as the second messenger.

Still other hormones produce their effects by triggering the opening of calcium (Ca²⁺) channels in the target cell's membranes, as you can see in Figure 16-9. Binding of a hormone to a fixed membrane receptor activates a chain of membrane proteins (G protein and phosphodiesterase, PIP₂) that in turn trigger the opening of calcium channels in the plasma membrane. Ca²⁺ ions that enter the cytosol when the channels open bind to an intracellular molecule called calmodulin. The Ca²⁺-calmodulin complex thus formed acts as a second messenger, influencing the enzymes that produce the target cell's response.

Recent research findings also show that in second messenger systems, the hormone-receptor complexes may be taken into the cell by means of endocytosis. Although the purpose of this may be primarily to break down the complexes and recycle the receptors, the hormone-receptor complex may continue to have physiological effects after it is taken into the cell.
The second messenger mechanism produces target cell effects that differ from steroid hormone effects in several important ways. First, the cascade of reactions produced in the second messenger mechanism greatly amplifies the effects of the hormone. Thus the effects of many nonsteroid hormones are disproportionally great when compared to the amount of hormone present. Recall that steroid hormones produce effects in proportion to the amount of hormone present. Also, the second messenger mechanism operates much more quickly than the steroid mechanism. Many nonsteroid hormones produce their full effects within seconds or minutes of initial binding to the target cell receptors—not the hours or days sometimes seen with steroid hormones.

**The nuclear receptor mechanism.** Not all nonsteroid hormones operate according to the second messenger model. The notable exception is the pair of thyroid hormones, thyroxine ($T_4$) and triiodothyronine ($T_3$). These small iodinated amino acids apparently enter their target cells and bind to receptors already associated with a DNA molecule within the nucleus of the target cell. Formation of a hormone-receptor complex triggers transcription of mRNA and the synthesis of new enzymes in a manner similar to the steroid mechanism. More information on these hormones is given later in this chapter.

**REGULATION OF HORMONE SECRETION**

The control of hormonal secretion is usually part of a negative feedback loop. Recall from Chapter 1 (Figure 1-4, p. 24) that negative feedback loops tend to reverse any deviation of the internal environment away from its stable point (the set point value). Rarely, a positive feedback loop controls the secretion of a hormone. Recall that in positive feedback control, deviation from the stable point is exaggerated rather than reversed. Responses that result from the operation of feedback loops within the endocrine system are called endocrine reflexes, just as responses to nervous feedback loops (reflex arcs) are called nervous reflexes.

For a moment, let us focus our attention on the specific mechanisms that regulate the release of hormones from endocrine cells (Box 16-1). The simplest mechanism operates when an endocrine cell is sensitive to the physiological changes
produced by its target cells (Figure 16-10). For example, parathyroid hormone (PTH) produces responses in its target cells that increase Ca\[^{++}\] concentration in the blood. When blood Ca\[^{++}\] concentration exceeds the set point value, parathyroid cells sense it and reflexively reduce their output of PTH. Secretion by many endocrine glands is regulated by a hormone produced by another gland. For example, the pituitary gland (specifically, the anterior portion) produces thyroid-stimulating hormone (TSH), which stimulates the thyroid gland to release its hormones. The anterior pituitary responds to changes in the controlled physiological variable and to changes in the blood concentration of hormones secreted by its target gland. Secretion by the anterior pituitary can, in turn, be regulated by releasing hormones or inhibiting hormones secreted by the hypothalamus. Hypothalamic secretion is responsive to changes in the controlled variable, as well as changes in the blood concentration of anterior pituitary and target gland hormones. Although the target gland may be able to adjust its own output, the additional controls exerted by long feedback loops involving the anterior pituitary and hypothalamus allow more precise regulation of hormone secretion—and thus more precise regulation of the internal environment.

Another mechanism that may influence the secretion of hormones by a gland is input from the nervous system. For example, secretion by the posterior pituitary is not regulated by releasing hormones but by direct nervous input from the hypothalamus. Likewise, sympathetic nerve impulses that reach the medulla of the adrenal glands trigger the secretion of epinephrine and norepinephrine. Many other glands, including the pancreas, are also influenced to some degree by nervous input. That the nervous system operates with hormonal mechanisms to produce endocrine reflexes emphasizes the close functional relationship between these two systems.

Although the operation of long feedback loops tends to minimize wide fluctuations in secretion rates, the output of several hormones typically rises and falls dramatically

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**Figure 16-9** Calcium-calmodulin as a second messenger. In this example of a second messenger mechanism, a nonsteroid hormone (first messenger) first binds to a fixed receptor in the plasma membrane (1), which activates membrane-bound proteins (G protein and PIP\(_2\)) that trigger the opening of calcium channels (2). Calcium ions, which are normally at a higher concentration in the extracellular fluid, diffuse into the cell and bind to a calmodulin molecule (3). The Ca\[^{++}\]-calmodulin complex thus formed is a second messenger that binds to an enzyme to produce an allosteric effect that promotes or inhibits the enzyme’s regulatory effect in the target cell (4).
within a short period. For example, the concentration of insulin—a hormone that can correct a rise in blood glucose concentration—increases to a high level just after a meal high in carbohydrates. The level of insulin decreases only after the blood glucose concentration returns to its set point value. Likewise, threatening stimuli can cause a sudden, dramatic increase in the secretion of epinephrine from the adrenal medulla as part of the fight-or-flight response.

Specific examples of feedback control of hormone secretion are given later in this chapter.
Before continuing with our discussion of endocrine glands and hormones, let us pause a moment to consider the prostaglandins (PGs) and related compounds. The prostaglandins are a unique group of lipid molecules that serve important and widespread integrative functions in the body but do not meet the usual definition of a hormone. Prostaglandins are derived from 20-carbon unsaturated fatty acids and contain a 5-carbon ring (Figure 16-11). Although they may be secreted directly into the bloodstream, they are rapidly metabolized, so that circulating levels are extremely low.

The sensitivity of a target cell to any particular hormone depends on how many receptors for that hormone it has. The more receptors, the more sensitive the target cell. Hormone receptors, as with other cell components, are constantly broken down by the cell and replaced with newly synthesized receptors. This mechanism not only ensures that all cell parts are ‘new’ and working properly, but also provides a method by which the number of receptors can be changed from time to time.

If synthesis of new receptors occurs faster than degradation of old receptors, the target cell will have more receptors and thus be more sensitive to the hormone. This phenomenon, illustrated in part A of the figure, is often called up-regulation because the number of receptors “goes up.” If, on the other hand, the rate of receptor degradation exceeds the rate of receptor synthesis, the target cell’s number of receptors will decrease (part B). Because the number of receptors, and thus the sensitivity of the target cell, “goes down,” this phenomenon is often called down-regulation.

Endocrinologists are just now learning the mechanisms that control the process of receptor turnover in the cell and how this affects the functions of the target cell. Information uncovered so far has already led to a better understanding of important and widespread endocrine disorders such as diabetes mellitus.
from a variety of tissues. The first prostaglandin was discovered in semen, so it was attributed to the prostate gland (hence the name, prostaglandin). Later, researchers found that the seminal vesicles, not the prostate, secreted the prostaglandin that they had found. Other tissues known to secrete prostaglandins include the kidneys, lungs, iris, brain, and thymus. As a group, the prostaglandins have diverse physiological effects and are among the most varied and potent of any naturally occurring biological compounds. They are intimately involved in overall endocrine regulation by influencing adenyl cyclase–cAMP interaction within the cell’s plasma membrane (see Figure 16-8). Specific biological effects depend on the class of prostaglandin.

Intraarterial infusion of prostaglandins A (PGAs) results in an immediate fall in blood pressure accompanied by an increase in regional blood flow to several areas, including the coronary and renal systems. PGAs apparently produce this effect by causing relaxation of smooth muscle fibers in the walls of certain arteries and arterioles.

Prostaglandins E (PGEs) have an important role in various vascular, metabolic, and gastrointestinal functions. Vascular effects include regulation of red blood cell deformability and platelet aggregation (see Chapter 17). PGEs also have a role in systemic inflammations such as fever. Common anti-inflammatory agents, such as aspirin, produce some of their effects by inhibiting PGE synthesis. PGE also regulates hydrochloric acid secretion in the stomach, helping to prevent gastric ulcers.

Prostaglandins F (PGFs) have an especially important role in the reproductive system. They cause uterine muscle contractions, so they have been used to induce labor and thus accelerate delivery of a baby. PGFs also affect intestinal motility and are required for normal peristalsis.

In addition to prostaglandins, various tissues also synthesize other fatty acid compounds that are structurally and functionally similar to prostaglandins. Examples include the thromboxanes and leukotrienes. As with prostaglandins, these compounds may also be referred to as tissue hormones because of their local, yet potent, regulatory effects.

The potential therapeutic use of prostaglandins and related compounds, which are found in almost every body tissue and are capable of regulating hormone activity on the cellular level, has been described as the most revolutionary development in medicine since the advent of antibiotics. They are likely to play increasingly important roles in the treatment of such diverse conditions as hypertension, coronary thrombosis, asthma, and ulcers.

**PITUITARY GLAND**

**STRUCTURE OF THE PITUITARY GLAND**

The pituitary gland, or hypophysis, is a small but mighty structure. It measures only 1.2 to 1.5 cm (about ½ inch) across. By weight, it is even less impressive—only about 0.5 g (⅙ ounce)! And yet so crucial are the functions of the anterior lobe of the pituitary gland that, years ago, it was referred to as the “master gland.”

The hypophysis has a well-protected location within the skull on the ventral surface of the brain (Figure 16-12). It lies in the pituitary fossa of the sella turcica and is covered by a
portion of the dura mater called the *pituitary diaphragm*. The gland has a stemlike stalk, the *infundibulum*, which connects it to the hypothalamus of the brain.

Although the pituitary looks like one gland, it actually consists of two separate glands—the *adenohypophysis*, or anterior pituitary gland, and the *neurohypophysis*, or posterior pituitary gland. In the embryo, the adenohypophysis develops from an upward projection of the pharynx and is composed of regular endocrine tissue. The neurohypophysis, on the other hand, develops from a downward projection of the brain and is composed of neurosecretory tissue. These histological differences are incorporated into their names—*adeno* means “gland” and *neuro* means “nervous.” As you may suspect, the hormones secreted by the adenohypophysis serve very different functions from those released by the neurohypophysis.

**ADENOHYPOPHYSIS (ANTERIOR PITUITARY)**

The *adenohypophysis*, the anterior portion of the pituitary gland, is divided into two parts—the *pars anterior* and the *pars intermedia*. The pars anterior forms the major portion of the adenohypophysis and is divided from the tiny pars intermedia by a narrow cleft and some connective tissue (Figure 16-12).

The tissue of the adenohypophysis is composed of irregular clumps of secretory cells supported by fine connective tissue fibers and surrounded by a rich vascular network.

Traditionally, histologists have identified three types of cells according to their affinity for certain types of stains: *chromophobes* (literally “afraid of color”), *acidophils* (“acid [stain] lover”), and *basophils* (“base [stain] lover”). All three types are visible in the photomicrograph shown in Figure 16-13. Currently, however, cells of the adenohypophysis are more often classified by their secretions into five types:

1. **Somatotrophs**—secrete growth hormone (GH)
2. **Corticotrophs**—secrete adrenocorticotropic hormone (ACTH)
3. **Thyrotrophs**—secrete thyroid-stimulating hormone (TSH)
4. **Lactotrophs**—secrete prolactin (PRL)
5. **Gonadotrophs**—secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH)

Figure 16-14 summarizes the hormones of the adenohypophysis and shows the primary locations of their target cells.

**Growth Hormone**

**Growth hormone (GH), or somatotropin (STH),** is thought to promote bodily growth indirectly by stimulating the liver to produce certain growth factors, which, in turn, accelerate amino acid transport into cells. Rapid entrance of amino acids from the blood into the cells allows protein anabolism within the cells to accelerate. Increased protein anabolism allows increased rate of growth. GH promotes the growth of bone, muscle, and other tissues.

![Figure 16-15  Histology of the adenohypophysis. In this light micrograph, nonstaining chromophobes are indicated by arrowheads. Examples of hormone-secreting cells are labeled a (acidophil) and b (basophil).](image)

In addition to stimulating protein anabolism, GH also stimulates fat metabolism. GH accelerates mobilization of lipids from storage in adipose cells and also speeds up the catabolism of those lipids after they have entered another cell. In this way, GH tends to shift a cell’s use of nutrients away from carbohydrate (glucose) catabolism and toward lipid catabolism as an energy source. Because less glucose is then removed from the blood by cells, the blood glucose levels tend to rise. Thus GH is said to have a *hyperglycemic effect*. Insulin (from the pancreas) has the opposite effect—it promotes glucose entry into cells, producing a *hypoglycemic effect*. Therefore GH and insulin function as antagonists. The balance between these two hormones is vital to maintaining a homeostasis of blood glucose levels.

