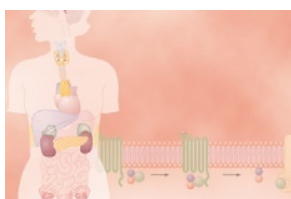


# Introduction to Endocrinology



## Coordination of Body Functions by Chemical Messengers

The multiple activities of the cells, tissues, and organs of the body are coordinated by the interplay of several types of chemical messenger systems:

1. **Neurotransmitters** are released by axon terminals of neurons into the synaptic junctions and act locally to control nerve cell functions.
2. **Endocrine hormones** are released by glands or specialized cells into the circulating blood and influence the function of target cells at another location in the body.
3. **Neuroendocrine hormones** are secreted by neurons into the circulating blood and influence the function of target cells at another location in the body.
4. **Paracrines** are secreted by cells into the extracellular fluid and affect neighboring target cells of a different type.
5. **Autocrines** are secreted by cells into the extracellular fluid and affect the function of the same cells that produced them.
6. **Cytokines** are peptides secreted by cells into the extracellular fluid and can function as autocrines, paracrines, or endocrine hormones. Examples of cytokines include the *interleukins* and other *lymphokines* that are secreted by helper cells and act on other cells of the immune system (see Chapter 34). Cytokine hormones (e.g., *leptin*) produced by adipocytes are sometimes called *adipokines*.

In the next few chapters, we discuss mainly the endocrine and neuroendocrine hormone systems, keeping in mind that many of the body's chemical messenger systems interact with one another to maintain homeostasis. For example, the adrenal medullae and the pituitary gland secrete their hormones primarily in response to neural stimuli. The neuroendocrine cells, located in the hypothalamus, have axons that terminate in the posterior pituitary gland and median eminence and secrete several neurohormones, including *antidiuretic hormone* (ADH), *oxytocin*, and *hypophysiotropic hormones*, which control the secretion of anterior pituitary hormones.

The *endocrine hormones* are carried by the circulatory system to cells throughout the body, including the nervous system in some cases, where they bind with receptors and initiate many cell reactions. Some endocrine hormones affect many different types of cells of the body; for example, *growth hormone* (from the anterior pituitary gland) causes growth in most parts of the body, and *thyroxine* (from the thyroid gland) increases the rate of many chemical reactions in almost all the body's cells.

Other hormones affect mainly specific *target tissues* because these tissues have abundant receptors for the hormone. For example, *adrenocorticotrophic hormone* (ACTH) from the anterior pituitary gland specifically stimulates the adrenal cortex, causing it to secrete adrenocortical hormones, and the *ovarian hormones* have their main effects on the female sex organs and the secondary sexual characteristics of the female body.

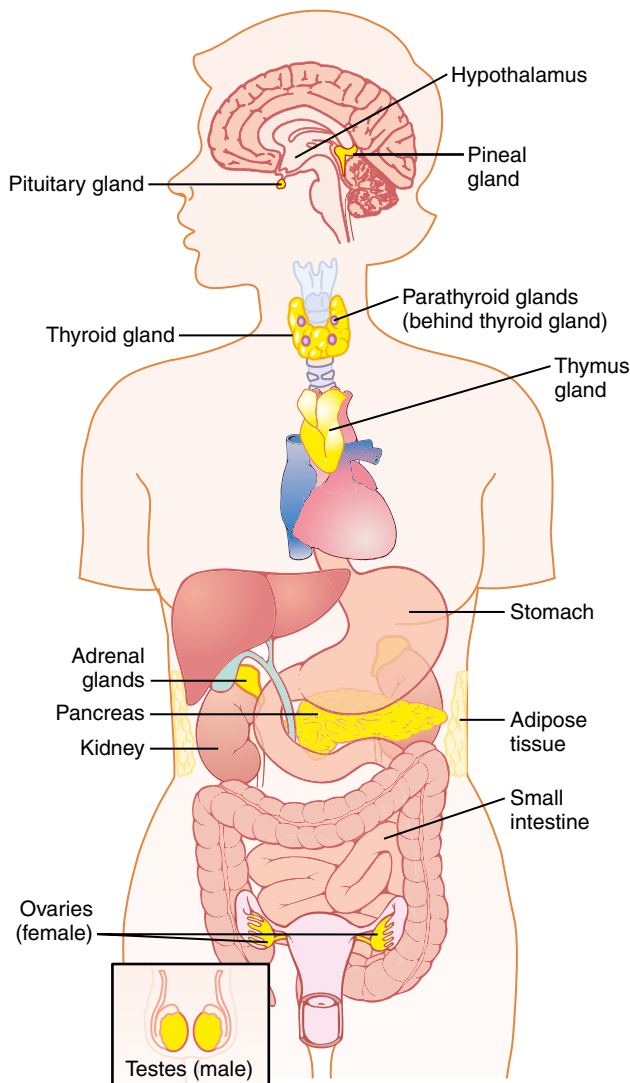
Figure 74-1 shows the anatomical loci of the major endocrine glands and endocrine tissues of the body, except for the placenta, which is an additional source of the sex hormones. Table 74-1 provides an overview of the different hormone systems and their most important actions.

The multiple hormone systems play a key role in regulating almost all body functions, including metabolism, growth and development, water and electrolyte balance, reproduction, and behavior. For instance, without growth hormone, a person would be a dwarf. Without thyroxine and triiodothyronine from the thyroid gland, almost all the chemical reactions of the body would become sluggish and the person would become sluggish as well. Without insulin from the pancreas, the body's cells could use little of the food carbohydrates for energy. And without the sex hormones, sexual development and sexual functions would be absent.

## Chemical Structure and Synthesis of Hormones

Three general classes of hormones exist:

1. **Proteins and polypeptides**, including hormones secreted by the anterior and posterior pituitary gland, the pancreas (insulin and glucagon), the parathyroid gland (parathyroid hormone), and many others (see Table 74-1).



**Figure 74-1** Anatomical loci of the principal endocrine glands and tissues of the body.

2. *Steroids* secreted by the adrenal cortex (cortisol and aldosterone), the ovaries (estrogen and progesterone), the testes (testosterone), and the placenta (estrogen and progesterone).
3. *Derivatives of the amino acid tyrosine*, secreted by the thyroid (thyroxine and triiodothyronine) and the adrenal medullae (epinephrine and norepinephrine). There are no known polysaccharides or nucleic acid hormones.

**Polypeptide and Protein Hormones Are Stored in Secretory Vesicles Until Needed.** Most of the hormones in the body are polypeptides and proteins. These hormones range in size from small peptides with as few as 3 amino acids (thyrotropin-releasing hormone) to proteins with almost 200 amino acids (growth hormone and prolactin). In general, polypeptides with 100 or more amino acids are called *proteins*, and those with fewer than 100 amino acids are referred to as *peptides*.

Protein and peptide hormones are synthesized on the rough end of the endoplasmic reticulum of the different endocrine cells, in the same fashion as most other proteins (Figure 74-2). They are usually synthesized first as larger proteins that are not biologically active (*preprohormones*) and are cleaved to form smaller *prohormones* in the endoplasmic reticulum. These are then transferred to the Golgi apparatus for packaging into secretory vesicles. In this process, enzymes in the vesicles cleave the prohormones to produce smaller, biologically active hormones and inactive fragments. The vesicles are stored within the cytoplasm, and many are bound to the cell membrane until their secretion is needed. Secretion of the hormones (as well as the inactive fragments) occurs when the secretory vesicles fuse with the cell membrane and the granular contents are extruded into the interstitial fluid or directly into the blood stream by *exocytosis*.

In many cases, the stimulus for exocytosis is an increase in cytosolic calcium concentration caused by depolarization of the plasma membrane. In other instances, stimulation of an endocrine cell surface receptor causes increased cyclic adenosine monophosphate (cAMP) and subsequently activation of protein kinases that initiate secretion of the hormone. The peptide hormones are water soluble, allowing them to enter the circulatory system easily, where they are carried to their target tissues.

**Steroid Hormones Are Usually Synthesized from Cholesterol and Are Not Stored.** The chemical structure of steroid hormones is similar to that of cholesterol, and in most instances hormones are synthesized from cholesterol itself. They are lipid soluble and consist of three cyclohexyl rings and one cyclopentyl ring combined into a single structure (Figure 74-3).

Although there is usually very little hormone storage in steroid-producing endocrine cells, large stores of cholesterol esters in cytoplasm vacuoles can be rapidly mobilized for steroid synthesis after a stimulus. Much of the cholesterol in steroid-producing cells comes from the plasma, but there is also *de novo* synthesis of cholesterol in steroid-producing cells. Because the steroids are highly lipid soluble, once they are synthesized, they simply diffuse across the cell membrane and enter the interstitial fluid and then the blood.

**Amine Hormones Are Derived from Tyrosine.** The two groups of hormones derived from tyrosine, the thyroid and the adrenal medullary hormones, are formed by the actions of enzymes in the cytoplasmic compartments of the glandular cells. The thyroid hormones are synthesized and stored in the thyroid gland and incorporated into macromolecules of the protein *thyroglobulin*, which is stored in large follicles within the thyroid gland. Hormone secretion occurs when the amines are split from thyroglobulin, and the free hormones are then released into the blood stream. After entering the blood, most of the thyroid hormones combine with plasma proteins, especially *thyroxine-binding globulin*, which slowly releases the hormones to the target tissues.

**Table 74-1** Endocrine Glands, Hormones, and Their Functions and Structure

Gland/Tissue	Hormones	Major Functions	Chemical Structure
Hypothalamus (Chapter 75)	Thyrotropin-releasing hormone (TRH)	Stimulates secretion of thyroid-stimulating hormone (TSH) and prolactin	Peptide
	Corticotropin-releasing hormone (CRH)	Causes release of adrenocorticotrophic hormone (ACTH)	Peptide
	Growth hormone-releasing hormone (GHRH)	Causes release of growth hormone	Peptide
	Growth hormone inhibitory hormone (GHIH) (somatostatin)	Inhibits release of growth hormone	Peptide
	Gonadotropin-releasing hormone (GnRH)	Causes release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)	
	Dopamine or prolactin-inhibiting factor (PIF)	Inhibits release of prolactin	Amine
Anterior pituitary (Chapter 75)	Growth hormone	Stimulates protein synthesis and overall growth of most cells and tissues	Peptide
	TSH	Stimulates synthesis and secretion of thyroid hormones (thyroxine and triiodothyronine)	Peptide
	ACTH	Stimulates synthesis and secretion of adrenocortical hormones (cortisol, androgens, and aldosterone)	Peptide
	Prolactin	Promotes development of the female breasts and secretion of milk	Peptide
	FSH	Causes growth of follicles in the ovaries and sperm maturation in Sertoli cells of testes	Peptide
	LH	Stimulates testosterone synthesis in Leydig cells of testes; stimulates ovulation, formation of corpus luteum, and estrogen and progesterone synthesis in ovaries	Peptide
Posterior pituitary (Chapter 75)	Antidiuretic hormone (ADH) (also called <i>vasopressin</i> )	Increases water reabsorption by the kidneys and causes vasoconstriction and increased blood pressure	Peptide
	Oxytocin	Stimulates milk ejection from breasts and uterine contractions	Peptide
Thyroid (Chapter 76)	Thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ )	Increases the rates of chemical reactions in most cells, thus increasing body metabolic rate	Amine
	Calcitonin	Promotes deposition of calcium in the bones and decreases extracellular fluid calcium ion concentration	Peptide
Adrenal cortex (Chapter 77)	Cortisol	Has multiple metabolic functions for controlling metabolism of proteins, carbohydrates, and fats; also has anti-inflammatory effects	Steroid
	Aldosterone	Increases renal sodium reabsorption, potassium secretion, and hydrogen ion secretion	Steroid
Adrenal medulla (Chapter 60)	Norepinephrine, epinephrine	Same effects as sympathetic stimulation	Amine
Pancreas (Chapter 78)	Insulin ( $\beta$ cells)	Promotes glucose entry in many cells, and in this way controls carbohydrate metabolism	Peptide

(Continued)

**Table 74-1** Endocrine Glands, Hormones, and Their Functions and Structure—Cont'd

Gland/Tissue	Hormones	Major Functions	Chemical Structure
	Glucagon ( $\alpha$ cells)	Increases synthesis and release of glucose from the liver into the body fluids	Peptide
Parathyroid (Chapter 79)	Parathyroid hormone (PTH)	Controls serum calcium ion concentration by increasing calcium absorption by the gut and kidneys and releasing calcium from bones	Peptide
Testes (Chapter 80)	Testosterone	Promotes development of male reproductive system and male secondary sexual characteristics	Steroid
Ovaries (Chapter 81)	Estrogens	Promotes growth and development of female reproductive system, female breasts, and female secondary sexual characteristics	Steroid
	Progesterone	Stimulates secretion of "uterine milk" by the uterine endometrial glands and promotes development of secretory apparatus of breasts	Steroid
Placenta (Chapter 82)	Human chorionic gonadotropin (HCG)	Promotes growth of corpus luteum and secretion of estrogens and progesterone by corpus luteum	Peptide
	Human somatomammotropin	Probably helps promote development of some fetal tissues as well as the mother's breasts	Peptide
	Estrogens	See actions of estrogens from ovaries	Steroid
	Progesterone	See actions of progesterone from ovaries	Steroid
Kidney (Chapter 26)	Renin	Catalyzes conversion of angiotensinogen to angiotensin I (acts as an enzyme)	Peptide
	1,25-Dihydroxycholecalciferol	Increases intestinal absorption of calcium and bone mineralization	Steroid
	Erythropoietin	Increases erythrocyte production	Peptide
Heart (Chapter 22)	Atrial natriuretic peptide (ANP)	Increases sodium excretion by kidneys, reduces blood pressure	Peptide
Stomach (Chapter 64)	Gastrin	Stimulates HCl secretion by parietal cells	Peptide
Small intestine (Chapter 64)	Secretin	Stimulates pancreatic acinar cells to release bicarbonate and water	Peptide
	Cholecystokinin (CCK)	Stimulates gallbladder contraction and release of pancreatic enzymes	Peptide
Adipocytes (Chapter 71)	Leptin	Inhibits appetite, stimulates thermogenesis	Peptide

Epinephrine and norepinephrine are formed in the adrenal medulla, which normally secretes about four times more epinephrine than norepinephrine. Catecholamines are taken up into preformed vesicles and stored until secreted. Similar to the protein hormones stored in secretory granules, catecholamines are also released from adrenal medullary cells by exocytosis. Once the catecholamines enter the circulation, they can exist in the plasma in free form or in conjugation with other substances.

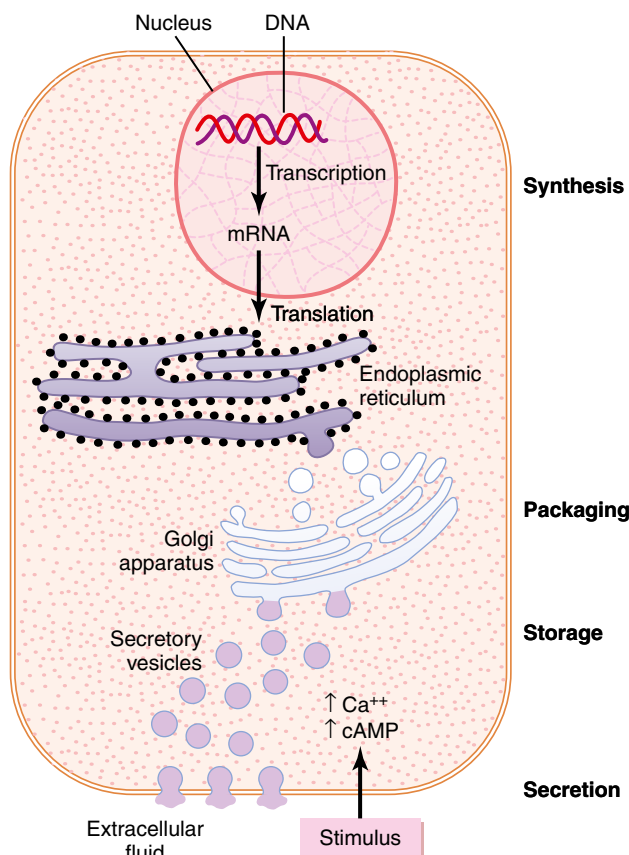
### Hormone Secretion, Transport, and Clearance from the Blood

**Onset of Hormone Secretion After a Stimulus, and Duration of Action of Different Hormones.** Some hormones, such as norepinephrine and epinephrine, are secreted within seconds after the gland is stimulated, and

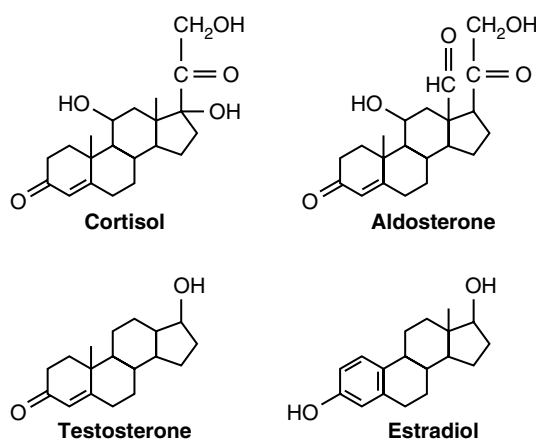
they may develop full action within another few seconds to minutes; the actions of other hormones, such as thyroxine or growth hormone, may require months for full effect. Thus, each of the different hormones has its own characteristic onset and duration of action—each tailored to perform its specific control function.

**Concentrations of Hormones in the Circulating Blood, and Hormonal Secretion Rates.** The concentrations of hormones required to control most metabolic and endocrine functions are incredibly small. Their concentrations in the blood range from as little as 1 picogram (which is one millionth of one millionth of a gram) in each milliliter of blood up to at most a few micrograms (a few millionths of a gram) per milliliter of blood. Similarly, the rates of secretion of the various hormones are extremely small, usually measured in micrograms or milligrams per day. We shall see later in this





**Figure 74-2** Synthesis and secretion of peptide hormones. The stimulus for hormone secretion often involves changes in intracellular calcium or changes in cyclic adenosine monophosphate (cAMP) in the cell.



**Figure 74-3** Chemical structures of several steroid hormones.

chapter that highly specialized mechanisms are available in the target tissues that allow even these minute quantities of hormones to exert powerful control over the physiological systems.

### Feedback Control of Hormone Secretion

**Negative Feedback Prevents Overactivity of Hormone Systems.** Although the plasma concentrations of many hormones fluctuate in response to vari-

ous stimuli that occur throughout the day, all hormones studied thus far appear to be closely controlled. In most instances, this control is exerted through *negative feedback mechanisms* that ensure a proper level of hormone activity at the target tissue. After a stimulus causes release of the hormone, conditions or products resulting from the action of the hormone tend to suppress its further release. In other words, the hormone (or one of its products) has a negative feedback effect to prevent oversecretion of the hormone or overactivity at the target tissue.

The controlled variable is sometimes not the secretory rate of the hormone itself but the degree of activity of the target tissue. Therefore, only when the target tissue activity rises to an appropriate level will feedback signals to the endocrine gland become powerful enough to slow further secretion of the hormone. Feedback regulation of hormones can occur at all levels, including gene transcription and translation steps involved in the synthesis of hormones and steps involved in processing hormones or releasing stored hormones.

**Surges of Hormones Can Occur with Positive Feedback.** In a few instances, *positive feedback* occurs when the biological action of the hormone causes additional secretion of the hormone. One example of this is the surge of *luteinizing hormone* (LH) that occurs as a result of the stimulatory effect of estrogen on the anterior pituitary before ovulation. The secreted LH then acts on the ovaries to stimulate additional secretion of estrogen, which in turn causes more secretion of LH. Eventually, LH reaches an appropriate concentration and typical negative feedback control of hormone secretion is then exerted.

**Cyclical Variations Occur in Hormone Release.** Superimposed on the negative and positive feedback control of hormone secretion are periodic variations in hormone release that are influenced by seasonal changes, various stages of development and aging, the diurnal (daily) cycle, and sleep. For example, the secretion of growth hormone is markedly increased during the early period of sleep but is reduced during the later stages of sleep. In many cases, these cyclical variations in hormone secretion are due to changes in activity of neural pathways involved in controlling hormone release.

### Transport of Hormones in the Blood

*Water-soluble hormones* (peptides and catecholamines) are dissolved in the plasma and transported from their sites of synthesis to target tissues, where they diffuse out of the capillaries, into the interstitial fluid, and ultimately to target cells.

*Steroid and thyroid hormones*, in contrast, circulate in the blood mainly bound to plasma proteins. Usually less than 10 percent of steroid or thyroid hormones in the plasma exist free in solution. For example, more than 99 percent of the thyroxine in the blood is bound to plasma proteins. However, protein-bound hormones cannot easily diffuse across the capillaries and gain access to their

target cells and are therefore biologically inactive until they dissociate from plasma proteins.

The relatively large amounts of hormones bound to proteins serve as reservoirs, replenishing the concentration of free hormones when they are bound to target receptors or lost from the circulation. Binding of hormones to plasma proteins greatly slows their clearance from the plasma.

### "Clearance" of Hormones from the Blood

Two factors can increase or decrease the concentration of a hormone in the blood. One of these is the rate of hormone secretion into the blood. The second is the rate of removal of the hormone from the blood, which is called the *metabolic clearance rate*. This is usually expressed in terms of the number of milliliters of plasma cleared of the hormone per minute. To calculate this clearance rate, one measures (1) the rate of disappearance of the hormone from the plasma (e.g., nanograms per minute) and (2) the plasma concentration of the hormone (e.g., nanograms per milliliter of plasma). Then, the metabolic clearance rate is calculated by the following formula:

$$\text{Metabolic clearance rate} = \frac{\text{Rate of disappearance of hormone from the plasma}}{\text{Concentration of hormone}}$$

The usual procedure for making this measurement is the following: A purified solution of the hormone to be measured is tagged with a radioactive substance. Then the radioactive hormone is infused at a constant rate into the blood stream until the radioactive concentration in the plasma becomes steady. At this time, the rate of disappearance of the radioactive hormone from the plasma equals the rate at which it is infused, which gives one the rate of disappearance. At the same time, the plasma concentration of the radioactive hormone is measured using a standard radioactive counting procedure. Then, using the formula just cited, the metabolic clearance rate is calculated.

Hormones are "cleared" from the plasma in several ways, including (1) metabolic destruction by the tissues, (2) binding with the tissues, (3) excretion by the liver into the bile, and (4) excretion by the kidneys into the urine. For certain hormones, a decreased metabolic clearance rate may cause an excessively high concentration of the hormone in the circulating body fluids. For instance, this occurs for several of the steroid hormones when the liver is diseased because these hormones are conjugated mainly in the liver and then "cleared" into the bile.

Hormones are sometimes degraded at their target cells by enzymatic processes that cause endocytosis of the cell membrane hormone-receptor complex; the hormone is then metabolized in the cell, and the receptors are usually recycled back to the cell membrane.

Most of the peptide hormones and catecholamines are water soluble and circulate freely in the blood. They are usually degraded by enzymes in the blood and tissues and

rapidly excreted by the kidneys and liver, thus remaining in the blood for only a short time. For example, the half-life of angiotensin II circulating in the blood is less than a minute.

Hormones that are bound to plasma proteins are cleared from the blood at much slower rates and may remain in the circulation for several hours or even days. The half-life of adrenal steroids in the circulation, for example, ranges between 20 and 100 minutes, whereas the half-life of the protein-bound thyroid hormones may be as long as 1 to 6 days.

## Mechanisms of Action of Hormones

### Hormone Receptors and Their Activation

The first step of a hormone's action is to bind to specific *receptors* at the target cell. Cells that lack receptors for the hormones do not respond. Receptors for some hormones are located on the target cell membrane, whereas other hormone receptors are located in the cytoplasm or the nucleus. When the hormone combines with its receptor, this usually initiates a cascade of reactions in the cell, with each stage becoming more powerfully activated so that even small concentrations of the hormone can have a large effect.

Hormonal receptors are large proteins, and each cell that is to be stimulated usually has some 2000 to 100,000 receptors. Also, each receptor is usually highly specific for a single hormone; this determines the type of hormone that will act on a particular tissue. The target tissues that are affected by a hormone are those that contain its specific receptors.

The locations for the different types of hormone receptors are generally the following:

1. *In or on the surface of the cell membrane.* The membrane receptors are specific mostly for the protein, peptide, and catecholamine hormones.
2. *In the cell cytoplasm.* The primary receptors for the different steroid hormones are found mainly in the cytoplasm.
3. *In the cell nucleus.* The receptors for the thyroid hormones are found in the nucleus and are believed to be located in direct association with one or more of the chromosomes.

**The Number and Sensitivity of Hormone Receptors Are Regulated.** The number of receptors in a target cell usually does not remain constant from day to day, or even from minute to minute. The receptor proteins themselves are often inactivated or destroyed during the course of their function, and at other times they are reactivated or new ones are manufactured by the protein-manufacturing mechanism of the cell. For instance, increased hormone concentration and increased binding with its target cell receptors sometimes cause the number of active receptors to decrease. This *down-regulation* of the receptors can occur as a result of (1) inactivation of some of the receptor molecules; (2) inactivation of some of the intracellular

protein signaling molecules; (3) temporary sequestration of the receptor to the inside of the cell, away from the site of action of hormones that interact with cell membrane receptors; (4) destruction of the receptors by lysosomes after they are internalized; or (5) decreased production of the receptors. In each case, receptor down-regulation decreases the target tissue's responsiveness to the hormone.

Some hormones cause *up-regulation* of receptors and intracellular signaling proteins; that is, the stimulating hormone induces greater than normal formation of receptor or intracellular signaling molecules by the protein-manufacturing machinery of the target cell, or greater availability of the receptor for interaction with the hormone. When this occurs, the target tissue becomes progressively more sensitive to the stimulating effects of the hormone.

### Intracellular Signaling After Hormone Receptor Activation

Almost without exception, a hormone affects its target tissues by first forming a hormone-receptor complex. This alters the function of the receptor itself, and the activated receptor initiates the hormonal effects. To explain this, let us give a few examples of the different types of interactions.

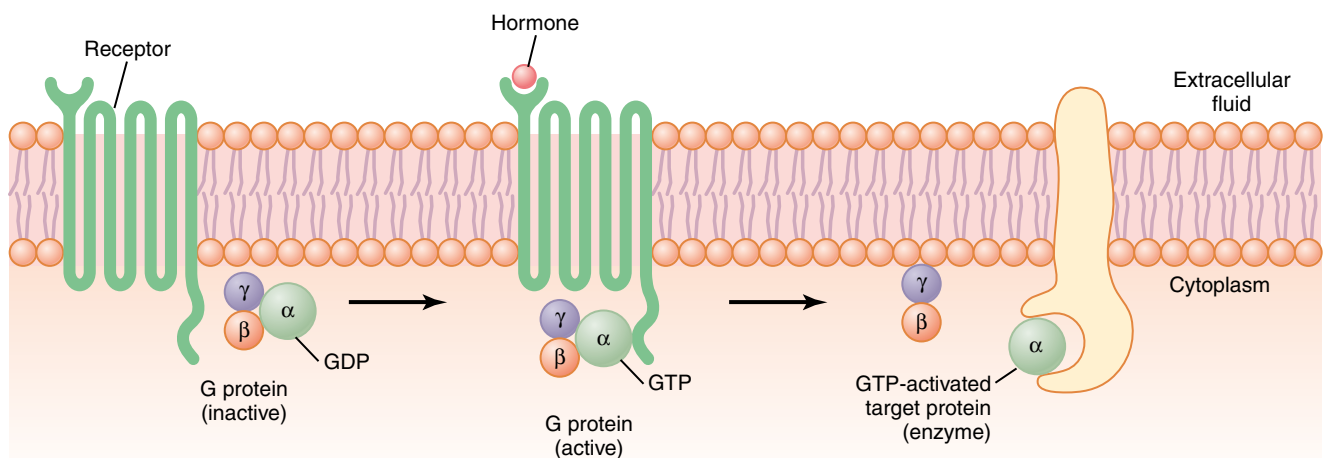
**Ion Channel–Linked Receptors.** Virtually all the neurotransmitter substances, such as acetylcholine and norepinephrine, combine with receptors in the postsynaptic membrane. This almost always causes a change in the structure of the receptor, usually opening or closing a channel for one or more ions. Some of these *ion channel-linked receptors* open (or close) channels for sodium ions, others for potassium ions, others for calcium ions, and so forth. The altered movement of these ions through the channels causes the subsequent effects on the postsynaptic cells. Although a few hormones may exert some of their actions through activation of ion channel receptors, most hormones that open or close ions channels

do this indirectly by coupling with G protein–linked or enzyme-linked receptors, as discussed next.

**G Protein–Linked Hormone Receptors.** Many hormones activate receptors that indirectly regulate the activity of target proteins (e.g., enzymes or ion channels) by coupling with groups of cell membrane proteins called *heterotrimeric GTP-binding proteins* (*G proteins*) (Figure 74-4). Of more than 1000 known G protein–coupled receptors, all have seven transmembrane segments that loop in and out of the cell membrane. Some parts of the receptor that protrude into the cell cytoplasm (especially the cytoplasmic tail of the receptor) are coupled to G proteins that include three (i.e., trimeric) parts—the  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits. When the ligand (hormone) binds to the extracellular part of the receptor, a conformational change occurs in the receptor that activates the G proteins and induces intracellular signals that either (1) open or close cell membrane ion channels or (2) change the activity of an enzyme in the cytoplasm of the cell.

The trimeric G proteins are named for their ability to bind *guanosine nucleotides*. In their inactive state, the  $\alpha$ ,  $\beta$ , and  $\gamma$  subunits of G proteins form a complex that binds *guanosine diphosphate* (GDP) on the  $\alpha$  subunit. When the receptor is activated, it undergoes a conformational change that causes the GDP-bound trimeric G protein to associate with the cytoplasmic part of the receptor and to exchange GDP for *guanosine triphosphate* (GTP). Displacement of GDP by GTP causes the  $\alpha$  subunit to dissociate from the trimeric complex and to associate with other intracellular signaling proteins; these proteins, in turn, alter the activity of ion channels or intracellular enzymes such as *adenylyl cyclase* or *phospholipase C*, which alters cell function.

The signaling event is terminated when the hormone is removed and the  $\alpha$  subunit inactivates itself by converting its bound GTP to GDP; then the  $\alpha$  subunit once again combines with the  $\beta$  and  $\gamma$  subunits to form an inactive, membrane-bound trimeric G protein.



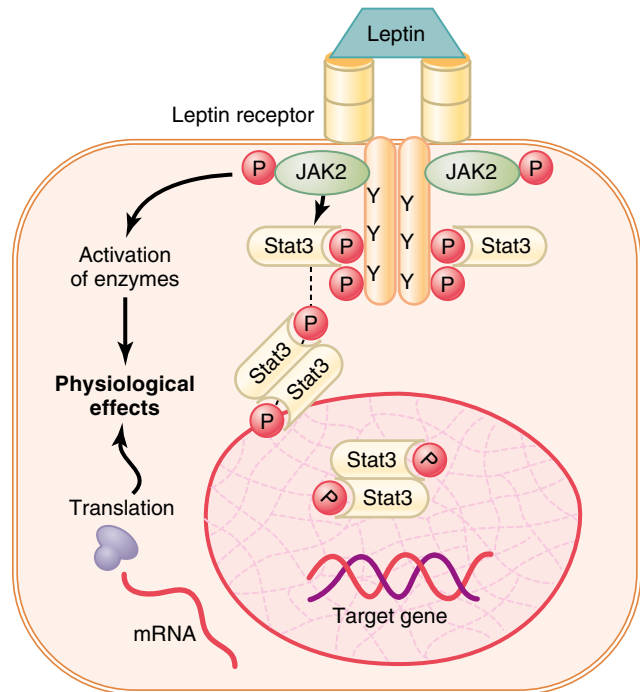
**Figure 74-4** Mechanism of activation of a G protein–coupled receptor. When the hormone activates the receptor, the inactive  $\alpha$ ,  $\beta$ , and  $\gamma$  G protein complex associates with the receptor and is activated, with an exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP). This causes the  $\alpha$  subunit (to which the GTP is bound) to dissociate from the  $\beta$  and  $\gamma$  subunits of the G protein and to interact with membrane-bound target proteins (enzymes) that initiate intracellular signals.

Some hormones are coupled to *inhibitory G proteins* (denoted  $G_i$  proteins), whereas others are coupled to *stimulatory G proteins* (denoted  $G_s$  proteins). Thus, depending on the coupling of a hormone receptor to an inhibitory or stimulatory G protein, a hormone can either increase or decrease the activity of intracellular enzymes. This complex system of cell membrane G proteins provides a vast array of potential cell responses to different hormones in the various target tissues of the body.

**Enzyme-Linked Hormone Receptors.** Some receptors, when activated, function directly as enzymes or are closely associated with enzymes that they activate. These *enzyme-linked receptors* are proteins that pass through the membrane only once, in contrast to the seven-transmembrane G protein-coupled receptors. Enzyme-linked receptors have their hormone-binding site on the outside of the cell membrane and their catalytic or enzyme-binding site on the inside. When the hormone binds to the extracellular part of the receptor, an enzyme immediately inside the cell membrane is activated (or occasionally inactivated). Although many enzyme-linked receptors have intrinsic enzyme activity, others rely on enzymes that are closely associated with the receptor to produce changes in cell function.

One example of an enzyme-linked receptor is the *leptin receptor* (Figure 74-5). Leptin is a hormone secreted by fat cells and has many physiological effects, but it is especially important in regulating appetite and energy balance, as discussed in Chapter 71. The leptin receptor is a member of a large family of *cytokine receptors* that do not themselves contain enzymatic activity but signal through associated enzymes. In the case of the leptin receptor, one of the signaling pathways occurs through a *tyrosine kinase* of the *janus kinase* (JAK) family, *JAK2*. The leptin receptor exists as a dimer (i.e., in two parts), and binding of leptin to the extracellular part of the receptor alters its conformation, enabling phosphorylation and activation of the intracellular associated JAK2 molecules. The activated JAK2 molecules then phosphorylate other tyrosine residues within the leptin receptor–JAK2 complex to mediate intracellular signaling. The intracellular signals include phosphorylation of *signal transducer and activator of transcription* (STAT) proteins, which activates transcription by leptin target genes to initiate protein synthesis. Phosphorylation of JAK2 also leads to activation of other intracellular enzyme pathways such as *mitogen-activated protein kinases* (MAPK) and *phosphatidylinositol 3-kinase* (PI3K). Some of the effects of leptin occur rapidly as a result of activation of these intracellular enzymes, whereas other actions occur more slowly and require synthesis of new proteins.

Another example, one widely used in hormonal control of cell function, is for the hormone to bind with a special transmembrane receptor, which then becomes the activated enzyme *adenylyl cyclase* at the end that protrudes to the interior of the cell. This cyclase catalyzes



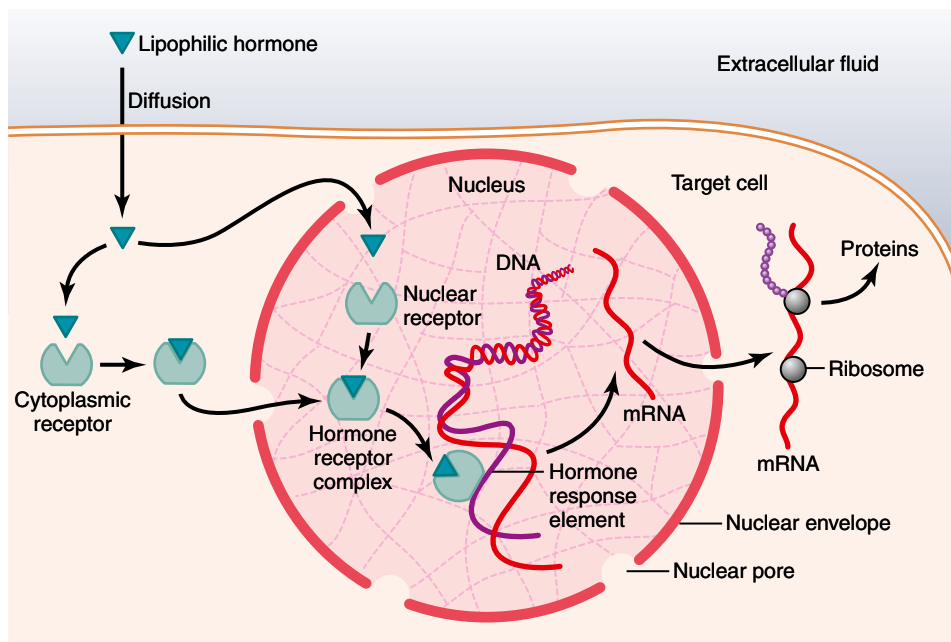
**Figure 74-5** An enzyme-linked receptor—the leptin receptor. The receptor exists as a homodimer (two identical parts), and leptin binds to the extracellular part of the receptor, causing phosphorylation and activation of the intracellular associated janus kinase 2 (JAK2). This causes phosphorylation of signal transducer and activator of transcription (STAT) proteins, which then activates the transcription of target genes and the synthesis of proteins. JAK2 phosphorylation also activates several other enzyme systems that mediate some of the more rapid effects of leptin.

the formation of cAMP, which has a multitude of effects inside the cell to control cell activity, as discussed later. cAMP is called a *second messenger* because it is not the hormone itself that directly institutes the intracellular changes; instead, the cAMP serves as a second messenger to cause these effects.

For a few peptide hormones, such as atrial natriuretic peptide (ANP), *cyclic guanosine monophosphate* (cGMP), which is only slightly different from cAMP, serves in a similar manner as a second messenger.

**Intracellular Hormone Receptors and Activation of Genes.** Several hormones, including adrenal and gonadal steroid hormones, thyroid hormones, retinoid hormones, and vitamin D, bind with protein receptors inside the cell rather than in the cell membrane. Because these hormones are lipid soluble, they readily cross the cell membrane and interact with receptors in the cytoplasm or nucleus. The activated hormone-receptor complex then binds with a specific regulatory (promoter) sequence of the DNA called the *hormone response element*, and in this manner either activates or represses transcription of specific genes and formation of messenger RNA (mRNA) (Figure 74-6). Therefore, minutes, hours, or even days after the hormone has entered the cell, newly formed proteins appear in the cell and become the controllers of new or altered cellular functions.





**Figure 74-6** Mechanisms of interaction of lipophilic hormones, such as steroids, with intracellular receptors in target cells. After the hormone binds to the receptor in the cytoplasm or in the nucleus, the hormone-receptor complex binds to the hormone response element (promoter) on the DNA. This either activates or inhibits gene transcription, formation of messenger RNA (mRNA), and protein synthesis.

Many different tissues have identical intracellular hormone receptors, but the genes that the receptors regulate are different in the various tissues. An intracellular receptor can activate a gene response only if the appropriate combination of gene regulatory proteins is present, and many of these regulatory proteins are tissue specific. Thus, the responses of different tissues to a hormone are determined not only by the specificity of the receptors but also by the expression of genes that the receptor regulates.

### Second Messenger Mechanisms for Mediating Intracellular Hormonal Functions

We noted earlier that one of the means by which hormones exert intracellular actions is to stimulate formation of the second messenger cAMP inside the cell membrane. The cAMP then causes subsequent intracellular effects of the hormone. Thus, the only direct effect that the hormone has on the cell is to activate a single type of membrane receptor. The second messenger does the rest.

cAMP is not the only second messenger used by the different hormones. Two other especially important ones are (1) calcium ions and associated *calmodulin* and (2) products of membrane phospholipid breakdown.

### Adenylyl Cyclase–cAMP Second Messenger System

Table 74-2 shows a few of the many hormones that use the adenylyl cyclase–cAMP mechanism to stimulate their target tissues, and Figure 74-7 shows the adenylyl cyclase–cAMP second messenger system. Binding of the hormones with the receptor allows coupling of the receptor to a *G protein*. If the G protein stimulates the adenylyl cyclase–cAMP system, it is called a *G<sub>s</sub> protein*, denoting a stimulatory G protein. Stimulation of adenylyl cyclase, a membrane-bound enzyme, by the *G<sub>s</sub>* protein then

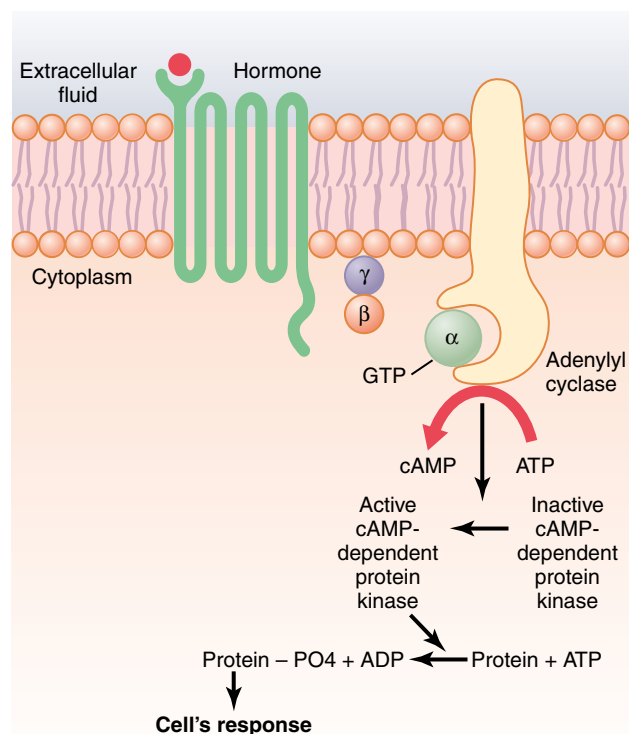
**Table 74-2** Hormones That Use the Adenylyl Cyclase–cAMP Second Messenger System

Adrenocorticotrophic hormone (ACTH)
Angiotensin II (epithelial cells)
Calcitonin
Catecholamines ( $\beta$ receptors)
Corticotropin-releasing hormone (CRH)
Follicle-stimulating hormone (FSH)
Glucagon
Human chorionic gonadotropin (HCG)
Luteinizing hormone (LH)
Parathyroid hormone (PTH)
Secretin
Somatostatin
Thyroid-stimulating hormone (TSH)
Vasopressin ( $V_2$ receptor, epithelial cells)

catalyzes the conversion of a small amount of cytoplasmic *adenosine triphosphate* (ATP) into cAMP inside the cell. This then activates *cAMP-dependent protein kinase*, which phosphorylates specific proteins in the cell, triggering biochemical reactions that ultimately lead to the cell's response to the hormone.

Once cAMP is formed inside the cell, it usually activates a *cascade of enzymes*. That is, first one enzyme is activated, which activates a second enzyme, which activates a third, and so forth. The importance of this mechanism is that only a few molecules of activated adenylyl cyclase immediately inside the cell membrane can cause many more molecules of the next enzyme to be activated, which can cause still more molecules of the third enzyme to be activated, and so forth. In this way, even the slightest amount of hormone acting on the cell surface can initiate a powerful cascading activating force for the entire cell.





**Figure 74-7** Cyclic adenosine monophosphate (cAMP) mechanism by which many hormones exert their control of cell function. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

If binding of the hormone to its receptors is coupled to an inhibitory G protein (denoted  $G_i$  protein), adenylyl cyclase will be inhibited, reducing the formation of cAMP and ultimately leading to an inhibitory action in the cell. Thus, depending on the coupling of the hormone receptor to an inhibitory or a stimulatory G protein, a hormone can either increase or decrease the concentration of cAMP and phosphorylation of key proteins inside the cell.

The specific action that occurs in response to increases or decreases of cAMP in each type of target cell depends on the nature of the intracellular machinery—some cells have one set of enzymes, and other cells have other enzymes. Therefore, different functions are elicited in different target cells, such as initiating synthesis of specific intracellular chemicals, causing muscle contraction or relaxation, initiating secretion by the cells, and altering cell permeability.

Thus, a thyroid cell stimulated by cAMP forms the metabolic hormones thyroxine and triiodothyronine, whereas the same cAMP in an adrenocortical cell causes secretion of the adrenocortical steroid hormones. In epithelial cells of the renal tubules, cAMP increases their permeability to water.

### Cell Membrane Phospholipid Second Messenger System

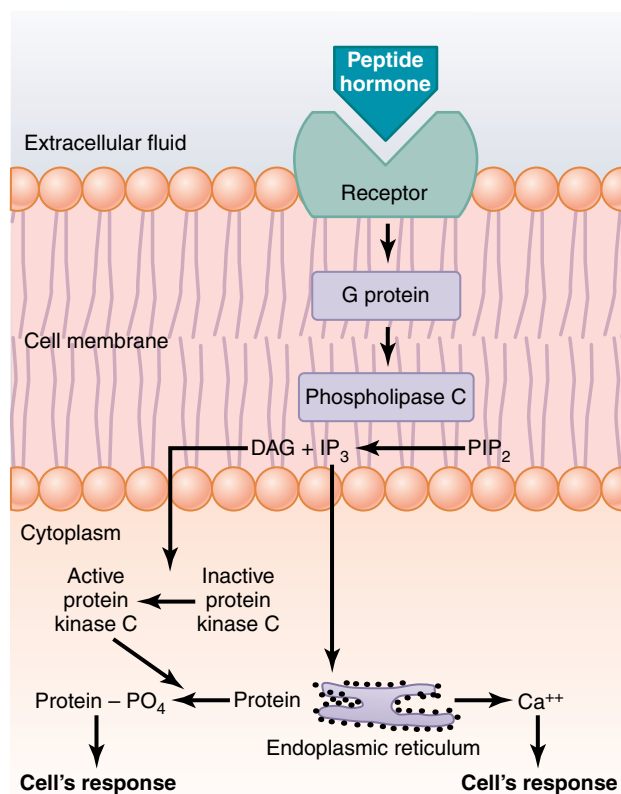
Some hormones activate transmembrane receptors that activate the enzyme *phospholipase C* attached to the inside projections of the receptors (Table 74-3). This enzyme catalyzes the breakdown of some phospholipids in the cell membrane, especially *phosphatidylinositol bi-*

**Table 74-3** Hormones That Use the Phospholipase C Second Messenger System

Angiotensin II (vascular smooth muscle)
Catecholamines ( $\alpha$ receptors)
Gonadotropin-releasing hormone (GnRH)
Growth hormone–releasing hormone (GHRH)
Oxytocin
Thyrotropin releasing hormone (TRH)
Vasopressin (V1 receptor, vascular smooth muscle)

*phosphate* (PIP<sub>2</sub>), into two different second messenger products: *inositol triphosphate* (IP<sub>3</sub>) and *diacylglycerol* (DAG). The IP<sub>3</sub> mobilizes calcium ions from mitochondria and the endoplasmic reticulum, and the calcium ions then have their own second messenger effects, such as smooth muscle contraction and changes in cell secretion.

DAG, the other lipid second messenger, activates the enzyme *protein kinase C* (PKC), which then phosphorylates a large number of proteins, leading to the cell's response (Figure 74-8). In addition to these effects, the lipid portion of DAG is *arachidonic acid*, which is the precursor for the *prostaglandins* and other local hormones that cause multiple effects in tissues throughout the body.



**Figure 74-8** The cell membrane phospholipid second messenger system by which some hormones exert their control of cell function. DAG, diacylglycerol; IP<sub>3</sub>, inositol triphosphate; PIP<sub>2</sub>, phosphatidylinositol biphosphate.

### Calcium-Calmodulin Second Messenger System

Another second messenger system operates in response to the entry of calcium into the cells. Calcium entry may be initiated by (1) changes in membrane potential that open calcium channels or (2) a hormone interacting with membrane receptors that open calcium channels.

On entering a cell, calcium ions bind with the protein *calmodulin*. This protein has four calcium sites, and when three or four of these sites have bound with calcium, the calmodulin changes its shape and initiates multiple effects inside the cell, including activation or inhibition of protein kinases. Activation of calmodulin-dependent protein kinases causes, via phosphorylation, activation or inhibition of proteins involved in the cell's response to the hormone. For example, one specific function of calmodulin is to activate *myosin light chain kinase*, which acts directly on the myosin of smooth muscle to cause smooth muscle contraction.

The normal calcium ion concentration in most cells of the body is  $10^{-8}$  to  $10^{-7}$  mol/L, which is not enough to activate the calmodulin system. But when the calcium ion concentration rises to  $10^{-6}$  to  $10^{-5}$  mol/L, enough binding occurs to cause all the intracellular actions of calmodulin. This is almost exactly the same amount of calcium ion change that is required in skeletal muscle to activate troponin C, which causes skeletal muscle contraction, as explained in Chapter 7. It is interesting that troponin C is similar to calmodulin in both function and protein structure.

### Hormones That Act Mainly on the Genetic Machinery of the Cell

#### Steroid Hormones Increase Protein Synthesis

Another means by which hormones act—specifically, the steroid hormones secreted by the adrenal cortex, ovaries, and testes—is to cause synthesis of proteins in the target cells. These proteins then function as enzymes, transport proteins, or structural proteins, which in turn provide other functions of the cells.

The sequence of events in steroid function is essentially the following:

1. The steroid hormone diffuses across the cell membrane and enters the cytoplasm of the cell, where it binds with a specific *receptor protein*.
2. The combined receptor protein–hormone then diffuses into or is transported into the nucleus.
3. The combination binds at specific points on the DNA strands in the chromosomes, which activates the transcription process of specific genes to form mRNA.
4. The mRNA diffuses into the cytoplasm, where it promotes the translation process at the ribosomes to form new proteins.

To give an example, *aldosterone*, one of the hormones secreted by the adrenal cortex, enters the cytoplasm of renal tubular cells, which contain a specific receptor protein

often called the *mineralocorticoid receptor*. Therefore, in these cells, the sequence of events cited earlier ensues. After about 45 minutes, proteins begin to appear in the renal tubular cells and promote sodium reabsorption from the tubules and potassium secretion into the tubules. Thus, the full action of the steroid hormone is characteristically delayed for at least 45 minutes—up to several hours or even days. This is in marked contrast to the almost instantaneous action of some of the peptide and amino acid–derived hormones, such as vasopressin and norepinephrine.

### Thyroid Hormones Increase Gene Transcription in the Cell Nucleus

The thyroid hormones *thyroxine* and *triiodothyronine* cause increased transcription by specific genes in the nucleus. To accomplish this, these hormones first bind directly with receptor proteins in the nucleus; these receptors are *activated transcription factors* located within the chromosomal complex, and they control the function of the gene promoters, as explained in Chapter 3.

Two important features of thyroid hormone function in the nucleus are the following:

1. They activate the genetic mechanisms for the formation of many types of intracellular proteins—probably 100 or more. Many of these are enzymes that promote enhanced intracellular metabolic activity in virtually all cells of the body.
2. Once bound to the intranuclear receptors, the thyroid hormones can continue to express their control functions for days or even weeks.

### Measurement of Hormone Concentrations in the Blood

Most hormones are present in the blood in extremely minute quantities; some concentrations are as low as one billionth of a milligram (1 picogram) per milliliter. Therefore, it was difficult to measure these concentrations by the usual chemical means. An extremely sensitive method, however, was developed about 45 years ago that revolutionized the measurement of hormones, their precursors, and their metabolic end products. This method is called *radioimmunoassay*.

#### Radioimmunoassay

The method of performing radioimmunoassay is as follows. First, an antibody that is highly specific for the hormone to be measured is produced.

Second, a small quantity of this antibody is (1) mixed with a quantity of fluid from the animal containing the hormone to be measured and (2) mixed simultaneously with an appropriate amount of purified standard hormone that has been tagged with a radioactive isotope. However, one specific condition must be met: There must be too little antibody to bind completely both the

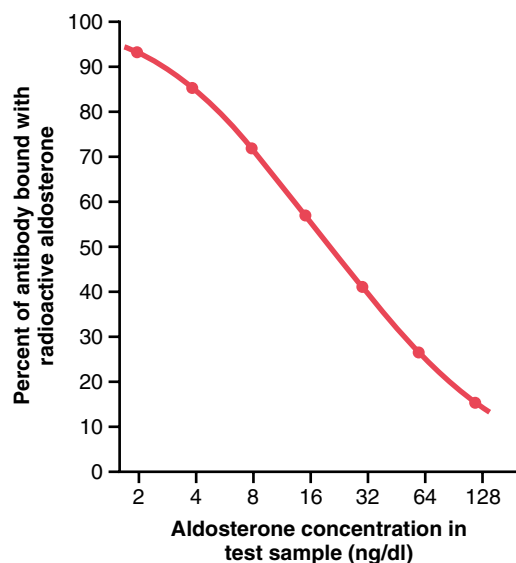
radioactively tagged hormone and the hormone in the fluid to be assayed. Therefore, the natural hormone in the assay fluid and the radioactive standard hormone *compete for the binding sites* of the antibody. In the process of competing, the quantity of each of the two hormones, the natural and the radioactive, that binds is proportional to its concentration in the assay fluid.

Third, after binding has reached equilibrium, the antibody-hormone complex is separated from the remainder of the solution, and the quantity of radioactive hormone bound in this complex is measured by radioactive counting techniques. If a large amount of radioactive hormone has bound with the antibody, it is clear that there was only a small amount of natural hormone to compete with the radioactive hormone, and therefore the concentration of the natural hormone in the assayed fluid was small. Conversely, if only a small amount of radioactive hormone has bound, it is clear that there was a large amount of natural hormone to compete for the binding sites.

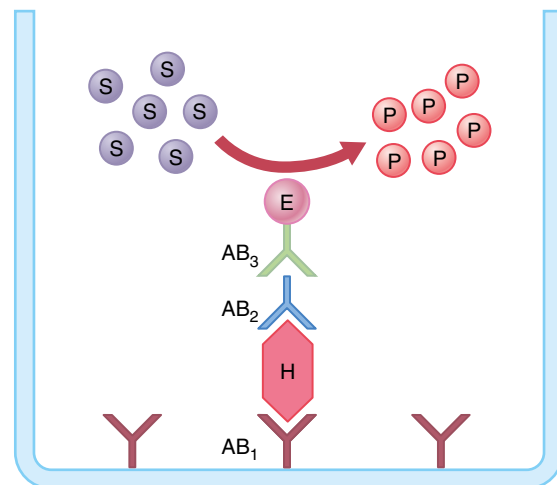
Fourth, to make the assay highly quantitative, the radioimmunoassay procedure is also performed for “standard” solutions of untagged hormone at several concentration levels. Then a “standard curve” is plotted, as shown in Figure 74-9. By comparing the radioactive counts recorded from the “unknown” assay procedures with the standard curve, one can determine within an error of 10 to 15 percent the concentration of the hormone in the “unknown” assayed fluid. As little as billionths or even trillionths of a gram of hormone can often be assayed in this way.

### Enzyme-Linked Immunosorbent Assay

Enzyme-linked immunosorbent assays (ELISAs) can be used to measure almost any protein, including hormones. This test combines the specificity of antibodies with the sensitivity of simple enzyme assays. Figure 74-10 shows the basic elements of this method, which is often



**Figure 74-9** “Standard curve” for radioimmunoassay of aldosterone. (Courtesy Dr. Manis Smith.)



**Figure 74-10** Basic principles of the enzyme-linked immunosorbent assay (ELISA) for measuring the concentration of a hormone (H). AB<sub>1</sub> and AB<sub>2</sub> are antibodies that recognize the hormone at different binding sites, and AB<sub>3</sub> is an antibody that recognizes AB<sub>2</sub>. E is an enzyme linked to AB<sub>3</sub> that catalyzes the formation of a colored fluorescent product (P) from a substrate (S). The amount of the product is measured using optical methods and is proportional to the amount of hormone in the well if there are excess antibodies in the well.

performed on plastic plates that each have 96 small wells. Each well is coated with an antibody (AB<sub>1</sub>) that is specific for the hormone being assayed. Samples or standards are added to each of the wells, followed by a second antibody (AB<sub>2</sub>) that is also specific for the hormone but binds to a different site of the hormone molecule. A third antibody (AB<sub>3</sub>) that is added recognizes AB<sub>2</sub> and is coupled to an enzyme that converts a suitable substrate to a product that can be easily detected by colorimetric or fluorescent optical methods.

Because each molecule of enzyme catalyzes the formation of many thousands of product molecules, even small amounts of hormone molecules can be detected. In contrast to competitive radioimmunoassay methods, ELISA methods use excess antibodies so that all hormone molecules are captured in antibody-hormone complexes. Therefore, the amount of hormone present in the sample or in the standard is proportional to the amount of product formed.

The ELISA method has become widely used in clinical laboratories because (1) it does not employ radioactive isotopes, (2) much of the assay can be automated using 96-well plates, and (3) it has proved to be a cost-effective and accurate method for assessing hormone levels.

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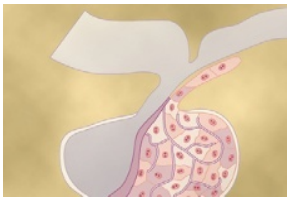
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# Pituitary Hormones and Their Control by the Hypothalamus



## Pituitary Gland and Its Relation to the Hypothalamus

### The Pituitary Gland Has Two Distinct Parts—

**The Anterior and Posterior Lobes.** The *pituitary gland* (Figure 75-1), also called the *hypophysis*, is a small gland—about 1 centimeter in diameter and 0.5 to 1 gram in weight—that lies in the *sella turcica*, a bony cavity at the base of the brain, and is connected to the hypothalamus by the *pituitary* (or *hypophysial*) stalk. Physiologically, the pituitary gland is divisible into two distinct portions: the *anterior pituitary*, also known as the *adenohypophysis*, and the *posterior pituitary*, also known as the *neurohypophysis*. Between these is a small, relatively avascular zone called the *pars intermedia*, which is much less developed in the human being but is larger and much more functional in some lower animals.

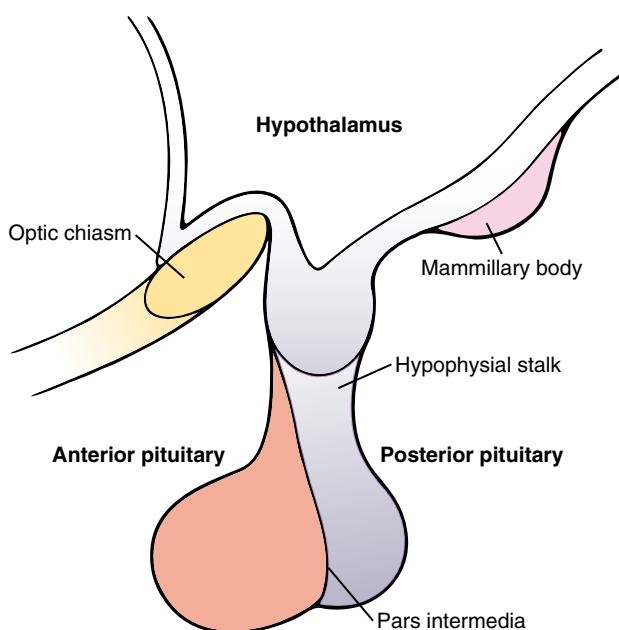


Figure 75-1 Pituitary gland.

Embryologically, the two portions of the pituitary originate from different sources—the anterior pituitary from *Rathke's pouch*, which is an embryonic invagination of the pharyngeal epithelium, and the posterior pituitary from a neural tissue outgrowth from the hypothalamus. The origin of the anterior pituitary from the pharyngeal epithelium explains the epithelioid nature of its cells, and the origin of the posterior pituitary from neural tissue explains the presence of large numbers of glial-type cells in this gland.

Six important peptide hormones plus several hormones of lesser importance are secreted by the *anterior* pituitary, and two important peptide hormones are secreted by the *posterior* pituitary. The hormones of the anterior pituitary play major roles in the control of metabolic functions throughout the body, as shown in Figure 75-2.

- *Growth hormone* promotes growth of the entire body by affecting protein formation, cell multiplication, and cell differentiation.

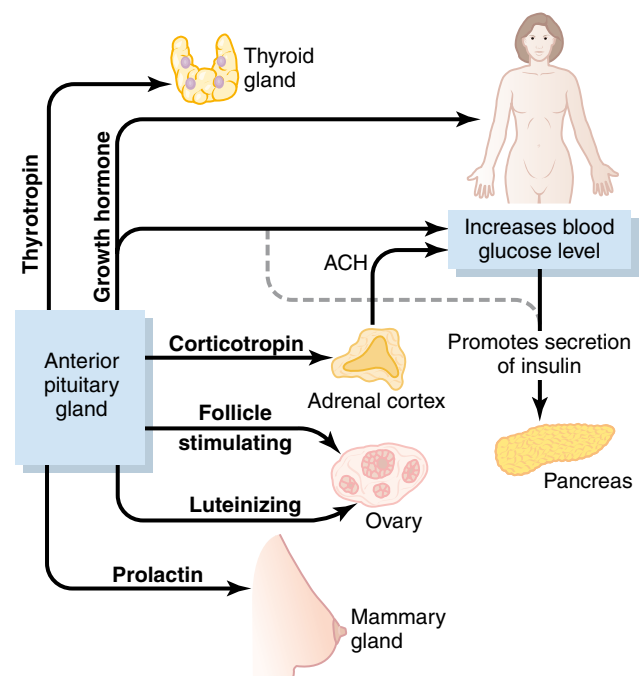


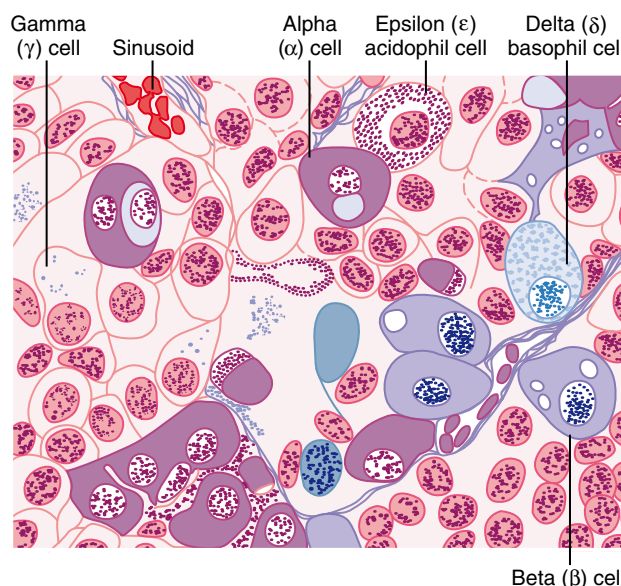
Figure 75-2 Metabolic functions of the anterior pituitary hormones. ACH, adrenal corticosteroid hormones.

- *Adrenocorticotropin (corticotropin)* controls the secretion of some of the adrenocortical hormones, which affect the metabolism of glucose, proteins, and fats.
- *Thyroid-stimulating hormone (thyrotropin)* controls the rate of secretion of thyroxine and triiodothyronine by the thyroid gland, and these hormones control the rates of most intracellular chemical reactions in the body.
- *Prolactin* promotes mammary gland development and milk production.
- Two separate gonadotrophic hormones, *follicle-stimulating hormone* and *luteinizing hormone*, control growth of the ovaries and testes, as well as their hormonal and reproductive activities.

The two hormones secreted by the posterior pituitary play other roles.

- *Antidiuretic hormone* (also called *vasopressin*) controls the rate of water excretion into the urine, thus helping to control the concentration of water in the body fluids.
- *Oxytocin* helps express milk from the glands of the breast to the nipples during suckling and helps in the delivery of the baby at the end of gestation.

**Anterior Pituitary Gland Contains Several Different Cell Types That Synthesize and Secrete Hormones.** Usually, there is one cell type for each major hormone formed in the anterior pituitary gland. With special stains attached to high-affinity antibodies that bind with the distinctive hormones, at least five cell types can be differentiated (Figure 75-3). Table 75-1 provides



**Figure 75-3** Cellular structure of the anterior pituitary gland. (Redrawn from Guyton AC: *Physiology of the Human Body*, 6th ed. Philadelphia: Saunders College Publishing, 1984.)

a summary of these cell types, the hormones they produce, and their physiological actions. These five cell types are:

1. *Somatotropes*—human growth hormone (hGH)
2. *Corticotropes*—adrenocorticotropin (ACTH)
3. *Thyrotropes*—thyroid-stimulating hormone (TSH)
4. *Gonadotropes*—gonadotrophic hormones, which include both luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
5. *Lactotropes*—prolactin (PRL)

**Table 75-1** Cells and Hormones of the Anterior Pituitary Gland and Their Physiological Functions

Cell	Hormone	Chemistry	Physiological Action
Somatotropes	Growth hormone (GH; somatotropin)	Single chain of 191 amino acids	Stimulates body growth; stimulates secretion of IGF-1; stimulates lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism
Corticotropes	Adrenocorticotrophic hormone (ACTH; corticotropin)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (TSH; thyrotropin)	Glycoprotein of two subunits, $\alpha$ (89 amino acids) and $\beta$ (112 amino acids)	Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)  Luteinizing hormone (LH)	Glycoprotein of two subunits, $\alpha$ (89 amino acids) and $\beta$ (112 amino acids)  Glycoprotein of two subunits, $\alpha$ (89 amino acids) and $\beta$ (115 amino acids)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Lactotropes Mammotropes	Prolactin (PRL)	Single chain of 198 amino acids	Stimulates milk secretion and production

IGF, insulin-like growth factor.

About 30 to 40 percent of the anterior pituitary cells are somatotropes that secrete growth hormone, and about 20 percent are corticotropes that secrete ACTH. Each of the other cell types accounts for only 3 to 5 percent of the total; nevertheless, they secrete powerful hormones for controlling thyroid function, sexual functions, and milk secretion by the breasts.

Somatotropes stain strongly with acid dyes and are therefore called *acidophils*. Thus, pituitary tumors that secrete large quantities of human growth hormone are called *acidophilic tumors*.

**Posterior Pituitary Hormones Are Synthesized by Cell Bodies in the Hypothalamus.** The bodies of the cells that secrete the *posterior* pituitary hormones are not located in the pituitary gland itself but are large neurons, called *magnocellular neurons*, located in the *supraoptic* and *paraventricular nuclei* of the hypothalamus. The hormones are then transported in the axoplasm of the neurons' nerve fibers passing from the hypothalamus to the posterior pituitary gland. This is discussed later in the chapter.

### Hypothalamus Controls Pituitary Secretion

Almost all secretion by the pituitary is controlled by either hormonal or nervous signals from the hypothalamus. Indeed, when the pituitary gland is removed from its normal position beneath the hypothalamus and transplanted to some other part of the body, its rates of secretion of the different hormones (except for prolactin) fall to very low levels.

Secretion from the posterior pituitary is controlled by nerve signals that originate in the hypothalamus and terminate in the posterior pituitary. In contrast, secretion by the anterior pituitary is controlled by hormones called *hypothalamic releasing* and *hypothalamic inhibitory hormones* (or *factors*) secreted within the hypothalamus and then conducted, as shown in Figure 75-4, to the anterior pituitary through minute blood vessels called *hypothalamic-hypophyseal portal vessels*. In the anterior pituitary, these releasing and inhibitory hormones act on the glandular cells to control their secretion. This system of control is discussed in the next section of this chapter.

