

Human pancreas. Light zones in the middle are the insulin-producing islets.

## CHAPTER

# 17

## The Endocrine System

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### Brushing Up

To understand this chapter, it is important that you understand or brush up on the following concepts:

- Structure and function of the plasma membrane (p. 98)
- G proteins, cAMP, and other second messengers (p. 102)
- Active transport and the transport maximum (pp. 109–110)
- Monoamines, especially catecholamines (p. 464)
- The hypothalamus (p. 530)

636 Part Three Integration and Control

**F**or the body to maintain homeostasis, cells must be able to communicate and integrate their activities with each other. For the last five chapters, we have examined how this is achieved through the nervous system. We now turn to two modes of chemical communication called *endocrine* and *paracrine* signaling, with an emphasis on the former. This chapter is primarily about **endocrinology**, the study of the endocrine system and the diagnosis and treatment of its dysfunctions.

You probably have at least some prior acquaintance with this system. Perhaps you have heard of the pituitary gland and thyroid gland, secretions such as growth hormone, estrogen, and insulin, and endocrine disorders such as dwarfism, goiter, and diabetes mellitus. Fewer readers, perhaps, are familiar with what hormones are at a chemical level or exactly how they work. Therefore, this chapter starts with the relatively familiar—a survey of the endocrine glands, their hormones, and the principal effects of these hormones. We will then work our way down to the finer and less familiar details—the chemical identity of hormones, how they are made and transported, and how they produce their effects on their target cells. Shorter sections at the end of the chapter discuss the role of the endocrine system in adapting to stress, some hormonelike paracrine secretions, and the pathologies that result from endocrine dysfunction.

## Overview of the Endocrine System

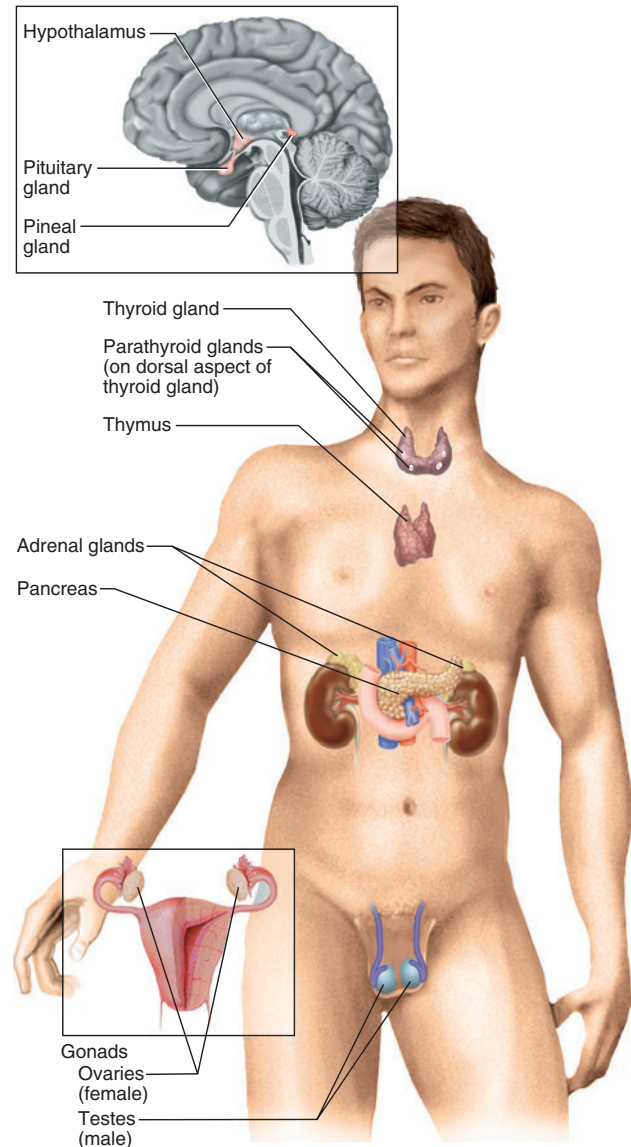
### Objectives

When you have completed this section, you should be able to

- define *hormone* and *endocrine system*;
- list the major organs of the endocrine system;
- recognize the standard abbreviations for many hormones; and
- compare and contrast the nervous and endocrine systems.

Cells communicate with each other in four ways:

1. **Gap junctions** join single-unit smooth muscle, cardiac muscle, epithelial, and other cells to each other. They enable cells to pass nutrients, electrolytes, and signaling molecules directly from the cytoplasm of one cell to the cytoplasm of the next through adjacent pores in their plasma membranes (fig. 5.29, p. 178).
2. **Neurotransmitters** are released by neurons, diffuse across a narrow synaptic cleft, and bind to receptors on the surface of the next cell.
3. **Paracrines**<sup>1</sup> are secreted into the tissue fluid by a cell, diffuse to nearby cells in the same tissue, and stimulate their physiology. They are sometimes called *local hormones*.



**Figure 17.1 Major Organs of the Endocrine System.** This system also includes gland cells in many other organs not shown here.

4. **Hormones**<sup>2</sup> are chemical messengers that are secreted into the bloodstream and stimulate the physiology of cells in another tissue or organ, often a considerable distance away. Hormones produced by the pituitary gland in the head, for example, can act on organs in the abdominal and pelvic cavities. (Some authorities define *hormone* so broadly as to include paracrines and neurotransmitters. This book

<sup>1</sup>*para* = next to + *crin* = secrete

<sup>2</sup>*hormone* = to excite, set in motion

adopts the stricter definition of hormones as blood-borne messengers secreted by endocrine cells.)

Our focus in this chapter will be primarily on hormones and the **endocrine<sup>3</sup> glands** that secrete them (fig. 17.1). The **endocrine system** is composed of these glands as well as hormone-secreting cells in many organs not usually thought of as glands, such as the brain, heart, and small intestine. Hormones travel anywhere the blood goes, but they affect only those cells that have receptors for them. These are called the **target cells** for a particular hormone.

In chapter 5, we saw that glands can be classified as exocrine or endocrine. One way in which these differ is that exocrine glands have ducts to carry their secretion to the body surface (as in sweat) or to the cavity of another organ (as in digestive enzymes). Endocrine glands have no ducts but do have dense blood capillary networks. Endocrine cells release their hormones into the surrounding tissue fluid, and then the bloodstream quickly picks up and distributes the hormones. Exocrine secretions have extracellular effects such as the digestion of food, whereas endocrine secretions have intracellular effects—they alter the metabolism of their target cells.

## Comparison of the Nervous and Endocrine Systems

Although the nervous and endocrine systems both serve for internal communication, they are not redundant; they complement rather than duplicate each other's function (table 17.1). The systems differ in their means of communication—both electrical and chemical in the nervous system and solely chemical in the endocrine system (fig. 17.2)—yet as we shall see, they have many similarities on this point as well. They differ also in how quickly they start and stop responding to stimuli. The nervous system typically responds in just a few milliseconds, whereas hormone release may follow from several seconds to several days after the stimulus that caused it. Furthermore, when a stimulus ceases, the nervous system stops responding almost immediately, whereas some endocrine effects persist for several days or even weeks. On the other hand, under long-term stimulation, neurons soon adapt and their response declines. The endocrine system shows more persistent responses. For example, thyroid hormone secretion rises in cold weather and remains elevated as long as it remains cold. Another difference between the two systems is that an efferent nerve fiber innervates only one organ and a limited number of cells within that organ; its effects, therefore, are precisely targeted and relatively specific. Hormones, by contrast, circulate throughout the body and some of them, such as growth hormone, epinephrine, and thyroid hormone, have very widespread effects.

But these differences should not blind us to the similarities between the two systems. Several chemicals function as both neurotransmitters and hormones, including norepinephrine, cholecystokinin, thyrotropin-releasing hormone, dopamine, and antidiuretic hormone (= vasopressin). Some hormones, such as oxytocin and the catecholamines, are secreted by **neuroendocrine cells**—neurons that release their secretions into the extracellular fluid. Some hormones and neurotransmitters produce overlapping effects on the same target cells. For example, norepinephrine and glucagon cause glycogen hydrolysis in the liver. The nervous and endocrine systems continually regulate each other as they coordinate the activities of other organ systems. Neurons often trigger hormone secretion, and hormones often stimulate or inhibit neurons.

## Hormone Nomenclature

Many hormones are denoted by standard abbreviations which are used repeatedly in this chapter. These abbreviations are listed alphabetically in table 17.2 so that you can use this as a convenient reference while you work through the chapter. This is by no means a complete list. It does not include hormones that have no abbreviation, such as estrogen and insulin, and it omits hormones that are not discussed much in this chapter. Synonyms used by many authors are indicated in parentheses, but the first name listed is the one that is used in this book.

### Before You Go On

Answer the following questions to test your understanding of the preceding section:

1. Define the word *hormone* and distinguish a hormone from a neurotransmitter. Why is this an imperfect distinction?
2. Describe some ways in which endocrine glands differ from exocrine glands.
3. Name some sources of hormones other than purely endocrine glands.
4. List some similarities and differences between the endocrine and nervous systems.

## The Hypothalamus and Pituitary Gland

### Objectives

When you have completed this section, you should be able to

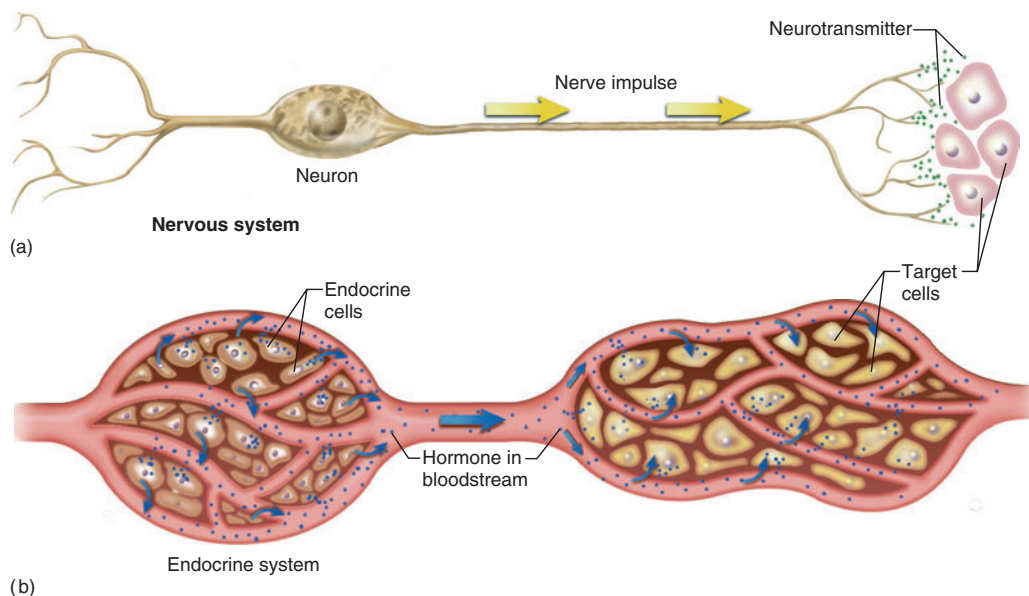
- list the hormones produced by the hypothalamus and pituitary gland;
- explain how the hypothalamus and pituitary are controlled and coordinated with each other;
- describe the functions of growth hormone; and
- describe the effects of pituitary hypo- and hypersecretion.

<sup>3</sup>endo = into; crin = to separate or secrete



**Table 17.1 Comparison of the Nervous and Endocrine Systems**

Nervous System	Endocrine System
Communicates by means of electrical impulses and neurotransmitters	Communicates by means of hormones
Releases neurotransmitters at synapses at specific target cells	Releases hormones into bloodstream for general distribution throughout body
Usually has relatively local, specific effects	Sometimes has very general, widespread effects
Reacts quickly to stimuli, usually within 1 to 10 msec	Reacts more slowly to stimuli, often taking seconds to days
Stops quickly when stimulus stops	May continue responding long after stimulus stops
Adapts relatively quickly to continual stimulation	Adapts relatively slowly; may continue responding for days to weeks of stimulation



**Figure 17.2 Communication by the Nervous and Endocrine Systems.** (a) A neuron has a long fiber that delivers its neurotransmitter to the immediate vicinity of its target cells. (b) Endocrine cells secrete a hormone into the bloodstream. The hormone binds to target cells at places often remote from the gland cells.

There is no “master control center” that regulates the entire endocrine system, but the pituitary gland and a nearby region of the brain, the hypothalamus, have a more wide-ranging influence than any other part of the system. This is an appropriate place to begin a survey of the endocrine system.

## Anatomy

The hypothalamus forms the floor and walls of the third ventricle of the brain (see fig. 14.12, p. 530). It regulates primitive functions of the body ranging from water balance to sex drive. Many of its functions are carried out by way of the pituitary gland, which is closely associated with it.

The **pituitary gland (hypophysis<sup>4</sup>)** is suspended from the hypothalamus by a stalk (*infundibulum<sup>5</sup>*) and housed in the sella turcica of the sphenoid bone. It is usually about 1.3 cm in diameter, but grows about 50% larger in pregnancy. It is actually composed of two structures—the **adenohypophysis** and **neurohypophysis**—that arise independently in the embryo and have entirely separate functions. The **adenohypophysis** arises from a *hypophyseal pouch* that grows upward from the pharynx, while the **neurohypophysis** arises as a downgrowth of the brain, the *neurohypophyseal bud* (fig. 17.3). They come to lie

<sup>4</sup>*hypo* = below + *physis* = growth

<sup>5</sup>*infundibulum* = funnel

**Table 17.2 Names and Abbreviations for Hormones**

Abbreviation	Name	Source
ACTH	Adrenocorticotrophic hormone (corticotropin)	Anterior pituitary
ADH	Antidiuretic hormone (vasopressin)	Posterior pituitary
ANP	Atrial natriuretic peptide	Heart
CRH	Corticotropin-releasing hormone	Hypothalamus
DHEA	Dehydroepiandrosterone	Adrenal cortex
EPO	Erythropoietin	Kidney, liver
FSH	Follicle-stimulating hormone	Anterior pituitary
GH	Growth hormone (somatotropin)	Anterior pituitary
GHRH	Growth hormone–releasing hormone	Hypothalamus
GnRH	Gonadotropin-releasing hormone	Hypothalamus
IGFs	Insulin-like growth factors (somatomedins)	Liver, other tissues
LH	Luteinizing hormone	Anterior pituitary
NE	Norepinephrine	Adrenal medulla
OT	Oxytocin	Posterior pituitary
PIH	Prolactin-inhibiting hormone (dopamine)	Hypothalamus
PRH	Prolactin-releasing hormone	Hypothalamus
PRL	Prolactin	Anterior pituitary
PTH	Parathyroid hormone (parathormone)	Parathyroids
T <sub>3</sub>	Triiodothyronine	Thyroid
T <sub>4</sub>	Thyroxine (tetraiodothyronine)	Thyroid
TH	Thyroid hormone (T <sub>3</sub> and T <sub>4</sub> )	Thyroid
TRH	Thyrotropin-releasing hormone	Hypothalamus
TSH	Thyroid-stimulating hormone	Anterior pituitary

side by side and are so closely joined that they look like a single gland.

The **adenohypophysis**<sup>6</sup> (AD-eh-no-hy-POFF-ih-sis) constitutes the anterior three-quarters of the pituitary (fig. 17.4a). It has two parts: a large **anterior lobe**, also called the *pars distalis* (“distal part”) because it is most distal to the pituitary stalk, and the *pars tuberalis*, a small mass of cells adhering to the anterior side of the stalk. In the fetus there is also a *pars intermedia*, a strip of tissue between the anterior lobe and neurohypophysis. During subsequent development, its cells mingle with those of the anterior lobe; in adults, there is no longer a separate *pars intermedia*.

The anterior pituitary has no nervous connection to the hypothalamus but is connected to it by a complex of blood vessels called the **hypophyseal portal system** (fig. 17.4b). This begins with a network of *primary capillaries* in the hypothalamus, leading to *portal venules* (small veins) that travel down the pituitary stalk to a complex of *secondary capillaries* in the anterior pitu-

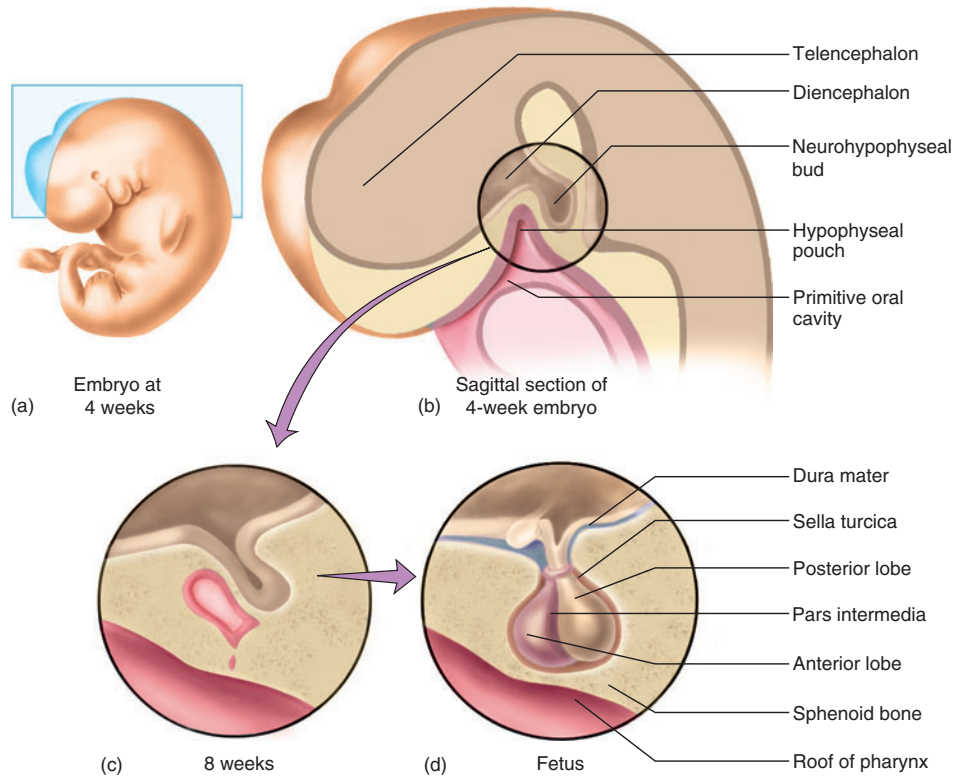
itary. The primary capillaries pick up hormones from the hypothalamus, the venules deliver them to the anterior pituitary, and the hormones leave the circulation at the secondary capillaries.

The **neurohypophysis** constitutes the posterior one-quarter of the pituitary. It has three parts: an extension of the hypothalamus called the *median eminence*; the *stalk*; and the largest part, the **posterior lobe** (*pars nervosa*). The neurohypophysis is not a true gland but a mass of neuroglia and nerve fibers. The nerve fibers arise from cell bodies in the hypothalamus, travel down the stalk as a bundle called the **hypothalamo-hypophyseal tract**, and end in the posterior lobe. The hypothalamic neurons synthesize hormones, transport them down the stalk, and store them in the posterior pituitary until a nerve signal triggers their release.

## Hypothalamic Hormones

The hypothalamus produces nine hormones important to our discussion. Seven of them, listed in figure 17.4 and table 17.3, travel through the portal system and regulate

<sup>6</sup>adeno = gland



**Figure 17.3 Embryonic Development of the Pituitary Gland.** (a) Plane of section seen in b. (b) Sagittal section of the embryo showing the early beginnings of the adenohypophysis and neurohypophysis. (c) Separation of the hypophyseal pouch from the pharynx at about 8 weeks. (d) Development nearly completed. The pars intermedia largely disappears by birth.

the activities of the anterior pituitary. Five of these are *releasing hormones* that stimulate the anterior pituitary to secrete its hormones, and two are *inhibiting hormones* that suppress pituitary secretion. Most of these hypothalamic hormones control the release of just one anterior pituitary hormone. Gonadotropin-releasing hormone, however, controls the release of both follicle-stimulating hormone and luteinizing hormone.

The other two hypothalamic hormones are secreted by way of the posterior pituitary. These are **oxytocin (OT)** and **antidiuretic hormone (ADH)**. OT is produced mainly by neurons in the **paraventricular<sup>7</sup> nuclei** of the hypothalamus, so-called because they lie in the walls of the third ventricle (the nuclei are paired right and left). ADH is produced mainly by the **supraoptic<sup>8</sup> nuclei**, so-called because they lie just above the optic chiasm on each side. Each nucleus also produces smaller quantities of the other hormone.