GH affects metabolism in these ways:

- It promotes protein anabolism (growth, tissue repair)
- It promotes lipid mobilization and catabolism
- It indirectly inhibits glucose metabolism
- It indirectly increases blood glucose levels

**Prolactin**

**Prolactin (PRL),** produced by acidophils in the pars anterior, is also called *lactogenic hormone*. Both names of this hormone suggest its function in “generating” or initiating milk secretion (lactation). During pregnancy, a high level of PRL promotes the development of the breasts in anticipation of milk secretion. At the birth of an infant, PRL in the mother stimulates the mammary glands to begin milk secretion.

Hypersecretion of PRL may cause lactation in nonnursing women, disruption of the menstrual cycle, and impotence in men. Hyposecretion of PRL is usually insignificant except in women who want to nurse their children. Milk production cannot be initiated or maintained without PRL.

**Tropic Hormones**

**Tropic hormones** are hormones that have a stimulating effect on other endocrine glands. These hormones stimulate the
Hypersecretion of GH during the growth years (before ossification of the epiphyseal plates) causes an abnormally rapid rate of skeletal growth. This condition is known as gigantism (see figure, left). Hypersecretion after skeletal fusion has occurred can result in acromegaly, a condition in which cartilage still left in the skeleton continues to form new bone. This abnormal growth may result in a distorted appearance because of the enlargement of the hands, feet, face, jaw (causing separation of the teeth), and other body parts. Overlying soft tissue may also be affected—for instance, the skin often thickens and the pores become more prominent.

Hyposecretion of GH during growth years may result in stunted body growth, known as pituitary dwarfism (see figure, right). Formerly, patients were treated only with GH extracted from human tissues. Since the 1980s, the availability of human GH produced by genetically engineered bacteria has made the treatment obtainable for many more patients. However, concerns have been raised about possible adverse side effects associated with human GH from bacterial sources.
Development of their target glands and tend to stimulate synthesis and secretion of the target hormone. Four principal tropic hormones are produced and secreted by the basophils of the pars anterior:

1. **Thyroid-stimulating hormone (TSH), or thyrotropin,** promotes and maintains the growth and development of its target gland—the thyroid. TSH also causes the thyroid gland to secrete its hormones.

2. **Adrenocorticotropic hormone (ACTH), or adrenocorticotropin,** promotes and maintains normal growth and development of the cortex of the adrenal gland. ACTH also stimulates the adrenal cortex to synthesize and secrete some of its hormones.

3. **Follicle-stimulating hormone (FSH),** stimulates structures within the ovaries, primary follicles, to grow toward maturity. Each follicle contains a developing egg cell (ovum), which is released from the ovary during ovulation. FSH also stimulates the follicle cells to synthesize and secrete estrogens (female sex hormones). In the male, FSH stimulates the development of the seminiferous tubules of the testes and maintains spermatogenesis (sperm production) by them.

4. **Luteinizing hormone (LH)** stimulates the formation and activity of the corpus luteum of the ovary. The corpus luteum (meaning “yellow body”) is the tissue left behind when a follicle ruptures to release its egg during ovulation. The corpus luteum secretes progesterone and estrogens when stimulated by LH. LH also supports FSH in stimulating the maturation of follicles. In males, LH stimulates interstitial cells in the testes to develop, then synthesize and secrete testosterone (the male sex hormone).

FSH and LH are called **gonadotropins** because they stimulate the growth and maintenance of the gonads (ovaries and testes). During childhood the adenohypophysis secretes insignificant amounts of the gonadotropins. A few years before puberty, gonadotropin secretion is gradually increased. Then, suddenly, their secretion spurts, and the gonads are stimulated to develop and begin their normal functions.

**Control of Secretion in the Adenohypophysis**
The cell bodies of neurons in certain parts of the hypothalamus synthesize chemicals that their axons secrete into the blood. These chemicals, generally called **releasing hormones,** travel through a complex of small blood vessels called the **hypophyseal portal system** (Figure 16-15). A **portal system** is an arrangement of blood vessels in which blood exiting one tissue is immediately carried to a second tissue before being returned to the heart and lungs for oxygenation and redistribution. The hypophyseal portal system carries blood from the hypothalamus directly to the adenohypophysis, where the target cells of the releasing hormones are located. The advantage of a portal system in the hypophysis is that a small amount of hormone can be delivered directly to its target tissue without the great dilution that would occur in the general circulation. The releasing hormones that arrive in the adenohypophysis by means of this portal system influence the secretion of hormones by acidophils and ba-
sophils. In this manner, the hypothalamus directly regulates the secretion of the adenohypophysis. You can see that the supposed “master gland” really has a master of its own—the hypothalamus.

The following is a list of some of the important hormones secreted by the hypothalamus into the hypophyseal portal system:

- Growth hormone-releasing hormone (GRH)
- Growth hormone-inhibiting hormone (GIH) (also called somatostatin)
- Corticotropin-releasing hormone (CRH)
- Thyrotropin-releasing hormone (TRH)
- Gonadotropin-releasing hormone (GnRH)
- Prolactin-releasing hormone (PRH)
- Prolactin-inhibiting hormone (PIH)

Table 16-3 lists the functions of each releasing hormone. Before consulting the table, try to deduce their functions from their names.

Through negative feedback mechanisms, the hypothalamus adjusts the secretions of the adenohypophysis, and the adenohypophysis adjusts the secretions of its target glands, which in turn adjust the activity of their target tissues. For example, Figure 16-16 shows the negative feedback control of the secretion of TSH and thyroid hormone (T₃ and T₄).

Before leaving the subject of control of pituitary secretion, we want to call attention to another concept about the hypothalamus. It functions as an important part of the body’s complex machinery for responding to stress situations. For example, in severe pain or intense emotions, the cerebral cortex—especially the limbic area—sends impulses to the hypothalamus. The impulses stimulate the hypothalamus to secrete its releasing hormones into the hypophyseal portal veins. Circulating quickly to the adenohypophysis, they stimulate it to secrete more of its hormones. These, in

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Source</th>
<th>Target</th>
<th>Principal Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone-releasing hormone (GRH)</td>
<td>Hypothalamus</td>
<td>Adenohypophysis (somatotrophs)</td>
<td>Stimulates secretion (release) of growth hormone</td>
</tr>
<tr>
<td>Growth hormone-inhibiting hormone (GIH), or somatostatin</td>
<td>Hypothalamus</td>
<td>Adenohypophysis (somatotrophs)</td>
<td>Inhibits secretion of growth hormone</td>
</tr>
<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
<td>Hypothalamus</td>
<td>Adenohypophysis (corticotrophs)</td>
<td>Stimulates release of adrenocorticotropic hormone (ACTH)</td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone (TRH)</td>
<td>Hypothalamus</td>
<td>Adenohypophysis (thyrotrophs)</td>
<td>Stimulates release of thyroid-stimulating hormone (TSH)</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone (GnRH)</td>
<td>Hypothalamus</td>
<td>Adenohypophysis (gonadotrophs)</td>
<td>Stimulates release of gonadotropins (FSH and LH)</td>
</tr>
<tr>
<td>Prolactin-releasing hormone (PRH)</td>
<td>Hypothalamus</td>
<td>Adenohypophysis (corticotrophs)</td>
<td>Stimulates secretion of prolactin</td>
</tr>
<tr>
<td>Prolactin-inhibiting hormone (PIH)</td>
<td>Hypothalamus</td>
<td>Adenohypophysis (corticotrophs)</td>
<td>Inhibits secretion of prolactin</td>
</tr>
</tbody>
</table>

Table 16-3  Hormones of the Hypothalamus

Figure 16-16  Negative feedback control by the hypothalamus.

In this example, the secretion of thyroid hormone (T₁ and T₄) is regulated by a number of negative feedback loops. A long negative feedback loop (thin line) allows the CNS to influence hypothalamic secretion of thyrotropin-releasing hormone (TRH) by nervous feedback from the targets of T₁/T₄ (and from other nerve inputs). The secretion of TRH by the hypothalamus and thyroid-stimulating hormone (TSH) by the adenohypophysis is also influenced by shorter feedback loops (thicker lines), allowing great precision in the control of this system.
thus, stimulate increased activity by the pituitary’s target structures. In essence, what the hypothalamus does through its releasing hormones is to translate nerve impulses into hormone secretion by endocrine glands. Thus the hypothalamus links the nervous system to the endocrine system. It integrates the activities of these two great integrating systems—particularly, it seems, in times of stress. When survival is threatened, the hypothalamus can take over the adenohypophysis and thus gain control of literally every cell in the body.

The mind-body link provided by the hypothalamus has tremendous implications. It means that the cerebrum can do more than just receive sensory impulses and send out impulses to muscles and glands. It means that our thoughts and emotions—our minds—can, by way of the hypothalamus, influence the functions of all of our billions of cells. In short, the brain has two-way contact with every tissue of the body.

Thus the state of the body can influence mental processes, and the state of the mind can affect the functioning of the body. Therefore both psychosomatic (mind influencing the body) and somatopsychic (body influencing the mind) relationships exist between human body systems and the brain.

**Neurohypophysis (Posterior Pituitary)**

The neurohypophysis serves as a storage and release site for two hormones: antidiuretic hormone (ADH) and oxytocin (OT). The cells of the neurohypophysis do not themselves make these hormones. Instead, neurons whose bodies are in either the supraoptic or the paraventricular nuclei of the hypothalamus synthesize them (Figure 16-17).

From the cell bodies of these neurons in the hypothalamus, the hormones pass down along axons (in the hypothalamo-hypophysial tract) into the neurohypophysis. Instead of the chemical-releasing factors that triggered secretion of hormones from the adenohypophysis, release of ADH and OT into the blood is controlled by nervous stimulation.

**Antidiuretic Hormone**

The term antidiuresis literally means “opposing the production of a large urine volume.” And this is exactly what ADH
does—it prevents the formation of a large volume of urine. In preventing large losses of fluid through the excretion of dilute urine, ADH helps the body conserve water. In other words, ADH maintains water balance in the body. When the body dehydrates, the increased osmotic pressure of the blood is detected by special osmoreceptors near the supraoptic nucleus. This triggers the release of ADH from the neurohypophysis. ADH causes water to be reabsorbed from the tubules of the kidney and returned to the blood (see Chapter 28). This increases the water content of the blood, restoring the osmotic pressure to its normal lower level.

**Oxytocin**

Oxytocin has two actions: it stimulates contraction of uterine muscles and it causes milk ejection from the breasts of lactating women. Under the influence of OT, milk-producing alveolar cells release their secretion into the ducts of the breast. This is very important because milk cannot be removed by sucking unless it has first been ejected into the ducts. Throughout nursing, the mechanical and psychological stimulation of the baby’s suckling action trigger the release of more OT. In other words, OT secretion is regulated by a positive feedback mechanism: the baby suckles, which increases OT levels, which provides more milk, so the baby continues to suckle, which increases OT levels, and so on. OT, together with prolactin, ensures successful nursing. Prolactin prepares the breast for milk production and stimulates cells to produce milk. The milk is not released, however, until OT permits it to do so.

It is OT’s other action—its stimulation of uterine contractions—that gives it its name: oxytocin (literally “swift childbirth”). OT stimulates the uterus to strengthen the strong, muscular labor contractions that occur during childbirth. OT secretion is regulated here again by means of a positive feedback mechanism. After they have begun, uterine contractions push on receptors in the pelvis, which triggers the release of more OT, which again pushes on the pelvic receptors, and so on. The wavelike contractions continue to some degree after childbirth, which helps the uterus expel the placenta and then return to its unstretched shape. Commercial preparations of OT have been given to stimulate contractions after childbirth to lessen the danger of uterine hemorrhage. Important characteristics of the hormones secreted by the pituitary—both the adenohypophysis and the neurohypophysis—are summarized in Table 16-4.

### Box 16-6 HEALTH MATTERS

**Antidiuretic Hormone (ADH) Abnormalities**

Hyposecretion of ADH can lead to diabetes insipidus, a condition in which the patient produces abnormally large amounts of urine. ADH, administered under the name vasopressin (Pitressin), can alleviate this symptom. Studies have shown that ADH may be involved in learning and memory, so investigators are looking into the possibility of administering ADH to reverse the memory loss associated with senility.