The hypothalamus receives signals from many sources in the nervous system. Thus, when a person is exposed to pain, a portion of the pain signal is transmitted into the hypothalamus. Likewise, when a person experiences some powerful depressing or exciting thought, a portion of the signal is transmitted into the hypothalamus. Olfactory stimuli denoting pleasant or unpleasant smells transmit strong signal components directly and through the amygdaloid nuclei into the hypothalamus. Even the concentrations of nutrients, electrolytes, water, and various hormones in the blood excite or inhibit various portions of the hypothalamus. Thus, the hypothalamus is a collecting center for information concerning the internal well-being

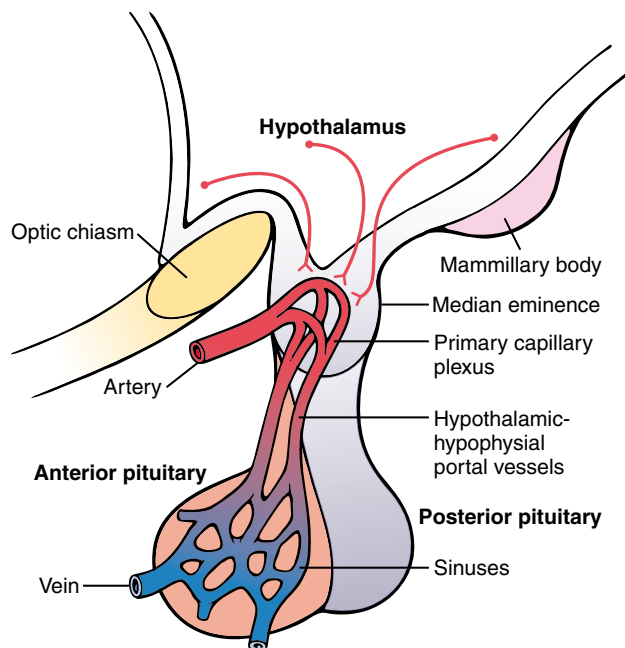


Figure 75-4 Hypothalamic-hypophyseal portal system.

of the body, and much of this information is used to control secretions of the many globally important pituitary hormones.

### Hypothalamic-Hypophyseal Portal Blood Vessels of the Anterior Pituitary Gland

The anterior pituitary is a highly vascular gland with extensive capillary sinuses among the glandular cells. Almost all the blood that enters these sinuses passes first through another capillary bed in the lower hypothalamus. The blood then flows through small *hypothalamic-hypophyseal portal blood vessels* into the anterior pituitary sinuses. Figure 75-4 shows the lowermost portion of the hypothalamus, called the *median eminence*, which connects inferiorly with the pituitary stalk. Small arteries penetrate into the median eminence and then additional small vessels return to its surface, coalescing to form the hypothalamic-hypophyseal portal blood vessels. These pass downward along the pituitary stalk to supply blood to the anterior pituitary sinuses.

**Hypothalamic Releasing and Inhibitory Hormones Are Secreted into the Median Eminence.** Special neurons in the hypothalamus synthesize and secrete the *hypothalamic releasing* and *inhibitory hormones* that control secretion of the anterior pituitary hormones. These neurons originate in various parts of the hypothalamus and send their nerve fibers to the median eminence and *tuber cinereum*, an extension of hypothalamic tissue into the pituitary stalk.

The endings of these fibers are different from most endings in the central nervous system, in that their function is not to transmit signals from one neuron to another but rather to secrete the hypothalamic releasing and inhibitory hormones into the tissue fluids. These hormones are

immediately absorbed into the hypothalamic-hypophyseal portal system and carried directly to the sinuses of the anterior pituitary gland.

**Hypothalamic Releasing and Inhibitory Hormones Control Anterior Pituitary Secretion.** The function of the releasing and inhibitory hormones is to control secretion of the anterior pituitary hormones. For most of the anterior pituitary hormones, it is the releasing hormones that are important, but for prolactin, a hypothalamic inhibitory hormone probably exerts more control. The major hypothalamic releasing and inhibitory hormones are summarized in Table 75-2 and are the following:

1. *Thyrotropin-releasing hormone* (TRH), which causes release of thyroid-stimulating hormone
2. *Corticotropin-releasing hormone* (CRH), which causes release of adrenocorticotropin
3. *Growth hormone–releasing hormone* (GHRH), which causes release of growth hormone, and *growth hormone inhibitory hormone* (GHIH), also called *somatostatin*, which inhibits release of growth hormone
4. *Gonadotropin-releasing hormone* (GnRH), which causes release of the two gonadotropic hormones, luteinizing hormone and follicle-stimulating hormone
5. *Prolactin inhibitory hormone* (PIH), which causes inhibition of prolactin secretion

Additional hypothalamic hormones include one that stimulates prolactin secretion and perhaps others that inhibit release of the anterior pituitary hormones. Each of the more important hypothalamic hormones is discussed in detail as the specific hormonal systems controlled by them are presented in this and subsequent chapters.

**Specific Areas in the Hypothalamus Control Secretion of Specific Hypothalamic Releasing and Inhibitory Hormones.** All or most of the hypothalamic hormones are secreted at nerve endings in the median eminence before being transported to the anterior pituitary

gland. Electrical stimulation of this region excites these nerve endings and, therefore, causes release of essentially all the hypothalamic hormones. However, the neuronal cell bodies that give rise to these median eminence nerve endings are located in other discrete areas of the hypothalamus or in closely related areas of the basal brain. The specific loci of the neuronal cell bodies that form the different hypothalamic releasing or inhibitory hormones are still poorly known, so it would be misleading to attempt delineation here.

### Physiological Functions of Growth Hormone

All the major anterior pituitary hormones, except for growth hormone, exert their principal effects by stimulating target glands, including thyroid gland, adrenal cortex, ovaries, testicles, and mammary glands. The functions of each of these pituitary hormones are so intimately concerned with the functions of the respective target glands that, except for growth hormone, their functions are discussed in subsequent chapters along with the target glands. Growth hormone, in contrast to other hormones, does not function through a target gland but exerts its effects directly on all or almost all tissues of the body.

### Growth Hormone Promotes Growth of Many Body Tissues

Growth hormone, also called *somatotropic hormone* or *somatotropin*, is a small protein molecule that contains 191 amino acids in a single chain and has a molecular weight of 22,005. It causes growth of almost all tissues of the body that are capable of growing. It promotes increased sizes of the cells and increased mitosis, with development of greater numbers of cells and specific differentiation of certain types of cells such as bone growth cells and early muscle cells.

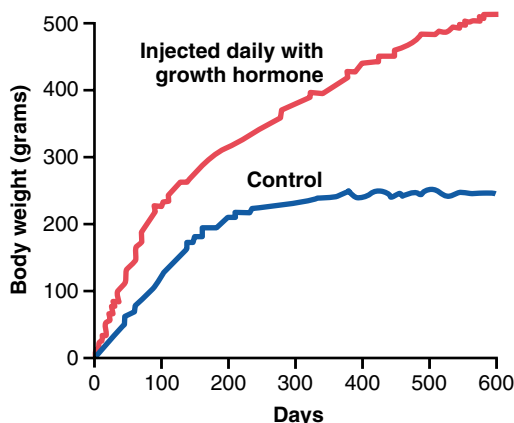
Figure 75-5 shows typical weight charts of two growing littermate rats, one of which received daily injections of growth hormone and the other of which did not receive

**Table 75-2** Hypothalamic Releasing and Inhibitory Hormones That Control Secretion of the Anterior Pituitary Gland

Hormone	Structure	Primary Action on Anterior Pituitary
Thyrotropin-releasing hormone (TRH)	Peptide of 3 amino acids	Stimulates secretion of TSH by thyrotropes
Gonadotropin-releasing hormone (GnRH)	Single chain of 10 amino acids	Stimulates secretion of FSH and LH by gonadotropes
Corticotropin-releasing hormone (CRH)	Single chain of 41 amino acids	Stimulates secretion of ACTH by corticotropes
Growth hormone–releasing hormone (GHRH)	Single chain of 44 amino acids	Stimulates secretion of growth hormone by somatotropes
Growth hormone inhibitory hormone (somatostatin)	Single chain of 14 amino acids	Inhibits secretion of growth hormone by somatotropes
Prolactin-inhibiting hormone (PIH)	Dopamine (a catecholamine)	Inhibits synthesis and secretion of prolactin by lactotropes

ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.





**Figure 75-5** Comparison of weight gain of a rat injected daily with growth hormone with that of a normal littermate.

growth hormone. This figure shows marked enhancement of growth in the rat given growth hormone, in the early days of life and even after the two rats reached adulthood. In the early stages of development, all organs of the treated rat increased proportionately in size; after adulthood was reached, most of the bones stopped lengthening, but many of the soft tissues continued to grow. This results from the fact that once the epiphyses of the long bones have united with the shafts, further lengthening of bone cannot occur, even though most other tissues of the body can continue to grow throughout life.

### Growth Hormone Has Several Metabolic Effects

Aside from its general effect in causing growth, growth hormone has multiple specific metabolic effects, including (1) increased rate of protein synthesis in most cells of the body; (2) increased mobilization of fatty acids from adipose tissue, increased free fatty acids in the blood, and increased use of fatty acids for energy; and (3) decreased rate of glucose utilization throughout the body. Thus, in effect, growth hormone enhances body protein, uses up fat stores, and conserves carbohydrates.

### Growth Hormone Promotes Protein Deposition in Tissues

Although the precise mechanisms by which growth hormone increases protein deposition are not known, a series of different effects are known, all of which could lead to enhanced protein deposition.

**Enhancement of Amino Acid Transport Through the Cell Membranes.** Growth hormone directly enhances transport of most amino acids through the cell membranes to the interior of the cells. This increases the amino acid concentrations in the cells and is presumed to be at least partly responsible for the increased protein synthesis. This control of amino acid transport is similar to the effect of insulin in controlling glucose transport through the membrane, as discussed in Chapters 67 and 78.

**Enhancement of RNA Translation to Cause Protein Synthesis by the Ribosomes.** Even when the amino acid concentrations are not increased in the cells, growth

hormone still increases RNA translation, causing protein to be synthesized in greater amounts by the ribosomes in the cytoplasm.

**Increased Nuclear Transcription of DNA to Form RNA.** Over more prolonged periods (24 to 48 hours), growth hormone also stimulates the transcription of DNA in the nucleus, causing the formation of increased quantities of RNA. This promotes more protein synthesis and promotes growth if sufficient energy, amino acids, vitamins, and other requisites for growth are available. In the long run, this may be the most important function of growth hormone.

### Decreased Catabolism of Protein and Amino Acids.

In addition to the increase in protein synthesis, there is a decrease in the breakdown of cell protein. A probable reason for this is that growth hormone also mobilizes large quantities of free fatty acids from the adipose tissue, and these are used to supply most of the energy for the body's cells, thus acting as a potent "protein sparer."

**Summary.** Growth hormone enhances almost all facets of amino acid uptake and protein synthesis by cells, while at the same time reducing the breakdown of proteins.

### Growth Hormone Enhances Fat Utilization for Energy

Growth hormone has a specific effect in causing the release of fatty acids from adipose tissue and, therefore, increasing the concentration of fatty acids in the body fluids. In addition, in tissues throughout the body, growth hormone enhances the conversion of fatty acids to acetyl coenzyme A (acetyl-CoA) and its subsequent utilization for energy. Therefore, under the influence of growth hormone, fat is used for energy in preference to the use of carbohydrates and proteins.

Growth hormone's ability to promote fat utilization, together with its protein anabolic effect, causes an increase in lean body mass. However, mobilization of fat by growth hormone requires several hours to occur, whereas enhancement of protein synthesis can begin in minutes under the influence of growth hormone.

### "Ketogenic" Effect of Excessive Growth Hormone.

Under the influence of excessive amounts of growth hormone, fat mobilization from adipose tissue sometimes becomes so great that large quantities of acetoacetic acid are formed by the liver and released into the body fluids, thus causing *ketosis*. This excessive mobilization of fat from the adipose tissue also frequently causes a fatty liver.

### Growth Hormone Decreases Carbohydrate Utilization

Growth hormone causes multiple effects that influence carbohydrate metabolism, including (1) decreased glucose uptake in tissues such as skeletal muscle and fat, (2) increased glucose production by the liver, and (3) increased insulin secretion.



Each of these changes results from growth hormone–induced “insulin resistance,” which attenuates insulin’s actions to stimulate the uptake and utilization of glucose in skeletal muscle and adipose tissue and to inhibit gluconeogenesis (glucose production) by the liver; this leads to increased blood glucose concentration and a compensatory increase in insulin secretion. For these reasons, growth hormone’s effects are called *diabetogenic*, and excess secretion of growth hormone can produce metabolic disturbances similar to those found in patients with type II (non-insulin-dependent) diabetes, who are also resistant to the metabolic effects of insulin.

We do not know the precise mechanism by which growth hormone causes insulin resistance and decreased glucose utilization by the cells. However, growth hormone–induced increases in blood concentrations of fatty acids likely contribute to impairment of insulin’s actions on tissue glucose utilization. Experimental studies indicate that raising blood levels of fatty acids above normal rapidly decreases the sensitivity of the liver and skeletal muscle to insulin’s effects on carbohydrate metabolism.

**Necessity of Insulin and Carbohydrate for the Growth-Promoting Action of Growth Hormone.** Growth hormone fails to cause growth in animals that lack a pancreas; it also fails to cause growth if carbohydrates are excluded from the diet. This shows that adequate insulin activity and adequate availability of carbohydrates are necessary for growth hormone to be effective. Part of this requirement for carbohydrates and insulin is to provide the energy needed for the metabolism of growth, but there seem to be other effects as well. Especially important is insulin’s ability to enhance the transport of some amino acids into cells, in the same way that it stimulates glucose transport.

### Growth Hormone Stimulates Cartilage and Bone Growth

Although growth hormone stimulates increased deposition of protein and increased growth in almost all tissues of the body, its most obvious effect is to increase growth of the skeletal frame. This results from multiple effects of growth hormone on bone, including (1) increased deposition of protein by the chondrocytic and osteogenic cells that cause bone growth, (2) increased rate of reproduction of these cells, and (3) a specific effect of converting chondrocytes into osteogenic cells, thus causing deposition of new bone.

There are two principal mechanisms of bone growth. First, in response to growth hormone stimulation, the long bones grow in length at the epiphyseal cartilages, where the epiphyses at the ends of the bone are separated from the shaft. This growth first causes deposition of new cartilage, followed by its conversion into new bone, thus elongating the shaft and pushing the epiphyses farther and farther apart. At the same time, the epiphyseal cartilage itself is progressively used up, so by late adolescence, no additional epiphyseal cartilage remains to provide

for further long bone growth. At this time, bony fusion occurs between the shaft and the epiphysis at each end, so no further lengthening of the long bone can occur.

Second, *osteoblasts* in the bone periosteum and in some bone cavities deposit new bone on the surfaces of older bone. Simultaneously, *osteoclasts* in the bone (discussed in detail in Chapter 79) remove old bone. When the rate of deposition is greater than that of resorption, the thickness of the bone increases. *Growth hormone strongly stimulates osteoblasts*. Therefore, the bones can continue to become thicker throughout life under the influence of growth hormone; this is especially true for the membranous bones. For instance, the jaw bones can be stimulated to grow even after adolescence, causing forward protrusion of the chin and lower teeth. Likewise, the bones of the skull can grow in thickness and give rise to bony protrusions over the eyes.

### Growth Hormone Exerts Much of Its Effect Through Intermediate Substances Called “Somatomedins” (Also Called “Insulin-Like Growth Factors”)

When growth hormone is supplied directly to cartilage chondrocytes cultured outside the body, proliferation or enlargement of the chondrocytes usually fails to occur. Yet growth hormone injected into the intact animal does cause proliferation and growth of the same cells.

In brief, it has been found that growth hormone causes the liver (and, to a much less extent, other tissues) to form several small proteins called *somatomedins* that have the potent effect of increasing all aspects of bone growth. Many of the somatomedin effects on growth are similar to the effects of insulin on growth. Therefore, the somatomedins are also called insulin-like growth factors (IGFs).

At least four somatomedins have been isolated, but by far the most important of these is *somatomedin C* (also called insulin-like growth factor-1, or IGF-1). The molecular weight of somatomedin C is about 7500, and its concentration in the plasma closely follows the rate of growth hormone secretion.

The pygmies of Africa have a congenital inability to synthesize significant amounts of somatomedin C. Therefore, even though their plasma concentration of growth hormone is either normal or high, they have diminished amounts of somatomedin C in the plasma; this apparently accounts for the small stature of these people. Some other dwarfs (e.g., the Lévi-Lorain dwarf) also have this problem.

It has been postulated that most, if not all, of the growth effects of growth hormone result from somatomedin C and other somatomedins, rather than from direct effects of growth hormone on the bones and other peripheral tissues. Even so, experiments have demonstrated that injection of growth hormone directly into the epiphyseal cartilages of bones of living animals causes the specific growth of these cartilage areas, and the amount of growth hormone required for this is minute. Some aspects of the somatomedin hypothesis are still questionable.

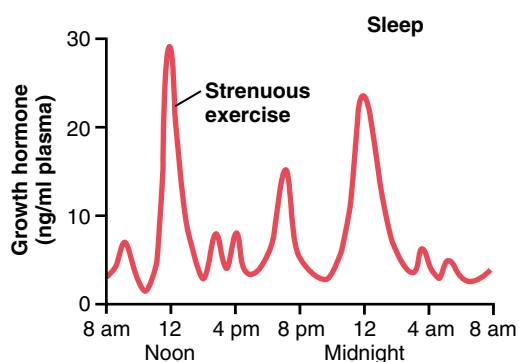
One possibility is that growth hormone can cause the formation of enough somatomedin C in the local tissue to cause local growth. It is also possible that growth hormone itself is directly responsible for increased growth in some tissues and that the somatomedin mechanism is an alternative means of increasing growth but not always a necessary one.

**Short Duration of Action of Growth Hormone but Prolonged Action of Somatomedin C.** Growth hormone attaches only weakly to the plasma proteins in the blood. Therefore, it is released from the blood into the tissues rapidly, having a half-time in the blood of less than 20 minutes. By contrast, somatomedin C attaches strongly to a carrier protein in the blood that, like somatomedin C, is produced in response to growth hormone. As a result, somatomedin C is released only slowly from the blood to the tissues, with a half-time of about 20 hours. This greatly prolongs the growth-promoting effects of the bursts of growth hormone secretion shown in Figure 75-6.

### Regulation of Growth Hormone Secretion

For many years it was believed that growth hormone was secreted primarily during the period of growth but then disappeared from the blood at adolescence. This has proved to be untrue. After adolescence, secretion decreases slowly with aging, finally falling to about 25 percent of the adolescent level in very old age.

Growth hormone is secreted in a pulsatile pattern, increasing and decreasing. The precise mechanisms that control secretion of growth hormone are not fully understood, but several factors related to a person's state of nutrition or stress are known to stimulate secretion: (1) *starvation*, especially with severe *protein deficiency*; (2) *hypoglycemia* or *low concentration of fatty acids in the blood*; (3) *exercise*; (4) *excitement*; (5) *trauma*; and (6) *ghrelin*, a hormone secreted by the stomach before meals. Growth hormone also characteristically increases during the first 2 hours of *deep sleep*, as shown in Figure 75-6. Table 75-3 summarizes some of the factors that are known to influence growth hormone secretion.



**Figure 75-6** Typical variations in growth hormone secretion throughout the day, demonstrating the especially powerful effect of strenuous exercise and also the high rate of growth hormone secretion that occurs during the first few hours of deep sleep.

**Table 75-3** Factors That Stimulate or Inhibit Secretion of Growth Hormone

Stimulate Growth Hormone Secretion	Inhibit Growth Hormone Secretion
Decreased blood glucose	Increased blood glucose
Decreased blood free fatty acids	Increased blood free fatty acids
Increased blood amino acids (arginine)	Aging
Starvation or fasting, protein deficiency	Obesity
Trauma, stress, excitement	Growth hormone inhibitory hormone (somatostatin)
Exercise	Growth hormone (exogenous)
Testosterone, estrogen	Somatomedins (insulin-like growth factors)
Deep sleep (stages II and IV)	
Growth hormone–releasing hormone	
Ghrelin	

The normal concentration of growth hormone in the plasma of an adult is between 1.6 and 3 ng/ml; in a child or adolescent, it is about 6 ng/ml. These values often increase to as high as 50 ng/ml after depletion of the body stores of proteins or carbohydrates during prolonged starvation.

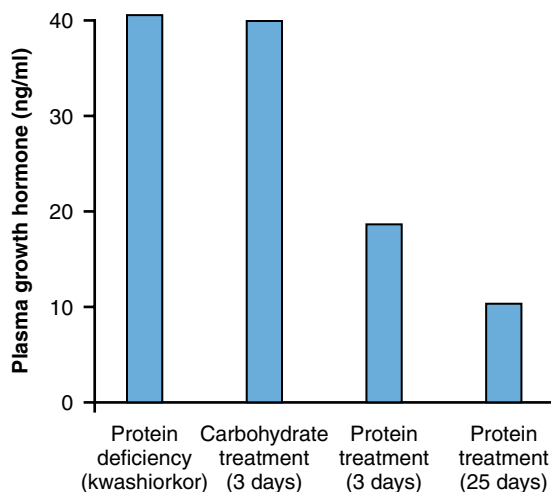
Under acute conditions, hypoglycemia is a far more potent stimulator of growth hormone secretion than is an acute decrease in protein intake. Conversely, in chronic conditions, growth hormone secretion seems to correlate more with the degree of cellular protein depletion than with the degree of glucose insufficiency. For instance, the extremely high levels of growth hormone that occur during starvation are closely related to the amount of protein depletion.

Figure 75-7 demonstrates the effect of protein deficiency on plasma growth hormone and then the effect of adding protein to the diet. The first column shows very high levels of growth hormone in children with extreme protein deficiency during the protein malnutrition condition called *kwashiorkor*; the second column shows the levels in the same children after 3 days of treatment with more than adequate quantities of carbohydrates in their diets, demonstrating that the carbohydrates did not lower the plasma growth hormone concentration. The third and fourth columns show the levels after treatment with protein supplements for 3 and 25 days, respectively, with a concomitant decrease in the hormone.

These results demonstrate that under severe conditions of protein malnutrition, adequate calories alone are not sufficient to correct the excess production of growth hormone. The protein deficiency must also be corrected before the growth hormone concentration will return to normal.

### Role of the Hypothalamus, Growth Hormone-Releasing Hormone, and Somatostatin in the Control of Growth Hormone Secretion

From the preceding description of the many factors that can affect growth hormone secretion, one can readily understand the perplexity of physiologists as they attempted



**Figure 75-7** Effect of extreme protein deficiency on the plasma concentration of growth hormone in the disease kwashiorkor. Also shown is the failure of carbohydrate treatment but the effectiveness of protein treatment in lowering growth hormone concentration. (Drawn from data in Pimstone BL, Barbezat G, Hansen JD, et al: Studies on growth hormone secretion in protein-calorie malnutrition. *Am J Clin Nutr* 21:482, 1968.)

to unravel the mysteries of regulation of growth hormone secretion. It is known that growth hormone secretion is controlled by two factors secreted in the hypothalamus and then transported to the anterior pituitary gland through the hypothalamic-hypophyseal portal vessels. They are *growth hormone-releasing hormone* and *growth hormone inhibitory hormone* (also called *somatostatin*). Both of these are polypeptides; GHRH is composed of 44 amino acids, and somatostatin is composed of 14 amino acids.

The part of the hypothalamus that causes secretion of GHRH is the ventromedial nucleus; this is the same area of the hypothalamus that is sensitive to blood glucose concentration, causing satiety in hyperglycemic states and hunger in hypoglycemic states. The secretion of somatostatin is controlled by other nearby areas of the hypothalamus. Therefore, it is reasonable to believe that some of the same signals that modify a person's behavioral feeding instincts also alter the rate of growth hormone secretion.

In a similar manner, hypothalamic signals depicting emotions, stress, and trauma can all affect hypothalamic control of growth hormone secretion. In fact, experiments have shown that catecholamines, dopamine, and serotonin, each of which is released by a different neuronal system in the hypothalamus, all increase the rate of growth hormone secretion.

Most of the control of growth hormone secretion is probably mediated through GHRH rather than through the inhibitory hormone somatostatin. GHRH stimulates growth hormone secretion by attaching to specific cell membrane receptors on the outer surfaces of the growth hormone cells in the pituitary gland. The receptors activate the adenyl cyclase system inside the cell membrane, increasing the intracellular level of cyclic adenosine monophosphate (cAMP). This has both short-term and

long-term effects. The short-term effect is to increase calcium ion transport into the cell; within minutes, this causes fusion of the growth hormone secretory vesicles with the cell membrane and release of the hormone into the blood. The long-term effect is to increase transcription in the nucleus by the genes to stimulate the synthesis of new growth hormone.

When growth hormone is administered directly into the blood of an animal over a period of hours, the rate of endogenous growth hormone secretion decreases. This demonstrates that growth hormone secretion is subject to typical negative feedback control, as is true for essentially all hormones. The nature of this feedback mechanism and whether it is mediated mainly through inhibition of GHRH or enhancement of somatostatin, which inhibits growth hormone secretion, are uncertain.

In summary, our knowledge of the regulation of growth hormone secretion is not sufficient to describe a composite picture. Yet because of the extreme secretion of growth hormone during starvation and its important long-term effect to promote protein synthesis and tissue growth, we can propose the following: the major long-term controller of growth hormone secretion is the long-term state of nutrition of the tissues themselves, especially their level of protein nutrition. That is, nutritional deficiency or excess tissue need for cellular proteins—for instance, after a severe bout of exercise when the muscles' nutritional status has been taxed—in some way increases the rate of growth hormone secretion. Growth hormone, in turn, promotes synthesis of new proteins while at the same time conserving the proteins already present in the cells.

### Abnormalities of Growth Hormone Secretion

**Panhypopituitarism.** This term means decreased secretion of all the anterior pituitary hormones. The decrease in secretion may be congenital (present from birth), or it may occur suddenly or slowly at any time during life, most often resulting from a pituitary tumor that destroys the pituitary gland.

**Dwarfism.** Most instances of dwarfism result from generalized deficiency of anterior pituitary secretion (panhypopituitarism) during childhood. In general, all the physical parts of the body develop in appropriate proportion to one another, but the rate of development is greatly decreased. A child who has reached the age of 10 years may have the bodily development of a child aged 4 to 5 years, and the same person at age 20 years may have the bodily development of a child aged 7 to 10 years.

A person with panhypopituitary dwarfism does not pass through puberty and never secretes sufficient quantities of gonadotropic hormones to develop adult sexual functions. In one third of such dwarfs, however, only growth hormone is deficient; these persons do mature sexually and occasionally reproduce. In one type of dwarfism (the African pygmy and the Lévi-Lorain dwarf), the rate of growth hormone secretion is normal or high, but there is a hereditary inability to form somatomedin C, which is a key step for the promotion of growth by growth hormone.

**Treatment with Human Growth Hormone.** Growth hormones from different species of animals are sufficiently



different from one another that they will cause growth only in the one species or, at most, closely related species. For this reason, growth hormone prepared from lower animals (except, to some extent, from primates) is not effective in human beings. Therefore, the growth hormone of the human being is called *human growth hormone* to distinguish it from the others.

In the past, because growth hormone had to be prepared from human pituitary glands, it was difficult to obtain sufficient quantities to treat patients with growth hormone deficiency, except on an experimental basis. However, human growth hormone can now be synthesized by *Escherichia coli* bacteria as a result of successful application of recombinant DNA technology. Therefore, this hormone is now available in sufficient quantities for treatment purposes. Dwarfs who have pure growth hormone deficiency can be completely cured if treated early in life. Human growth hormone may also prove to be beneficial in other metabolic disorders because of its widespread metabolic functions.

**Panhypopituitarism in the Adult.** Panhypopituitarism first occurring in adulthood frequently results from one of three common abnormalities. Two tumorous conditions, craniopharyngiomas or chromophobe tumors, may compress the pituitary gland until the functioning anterior pituitary cells are totally or almost totally destroyed. The third cause is thrombosis of the pituitary blood vessels. This abnormality occasionally occurs when a new mother develops circulatory shock after the birth of her baby.

The general effects of adult panhypopituitarism are (1) hypothyroidism, (2) depressed production of glucocorticoids by the adrenal glands, and (3) suppressed secretion of the gonadotropic hormones so that sexual functions are lost. Thus, the picture is that of a lethargic person (from lack of thyroid hormones) who is gaining weight (because of lack of fat mobilization by growth, adrenocorticotrophic, adrenocortical, and thyroid hormones) and has lost all sexual functions. Except for the abnormal sexual functions, the patient can usually be treated satisfactorily by administering adrenocortical and thyroid hormones.

**Gigantism.** Occasionally, the acidophilic, growth hormone-producing cells of the anterior pituitary gland become excessively active, and sometimes even acidophilic tumors occur in the gland. As a result, large quantities of growth hormone are produced. All body tissues grow rapidly, including the bones. If the condition occurs before adolescence, before the epiphyses of the long bones have become fused with the shafts, height increases so that the person becomes a giant—up to 8 feet tall.

The giant ordinarily has *hyperglycemia*, and the beta cells of the islets of Langerhans in the pancreas are prone to degenerate because they become overactive owing to the hyperglycemia. Consequently, in about 10 percent of giants, full-blown *diabetes mellitus* eventually develops.

In most giants, panhypopituitarism eventually develops if they remain untreated because the gigantism is usually caused by a tumor of the pituitary gland that grows until the gland itself is destroyed. This eventual general deficiency of pituitary hormones usually causes death in early adulthood. However, once gigantism is diagnosed, further effects can often be blocked by microsurgical removal of the tumor or by irradiation of the pituitary gland.

**Acromegaly.** If an acidophilic tumor occurs after adolescence—that is, after the epiphyses of the long bones have fused with the shafts—the person cannot grow taller, but the bones can become thicker and the soft tissues can continue to grow. This condition, shown in Figure 75-8, is known as *acromegaly*. Enlargement is especially marked in the bones of the hands and feet and in the *membranous bones*, including the cranium, nose, bosses on the forehead, supraorbital ridges, lower jawbone, and portions of the vertebrae, because their growth does not cease at adolescence. Consequently, the lower jaw protrudes forward, sometimes as much as half an inch, the forehead slants forward because of excess development of the supraorbital ridges, the nose increases to as much as twice normal size, the feet require size 14 or larger shoes, and the fingers become extremely thickened so that the hands are almost twice normal size. In addition to these effects, changes in the vertebrae ordinarily cause a hunched



Figure 75-8 Acromegalic patient

back, which is known clinically as *kyphosis*. Finally, many soft tissue organs, such as the tongue, the liver, and especially the kidneys, become greatly enlarged.

#### Possible Role of Decreased Growth Hormone Secretion in Causing Changes Associated with Aging

In people who have lost the ability to secrete growth hormone, some features of the aging process accelerate. For instance, a 50-year-old person who has been without growth hormone for many years may have the appearance of a person aged 65. The aged appearance seems to result mainly from decreased protein deposition in most tissues of the body and increased fat deposition in its place. The physical and physiological effects are increased wrinkling of the skin, diminished rates of function of some of the organs, and diminished muscle mass and strength.

As one ages, the average plasma concentration of growth hormone in an otherwise normal person changes approximately as follows:

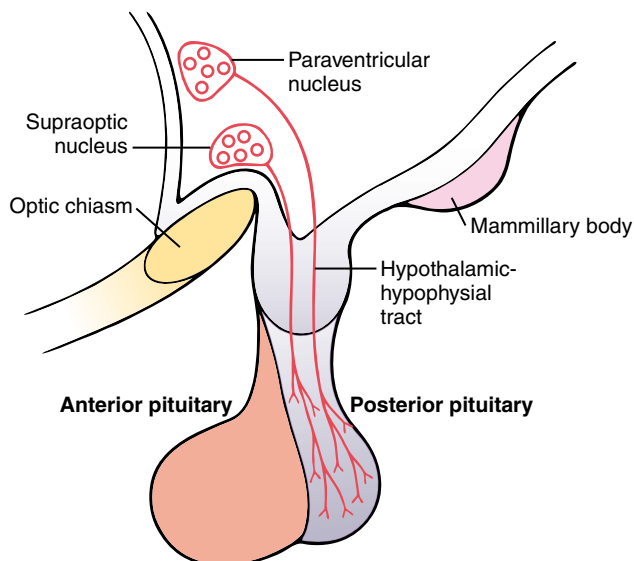
	ng/ml
5 to 20 years	6
20 to 40 years	3
40 to 70 years	1.6

Thus, it is possible that some of the normal aging effects result from diminished growth hormone secretion. In fact, some studies of growth hormone therapy in older people have demonstrated three important beneficial effects: (1) increased protein deposition in the body, especially in the muscles; (2) decreased fat deposits; and (3) a feeling of increased energy. Other studies, however, have shown that treatment of elderly patients with recombinant growth hormone may produce several undesirable side effects including insulin resistance and diabetes, edema, carpal tunnel syndrome, and arthralgias (joint pain). Therefore, recombinant growth hormone therapy is generally not recommended for use in healthy elderly patients with normal endocrine function.

### Posterior Pituitary Gland and Its Relation to the Hypothalamus

The *posterior pituitary gland*, also called the *neurohypophysis*, is composed mainly of glial-like cells called *pituicytes*. The pituicytes do not secrete hormones; they act simply as a supporting structure for large numbers of *terminal nerve fibers* and *terminal nerve endings* from nerve tracts that originate in the *supraoptic* and *paraventricular nuclei* of the hypothalamus, as shown in Figure 75-9. These tracts pass to the neurohypophysis through the *pituitary stalk* (hypophyseal stalk). The nerve endings are bulbous knobs that contain many secretory granules. These endings lie on the surfaces of capillaries, where they secrete two posterior pituitary hormones: (1) *antidiuretic hormone* (ADH), also called *vasopressin*, and (2) *oxytocin*.

If the pituitary stalk is cut above the pituitary gland but the entire hypothalamus is left intact, the posterior pituitary hormones continue to be secreted normally, after a transient decrease for a few days; they are then secreted by the cut ends of the fibers within the hypothalamus and not by the



**Figure 75-9** Hypothalamic control of the posterior pituitary.

nerve endings in the posterior pituitary. The reason for this is that the hormones are initially synthesized in the cell bodies of the supraoptic and paraventricular nuclei and are then transported in combination with “carrier” proteins called *neurophysins* down to the nerve endings in the posterior pituitary gland, requiring several days to reach the gland.

*ADH is formed primarily in the supraoptic nuclei, whereas oxytocin is formed primarily in the paraventricular nuclei.* Each of these nuclei can synthesize about one sixth as much of the second hormone as of its primary hormone.

When nerve impulses are transmitted downward along the fibers from the supraoptic or paraventricular nuclei, the hormone is immediately released from the secretory granules in the nerve endings by the usual secretory mechanism of *exocytosis* and is absorbed into adjacent capillaries. Both the neurophysin and the hormone are secreted together, but because they are only loosely bound to each other, the hormone separates almost immediately. The neurophysin has no known function after leaving the nerve terminals.

#### Chemical Structures of Antidiuretic Hormone and Oxytocin

Both oxytocin and ADH (vasopressin) are polypeptides, each containing nine amino acids. Their amino acid sequences are the following:

**Vasopressin:** Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-GlyNH<sub>2</sub>

**Oxytocin:** Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-GlyNH<sub>2</sub>

Note that these two hormones are almost identical except that in vasopressin, phenylalanine and arginine replace isoleucine and leucine of the oxytocin molecule. The similarity of the molecules explains their partial functional similarities.

#### Physiological Functions of Antidiuretic Hormone

The injection of extremely minute quantities of ADH—as small as 2 nanograms—can cause decreased excretion of water by the kidneys (antidiuresis). This antidiuretic effect is discussed in detail in Chapter 28. Briefly, in the absence of ADH, the collecting tubules and ducts become almost impermeable to water, which prevents significant reabsorption of water and therefore allows extreme loss



of water into the urine, also causing extreme dilution of the urine. Conversely, in the presence of ADH, the permeability of the collecting ducts and tubules to water increases greatly and allows most of the water to be reabsorbed as the tubular fluid passes through these ducts, thereby conserving water in the body and producing very concentrated urine.

The precise mechanism by which ADH acts on the collecting ducts to increase their permeability is only partially known. Without ADH, the luminal membranes of the tubular epithelial cells of the collecting ducts are almost impermeable to water. However, immediately inside the cell membrane are a large number of special vesicles that have highly water-permeable pores called *aquaporins*. When ADH acts on the cell, it first combines with membrane receptors that activate adenylyl cyclase and cause the formation of cAMP inside the tubular cell cytoplasm. This causes phosphorylation of elements in the special vesicles, which then causes the vesicles to insert into the apical cell membranes, thus providing many areas of high water permeability. All this occurs within 5 to 10 minutes. Then, in the absence of ADH, the entire process reverses in another 5 to 10 minutes. Thus, this process temporarily provides many new pores that allow free diffusion of water from the tubular fluid through the tubular epithelial cells and into the renal interstitial fluid. Water is then absorbed from the collecting tubules and ducts by osmosis, as explained in Chapter 28 in relation to the urine-concentrating mechanism of the kidneys.

### Regulation of Antidiuretic Hormone Production

**Increased Extracellular Fluid Osmolarity Stimulates Antidiuretic Hormone Secretion.** When a concentrated electrolyte solution is injected into the artery that supplies the hypothalamus, the ADH neurons in the supraoptic and paraventricular nuclei immediately transmit impulses into the posterior pituitary to release large quantities of ADH into the circulating blood, sometimes increasing the ADH secretion to as high as 20 times normal. Conversely, injection of a dilute solution into this artery causes cessation of the impulses and therefore almost total cessation of ADH secretion. Thus, the concentration of ADH in the body fluids can change from small amounts to large amounts, or vice versa, in only a few minutes.

Somewhere in or near the hypothalamus are modified neuron receptors called *osmoreceptors*. When the extracellular fluid becomes too concentrated, fluid is pulled by osmosis out of the osmoreceptor cell, decreasing its size and initiating appropriate nerve signals in the hypothalamus to cause additional ADH secretion. Conversely, when the extracellular fluid becomes too dilute, water moves by osmosis in the opposite direction, into the cell, and this decreases the signal for ADH secretion. Although some researchers place these osmoreceptors in the hypothalamus itself (possibly even in the supraoptic nuclei), others believe that they are located in the *organum vasculosum*,

a highly vascular structure in the anteroventral wall of the third ventricle.

Regardless of the mechanism, concentrated body fluids stimulate the supraoptic nuclei, whereas dilute body fluids inhibit them. A feedback control system is available to control the total osmotic pressure of the body fluids.

Further details on the control of ADH secretion and the role of ADH in controlling renal function and body fluid osmolality are presented in Chapter 28.

### Low Blood Volume and Low Blood Pressure Stimulate ADH Secretion—Vasoconstrictor Effects of ADH

Whereas minute concentrations of ADH cause increased water conservation by the kidneys, higher concentrations of ADH have a potent effect of constricting the arterioles throughout the body and therefore increasing the arterial pressure. For this reason, ADH has another name, *vasopressin*.

One of the stimuli for causing intense ADH secretion is decreased blood volume. This occurs strongly when the blood volume decreases 15 to 25 percent or more; the secretory rate then sometimes rises to as high as 50 times normal. The cause of this is the following.

The atria have stretch receptors that are excited by overfilling. When excited, they send signals to the brain to inhibit ADH secretion. Conversely, when the receptors are unexcited as a result of underfilling, the opposite occurs, with greatly increased ADH secretion. Decreased stretch of the baroreceptors of the carotid, aortic, and pulmonary regions also stimulates ADH secretion. For further details about this blood volume-pressure feedback mechanism, refer to Chapter 28.

### Oxytocic Hormone

**Oxytocin Causes Contraction of the Pregnant Uterus.** The hormone *oxytocin*, in accordance with its name, powerfully stimulates contraction of the pregnant uterus, especially toward the end of gestation. Therefore, many obstetricians believe that this hormone is at least partially responsible for causing birth of the baby. This is supported by the following facts: (1) In a hypophysectomized animal, the duration of labor is prolonged, indicating a possible effect of oxytocin during delivery. (2) The amount of oxytocin in the plasma increases during labor, especially during the last stage. (3) Stimulation of the cervix in a pregnant animal elicits nervous signals that pass to the hypothalamus and cause increased secretion of oxytocin. These effects and this possible mechanism for aiding in the birth process are discussed in more detail in Chapter 82.

**Oxytocin Aids in Milk Ejection by the Breasts.** Oxytocin also plays an especially important role in lactation—a role that is far better understood than its role in delivery. In lactation, oxytocin causes milk to be expressed from the alveoli into the ducts of the breast so that the baby can obtain it by suckling.

This mechanism works as follows: The suckling stimulus on the nipple of the breast causes signals to be transmitted through sensory nerves to the oxytocin neurons in the paraventricular and supraoptic nuclei in the hypothalamus, which causes release of oxytocin by the posterior pituitary gland. The oxytocin is then carried by the blood to the breasts, where it causes contraction of *myoepithelial cells* that lie outside of and form a lattice-work surrounding the alveoli of the mammary glands. In less than a minute after the beginning of suckling, milk begins to flow. This mechanism is called *milk letdown* or *milk ejection*. It is discussed further in Chapter 82 in relation to the physiology of lactation.

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# Thyroid Metabolic Hormones



The thyroid gland, located immediately below the larynx on each side of and anterior to the trachea, is one of the largest of the endocrine glands, normally weighing 15 to 20 grams in adults.

The thyroid secretes two major hormones, *thyroxine* and *triiodothyronine*, commonly called  $T_4$  and  $T_3$ , respectively. Both of these hormones profoundly increase the metabolic rate of the body. Complete lack of thyroid secretion usually causes the basal metabolic rate to fall 40 to 50 percent below normal, and extreme excesses of thyroid secretion can increase the basal metabolic rate to 60 to 100 percent above normal. Thyroid secretion is controlled primarily by *thyroid-stimulating hormone* (TSH) secreted by the anterior pituitary gland.

The thyroid gland also secretes *calcitonin*, an important hormone for calcium metabolism that is considered in detail in Chapter 79.

The purpose of this chapter is to discuss the formation and secretion of the thyroid hormones, their metabolic functions, and regulation of their secretion.

## Synthesis and Secretion of the Thyroid Metabolic Hormones

About 93 percent of the metabolically active hormones secreted by the thyroid gland is *thyroxine*, and 7 percent *triiodothyronine*. However, almost all the thyroxine is eventually converted to triiodothyronine in the tissues, so both are functionally important. The functions of these two hormones are qualitatively the same, but they differ in rapidity and intensity of action. Triiodothyronine is about four times as potent as thyroxine, but it is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine.

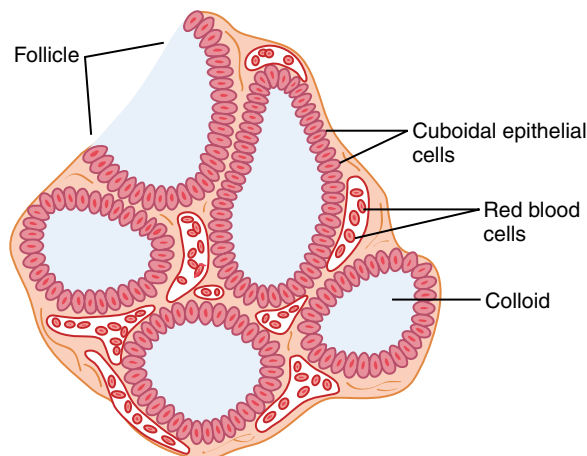
**Physiologic Anatomy of the Thyroid Gland.** The thyroid gland is composed, as shown in Figure 76-1, of large numbers of closed *follicles* (100 to 300 micrometers in diameter) filled with a secretory substance called

*colloid* and lined with *cuboidal epithelial cells* that secrete into the interior of the follicles. The major constituent of colloid is the large glycoprotein *thyroglobulin*, which contains the thyroid hormones. Once the secretion has entered the follicles, it must be absorbed back through the follicular epithelium into the blood before it can function in the body. The thyroid gland has a blood flow about five times the weight of the gland each minute, which is a blood supply as great as that of any other area of the body, with the possible exception of the adrenal cortex.

## Iodine Is Required for Formation of Thyroxine

To form normal quantities of thyroxine, about 50 milligrams of ingested iodine in the form of iodides are required *each year*, or about *1 mg/week*. To prevent iodine deficiency, common table salt is iodized with about 1 part sodium iodide to every 100,000 parts sodium chloride.

**Fate of Ingested Iodides.** Iodides ingested orally are absorbed from the gastrointestinal tract into the blood in about the same manner as chlorides. Normally, most of the iodides are rapidly excreted by the kidneys, but only after about one fifth are selectively removed from the circulating blood by the cells of the thyroid gland and used for synthesis of the thyroid hormones.



**Figure 76-1** Microscopic appearance of the thyroid gland, showing secretion of thyroglobulin into the follicles.

## Iodide Pump—the Sodium-Iodide Symporter (Iodide Trapping)

The first stage in the formation of thyroid hormones, shown in Figure 76-2, is transport of iodides from the blood into the thyroid glandular cells and follicles. The basal membrane of the thyroid cell has the specific ability to pump the iodide actively to the interior of the cell. This is achieved by the action of a *sodium-iodide symporter* (NIS), which co-transporters one iodide ion along with two sodium ions across the basolateral (plasma) membrane into the cell. The energy for transporting iodide against a concentration gradient comes from the sodium-potassium ATPase pump, which pumps sodium out of the cell, thereby establishing a low intracellular sodium concentration and a gradient for facilitated diffusion of sodium into the cell.

This process of concentrating the iodide in the cell is called *iodide trapping*. In a normal gland, the iodide pump concentrates the iodide to about 30 times its concentration in the blood. When the thyroid gland becomes maximally active, this concentration ratio can rise to as high as 250 times. The rate of iodide trapping by the thyroid is influenced by several factors, the most important being the concentration of TSH; TSH stimulates and hypophysectomy greatly diminishes the activity of the iodide pump in thyroid cells.

Iodide is transported out of the thyroid cells across the apical membrane into the follicle by a chloride-iodide ion counter-transporter molecule called *pendrin*. The thyroid epithelial cells also secrete into the follicle thyroglobulin that contains tyrosine amino acids to which the iodide ions will bind, as discussed in the next section.

## Thyroglobulin and Chemistry of Thyroxine and Triiodothyronine Formation

**Formation and Secretion of Thyroglobulin by the Thyroid Cells.** The thyroid cells are typical protein-secreting glandular cells, as shown in Figure 76-2. The

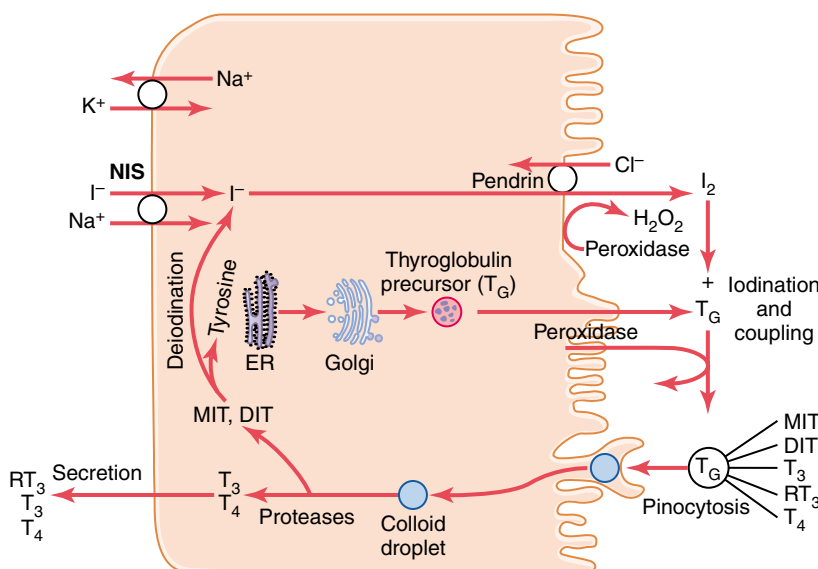
endoplasmic reticulum and Golgi apparatus synthesize and secrete into the follicles a large glycoprotein molecule called *thyroglobulin*, with a molecular weight of about 335,000.

Each molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. Thus, the thyroid hormones form *within* the thyroglobulin molecule. That is, the thyroxine and triiodothyronine hormones formed from the tyrosine amino acids remain part of the thyroglobulin molecule during synthesis of the thyroid hormones and even afterward as stored hormones in the follicular colloid.

**Oxidation of the Iodide Ion.** The first essential step in the formation of the thyroid hormones is conversion of the iodide ions to an *oxidized form of iodine*, either nascent iodine ( $I^0$ ) or  $I_3^-$ , that is then capable of combining directly with the amino acid tyrosine. This oxidation of iodine is promoted by the enzyme *peroxidase* and its accompanying *hydrogen peroxide*, which provide a potent system capable of oxidizing iodides. The peroxidase is either located in the apical membrane of the cell or attached to it, thus providing the oxidized iodine at exactly the point in the cell where the thyroglobulin molecule issues forth from the Golgi apparatus and through the cell membrane into the stored thyroid gland colloid. When the peroxidase system is blocked or when it is hereditarily absent from the cells, the rate of formation of thyroid hormones falls to zero.

**Iodination of Tyrosine and Formation of the Thyroid Hormones—"Organification" of Thyroglobulin.** The binding of iodine with the thyroglobulin molecule is called *organification* of the thyroglobulin. Oxidized iodine even in the molecular form will bind directly but slowly with the amino acid tyrosine. In the thyroid cells, however, the oxidized iodine is associated with thyroid

**Figure 76-2** Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. DIT, diiodotyrosine; MIT, monoiodotyrosine; NIS, sodium-iodide symporter;  $RT_3$ , reverse triiodothyronine;  $T_3$ , triiodothyronine;  $T_4$ , thyroxine;  $T_G$ , thyroglobulin.





peroxidase enzyme (Figure 76-2) that causes the process to occur within seconds or minutes. Therefore, almost as rapidly as the thyroglobulin molecule is released from the Golgi apparatus or as it is secreted through the apical cell membrane into the follicle, iodine binds with about one sixth of the tyrosine amino acids within the thyroglobulin molecule.

Figure 76-3 shows the successive stages of iodination of tyrosine and final formation of the two important thyroid hormones, thyroxine and triiodothyronine. Tyrosine is first iodized to *monoiodotyrosine* and then to *diiodotyrosine*. Then, during the next few minutes, hours, and even days, more and more of the diiodotyrosine residues become *coupled* with one another.

The major hormonal product of the coupling reaction is the molecule *thyroxine* ( $T_4$ ), which is formed when two molecules of diiodotyrosine are joined together; the thyroxine then remains part of the thyroglobulin molecule. Or one molecule of monoiodotyrosine couples with one molecule of diiodotyrosine to form *triiodothyronine* ( $T_3$ ), which represents about one fifteenth of the final hormones. Small amounts of *reverse*  $T_3$  ( $RT_3$ ) are formed by coupling of diiodotyrosine with monoiodotyrosine, but  $RT_3$  does not appear to be of functional significance in humans.

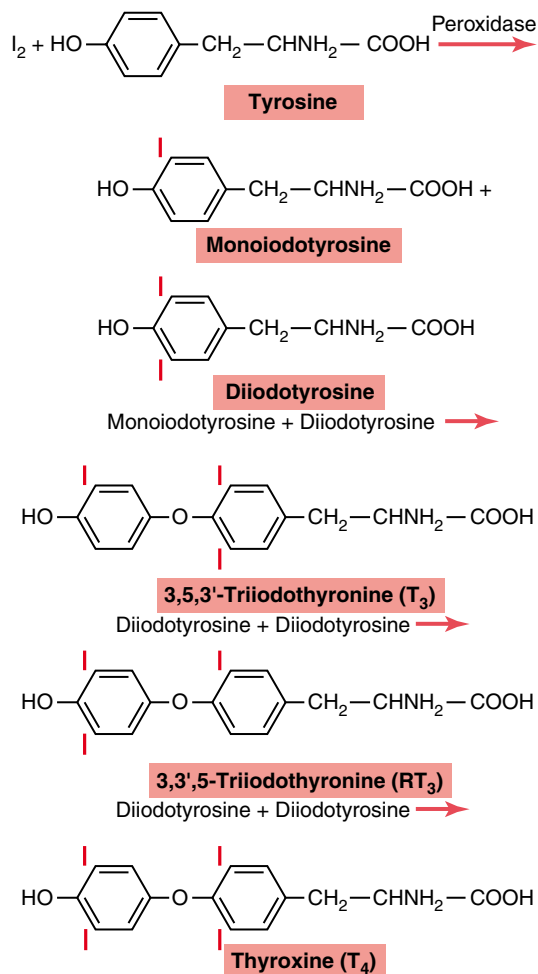


Figure 76-3 Chemistry of thyroxine and triiodothyronine formation.

**Storage of Thyroglobulin.** The thyroid gland is unusual among the endocrine glands in its ability to store large amounts of hormone. After synthesis of the thyroid hormones has run its course, each thyroglobulin molecule contains up to 30 thyroxine molecules and a few triiodothyronine molecules. In this form, the thyroid hormones are stored in the follicles in an amount sufficient to supply the body with its normal requirements of thyroid hormones for 2 to 3 months. Therefore, when synthesis of thyroid hormone ceases, the physiologic effects of deficiency are not observed for several months.

### Release of Thyroxine and Triiodothyronine from the Thyroid Gland

Thyroglobulin itself is not released into the circulating blood in measurable amounts; instead, thyroxine and triiodothyronine must first be cleaved from the thyroglobulin molecule, and then these free hormones are released. This process occurs as follows: The apical surface of the thyroid cells sends out pseudopod extensions that close around small portions of the colloid to form *pinocytic vesicles* that enter the apex of the thyroid cell. Then *lysosomes* in the cell cytoplasm immediately fuse with these vesicles to form digestive vesicles containing digestive enzymes from the lysosomes mixed with the colloid. Multiple *proteases* among the enzymes digest the thyroglobulin molecules and release thyroxine and triiodothyronine in free form. These then diffuse through the base of the thyroid cell into the surrounding capillaries. Thus, the thyroid hormones are released into the blood.

About three quarters of the iodinated tyrosine in the thyroglobulin never become thyroid hormones but remain monoiodotyrosine and diiodotyrosine. During the digestion of the thyroglobulin molecule to cause release of thyroxine and triiodothyronine, these iodinated tyrosines also are freed from the thyroglobulin molecules. However, they are not secreted into the blood. Instead, their iodine is cleaved from them by a *deiodinase* enzyme that makes virtually all this iodine available again for recycling within the gland for forming additional thyroid hormones. In the congenital absence of this deiodinase enzyme, many persons become iodine deficient because of failure of this recycling process.

**Daily Rate of Secretion of Thyroxine and Triiodothyronine.** About 93 percent of the thyroid hormone released from the thyroid gland is normally thyroxine and only 7 percent is triiodothyronine. However, during the ensuing few days, about one half of the thyroxine is slowly deiodinated to form additional triiodothyronine. Therefore, the hormone finally delivered to and used by the tissues is mainly triiodothyronine, a total of about 35 micrograms of triiodothyronine per day.

### Transport of Thyroxine and Triiodothyronine to Tissues

Thyroxine and Triiodothyronine Are Bound to Plasma Proteins. On entering the blood, more than



99 percent of the thyroxine and triiodothyronine combines immediately with several of the plasma proteins, all of which are synthesized by the liver. They combine mainly with *thyroxine-binding globulin* and much less so with *thyroxine-binding prealbumin* and *albumin*.

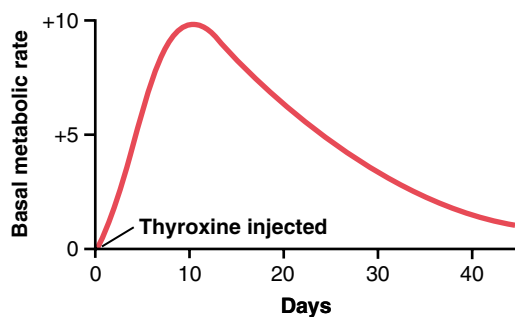
**Thyroxine and Triiodothyronine Are Released Slowly to Tissue Cells.** Because of high affinity of the plasma-binding proteins for the thyroid hormones, these substances—in particular, thyroxine—are released to the tissue cells slowly. Half the thyroxine in the blood is released to the tissue cells about every 6 days, whereas half the triiodothyronine—because of its lower affinity—is released to the cells in about 1 day.

On entering the tissue cells, both thyroxine and triiodothyronine again bind with intracellular proteins, the thyroxine binding more strongly than the triiodothyronine. Therefore, they are again stored, but this time in the target cells themselves, and they are used slowly over a period of days or weeks.

**Thyroid Hormones Have Slow Onset and Long Duration of Action.** After injection of a large quantity of thyroxine into a human being, essentially no effect on the metabolic rate can be discerned for 2 to 3 days, thereby demonstrating that there is a *long latent* period before thyroxine activity begins. Once activity does begin, it increases progressively and reaches a maximum in 10 to 12 days, as shown in Figure 76-4. Thereafter, it decreases with a half-life of about 15 days. Some of the activity persists for as long as 6 weeks to 2 months.

The actions of triiodothyronine occur about four times as rapidly as those of thyroxine, with a latent period as short as 6 to 12 hours and maximal cellular activity occurring within 2 to 3 days.

Most of the latency and prolonged period of action of these hormones are probably caused by their binding with proteins both in the plasma and in the tissue cells, followed by their slow release. However, we shall see in subsequent discussions that part of the latent period also results from the manner in which these hormones perform their functions in the cells themselves.



**Figure 76-4** Approximate prolonged effect on the basal metabolic rate caused by administering a single large dose of thyroxine.

## Physiological Functions of the Thyroid Hormones

### Thyroid Hormones Increase the Transcription of Large Numbers of Genes

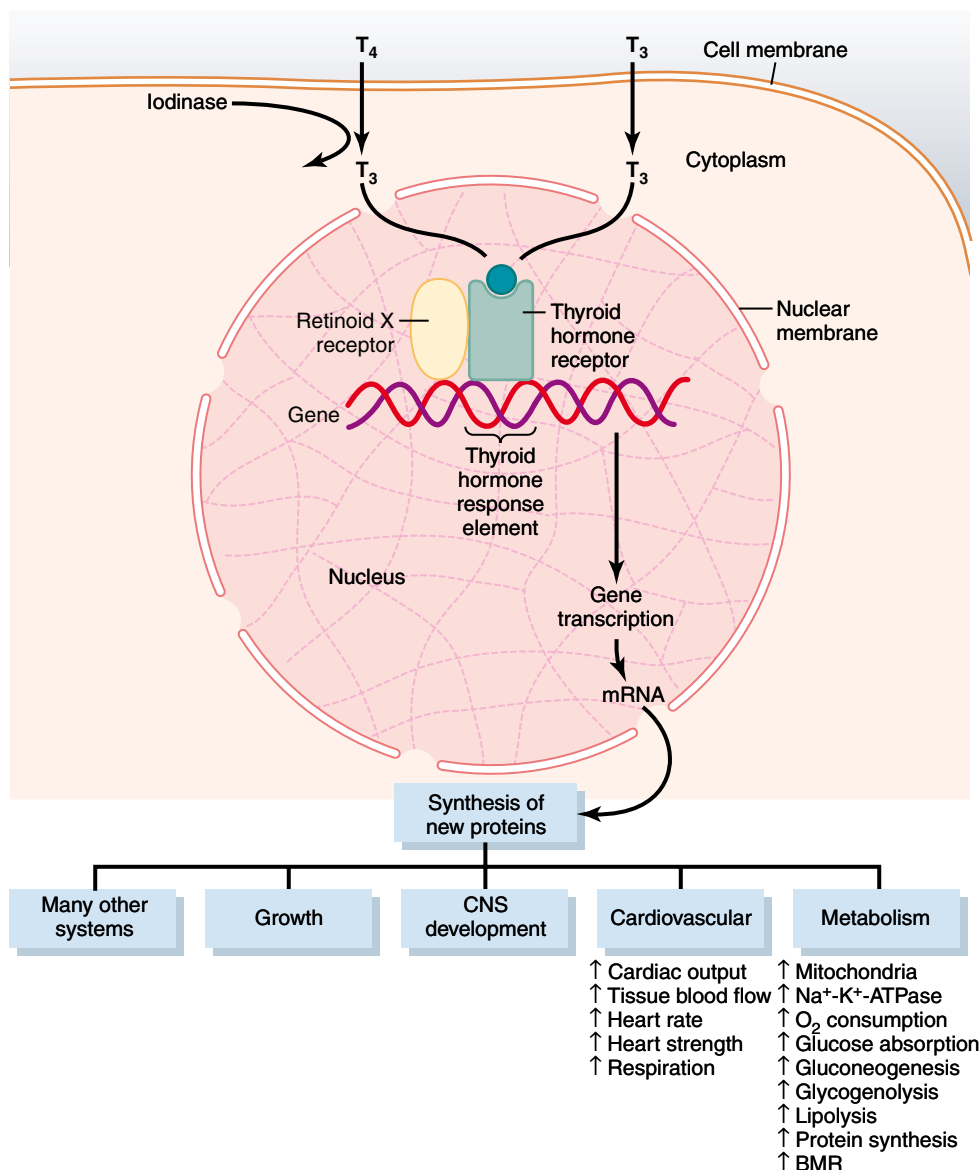
The general effect of thyroid hormone is to activate nuclear transcription of large numbers of genes (Figure 76-5). Therefore, in virtually all cells of the body, great numbers of protein enzymes, structural proteins, transport proteins, and other substances are synthesized. The net result is generalized increase in functional activity throughout the body.

**Most of the Thyroxine Secreted by the Thyroid Is Converted to Triiodothyronine.** Before acting on the genes to increase genetic transcription, one iodide is removed from almost all the thyroxine, thus forming triiodothyronine. Intracellular thyroid hormone receptors have a high affinity for triiodothyronine. Consequently, more than 90 percent of the thyroid hormone molecules that bind with the receptors is triiodothyronine.

### Thyroid Hormones Activate Nuclear Receptors.

The thyroid hormone receptors are either attached to the DNA genetic strands or located in proximity to them. The thyroid hormone receptor usually forms a heterodimer with *retinoid X receptor* (RXR) at specific *thyroid hormone response elements* on the DNA. On binding with thyroid hormone, the receptors become activated and initiate the transcription process. Then large numbers of different types of messenger RNA are formed, followed within another few minutes or hours by RNA translation on the cytoplasmic ribosomes to form hundreds of new intracellular proteins. However, not all the proteins are increased by similar percentages—some only slightly, and others at least as much as sixfold. It is believed that most of the actions of thyroid hormone result from the subsequent enzymatic and other functions of these new proteins.

Thyroid hormones also appear to have *nongenomic* cellular effects that are independent of their effects on gene transcription. For example, some effects of thyroid hormones occur within minutes, too rapidly to be explained by changes in protein synthesis, and are not affected by inhibitors of gene transcription and translation. Such actions have been described in several tissues, including the heart and pituitary, as well as adipose tissue. The site of nongenomic thyroid hormone action appears to be the plasma membrane, cytoplasm, and perhaps some cell organelles such as mitochondria. Nongenomic actions of thyroid hormone include the regulation of ion channels and oxidative phosphorylation and appear to involve the activation of intracellular secondary messengers such as cyclic AMP or protein kinase signaling cascades.



**Figure 76-5** Thyroid hormone activation of target cells. Thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) readily diffuse through the cell membrane. Much of the  $T_4$  is deiodinated to form  $T_3$ , which interacts with the thyroid hormone receptor, bound as a heterodimer with a retinoid X receptor, of the thyroid hormone response element of the gene. This causes either increases or decreases in transcription of genes that lead to formation of proteins, thus producing the thyroid hormone response of the cell. The actions of thyroid hormone on cells of several different systems are shown. mRNA, messenger ribonucleic acid.

### Thyroid Hormones Increase Cellular Metabolic Activity

The thyroid hormones increase the metabolic activities of almost all the tissues of the body. The basal metabolic rate can increase to 60 to 100 percent above normal when large quantities of the hormones are secreted. The rate of utilization of foods for energy is greatly accelerated. Although the rate of protein synthesis is increased, at the same time the rate of protein catabolism is also increased. The growth rate of young people is greatly accelerated. The mental processes are excited, and the activities of most of the other endocrine glands are increased.

**Thyroid Hormones Increase the Number and Activity of Mitochondria.** When thyroxine or triiodothyronine is given to an animal, the mitochondria in most cells of the animal's body increase in size and number. Furthermore, the total membrane surface area of the mitochondria increases almost directly in proportion to the increased metabolic rate of the whole animal. Therefore, one of the principal functions of thyroxine might be simply to increase the number and activity of mitochondria, which in turn increases the rate of formation of adenosine triphosphate (ATP) to energize cellular function. However, the increase in the

number and activity of mitochondria could be the *result* of increased activity of the cells as well as the cause of the increase.

**Thyroid Hormones Increase Active Transport of Ions through Cell Membranes.** One of the enzymes that increases its activity in response to thyroid hormone is *Na-K-ATPase*. This in turn increases the rate of transport of both sodium and potassium ions through the cell membranes of some tissues. Because this process uses energy and increases the amount of heat produced in the body, it has been suggested that this might be one of the mechanisms by which thyroid hormone increases the body's metabolic rate. In fact, thyroid hormone also causes the cell membranes of most cells to become leaky to sodium ions, which further activates the sodium pump and further increases heat production.

### Effect of Thyroid Hormone on Growth

Thyroid hormone has both general and specific effects on growth. For instance, it has long been known that thyroid hormone is essential for the metamorphic change of the tadpole into the frog.

In humans, the effect of thyroid hormone on growth is manifest mainly in growing children. In those who are hypothyroid, the rate of growth is greatly retarded. In those who are hyperthyroid, excessive skeletal growth often occurs, causing the child to become considerably taller at an earlier age. However, the bones also mature more rapidly and the epiphyses close at an early age, so the duration of growth and the eventual height of the adult may actually be shortened.

An important effect of thyroid hormone is to promote growth and development of the brain during fetal life and for the first few years of postnatal life. If the fetus does not secrete sufficient quantities of thyroid hormone, growth and maturation of the brain both before birth and afterward are greatly retarded and the brain remains smaller than normal. Without specific thyroid therapy within days or weeks after birth, the child without a thyroid gland will remain mentally deficient throughout life. This is discussed more fully later in the chapter.

### Effects of Thyroid Hormone on Specific Bodily Mechanisms

**Stimulation of Carbohydrate Metabolism.** Thyroid hormone stimulates almost all aspects of carbohydrate metabolism, including rapid uptake of glucose by the cells, enhanced glycolysis, enhanced gluconeogenesis, increased rate of absorption from the gastrointestinal tract, and even increased insulin secretion with its resultant secondary effects on carbohydrate metabolism. All these effects probably result from the overall increase in cellular metabolic enzymes caused by thyroid hormone.

**Stimulation of Fat Metabolism.** Essentially all aspects of fat metabolism are also enhanced under the

influence of thyroid hormone. In particular, lipids are mobilized rapidly from the fat tissue, which decreases the fat stores of the body to a greater extent than almost any other tissue element. This also increases the free fatty acid concentration in the plasma and greatly accelerates the oxidation of free fatty acids by the cells.