<sup>7</sup>*para* = next to + *ventricular* = pertaining to the ventricle

<sup>8</sup>*supra* = above

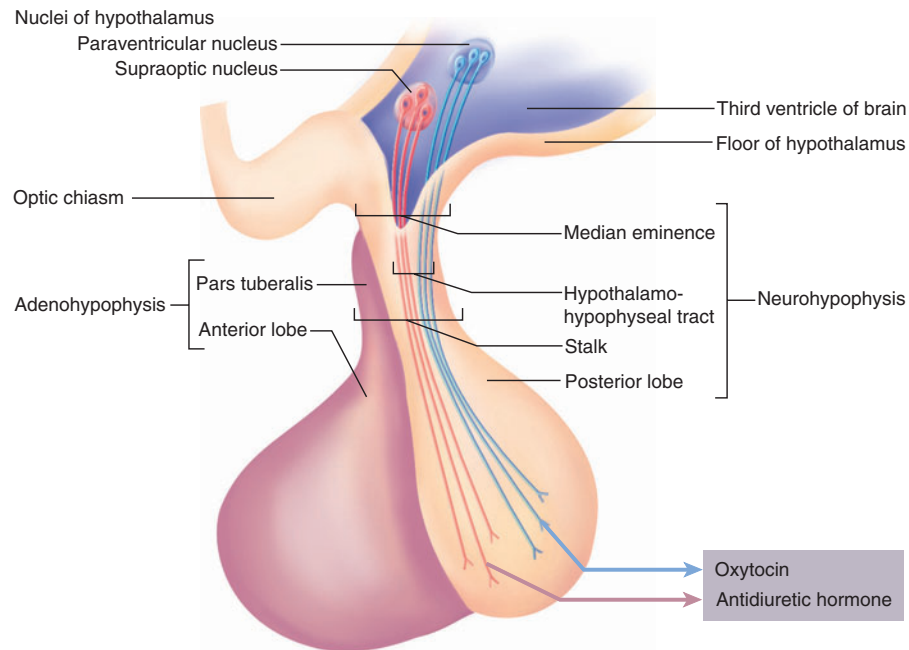
## Pituitary Hormones

The secretions of the pituitary gland are as follows:

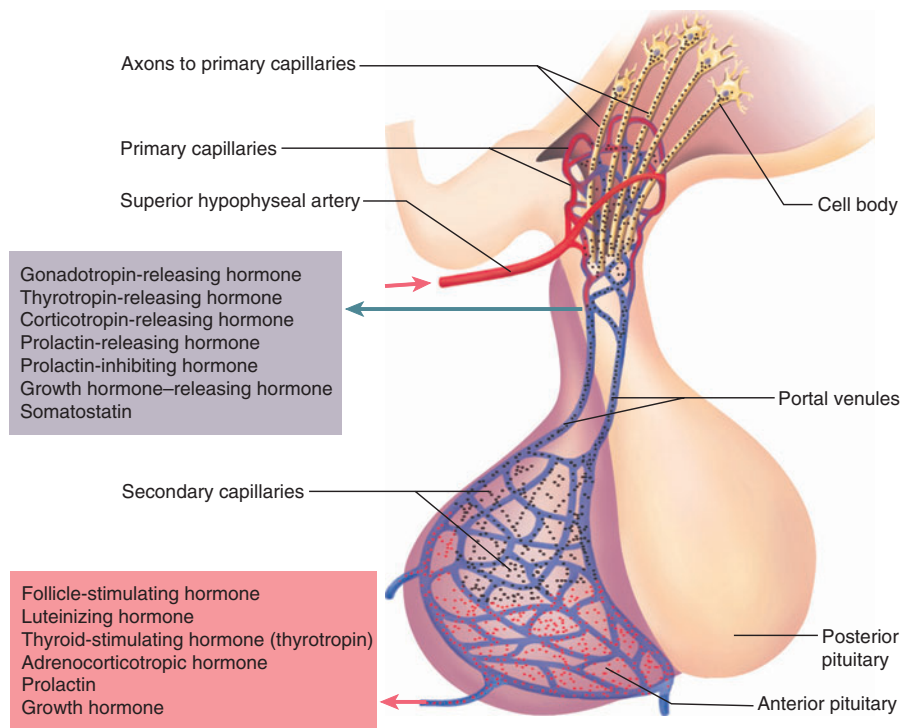
- The **anterior lobe** synthesizes and secretes six principal hormones: follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), growth hormone (GH), and prolactin (PRL) (table 17.4). The first five of these are **tropic**, or **trophic<sup>9</sup> hormones**—pituitary hormones that stimulate endocrine cells elsewhere to release their own hormones. More specifically, the first two are called **gonadotropins** because their target organs are the gonads.

The hormonal relationship between the hypothalamus, pituitary, and a more remote endocrine gland is called an **axis**. There are three such axes: the **hypothalamic-pituitary-gonadal axis** involving GnRH, FSH, and LH, the **hypothalamic-pituitary-thyroid axis**

<sup>9</sup>*trop* = to turn, change; *troph* = to feed, nourish



(a)



(b)

**Figure 17.4 Anatomy of the Pituitary Gland.** (a) Major structures of the pituitary and hormones of the neurohypophysis. Note that these hormones are produced by two nuclei in the hypothalamus and later released from the posterior lobe of the pituitary. (b) The hypophyseal portal system. The hormones in the *violet box* are secreted by the hypothalamus and travel in the portal system to the anterior pituitary. The hormones in the *red box* are secreted by the anterior pituitary under the control of the hypothalamic releasers and inhibitors.

**Which lobe of the pituitary is essentially composed of brain tissue?**

**Table 17.3 Hypothalamic Releasing and Inhibiting Hormones that Regulate the Anterior Pituitary**

Hormone	Principal Effects
TRH: Thyrotropin-releasing hormone	Promotes TSH and PRL secretion
CRH: Corticotropin-releasing hormone	Promotes ACTH secretion
GnRH: Gonadotropin-releasing hormone	Promotes FSH and LH secretion
PRH: Prolactin-releasing hormone	Promotes PRL secretion
PIH: Prolactin-inhibiting hormone	Inhibits PRL secretion
GHRH: Growth hormone–releasing hormone	Promotes GH secretion
Somatostatin	Inhibits GH and TSH secretion

involving TRH and TSH, and the **hypothalamic-pituitary-adrenal axis** involving CRH and ACTH (fig. 17.5).

- The *pars intermedia* is absent from the adult human pituitary, but is present in other animals and the human fetus. In other species, it secretes *melanocyte-stimulating hormone (MSH)*, which influences pigmentation of the skin, hair, or feathers. Humans, however, apparently produce no circulating MSH. Some anterior pituitary cells derived from the *pars intermedia* produce a large polypeptide called *pro-opiomelanocortin (POMC)*. POMC is not secreted but is processed within the pituitary to yield smaller fragments such as ACTH and endorphins.
- The *posterior lobe* produces no hormones of its own but only stores and releases OT and ADH. Since they are released into the blood by the posterior pituitary, however, these are treated as pituitary hormones for convenience.

## Actions of the Pituitary Hormones

Now for a closer look at what all of these pituitary hormones do. Most of these hormones receive their fullest treatment in later chapters on such topics as the urinary and reproductive systems, but growth hormone gets its fullest treatment here.

### Anterior Lobe Hormones

**Follicle-Stimulating Hormone (FSH)** FSH, one of the gonadotropins, is secreted by pituitary cells called *gonadotropes*. Its target organs are the ovaries and testes. In the ovaries, it stimulates the development of eggs and the follicles that contain them. In the testes, it stimulates sperm production.

**Luteinizing Hormone (LH)** LH, the other gonadotropin, is also secreted by the gonadotropes. In females, it stimu-

lates *ovulation* (the release of an egg). LH is named for the fact that after ovulation, the remainder of a follicle is called the *corpus luteum* (“yellow body”). LH stimulates the corpus luteum to secrete estrogen and progesterone, hormones important to pregnancy. In males, LH stimulates *interstitial cells* of the testes to secrete testosterone.

**Thyroid-Stimulating Hormone (TSH), or Thyrotropin** TSH is secreted by pituitary cells called *thyrotropes*. It stimulates growth of the thyroid gland and the secretion of thyroid hormone, which has widespread effects on the body’s metabolism considered later in this chapter.

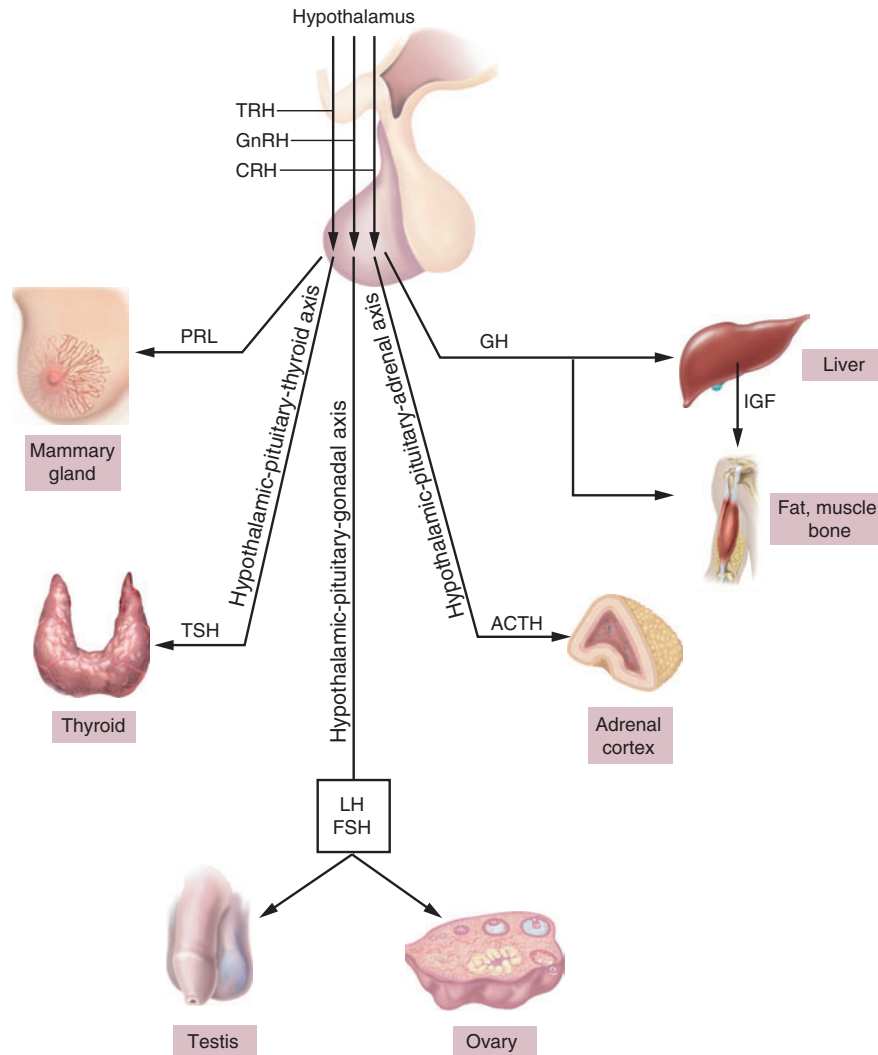
**Adrenocorticotropic Hormone (ACTH), or Corticotropin** ACTH is secreted by pituitary cells called *corticotropes*. ACTH stimulates the adrenal cortex to secrete its hormones (*corticosteroids*), especially cortisol, which regulates glucose, fat, and protein metabolism. ACTH plays a central role in the body’s response to stress, which we will examine more fully later in this chapter.

**Prolactin<sup>10</sup> (PRL)** PRL is secreted by *lactotropes* (*mam-motropes*), which increase greatly in size and number during pregnancy. PRL level rises during pregnancy, but it has no effect until after a woman gives birth. Then, it stimulates the mammary glands to synthesize milk. In males, PRL has a gonadotropic effect that makes the testes more sensitive to LH. Thus, it indirectly enhances their secretion of testosterone.

**Growth Hormone (GH), or Somatotropin** GH is secreted by *somatotropes*, the most numerous cells in the anterior pituitary. The pituitary produces at least a thousand times as much GH as any other hormone. The general effect of GH is to promote mitosis and cellular differentiation and thus to promote widespread tissue growth. Unlike the foregoing hormones, GH is not targeted to any one or few organs, but has widespread effects on the body, especially

<sup>10</sup>*pro* = favoring + *lact* = milk





**Figure 17.5 Principal Hormones of the Anterior Pituitary Gland and Their Target Organs.** The three axes physiologically link pituitary function to the function of other endocrine glands.

on cartilage, bone, muscle, and fat. It exerts these effects both directly and indirectly. GH itself directly stimulates these tissues, but it also induces the liver and other tissues to produce growth stimulants called **insulin-like growth factors (IGF-I and II)**, or **somatomedins**,<sup>11</sup> which then stimulate target cells in diverse tissues. Most of these effects are caused by IGF-I, but IGF-II is important in fetal growth.

Hormones have a **half-life**, the time required for half of the hormone to be cleared from the blood. GH is short-lived; it has a half-life of 6 to 20 minutes. IGFs, by contrast,

have half-lives of about 20 hours, so they greatly prolong the effect of GH. The mechanisms of GH-IGF action include:

- **Protein synthesis.** Tissue growth requires protein synthesis, and protein synthesis needs two things: amino acids for building material, and messenger RNA (mRNA) for instructions. Within minutes of GH secretion, preexisting mRNA is translated and proteins synthesized; within a few hours, DNA is transcribed and more mRNA is produced. GH enhances amino acid transport into cells, and to ensure that protein synthesis outpaces breakdown, it suppresses protein catabolism.
- **Lipid metabolism.** To provide energy for growing tissues, GH stimulates adipocytes to catabolize fat and

<sup>11</sup>Acronym for *somatotropin mediating protein*

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release free fatty acids (FFAs) and glycerol into the blood. GH has a **protein-sparing effect**—by liberating FFAs and glycerol for energy, it makes it unnecessary for cells to consume their proteins.

- **Carbohydrate metabolism.** GH also has a **glucose-sparing effect**. Its role in mobilizing FFAs reduces the body's dependence on glucose, which is used instead for glycogen synthesis and storage.
- **Electrolyte balance.** GH promotes  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Cl}^-$  retention by the kidneys, enhances  $\text{Ca}^{2+}$  absorption by the small intestine, and makes these electrolytes available to the growing tissues.

The most conspicuous effects of GH are on bone, cartilage, and muscle growth, especially during childhood and adolescence. IGF-I stimulates bone growth at the epiphyseal plates. It promotes the multiplication of chondrocytes and osteogenic cells and stimulates protein deposition in the cartilage and bone matrix. In adulthood, it stimulates osteoblast activity and the appositional growth of bone; thus, it continues to influence bone thickening and remodeling.

The blood GH concentration declines gradually with age—averaging about 6 ng/mL (ng = nanograms) in adolescence and one-quarter of that in very old age. The resulting decline in protein synthesis may contribute to aging of the tissues, including wrinkling of the skin and decreasing muscular mass and strength. At age 30, the average adult body is 10% bone, 30% muscle, and 20% fat; at age 75, it averages 8% bone, 15% muscle, and 40% fat.

GH concentration fluctuates greatly over the course of a day. It rises to 20 ng/mL or higher during the first 2 hours of deep sleep and may reach 30 ng/mL in response to vigorous exercise. Smaller peaks occur after high-protein meals, but high-carbohydrate meals tend to suppress GH secretion. Trauma, hypoglycemia (low blood sugar), and other conditions also stimulate GH secretion.

## Posterior Lobe Hormones

**Antidiuretic<sup>12</sup> Hormone (ADH).** ADH acts on the kidneys to increase water retention, reduce urine volume, and help prevent dehydration. We will study this hormone more extensively when we deal with the urinary system. ADH is also called *vasopressin* because it causes vasoconstriction at high concentrations. These concentrations are so unnatural for the human body, however, that this effect is of doubtful significance except in pathological states. ADH also functions as a brain neurotransmitter and is usually called vasopressin, or arginine vasopressin (AVP), in the neurobiology literature.

**Oxytocin<sup>13</sup> (OT).** OT has various reproductive roles. In childbirth, it stimulates smooth muscle of the uterus to

contract, thus contributing to the labor contractions that expel the infant. In lactating mothers, it stimulates muscle-like cells of the mammary glands to squeeze on the glandular acini and force milk to flow down the ducts to the nipple. In both sexes, OT secretion surges during sexual arousal and orgasm. It may play a role in the propulsion of semen through the male reproductive tract, in uterine contractions that help transport sperm up the female reproductive tract, and in feelings of sexual satisfaction and emotional bonding.

Hormones of the pituitary gland are summarized in table 17.4.

## Control of Pituitary Secretion

Pituitary hormones are not secreted at a steady rate. GH is secreted mainly at night, LH peaks at the middle of the menstrual cycle, and OT surges during labor and nursing, for example. The timing and amount of pituitary secretion are regulated by the hypothalamus, other brain centers, and feedback from the target organs.

## Hypothalamic and Cerebral Control

Both lobes of the pituitary gland are strongly subject to control by the brain. As we have seen, the anterior lobe is regulated by releasing and inhibiting hormones from the hypothalamus. Thus, the brain can monitor conditions within and outside of the body and stimulate or inhibit the release of anterior lobe hormones appropriately. For example, in cold weather, the hypothalamus stimulates the pituitary to secrete thyroid-stimulating hormone, which indirectly helps generate body heat; in times of stress, it triggers ACTH secretion, which indirectly mobilizes materials needed for tissue repair; during pregnancy, it induces prolactin secretion so a woman will be prepared to lactate; after a high-protein meal, it triggers the release of growth hormone so we can best use the amino acids for tissue growth.

The posterior lobe of the pituitary is controlled by **neuroendocrine reflexes**—the release of hormones in response to signals from the nervous system. For example, the suckling of an infant stimulates nerve endings in the nipple. Sensory signals are transmitted through the spinal cord and brainstem to the hypothalamus and from there to the posterior pituitary. This causes the release of oxytocin, which results in milk ejection.

Antidiuretic hormone (ADH) is also controlled by a neuroendocrine reflex. Dehydration raises the osmolarity of the blood, which is detected by hypothalamic neurons called *osmoreceptors*. The osmoreceptors trigger ADH release, and ADH promotes water conservation. Excessive blood pressure, by contrast, stimulates stretch receptors in the heart and certain arteries. By another neuroendocrine reflex, this inhibits ADH release, increases urine output, and brings blood volume and pressure back to normal.

Neuroendocrine reflexes can also involve higher brain centers. For example, the milk-ejection reflex can be

<sup>12</sup>anti = against + diuret = to pass through, urinate

<sup>13</sup>oxy = sharp, quick + toc = childbirth

**Table 17.4 Pituitary Hormones**

Hormone	Target Organ	Principal Effects
<b>Anterior Pituitary</b>		
FSH: Follicle-stimulating hormone	Ovaries, testes	Female: growth of ovarian follicles and secretion of estrogen Male: sperm production
LH: Luteinizing hormone	Ovaries, testes	Female: ovulation, maintenance of corpus luteum Male: testosterone secretion
TSH: Thyroid-stimulating hormone	Thyroid gland	Growth of thyroid, secretion of thyroid hormone
ACTH: Adrenocorticotropic hormone	Adrenal cortex	Growth of adrenal cortex, secretion of corticosteroids
PRL: Prolactin	Mammary glands, testes	Female: milk synthesis Male: increased LH sensitivity and testosterone secretion
GH: Growth hormone (somatotropin)	Liver	Somatomedin secretion, widespread tissue growth
<b>Posterior Pituitary</b>		
ADH: Antidiuretic hormone	Kidneys	Water retention
OT: Oxytocin	Uterus, mammary glands	Labor contractions, milk release; possibly involved in ejaculation, sperm transport, and sexual affection

triggered when a lactating mother simply hears a baby cry. Emotional stress can affect the secretion of gonadotropins, thus disrupting ovulation, the menstrual rhythm, and fertility.

### Think About It

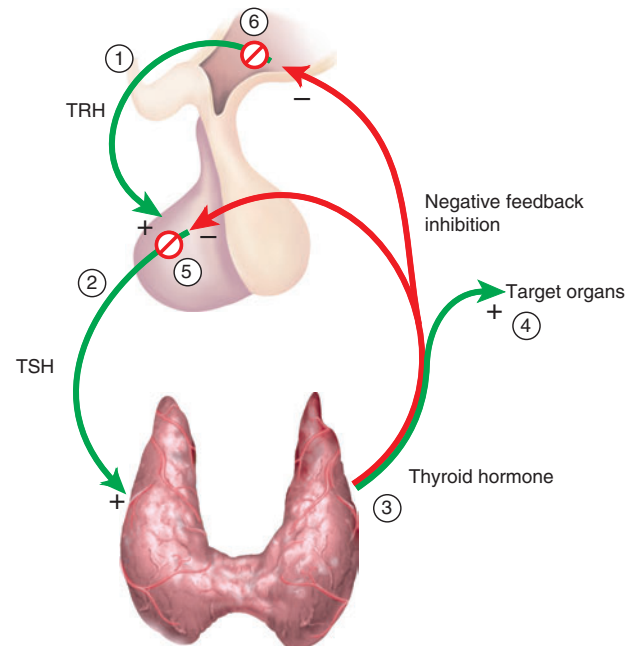
Which of the unifying themes at the end of chapter 1 (p. 21) is best exemplified by the neuroendocrine reflexes that govern ADH secretion?

### Feedback from Target Organs

The regulation of other endocrine glands by the pituitary is not simply a system of “command from the top down.” Those target organs also regulate the pituitary and hypothalamus through various feedback loops.

Most often, this takes the form of **negative feedback inhibition**—the pituitary stimulates another endocrine gland to secrete its hormone, and that hormone feeds back to the pituitary and inhibits further secretion of the tropic hormone. All of the pituitary axes are controlled this way. Figure 17.6 shows negative feedback inhibition in the pituitary-thyroid axis as an example. The figure is numbered to correspond to the following description:

1. The hypothalamus secretes thyrotropin-releasing hormone (TRH).
2. TRH stimulates the anterior pituitary to secrete thyroid-stimulating hormone (TSH).
3. TSH stimulates the thyroid gland to secrete the two thyroid hormones,  $T_3$  and  $T_4$ .
4.  $T_3$  and  $T_4$  stimulate the metabolism of most cells throughout the body.



**Figure 17.6 Negative Feedback Inhibition in the Pituitary-Thyroid Axis.** See text for explanation of numbered steps. Plus signs and green arrows represent stimulatory effects; minus signs and red arrows indicate inhibitory effects.

5.  $T_3$  and  $T_4$  also *inhibit* the release of TSH by the pituitary.
6. To a lesser extent,  $T_3$  and  $T_4$  also *inhibit* the release of TRH by the hypothalamus.

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Steps 5 and 6 are negative feedback inhibition of the pituitary and hypothalamus. These steps ensure that when thyroid hormone levels are high, TSH secretion remains low. If thyroid hormone secretion drops, TSH secretion rises and stimulates the thyroid to secrete more hormone. This negative feedback keeps thyroid hormone levels oscillating around a set point in typical homeostatic fashion.

### Think About It

If the thyroid gland were removed from a cancer patient, would you expect the level of TSH to rise or fall? Why?

Feedback from a target organ is not always inhibitory. During labor, oxytocin triggers a positive feedback cycle. Uterine stretching sends a nerve signal to the brain that stimulates OT release. OT stimulates uterine contractions, which push the infant downward. This stretches the lower end of the uterus some more, which results in a nerve signal that stimulates still more OT release. This positive feedback cycle continues until the infant is born (see fig. 1.13, p. 19).

### Before You Go On

Answer the following questions to test your understanding of the preceding section:

- What are two good reasons for considering the pituitary to be two separate glands?
- Name three anterior lobe hormones that have reproductive functions and three that have nonreproductive roles. What target organs are stimulated by each of these hormones?
- Briefly contrast hypothalamic control of the anterior pituitary with its control of the posterior pituitary.
- In what sense does the pituitary “take orders” from the target organs under its command?