### Table 16-4 Hormones of the Pituitary Gland (Hypophysis)

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Source</th>
<th>Target</th>
<th>Principal Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone (GH)</td>
<td>Adenohypophysis</td>
<td>General</td>
<td>Promotes growth by stimulating protein anabolism and fat mobilization</td>
</tr>
<tr>
<td>(somatotropin [STH])</td>
<td>(somatotrophs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin (PRL)</td>
<td>Adenohypophysis</td>
<td>Mammary glands (alveolar secretory cells)</td>
<td>Promotes milk secretion</td>
</tr>
<tr>
<td>(lactogenic hormone)</td>
<td>(lactotrophs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH)*</td>
<td>Adenohypophysis (thyrotrophs)</td>
<td>Thyroid gland</td>
<td>Stimulates development and secretion in the thyroid gland</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone (ACTH)*</td>
<td>Adenohypophysis (corticotrophs)</td>
<td>Adrenal cortex</td>
<td>Promotes development and secretion in the adrenal cortex</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)*</td>
<td>Adenohypophysis (gonadotrophs)</td>
<td>Gonads (primary sex organs)</td>
<td>Female: promotes development of ovarian follicle; stimulates estrogen secretion</td>
</tr>
<tr>
<td>Luteinizing hormone (LH)*</td>
<td>Adenohypophysis (gonadotrophs)</td>
<td>Gonads</td>
<td>Male: promotes development of testis; stimulates sperm production</td>
</tr>
<tr>
<td>Antidiuretic hormone (ADH)</td>
<td>Neurohypophysis</td>
<td>Kidney</td>
<td>Female: triggers ovulation; promotes development of corpus luteum</td>
</tr>
<tr>
<td>Oxytocin (OT)</td>
<td>Neurohypophysis</td>
<td>Uterus and mammary glands</td>
<td>Male: stimulates production of testosterone</td>
</tr>
</tbody>
</table>

*Tropic hormones.
**PINEAL GLAND**

The pineal gland, or pineal body, is a tiny (1 cm [or about \( \frac{3}{8} \) in]) pine cone–shaped structure located on the dorsal aspect of the brain's diencephalon region (see Figure 16-12). It is a member of two systems because it acts as a part of the nervous system (it receives visual nerve stimuli) and as a part of the endocrine system (it secretes a hormone).

Although full understanding of the pineal gland is a long way off, we do know that it functions to support the body's biological clock. It is the biological clock that regulates our patterns of eating (hunger), sleeping, reproduction (female reproductive cycle), and behavior. One hypothesis states that visual signals received by the pineal allow it to determine day length and lunar cycles (changing phases of the moon). Day-length information helps to keep daily and seasonal cycles “on time,” whereas lunar-cycle information helps keep the menstrual cycle “on time.” Melatonin, the principal pineal secretion, is thought to induce sleep.

Melatonin, whose secretion is inhibited by the presence of sunlight, may also affect a person's mood. A mental disorder, called seasonal affective disorder (SAD), in which a patient suffers severe depression only in winter (when day length is shorter), has been linked to the pineal gland. Patients suffering from this “winter depression” are often advised to expose themselves to special high-intensity lights for several hours each evening during the winter months. Apparently, light stimulates the pineal gland for a longer period, which reduces the blood levels of mood-altering melatonin. The symptoms of depression are thus reduced or eliminated.

**THYROID GLAND**

**STRUCTURE OF THE THYROID GLAND**

Two large lateral lobes and a narrow connecting isthmus make up the thyroid gland (Figure 16-18). There is often a thin wormlike piece of thyroid tissue, called the pyramidal lobe, extending upward from the isthmus. The weight of the gland in the adult is variable, but it's around 30 g (1 oz). The thyroid is located in the neck, on the anterior and lateral surfaces of the trachea, just below the larynx.

Thyroid tissue is composed of tiny structural units called follicles, the site of thyroid hormone synthesis. Each follicle is a small hollow sphere with a wall of simple cuboidal glandular epithelium (Figure 16-19). The interior is filled with a thick fluid called thyroid colloid. The colloid is produced by the cuboidal cells of the follicle wall (follicular cells) and contains protein-iodine complexes known as thyroglobulins—the precursors of thyroid hormones.

**THYROID HORMONE**

The substance that is often called thyroid hormone (TH) is actually two different hormones. The most abundant TH is...
tetraiodothyronine (T₄), or thyroxine. The other is called triiodothyronine (T₃). One molecule of T₄ contains four iodine atoms, and one molecule of T₃ contains three iodine atoms. After synthesizing a preliminary form of its hormones, the thyroid gland stores considerable amounts of them before secreting them. This is unusual because none of the other endocrine glands stores its hormones in another form for later release. T₃ and T₄ form in the colloid of the follicles on globulin molecules, forming thyroglobulin complexes. When they are to be released, T₃ and T₄ detach from the globulin and enter the blood. Once in the bloodstream, however, they attach to plasma proteins, principally a globulin called thyroxine-binding globulin (TBG) and albumin, and circulate as a hormone-globulin complex. When they near their target cells, T₃ and T₄ detach from the plasma globulin.

Although the thyroid gland releases about 20 times more T₄ than T₃, T₃ is much more potent than T₄ and is considered by physiologists to be the principal thyroid hormone. Why is this? T₃ binds more strongly to plasma globulins than T₄, so T₄ is not removed from the blood by target cells as quickly as T₃. The small amount of T₄ that enters target tissues is usually converted to T₃. Add this to the fact that experiments have shown that T₃ binds more efficiently than T₄ to nuclear receptors in target cells and the evidence is overwhelming that T₃ is the principal thyroid hormone. Although T₄ may influence target cells to some extent, its major importance is as a precursor to T₃. Such hormone precursors are often called prohormones.

Thyroid hormone helps regulate the metabolic rate of all cells, as well as the processes of cell growth and tissue differentiation. Because thyroid hormone can potentially interact with any cell in the body, it is said to have a “general” target.

**CALCITONIN**

Besides thyroid hormone (T₃ and T₄), the thyroid gland also produces a hormone called calcitonin (CT). You might wonder why some hormones of the thyroid qualify for the name “thyroid hormone,” whereas calcitonin does not. The answer lies in the simple fact that for many years, we had no idea that a hormone other than thyroid hormone was produced by the thyroid gland. By the time calcitonin was discovered, and later shown to be made in the thyroid gland, the term thyroid hormone was too well established to change it easily.

Produced by parafollicular cells (cells between the thyroid follicles), or simply c cells, calcitonin influences the processing of calcium by bone cells. Calcitonin apparently controls calcium content of the blood by increasing bone formation by osteoblasts and inhibiting bone breakdown by osteoclasts. This means more calcium is removed from the blood by the osteoblasts, and less calcium is released into the blood by osteoclasts. Calcitonin, then, tends to decrease blood calcium levels and promote conservation of hard bone matrix. Parathyroid hormone, discussed later, is an antagonist to calcitonin, because it has the opposite effects. Together, calcitonin and parathyroid hormone help maintain calcium homeostasis (see Figure 16-21).

Hormones of the thyroid gland are summarized in Table 16-5.

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**Figure 16-19** Thyroid gland tissue. Note that each of the follicles is filled with colloid. (x 140.)

**Table 16-5** Hormones of the Thyroid and Parathyroid Glands

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Source</th>
<th>Target</th>
<th>Principal Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triiodothyronine (T₃)</td>
<td>Thyroid gland (follicular cells)</td>
<td>General</td>
<td>Increases rate of metabolism</td>
</tr>
<tr>
<td>Tetraiodothyronine (T₄), or thyroxine</td>
<td>Thyroid gland (follicular cells)</td>
<td>General</td>
<td>Increases rate of metabolism (usually converted to T₃ first)</td>
</tr>
<tr>
<td>Calcitonin (CT)</td>
<td>Thyroid gland (parafollicular cells)</td>
<td>Bone tissue</td>
<td>Increases calcium storage in bone, lowering blood Ca²⁺ levels</td>
</tr>
<tr>
<td>Parathyroid hormone (PTH) or parathormone</td>
<td>Parathyroid glands</td>
<td>Bone tissue and kidney</td>
<td>Increases calcium removal from storage in bone and produces the active form of vitamin D in the kidneys, increasing absorption of calcium by intestines and increasing blood Ca²⁺ levels</td>
</tr>
</tbody>
</table>
HYPERSECRETION of thyroid hormone occurs in Graves disease, which is thought to be an autoimmune condition. Graves disease patients may suffer from unexplained weight loss, nervousness, increased heart rate, and exophthalmos (protrusion of the eyeballs resulting, in part, to edema of tissue at the back of the eye socket; see part A of the figure).

HYPOSECRETION of thyroid hormone during growth years may lead to cretinism. Cretinism is a condition characterized by a low metabolic rate, retarded growth and sexual development, and, possibly, mental retardation. People with profound manifestations of this condition are said to have deformed dwarfism (as opposed to the proportional dwarfism caused by hyposecretion of growth hormone). Hyposcretion later in life produces a condition characterized by decreased metabolic rate, loss of mental and physical vigor, gain in weight, loss of hair, yellow dullness of the skin, and myxedema. Myxedema is a swelling (edema) and firmness of the skin caused by accumulation of mucopolysaccharides in the skin.

In a condition called simple goiter, the thyroid enlarges when there is a lack of iodine in the diet (part B of the figure). This condition is an interesting example of how the feedback control mechanisms illustrated in Figure 16-16 operate. Because iodine is required for the synthesis of T3 and T4, lack of iodine in the diet results in a drop in the production of these hormones. When the reserve (in thyroid colloid) is exhausted, feedback informs the hypothalamus and adenohypophysis of the deficiency. In response, the secretion of thyrotropin-releasing hormone (TRH) and thyroid-stimulating hormone (TSH) increases in an attempt to stimulate the thyroid to produce more thyroid hormone. Because there is no iodine available to do this, the only effect is to increase the size of the thyroid gland. This information feeds back to the hypothalamus and adenohypophysis, and both increase their secretions in response. Thus the thyroid gets larger and larger and larger—all in a futile attempt to increase thyroid hormone secretion to normal levels. This condition is still common in areas of the world where the soil and water contain little or no iodine. The use of iodized salt has dramatically reduced the incidence of simple goiter in the United States.
PARATHYROID GLANDS

STRUCTURE OF THE PARATHYROID GLANDS

There are usually four or five parathyroid glands embedded in the posterior surface of the thyroid’s lateral lobes (see Figure 16-18). They appear as tiny rounded bodies within thyroid tissue formed by compact, irregular rows of cells (Figure 16-20).

PARATHYROID HORMONE

The parathyroid glands secrete parathyroid hormone (PTH), or parathormone (see Table 16-5). PTH is an antagonist to calcitonin and so helps maintain calcium homeostasis. PTH acts on bone and kidney cells by increasing the release of calcium into the blood. The bone cells are especially affected, causing less new bone to be formed and more old bone to be dissolved, yielding calcium and phosphate. These minerals are then free to move into the blood, elevating blood levels of calcium and phosphate. In the kidney, however, only calcium is reabsorbed from urine into the blood. Under the influence of PTH, phosphate is secreted by kidney cells out of the blood and into the urine to be excreted. PTH also increases the body’s absorption of calcium from food by activating vitamin D (cholecalciferol) in the kidney, which then permits Ca$^{++}$ to be transported through intestinal cells and into the blood.

The maintenance of calcium homeostasis, achieved through the interaction of PTH and calcitonin, is very important for healthy survival (Figure 16-21). Normal neuromuscular excitability, blood clotting, cell membrane permeability, and normal functioning of certain enzymes, all depend on the maintenance of normal levels of calcium in the blood. For example, hyposcretion of PTH can lead to hypocalcemia. Hypocalcemia increases neuromuscular irritability—sometimes so much that it produces muscle spasms and convulsions. Conversely, high blood calcium levels decrease the irritability of muscle and nerve tissue so that constipation, lethargy, and even coma can result.

1. Where is the thyroid located? What does it look like?
2. Thyroid hormone is really two distinct compounds—what are they? Which of the two is considered more physiologically active?
3. How do calcitonin and parathyroid hormone act together to regulate homeostasis of blood calcium concentration?
**ADRENAL GLANDS**

**STRUCTURE OF THE ADRENAL GLANDS**

The *adrenal,* or *suprarenal,* glands are located atop the kidneys, fitting like a cap over these organs (see Figure 16-22). The outer portion of the gland is called the *adrenal cortex,* and the inner portion of the gland is called the *adrenal medulla.* Even though the adrenal cortex and adrenal medulla are part of the same organ, they have different embryological origins and are structurally and functionally so different that they are often spoken of as if they were separate glands. The adrenal cortex is composed of regular endocrine tissue, but the adrenal medulla is made of neurosecretory tissue. As you might guess, each of these tissues synthesizes and secretes a different set of hormones (Table 16-6).

**ADRENAL CORTEX**

The adrenal cortex is composed of three distinct layers, or zones, of secreting cells (see Figure 16-22). Starting with the

### Table 16-6  Hormones of the Adrenal Glands

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Source</th>
<th>Target</th>
<th>Principal Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldosterone</td>
<td>Adrenal cortex (zona glomerulosa)</td>
<td>Kidney</td>
<td>Stimulates kidney tubules to conserve sodium, which, in turn, triggers the release of ADH and the resulting conservation of water by the kidney</td>
</tr>
<tr>
<td>Cortisol (hydrocortisone)</td>
<td>Adrenal cortex (zona fasciculata)</td>
<td>General</td>
<td>Influences metabolism of food molecules; in large amounts, it has an antiinflammatory effect</td>
</tr>
<tr>
<td>Adrenal androgens</td>
<td>Adrenal cortex (zona reticularis)</td>
<td>Sex organs, other effectors</td>
<td>Exact role uncertain, but may support sexual function</td>
</tr>
<tr>
<td>Adrenal estrogens</td>
<td>Adrenal cortex (zona reticularis)</td>
<td>Sex organs</td>
<td>Thought to be physiologically insignificant</td>
</tr>
<tr>
<td>Epinephrine (adrenaline)</td>
<td>Adrenal medulla</td>
<td>Sympathetic effectors</td>
<td>Enhances and prolongs the effects of the sympathetic division of the autonomic nervous system</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Adrenal medulla</td>
<td>Sympathetic effectors</td>
<td>Enhances and prolongs the effects of the sympathetic division of the autonomic nervous system</td>
</tr>
</tbody>
</table>
zone directly under the outer connective tissue capsule of the gland, they are *zona glomerulosa*, *zona fasciculata*, and *zona reticularis*. Cells of the outer zone secrete a class of hormones called *mineralocorticoids*. Cells of the middle zone secrete *glucocorticoids*. The inner zone secretes small amounts of *glucocorticoids* and *gonadocorticoids* (sex hormones). All of these cortical hormones are steroids, so, together, they are known as corticosteroids.