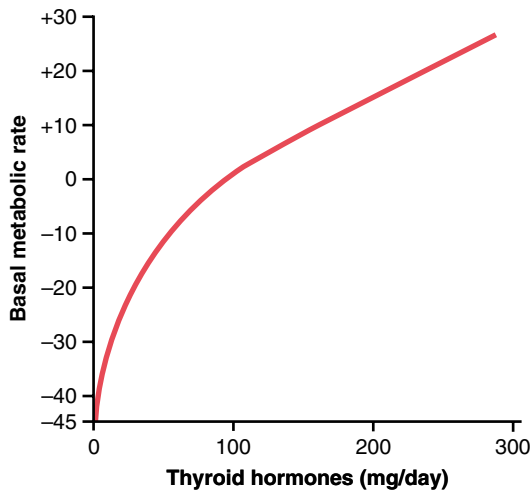
**Effect on Plasma and Liver Fats.** *Increased* thyroid hormone *decreases* the concentrations of cholesterol, phospholipids, and triglycerides in the plasma, even though it *increases* the free fatty acids. Conversely, *decreased* thyroid secretion greatly *increases* the plasma concentrations of cholesterol, phospholipids, and triglycerides and almost always causes excessive deposition of fat in the liver as well. The large increase in circulating plasma cholesterol in prolonged hypothyroidism is often associated with severe atherosclerosis, discussed in Chapter 68.

One of the mechanisms by which thyroid hormone decreases the plasma cholesterol concentration is to increase significantly the rate of cholesterol secretion in the bile and consequent loss in the feces. A possible mechanism for the increased cholesterol secretion is that thyroid hormone induces increased numbers of low-density lipoprotein receptors on the liver cells, leading to rapid removal of low-density lipoproteins from the plasma by the liver and subsequent secretion of cholesterol in these lipoproteins by the liver cells.

**Increased Requirement for Vitamins.** Because thyroid hormone increases the quantities of many bodily enzymes and because vitamins are essential parts of some of the enzymes or coenzymes, thyroid hormone increases the need for vitamins. Therefore, a relative vitamin deficiency can occur when excess thyroid hormone is secreted, unless at the same time increased quantities of vitamins are made available.

**Increased Basal Metabolic Rate.** Because thyroid hormone increases metabolism in almost all cells of the body, excessive quantities of the hormone can occasionally increase the basal metabolic rate 60 to 100 percent above normal. Conversely, when no thyroid hormone is produced, the basal metabolic rate falls to almost one-half normal. Figure 76-6 shows the approximate relation between the daily supply of thyroid hormones and the basal metabolic rate. Extreme amounts of the hormones are required to cause high basal metabolic rates.

**Decreased Body Weight.** Greatly increased thyroid hormone almost always decreases the body weight, and greatly decreased thyroid hormone almost always increases the body weight; these effects do not always occur because thyroid hormone also increases the appetite, and this may counterbalance the change in the metabolic rate.



**Figure 76-6** Approximate relation of daily rate of thyroid hormone ( $T_4$  and  $T_3$ ) secretion to the basal metabolic rate.

### Effect of Thyroid Hormones on the Cardiovascular System

**Increased Blood Flow and Cardiac Output.** Increased metabolism in the tissues causes more rapid utilization of oxygen than normal and release of greater than normal quantities of metabolic end products from the tissues. These effects cause vasodilation in most body tissues, thus increasing blood flow. The rate of blood flow in the skin especially increases because of the increased need for heat elimination from the body. As a consequence of the increased blood flow, cardiac output also increases, sometimes rising to 60 percent or more above normal when excessive thyroid hormone is present and falling to only 50 percent of normal in severe hypothyroidism.

**Increased Heart Rate.** The heart rate increases considerably more under the influence of thyroid hormone than would be expected from the increase in cardiac output. Therefore, thyroid hormone seems to have a direct effect on the excitability of the heart, which in turn increases the heart rate. This effect is of particular importance because the heart rate is one of the sensitive physical signs that the clinician uses in determining whether a patient has excessive or diminished thyroid hormone production.

**Increased Heart Strength.** The increased enzymatic activity caused by increased thyroid hormone production apparently increases the strength of the heart when only a slight excess of thyroid hormone is secreted. This is analogous to the increase in heart strength that occurs in mild fevers and during exercise. However, when thyroid hormone is increased markedly, the heart muscle strength becomes depressed because of long-term excessive protein catabolism. Indeed, some severely thyrotoxic patients die of cardiac decompensation secondary to myocardial failure and to increased cardiac load imposed by the increase in cardiac output.

**Normal Arterial Pressure.** The *mean* arterial pressure usually remains about normal after administration of thyroid hormone. Because of increased blood flow through the tissues between heartbeats, the pulse pressure is often

increased, with the systolic pressure elevated in hyperthyroidism 10 to 15 mm Hg and the diastolic pressure reduced a corresponding amount.

**Increased Respiration.** The increased rate of metabolism increases the utilization of oxygen and formation of carbon dioxide; these effects activate all the mechanisms that increase the rate and depth of respiration.

**Increased Gastrointestinal Motility.** In addition to increased appetite and food intake, which has been discussed, thyroid hormone increases both the rates of secretion of the digestive juices and the motility of the gastrointestinal tract. Hyperthyroidism therefore often results in diarrhea, whereas lack of thyroid hormone can cause constipation.

**Excitatory Effects on the Central Nervous System.** In general, thyroid hormone increases the rapidity of cerebration but also often dissociates this; conversely, lack of thyroid hormone decreases this function. The hyperthyroid individual is likely to have extreme nervousness and many psychoneurotic tendencies, such as anxiety complexes, extreme worry, and paranoia.

**Effect on the Function of the Muscles.** Slight increase in thyroid hormone usually makes the muscles react with vigor, but when the quantity of hormone becomes excessive, the muscles become weakened because of excess protein catabolism. Conversely, lack of thyroid hormone causes the muscles to become sluggish and they relax slowly after a contraction.

**Muscle Tremor.** One of the most characteristic signs of hyperthyroidism is a fine muscle tremor. This is not the coarse tremor that occurs in Parkinson disease or in shivering because it occurs at the rapid frequency of 10 to 15 times per second. The tremor can be observed easily by placing a sheet of paper on the extended fingers and noting the degree of vibration of the paper. This tremor is believed to be caused by increased reactivity of the neuronal synapses in the areas of the spinal cord that control muscle tone. The tremor is an important means for assessing the degree of thyroid hormone effect on the central nervous system.

**Effect on Sleep.** Because of the exhausting effect of thyroid hormone on the musculature and on the central nervous system, the hyperthyroid subject often has a feeling of constant tiredness, but because of the excitable effects of thyroid hormone on the synapses, it is difficult to sleep. Conversely, extreme somnolence is characteristic of hypothyroidism, with sleep sometimes lasting 12 to 14 hours a day.

**Effect on Other Endocrine Glands.** Increased thyroid hormone increases the rates of secretion of several other endocrine glands, but it also increases the need of the tissues for the hormones. For instance, increased thyroxine secretion increases the rate of glucose metabolism everywhere in the body and therefore causes a corresponding need for increased insulin secretion by the pancreas. Also, thyroid hormone increases many metabolic activities related to bone formation and, as a consequence, increases the need for parathyroid hormone. Thyroid hormone also



increases the rate at which adrenal glucocorticoids are inactivated by the liver. This leads to feedback increase in adrenocorticotrophic hormone (ACTH) production by the anterior pituitary and, therefore, increased rate of glucocorticoid secretion by the adrenal glands.

**Effect of Thyroid Hormone on Sexual Function.** For normal sexual function, thyroid secretion needs to be approximately normal. In men, lack of thyroid hormone is likely to cause loss of libido; great excesses of the hormone, however, sometimes cause impotence.

In women, lack of thyroid hormone often causes *menorrhagia* and *polymenorrhea*—that is, respectively, excessive and frequent menstrual bleeding. Yet, strangely enough, in other women thyroid lack may cause irregular periods and occasionally even *amenorrhea*.

A hypothyroid woman, like a man, is likely to have greatly decreased libido. To make the picture still more confusing, in the hyperthyroid woman, *oligomenorrhea*, which means greatly reduced bleeding, is common, and occasionally amenorrhea results.

The action of thyroid hormone on the gonads cannot be pinpointed to a specific function but probably results from a combination of direct metabolic effects on the gonads, as well as excitatory and inhibitory feedback effects operating through the anterior pituitary hormones that control the sexual functions.

### Regulation of Thyroid Hormone Secretion

To maintain normal levels of metabolic activity in the body, precisely the right amount of thyroid hormone must be secreted at all times; to achieve this, specific feedback mechanisms operate through the hypothalamus and anterior pituitary gland to control the rate of thyroid secretion. These mechanisms are as follows.

**TSH (from the Anterior Pituitary Gland) Increases Thyroid Secretion.** TSH, also known as *thyrotropin*, is an anterior pituitary hormone, a glycoprotein with a molecular weight of about 28,000. This hormone, also discussed in Chapter 74, increases the secretion of thyroxine and triiodothyronine by the thyroid gland. Its specific effects on the thyroid gland are as follows:

1. *Increased proteolysis of the thyroglobulin* that has already been stored in the follicles, with resultant release of the thyroid hormones into the circulating blood and diminishment of the follicular substance itself
2. *Increased activity of the iodide pump*, which increases the rate of “iodide trapping” in the glandular cells, sometimes increasing the ratio of intracellular to extracellular iodide concentration in the glandular substance to as much as eight times normal
3. *Increased iodination of tyrosine* to form the thyroid hormones
4. *Increased size and increased secretory activity of the thyroid cells*
5. *Increased number of thyroid cells* plus a change from cuboidal to columnar cells and much infolding of the thyroid epithelium into the follicles

In summary, TSH increases all the known secretory activities of the thyroid glandular cells.

The most important early effect after administration of TSH is to initiate proteolysis of the thyroglobulin, which causes release of thyroxine and triiodothyronine into the blood within 30 minutes. The other effects require hours or even days and weeks to develop fully.

**Cyclic Adenosine Monophosphate Mediates the Stimulatory Effect of TSH.** In the past, it was difficult to explain the many and varied effects of TSH on the thyroid cell. It is now clear that most of these effects result from activation of the “second messenger” *cyclic adenosine monophosphate* (cAMP) system of the cell.

The first event in this activation is binding of TSH with specific TSH receptors on the basal membrane surfaces of the thyroid cell. This then activates *adenylyl cyclase* in the membrane, which increases the formation of cAMP inside the cell. Finally, the cAMP acts as a *second messenger* to activate protein kinase, which causes multiple phosphorylations throughout the cell. The result is both an immediate increase in secretion of thyroid hormones and prolonged growth of the thyroid glandular tissue itself.

This method for control of thyroid cell activity is similar to the function of cAMP as a “second messenger” in many other target tissues of the body, as discussed in Chapter 74.

### Anterior Pituitary Secretion of TSH Is Regulated by Thyrotropin-Releasing Hormone from the Hypothalamus

Anterior pituitary secretion of TSH is controlled by a hypothalamic hormone, *thyrotropin-releasing hormone* (TRH), which is secreted by nerve endings in the median eminence of the hypothalamus. From the median eminence, the TRH is then transported to the anterior pituitary by way of the hypothalamic-hypophyseal portal blood, as explained in Chapter 74.

TRH has been obtained in pure form. It is a simple substance, a tripeptide amide—*pyroglutamyl-histidyl-proline-amide*. TRH directly affects the anterior pituitary gland cells to increase their output of TSH. When the blood portal system from the hypothalamus to the anterior pituitary gland becomes blocked, the rate of secretion of TSH by the anterior pituitary decreases greatly but is not reduced to zero.

The molecular mechanism by which TRH causes the TSH-secreting cells of the anterior pituitary to produce TSH is first to bind with TRH receptors in the pituitary cell membrane. This in turn *activates the phospholipase second messenger system* inside the pituitary cells to produce large amounts of phospholipase C, followed by a cascade of other second messengers, including calcium ions and diacyl glycerol, which eventually leads to TSH release.

**Effects of Cold and Other Neurogenic Stimuli on TRH and TSH Secretion.** One of the best-known stimuli for increasing the rate of TRH secretion by the hypothalamus, and therefore TSH secretion by the anterior pituitary gland, is exposure of an animal to cold. This effect almost certainly results from excitation of the hypothalamic centers for body temperature control. Exposure of rats for several weeks to severe cold increases the output of thyroid hormones sometimes to more than 100 percent of normal and can increase the basal metabolic rate as much as 50 percent. Indeed, persons moving to arctic regions have been known to develop basal metabolic rates 15 to 20 percent above normal.

Various emotional reactions can also affect the output of TRH and TSH and therefore indirectly affect the secretion of thyroid hormones. Excitement and anxiety—conditions that greatly stimulate the sympathetic nervous system—cause an acute decrease in secretion of TSH, perhaps because these states increase the metabolic rate and body heat and therefore exert an inverse effect on the heat control center.

Neither these emotional effects nor the effect of cold is observed after the hypophyseal stalk has been cut, demonstrating that both of these effects are mediated by way of the hypothalamus.

### Feedback Effect of Thyroid Hormone to Decrease Anterior Pituitary Secretion of TSH

Increased thyroid hormone in the body fluids decreases secretion of TSH by the anterior pituitary. When the rate of thyroid hormone secretion rises to about 1.75 times normal, the rate of TSH secretion falls essentially to zero. Almost all this feedback depressant effect occurs even when the anterior pituitary has been separated from the hypothalamus. Therefore, as shown in Figure 76-7, it is probable that increased thyroid hormone inhibits anterior pituitary secretion of TSH mainly by a direct effect on the anterior pituitary gland itself. Regardless of the mechanism of the feedback, its effect is to maintain an almost

constant concentration of free thyroid hormones in the circulating body fluids.

### Antithyroid Substances Suppress Thyroid Secretion

The best known antithyroid drugs are *thiocyanate*, *propylthiouracil*, and high concentrations of *inorganic iodides*. The mechanism by which each of these drugs blocks thyroid secretion is different from the others, and can be explained as follows.

**Thiocyanate Ions Decrease Iodide Trapping.** The same active pump that transports iodide ions into the thyroid cells can also pump thiocyanate ions, perchlorate ions, and nitrate ions. Therefore, the administration of thiocyanate (or one of the other ions as well) in high enough concentration can cause competitive inhibition of iodide transport into the cell—that is, inhibition of the iodide-trapping mechanism.

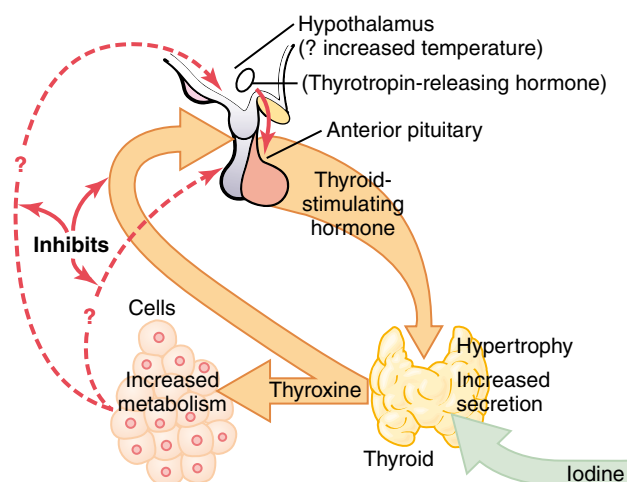
The decreased availability of iodide in the glandular cells does not stop the formation of thyroglobulin; it merely prevents the thyroglobulin that is formed from becoming iodinated and therefore from forming the thyroid hormones. This deficiency of the thyroid hormones in turn leads to increased secretion of TSH by the anterior pituitary gland, which causes overgrowth of the thyroid gland even though the gland still does not form adequate quantities of thyroid hormones. Therefore, the use of thiocyanates and some other ions to block thyroid secretion can lead to development of a greatly enlarged thyroid gland, which is called a *goiter*.

**Propylthiouracil Decreases Thyroid Hormone Formation.** Propylthiouracil (and other, similar compounds, such as methimazole and carbimazole) prevents formation of thyroid hormone from iodides and tyrosine. The mechanism of this is partly to block the peroxidase enzyme that is required for iodination of tyrosine and partly to block the coupling of two iodinated tyrosines to form thyroxine or triiodothyronine.

Propylthiouracil, like thiocyanate, does not prevent formation of thyroglobulin. The absence of thyroxine and triiodothyronine in the thyroglobulin can lead to tremendous feedback enhancement of TSH secretion by the anterior pituitary gland, thus promoting growth of the glandular tissue and forming a goiter.

**Iodides in High Concentrations Decrease Thyroid Activity and Thyroid Gland Size.** When iodides are present in the blood in *high concentration* (100 times the normal plasma level), most activities of the thyroid gland are decreased, but often they remain decreased for only a few weeks. The effect is to reduce the rate of iodide trapping so that the rate of iodination of tyrosine to form thyroid hormones is also decreased. Even more important, the normal endocytosis of colloid from the follicles by the thyroid glandular cells is paralyzed by the high iodide concentrations. Because this is the first step in release of the thyroid hormones from the storage colloid, there is almost immediate shutdown of thyroid hormone secretion into the blood.

Because iodides in high concentrations decrease all phases of thyroid activity, they slightly decrease the size of the thyroid gland and especially decrease its blood supply, in contradistinction to the opposite effects caused by most of the other antithyroid agents. For this reason, iodides are frequently administered to patients for 2 to 3 weeks before surgical removal of the thyroid gland to decrease the necessary amount of surgery, especially to decrease the amount of bleeding.



**Figure 76-7** Regulation of thyroid secretion.

## Diseases of the Thyroid

### Hyperthyroidism

Most effects of hyperthyroidism are obvious from the preceding discussion of the various physiologic effects of thyroid hormone. However, some specific effects should be mentioned in connection especially with the development, diagnosis, and treatment of hyperthyroidism.

**Causes of Hyperthyroidism (Toxic Goiter, Thyrotoxicosis, Graves' Disease).** In most patients with hyperthyroidism, the thyroid gland is increased to two to three times' normal size, with tremendous hyperplasia and infolding of the follicular cell lining into the follicles, so the number of cells is increased greatly. Also, each cell increases its rate of secretion several-fold; radioactive iodine uptake studies indicate that some of these hyperplastic glands secrete thyroid hormone at rates 5 to 15 times normal.

*Graves' disease*, the most common form of hyperthyroidism, is an autoimmune disease in which antibodies called *thyroid-stimulating immunoglobulins* (TSIs) form against the TSH receptor in the thyroid gland. These antibodies bind with the same membrane receptors that bind TSH and induce continual activation of the cAMP system of the cells, with resultant development of hyperthyroidism. The TSI antibodies have a prolonged stimulating effect on the thyroid gland, lasting for as long as 12 hours, in contrast to a little over 1 hour for TSH. The high level of thyroid hormone secretion caused by TSI in turn suppresses anterior pituitary formation of TSH. Therefore, TSH concentrations are less than normal (often essentially zero) rather than enhanced in almost all patients with Graves' disease.

The antibodies that cause hyperthyroidism almost certainly occur as the result of autoimmunity that has developed against thyroid tissue. Presumably, at some time in the history of the person, an excess of thyroid cell antigens was released from the thyroid cells and this has resulted in the formation of antibodies against the thyroid gland itself.

**Thyroid Adenoma.** Hyperthyroidism occasionally results from a localized adenoma (a tumor) that develops in the thyroid tissue and secretes large quantities of thyroid hormone. This is different from the more usual type of hyperthyroidism in that it is usually not associated with evidence of any autoimmune disease. An interesting effect of the adenoma is that as long as it continues to secrete large quantities of thyroid hormone, secretory function in the remainder of the thyroid gland is almost totally inhibited because the thyroid hormone from the adenoma depresses the production of TSH by the pituitary gland.

### Symptoms of Hyperthyroidism

The symptoms of hyperthyroidism are obvious from the preceding discussion of the physiology of the thyroid hormones: (1) a high state of excitability, (2) intolerance to heat, (3) increased sweating, (4) mild to extreme weight loss (sometimes as much as 100 pounds), (5) varying degrees of diarrhea, (6) muscle weakness, (7) nervousness or other psychic disorders, (8) extreme fatigue but inability to sleep, and (9) tremor of the hands.

**Exophthalmos.** Most people with hyperthyroidism develop some degree of protrusion of the eyeballs, as shown in Figure 76-8. This condition is called *exophthalmos*. A major degree of exophthalmos occurs in about one third of



**Figure 76-8** Patient with exophthalmic hyperthyroidism. Note protrusion of the eyes and retraction of the superior eyelids. The basal metabolic rate was +40. (Courtesy Dr. Leonard Posey.)

hyperthyroid patients, and the condition sometimes becomes so severe that the eyeball protrusion stretches the optic nerve enough to damage vision. Much more often, the eyes are damaged because the eyelids do not close completely when the person blinks or is asleep. As a result, the epithelial surfaces of the eyes become dry and irritated and often infected, resulting in ulceration of the cornea.

The cause of the protruding eyes is edematous swelling of the retro-orbital tissues and degenerative changes in the extraocular muscles. In most patients, immunoglobulins that react with the eye muscles can be found in the blood. Furthermore, the concentration of these immunoglobulins is usually highest in patients who have high concentrations of TSIs. Therefore, there is much reason to believe that exophthalmos, like hyperthyroidism itself, is an autoimmune process. The exophthalmos is usually greatly ameliorated with treatment of the hyperthyroidism.

**Diagnostic Tests for Hyperthyroidism.** For the usual case of hyperthyroidism, the most accurate diagnostic test is direct measurement of the concentration of "free" thyroxine (and sometimes triiodothyronine) in the plasma, using appropriate radioimmunoassay procedures.

Other tests that are sometimes used are as follows:

1. The basal metabolic rate is usually increased to +30 to +60 in severe hyperthyroidism.
2. The concentration of TSH in the plasma is measured by radioimmunoassay. In the usual type of thyrotoxicosis, anterior pituitary secretion of TSH is so completely suppressed by the large amounts of circulating thyroxine and triiodothyronine that there is almost no plasma TSH.
3. The concentration of TSI is measured by radioimmunoassay. This is usually high in thyrotoxicosis but low in thyroid adenoma.



**Physiology of Treatment in Hyperthyroidism.** The most direct treatment for hyperthyroidism is surgical removal of most of the thyroid gland. In general, it is desirable to prepare the patient for surgical removal of the gland before the operation. This is done by administering propylthiouracil, usually for several weeks, until the basal metabolic rate of the patient has returned to normal. Then, administration of high concentrations of iodides for 1 to 2 weeks immediately before operation causes the gland itself to recede in size and its blood supply to diminish. By using these preoperative procedures, the operative mortality is less than 1 in 1000 in the better hospitals, whereas before development of modern procedures, operative mortality was 1 in 25.

#### Treatment of the Hyperplastic Thyroid Gland with Radioactive Iodine

Eighty to 90 percent of an injected dose of iodide is absorbed by the hyperplastic, toxic thyroid gland within 1 day after injection. If this injected iodine is radioactive, it can destroy most of the secretory cells of the thyroid gland. Usually 5 millicuries of radioactive iodine is given to the patient, whose condition is reassessed several weeks later. If the patient is still hyperthyroid, additional doses are administered until normal thyroid status is reached.

#### Hypothyroidism

The effects of hypothyroidism, in general, are opposite to those of hyperthyroidism, but there are a few physiological mechanisms peculiar to hypothyroidism. Hypothyroidism, like hyperthyroidism, is often initiated by autoimmunity against the thyroid gland (*Hashimoto disease*), but immunity that destroys the gland rather than stimulates it. The thyroid glands of most of these patients first have autoimmune “thyroiditis,” which means thyroid inflammation. This causes progressive deterioration and finally fibrosis of the gland, with resultant diminished or absent secretion of thyroid hormone. Several other types of hypothyroidism also occur, often associated with development of enlarged thyroid glands, called *thyroid goiter*, as follows.

**Endemic Colloid Goiter Caused by Dietary Iodide Deficiency.** The term “goiter” means a greatly enlarged thyroid gland. As pointed out in the discussion of iodine metabolism, about 50 milligrams of iodine are required *each year* for the formation of adequate quantities of thyroid hormone. In certain areas of the world, notably in the Swiss Alps, the Andes, and the Great Lakes region of the United States, insufficient iodine is present in the soil for the food-stuffs to contain even this minute quantity. Therefore, in the days before iodized table salt, many people who lived in these areas developed extremely large thyroid glands, called *endemic goiters*.

The mechanism for development of large endemic goiters is the following: Lack of iodine prevents production of both thyroxine and triiodothyronine. As a result, no hormone is available to inhibit production of TSH by the anterior pituitary; this causes the pituitary to secrete excessively large quantities of TSH. The TSH then stimulates the thyroid cells to secrete tremendous amounts of thyroglobulin colloid into the follicles, and the gland grows larger and larger. But because of lack of iodine, thyroxine and triiodothyronine production does not occur in the thyroglobulin molecule and therefore does not cause the normal suppression of TSH

production by the anterior pituitary. The follicles become tremendous in size, and the thyroid gland may increase to 10 to 20 times' normal size.

**Idiopathic Nontoxic Colloid Goiter.** Enlarged thyroid glands similar to those of endemic colloid goiter can also occur in people who do not have iodine deficiency. These goitrous glands may secrete normal quantities of thyroid hormones, but more frequently, the secretion of hormone is depressed, as in endemic colloid goiter.

The exact cause of the enlarged thyroid gland in patients with idiopathic colloid goiter is not known, but most of these patients show signs of mild thyroiditis; therefore, it has been suggested that the thyroiditis causes slight hypothyroidism, which then leads to increased TSH secretion and progressive growth of the noninflamed portions of the gland. This could explain why these glands are usually nodular, with some portions of the gland growing while other portions are being destroyed by thyroiditis.

In some persons with colloid goiter, the thyroid gland has an abnormality of the enzyme system required for formation of the thyroid hormones. Among the abnormalities often encountered are the following:

1. *Deficient iodide-trapping mechanism*, in which iodine is not pumped adequately into the thyroid cells
2. *Deficient peroxidase system*, in which the iodides are not oxidized to the iodine state
3. *Deficient coupling of iodinated tyrosines in the thyroglobulin molecule* so that the final thyroid hormones cannot be formed
4. *Deficiency of the deiodinase enzyme*, which prevents recovery of iodine from the iodinated tyrosines that are not coupled to form the thyroid hormones (this is about two thirds of the iodine), thus leading to iodine deficiency

Finally, some foods contain *goitrogenic substances* that have a propylthiouracil-type of antithyroid activity, thus also leading to TSH-stimulated enlargement of the thyroid gland. Such goitrogenic substances are found especially in some varieties of turnips and cabbages.

**Physiological Characteristics of Hypothyroidism.** Whether hypothyroidism is due to thyroiditis, endemic colloid goiter, idiopathic colloid goiter, destruction of the thyroid gland by irradiation, or surgical removal of the thyroid gland, the physiological effects are the same. They include fatigue and extreme somnolence with sleeping up to 12 to 14 hours a day, extreme muscular sluggishness, slowed heart rate, decreased cardiac output, decreased blood volume, sometimes increased body weight, constipation, mental sluggishness, failure of many trophic functions in the body evidenced by depressed growth of hair and scaliness of the skin, development of a froglike husky voice, and, in severe cases, development of an edematous appearance throughout the body called *myxedema*.

**Myxedema.** *Myxedema* develops in the patient with almost total lack of thyroid hormone function. Figure 76-9 shows such a patient, demonstrating bagginess under the eyes and swelling of the face. In this condition, for reasons not explained, greatly increased quantities of hyaluronic acid and chondroitin sulfate bound with protein form excessive tissue gel in the interstitial spaces, and this causes the total quantity of interstitial fluid to increase. Because of the





**Figure 76-9** Patient with myxedema. (Courtesy Dr. Herbert Langford.)

gel nature of the excess fluid, it is mainly immobile and the edema is the nonpitting type.

**Atherosclerosis in Hypothyroidism.** As pointed out earlier, lack of thyroid hormone increases the quantity of blood cholesterol because of altered fat and cholesterol metabolism and diminished liver excretion of cholesterol in the bile. The increase in blood cholesterol is usually associated with increased atherosclerosis. Therefore, many hypothyroid patients, particularly those with myxedema, develop atherosclerosis, which in turn results in peripheral vascular disease, deafness, and coronary artery disease with consequent early death.

**Diagnostic Tests in Hypothyroidism.** The tests already described for diagnosis of hyperthyroidism give opposite results in hypothyroidism. The free thyroxine in the blood is low. The basal metabolic rate in myxedema ranges between  $-30$  and  $-50$ . And the secretion of TSH by the anterior pituitary when a test dose of TRH is administered is usually greatly increased (except in those rare instances of hypothyroidism caused by depressed response of the pituitary gland to TRH).

**Treatment of Hypothyroidism.** Figure 76-4 shows the effect of thyroxine on the basal metabolic rate, demonstrating that the hormone normally has a duration of action of more than 1 month. Consequently, it is easy to maintain a steady level of thyroid hormone activity in the body by daily oral ingestion of a tablet or more containing thyroxine. Furthermore, proper treatment of the hypothyroid patient results in such complete normality that formerly myxedematous patients have lived into their 90s after treatment for more than 50 years.

## Cretinism

Cretinism is caused by extreme hypothyroidism during fetal life, infancy, or childhood. This condition is characterized especially by failure of body growth and by mental retardation. It results from congenital lack of a thyroid gland (*congenital cretinism*), from failure of the thyroid gland to produce thyroid hormone because of a genetic defect of the gland, or from iodine lack in the diet (*endemic cretinism*). The severity of endemic cretinism varies greatly, depending on the amount of iodine in the diet, and whole populations of an endemic geographic iodine-deficient soil area have been known to have cretinoid tendencies.

A neonate without a thyroid gland may have normal appearance and function because it was supplied with some (but usually not enough) thyroid hormone by the mother while in utero. A few weeks after birth, however, the neonate's movements become sluggish and both physical and mental growth begin to be greatly retarded. Treatment of the neonate with cretinism at any time with adequate iodine or thyroxine usually causes normal return of physical growth, but unless the cretinism is treated within a few weeks after birth, mental growth remains permanently retarded. This results from retardation of the growth, branching, and myelination of the neuronal cells of the central nervous system at this critical time in the normal development of the mental powers.

Skeletal growth in the child with cretinism is characteristically more inhibited than is soft tissue growth. As a result of this disproportionate rate of growth, the soft tissues are likely to enlarge excessively, giving the child with cretinism an obese, stocky, and short appearance. Occasionally the tongue becomes so large in relation to the skeletal growth that it obstructs swallowing and breathing, inducing a characteristic guttural breathing that sometimes chokes the child.

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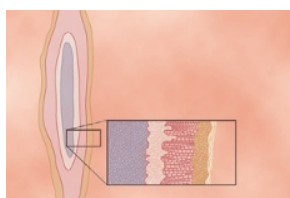
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# Adrenocortical Hormones



The two *adrenal glands*, each of which weighs about 4 grams, lie at the superior poles of the two kidneys. As shown in Figure 77-1, each gland is composed of two distinct parts, the *adrenal medulla* and the *adrenal cortex*. The adrenal medulla, the central 20 percent of the gland, is functionally related to the sympathetic nervous system; it secretes the hormones *epinephrine* and *norepinephrine* in response to sympathetic stimulation. In turn, these hormones cause almost the same effects as direct stimulation of the sympathetic nerves in all parts of the body. These hormones and their effects are discussed in detail in Chapter 60 in relation to the sympathetic nervous system.

The adrenal cortex secretes an entirely different group of hormones, called *corticosteroids*. These hormones are all synthesized from the steroid cholesterol, and they all have similar chemical formulas. However, slight differences in their molecular structures give them several different but very important functions.

**Corticosteroids: Mineralocorticoids, Glucocorticoids, and Androgens.** Two major types of adrenocortical hormones, the *mineralocorticoids* and the *glucocorticoids*, are secreted by the adrenal cortex. In addition to these, small amounts of sex hormones are secreted, especially *androgenic hormones*, which exhibit about the same effects in the body as the male sex hormone testosterone. They are normally of only slight importance, although in certain abnormalities of the adrenal cortices, extreme quantities can be secreted (which is discussed later in the chapter) and can result in masculinizing effects.

The *mineralocorticoids* have gained this name because they especially affect the electrolytes (the “minerals”) of the extracellular fluids, especially sodium and potassium. The *glucocorticoids* have gained their name because they exhibit important effects that increase blood glucose concentration. They have additional effects on both protein and fat metabolism that are equally as important to body function as their effects on carbohydrate metabolism.

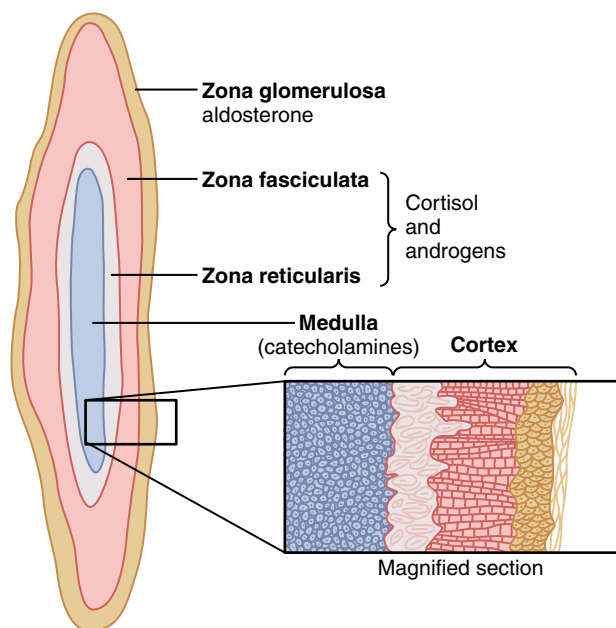
More than 30 steroids have been isolated from the adrenal cortex, but two are of exceptional importance to the normal endocrine function of the human body: *aldosterone*, which is the principal mineralocorticoid, and *cortisol*, which is the principal glucocorticoid.

## Synthesis and Secretion of Adrenocortical Hormones

### The Adrenal Cortex Has Three Distinct Layers.

Figure 77-1 shows that the adrenal cortex is composed of three relatively distinct layers:

1. The *zona glomerulosa*, a thin layer of cells that lies just underneath the capsule, constitutes about 15 percent of the adrenal cortex. These cells are the only ones in the adrenal gland capable of secreting significant amounts of *aldosterone* because they contain the enzyme *aldosterone synthase*, which is necessary for



**Figure 77-1** Secretion of adrenocortical hormones by the different zones of the adrenal cortex and secretion of catecholamines by the adrenal medulla.



synthesis of aldosterone. The secretion of these cells is controlled mainly by the extracellular fluid concentrations of *angiotensin II* and *potassium*, both of which stimulate aldosterone secretion.

2. The *zona fasciculata*, the middle and widest layer, constitutes about 75 percent of the adrenal cortex and secretes the glucocorticoids *cortisol* and *corticosterone*, as well as small amounts of *adrenal androgens* and *estrogens*. The secretion of these cells is controlled in large part by the hypothalamic-pituitary axis via *adrenocorticotrophic hormone* (ACTH).
3. The *zona reticularis*, the deep layer of the cortex, secretes the adrenal androgens *dehydroepiandrosterone* (DHEA) and *androstenedione*, as well as small amounts of estrogens and some glucocorticoids. ACTH also regulates secretion of these cells, although other factors such as *cortical androgen-stimulating hormone*, released from the pituitary, may also be involved. The mechanisms for controlling adrenal androgen production, however, are not nearly as well understood as those for glucocorticoids and mineralocorticoids.

Aldosterone and cortisol secretion are regulated by independent mechanisms. Factors such as angiotensin II that specifically increase the output of aldosterone and cause hypertrophy of the zona glomerulosa have no effect on the other two zones. Similarly, factors such as ACTH that increase secretion of cortisol and adrenal androgens and cause hypertrophy of the zona fasciculata and zona reticularis have little effect on the zona glomerulosa.

**Adrenocortical Hormones Are Steroids Derived from Cholesterol.** All human steroid hormones, including those produced by the adrenal cortex, are synthesized from cholesterol. Although the cells of the adrenal cortex can synthesize *de novo* small amounts of cholesterol from acetate, approximately 80 percent of the cholesterol used for steroid synthesis is provided by low-density lipoproteins (LDL) in the circulating plasma. The LDLs, which have high concentrations of cholesterol, diffuse from the plasma into the interstitial fluid and attach to specific receptors contained in structures called *coated pits* on the adrenocortical cell membranes. The coated pits are then internalized by *endocytosis*, forming vesicles that eventually fuse with cell lysosomes and release cholesterol that can be used to synthesize adrenal steroid hormones.

Transport of cholesterol into the adrenal cells is regulated by feedback mechanisms that can markedly alter the amount available for steroid synthesis. For example, ACTH, which stimulates adrenal steroid synthesis, increases the number of adrenocortical cell receptors for LDL, as well as the activity of enzymes that liberate cholesterol from LDL.

Once the cholesterol enters the cell, it is delivered to the mitochondria, where it is cleaved by the enzyme *cholesterol desmolase* to form *pregnenolone*; this is the rate-limiting step in the eventual formation of adrenal steroids (Figure 77-2). In all three zones of the adrenal cortex, this initial step in steroid synthesis is stimulated by the different factors that control secretion of the major hormone products aldosterone and cortisol. For example, both ACTH, which stimulates cortisol secretion, and angiotensin II, which stimulates

aldosterone secretion, increase the conversion of cholesterol to pregnenolone.

**Synthetic Pathways for Adrenal Steroids.** Figure 77-2 gives the principal steps in the formation of the important steroid products of the adrenal cortex: aldosterone, cortisol, and the androgens. Essentially all these steps occur in two of the organelles of the cell, the *mitochondria* and the *endoplasmic reticulum*, some steps occurring in one of these organelles and some in the other. Each step is catalyzed by a specific enzyme system. A change in even a single enzyme in the schema can cause vastly different types and relative proportions of hormones to be formed. For example, very large quantities of masculinizing sex hormones or other steroid compounds not normally present in the blood can occur with altered activity of only one of the enzymes in this pathway.

The chemical formulas of aldosterone and cortisol, which are the most important mineralocorticoid and glucocorticoid hormones, respectively, are shown in Figure 77-2. Cortisol has a keto-oxygen on carbon number 3 and is hydroxylated at carbon numbers 11 and 21. The mineralocorticoid aldosterone has an oxygen atom bound at the number 18 carbon.

In addition to aldosterone and cortisol, other steroids having glucocorticoid or mineralocorticoid activities, or both, are normally secreted in small amounts by the adrenal cortex. And several additional potent steroid hormones not normally formed in the adrenal glands have been synthesized and are used in various forms of therapy. Some of the more important of the corticosteroid hormones, including the synthetic ones, are the following, as summarized in Table 77-1.

#### Mineralocorticoids

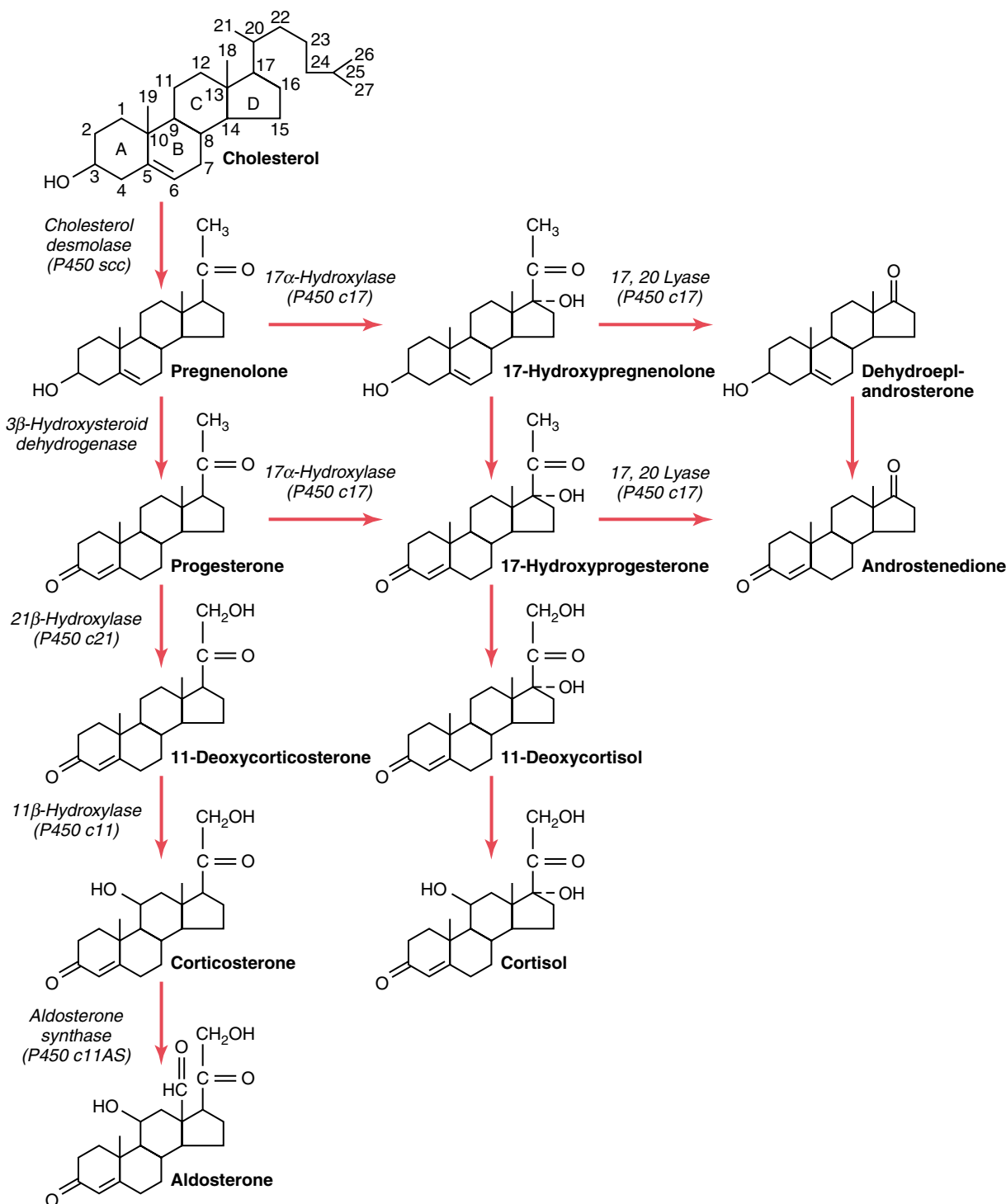
- Aldosterone (very potent, accounts for about 90 percent of all mineralocorticoid activity)
- Deoxycorticosterone (1/30 as potent as aldosterone, but very small quantities secreted)
- Corticosterone (slight mineralocorticoid activity)
- 9 $\alpha$ -Fluorocortisol (synthetic, slightly more potent than aldosterone)
- Cortisol (very slight mineralocorticoid activity, but large quantity secreted)
- Cortisone (slight mineralocorticoid activity)

#### Glucocorticoids

- Cortisol (very potent, accounts for about 95 percent of all glucocorticoid activity)
- Corticosterone (provides about 4 percent of total glucocorticoid activity, but much less potent than cortisol)
- Cortisone (almost as potent as cortisol)
- Prednisone (synthetic, four times as potent as cortisol)
- Methylprednisone (synthetic, five times as potent as cortisol)
- Dexamethasone (synthetic, 30 times as potent as cortisol)

*It is clear from this list that some of these hormones have both glucocorticoid and mineralocorticoid activities.* It is especially significant that cortisol normally has some mineralocorticoid activity, because some syndromes of excess cortisol secretion can cause significant mineralocorticoid effects, along with its much more potent glucocorticoid effects.

The intense glucocorticoid activity of the synthetic hormone dexamethasone, which has almost zero



**Figure 77-2** Pathways for synthesis of steroid hormones by the adrenal cortex. The enzymes are shown in italics.

mineralocorticoid activity, makes this an especially important drug for stimulating specific glucocorticoid activity.

**Adrenocortical Hormones Are Bound to Plasma Proteins.** Approximately 90 to 95 percent of the cortisol in the plasma binds to plasma proteins, especially a globulin called *cortisol-binding globulin* or *transcortin* and, to a lesser extent, to albumin. This high degree of binding to plasma proteins slows the elimination of cortisol from the plasma; therefore, cortisol has a relatively long half-life of 60 to 90 minutes. Only about 60 percent of circulating aldosterone

combines with the plasma proteins, so about 40 percent is in the free form; as a result, aldosterone has a relatively short half-life of about 20 minutes. These hormones are transported throughout the extracellular fluid compartment in both the combined and free forms.

Binding of adrenal steroids to the plasma proteins may serve as a reservoir to lessen rapid fluctuations in free hormone concentrations, as would occur, for example, with cortisol during brief periods of stress and episodic secretion of ACTH. This reservoir function may also help to ensure a

**Table 77-1** Adrenal Steroid Hormones in Adults; Synthetic Steroids and Their Relative Glucocorticoid and Mineralocorticoid Activities

Steroids	Average Plasma Concentration (free and bound, $\mu\text{g}/100\text{ ml}$ )	Average Amount Secreted ( $\text{mg}/24\text{ hr}$ )	Glucocorticoid Activity	Mineralocorticoid Activity
<b>Adrenal Steroids</b>				
Cortisol	12	15	1.0	1.0
Corticosterone	0.4	3	0.3	15.0
Aldosterone	0.006	0.15	0.3	3000
Deoxycorticosterone	0.006	0.2	0.2	100
Dehydroepiandrosterone	175	20	—	—
<b>Synthetic Steroids</b>				
Cortisone	—	—	0.8	1.0
Prednisolone	—	—	4	0.8
Methylprednisone	—	—	5	—
Dexamethasone	—	—	30	—
9 $\alpha$ -fluorocortisol	—	—	10	125

Glucocorticoid and mineralocorticoid activities of the steroids are relative to cortisol, with cortisol being 1.0.

relatively uniform distribution of the adrenal hormones to the tissues.

#### Adrenocortical Hormones Are Metabolized in the Liver.

The adrenal steroids are degraded mainly in the liver and conjugated especially to *glucuronic acid* and, to a lesser extent, sulfates. These substances are inactive and do not have mineralocorticoid or glucocorticoid activity. About 25 percent of these conjugates are excreted in the bile and then in the feces. The remaining conjugates formed by the liver enter the circulation but are not bound to plasma proteins, are highly soluble in the plasma, and are therefore filtered readily by the kidneys and excreted in the urine. Diseases of the liver markedly depress the rate of inactivation of adrenocortical hormones, and kidney diseases reduce the excretion of the inactive conjugates.

The normal concentration of aldosterone in blood is about 6 nanograms (6 billionths of a gram) per 100 milliliters, and the average secretory rate is approximately 150  $\mu\text{g}/\text{day}$  (0.15  $\text{mg}/\text{day}$ ). The blood concentration of aldosterone, however, depends greatly on several factors including dietary intake of sodium and potassium.

The concentration of cortisol in the blood averages 12  $\mu\text{g}/100\text{ ml}$ , and the secretory rate averages 15 to 20  $\text{mg}/\text{day}$ . However, blood concentration and secretion rate of cortisol fluctuate throughout the day, rising in the early morning and declining in the evening, as discussed later.

### Functions of the Mineralocorticoids—Aldosterone

**Mineralocorticoid Deficiency Causes Severe Renal Sodium Chloride Wasting and Hyperkalemia.** Total loss of adrenocortical secretion usually causes death within 3 days to 2 weeks unless the person receives extensive salt therapy or injection of mineralocorticoids.

Without mineralocorticoids, potassium ion concentration of the extracellular fluid rises markedly, sodium

and chloride are rapidly lost from the body, and the total extracellular fluid volume and blood volume become greatly reduced. The person soon develops diminished cardiac output, which progresses to a shocklike state, followed by death. This entire sequence can be prevented by the administration of aldosterone or some other mineralocorticoid. Therefore, the mineralocorticoids are said to be the acute “lifesaving” portion of the adrenocortical hormones. The glucocorticoids are equally necessary, however, allowing the person to resist the destructive effects of life’s intermittent physical and mental “stresses,” as discussed later in the chapter.

**Aldosterone Is the Major Mineralocorticoid Secreted by the Adrenals.** Aldosterone exerts nearly 90 percent of the mineralocorticoid activity of the adrenocortical secretions, but cortisol, the major glucocorticoid secreted by the adrenal cortex, also provides a significant amount of mineralocorticoid activity. Aldosterone’s mineralocorticoid activity is about 3000 times greater than that of cortisol, but the plasma concentration of cortisol is nearly 2000 times that of aldosterone.

Cortisol can also bind to mineralocorticoid receptors with high affinity. However, the renal epithelial cells also contain the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 2, which converts cortisol to cortisone. Because cortisone does not avidly bind mineralocorticoid receptors, cortisol does not normally exert significant mineralocorticoid effects. However, in patients with genetic deficiency of 11 $\beta$ -hydroxysteroid dehydrogenase type 2 activity, cortisol may have substantial mineralocorticoid effects. This condition is called *apparent mineralocorticoid excess syndrome* (AME) because the patient has essentially the same pathophysiological changes as a patient with excess aldosterone secretion, except that plasma aldosterone

levels are very low. Ingestion of large amounts of licorice, which contains glycyrrhetic acid, may also cause AME due to its ability to block  $11\beta$ -hydroxysteroid dehydrogenase type 2 enzyme activity.

### Renal and Circulatory Effects of Aldosterone

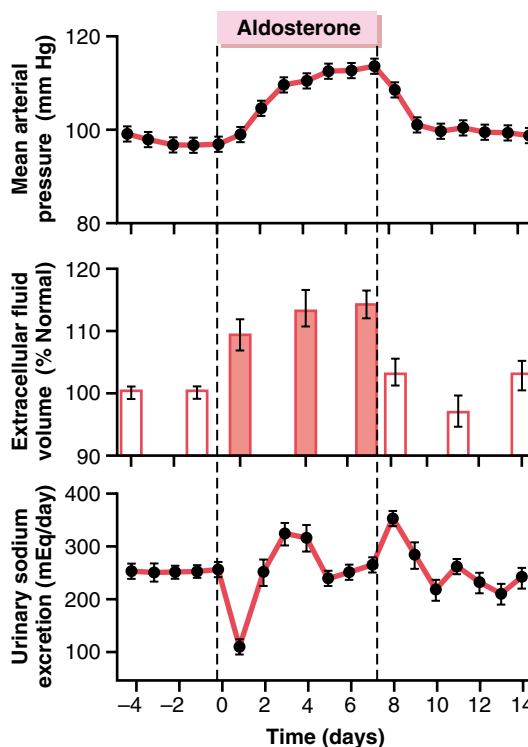
**Aldosterone Increases Renal Tubular Reabsorption of Sodium and Secretion of Potassium.** It will be recalled from Chapter 27 that aldosterone increases reabsorption of sodium and simultaneously increases secretion of potassium by the renal tubular epithelial cells, especially in the *principal cells of the collecting tubules* and, to a lesser extent, in the distal tubules and collecting ducts. Therefore, aldosterone causes sodium to be conserved in the extracellular fluid while increasing potassium excretion in the urine.

A high concentration of aldosterone in the plasma can transiently decrease the sodium loss into the urine to as little as a few milliequivalents a day. At the same time, potassium loss into the urine transiently increases severalfold. Therefore, the net effect of excess aldosterone in the plasma is to increase the total quantity of sodium in the extracellular fluid while decreasing the potassium.

Conversely, total lack of aldosterone secretion can cause transient loss of 10 to 20 grams of sodium in the urine a day, an amount equal to one tenth to one fifth of all the sodium in the body. At the same time, potassium is conserved tenaciously in the extracellular fluid.

**Excess Aldosterone Increases Extracellular Fluid Volume and Arterial Pressure but Has Only a Small Effect on Plasma Sodium Concentration.** Although aldosterone has a potent effect in decreasing the rate of sodium ion excretion by the kidneys, the concentration of sodium in the extracellular fluid often rises only a few milliequivalents. The reason for this is that when sodium is reabsorbed by the tubules, there is simultaneous osmotic absorption of almost equivalent amounts of water. Also, small increases in extracellular fluid sodium concentration stimulate thirst and increased water intake, if water is available. Therefore, the extracellular fluid volume increases almost as much as the retained sodium, but without much change in sodium concentration.

Even though aldosterone is one of the body's most powerful sodium-retaining hormones, only transient sodium retention occurs when excess amounts are secreted. An aldosterone-mediated increase in extracellular fluid volume lasting more than 1 to 2 days also leads to an increase in arterial pressure, as explained in Chapter 19. The rise in arterial pressure then increases kidney excretion of both salt and water, called *pressure natriuresis* and *pressure diuresis*, respectively. Thus, after the extracellular fluid volume increases 5 to 15 percent above normal, arterial pressure also increases 15 to 25 mm Hg, and this elevated blood pressure returns the renal output of salt and water to normal despite the excess aldosterone (Figure 77-3).



**Figure 77-3** Effect of aldosterone infusion on arterial pressure, extracellular fluid volume, and sodium excretion in dogs. Although aldosterone was infused at a rate that raised plasma concentrations to about 20 times normal, note the “escape” from sodium retention on the second day of infusion as arterial pressure increased and urinary sodium excretion returned to normal. (Drawn from data in Hall JE, Granger JP, Smith MJ Jr, et al: Role of hemodynamics and arterial pressure in aldosterone “escape.” *Hypertension* 6 (suppl 1):183-192, 1984.)

This return to normal of salt and water excretion by the kidneys as a result of pressure natriuresis and diuresis is called *aldosterone escape*. Thereafter, the rate of gain of salt and water by the body is zero, and balance is maintained between salt and water intake and output by the kidneys despite continued excess aldosterone. In the meantime, however, the person has developed hypertension, which lasts as long as the person remains exposed to high levels of aldosterone.

Conversely, when aldosterone secretion becomes zero, large amounts of salt are lost in the urine, not only diminishing the amount of sodium chloride in the extracellular fluid but also decreasing the extracellular fluid volume. The result is severe extracellular fluid dehydration and low blood volume, leading to *circulatory shock*. Without therapy, this usually causes death within a few days after the adrenal glands suddenly stop secreting aldosterone.

**Excess Aldosterone Causes Hypokalemia and Muscle Weakness; Too Little Aldosterone Causes Hyperkalemia and Cardiac Toxicity.** Excess aldosterone not only causes loss of potassium ions from the extracellular fluid into the urine but also stimulates transport of potassium from the extracellular fluid into most cells of the body. Therefore, excessive secretion of aldosterone, as occurs with some types of adrenal tumors, may cause a

serious decrease in the plasma potassium concentration, sometimes from the normal value of 4.5 mEq/L to as low as 2 mEq/L. This condition is called *hypokalemia*. When the potassium ion concentration falls below about one-half normal, severe muscle weakness often develops. This is caused by alteration of the electrical excitability of the nerve and muscle fiber membranes (see Chapter 5), which prevents transmission of normal action potentials.

Conversely, when aldosterone is deficient, the extracellular fluid potassium ion concentration can rise far above normal. When it rises to 60 to 100 percent above normal, serious cardiac toxicity, including weakness of heart contraction and development of arrhythmia, becomes evident; progressively higher concentrations of potassium lead inevitably to heart failure.

**Excess Aldosterone Increases Tubular Hydrogen Ion Secretion and Causes Alkalosis.** Aldosterone not only causes potassium to be secreted into the tubules in exchange for sodium reabsorption in the principal cells of the renal collecting tubules but also causes secretion of hydrogen ions in exchange for sodium in the *intercalated cells* of the cortical collecting tubules. This decreases the hydrogen ion concentration in the extracellular fluid, causing a metabolic alkalosis.

### Aldosterone Stimulates Sodium and Potassium Transport in Sweat Glands, Salivary Glands, and Intestinal Epithelial Cells

Aldosterone has almost the same effects on sweat glands and salivary glands as it has on the renal tubules. Both these glands form a primary secretion that contains large quantities of sodium chloride, but much of the sodium chloride, on passing through the excretory ducts, is reabsorbed, whereas potassium and bicarbonate ions are secreted. Aldosterone greatly increases the reabsorption of sodium chloride and the secretion of potassium by the ducts. The effect on the sweat glands is important to conserve body salt in hot environments, and the effect on the salivary glands is necessary to conserve salt when excessive quantities of saliva are lost.

Aldosterone also greatly enhances sodium absorption by the intestines, especially in the colon, which prevents loss of sodium in the stools. Conversely, in the absence of aldosterone, sodium absorption can be poor, leading to failure to absorb chloride and other anions and water as well. The unabsorbed sodium chloride and water then lead to diarrhea, with further loss of salt from the body.

### Cellular Mechanism of Aldosterone Action

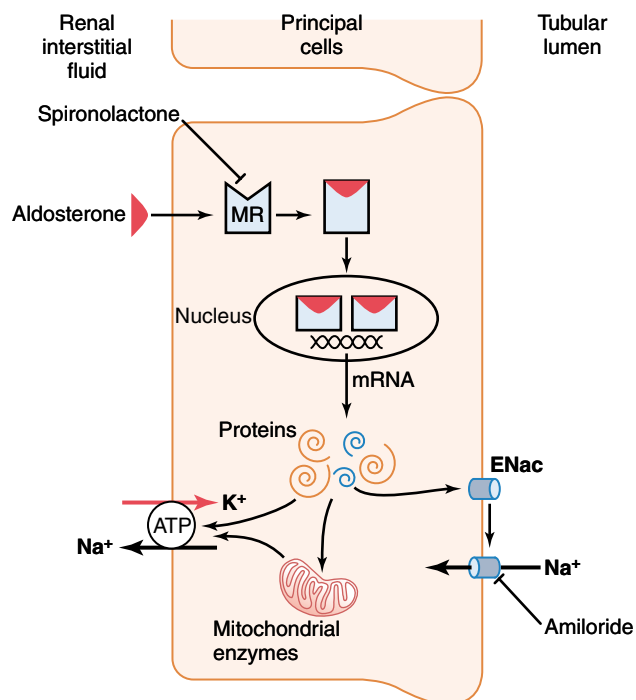
Although for many years we have known the overall effects of mineralocorticoids on the body, the molecular mechanisms of aldosterone's actions on the tubular cells to increase transport of sodium are still not fully understood. However, the cellular sequence of events that leads to increased sodium reabsorption seems to be the following.

First, because of its lipid solubility in the cellular membranes, aldosterone diffuses readily to the interior of the tubular epithelial cells.

Second, in the cytoplasm of the tubular cells, aldosterone combines with a highly specific cytoplasmic *mineralocorticoid receptor* (MR) protein (Figure 77-4), a protein that has a stereomolecular configuration that allows only aldosterone or similar compounds to combine with it. Although renal tubular epithelial cell MR receptors also have a high affinity for cortisol, the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 2 normally converts most of the cortisol to cortisone, which does not readily bind to MR receptors, as discussed previously.

Third, the aldosterone-receptor complex or a product of this complex diffuses into the nucleus, where it may undergo further alterations, finally inducing one or more specific portions of the DNA to form one or more types of messenger RNA related to the process of sodium and potassium transport.

Fourth, the messenger RNA diffuses back into the cytoplasm, where, operating in conjunction with the ribosomes, it causes protein formation. The proteins formed are a mixture of (1) one or more enzymes and (2) membrane transport proteins that, all acting together, are required for sodium, potassium, and hydrogen transport through the cell membrane (see Figure 77-4). One of the enzymes especially increased is *sodium-potassium adenosine triphosphatase*, which serves as the principal part of the pump for sodium and potassium exchange at the *basolateral membranes* of the renal tubular cells.



**Figure 77-4** Aldosterone-responsive epithelial cell signaling pathways. ENaC, epithelial sodium channel proteins; MR, mineralocorticoid receptor. Activation of the MR by aldosterone can be antagonized with spironolactone. Amiloride is a drug that can be used to block ENaC.



Additional proteins, perhaps equally important, are *epithelial sodium channel* (ENaC) proteins inserted into the *luminal membrane* of the same tubular cells that allow rapid diffusion of sodium ions from the tubular lumen into the cell; then the sodium is pumped the rest of the way by the sodium-potassium pump located in the basolateral membranes of the cell.

Thus, aldosterone does not have a major immediate effect on sodium transport; rather, this effect must await the sequence of events that leads to the formation of the specific intracellular substances required for sodium transport. About 30 minutes is required before new RNA appears in the cells, and about 45 minutes is required before the rate of sodium transport begins to increase; the effect reaches maximum only after several hours.

### Possible Nongenomic Actions of Aldosterone and Other Steroid Hormones

Recent studies suggest that many steroids, including aldosterone, elicit not only slowly developing *genomic* effects that have a latency of 60 to 90 minutes and require gene transcription and synthesis of new proteins, but also more rapid *nongenomic* effects that take place in a few seconds or minutes.

These nongenomic actions are believed to be mediated by binding of steroids to cell membrane receptors that are coupled to second messenger systems, similar to those used for peptide hormone signal transduction. For example, aldosterone has been shown to increase formation of cAMP in vascular smooth muscle cells and in epithelial cells of the renal collecting tubules in less than 2 minutes, a time period that is far too short for gene transcription and synthesis of new proteins. In other cell types, aldosterone has been shown to rapidly stimulate the phosphatidylinositol second messenger system. However, the precise structure of receptors responsible for the rapid effects of aldosterone has not been determined, nor is the physiological significance of these nongenomic actions of steroids well understood.

### Regulation of Aldosterone Secretion

The regulation of aldosterone secretion is so deeply intertwined with the regulation of extracellular fluid electrolyte concentrations, extracellular fluid volume, blood volume, arterial pressure, and many special aspects of renal function that it is difficult to discuss the regulation of aldosterone secretion independently of all these other factors. This subject is presented in detail in Chapters 28 and 29, to which the reader is referred. However, it is important to list here some of the more important points of aldosterone secretion control.

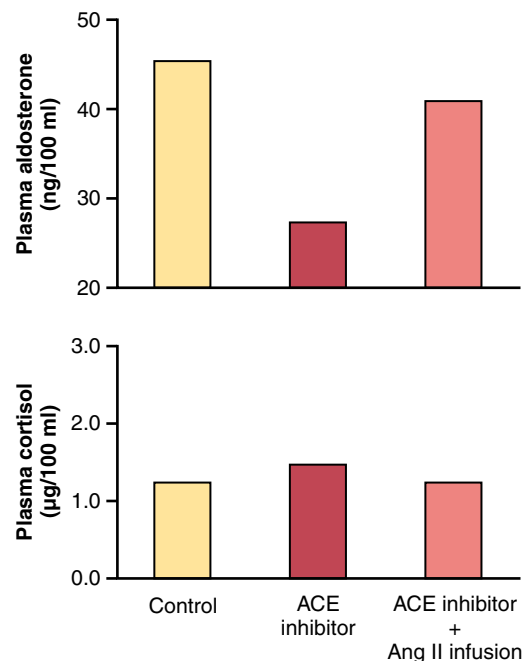
The regulation of aldosterone secretion by the zona glomerulosa cells is almost entirely independent of the regulation of cortisol and androgens by the zona fasciculata and zona reticularis.

Four factors are known to play essential roles in the regulation of aldosterone. In the probable order of their importance, they are as follows:

1. Increased potassium ion concentration in the extracellular fluid greatly *increases* aldosterone secretion.
2. Increased angiotensin II concentration in the extracellular fluid also greatly *increases* aldosterone secretion.
3. Increased sodium ion concentration in the extracellular fluid *very slightly decreases* aldosterone secretion.
4. ACTH from the anterior pituitary gland is necessary for aldosterone secretion but has little effect in controlling the rate of secretion in most physiological conditions.

Of these factors, *potassium ion concentration* and the *renin-angiotensin system* are by far the most potent in regulating aldosterone secretion. A small percentage increase in potassium concentration can cause a severalfold increase in aldosterone secretion. Likewise, activation of the renin-angiotensin system, usually in response to diminished blood flow to the kidneys or to sodium loss, can increase in aldosterone secretion severalfold. In turn, the aldosterone acts on the kidneys (1) to help them excrete the excess potassium ions and (2) to increase the blood volume and arterial pressure, thus returning the renin-angiotensin system toward its normal level of activity. These feedback control mechanisms are essential for maintaining life, and the reader is referred again to Chapters 27 and 29 for a more complete description of their functions.

Figure 77-5 shows the effects on plasma aldosterone concentration caused by blocking the formation of angiotensin



**Figure 77-5** Effects of treating sodium-depleted dogs with an angiotensin-converting enzyme (ACE) inhibitor for 7 days to block formation of angiotensin II (Ang II) and of infusing exogenous Ang II to restore plasma Ang II levels after ACE inhibition. Note that blocking Ang II formation reduced plasma aldosterone concentration with little effect on cortisol, demonstrating the important role of Ang II in stimulating aldosterone secretion during sodium depletion. (Drawn from data in Hall JE, Guyton AC, Smith MJ Jr, et al: Chronic blockade of angiotensin II formation during sodium deprivation. *Am J Physiol* 237:F424, 1979.)

II with an angiotensin-converting enzyme inhibitor after several weeks of a low-sodium diet that increases plasma aldosterone concentration. Note that blocking angiotensin II formation markedly decreases plasma aldosterone concentration without significantly changing cortisol concentration; this indicates the important role of angiotensin II in stimulating aldosterone secretion when sodium intake and extracellular fluid volume are reduced.

By contrast, the effects of sodium ion concentration per se and of ACTH in controlling aldosterone secretion are usually minor. Nevertheless, a 10 to 20 percent decrease in extracellular fluid sodium ion concentration, which occurs on rare occasions, can perhaps increase aldosterone secretion by about 50 percent. In the case of ACTH, if there is even a small amount of ACTH secreted by the anterior pituitary gland, it is usually enough to permit the adrenal glands to secrete whatever amount of aldosterone is required, but total absence of ACTH can significantly reduce aldosterone secretion. Therefore, ACTH appears to play a “permissive” role in regulation of aldosterone secretion.

## Functions of the Glucocorticoids

Even though mineralocorticoids can save the life of an acutely adrenalectomized animal, the animal still is far from normal. Instead, its metabolic systems for utilization of proteins, carbohydrates, and fats remain considerably deranged. Furthermore, the animal cannot resist different types of physical or even mental stress, and minor illnesses such as respiratory tract infections can lead to death. Therefore, the glucocorticoids have functions just as important to the long-continued life of the animal as those of the mineralocorticoids. They are explained in the following sections.

At least 95 percent of the glucocorticoid activity of the adrenocortical secretions results from the secretion of *cortisol*, known also as *hydrocortisone*. In addition to this, a small but significant amount of glucocorticoid activity is provided by *corticosterone*.

### Effects of Cortisol on Carbohydrate Metabolism

**Stimulation of Gluconeogenesis.** By far the best-known metabolic effect of cortisol and other glucocorticoids on metabolism is the ability to stimulate gluconeogenesis (formation of carbohydrate from proteins and some other substances) by the liver, often increasing the rate of gluconeogenesis as much as 6- to 10-fold. This results mainly from two effects of cortisol.

1. *Cortisol increases the enzymes required to convert amino acids into glucose in the liver cells.* This results from the effect of the glucocorticoids to activate DNA transcription in the liver cell nuclei in the same way that aldosterone functions in the renal tubular cells, with formation of messenger RNAs that in turn lead to the array of enzymes required for gluconeogenesis.

2. *Cortisol causes mobilization of amino acids from the extrahepatic tissues mainly from muscle.* As a result, more amino acids become available in the plasma to enter into the gluconeogenesis process of the liver and thereby to promote the formation of glucose.

One of the effects of increased gluconeogenesis is a marked increase in glycogen storage in the liver cells. This effect of cortisol allows other glycolytic hormones, such as epinephrine and glucagon, to mobilize glucose in times of need, such as between meals.

**Decreased Glucose Utilization by Cells.** Cortisol also causes a moderate decrease in the rate of glucose utilization by most cells in the body. Although the cause of this decrease is unknown, most physiologists believe that somewhere between the point of entry of glucose into the cells and its final degradation, cortisol directly delays the rate of glucose utilization. A suggested mechanism is based on the observation that glucocorticoids depress the oxidation of nicotinamide-adenine dinucleotide (NADH) to form NAD<sup>+</sup>. Because NADH must be oxidized to allow glycolysis, this effect could account for the diminished utilization of glucose by the cells.