## Other Endocrine Glands

### Objectives

When you have completed this section, you should be able to

- describe the structure and location of the remaining organs of the endocrine system; and
- name the hormones these endocrine organs produce and state their functions.

## The Pineal Gland

The **pineal**<sup>14</sup> (PIN-ee-ul) **gland** is a pine cone-shaped growth on the roof of the third ventricle of the brain, beneath

the posterior end of the corpus callosum (see fig. 17.1). The philosopher René Descartes (1596–1650) thought it was the seat of the human soul. If so, children must have more soul than adults—a child’s pineal gland is about 8 mm long and 5 mm wide, but after age seven it regresses rapidly and is no more than a tiny shrunken mass of fibrous tissue in the adult. Such shrinkage of an organ is called **involution**.<sup>15</sup> Pineal secretion peaks between the ages of 1 and 5 years and declines 75% by the end of puberty.

We no longer look for the human soul in the pineal gland, but this little organ remains an intriguing mystery. It produces **serotonin** by day and **melatonin** at night. In animals with seasonal breeding, it regulates the gonads and the annual breeding cycle. Melatonin may suppress gonadotropin secretion; removal of the pineal from animals causes premature sexual maturation. Some physiologists think that the pineal gland may regulate the timing of puberty in humans, but a clear demonstration of its role has remained elusive. Pineal tumors cause premature onset of puberty in boys, but such tumors also damage the hypothalamus, so we cannot be sure the effect is due specifically to pineal damage.

### Insight 17.1 Clinical Application

#### Melatonin, SAD, and PMS

There seems to be a relationship between melatonin and mood disorders, including depression and sleep disturbances. Some people experience a mood dysfunction called *seasonal affective disorder (SAD)*, especially in winter when the days are shorter and they get less exposure to sunlight, and in extreme northern and southern latitudes where sunlight may be dim to nonexistent for months at a time. SAD thus affects about 20% of the population in Alaska but only 2.5% in Florida. The symptoms—which include depression, sleepiness, irritability, and carbohydrate craving—can be relieved by 2 or 3 hours of exposure to bright light each day (*phototherapy*). Premenstrual syndrome (PMS) is similar to SAD and is also relieved by phototherapy. The melatonin level is elevated in both SAD and PMS and is reduced by phototherapy. However, there is also evidence that casts doubt on any causal link between melatonin and these mood disorders, so for now, “the jury is still out.” Many people are taking melatonin for jet lag, and it is quite effective, but it is also risky to use when we know so little, as yet, about its potential effect on reproductive function.

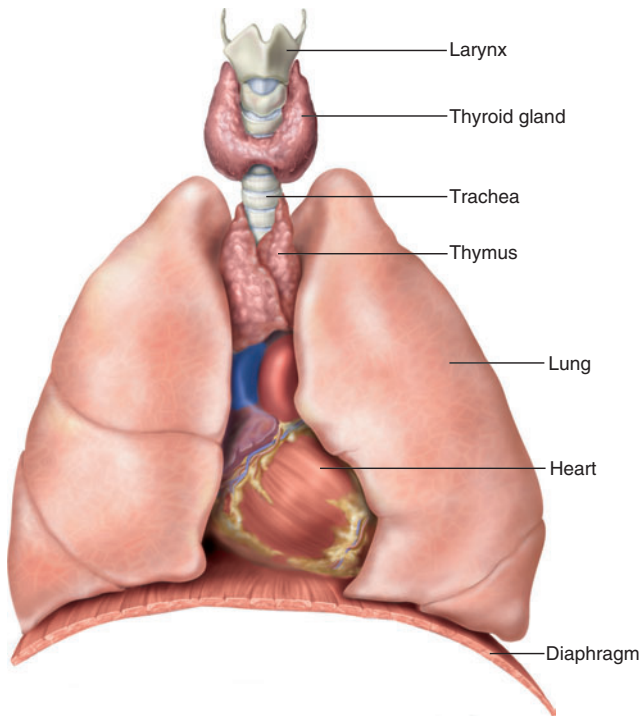
## The Thymus

The **thymus** is located in the mediastinum superior to the heart (fig. 17.7). Like the pineal, it is large in infants and children but involutes after puberty. In elderly people,

<sup>14</sup>pineal = pine cone

<sup>15</sup>in = inward + volution = rolling or turning





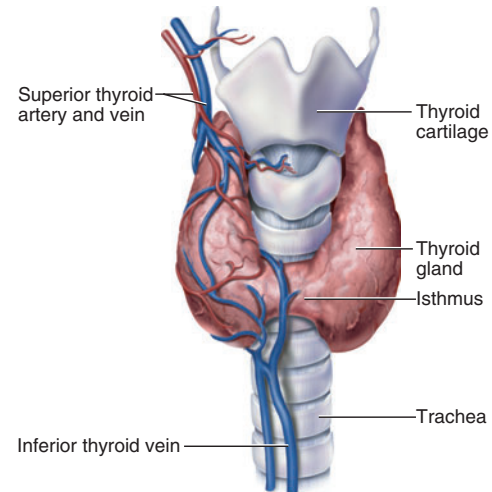
**Figure 17.7** Locations of the Thyroid Gland and Thymus. Which of these glands will be markedly smaller than the other in a 50-year-old?

it is a shriveled vestige of its former self, with most of its parenchyma replaced by fibrous and adipose tissue. The thymus secretes *thymopoietin* and *thymosins*, hormones that regulate the development and later activation of disease-fighting blood cells called T lymphocytes (*T* for *thymus*). This is discussed in detail in chapter 21.

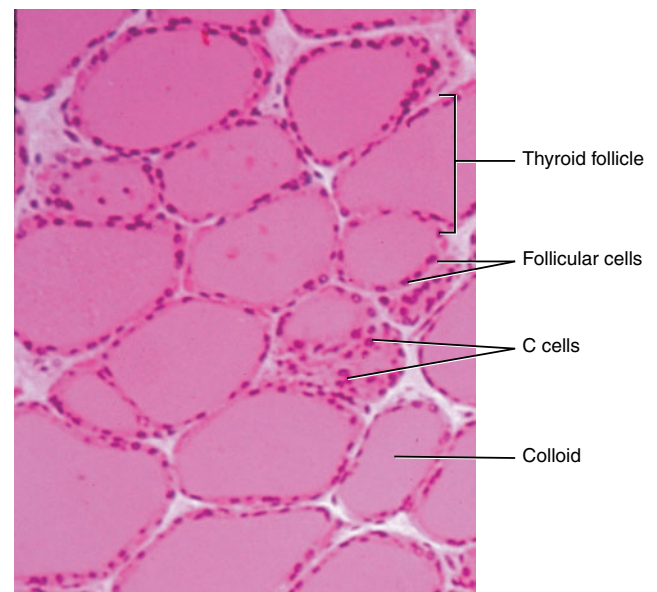
## The Thyroid Gland

The **thyroid gland** is the largest endocrine gland; it weighs 20 to 25 g and receives one of the body's highest rates of blood flow per gram of tissue. It is wrapped around the anterior and lateral aspects of the trachea, immediately below the larynx. It consists of two large lobes, one on each side of the trachea, connected by a narrow anterior **isthmus** (fig. 17.8a).

Histologically, the thyroid is composed mostly of sacs called **thyroid follicles** (fig. 17.8b). Each is filled with a protein-rich colloid and lined by a simple cuboidal epithelium of **follicular cells**. These cells secrete two main thyroid hormones—**T<sub>3</sub>**, or **triiodothyronine** (try-EYE-oh-doe-THY-ro-neen), and **thyroxine**, also known as **T<sub>4</sub>** or **tetraiodothyronine** (TET-ra-EYE-oh-doe-THY-ro-neen). These names refer to the fact that the two hormones con-



(a)



(b)

**Figure 17.8** The Thyroid Gland. (a) Gross anatomy; (b) histology.

tain three (T<sub>3</sub>) and four (T<sub>4</sub>) iodine atoms. The expression **thyroid hormone** refers to T<sub>3</sub> and T<sub>4</sub> collectively.

Thyroid hormone is secreted in response to TSH from the pituitary. The primary effect of TH is to increase the body's metabolic rate. As a result, it raises oxygen consumption and has a **calorigenic**<sup>16</sup> effect—it increases heat production. TH secretion rises in cold weather and

<sup>16</sup>*calor* = heat + *genic* = producing

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thus helps to compensate for increased heat loss. To ensure an adequate blood and oxygen supply to meet this increased metabolic demand, thyroid hormone also raises the heart rate and contraction strength and raises the respiratory rate. It accelerates the breakdown of carbohydrates, fats, and protein for fuel and stimulates the appetite. Thyroid hormone promotes alertness, bone growth and remodeling, the development of the skin, hair, nails, and teeth, and fetal nervous system and skeletal development. It also stimulates the pituitary gland to secrete growth hormone.

**Calcitonin** is another hormone produced by the thyroid gland. It comes from **C (calcitonin) cells**, also called *parafollicular cells*, found in clusters between the thyroid follicles. Calcitonin is secreted when blood calcium level rises. It antagonizes the action of parathyroid hormone (described shortly) and promotes calcium deposition and bone formation by stimulating osteoblast activity. Calcitonin is important mainly to children. It has relatively little effect in adults for reasons explained earlier (p. 232).

## The Parathyroid Glands

The **parathyroid glands** are partially embedded in the posterior surface of the thyroid (fig. 17.9). There are usually four, each about 3 to 8 mm long and 2 to 5 mm wide. They secrete **parathyroid hormone (PTH)** in response to hypocalcemia. PTH raises blood calcium levels by promoting the synthesis of calcitriol, which in turn promotes intestinal calcium absorption; by inhibiting urinary calcium excretion; by promoting phosphate excretion (so the phosphate does not combine with calcium and deposit into the bones); and by indirectly stimulating osteoclasts to resorb bone. PTH and calcium metabolism are discussed in more detail in chapter 7.

## The Adrenal Glands

An **adrenal (suprarenal) gland** sits like a cap on the superior pole of each kidney (fig. 17.10). In adults, the adrenal is about 5 cm (2 in.) long, 3 cm (1.2 in.) wide, and weighs about 4 g; it weighs about twice this much at birth. Like the pituitary gland, the adrenal gland is formed by the merger of two fetal glands with different origins and functions. Its inner core, the *adrenal medulla*, is a small portion of the total gland. Surrounding it is a much thicker *adrenal cortex*.

### The Adrenal Medulla

The **adrenal medulla** was discussed as part of the sympathetic nervous system in chapter 15. It arises from the neural crest and is not fully formed until the age of three. It is actually a sympathetic ganglion consisting of modified neu-

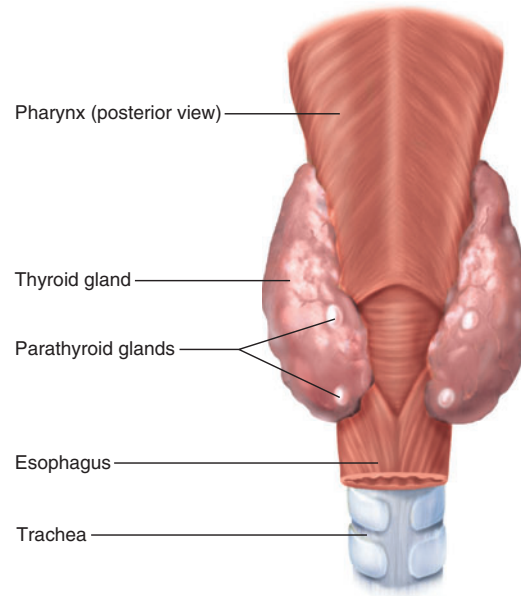
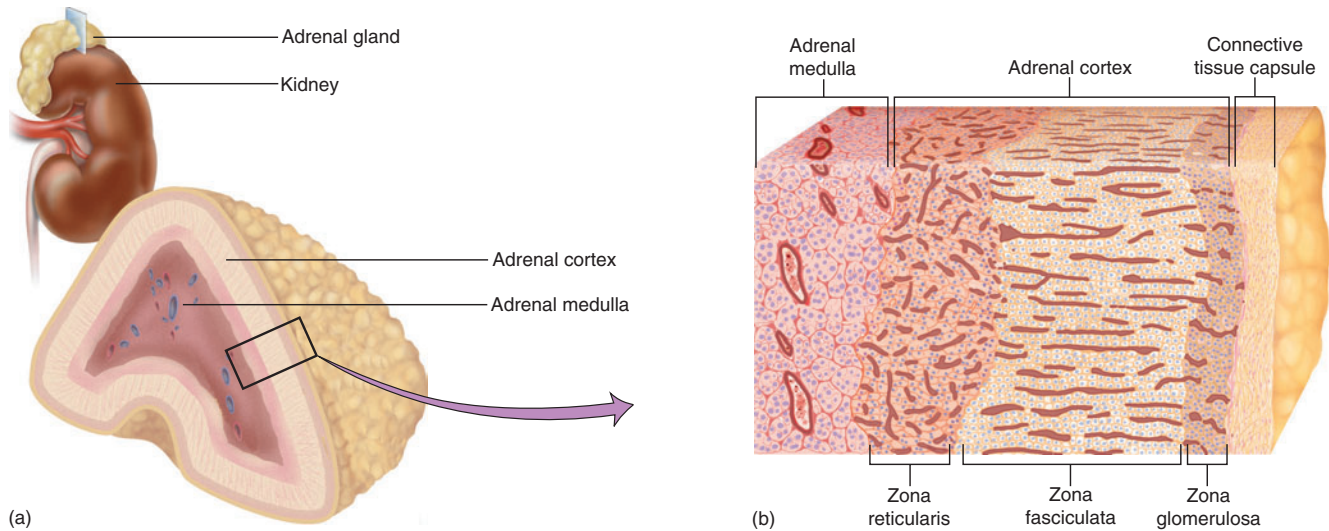


Figure 17.9 The Parathyroid Glands.

rons, called *chromaffin cells*, that lack dendrites and axons. These cells are richly innervated by sympathetic preganglionic fibers and respond to stimulation by secreting catecholamines, especially epinephrine and norepinephrine. About three-quarters of the output is epinephrine.

These hormones supplement the effects of the sympathetic nervous system, but their effects last much longer (about 30 min.) because the hormones circulate in the blood. They prepare the body for physical activity in several ways. They raise the blood pressure and heart rate, increase circulation to the skeletal muscles, increase pulmonary airflow, and inhibit such temporarily inessential functions as digestion and urine formation. They stimulate **glycogenolysis** (hydrolysis of glycogen to glucose) and **gluconeogenesis** (the synthesis of glucose from amino acids and other substrates), thus raising the blood glucose level. In order to further ensure an adequate supply of glucose to the brain, epinephrine inhibits insulin secretion and thus, the uptake and use of glucose by the muscles and other insulin-dependent organs. Thus, epinephrine has a glucose-sparing effect, sparing it from needless consumption by organs that can use alternative fuels to ensure that the nervous system has an adequate supply.

The medulla and cortex are not as functionally independent as once thought. The boundary between them is indistinct and some cells of the medulla extend into the cortex. When stress activates the sympathetic nervous system, these medullary cells secrete catecholamines that stimulate the cortex to secrete corticosterone.



**Figure 17.10** The Adrenal Gland. (a) Gross anatomy; (b) histology.

## The Adrenal Cortex

The **adrenal cortex** has three layers of glandular tissue (fig. 17.10b)—an outer **zona glomerulosa**<sup>17</sup> (glo-MER-you-LO-suh) composed of globular cell clusters; a thick middle **zona fasciculata**<sup>18</sup> (fah-SIC-you-LAH-ta) composed of cell columns separated by blood sinuses; and an inner **zona reticularis**<sup>19</sup> (reh-TIC-you-LAR-iss), where the cells form a network. The cortex synthesizes more than 25 steroid hormones known collectively as the **corticosteroids**, or **corticoids**. The three tissue layers secrete, in the same order, the following corticosteroids:

1. **Mineralocorticoids** (zona glomerulosa only), which act on the kidneys to control electrolyte balance. The principal mineralocorticoid is **aldosterone**, which promotes  $\text{Na}^+$  retention and  $\text{K}^+$  excretion by the kidneys. Aldosterone is discussed more fully in chapter 24.
2. **Glucocorticoids** (mainly zona fasciculata), especially **cortisol (hydrocortisone)**; **corticosterone** is a less potent relative. Glucocorticoids stimulate fat and protein catabolism, gluconeogenesis, and the release of fatty acids and glucose into the blood. This helps the body adapt to stress and repair damaged tissues. Glucocorticoids also have an anti-

inflammatory effect and are widely used in ointments to relieve swelling and other signs of inflammation. Long-term secretion, however, suppresses the immune system for reasons we will see later in the discussion of stress.

3. **Sex steroids** (mainly zona reticularis), including weak **androgens** and smaller amounts of **estrogens**. Androgens control many aspects of male development and reproductive physiology. The principal adrenal androgen is **dehydroepiandrosterone (DHEA)** (de-HY-dro-EP-ee-an-DROSS-tur-own). DHEA has weak hormonal effects in itself, but more importantly, other tissues convert it to the more potent androgen, **testosterone**. This source is relatively unimportant in men because the testes produce so much more testosterone than this. In women, however, the adrenal glands meet about 50% of the total androgen requirement. In both sexes, androgens stimulate the development of pubic and axillary hair and apocrine scent glands at puberty, and they sustain the libido (sex drive) throughout adult life.

Adrenal estrogen (estradiol) is of minor importance to women of reproductive age because its quantity is small compared to estrogen from the ovaries. After menopause, however, the ovaries no longer function and the adrenals are the only remaining estrogen source. Both androgens and estrogens promote adolescent skeletal growth and help to sustain adult bone mass.

<sup>17</sup>zona = zone + glomerul = little balls + osa = full of

<sup>18</sup>fascicul = little cords + ata = possessing

<sup>19</sup>reticul = little network + aris = like



### Think About It

Which could a person more easily live without—the adrenal medulla or adrenal cortex? Why?

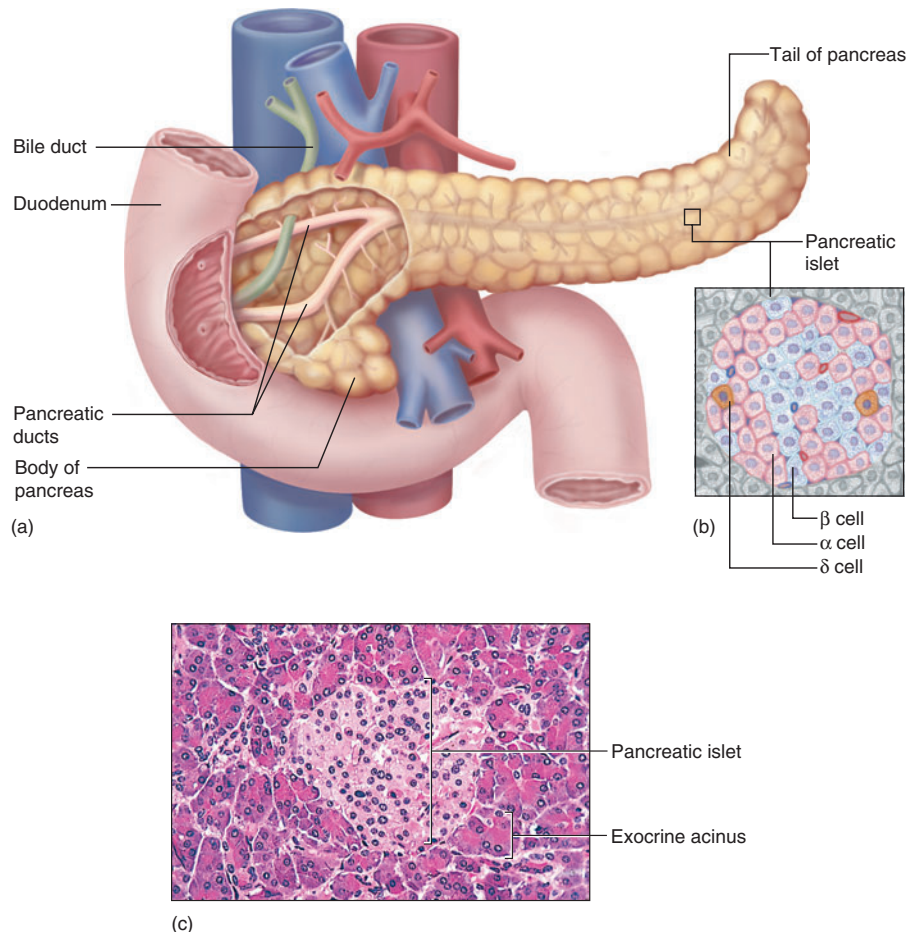
## The Pancreas

The elongated spongy **pancreas** is located retroperitoneally, inferior and dorsal to the stomach (fig. 17.11). It is approximately 15 cm long and 2.5 cm thick. Most of it is an exocrine digestive gland, but scattered through the exocrine tissue are endocrine cell clusters called **pancreatic islets (islets of Langerhans<sup>20</sup>)**. There are 1 to 2 million islets, but they constitute only about 2% of the pancreatic tissue. The islets secrete at least five hormones and

paracrine products, the most important of which are insulin, glucagon, and somatostatin.

- **Insulin** is secreted by the **beta ( $\beta$ ) cells** of the islets when we digest a meal and the level of glucose and amino acids in the blood rises. In such times of plenty, insulin stimulates cells to absorb glucose and amino acids from the blood and especially stimulates muscle and adipose tissue to store glycogen and fat. Essentially, insulin stimulates cells to store excess nutrients for later use, and it suppresses the use of already-stored fuels. The stored nutrients are then available for use between meals and overnight. By stimulating glycogen, fat, and protein synthesis, insulin promotes cell growth and differentiation. Insulin also antagonizes the effects of glucagon. Some cells and organs that do not depend on insulin for glucose uptake include the kidneys, brain, liver, and red blood cells. Insulin

<sup>20</sup>Paul Langerhans (1847–88), German anatomist



**Figure 17.11 The Pancreas.** (a) Gross anatomy and relationship to the duodenum and other nearby organs; (b) the  $\alpha$ ,  $\beta$ , and  $\delta$  cells of a pancreatic islet; (c) light micrograph of a pancreatic islet amid the exocrine acini.



does, however, promote the liver's synthesis of glycogen from the absorbed glucose.