**Mineralocorticoids**

Mineralocorticoids, as their name suggests, have an important role in regulating how mineral salts (electrolytes) are processed in the body. In the human, *aldosterone* is the only physiologically important mineralocorticoid. Its primary function is in the maintenance of sodium homeostasis in the blood. Aldosterone accomplishes this by increasing sodium reabsorption in the kidneys. Sodium ions are reabsorbed from the urine back into the blood in exchange for potassium or hydrogen ions. In this way, aldosterone not only adjusts blood sodium levels but can also influence potassium and pH levels in the blood.

Because the reabsorption of sodium ions causes water to also be reabsorbed (partly by triggering the secretion of ADH), aldosterone promotes water retention by the body. Altogether, aldosterone can increase sodium and water retention and promote the loss of potassium and hydrogen ions.

Aldosterone secretion is controlled mainly by the *renin-angiotensin mechanism* and by blood potassium concentration. The renin-angiotensin mechanism (Figure 16-23) operates as indicated in this sequence of steps:

1. When the incoming blood pressure in the kidneys drops below a certain level, a piece of tissue near the vessels (the *juxtaglomerular apparatus*) secretes *renin* into the blood.
2. Renin, an enzyme, causes *angiotensinogen* (a normal constituent of blood) to be converted to *angiotensin I*.
3. Angiotensin I circulates to the lungs, where converting enzymes in the capillaries split the molecule, forming *angiotensin II*.
4. Angiotensin II circulates to the adrenal cortex, where it stimulates the secretion of aldosterone.
5. Aldosterone causes increased reabsorption of sodium, which causes increased water retention. As water is retained, the volume of blood increases. The increased volume of blood creates higher blood pressure—which then causes the renin-angiotensin mechanism to stop.

*Figure 16-22* Structure of the adrenal gland. The zona glomerulosa of the cortex secretes aldosterone. The zona fasciculata secretes abundant amounts of glucocorticoids, chiefly cortisol. The zona reticularis secretes minute amounts of sex hormones and glucocorticoids. A portion of the medulla is visible at lower right in the photomicrograph (x 35) and at the bottom of the drawing.
The renin-angiotensin mechanism is a negative feedback mechanism that helps maintain homeostasis of blood pressure.

Glucocorticoids

The chief glucocorticoids secreted by the zona fasciculata of the adrenal cortex are cortisol (also called hydrocortisone), cortisone, and corticosterone. Of these, only cortisol is secreted in significant quantities in the human. Glucocorticoids affect every cell in the body. Although much remains to be discovered about their precise mechanisms of action, we do know enough to make some generalizations:

- Glucocorticoids accelerate the breakdown of proteins into amino acids (except in liver cells). These “mobilized” amino acids move out of the tissue cells and into the blood. From there, they circulate to the liver cells, where they are changed to glucose in a process called gluconeogenesis. A prolonged high blood concentration of glucocorticoids in the blood, therefore, results in a net loss of tissue proteins ("tissue wasting") and hyperglycemia (high blood glucose). Glucocorticoids are protein-mobilizing, gluconeogenic, and hyperglycemic.
- Glucocorticoids tend to accelerate mobilization of both lipids from adipose cells and lipid catabolism by nearly every cell in the body. In other words, glucocorticoids tend to cause a shift from carbohydrate catabolism to lipid catabolism as an energy source. The mobilized lipids may also be used in the liver for gluconeogenesis. This effect contributes to the hyperglycemic effect already observed.
- Glucocorticoids are essential for maintaining a normal blood pressure. Without adequate amounts
of glucocorticoids in the blood, the hormones norepinephrine and epinephrine cannot produce their vasoconstricting effect on blood vessels, and blood pressure falls. In other words, glucocorticoids exhibit permissiveness in that they permit norepinephrine and epinephrine to have their full effects. When glucocorticoids are present in high concentrations for a prolonged period of time, they may elevate blood pressure beyond normal (hypertension).

- A high blood concentration of glucocorticoids rather quickly causes a marked decrease in the number of white blood cells, called eosinophils, in the blood (eosinopenia) and marked atrophy of lymphatic tissues. The thymus gland and lymph nodes are particularly affected. This, in turn, leads to a decrease in the number of lymphocytes and plasma cells in the blood. Because of the decreased number of lymphocytes and plasma cells (antibody-processing cells), antibody formation decreases. Antibody formation is an important part of immunity—the body’s defense against infection.

- Normal amounts of glucocorticoids act with epinephrine, a hormone secreted by the adrenal medulla, to bring about normal recovery from injury produced by inflammatory agents. How they act together to bring about this antiinflammatory effect is still uncertain.

- Glucocorticoid secretion increases as part of the stress response. One advantage gained by increased secretion may be the increase in glucose available for skeletal muscles needed in fight-or-flight responses. However, prolonged stress can lead to immune dys-

function, probably as a result of prolonged exposure to high levels of glucocorticoids (see Chapter 22).

- Except during the stress response, glucocorticoid secretion is controlled mainly by means of a negative feedback mechanism that involves ACTH from the adenohypophysis.

**Gonadocorticoids**

The term gonadocorticoid refers to sex hormones that are released from the zona fasciculata and zona reticularis of the adrenal cortex rather than the gonads. The normal adrenal cortex secretes small amounts of male hormones (androgens). Normally, there is not enough androgen produced to give women masculine characteristics, but it is sufficient to influence the appearance of pubic and axillary hair in both boys and girls.

**ADRENAL MEDULLA**

The adrenal medulla is composed of neurosecretory tissue; that is, tissue composed of neurons specialized to secrete their products into the blood rather than across a synapse. Actually, the medullary cells are modified versions of sympathetic postganglionic fibers of the autonomic nervous system. They are innervated by sympathetic preganglionic fibers, so that when the sympathetic nervous system is activated (as in the stress response), the medullary cells secrete their hormones directly into the blood.

The adrenal medulla secretes two important hormones, both of which are in the class of nonsteroid hormones called catecholamines. **Epinephrine**, or **adrenaline**, accounts for about 80% of the medulla’s secretion. The other 20% is **norepinephrine** (NE or NR). You may recall that norepinephrine
is also the neurotransmitter produced by postganglionic sympathetic fibers. Sympathetic effectors such as the heart, smooth muscle, and glands have receptors for norepinephrine. Both epinephrine and norepinephrine produced by the adrenal medulla can bind to the receptors of sympathetic effectors to prolong and enhance the effects of sympathetic stimulation by the autonomic nervous system (Figure 16-24).

**PANCREATIC ISLETS**

**STRUCTURE OF THE PANCREATIC ISLETS**

The pancreas is an elongated gland (12 to 15 cm [or about 5 to 6 inches] long) weighing up to 100 g (3.5 ounces) (Figure 16-25). The “head” of the gland lies in the C-shaped beginning of the small intestine (duodenum), with its body extending horizontally behind the stomach and its tail touching the spleen.

The tissue of the pancreas is composed of both endocrine and exocrine tissues. The endocrine portion is made up of scattered, tiny islands of cells, called pancreatic islets (islets of Langerhans) that account for only about 2% or 3% of the total mass of the pancreas. These hormone-producing islets are surrounded by cells called acini, which secrete a serous fluid containing digestive enzymes into ducts that drain into the small intestine (see Figure 16-25). The digestive roles of the pancreas are discussed in Chapters 25 and 26. For the moment, we will concentrate on the endocrine part of this gland, the pancreatic islets.

Each of the one to two million pancreatic islets in the pancreas contains a combination of four primary types of endocrine cells, all joined to each other by gap junctions. Each type of cell secretes a different hormone, but the gap junctions may allow for some coordination of these functions as a single secretory unit. One type of pancreatic islet cell is the alpha cell (also called the A cell), which secretes the hormone glucagon. Beta cells (B cells) secrete the hormone insulin; delta cells (D cells) secrete the hormone somatostatin; and pancreatic polypeptide cells (F, or PP, cells) secrete pancreatic polypeptide. Beta cells, which account for about three-fourths of all the pancreatic islet cells, are usually found near the center of each islet, whereas cells of the other three types are more often found in the outer portion. Figure 16-26 shows how the different cell types can be distinguished by the microscope with special staining techniques.

**PANCREATIC HORMONES**

The pancreatic islets produce several hormones, the most important of which are described in Table 16-7 and in the following paragraphs:
**Figure 16-25** Pancreas. Two pancreatic islets, or hormone-producing areas, are evident among the pancreatic cells that produce the pancreatic digestive juice. The pancreatic islets are more abundant in the tail of the pancreas than in the body or head.

**Figure 16-26** Cells of the pancreatic islet. A special technique of microscopy, called immunofluorescent staining, allows cells to be distinguished by the different molecules that they contain. A, Micrograph shows a central cluster of beta, or $b$, cells outlined by green dots. The green dots are insulin molecules stained by a special type of antibody coupled to a fluorescent dye. B, In this micrograph, peripheral alpha, or $a$, cells are stained green and delta, or $d$, cells are stained red. The central beta cells are not stained in this specimen, so they appear only as black spaces in the micrograph.
• **Glucagon**, produced by alpha cells, tends to increase blood glucose levels by stimulating the conversion of glycogen to glucose in liver cells. It also stimulates gluconeogenesis (transformation of fatty acids and amino acids into glucose) in liver cells. The glucose produced via the breakdown of glycogen and by gluconeogenesis is released into the bloodstream, producing a hyperglycemic effect.

• **Insulin**, produced by beta cells, tends to promote the movement of glucose, amino acids, and fatty acids out of the blood and into tissue cells. Hence insulin tends to lower the blood concentrations of these food molecules and to promote their metabolism by tissue cells. The antagonistic effects that glucagon and insulin have on blood glucose levels are summarized in Figure 16-27 and discussed further in Chapter 27. (See Box 16-12 for a discussion of diabetes mellitus.)

• **Somatostatin**, produced by delta cells, may affect many different tissues in the body, but its primary role seems to be in regulating the other endocrine cells of the pancreatic islets. Somatostatin inhibits the secretion of glucagon, insulin, and pancreatic polypeptide. It also inhibits the secretion of growth hormone (somatotropin) from the anterior pituitary.

• **Pancreatic polypeptide** is produced by PP (or F) cells in the periphery of pancreatic islets. Although much is yet to be learned about pancreatic polypeptide, we do know that it influences the digestion and distribution of food molecules to some degree.

All four of these pancreatic hormones probably work together as a team to maintain a homeostasis of food molecules (glucose, fatty acids, and amino acids). More about their respective roles in overall nutrient metabolism is discussed in Chapter 27.

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**Figure 16-27 Regulation of blood glucose levels.** Insulin and glucagon, two of the major pancreatic hormones, have antagonistic (opposite) effects on glucose concentration in the blood.

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1. Name two of the four principal hormones secreted by the pancreatic islets.

2. In what way do insulin and glucagon exert antagonistic influences on the concentration of glucose in the blood?
GONADS

Gonads are the primary sex organs in the male (testes; singular, testis) and in the female (ovaries). Each is structured differently, and each produces its own unique set of hormones.

TESTES

The testes are paired organs within a sac of skin called the scrotum, which hangs from the groin area of the trunk (see Figure 16-2). Composed mainly of coils of sperm-producing seminiferous tubules, there is a scattering of endocrine interstitial cells found in areas between the tubules. These interstitial cells produce androgens (male sex hormones); the principal androgen is testosterone. Testosterone is responsible for the growth and maintenance of male sexual characteristics and for sperm production. Testosterone secretion is regulated principally by gonadotropin (especially luteinizing hormone [LH]) levels in the blood.

OVARIES

Ovaries are a set of paired glands in the pelvis (see Figure 16-2) that produce several types of sex hormones, including those described briefly in the following paragraphs:

- **Estrogens**, including estradiol and estrone, are steroid hormones secreted by the cells of the ovarian follicles that promote the development and maintenance of female sexual characteristics. With other hormones, they are responsible for breast development and the proper sequence of events in the female reproductive cycle (menstrual cycle). More details of its function are discussed in Chapter 32.

- **Progesterone** is a hormone whose name, which means “pregnancy-promoting steroid,” is an indicator of its chief function. Secreted by the corpus luteum (the tissue left behind after the rupture of a follicle during ovulation), progesterone (along with estrogen) maintains the lining of the uterus necessary for successful pregnancy (gestation). This hormone, along with others, is discussed in detail in Chapter 32.