**Elevated Blood Glucose Concentration and “Adrenal Diabetes.”** Both the increased rate of gluconeogenesis and the moderate reduction in the rate of glucose utilization by the cells cause the blood glucose concentrations to rise. The rise in blood glucose in turn stimulates secretion of insulin. The increased plasma levels of insulin, however, are not as effective in maintaining plasma glucose as they are under normal conditions. For reasons that are not entirely clear, high levels of glucocorticoid reduce the sensitivity of many tissues, especially skeletal muscle and adipose tissue, to the stimulatory effects of insulin on glucose uptake and utilization. One possible explanation is that high levels of fatty acids, caused by the effect of glucocorticoids to mobilize lipids from fat depots, may impair insulin’s actions on the tissues. In this way, excess secretion of glucocorticoids may produce disturbances of carbohydrate metabolism similar to those found in patients with excess levels of growth hormone.

The increase in blood glucose concentration is occasionally great enough (50 percent or more above normal) that the condition is called *adrenal diabetes*. Administration of insulin lowers the blood glucose concentration only a moderate amount in adrenal diabetes—not nearly as much as it does in pancreatic diabetes—because the tissues are resistant to the effects of insulin.

### Effects of Cortisol on Protein Metabolism

**Reduction in Cellular Protein.** One of the principal effects of cortisol on the metabolic systems of the body is reduction of the protein stores in essentially all body cells except those of the liver. This is caused by both decreased protein synthesis and increased catabolism of protein already in the cells. Both these effects may result partly

from decreased amino acid transport into extrahepatic tissues, as discussed later; this is probably not the major cause because cortisol also depresses the formation of RNA and subsequent protein synthesis in many extrahepatic tissues, especially in muscle and lymphoid tissue.

In the presence of great excesses of cortisol, the muscles can become so weak that the person cannot rise from the squatting position. And the immunity functions of the lymphoid tissue can be decreased to a small fraction of normal.

### Cortisol Increases Liver and Plasma Proteins.

Coincidentally with the reduced proteins elsewhere in the body, the liver proteins become enhanced. Furthermore, the plasma proteins (which are produced by the liver and then released into the blood) are also increased. These increases are exceptions to the protein depletion that occurs elsewhere in the body. It is believed that this difference results from a possible effect of cortisol to enhance amino acid transport into liver cells (but not into most other cells) and to enhance the liver enzymes required for protein synthesis.

**Increased Blood Amino Acids, Diminished Transport of Amino Acids into Extrahepatic Cells, and Enhanced Transport into Hepatic Cells.** Studies in isolated tissues have demonstrated that cortisol depresses amino acid transport into muscle cells and perhaps into other extrahepatic cells.

The decreased transport of amino acids into extrahepatic cells decreases their intracellular amino acid concentrations and consequently decreases the synthesis of protein. Yet catabolism of proteins in the cells continues to release amino acids from the already existing proteins, and these diffuse out of the cells to increase the plasma amino acid concentration. Therefore, *cortisol mobilizes amino acids from the nonhepatic tissues* and in doing so diminishes the tissue stores of protein.

The increased plasma concentration of amino acids and enhanced transport of amino acids into the hepatic cells by cortisol could also account for enhanced utilization of amino acids by the liver to cause such effects as (1) increased rate of deamination of amino acids by the liver, (2) increased protein synthesis in the liver, (3) increased formation of plasma proteins by the liver, and (4) increased conversion of amino acids to glucose—that is, enhanced gluconeogenesis. Thus, it is possible that many of the effects of cortisol on the metabolic systems of the body result mainly from this ability of cortisol to mobilize amino acids from the peripheral tissues while at the same time increasing the liver enzymes required for the hepatic effects.

### Effects of Cortisol on Fat Metabolism

**Mobilization of Fatty Acids.** In much the same manner that cortisol promotes amino acid mobilization from muscle, it also promotes mobilization of fatty acids from

adipose tissue. This increases the concentration of free fatty acids in the plasma, which also increases their utilization for energy. Cortisol also seems to have a direct effect to enhance the oxidation of fatty acids in the cells.

The mechanism by which cortisol promotes fatty acid mobilization is not completely understood. However, part of the effect probably results from diminished transport of glucose into the fat cells. Recall that  $\alpha$ -glycerophosphate, which is derived from glucose, is required for both deposition and maintenance of triglycerides in these cells. In its absence the fat cells begin to release fatty acids.

The increased mobilization of fats by cortisol, combined with increased oxidation of fatty acids in the cells, helps shift the metabolic systems of the cells from utilization of glucose for energy to utilization of fatty acids in times of starvation or other stresses. This cortisol mechanism, however, requires several hours to become fully developed—not nearly so rapid or so powerful an effect as a similar shift elicited by a decrease in insulin, as we discuss in Chapter 78. Nevertheless, the increased use of fatty acids for metabolic energy is an important factor for long-term conservation of body glucose and glycogen.

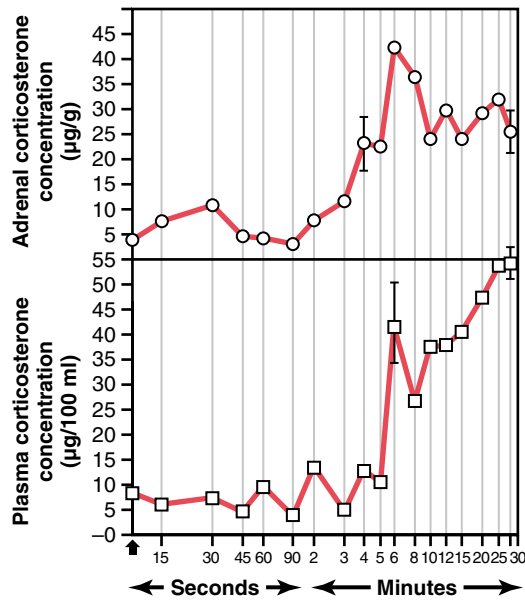
**Obesity Caused by Excess Cortisol.** Despite the fact that cortisol can cause a moderate degree of fatty acid mobilization from adipose tissue, many people with excess cortisol secretion develop a peculiar type of obesity, with excess deposition of fat in the chest and head regions of the body, giving a buffalo-like torso and a rounded “moon face.” Although the cause is unknown, it has been suggested that this obesity results from excess stimulation of food intake, with fat being generated in some tissues of the body more rapidly than it is mobilized and oxidized.

### Cortisol Is Important in Resisting Stress and Inflammation

Almost any type of stress, whether physical or neurogenic, causes an immediate and marked increase in ACTH secretion by the anterior pituitary gland, followed within minutes by greatly increased adrenocortical secretion of cortisol. This is demonstrated dramatically by the experiment shown in Figure 77-6, in which corticosteroid formation and secretion increased sixfold in a rat within 4 to 20 minutes after fracture of two leg bones.

Some of the different types of stress that increase cortisol release are the following:

1. Trauma of almost any type
2. Infection
3. Intense heat or cold
4. Injection of norepinephrine and other sympathomimetic drugs
5. Surgery
6. Injection of necrotizing substances beneath the skin
7. Restraining an animal so that it cannot move
8. Almost any debilitating disease



**Figure 77-6** Rapid reaction of the adrenal cortex of a rat to stress caused by fracture of the tibia and fibula at time zero. (In the rat, corticosterone is secreted in place of cortisol.) (Courtesy Drs. Guillemin, Dear, and Lipscomb.)

Even though we know that cortisol secretion often increases greatly in stressful situations, we are not sure why this is of significant benefit to the animal. One possibility is that the glucocorticoids cause rapid mobilization of amino acids and fats from their cellular stores, making them immediately available both for energy and for synthesis of other compounds, including glucose, needed by the different tissues of the body. Indeed, it has been shown in a few instances that damaged tissues that are momentarily depleted of proteins can use the newly available amino acids to form new proteins that are essential to the lives of the cells. Also, the amino acids are perhaps used to synthesize other essential intracellular substances, such as purines, pyrimidines, and creatine phosphate, which are necessary for maintenance of cellular life and reproduction of new cells.

But all this is mainly supposition. It is supported only by the fact that cortisol usually does not mobilize the basic functional proteins of the cells, such as the muscle contractile proteins and the proteins of neurons, until almost all other proteins have been released. This preferential effect of cortisol in mobilizing labile proteins could make amino acids available to needy cells to synthesize substances essential to life.

### Anti-Inflammatory Effects of High Levels of Cortisol

When tissues are damaged by trauma, by infection with bacteria, or in other ways, they almost always become "inflamed." In some conditions, such as in rheumatoid arthritis, the inflammation is more damaging than the trauma or disease itself. The administration of large amounts of cortisol can usually block this inflammation or even reverse many of its effects once it has begun. Before attempting to explain the way in which cortisol

functions to block inflammation, let us review the basic steps in the inflammation process, discussed in more detail in Chapter 33.

Five main stages of inflammation occur: (1) release from the damaged tissue cells of chemical substances that activate the inflammation process—chemicals such as histamine, bradykinin, proteolytic enzymes, prostaglandins, and leukotrienes; (2) an increase in blood flow in the inflamed area caused by some of the released products from the tissues, an effect called *erythema*; (3) leakage of large quantities of almost pure plasma out of the capillaries into the damaged areas because of increased capillary permeability, followed by clotting of the tissue fluid, thus causing a *nonpitting type of edema*; (4) infiltration of the area by leukocytes; and (5) after days or weeks, ingrowth of fibrous tissue that often helps in the healing process.

When large amounts of cortisol are secreted or injected into a person, the cortisol has two basic *anti-inflammatory effects*: (1) it can block the early stages of the inflammation process before inflammation even begins, or (2) if inflammation has already begun, it causes rapid resolution of the inflammation and increased rapidity of healing. These effects are explained further as follows.

**Cortisol Prevents the Development of Inflammation by Stabilizing Lysosomes and by Other Effects.** Cortisol has the following effects in preventing inflammation:

1. *Cortisol stabilizes the lysosomal membranes.* This is one of its most important anti-inflammatory effects because it is much more difficult than normal for the membranes of the intracellular lysosomes to rupture. Therefore, most of the proteolytic enzymes that are released by damaged cells to cause inflammation, which are mainly stored in the lysosomes, are released in greatly decreased quantity.
2. *Cortisol decreases the permeability of the capillaries,* probably as a secondary effect of the reduced release of proteolytic enzymes. This prevents loss of plasma into the tissues.
3. *Cortisol decreases both migration of white blood cells into the inflamed area and phagocytosis of the damaged cells.* These effects probably result from the fact that cortisol diminishes the formation of prostaglandins and leukotrienes that otherwise would increase vasodilation, capillary permeability, and mobility of white blood cells.
4. *Cortisol suppresses the immune system, causing lymphocyte reproduction to decrease markedly.* The T lymphocytes are especially suppressed. In turn, reduced amounts of T cells and antibodies in the inflamed area lessen the tissue reactions that would otherwise promote the inflammation process.
5. *Cortisol attenuates fever mainly because it reduces the release of interleukin-1 from the white blood cells,* which is one of the principal excitants to the hypothalamic temperature control system. The decreased temperature in turn reduces the degree of vasodilation.



Thus, cortisol has an almost global effect in reducing all aspects of the inflammatory process. How much of this results from the simple effect of cortisol in stabilizing lysosomal and cell membranes versus its effect to reduce the formation of prostaglandins and leukotrienes from arachidonic acid in damaged cell membranes and other effects of cortisol is unclear.

**Cortisol Causes Resolution of Inflammation.** Even after inflammation has become well established, the administration of cortisol can often reduce inflammation within hours to a few days. The immediate effect is to block most of the factors that promote the inflammation. But in addition, the rate of healing is enhanced. This probably results from the same, mainly undefined, factors that allow the body to resist many other types of physical stress when large quantities of cortisol are secreted. Perhaps this results from the mobilization of amino acids and use of these to repair the damaged tissues; perhaps it results from the increased glucogenesis that makes extra glucose available in critical metabolic systems; perhaps it results from increased amounts of fatty acids available for cellular energy; or perhaps it depends on some effect of cortisol for inactivating or removing inflammatory products.

Regardless of the precise mechanisms by which the anti-inflammatory effect occurs, this effect of cortisol plays a major role in combating certain types of diseases, such as rheumatoid arthritis, rheumatic fever, and acute glomerulonephritis. All these diseases are characterized by severe local inflammation, and the harmful effects on the body are caused mainly by the inflammation itself and not by other aspects of the disease.

When cortisol or other glucocorticoids are administered to patients with these diseases, almost invariably the inflammation begins to subside within 24 hours. And even though the cortisol does not correct the basic disease condition, merely preventing the damaging effects of the inflammatory response, this alone can often be a lifesaving measure.

#### Other Effects of Cortisol

**Cortisol Blocks the Inflammatory Response to Allergic Reactions.** The basic allergic reaction between antigen and antibody is not affected by cortisol, and even some of the secondary effects of the allergic reaction still occur. However, because the inflammatory response is responsible for many of the serious and sometimes lethal effects of allergic reactions, administration of cortisol, followed by its effect in reducing inflammation and the release of inflammatory products, can be lifesaving. For instance, cortisol effectively prevents shock or death in anaphylaxis, which otherwise kills many people, as explained in Chapter 34.

**Effect on Blood Cells and on Immunity in Infectious Diseases.** Cortisol decreases the number of eosinophils and lymphocytes in the blood; this effect begins within a few minutes after the injection of cortisol and becomes marked within a few hours. Indeed, a finding of lymphocytopenia or eosinopenia is an important diagnostic criterion for overproduction of cortisol by the adrenal gland.

Likewise, the administration of large doses of cortisol causes significant atrophy of all the lymphoid tissue throughout the body, which in turn decreases the output of both T cells and antibodies from the lymphoid tissue. As a result, the level of immunity for almost all foreign invaders of the body is decreased. This occasionally can lead to fulminating infection and death from diseases that would otherwise not be lethal, such as fulminating tuberculosis in a person whose disease had previously been arrested. Conversely, this ability of cortisol and other glucocorticoids to suppress immunity makes them useful drugs in preventing immunological rejection of transplanted hearts, kidneys, and other tissues.

Cortisol increases the production of red blood cells by mechanisms that are unclear. When excess cortisol is secreted by the adrenal glands, polycythemia often results, and conversely, when the adrenal glands secrete no cortisol, anemia often results.

#### Cellular Mechanism of Cortisol Action

Cortisol, like other steroid hormones, exerts its effects by first interacting with intracellular receptors in target cells. Because cortisol is lipid soluble, it can easily diffuse through the cell membrane. Once inside the cell, cortisol binds with its protein receptor in the cytoplasm, and the hormone-receptor complex then interacts with specific regulatory DNA sequences, called *glucocorticoid response elements*, to induce or repress gene transcription. Other proteins in the cell, called *transcription factors*, are also necessary for the hormone-receptor complex to interact appropriately with the glucocorticoid response elements.

Glucocorticoids increase or decrease transcription of many genes to alter synthesis of mRNA for the proteins that mediate their multiple physiological effects. Thus, most of the metabolic effects of cortisol are not immediate but require 45 to 60 minutes for proteins to be synthesized, and up to several hours or days to fully develop. Recent evidence suggests that glucocorticoids, especially at high concentrations, may also have some rapid *nongenomic effects* on cell membrane ion transport that may contribute to their therapeutic benefits.

### Regulation of Cortisol Secretion by Adrenocorticotrophic Hormone from the Pituitary Gland

**ACTH Stimulates Cortisol Secretion.** Unlike aldosterone secretion by the zona glomerulosa, which is controlled mainly by potassium and angiotensin acting directly on the adrenocortical cells, secretion of cortisol is controlled almost entirely by ACTH secreted by the anterior pituitary gland. This hormone, also called *corticotropin* or *adrenocorticotropin*, also enhances the production of adrenal androgens.

**Chemistry of ACTH.** ACTH has been isolated in pure form from the anterior pituitary. It is a large polypeptide, having a chain length of 39 amino acids. A smaller polypeptide, a digested product of ACTH having a chain length of 24 amino acids, has all the effects of the total molecule.

**ACTH Secretion Is Controlled by Corticotropin-Releasing Factor from the Hypothalamus.** In the same way that other pituitary hormones are controlled by releasing

factors from the hypothalamus, an important releasing factor also controls ACTH secretion. This is called *corticotropin-releasing factor* (CRF). It is secreted into the primary capillary plexus of the hypophyseal portal system in the median eminence of the hypothalamus and then carried to the anterior pituitary gland, where it induces ACTH secretion. CRF is a peptide composed of 41 amino acids. The cell bodies of the neurons that secrete CRF are located mainly in the paraventricular nucleus of the hypothalamus. This nucleus in turn receives many nervous connections from the limbic system and lower brain stem.

The anterior pituitary gland can secrete only minute quantities of ACTH in the absence of CRF. Instead, most conditions that cause high ACTH secretory rates initiate this secretion by signals that begin in the basal regions of the brain, including the hypothalamus, and are then transmitted by CRF to the anterior pituitary gland.

**ACTH Activates Adrenocortical Cells to Produce Steroids by Increasing Cyclic Adenosine Monophosphate (cAMP).** The principal effect of ACTH on the adrenocortical cells is to activate *adenylyl cyclase* in the cell membrane. This then induces the formation of *cAMP* in the cell cytoplasm, reaching its maximal effect in about 3 minutes. The cAMP in turn activates the intracellular enzymes that cause formation of the adrenocortical hormones. This is another example of cAMP as a *second messenger* signal system.

The most important of all the ACTH-stimulated steps for controlling adrenocortical secretion is activation of the enzyme *protein kinase A*, which *causes initial conversion of cholesterol to pregnenolone*. This initial conversion is the “rate-limiting” step for all the adrenocortical hormones, which explains why ACTH is normally necessary for any

adrenocortical hormones to be formed. Long-term stimulation of the adrenal cortex by ACTH not only increases secretory activity but also causes hypertrophy and proliferation of the adrenocortical cells, especially in the zona fasciculata and zona reticularis, where cortisol and the androgens are secreted.

### Physiological Stress Increases ACTH and Adrenocortical Secretion

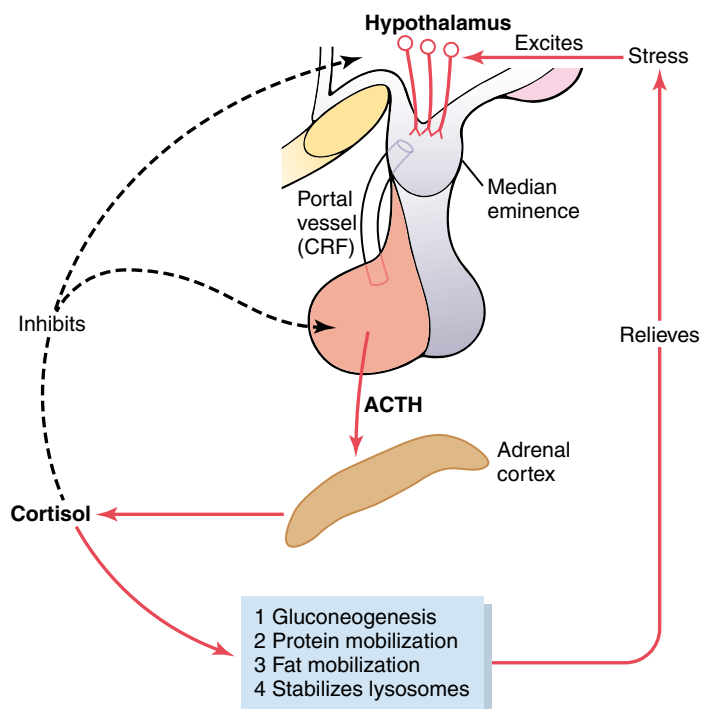
As pointed out earlier in the chapter, almost any type of physical or mental stress can lead within minutes to greatly enhanced secretion of ACTH and consequently cortisol as well, often increasing cortisol secretion as much as 20-fold. This effect was demonstrated by the rapid and strong adrenocortical secretory responses after trauma shown in Figure 77-6.

Pain stimuli caused by physical stress or tissue damage are transmitted first upward through the brain stem and eventually to the median eminence of the hypothalamus, as shown in Figure 77-7. Here CRF is secreted into the hypophyseal portal system. Within minutes the entire control sequence leads to large quantities of cortisol in the blood.

Mental stress can cause an equally rapid increase in ACTH secretion. This is believed to result from increased activity in the limbic system, especially in the region of the amygdala and hippocampus, both of which then transmit signals to the posterior medial hypothalamus.

**Inhibitory Effect of Cortisol on the Hypothalamus and on the Anterior Pituitary to Decrease ACTH Secretion.** Cortisol has direct negative feedback effects on (1) the hypothalamus to decrease the formation of CRF and (2) the anterior pituitary gland to decrease the formation of ACTH. Both of these feedbacks help regulate

**Figure 77-7** Mechanism for regulation of glucocorticoid secretion. ACTH, adrenocorticotrophic hormone; CRF, corticotropin-releasing factor.

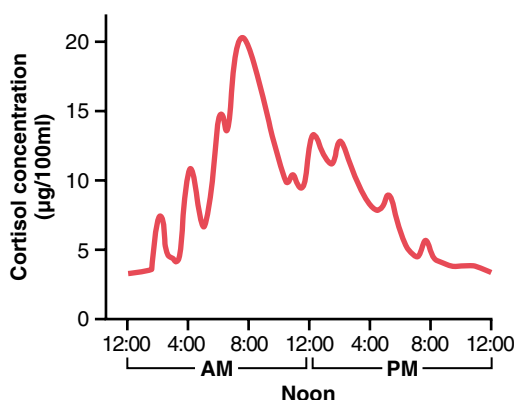


the plasma concentration of cortisol. That is, whenever the cortisol concentration becomes too great, the feedbacks automatically reduce the ACTH toward a normal control level.

### Summary of the Cortisol Control System

Figure 77-7 shows the overall system for control of cortisol secretion. The key to this control is the excitation of the hypothalamus by different types of stress. Stress stimuli activate the entire system to cause rapid release of cortisol, and the cortisol in turn initiates a series of metabolic effects directed toward relieving the damaging nature of the stressful state.

There is also direct feedback of the cortisol to both the hypothalamus and the anterior pituitary gland to decrease the concentration of cortisol in the plasma at times when the body is not experiencing stress. However, the stress stimuli are the prepotent ones; they can always break through this direct inhibitory feedback of cortisol, causing either periodic exacerbations of cortisol secretion at multiple times during the day (Figure 77-8) or prolonged cortisol secretion in times of chronic stress.



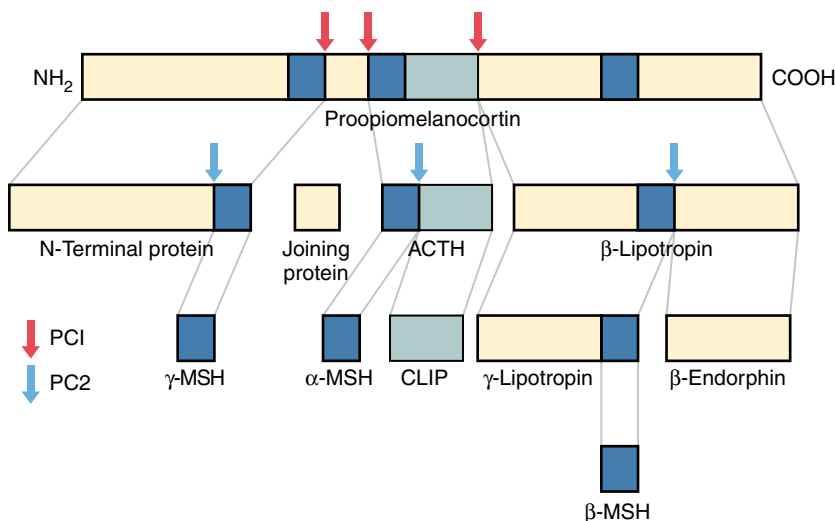
**Figure 77-8** Typical pattern of cortisol concentration during the day. Note the oscillations in secretion as well as a daily secretory surge an hour or so after awaking in the morning.

**Circadian Rhythm of Glucocorticoid Secretion.** The secretory rates of CRF, ACTH, and cortisol are high in the early morning but low in the late evening, as shown in Figure 77-8; the plasma cortisol level ranges between a high of about 20 µg/dl an hour before arising in the morning and a low of about 5 µg/dl around midnight. This effect results from a 24-hour cyclical alteration in the signals from the hypothalamus that cause cortisol secretion. When a person changes daily sleeping habits, the cycle changes correspondingly. Therefore, measurements of blood cortisol levels are meaningful only when expressed in terms of the time in the cycle at which the measurements are made.

### Synthesis and Secretion of ACTH in Association with Melanocyte-Stimulating Hormone, Lipotropin, and Endorphin

When ACTH is secreted by the anterior pituitary gland, several other hormones that have similar chemical structures are secreted simultaneously. The reason for this is that the gene that is transcribed to form the RNA molecule that causes ACTH synthesis initially causes the formation of a considerably larger protein, a prohormone called *proopiomelanocortin* (POMC), which is the precursor of ACTH and several other peptides, including *melanocyte-stimulating hormone* (MSH), *β-lipotropin*, *β-endorphin*, and a few others (Figure 77-9). Under normal conditions, none of these hormones is secreted in enough quantity by the pituitary to have a significant effect on the human body, but when the rate of secretion of ACTH is high, as may occur in Addison's disease, formation of some of the other POMC-derived hormones may also be increased.

The POMC gene is actively transcribed in several tissues, including the corticotroph cells of the anterior pituitary, POMC neurons in the arcuate nucleus of the hypothalamus, cells of the dermis, and lymphoid tissue. In all of these cell types, POMC is processed to form a series of smaller peptides. The precise type of POMC-derived products from a particular tissue depends on the type of processing enzymes present in the tissue. Thus, pituitary corticotroph cells express *prohormone convertase 1* (PC1),



**Figure 77-9** Proopiomelanocortin (POMC) processing by prohormone convertase 1 (PC1, red arrows) and PC 2 (blue arrows). Tissue-specific expression of these two enzymes results in different peptides produced in various tissues. The anterior pituitary expresses PC1, resulting in formation of N-terminal peptide, joining peptide, ACTH, and  $\beta$ -lipotropin. Expression of PC2 within the hypothalamus leads to the production of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -melanocyte stimulating hormone (MSH), but not ACTH. CLIP, corticotropin-like intermediate peptide.

but not PC2, resulting in the production of N-terminal peptide, joining peptide, ACTH, and  $\beta$ -lipotropin. In the hypothalamus, the expression of PC2 leads to the production of  $\alpha$ -,  $\beta$ -, and  $\gamma$ -MSH and  $\beta$ -endorphin but not ACTH. As discussed in Chapter 71,  $\alpha$ -MSH formed by neurons of the hypothalamus plays a major role in appetite regulation.

In *melanocytes* located in abundance between the dermis and epidermis of the skin, MSH stimulates formation of the black pigment *melanin* and disperses it to the epidermis. Injection of MSH into a person over 8 to 10 days can greatly increase darkening of the skin. The effect is much greater in people who have genetically dark skins than in light-skinned people.

In some lower animals, an intermediate “lobe” of the pituitary gland, called the *pars intermedia*, is highly developed, lying between the anterior and posterior pituitary lobes. This lobe secretes an especially large amount of MSH. Furthermore, this secretion is independently controlled by the hypothalamus in response to the amount of light to which the animal is exposed or in response to other environmental factors. For instance, some arctic animals develop darkened fur in the summer and yet have entirely white fur in the winter.

ACTH, because it contains an MSH sequence, has about 1/30 as much melanocyte-stimulating effect as MSH. Furthermore, because the quantities of pure MSH secreted in the human being are extremely small, whereas those of ACTH are large, it is likely that ACTH is normally more important than MSH in determining the amount of melanin in the skin.

### Adrenal Androgens

Several moderately active male sex hormones called *adrenal androgens* (the most important of which is *dehydroepiandrosterone*) are continually secreted by the adrenal cortex, especially during fetal life, as discussed more fully in Chapter 83. Also, progesterone and estrogens, which are female sex hormones, are secreted in minute quantities.

Normally, the adrenal androgens have only weak effects in humans. It is possible that part of the early development of the male sex organs results from childhood secretion of adrenal androgens. The adrenal androgens also exert mild effects in the female, not only before puberty but also throughout life. Much of the growth of the pubic and axillary hair in the female results from the action of these hormones.

In extra-adrenal tissues, some of the adrenal androgens are converted to testosterone, the primary male sex hormone, which probably accounts for much of their androgenic activity. The physiological effects of androgens are discussed in Chapter 80 in relation to male sexual function.

### Abnormalities of Adrenocortical Secretion

#### Hypoadrenalism (Adrenal Insufficiency)—Addison’s Disease

Addison’s disease results from an inability of the adrenal cortices to produce sufficient adrenocortical hormones, and

this in turn is most frequently caused by *primary atrophy or injury* of the adrenal cortices. In about 80 percent of the cases, the atrophy is caused by autoimmunity against the cortices. Adrenal gland hypofunction is also frequently caused by tuberculous destruction of the adrenal glands or invasion of the adrenal cortices by cancer.

In some cases, adrenal insufficiency is secondary to impaired function of the pituitary gland, which fails to produce sufficient ACTH. When ACTH output is too low, cortisol and aldosterone production decrease and eventually, the adrenal glands may atrophy due to lack of ACTH stimulation. Secondary adrenal insufficiency is much more common than Addison’s disease, which is sometimes called *primary adrenal insufficiency*. Disturbances in severe adrenal insufficiency are as follows.

**Mineralocorticoid Deficiency.** Lack of aldosterone secretion greatly decreases renal tubular sodium reabsorption and consequently allows sodium ions, chloride ions, and water to be lost into urine in great profusion. The net result is a greatly decreased extracellular fluid volume. Furthermore, hyponatremia, hyperkalemia, and mild acidosis develop because of failure of potassium and hydrogen ions to be secreted in exchange for sodium reabsorption.

As the extracellular fluid becomes depleted, plasma volume falls, red blood cell concentration rises markedly, cardiac output and blood pressure decrease, and the patient dies in shock, death usually occurring in the untreated patient 4 days to 2 weeks after complete cessation of mineralocorticoid secretion.

**Glucocorticoid Deficiency.** Loss of cortisol secretion makes it impossible for a person with Addison’s disease to maintain normal blood glucose concentration between meals because he or she cannot synthesize significant quantities of glucose by gluconeogenesis. Furthermore, lack of cortisol reduces the mobilization of both proteins and fats from the tissues, thereby depressing many other metabolic functions of the body. This sluggishness of energy mobilization when cortisol is not available is one of the major detrimental effects of glucocorticoid lack. Even when excess quantities of glucose and other nutrients are available, the person’s muscles are weak, indicating that glucocorticoids are necessary to maintain other metabolic functions of the tissues in addition to energy metabolism.

Lack of adequate glucocorticoid secretion also makes a person with Addison’s disease highly susceptible to the deteriorating effects of different types of stress, and even a mild respiratory infection can cause death.

**Melanin Pigmentation.** Another characteristic of most people with Addison’s disease is melanin pigmentation of the mucous membranes and skin. This melanin is not always deposited evenly but occasionally is deposited in blotches, and it is deposited especially in the thin skin areas, such as the mucous membranes of the lips and the thin skin of the nipples.

The cause of the melanin deposition is believed to be the following: When cortisol secretion is depressed, the normal negative feedback to the hypothalamus and anterior pituitary gland is also depressed, therefore allowing tremendous rates of ACTH secretion, as well as simultaneous secretion of increased amounts of MSH. Probably the tremendous amounts of ACTH cause most of the pigmenting effect because they can stimulate formation of melanin by the melanocytes in the same way that MSH does.



**Treatment of People with Addison's Disease.** An untreated person with total adrenal destruction dies within a few days to a few weeks because of weakness and usually circulatory shock. Yet such a person can live for years if small quantities of mineralocorticoids and glucocorticoids are administered daily.

**Addisonian Crisis.** As noted earlier in the chapter, great quantities of glucocorticoids are occasionally secreted in response to different types of physical or mental stress. In a person with Addison's disease, the output of glucocorticoids does not increase during stress. Yet whenever different types of trauma, disease, or other stresses, such as surgical operations, supervene, a person is likely to have an acute need for excessive amounts of glucocorticoids and often must be given 10 or more times the normal quantities of glucocorticoids to prevent death.

This critical need for extra glucocorticoids and the associated severe debility in times of stress is called an *addisonian crisis*.

### Hyperadrenalism—Cushing's Syndrome

Hypersecretion by the adrenal cortex causes a complex cascade of hormone effects called *Cushing's syndrome*. Many of the abnormalities of Cushing's syndrome are ascribable to abnormal amounts of cortisol, but excess secretion of androgens may also cause important effects. Hypercortisolism can occur from multiple causes, including (1) adenomas of the anterior pituitary that secrete large amounts of ACTH, which then causes adrenal hyperplasia and excess cortisol secretion; (2) abnormal function of the hypothalamus that causes high levels of corticotropin-releasing hormone (CRH), which stimulates excess ACTH release; (3) "ectopic secretion" of ACTH by a tumor elsewhere in the body, such as an abdominal carcinoma; and (4) adenomas of the adrenal cortex. When Cushing's syndrome is secondary to excess secretion of ACTH by the anterior pituitary, this is referred to as *Cushing's disease*.

Excess ACTH secretion is the most common cause of Cushing's syndrome and is characterized by high plasma levels of ACTH and cortisol. Primary overproduction of cortisol

by the adrenal glands accounts for about 20 to 25 percent of clinical cases of Cushing's syndrome and is usually associated with reduced ACTH levels due to cortisol feedback inhibition of ACTH secretion by the anterior pituitary gland.

Administration of large doses of dexamethasone, a synthetic glucocorticoid, can be used to distinguish between *ACTH-dependent* and *ACTH-independent* Cushing's syndrome. In patients who have overproduction of ACTH due to an ACTH-secreting pituitary adenoma or to hypothalamic-pituitary dysfunction, even large doses of dexamethasone usually do not suppress ACTH secretion. In contrast, patients with primary adrenal overproduction of cortisol (ACTH-independent) usually have low or undetectable levels of ACTH. The dexamethasone test, although widely used, can sometimes give an incorrect diagnosis because some ACTH-secreting pituitary tumors respond to dexamethasone with suppressed ACTH secretion. Therefore, it is usually considered to be a first step in the differential diagnosis of Cushing's syndrome.

Cushing's syndrome can also occur when large amounts of glucocorticoids are administered over prolonged periods for therapeutic purposes. For example, patients with chronic inflammation associated with diseases such as rheumatoid arthritis are often treated with glucocorticoids and may develop some of the clinical symptoms of Cushing's syndrome.

A special characteristic of Cushing's syndrome is mobilization of fat from the lower part of the body, with concomitant extra deposition of fat in the thoracic and upper abdominal regions, giving rise to a buffalo torso. The excess secretion of steroids also leads to an edematous appearance of the face, and the androgenic potency of some of the hormones sometimes causes acne and hirsutism (excess growth of facial hair). The appearance of the face is frequently described as a "moon face," as demonstrated in the untreated patient with Cushing's syndrome to the left in Figure 77-10. About 80 percent of patients have hypertension, presumably because of the mineralocorticoid effects of cortisol.

**Effects on Carbohydrate and Protein Metabolism.** The abundance of cortisol secreted in Cushing's syndrome can cause increased blood glucose concentration, sometimes to



**Figure 77-10** A person with Cushing's syndrome before (*left*) and after (*right*) subtotal adrenalectomy. (Courtesy Dr. Leonard Posey.)

values as high as 200 mg/dl after meals—as much as twice normal. This results mainly from enhanced gluconeogenesis and decreased glucose utilization by the tissues.

The effects of glucocorticoids on protein catabolism are often profound in Cushing's syndrome, causing greatly decreased tissue proteins almost everywhere in the body with the exception of the liver; the plasma proteins also remain unaffected. The loss of protein from the muscles in particular causes severe weakness. The loss of protein synthesis in the lymphoid tissues leads to a suppressed immune system, so many of these patients die of infections. Even the protein collagen fibers in the subcutaneous tissue are diminished so that the subcutaneous tissues tear easily, resulting in development of large *purplish striae* where they have torn apart. In addition, severely diminished protein deposition in the bones often causes severe *osteoporosis* with consequent weakness of the bones.

**Treatment of Cushing's Syndrome.** Treatment of Cushing's syndrome consists of removing an adrenal tumor if this is the cause or decreasing the secretion of ACTH, if this is possible. Hypertrophied pituitary glands or even small tumors in the pituitary that oversecrete ACTH can sometimes be surgically removed or destroyed by radiation. Drugs that block steroidogenesis, such as *metirapone*, *ketoconazole*, and *aminoglutethimide*, or that inhibit ACTH secretion, such as *serotonin antagonists* and *GABA-transaminase inhibitors*, can also be used when surgery is not feasible. If ACTH secretion cannot easily be decreased, the only satisfactory treatment is usually bilateral partial (or even total) adrenalectomy, followed by administration of adrenal steroids to make up for any insufficiency that develops.

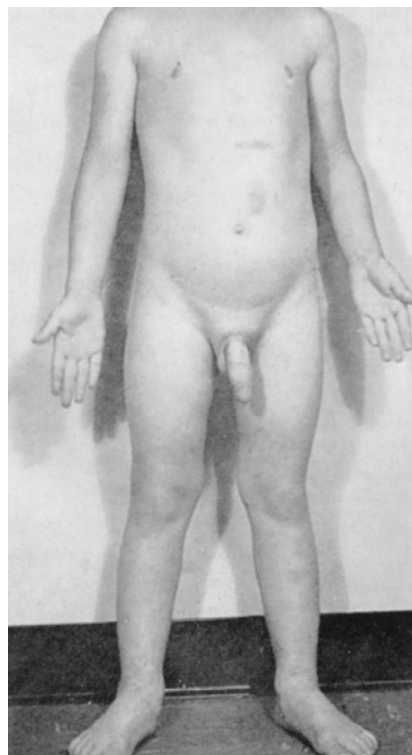
### Primary Aldosteronism (Conn's Syndrome)

Occasionally a small tumor of the zona glomerulosa cells occurs and secretes large amounts of aldosterone; the resulting condition is called "primary aldosteronism" or "Conn's syndrome." Also, in a few instances, hyperplastic adrenal cortices secrete aldosterone rather than cortisol. The effects of the excess aldosterone are discussed in detail earlier in the chapter. The most important effects are hypokalemia, mild metabolic alkalosis, slight increase in extracellular fluid volume and blood volume, very slight increase in plasma sodium concentration (usually  $> 4$  to  $6$  mEq/L increase), and, almost always, hypertension. Especially interesting in primary aldosteronism are occasional periods of muscle paralysis caused by the hypokalemia. The paralysis is caused by a depressant effect of low extracellular potassium concentration on action potential transmission by the nerve fibers, as explained in Chapter 5.

One of the diagnostic criteria of primary aldosteronism is a decreased plasma renin concentration. This results from feedback suppression of renin secretion caused by the excess aldosterone or by the excess extracellular fluid volume and arterial pressure resulting from the aldosteronism. Treatment of primary aldosteronism may include surgical removal of the tumor or of most of the adrenal tissue when hyperplasia is the cause. Another option for treatment is pharmacological antagonism of the mineralocorticoid receptor with spironolactone or eplerenone.

### Adrenogenital Syndrome

An occasional adrenocortical tumor secretes excessive quantities of androgens that cause intense masculinizing effects



**Figure 77-11** Adrenogenital syndrome in a 4-year-old boy. (Courtesy Dr. Leonard Posey.)

throughout the body. If this occurs in a female, she develops virile characteristics, including growth of a beard, a much deeper voice, occasionally baldness if she also has the genetic trait for baldness, masculine distribution of hair on the body and the pubis, growth of the clitoris to resemble a penis, and deposition of proteins in the skin and especially in the muscles to give typical masculine characteristics.

In the prepubertal male, a virilizing adrenal tumor causes the same characteristics as in the female plus rapid development of the male sexual organs, as shown in Figure 77-11, which depicts a 4-year-old boy with adrenogenital syndrome. In the adult male, the virilizing characteristics of adrenogenital syndrome are usually obscured by the normal virilizing characteristics of the testosterone secreted by the testes. It is often difficult to make a diagnosis of adrenogenital syndrome in the adult male. In adrenogenital syndrome, the excretion of 17-ketosteroids (which are derived from androgens) in the urine may be 10 to 15 times normal. This finding can be used in diagnosing the disease.

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# Insulin, Glucagon, and Diabetes Mellitus



The pancreas, in addition to its digestive functions, secretes two important hormones, *insulin* and *glucagon*, that are crucial for normal regulation of glucose, lipid, and protein

metabolism. Although the pancreas secretes other hormones, such as *amylin*, *somatostatin*, and *pancreatic polypeptide*, their functions are not as well established. The main purpose of this chapter is to discuss the physiological roles of insulin and glucagon and the pathophysiology of diseases, especially *diabetes mellitus*, caused by abnormal secretion or activity of these hormones.

**Physiologic Anatomy of the Pancreas.** The pancreas is composed of two major types of tissues, as shown in Figure 78-1: (1) the *acini*, which secrete digestive juices into the duodenum, and (2) the *islets of Langerhans*, which secrete insulin and glucagon directly into the blood. The digestive secretions of the pancreas are discussed in Chapter 64.

The human pancreas has 1 to 2 million islets of Langerhans, each only about 0.3 millimeter in diameter and organized around small capillaries into which its cells secrete their hormones. The islets contain three major types of cells, *alpha*, *beta*, and *delta* cells, which are distinguished from one another by their morphological and staining characteristics.

The beta cells, constituting about 60 percent of all the cells of the islets, lie mainly in the middle of each islet and secrete *insulin* and *amylin*, a hormone that is often secreted in parallel with insulin, although its function is unclear. The alpha cells, about 25 percent of the total, secrete *glucagon*. And the delta cells, about 10 percent of the total, secrete *somatostatin*. In addition, at least one other type of cell, the *PP cell*, is present in small numbers in the islets and secretes a hormone of uncertain function called *pancreatic polypeptide*.

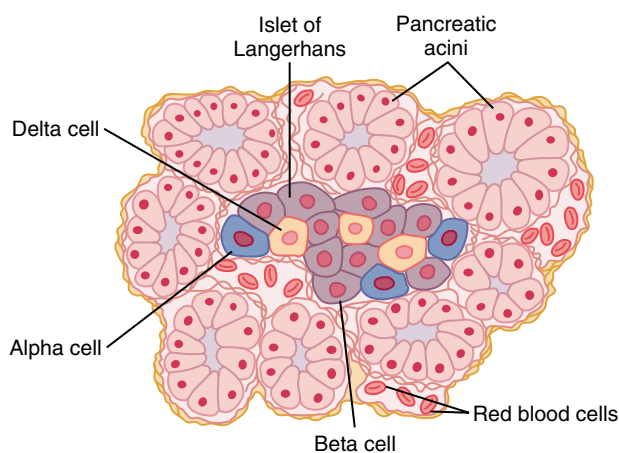
The close interrelations among these cell types in the islets of Langerhans allow cell-to-cell communication and direct control of secretion of some of the hormones by the other hormones. For instance, insulin inhibits glucagon secretion, amylin inhibits insulin secretion, and somatostatin inhibits the secretion of both insulin and glucagon.

## Insulin and Its Metabolic Effects

Insulin was first isolated from the pancreas in 1922 by Banting and Best, and almost overnight the outlook for the severely diabetic patient changed from one of rapid decline and death to that of a nearly normal person. Historically, insulin has been associated with “blood sugar,” and true enough, insulin has profound effects on carbohydrate metabolism. Yet it is abnormalities of fat metabolism, causing such conditions as acidosis and arteriosclerosis, that are the usual causes of death in diabetic patients. Also, in patients with prolonged diabetes, diminished ability to synthesize proteins leads to wasting of the tissues and many cellular functional disorders. Therefore, it is clear that insulin affects fat and protein metabolism almost as much as it does carbohydrate metabolism.

## Insulin Is a Hormone Associated with Energy Abundance

As we discuss insulin in the next few pages, it will become apparent that insulin secretion is associated with energy abundance. That is, when there is great abundance of energy-giving foods in the diet, especially excess amounts of carbohydrates, insulin secretion increases. In turn, the insulin plays an important role in storing the excess



**Figure 78-1** Physiologic anatomy of an islet of Langerhans in the pancreas.

energy. In the case of excess carbohydrates, it causes them to be stored as glycogen mainly in the liver and muscles. Also, all the excess carbohydrates that cannot be stored as glycogen are converted under the stimulus of insulin into fats and stored in the adipose tissue. In the case of proteins, insulin has a direct effect in promoting amino acid uptake by cells and conversion of these amino acids into protein. In addition, it inhibits the breakdown of the proteins that are already in the cells.

### Insulin Chemistry and Synthesis

Insulin is a small protein; human insulin has a molecular weight of 5808. It is composed of two amino acid chains, shown in Figure 78-2, connected to each other by disulfide linkages. When the two amino acid chains are split apart, the functional activity of the insulin molecule is lost.

Insulin is synthesized in the beta cells by the usual cell machinery for protein synthesis, as explained in Chapter 3, beginning with translation of the insulin RNA by ribosomes attached to the endoplasmic reticulum to form *preproinsulin*. This initial preproinsulin has a molecular weight of about 11,500, but it is then cleaved in the endoplasmic reticulum to form a *proinsulin* with a molecular weight of about 9000 and consisting of three

chains of peptides, A, B, and C. Most of the proinsulin is further cleaved in the Golgi apparatus to form insulin, composed of the A and B chain connected by disulfide linkages, and the C chain peptide, called *connecting peptide* (*C peptide*). The insulin and C peptide are packaged in the secretory granules and secreted in equimolar amounts. About 5 to 10 percent of the final secreted product is still in the form of proinsulin.

The proinsulin and C peptide have virtually no insulin activity. However, C peptide binds to a membrane structure, most likely a G protein-coupled membrane receptor, and elicits activation of at least two enzyme systems, sodium-potassium ATPase and endothelial nitric oxide synthase. Although both of these enzymes have multiple physiological functions, the importance of C peptide in regulating these enzymes is still uncertain.

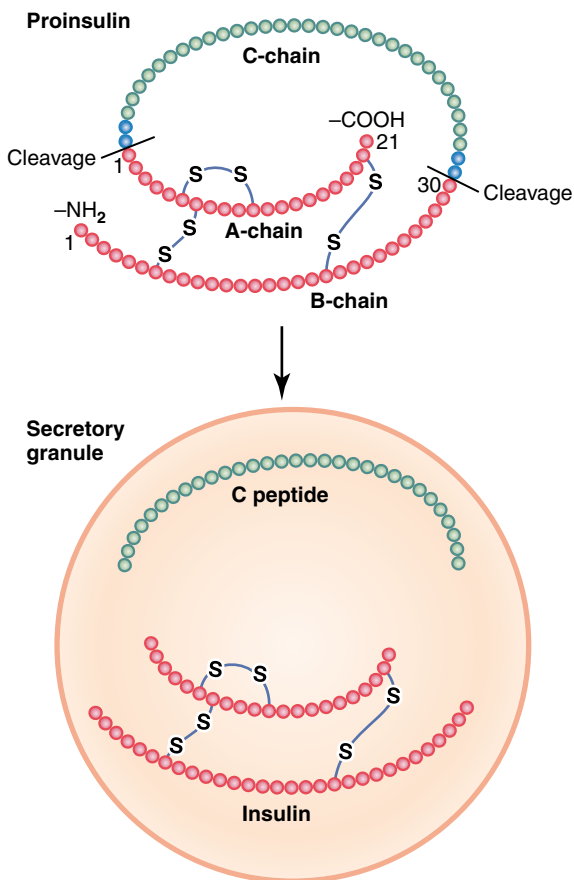
Measurement of C peptide levels by radioimmunoassay can be used in insulin-treated diabetic patients to determine how much of their own natural insulin they are still producing. Patients with type 1 diabetes who are unable to produce insulin will usually have greatly decreased levels of C peptide.

When insulin is secreted into the blood, it circulates almost entirely in an unbound form; it has a plasma half-life that averages only about 6 minutes, so it is mainly cleared from the circulation within 10 to 15 minutes. Except for that portion of the insulin that combines with receptors in the target cells, the remainder is degraded by the enzyme *insulinase* mainly in the liver, to a lesser extent in the kidneys and muscles, and slightly in most other tissues. This rapid removal from the plasma is important because, at times, it is as important to turn off rapidly as to turn on the control functions of insulin.

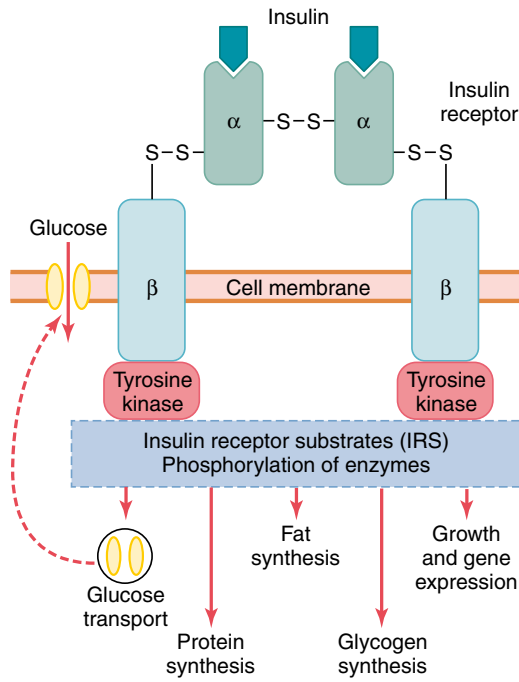
### Activation of Target Cell Receptors by Insulin and the Resulting Cellular Effects

To initiate its effects on target cells, insulin first binds with and activates a membrane receptor protein that has a molecular weight of about 300,000 (Figure 78-3). It is the activated receptor that causes the subsequent effects.

The insulin receptor is a combination of four subunits held together by disulfide linkages: *two alpha subunits* that lie entirely outside the cell membrane and *two beta subunits* that penetrate through the membrane, protruding into the cell cytoplasm. The insulin binds with the alpha subunits on the outside of the cell, but because of the linkages with the beta subunits, the portions of the beta subunits protruding into the cell become autophosphorylated. Thus, the insulin receptor is an example of an *enzyme-linked receptor*, discussed in Chapter 74. Autophosphorylation of the beta subunits of the receptor activates a local *tyrosine kinase*, which in turn causes phosphorylation of multiple other intracellular enzymes including a group called *insulin-receptor substrates (IRS)*. Different types of IRS (e.g., IRS-1, IRS-2, IRS-3) are expressed in different tissues. The net effect is to activate some of these enzymes while inactivating others. In this



**Figure 78-2** Schematic of the human proinsulin molecule, which is cleaved in the Golgi apparatus of the pancreatic beta cells to form connecting peptide (C peptide), and insulin, which is composed of the A and B chains connected by disulfide bonds. The C peptide and insulin are packaged in granules and secreted in equimolar amounts, along with a small amount of proinsulin.



**Figure 78-3** Schematic of the insulin receptor. Insulin binds to the  $\alpha$ -subunit of its receptor, which causes autophosphorylation of the  $\beta$ -subunit receptor, which in turn induces tyrosine kinase activity. The receptor tyrosine kinase activity begins a cascade of cell phosphorylation that increases or decreases the activity of enzymes, including insulin receptor substrates, that mediate the effects on glucose, fat, and protein metabolism. For example, glucose transporters are moved to the cell membrane to assist glucose entry into the cell.

way, insulin directs the intracellular metabolic machinery to produce the desired effects on carbohydrate, fat, and protein metabolism. The end effects of insulin stimulation are the following:

1. Within seconds after insulin binds with its membrane receptors, the membranes of about 80 percent of the body's cells markedly increase their uptake of glucose. This is especially true of muscle cells and adipose cells but *is not true of most neurons in the brain*. The increased glucose transported into the cells is immediately phosphorylated and becomes a substrate for all the usual carbohydrate metabolic functions. The increased glucose transport is believed to result from translocation of multiple intracellular vesicles to the cell membranes; these vesicles carry multiple molecules of glucose transport proteins, which bind with the cell membrane and facilitate glucose uptake into the cells. When insulin is no longer available, these vesicles separate from the cell membrane within about 3 to 5 minutes and move back to the cell interior to be used again and again as needed.
2. The cell membrane becomes more permeable to many of the amino acids, potassium ions, and phosphate ions, causing increased transport of these substances into the cell.
3. Slower effects occur during the next 10 to 15 minutes to change the activity levels of many more intracellular metabolic enzymes. These effects result mainly from the changed states of phosphorylation of the enzymes.

4. Much slower effects continue to occur for hours and even several days. They result from changed rates of translation of messenger RNAs at the ribosomes to form new proteins and still slower effects from changed rates of transcription of DNA in the cell nucleus. In this way, insulin remolds much of the cellular enzymatic machinery to achieve its metabolic goals.

### Effect of Insulin on Carbohydrate Metabolism

Immediately after a high-carbohydrate meal, the glucose that is absorbed into the blood causes rapid secretion of insulin, which is discussed in detail later in the chapter. The insulin in turn causes rapid uptake, storage, and use of glucose by almost all tissues of the body, but especially by the muscles, adipose tissue, and liver.

### Insulin Promotes Muscle Glucose Uptake and Metabolism

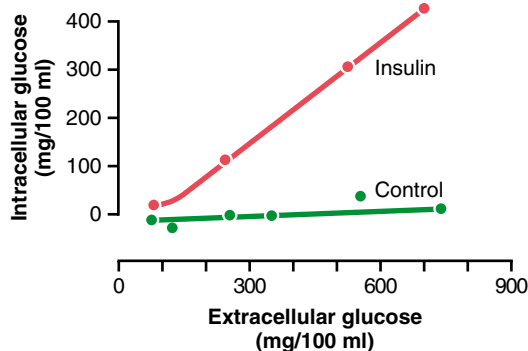
During much of the day, muscle tissue depends not on glucose for its energy but on fatty acids. The principal reason for this is that the normal *resting muscle* membrane is only slightly permeable to glucose, except when the muscle fiber is stimulated by insulin; between meals, the amount of insulin that is secreted is too small to promote significant amounts of glucose entry into the muscle cells.

However, under two conditions the muscles do use large amounts of glucose. One of these is during moderate or heavy exercise. This usage of glucose does not require large amounts of insulin because exercising muscle fibers become more permeable to glucose even in the absence of insulin because of the contraction process itself.

The second condition for muscle usage of large amounts of glucose is during the few hours after a meal. At this time the blood glucose concentration is high and the pancreas is secreting large quantities of insulin. The extra insulin causes rapid transport of glucose into the muscle cells. This causes the muscle cell during this period to use glucose preferentially over fatty acids, as discussed later.

**Storage of Glycogen in Muscle.** If the muscles are not exercising after a meal and yet glucose is transported into the muscle cells in abundance, then most of the glucose is stored in the form of muscle glycogen instead of being used for energy, up to a limit of 2 to 3 percent concentration. The glycogen can later be used for energy by the muscle. It is especially useful for short periods of extreme energy use by the muscles and even to provide spurts of anaerobic energy for a few minutes at a time by glycolytic breakdown of the glycogen to lactic acid, which can occur even in the absence of oxygen.

**Quantitative Effect of Insulin to Assist Glucose Transport through the Muscle Cell Membrane.** The quantitative effect of insulin to facilitate glucose transport through the muscle cell membrane is demonstrated by the experimental results shown in Figure 78-4. The lower curve labeled "control" shows the concentration of free glucose measured inside the cell, demonstrating that the glucose concentration remained almost zero despite



**Figure 78-4** Effect of insulin in enhancing the concentration of glucose inside muscle cells. Note that in the absence of insulin (control), the intracellular glucose concentration remains near zero, despite high extracellular glucose concentrations. (Data from Eisenstein AB: *The Biochemical Aspects of Hormone Action*. Boston: Little, Brown, 1964.)

increased extracellular glucose concentration up to as high as 750 mg/100 ml. In contrast, the curve labeled “insulin” demonstrates that the intracellular glucose concentration rose to as high as 400 mg/100 ml when insulin was added. Thus, it is clear that insulin can increase the rate of transport of glucose into the resting muscle cell by at least 15-fold.

### Insulin Promotes Liver Uptake, Storage, and Use of Glucose

One of the most important of all the effects of insulin is to cause most of the glucose absorbed after a meal to be stored almost immediately in the liver in the form of glycogen. Then, between meals, when food is not available and the blood glucose concentration begins to fall, insulin secretion decreases rapidly and the liver glycogen is split back into glucose, which is released back into the blood to keep the glucose concentration from falling too low.

The mechanism by which insulin causes glucose uptake and storage in the liver includes several almost simultaneous steps:

1. Insulin *inactivates liver phosphorylase*, the principal enzyme that causes liver glycogen to split into glucose. This prevents breakdown of the glycogen that has been stored in the liver cells.
2. Insulin causes *enhanced uptake of glucose* from the blood by the liver cells. It does this by *increasing the activity of the enzyme glucokinase*, which is one of the enzymes that causes the initial phosphorylation of glucose after it diffuses into the liver cells. Once phosphorylated, the glucose is *temporarily* trapped inside the liver cells because phosphorylated glucose cannot diffuse back through the cell membrane.
3. Insulin also increases the activities of the enzymes that promote glycogen synthesis, including especially *glycogen synthase*, which is responsible for polymerization of the monosaccharide units to form the glycogen molecules.

The net effect of all these actions is to increase the amount of glycogen in the liver. The glycogen can increase to a total of about 5 to 6 percent of the liver mass, which is equivalent to almost 100 grams of stored glycogen in the whole liver.

**Glucose Is Released from the Liver Between Meals.** When the blood glucose level begins to fall to a low level between meals, several events transpire that cause the liver to release glucose back into the circulating blood:

1. The decreasing blood glucose causes the pancreas to decrease its insulin secretion.
2. The lack of insulin then reverses all the effects listed earlier for glycogen storage, essentially stopping further synthesis of glycogen in the liver and preventing further uptake of glucose by the liver from the blood.
3. The lack of insulin (along with increase of glucagon, which is discussed later) activates the enzyme *phosphorylase*, which causes the splitting of glycogen into *glucose phosphate*.
4. The enzyme *glucose phosphatase*, which had been inhibited by insulin, now becomes activated by the insulin lack and causes the phosphate radical to split away from the glucose; this allows the free glucose to diffuse back into the blood.

Thus, the liver removes glucose from the blood when it is present in excess after a meal and returns it to the blood when the blood glucose concentration falls between meals. Ordinarily, about 60 percent of the glucose in the meal is stored in this way in the liver and then returned later.

**Insulin Promotes Conversion of Excess Glucose into Fatty Acids and Inhibits Gluconeogenesis in the Liver.** When the quantity of glucose entering the liver cells is more than can be stored as glycogen or can be used for local hepatocyte metabolism, *insulin promotes the conversion of all this excess glucose into fatty acids*. These fatty acids are subsequently packaged as triglycerides in very-low-density lipoproteins and transported in this form by way of the blood to the adipose tissue and deposited as fat.

Insulin also *inhibits gluconeogenesis*. It does this mainly by decreasing the quantities and activities of the liver enzymes required for gluconeogenesis. However, part of the effect is caused by an action of insulin that decreases the release of amino acids from muscle and other extra-hepatic tissues and in turn the availability of these necessary precursors required for gluconeogenesis. This is discussed further in relation to the effect of insulin on protein metabolism.

### Lack of Effect of Insulin on Glucose Uptake and Usage by the Brain

The brain is quite different from most other tissues of the body in that insulin has little effect on uptake or use of glucose. Instead, *most of the brain cells are permeable to*



*glucose and can use glucose without the intermediation of insulin.*

The brain cells are also quite different from most other cells of the body in that they normally use only glucose for energy and can use other energy substrates, such as fats, only with difficulty. Therefore, it is essential that the blood glucose level always be maintained above a critical level, which is one of the most important functions of the blood glucose control system. When the blood glucose falls too low, into the range of 20 to 50 mg/100 ml, symptoms of *hypoglycemic shock* develop, characterized by progressive nervous irritability that leads to fainting, seizures, and even coma.

### Effect of Insulin on Carbohydrate Metabolism in Other Cells

Insulin increases glucose transport into and glucose usage by most other cells of the body (with the exception of the brain cells, as noted) in the same way that it affects glucose transport and usage in muscle cells. The transport of glucose into adipose cells mainly provides substrate for the glycerol portion of the fat molecule. Therefore, in this indirect way, insulin promotes deposition of fat in these cells.

### Effect of Insulin on Fat Metabolism

Although not quite as visible as the acute effects of insulin on carbohydrate metabolism, insulin's effects on fat metabolism are, in the long run, equally important. Especially dramatic is the long-term effect of *insulin lack* in causing extreme atherosclerosis, often leading to heart attacks, cerebral strokes, and other vascular accidents. But first, let us discuss the acute effects of insulin on fat metabolism.

### Insulin Promotes Fat Synthesis and Storage

Insulin has several effects that lead to fat storage in adipose tissue. First, insulin increases the utilization of glucose by most of the body's tissues, which automatically decreases the utilization of fat, thus functioning as a fat sparer. However, insulin also promotes fatty acid synthesis. This is especially true when more carbohydrates are ingested than can be used for immediate energy, thus providing the substrate for fat synthesis. Almost all this synthesis occurs in the liver cells, and the fatty acids are then transported from the liver by way of the blood lipoproteins to the adipose cells to be stored. The different factors that lead to increased fatty acid synthesis in the liver include the following:

1. *Insulin increases the transport of glucose into the liver cells.* After the liver glycogen concentration reaches 5 to 6 percent, this in itself inhibits further glycogen synthesis. Then all the additional glucose entering the liver cells becomes available to form fat. The glucose is first split to pyruvate in the glycolytic pathway, and the pyruvate subsequently is converted to acetyl coenzyme A (acetyl-CoA), the substrate from which fatty acids are synthesized.

2. *An excess of citrate and isocitrate ions is formed by the citric acid cycle when excess amounts of glucose are being used for energy.* These ions then have a direct effect in activating *acetyl-CoA carboxylase*, the enzyme required to carboxylate acetyl-CoA to form *malonyl-CoA*, the first stage of fatty acid synthesis.
3. *Most of the fatty acids are then synthesized within the liver and used to form triglycerides*, the usual form of storage fat. They are released from the liver cells to the blood in the lipoproteins. Insulin activates *lipoprotein lipase* in the capillary walls of the adipose tissue, which splits the triglycerides again into fatty acids, a requirement for them to be absorbed into the adipose cells, where they are again converted to triglycerides and stored.

**Role of Insulin in Storage of Fat in the Adipose Cells.** Insulin has two other essential effects that are required for fat storage in adipose cells:

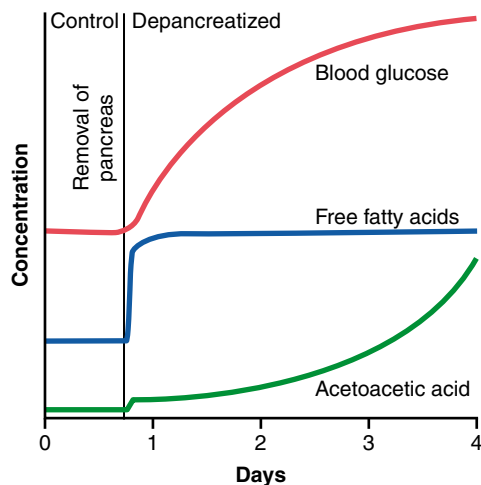
1. *Insulin inhibits the action of hormone-sensitive lipase.* This is the enzyme that causes hydrolysis of the triglycerides already stored in the fat cells. Therefore, the release of fatty acids from the adipose tissue into the circulating blood is inhibited.
2. *Insulin promotes glucose transport through the cell membrane into the fat cells* in the same way that it promotes glucose transport into muscle cells. Some of this glucose is then used to synthesize minute amounts of fatty acids, but more important, it also forms large quantities of  $\alpha$ -glycerol phosphate. This substance supplies the *glycerol* that combines with fatty acids to form the triglycerides that are the storage form of fat in adipose cells. Therefore, when insulin is not available, even storage of the large amounts of fatty acids transported from the liver in the lipoproteins is almost blocked.

### Insulin Deficiency Increases Use of Fat for Energy

All aspects of fat breakdown and use for providing energy are greatly enhanced in the absence of insulin. This occurs even normally between meals when secretion of insulin is minimal, but it becomes extreme in diabetes mellitus when secretion of insulin is almost zero. The resulting effects are as follows.

**Insulin Deficiency Causes Lipolysis of Storage Fat and Release of Free Fatty Acids.** In the absence of insulin, all the effects of insulin noted earlier that cause storage of fat are reversed. The most important effect is that the enzyme *hormone-sensitive lipase* in the fat cells becomes strongly activated. This causes hydrolysis of the stored triglycerides, releasing large quantities of fatty acids and glycerol into the circulating blood. Consequently, the plasma concentration of free fatty acids begins to rise within minutes. These free fatty acids then become the main energy substrate used by essentially all tissues of the body except the brain.

Figure 78-5 shows the effect of insulin lack on the plasma concentrations of free fatty acids, glucose, and



**Figure 78-5** Effect of removing the pancreas on the approximate concentrations of blood glucose, plasma free fatty acids, and acetoacetic acid.

acetoacetic acid. Note that almost immediately after removal of the pancreas, the free fatty acid concentration in the plasma begins to rise, more rapidly even than the concentration of glucose.

**Insulin Deficiency Increases Plasma Cholesterol and Phospholipid Concentrations.** The excess of fatty acids in the plasma associated with insulin deficiency also promotes liver conversion of some of the fatty acids into phospholipids and cholesterol, two of the major products of fat metabolism. These two substances, along with excess triglycerides formed at the same time in the liver, are then discharged into the blood in the lipoproteins. Occasionally the plasma lipoproteins increase as much as threefold in the absence of insulin, giving a total concentration of plasma lipids of several percent rather than the normal 0.6 percent. This high lipid concentration—especially the high concentration of cholesterol—promotes the development of atherosclerosis in people with serious diabetes.

**Excess Usage of Fats During Insulin Lack Causes Ketosis and Acidosis.** Insulin lack also causes excessive amounts of *acetoacetic acid* to be formed in the liver cells due to the following effect: In the absence of insulin but in the presence of excess fatty acids in the liver cells, the carnitine transport mechanism for transporting fatty acids into the mitochondria becomes increasingly activated. In the mitochondria, beta oxidation of the fatty acids then proceeds rapidly, releasing extreme amounts of acetyl-CoA. A large part of this excess acetyl-CoA is then condensed to form acetoacetic acid, which is then released into the circulating blood. Most of this passes to the peripheral cells, where it is again converted into acetyl-CoA and used for energy in the usual manner.

At the same time, the absence of insulin also depresses the utilization of acetoacetic acid in the peripheral tissues. Thus, so much acetoacetic acid is released from the liver that it cannot all be metabolized by the tissues. As shown

in Figure 78-5, the concentration of acetoacetic acid rises during the days after cessation of insulin secretion, sometimes reaching concentrations of 10 mEq/L or more, which is a severe state of body fluid acidosis.

As explained in Chapter 68, some of the acetoacetic acid is also converted into  $\beta$ -hydroxybutyric acid and *acetone*. These two substances, along with the acetoacetic acid, are called *ketone bodies*, and their presence in large quantities in the body fluids is called *ketosis*. We see later that in severe diabetes the acetoacetic acid and the  $\beta$ -hydroxybutyric acid can cause severe *acidosis* and *coma*, which may lead to death.