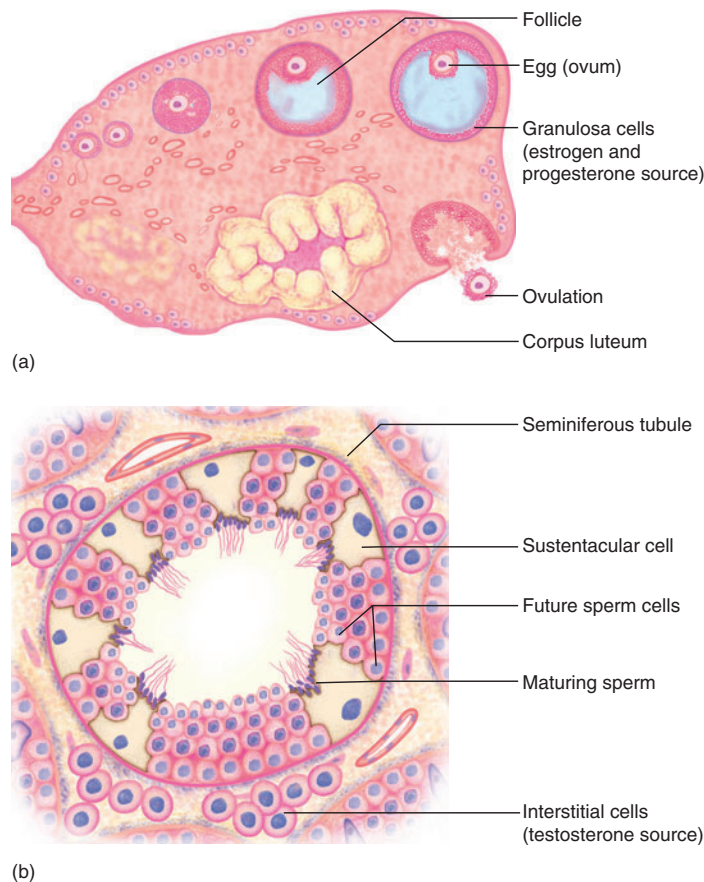
- **Glucagon** is secreted by **alpha ( $\alpha$ ) cells** when blood glucose concentration falls between meals. In the liver, it stimulates gluconeogenesis, glycogenolysis, and the release of glucose into circulation. In adipose tissue, it stimulates fat catabolism and the release of free fatty acids. Glucagon is also secreted in response to rising amino acid levels in the blood after a high-protein meal. By promoting amino acid absorption, it provides cells with raw material for gluconeogenesis.
- **Somatostatin** is secreted by the **delta ( $\delta$ ) cells** when blood glucose and amino acids rise after a meal. Somatostatin travels briefly in the blood and inhibits various digestive functions, but also acts locally in the pancreas as a *paracrine* secretion—a chemical messenger that diffuses through the tissue fluid to target cells a short distance away. Somatostatin inhibits the secretion of glucagon and insulin by the neighboring  $\alpha$  and  $\beta$  cells.

Any hormone that raises blood glucose concentration is called a *hyperglycemic hormone*. You may have noticed that glucagon is not the only hormone that does so; so do growth hormone, epinephrine, norepinephrine, cortisol, and corticosterone. Insulin is called a *hypoglycemic hormone* because it lowers blood glucose levels.

## The Gonads

Like the pancreas, the **gonads** are both endocrine and exocrine. Their exocrine products are eggs and sperm, and their endocrine products are the gonadal hormones, most of which are steroids.

Each follicle of the ovary contains an egg cell surrounded by a wall of **granulosa cells** (fig. 17.12a). The granulosa cells produce an estrogen called **estradiol** in the first half of the menstrual cycle. After ovulation, the corpus luteum secretes estradiol and **progesterone** for 12 days or so, or for 8 to 12 weeks in the event of pregnancy. The functions of estradiol and progesterone are discussed in chapter 28. In brief, they contribute to the development of the



**Figure 17.12 The Gonads.** (a) Histology of the ovary; (b) histology of the testis. The granulosa cells of the ovary and interstitial cells of the testis are endocrine cells.

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reproductive system and feminine physique, they promote adolescent bone growth, they regulate the menstrual cycle, they sustain pregnancy, and they prepare the mammary glands for lactation. The follicle and corpus luteum also secrete **inhibin**, which suppresses FSH secretion by means of negative feedback inhibition of the anterior pituitary.

The testis consists mainly of microscopic *seminiferous tubules* that produce sperm. Nestled between them are clusters of **interstitial cells** (fig. 17.12b), which produce testosterone and lesser amounts of weaker androgens and estrogen. Testosterone stimulates development of the male reproductive system in the fetus and adolescent, the development of the masculine physique in adolescence, and the sex drive. It sustains sperm production and the sexual instinct throughout adult life. **Sustentacular (Sertoli)<sup>21</sup> cells** of the testis secrete inhibin, which suppresses FSH secretion and thus homeostatically stabilizes the rate of sperm production.

## Endocrine Functions of Other Organs

Several other organs have hormone-secreting cells:

- **The heart.** High blood pressure stretches the heart wall and stimulates muscle cells in the atria to secrete **atrial natriuretic<sup>22</sup> peptide (ANP)**. ANP increases sodium excretion and urine output and opposes the action of angiotensin II, described shortly. Together, these effects lower the blood pressure.
- **The skin.** Keratinocytes of the epidermis produce vitamin D<sub>3</sub>, the first step in the synthesis of **calcitriol**. Its synthesis is completed by the liver and kidneys, as detailed in chapter 7.
- **The liver.** The liver converts vitamin D<sub>3</sub> to calcidiol, the second step in calcitriol synthesis. It is one of the sources of IGF-I, which mediates the action of growth hormone. It secretes about 15% of the body's **erythropoietin (EPO)** (eh-RITH-ro-POY-eh-tin), a hormone that stimulates the bone marrow to produce red blood cells. The liver also secretes a hormone precursor called *angiotensinogen*. In the blood, angiotensinogen is converted to angiotensin I by a kidney enzyme (*renin*) and then to angiotensin II by a lung enzyme (*angiotensin-converting enzyme, ACE*). Angiotensin II is a hormone that stimulates vasoconstriction and aldosterone secretion. Together, these effects raise blood pressure.
- **The kidneys.** The kidneys convert calcidiol to calcitriol, the active form of vitamin D. Calcitriol promotes calcium absorption by the small intestine, somewhat inhibits calcium loss in the urine, and thus

makes more calcium available for bone deposition and other metabolic needs. The kidneys also produce about 85% of our EPO, and convert angiotensinogen to angiotensin I.

- **The stomach and small intestine.** These have various *enteroendocrine cells*,<sup>23</sup> which secrete at least 10 **enteric hormones**. In general, they coordinate the different regions and glands of the digestive system with each other (see chapter 25).
- **The placenta.** This organ performs many functions in pregnancy, including fetal nutrition and waste removal. But it also secretes estrogen (estriol and estradiol), progesterone, and other hormones that regulate pregnancy and stimulate development of the fetus and the mother's mammary glands (see chapter 28).

You can see that the endocrine system is extensive. It includes numerous discrete glands as well as individual cells in the tissues of other organs. The endocrine organs and tissues other than the hypothalamus and pituitary are reviewed in table 17.5.

### Before You Go On

Answer the following questions to test your understanding of the preceding section:

9. Name three endocrine glands that are larger in children than in adults.
10. What is the value of the calorogenic effect of thyroid hormone?
11. Name a glucocorticoid, a mineralocorticoid, and a catecholamine secreted by the adrenal gland.
12. Does the action of glucocorticoids more closely resemble that of glucagon or insulin? Explain.
13. What is the difference between a gonadal hormone and a gonadotropin?

## Hormones and Their Actions

### Objectives

When you have completed this section, you should be able to

- identify the chemical classes to which various hormones belong;
- describe how hormones are synthesized and transported to their target organs;
- describe how hormones stimulate their target cells;
- explain how target cells regulate their sensitivity to circulating hormones;
- explain how hormones are removed from circulation after they have performed their roles; and
- explain how hormones affect each other when two or more of them stimulate the same target cells.

<sup>21</sup>Enrico Sertoli (1824–1910), Italian histologist

<sup>22</sup>*natri* = sodium + *uretic* = pertaining to urine

<sup>23</sup>*entero* = intestine

**Table 17.5 Hormones from Sources Other than the Hypothalamus and Pituitary**

Hormone	Target	Principal Effects
<b>Pineal Gland</b>		
Melatonin and serotonin	Brain	Influence mood; may regulate the timing of puberty
<b>Thymus</b>		
Thymopoietin and thymosins	T lymphocytes	Stimulate T lymphocytes
<b>Thyroid</b>		
Triiodothyronine (T <sub>3</sub> ) and thyroxine (T <sub>4</sub> )	Most tissues	Elevate metabolic rate, O <sub>2</sub> consumption, and heat production; stimulate circulation and respiration; promote nervous system and skeletal development
Calcitonin	Bone	Promotes Ca <sup>2+</sup> deposition and ossification; reduces blood Ca <sup>2+</sup> level
<b>Parathyroids</b>		
Parathyroid hormone (PTH)	Bone, kidneys	Increases blood Ca <sup>2+</sup> level by stimulating bone resorption and calcitriol synthesis and reducing urinary Ca <sup>2+</sup> excretion
<b>Adrenal Medulla</b>		
Epinephrine, norepinephrine, dopamine	Most tissues	Complement effects of sympathetic nervous system
<b>Adrenal Cortex</b>		
Aldosterone	Kidney	Promotes Na <sup>+</sup> retention and K <sup>+</sup> excretion, maintains blood pressure and volume
Cortisol and corticosterone	Most tissues	Stimulate fat and protein catabolism, gluconeogenesis, stress resistance, and tissue repair; inhibit immune system
Androgen (DHEA) and estrogen	Bone, muscle, integument, many other tissues	Growth of pubic and axillary hair, bone growth, sex drive, male prenatal development
<b>Pancreatic Islets</b>		
Insulin	Most tissues	Stimulates glucose and amino acid uptake; lowers blood glucose level; promotes glycogen, fat, and protein synthesis
Glucagon	Primarily liver	Stimulates gluconeogenesis, glycogen and fat breakdown, release of glucose and fatty acids into circulation
<b>Ovaries</b>		
Estradiol	Many tissues	Stimulates female reproductive development, regulates menstrual cycle and pregnancy, prepares mammary glands for lactation
Progesterone	Uterus, mammary glands	Regulates menstrual cycle and pregnancy, prepares mammary glands for lactation
Inhibin	Anterior pituitary	Inhibits FSH secretion
<b>Testes</b>		
Testosterone	Many tissues	Stimulates reproductive development, skeletomuscular growth, sperm production, and libido
Inhibin	Anterior pituitary	Inhibits FSH secretion
<b>Heart</b>		
Atrial natriuretic peptide	Kidney	Lowers blood volume and pressure by promoting Na <sup>+</sup> and water loss

(continued)

**Table 17.5 Hormones from Sources Other than the Hypothalamus and Pituitary (continued)**

Hormone	Target	Principal Effects
<b>Skin</b>		
Vitamin D <sub>3</sub>	—	First step in calcitriol synthesis (see kidneys)
<b>Liver</b>		
Calcidiol	—	Second step in calcitriol synthesis (see kidneys)
IGF-I	Many tissues	Mediates action of growth hormone
Erythropoietin	Red bone marrow	Promotes red blood cell production
Angiotensinogen (a prohormone)	Blood vessels	Precursor of angiotensin II, a vasoconstrictor
<b>Kidneys</b>		
Calcitriol	Small intestine, kidneys	Promotes bone deposition by increasing calcium and phosphate absorption in small intestine and reducing their urinary loss
Erythropoietin	Red bone marrow	Promotes red blood cell production
<b>Stomach and Small Intestine</b>		
Enteric hormones	Stomach and intestines	Coordinate digestive motility and secretion
<b>Placenta</b>		
Estrogen, progesterone, and others	Many tissues of mother and fetus	Enhance effects of ovarian hormones on fetal development, maternal reproductive system, and preparation for lactation

Having surveyed the body's major hormones and their effects, we are left with some deeper questions: Exactly what is a hormone? How are hormones synthesized and transported to their destinations? How does a hormone produce its effects on a target organ? Thus, we now address endocrinology at the molecular and cellular levels.

## Hormone Chemistry

Most hormones fall into three chemical classes—*steroids*, *peptides*, and *monoamines* (table 17.6).

1. **Steroid hormones** are derived from cholesterol. They include sex steroids produced by the testes and ovaries (such as estrogens, progesterone, and testosterone) and corticosteroids produced by the adrenal gland (such as cortisol, corticosterone, aldosterone, and DHEA). Calcitriol, the calcium-regulating hormone, is not a steroid but is derived from one and has the same hydrophobic character and mode of action as the steroids.
2. **Peptide hormones** are chains of 3 to 200 or more amino acids. The two posterior pituitary hormones, oxytocin and antidiuretic hormone, are very similar oligopeptides; they differ in only two of their nine amino acids (fig. 17.13). Except for dopamine, the

releasing and inhibiting hormones produced by the hypothalamus are polypeptides. Most hormones of the anterior pituitary are polypeptides or glycoproteins—polypeptides conjugated with short carbohydrate chains. All glycoprotein hormones have an identical  $\alpha$  chain of 92 amino acids and a variable  $\beta$  chain that distinguishes them from each other.

3. **Monoamines (biogenic amines)** were introduced in chapter 12, since this class also includes several neurotransmitters (see fig. 12.18, p. 465). The monoamine hormones include epinephrine, norepinephrine, dopamine, melatonin, and thyroid hormone. The first three of these are also called *catecholamines*. Monoamines are made from amino acids and retain an amino group, from which this hormone class gets its name.

## Hormone Synthesis

All hormones are made from either cholesterol or amino acids.

### Steroids

Steroid hormones are synthesized from cholesterol and differ mainly in the functional groups attached to the four-



**Table 17.6 Chemical Classification of Hormones**

**Steroids and Steroid Derivatives**

Aldosterone  
Calcitriol  
Corticosterone  
Cortisone  
Estrogens  
Progesterone  
Testosterone

**Oligopeptides (3–10 amino acids)**

Angiotensin II  
Antidiuretic hormone  
Gonadotropin-releasing hormone  
Oxytocin  
Thyrotropin-releasing hormone

**Polypeptides (14–199 amino acids)**

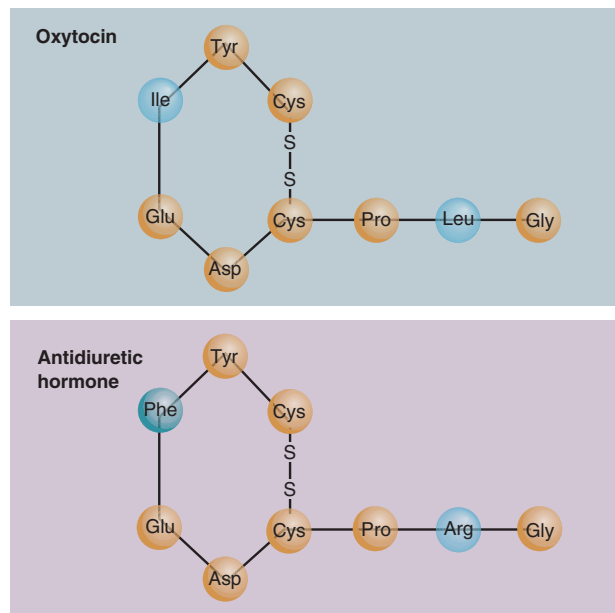
Adrenocorticotrophic hormone  
Atrial natriuretic peptide  
Calcitonin  
Corticotropin-releasing hormone  
Glucagon  
Growth hormone  
Growth hormone–releasing hormone  
Insulin  
Parathyroid hormone  
Prolactin  
Somatostatin

**Glycoproteins (92 amino acids in the  $\alpha$  chain, 112–18 amino acids in the  $\beta$  chain)**

Follicle-stimulating hormone  
Human chorionic gonadotropin  
Inhibin  
Luteinizing hormone  
Thyroid-stimulating hormone

**Monoamines**

Dopamine  
Epinephrine  
Melatonin  
Norepinephrine  
Serotonin  
Thyroxine ( $T_4$ )  
Triiodothyronine ( $T_3$ )



**Figure 17.13 Oxytocin and Antidiuretic Hormone.** Note the structural similarity of these two hormones of the posterior pituitary.

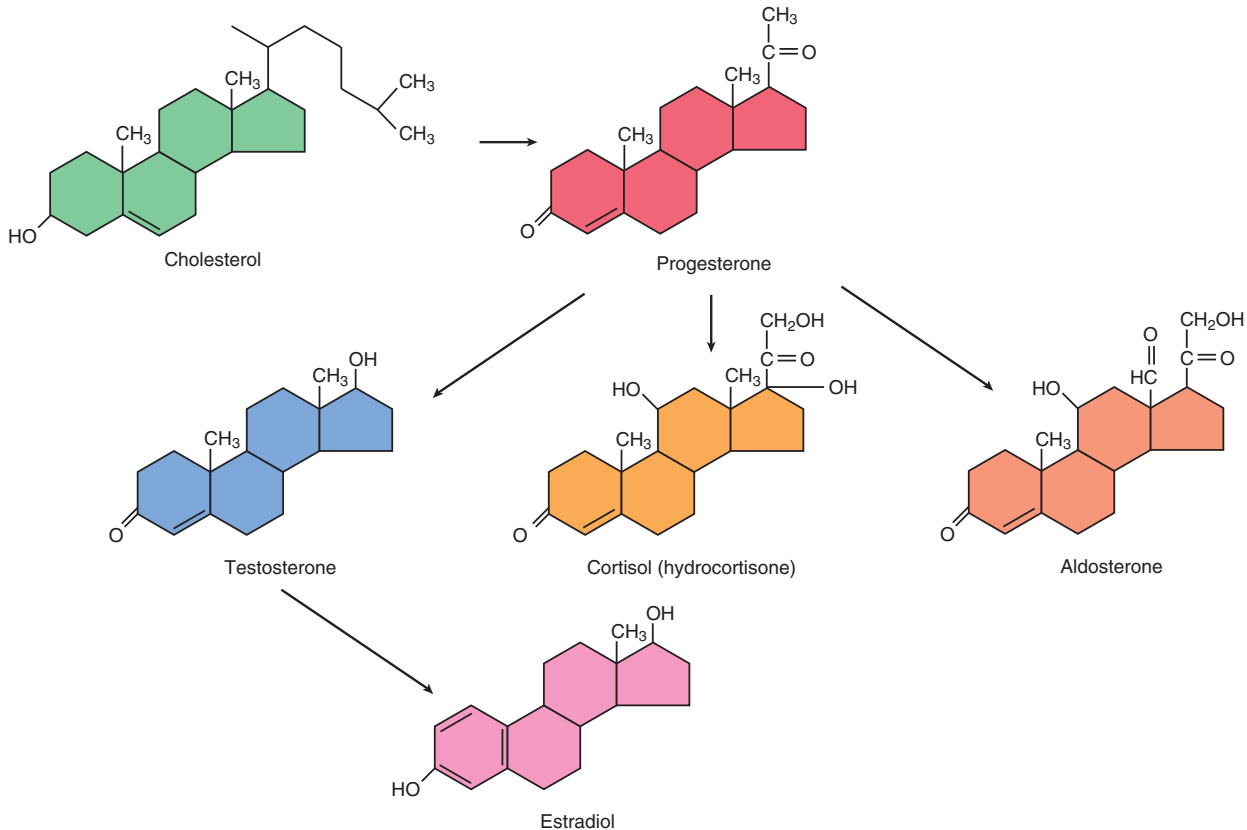
ringed steroid backbone. Figure 17.14 shows the synthetic pathway for several steroid hormones. Notice that while estrogen and progesterone are typically thought of as “female” hormones and testosterone as a “male” hormone, these sex steroids are interrelated in their synthesis and thus have roles in both sexes.

## Peptides

Peptide hormones are synthesized the same way as any other protein. The gene for the hormone is transcribed to form a molecule of mRNA, and ribosomes translate the mRNA and assemble amino acids in the right order to make the hormone. The newly synthesized polypeptide is an inactive **preprohormone**. It has a signal peptide of hydrophobic amino acids that guide it into the cisterna of the rough endoplasmic reticulum (as explained on p. 139). Here, the signal peptide is split off and the remainder of the polypeptide is now a **prohormone**. The prohormone is transferred to the Golgi complex, which may further cut and splice it and then package the hormone for secretion.

Insulin, for example, begins as *preproinsulin*. When the signal peptide is removed, the chain folds back on itself and forms three disulfide bridges. It is now called *proinsulin*. Enzymes in the Golgi complex then remove a large middle segment called the *connecting (C) peptide*. The remainder is now insulin, composed of two polypeptide chains totaling 51 amino acids, connected to each other by two of the three disulfide bridges (fig. 17.15). The

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**Figure 17.14 The Synthesis of Steroid Hormones from Cholesterol.** The ovaries secrete progesterone and estradiol, the testes and adrenal cortex secrete testosterone, and the adrenal cortex secretes cortisol and aldosterone.

C peptide is not wasted; it has recently been found to have some hormonal effects of its own, binding to cellular receptors and reducing some of the pathological effects of diabetes mellitus.

### Think About It

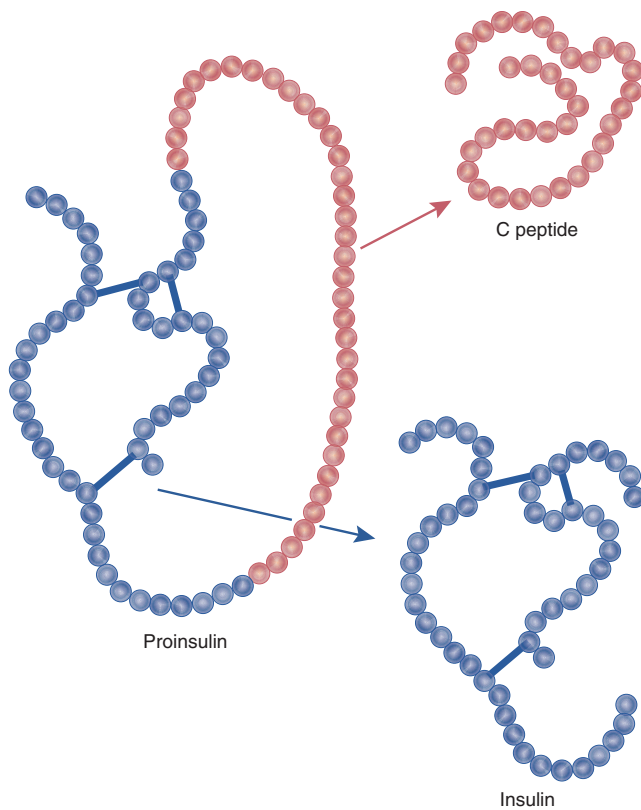
During the synthesis of glycoprotein hormones, where in the cell would the carbohydrate be added? (See chapter 4.)