Regulation of ovarian hormone secretion is complex, to say the least, but basically depends on the changing levels of follicle-stimulating hormone (FSH) and LH (gonadotropins) from the adenohypophysis.

PLACENTA

Another reproductive tissue that functions as an important endocrine gland is the placenta. The placenta, the tissue that forms on the lining of the uterus as an interface between the circulatory systems of the mother and developing child, serves as a temporary endocrine gland. The placenta produces human chorionic gonadotropin (hCG). This hormone is called “chorionic” because it is secreted by the chorion, a fetal tissue component of the placenta. It is called “gonadotropin” because, as with the gonadotropins of the adenohypophysis, it stimulates development and hormone secretion by maternal ovarian tissues. Chorionic gonadotropin secretion is high during the early part of preg-
nancy and serves as a signal to the mother’s gonads to maintain the uterine lining rather than allow it to degenerate and fall away (as in menstruation).

The discovery of hCG many years ago led to the development of early pregnancy tests. The high levels of hCG in the urine of women who are in the early part of their pregnancies can be detected through several means. The most familiar test involves the use of an over-the-counter kit, which tests for hCG in urine by means of an antigen-antibody reaction that can be easily interpreted.

As the placenta develops past the first trimester (3 months) of pregnancy, its production of hCG drops as its production of estrogens and progesterone increase. The placenta therefore more or less takes over the job of ovaries in producing these hormones necessary for a successful pregnancy. More about how this works is discussed in Chapter 33.

THYMUS
The thymus is a gland in the mediastinum, just beneath the sternum (see Figure 16-2). It is large in children until puberty, when it begins to atrophy. It continues to atrophy throughout adulthood, so that by the time an individual reaches old age, the gland is but a vestige of fat and fibrous tissue.

The anatomy of the thymus is described in Chapter 20.

Although it is considered to be primarily a lymphatic organ (see Chapter 20), the hormones thymosin and thymopoietin have been isolated from thymus tissue and are considered to be largely responsible for its endocrine activity. Thymosin and thymopoietin actually refer to two entire families of peptides that, together, have a critical role in the development of the immune system. Specifically, thymosin and thymopoietin are thought to stimulate the production of specialized lymphocytes involved in the immune response called \textit{T cells}. The role of T cells in the immune system is discussed in Chapter 21.

GASTRIC AND INTESTINAL MUCOSA
The mucous lining of the gastrointestinal (GI) tract, like the pancreas, contains cells that produce both endocrine and exocrine secretions. GI hormones such as gastrin, secretin, cholecystokinin-pancreozymin (CCK), and others, have important regulatory roles in coordinating the secretory and motor activities involved in the digestive process. For example, secretin is released when acids make contact with the intestinal mucosa. Secretin carried by the blood triggers its target cells in the stomach to reduce acid secretion. Secretin also triggers its target cells in the pancreas to release an alkaline fluid and it acts with CCK to trigger the pancreas to release digestive enzymes. CCK triggers the gallbladder to release more bile, which helps break up fat droplets. In effect, secretin and CCK are signals from the intestine to other parts of the digestive system that promote an effective coordination of GI functions.

The hormone \textit{ghrelin} is secreted by endocrine cells in the gastric mucosa. It acts by stimulating the hypothalamus to boost appetite. Since it also acts on other body tissues to slow metabolism and reduce fat burning, it may play an important role in contributing to obesity.

Chapter 26 describes the hormonal control of digestion in the stomach and small intestine in more detail (see Table 26-5, p. 782).

HEART
The heart is another organ that has a secondary endocrine role. Although the heart’s main function is to pump blood, a specific area in its wall contains some hormone-producing cells. These cells produce a hormone called \textit{atrial natriuretic hormone} (ANH). The name of this hormone reveals much about its role in the body. The term \textit{atrial} refers to the fact that ANH is secreted by cells in an upper chamber of the heart called an atrium. Atrial cells increase their secretion of ANH in response to an increase in the stretch of the atrial wall caused by abnormally high blood volume or blood pressure. The term \textit{natriuretic} refers to the fact that its principal effect is to promote the loss of sodium (Latin, \textit{natrium}) from the body by means of the urine. When sodium is thus lost from the internal environment, water follows. Water loss results in a decrease in blood volume (and thus a decrease in blood pressure). We can then state that the primary effect of ANH is to oppose increases in blood volume or blood pressure. We can also state that ANH is an antagonist to ADH and aldosterone. ANH is also known by several other names, including \textit{atrial natriuretic factor (ANF), atrial natriuretic peptide}, and, simply, \textit{atrial peptide}. 

1. What are the major hormones secreted by reproductive tissues (gonads and the placenta)?
2. Which gland produces a hormone that regulates the development of cells important to the immune system?
3. Secretin was the first substance in the body to be identified as a hormone. What structure produces secretin?
Diabetes Mellitus

Diabetes mellitus is one of the most common endocrine disorders. It affects more than 14 million Americans and will have a significant impact on the health of about 7% of the population at some point in their lives. Diabetes is best described as a syndrome—a collection of features that characterizes the disease. Although the features of diabetes tend to vary between individuals and on the type, severity, and length of the illness, each sign or symptom is related in some way to abnormal metabolism of nutrients and the consequences that follow (see the figure on p. 517).

In diabetics, an inadequate amount or abnormal type of insulin may be produced. In other affected individuals, diminished numbers of normal insulin receptors or second messenger systems in target cells impair glucose entry into cells even if normal insulin in adequate amounts is present. A newly discovered hormone secreted by fat cells, called resistin, may also interfere with insulin action. Research on resistin may help explain the relationship between obesity and Type 2 diabetes (see discussion below). The possible causes of all of these insulin-related problems are still under investigation. Probably one or a combination of factors such as genetic predisposition, hormone problems, viral infection, nutrition and diet, obesity, autoimmune disorders, and exposure to damaging agents are involved in most cases of diabetes mellitus.

The term insulin resistance refers to an inability of fat, muscle, and other cells to respond normally to insulin and permit the entry of blood sugar that the hormone is trying to accomplish. Insulin insensitivity is the opposite of insulin resistance. It involves the rapid response of cells to insulin action and subsequent entry of sugar.

The presence of adequate amounts of normal insulin, and sufficient sensitivity to insulin, is key to the entry of glucose into cells. If there are no insulin problems and if the major target tissues such as skeletal muscle, fat, and liver have adequate, normal insulin receptors and signaling mechanisms, glucose will transfer from blood into cells. In diabetes, glucose cannot enter cells normally. The result is one of the most universal symptoms of the disease—chronic elevation in blood glucose levels, a condition called hyperglycemia. Glucose is normally filtered out of the blood and then resorbed from the kidney tubules. However, as blood sugar levels rise in diabetes, the amount of glucose filtered out of the blood exceeds the ability of the kidney tubules to resorb it. The result is a “spilling over” of sugar into the urine. This condition, called glycosuria, causes increased urine production (polyuria), since additional water is required to carry the sugar load. In effect, the excess glucose acts like an osmotic diuretic. As large quantities of water are lost in the urine, the body dehydrates. The resulting sense of excessive and ongoing thirst (polydipsia) and the tendency to drink large quantities of liquid are also classic symptoms of the disease. In addition, since cells are deprived of glucose to burn as energy, people with diabetes often suffer from intense and continuous hunger (polyphagia). Their blood sugar level is high, but the cells are literally starving to death, and the body craves food. In screening for diabetes, health care professionals look for glycosuria and the “three polys”: polyuria, polydipsia, and polyphagia.

The untreated person with diabetes is unable to utilize glucose for energy, and the body is forced to burn protein and fat. This abnormal metabolic shift results in fatigue and weight loss. If glucose metabolism is severely restricted, the large quantities of fat that must be burned produce toxic quantities of acetoacetic acid and other acidic metabolites called ketone bodies. Buildup of these organic acids lowers blood pH, causing acidosis, and disturbs the normal acid-base balance of the body. (Mechanisms that attempt to restore homeostasis are described in Chapter 30.) Accumulation of ketone bodies in the blood results in diabetic ketoacidosis. Signs and symptoms include abdominal pain, nausea, vomiting, fruity odor of the breath, possible alterations in level of consciousness, coma, and even death, if left untreated.

Types of Diabetes Mellitus

There are two major types of diabetes mellitus: type 1 and type 2. Hereditary factors play an important role in both types.

Type 1

Type 1 diabetes mellitus was formerly referred to as juvenile-onset diabetes because it usually strikes before age 30. In this form of the disease the beta cells of the pancreatic islets are destroyed and there is an absolute deficiency of insulin production. Individuals with type 1 diabetes are required to take insulin injections daily to prevent ketosis and to control hyperglycemia. As a result, type 1 diabetes was sometimes called insulin-dependent diabetes mellitus (IDDM). This form of the disease accounts for only about 10% of the total number of diabetic individuals.

The cause of beta cell destruction in type 1 diabetes is still uncertain. Current research, however, suggests that type 1 diabetes is an autoimmune disease that is probably triggered by some type of viral infection in genetically susceptible individuals. Anyone who has a parent, brother, or sister with type 1 diabetes has about a 5% to 7% chance of getting the disease. If an identical twin has type 1 diabetes, the risk increases to about 50%.

Type 2

Type 2 diabetes mellitus, previously called non–insulin-dependent diabetes mellitus (NIDDM), is the most common form of the disease, accounting for about 90% of all cases. Because it most often occurs after age 40 years, it was formerly also called maturity-onset diabetes. In susceptible individuals who are overweight, the incidence increases with age. In this form of diabetes, insulin is still produced by the beta cells but generally in reduced amounts. In addition, loss of insulin receptors on the surface membranes of target cells leading to insulin resistance also reduces effectiveness of glucose uptake from the blood.

Continued.
Diabetes Mellitus—cont’d

The older name NIDDM was inappropriate because insulin injections, often combined with oral diabetic medicines, may be required to control the disease. However, in many type 2 diabetics, hyperglycemia will frequently respond to changes in lifestyle that result in eating a balanced diet high in fiber, achieving an ideal body weight, getting adequate exercise, and maintaining body weight within normal limits.

Hereditary and ethnic background are important determinants in type 2 diabetes. Those who have a family history of the disease are particularly susceptible if overweight and sedentary. Native Americans are at increased risk for type 2 diabetes. In addition, Hispanics and African Americans are more likely than Caucasians to develop this type of diabetes. A specific gene defect is responsible for at least some forms of type 2 diabetes. The gene in question is involved in regulating insulin secretion.

The symptoms of type 1 diabetes are dramatic and, as a result, most individuals seek medical care soon after the disease occurs. The symptoms of type 2 diabetes, although of the same type as seen in type 1 diabetes, can be much more subtle and hard to recognize. The American Diabetes Association estimates that more than 7 million Americans have diabetes and are unaware of it. Unfortunately, if left untreated, over time the hyperglycemia and other effects of diabetes results in many complications affecting almost every area of the body. Reduced blood flow caused by a buildup of fatty materials in blood vessels (atherosclerosis) is one of the most serious complications. It causes such diverse problems as heart attack, stroke, and reduced circulation to the extremities, resulting in tingling or numbness in the feet and, in severe cases, gangrene. Retinal changes (diabetic retinopathy) may cause blindness in some people with diabetes who have battled the disease for decades. As you read in Chapter 12, nerve damage or neuropathy can also result from diabetes. Kidney disease is another common diabetic complication. Most authorities agree that careful regulation of blood sugar levels and reducing cardiovascular risk factors such as hypertension and “bad” (LDL) cholesterol levels are the most important measure that people with diabetes can take to reduce the number of long-term complications of the disease.

Treatment of Type 1 Diabetes

The discovery of insulin in 1921 was one of the most important advances in medicine of the last century. Problems associated with the injection of insulin harvested from animal pancreatic tissue were solved when synthetic human insulin became available.

Insulin can be introduced into the body by regular injection using a needle and syringe or by implanting miniaturized pumps to deliver the insulin as needed. Oral (non-injectable) insulin in pill form that can withstand the destructive action of digestive enzymes may become a reality in the not-too-distant future. In addition, development of alternate ways to administer new types of insulin also show promise. Special inhalers are being tested to deliver a powder form of insulin into the lungs. A liquid aerosol form of insulin is also under study. It is sprayed into the mouth and absorbed through the epithelial lining of the oral cavity.

Pancreas transplants eliminate the need for insulin injection or administration altogether and the number of successful pancreatic transplants is increasing with the advent of new surgical techniques and more effective anti-rejection drugs (see Chapter 21). However, transplantation of islet cells rather than the entire pancreas shows even greater promise for treatment of the most serious cases of type 1 diabetes.

One of the newest and most promising of the experimental islet cell transplant techniques is called the “Edmonton Protocol.” It was developed at the University of Alberta in Edmonton, Canada. The procedure begins with the separation and harvesting of islets from a donor pancreas; the islets are then injected into a diabetic patient’s portal vein that goes to the liver. After injection, the islets pass into the liver, become lodged there, and produce insulin. The protocol differs from other islet cell transplant procedures by increasing the number of functional islet cells that can be recovered from a donor pancreas and by elimination of steroids and other substances that decrease rejection rates. The procedure, while still experimental, shows great promise in treating severe type 1 diabetics.