## Effect of Insulin on Protein Metabolism and on Growth

### Insulin Promotes Protein Synthesis and Storage.

During the few hours after a meal when excess quantities of nutrients are available in the circulating blood, proteins, carbohydrates, and fats are stored in the tissues; insulin is required for this to occur. The manner in which insulin causes protein storage is not as well understood as the mechanisms for both glucose and fat storage. Some of the facts follow.

1. *Insulin stimulates transport of many of the amino acids into the cells.* Among the amino acids most strongly transported are *valine, leucine, isoleucine, tyrosine, and phenylalanine*. Thus, insulin shares with growth hormone the capability of increasing the uptake of amino acids into cells. However, the amino acids affected are not necessarily the same ones.
2. *Insulin increases the translation of messenger RNA*, thus forming new proteins. In some unexplained way, insulin “turns on” the ribosomal machinery. In the absence of insulin, the ribosomes simply stop working, almost as if insulin operates an “on-off” mechanism.
3. Over a longer period of time, *insulin also increases the rate of transcription of selected DNA genetic sequences* in the cell nuclei, thus forming increased quantities of RNA and still more protein synthesis—especially promoting a vast array of enzymes for storage of carbohydrates, fats, and proteins.
4. *Insulin inhibits the catabolism of proteins*, thus decreasing the rate of amino acid release from the cells, especially from the muscle cells. Presumably this results from the ability of insulin to diminish the normal degradation of proteins by the cellular lysosomes.
5. *In the liver, insulin depresses the rate of gluconeogenesis.* It does this by decreasing the activity of the enzymes that promote gluconeogenesis. Because the substrates most used for synthesis of glucose by gluconeogenesis are the plasma amino acids, this suppression of gluconeogenesis conserves the amino acids in the protein stores of the body.

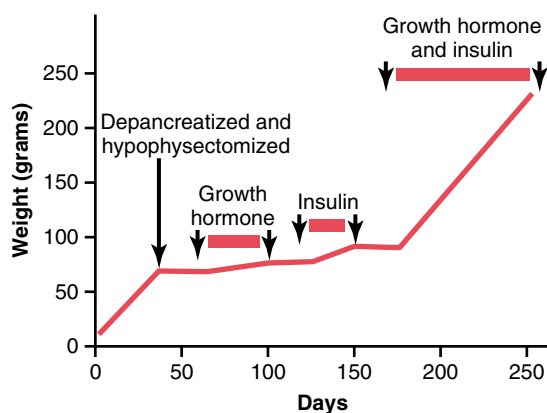
In summary, insulin promotes protein formation and prevents the degradation of proteins.

**Insulin Deficiency Causes Protein Depletion and Increased Plasma Amino Acids.** Virtually all protein storage comes to a halt when insulin is not available. The catabolism of proteins increases, protein synthesis stops, and large quantities of amino acids are dumped into the plasma. The plasma amino acid concentration rises considerably, and most of the excess amino acids are used either directly for energy or as substrates for gluconeogenesis. This degradation of the amino acids also leads to enhanced urea excretion in the urine. The resulting protein wasting is one of the most serious of all the effects of severe diabetes mellitus. It can lead to extreme weakness and many deranged functions of the organs.

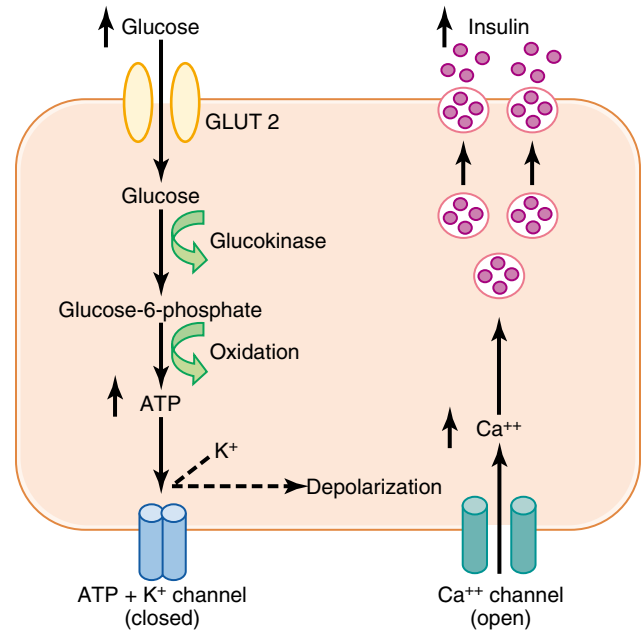
**Insulin and Growth Hormone Interact Synergistically to Promote Growth.** Because insulin is required for the synthesis of proteins, it is as essential for growth of an animal as growth hormone is. This is demonstrated in Figure 78-6, which shows that a depancreatized, hypophysectomized rat without therapy hardly grows at all. Furthermore, the administration of either growth hormone or insulin one at a time causes almost no growth. Yet a combination of these hormones causes dramatic growth. Thus, it appears that the two hormones function synergistically to promote growth, each performing a specific function that is separate from that of the other. Perhaps a small part of this necessity for both hormones results from the fact that each promotes cellular uptake of a different selection of amino acids, all of which are required if growth is to be achieved.

### Mechanisms of Insulin Secretion

Figure 78-7 shows the basic cellular mechanisms for insulin secretion by the pancreatic beta cells in response to increased blood glucose concentration, the primary controller of insulin secretion. The beta cells have a large number of *glucose transporters* (GLUT 2) that permit a rate of glucose influx that is proportional to the blood concentration in the physiological range. Once inside the cells, glucose is phosphorylated to glucose-6-phosphate by



**Figure 78-6** Effect of growth hormone, insulin, and growth hormone plus insulin on growth in a depancreatized and hypophysectomized rat.



**Figure 78-7** Basic mechanisms of glucose stimulation of insulin secretion by beta cells of the pancreas. GLUT, glucose transporter.

*glucokinase*. This appears to be the rate limiting step for glucose metabolism in the beta cell and is considered the major mechanism for glucose sensing and adjustment of the amount of secreted insulin to the blood glucose levels.

The glucose-6-phosphate is subsequently oxidized to form adenosine triphosphate (ATP), which inhibits the *ATP-sensitive potassium channels* of the cell. Closure of the potassium channels depolarizes the cell membrane, thereby opening *voltage-gated calcium channels*, which are sensitive to changes in membrane voltage. This produces an influx of calcium that stimulates fusion of the docked insulin-containing vesicles with the cell membrane and secretion of insulin into the extracellular fluid by *exocytosis*.

Other nutrients, such as certain amino acids, can also be metabolized by the beta cells to increase intracellular ATP levels and stimulate insulin secretion. Some hormones, such as glucagon, glucose-dependent insulinotropic peptide (gastric inhibitory peptide), and acetylcholine, increase intracellular calcium levels through other signaling pathways and enhance the effect of glucose, although they do not have major effects on insulin secretion in the absence of glucose. Other hormones, including somatostatin and norepinephrine (by activating  $\alpha$ -adrenergic receptors), inhibit exocytosis of insulin.

Sulfonylurea drugs stimulate insulin secretion by binding to the ATP-sensitive potassium channels and blocking their activity. This results in a depolarizing effect that triggers insulin secretion, making these drugs useful in stimulating insulin secretion in patients with type II diabetes, as we discuss later. Table 78-1 summarizes some of the factors that can increase or decrease insulin secretion.

### Control of Insulin Secretion

Formerly, it was believed that insulin secretion was controlled almost entirely by the blood glucose concentration.

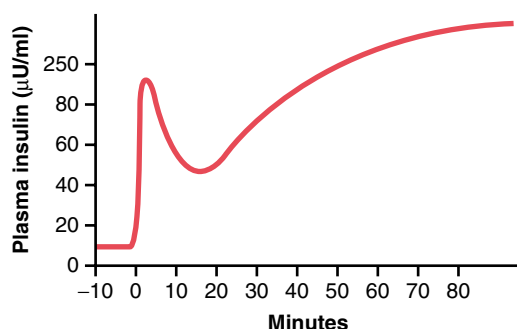
**Table 78-1** Factors and Conditions That Increase or Decrease Insulin Secretion

Increase Insulin Secretion	Decrease Insulin Secretion
Increased blood glucose	Decreased blood glucose
Increased blood free fatty acids	Fasting
Increased blood amino acids	Somatostatin
Gastrointestinal hormones (gastrin, cholecystokinin, secretin, gastric inhibitory peptide)	$\alpha$ -Adrenergic activity
Glucagon, growth hormone, cortisol	Leptin
Parasympathetic stimulation; acetylcholine	
$\beta$ -Adrenergic stimulation	
Insulin resistance; obesity	
Sulfonylurea drugs (glyburide, tolbutamide)	

However, as more has been learned about the metabolic functions of insulin for protein and fat metabolism, it has become apparent that blood amino acids and other factors also play important roles in controlling insulin secretion (see Table 78-1).

**Increased Blood Glucose Stimulates Insulin Secretion.** At the normal *fasting* level of blood glucose of 80 to 90 mg/100 ml, the rate of insulin secretion is minimal—on the order of 25 ng/min/kg of body weight, a level that has only slight physiological activity. If the blood glucose concentration is suddenly increased to a level two to three times normal and kept at this high level thereafter, insulin secretion increases markedly in two stages, as shown by the changes in plasma insulin concentration seen in Figure 78-8.

1. Plasma insulin concentration increases almost 10-fold within 3 to 5 minutes after the acute elevation of the blood glucose; this results from immediate dumping of preformed insulin from the beta cells of the islets



**Figure 78-8** Increase in plasma insulin concentration after a sudden increase in blood glucose to two to three times the normal range. Note an initial rapid surge in insulin concentration and then a delayed but higher and continuing increase in concentration beginning 15 to 20 minutes later.

of Langerhans. However, the initial high rate of secretion is not maintained; instead, the insulin concentration decreases about halfway back toward normal in another 5 to 10 minutes.

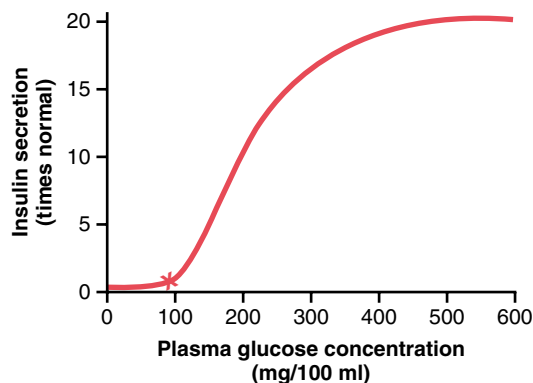
2. Beginning at about 15 minutes, insulin secretion rises a second time and reaches a new plateau in 2 to 3 hours, this time usually at a rate of secretion even greater than that in the initial phase. This secretion results both from additional release of preformed insulin and from activation of the enzyme system that synthesizes and releases new insulin from the cells.

**Feedback Relation between Blood Glucose Concentration and Insulin Secretion Rate.** As the concentration of blood glucose rises above 100 mg/100 ml of blood, the rate of insulin secretion rises rapidly, reaching a peak some 10 to 25 times the basal level at blood glucose concentrations between 400 and 600 mg/100 ml, as shown in Figure 78-9. Thus, the increase in insulin secretion under a glucose stimulus is dramatic both in its rapidity and in the tremendous level of secretion achieved. Furthermore, the turn-off of insulin secretion is almost equally as rapid, occurring within 3 to 5 minutes after reduction in blood glucose concentration back to the fasting level.

This response of insulin secretion to an elevated blood glucose concentration provides an extremely important feedback mechanism for regulating blood glucose concentration. That is, any rise in blood glucose increases insulin secretion and the insulin in turn increases transport of glucose into liver, muscle, and other cells, thereby reducing the blood glucose concentration back toward the normal value.

#### Other Factors That Stimulate Insulin Secretion

**Amino Acids.** In addition to the stimulation of insulin secretion by excess blood glucose, some of the amino acids have a similar effect. The most potent of these are *arginine* and *lysine*. This effect differs from glucose stimulation of insulin secretion in the following way: Amino acids administered in the absence of a rise in blood glucose cause only a small increase in insulin secretion. However, when administered at the same time that the blood glucose concentration



**Figure 78-9** Approximate insulin secretion at different plasma glucose levels.



is elevated, the glucose-induced secretion of insulin may be as much as doubled in the presence of the excess amino acids. Thus, the *amino acids strongly potentiate the glucose stimulus for insulin secretion*.

The stimulation of insulin secretion by amino acids is important because the insulin in turn promotes transport of amino acids into the tissue cells, as well as intracellular formation of protein. That is, insulin is important for proper utilization of excess amino acids in the same way that it is important for the utilization of carbohydrates.

**Gastrointestinal Hormones.** A mixture of several important gastrointestinal hormones—*gastrin*, *secretin*, *cholecystokinin*, and *glucose-dependent insulintrophic peptide* (which seems to be the most potent)—causes a moderate increase in insulin secretion. These hormones are released in the gastrointestinal tract after a person eats a meal. They then cause an “anticipatory” increase in blood insulin in preparation for the glucose and amino acids to be absorbed from the meal. These gastrointestinal hormones generally act the same way as amino acids to increase the sensitivity of insulin response to increased blood glucose, almost doubling the rate of insulin secretion as the blood glucose level rises.

**Other Hormones and the Autonomic Nervous System.** Other hormones that either directly increase insulin secretion or potentiate the glucose stimulus for insulin secretion include *glucagon*, *growth hormone*, *cortisol*, and, to a lesser extent, *progesterone* and *estrogen*. The importance of the stimulatory effects of these hormones is that prolonged secretion of any one of them in large quantities can occasionally lead to exhaustion of the beta cells of the islets of Langerhans and thereby increase the risk for developing diabetes mellitus. Indeed, diabetes often occurs in people who are maintained on high pharmacological doses of some of these hormones. Diabetes is particularly common in giants or acromegalic people with growth hormone-secreting tumors, or in people whose adrenal glands secrete excess glucocorticoids.

Under some conditions, stimulation of the parasympathetic nerves to the pancreas can increase insulin secretion, whereas sympathetic nerve stimulation may decrease insulin secretion. However, it is doubtful that these effects play a major role in physiological regulation of insulin secretion.

### Role of Insulin (and Other Hormones) in “Switching” Between Carbohydrate and Lipid Metabolism

From the preceding discussions, it should be clear that insulin promotes the utilization of carbohydrates for energy, whereas it depresses the utilization of fats. Conversely, lack of insulin causes fat utilization mainly to the exclusion of glucose utilization, except by brain tissue. Furthermore, the signal that controls this switching mechanism is principally the blood glucose concentration. When the glucose concentration is low, insulin secretion is suppressed and fat is used almost exclusively for energy everywhere except in the brain. When the glucose concentration is high, insulin secretion is stimulated and carbohydrate is used instead of fat. The excess blood glucose is stored in the form of liver glycogen, liver fat, and muscle glycogen. Therefore, one of the most important functional roles of insulin in the body is to control which of

these two foods from moment to moment will be used by the cells for energy.

At least four other known hormones also play important roles in this switching mechanism: *growth hormone* from the anterior pituitary gland, *cortisol* from the adrenal cortex, *epinephrine* from the adrenal medulla, and *glucagon* from the alpha cells of the islets of Langerhans in the pancreas. Glucagon is discussed in the next section of this chapter. Both growth hormone and cortisol are secreted in response to hypoglycemia, and both inhibit cellular utilization of glucose while promoting fat utilization. However, the effects of both of these hormones develop slowly, usually requiring many hours for maximal expression.

Epinephrine is especially important in increasing plasma glucose concentration during periods of stress when the sympathetic nervous system is excited. However, epinephrine acts differently from the other hormones in that it increases the plasma fatty acid concentration at the same time. The reasons for these effects are as follows: (1) epinephrine has the potent effect of causing glycogenolysis in the liver, thus releasing within minutes large quantities of glucose into the blood; (2) it also has a direct lipolytic effect on the adipose cells because it activates adipose tissue hormone-sensitive lipase, thus greatly enhancing the blood concentration of fatty acids as well. Quantitatively, the enhancement of fatty acids is far greater than the enhancement of blood glucose. Therefore, epinephrine especially enhances the utilization of fat in such stressful states as exercise, circulatory shock, and anxiety.

### Glucagon and Its Functions

Glucagon, a hormone secreted by the *alpha cells* of the islets of Langerhans when the blood glucose concentration falls, has several functions that are diametrically opposed to those of insulin. Most important of these functions is to increase the blood glucose concentration, an effect that is exactly the opposite that of insulin.

Like insulin, glucagon is a large polypeptide. It has a molecular weight of 3485 and is composed of a chain of 29 amino acids. On injection of purified glucagon into an animal, a profound *hyperglycemic* effect occurs. Only 1 µg/kg of glucagon can elevate the blood glucose concentration about 20 mg/100 ml of blood (a 25 percent increase) in about 20 minutes. For this reason, glucagon is also called the *hyperglycemic hormone*.

### Effects on Glucose Metabolism

The major effects of glucagon on glucose metabolism are (1) breakdown of liver glycogen (*glycogenolysis*) and (2) increased *gluconeogenesis* in the liver. Both of these effects greatly enhance the availability of glucose to the other organs of the body.

**Glucagon Causes Glycogenolysis and Increased Blood Glucose Concentration.** The most dramatic effect of glucagon is its ability to cause glycogenolysis in

the liver, which in turn increases the blood glucose concentration within minutes.

It does this by the following complex cascade of events:

1. Glucagon activates *adenylyl cyclase* in the hepatic cell membrane,
2. Which causes the formation of *cyclic adenosine monophosphate*,
3. Which activates *protein kinase regulator protein*,
4. Which activates *protein kinase*,
5. Which activates *phosphorylase b kinase*,
6. Which converts *phosphorylase b* into *phosphorylase a*,
7. Which promotes the degradation of glycogen into glucose-1-phosphate,
8. Which is then dephosphorylated; and the glucose is released from the liver cells.

This sequence of events is exceedingly important for several reasons. First, it is one of the most thoroughly studied of all the *second messenger* functions of cyclic adenosine monophosphate. Second, it demonstrates a cascade system in which *each succeeding product is produced in greater quantity than the preceding product*. Therefore, it represents a potent *amplifying* mechanism; this type of amplifying mechanism is widely used throughout the body for controlling many, if not most, cellular metabolic systems, often causing as much as a millionfold amplification in response. This explains how *only a few micrograms of glucagon can cause the blood glucose level to double or increase even more within a few minutes*.

Infusion of glucagon for about 4 hours can cause such intensive liver glycogenolysis that all the liver stores of glycogen become depleted.

### Glucagon Increases Gluconeogenesis

Even after all the glycogen in the liver has been exhausted under the influence of glucagon, continued infusion of this hormone still causes continued hyperglycemia. This results from the effect of glucagon to increase the rate of amino acid uptake by the liver cells and then the conversion of many of the amino acids to glucose by gluconeogenesis. This is achieved by activating multiple enzymes that are required for amino acid transport and gluconeogenesis, especially activation of the enzyme system for converting pyruvate to phosphoenolpyruvate, a rate-limiting step in gluconeogenesis.

### Other Effects of Glucagon

Most other effects of glucagon occur only when its concentration rises well above the maximum normally found in the blood. Perhaps the most important effect is that *glucagon activates adipose cell lipase*, making increased quantities of fatty acids available to the energy systems of the body. Glucagon also inhibits the storage of triglycerides in the liver, which prevents the liver from removing fatty acids from the blood; this also helps make additional

amounts of fatty acids available for the other tissues of the body.

Glucagon in high concentrations also (1) enhances the strength of the heart; (2) increases blood flow in some tissues, especially the kidneys; (3) enhances bile secretion; and (4) inhibits gastric acid secretion. All these effects are probably of minimal importance in the normal function of the body.

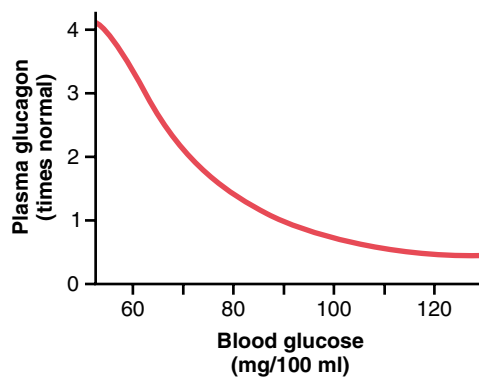
### Regulation of Glucagon Secretion

**Increased Blood Glucose Inhibits Glucagon Secretion.** The blood glucose concentration is by far the most potent factor that controls glucagon secretion. Note specifically, however, that *the effect of blood glucose concentration on glucagon secretion is in exactly the opposite direction from the effect of glucose on insulin secretion*.

This is demonstrated in Figure 78-10, showing that a *decrease* in the blood glucose concentration from its normal fasting level of about 90 mg/100 ml of blood down to hypoglycemic levels can increase the plasma concentration of glucagon severalfold. Conversely, increasing the blood glucose to hyperglycemic levels decreases plasma glucagon. Thus, in hypoglycemia, glucagon is secreted in large amounts; it then greatly increases the output of glucose from the liver and thereby serves the important function of correcting the hypoglycemia.

**Increased Blood Amino Acids Stimulate Glucagon Secretion.** High concentrations of amino acids, as occur in the blood after a protein meal (especially the amino acids *alanine* and *arginine*), *stimulate* the secretion of glucagon. This is the same effect that amino acids have in stimulating insulin secretion. Thus, in this instance, the glucagon and insulin responses are not opposites. The importance of amino acid stimulation of glucagon secretion is that the glucagon then promotes rapid conversion of the amino acids to glucose, thus making even more glucose available to the tissues.

**Exercise Stimulates Glucagon Secretion.** In exhaustive exercise, the blood concentration of glucagon often increases fourfold to fivefold. What causes this is not understood because the blood glucose concentration



**Figure 78-10** Approximate plasma glucagon concentration at different blood glucose levels.

does not necessarily fall. A beneficial effect of the glucagon is that it prevents a decrease in blood glucose.

One of the factors that might increase glucagon secretion in exercise is increased circulating amino acids. Other factors, such as  $\beta$ -adrenergic stimulation of the islets of Langerhans, may also play a role.

### Somatostatin Inhibits Glucagon and Insulin Secretion

The *delta cells* of the islets of Langerhans secrete the hormone *somatostatin*, a 14 amino acid polypeptide that has an extremely short half-life of only 3 minutes in the circulating blood. Almost all factors related to the ingestion of food stimulate somatostatin secretion. They include (1) increased blood glucose, (2) increased amino acids, (3) increased fatty acids, and (4) increased concentrations of several of the gastrointestinal hormones released from the upper gastrointestinal tract in response to food intake.

In turn, somatostatin has multiple inhibitory effects as follows:

1. Somatostatin acts locally within the islets of Langerhans themselves to depress the secretion of both insulin and glucagon.
2. Somatostatin decreases the motility of the stomach, duodenum, and gallbladder.
3. Somatostatin decreases both secretion and absorption in the gastrointestinal tract.

Putting all this information together, it has been suggested that the principal role of somatostatin is to extend the period of time over which the food nutrients are assimilated into the blood. At the same time, the effect of somatostatin to depress insulin and glucagon secretion decreases the utilization of the absorbed nutrients by the tissues, thus preventing rapid exhaustion of the food and therefore making it available over a longer period of time.

It should also be recalled that somatostatin is the same chemical substance as *growth hormone inhibitory hormone*, which is secreted in the hypothalamus and suppresses anterior pituitary gland growth hormone secretion.

### Summary of Blood Glucose Regulation

In a normal person, the blood glucose concentration is narrowly controlled, usually between 80 and 90 mg/100 ml of blood in the fasting person each morning before breakfast. This concentration increases to 120 to 140 mg/100 ml during the first hour or so after a meal, but the feedback systems for control of blood glucose return the glucose concentration rapidly back to the control level, usually within 2 hours after the last absorption of carbohydrates. Conversely, in starvation, the gluconeogenesis function of the liver provides the glucose that is required to maintain the fasting blood glucose level.

The mechanisms for achieving this high degree of control have been presented in this chapter. Let us summarize them.

1. *The liver functions as an important blood glucose buffer system.* That is, when the blood glucose rises to a high concentration after a meal and the rate of insulin secretion also increases, as much as two thirds of the glucose absorbed from the gut is almost immediately stored in the liver in the form of glycogen. Then, during the succeeding hours, when both the blood glucose concentration and the rate of insulin secretion fall, the liver releases the glucose back into the blood. In this way, the liver decreases the fluctuations in blood glucose concentration to about one third of what they would otherwise be. In fact, in patients with severe liver disease, it becomes almost impossible to maintain a narrow range of blood glucose concentration.
2. *Both insulin and glucagon function as important feedback control systems for maintaining a normal blood glucose concentration.* When the glucose concentration rises too high, increased insulin secretion causes the blood glucose concentration to decrease toward normal. Conversely, a decrease in blood glucose stimulates glucagon secretion; the glucagon then functions in the opposite direction to increase the glucose toward normal. Under most normal conditions, the insulin feedback mechanism is much more important than the glucagon mechanism, but in instances of starvation or excessive utilization of glucose during exercise and other stressful situations, the glucagon mechanism also becomes valuable.
3. Also, in severe hypoglycemia, a direct effect of low blood glucose on the hypothalamus stimulates the sympathetic nervous system. The epinephrine secreted by the adrenal glands further increases release of glucose from the liver. This also helps protect against severe hypoglycemia.
4. And finally, over a period of hours and days, both growth hormone and cortisol are secreted in response to prolonged hypoglycemia. They both decrease the rate of glucose utilization by most cells of the body, converting instead to greater amounts of fat utilization. This, too, helps return the blood glucose concentration toward normal.

**Importance of Blood Glucose Regulation.** One might ask the question: Why is it so important to maintain a constant blood glucose concentration, particularly because most tissues can shift to utilization of fats and proteins for energy in the absence of glucose? The answer is that glucose is the only nutrient that normally can be used by the *brain, retina, and germinal epithelium of the gonads* in sufficient quantities to supply them optimally with their required energy. Therefore, it is important to maintain the blood glucose concentration at a sufficiently high level to provide this necessary nutrition.

Most of the glucose formed by gluconeogenesis during the interdigestive period is used for metabolism in the brain. Indeed, it is important that the pancreas not secrete any insulin during this time; otherwise, the scant supplies



of glucose that are available would all go into the muscles and other peripheral tissues, leaving the brain without a nutritive source.

It is also important that the blood glucose concentration not rise too high for four reasons: (1) Glucose can exert a large amount of osmotic pressure in the extracellular fluid, and if the glucose concentration rises to excessive values, this can cause considerable cellular dehydration. (2) An excessively high level of blood glucose concentration causes loss of glucose in the urine. (3) Loss of glucose in the urine also causes osmotic diuresis by the kidneys, which can deplete the body of its fluids and electrolytes. (4) Long-term increases in blood glucose may cause damage to many tissues, especially to blood vessels. Vascular injury associated with uncontrolled diabetes mellitus leads to increased risk for heart attack, stroke, end-stage renal disease, and blindness.

### Diabetes Mellitus

Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin. There are two general types of diabetes mellitus:

1. *Type I diabetes*, also called *insulin-dependent diabetes mellitus* (IDDM), is caused by lack of insulin secretion.
2. *Type II diabetes*, also called *non-insulin-dependent diabetes mellitus* (NIDDM), is initially caused by decreased sensitivity of target tissues to the metabolic effect of insulin. This reduced sensitivity to insulin is often called *insulin resistance*.

In both types of diabetes mellitus, metabolism of all the main foodstuffs is altered. The basic effect of insulin lack or insulin resistance on glucose metabolism is to prevent the efficient uptake and utilization of glucose by most cells of the body, except those of the brain. As a result, blood glucose concentration increases, cell utilization of glucose falls increasingly lower, and utilization of fats and proteins increases.

#### Type I Diabetes—Deficiency of Insulin Production by Beta Cells of the Pancreas

Injury to the beta cells of the pancreas or diseases that impair insulin production can lead to type I diabetes. *Viral infections* or *autoimmune disorders* may be involved in the destruction of beta cells in many patients with type I diabetes, although heredity also plays a major role in determining the susceptibility of the beta cells to destruction by these insults. In some instances, there may be a hereditary tendency for beta cell degeneration even without viral infections or autoimmune disorders.

The usual onset of type I diabetes occurs at about 14 years of age in the United States, and for this reason it is often called *juvenile diabetes mellitus*. However, type I diabetes can occur at any age, including adulthood, following disorders that lead to destruction of pancreatic beta cells. Type I diabetes may develop abruptly, over a period of a few days or weeks, with three principal sequelae: (1) increased blood glucose, (2) increased utilization of fats for energy and

for formation of cholesterol by the liver, and (3) depletion of the body's proteins. Approximately 5 to 10 percent of people with diabetes mellitus have the type I form of the disease.

**Blood Glucose Concentration Rises to High Levels in Diabetes Mellitus.** The lack of insulin decreases the efficiency of peripheral glucose utilization and augments glucose production, raising plasma glucose to 300 to 1200 mg/100 ml. The increased plasma glucose then has multiple effects throughout the body.

**Increased Blood Glucose Causes Loss of Glucose in the Urine.** The high blood glucose causes more glucose to filter into the renal tubules than can be reabsorbed, and the excess glucose spills into the urine. This normally occurs when the blood glucose concentration rises above 180 mg/100 ml, a level that is called the blood "threshold" for the appearance of glucose in the urine. When the blood glucose level rises to 300 to 500 mg/100 ml—common values in people with severe untreated diabetes—100 or more grams of glucose can be lost into the urine each day.

**Increased Blood Glucose Causes Dehydration.** The very high levels of blood glucose (sometimes as high as 8 to 10 times normal in severe untreated diabetes) can cause severe cell dehydration throughout the body. This occurs partly because glucose does not diffuse easily through the pores of the cell membrane, and the increased osmotic pressure in the extracellular fluids causes osmotic transfer of water out of the cells.

In addition to the direct cellular dehydrating effect of excessive glucose, the loss of glucose in the urine causes *osmotic diuresis*. That is, the osmotic effect of glucose in the renal tubules greatly decreases tubular reabsorption of fluid. The overall effect is massive loss of fluid in the urine, causing dehydration of the extracellular fluid, which in turn causes compensatory dehydration of the intracellular fluid, for reasons discussed in Chapter 26. Thus, *polyuria* (excessive urine excretion), *intracellular and extracellular dehydration*, and *increased thirst* are classic symptoms of diabetes.

**Chronic High Glucose Concentration Causes Tissue Injury.** When blood glucose is poorly controlled over long periods in diabetes mellitus, blood vessels in multiple tissues throughout the body begin to function abnormally and undergo structural changes that result in inadequate blood supply to the tissues. This in turn leads to increased risk for heart attack, stroke, end-stage kidney disease, retinopathy and blindness, and ischemia and gangrene of the limbs.

Chronic high glucose concentration also causes damage to many other tissues. For example, *peripheral neuropathy*, which is abnormal function of peripheral nerves, and *autonomic nervous system dysfunction* are frequent complications of chronic, uncontrolled diabetes mellitus. These abnormalities can result in impaired cardiovascular reflexes, impaired bladder control, decreased sensation in the extremities, and other symptoms of peripheral nerve damage.

The precise mechanisms that cause tissue injury in diabetes are not well understood but probably involve multiple effects of high glucose concentrations and other metabolic abnormalities on proteins of endothelial and vascular smooth muscle cells, as well as other tissues. In addition, *hypertension*, secondary to renal injury, and *atherosclerosis*, secondary to abnormal lipid metabolism, often develop in patients with diabetes and amplify the tissue damage caused by the elevated glucose.



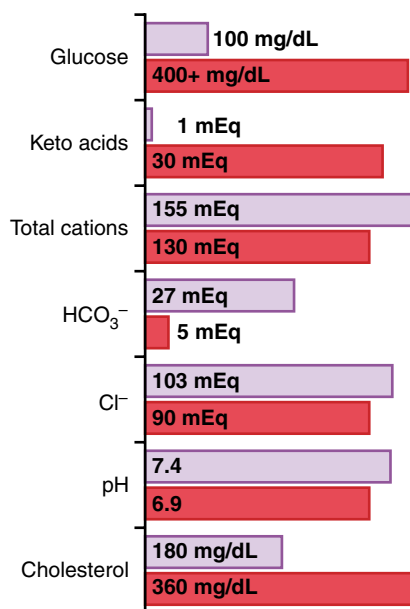
**Diabetes Mellitus Causes Increased Utilization of Fats and Metabolic Acidosis.** The shift from carbohydrate to fat metabolism in diabetes increases the release of keto acids, such as acetoacetic acid and  $\beta$ -hydroxybutyric acid, into the plasma more rapidly than they can be taken up and oxidized by the tissue cells. As a result, the patient develops severe *metabolic acidosis* from the excess keto acids, which, in association with dehydration due to the excessive urine formation, can cause severe acidosis. This leads rapidly to *diabetic coma* and death unless the condition is treated immediately with large amounts of insulin.

All the usual physiological compensations that occur in metabolic acidosis take place in diabetic acidosis. They include *rapid and deep breathing*, which causes increased expiration of carbon dioxide; this buffers the acidosis but also depletes extracellular fluid bicarbonate stores. The kidneys compensate by decreasing bicarbonate excretion and generating new bicarbonate that is added back to the extracellular fluid.

Although extreme acidosis occurs only in the most severe instances of uncontrolled diabetes, when the pH of the blood falls below about 7.0, *acidotic coma* and death can occur within hours. The overall changes in the electrolytes of the blood as a result of severe diabetic acidosis are shown in Figure 78-11.

Excess fat utilization in the liver occurring over a long time causes large amounts of cholesterol in the circulating blood and increased deposition of cholesterol in the arterial walls. This leads to severe *arteriosclerosis* and other vascular lesions, as discussed earlier.

**Diabetes Causes Depletion of the Body's Proteins.** Failure to use glucose for energy leads to increased utilization and decreased storage of proteins and fat. Therefore, a person with severe untreated diabetes mellitus suffers rapid weight loss and *asthenia* (lack of energy) despite eating large amounts of food (*polyphagia*). Without treatment, these metabolic abnormalities can cause severe wasting of the body tissues and death within a few weeks.



**Figure 78-11** Changes in blood constituents in diabetic coma, showing normal values (lavender bars) and diabetic coma values (red bars).

### Type II Diabetes—Resistance to the Metabolic Effects of Insulin

Type II diabetes is far more common than type I, accounting for about 90 to 95 percent of all cases of diabetes mellitus. In most cases, the onset of type II diabetes occurs after age 30, often between the ages of 50 and 60 years, and the disease develops gradually. Therefore, this syndrome is often referred to as *adult-onset diabetes*. In recent years, however, there has been a steady increase in the number of younger individuals, some younger than 20 years old, with type II diabetes. This trend appears to be related mainly to the increasing prevalence of *obesity*, the most important risk factor for type II diabetes in children and adults.

**Obesity, Insulin Resistance, and “Metabolic Syndrome” Usually Precede Development of Type II Diabetes.** Type II diabetes, in contrast to type I, is associated with *increased* plasma insulin concentration (*hyperinsulinemia*). This occurs as a compensatory response by the pancreatic beta cells for diminished sensitivity of target tissues to the metabolic effects of insulin, a condition referred to as *insulin resistance*. The decrease in insulin sensitivity impairs carbohydrate utilization and storage, raising blood glucose and stimulating a compensatory increase in insulin secretion.

Development of insulin resistance and impaired glucose metabolism is usually a gradual process, beginning with excess weight gain and obesity. The mechanisms that link obesity with insulin resistance, however, are still uncertain. Some studies suggest that there are fewer insulin receptors, especially in the skeletal muscle, liver, and adipose tissue, in obese than in lean subjects. However, most of the insulin resistance appears to be caused by abnormalities of the signaling pathways that link receptor activation with multiple cellular effects. Impaired insulin signaling appears to be closely related to toxic effects of lipid accumulation in tissues such as skeletal muscle and liver secondary to excess weight gain.

Insulin resistance is part of a cascade of disorders that is often called the “*metabolic syndrome*.” Some of the features of the metabolic syndrome include (1) obesity, especially accumulation of abdominal fat; (2) insulin resistance; (3) fasting hyperglycemia; (4) lipid abnormalities, such as increased blood triglycerides and decreased blood high-density lipoprotein-cholesterol; and (5) hypertension. All of the features of the metabolic syndrome are closely related to accumulation of excess adipose tissue in the abdominal cavity around the visceral organs.

The role of insulin resistance in contributing to some of the components of the metabolic syndrome is uncertain, although it is clear that insulin resistance is the primary cause of increased blood glucose concentration. The major adverse consequence of the metabolic syndrome is cardiovascular disease including atherosclerosis and injury to various organs throughout the body. Several of the metabolic abnormalities associated with the syndrome increase the risk for cardiovascular disease, and insulin resistance predisposes to the development of type II diabetes mellitus, also a major cause of cardiovascular disease.

**Other Factors That Can Cause Insulin Resistance and Type II Diabetes.** Although most patients with type II diabetes are overweight or have substantial accumulation of visceral fat, severe insulin resistance and type II diabetes can also occur as a result of other acquired or genetic conditions that impair insulin signaling in peripheral tissues (Table 78-2).

**Table 78-2** Some Causes of Insulin Resistance

• Obesity/overweight (especially excess visceral adiposity)
• Excess glucocorticoids (Cushing's syndrome or steroid therapy)
• Excess growth hormone (acromegaly)
• Pregnancy, gestational diabetes
• Polycystic ovary disease
• Lipodystrophy (acquired or genetic; associated with lipid accumulation in liver)
• Autoantibodies to the insulin receptor
• Mutations of insulin receptor
• Mutations of the peroxisome proliferators' activator receptor $\gamma$ (PPAR $\gamma$ )
• Mutations that cause genetic obesity (e.g., melanocortin receptor mutations)
• Hemochromatosis (a hereditary disease that causes tissue iron accumulation)

*Polycystic ovary syndrome* (PCOS), for example, is associated with marked increases in ovarian androgen production and insulin resistance and is one of the most common endocrine disorders in women, affecting approximately 6 percent of all women during their reproductive life. Although the pathogenesis of PCOS remains uncertain, insulin resistance and hyperinsulinemia are found in approximately 80 percent of affected women. The long-term consequences include increased risk for diabetes mellitus, increased blood lipids, and cardiovascular disease.

*Excess formation of glucocorticoids* (Cushing's syndrome) or *growth hormone* (acromegaly) also decreases the sensitivity of various tissues to the metabolic effects of insulin and can lead to development of diabetes mellitus. Genetic causes of obesity and insulin resistance, if severe enough, also can lead to type II diabetes and many other features of the metabolic syndrome including cardiovascular disease.

**Development of Type II Diabetes During Prolonged Insulin Resistance.** With prolonged and severe insulin resistance, even the increased levels of insulin are not sufficient to maintain normal glucose regulation. As a result, moderate hyperglycemia occurs after ingestion of carbohydrates in the early stages of the disease.

In the later stages of type II diabetes, the pancreatic beta cells become "exhausted" or damaged and are unable to produce enough insulin to prevent more severe hyperglycemia, especially after the person ingests a carbohydrate-rich meal.

Some obese people, although having marked insulin resistance and greater than normal increases in blood glucose after a meal, never develop clinically significant diabetes mellitus; apparently, the pancreas in these people produces enough insulin to prevent severe abnormalities of glucose metabolism. In others, however, the pancreas gradually becomes exhausted from secreting large amounts of insulin or damaged by factors associated with lipid accumulation in the pancreas, and full-blown diabetes mellitus occurs. Some studies suggest that genetic factors play an important role in determining whether an individual's pancreas can sustain the high output of insulin over many years that is necessary to avoid the severe abnormalities of glucose metabolism in type II diabetes.

In many instances, type II diabetes can be effectively treated, at least in the early stages, with exercise, caloric restriction, and weight reduction, and no exogenous insulin administration is required. Drugs that increase insulin sensitivity, such as *thiazolidinediones*, drugs that suppress liver glucose production, such as *metformin*, or drugs that cause additional release of insulin by the pancreas, such as *sulfonylureas*, may also be used. However, in the later stages of type II diabetes, insulin administration is usually required to control plasma glucose.

### Physiology of Diagnosis of Diabetes Mellitus

Table 78-3 compares some of clinical features of type I and type II diabetes mellitus. The usual methods for diagnosing diabetes are based on various chemical tests of the urine and the blood.

**Urinary Glucose.** Simple office tests or more complicated quantitative laboratory tests may be used to determine the quantity of glucose lost in the urine. In general, a normal person loses undetectable amounts of glucose, whereas a person with diabetes loses glucose in small to large amounts, in proportion to the severity of disease and the intake of carbohydrates.

**Fasting Blood Glucose and Insulin Levels.** The fasting blood glucose level in the early morning is normally 80 to 90 mg/100 ml, and 110 mg/100 ml is considered to be the upper limit of normal. A fasting blood glucose level above this value often indicates diabetes mellitus or at least marked insulin resistance.

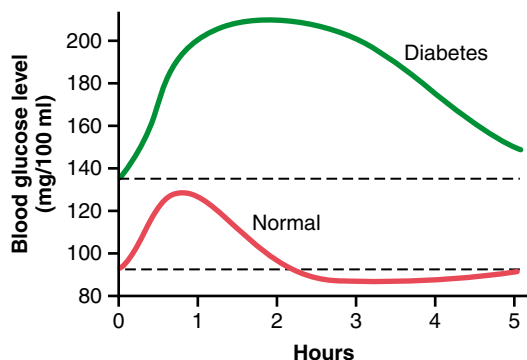
In type I diabetes, plasma insulin levels are very low or undetectable during fasting and even after a meal. In type II diabetes, plasma insulin concentration may be severalfold higher than normal and usually increases to a greater extent after ingestion of a standard glucose load during a glucose tolerance test (see the next paragraph).

**Glucose Tolerance Test.** As demonstrated by the bottom curve in Figure 78-12, called a "glucose tolerance curve," when a normal, fasting person ingests 1 gram of glucose per kilogram of body weight, the blood glucose level rises from about 90 mg/100 ml to 120 to 140 mg/100 ml and falls back to below normal in about 2 hours.

In a person with diabetes, the fasting blood glucose concentration is almost always above 110 mg/100 ml and often

**Table 78-3** Clinical Characteristics of Patients with Type I and Type II Diabetes Mellitus

Feature	Type I	Type II
Age at onset	Usually <20 yr	Usually >30 yr
Body mass	Low (wasted) to Normal	Obese
Plasma insulin	Low or absent	Normal to high initially
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin



**Figure 78-12** Glucose tolerance curve in a normal person and in a person with diabetes.

above 140 mg/100 ml. Also, the glucose tolerance test is almost always abnormal. On ingestion of glucose, these people exhibit a much greater than normal rise in blood glucose level, as demonstrated by the upper curve in Figure 78-12, and the glucose level falls back to the control value only after 4 to 6 hours; furthermore, it fails to fall *below* the control level. The slow fall of this curve and its failure to fall below the control level demonstrate that either (1) the normal increase in insulin secretion after glucose ingestion does not occur or (2) there is decreased sensitivity to insulin. A diagnosis of diabetes mellitus can usually be established on the basis of such a curve, and type I and type II diabetes can be distinguished from each other by measurements of plasma insulin, with plasma insulin being low or undetectable in type I diabetes and increased in type II diabetes.

**Acetone Breath.** As pointed out in Chapter 68, small quantities of acetoacetic acid in the blood, which increase greatly in severe diabetes, are converted to acetone. This is volatile and vaporized into the expired air. Consequently, one can frequently make a diagnosis of type I diabetes mellitus simply by smelling acetone on the breath of a patient. Also, keto acids can be detected by chemical means in the urine and their quantitation aids in determining the severity of the diabetes. In the early stages of type II diabetes, however, keto acids are usually not produced in excess amounts. However, when insulin resistance becomes severe and there is greatly increased utilization of fats for energy, keto acids are then produced in persons with type II diabetes.

### Treatment of Diabetes

Effective treatment of type I diabetes mellitus requires administration of enough insulin so that the patient will have carbohydrate, fat, and protein metabolism that is as normal as possible. Insulin is available in several forms. “Regular” insulin has a duration of action that lasts from 3 to 8 hours, whereas other forms of insulin (precipitated with zinc or with various protein derivatives) are absorbed slowly from the injection site and therefore have effects that last as long as 10 to 48 hours. Ordinarily, a patient with severe type I diabetes is given a single dose of one of the longer-acting insulins each day to increase overall carbohydrate metabolism throughout the day. Then additional quantities of regular insulin are given during the day at those times when the blood glucose level tends to rise too high, such as at mealtimes. Thus, each patient is provided with an individualized pattern of treatment.

In persons with type II diabetes, dieting and exercise are usually recommended in an attempt to induce weight loss

and to reverse the insulin resistance. If this fails, drugs may be administered to increase insulin sensitivity or to stimulate increased production of insulin by the pancreas. In many persons, however, exogenous insulin must be used to regulate blood glucose.

In the past, the insulin used for treatment was derived from animal pancreata. However, human insulin produced by the recombinant DNA process has become more widely used because some patients develop immunity and sensitization against animal insulin, thus limiting its effectiveness.

**Relation of Treatment to Arteriosclerosis.** Diabetic patients, mainly because of their high levels of circulating cholesterol and other lipids, develop atherosclerosis, arteriosclerosis, severe coronary heart disease, and multiple microcirculatory lesions far more easily than do normal people. Indeed, those who have poorly controlled diabetes throughout childhood are likely to die of heart disease in early adulthood.

In the early days of treating diabetes, the tendency was to severely reduce the carbohydrates in the diet so that the insulin requirements would be minimized. This procedure kept the blood glucose from increasing too high and attenuated loss of glucose in the urine, but it did not prevent many of the abnormalities of fat metabolism. Consequently, the current tendency is to allow the patient an almost normal carbohydrate diet and to give enough insulin to metabolize the carbohydrates. This decreases the rate of fat metabolism and depresses the high level of blood cholesterol.

Because the complications of diabetes, such as atherosclerosis, increased susceptibility to infection, diabetic retinopathy, cataracts, hypertension, and chronic renal disease, are closely associated with the levels of blood lipids and blood glucose, most physicians also use lipid-lowering drugs to help prevent these disturbances.

### Insulinoma—Hyperinsulinism

Although much rarer than diabetes, excessive insulin production occasionally occurs from an adenoma of an islet of Langerhans. About 10 to 15 percent of these adenomas are malignant, and occasionally metastases from the islets of Langerhans spread throughout the body, causing tremendous production of insulin by both the primary and metastatic cancers. Indeed, more than 1000 grams of glucose have had to be administered every 24 hours to prevent hypoglycemia in some of these patients.

**Insulin Shock and Hypoglycemia.** As already emphasized, the central nervous system normally derives essentially all its energy from glucose metabolism, and insulin is not necessary for this use of glucose. However, if high levels of insulin cause blood glucose to fall to low values, the metabolism of the central nervous system becomes depressed. Consequently, in patients with insulin-secreting tumors or in patients with diabetes who administer too much insulin to themselves, the syndrome called *insulin shock* may occur as follows.

As the blood glucose level falls into the range of 50 to 70 mg/100 ml, the central nervous system usually becomes excitable because this degree of hypoglycemia sensitizes neuronal activity. Sometimes various forms of hallucinations result, but more often the patient simply experiences extreme nervousness, trembles all over, and breaks out in a sweat. As the blood glucose level falls to 20 to 50 mg/100 ml, clonic seizures and loss of consciousness are likely to occur. As the glucose level falls still lower, the seizures cease and

only a state of coma remains. Indeed, at times it is difficult by simple clinical observation to distinguish between diabetic coma as a result of insulin-lack acidosis and coma due to hypoglycemia caused by excess insulin. The acetone breath and the rapid, deep breathing of diabetic coma are not present in hypoglycemic coma.

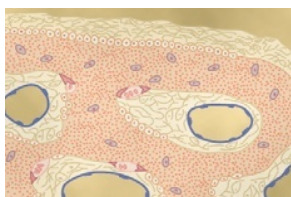
Proper treatment for a patient who has hypoglycemic shock or coma is immediate intravenous administration of large quantities of glucose. This usually brings the patient out of shock within a minute or more. Also, the administration of glucagon (or, less effectively, epinephrine) can cause glycogenolysis in the liver and thereby increase the blood glucose level extremely rapidly. If treatment is not administered immediately, permanent damage to the neuronal cells of the central nervous system often occurs.

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# Parathyroid Hormone, Calcitonin, Calcium and Phosphate Metabolism, Vitamin D, Bone, and Teeth



The physiology of calcium and phosphate metabolism, formation of bone and teeth, and regulation of *vitamin D*, *parathyroid hormone* (PTH), and *calcitonin* are all closely intertwined.

Extracellular calcium ion concentration, for example, is determined by the interplay of calcium absorption from the intestine, renal excretion of calcium, and bone uptake and release of calcium, each of which is regulated by the hormones just noted. Because phosphate homeostasis and calcium homeostasis are closely associated, they are discussed together in this chapter.

## Overview of Calcium and Phosphate Regulation in the Extracellular Fluid and Plasma

Extracellular fluid calcium concentration is normally regulated precisely, seldom rising or falling more than a few percent from the normal value of about 9.4 mg/dl, which is equivalent to 2.4 mmol calcium per liter. This precise control is essential because calcium plays a key role in many physiologic processes, including contraction of skeletal, cardiac, and smooth muscles; blood clotting; and transmission of nerve impulses, to name just a few. Excitable cells, such as neurons, are sensitive to changes in calcium ion concentrations, and increases in calcium ion concentration above normal (*hypercalcemia*) cause progressive depression of the nervous system; conversely, decreases in calcium concentration (*hypocalcemia*) cause the nervous system to become more excited.

An important feature of extracellular calcium regulation is that only about 0.1 percent of the total body calcium is in the extracellular fluid, about 1 percent is in the cells and its organelles, and the rest is stored in bones. Therefore, the bones can serve as large reservoirs, releasing calcium when extracellular fluid concentration decreases and storing excess calcium.

Approximately 85 percent of the body's phosphate is stored in bones, 14 to 15 percent is in the cells, and less

than 1 percent is in the extracellular fluid. Although extracellular fluid phosphate concentration is not nearly as well regulated as calcium concentration, phosphate serves several important functions and is controlled by many of the same factors that regulate calcium.

## Calcium in the Plasma and Interstitial Fluid

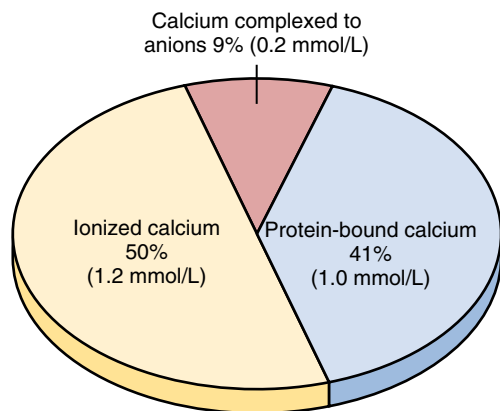
The calcium in the plasma is present in three forms, as shown in Figure 79-1: (1) About 41 percent (1 mmol/L) of the calcium is combined with the plasma proteins and in this form is nondiffusible through the capillary membrane; (2) about 9 percent of the calcium (0.2 mmol/L) is diffusible through the capillary membrane but is combined with anionic substances of the plasma and interstitial fluids (citrate and phosphate, for instance) in such a manner that it is not ionized; and (3) the remaining 50 percent of the calcium in the plasma is both diffusible through the capillary membrane and ionized.

Thus, the plasma and interstitial fluids have a normal calcium *ion* concentration of about 1.2 mmol/L (or 2.4 mEq/L, because it is a divalent ion), a level only one-half the total plasma calcium concentration. This ionic calcium is the form that is important for most functions of calcium in the body, including the effect of calcium on the heart, the nervous system, and bone formation.

## Inorganic Phosphate in the Extracellular Fluids

Inorganic phosphate in the plasma is mainly in two forms:  $\text{HPO}_4^-$  and  $\text{H}_2\text{PO}_4^-$ . The concentration of  $\text{HPO}_4^-$  is about 1.05 mmol/L, and the concentration of  $\text{H}_2\text{PO}_4^-$  is about 0.26 mmol/L. When the total quantity of phosphate in the extracellular fluid rises, so does the quantity of each of these two types of phosphate ions. Furthermore, when the pH of the extracellular fluid becomes more acidic, there is a relative increase in  $\text{H}_2\text{PO}_4^-$  and a decrease in  $\text{HPO}_4^-$ , whereas the opposite occurs when the extracellular fluid becomes alkaline. These relations were presented in the discussion of acid-base balance in Chapter 30.

Because it is difficult to determine chemically the exact quantities of  $\text{HPO}_4^-$  and  $\text{H}_2\text{PO}_4^-$  in the blood, ordinarily the total quantity of phosphate is expressed in terms of milligrams of *phosphorus* per deciliter (100 ml) of blood. The average total quantity of inorganic phosphorus



**Figure 79-1** Distribution of ionized calcium ( $\text{Ca}^{++}$ ), diffusible but un-ionized calcium complexed to anions, and nondiffusible protein-bound calcium in blood plasma.

represented by both phosphate ions is about 4 mg/dl, varying between normal limits of 3 to 4 mg/dl in adults and 4 to 5 mg/dl in children.

### Nonbone Physiologic Effects of Altered Calcium and Phosphate Concentrations in the Body Fluids

Changing the level of phosphate in the extracellular fluid from far below normal to two to three times normal does not cause major immediate effects on the body. In contrast, even slight increases or decreases of calcium ion in the extracellular fluid can cause extreme immediate physiological effects. In addition, chronic hypocalcemia or hypophosphatemia greatly decreases bone mineralization, as explained later in the chapter.

**Hypocalcemia Causes Nervous System Excitement and Tetany.** When the extracellular fluid concentration of calcium ions falls below normal, the nervous system becomes progressively more excitable because this causes increased neuronal membrane permeability to sodium ions, allowing easy initiation of action potentials. At plasma calcium ion concentrations about 50 percent below normal, the peripheral nerve fibers become so excitable that they begin to discharge spontaneously, initiating trains of nerve impulses that pass to the peripheral skeletal muscles to elicit tetanic muscle contraction. Consequently, hypocalcemia causes tetany. It also occasionally causes seizures because of its action of increasing excitability in the brain.

Figure 79-2 shows tetany in the hand, which usually occurs before tetany develops in most other parts of the body. This is called “carpopedal spasm.”

Tetany ordinarily occurs when the blood concentration of calcium falls from its normal level of 9.4 mg/dl to about 6 mg/dl, which is only 35 percent below the normal calcium concentration, and it is usually lethal at about 4 mg/dl.

In laboratory animals, in which calcium can gradually be reduced beyond the usual lethal levels, very extreme hypocalcemia can cause other effects that are seldom



**Figure 79-2** Hypocalcemic tetany in the hand, called *carpopedal spasm*.

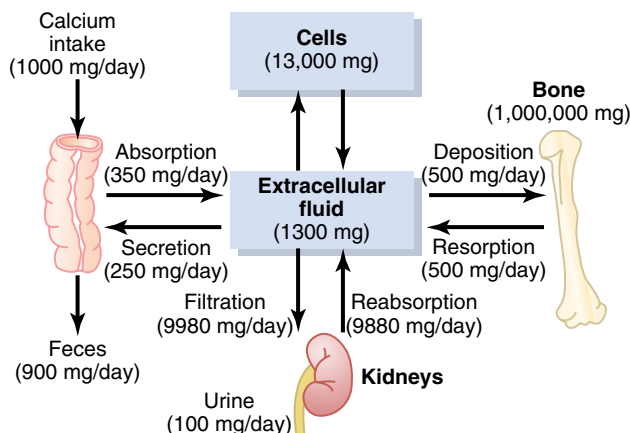
evident in patients, such as marked dilatation of the heart, changes in cellular enzyme activities, increased membrane permeability in some cells (in addition to nerve cells), and impaired blood clotting.

**Hypercalcemia Depresses Nervous System and Muscle Activity.** When the level of calcium in the body fluids rises above normal, the nervous system becomes depressed and reflex activities of the central nervous system are sluggish. Also, increased calcium ion concentration decreases the QT interval of the heart and causes lack of appetite and constipation, probably because of depressed contractility of the muscle walls of the gastrointestinal tract.

These depressive effects begin to appear when the blood level of calcium rises above about 12 mg/dl, and they can become marked as the calcium level rises above 15 mg/dl. When the level of calcium rises above about 17 mg/dl in the blood, calcium phosphate crystals are likely to precipitate throughout the body; this condition is discussed later in connection with parathyroid poisoning.

### Absorption and Excretion of Calcium and Phosphate

**Intestinal Absorption and Fecal Excretion of Calcium and Phosphate.** The usual rates of intake are about 1000 mg/day each for calcium and phosphorus, about the amounts in 1 liter of milk. Normally, divalent cations such as calcium ions are poorly absorbed from the intestines. However, as discussed later, *vitamin D* promotes calcium absorption by the intestines, and about 35 percent (350 mg/day) of the ingested calcium is usually absorbed; the calcium remaining in the intestine is excreted in the feces. An additional 250 mg/day of calcium enters the intestines via secreted gastrointestinal juices and sloughed mucosal cells. Thus, about 90 percent (900 mg/day) of the daily intake of calcium is excreted in the feces (Figure 79-3).



**Figure 79-3** Overview of calcium exchange between different tissue compartments in a person ingesting 1000 mg of calcium per day. Note that most of the ingested calcium is normally eliminated in the feces, although the kidneys have the capacity to excrete large amounts by reducing tubular reabsorption of calcium.

Intestinal absorption of phosphate occurs easily. Except for the portion of phosphate that is excreted in the feces in combination with nonabsorbed calcium, almost all the dietary phosphate is absorbed into the blood from the gut and later excreted in the urine.

**Renal Excretion of Calcium and Phosphate.** Approximately 10 percent (100 mg/day) of the ingested calcium is excreted in the urine. About 41 percent of the plasma calcium is bound to plasma proteins and is therefore not filtered by the glomerular capillaries. The rest is combined with anions such as phosphate (9 percent) or ionized (50 percent) and is filtered through the glomeruli into the renal tubules.

Normally, the renal tubules reabsorb 99 percent of the filtered calcium and about 100 mg/day are excreted in the urine. Approximately 90 percent of the calcium in the glomerular filtrate is reabsorbed in the proximal tubules, loops of Henle, and early distal tubules.

Then in the late distal tubules and early collecting ducts, reabsorption of the remaining 10 percent is selective, depending on the calcium ion concentration in the blood.

When calcium concentration is low, this reabsorption is great, so almost no calcium is lost in the urine. Conversely, even a minute increase in blood calcium ion concentration above normal increases calcium excretion markedly. We shall see later in the chapter that the most important factor controlling this reabsorption of calcium in the distal portions of the nephron, and therefore controlling the rate of calcium excretion, is PTH.

Renal phosphate excretion is controlled by an *overflow mechanism*, as explained in Chapter 29. That is, when phosphate concentration in the plasma is below the critical value of about 1 mmol/L, all the phosphate in the glomerular filtrate is reabsorbed and no phosphate is lost in the urine. But above this critical concentration, the rate of phosphate loss is directly proportional to the additional

increase. Thus, the kidneys regulate the phosphate concentration in the extracellular fluid by altering the rate of phosphate excretion in accordance with the plasma phosphate concentration and the rate of phosphate filtration by the kidneys.

However, as discussed later in the chapter, PTH can greatly increase phosphate excretion by the kidneys, thereby playing an important role in the control of plasma phosphate concentration and calcium concentration.

### Bone and Its Relation to Extracellular Calcium and Phosphate

Bone is composed of a tough *organic matrix* that is greatly strengthened by deposits of *calcium salts*. Average *compact bone* contains by weight about 30 percent matrix and 70 percent salts. *Newly formed bone* may have a considerably higher percentage of matrix in relation to salts.

**Organic Matrix of Bone.** The organic matrix of bone is 90 to 95 percent *collagen fibers*, and the remainder is a homogeneous gelatinous medium called *ground substance*. The collagen fibers extend primarily along the lines of tensional force and give bone its powerful tensile strength.

The ground substance is composed of extracellular fluid plus *proteoglycans*, especially *chondroitin sulfate* and *hyaluronic acid*. The precise function of each of these is not known, although they do help to control the deposition of calcium salts.

**Bone Salts.** The crystalline salts deposited in the organic matrix of bone are composed principally of *calcium* and *phosphate*. The formula for the major crystalline salt, known as *hydroxyapatite*, is the following:



Each crystal—about 400 angstroms long, 10 to 30 angstroms thick, and 100 angstroms wide—is shaped like a long, flat plate. The relative ratio of calcium to phosphorus can vary markedly under different nutritional conditions, the Ca/P ratio on a weight basis varying between 1.3 and 2.0.

*Magnesium, sodium, potassium, and carbonate* ions are also present among the bone salts, although x-ray diffraction studies fail to show definite crystals formed by them. Therefore, they are believed to be conjugated to the hydroxyapatite crystals rather than organized into distinct crystals of their own. This ability of many types of ions to conjugate to bone crystals extends to many ions normally foreign to bone, such as *strontium, uranium, plutonium, the other transuranic elements, lead, gold, other heavy metals*, and *at least 9 of 14 of the major radioactive products released by explosion of the hydrogen bomb*. Deposition of radioactive substances in the bone can cause prolonged irradiation of the bone tissues, and if a sufficient amount

is deposited, an osteogenic sarcoma (bone cancer) eventually develops in most cases.

### Tensile and Compressional Strength of Bone.

Each collagen fiber of *compact* bone is composed of repeating periodic segments every 640 angstroms along its length; hydroxyapatite crystals lie adjacent to each segment of the fiber, bound tightly to it. This intimate bonding prevents “shear” in the bone; that is, it prevents the crystals and collagen fibers from slipping out of place, which is essential in providing strength to the bone. In addition, the segments of adjacent collagen fibers overlap one another, also causing hydroxyapatite crystals to be overlapped like bricks keyed to one another in a brick wall.

The collagen fibers of bone, like those of tendons, have great tensile strength, whereas the calcium salts have great compressional strength. These combined properties plus the degree of bondage between the collagen fibers and the crystals provide a bony structure that has both extreme tensile strength and compressional strength.

### Precipitation and Absorption of Calcium and Phosphate in Bone—Equilibrium with the Extracellular Fluids

**Hydroxyapatite Does Not Precipitate in Extracellular Fluid Despite Supersaturation of Calcium and Phosphate Ions.** The concentrations of calcium and phosphate ions in extracellular fluid are considerably greater than those required to cause precipitation of hydroxyapatite. However, inhibitors are present in almost all tissues of the body, as well as in plasma, to prevent such precipitation; one such inhibitor is *pyrophosphate*. Therefore, hydroxyapatite crystals fail to precipitate in normal tissues except in bone despite the state of supersaturation of the ions.

**Mechanism of Bone Calcification.** The initial stage in bone production is the secretion of *collagen molecules* (called collagen monomers) and *ground substance* (mainly proteoglycans) by *osteoblasts*. The collagen monomers polymerize rapidly to form collagen fibers; the resultant tissue becomes *osteoid*, a cartilage-like material differing from cartilage in that calcium salts readily precipitate in it. As the osteoid is formed, some of the osteoblasts become entrapped in the osteoid and become quiescent. At this stage they are called *osteocytes*.

Within a few days after the osteoid is formed, calcium salts begin to precipitate on the surfaces of the collagen fibers. The precipitates first appear at intervals along each collagen fiber, forming minute nidi that rapidly multiply and grow over a period of days and weeks into the finished product, *hydroxyapatite crystals*.

The initial calcium salts to be deposited are not hydroxyapatite crystals but amorphous compounds (non-crystalline), a mixture of salts such as  $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ ,  $\text{Ca}_3(\text{PO}_4)_2 \cdot 3\text{H}_2\text{O}$ , and others. Then by a process of substitution and addition of atoms, or reabsorption and

reprecipitation, these salts are converted into the hydroxyapatite crystals over a period of weeks or months. A few percent may remain permanently in the amorphous form. This is important because these amorphous salts can be absorbed rapidly when there is need for extra calcium in the extracellular fluid.

The mechanism that causes calcium salts to be deposited in osteoid is not fully understood. One theory holds that at the time of formation, the collagen fibers are specially constituted in advance for causing precipitation of calcium salts. The osteoblasts supposedly also secrete a substance into the osteoid to neutralize an inhibitor (believed to be pyrophosphate) that normally prevents hydroxyapatite crystallization. Once the pyrophosphate has been neutralized, the natural affinity of the collagen fibers for calcium salts causes the precipitation.

**Precipitation of Calcium in Nonosseous Tissues Under Abnormal Conditions.** Although calcium salts almost never precipitate in normal tissues besides bone, under abnormal conditions, they do precipitate. For instance, they precipitate in arterial walls in *arteriosclerosis* and cause the arteries to become bonelike tubes. Likewise, calcium salts frequently deposit in degenerating tissues or in old blood clots. Presumably, in these instances, the inhibitor factors that normally prevent deposition of calcium salts disappear from the tissues, thereby allowing precipitation.

### Calcium Exchange Between Bone and Extracellular Fluid

If soluble calcium salts are injected intravenously, the calcium ion concentration may increase immediately to high levels. However, within 30 to 60 minutes, the calcium ion concentration returns to normal. Likewise, if large quantities of calcium ions are removed from the circulating body fluids, the calcium ion concentration again returns to normal within 30 minutes to about 1 hour. These effects result in great part from the fact that the bone contains a type of *exchangeable* calcium that is always in equilibrium with the calcium ions in the extracellular fluids.

A small portion of this exchangeable calcium is also the calcium found in all tissue cells, especially in highly permeable types of cells such as those of the liver and the gastrointestinal tract. However, most of the exchangeable calcium is in the bone. It normally amounts to about 0.4 to 1 percent of the total bone calcium. This calcium is deposited in the bones in a form of readily mobilizable salt such as  $\text{CaHPO}_4$  and other amorphous calcium salts.

The importance of exchangeable calcium is that it provides a rapid *buffering* mechanism to keep the calcium ion concentration in the extracellular fluids from rising to excessive levels or falling to low levels under transient conditions of excess or decreased availability of calcium.



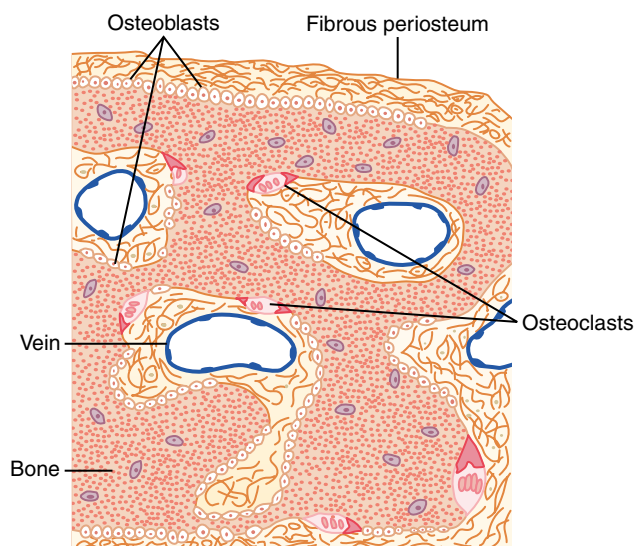
**Deposition and Absorption of Bone—Remodeling of Bone**

**Deposition of Bone by the Osteoblasts.** Bone is continually being deposited by *osteoblasts*, and it is continually being absorbed where *osteoclasts* are active (Figure 79-4). Osteoblasts are found on the outer surfaces of the bones and in the bone cavities. A small amount of osteoblastic activity occurs continually in all living bones (on about 4 percent of all surfaces at any given time in an adult), so at least some new bone is being formed constantly.