## Monoamines

Melatonin is synthesized from the amino acid tryptophan and the other monoamines from the amino acid tyrosine. Thyroid hormone (TH) is an unusual case in three respects: (1) its synthesis begins with the production of a large protein called **thyroglobulin**, although this protein is not part of the finished TH; (2) TH is composed of *two* tyrosine molecules linked together; and (3) the synthesis of TH requires a mineral, iodine. TH is synthesized in the

follicles of the thyroid gland by the process shown in figure 17.16, numbered to correspond to the following description.

1. The thyroid follicle cells secrete thyroglobulin into the lumen of the follicle, forming a colloid that fills an active follicle. Thyroglobulin has 123 tyrosines, but only 4 to 8 of them are destined to become incorporated into thyroid hormone.
2. The follicle cells actively transport iodide ions ( $I^-$ ) from the blood into the cell and release them into the lumen. Here, the iodine is immediately oxidized to neutral iodine (I).
3. An iodine is added to a tyrosine of the thyroglobulin molecule, converting it to *monoiodotyrosine* (MON-oh-eye-OH-doe-TIE-ro-see), or *MIT*.
4. Another iodine *may* be added, converting MIT to *diiodotyrosine*, or *DIT*.
5. DIT can combine either with an MIT, as shown in the figure, or with another DIT. The small arrow in the figure shows where the oxygen of DIT bonds with



**Figure 17.15 The Synthesis of Insulin, a Representative Polypeptide Hormone.** Proinsulin has a connecting (C) peptide, 35 amino acids long, that is removed to leave insulin. Insulin has two polypeptide chains, 30 and 21 amino acids long, joined by two disulfide (–S–S–) bridges.

the carbon ring of the MIT. MIT splits away from its thyroglobulin backbone at this stage, but the DIT remains linked to the thyroglobulin. At this point, the hormone  $T_3$  is essentially formed. (If two DITs combine, the hormone produced is  $T_4$ . It has another iodine at the point indicated by the red arrow.)

6. When stimulated by TSH, the follicle cells take up droplets of colloid by pinocytosis (return to the top of the figure). A lysosome fuses with the pinocytotic vesicle and contributes an enzyme that hydrolyzes the thyroglobulin and liberates the thyroid hormone (step 6 at the bottom).
7. TH is released into the blood as a mixture of about 10%  $T_3$  and 90%  $T_4$ .

## Hormone Transport

To get from an endocrine cell to a target cell, a hormone must travel in the blood, which is mostly water. Most of the monoamines and peptides are hydrophilic, so mixing

with the blood plasma presents no problem for them. Steroids and thyroid hormone, however, are hydrophobic and must bind to hydrophilic **transport proteins** to get to their destination. The transport proteins are albumins and globulins synthesized by the liver. A hormone attached to a transport protein is called **bound hormone**, and one that is not attached is an **unbound (free) hormone**. Only the unbound hormone can leave a blood capillary and get to a target cell (fig. 17.17).

Transport proteins not only enable hydrophobic hormones to travel in the blood, they also prolong their half-lives. They protect circulating hormones from being broken down by enzymes in the blood plasma and liver and from being filtered out of the blood by the kidneys. Free hormone may be broken down or removed from the blood in a few minutes, whereas bound hormone may circulate for hours to weeks.

Thyroid hormone binds to three transport proteins in the blood plasma: *albumin*, an albumin-like protein called *thyretin*, and an  $\alpha$ -globulin named *thyroxine-binding globulin* (TBG). TBG binds the greatest amount. About 99.8% of  $T_3$  and 99.98% of  $T_4$  are protein-bound. Bound TH serves as a long-lasting blood reservoir, so even if the thyroid is surgically removed (as for cancer surgery), no signs of TH deficiency appear for about 2 weeks. Steroid hormones bind to globulins such as *transcortin*, the transport protein for cortisol. Aldosterone is unusual. It has no specific transport protein, but binds weakly to albumin and others. However, 85% of it remains unbound, and correspondingly, it has a half-life of only 20 minutes.

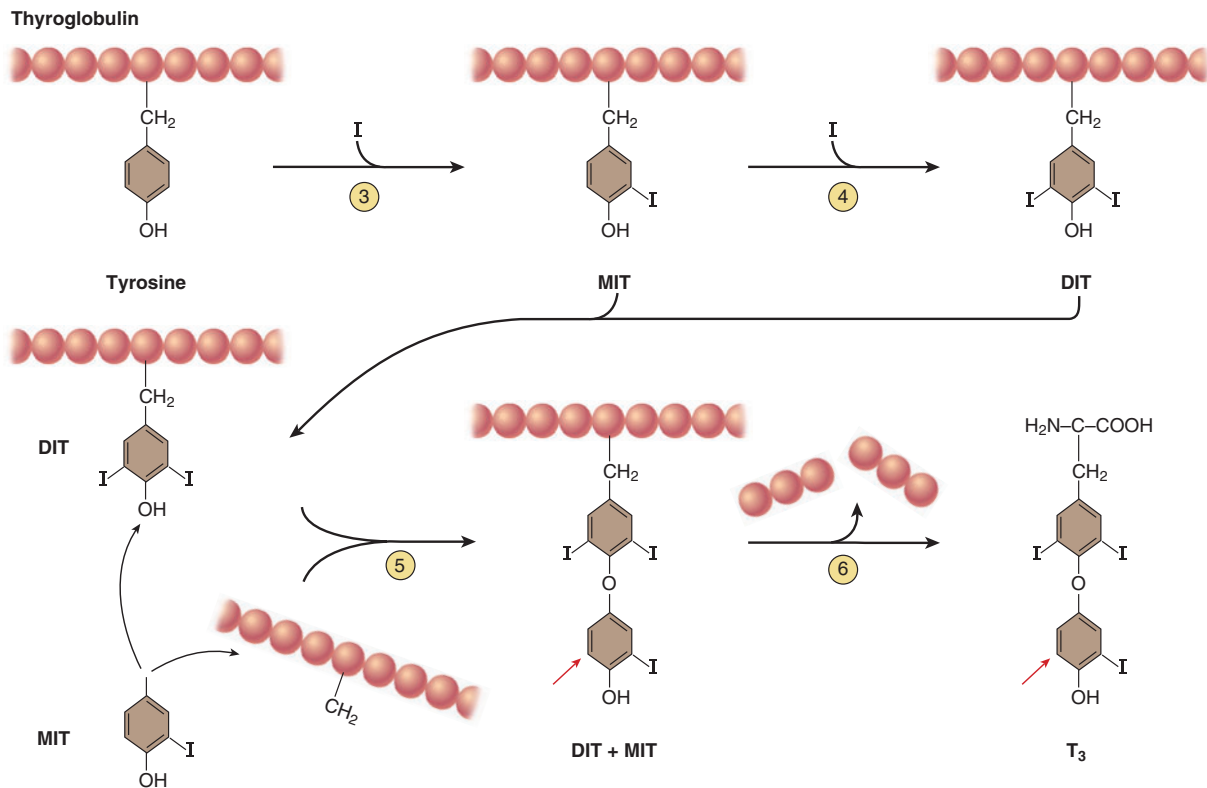
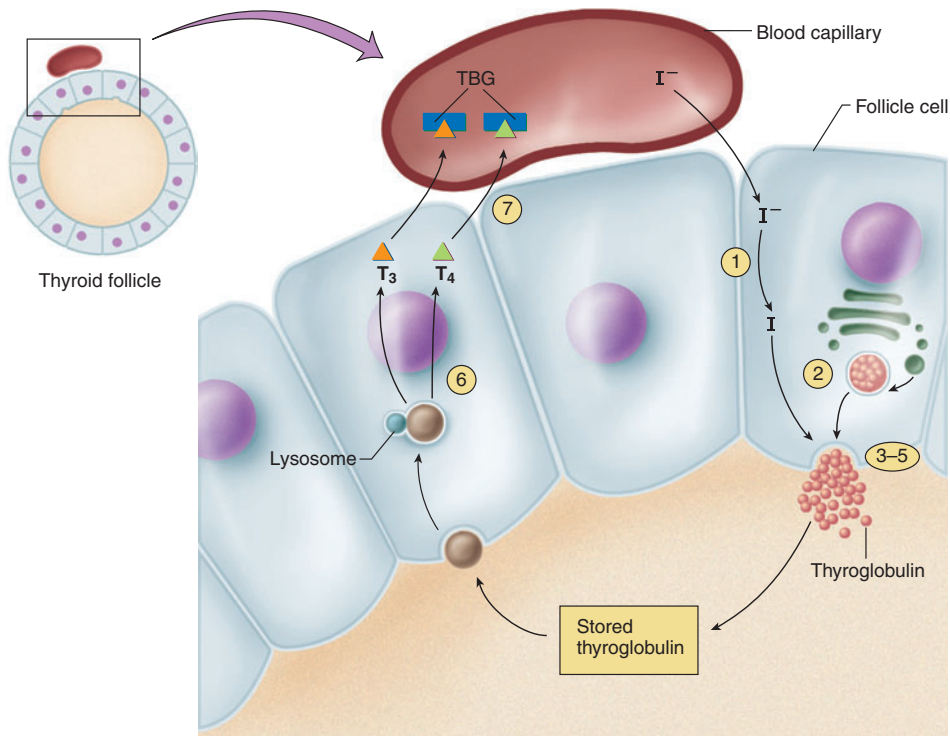
## Hormone Receptors and Mode of Action

Hormones stimulate only those cells that have receptors for them. The receptors are protein or glycoprotein molecules located on the plasma membrane, on mitochondria and other organelles in the cytoplasm, or in the nucleus. They act like switches to turn certain metabolic pathways on or off when the hormone binds to them. A target cell usually has a few thousand receptors for a given hormone. Receptor defects lie at the heart of several endocrine diseases (see insight 17.2).

### Insight 17.2 Clinical Application

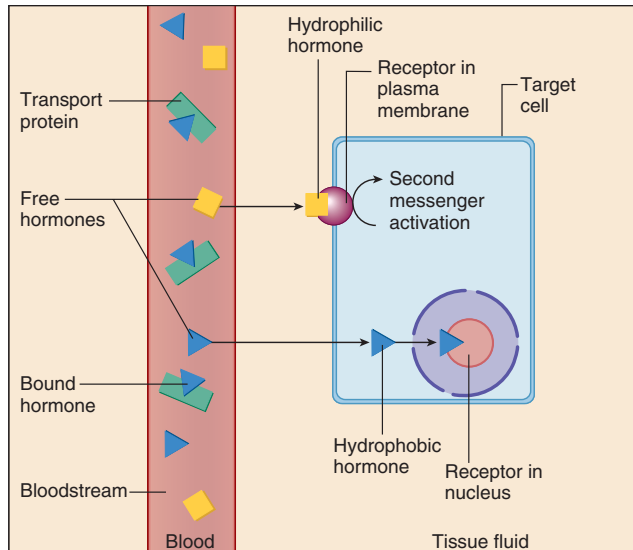
#### Hormone Receptors and Therapy

In treating endocrine disorders, it is essential to understand the role of hormone receptors. For example, type II diabetes mellitus is thought to result from an insulin receptor defect or deficiency (among other possible causes). No amount of insulin replacement can correct this. And while growth hormone is now abundantly available thanks to genetic engineering, it is useless to children with *Laron dwarfism*, who have a



**Figure 17.16 Synthesis of Thyroid Hormone (TH).** See text for explanation of numbered steps. The *upper part* of the figure shows where the processes of TH synthesis and secretion occur. The *lower part* shows the chemistry of steps 3 to 6.  $T_3$  synthesis is used as an example to show the roles played by both MIT and DIT. In  $T_4$  synthesis, two DITs would combine at step 5 and there would be another iodine atom at the point marked by the *red arrows*.





**Figure 17.17 Transport and Action of Hormones.**

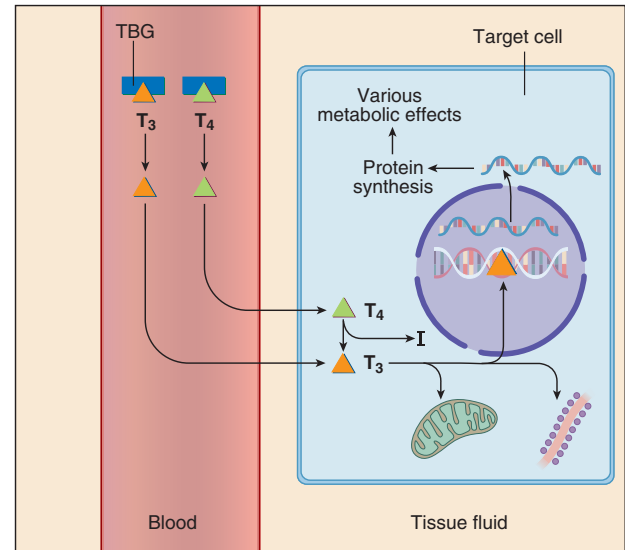
Hydrophobic hormones are carried in the blood by transport proteins. They enter the target cell and bind to receptors in the cytoplasm or nucleus. Hydrophilic hormones usually do not employ transport proteins. They bind to receptors at the target cell surface and activate the formation of second messengers in the target cell.

hereditary defect in their GH receptors. *Androgen insensitivity syndrome* is due to an androgen receptor defect or deficiency; it causes genetic males to develop feminine genitalia and other features (see insight 27.1, p. 1021). Estrogen stimulates the growth of some malignant tumors with estrogen receptors. For this reason, estrogen replacement therapy should not be used for women with estrogen-dependent cancer.

Receptor-hormone interactions are similar to the enzyme-substrate interactions described in chapter 2. Unlike enzymes, receptors do not chemically change their ligands, but they do exhibit enzymelike specificity and saturation. *Specificity* means that the receptor for one hormone will not bind other hormones. *Saturation* is the condition in which all the receptor molecules are occupied by hormone molecules. Adding more hormone cannot produce any greater effect.

## Steroids and Thyroid Hormone

The hydrophilic steroid and thyroid hormones easily penetrate the phospholipid plasma membrane of a target cell and enter the cytoplasm. Steroids enter the nucleus and bind to a receptor associated with the DNA. The receptor has three functional regions that explain its action on the DNA: one that binds the hormone, one that binds to an *acceptor site* on the chromatin, and one that activates DNA transcription at that site. Transcription produces new



**Figure 17.18 The Action of Thyroid Hormone on a Target Cell.**

T<sub>3</sub> and T<sub>4</sub> dissociate from thyroxine-binding globulin (TBG), leave the bloodstream, and enter the target cell cytoplasm. Here, T<sub>4</sub> is converted to T<sub>3</sub> by the removal of one iodine atom. T<sub>3</sub> may bind to receptors on the mitochondria or ribosomes, or enter the nucleus and activate genetic transcription.

mRNA that leads to the synthesis of proteins, which then alter the metabolism of the target cell. Estrogen, for example, stimulates cells of the uterine lining to synthesize proteins that act as progesterone receptors. Progesterone, which comes later in the menstrual cycle, then binds to these receptors and stimulates the cells to produce enzymes that synthesize glycogen. Glycogen prepares the uterus to nourish an embryo in the event of pregnancy.

Even though T<sub>4</sub> constitutes 90% of the secreted thyroid hormone, it has little direct metabolic effect on the target cells. Unbound T<sub>3</sub> and T<sub>4</sub> enter the target cell cytoplasm, where an enzyme converts the T<sub>4</sub> to T<sub>3</sub> by removing one iodine. T<sub>3</sub> binds to receptors in three sites: on mitochondria, where it increases the rate of aerobic respiration; on ribosomes, where it stimulates the translation of mRNA and thus increases the rate of protein synthesis; and in the nucleus, where it binds to receptors in the chromatin and stimulates DNA transcription (mRNA synthesis) (fig. 17.18). One of the proteins produced under the influence of T<sub>3</sub> is Na<sup>+</sup>-K<sup>+</sup> ATPase—the sodium-potassium pump. As we saw in chapter 3 (p. 111), one of the functions of Na<sup>+</sup>-K<sup>+</sup> ATPase is to generate heat, thus accounting for the calorogenic effect of thyroid hormone.

## Peptides and Catecholamines

Peptides and catecholamines (hydrophilic hormones) cannot penetrate into a target cell, so they must stimulate its

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physiology indirectly. They bind to cell-surface receptors, which are linked to second-messenger systems on the other side of the plasma membrane (see fig. 17.17). The best-known second messenger is cyclic adenosine monophosphate (cAMP). When glucagon binds to liver cell receptors, for example, the receptor activates a G protein, which in turn activates adenylate cyclase, the membrane enzyme that produces cAMP. cAMP leads ultimately to the activation of enzymes that hydrolyze glycogen stored in the liver cell (fig. 17.19). Somatostatin, however, works by *inhibiting* cAMP synthesis. Atrial natriuretic peptide (ANP) works through a similar second messenger, cyclic guanosine monophosphate (cGMP). These second messengers do not linger in the cell for long. cAMP, for example, is broken down very quickly by an enzyme called **phosphodiesterase**.

Other second messengers include **diacylglycerol (diglyceride)** and **inositol triphosphate (IP<sub>3</sub>)** (fig. 17.20). In oxytocin action, for example, the receptor activates a G protein and the G protein activates a membrane enzyme, *phospholipase*. Phospholipase breaks down certain phospholipids of the plasma membrane into diacylglycerol and IP<sub>3</sub>. Diacylglycerol activates protein kinases much like cAMP does, with similarly diverse effects. IP<sub>3</sub> binds to the smooth endoplasmic reticulum or to ligand-gated calcium channels in the plasma membrane. In either case, it triggers a flood of Ca<sup>2+</sup> into the cytoplasm. Calcium, the *third messenger*, can do several things: open or close channels that alter the permeability and membrane potential of the cell; directly activate certain enzymes; or bind to a cytoplasmic receptor called **calmodulin**, which in turn activates protein kinases.

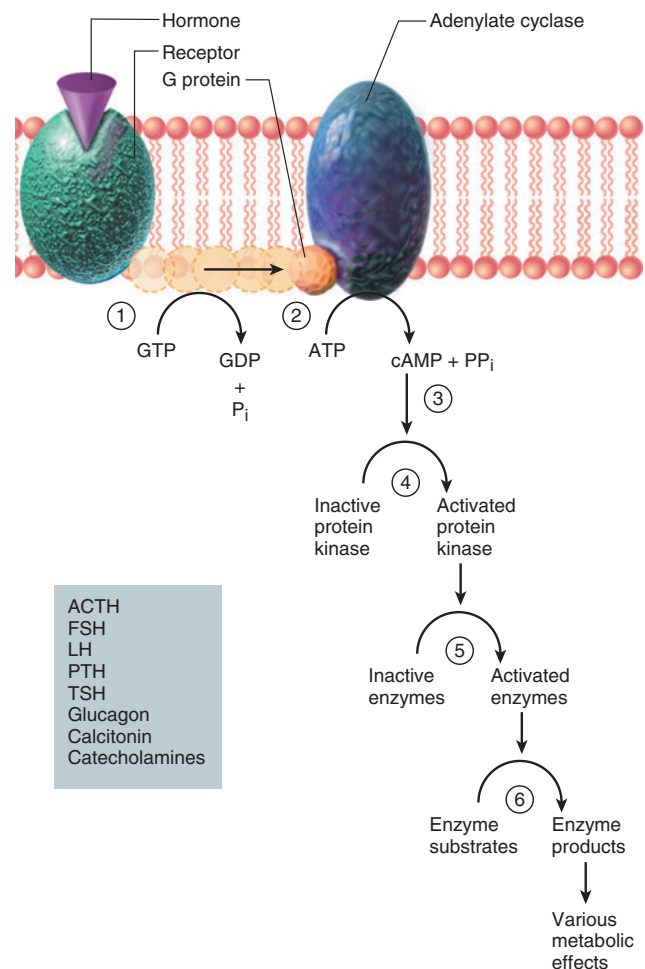
A given hormone doesn't always employ the same second messenger. Antidiuretic hormone (ADH) employs the IP<sub>3</sub>-calcium system in smooth muscle but the cAMP system in kidney tubules. Insulin is unusual in comparison to other peptide hormones. Rather than using a second-messenger system, it binds to a plasma membrane enzyme, tyrosine kinase, that directly phosphorylates cytoplasmic proteins.

### Think About It

From the moment either hormone enters the bloodstream, insulin works much more quickly than estrogen. In view of how each hormone acts on its target cells, explain why.