Treatment of Type 2 Diabetes

If the lifestyle changes described earlier in this discussion are not totally effective in lowering elevated blood glucose levels in individuals with type 2 diabetes, medicines called oral hypoglycemic agents may be prescribed. One group of oral hypoglycemic agents, called sulfonylureas, act by stimulating beta cells to increase insulin supplies (for example, Micronase and Glucotrol). Other short-acting “insulin stimulators” act like sulfonylureas but much more rapidly (for example, Prandin and Starlix). Another group of oral agents, called biguanides, act by inhibiting the release of glucose from the liver (for example, Glucophage). Others, such as the drugs Avandia and Actos (thiazolidinediones or TZDs) reduce blood levels of resistin, thus decreasing insulin resistance. Newer oral treatments for type 2 diabetes often involve administration of lower doses of more than one drug. A popular combination called Glucovance combines metformin (Glucophage) and the sulfonylurea glyburide (Micronase). In addition, oral agents are also given in combination with insulin injections in many patients with type 2 diabetes.
**Box 16-12**

**Diabetes Mellitus—cont’d**

Diabetes mellitus. Each of the many diverse signs and symptoms often associated with this disorder (highlighted in yellow) ultimately can be traced to insulin-deficiency problems.
Endocrine regulation of body processes first begins during early development in the womb. By the time a baby is born, many of the hormones are already at work influencing the activity of target cells throughout the body. As a matter of fact, new evidence suggests that it is a hormonal signal from the fetus to the mother that signals the onset of labor and delivery. Many of the basic hormones are active from birth, but most of the hormones related to reproductive functions are not produced or secreted until puberty. Secretion of male reproductive hormones follows the same pattern as most nonreproductive hormones: continuous secretion from puberty until there is a slight tapering off in late adulthood. The secretion of female reproductive hormones such as estrogens also declines late in life, but more suddenly and completely—often during or just at the end of middle adulthood.

It is important to appreciate the precision of control afforded by the partnership of the two major regulatory systems: the endocrine system and the nervous system. The neuroendocrine system is able to finely adjust the availability and processing of nutrients through a diverse array of mechanisms: growth hormone, thyroid hormone, cortisol, epinephrine, somatostatin, autonomic nervous regulation, and so on. The absorption, storage, and transport of calcium ions are kept in balance by the antagonistic actions of calcitonin and parathyroid hormone (and its effects on vitamin D). Reproductive ability is triggered, developed, maintained, and timed by the complex interaction of the nervous system with follicle-stimulating hormone, luteinizing hormone, estrogen, progesterone, testosterone, chorionic gonadotropin, prolactin, oxytocin, and melatonin. Nearly every process in the human organism is kept in balance by the incredibly complex, but precise, interaction of all these different nervous and endocrine regulatory chemicals.

As we have stated throughout this chapter, endocrine disorders typically result from either elevated or depressed hormone levels (hypersecretion or hyposecretion). At first thought, this may seem very simple and straightforward. In reality, however, nothing could be further from the truth. A variety of specific mechanisms may produce hypersecretion or hyposecretion of hormones. A few of the more well-known mechanisms are briefly explained here. Examples of a few major endocrine disorders and their mechanisms are listed in Table 16-8.

Mechanisms of Hypersecretion
Excessively high blood concentration of a hormone—or any condition that mimics high hormone levels—is called hypersecretion. Specific types of hypersecretion are usually named hyper- in front of the name of the source gland and the suffix -ism at the end. For example, hypersecretion of thyroid hormone—no matter what the specific cause—is called hyperthyroidism. Hyperthyroidism is not a disease itself but a condition that characterizes several different diseases (e.g., Graves’ disease and toxic nodular goiter).

Any of several different mechanisms may be responsible for a particular case of hypersecretion. For example, tumors are often responsible for an abnormal proliferation of endocrine cells and the resulting increase in hormone secretion. Pituitary adenomas, for example, are benign tumors that may cause hyperpituitarism. As many as one in five people may have pituitary adenomas, but the majority of tumors are microscopic and asymptomatic. Larger tumors may, however, cause hyperpituitarism with a possible outcome of gigantism, or acromegaly.

Another cause of hypersecretion is a phenomenon called autoimmunity. In autoimmunity, the immune system functions abnormally. In Graves’ disease, for example, autoimmune antibodies against the TSH receptor actually stimulate the receptor and mimic the activity of TSH. As a result, the thyroid gland hypertrophies and excess thyroid hormone is produced. Another possible cause of hypersecretion of a hormone is a failure of the feedback mechanisms that regulate secretion.
### Table 16-8 Examples of Endocrine Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acromegaly</td>
<td>Hypersecretion of growth hormone (GH) during adulthood</td>
<td>Chronic metabolic disorder characterized by gradual enlargement or elongation of facial bones and extremities</td>
</tr>
<tr>
<td>Addison disease</td>
<td>Hyposcretion of adrenal cortical hormones (adrenal cortical insufficiency)</td>
<td>Caused by tuberculosis, autoimmunity, or other factors, this life-threatening condition is characterized by weakness, anorexia, weight loss, nausea, irritability, decreased cold tolerance, dehydration, increased skin pigmentation, and emotional disturbance; it may lead to an acute phase (adrenal crisis) characterized by circulatory shock</td>
</tr>
<tr>
<td>Aldosteronism</td>
<td>Hypersecretion of aldosterone</td>
<td>Often caused by adrenal hyperplasia, this condition is characterized by sodium retention and potassium loss—producing Conn syndrome: severe muscle weakness, hypertension (high blood pressure), kidney dysfunction, and cardiac problems</td>
</tr>
<tr>
<td>Cretinism</td>
<td>Hyposcretion of thyroid hormone during early development</td>
<td>Congenital condition characterized by dwarfism, retarded mental development, facial puffy, dry skin, umbilical hernia, and lack of muscle coordination</td>
</tr>
<tr>
<td>Cushing disease</td>
<td>Hypersecretion of adrenocorticotropic hormone (ACTH)</td>
<td>Caused by adenoma of the anterior pituitary, increased ACTH causes hypersecretion of adrenal cortical hormones, producing Cushing syndrome</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Hypersecretion (or injection) of glucocorticoids</td>
<td>Metabolic disorder characterized by fat deposits on upper back, striated pad of fat on chest and abdomen, rounded “moon” face, muscular atrophy, edema, hypokalemia (low blood potassium level), and possible abnormal skin pigmentation; occurs in Cushing disease</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>Hyposcretion of (or insensitivity to) antidiuretic hormone (ADH)</td>
<td>Metabolic disorder characterized by extreme polyuria (excessive urination) and polydipsia (excessive thirst) due to a decrease in the kidney’s retention of water</td>
</tr>
<tr>
<td>Gestational diabetes mellitus (GDM)</td>
<td>Temporary decrease in blood levels of insulin during pregnancy</td>
<td>Carbohydrate-metabolism disorder occurring in some pregnant women; characterized by polydipsia, polyuria, overeating, weight loss, fatigue, and irritability</td>
</tr>
<tr>
<td>Gigantism</td>
<td>Hypersecretion of GH before age 25</td>
<td>Condition characterized by extreme skeletal size caused by excess protein anabolism during skeletal development</td>
</tr>
<tr>
<td>Graves disease</td>
<td>Hypersecretion of thyroid hormone</td>
<td>Inherited, possibly autoimmune disease characterized by hyperthyroidism, exophthalmos (protruding eyes)</td>
</tr>
<tr>
<td>Hashimoto disease</td>
<td>Autoimmune damage to thyroid causing hyposcretion of thyroid hormone</td>
<td>Enlargement of thyroid (goiter) is sometimes accompanied by hyperthyroidism, typically occurring between ages 30 and 50; it is 20 times more common in females than males</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>Hypersecretion of parathyroid hormone (PTH)</td>
<td>Condition characterized by increased reabsorption of calcium from bone tissue and kidneys and increased absorption by the gastrointestinal tract; produces hypercalcemia, resulting in confusion, anorexia, abdominal pain, muscle pain, and fatigue, possibly progressing to circulatory shock, kidney failure, and death</td>
</tr>
<tr>
<td>Hyperthyroidism (adult)</td>
<td>Hypersecretion of thyroid hormone</td>
<td>Condition characterized by nervousness, tremor, weight loss, excessive hunger, fatigue, heat intolerance, heart arrhythmia, and diarrhea, is caused by a general acceleration of body function</td>
</tr>
<tr>
<td>Hypothyroidism (adult)</td>
<td>Hyposcretion of thyroid hormone</td>
<td>Condition characterized by sluggishness, weight gain, skin dryness, constipation, arthritis, and general slowing of body function, may lead to myxedema, coma, or death if untreated</td>
</tr>
<tr>
<td>Insulin shock</td>
<td>Hypersecretion (or overdose injection) of insulin, decreased food intake, and excessive exercise</td>
<td>Hypoglycemic (low blood glucose) shock characterized by nervousness, sweating and chills, irritability, hunger, and pallor—progressing to convulsion, coma, and death if untreated</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>Hyposcretion of insulin</td>
<td>Inherited condition with sudden childhood onset characterized by polydipsia, polyuria, overeating, weight loss, fatigue, and irritability, resulting from the inability of cells to secure and metabolize carbohydrates</td>
</tr>
<tr>
<td>Myxedema</td>
<td>Extreme hyposcretion of thyroid hormone during adulthood</td>
<td>Severe form of adult hypothyroidism characterized by edema of the face and extremities; often progressing to coma and death</td>
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*Continued*
of a particular hormone. For example, a condition called primary hyperparathyroidism is characterized by a failure of the parathyroid gland to adjust its output to compensate for changes in blood calcium levels. Instead, the parathyroid gland seems to operate independently of the normal feedback loop and thus overproduces parathyroid hormone.

### Mechanisms of Hyposecretion

Depressed blood hormone levels—or any condition that mimics low hormone levels—is termed hyposecretion. Specific types of hyposecretion are named in a manner similar to that in which hypersecretion disorders are named: by the addition of the hypo- prefix and the -ism suffix. For example, hyposecretion of thyroid hormone is called hypothyroidism.

Various different mechanisms have been shown to cause hyposecretion of hormones. For example, although most tumors cause oversecretion of a hormone, they may instead cause a gland to undersecrete its hormone(s). Tissue death, perhaps caused by a blockage or other failure of the blood supply, can also cause a gland to reduce its hormonal output. Hypopituitarism (hyposecretion by the anterior pituitary) can occur this way. Still another way in which a gland may reduce its secretion below normal levels is through abnormal operation of regulatory feedback loops. An example of this is in the case of hyposecretion of testosterone and gonadotropic hormones in males who abuse anabolic steroids. Men who take testosterone steroids increase their blood concentration of this hormone above set point levels. The body responds to this overabundance by reducing its own output of testosterone by reducing its output of gonadotropins. This may lead to sterility and other complications.

Abnormalities of immune function may also cause hyposecretion. For example, an autoimmune attack on glandular tissue sometimes has the effect of reducing hormone output. Some endocrinologists theorize that autoimmune destruction of pancreatic islet cells, perhaps in combination with viral and genetic mechanisms, is a culprit in many cases of type 1 (insulin-dependent) diabetes mellitus.

Many types of hyposecretion disorders have recently been shown to be caused by insensitivity of the target cells to tropic hormones rather than from actual hyposecretion. A few major types of abnormal responses in target cells are:

- An abnormal decrease in the number of hormone receptors
- Abnormal function of hormone receptors, resulting in failure to bind to hormones properly
- Antibodies bind to hormone receptors, thus blocking binding of hormone molecules
- Abnormal metabolic response to the hormone-receptor complex by the target cell
- Failure of the target cell to produce enough second messenger molecules

Type 2 (non–insulin-dependent) diabetes mellitus is thought to be caused by target cell abnormalities that render the cells insensitive to insulin.
CASE STUDY

Sonia Dawson, a 30-year-old female, has been diagnosed with Graves’ disease. She has recently lost 25 pounds despite an increased appetite. Her vision is blurry; her heart races and pounds. She has been irritable but attributes the irritability to insomnia. She has had bouts of diarrhea. She feels hot, even if others are comfortable. The collars on her clothing are becoming too tight. Her last menstrual period was 2 months ago. Before that time her menses were regular.

On physical examination, the nurse notes that Ms. Dawson is thin, pale, and anxious. She moves restlessly around the room. Her eyes are bulging and have a staring appearance. Her eyelids and hands have fine tremors. Her skin is smooth, warm, and moist. She is sweating profusely, although the room temperature is ambient. Her hair is very fine and soft. She weighs 112 pounds. Her oral temperature is 99°F (37.2°C), heart rate is 120 at rest, respirations are 20, and blood pressure is 110/50. Her thyroid gland is enlarged with auscultation of a bruit. Laboratory results reveal a serum T₃ level of 200 µg/dl (high), a T₄ level of 20 µg/dl (low), and a TSH level that is 2.5 µU/ml, which is normal. A thyroid antibody test shows a high titer of thyroglobulin antibodies. Radioactive iodine uptake test shows a 40% uptake in 6 hours, which is elevated.