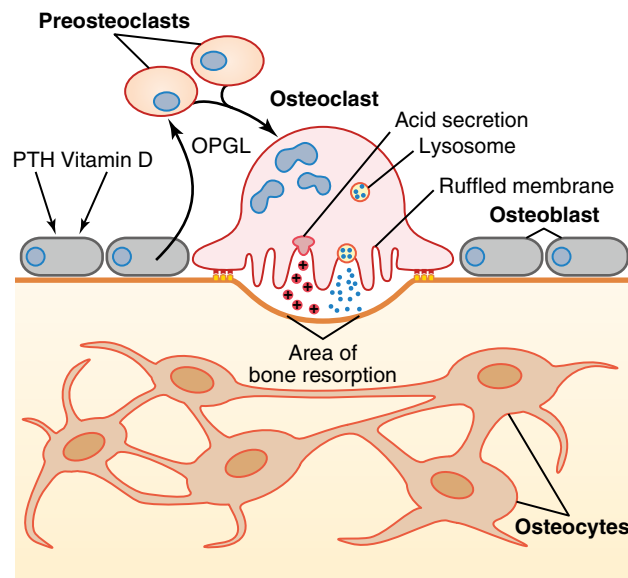
**Absorption of Bone—Function of the Osteoclasts.** Bone is also being continually absorbed in the presence of osteoclasts, which are large, phagocytic, multinucleated cells (as many as 50 nuclei), derivatives of monocytes or monocyte-like cells formed in the bone marrow. The osteoclasts are normally active on less than 1 percent of the bone surfaces of an adult. Later in the chapter we see that PTH controls the bone absorptive activity of osteoclasts.

Histologically, bone absorption occurs immediately adjacent to the osteoclasts. The mechanism of this absorption is believed to be the following: The osteoclasts send out villus-like projections toward the bone, forming a ruffled border adjacent to the bone (Figure 79-5). The villi secrete two types of substances: (1) proteolytic enzymes, released from the lysosomes of the osteoclasts, and (2) several acids, including citric acid and lactic acid, released from the mitochondria and secretory vesicles. The enzymes digest or dissolve the organic matrix of the bone, and the acids cause dissolution of the bone salts. The osteoclastic cells also imbibe by phagocytosis minute particles of bone matrix and crystals, eventually also dissolving these and releasing the products into the blood.

As discussed later, parathyroid hormone (PTH) stimulates osteoclast activity and bone resorption, but this occurs through an indirect mechanism. PTH binds to receptors on the adjacent osteoblasts, causing them to release cytokines, including *osteoprotegerin ligand* (OPGL), which is also called *RANK ligand*. OPGL activates receptors on preosteoclast cells, causing them to differentiate into mature multinucleated osteoclasts. The mature osteoclasts then develop



**Figure 79-4** Osteoblastic and osteoclastic activity in the same bone.



**Figure 79-5** Bone resorption by osteoclasts. Parathyroid hormone (PTH) binds to receptors on osteoblasts, causing them to release osteoprotegerin ligand (OPGL), which binds to receptors on preosteoclast cells. This causes the cells to differentiate into mature osteoclasts. The osteoclasts then develop a ruffled border and release enzymes from lysosomes, as well as acids that promote bone resorption. Osteocytes are osteoblasts that have become encased in bone matrix during bone tissue production; the osteocytes form a system of interconnected cells that spreads all through the bone.

a ruffled border and release enzymes and acids that promote bone resorption.

Osteoblasts also produce osteoprotegerin (OPG), sometimes called *osteoclastogenesis inhibitory factor* (OCIF), a cytokine which inhibits bone resorption. OPG acts as a “decoy” receptor, binding to OPGL and preventing OPGL from interacting with its receptor, thereby inhibiting differentiation of preosteoclasts into mature osteoclasts that resorb bone. OPG opposes the bone resorptive activity of PTH and mice with genetic deficiency of OPG have severe decreases in bone mass compared with mice with normal OPG formation. Although the factors that regulate OPG are not well understood, vitamin D and PTH appear to stimulate production of mature osteoclasts through the dual action of inhibiting OPG production and stimulating OPGL formation. On the other hand, the hormone estrogen stimulates OPG production.

The therapeutic importance of the OPG-OPGL pathway is currently being exploited. Novel drugs that mimic the action of OPG by blocking the interaction of OPGL with its receptor appear to be useful for treating bone loss in postmenopausal women and in some patients with bone cancer.

**Bone Deposition and Absorption Are Normally in Equilibrium.** Normally, except in growing bones, the rates of bone deposition and absorption are equal to each other, so the total mass of bone remains constant. Osteoclasts usually exist in small but concentrated masses, and once a mass of osteoclasts begins to develop, it usually eats away at the bone for about 3 weeks, creating a tunnel that ranges in diameter from 0.2 to 1 millimeter and is several millimeters long. At the end of this time, the osteoclasts disappear and the tunnel

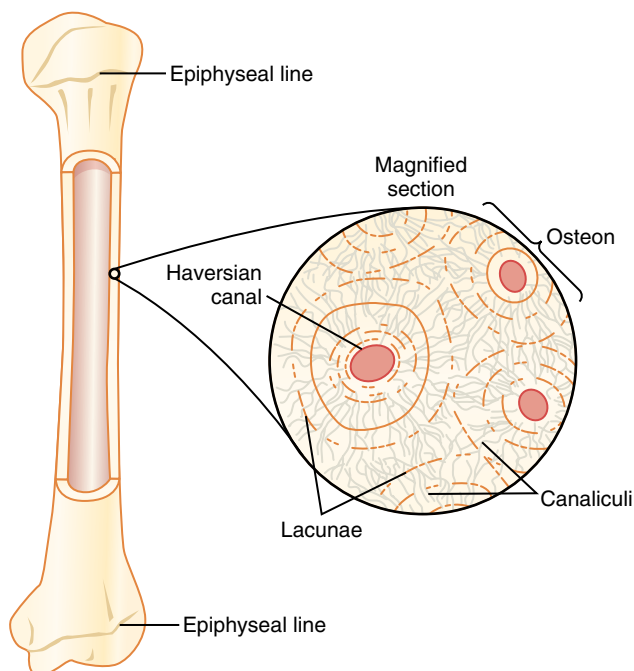


Figure 79-6 Structure of bone.

is invaded by osteoblasts instead; then new bone begins to develop. Bone deposition then continues for several months, the new bone being laid down in successive layers of concentric circles (*lamellae*) on the inner surfaces of the cavity until the tunnel is filled. Deposition of new bone ceases when the bone begins to encroach on the blood vessels supplying the area. The canal through which these vessels run, called the *haversian canal*, is all that remains of the original cavity. Each new area of bone deposited in this way is called an *osteon*, as shown in Figure 79-6.

**Value of Continual Bone Remodeling.** The continual deposition and absorption of bone have several physiologically important functions. First, bone ordinarily adjusts its strength in proportion to the degree of bone stress. Consequently, bones thicken when subjected to heavy loads. Second, even the shape of the bone can be rearranged for proper support of mechanical forces by deposition and absorption of bone in accordance with stress patterns. Third, because old bone becomes relatively brittle and weak, new organic matrix is needed as the old organic matrix degenerates. In this manner, the normal toughness of bone is maintained. Indeed, the bones of children, in whom the rates of deposition and absorption are rapid, show little brittleness in comparison with the bones of the elderly, in whom the rates of deposition and absorption are slow.

**Control of the Rate of Bone Deposition by Bone "Stress."** Bone is deposited in proportion to the compressional load that the bone must carry. For instance, the bones of athletes become considerably heavier than those of non-athletes. Also, if a person has one leg in a cast but continues to walk on the opposite leg, the bone of the leg in the cast becomes thin and as much as 30 percent decalcified within a few weeks, whereas the opposite bone remains thick and normally calcified. Therefore, continual physical stress stimulates osteoblastic deposition and calcification of bone.

Bone stress also determines the shape of bones under certain circumstances. For instance, if a long bone of the leg

breaks in its center and then heals at an angle, the compression stress on the inside of the angle causes increased deposition of bone. Increased absorption occurs on the outer side of the angle where the bone is not compressed. After many years of increased deposition on the inner side of the angulated bone and absorption on the outer side, the bone can become almost straight, especially in children because of the rapid remodeling of bone at younger ages.

**Repair of a Fracture Activates Osteoblasts.** Fracture of a bone in some way maximally activates all the periosteal and intraosseous osteoblasts involved in the break. Also, immense numbers of new osteoblasts are formed almost immediately from *osteoprogenitor cells*, which are bone stem cells in the surface tissue lining bone, called the "*bone membrane*." Therefore, within a short time, a large bulge of osteoblastic tissue and new organic bone matrix, followed shortly by the deposition of calcium salts, develops between the two broken ends of the bone. This is called a *callus*.

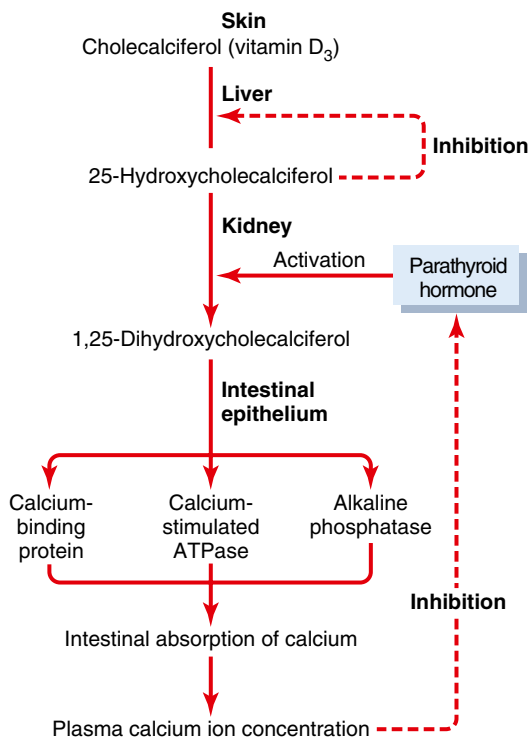
Many orthopedic surgeons use the phenomenon of bone stress to accelerate the rate of fracture healing. This is done by use of special mechanical fixation apparatuses for holding the ends of the broken bone together so that the patient can continue to use the bone immediately. This causes stress on the opposed ends of the broken bones, which accelerates osteoblastic activity at the break and often shortens convalescence.

## Vitamin D

Vitamin D has a potent effect to increase calcium absorption from the intestinal tract; it also has important effects on bone deposition and bone absorption, as discussed later. However, vitamin D itself is not the active substance that actually causes these effects. Instead, vitamin D must first be converted through a succession of reactions in the liver and the kidneys to the final active product, *1,25-dihydroxycholecalciferol*, also called  $1,25(\text{OH})_2\text{D}_3$ . Figure 79-7 shows the succession of steps that lead to the formation of this substance from vitamin D. Let us discuss these steps.

**Cholecalciferol (Vitamin  $\text{D}_3$ ) Is Formed in the Skin.** Several compounds derived from sterols belong to the vitamin D family, and they all perform more or less the same functions. Vitamin  $\text{D}_3$  (also called *cholecalciferol*) is the most important of these and is formed in the skin as a result of irradiation of *7-dehydrocholesterol*, a substance normally in the skin, by ultraviolet rays from the sun. Consequently, appropriate exposure to the sun prevents vitamin D deficiency. The additional vitamin D compounds that we ingest in food are identical to the cholecalciferol formed in the skin, except for the substitution of one or more atoms that do not affect their function.

**Cholecalciferol Is Converted to 25-Hydroxycholecalciferol in the Liver.** The first step in the activation of cholecalciferol is to convert it to 25-hydroxycholecalciferol; this occurs in the liver. The process is limited because the 25-hydroxycholecalciferol has a feedback inhibitory

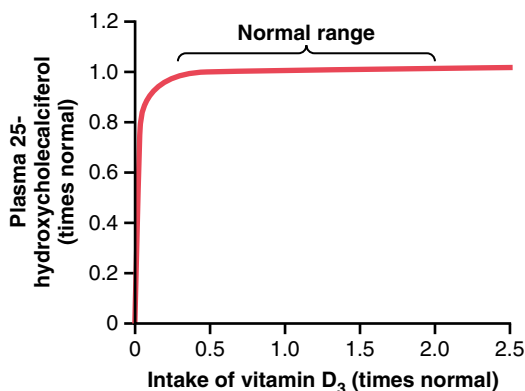


**Figure 79-7** Activation of vitamin D<sub>3</sub> to form 1,25-dihydroxycholecalciferol and the role of vitamin D in controlling the plasma calcium concentration.

effect on the conversion reactions. This feedback effect is extremely important for two reasons.

First, the feedback mechanism precisely regulates the concentration of 25-hydroxycholecalciferol in the plasma, an effect that is shown in Figure 79-8. Note that the intake of vitamin D<sub>3</sub> can increase many times and yet the concentration of 25-hydroxycholecalciferol remains nearly normal. This high degree of feedback control prevents excessive action of vitamin D when intake of vitamin D<sub>3</sub> is altered over a wide range.

Second, this controlled conversion of vitamin D<sub>3</sub> to 25-hydroxycholecalciferol conserves the vitamin D



**Figure 79-8** Effect of increasing vitamin D<sub>3</sub> intake on the plasma concentration of 25-hydroxycholecalciferol. This figure shows that increases in vitamin D intake, up to 2.5 times normal, have little effect on the final quantity of activated vitamin D that is formed. Deficiency of activated vitamin D occurs only at very low levels of vitamin D intake.

stored in the liver for future use. Once it is converted, it persists in the body for only a few weeks, whereas in the vitamin D form, it can be stored in the liver for many months.

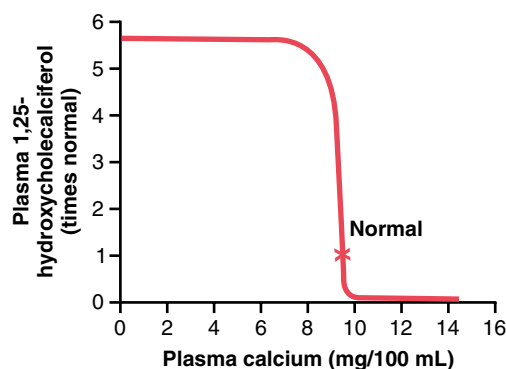
### Formation of 1,25-Dihydroxycholecalciferol in the Kidneys and Its Control by Parathyroid Hormone.

Figure 79-7 also shows the conversion in the proximal tubules of the kidneys of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. This latter substance is by far the most active form of vitamin D because the previous products in the scheme of Figure 79-7 have less than 1/1000 of the vitamin D effect. Therefore, in the absence of the kidneys, vitamin D loses almost all its effectiveness.

Note also in Figure 79-7 that the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol requires PTH. In the absence of PTH, almost none of the 1,25-dihydroxycholecalciferol is formed. Therefore, PTH exerts a potent influence in determining the functional effects of vitamin D in the body.

### Calcium Ion Concentration Controls the Formation of 1,25-Dihydroxycholecalciferol.

Figure 79-9 demonstrates that the plasma concentration of 1,25-dihydroxycholecalciferol is inversely affected by the concentration of calcium in the plasma. There are two reasons for this. First, the calcium ion itself has a slight effect in preventing the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. Second, and even more important, as we shall see later in the chapter, the rate of secretion of PTH is greatly suppressed when the plasma calcium ion concentration rises above 9 to 10 mg/100 ml. Therefore, at calcium concentrations below this level, PTH promotes the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol in the kidneys. At higher calcium concentrations, when PTH is suppressed, the 25-hydroxycholecalciferol is converted to a different



**Figure 79-9** Effect of plasma calcium concentration on the plasma concentration of 1,25-dihydroxycholecalciferol. This figure shows that a slight decrease in calcium concentration below normal causes increased formation of activated vitamin D, which in turn leads to greatly increased absorption of calcium from the intestine.

compound—24,25-dihydroxycholecalciferol—that has almost no vitamin D effect.

When the plasma calcium concentration is already too high, the formation of 1,25-dihydroxycholecalciferol is greatly depressed. Lack of this in turn decreases the absorption of calcium from the intestines, the bones, and the renal tubules, thus causing the calcium ion concentration to fall back toward its normal level.

### Actions of Vitamin D

The active form of vitamin D, 1,25-dihydroxycholecalciferol, has several effects on the intestines, kidneys, and bones that increase absorption of calcium and phosphate into the extracellular fluid and contribute to feedback regulation of these substances.

Vitamin D receptors are present in most cells in the body and are located mainly in the nuclei of target cells. Similar to receptors for steroids and thyroid hormone, the vitamin D receptor has hormone-binding and DNA-binding domains. The vitamin D receptor forms a complex with another intracellular receptor, the *retinoid-X receptor*, and this complex binds to DNA and activates transcription in most instances. In some cases, however, vitamin D suppresses transcription. Although the vitamin D receptor binds several forms of cholecalciferol, its affinity for 1,25-dihydroxycholecalciferol is roughly 1000 times that for 25-hydroxycholecalciferol, which explains their relative biological potencies.

**“Hormonal” Effect of Vitamin D to Promote Intestinal Calcium Absorption.** 1,25-Dihydroxycholecalciferol itself functions as a type of “hormone” to promote intestinal absorption of calcium. It does this principally by increasing, over a period of about 2 days, formation of *calbindin*, a *calcium-binding protein*, in the intestinal epithelial cells. This protein functions in the brush border of these cells to transport calcium into the cell cytoplasm. Then the calcium moves through the basolateral membrane of the cell by facilitated diffusion. The rate of calcium absorption is directly proportional to the quantity of this calcium-binding protein. Furthermore, this protein remains in the cells for several weeks after the 1,25-dihydroxycholecalciferol has been removed from the body, thus causing a prolonged effect on calcium absorption.

Other effects of 1,25-dihydroxycholecalciferol that might play a role in promoting calcium absorption are the formation of (1) a calcium-stimulated ATPase in the brush border of the epithelial cells and (2) an alkaline phosphatase in the epithelial cells. The precise details of all these effects are unclear.

**Vitamin D Promotes Phosphate Absorption by the Intestines.** Although phosphate is usually absorbed easily, phosphate flux through the gastrointestinal epithelium is enhanced by vitamin D. It is believed that this results from a direct effect of 1,25-dihydroxycholecalciferol, but it is possible that it results secondarily from this hor-

mon’s action on calcium absorption, the calcium in turn acting as a transport mediator for the phosphate.

**Vitamin D Decreases Renal Calcium and Phosphate Excretion.** Vitamin D also increases calcium and phosphate reabsorption by the epithelial cells of the renal tubules, thereby tending to decrease excretion of these substances in the urine. However, this is a weak effect and probably not of major importance in regulating the extracellular fluid concentration of these substances.

**Effect of Vitamin D on Bone and Its Relation to Parathyroid Hormone Activity.** Vitamin D plays important roles in both bone absorption and bone deposition. The administration of *extreme quantities of vitamin D causes absorption of bone*. In the absence of vitamin D, the effect of PTH in causing bone absorption (discussed in the next section) is greatly reduced or even prevented. The mechanism of this action of vitamin D is not known, but it is believed to result from the effect of 1,25-dihydroxycholecalciferol to increase calcium transport through cellular membranes.

*Vitamin D in smaller quantities promotes bone calcification.* One of the ways in which it does this is to increase calcium and phosphate absorption from the intestines. However, even in the absence of such increase, it enhances the mineralization of bone. Here again, the mechanism of the effect is unknown, but it probably also results from the ability of 1,25-dihydroxycholecalciferol to cause transport of calcium ions through cell membranes—but in this instance, perhaps in the opposite direction through the osteoblastic or osteocytic cell membranes.

## Parathyroid Hormone

Parathyroid hormone provides a powerful mechanism for controlling extracellular calcium and phosphate concentrations by regulating intestinal reabsorption, renal excretion, and exchange between the extracellular fluid and bone of these ions. Excess activity of the parathyroid gland causes rapid absorption of calcium salts from the bones, with resultant *hypercalcemia* in the extracellular fluid; conversely, hypofunction of the parathyroid glands causes *hypocalcemia*, often with resultant tetany.

**Physiologic Anatomy of the Parathyroid Glands.** Normally there are four parathyroid glands in humans; they are located immediately behind the thyroid gland—one behind each of the upper and each of the lower poles of the thyroid. Each parathyroid gland is about 6 millimeters long, 3 millimeters wide, and 2 millimeters thick and has a macroscopic appearance of dark brown fat. The parathyroid glands are difficult to locate during thyroid operations because they often look like just another lobule of the thyroid gland. For this reason, before the importance of these glands was generally recognized, total or



subtotal thyroidectomy frequently resulted in removal of the parathyroid glands as well.

Removal of half the parathyroid glands usually causes no major physiologic abnormalities. However, removal of three of the four normal glands causes transient hypoparathyroidism. But even a small quantity of remaining parathyroid tissue is usually capable of hypertrophying to satisfactorily perform the function of all the glands.

The parathyroid gland of the adult human being, shown in Figure 79-10, contains mainly *chief cells* and a small to moderate number of *oxyphil cells*, but oxyphil cells are absent in many animals and in young humans. The chief cells are believed to secrete most, if not all, of the PTH. The function of the oxyphil cells is not certain, but the cells are believed to be modified or depleted chief cells that no longer secrete hormone.

**Chemistry of Parathyroid Hormone.** PTH has been isolated in a pure form. It is first synthesized on the ribosomes in the form of a preprohormone, a polypeptide chain of 110 amino acids. This is cleaved first to a prohormone with 90 amino acids, then to the hormone itself with 84 amino acids by the endoplasmic reticulum and Golgi apparatus, and finally packaged in secretory granules in the cytoplasm of the cells. The final hormone has a molecular weight of about 9500. Smaller compounds with as few as 34 amino acids adjacent to the N terminus of the molecule have also been isolated from the parathyroid glands that exhibit full PTH activity. In fact, because the kidneys rapidly remove the whole 84-amino acid hormone within minutes but fail to remove many of the fragments

for hours, a large share of the hormonal activity is caused by the fragments.

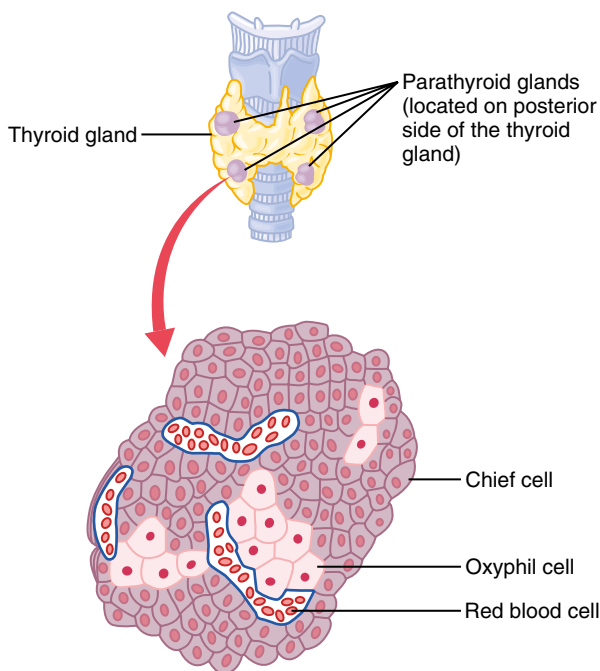
### Effect of Parathyroid Hormone on Calcium and Phosphate Concentrations in the Extracellular Fluid

Figure 79-11 shows the approximate effects on the blood calcium and phosphate concentrations caused by suddenly infusing PTH into an animal and continuing this for several hours. Note that at the onset of infusion the calcium ion concentration begins to rise and reaches a plateau in about 4 hours. The phosphate concentration, however, falls more rapidly than the calcium rises and reaches a depressed level within 1 or 2 hours. The rise in calcium concentration is caused principally by two effects: (1) an effect of PTH to increase calcium and phosphate absorption from the bone and (2) a rapid effect of PTH to decrease the excretion of calcium by the kidneys. The decline in phosphate concentration is caused by a strong effect of PTH to increase renal phosphate excretion, an effect that is usually great enough to override increased phosphate absorption from the bone.

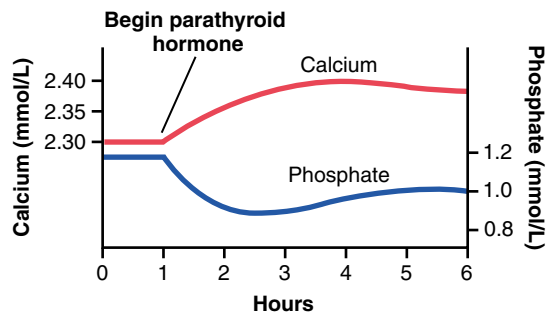
### Parathyroid Hormone Increases Calcium and Phosphate Absorption from the Bone

PTH has two effects on bone in causing absorption of calcium and phosphate. One is a rapid phase that begins in minutes and increases progressively for several hours. This phase results from activation of the already existing bone cells (mainly the osteocytes) to promote calcium and phosphate absorption. The second phase is a much slower one, requiring several days or even weeks to become fully developed; it results from proliferation of the osteoclasts, followed by greatly increased osteoclastic reabsorption of the bone itself, not merely absorption of the calcium phosphate salts from the bone.

**Rapid Phase of Calcium and Phosphate Absorption from Bone—Osteolysis.** When large quantities of PTH are injected, the calcium ion concentration in the blood begins to rise within minutes, long before any new bone cells can be developed. Histological and physiological studies have shown that PTH causes removal of bone salts from two areas in the bone: (1) from the bone matrix in



**Figure 79-10** The four parathyroid glands lie immediately behind the thyroid gland. Almost all of the parathyroid hormone (PTH) is synthesized and secreted by the chief cells. The function of the oxyphil cells is uncertain, but they may be modified or depleted chief cells that no longer secrete PTH.



**Figure 79-11** Approximate changes in calcium and phosphate concentrations during the first 5 hours of parathyroid hormone infusion at a moderate rate.

the vicinity of the osteocytes lying within the bone itself and (2) in the vicinity of the osteoblasts along the bone surface.

One does not usually think of either osteoblasts or osteocytes functioning to cause bone salt absorption, because both these types of cells are osteoblastic in nature and normally associated with bone deposition and its calcification. However, studies have shown that the osteoblasts and osteocytes form a system of interconnected cells that spreads all through the bone and over all the bone surfaces except the small surface areas adjacent to the osteoclasts (see Figure 79-5). In fact, long, filmy processes extend from osteocyte to osteocyte throughout the bone structure, and these processes also connect with the surface osteocytes and osteoblasts. This extensive system is called the *osteocytic membrane system*, and it is believed to provide a membrane that separates the bone itself from the extracellular fluid.

Between the osteocytic membrane and the bone is a small amount of *bone fluid*. Experiments suggest that the osteocytic membrane pumps calcium ions from the bone fluid into the extracellular fluid, creating a calcium ion concentration in the bone fluid only one-third that in the extracellular fluid. When the osteocytic pump becomes excessively activated, the bone fluid calcium concentration falls even lower, and calcium phosphate salts are then absorbed from the bone. This effect is called *osteolysis*, and it occurs without absorption of the bone's fibrous and gel matrix. When the pump is inactivated, the bone fluid calcium concentration rises to a higher level and calcium phosphate salts are redeposited in the matrix.

But where does PTH fit into this picture? First, the cell membranes of both the osteoblasts and the osteocytes have receptor proteins for binding PTH. PTH can activate the calcium pump strongly, thereby causing rapid removal of calcium phosphate salts from those amorphous bone crystals that lie near the cells. PTH is believed to stimulate this pump by increasing the calcium permeability of the bone fluid side of the osteocytic membrane, thus allowing calcium ions to diffuse into the membrane cells from the bone fluid. Then the calcium pump on the other side of the cell membrane transfers the calcium ions the rest of the way into the extracellular fluid.

**Slow Phase of Bone Absorption and Calcium Phosphate Release—Activation of the Osteoclasts.** A much better known effect of PTH and one for which the evidence is much clearer is its activation of the osteoclasts. Yet the osteoclasts do not themselves have membrane receptor proteins for PTH. Instead, it is believed that the activated osteoblasts and osteocytes send secondary “signals” to the osteoclasts. As discussed previously, a major secondary signal is *osteoprotegerin ligand*, which activates receptors on preosteoclast cells and transforms them into mature osteoclasts that set about their usual task of gobbling up the bone over a period of weeks or months.

Activation of the osteoclastic system occurs in two stages: (1) immediate activation of the osteoclasts that are already formed and (2) formation of new osteoclasts.

Several days of excess PTH usually cause the osteoclastic system to become well developed, but it can continue to grow for months under the influence of strong PTH stimulation.

After a few months of excess PTH, osteoclastic resorption of bone can lead to weakened bones and secondary stimulation of the osteoblasts that attempt to correct the weakened state. Therefore, the late effect is actually to enhance both osteoblastic and osteoclastic activity. Still, even in the late stages, there is more bone absorption than bone deposition in the presence of continued excess PTH.

Bone contains such great amounts of calcium in comparison with the total amount in all the extracellular fluids (about 1000 times as much) that even when PTH causes a great rise in calcium concentration in the fluids, it is impossible to discern any immediate effect on the bones. Prolonged administration or secretion of PTH—over a period of many months or years—finally results in very evident absorption in all the bones and even development of large cavities filled with large, multinucleated osteoclasts.

### Parathyroid Hormone Decreases Calcium Excretion and Increases Phosphate Excretion by the Kidneys

Administration of PTH causes rapid loss of phosphate in the urine owing to the effect of the hormone to diminish proximal tubular reabsorption of phosphate ions.

PTH also increases renal tubular reabsorption of calcium at the same time that it diminishes phosphate reabsorption. Moreover, it increases the rate of reabsorption of magnesium ions and hydrogen ions while it decreases the reabsorption of sodium, potassium, and amino acid ions in much the same way that it affects phosphate. The increased calcium absorption occurs mainly in the *late distal tubules*, the *collecting tubules*, the early collecting ducts, and possibly the ascending loop of Henle to a lesser extent.

Were it not for the effect of PTH on the kidneys to increase calcium reabsorption, continual loss of calcium into the urine would eventually deplete both the extracellular fluid and the bones of this mineral.

### Parathyroid Hormone Increases Intestinal Absorption of Calcium and Phosphate

At this point, we should be reminded again that PTH greatly enhances both calcium and phosphate absorption from the intestines by increasing the formation in the kidneys of 1,25-dihydroxycholecalciferol from vitamin D, as discussed earlier in the chapter.

**Cyclic Adenosine Monophosphate Mediates the Effects of Parathyroid Hormone.** A large share of the effect of PTH on its target organs is mediated by the cyclic adenosine monophosphate (cAMP) *second messenger* mechanism. Within a few minutes after PTH administration, the concentration of cAMP increases in the osteocytes, osteoclasts, and other target cells. This

cAMP in turn is probably responsible for such functions as osteoclastic secretion of enzymes and acids to cause bone reabsorption and formation of 1,25-dihydroxycholecalciferol in the kidneys. Other direct effects of PTH probably function independently of the second messenger mechanism.

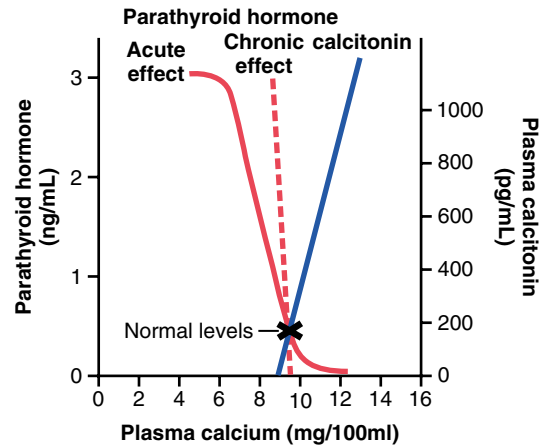
### Control of Parathyroid Secretion by Calcium Ion Concentration

Even the slightest decrease in calcium ion concentration in the extracellular fluid causes the parathyroid glands to increase their rate of secretion within minutes; if the decreased calcium concentration persists, the glands will hypertrophy, sometimes fivefold or more. For instance, the parathyroid glands become greatly enlarged in *rickets*, in which the level of calcium is usually depressed only a small amount. They also become greatly enlarged in *pregnancy*, even though the decrease in calcium ion concentration in the mother's extracellular fluid is hardly measurable, and they are greatly enlarged during *lactation* because calcium is used for milk formation.

Conversely, conditions that increase the calcium ion concentration above normal cause decreased activity and reduced size of the parathyroid glands. Such conditions include (1) excess quantities of calcium in the diet, (2) increased vitamin D in the diet, and (3) bone absorption caused by factors other than PTH (e.g., bone absorption caused by disuse of the bones).

Changes in extracellular fluid calcium ion concentration are detected by a *calcium-sensing receptor* (CaSR) in parathyroid cell membranes. The CaSR is a G protein-coupled receptor that, when stimulated by calcium ions, activates phospholipase C and increases intracellular inositol 1,4,5-triphosphate and diacylglycerol formation. This stimulates release of calcium from intracellular stores, which, in turn, *decreases* PTH secretion. Conversely, decreased extracellular fluid calcium ion concentration inhibits these pathways and stimulates PTH secretion. This contrasts with many endocrine tissues in which hormone secretion is stimulated when these pathways are activated.

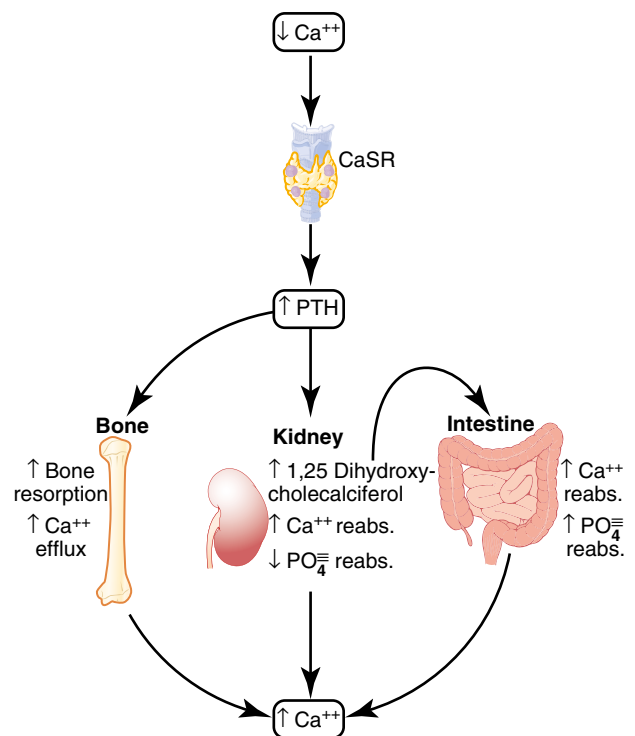
Figure 79-12 shows the approximate relation between plasma calcium concentration and plasma PTH concentration. The solid red curve shows the acute effect when the calcium concentration is changed over a period of a few hours. This shows that even small decreases in calcium concentration from the normal value can double or triple the plasma PTH. The approximate chronic effect that one finds when the calcium ion concentration changes over a period of many weeks, thus allowing time for the glands to hypertrophy greatly, is shown by the dashed red line; this demonstrates that a decrease of only a fraction of a milligram per deciliter in plasma calcium concentration can double PTH secretion. This is the basis of the body's extremely potent feedback system for long-term control of plasma calcium ion concentration.



**Figure 79-12** Approximate effect of plasma calcium concentration on the plasma concentrations of parathyroid hormone and calcitonin. Note especially that long-term, chronic changes in calcium concentration of only a few percentage points can cause as much as 100 percent change in parathyroid hormone concentration.

### Summary of Effects of Parathyroid Hormone.

Figure 79-13 summarizes the main effects of increased PTH secretion in response to decreased extracellular fluid calcium ion concentration: (1) PTH stimulates bone resorption, causing release of calcium into the extracellular fluid; (2) PTH increases reabsorption of calcium and decreases phosphate reabsorption by the renal tubules, leading to decreased excretion of calcium and increased excretion of phosphate; and (3) PTH is



**Figure 79-13** Summary of effects of parathyroid hormone (PTH) on bone, the kidneys, and the intestine in response to decreased extracellular fluid calcium ion concentration. CaSR, calcium sensing receptor.

necessary for conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol, which, in turn, increases calcium absorption by the intestines. These actions together provide a powerful means of regulating extracellular fluid calcium concentration.

## Calcitonin

Calcitonin, a peptide hormone secreted by the thyroid gland, tends to *decrease* plasma calcium concentration and, in general, has effects opposite to those of PTH. However, the quantitative role of calcitonin in humans is far less than that of PTH in regulating calcium ion concentration.

Synthesis and secretion of calcitonin occur in the *parafollicular cells*, or *C cells*, lying in the interstitial fluid between the follicles of the thyroid gland. These cells constitute only about 0.1 percent of the human thyroid gland and are the remnants of the *ultimobranchial glands* of lower animals, such as fish, amphibians, reptiles, and birds. Calcitonin is a 32-amino acid peptide with a molecular weight of about 3400.

**Increased Plasma Calcium Concentration Stimulates Calcitonin Secretion.** The primary stimulus for calcitonin secretion is increased extracellular fluid calcium ion concentration. This contrasts with PTH secretion, which is stimulated by decreased calcium concentration.

In young animals, but much less so in older animals and in humans, an increase in plasma calcium concentration of about 10 percent causes an immediate twofold or more increase in the rate of secretion of calcitonin, which is shown by the blue line in Figure 79-12. This provides a second hormonal feedback mechanism for controlling the plasma calcium ion concentration, but one that is relatively weak and works in a way opposite that of the PTH system.

**Calcitonin Decreases Plasma Calcium Concentration.** In some young animals, calcitonin decreases blood calcium ion concentration rapidly, beginning within minutes after injection of the calcitonin, in at least two ways.

1. The immediate effect is to decrease the absorptive activities of the osteoclasts and possibly the osteolytic effect of the osteocytic membrane throughout the bone, thus shifting the balance in favor of deposition of calcium in the exchangeable bone calcium salts. This effect is especially significant in young animals because of the rapid interchange of absorbed and deposited calcium.
2. The second and more prolonged effect of calcitonin is to decrease the formation of new osteoclasts. Also, because osteoclastic resorption of bone leads secondarily to osteoblastic activity, decreased numbers

of osteoclasts are followed by decreased numbers of osteoblasts. Therefore, over a long period, the net result is reduced osteoclastic and osteoblastic activity and, consequently, little prolonged effect on plasma calcium ion concentration. That is, the effect on plasma calcium is mainly a transient one, lasting for a few hours to a few days at most.

Calcitonin also has minor effects on calcium handling in the kidney tubules and the intestines. Again, the effects are opposite those of PTH, but they appear to be of such little importance that they are seldom considered.

**Calcitonin Has a Weak Effect on Plasma Calcium Concentration in the Adult Human.** The reason for the weak effect of calcitonin on plasma calcium is twofold. First, any initial reduction of the calcium ion concentration caused by calcitonin leads within hours to a powerful stimulation of PTH secretion, which almost overrides the calcitonin effect. When the thyroid gland is removed and calcitonin is no longer secreted, the long-term blood calcium ion concentration is not measurably altered, which again demonstrates the overriding effect of the PTH system of control.

Second, in the adult, the daily rates of absorption and deposition of calcium are small, and even after the rate of absorption is slowed by calcitonin, this still has only a small effect on plasma calcium ion concentration. The effect of calcitonin in children is much greater because bone remodeling occurs rapidly in children, with absorption and deposition of calcium as great as 5 grams or more per day—equal to 5 to 10 times the total calcium in all the extracellular fluid. Also, in certain bone diseases, such as *Paget disease*, in which osteoclastic activity is greatly accelerated, calcitonin has a much more potent effect of reducing the calcium absorption.

## Summary of Control of Calcium Ion Concentration

At times, the amount of calcium absorbed into or lost from the body fluids is as much as 0.3 gram in 1 hour. For instance, in cases of diarrhea, several grams of calcium can be secreted in the intestinal juices, passed into the intestinal tract, and lost into the feces each day.

Conversely, after ingestion of large quantities of calcium, particularly when there is also an excess of vitamin D activity, a person may absorb as much as 0.3 gram in 1 hour. This figure compares with a *total quantity of calcium in all the extracellular fluid of about 1 gram*. The addition or subtraction of 0.3 gram to or from such a small amount of calcium in the extracellular fluid would cause serious hypercalcemia or hypocalcemia. However, there is a first line of defense to prevent this from occurring even before the parathyroid and calcitonin hormonal feedback systems have a chance to act.



**Buffer Function of the Exchangeable Calcium in Bones—The First Line of Defense.** The exchangeable calcium salts in the bones, discussed earlier in this chapter, are amorphous calcium phosphate compounds, probably mainly  $\text{CaHPO}_4$  or some similar compound loosely bound in the bone and in reversible equilibrium with the calcium and phosphate ions in the extracellular fluid.

The quantity of these salts that is available for exchange is about 0.5 to 1 percent of the total calcium salts of the bone, a total of 5 to 10 grams of calcium. Because of the ease of deposition of these exchangeable salts and their ease of resolubility, an increase in the concentrations of extracellular fluid calcium and phosphate ions above normal causes immediate deposition of exchangeable salt. Conversely, a decrease in these concentrations causes immediate absorption of exchangeable salt. This reaction is rapid because the amorphous bone crystals are extremely small and their total surface area exposed to the fluids of the bone is perhaps 1 acre or more.

Also, about 5 percent of all the blood flows through the bones each minute—that is, about 1 percent of all the extracellular fluid each minute. Therefore, about one half of any excess calcium that appears in the extracellular fluid is removed by this buffer function of the bones in about 70 minutes.

In addition to the buffer function of the bones, the *mitochondria* of many of the tissues of the body, especially of the liver and intestine, contain a significant amount of exchangeable calcium (a total of about 10 grams in the whole body) that provides an additional buffer system for helping to maintain constancy of the extracellular fluid calcium ion concentration.

**Hormonal Control of Calcium Ion Concentration—The Second Line of Defense.** At the same time that the exchangeable calcium mechanism in the bones is “buffering” the calcium in the extracellular fluid, both the parathyroid and the calcitonin hormonal systems are beginning to act. Within 3 to 5 minutes after an acute increase in the calcium ion concentration, the rate of PTH secretion decreases. As already explained, this sets into play multiple mechanisms for reducing the calcium ion concentration back toward normal.

At the same time that PTH decreases, calcitonin increases. In young animals and possibly in young children (but probably to a smaller extent in adults), the calcitonin causes rapid deposition of calcium in the bones, and perhaps in some cells of other tissues. Therefore, in very young animals, excess calcitonin can cause a high calcium ion concentration to return to normal perhaps considerably more rapidly than can be achieved by the exchangeable calcium-buffering mechanism alone.

In prolonged calcium excess or prolonged calcium deficiency, only the PTH mechanism seems to be really important in maintaining a normal plasma calcium ion concentration. When a person has a continuing deficiency of calcium in the diet, PTH can often stimulate enough calcium absorption from the bones to maintain a normal

plasma calcium ion concentration for 1 year or more, but eventually, even the bones will run out of calcium. Thus, in effect, the bones are a large buffer-reservoir of calcium that can be manipulated by PTH. Yet when the bone reservoir either runs out of calcium or, oppositely, becomes saturated with calcium, the long-term control of extracellular calcium ion concentration resides almost entirely in the roles of PTH and vitamin D in controlling calcium absorption from the gut and calcium excretion in the urine.

### Pathophysiology of Parathyroid Hormone, Vitamin D, and Bone Disease

#### Hypoparathyroidism

When the parathyroid glands do not secrete sufficient PTH, the osteocytic resorption of exchangeable calcium decreases and the osteoclasts become almost totally inactive. As a result, calcium reabsorption from the bones is so depressed that the level of calcium in the body fluids decreases. Yet because calcium and phosphates are not being absorbed from the bone, the bone usually remains strong.

When the parathyroid glands are suddenly removed, the calcium level in the blood falls from the normal of 9.4 mg/dl to 6 to 7 mg/dl within 2 to 3 days and the blood phosphate concentration may double. When this low calcium level is reached, the usual signs of tetany develop. Among the muscles of the body especially sensitive to tetanic spasm are the laryngeal muscles. Spasm of these muscles obstructs respiration, which is the usual cause of death in tetany unless appropriate treatment is applied.

**Treatment of Hypoparathyroidism with PTH and Vitamin D.** PTH is occasionally used for treating hypoparathyroidism. However, because of the expense of this hormone, because its effect lasts for a few hours at most, and because the tendency of the body to develop antibodies against it makes it progressively less and less effective, hypoparathyroidism is usually not treated with PTH administration.

In most patients with hypoparathyroidism, the administration of extremely large quantities of vitamin D, to as high as 100,000 units per day, along with intake of 1 to 2 grams of calcium, keeps the calcium ion concentration in a normal range. At times, it might be necessary to administer 1,25-dihydroxycholecalciferol instead of the nonactivated form of vitamin D because of its much more potent and much more rapid action. This can also cause unwanted effects because it is sometimes difficult to prevent overactivity by this activated form of vitamin D.

#### Primary Hyperparathyroidism

In primary hyperparathyroidism, an abnormality of the parathyroid glands causes inappropriate, excess PTH secretion. The cause of primary hyperparathyroidism ordinarily is a tumor of one of the parathyroid glands; such tumors occur much more frequently in women than in men or children, mainly because pregnancy and lactation stimulate the parathyroid glands and therefore predispose to the development of such a tumor.

Hyperparathyroidism causes extreme osteoclastic activity in the bones. This elevates the calcium ion concentration in

the extracellular fluid while usually depressing the concentration of phosphate ions because of increased renal excretion of phosphate.

**Bone Disease in Hyperparathyroidism.** Although in mild hyperparathyroidism new bone can be deposited rapidly enough to compensate for the increased osteoclastic resorption of bone, in severe hyperparathyroidism the osteoclastic absorption soon far outstrips osteoblastic deposition, and the bone may be eaten away almost entirely. Indeed, the reason a hyperparathyroid person seeks medical attention is often a broken bone. Radiographs of the bone typically show extensive decalcification and, occasionally, large punched-out cystic areas of the bone that are filled with osteoclasts in the form of so-called giant cell osteoclast "tumors." Multiple fractures of the weakened bones can result from only slight trauma, especially where cysts develop. The cystic bone disease of hyperparathyroidism is called *osteitis fibrosa cystica*.

Osteoblastic activity in the bones also increases greatly in a vain attempt to form enough new bone to make up for the old bone absorbed by the osteoclastic activity. When the osteoblasts become active, they secrete large quantities of *alkaline phosphatase*. Therefore, one of the important diagnostic findings in hyperparathyroidism is a high level of plasma alkaline phosphatase.

**Effects of Hypercalcemia in Hyperparathyroidism.** Hyperparathyroidism can at times cause the plasma calcium level to rise to 12 to 15 mg/dl and, rarely, even higher. The effects of such elevated calcium levels, as detailed earlier in the chapter, are depression of the central and peripheral nervous systems, muscle weakness, constipation, abdominal pain, peptic ulcer, lack of appetite, and depressed relaxation of the heart during diastole.

**Parathyroid Poisoning and Metastatic Calcification.** When, on rare occasions, extreme quantities of PTH are secreted, the level of calcium in the body fluids rises rapidly to high values. Even the extracellular fluid phosphate concentration often rises markedly instead of falling, as is usually the case, probably because the kidneys cannot excrete rapidly enough all the phosphate being absorbed from the bone. Therefore, the calcium and phosphate in the body fluids become greatly supersaturated, so calcium phosphate ( $\text{CaHPO}_4$ ) crystals begin to deposit in the alveoli of the lungs, the tubules of the kidneys, the thyroid gland, the acid-producing area of the stomach mucosa, and the walls of the arteries throughout the body. This extensive *metastatic* deposition of calcium phosphate can develop within a few days.

Ordinarily, the level of calcium in the blood must rise above 17 mg/dl before there is danger of parathyroid poisoning, but once such elevation develops along with concurrent elevation of phosphate, death can occur in only a few days.

**Formation of Kidney Stones in Hyperparathyroidism.** Most patients with mild hyperparathyroidism show few signs of bone disease and few general abnormalities as a result of elevated calcium, but they do have an extreme tendency to form kidney stones. The reason is that the excess calcium and phosphate absorbed from the intestines or mobilized from the bones in hyperparathyroidism must eventually be excreted by the kidneys, causing a proportionate increase in the concentrations of these substances in the urine. As a result, crystals of calcium phosphate tend to precipitate in the kidney, forming calcium phosphate stones. Also, calcium oxalate stones develop because even normal levels of oxalate cause calcium precipitation at high calcium levels.

Because the solubility of most renal stones is slight in alkaline media, the tendency for formation of renal calculi is considerably greater in alkaline urine than in acid urine. For this reason, acidotic diets and acidic drugs are frequently used for treating renal calculi.

### Secondary Hyperparathyroidism

In secondary hyperparathyroidism, high levels of PTH occur as a compensation for *hypocalcemia* rather than as a primary abnormality of the parathyroid glands. This contrasts with primary hyperparathyroidism, which is associated with hypercalcemia.

Secondary hyperparathyroidism can be caused by vitamin D deficiency or chronic renal disease in which the damaged kidneys are unable to produce sufficient amounts of the active form of vitamin D, 1,25-dihydroxycholecalciferol. As discussed in more detail in the next section, the vitamin D deficiency leads to *osteomalacia* (inadequate mineralization of the bones) and high levels of PTH cause absorption of the bones.

### Rickets Caused by Vitamin D Deficiency

Rickets occurs mainly in children. It results from calcium or phosphate deficiency in the extracellular fluid, usually caused by lack of vitamin D. If the child is adequately exposed to sunlight, the 7-dehydrocholesterol in the skin becomes activated by the ultraviolet rays and forms vitamin  $\text{D}_3$ , which prevents rickets by promoting calcium and phosphate absorption from the intestines, as discussed earlier in the chapter.

Children who remain indoors through the winter in general do not receive adequate quantities of vitamin D without some supplementation in the diet. Rickets tends to occur especially in the spring months because vitamin D formed during the preceding summer is stored in the liver and available for use during the early winter months. Also, calcium and phosphate absorption from the bones can prevent clinical signs of rickets for the first few months of vitamin D deficiency.

**Plasma Concentrations of Calcium and Phosphate Decrease in Rickets.** The plasma calcium concentration in rickets is only slightly depressed, but the level of phosphate is greatly depressed. This is because the parathyroid glands prevent the calcium level from falling by promoting bone absorption every time the calcium level begins to fall. However, there is no good regulatory system for preventing a falling level of phosphate, and the increased parathyroid activity actually increases the excretion of phosphates in the urine.

**Rickets Weakens the Bones.** During prolonged rickets, the marked compensatory increase in PTH secretion causes extreme osteoclastic absorption of the bone; this in turn causes the bone to become progressively weaker and imposes marked physical stress on the bone, resulting in rapid osteoblastic activity as well. The osteoblasts lay down large quantities of osteoid, which does not become calcified because of insufficient calcium and phosphate ions. Consequently, the newly formed, uncalcified, and weak osteoid gradually takes the place of the older bone that is being reabsorbed.

**Tetany in Rickets.** In the early stages of rickets, tetany almost never occurs because the parathyroid glands continually stimulate osteoclastic absorption of bone and, therefore, maintain an almost normal level of calcium in the extracellular fluid. However, when the bones finally become exhausted of calcium, the level of calcium may fall rapidly. As the blood

level of calcium falls below 7 mg/dl, the usual signs of tetany develop and the child may die of tetanic respiratory spasm unless intravenous calcium is administered, which relieves the tetany immediately.

**Treatment of Rickets.** The treatment of rickets depends on supplying adequate calcium and phosphate in the diet and, equally important, on administering large amounts of vitamin D. If vitamin D is not administered, little calcium and phosphate are absorbed from the gut.

**Osteomalacia—"Adult Rickets."** Adults seldom have a serious *dietary* deficiency of vitamin D or calcium because large quantities of calcium are not needed for bone growth as in children. However, serious deficiencies of both vitamin D and calcium occasionally occur as a result of *steatorrhea* (failure to absorb fat) because vitamin D is fat-soluble and calcium tends to form insoluble soaps with fat; consequently, in *steatorrhea*, both vitamin D and calcium tend to pass into the feces. Under these conditions, an adult occasionally has such poor calcium and phosphate absorption that adult rickets can occur, although this almost never proceeds to the stage of tetany but often is a cause of severe bone disability.

**Osteomalacia and Rickets Caused by Renal Disease.** "Renal rickets" is a type of osteomalacia that results from prolonged kidney damage. The cause of this condition is mainly failure of the damaged kidneys to form 1,25-dihydroxycholecalciferol, the active form of vitamin D. In patients whose kidneys have been removed or destroyed and who are being treated by hemodialysis, the problem of renal rickets is often a severe one.

Another type of renal disease that leads to rickets and osteomalacia is *congenital hypophosphatemia*, resulting from congenitally reduced reabsorption of phosphates by the renal tubules. This type of rickets must be treated with phosphate compounds instead of calcium and vitamin D, and it is called *vitamin D-resistant rickets*.

### Osteoporosis—Decreased Bone Matrix

Osteoporosis is the most common of all bone diseases in adults, especially in old age. It is different from osteomalacia and rickets because it results from diminished organic bone matrix rather than from poor bone calcification. In osteoporosis the osteoblastic activity in the bone is usually less than normal, and consequently the rate of bone osteoid deposition is depressed. But occasionally, as in hyperparathyroidism, the cause of the diminished bone is excess osteoclastic activity.

The many common causes of osteoporosis are (1) *lack of physical stress on the bones* because of inactivity; (2) *malnutrition* to the extent that sufficient protein matrix cannot be formed; (3) *lack of vitamin C*, which is necessary for the secretion of intercellular substances by all cells, including formation of osteoid by the osteoblasts; (4) *postmenopausal lack of estrogen secretion* because estrogens decrease the number and activity of osteoclasts; (5) *old age*, in which growth hormone and other growth factors diminish greatly, plus the fact that many of the protein anabolic functions also deteriorate with age, so bone matrix cannot be deposited satisfactorily; and (6) *Cushing's syndrome*, because massive quantities of glucocorticoids secreted in this disease cause decreased deposition of protein throughout the body and increased catabolism of protein and have the specific effect of depressing osteoblastic activity. Thus, many diseases of deficiency of protein metabolism can cause osteoporosis.

## Physiology of the Teeth

The teeth cut, grind, and mix the food eaten. To perform these functions, the jaws have powerful muscles capable of providing an occlusive force between the front teeth of 50 to 100 pounds and for the jaw teeth, 150 to 200 pounds. Also, the upper and lower teeth are provided with projections and facets that interdigitate, so the upper set of teeth fits with the lower. This fitting is called *occlusion*, and it allows even small particles of food to be caught and ground between the tooth surfaces.

### Function of the Different Parts of the Teeth

Figure 79-14 shows a sagittal section of a tooth, demonstrating its major functional parts: the *enamel*, *dentin*, *cementum*, and *pulp*. The tooth can also be divided into the *crown*, which is the portion that protrudes out from the gum into the mouth, and the *root*, which is the portion within the bony socket of the jaw. The collar between the crown and the root where the tooth is surrounded by the gum is called the *neck*.

**Enamel.** The outer surface of the tooth is covered by a layer of enamel that is formed before eruption of the tooth by special epithelial cells called *ameloblasts*. Once the tooth has erupted, no more enamel is formed. Enamel is composed of large and dense crystals of hydroxyapatite with adsorbed carbonate, magnesium, sodium, potassium, and other ions embedded in a fine meshwork of strong and almost insoluble protein fibers that are similar in physical characteristics (but not chemically identical) to the keratin of hair.

The crystalline structure of the salts makes the enamel extremely hard, much harder than the dentin. Also, the special protein fiber meshwork, although constituting

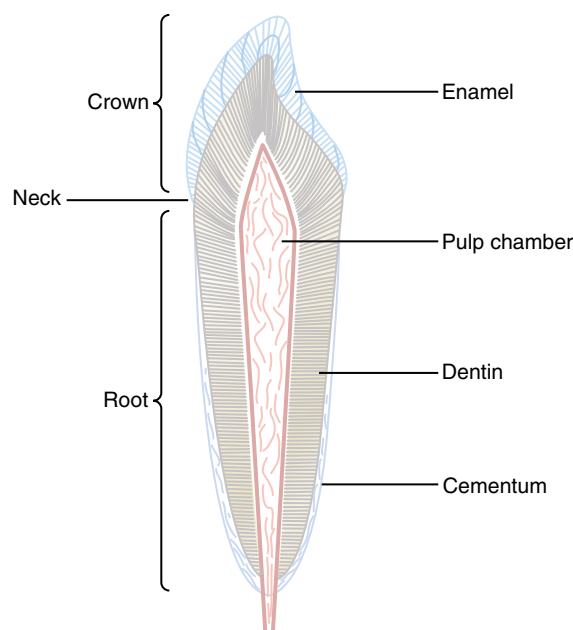


Figure 79-14 Functional parts of a tooth.



only about 1 percent of the enamel mass, makes enamel resistant to acids, enzymes, and other corrosive agents because this protein is one of the most insoluble and resistant proteins known.

**Dentin.** The main body of the tooth is composed of dentin, which has a strong, bony structure. Dentin is made up principally of hydroxyapatite crystals similar to those in bone but much denser. These crystals are embedded in a strong meshwork of collagen fibers. In other words, the principal constituents of dentin are much the same as those of bone. The major difference is its histological organization because dentin does not contain any osteoblasts, osteocytes, osteoclasts, or spaces for blood vessels or nerves. Instead, it is deposited and nourished by a layer of cells called *odontoblasts*, which line its inner surface along the wall of the pulp cavity.

The calcium salts in dentin make it extremely resistant to compressional forces, and the collagen fibers make it tough and resistant to tensional forces that might result when the teeth are struck by solid objects.

**Cementum.** Cementum is a bony substance secreted by cells of the *periodontal membrane*, which lines the tooth socket. Many collagen fibers pass directly from the bone of the jaw, through the periodontal membrane, and then into the cementum. These collagen fibers and the cementum hold the tooth in place. When the teeth are exposed to excessive strain, the layer of cementum becomes thicker and stronger. Also, it increases in thickness and strength with age, causing the teeth to become more firmly seated in the jaws by adulthood and later.

**Pulp.** The pulp cavity of each tooth is filled with *pulp*, which is composed of connective tissue with an abundant supply of nerve fibers, blood vessels, and lymphatics. The cells lining the surface of the pulp cavity are the odontoblasts, which, during the formative years of the tooth, lay down the dentin but at the same time encroach more and more on the pulp cavity, making it smaller. In later life, the dentin stops growing and the pulp cavity remains essentially constant in size. However, the odontoblasts are still viable and send projections into small *dentinal tubules* that penetrate all the way through the dentin; they are of importance for exchange of calcium, phosphate, and other minerals with the dentin.

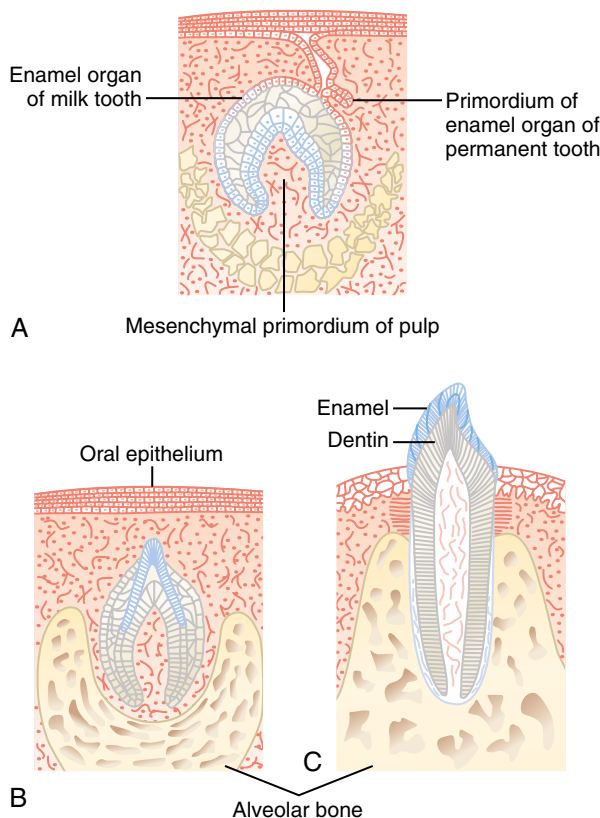
## Dentition

Humans and most other mammals develop two sets of teeth during a lifetime. The first teeth are called the deciduous teeth, or milk teeth, and they number 20 in humans. They erupt between the seventh month and the second year of life, and they last until the sixth to the 13th year. After each deciduous tooth is lost, a permanent tooth replaces it and an additional 8 to 12 molars appear posteriorly in the jaws, making the total number of permanent teeth 28 to 32, depending on whether the four wisdom teeth finally appear, which does not occur in everyone.

**Formation of the Teeth.** Figure 79-15 shows the formation and eruption of teeth. Figure 79-15A shows invagination of the oral epithelium into the *dental lamina*; this is followed by the development of a tooth-producing organ. The epithelial cells above form ameloblasts, which form the enamel on the outside of the tooth. The epithelial cells below invaginate upward into the middle of the tooth to form the pulp cavity and the odontoblasts that secrete dentin. Thus, enamel is formed on the outside of the tooth, and dentin is formed on the inside, giving rise to an early tooth, as shown in Figure 79-15B.

**Eruption of Teeth.** During early childhood, the teeth begin to protrude outward from the bone through the oral epithelium into the mouth. The cause of “eruption” is unknown, although several theories have been offered in an attempt to explain this phenomenon. The most likely theory is that growth of the tooth root and the bone underneath the tooth progressively shoves the tooth forward.

**Development of the Permanent Teeth.** During embryonic life, a tooth-forming organ also develops in the deeper dental lamina for each permanent tooth that will be needed after the deciduous teeth are gone. These tooth-producing organs slowly form the permanent teeth throughout the first 6 to 20 years of life. When each permanent tooth becomes fully formed, it, like the deciduous tooth, pushes outward through the bone. In so doing, it erodes the root of the deciduous tooth and



**Figure 79-15** A, Primordial tooth organ. B, Developing tooth. C, Erupting tooth.



eventually causes it to loosen and fall out. Soon thereafter, the permanent tooth erupts to take the place of the original one.

**Metabolic Factors Influence Development of the Teeth.** The rate of development and the speed of eruption of teeth can be accelerated by both thyroid and growth hormones. Also, the deposition of salts in the early-forming teeth is affected considerably by various factors of metabolism, such as the availability of calcium and phosphate in the diet, the amount of vitamin D present, and the rate of PTH secretion. When all these factors are normal, the dentin and enamel will be correspondingly healthy, but when they are deficient, the calcification of the teeth also may be defective and the teeth will be abnormal throughout life.

### Mineral Exchange in Teeth

The salts of teeth, like those of bone, are composed of hydroxyapatite with adsorbed carbonates and various cations bound together in a hard crystalline substance. Also, new salts are constantly being deposited while old salts are being reabsorbed from the teeth, as occurs in bone. Deposition and reabsorption occur mainly in the dentin and cementum and to a limited extent in the enamel. In the enamel, these processes occur mostly by diffusional exchange of minerals with the saliva instead of with the fluids of the pulp cavity.

The rate of absorption and deposition of minerals in the cementum is about equal to that in the surrounding bone of the jaw, whereas the rate of deposition and absorption of minerals in the dentin is only one-third that of bone. The cementum has characteristics almost identical to those of usual bone, including the presence of osteoblasts and osteoclasts, whereas dentin does not have these characteristics, as explained earlier. This difference undoubtedly explains the different rates of mineral exchange.

In summary, continual mineral exchange occurs in the dentin and cementum of teeth, although the mechanism of this exchange in dentin is unclear. However, enamel exhibits extremely slow mineral exchange, so it maintains most of its original mineral complement throughout life.

### Dental Abnormalities

The two most common dental abnormalities are *caries* and *malocclusion*. Caries refers to erosion of the teeth, whereas malocclusion is failure of the projections of the upper and lower teeth to interdigitate properly.

**Caries and the Role of Bacteria and Ingested Carbohydrates.** It is generally agreed that caries result from the action of bacteria on the teeth, the most common of which is *Streptococcus mutans*. The first event in the development of caries is the deposit of *plaque*, a film of precipitated products of saliva and food, on the

teeth. Large numbers of bacteria inhabit this plaque and are readily available to cause caries. These bacteria depend to a great extent on carbohydrates for their food. When carbohydrates are available, their metabolic systems are strongly activated and they multiply. In addition, they form acids (particularly lactic acid) and proteolytic enzymes. The acids are the major culprit in causing caries because the calcium salts of teeth are slowly dissolved in a highly acidic medium. And once the salts have become absorbed, the remaining organic matrix is rapidly digested by the proteolytic enzymes.

The enamel of the tooth is the primary barrier to the development of caries. Enamel is far more resistant to demineralization by acids than is dentin, primarily because the crystals of enamel are dense, but also because each enamel crystal is about 200 times as large in volume as each dentin crystal. Once the carious process has penetrated through the enamel to the dentin, it proceeds many times as rapidly because of the high degree of solubility of the dentin salts.

Because of the dependence of the caries bacteria on carbohydrates for their nutrition, it has frequently been taught that eating a diet high in carbohydrate content will lead to excessive development of caries. However, it is not the quantity of carbohydrate ingested but the frequency with which it is eaten that is important. If carbohydrates are eaten in many small parcels throughout the day, such as in the form of candy, the bacteria are supplied with their preferential metabolic substrate for many hours of the day and the development of caries is greatly increased.

**Role of Fluorine in Preventing Caries.** Teeth formed in children who drink water that contains small amounts of fluorine develop enamel that is more resistant to caries than the enamel in children who drink water that does not contain fluorine. Fluorine does not make the enamel harder than usual, but fluorine ions replace many of the hydroxyl ions in the hydroxyapatite crystals, which in turn makes the enamel several times less soluble. Fluorine may also be toxic to the bacteria. Finally, when small pits do develop in the enamel, fluorine is believed to promote deposition of calcium phosphate to “heal” the enamel surface. Regardless of the precise means by which fluorine protects the teeth, it is known that small amounts of fluorine deposited in enamel make teeth about three times as resistant to caries as teeth without fluorine.

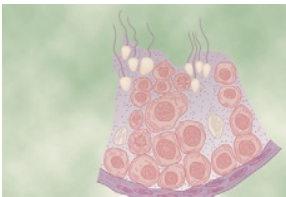
**Malocclusion.** Malocclusion is usually caused by a hereditary abnormality that causes the teeth of one jaw to grow to abnormal positions. In malocclusion, the teeth do not interdigitate properly and therefore cannot perform their normal grinding or cutting action adequately. Malocclusion occasionally also results in abnormal displacement of the lower jaw in relation to the upper jaw, causing such undesirable effects as pain in the mandibular joint and deterioration of the teeth.

The orthodontist can usually correct malocclusion by applying prolonged gentle pressure against the teeth with appropriate braces. The gentle pressure causes absorption of alveolar jaw bone on the compressed side of the tooth and deposition of new bone on the tensional side of the tooth. In this way, the tooth gradually moves to a new position as directed by the applied pressure.

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# Reproductive and Hormonal Functions of the Male (and Function of the Pineal Gland)



The reproductive functions of the male can be divided into three major subdivisions: (1) spermatogenesis, which means the formation of sperm; (2) performance of the male sexual act; and

(3) regulation of male reproductive functions by the various hormones. Associated with these reproductive functions are the effects of the male sex hormones on the accessory sexual organs, cellular metabolism, growth, and other functions of the body.