## Enzyme Amplification

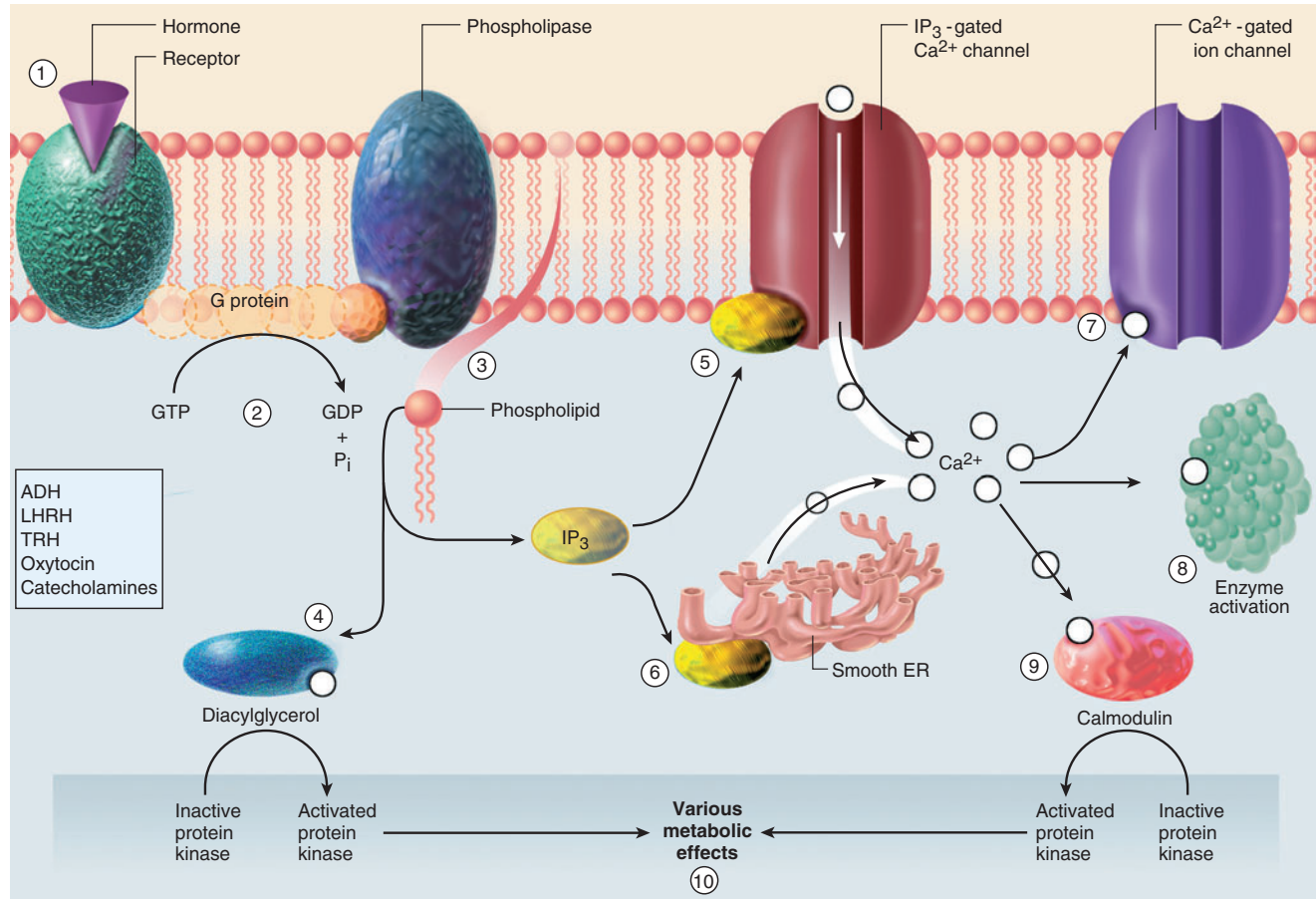
One hormone molecule does not trigger the synthesis or activation of just one enzyme molecule. It activates thousands of enzyme molecules through a cascade effect called **enzyme amplification** (fig. 17.21). To put it in a simplistic but illustrative way, suppose one glucagon molecule trig-



**Figure 17.19 Cyclic AMP as a Second Messenger.** (1) The binding of a hormone to a membrane receptor activates a G protein. (2) The G protein activates adenylate cyclase. (3) Adenylate cyclase produces cAMP. (4) cAMP activates protein kinases. (5) Protein kinases phosphorylate enzymes and other proteins in the cytoplasm. Some enzymes are activated and others are deactivated by this phosphorylation. (6) Activated enzymes catalyze metabolic reactions with a wide range of possible effects on the cell, such as synthesis, secretion, and changes in plasma membrane potential. Some hormones acting through cAMP are listed in the box.

**Why are no steroid hormones listed?**

gered the formation of 1,000 molecules of cAMP; cAMP activated a protein kinase; each protein kinase activated 1,000 other enzyme molecules; and each of those enzymes produced 1,000 molecules of a reaction product. These are modest numbers as chemical reactions go, and yet even at this low estimate, that one glucagon molecule would have triggered the production of 1 billion molecules of reaction product. Whatever the actual numbers may be, you can see how enzyme amplification enables a very small stimulus



**Figure 17.20** Diacylglycerol and Inositol Triphosphate (IP<sub>3</sub>) as Second Messengers. (1) The binding of a hormone to a membrane receptor activates a G protein. (2) The G protein activates a membrane enzyme, phospholipase. (3) Phospholipase breaks down membrane phospholipids into diacylglycerol and inositol triphosphate (IP<sub>3</sub>). (4) Diacylglycerol activates protein kinases. (5) Inositol triphosphate binds to gated calcium channels in the plasma membrane, admitting calcium to the cell from the ECF, or (6) it triggers calcium release from the smooth ER. Calcium ions can have a variety of effects: (7) Ca<sup>2+</sup> can open other ion channels in the plasma membrane, (8) Ca<sup>2+</sup> can function as a cofactor that activates enzymes, or (9) Ca<sup>2+</sup> can bind to calmodulin, a protein that activates protein kinases. (10) Protein kinases exert the same variety of metabolic effects here as they do in the cAMP system.

to produce a very large effect. Hormones are therefore needed in only very small quantities. Their circulating concentrations are very low compared to other blood substances: on the order of nanograms per deciliter. Blood glucose, for example, is about 100 million times this concentrated. Because of enzyme amplification, target cells do not need a great number of hormone receptors.

## Hormone Clearance

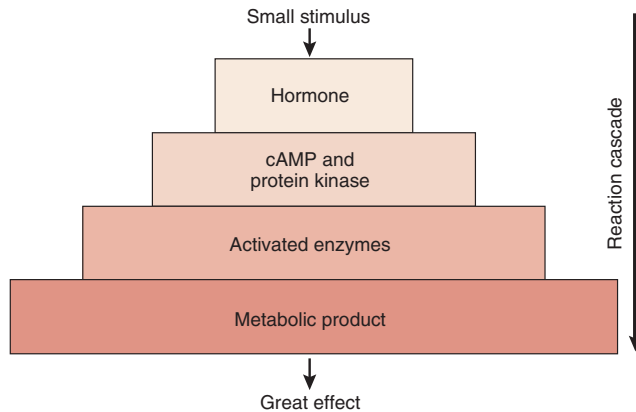
Hormonal signals, like nervous signals, must be turned off when they have served their purpose. Most hormones are taken up and degraded by the liver and kidneys and then excreted in the bile or urine. Some are degraded by their

target cells. As noted earlier, hormones that bind to transport proteins are removed from the blood much more slowly than hormones that do not employ transport proteins. The rate of hormone removal is called the *metabolic clearance rate (MCR)*, and the length of time required to clear 50% of the hormone from the blood is the half-life. The faster the MCR, the shorter is the half-life.

## Modulation of Target Cell Sensitivity

Target cells can modulate (adjust) their sensitivity to a hormone, and one hormone can alter a target cell's sensitivity to another. In **up-regulation**, a cell increases the number of hormone receptors and becomes more sensitive to the hormone

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**Figure 17.21 Enzyme Amplification.** A single hormone molecule can trigger the production of many cAMP molecules and activation of many molecules of protein kinase. Every protein kinase molecule can phosphorylate and activate many other enzymes. Each of those enzyme molecules can produce many molecules of a metabolic product. Amplification of the process at each step allows for a very small hormonal stimulus to cause a very large metabolic effect.

(fig. 17.22a). In late pregnancy, for example, the uterus produces oxytocin receptors, preparing it for the surge of oxytocin that will occur during childbirth.

**Down-regulation** is the process in which a cell reduces its receptor population and thus becomes less sensitive to a hormone (fig. 17.22b). This sometimes happens in response to long-term exposure to a high hormone concentration. For example, adipocytes down-regulate when exposed to high concentrations of insulin, and cells of the testis down-regulate in response to high concentrations of luteinizing hormone.

Hormone therapy often involves long-term use of abnormally high *pharmacological doses* of hormone, which may have undesirable side effects. Long-term treatment of inflammation with hydrocortisone, for example, has undesirable effects on bone metabolism. Two ways in which these abnormal effects can be produced are: (1) excess hormone may bind to receptor sites for other related hormones and mimic their effects, and (2) a target cell may convert one hormone into another, such as testosterone to estrogen. Thus, long-term high doses of testosterone can, paradoxically, have feminizing effects.

## Hormone Interactions

No hormone travels in the bloodstream alone, and no cell is exposed to only one hormone. Rather, there are many hormones in the blood and tissue fluid at once. Cells ignore the majority of them because they have no receptors for them, but most cells are sensitive to more than one. In

these cases, the hormones may have three kinds of interactive effects:

1. **Synergistic effects**, in which two or more hormones act together to produce an effect that is greater than the sum of their separate effects. Neither FSH nor testosterone alone, for example, can stimulate significant sperm production. When they act together, however, the testes produce some 300,000 sperm per minute.
2. **Permissive effects**, in which one hormone enhances the target organ's response to a second hormone that is secreted later. Estrogen stimulates the up-regulation of progesterone receptors in the uterus. The uterus would respond poorly to progesterone, if at all, had it not been primed by the first hormone. Estrogen thus has a permissive effect on progesterone action.
3. **Antagonistic effects**, in which one hormone opposes the action of another. For example, insulin lowers blood glucose level and glucagon raises it. During pregnancy, estrogen from the placenta inhibits the mammary glands from responding to prolactin; thus milk is not secreted until the placenta is shed at birth.

## Before You Go On

Answer the following questions to test your understanding of the preceding section:

14. What are the three chemical classes of hormones? Name at least one hormone in each class.
15. Why do corticosteroids and thyroid hormones require transport proteins to travel in the bloodstream?
16. Explain how MIT, DIT, T<sub>3</sub>, and T<sub>4</sub> relate to each other structurally.
17. Where are hormone receptors located in target cells? Name one hormone that employs each receptor location.
18. Explain how one hormone molecule can activate millions of enzyme molecules.

## Stress and Adaptation

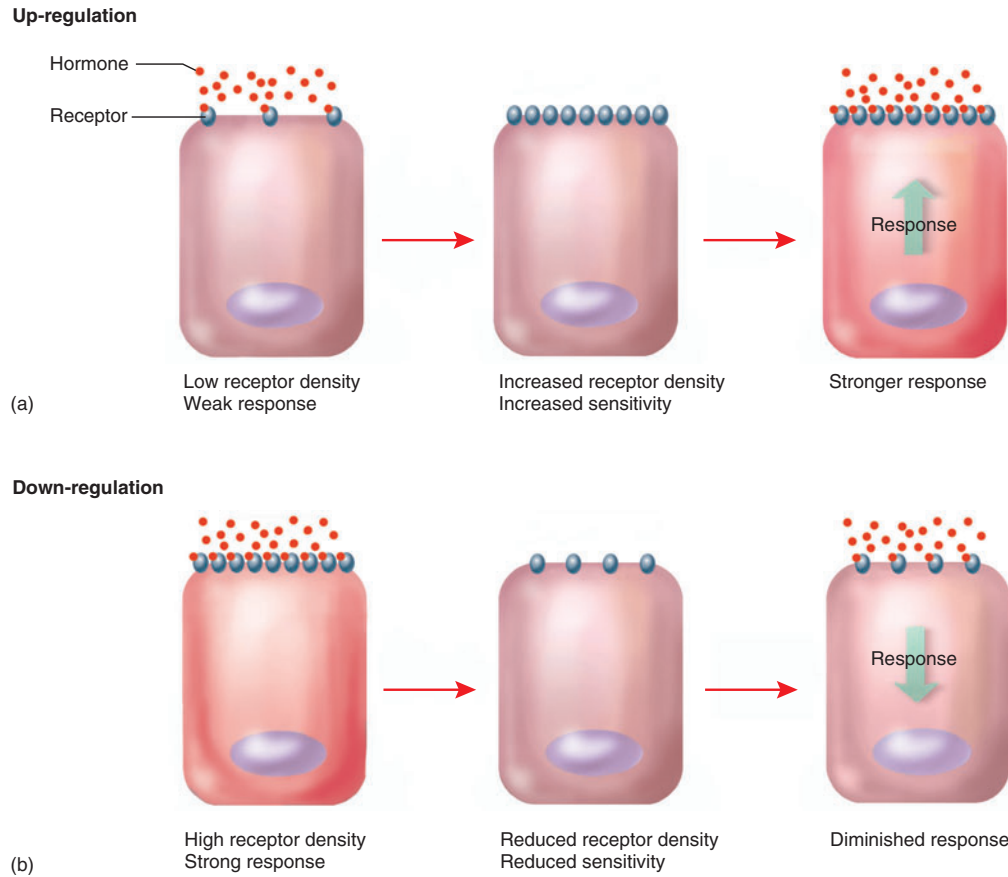
### Objectives

When you have completed this section, you should be able to

- give a physiological definition of stress; and
- discuss how the body adapts to stress through its endocrine system.

Stress affects us all from time to time, and we react to it in ways that are mediated mainly by the endocrine and sympathetic nervous systems. **Stress** is defined as any situation that upsets homeostasis and threatens one's physical or emotional well-being. Physical causes of stress (*stressors*) include injury, surgery, hemorrhage, infection,





**Figure 17.22 Modulation of Target Cell Sensitivity.** (a) Up-regulation, in which a cell produces more receptors and increases its own sensitivity to a hormone. (b) Down-regulation, in which a cell reduces the density of its receptors and lessens its sensitivity to a hormone.

intense exercise, temperature extremes, pain, and malnutrition. Emotional causes include anger, grief, depression, anxiety, and guilt.

Whatever the cause, the body reacts to stress in a fairly consistent way called the **stress response** or **general adaptation syndrome (GAS)**. The response typically involves elevated levels of epinephrine and glucocorticoids, especially cortisol; some physiologists now define stress as any situation that raises the cortisol level. A pioneering researcher on stress physiology, Canadian biochemist Hans Selye, showed in 1936 that the GAS typically occurs in three stages, which he called the *alarm reaction*, the *stage of resistance*, and the *stage of exhaustion*.

## The Alarm Reaction

The initial response to stress is an **alarm reaction** mediated mainly by norepinephrine from the sympathetic

nervous system and epinephrine from the adrenal medulla. These catecholamines prepare the body to take action such as fighting or escaping danger. One of their effects, the consumption of stored glycogen, is particularly important to the transition to the next stage of the stress response. Aldosterone and angiotensin levels also rise during the alarm reaction. Angiotensin helps to raise the blood pressure, and aldosterone promotes sodium and water conservation, which helps to offset possible losses by sweating and bleeding.

## The Stage of Resistance

After a few hours, the body's glycogen reserves are exhausted, and yet the nervous system continues to demand glucose. If a stressful situation is not resolved before the glycogen is gone, the body enters the **stage of resistance**, in which the first priority is to provide alternative fuels for metabolism. This stage is dominated



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by cortisol. The hypothalamus secretes corticotropin-releasing hormone (CRH), the pituitary responds by secreting adrenocorticotrophic hormone (ACTH), and this, in turn, stimulates the adrenal cortex to secrete cortisol and other glucocorticoids. Cortisol promotes the breakdown of fat and protein into glycerol, fatty acids, and amino acids, providing the liver with raw material for gluconeogenesis (glucose synthesis). Like epinephrine, cortisol inhibits glucose uptake by most organs and thus has a glucose-sparing effect. It also inhibits protein synthesis, leaving the free amino acids available for gluconeogenesis. The immune system, which depends heavily on the synthesis of antibodies and other proteins, is depressed by long-term cortisol exposure. Lymphoid tissues atrophy, antibody levels drop, the number of circulating leukocytes declines, and inflammatory cells such as *mast cells* (see chapter 21) release less histamine and other inflammatory chemicals. Wounds heal poorly, and a person in chronic stress becomes more susceptible to infections and some forms of cancer. Cortisol stimulates gastric secretion, which may account for the ulcers that occur in chronic stress, but it suppresses the secretion of sex hormones such as estrogen, testosterone, and luteinizing hormone, causing disturbances of fertility and sexual function.

## The Stage of Exhaustion

The body's fat reserves can carry it through months of stress, but when fat is depleted, stress overwhelms homeostasis. The **stage of exhaustion** sets in, often marked by rapid decline and death. With its fat stores gone, the body now relies primarily on protein breakdown to meet its energy needs. Thus, there is a progressive wasting away of the muscles and weakening of the body. After prolonged stimulation, the adrenal cortex may stop producing glucocorticoids, making it all the more difficult to maintain glucose homeostasis. Aldosterone sometimes promotes so much water retention that it creates a state of hypertension; and while it conserves sodium, it hastens the elimination of potassium and hydrogen ions. This creates a state of hypokalemia (potassium deficiency in the blood) and alkalosis (excessively high blood pH), resulting in nervous and muscular system dysfunctions. Death frequently results from heart failure, kidney failure, or overwhelming infection.

### Before You Go On

Answer the following questions to test your understanding of the preceding section:

19. Define *stress* from the standpoint of endocrinology.
20. Describe the stages of the general adaptation syndrome.
21. List six hormones that show increased secretion in the stress response. Describe how each one contributes to recovery from stress.

## Eicosanoids and Paracrine Signaling

### Objectives

When you have completed this section, you should be able to

- explain what eicosanoids are and how they are produced;
- identify some classes and functions of eicosanoids; and
- describe several physiological roles of prostaglandins.

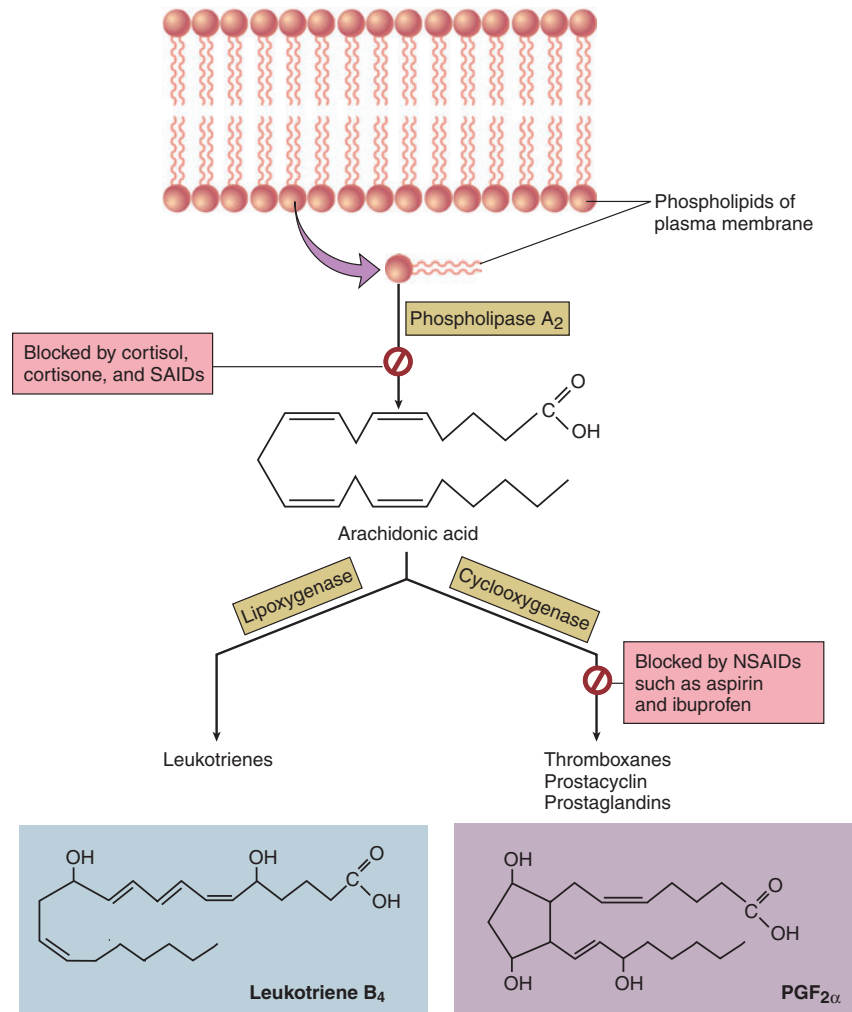
Neurotransmitters and hormones are not the only chemical messengers in the body. Here we briefly consider the *paracrine* messengers. These are chemical signals released by cells into the tissue fluid; they do not travel to their target cells by way of the blood, but diffuse from their source to nearby cells in the same tissue. Histamine, for example, is released by mast cells that lie alongside the blood vessels in a connective tissue. It diffuses to the smooth muscle of the blood vessel, relaxing it and allowing vasodilation. Nitric oxide, another paracrine vasodilator, is released by the endothelial cells of the blood vessel itself. In the pancreas, somatostatin acts as a paracrine signal when it is released by  $\delta$  cells and diffuses to the  $\alpha$  and  $\beta$  cells in the same islet, inhibiting their secretion of glucagon and insulin. Catecholamines diffuse from the adrenal medulla to the cortex to stimulate corticosterone secretion. A single chemical can act as a hormone, a paracrine, or even a neurotransmitter in different locations and circumstances.

The **eicosanoids**<sup>24</sup> (eye-CO-sah-noyds) are an important family of paracrine secretions. They have 20-carbon backbones derived from a polyunsaturated fatty acid called **arachidonic** (ah-RACK-ih-DON-ic) **acid**. Some peptide hormones and other stimuli liberate arachidonic acid from one of the phospholipids of the plasma membrane, and the following two enzymes then convert it to various eicosanoids (fig. 17.23).

**Lipoxygenase** helps to convert arachidonic acid to **leukotrienes**, eicosanoids that mediate allergic and inflammatory reactions (see chapter 21). **Cyclooxygenase** converts arachidonic acid to three other types of eicosanoids:

1. **Prostacyclin** is produced by the walls of the blood vessels, where it inhibits blood clotting and vasoconstriction.
2. **Thromboxanes** are produced by blood platelets. In the event of injury, they override prostacyclin and stimulate vasoconstriction and clotting. Prostacyclin and thromboxanes are further discussed in chapter 18.

<sup>24</sup>eicosa (variation of ico) = 20



**Figure 17.23 Eicosanoid Synthesis and Related Drug Actions.** NSAIDs are nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen. SAIDs are steroidal anti-inflammatory drugs such as hydrocortisone; NSAIDs are nonsteroidal anti-inflammatory drugs such as aspirin and ibuprofen.

How would the body be affected by a drug that inhibited lipoxygenase?

3. **Prostaglandins (PGs)** are the most diverse eicosanoids. They have a five-sided carbon ring in their backbone. They are named PG for *prostaglandin*, plus a third letter that indicates the type of ring structure (PGE, PGF, etc.) and a subscript that indicates the number of C=C double bonds in the side chain. They were first found in bull semen and the prostate gland, hence their name, but they are now thought to be produced in most organs of the body. The PGEs are usually antagonized by PGFs. For example, the PGE family relaxes smooth

muscle in the bladder, intestines, bronchioles, and uterus and stimulates contraction of the smooth muscle of blood vessels. PGF<sub>2α</sub> has precisely the opposite effects. Some other roles of prostaglandins are described in table 17.7.