The decision to treat nonsurgically is made. Ms. Dawson is started on methimazole 10 mg by mouth every day to suppress her thyroid gland and propranolol 10 mg twice a day to decrease her heart rate and control her cardiac symptoms.

1. Which of the following reasons is the most likely cause of Sonia Dawson’s increased thyroid function?
   A. Hyperplasia of the thyroid
   B. Anterior pituitary tumor
   C. Thyroid carcinoma
   D. Autoimmune response

2. After 1 month of treatment Sonia returns to the clinic for a checkup. She has not been feeling well and is very tired. However, her previous symptoms have resolved. A TSH level from a few days ago is now 7.5, which is greatly elevated. Which one of the following explanations for this recent elevation would be considered reasonable in Ms. Dawson’s case?
   A. Pituitary failure has occurred.
   B. The thyroid gland has been suppressed too much.
   C. The hypothalamus has been suppressed.
   D. The thyroid gland has been overstimulated.

3. Based on the elevated TSH level and the change in Ms. Dawson’s condition, what symptoms would you expect her to exhibit?
   A. Dyspnea, increased heart rate, and constipation
   B. Slower heart rate, lethargy, and nervousness
   C. Dyspnea, slight fever, and increased heart rate
   D. Slower heart rate, lethargy, and hair loss

CHAPTER SUMMARY

INTRODUCTION

A. The endocrine and nervous systems function to achieve and maintain homeostasis
B. When the two systems work together, referred to as the neuroendocrine system, they perform the same general functions: communication, integration, and control
C. In the endocrine system, secreting cells send hormone molecules via the blood to specific target cells contained in target tissues or target organs
D. Hormones—carried to almost every point in the body; can regulate most cells; effects work more slowly and last longer than those of neurotransmitters
E. Endocrine glands are “ductless glands”; many are made of glandular epithelium whose cells manufacture and secrete hormones; a few endocrine glands are made of neurosecretory tissue
F. Glands of the endocrine system are widely scattered throughout the body (Figure 16-2)

HORMONES

A. Classification of hormones
   1. Classification by general function
      a. Tropic hormones—hormones that target other endocrine glands and stimulate their growth and secretion
      b. Sex hormones—hormones that target reproductive tissues
      c. Anabolic hormones—hormones that stimulate anabolism in target cells
   2. Classification by chemical structure (Figure 16-3)
      a. Steroid hormones
      b. Nonsteroid hormones
   3. Steroid hormones (Figure 16-4)
      a. Synthesized from cholesterol
      b. Lipid-soluble and can easily pass through the phospholipid plasma membrane of target cells
      c. Examples of steroid hormones: cortisol, aldosterone, estrogen, progesterone, and testosterone
4. Nonsteroid hormones (Figure 16-5)
   a. Synthesized primarily from amino acids
   b. Protein hormones—long, folded chains of amino acids; e.g., insulin and parathyroid hormone
   c. Glycoprotein hormones—protein hormones with carbohydrate groups attached to the amino acid chain
   d. Peptide hormones—smaller than protein hormones; short chain of amino acids; e.g., oxytocin and antidiuretic hormone (ADH)
   e. Amino acid derivative hormones—each is derived from a single amino acid molecule
      (1) Amine hormones—synthesized by modifying a single molecule of tyrosine; produced by neurosecretory cells and by neurons; e.g., epinephrine and norepinephrine
      (2) Amino acid derivatives produced by the thyroid gland; synthesized by adding iodine to tyrosine

B. How hormones work
   1. General principles of hormone action
      a. Hormones signal a cell by binding to the target cell’s specific receptors in a “lock-and-key” mechanism (Figure 16-6)
      b. Different hormone-receptor interactions produce different regulatory changes within the target cell through chemical reactions
      c. Combined hormone actions:
         (1) Synergism—combinations of hormones acting together have a greater effect on a target cell than the sum of the effects that each would have if acting alone
         (2) Permissiveness—when a small amount of one hormone allows a second one to have its full effects on a target cell
         (3) Antagonism—one hormone produces the opposite effects of another hormone; used to “fine tune” the activity of target cells with great accuracy
      d. Endocrine glands produce more hormone molecules than actually are needed; the unused hormones are quickly excreted by the kidneys or broken down by metabolic processes
   2. Mechanism of steroid hormone action (Figure 16-7)
      a. Steroid hormones are lipid-soluble, and their receptors are normally found in the target cell’s cytosol
      b. After a steroid hormone molecule has diffused into the target cell, it binds to a receptor molecule to form a hormone-receptor complex
      c. Mobile-receptor hypothesis—the hormone passes into the nucleus, where it binds to mobile receptor and activates a certain gene sequence to begin transcription of mRNA; newly formed mRNA molecules move into the cytosol, associate with ribosomes, and begin synthesizing protein molecules that produce the effects of the hormone
      d. Steroid hormones regulate cells by regulating production of certain critical proteins
      e. The amount of steroid hormone present determines the magnitude of a target cell’s response
      f. Because transcription and protein synthesis take time, responses to steroid hormones are often slow
   3. Mechanisms of nonsteroid hormone action
      a. The second messenger mechanism—also known as the fixed-membrane-receptor hypothesis (Figure 16-8)
         (1) A nonsteroid hormone molecule acts as a “first messenger” and delivers its chemical message to fixed receptors in the target cell’s plasma membrane
         (2) The “message” is then passed by way of a G protein into the cell where a “second messenger” triggers the appropriate cellular changes
         (3) Second messenger mechanism—produces target cell effects that differ from steroid hormone effects in several important ways:
            (a) The effects of the hormone are amplified by the cascade of reactions
            (b) There are a variety of second messenger mechanisms—examples: IP3, GMP, calcium-calmodulin mechanisms (Figure 16-9)
            (c) The second messenger mechanism operates much more quickly than the steroid mechanism
      b. The nuclear receptor mechanism—small iodinated amino acids (T4 and T3) enter the target cell and bind to receptors associated with a DNA molecule in the nucleus; this binding triggers transcription of mRNA and synthesis of new enzymes

C. Regulation of hormone secretion
   1. Control of hormonal secretion is usually part of a negative feedback loop and is called endocrine reflexes (Figure 16-10)
   2. Simplest mechanism—when an endocrine gland is sensitive to the physiological changes produced by its target cells
   3. Endocrine gland secretion may also be regulated by a hormone produced by another gland
   4. Endocrine gland secretions may be influenced by nervous system input; this fact emphasizes the close functional relationship between the two systems

PROSTAGLANDINS
   A. Unique group of lipid molecules (20-carbon fatty acid with 5-carbon ring) that serves important and widespread integrative functions in the body but do not meet the usual definition of a hormone (Figure 16-11)
   B. Called tissue hormones because the secretion is produced in a tissue and diffuses only a short distance to other cells within the same tissue; PGs tend to integrate activities of neighboring cells
C. Many structural classes of prostaglandins have been isolated and identified
1. Prostaglandin A (PGA)—intraarterial infusion resulting in an immediate fall in blood pressure accompanied by an increase in regional blood flow to several areas
2. Prostaglandin E (PGE)—vascular effects: regulation of red blood cell deformability and platelet aggregation; gastrointestinal effects: regulates hydrochloric acid secretion
3. Prostaglandin F (PGF)—especially important in reproductive system, causing uterine contractions; also affects intestinal motility and is required for normal peristalsis
D. Tissues known to secrete PGs—kidneys, lungs, iris, brain, thymus
E. PGs have diverse physiological effects

**PITUITARY GLAND**

**A. Structure of the pituitary gland**
1. Also known as hypophysis and called the “master gland”
2. Size: 1.2 to 1.5 cm (about ½ inch) across; weight: 0.5 g (¼ ounce)
3. Located on the ventral surface of the brain within the skull (Figure 16-12)
4. Infundibulum—stemlike stalk that connects pituitary to the hypothalamus
5. Made up of two separate glands, the adenohypophysis (anterior pituitary gland) and the neurohypophysis (posterior pituitary gland)

**B. Adenohypophysis (anterior pituitary)**
1. Divided into two parts
   a. Pars anterior—forms the major portion of the adenohypophysis
   b. Pars intermedia
2. Tissue is composed of irregular clumps of secretory cells supported by fine connective tissue fibers and surrounded by a rich vascular network
3. Three types of cells can be identified according to their affinity for certain stains (Figure 16-13)
   a. Chromophobes—do not stain
   b. Acidophils—stain with acid stains
   c. Basophils—stain with basic stains
4. Five functional types of secretory cells exist:
   a. Somatotrophs—secrete GH
   b. Corticotrophs—secrete ACTH
   c. Thyrotrophs—secrete TSH
   d. Lactotrophs—secrete prolactin (PRL)
   e. Gonadotrophs—secrete LH and FSH
5. Growth hormone (GH) (Figure 16-14)
   a. Also known as somatotropin (STH)
   b. Promotes growth of bone, muscle, and other tissues by accelerating amino acid transport into the cells
   c. Stimulates fat metabolism by mobilizing lipids from storage in adipose cells and speeding up catabolism of the lipids after they have entered another cell
   d. GH tends to shift cell chemistry away from glucose catabolism and toward lipid catabolism as an energy source; this leads to increased blood glucose levels
   e. GH functions as an insulin antagonist and is vital to maintaining homeostasis of blood glucose levels

6. Prolactin (PRL)
   a. Produced by acidophils in the pars anterior
   b. Also known as lactogenic hormone
   c. During pregnancy, PRL promotes development of the breasts, anticipating milk secretion; after the baby is born, PRL stimulates the mother’s mammary glands to produce milk

7. Tropic hormones—hormones that have a stimulating effect on other endocrine glands; four principal tropic hormones are produced and secreted by the basophils of the pars anterior
   a. Thyroid-stimulating hormone (TSH), or thyrotropin—promotes and maintains the growth and development of the thyroid; also causes the thyroid to secrete its hormones
   b. Adrenocorticotropic hormone (ACTH), or adrenocorticotropic—promotes and maintains normal growth and development of the cortex of the adrenal gland; also stimulates the adrenal cortex to secrete some of its hormones
   c. Follicle-stimulating hormone (FSH)—in the female, stimulates primary graafian follicles to grow toward maturity; also stimulates the follicle cells to secrete estrogens; in the male, FSH stimulates the development of the seminiferous tubules of the testes and maintains spermatogenesis
   d. Luteinizing hormone (LH)—in the female, stimulates the formation and activity of the corpus luteum of the ovary; corpus luteum secretes progesterone and estrogens when stimulated by LH; LH also supports FSH in stimulating maturation of follicles; in the male, LH stimulates interstitial cells in the testes to develop and secrete testosterone; FSH and LH are called gonadotropins because they stimulate the growth and maintenance of the gonads

8. Control of secretion in the adenohypophysis
   a. Hypothalamus secretes releasing hormones into the blood, which are then carried to the hypothalamic portal system (Figure 16-15)
   b. Hypophyseal portal system carries blood from the hypothalamus directly to the adenohypophysis where the target cells of the releasing hormones are located
   c. Releasing hormones influence the secretion of hormones by acidophils and basophils
   d. Through negative feedback, the hypothalamus adjusts the secretions of the adenohypophysis, which then adjusts the secretions of the target glands
that, in turn, adjust the activity of their target tissues (Figure 16-16)
e. In stress, the hypothalamus translates nerve impulses into hormone secretions by endocrine glands, basically creating a mind-body link

C. Neurohypophysis (posterior pituitary)
1. Serves as storage and release site for antidiuretic hormone (ADH) and oxytocin (OT), which are synthesized in the hypothalamus (Figure 16-17)
2. Release of ADH and OT into the blood is controlled by nervous stimulation
3. Antidiuretic hormone (ADH)
   a. Prevents the formation of a large volume of urine, thereby helping the body conserve water
   b. Causes a portion of each tubule in the kidney to reabsorb water from the urine it is forming
   c. Dehydration triggers the release of ADH
4. Oxytocin (OT)—has two actions
   a. Causes milk ejection from the lactating breast; regulated by positive feedback mechanism; PRL cooperates with oxytocin
   b. Stimulates contraction of uterine muscles that occurs during childbirth; regulated by positive feedback mechanism

PINEAL GLAND
A. Tiny, pine cone–shaped structure located on the dorsal aspect of the brain’s diencephalon
B. Member of the nervous system, because it receives visual stimuli, and also a member of the endocrine system, because it secretes hormones
C. Pineal gland supports the body’s biological clock
D. Principal pineal secretion is melatonin