## Physiologic Anatomy of the Male Sexual Organs

Figure 80-1A shows the various portions of the male reproductive system, and Figure 80-1B gives a more detailed structure of the testis and epididymis. The testis is composed of up to 900 coiled *seminiferous tubules*, each averaging more than one-half meter long, in which the sperm are formed. The sperm then empty into the *epididymis*, another coiled tube about 6 meters long. The epididymis leads into the *vas deferens*, which enlarges into the *ampulla of the vas deferens* immediately before the vas enters the body of the *prostate gland*.

Two *seminal vesicles*, one located on each side of the prostate, empty into the prostatic end of the ampulla, and the contents from both the ampulla and the seminal vesicles pass into an *ejaculatory duct* leading through the body of the prostate gland and then emptying into the *internal urethra*. *Prostatic ducts* also empty from the prostate gland into the ejaculatory duct and from there into the prostatic urethra.

Finally, the *urethra* is the last connecting link from the testis to the exterior. The urethra is supplied with mucus derived from a large number of minute *urethral glands* located along its entire extent and even more so from bilateral *bulbourethral glands* (Cowper glands) located near the origin of the urethra.

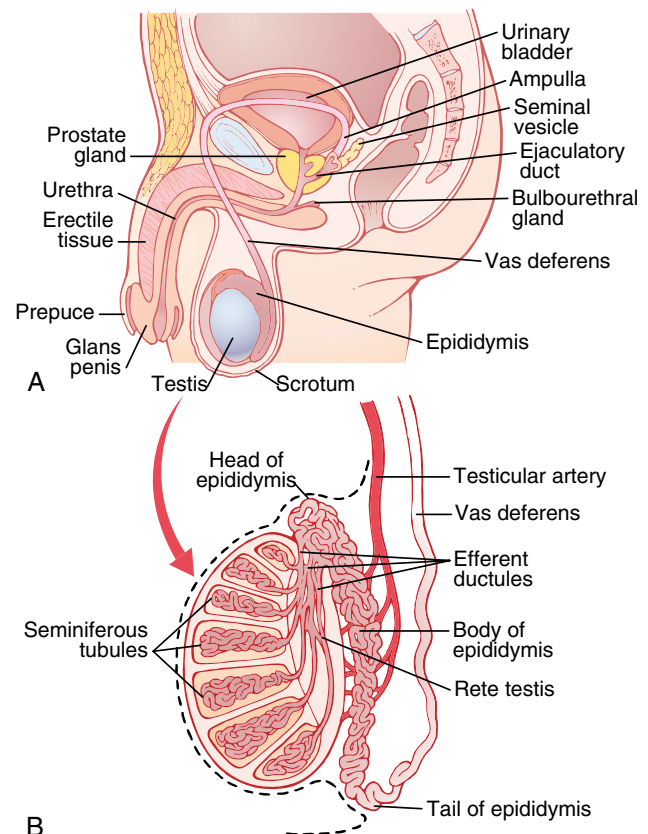
## Spermatogenesis

During formation of the embryo, the *primordial germ cells* migrate into the testes and become immature germ cells called *spermatogonia*, which lie in two or

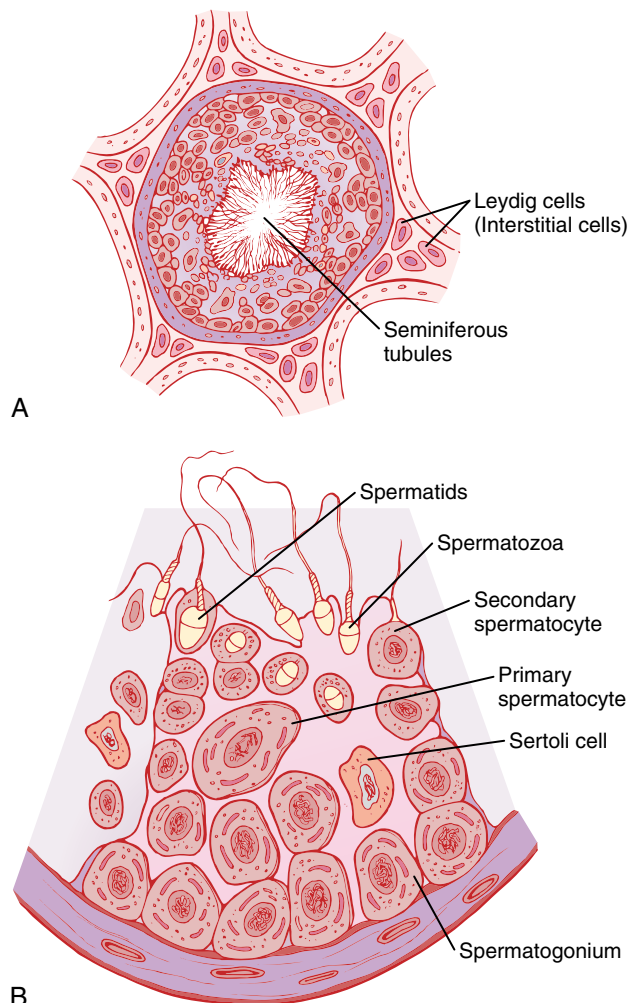
three layers of the inner surfaces of the *seminiferous tubules* (a cross section of one is shown in Figure 80-2A). The spermatogonia begin to undergo mitotic division, beginning at puberty, and continually proliferate and differentiate through definite stages of development to form sperm, as shown in Figure 80-2B.

## Steps of Spermatogenesis

Spermatogenesis occurs in the seminiferous tubules during active sexual life as the result of stimulation by anterior



**Figure 80-1** A, Male reproduction system. (Modified from Bloom V, Fawcett DW: Textbook of Histology, 10th ed. Philadelphia: WB Saunders, 1975.) B, Internal structure of the testis and relation of the testis to the epididymis. (Redrawn from Guyton AC: Anatomy and Physiology. Philadelphia: Saunders College Publishing, 1985.)



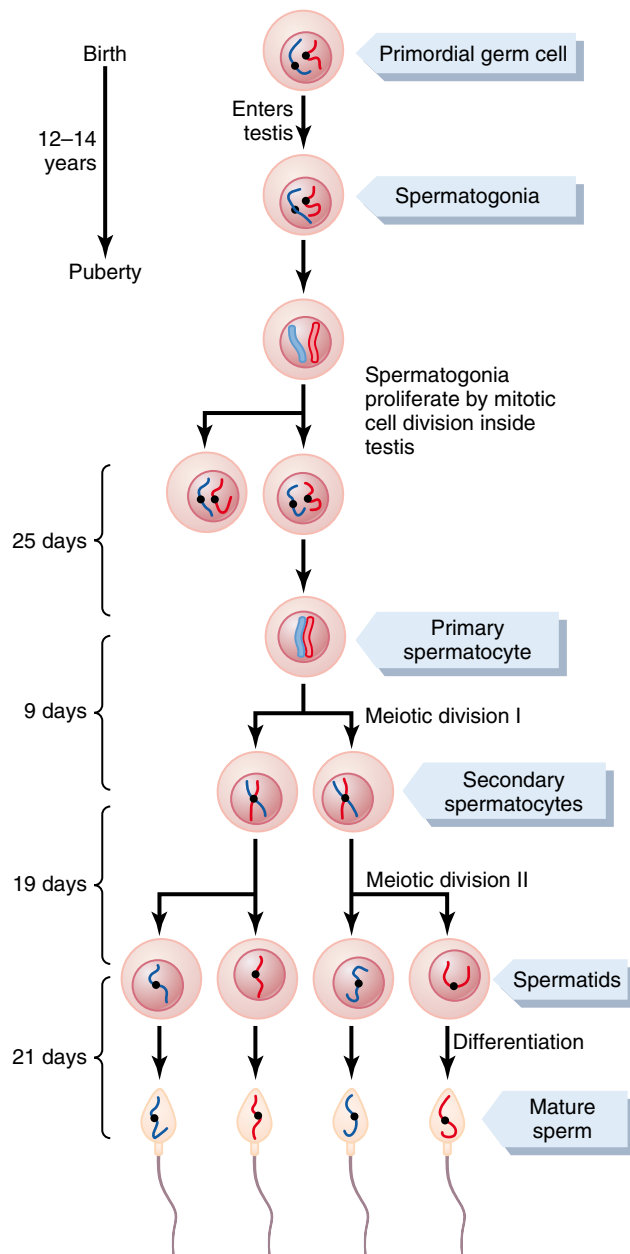
**Figure 80-2** A, Cross section of a seminiferous tubule. B, Stages in the development of sperm from spermatogonia.

pituitary gonadotropic hormones, beginning at an average age of 13 years and continuing throughout most of the remainder of life but decreasing markedly in old age.

In the first stage of spermatogenesis, the spermatogonia migrate among *Sertoli cells* toward the central lumen of the seminiferous tubule. The Sertoli cells are large, with overflowing cytoplasmic envelopes that surround the developing spermatogonia all the way to the central lumen of the tubule.

**Meiosis.** Spermatogonia that cross the barrier into the Sertoli cell layer become progressively modified and enlarged to form large *primary spermatocytes* (Figure 80-3). Each of these, in turn, undergoes meiotic division to form two *secondary spermatocytes*. After another few days, these too divide to form *spermatids* that are eventually modified to become *spermatozoa* (sperm).

During the change from the spermatocyte stage to the spermatid stage, the 46 chromosomes (23 pairs of chromosomes) of the spermatocyte are divided, so 23 chromosomes go to one spermatid and the other 23 to the second spermatid. This also divides the chromosomal genes so that only one half of the genetic characteristics



**Figure 80-3** Cell divisions during spermatogenesis. During embryonic development the primordial germ cells migrate to the testis, where they become spermatogonia. At puberty (usually 12 to 14 years after birth), the spermatogonia proliferate rapidly by mitosis. Some begin meiosis to become primary spermatocytes and continue through meiotic division I to become secondary spermatocytes. After completion of meiotic division II, the secondary spermatocytes produce spermatids, which differentiate to form spermatozoa.

of the eventual fetus are provided by the father, whereas the other half are derived from the oocyte provided by the mother.

The entire period of spermatogenesis, from spermatogonia to spermatozoa, takes about 74 days.

**Sex Chromosomes.** In each spermatogonium, one of the 23 pairs of chromosomes carries the genetic information that determines the sex of each eventual



offspring. This pair is composed of one X chromosome, which is called the *female chromosome*, and one Y chromosome, the *male chromosome*. During meiotic division, the male Y chromosome goes to one spermatid that then becomes a *male sperm*, and the female X chromosome goes to another spermatid that becomes a *female sperm*. The sex of the eventual offspring is determined by which of these two types of sperm fertilizes the ovum. This is discussed further in Chapter 82.

**Formation of Sperm.** When the spermatids are first formed, they still have the usual characteristics of epithelioid cells, but soon they begin to differentiate and elongate into spermatozoa. As shown in Figure 80-4, each spermatozoon is composed of a *head* and a *tail*. The head comprises the condensed nucleus of the cell with only a thin cytoplasmic and cell membrane layer around its surface. On the outside of the anterior two thirds of the head is a thick cap called the *acrosome* that is formed mainly from the Golgi apparatus. This contains a number of enzymes similar to those found in lysosomes of the typical cell, including *hyaluronidase* (which can digest proteoglycan filaments of tissues) and powerful *proteolytic enzymes* (which can digest proteins). These enzymes play important roles in allowing the sperm to enter the ovum and fertilize it.

The tail of the sperm, called the *flagellum*, has three major components: (1) a central skeleton constructed of 11 microtubules, collectively called the *axoneme*—the structure of this is similar to that of cilia found on the surfaces of other types of cells described in Chapter 2; (2) a thin cell membrane covering the axoneme; and (3) a collection of

mitochondria surrounding the axoneme in the proximal portion of the tail (called the *body of the tail*).

Back-and-forth movement of the tail (flagellar movement) provides motility for the sperm. This movement results from a rhythmical longitudinal sliding motion between the anterior and posterior tubules that make up the axoneme. The energy for this process is supplied in the form of adenosine triphosphate, which is synthesized by the mitochondria in the body of the tail.

Normal sperm move in a fluid medium at a velocity of 1 to 4 mm/min. This allows them to move through the female genital tract in quest of the ovum.

### Hormonal Factors That Stimulate Spermatogenesis

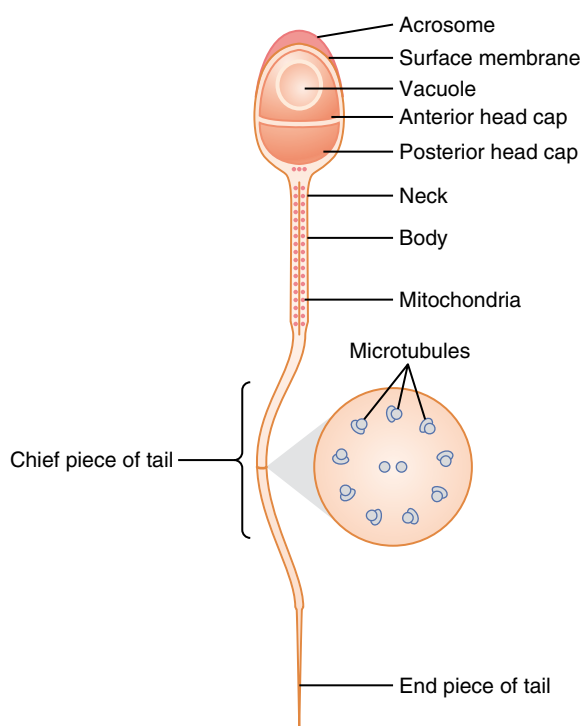
The role of hormones in reproduction is discussed later, but at this point, let us note that several hormones play essential roles in spermatogenesis. Some of these are as follows:

1. **Testosterone**, secreted by the *Leydig cells* located in the interstitium of the testis (see Figure 80-2), is essential for growth and division of the testicular germinal cells, which is the first stage in forming sperm.
2. **Luteinizing hormone**, secreted by the anterior pituitary gland, stimulates the Leydig cells to secrete testosterone.
3. **Follicle-stimulating hormone**, also secreted by the anterior pituitary gland, stimulates the *Sertoli cells*; without this stimulation, the conversion of the spermatids to sperm (the process of spermiogenesis) will not occur.
4. **Estrogens**, formed from testosterone by the Sertoli cells when they are stimulated by follicle-stimulating hormone, are probably also essential for spermiogenesis.
5. **Growth hormone** (as well as most of the other body hormones) is necessary for controlling background metabolic functions of the testes. Growth hormone specifically promotes early division of the spermatogonia themselves; in its absence, as in pituitary dwarfs, spermatogenesis is severely deficient or absent, thus causing infertility.

### Maturation of Sperm in the Epididymis

After formation in the seminiferous tubules, the sperm require several days to pass through the 6-meter-long tubule of the *epididymis*. Sperm removed from the seminiferous tubules and from the early portions of the epididymis are nonmotile, and they cannot fertilize an ovum. However, after the sperm have been in the epididymis for 18 to 24 hours, they develop the *capability of motility*, even though several inhibitory proteins in the epididymal fluid still prevent final motility until after ejaculation.

**Storage of Sperm in the Testes.** The two testes of the human adult form up to 120 million sperm each day. A small quantity of these can be stored in the epididymis,



**Figure 80-4** Structure of the human spermatozoon.

but most are stored in the vas deferens. They can remain stored, maintaining their fertility, for at least a month. During this time, they are kept in a deeply suppressed, inactive state by multiple inhibitory substances in the secretions of the ducts. Conversely, with a high level of sexual activity and ejaculations, storage may be no longer than a few days.

After ejaculation, the sperm become motile, and they also become capable of fertilizing the ovum, a process called *maturation*. The Sertoli cells and the epithelium of the epididymis secrete a special nutrient fluid that is ejaculated along with the sperm. This fluid contains hormones (including both testosterone and estrogens), enzymes, and special nutrients that are essential for sperm maturation.

**Physiology of the Mature Sperm.** The normal motile, fertile sperm are capable of flagellated movement through the fluid medium at velocities of 1 to 4 mm/min. The activity of sperm is greatly enhanced in a neutral and slightly alkaline medium, as exists in the ejaculated semen, but it is greatly depressed in a mildly acidic medium. A strong acidic medium can cause rapid death of sperm.

The activity of sperm increases markedly with increasing temperature, but so does the rate of metabolism, causing the life of the sperm to be considerably shortened. Although sperm can live for many weeks in the suppressed state in the genital ducts of the testes, life expectancy of ejaculated sperm in the female genital tract is only 1 to 2 days.

### Function of the Seminal Vesicles

Each seminal vesicle is a tortuous, loculated tube lined with a secretory epithelium that secretes a mucoid material containing an abundance of *fructose*, *citric acid*, and other nutrient substances, as well as large quantities of *prostaglandins* and *fibrinogen*. During the process of emission and ejaculation, each seminal vesicle empties its contents into the ejaculatory duct shortly after the vas deferens empties the sperm. This adds greatly to the bulk of the ejaculated semen, and the fructose and other substances in the seminal fluid are of considerable nutrient value for the ejaculated sperm until one of the sperm fertilizes the ovum.

Prostaglandins are believed to aid fertilization in two ways: (1) by reacting with the female cervical mucus to make it more receptive to sperm movement and (2) by possibly causing backward, reverse peristaltic contractions in the uterus and fallopian tubes to move the ejaculated sperm toward the ovaries (a few sperm reach the upper ends of the fallopian tubes within 5 minutes).

### Function of the Prostate Gland

The prostate gland secretes a thin, milky fluid that contains calcium, citrate ion, phosphate ion, a clotting enzyme, and a profibrinolysin. During emission, the capsule of the prostate gland contracts simultaneously with the contractions of the vas deferens so that the thin, milky

fluid of the prostate gland adds further to the bulk of the semen. A slightly alkaline characteristic of the prostatic fluid may be quite important for successful fertilization of the ovum because the fluid of the vas deferens is relatively acidic owing to the presence of citric acid and metabolic end products of the sperm and, consequently, helps to inhibit sperm fertility. Also, the vaginal secretions of the female are acidic (pH of 3.5 to 4.0). Sperm do not become optimally motile until the pH of the surrounding fluids rises to about 6.0 to 6.5. Consequently, it is probable that the slightly alkaline prostatic fluid helps to neutralize the acidity of the other seminal fluids during ejaculation and thus enhances the motility and fertility of the sperm.

### Semen

Semen, which is ejaculated during the male sexual act, is composed of the fluid and sperm from the vas deferens (about 10 percent of the total), fluid from the seminal vesicles (almost 60 percent), fluid from the prostate gland (about 30 percent), and small amounts from the mucous glands, especially the bulbourethral glands. Thus, the bulk of the semen is seminal vesicle fluid, which is the last to be ejaculated and serves to wash the sperm through the ejaculatory duct and urethra.

The average pH of the combined semen is about 7.5, the alkaline prostatic fluid having more than neutralized the mild acidity of the other portions of the semen. The prostatic fluid gives the semen a milky appearance, and fluid from the seminal vesicles and mucous glands gives the semen a mucoid consistency. Also, a clotting enzyme from the prostatic fluid causes the fibrinogen of the seminal vesicle fluid to form a weak fibrin coagulum that holds the semen in the deeper regions of the vagina where the uterine cervix lies. The coagulum then dissolves during the next 15 to 30 minutes because of lysis by fibrinolysin formed from the prostatic profibrinolysin. In the early minutes after ejaculation, the sperm remain relatively immobile, possibly because of the viscosity of the coagulum. As the coagulum dissolves, the sperm simultaneously become highly motile.

Although sperm can live for many weeks in the male genital ducts, once they are ejaculated in the semen, their maximal life span is only 24 to 48 hours at body temperature. At lowered temperatures, however, semen can be stored for several weeks, and when frozen at temperatures below  $-100^{\circ}\text{C}$ , sperm have been preserved for years.

### "Capacitation" of Spermatozoa Is Required for Fertilization of the Ovum

Although spermatozoa are said to be "mature" when they leave the epididymis, their activity is held in check by multiple inhibitory factors secreted by the genital duct epithelia. Therefore, when they are first expelled in the semen, they are unable to fertilize the ovum. However, on coming in contact with the fluids of the female genital tract, multiple changes occur that activate the sperm for the final processes of fertilization. These collective

changes are called *capacitation of the spermatozoa*. This normally requires from 1 to 10 hours. Some changes that are believed to occur are the following:

1. The uterine and fallopian tube fluids wash away the various inhibitory factors that suppress sperm activity in the male genital ducts.
2. While the spermatozoa remain in the fluid of the male genital ducts, they are continually exposed to many floating vesicles from the seminiferous tubules containing large amounts of cholesterol. This cholesterol is continually added to the cellular membrane covering the sperm acrosome, toughening this membrane and preventing release of its enzymes. After ejaculation, the sperm deposited in the vagina swim away from the cholesterol vesicles upward into the uterine cavity, and they gradually lose much of their other excess cholesterol over the next few hours. In so doing, the membrane at the head of the sperm (the acrosome) becomes much weaker.
3. The membrane of the sperm also becomes much more permeable to calcium ions, so calcium now enters the sperm in abundance and changes the activity of the flagellum, giving it a powerful whiplash motion in contrast to its previously weak undulating motion. In addition, the calcium ions cause changes in the cellular membrane that cover the leading edge of the acrosome, making it possible for the acrosome to release its enzymes rapidly and easily as the sperm penetrates the granulosa cell mass surrounding the ovum, and even more so as it attempts to penetrate the zona pellucida of the ovum itself.

Thus, multiple changes occur during the process of capacitation. Without these, the sperm cannot make its way to the interior of the ovum to cause fertilization.

### Acrosome Enzymes, the "Acrosome Reaction," and Penetration of the Ovum

Stored in the acrosome of the sperm are large quantities of *hyaluronidase* and *proteolytic enzymes*. Hyaluronidase depolymerizes the hyaluronic acid polymers in the intercellular cement that holds the ovarian granulosa cells together. The proteolytic enzymes digest proteins in the structural elements of tissue cells that still adhere to the ovum.

When the ovum is expelled from the ovarian follicle into the fallopian tube, it still carries with it multiple layers of granulosa cells. Before a sperm can fertilize the ovum, it must dissolve these granulosa cell layers, and then it must penetrate through the thick covering of the ovum itself, the *zona pellucida*. To achieve this, the stored enzymes in the acrosome begin to be released. It is believed that the hyaluronidase among these enzymes is especially important in opening pathways between the granulosa cells so that the sperm can reach the ovum.

When the sperm reaches the zona pellucida of the ovum, the anterior membrane of the sperm binds spe-

cifically with receptor proteins in the zona pellucida. Next, the entire acrosome rapidly dissolves and all the acrosomal enzymes are released. Within minutes, these enzymes open a penetrating pathway for passage of the sperm head through the zona pellucida to the inside of the ovum. Within another 30 minutes, the cell membranes of the sperm head and of the oocyte fuse with each other to form a single cell. At the same time, the genetic material of the sperm and the oocyte combine to form a completely new cell genome, containing equal numbers of chromosomes and genes from mother and father. This is the process of *fertilization*; then the embryo begins to develop, as discussed in Chapter 82.

**Why Does Only One Sperm Enter the Oocyte?** With as many sperm as there are, why does only one enter the oocyte? The reason is not entirely known, but within a few minutes after the first sperm penetrates the zona pellucida of the ovum, calcium ions diffuse inward through the oocyte membrane and cause multiple cortical granules to be released by exocytosis from the oocyte into the perivitelline space. These granules contain substances that permeate all portions of the zona pellucida and prevent binding of additional sperm, and they even cause any sperm that have already begun to bind to fall off. Thus, almost never does more than one sperm enter the oocyte during fertilization.

### Abnormal Spermatogenesis and Male Fertility

The seminiferous tubular epithelium can be destroyed by a number of diseases. For instance, bilateral *orchitis* (inflammation) of the testes resulting from *mumps* causes sterility in some affected males. Also, some male infants are born with degenerate tubular epithelia as a result of strictures in the genital ducts or other abnormalities. Finally, another cause of sterility, usually temporary, is *excessive temperature of the testes*.

**Effect of Temperature on Spermatogenesis.** Increasing the temperature of the testes can prevent spermatogenesis by causing degeneration of most cells of the seminiferous tubules besides the spermatogonia. It has often been stated that the reason the testes are located in the dangling scrotum is to maintain the temperature of these glands below the internal temperature of the body, although usually only about 2°C below the internal temperature. On cold days, scrotal reflexes cause the musculature of the scrotum to contract, pulling the testes close to the body to maintain this 2° differential. Thus, the scrotum acts as a cooling mechanism for the testes (but a *controlled* cooling), without which spermatogenesis might be deficient during hot weather.

### Cryptorchidism

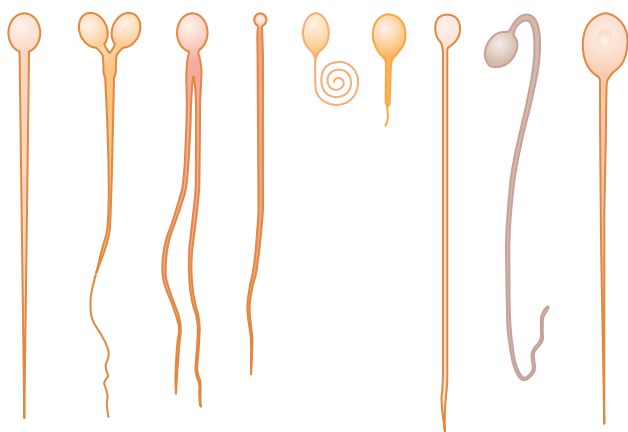
Cryptorchidism means failure of a testis to descend from the abdomen into the scrotum at or near the time of birth of a fetus. During development of the male fetus, the testes are derived from the genital ridges in the abdomen. However, at about 3 weeks to 1 month before birth of the baby, the testes normally descend through the inguinal canals into the scrotum. Occasionally this descent does not occur or occurs incompletely, so one or both testes remain in the abdomen, in the inguinal canal, or elsewhere along the route of descent.

A testis that remains throughout life in the abdominal cavity is incapable of forming sperm. The tubular epithelium becomes degenerate, leaving only the interstitial structures of the testis. It has been claimed that even the few degrees' higher temperature in the abdomen than in the scrotum is sufficient to cause this degeneration of the tubular epithelium and, consequently, to cause sterility, although this is not certain. Nevertheless, for this reason, operations to relocate the cryptorchid testes from the abdominal cavity into the scrotum before the beginning of adult sexual life can be performed on boys who have undescended testes.

Testosterone secretion by the fetal testes is the normal stimulus that causes the testes to descend into the scrotum from the abdomen. Therefore, many, if not most, instances of cryptorchidism are caused by abnormally formed testes that are unable to secrete enough testosterone. The surgical operation for cryptorchidism in these patients is unlikely to be successful.

**Effect of Sperm Count on Fertility.** The usual quantity of semen ejaculated during each coitus averages about 3.5 milliliters, and in each milliliter of semen is an average of about 120 million sperm, although even in "normal" males this can vary from 35 million to 200 million. This means an average total of 400 million sperm are usually present in the several milliliters of each ejaculate. When the number of sperm in each milliliter falls below about 20 million, the person is likely to be infertile. Thus, even though only a single sperm is necessary to fertilize the ovum, for reasons not understood, the ejaculate usually must contain a tremendous number of sperm for only one sperm to fertilize the ovum.

**Effect of Sperm Morphology and Motility on Fertility.** Occasionally a man has a normal number of sperm but is still infertile. When this occurs, sometimes as many as one-half the sperm are found to be abnormal physically, having two heads, abnormally shaped heads, or abnormal tails, as shown in Figure 80-5. At other times, the sperm appear to be structurally normal, but for reasons not understood, they are either entirely nonmotile or relatively nonmotile. Whenever the majority of the sperm are morphologically abnormal or are nonmotile, the person is likely to be infertile, even though the remainder of the sperm appear to be normal.



**Figure 80-5** Abnormal infertile sperm, compared with a normal sperm on the right.

## Male Sexual Act

### Neuronal Stimulus for Performance of the Male Sexual Act

The most important source of sensory nerve signals for initiating the male sexual act is the *glans penis*. The glans contains an especially sensitive sensory end-organ system that transmits into the central nervous system that special modality of sensation called *sexual sensation*. The slippery massaging action of intercourse on the glans stimulates the sensory end-organs, and the sexual signals in turn pass through the pudendal nerve, then through the sacral plexus into the sacral portion of the spinal cord, and finally up the cord to undefined areas of the brain.

Impulses may also enter the spinal cord from areas adjacent to the penis to aid in stimulating the sexual act. For instance, stimulation of the anal epithelium, the scrotum, and perineal structures in general can send signals into the cord that add to the sexual sensation. Sexual sensations can even originate in internal structures, such as in areas of the urethra, bladder, prostate, seminal vesicles, testes, and vas deferens. Indeed, one of the causes of "sexual drive" is filling of the sexual organs with secretions. Mild infection and inflammation of these sexual organs sometimes cause almost continual sexual desire, and some "aphrodisiac" drugs, such as cantharidin, irritate the bladder and urethral mucosa, inducing inflammation and vascular congestion.

### Psychic Element of Male Sexual Stimulation.

Appropriate psychic stimuli can greatly enhance the ability of a person to perform the sexual act. Simply thinking sexual thoughts or even dreaming that the act of intercourse is being performed can initiate the male act, culminating in ejaculation. Indeed, *nocturnal emissions* during dreams occur in many males during some stages of sexual life, especially during the teens.

**Integration of the Male Sexual Act in the Spinal Cord.** Although psychic factors usually play an important part in the male sexual act and can initiate or inhibit it, brain function is probably not necessary for its performance because appropriate genital stimulation can cause ejaculation in some animals and occasionally in humans after their spinal cords have been cut above the lumbar region. The male sexual act results from inherent reflex mechanisms integrated in the sacral and lumbar spinal cord, and these mechanisms can be initiated by either psychic stimulation from the brain or actual sexual stimulation from the sex organs, but usually it is a combination of both.

### Stages of the Male Sexual Act

**Penile Erection—Role of the Parasympathetic Nerves.** Penile erection is the first effect of male sexual stimulation, and the degree of erection is proportional



to the degree of stimulation, whether psychic or physical. Erection is caused by parasympathetic impulses that pass from the sacral portion of the spinal cord through the pelvic nerves to the penis. These parasympathetic nerve fibers, in contrast to most other parasympathetic fibers, are believed to release *nitric oxide* and/or *vasoactive intestinal peptide* in addition to acetylcholine. Nitric oxide activates the enzyme *guanylyl cyclase*, causing increased formation of *cyclic guanosine monophosphate* (GMP). The cyclic GMP especially relaxes the arteries of the penis and the trabecular meshwork of smooth muscle fibers in the *erectile tissue* of the *corpora cavernosa* and *corpus spongiosum* in the shaft of the penis, shown in Figure 80-6. As the vascular smooth muscles relax, blood flow into the penis increases, causing release of nitric oxide from the vascular endothelial cells and further vasodilation.

The erectile tissue of the penis consists of large cavernous sinusoids, which are normally relatively empty of blood but become dilated tremendously when arterial blood flows rapidly into them under pressure while the venous outflow is partially occluded. Also, the erectile bodies, especially the two corpora cavernosa, are surrounded by strong fibrous coats; therefore, high pressure within the sinusoids causes ballooning of the erectile tissue to such an extent that the penis becomes hard and elongated. This is the phenomenon of *erection*.

**Lubrication Is a Parasympathetic Function.** During sexual stimulation, the parasympathetic impulses, in addition to promoting erection, cause the urethral glands and the bulbourethral glands to secrete mucus. This mucus flows through the urethra during intercourse to aid in the lubrication during coitus. However, most of the lubrication of coitus is provided by the female sexual organs rather than by the male. Without satisfactory lubrication, the male sexual act is seldom successful because unlubricated intercourse causes grating, painful sensations that inhibit rather than excite sexual sensations.

**Emission and Ejaculation Are Functions of the Sympathetic Nerves.** Emission and ejaculation are the culmination of the male sexual act. When the sexual stimulus becomes extremely intense, the reflex centers

of the spinal cord begin to emit *sympathetic impulses* that leave the cord at T-12 to L-2 and pass to the genital organs through the hypogastric and pelvic sympathetic nerve plexuses to initiate *emission*, the forerunner of ejaculation.

Emission begins with contraction of the vas deferens and the ampulla to cause expulsion of sperm into the internal urethra. Then, contractions of the muscular coat of the prostate gland followed by contraction of the seminal vesicles expel prostatic and seminal fluid also into the urethra, forcing the sperm forward. All these fluids mix in the internal urethra with mucus already secreted by the bulbourethral glands to form the semen. The process to this point is *emission*.

The filling of the internal urethra with semen elicits sensory signals that are transmitted through the pudendal nerves to the sacral regions of the cord, giving the feeling of sudden fullness in the internal genital organs. Also, these sensory signals further excite rhythmical contraction of the internal genital organs and cause contraction of the ischiocavernosus and bulbocavernosus muscles that compress the bases of the penile erectile tissue. These effects together cause rhythmical, wavelike increases in pressure in both the erectile tissue of the penis and the genital ducts and urethra, which “ejaculate” the semen from the urethra to the exterior. This final process is called *ejaculation*. At the same time, rhythmical contractions of the pelvic muscles and even of some of the muscles of the body trunk cause thrusting movements of the pelvis and penis, which also help propel the semen into the deepest recesses of the vagina and perhaps even slightly into the cervix of the uterus.

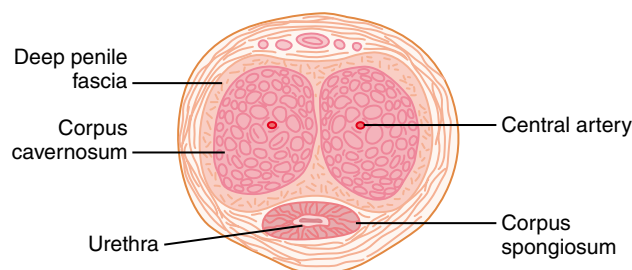
This entire period of emission and ejaculation is called the *male orgasm*. At its termination, the male sexual excitement disappears almost entirely within 1 to 2 minutes and erection ceases, a process called *resolution*.

## Testosterone and Other Male Sex Hormones

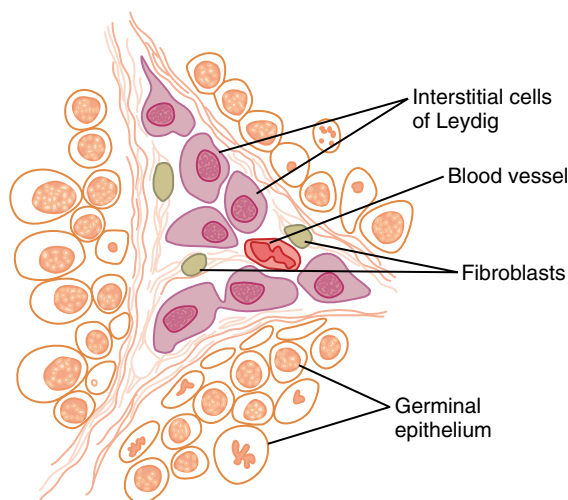
### Secretion, Metabolism, and Chemistry of the Male Sex Hormone

**Secretion of Testosterone by the Interstitial Cells of Leydig in the Testes.** The testes secrete several male sex hormones, which are collectively called *androgens*, including *testosterone*, *dihydrotestosterone*, and *androstenedione*. Testosterone is so much more abundant than the others that one can consider it to be the primary testicular hormone, although as we shall see, much, if not most, of the testosterone is eventually converted into the more active hormone dihydrotestosterone in the target tissues.

Testosterone is formed by the *interstitial cells of Leydig*, which lie in the interstices between the seminiferous tubules and constitute about 20 percent of the mass of the adult testes, as shown in Figure 80-7. Leydig cells



**Figure 80-6** Erectile tissue of the penis.



**Figure 80-7** Interstitial cells of Leydig, the cells that secrete testosterone, located in the interstices between the seminiferous tubules.

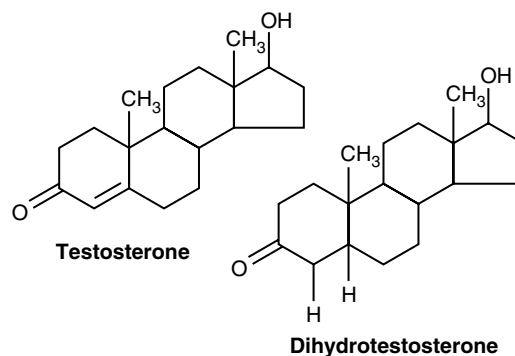
are almost nonexistent in the testes during childhood when the testes secrete almost no testosterone, but they *are* numerous in the newborn male infant for the first few months of life and in the adult male after puberty; at both these times the testes secrete large quantities of testosterone. Furthermore, when tumors develop from the interstitial cells of Leydig, great quantities of testosterone are secreted. Finally, when the germinal epithelium of the testes is destroyed by x-ray treatment or excessive heat, the Leydig cells, which are less easily destroyed, often continue to produce testosterone.

**Secretion of Androgens Elsewhere in the Body.** The term “androgen” means any steroid hormone that has masculinizing effects, including testosterone; it also includes male sex hormones produced elsewhere in the body besides the testes. For instance, the adrenal glands secrete at least five androgens, although the total masculinizing activity of all these is normally so slight (<5 percent of the total in the adult male) that even in women they do not cause significant masculine characteristics, except for causing growth of pubic and axillary hair. But when an adrenal tumor of the adrenal androgen-producing cells occurs, the quantity of androgenic hormones may then become great enough to cause all the usual male secondary sexual characteristics to occur even in the female. These effects are described in connection with the adrenogenital syndrome in Chapter 77.

Rarely, embryonic rest cells in the ovary can develop into a tumor that produces excessive quantities of androgens in women; one such tumor is the *arrhenoblastoma*. The normal ovary also produces minute quantities of androgens, but they are not significant.

**Chemistry of the Androgens.** All androgens are steroid compounds, as shown by the formulas in Figure 80-8 for *testosterone* and *dihydrotestosterone*. Both in the testes and in the adrenals, the androgens can be synthesized either from cholesterol or directly from acetyl coenzyme A.

**Metabolism of Testosterone.** After secretion by the testes, about 97 percent of the testosterone becomes either loosely bound with plasma albumin or more tightly bound with a beta globulin called *sex hormone-binding globulin*



**Figure 80-8** Testosterone and dihydrotestosterone.

and circulates in the blood in these states for 30 minutes to several hours. By that time, the testosterone is either transferred to the tissues or degraded into inactive products that are subsequently excreted.

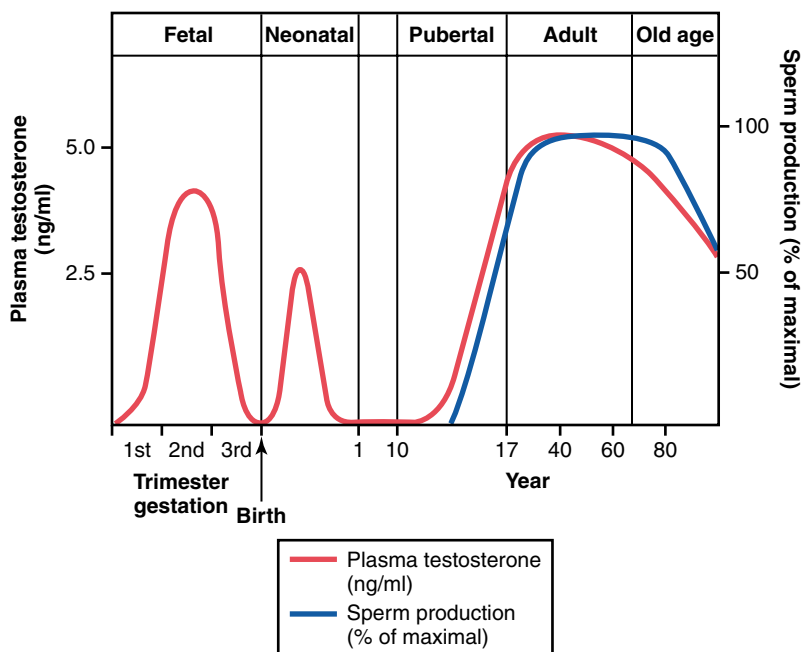
Much of the testosterone that becomes fixed to the tissues is converted within the tissue cells to *dihydrotestosterone*, especially in certain target organs such as the prostate gland in the adult and the external genitalia of the male fetus. Some actions of testosterone are dependent on this conversion, whereas other actions are not. The intracellular functions are discussed later in the chapter.

**Degradation and Excretion of Testosterone.** The testosterone that does not become fixed to the tissues is rapidly converted, mainly by the liver, into *androsterone* and *dehydroepiandrosterone* and simultaneously conjugated as either glucuronides or sulfates (glucuronides, particularly). These are excreted either into the gut by way of the liver bile or into the urine through the kidneys.

**Production of Estrogen in the Male.** In addition to testosterone, small amounts of estrogens are formed in the male (about one-fifth the amount in the nonpregnant female) and a reasonable quantity of estrogens can be recovered from a man's urine. The exact source of estrogens in the male is unclear, but the following are known: (1) the concentration of estrogens in the fluid of the seminiferous tubules is quite high and probably plays an important role in spermiogenesis. This estrogen is believed to be formed by the Sertoli cells by converting testosterone to estradiol. (2) Much larger amounts of estrogens are formed from testosterone and androstenediol in other tissues of the body, especially the liver, probably accounting for as much as 80 percent of the total male estrogen production.

## Functions of Testosterone

In general, testosterone is responsible for the distinguishing characteristics of the masculine body. Even during fetal life, the testes are stimulated by chorionic gonadotropin from the placenta to produce moderate quantities of testosterone throughout the entire period of fetal development and for 10 or more weeks after birth; thereafter, essentially no testosterone is produced during childhood until about the ages of 10 to 13 years. Then testosterone production increases rapidly under the stimulus of anterior pituitary gonadotropic hormones at the onset of puberty and lasts throughout most of the remainder of life, as shown in Figure 80-9, dwindling rapidly beyond age 50 to become 20 to 50 percent of the peak value by age 80.



**Figure 80-9** The different stages of male sexual function as reflected by average plasma testosterone concentrations (*red line*) and sperm production (*blue line*) at different ages. (Modified from Griffin JF, Wilson JD: The testis. In: Bondy PK, Rosenberg LE [eds]: Metabolic Control and Disease, 8th ed. Philadelphia: WB Saunders, 1980.)

### Functions of Testosterone During Fetal Development

Testosterone begins to be elaborated by the male fetal testes at about the seventh week of embryonic life. Indeed, one of the major functional differences between the female and the male sex chromosome is that the male chromosome has the *SRY* (*sex-determining region Y*) gene that encodes a protein called the *testis determining factor* (also called the *SRY protein*). The SRY protein initiates a cascade of gene activations that cause the genital ridge cells to differentiate into cells that secrete testosterone and eventually become the testes, whereas the female chromosome causes this ridge to differentiate into cells that secrete estrogens.

Injection of large quantities of male sex hormone into pregnant animals causes development of male sexual organs even though the fetus is female. Also, removal of the testes in the early male fetus causes development of female sexual organs.

Thus, testosterone secreted first by the genital ridges and later by the fetal testes is responsible for the development of the male body characteristics, including the formation of a penis and a scrotum rather than formation of a clitoris and a vagina. Also, it causes formation of the prostate gland, seminal vesicles, and male genital ducts, while at the same time suppressing the formation of female genital organs.

**Effect of Testosterone to Cause Descent of the Testes.** The testes usually descend into the scrotum during the last 2 to 3 months of gestation when the testes begin secreting reasonable quantities of testosterone. If a male child is born with undescended but otherwise normal testes, administration of testosterone usually causes the testes to descend in the usual manner if the inguinal canals are large enough to allow the testes to pass.

Administration of gonadotropic hormones, which stimulate the Leydig cells of the newborn child's testes to produce testosterone, can also cause the testes to descend. Thus, the stimulus for descent of the testes is testosterone, indicating again that testosterone is an important hormone for male sexual development during fetal life.

### Effect of Testosterone on Development of Adult Primary and Secondary Sexual Characteristics

After puberty, increasing amounts of testosterone secretion cause the penis, scrotum, and testes to enlarge about eightfold before the age of 20 years. In addition, testosterone causes the secondary sexual characteristics of the male to develop, beginning at puberty and ending at maturity. These secondary sexual characteristics, in addition to the sexual organs themselves, distinguish the male from the female as follows.

**Effect on the Distribution of Body Hair.** Testosterone causes growth of hair (1) over the pubis, (2) upward along the linea alba of the abdomen sometimes to the umbilicus and above, (3) on the face, (4) usually on the chest, and (5) less often on other regions of the body, such as the back. It also causes the hair on most other portions of the body to become more prolific.

**Baldness.** Testosterone decreases the growth of hair on the top of the head; a man who does not have functional testes does not become bald. However, many virile men never become bald because baldness is a result of two factors: first, a *genetic background* for the development of baldness and, second, superimposed on this genetic background, *large quantities of androgenic hormones*. A woman who has the appropriate genetic background and who develops a long-sustained androgenic tumor becomes bald in the same manner as does a man.

**Effect on the Voice.** Testosterone secreted by the testes or injected into the body causes hypertrophy of the laryngeal mucosa and enlargement of the larynx. The effects cause at first a relatively discordant, “cracking” voice, but this gradually changes into the typical adult masculine voice.

**Testosterone Increases Thickness of the Skin and Can Contribute to Development of Acne.** Testosterone increases the thickness of the skin over the entire body and increases the ruggedness of the subcutaneous tissues. Testosterone also increases the rate of secretion by some or perhaps all the body’s sebaceous glands. Especially important is excessive secretion by the sebaceous glands of the face because this can result in *acne*. Therefore, acne is one of the most common features of male adolescence when the body is first becoming introduced to increased testosterone. After several years of testosterone secretion, the skin normally adapts to the testosterone in a way that allows it to overcome the acne.

**Testosterone Increases Protein Formation and Muscle Development.** One of the most important male characteristics is development of increasing musculature after puberty, averaging about a 50 percent increase in muscle mass over that in the female. This is associated with increased protein in the nonmuscle parts of the body as well. Many of the changes in the skin are due to deposition of proteins in the skin, and the changes in the voice also result partly from this protein anabolic function of testosterone.

Because of the great effect that testosterone and other androgens have on the body musculature, synthetic androgens are widely used by athletes to improve their muscular performance. This practice is to be severely deprecated because of prolonged harmful effects of excess androgens, as we discuss in Chapter 84 in relation to sports physiology. Testosterone or synthetic androgens are also occasionally used in old age as a “youth hormone” to improve muscle strength and vigor, but with questionable results.

**Testosterone Increases Bone Matrix and Causes Calcium Retention.** After the great increase in circulating testosterone that occurs at puberty (or after prolonged injection of testosterone), the bones grow considerably thicker and deposit considerable additional calcium salts. Thus, testosterone increases the total quantity of bone matrix and causes calcium retention. The increase in bone matrix is believed to result from the general protein anabolic function of testosterone plus deposition of calcium salts in response to the increased protein.

Testosterone has a specific effect on the pelvis to (1) narrow the pelvic outlet, (2) lengthen it, (3) cause a funnel-like shape instead of the broad ovoid shape of the female pelvis, and (4) greatly increase the strength of the entire pelvis for load-bearing. In the absence of testosterone, the male pelvis develops into a pelvis that is similar to that of the female.

Because of the ability of testosterone to increase the size and strength of bones, it is sometimes used in older men to treat osteoporosis.

When great quantities of testosterone (or any other androgen) are secreted abnormally in the still-growing child, the rate of bone growth increases markedly, causing a spurt in total body height. However, the testosterone also causes the epiphyses of the long bones to unite with the shafts of the bones at an early age. Therefore, despite the rapidity of growth, this early uniting of the epiphyses prevents the person from growing as tall as he would have grown had testosterone not been secreted at all. Even in normal men, the final adult height is slightly less than that which occurs in males castrated before puberty.

**Testosterone Increases Basal Metabolic Rate.** Injection of large quantities of testosterone can increase the basal metabolic rate by as much as 15 percent. Also, even the usual quantity of testosterone secreted by the testes during adolescence and early adult life increases the rate of metabolism some 5 to 10 percent above the value that it would be were the testes not active. This increased rate of metabolism is possibly an indirect result of the effect of testosterone on protein anabolism, the increased quantity of proteins—the enzymes especially—increasing the activities of all cells.

**Testosterone Increases Red Blood Cells.** When normal quantities of testosterone are injected into a castrated adult, the number of red blood cells per cubic millimeter of blood increases 15 to 20 percent. Also, the average man has about 700,000 more red blood cells per cubic millimeter than the average woman. Despite the strong association of testosterone and increased hematocrit, testosterone does not appear to directly increase erythropoietin levels or have a direct effect on red blood cell production. The effect of testosterone to increase red blood cell production may be at least partly indirect due to the increased metabolic rate that occurs after testosterone administration.

**Effect on Electrolyte and Water Balance.** As pointed out in Chapter 77, many steroid hormones can increase the reabsorption of sodium in the distal tubules of the kidneys. Testosterone also has such an effect, but only to a minor degree in comparison with the adrenal mineralocorticoids. Nevertheless, after puberty, the blood and extracellular fluid volumes of the male in relation to body weight increase as much as 5 to 10 percent.

### Basic Intracellular Mechanism of Action of Testosterone

Most of the effects of testosterone result basically from increased rate of protein formation in the target cells. This has been studied extensively in the prostate gland, one of the organs that is most affected by testosterone. In this gland, testosterone enters the prostatic cells within a few minutes after secretion. Then it is most often converted, under the influence of the intracellular enzyme *5 $\alpha$ -reductase*, to *dihydrotestosterone*, and this in turn binds with a cytoplasmic “receptor protein.” This combination migrates to the cell nucleus, where it binds with a nuclear protein and induces DNA-RNA transcription.



Within 30 minutes, RNA polymerase has become activated and the concentration of RNA begins to increase in the prostatic cells; this is followed by progressive increase in cellular protein. After several days, the quantity of DNA in the prostate gland has also increased and there has been a simultaneous increase in the number of prostatic cells.

Testosterone stimulates production of proteins virtually everywhere in the body, although more specifically affecting those proteins in “target” organs or tissues responsible for the development of both primary and secondary male sexual characteristics.

Recent studies suggest that testosterone, like other steroid hormones, may also exert some rapid, *nongenomic effects* that do not require synthesis of new proteins. The physiological role of these nongenomic actions of testosterone, however, has yet to be determined.

### Control of Male Sexual Functions by Hormones from the Hypothalamus and Anterior Pituitary Gland

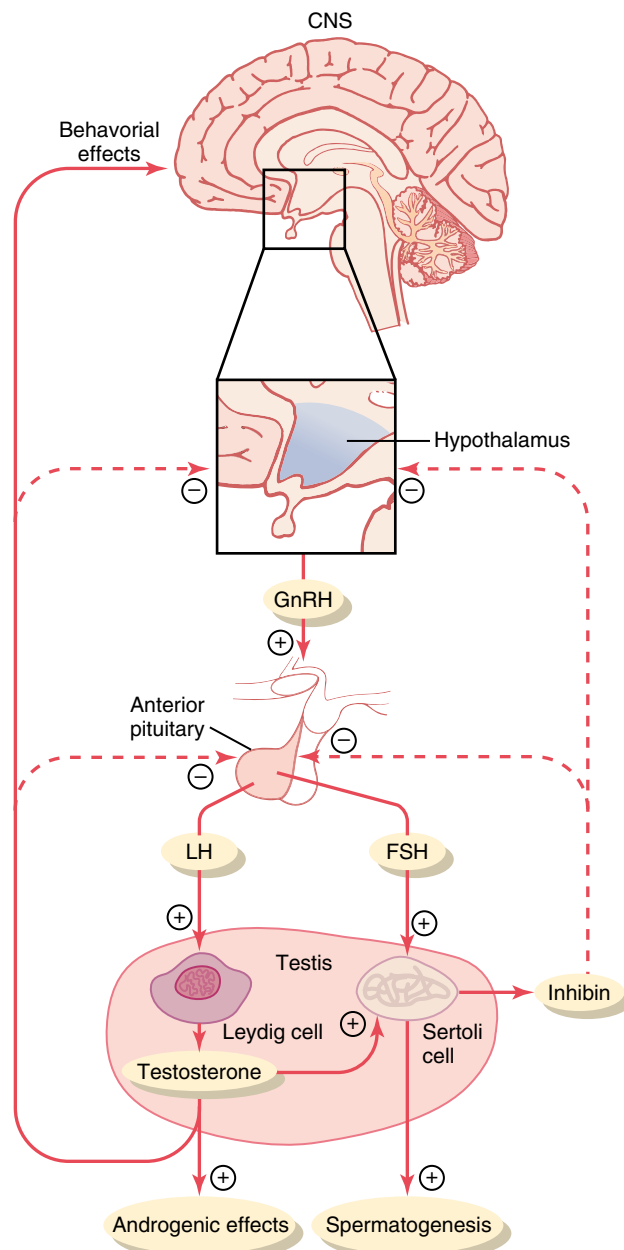
A major share of the control of sexual functions in both the male and the female begins with secretion of *gonadotropin-releasing hormone* (GnRH) by the hypothalamus (Figure 80-10). This hormone in turn stimulates the anterior pituitary gland to secrete two other hormones called *gonadotropic hormones*: (1) *luteinizing hormone* (LH) and (2) *follicle-stimulating hormone* (FSH). In turn, LH is the primary stimulus for the secretion of testosterone by the testes, and FSH mainly stimulates spermatogenesis.

#### GnRH and Its Effect in Increasing the Secretion of LH and FSH

GnRH is a 10-amino acid peptide secreted by neurons whose cell bodies are located in the *arcuate nuclei of the hypothalamus*. The endings of these neurons terminate mainly in the median eminence of the hypothalamus, where they release GnRH into the hypothalamic-hypophyseal portal vascular system. Then the GnRH is transported to the anterior pituitary gland in the hypophyseal portal blood and stimulates the release of the two gonadotropins, LH and FSH.

GnRH is secreted intermittently a few minutes at a time once every 1 to 3 hours. The intensity of this hormone's stimulus is determined in two ways: (1) by the frequency of these cycles of secretion and (2) by the quantity of GnRH released with each cycle.

The secretion of LH by the anterior pituitary gland is also cyclical, with LH following fairly faithfully the pulsatile release of GnRH. Conversely, FSH secretion increases and decreases only slightly with each fluctuation of GnRH secretion; instead, it changes more slowly over a period of many hours in response to longer-term changes in GnRH. Because of the much closer relation between GnRH secretion and LH secretion, GnRH is also widely known as *LH-releasing hormone*.



**Figure 80-10** Feedback regulation of the hypothalamic-pituitary-testicular axis in males. Stimulatory effects are shown by ⊕ and negative feedback inhibitory effects are shown by ⊖. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

#### Gonadotropic Hormones: LH and FSH

Both of the gonadotropic hormones, LH and FSH, are secreted by the same cells, called *gonadotropes*, in the anterior pituitary gland. In the absence of GnRH secretion from the hypothalamus, the gonadotropes in the pituitary gland secrete almost no LH or FSH.

LH and FSH are *glycoproteins*. They exert their effects on their target tissues in the testes mainly by *activating the cyclic adenosine monophosphate second messenger system*, which in turn activates specific enzyme systems in the respective target cells.

**Regulation of Testosterone Production by LH.**

*Testosterone* is secreted by the *interstitial cells of Leydig* in the testes, but only when they are stimulated by LH from the anterior pituitary gland. Furthermore, the quantity of testosterone secreted increases approximately in direct proportion to the amount of LH available.

Mature Leydig cells are normally found in a child's testes for a few weeks after birth but then disappear until after the age of about 10 years. However, injection of purified LH into a child at any age or secretion of LH at puberty causes testicular interstitial cells that look like fibroblasts to evolve into functioning Leydig cells.

**Inhibition of Anterior Pituitary Secretion of LH and FSH by Testosterone-Negative Feedback Control of Testosterone Secretion.** The testosterone secreted by the testes in response to LH has the reciprocal effect of inhibiting anterior pituitary secretion of LH (see Figure 80-10). Most of this inhibition probably results from a direct effect of testosterone on the hypothalamus to decrease the secretion of GnRH. This in turn causes a corresponding decrease in secretion of both LH and FSH by the anterior pituitary, and the decrease in LH reduces the secretion of testosterone by the testes. Thus, whenever secretion of testosterone becomes too great, this automatic negative feedback effect, operating through the hypothalamus and anterior pituitary gland, reduces the testosterone secretion back toward the desired operating level. Conversely, too little testosterone allows the hypothalamus to secrete large amounts of GnRH, with a corresponding increase in anterior pituitary LH and FSH secretion and consequent increase in testicular testosterone secretion.

**Regulation of Spermatogenesis by FSH and Testosterone**

FSH binds with specific FSH receptors attached to the Sertoli cells in the seminiferous tubules. This causes the Sertoli cells to grow and secrete various spermatogenic substances. Simultaneously, testosterone (and dihydrotestosterone) diffusing into the seminiferous tubules from the Leydig cells in the interstitial spaces also has a strong tropic effect on spermatogenesis. Thus, to initiate spermatogenesis, both FSH and testosterone are necessary.

**Role of Inhibin in Negative Feedback Control of Seminiferous Tubule Activity.** When the seminiferous tubules fail to produce sperm, secretion of FSH by the anterior pituitary gland increases markedly. Conversely, when spermatogenesis proceeds too rapidly, pituitary secretion of FSH diminishes. The cause of this negative feedback effect on the anterior pituitary is believed to be secretion by the Sertoli cells of still another hormone called *inhibin* (see Figure 80-10). This hormone has a strong direct effect on the anterior pituitary gland to inhibit the secretion of FSH and possibly a slight effect on the hypothalamus to inhibit secretion of GnRH.

Inhibin is a glycoprotein, like both LH and FSH, having a molecular weight between 10,000 and 30,000. It has been isolated from cultured Sertoli cells. Its potent inhibitory feedback effect on the anterior pituitary gland

provides an important negative feedback mechanism for control of spermatogenesis, operating simultaneously with and in parallel to the negative feedback mechanism for control of testosterone secretion.

**Human Chorionic Gonadotropin Secreted by the Placenta During Pregnancy Stimulates Testosterone Secretion by the Fetal Testes**

During pregnancy the hormone *human chorionic gonadotropin* (hCG) is secreted by the placenta, and it circulates both in the mother and in the fetus. This hormone has almost the same effects on the sexual organs as LH.

During pregnancy, if the fetus is a male, hCG from the placenta causes the testes of the fetus to secrete testosterone. This testosterone is critical for promoting formation of the male sexual organs, as pointed out earlier. We discuss hCG and its functions during pregnancy in greater detail in Chapter 82.

**Puberty and Regulation of Its Onset**

Initiation of the onset of puberty has long been a mystery. But it has now been determined that *during childhood the hypothalamus simply does not secrete significant amounts of GnRH*. One of the reasons for this is that, during childhood, the slightest secretion of any sex steroid hormones exerts a strong inhibitory effect on hypothalamic secretion of GnRH. Yet for reasons still not understood, at the time of puberty, the secretion of hypothalamic GnRH breaks through the childhood inhibition and adult sexual life begins.

**Male Adult Sexual Life and Male Climacteric.** After puberty, gonadotropic hormones are produced by the male pituitary gland for the remainder of life, and at least some spermatogenesis usually continues until death. Most men, however, begin to exhibit slowly decreasing sexual functions in their late 50s or 60s, and one study showed that the average age for terminating intersexual relations was 68, although the variation was great. This decline in sexual function is related to decrease in testosterone secretion, as shown in Figure 80-9. The decrease in male sexual function is called the *male climacteric*. Occasionally the male climacteric is associated with symptoms of hot flashes, suffocation, and psychic disorders similar to the menopausal symptoms of the female. These symptoms can be abrogated by administration of testosterone, synthetic androgens, or even estrogens that are used for treatment of menopausal symptoms in the female.

**Abnormalities of Male Sexual Function****Prostate Gland and Its Abnormalities**

The prostate gland remains relatively small throughout childhood and begins to grow at puberty under the stimulus of testosterone. This gland reaches an almost stationary size by the age of 20 years and remains at this size up to the age of about 50 years. At that time, in some men it begins to involute, along with decreased production of testosterone by the testes.

A benign prostatic fibroadenoma frequently develops in the prostate in many older men and can cause urinary

obstruction. This hypertrophy is caused not by testosterone but instead by abnormal overgrowth of prostate tissue itself.

Cancer of the prostate gland is a different problem and accounts for about 2 to 3 percent of all male deaths. Once cancer of the prostate gland does occur, the cancerous cells are usually stimulated to more rapid growth by testosterone and are inhibited by removal of both testes so that testosterone cannot be formed. Prostatic cancer usually can be inhibited by administration of estrogens. Even some patients who have prostatic cancer that has already metastasized to almost all the bones of the body can be successfully treated for a few months to years by removal of the testes, by estrogen therapy, or by both; after this therapy the metastases usually diminish in size and the bones partially heal. This treatment does not stop the cancer but does slow it and sometimes greatly diminishes the severe bone pain.

### Hypogonadism in the Male

When the testes of a male fetus are nonfunctional during fetal life, none of the male sexual characteristics develop in the fetus. Instead, female organs are formed. The reason for this is that the basic genetic characteristic of the fetus, whether male or female, is to form female sexual organs if there are no sex hormones. But in the presence of testosterone, formation of female sexual organs is suppressed, and instead, male organs are induced.

When a boy loses his testes before puberty, a state of eunuchism ensues in which he continues to have infantile sex organs and other infantile sexual characteristics throughout life. The height of an adult eunuch is slightly greater than that of a normal man because the bone epiphyses are slow to unite, although the bones are quite thin and the muscles are considerably weaker than those of a normal man. The voice is childlike, there is no loss of hair on the head, and the normal adult masculine hair distribution on the face and elsewhere does not occur.

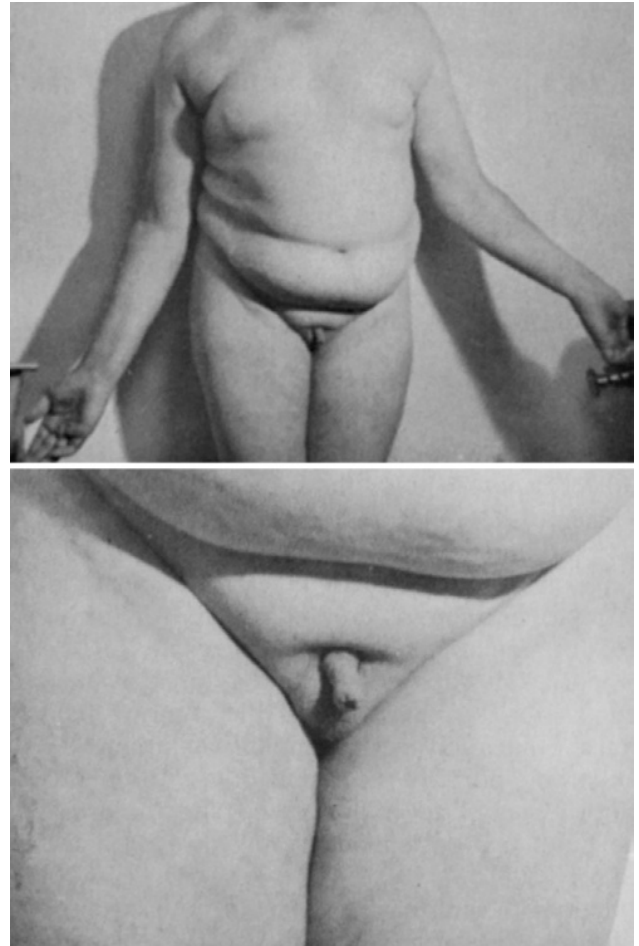
When a man is castrated after puberty, some of his male secondary sexual characteristics revert to those of a child and others remain of adult masculine character. The sexual organs regress slightly in size but not to a childlike state, and the voice regresses from the bass quality only slightly. However, there is loss of masculine hair production, loss of the thick masculine bones, and loss of the musculature of the virile male.

Also in a castrated adult male, sexual desires are decreased but not lost, provided sexual activities have been practiced previously. Erection can still occur as before, although with less ease, but it is rare that ejaculation can take place, primarily because the semen-forming organs degenerate and there has been a loss of the testosterone-driven psychic desire.

Some instances of hypogonadism are caused by a genetic inability of the hypothalamus to secrete normal amounts of GnRH. This is often associated with a simultaneous abnormality of the feeding center of the hypothalamus, causing the person to greatly overeat. Consequently, obesity occurs along with eunuchism. A patient with this condition is shown in Figure 80-11; the condition is called *adiposogenital syndrome*, *Fröhlich syndrome*, or *hypothalamic eunuchism*.

### Testicular Tumors and Hypergonadism in the Male

*Interstitial Leydig cell tumors* develop in rare instances in the testes, but when they do develop, they sometimes produce as much as 100 times the normal quantities of testosterone. When such tumors develop in young children, they cause



**Figure 80-11** Adiposogenital syndrome in an adolescent male. Note the obesity and childlike sexual organs. (Courtesy Dr. Leonard Posey.)

rapid growth of the musculature and bones but also cause early uniting of the epiphyses, so that the eventual adult height is actually considerably less than that which would have been achieved otherwise. Such interstitial cell tumors also cause excessive development of the male sexual organs, all skeletal muscles, and other male sexual characteristics. In the adult male, small interstitial cell tumors are difficult to diagnose because masculine features are already present.

Much more common than the interstitial Leydig cell tumors are tumors of the germinal epithelium. Because germinal cells are capable of differentiating into almost any type of cell, many of these tumors contain multiple tissues, such as placental tissue, hair, teeth, bone, skin, and so forth, all found together in the same tumorous mass called a *teratoma*. These tumors often secrete few hormones, but if a significant quantity of placental tissue develops in the tumor, it may secrete large quantities of hCG with functions similar to those of LH. Also, estrogenic hormones are sometimes secreted by these tumors and cause the condition called *gynecomastia* (overgrowth of the breasts).

### Erectile Dysfunction in the Male

Erectile dysfunction, also called “impotence,” is characterized by an inability of the man to develop or maintain an *erection* of sufficient rigidity for satisfactory sexual intercourse.



Neurological problems, such as trauma to the parasympathetic nerves from prostate surgery, deficient levels of testosterone, and some *drugs* (*nicotine, alcohol, antidepressants*) can also contribute to erectile dysfunction.

In men older than age 40, erectile dysfunction is most often caused by underlying vascular disease. As discussed previously, adequate blood flow and nitric oxide formation are essential for penile erection. Vascular disease, which can occur as a result of uncontrolled *hypertension, diabetes, and atherosclerosis*, reduces the ability of the body's blood vessels, including those in the penis, to dilate. Part of this impaired vasodilation is due to decreased release of nitric oxide.

Erectile dysfunction caused by vascular disease can often be successfully treated with *phosphodiesterase-5 (PDE-5) inhibitors* such as sildenafil (Viagra), vardenafil (Levitra) or tadalafil (Cialis). These drugs increase cyclic GMP levels in the erectile tissue by inhibiting the enzyme *phosphodiesterase-5*, which rapidly degrades cyclic GMP. Thus, by inhibiting the degradation of cyclic GMP, the PDE-5 inhibitors enhance and prolong the effect of cyclic GMP to cause erection.