Understanding the pathways of eicosanoid synthesis makes it possible to understand the action of several familiar drugs (see insight 17.3). The roles of prostaglandins and other eicosanoids are further explored in later chapters on blood, immunity, and reproduction.

**Table 17.7** Some of the Roles of Prostaglandins**Inflammatory**

Promote fever and pain, two cardinal signs of inflammation

**Endocrine**

Mimic effects of TSH, ACTH, and other hormones; alter sensitivity of anterior pituitary to hypothalamic hormones; work with glucagon, catecholamines, and other hormones in regulation of fat mobilization

**Nervous**

Function as neuromodulators, altering the release or effects of neurotransmitters in the brain

**Reproductive**

Promote ovulation and formation of corpus luteum; induce labor contractions

**Gastrointestinal**

Inhibit gastric secretion

**Vascular**

Act as vasodilators and vasoconstrictors

**Respiratory**

Constrict or dilate bronchioles

**Renal**

Promote blood circulation through the kidney, increase water and electrolyte excretion

**Insight 17.3** Clinical Application**Anti-Inflammatory Drugs**

Cortisol and corticosterone are used as *steroidal anti-inflammatory drugs (SAIDs)*. They inhibit inflammation by blocking the release of arachidonic acid from the plasma membrane, thus inhibiting the synthesis of all eicosanoids. Their main disadvantage is that prolonged use causes side effects that mimic Cushing syndrome (see p. 668). Aspirin and ibuprofen (Motrin) are *nonsteroidal anti-inflammatory drugs (NSAIDs)* with more selective effects. They stop the action of cyclooxygenase, thus blocking prostaglandin synthesis without affecting lipoxygenase or the leukotrienes. For similar reasons, aspirin inhibits blood clotting (see chapter 18). One theory of fever is that it results from the action of prostaglandins on the hypothalamus. Most antipyretic (fever-reducing) drugs work by inhibiting cyclooxygenase.

*Before You Go On*

Answer the following questions to test your understanding of the preceding section:

22. What are eicosanoids and how do they differ from neurotransmitters and hormones?
23. Distinguish between a paracrine and endocrine effect.
24. State four functions of prostaglandins.

**Endocrine Disorders****Objectives**

When you have completed this section, you should be able to

- explain some general causes and examples of hormone hyposecretion and hypersecretion;
- briefly describe some common disorders of pituitary, thyroid, parathyroid, and adrenal function; and
- in more detail, describe the causes and pathology of diabetes mellitus.

Hormones are very potent chemicals; as we saw in the discussion of enzyme amplification, a little hormone goes a long way. It is therefore necessary to tightly regulate their secretion and blood concentration. Variations in hormone concentration and target cell sensitivity often have very noticeable effects on the body. This section deals with some of the better-known dysfunctions of the endocrine system. The effects of aging on the endocrine system are described on page 1110.

**Hyposecretion and Hypersecretion**

Inadequate hormone release is called **hyposecretion**. It can result from tumors or lesions that destroy an endocrine gland or interfere with its ability to receive signals from another gland. For example, a fractured sphenoid bone can sever the hypothalamo-hypophyseal tract and thus prevent the transport of oxytocin and antidiuretic hormone to the posterior pituitary. The resulting ADH hyposecretion disables the water-conserving capability of the kidneys and leads to **diabetes insipidus**, a condition of chronic polyuria without glucose in the urine. (*Insipidus* means “without taste” and refers to the lack of sweetness of the glucose-free urine, in contrast to the sugary urine of diabetes mellitus.) Autoimmune diseases can also lead to hormone hyposecretion when misguided antibodies (autoantibodies) attack endocrine cells. This is thought to be one of the causes of diabetes mellitus, as explained shortly.

Excessive hormone release, called **hypersecretion**, has multiple causes. Some tumors result in the overgrowth of functional endocrine tissue. A **pheochromocytoma** (FEE-o-CRO-mo-sy-TOE-muh), for example, is a tumor of the adrenal medulla that secretes excessive amounts of epinephrine and norepinephrine (table 17.8). Some tumors in nonendocrine organs produce hormones. For example, some lung tumors secrete ACTH and thus overstimulate cortisol secretion by the adrenal gland. While certain autoimmune disorders can cause endocrine hyposecretion, others cause hypersecretion. An example of this is **toxic goiter (Graves<sup>25</sup> disease)**, in which autoan-

<sup>25</sup>Robert James Graves (1796–1853), Irish physician



Age 9



Age 16



Age 33



Age 52

**Figure 17.24 Acromegaly, a Condition Caused by Growth Hormone Hypersecretion in Adulthood.** These are four photographs of the same person taken at different ages. Note the characteristic thickening of the face and hands.  
**How would she have been affected if GH hypersecretion began at age 9?**

tibodies mimic the effect of TSH on the thyroid, causing thyroid hypersecretion (table 17.8). Endocrine hypersecretion disorders can also be mimicked by excess or long-term clinical administration of hormones such as cortisol.

Following are brief descriptions of some of the better-known disorders of the major endocrine glands. Table 17.8 provides further details on some of these and lists some additional endocrine disorders. Diabetes mellitus, by far the most prevalent endocrine disease, receives a more extended discussion.

## Pituitary Disorders

The hypersecretion of growth hormone (GH) in adults causes **acromegaly**—thickening of the bones and soft tissues with especially noticeable effects on the hands, feet, and face (fig. 17.24). When it begins in childhood or adolescence, GH hypersecretion causes **gigantism** and hyposecretion causes **pituitary dwarfism** (table 17.8). Now that growth hormone is plentiful, made by genetically engineered bacteria containing the human GH gene, pituitary dwarfism has become rare.

## Thyroid and Parathyroid Disorders

**Congenital hypothyroidism** is thyroid hyposecretion present from birth; it was formerly called *cretinism*, now regarded as an insensitive term. Severe or prolonged adult hypothyroidism can cause **myxedema** (MIX-eh-DEE-muh). Both syndromes are described in table 17.8, and both can be treated with oral thyroid hormone.

A **goiter** is any pathological enlargement of the thyroid gland. **Endemic goiter** (fig. 17.25) is due to dietary



**Figure 17.25 Endemic Goiter.** The thyroid gland has hypertrophied as a result of iodine deficiency, leading to TSH hypersecretion.

iodine deficiency. There is little iodine in soil or most foods, but seafood and iodized salt are good sources. Without iodine, the gland cannot synthesize TH. Without TH, the pituitary gland receives no feedback and acts as if the thyroid were understimulated. It produces extra TSH, which stimulates hypertrophy of the thyroid gland. In the earlier-described toxic goiter, by contrast, the overgrown thyroid produces functional TH.

Because of their location and small size, the parathyroids are sometimes accidentally removed in thyroid surgery. Without hormone replacement therapy, the resulting **hypoparathyroidism** causes a rapid decline in blood calcium levels and leads to fatal tetany within 3 or 4 days.



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**Hyperparathyroidism**, excess PTH secretion, is usually caused by a parathyroid tumor. It causes the bones to become soft, deformed, and fragile; it raises the blood levels of calcium and phosphate ions; and it promotes the formation of *renal calculi* (kidney stones) composed of calcium phosphate. Chapter 7 further describes the relationship between parathyroid function, blood calcium, and bone tissue.

## Adrenal Disorders

**Cushing<sup>26</sup> syndrome** is excess cortisol secretion owing to any of several causes: ACTH hypersecretion by the pituitary, ACTH-secreting tumors, or hyperactivity of the adrenal cortex independently of ACTH. Cushing syndrome disrupts carbohydrate and protein metabolism, leading to hyperglycemia, hypertension, muscular weakness, and edema. Muscle and bone mass are lost rapidly as protein is catabolized. Some patients exhibit abnormal fat deposition between the shoulders (“buffalo hump”) or in the face (“moon face”) (fig. 17.26). Long-term hydrocortisone therapy can have similar effects.

**Adrenogenital syndrome (AGS)**, a state of adrenal androgen hypersecretion, commonly accompanies Cushing syndrome. In children, AGS often causes enlargement of the penis or clitoris and the premature onset of puberty. Prenatal AGS can result in newborn girls exhibiting masculinized genitalia and being misidentified as boys (fig. 17.27). In women, AGS produces such masculinizing effects as increased body hair, deepening of the voice, and beard growth.

## Diabetes Mellitus

**Diabetes mellitus<sup>27</sup> (DM)** warrants special consideration. This is the world’s most prevalent metabolic disease, and is the leading cause of adult blindness, renal failure, gangrene, and the necessity for limb amputations.

Diabetes mellitus can be defined as a disruption of carbohydrate, fat, and protein metabolism resulting from the hyposecretion or inaction of insulin. Its classic signs and symptoms are “the three polys”: **polyuria<sup>28</sup>** (excessive urine output), **polydipsia<sup>29</sup>** (intense thirst), and **polyphagia<sup>30</sup>** (ravenous hunger). We can add to this list three clinical signs revealed by blood and urine tests: **hyperglycemia<sup>31</sup>** (elevated blood glucose), **glycosuria<sup>32</sup>** (glucose in the urine), and **ketonuria** (ketones in the urine).



(a)



(b)

**Figure 17.26 Cushing Syndrome.** (a) Patient before the onset of the syndrome. (b) The same boy, only 4 months later, showing the “moon face” characteristic of Cushing syndrome.

A little knowledge of kidney physiology is necessary to understand why glycosuria and polyuria occur. The kidneys filter blood plasma and convert the filtrate to urine. Normally, the kidney tubules remove all glucose from the filtrate and return it to the blood, so there is little or no glucose in the urine of a healthy person. Water follows the glucose and other solutes by osmosis, so the tubules also reclaim most of the water in the filtrate.

But like any other carrier-mediated transport system, there is a limit to how fast the glucose transporters of the kidney can reabsorb glucose. The maximum rate of reabsorption is called the transport maximum,  $T_m$  (see p. 109).

<sup>26</sup>Harvey Cushing (1869–1939), American physician

<sup>27</sup>*diabet* = to flow through + *melli* = honey

<sup>28</sup>*poly* = much, excessive + *uri* = urine

<sup>29</sup>*dipsia* = drinking

<sup>30</sup>*phagia* = eating

<sup>31</sup>*hyper* = excess + *glyc* = sugar, glucose + *emia* = blood condition

<sup>32</sup>*glyco* = glucose, sugar + *uria* = urine condition





**Figure 17.27 Adrenogenital Syndrome (AGS).** These are the genitals of a baby girl with AGS, masculinized by prenatal hypersecretion of adrenal androgens. Note the fusion of the labia majora to resemble a scrotum and enlargement of the clitoris to resemble a penis. Such infants are easily mistaken for boys and raised as such.

In diabetes mellitus, glucose enters the tubules so rapidly that it exceeds the  $T_m$  and the tubules cannot reabsorb it fast enough. The excess passes through into the urine. Glucose and ketones in the tubules also raise the osmolarity of the tubular fluid and cause **osmotic diuresis**—water remains in the tubules with these solutes, so large amounts of water are passed in the urine. This accounts for the polyuria, dehydration, and thirst of diabetes. Diabetics often pass 10 to 15 L of urine per day, compared with 1 or 2 L in a healthy person.

## Types and Treatment

There are two forms of diabetes mellitus—*type I* and *type II*. **Type I**, or **insulin-dependent diabetes mellitus (IDDM)**, accounts for about 10% of cases. The cause is still little understood, but at least some cases appear to result from the destruction of  $\beta$  cells by autoantibodies. There are several genes implicated in IDDM, but heredity alone is not the cause; IDDM results from the interaction of hereditary and environmental factors. Up to a point, the body can tolerate the loss of  $\beta$  cells. Signs of diabetes begin to appear when 80% to 90% of them are destroyed and insulin falls to critically low levels. However, the signs are not caused by a deficiency of insulin alone. The relative level of glucagon is elevated in IDDM, and it is the abnormally low *ratio* of insulin to glucagon that causes the signs. IDDM is most

often diagnosed around age 12 and used to be called *juvenile diabetes*, but it can also appear later in life. IDDM must be treated through meal planning, exercise, the self-monitoring of blood glucose level by the patient, and periodic insulin injections or the continual subcutaneous delivery of insulin by a pump worn on the body.

Most diabetics (90%) have **type II**, or **non-insulin-dependent diabetes mellitus (NIDDM)**. Nearly 7% of U.S. residents are diagnosed with NIDDM. Type II diabetics may have normal or even elevated insulin levels; the problem is *insulin resistance*—a failure of target cells to respond to insulin. There may be multiple reasons for resistance. One theory is that target cells have a shortage of insulin receptors, although research has failed to find any consistent relationship between NIDDM and defective receptors, so this theory is being increasingly questioned. The three major risk factors for NIDDM are heredity, age, and obesity. It tends to run in families; if an identical twin contracts NIDDM it is virtually certain that the other twin will too. NIDDM has a gradual onset, with signs usually not appearing until age 40 or beyond; it used to be called *adult-onset DM*. Type II diabetics are usually overweight and the incidence of NIDDM is increasing as obesity becomes more prevalent in our overfed, under-exercised society. In obesity, the adipocytes produce a hormonelike secretion that indirectly interferes with glucose transport into most kinds of cells. NIDDM can often be managed through a weight-loss program of diet and exercise. Some patients are helped with oral medications that improve insulin secretion or target cell sensitivity or help in other ways to lower blood glucose.

## Pathogenesis

When cells cannot absorb glucose, they rely on fat and protein for energy. Fat and protein breakdown results in emaciation, muscular atrophy, and weakness. Before insulin therapy was introduced in 1922, the victims of type I diabetes wasted away to an astonishing extent (see insight 17.4). Diabetes was described in the first century as “a melting down of the flesh and limbs into urine.” Adult patients weighed as little as 27 to 34 kg (60–75 lb) and looked like victims of a concentration camp or severe famine. Their breath had a sickeningly sweet ketone smell, like rotten apples. One typical patient was described by medical historian Michael Bliss as “barely able to lift his head from his pillow, crying most of the time from pain, hunger, and despair.” In the terminal stage of the disease, patients became increasingly drowsy, gasped for air, became comatose, and then died within a few hours. Most diabetic children lived less than 1 year after diagnosis—a year of utmost misery at that.

Rapid fat catabolism elevates blood concentrations of free fatty acids and their breakdown products, the ketone bodies (acetoacetic acid, acetone, and  $\beta$ -hydroxybutyric acid). Ketonuria promotes osmotic diuresis and flushes

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$\text{Na}^+$  and  $\text{K}^+$  from the body, thus creating electrolyte deficiencies that can lead to abdominal pain, vomiting, irregular heartbeat, and neurological dysfunction. As acids, ketones lower the pH of the blood and produce a condition called **ketoacidosis**. Ketoacidosis causes a deep, gasping breathing called *Kussmaul*<sup>33</sup> *respiration*, typical of terminal diabetes. It also depresses the nervous system and produces diabetic coma.

Diabetes mellitus also leads to long-term degenerative cardiovascular and neurological diseases—signs that were seldom seen before insulin therapy, when patients died too quickly to show the chronic effects. Despite years of research and debate, it remains unclear exactly how diabetes mellitus causes cardiovascular disease. It appears that chronic hyperglycemia activates a metabolic reaction cascade that leads to cellular damage in small to medium blood vessels and peripheral nerves. Nerve damage (*diabetic neuropathy*), the most common complication of diabetes mellitus, can lead to impotence, incontinence, and loss of sensation from affected areas. The last effect makes a patient dangerously unaware of minor injuries, which can thus fester from neglect and contribute (along with

lowered resistance to infection) to gangrene and the necessity of amputation. Many diabetics lose their toes, feet, or legs to the disease. Diabetes also promotes *atherosclerosis*, the blockage of blood vessels with fatty deposits, causing poor circulation. The effects include degeneration of the small arteries of the retina and the kidneys, leading to blindness and kidney failure as common complications. Atherosclerosis also contributes to gangrene. People with type I diabetes are much more likely to die of kidney failure than those with type II. In type II diabetes, the most common cause of death is heart failure stemming from atherosclerosis of the coronary arteries.

### Before You Go On

Answer the following questions to test your understanding of the preceding section:

25. Explain some causes of hormone hyposecretion, and give examples. Do the same for hypersecretion.
26. In diabetes mellitus, explain the chain of events that lead to (a) osmotic diuresis, (b) ketoacidosis and coma, and (c) gangrene of the lower limbs.

**Table 17.8 Some Disorders of the Endocrine System**

<i>Addison</i> <sup>34</sup> <i>disease</i>	Hyposecretion of adrenal glucocorticoids and mineralocorticoids, causing hypoglycemia, hypotension, weight loss, weakness, loss of stress resistance, darkening or bronzing (metallic discoloration) of the skin, and potentially fatal dehydration and electrolyte imbalances
<i>Congenital hypothyroidism</i>	Thyroid hormone hyposecretion present from birth, resulting in stunted physical development, thickened facial features, low body temperature, lethargy, and irreversible brain damage in infancy
<i>Diabetes insipidus</i>	Chronic polyuria due to ADH hyposecretion. Can result from tumors, skull fractures, or infections that destroy hypothalamic tissue or the hypothalamo-hypophyseal tract
<i>Hyperinsulinism</i>	Insulin excess caused by islet hypersecretion or injection of excess insulin, causing hypoglycemia, weakness, hunger, and sometimes <i>insulin shock</i> , which is characterized by disorientation, convulsions, or unconsciousness
<i>Myxedema</i>	A syndrome occurring in severe or prolonged adult hypothyroidism, characterized by low metabolic rate, sluggishness and sleepiness, weight gain, constipation, dry skin and hair, abnormal sensitivity to cold, hypertension, and tissue swelling
<i>Pheochromocytoma</i>	A tumor of the adrenal medulla that secretes excess epinephrine and norepinephrine. Causes hypertension, elevated metabolic rate, nervousness, indigestion, hyperglycemia, and glycosuria
<i>Toxic goiter (Graves disease)</i>	Thyroid hypertrophy and hypersecretion, occurring when autoantibodies mimic the effect of TSH and overstimulate the thyroid. Results in elevated metabolic rate and heart rate, nervousness, sleeplessness, weight loss, abnormal heat sensitivity and sweating, and bulging of the eyes (exophthalmos) resulting from eyelid retraction and edema of the orbital tissues
<i>Disorders described elsewhere</i>	
Acromegaly p. 667	Endemic goiter p. 667
Adrenogenital syndrome p. 668	Gigantism p. 667
Androgen-insensitivity syndrome p. 1021	Hyperparathyroidism p. 668
Cushing syndrome p. 668	Hypoparathyroidism p. 667
	Pituitary dwarfism p. 667

<sup>33</sup>Adolph Kussmaul (1822–1902), German physician

<sup>34</sup>Thomas Addison (1793–1860), English physician

## Insight 17.4 Medical History

### The Discovery of Insulin

At the start of the twentieth century, physicians felt nearly helpless in the face of diabetes mellitus. They put patients on useless diets—the oatmeal cure, the potato cure, and others—or on starvation diets as low as 750 Calories per day so as not to “stress the system.” They were resigned to the fact that their patients were doomed to die, and simple starvation seemed to produce the least suffering.

After the cause of diabetes was traced to the pancreatic islets in 1901, European researchers tried treating patients and experimental animals with extracts of pancreas, but became discouraged by the severe side effects of impurities in the extracts. They lacked the resources to pursue the problem to completion, and by 1913, the scientific community showed signs of giving up on diabetes.

But in 1920, Frederick Banting (1891–1941), a young Canadian physician with a failing medical practice, became intrigued with a possible method for isolating the islets from the pancreas and testing extracts of the islets alone. He returned to his alma mater, the University of Toronto, to present his idea to Professor J. J. R. Macleod (1876–1935), a leading authority on carbohydrate metabolism. Macleod was unimpressed with Banting, finding his knowledge of the diabetes literature and scientific method superficial. Nevertheless, he felt Banting’s idea was worth pursuing and thought that with his military surgical training, Banting might be able to make some progress where others had failed. He offered Banting laboratory space for the summer, giving him a marginal chance to test his idea. Banting was uncertain whether to accept, but when his fiancé broke off their engagement and an alternative job offer fell through, he closed his medical office, moved to Toronto, and began work. Little did either man realize that in two years’ time, they would share a Nobel Prize and would so thoroughly detest each other they would scarcely be on speaking terms.

#### A Modest Beginning

Macleod advised Banting on an experimental plan of attack and gave him an assistant, Charles Best (1899–1978). Best had just received his B.A. in physiology and looked forward to an interesting summer job with Banting before starting graduate school. He received no pay for his work, and Banting himself was desperately poor, living in a 7- by 9-foot room and supporting himself on two dollars a week earned by performing tonsillectomies. Over the summer of 1921, Banting and Best removed the pancreases from some dogs to render them diabetic and tied off the pancreatic ducts in other dogs to make most of the pancreas degenerate while leaving the islets intact. Their plan was to treat the diabetic dogs with extracts made from the degenerated pancreases of the others.

It was a difficult undertaking. Their laboratory was tiny, filthy, unbearably hot, and reeked of dog excrement. The pancreatic ducts were very small and difficult to tie, and it was hard to tell if all the pancreas had been removed from the dogs intended to become diabetic. Several dogs died of overanesthesia, infection, and bleeding from Banting’s clumsy surgical technique. Banting was also careless in reading his data and interpreting the results, and he had little interest in reading the literature to see what other diabetes researchers were doing. In Banting and Best’s first publication, in early 1922, the data in their discussion disagreed with the data in the tables, and both disagreed with the data in their laboratory notebooks. These were not the signs of promising researchers.

In spite of themselves, Banting and Best achieved modest positive results over the summer. Crude pancreatic extracts brought one dog back from a diabetic coma and reduced the hyperglycemia and glycosuria of others. Buoyed by these results, Banting demanded a salary, a better laboratory, and another assistant. Macleod grudgingly obtained salaries for the pair, but Banting began to loathe him for their disagreement over his demands, and he and Macleod grew in mutual contempt as the project progressed.