THYROID GLAND
A. Structure of the thyroid gland
1. Made up of two large lateral lobes and a narrow connecting isthmus (Figure 16-18)
2. A thin wormlike projection of thyroid tissue often extends upward from the isthmus
3. Weight of the thyroid in an adult is approximately 30 g (1 ounce)
4. Located in the neck, on the anterior and lateral surfaces of the trachea, just below the larynx
5. Composed of follicles (Figure 16-19)
   a. Small hollow spheres
   b. Filled with thyroid colloid that contains thyroglobulins
B. Thyroid hormone
1. Actually two different hormones
   a. Tetraiodothyronine (T4), or thyroxine—contains four iodine atoms; approximately 20 times more abundant than T3; major importance is as a precursor to T3
   b. Triiodothyronine (T3)—contains three iodine atoms; considered to be the principal thyroid hormone; T3 binds efficiently to nuclear receptors in target cells
2. Thyroid gland stores considerable amounts of a preliminary form of its hormones prior to secreting them
3. Before being stored in the colloid of follicles, T1 and T4 are attached to globulin molecules, forming thyroglobulin complexes
4. On release, T3 and T4 detach from globulin and enter the bloodstream
5. Once in the blood, T3 and T4 attach to plasma globulins and travel as a hormone-globulin complex
6. T3 and, to a lesser extent, T4 detach from plasma globulin as they near the target cells
7. Thyroid hormone—helps regulate the metabolic rate of all cells and cell growth and tissue differentiation; it is said to have a “general” target

PARATHYROID GLANDS
A. Structure of the parathyroid glands
1. Four or five parathyroid glands embedded in the posterior surface of the thyroid’s lateral lobes
2. Tiny, rounded bodies within thyroid tissue formed by compact, irregular rows of cells (Figure 16-20)
B. Parathyroid hormone (PTH)
1. PTH is an antagonist to calcitonin and acts to maintain calcium homeostasis (Figure 16-21)
2. PTH acts on bone and kidney
   a. Causes more bone to be dissolved, yielding calcium and phosphate, which enters the bloodstream
   b. Causes phosphate to be secreted by the kidney cells into the urine to be excreted
   c. Causes increased intestinal absorption of calcium by stimulating the kidney to produce active vitamin D, which increases calcium absorption in gut

ADRENAL GLANDS
A. Structure of the adrenal glands (Figure 16-22)
1. Located on top of the kidneys, fitting like caps
2. Made up of two portions (Table 16-6)
   a. Adrenal cortex—composed of endocrine tissue
   b. Adrenal medulla—composed of neurosecretory tissue
B. Adrenal cortex—all cortical hormones are steroids and known as corticosteroids
1. Composed of three distinct layers of secreting cells
   a. Zona glomerulosa—outermost layer, directly under the outer connective tissue capsule of the adrenal gland; secretes mineralocorticoids
   b. Zona fasciculata—middle layer; secretes glucocorticoids
   c. Zona reticularis—inner layer; secretes small amounts of glucocorticoids and gonadocorticoids
2. Mineralocorticoids
   a. Have an important role in the regulatory process of sodium in the body
   b. Aldosterone
      (1) Only physiologically important mineralocorticoid in the human; primary function is maintenance of sodium homeostasis in the blood by increasing sodium reabsorption in the kidneys
      (2) Aldosterone also increases water retention and promotes the loss of potassium and hydrogen ions
      (3) Aldosterone secretion is controlled by the renin-angiotensin mechanism and by blood potassium concentration (Figure 16-23)

3. Glucocorticoids
   a. Main glucocorticoids secreted by the zona fasciculata are cortisol, cortisone, and corticosterone, with cortisol the only one secreted in significant quantities
   b. Affect every cell in the body
   c. Are protein-mobilizing, gluconeogenic, and hyperglycemic
   d. Tend to cause a shift from carbohydrate catabolism to lipid catabolism as an energy source
   e. Essential for maintaining normal blood pressure by aiding norepinephrine and epinephrine to have their full effect, causing vasoconstriction
   f. High blood concentration causes eosinopenia and marked atrophy of lymphatic tissues
   g. Act with epinephrine to bring about normal recovery from injury produced by inflammatory agents
   h. Secretion increases in response to stress
   i. Except during stress response, secretion is mainly controlled by a negative feedback mechanism involving ACTH from the adenohypophysis

4. Gonadocorticoids—sex hormones (androgens) that are released from the adrenal cortex

C. Adrenal medulla
   1. Neurosecretory tissue—tissue composed of neurons specialized to secrete their products into the blood
   2. Adrenal medulla secretes two important hormones—epinephrine and norepinephrine; they are part of the class of nonsteroid hormones called catecholamines
   3. Both hormones bind to the receptors of sympathetic effectors to prolong and enhance the effects of sympathetic stimulation by the ANS (Figure 16-24)

PANCREATIC ISLETS
A. Structure of the pancreatic islets (Figure 16-25)
   1. Elongated gland, weighing approximately 100 g (3.5 ounce); its head lies in the duodenum, extends horizontally behind the stomach, and, then, touches the spleen
   2. Composed of endocrine and exocrine tissues
      a. Pancreatic islets (islets of Langerhans)—endocrine portion
      b. Acini—exocrine portion—secretes a serous fluid containing digestive enzymes into ducts draining into the small intestine

3. Pancreatic islets—each islet contains four primary types of endocrine glands joined by gap junctions
   a. Alpha cells (A cells)—secrete glucagon (Figure 16-26)
   b. Beta cells (B cells)—secrete insulin; account for up to 75% of all pancreatic islet cells
   c. Delta cells (D cells)—secrete somatostatin
   d. Pancreatic polypeptide cells (F, or PP, cells)—secrete pancreatic polypeptides

B. Pancreatic hormones (review Table 16-7)—work as a team to maintain homeostasis of food molecules (Figure 16-27)
   1. Glucagon—produced by alpha cells; tends to increase blood glucose levels; stimulates gluconeogenesis in liver cells
   2. Insulin—produced by beta cells; lowers blood concentration of glucose, amino acids, and fatty acids and promotes their metabolism by tissue cells
   3. Somatostatin—produced by delta cells; primary role is regulating the other endocrine cells of the pancreatic islets
   4. Pancreatic polypeptide—produced by F (PP) cells; influences the digestion and distribution of food molecules to some degree

GONADS
A. Testes (Figure 16-2)
   1. Paired organs within the scrotum in the male
   2. Composed of seminiferous tubules and a scattering of interstitial cells
   3. Testosterone is produced by the interstitial cells and responsible for the growth and maintenance of male sexual characteristics
   4. Testosterone secretion is mainly regulated by gonadotropin levels in the blood

B. Ovaries (Figure 16-2)
   1. Primary sex organs in the female
   2. Set of paired glands in the pelvis that produce several types of sex hormones
      a. Estrogens—steroid hormones secreted by ovarian follicles; promote development and maintenance of female sexual characteristics
      b. Progesterone—secreted by corpus luteum; maintains the lining of the uterus necessary for successful pregnancy
      c. Ovarian hormone secretion depends on the changing levels of FSH and LH from the adenohypophysis

PLACENTA
A. Tissues that form on the lining of the uterus as a connection between the circulatory systems of the mother and developing child
B. Serves as a temporary endocrine gland that produces human chorionic gonadotropin, estrogens, and progesterone
THYMUS (Figure 16-2)
A. Gland located in the mediastinum just beneath the sternum
B. Thymus is large in children, begins to atrophy at puberty, and, by old age, the gland is a vestige of fat and fibrous tissue
C. Considered to be primarily a lymphatic organ, but the hormone thymosin has been isolated from thymus tissue
D. Thymosin—stimulates development of T cells

GASTRIC AND INTESTINAL MUCOSA
A. The mucous lining of the GI tract contains cells that produce both endocrine and exocrine secretions
B. GI hormones such as gastrin, secretin, and cholecystokinin-pancreozymin (CCK) play regulatory roles in coordinating the secretory and motor activities involved in the digestive process
C. Ghrelin—hormone secreted by endocrine cells in gastric mucosa; stimulates hypothalamus to boost appetite; slows metabolism and fat burning; may be a contributor to obesity

HEART
A. The heart has a secondary endocrine role
B. Hormone-producing cells produce atrial natriuretic hormone (ANH)
C. ANH’s primary effect is to oppose increases in blood volume or blood pressure; also an antagonist to ADH and aldosterone

CYCLE OF LIFE: ENDOCRINE SYSTEM
A. Endocrine regulation begins in the womb
B. Many active hormones are active from birth
   1. Evidence that a hormonal signal from fetus to mother signals the onset of labor
C. Hormones related to reproduction begin at puberty
D. Secretion of male reproductive hormones—continuous production from puberty, slight decline in late adulthood
E. Secretion of female reproductive hormones declines suddenly and completely in middle adulthood

THE BIG PICTURE: THE ENDOCRINE SYSTEM AND THE WHOLE BODY
A. Nearly every process in the human organism is kept in balance by the intricate interaction of different nervous and endocrine regulatory chemicals
B. The endocrine system operates with the nervous system to finely adjust the many processes they regulate
C. Neuroendocrine system adjusts nutrient supply
D. Calcitonin, parathyroid hormone, and vitamin D balance calcium ion use
E. The nervous system and hormones regulate reproduction

REVIEW QUESTIONS
1. Define the terms hormone and target organ.
2. Describe the characteristic chemical group found at the core of each steroid hormone.
3. Identify the major categories of nonsteroid hormones.
4. Identify the sequence of events involved in a second messenger mechanism.
5. What is the function of calmodulin?
6. List the classes of prostaglandins. Identify the functions of three of these classes.
7. Name the two subdivisions of the adenohypophysis.
8. Discuss and identify, by staining tendency and relative percentages, the cell types present in the anterior pituitary gland.
9. Discuss the functions of growth hormone.
10. What effect does growth hormone have on blood glucose concentration? Fat mobilization and catabolism? Protein anabolism?
11. List the four tropic hormones secreted by the basophils of the anterior pituitary gland. Which of the tropic hormones are also called gonadotropins?
12. How does antidiuretic hormone act to alter urine volume?
13. Describe the positive feedback associated with oxytocin.
14. Discuss the synthesis and storage of thyroxine and triiodothyronine. How are they transported in the blood?
15. Discuss the functions of parathyroid hormone.
16. List the hormones produced by each “zone” of the adrenal cortex and describe the actions of these hormones.
17. Discuss the normal function of hormones produced by the adrenal medulla.
18. Identify the hormones produced by each of the cell types in the pancreatic islets.
19. Identify the “pregnancy-promoting” hormone.
20. Where is human chorionic gonadotropin produced? What does it do?
21. Describe the role of atrial natriuretic hormone.
22. Identify the conditions resulting from both hypersecretion and hyposecretion of growth hormone during growth years.
23. Describe the face of a patient with Cushing syndrome.
24. How does exercise affect diabetes mellitus?

CRITICAL THINKING QUESTIONS
1. Driving a car requires rapid response of selected muscles. The regulation of blood sugar level requires regulating almost every cell in the body. Based on the characteristics of each system, explain why driving would be a nervous system function and blood sugar regulation would be an endocrine function.
2. How would you explain the ways in which one hormone interacts with another and its impact on the cell?
3. Compare and contrast the action mechanisms of steroid and nonsteroid hormones.
4. Why are thyroid hormones exceptions to the usual mode of nonsteroid hormone functioning?
5. What examples can you find that apply the concept of a negative feedback loop to the regulation of hormone secretion?
6. A hyposecretion of which hormone would make it difficult for a mother to nurse her child? How would you summarize the effects of this hormone?
7. Why do you think the hypothalamus can be called the “mind-body link?”
8. How would you explain the hormonal interaction that helps maintain the set point value for the glucose in the blood?
9. Explain how the cell is able to become more or less sensitive to a specific hormone.
10. What is the relationship between increased blood level concentrations of FSH and menopause?
11. A lack of iodine in the diet will cause a simple goiter. Describe the feedback loop that will cause its formation.
12. A friend of yours is considering the use of anabolic steroids. Based on what you know of their effects, how would you explain not using these steroids?

The reward of chiropractic is quite clear—it helps a patient return to their optimum potential for health. Chiropractic is not a treatment for disease. The purpose of the chiropractic adjustment is to allow the inborn intelligence within the body to be more fully expressed. When the innate (inborn) intelligence within the body is fully expressed, the body functions at its maximum potential for health and healing. To see this occur is the biggest reward for me!

Chiropractors use anatomy and physiology in everyday practice. We use the five components of subluxation that affect the physiology of the body. Kinesiopathology deals with the biomechanics, neuropathology deals with the nerves, myopathology deals with the muscles, histopathology deals with the cells, and finally, we use the biochemical system. Chiropractic is concerned with the relationship of the spinal column and the musculoskeletal structures of the body to the nervous system. Proper alignment of the spinal column is essential for optimum health because the spine acts as a “switchboard” for the nervous system. When there is nerve interference caused by misalignment in the spine, known as subluxation, pain can occur, and the body’s natural defenses are diminished. The chiropractor adjusts the spinal joints to remove subluxation and restore normal nerve function.

The education of the chiropractor is long and challenging. First you must go to undergraduate school to obtain a B.S. with a concentration in the sciences. Then you attend chiropractic school for another 4 years (8 years is a big commitment!). To receive a Doctor of Chiropractic, you have to take four national boards and a state board in the state in which you wish to practice.