#### Success and Bitterness

Macleod brought biochemist J. B. Collip (1892–1965) into the project that fall in hopes that he could produce purer extracts. More competent in experimental science, Collip was the first to show that pancreatic extracts could eliminate ketosis and restore the liver’s ability to store glycogen. He obtained better and better results in diabetic rabbits until, by January 1922, the group felt ready for human trials. Banting was happy to have Collip on the team initially, but grew intensely jealous of him as Collip not only achieved better results than he had, but also developed a closer relationship with Macleod. Banting, who had no qualifications to perform human experiments, feared he would be pushed aside as the project moved to its clinical phase. At one point, the tension between Banting and Collip erupted into a near-fistfight in the laboratory.

Banting insisted that the first human trial be done with an extract he and Best prepared, not with Collip’s. The patient was a 14-year-old boy who weighed only 29 kg (65 lb) and was on the verge of death. He was injected on January 11 with the Banting and Best extract, described by one observer as “a thick brown muck.” The trial was an embarrassing failure, with only a slight lowering of his blood glucose and a severe reaction to the impurities in the extract. On January 23, the same boy was treated again, but with Collip’s extract. This time, his ketonuria and glycosuria were almost completely eliminated and his blood sugar dropped 77%. This was the first successful clinical trial of insulin. Six more patients were treated in February 1922 and quickly became stronger, more alert, and in better spirits. In April, the Toronto group began calling the product insulin, and at a medical conference in May, they gave the first significant public report of their success.

But Banting felt increasingly excluded from the project. He quit coming to the laboratory, stayed drunk much of the time, and daydreamed of leaving diabetes research to work on cancer. He remained only because Best pleaded with him to stay. Banting briefly operated a private diabetes clinic, but fearful of embarrassment over alienating the discoverer of insulin, the university soon lured him back with a salaried appointment and hospital privileges.

Banting had a number of high-profile, successful cases in 1922, such as 14-year-old Elizabeth Hughes, who weighed only 20 kg (45 lb) before treatment. She began treatment in August and showed immediate, dramatic improvement. She was a spirited, optimistic, and articulate girl who kept enthusiastic diaries of being allowed to eat bread, potatoes, and macaroni and cheese for the first time since the onset of her illness. “Oh it is simply too wonderful for words this stuff,” she exuberantly wrote to her mother—even though the still-impure extracts caused her considerable pain and swelling. The world quickly beat a path to Toronto begging for insulin. The pharmaceutical firm of Eli Lilly and Company entered into an agreement with the University of Toronto for the mass production of insulin, and by the fall of 1923, over 25,000 patients were being treated at more than 60 Canadian and U.S. clinics.

#### Recognition and Enmity

Banting’s self-confidence was restored. He had become a public hero, and the Canadian Parliament awarded him an endowment generous enough to ensure him a life of comfort. Several distinguished physiologists

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nominated Banting and Macleod for the 1923 Nobel Prize, and they won. When the award was announced, Banting was furious about having to share it with Macleod. At first, he threatened to refuse it, but when he cooled down, he announced that he would split his share of the prize money with Best. Macleod quickly announced that half of his share would go to Collip.

Banting subsequently made life at the university so unbearable that Macleod left in 1928 to accept a university post in Scotland. Banting stayed on at Toronto. Although now wealthy and surrounded by admiring students, he achieved nothing significant in science for the rest of his career. He was killed in a plane crash in 1941. Best replaced Macleod on the Toronto faculty, led a distinguished career, and developed the

anticoagulant heparin. Collip went on to play a lead role in the isolation of PTH, ACTH, and other hormones.

Insulin made an industry giant of Eli Lilly and Company. It became the first protein whose amino acid sequence was determined, for which Frederick Sanger received a Nobel Prize in 1958. Diabetics today no longer depend on a limited supply of insulin extracted from beef and pork pancreas. Human insulin is now in plentiful supply, made by genetically engineered bacteria. Paradoxically, while insulin has dramatically reduced the suffering caused by diabetes mellitus, it has increased the number of people who have the disease—because thanks to insulin, diabetics are now able to live long enough to raise families and pass on the diabetes genes.



# Connective Issues

## Interactions Between the ENDOCRINE SYSTEM and Other Organ Systems

- ← indicates ways in which this system affects other systems
- indicates ways in which other systems affect this one

### All Systems

Growth hormone, insulin-like growth factors, insulin, thyroid hormone, and glucocorticoids affect the development and metabolism of most tissues

### Integumentary System

- ← Sex hormones affect skin pigmentation, development of body hair and apocrine glands, and subcutaneous fat deposition
- Skin carries out a step in calcitriol (vitamin D) synthesis

### Skeletal System

- ← Parathyroid hormone, calcitonin, calcitriol, growth hormone, thyroid hormone, sex steroids, and other hormones affect bone development
- Protects some endocrine glands; stores calcium needed for endocrine function

### Muscular System

- ← Growth hormone and testosterone stimulate muscular growth; insulin regulates carbohydrate metabolism in muscle; other hormones affect electrolyte balance, which is critical to muscle function
- Skeletal muscles protect some endocrine glands

### Nervous System

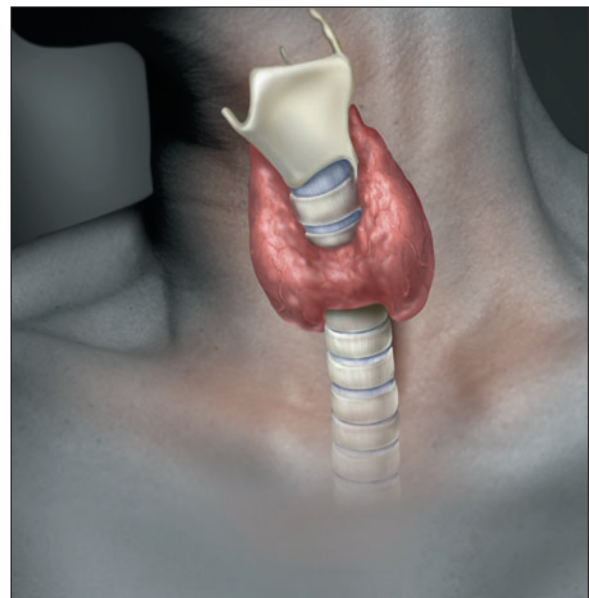
- ← Exerts negative feedback inhibition on hypothalamus; several hormones affect nervous system development, mood, and behavior; hormones regulate electrolyte balance, which is critical to neuron function
- Hypothalamus regulates secretion of anterior pituitary hormones and synthesizes the posterior pituitary hormones; sympathetic nervous system triggers secretion by adrenal medulla

### Circulatory System

- ← Angiotensin II, aldosterone, antidiuretic hormone, and atrial natriuretic peptide regulate blood volume and pressure; epinephrine, thyroid hormone, and other hormones affect heart rate and contraction force
- Blood transports hormones to their target organs; blood pressure and osmolarity variations trigger secretion of some hormones

### Lymphatic/Immune Systems

- ← Thymosin and other hormones activate immune cells; glucocorticoids suppress immunity and inflammation
- Lymphatic system maintains fluid balance in endocrine glands; lymphocytes protect endocrine glands from infection



### Respiratory System

- ← Epinephrine and norepinephrine increase pulmonary airflow
- Provides O<sub>2</sub> and removes CO<sub>2</sub>; lungs convert angiotensin I to angiotensin II

### Urinary System

- ← Antidiuretic hormone regulates water excretion; parathyroid hormone, calcitriol, and aldosterone regulate electrolyte excretion
- Disposes of wastes and maintains electrolyte and pH balance; degrades and excretes hormones

### Digestive System

- ← Parathyroid hormone affects intestinal calcium absorption; insulin and glucagon modulate nutrient storage and metabolism; several enteric hormones regulate gastrointestinal secretion and motility
- Provides nutrients; nutrient absorption triggers insulin secretion; gut-brain peptides act on hypothalamus and stimulate specific hungers; liver degrades and excretes hormones

### Reproductive System

- ← Gonadotropins and sex steroids regulate sexual development, sperm and egg production, sex drive, menstrual cycle, pregnancy, fetal development, and lactation
- Sex hormones inhibit secretion by hypothalamus and pituitary gland

# Chapter Review

## Review of Key Concepts

### Overview of the Endocrine System (p. 636)

1. Intercellular communication is necessary for homeostasis. Cells communicate through gap junctions, neurotransmitters, paracines, and hormones.
2. *Endocrinology* is the study of the endocrine system, which is composed of hormone-secreting cells and *endocrine glands*.
3. Hormones circulate throughout the body but stimulate only *target cells*, which have receptors for them.
4. Endocrine glands have no ducts, but secrete their products into the bloodstream.
5. The nervous and endocrine systems collaborate and have several overlapping functions and properties, but are not redundant. Differences are listed in table 17.1.

### The Hypothalamus and Pituitary Gland (p. 637)

1. The hypothalamus and pituitary gland have a more wide-ranging influence on the body than any other endocrine gland.
2. The pituitary gland is connected to the hypothalamus by a stalk. It is divided into an anterior *adenohypophysis*, whose main part is the *anterior lobe*, and a posterior *neurohypophysis*, whose main part is the *posterior lobe* of the pituitary.
3. The adenohypophysis is connected to the hypothalamus by a system of blood vessels called the hypophyseal portal system. The neurohypophysis is connected to the hypothalamus by a bundle of nerve fibers, the hypothalamo-hypophyseal tract.
4. The hypothalamus secretes seven hormones that travel through the portal system and regulate the anterior lobe. Five of these trigger hormone release and two of them inhibit hormone release by the anterior lobe (see table 17.3).
5. The hypothalamus synthesizes two hormones that are stored in the

posterior pituitary and released in response to nerve signals: oxytocin (OT) and antidiuretic hormone (ADH).

6. The anterior lobe secretes follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), prolactin (PRL), and growth hormone (GH). Their functions are summarized in table 17.4.
7. Growth hormone (GH) has an especially broad effect on the body, notably to stimulate the growth of cartilage, bone, muscle, and fat through its influence on protein, lipid, and carbohydrate metabolism. Many of its effects are mediated through insulin-like growth factors secreted by the liver.
8. The posterior lobe stores oxytocin (OT) and antidiuretic hormone (ADH) until the brain stimulates their release. OT promotes labor contractions and milk release and possibly contributes to semen propulsion, uterine contractions, and sexual emotion. ADH promotes water conservation.
9. The hypothalamus and pituitary are regulated by positive and negative feedback from their target organs.

### Other Endocrine Glands (p. 646)

1. The *pineal gland* secretes *serotonin* and *melatonin* and may contribute to the timing of puberty.
2. The *thymus* secretes *thymopoietin* and *thymosins*, which help to regulate immunity.
3. The *thyroid gland* secretes *triiodothyronine* ( $T_3$ ) and *thyroxine* ( $T_4$ ), which stimulate catabolism and heat production, tissue growth, nervous system development, and alertness. It also secretes calcitonin, which promotes bone deposition and lowers blood  $Ca^{2+}$  levels.
4. The four *parathyroid glands* secrete *parathyroid hormone*, which acts in several ways to increase blood  $Ca^{2+}$  levels.

5. The *adrenal medulla* secretes mainly *epinephrine* and *norepinephrine*, which raise blood glucose levels and help the body adapt to physical activity and stress.
6. The *adrenal cortex* secretes aldosterone, which promotes  $Na^+$  retention and  $K^+$  excretion; *cortisol* and *corticosterone*, which raise blood glucose and fatty acids levels and aid in stress adaptation and tissue repair; and *androgens* and *estrogens*, which contribute to reproductive development and physiology.
7. The *pancreatic islets* secrete *insulin*, which promotes glucose uptake by the tissues; *glucagon*, which stimulates the release of glucose from storage; and *somatostatin*, which regulates the insulin- and glucagon-secreting cells and inhibits some digestive functions.
8. The ovaries secrete estradiol and progesterone, which regulate reproductive development and physiology, and inhibin, which suppresses FSH secretion by the pituitary. The testes secrete testosterone and inhibin, with corresponding roles in the male.
9. Many other hormones are produced by cells that populate other organs but do not form discrete glands; *atrial natriuretic peptide* by the heart; *calcitriol* by sequential action of the skin, liver, and kidneys; *erythropoietin* by the liver and kidneys; *angiotensinogen* by the liver; several *enteric hormones* by the stomach and small intestine; and *estrogens* and *progesterone* by the placenta.

### Hormones and Their Actions (p. 652)

1. There are three chemical classes of hormones: steroids, peptides, and monoamines (table 17.6).
2. The steroids are synthesized from cholesterol.
3. Peptide hormones are synthesized by ribosomes and pass through inactive stages called the prohormone and

prohormone before being converted to active hormone.

4. Monoamines are synthesized from the amino acids tryptophan and tyrosine. Thyroid hormone is an unusual case in that its synthesis begins with a large protein, thyroglobulin. Iodine is added to its tyrosine residues, the modified tyrosines are linked in pairs, and then the tyrosines are cleaved from the protein to yield the two thyroid hormones,  $T_3$  and  $T_4$ .
5. Peptides and most monoamines travel easily in the watery blood plasma, but the hydrophobic steroids and thyroid hormone are carried by *transport proteins*, which also prolong the half-life of the hormones.
6. Hormone receptors are found in the plasma membranes, on the mitochondria and other organelles, and in the nuclei of the target cells. Steroids bind to nuclear receptors;  $T_3$  to receptors in the nucleus, mitochondria, and ribosomes; and peptides and catecholamines to plasma membrane receptors, which activate formation of second messengers in the cytosol.
7. Second messengers for hormone action include cAMP, cGMP, diacylglycerol, and inositol triphosphate.
8. Because of *enzyme amplification*, small amounts of hormone can have great physiological effects.
9. Hormones are cleared from the blood by metabolism in the liver and kidneys and excretion in the bile and urine.
10. Target cells can adjust their sensitivity to a hormone by *up-regulation* (increasing the number of hormone receptors) and *down-regulation* (decreasing the number of receptors).
11. Hormones do not act in isolation, but influence each other. One hormone

can have *synergistic*, *permissive*, or *antagonistic effects* on the action of another.

#### Stress and Adaptation (p. 662)

1. *Stress* is any situation that upsets homeostasis and threatens well-being.
2. Regardless of the cause of stress, the body reacts in a fairly consistent way called the *stress response* (*general adaptation syndrome*).
3. The first stage of the stress response, the *alarm reaction*, is characterized by elevated levels of norepinephrine, epinephrine, aldosterone, and angiotensin, resulting in glycogen breakdown, fluid and electrolyte retention, and elevated blood pressure.
4. The second stage, the *stage of resistance*, sets in when stored glycogen is exhausted. It is characterized by elevated levels of ACTH and cortisol, and the breakdown of fat and protein for fuel.
5. The third stage, the *stage of exhaustion*, sets in if fat reserves are depleted. It is characterized by increasing protein breakdown, weakening of the body, and often death.

#### Eicosanoids and Paracrine Signaling (p. 664)

1. *Paracrine*s are hormonelike messengers that travel only short distances and stimulate nearby cells.
2. Many paracrine are *eicosanoids*, which have 20-carbon backbones and are derived from arachidonic acid. Eicosanoids include leukotrienes, prostacyclin, thromboxanes, and prostaglandins.

#### Endocrine Disorders (p. 666)

1. Endocrine dysfunctions often stem from hormone hyposecretion or hypersecretion.

2. Some pituitary disorders include *acromegaly* and *gigantism* from GH hypersecretion, *pituitary dwarfism* from GH hyposecretion, and *diabetes insipidus* from ADH hyposecretion.
3. *Myxedema* and *endemic goiter* are thyroid hyposecretion disorders and *toxic goiter* is a thyroid hypersecretion disorder.
4. *Hypoparathyroidism* leads to low blood  $Ca^{2+}$  level and sometimes fatal tetany; *hyperparathyroidism* leads to excessive blood  $Ca^{2+}$  and bone fragility.
5. Hypersecretion by the adrenal cortex can result in *Cushing syndrome* (excess cortisol) or *adrenogenital syndrome* (excess androgen).
6. Diabetes mellitus (DM) is the most common endocrine dysfunction, resulting from the hyposecretion or inaction of insulin—type I or insulin-dependent DM (IDDM) and type II or non-insulin-dependent DM (NIDDM), respectively.
7. DM is characterized by *polyuria*, *polydipsia*, and *polyphagia* and clinically confirmed by findings of *hyperglycemia*, *glycosuria*, and *ketonuria*. Glycosuria and osmotic diuresis result in the extreme polyuria, dehydration, and thirst typical of DM.
8. IDDM results from destruction of insulin-secreting  $\beta$  cells of the pancreas and is treated with insulin. NIDDM results from insensitivity of target cells to insulin and is treated with exercise, weight-loss diets, and medications to enhance insulin sensitivity.
9. Untreated DM results in severe wasting away of the body, degenerative cardiovascular and neurological disease, gangrene, blindness, kidney failure, ketoacidosis, coma, and death.

## Selected Vocabulary

### Study tables 17.2 through 17.5 for hormone names.

endocrinology 636  
paracrine 636  
hormone 636  
target cell 637  
anterior lobe of pituitary 639  
posterior lobe of pituitary 639  
gonadotropin 640

neuroendocrine reflex 644  
negative feedback inhibition 645  
pineal gland 646  
thymus 646  
thyroid gland 647  
parathyroid glands 648  
adrenal gland 648  
adrenal cortex 649

androgen 649  
estrogen 649  
pancreatic islet 650  
 $\beta$  cell 650  
 $\alpha$  cell 651  
up- and down-regulation 661  
stress response 663  
eicosanoid 664  
arachidonic acid 664

leukotriene 664  
prostacyclin 664  
thromboxane 664  
prostaglandin 665  
hyposecretion 666  
hypersecretion 666  
IDDM 669  
NIDDM 669  
ketoacidosis 670

## Testing Your Recall

- CRH secretion would *not* raise the blood concentration of
  - ACTH.
  - thyroxine.
  - cortisol.
  - corticosterone.
  - glucose.
- Which of the following hormones has the least in common with the others?
  - adrenocorticotrophic hormone
  - follicle-stimulating hormone
  - thyrotropin
  - thyroxine
  - prolactin
- Which hormone would no longer be secreted if the hypothalamo-hypophyseal tract were destroyed?
  - oxytocin
  - follicle-stimulating hormone
  - growth hormone
  - adrenocorticotrophic hormone
  - corticosterone
- Which of the following is *not* a hormone?
  - prolactin
  - prolactin-inhibiting factor
  - thyroxine-binding globulin
  - atrial natriuretic factor
  - cortisol
- Where are the receptors for insulin located?
  - in the pancreatic  $\beta$  cells
  - in the blood plasma
  - on the target cell membrane
  - in the target cell cytoplasm
  - in the target cell nucleus
- What would be the consequence of defective ADH receptors?
  - diabetes mellitus
  - adrenogenital syndrome
  - dehydration
  - seasonal affective disorder
  - none of these
- Which of these has more exocrine than endocrine tissue?
  - the pineal gland
  - the adenohypophysis
  - the thyroid gland
  - the pancreas
  - the adrenal gland
- Which of these cells stimulate bone deposition?
  - $\alpha$  cells
  - $\beta$  cells
  - C cells
  - G cells
  - T cells
- Which of these hormones relies on cAMP as a second messenger?
  - ACTH
  - progesterone
  - thyroxine
  - testosterone
  - epinephrine
- Prostaglandins are derived from
  - pro-opiomelanocortin.
  - cyclooxygenase.
  - leukotriene.
  - lipoxygenase.
  - arachidonic acid.
- The \_\_\_\_\_ develops from the hypophyseal pouch of the embryo.
- Thyroxine ( $T_4$ ) is synthesized by combining two molecules of the amino acid \_\_\_\_\_.
- Growth hormone hypersecretion in adulthood causes a disease called \_\_\_\_\_.
- The dominant hormone in the stage of resistance of the stress response is \_\_\_\_\_.
- Adrenal steroids that regulate glucose metabolism are collectively called \_\_\_\_\_.
- Sex steroids are secreted by the \_\_\_\_\_ cells of the ovary and \_\_\_\_\_ cells of the testis.
- Target cells can reduce pituitary secretion by a process called \_\_\_\_\_.
- Hypothalamic releasing factors are delivered to the anterior pituitary by way of a network of blood vessels called the \_\_\_\_\_.
- A hormone is said to have a/an \_\_\_\_\_ effect when it stimulates the target cell to develop receptors for other hormones to follow.
- \_\_\_\_\_ is a process in which a cell increases its number of receptors for a hormone.

**Answers in Appendix B**

## True or False

Determine which five of the following statements are false, and briefly explain why.

- Castration would raise a man's blood gonadotropin concentration.
- Hormones in the glycoprotein class cannot have cytoplasmic or nuclear receptors in their target cells.
- Epinephrine and thyroid hormone have the same effects on metabolic rate and blood pressure.
- Tumors can lead to either hyposecretion or hypersecretion of various hormones.
- All hormones are secreted by endocrine glands.
- An atherosclerotic deposit that blocked blood flow in the hypophyseal portal system would cause the testes and ovaries to malfunction.
- The pineal gland and thymus become larger as one gets older.
- A deficiency of dietary iodine would lead to negative feedback inhibition of the hypothalamic-pituitary-thyroid axis.
- The tissue at the center of the adrenal gland is called the zona reticularis.
- Of the endocrine organs covered in this chapter, only the adrenal glands are paired; the rest are single.

**Answers in Appendix B**



## Testing Your Comprehension

1. Propose a model of enzyme amplification for the effect of a steroid hormone and construct a diagram similar to figure 17.21 for your model. A review of protein synthesis in chapter 4 may help.
2. Suppose you were browsing in a health-food store and saw a product advertised: "Put an end to heart disease. This herbal medicine will totally rid your body of cholesterol!" Would you buy it? Why or why not? If the product were as effective as claimed, what are some other effects it would produce?
3. A person with toxic goiter tends to sweat profusely. Explain this in terms of homeostasis.
4. How is the action of a peptide hormone similar to the action of the neurotransmitter norepinephrine?
5. Review the effects of anabolic steroid abuse (see insight 2.5, p. 87), and explain how some of these effects may relate to the concept of down-regulation explained in this chapter.

*Answers at the Online Learning Center*

## Answers to Figure Questions

- |   |   |  |
|---|---|--|
| 17.4 The neurohypophysis  | 17.23 Such a drug would block leukotriene synthesis and thus inhibit allergic and inflammatory responses. | 17.24 She would have been a pituitary giant. |
| 17.7 The thymus   |   |  |
| 17.19 Steroids enter the target cell; they do not bind to membrane receptors or activate second messengers. |   |  |

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