### Pineal Gland—Its Function in Controlling Seasonal Fertility in Some Animals

For as long as the pineal gland has been known to exist, myriad functions have been ascribed to it, including its (1) enhancing sex, (2) staving off infection, (3) promoting sleep, (4) enhancing mood, and (5) increasing longevity (as much as 10 to 25 percent). It is known from comparative anatomy that the pineal gland is a vestigial remnant of what was a third eye located high in the back of the head in some lower animals. Many physiologists have been content with the idea that this gland is a nonfunctional remnant, but others have claimed for many years that it plays important roles in the control of sexual activities and reproduction.

But now, after years of research, it appears that the pineal gland does indeed play a regulatory role in sexual and reproductive function. In lower animals that bear their young at certain seasons of the year and in which the pineal gland has been removed or the nervous circuits to the pineal gland have been sectioned, the normal periods of seasonal fertility are lost. To these animals, such seasonal fertility is important because it allows birth of the offspring at the time of year, usually springtime or early summer, when survival is most likely. The mechanism of this effect is not entirely clear, but it seems to be the following.

First, the pineal gland is controlled by the amount of light or “time pattern” of light seen by the eyes each day. For instance, in the hamster, greater than 13 hours of *darkness* each day activates the pineal gland, whereas less than that amount of darkness fails to activate it, with a critical balance between activation and nonactivation. The nervous pathway involves the passage of light signals from the eyes to the suprachiasmatic nucleus of the hypothalamus and then to the pineal gland, activating pineal secretion.

Second, the pineal gland secretes *melatonin* and several other, similar substances. Either melatonin or one of the other substances is believed to pass either by way of the blood or through the fluid of the third ventricle to the anterior pituitary gland to *decrease* gonadotropic hormone secretion.

Thus, in the presence of pineal gland secretion, gonadotropic hormone secretion is suppressed in some species of animals, and the gonads become inhibited and even partly involuted. This is what presumably occurs during the early winter months when there is increasing darkness. But after about 4 months of dysfunction, gonadotropic hormone secretion breaks through the inhibitory effect of the pineal gland and the gonads become functional once more, ready for a full springtime of activity.

But does the pineal gland have a similar function for control of reproduction in humans? The answer to this question is unknown. However, tumors often occur in the region of the pineal gland. Some of these secrete excessive quantities of pineal hormones, whereas others are tumors of surrounding tissue and press on the pineal gland to destroy it. Both types of tumors are often associated with hypogonadal or hypergonadal function. So perhaps the pineal gland does play at least some role in controlling sexual drive and reproduction in humans.

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# Female Physiology Before Pregnancy and Female Hormones



Female reproductive functions can be divided into two major phases: (1) preparation of the female body for conception and pregnancy and (2) the period of pregnancy itself. This chapter is concerned with preparation of the female body for pregnancy, and Chapter 82 presents the physiology of pregnancy and childbirth.

## Physiologic Anatomy of the Female Sexual Organs

Figures 81-1 and 81-2 show the principal organs of the human female reproductive tract, including the *ovaries*, *fallopian tubes* (also called *uterine tubes*), *uterus*, and *vagina*. Reproduction begins with the development of ova in the ovaries. In the middle of each monthly sexual cycle, a single ovum is expelled from an ovarian follicle into the abdominal cavity near the open fimbriated ends of the two fallopian tubes. This ovum then passes through one of the fallopian tubes into the uterus; if it has been fertilized by a sperm, it implants in the uterus, where it develops into a fetus, a placenta, and fetal membranes—and eventually into a baby.

During fetal life, the outer surface of the ovary is covered by a *germinal epithelium*, which embryologically is derived from the epithelium of the germinal ridges. As the female fetus develops, *primordial ova* differentiate from this germinal epithelium and migrate into the substance of the ovarian cortex. Each ovum then collects around it a layer of spindle cells from the ovarian *stroma* (the supporting tissue of the ovary) and causes them to take on epithelioid characteristics; they are then called *granulosa cells*. The ovum surrounded by a single layer of granulosa cells is called a *primordial follicle*. The ovum at this stage is still immature, requiring two more cell divisions before it can be fertilized by a sperm. At this time, the ovum is called a *primary oocyte*.

During all the reproductive years of adult life, between about 13 and 46 years of age, 400 to 500 of the primordial

follicles develop enough to expel their ova—one each month; the remainder degenerate (become *atretic*). At the end of reproductive capability (at *menopause*), only a few primordial follicles remain in the ovaries and even these degenerate soon thereafter.

## Female Hormonal System

The female hormonal system, like that of the male, consists of three hierarchies of hormones, as follows:

1. A hypothalamic releasing hormone, *gonadotropin-releasing hormone* (GnRH)
2. The anterior pituitary sex hormones, *follicle-stimulating hormone* (FSH) and *luteinizing hormone* (LH), both of which are secreted in response to the release of GnRH from the hypothalamus
3. The ovarian hormones, *estrogen* and *progesterone*, which are secreted by the ovaries in response to the two female sex hormones from the anterior pituitary gland

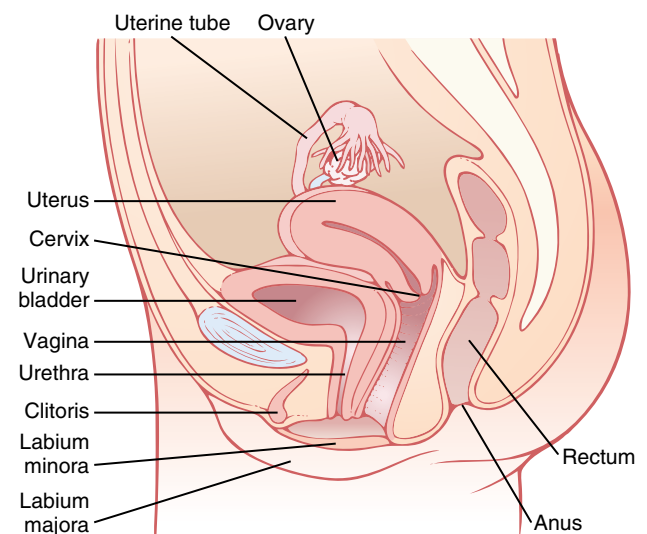
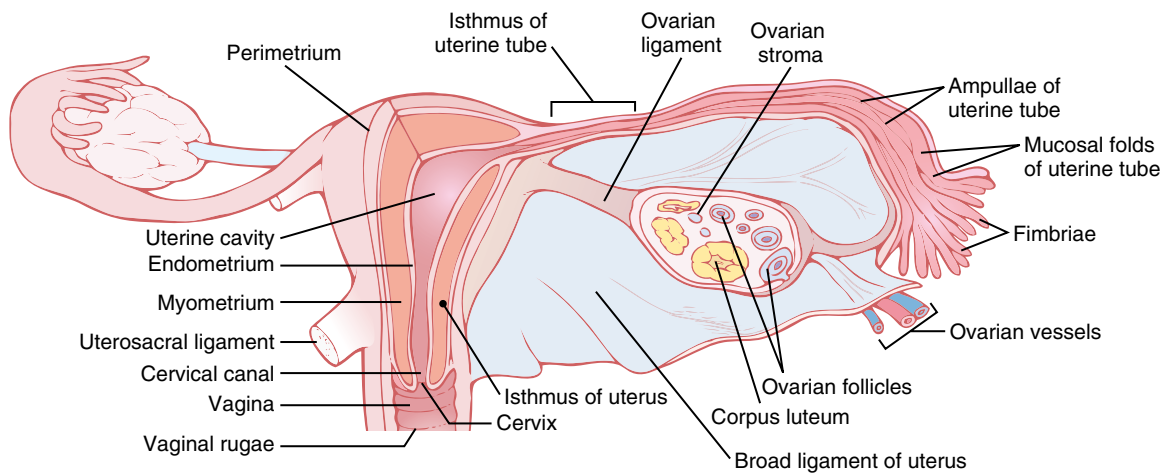
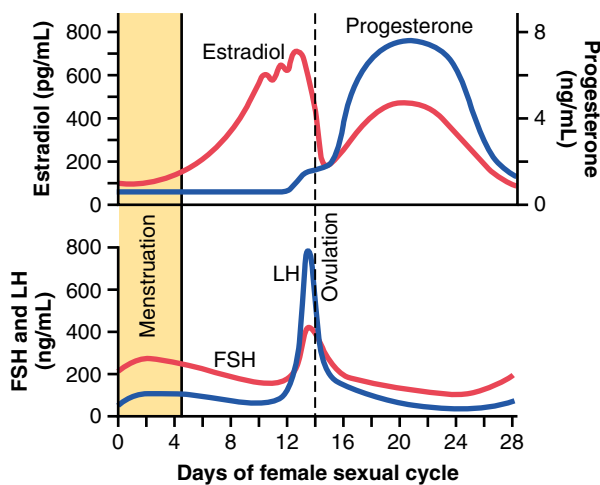


Figure 81-1 Female reproductive organs.



**Figure 81-2** Internal structures of the uterus, ovary, and a uterine tube. (Redrawn from Guyton AC: Physiology of the Human Body, 6th ed. Philadelphia: Saunders College Publishing, 1984.)



**Figure 81-3** Approximate plasma concentrations of the gonadotropins and ovarian hormones during the normal female sexual cycle. FSH, follicle-stimulating hormone; LH, luteinizing hormone.

These various hormones are secreted at drastically differing rates during different parts of the female monthly sexual cycle. Figure 81-3 shows the approximate changing concentrations of the anterior pituitary gonadotropic hormones FSH and LH (bottom two curves) and of the ovarian hormones estradiol (estrogen) and progesterone (top two curves).

The amount of GnRH released from the hypothalamus increases and decreases much less drastically during the monthly sexual cycle. It is secreted in short pulses averaging once every 90 minutes, as occurs in the male.

### Monthly Ovarian Cycle; Function of the Gonadotropic Hormones

The normal reproductive years of the female are characterized by monthly rhythmical changes in the rates of secretion of the female hormones and corresponding physical changes in the ovaries and other sexual organs. This rhythmical pattern is called the *female monthly*

*sexual cycle* (or, less accurately, the *menstrual cycle*). The duration of the cycle averages 28 days. It may be as short as 20 days or as long as 45 days in some women, although abnormal cycle length is frequently associated with decreased fertility.

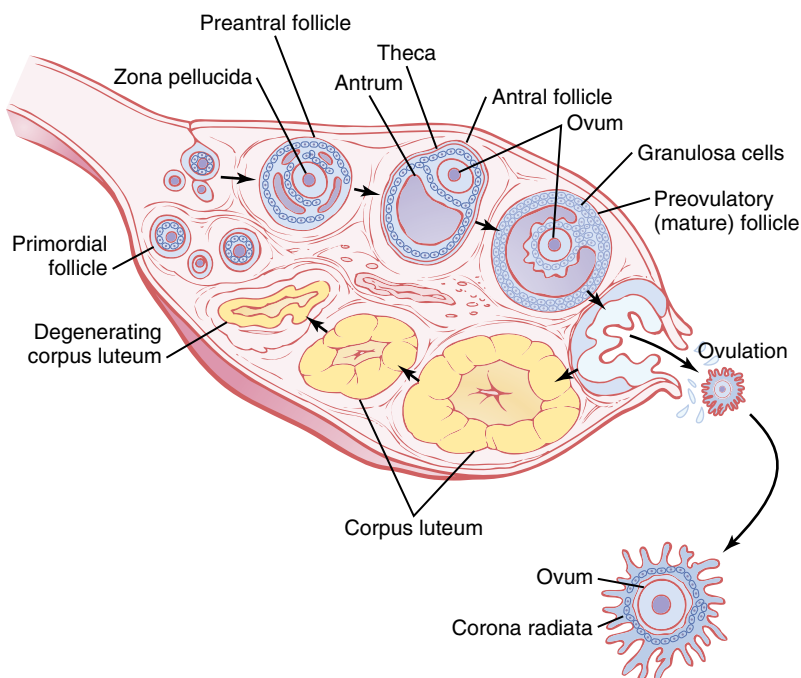
There are two significant results of the female sexual cycle. First, only a *single* ovum is normally released from the ovaries each month, so normally only a single fetus will begin to grow at a time. Second, the uterine endometrium is prepared in advance for implantation of the fertilized ovum at the required time of the month.

### Gonadotropic Hormones and Their Effects on the Ovaries

The ovarian changes that occur during the sexual cycle depend completely on the gonadotropic hormones FSH and LH, secreted by the anterior pituitary gland. In the absence of these hormones, the ovaries remain inactive, which is the case throughout childhood, when almost no pituitary gonadotropic hormones are secreted. At age 9 to 12 years, the pituitary begins to secrete progressively more FSH and LH, which leads to onset of normal monthly sexual cycles beginning between the ages of 11 and 15 years. This period of change is called *puberty*, and the time of the first menstrual cycle is called *menarche*. Both FSH and LH are small glycoproteins having molecular weights of about 30,000.

During each month of the female sexual cycle, there is a cyclical increase and decrease of both FSH and LH, as shown in the bottom of Figure 81-3. These cyclical variations cause cyclical ovarian changes, which are explained in the following sections.

Both FSH and LH stimulate their ovarian target cells by combining with highly specific FSH and LH receptors in the ovarian target cell membranes. In turn, the activated receptors increase the cells' rates of secretion and usually the growth and proliferation of the cells as well. Almost all these stimulatory effects result from *activation of the cyclic adenosine monophosphate second messenger*



**Figure 81-4** Stages of follicular growth in the ovary, also showing formation of the corpus luteum.

system in the cell cytoplasm, which causes the formation of *protein kinase* and multiple *phosphorylations* of *key enzymes* that stimulate sex hormone synthesis, as explained in Chapter 74.

### Ovarian Follicle Growth—"Follicular" Phase of the Ovarian Cycle

Figure 81-4 shows the progressive stages of follicular growth in the ovaries. When a female child is born, each ovum is surrounded by a single layer of granulosa cells; the ovum, with this granulosa cell sheath, is called a *primordial follicle*, as shown in the figure. Throughout childhood, the granulosa cells are believed to provide nourishment for the ovum and to secrete an *oocyte maturation-inhibiting factor* that keeps the ovum suspended in its primordial state in the prophase stage of meiotic division. Then, after puberty, when FSH and LH from the anterior pituitary gland begin to be secreted in significant quantities, the ovaries, together with some of the follicles within them, begin to grow.

The first stage of follicular growth is moderate enlargement of the ovum itself, which increases in diameter two-fold to threefold. Then follows growth of additional layers of granulosa cells in some of the follicles; these follicles are known as *primary follicles*.

#### Development of Antral and Vesicular Follicles.

During the first few days of each monthly female sexual cycle, the concentrations of both FSH and LH secreted by the anterior pituitary gland increase slightly to moderately, with the increase in FSH slightly greater than that of LH and preceding it by a few days. These hormones, especially FSH, cause accelerated growth of 6 to 12 primary follicles each month. The initial effect is rapid

proliferation of the granulosa cells, giving rise to many more layers of these cells. In addition, spindle cells derived from the ovary interstitium collect in several layers outside the granulosa cells, giving rise to a second mass of cells called the *theca*. This is divided into two layers. In the *theca interna*, the cells take on epithelioid characteristics similar to those of the granulosa cells and develop the ability to secrete additional steroid sex hormones (estrogen and progesterone). The outer layer, the *theca externa*, develops into a highly vascular connective tissue capsule that becomes the capsule of the developing follicle.

After the early proliferative phase of growth, lasting for a few days, the mass of granulosa cells secretes a *follicular fluid* that contains a high concentration of estrogen, one of the important female sex hormones (discussed later). Accumulation of this fluid causes an *antrum* to appear within the mass of granulosa cells, as shown in Figure 81-4.

The early growth of the primary follicle up to the antral stage is stimulated mainly by FSH alone. Then greatly accelerated growth occurs, leading to still larger follicles called *vesicular follicles*. This accelerated growth is caused by the following: (1) Estrogen is secreted into the follicle and causes the granulosa cells to form increasing numbers of FSH receptors; this causes a positive feedback effect because it makes the granulosa cells even more sensitive to FSH. (2) The pituitary FSH and the estrogens combine to promote LH receptors on the original granulosa cells, thus allowing LH stimulation to occur in addition to FSH stimulation and creating an even more rapid increase in follicular secretion. (3) The increasing estrogens from the follicle plus the increasing LH from the anterior pituitary gland act together to cause proliferation of the follicular thecal cells and increase their secretion as well.

Once the antral follicles begin to grow, their growth occurs almost explosively. The ovum itself also enlarges

in diameter another threefold to fourfold, giving a total ovum diameter increase up to 10-fold, or a mass increase of 1000-fold. As the follicle enlarges, the ovum remains embedded in a mass of granulosa cells located at one pole of the follicle.

**Only One Follicle Fully Matures Each Month, and the Remainder Undergo Atresia.** After a week or more of growth—but before ovulation occurs—one of the follicles begins to outgrow all the others; the remaining 5 to 11 developing follicles involute (a process called *atresia*), and these follicles are said to become *atretic*.

The cause of the atresia is unknown, but it has been postulated to be the following: The large amounts of estrogen from the most rapidly growing follicle act on the hypothalamus to depress further enhancement of FSH secretion by the anterior pituitary gland, in this way blocking further growth of the less well developed follicles. Therefore, the largest follicle continues to grow because of its intrinsic positive feedback effects, while all the other follicles stop growing and actually involute.

This process of atresia is important because it normally allows only one of the follicles to grow large enough each month to ovulate; this usually prevents more than one child from developing with each pregnancy. The single follicle reaches a diameter of 1 to 1.5 centimeters at the time of ovulation and is called the *mature follicle*.

## Ovulation

Ovulation in a woman who has a normal 28-day female sexual cycle occurs 14 days after the onset of menstruation. Shortly before ovulation the protruding outer wall of the follicle swells rapidly, and a small area in the center of the follicular capsule, called the *stigma*, protrudes like a nipple. In another 30 minutes or so, fluid begins to ooze from the follicle through the stigma, and about 2 minutes later, the stigma ruptures widely, allowing a more viscous fluid, which has occupied the central portion of the follicle, to evaginate outward. This viscous fluid carries with it the ovum surrounded by a mass of several thousand small granulosa cells, called the *corona radiata*.

**Surge of LH Is Necessary for Ovulation.** LH is necessary for final follicular growth and ovulation. Without this hormone, even when large quantities of FSH are available, the follicle will not progress to the stage of ovulation.

About 2 days before ovulation (for reasons that are not completely understood but are discussed in more detail later in the chapter), the rate of secretion of LH by the anterior pituitary gland increases markedly, rising 6- to 10-fold and peaking about 16 hours before ovulation. FSH also increases about twofold to threefold at the same time, and the FSH and LH act synergistically to cause rapid swelling of the follicle during the last few days before ovulation. The LH also has a specific effect on the granulosa and theca cells, converting them mainly to progesterone-secreting cells. Therefore, the rate of secretion of estrogen begins to fall about 1 day before ovula-

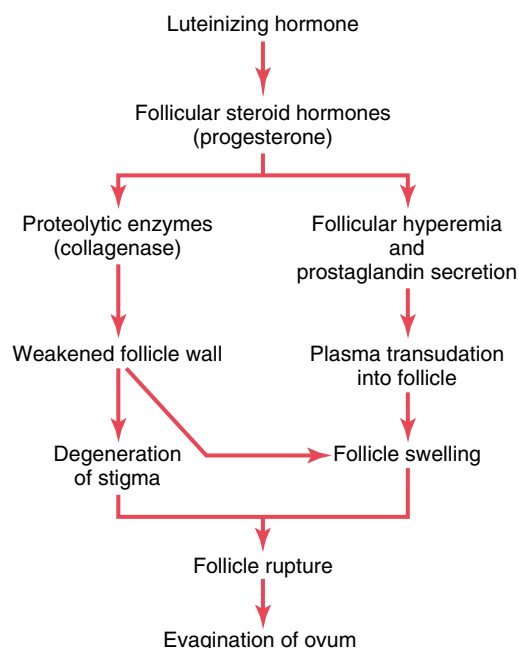
tion, while increasing amounts of progesterone begin to be secreted.

It is in this environment of (1) rapid growth of the follicle, (2) diminishing estrogen secretion after a prolonged phase of excessive estrogen secretion, and (3) initiation of secretion of progesterone that ovulation occurs. Without the initial preovulatory surge of LH, ovulation will not take place.

**Initiation of Ovulation.** Figure 81-5 gives a schema for the initiation of ovulation, showing the role of the large quantity of LH secreted by the anterior pituitary gland. This LH causes rapid secretion of follicular steroid hormones that contain progesterone. Within a few hours, two events occur, both of which are necessary for ovulation: (1) The *theca externa* (the capsule of the follicle) begins to release proteolytic enzymes from lysosomes, and these cause dissolution of the follicular capsular wall and consequent weakening of the wall, resulting in further swelling of the entire follicle and degeneration of the stigma. (2) Simultaneously there is rapid growth of new blood vessels into the follicle wall, and at the same time, prostaglandins (local hormones that cause vasodilation) are secreted into the follicular tissues. These two effects cause plasma transudation into the follicle, which contributes to follicle swelling. Finally, the combination of follicle swelling and simultaneous degeneration of the stigma causes follicle rupture, with discharge of the ovum.

## Corpus Luteum—"Luteal" Phase of the Ovarian Cycle

During the first few hours after expulsion of the ovum from the follicle, the remaining granulosa and theca interna cells change rapidly into *lutein cells*. They enlarge in diameter two or more times and become filled with lipid inclusions that give them a yellowish appearance.



**Figure 81-5** Postulated mechanism of ovulation.



This process is called *luteinization*, and the total mass of cells together is called the *corpus luteum*, which is shown in Figure 81-4. A well-developed vascular supply also grows into the corpus luteum.

The *granulosa cells* in the corpus luteum develop extensive intracellular smooth endoplasmic reticula that form large amounts of the female sex hormones *progesterone* and *estrogen* (more progesterone than estrogen during the luteal phase). The *theca cells* form mainly the androgens *androstenedione* and *testosterone* rather than female sex hormones. However, most of these hormones are also converted by the enzyme *aromatase* in the granulosa cells into estrogens, the female hormones.

The corpus luteum normally grows to about 1.5 centimeters in diameter, reaching this stage of development 7 to 8 days after ovulation. Then it begins to involute and eventually loses its secretory function and its yellowish, lipid characteristic about 12 days after ovulation, becoming the *corpus albicans*; during the ensuing few weeks, this is replaced by connective tissue and over months is absorbed.

**Luteinizing Function of LH.** The change of granulosa and theca interna cells into lutein cells is dependent mainly on LH secreted by the anterior pituitary gland. In fact, this function gives LH its name—"luteinizing," for "yellowing." Luteinization also depends on extrusion of the ovum from the follicle. A yet uncharacterized local hormone in the follicular fluid, called *luteinization-inhibiting factor*, seems to hold the luteinization process in check until after ovulation.

**Secretion by the Corpus Luteum: An Additional Function of LH.** The corpus luteum is a highly secretory organ, secreting large amounts of both *progesterone* and *estrogen*. Once LH (mainly that secreted during the ovulatory surge) has acted on the granulosa and theca cells to cause luteinization, the newly formed lutein cells seem to be programmed to go through a preordained sequence of (1) proliferation, (2) enlargement, and (3) secretion, followed by (4) degeneration. All this occurs in about 12 days. We shall see in the discussion of pregnancy in Chapter 82 that another hormone with almost exactly the same properties as LH, *chorionic gonadotropin*, which is secreted by the placenta, can act on the corpus luteum to prolong its life—usually maintaining it for at least the first 2 to 4 months of pregnancy.

**Involution of the Corpus Luteum and Onset of the Next Ovarian Cycle.** Estrogen in particular and progesterone to a lesser extent, secreted by the corpus luteum during the luteal phase of the ovarian cycle, have strong feedback effects on the anterior pituitary gland to maintain low secretory rates of both FSH and LH.

In addition, the lutein cells secrete small amounts of the hormone *inhibin*, the same as the inhibin secreted by the Sertoli cells of the male testes. This hormone inhibits secretion by the anterior pituitary gland, especially FSH

secretion. Low blood concentrations of both FSH and LH result, and loss of these hormones finally causes the corpus luteum to degenerate completely, a process called *involution* of the corpus luteum.

Final involution normally occurs at the end of almost exactly 12 days of corpus luteum life, which is around the 26th day of the normal female sexual cycle, 2 days before menstruation begins. At this time, the sudden cessation of secretion of estrogen, progesterone, and inhibin by the corpus luteum removes the feedback inhibition of the anterior pituitary gland, allowing it to begin secreting increasing amounts of FSH and LH again. FSH and LH initiate the growth of new follicles, beginning a new ovarian cycle. The paucity of secretion of progesterone and estrogen at this time also leads to menstruation by the uterus, as explained later.

## Summary

About every 28 days, gonadotropic hormones from the anterior pituitary gland cause about 8 to 12 new follicles to begin to grow in the ovaries. One of these follicles finally becomes "mature" and ovulates on the 14th day of the cycle. During growth of the follicles, mainly estrogen is secreted.

After ovulation, the secretory cells of the ovulating follicle develop into a corpus luteum that secretes large quantities of both the major female hormones, progesterone and estrogen. After another 2 weeks, the corpus luteum degenerates, whereupon the ovarian hormones estrogen and progesterone decrease greatly and menstruation begins. A new ovarian cycle then follows.

## Functions of the Ovarian Hormones—Estradiol and Progesterone

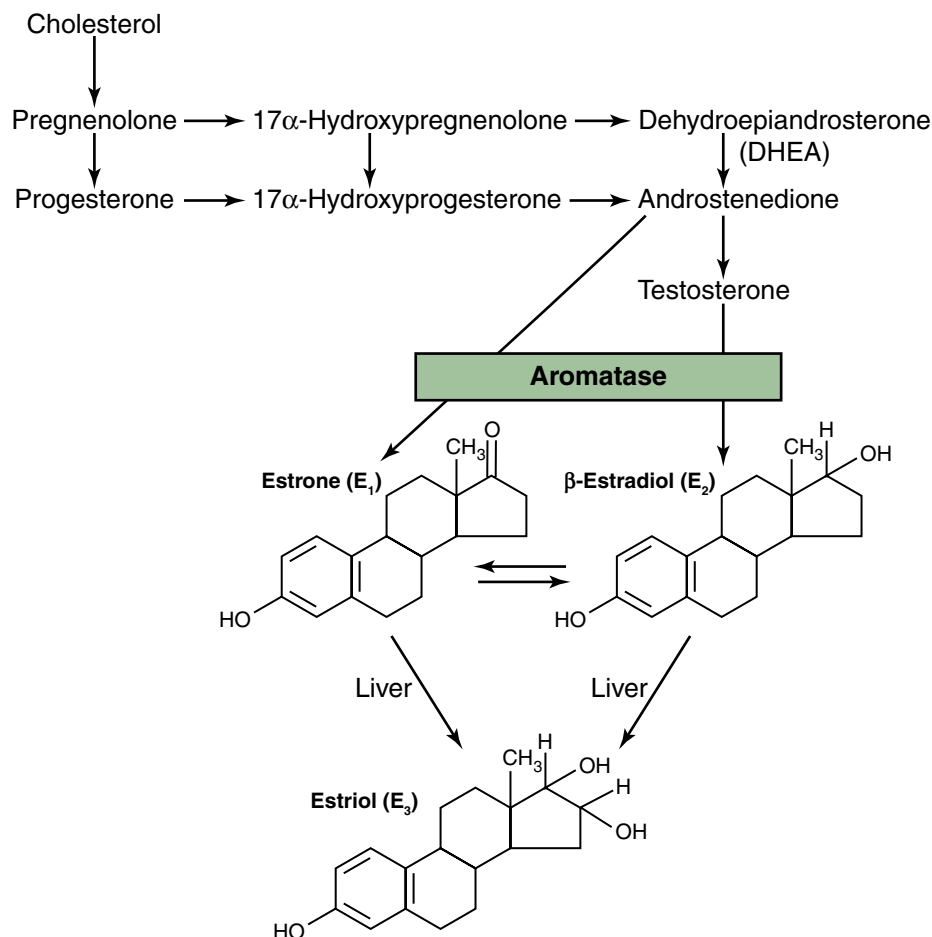
The two types of ovarian sex hormones are the *estrogens* and the *progestins*. By far the most important of the estrogens is the hormone *estradiol*, and by far the most important progestin is *progesterone*. The estrogens mainly promote proliferation and growth of specific cells in the body that are responsible for the development of most secondary sexual characteristics of the female. The progestins function mainly to prepare the uterus for pregnancy and the breasts for lactation.

## Chemistry of the Sex Hormones

**Estrogens.** In the normal *nonpregnant* female, estrogens are secreted in significant quantities only by the ovaries, although minute amounts are also secreted by the adrenal cortices. During *pregnancy*, tremendous quantities of estrogens are also secreted by the placenta, as discussed in Chapter 82.

Only three estrogens are present in significant quantities in the plasma of the human female:  $\beta$ -estradiol, estrone, and *estriol*, the formulas for which are shown in Figure 81-6. The principal estrogen secreted by the ovaries is  $\beta$ -estradiol. Small amounts of estrone are also secreted,

**Figure 81-6** Synthesis of the principal female hormones. The chemical structures of the precursor hormones, including progesterone, are shown in Figure 77-2.



but most of this is formed in the peripheral tissues from androgens secreted by the adrenal cortices and by ovarian thecal cells. Estriol is a weak estrogen; it is an oxidative product derived from both estradiol and estrone, with the conversion occurring mainly in the liver.

The estrogenic potency of  $\beta$ -estradiol is 12 times that of estrone and 80 times that of estriol. Considering these relative potencies, one can see that the total estrogenic effect of  $\beta$ -estradiol is usually many times that of the other two together. For this reason,  $\beta$ -estradiol is considered the major estrogen, although the estrogenic effects of estrone are not negligible.

**Progestins.** By far the most important of the progestins is progesterone. However, small amounts of another progestin, 17- $\alpha$ -hydroxyprogesterone, are secreted along with progesterone and have essentially the same effects. Yet for practical purposes, it is usually reasonable to consider progesterone the only important progestin.

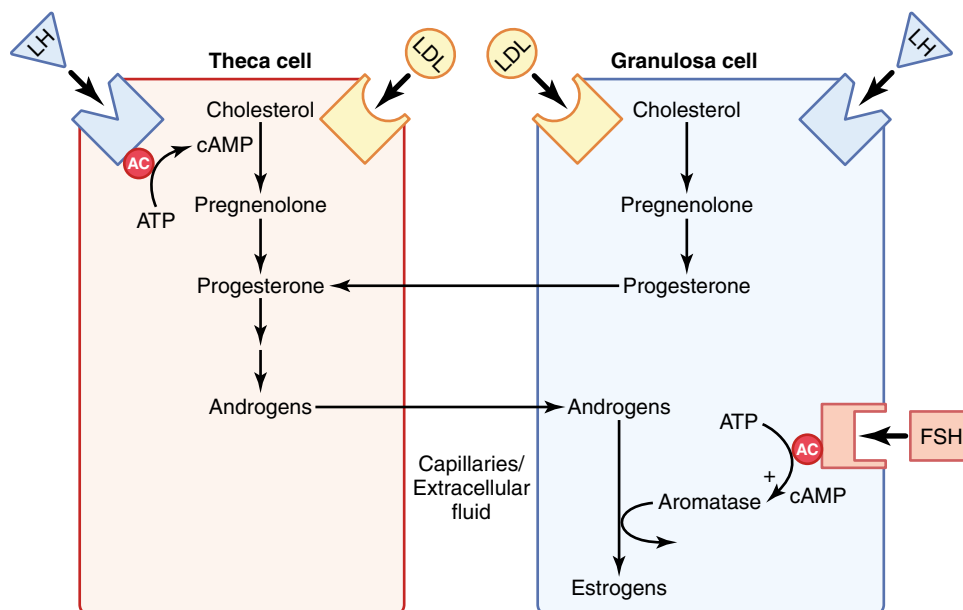
In the normal nonpregnant female, progesterone is secreted in significant amounts only during the latter half of each ovarian cycle, when it is secreted by the corpus luteum.

As we shall see in Chapter 82, large amounts of progesterone are also secreted by the placenta during pregnancy, especially after the fourth month of gestation.

**Synthesis of the Estrogens and Progestins.** Note from the chemical formulas of the estrogens and progesterone in Figure 81-6 that they are all steroids. They are synthesized in the ovaries mainly from cholesterol derived from the blood but also to a slight extent from acetyl coenzyme A, multiple molecules of which can combine to form the appropriate steroid nucleus.

During synthesis, mainly progesterone and androgens (testosterone and androstenedione) are synthesized first; then, during the follicular phase of the ovarian cycle, before these two initial hormones can leave the ovaries, almost all the androgens and much of the progesterone are converted into estrogens by the enzyme aromatase in the granulosa cells. Because the theca cells lack the aromatase, they cannot convert androgens to estrogens. However, androgens diffuse out of the theca cells into the adjacent granulosa cells, where they are converted to estrogens by aromatase, the activity of which is stimulated by FSH (Figure 81-7).

During the luteal phase of the cycle, far too much progesterone is formed for all of it to be converted, which accounts for the large secretion of progesterone into the circulating blood at this time. Also, about one-fifteenth as much testosterone is secreted into the plasma of the female by the ovaries as is secreted into the plasma of the male by the testes.



**Figure 81-7** Interaction of follicular theca and granulosa cells for production of estrogens. The theca cells, under the control of luteinizing hormone (LH), produce androgens that diffuse into the granulosa cells. In mature follicles, follicle stimulating hormone (FSH) acts on granulosa cells to stimulate aromatase activity, which converts the androgens to estrogens. AC, adenylate cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; LDL, low-density lipoproteins.

**Estrogens and Progesterone Are Transported in the Blood Bound to Plasma Proteins.** Both estrogens and progesterone are transported in the blood bound mainly with plasma albumin and with specific estrogen- and progesterone-binding globulins. The binding between these hormones and the plasma proteins is loose enough that they are rapidly released to the tissues over a period of 30 minutes or so.

**Functions of the Liver in Estrogen Degradation.** The liver conjugates the estrogens to form glucuronides and sulfates, and about one fifth of these conjugated products is excreted in the bile; most of the remainder is excreted in the urine. Also, the liver converts the potent estrogens estradiol and estrone into the almost totally impotent estrogen estriol. Therefore, diminished liver function actually *increases* the activity of estrogens in the body, sometimes causing *hyperestrinism*.

**Fate of Progesterone.** Within a few minutes after secretion, almost all the progesterone is degraded to other steroids that have no progestational effect. As with the estrogens, the liver is especially important for this metabolic degradation.

The major end product of progesterone degradation is *pregnanediol*. About 10 percent of the original progesterone is excreted in the urine in this form. Therefore, one can estimate the rate of progesterone formation in the body from the rate of this excretion.

### Functions of the Estrogens—Their Effects on the Primary and Secondary Female Sex Characteristics

A primary function of the estrogens is to cause cellular proliferation and growth of the tissues of the sex organs and other tissues related to reproduction.

**Effect of Estrogens on the Uterus and External Female Sex Organs.** During childhood, estrogens are secreted only in minute quantities, but at puberty, the quantity secreted in the female under the influence of the pituitary gonadotropic hormones increases 20-fold or more. At this time, the female sex organs change from those of a child to those of an adult. The ovaries, fallopian tubes, uterus, and vagina all increase several times in size. Also, the external genitalia enlarge, with deposition of fat in the mons pubis and labia majora and enlargement of the labia minora.

In addition, estrogens change the vaginal epithelium from a cuboidal into a stratified type, which is considerably more resistant to trauma and infection than is the prepubertal cuboidal cell epithelium. Vaginal infections in children can often be cured by the administration of estrogens simply because of the resulting increased resistance of the vaginal epithelium.

During the first few years after puberty, the size of the uterus increases twofold to threefold, but more important than the increase in uterus size are the changes that take place in the uterine endometrium under the influence of estrogens. Estrogens cause marked proliferation of the endometrial stroma and greatly increased development of the endometrial glands, which will later aid in providing nutrition to the implanted ovum. These effects are discussed later in the chapter in connection with the endometrial cycle.

**Effect of Estrogens on the Fallopian Tubes.** The estrogens' effect on the mucosal lining of the fallopian tubes is similar to that on the uterine endometrium. They cause the glandular tissues of this lining to proliferate; especially important, they cause the number of ciliated epithelial cells that line the fallopian tubes to increase. Also, activity of the cilia is considerably enhanced. These

cilia always beat toward the uterus, which helps propel the fertilized ovum in that direction.

**Effect of Estrogens on the Breasts.** The primordial breasts of females and males are exactly alike. In fact, under the influence of appropriate hormones, the masculine breast during the first 2 decades of life can develop sufficiently to produce milk in the same manner as the female breast.

Estrogens cause (1) development of the stromal tissues of the breasts, (2) growth of an extensive ductile system, and (3) deposition of fat in the breasts. The lobules and alveoli of the breast develop to a slight extent under the influence of estrogens alone, but it is progesterone and prolactin that cause the ultimate determinative growth and function of these structures.

In summary, the estrogens initiate growth of the breasts and of the milk-producing apparatus. They are also responsible for the characteristic growth and external appearance of the mature female breast. However, they do not complete the job of converting the breasts into milk-producing organs.

**Effect of Estrogens on the Skeleton.** Estrogens inhibit osteoclastic activity in the bones and therefore stimulate bone growth. As discussed in Chapter 79, at least part of this effect is due to stimulation of *osteoprotegerin*, also called *osteoclastogenesis inhibitory factor*, a cytokine that inhibits bone resorption.

At puberty, when the female enters her reproductive years, her growth in height becomes rapid for several years. However, estrogens have another potent effect on skeletal growth: They cause uniting of the epiphyses with the shafts of the long bones. This effect of estrogen in the female is much stronger than the similar effect of testosterone in the male. As a result, growth of the female usually ceases several years earlier than growth of the male. A female eunuch who is devoid of estrogen production usually grows several inches taller than a normal mature female because her epiphyses do not unite at the normal time.

**Osteoporosis of the Bones Caused by Estrogen Deficiency in Old Age.** After menopause, almost no estrogens are secreted by the ovaries. This estrogen deficiency leads to (1) increased osteoclastic activity in the bones, (2) decreased bone matrix, and (3) decreased deposition of bone calcium and phosphate. In some women this effect is extremely severe, and the resulting condition is *osteoporosis*, described in Chapter 79. Because this can greatly weaken the bones and lead to bone fracture, especially fracture of the vertebrae, many postmenopausal women are treated prophylactically with estrogen replacement to prevent the osteoporotic effects.

**Estrogens Slightly Increase Protein Deposition.** Estrogens cause a slight increase in total body protein, which is evidenced by a slight positive nitrogen balance

when estrogens are administered. This mainly results from the growth-promoting effect of estrogen on the sexual organs, the bones, and a few other tissues of the body. The enhanced protein deposition caused by testosterone is much more general and much more powerful than that caused by estrogens.

**Estrogens Increase Body Metabolism and Fat Deposition.** Estrogens increase the whole-body metabolic rate slightly, but only about one third as much as the increase caused by the male sex hormone testosterone. They also cause deposition of increased quantities of fat in the subcutaneous tissues. As a result, the percentage of body fat in the female body is considerably greater than that in the male body, which contains more protein. In addition to deposition of fat in the breasts and subcutaneous tissues, estrogens cause the deposition of fat in the buttocks and thighs, which is characteristic of the feminine figure.

**Estrogens Have Little Effect on Hair Distribution.** Estrogens do not greatly affect hair distribution. However, hair does develop in the pubic region and in the axillae after puberty. Androgens formed in increased quantities by the female adrenal glands after puberty are mainly responsible for this.

**Effect of Estrogens on the Skin.** Estrogens cause the skin to develop a texture that is soft and usually smooth, but even so, the skin of a woman is thicker than that of a child or a castrated female. Also, estrogens cause the skin to become more vascular; this is often associated with increased warmth of the skin and also promotes greater bleeding of cut surfaces than is observed in men.

**Effect of Estrogens on Electrolyte Balance.** The chemical similarity of estrogenic hormones to adrenocortical hormones has been pointed out. Estrogens, like aldosterone and some other adrenocortical hormones, cause sodium and water retention by the kidney tubules. This effect of estrogens is normally slight and rarely of significance, but during pregnancy, the tremendous formation of estrogens by the placenta may contribute to body fluid retention, as discussed in Chapter 82.

## Functions of Progesterone

**Progesterone Promotes Secretory Changes in the Uterus.** By far the most important function of progesterone is to promote secretory changes in the uterine endometrium during the latter half of the monthly female sexual cycle, thus preparing the uterus for implantation of the fertilized ovum. This function is discussed later in connection with the endometrial cycle of the uterus.

In addition to this effect on the endometrium, progesterone decreases the frequency and intensity of uterine contractions, thereby helping to prevent expulsion of the implanted ovum.



### Effect of Progesterone on the Fallopian Tubes.

Progesterone also promotes increased secretion by the mucosal lining of the fallopian tubes. These secretions are necessary for nutrition of the fertilized, dividing ovum as it traverses the fallopian tube before implantation.

**Progesterone Promotes Development of the Breasts.** Progesterone promotes development of the lobules and alveoli of the breasts, causing the alveolar cells to proliferate, enlarge, and become secretory in nature. However, progesterone does not cause the alveoli to secrete milk; as discussed in Chapter 82, milk is secreted only after the prepared breast is further stimulated by *prolactin* from the anterior pituitary gland.

Progesterone also causes the breasts to swell. Part of this swelling is due to the secretory development in the lobules and alveoli, but part also results from increased fluid in the tissue.

### Monthly Endometrial Cycle and Menstruation

Associated with the monthly cyclical production of estrogens and progesterone by the ovaries is an endometrial cycle in the lining of the uterus that operates through the following stages: (1) proliferation of the uterine endometrium; (2) development of secretory changes in the endometrium; and (3) desquamation of the endometrium, which is known as *menstruation*. The various phases of this endometrial cycle are shown in Figure 81-8.

**Proliferative Phase (Estrogen Phase) of the Endometrial Cycle, Occurring Before Ovulation.** At the beginning of each monthly cycle, most of the endometrium has been desquamated by menstruation. After menstruation, only a thin layer of endometrial stroma remains and the only epithelial cells that are left are those located in the remaining deeper portions of the glands and crypts of the endometrium. *Under the influence of estrogens*, secreted in increasing quantities by the ovary during the first part of the monthly ovarian cycle, the stromal cells and the epithelial cells proliferate rapidly. The endometrial surface is re-epithelialized within 4 to 7 days after the beginning of menstruation.

Then, during the next week and a half, before ovulation occurs, the endometrium increases greatly in thickness, owing to increasing numbers of stromal cells and

to progressive growth of the endometrial glands and new blood vessels into the endometrium. At the time of ovulation, the endometrium is 3 to 5 millimeters thick.

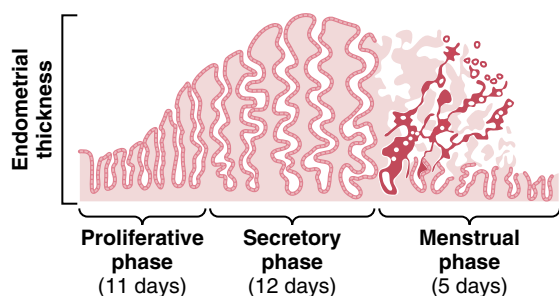
The endometrial glands, especially those of the cervical region, secrete a thin, stringy mucus. The mucus strings actually align themselves along the length of the cervical canal, forming channels that help guide sperm in the proper direction from the vagina into the uterus.

**Secretory Phase (Progestational Phase) of the Endometrial Cycle, Occurring After Ovulation.** During most of the latter half of the monthly cycle, after ovulation has occurred, progesterone and estrogen together are secreted in large quantities by the corpus luteum. The estrogens cause slight additional cellular proliferation in the endometrium during this phase of the cycle, whereas progesterone causes marked swelling and secretory development of the endometrium. The glands increase in tortuosity; an excess of secretory substances accumulates in the glandular epithelial cells. Also, the cytoplasm of the stromal cells increases; lipid and glycogen deposits increase greatly in the stromal cells; and the blood supply to the endometrium further increases in proportion to the developing secretory activity, with the blood vessels becoming highly tortuous. At the peak of the secretory phase, about 1 week after ovulation, the endometrium has a thickness of 5 to 6 millimeters.

The whole purpose of all these endometrial changes is to produce a highly secretory endometrium that contains large amounts of stored nutrients to provide appropriate conditions for implantation of a *fertilized* ovum during the latter half of the monthly cycle. From the time a fertilized ovum enters the uterine cavity from the fallopian tube (which occurs 3 to 4 days after ovulation) until the time the ovum implants (7 to 9 days after ovulation), the uterine secretions, called “uterine milk,” provide nutrition for the early dividing ovum. Then, once the ovum implants in the endometrium, the trophoblastic cells on the surface of the implanting ovum (in the blastocyst stage) begin to digest the endometrium and absorb the endometrial stored substances, thus making great quantities of nutrients available to the early implanting embryo.

**Menstruation.** If the ovum is not fertilized, about 2 days before the end of the monthly cycle, the corpus luteum in the ovary suddenly involutes and the ovarian hormones (estrogens and progesterone) decrease to low levels of secretion, as shown in Figure 81-3. Menstruation follows.

Menstruation is caused by the reduction of estrogens and progesterone, especially progesterone, at the end of the monthly ovarian cycle. The first effect is decreased stimulation of the endometrial cells by these two hormones, followed rapidly by involution of the endometrium itself to about 65 percent of its previous thickness. Then, during the 24 hours preceding the onset of menstruation, the tortuous blood vessels leading to the mucosal layers of the endometrium become vasospastic, presumably



**Figure 81-8** Phases of endometrial growth and menstruation during each monthly female sexual cycle.

because of some effect of involution, such as release of a vasoconstrictor material—possibly one of the vasoconstrictor types of prostaglandins that are present in abundance at this time.

The vasospasm, the decrease in nutrients to the endometrium, and the loss of hormonal stimulation initiate necrosis in the endometrium, especially of the blood vessels. As a result, blood at first seeps into the vascular layer of the endometrium and the hemorrhagic areas grow rapidly over a period of 24 to 36 hours. Gradually, the necrotic outer layers of the endometrium separate from the uterus at the sites of the hemorrhages until, about 48 hours after the onset of menstruation, all the superficial layers of the endometrium have desquamated. The mass of desquamated tissue and blood in the uterine cavity, plus contractile effects of prostaglandins or other substances in the decaying desquamate, all acting together, initiate uterine contractions that expel the uterine contents.

During normal menstruation, approximately 40 milliliters of blood and an additional 35 milliliters of serous fluid are lost. The menstrual fluid is normally nonclotting because a *fibrinolysin* is released along with the necrotic endometrial material. If excessive bleeding occurs from the uterine surface, the quantity of fibrinolysin may not be sufficient to prevent clotting. The presence of clots during menstruation is often clinical evidence of uterine pathology.

Within 4 to 7 days after menstruation starts, the loss of blood ceases because, by this time, the endometrium has become re-epithelialized.

**Leukorrhea During Menstruation.** During menstruation, tremendous numbers of leukocytes are released along with the necrotic material and blood. It is probable that some substance liberated by the endometrial necrosis causes this outflow of leukocytes. As a result of these leukocytes and possibly other factors, the uterus is highly resistant to infection during menstruation, even though the endometrial surfaces are denuded. This is of extreme protective value.

## Regulation of the Female Monthly Rhythm—Interplay Between the Ovarian and Hypothalamic-Pituitary Hormones

Now that we have presented the major cyclical changes that occur during the monthly female sexual cycle, we can attempt to explain the basic rhythmical mechanism that causes the cyclical variations.

### The Hypothalamus Secretes GnRH, Which Causes the Anterior Pituitary Gland to Secrete LH and FSH

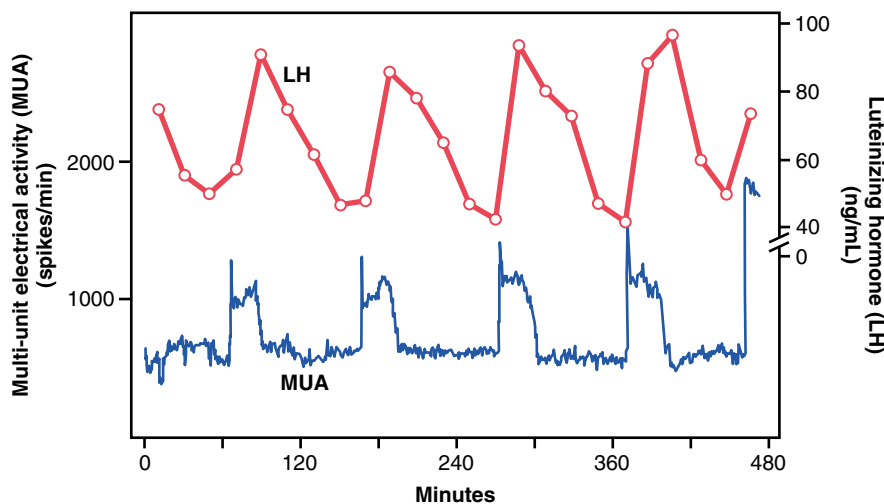
As pointed out in Chapter 74, secretion of most of the anterior pituitary hormones is controlled by “releasing hormones” formed in the hypothalamus and then transported to the anterior pituitary gland by way of the hypothalamic-hypophyseal portal system. In the case of the gonadotropins, one releasing hormone, *GnRH*, is important. This hormone has been purified and has been found to be a decapeptide with the following formula:



**Intermittent, Pulsatile Secretion of GnRH by the Hypothalamus Stimulates Pulsatile Release of LH from the Anterior Pituitary Gland.** The hypothalamus does not secrete GnRH continuously but instead secretes it in pulses lasting 5 to 25 minutes that occur every 1 to 2 hours. The lower curve in Figure 81-9 shows the electrical pulsatile signals in the hypothalamus that cause the hypothalamic pulsatile output of GnRH.

It is intriguing that when GnRH is infused continuously so that it is available all the time rather than in pulses, its ability to cause the release of LH and FSH by the anterior pituitary gland is lost. Therefore, for reasons unknown, the pulsatile nature of GnRH release is essential to its function.

**Figure 81-9** *Upper curve:* Pulsatile change in luteinizing hormone (LH) in the peripheral circulation of a pentobarbital-anesthetized ovariectomized rhesus monkey. *Lower curve:* Minute-by-minute recording of multi-unit electrical activity (MUA) in the mediobasal hypothalamus. (Data from Wilson RC, Kesner JS, Kaufman JM, et al: Central electrophysiologic correlates of pulsatile luteinizing hormone secretion. *Neuroendocrinology* 39:256, 1984.)



The pulsatile release of GnRH also causes intermittent output of LH secretion about every 90 minutes. This is shown by the upper curve in Figure 81-9.

**Hypothalamic Centers for Release of GnRH.** The neuronal activity that causes pulsatile release of GnRH occurs primarily in the mediobasal hypothalamus, especially in the arcuate nuclei of this area. Therefore, it is believed that these arcuate nuclei control most female sexual activity, although neurons located in the preoptic area of the anterior hypothalamus also secrete GnRH in moderate amounts. Multiple neuronal centers in the higher brain's "limbic" system (the system for psychic control) transmit signals into the arcuate nuclei to modify both the intensity of GnRH release and the frequency of the pulses, thus providing a partial explanation of why psychic factors often modify female sexual function.

### Negative Feedback Effects of Estrogen and Progesterone to Decrease LH and FSH Secretion

Estrogen in small amounts has a strong effect to inhibit the production of both LH and FSH. Also, when progesterone is available, the inhibitory effect of estrogen is multiplied, even though progesterone by itself has little effect (Figure 81-10).

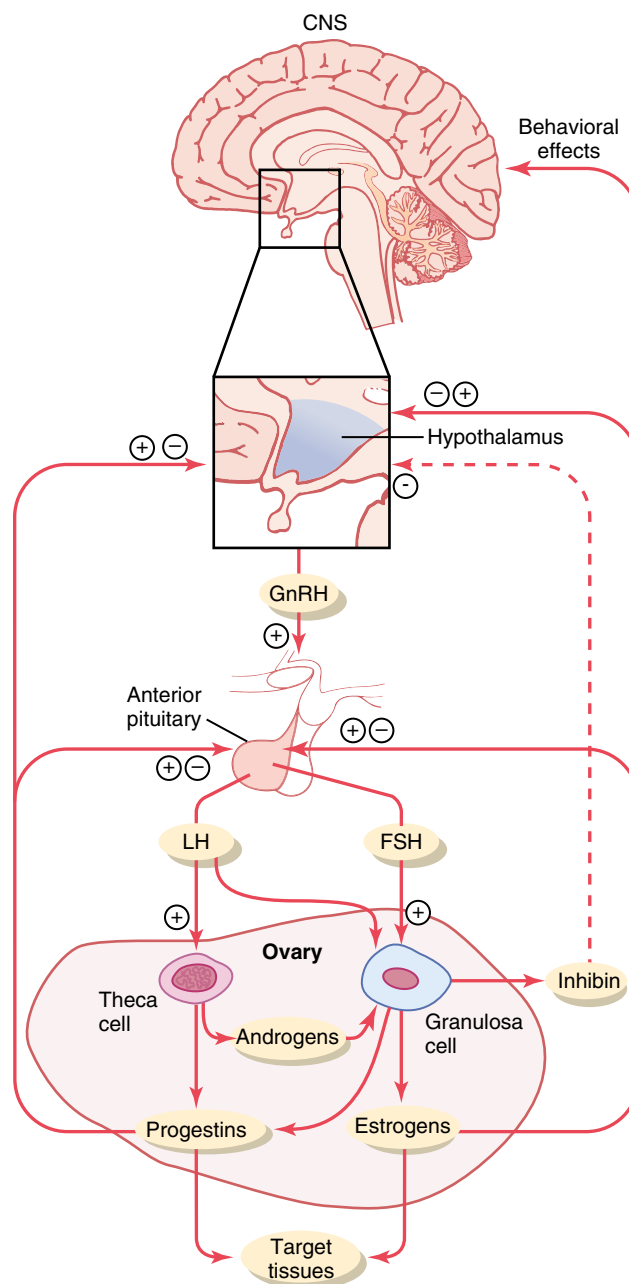
These feedback effects seem to operate mainly on the anterior pituitary gland directly, but they also operate to a lesser extent on the hypothalamus to decrease secretion of GnRH, especially by altering the frequency of the GnRH pulses.

**Inhibin from the Corpus Luteum Inhibits FSH and LH Secretion.** In addition to the feedback effects of estrogen and progesterone, other hormones seem to be involved, especially *inhibin*, which is secreted along with the steroid sex hormones by the granulosa cells of the ovarian corpus luteum in the same way that Sertoli cells secrete inhibin in the male testes (see Figure 81-10). This hormone has the same effect in the female as in the male—inhibiting the secretion of FSH and, to a lesser extent, LH by the anterior pituitary gland. Therefore, it is believed that inhibin might be especially important in causing the decrease in secretion of FSH and LH at the end of the monthly female sexual cycle.

### Positive Feedback Effect of Estrogen Before Ovulation—The Preovulatory LH Surge

For reasons not completely understood, the anterior pituitary gland secretes greatly increased amounts of LH for 1 to 2 days beginning 24 to 48 hours before ovulation. This effect is demonstrated in Figure 81-3. The figure shows a much smaller preovulatory surge of FSH as well.

Experiments have shown that infusion of estrogen into a female above a critical rate for 2 to 3 days during the latter part of the first half of the ovarian cycle will cause rapidly accelerating growth of the ovarian follicles, as well as rapidly accelerating secretion of ovarian estrogens. During



**Figure 81-10** Feedback regulation of the hypothalamic-pituitary-ovarian axis in females. Stimulatory effects are shown by  $\oplus$  and negative feedback inhibitory effects are shown by  $\ominus$ . Estrogens and progestins exert both negative and positive feedback effects on the anterior pituitary and hypothalamus depending on the stage of the ovarian cycle. Inhibin has a negative feedback effect on the anterior pituitary. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

this period, secretions of both FSH and LH by the anterior pituitary gland are at first slightly suppressed. Then secretion of LH increases abruptly sixfold to eightfold, and secretion of FSH increases about twofold. The greatly increased secretion of LH causes ovulation to occur.

The cause of this abrupt surge in LH secretion is not known. However, several possible explanations are as follows: (1) It has been suggested that estrogen at this point in the cycle has a peculiar *positive feedback effect*

of stimulating pituitary secretion of LH and, to a lesser extent, FSH (see Figure 81-10); this is in sharp contrast to its normal negative feedback effect that occurs during the remainder of the female monthly cycle. (2) The granulosa cells of the follicles begin to secrete small but increasing quantities of progesterone a day or so before the preovulatory LH surge, and it has been suggested that this might be the factor that stimulates the excess LH secretion.

Without this normal preovulatory surge of LH, ovulation will not occur.

### Feedback Oscillation of the Hypothalamic-Pituitary-Ovarian System

Now, after discussing much of the known information about the interrelations of the different components of the female hormonal system, we can explain the feedback oscillation that controls the rhythm of the female sexual cycle. It seems to operate in approximately the following sequence of three events.

#### 1. Postovulatory Secretion of the Ovarian Hormones, and Depression of the Pituitary Gonadotropins.

The easiest part of the cycle to explain is the events that occur during the postovulatory phase—between ovulation and the beginning of menstruation. During this time, the corpus luteum secretes large quantities of progesterone and estrogen, as well as the hormone inhibin. All these hormones together have a combined negative feedback effect on the anterior pituitary gland and hypothalamus, causing the suppression of both FSH and LH secretion and decreasing them to their lowest levels about 3 to 4 days before the onset of menstruation. These effects are shown in Figure 81-3.

**2. Follicular Growth Phase.** Two to 3 days before menstruation, the corpus luteum has regressed to almost total involution and the secretion of estrogen, progesterone, and inhibin from the corpus luteum decreases to a low ebb. This releases the hypothalamus and anterior pituitary from the negative feedback effect of these hormones. Therefore, a day or so later, at about the time that menstruation begins, pituitary secretion of FSH begins to increase again, as much as twofold; then, several days after menstruation begins, LH secretion increases slightly as well. These hormones initiate new ovarian follicle growth and a progressive increase in the secretion of estrogen, reaching a peak estrogen secretion at about 12.5 to 13 days after the onset of the new female monthly sexual cycle.

During the first 11 to 12 days of this follicle growth, the rates of pituitary secretion of the gonadotropins FSH and LH decrease slightly because of the negative feedback effect, mainly of estrogen, on the anterior pituitary gland. Then there is a sudden, marked increase in the secretion of LH and, to a lesser extent, FSH. This is the preovulatory surge of LH and FSH, which is followed by ovulation.

**3. Preovulatory Surge of LH and FSH Causes Ovulation.** About 11½ to 12 days after the onset of the monthly cycle, the decline in secretion of FSH and LH comes to an abrupt halt. It is believed that the high level of estrogens at this time (or the beginning of progesterone secretion by the follicles) causes a positive feedback stimulatory effect on the anterior pituitary, as explained earlier, which leads to a terrific surge in the secretion of LH and, to a lesser extent, FSH. Whatever the cause of this preovulatory LH and FSH surge, the great excess of LH leads to both ovulation and subsequent development of and secretion by the corpus luteum. Thus, the hormonal system begins its new round of secretions until the next ovulation.

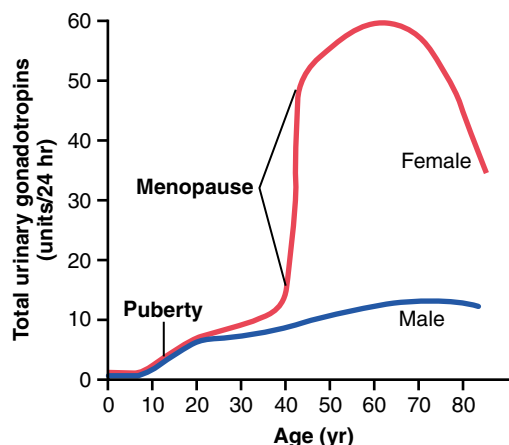
### Anovulatory Cycles—Sexual Cycles at Puberty

If the preovulatory surge of LH is not of sufficient magnitude, ovulation will not occur and the cycle is said to be “anovulatory.” The phases of the sexual cycle continue, but they are altered in the following ways: First, lack of ovulation causes failure of development of the corpus luteum, so there is almost no secretion of progesterone during the latter portion of the cycle. Second, the cycle is shortened by several days but the rhythm continues. Therefore, it is likely that progesterone is not required for maintenance of the cycle itself, although it can alter its rhythm.

The first few cycles after the onset of puberty are usually anovulatory, as are the cycles occurring several months to years before menopause, presumably because the LH surge is not potent enough at these times to cause ovulation.

### Puberty and Menarche

*Puberty* means the onset of adult sexual life, and *menarche* means the beginning of the cycle of menstruation. The period of puberty is caused by a gradual increase in gonadotropic hormone secretion by the pituitary, beginning in about the eighth year of life, as shown in Figure 81-11,



**Figure 81-11** Total rates of secretion of gonadotropic hormones throughout the sexual lives of female and male human beings, showing an especially abrupt increase in gonadotropic hormones at menopause in the female.



and usually culminating in the onset of puberty and menstruation between ages 11 and 16 years in girls (average, 13 years).

In the female, as in the male, the infantile pituitary gland and ovaries are capable of full function if appropriately stimulated. However, as is also true in the male, and for reasons not understood, the hypothalamus does not secrete significant quantities of GnRH during childhood. Experiments have shown that the hypothalamus is capable of secreting this hormone, but the appropriate signal from some other area of brain to cause the secretion is lacking. Therefore, it is now believed that the onset of puberty is initiated by some maturation process that occurs elsewhere in the brain, perhaps somewhere in the limbic system.

Figure 81-12 shows (1) the increasing levels of estrogen secretion at puberty, (2) the cyclical variation during the monthly sexual cycle, (3) the further increase in estrogen secretion during the first few years of reproductive life, (4) the progressive decrease in estrogen secretion toward the end of reproductive life, and, finally, (5) almost no estrogen or progesterone secretion beyond menopause.

## Menopause

At age 40 to 50 years, the sexual cycle usually becomes irregular and ovulation often fails to occur. After a few months to a few years, the cycle ceases altogether, as shown in Figure 81-12. The period during which the cycle ceases and the female sex hormones diminish to almost none is called *menopause*.

The cause of menopause is “burning out” of the ovaries. Throughout a woman’s reproductive life, about 400 of the primordial follicles grow into mature follicles and ovulate, and hundreds of thousands of ova degenerate. At about age 45 years, only a few primordial follicles remain to be stimulated by FSH and LH, and, as shown in Figure 81-12, the production of estrogens by the ovaries decreases as the number of primordial follicles approaches zero. When estrogen production falls below a critical value, the estrogens can no longer inhibit the production of the gonadotropins FSH and LH. Instead, as shown in Figure 81-11, the gonadotropins FSH and LH (mainly FSH) are produced

after menopause in large and continuous quantities, but as the remaining primordial follicles become atretic, the production of estrogens by the ovaries falls virtually to zero.

At the time of menopause, a woman must readjust her life from one that has been physiologically stimulated by estrogen and progesterone production to one devoid of these hormones. The loss of estrogens often causes marked physiological changes in the function of the body, including (1) “hot flushes” characterized by extreme flushing of the skin, (2) psychic sensations of dyspnea, (3) irritability, (4) fatigue, (5) anxiety, and (6) decreased strength and calcification of bones throughout the body. These symptoms are of sufficient magnitude in about 15 percent of women to warrant treatment. If counseling fails, daily administration of estrogen in small quantities usually reverses the symptoms, and by gradually decreasing the dose, postmenopausal women can likely avoid severe symptoms.

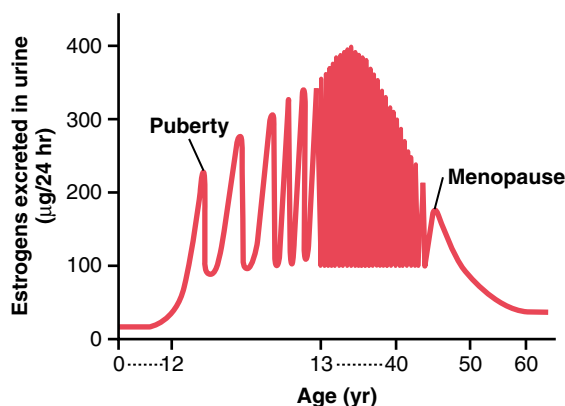
## Abnormalities of Secretion by the Ovaries

**Hypogonadism-Reduced Secretion by the Ovaries.** Less than normal secretion by the ovaries can result from poorly formed ovaries, lack of ovaries, or genetically abnormal ovaries that secrete the wrong hormones because of missing enzymes in the secretory cells. When ovaries are absent from birth or when they become nonfunctional before puberty, *female eunuchism* occurs. In this condition the usual secondary sexual characteristics do not appear, and the sexual organs remain infantile. Especially characteristic of this condition is prolonged growth of the long bones because the epiphyses do not unite with the shafts as early as they do in a normal woman. Consequently, the female eunuch is essentially as tall as or perhaps even slightly taller than her male counterpart of similar genetic background.

When the ovaries of a fully developed woman are removed, the sexual organs regress to some extent so that the uterus becomes almost infantile in size, the vagina becomes smaller, and the vaginal epithelium becomes thin and easily damaged. The breasts atrophy and become pendulous, and the pubic hair becomes thinner. The same changes occur in women after menopause.

**Irregularity of Menses, and Amenorrhea Caused by Hypogonadism.** As pointed out in the preceding discussion of menopause, the quantity of estrogens produced by the ovaries must rise above a critical value in order to cause rhythmic sexual cycles. Consequently, in hypogonadism or when the gonads are secreting small quantities of estrogens as a result of other factors, such as *hypothyroidism*, the ovarian cycle often does not occur normally. Instead, several months may elapse between menstrual periods or menstruation may cease altogether (amenorrhea). Prolonged ovarian cycles are frequently associated with failure of ovulation, presumably because of insufficient secretion of LH at the time of the pre-ovulatory surge of LH, which is necessary for ovulation.

**Hypersecretion by the Ovaries.** Extreme hypersecretion of ovarian hormones by the ovaries is a rare clinical entity because excessive secretion of estrogens automatically decreases the production of gonadotropins by the pituitary, and this limits



**Figure 81-12** Estrogen secretion throughout the sexual life of the female human being.

the production of ovarian hormones. Consequently, hypersecretion of feminizing hormones is usually recognized clinically only when a feminizing tumor develops.

A rare *granulosa cell tumor* can develop in an ovary, occurring more often after menopause than before. These tumors secrete large quantities of estrogens, which exert the usual estrogenic effects, including hypertrophy of the uterine endometrium and irregular bleeding from this endometrium. In fact, bleeding is often the first and only indication that such a tumor exists.

## Female Sexual Act

**Stimulation of the Female Sexual Act.** As is true in the male sexual act, successful performance of the female sexual act depends on both psychic stimulation and local sexual stimulation.

Thinking sexual thoughts can lead to female sexual desire, and this aids greatly in the performance of the female sexual act. Such desire is based on psychological and physiological drive, although sexual desire does increase in proportion to the level of sex hormones secreted. Desire also changes during the monthly sexual cycle, reaching a peak near the time of ovulation, probably because of the high levels of estrogen secretion during the preovulatory period.

Local sexual stimulation in women occurs in more or less the same manner as in men because massage and other types of stimulation of the vulva, vagina, and other perineal regions can create sexual sensations. The glans of the *clitoris* is especially sensitive for initiating sexual sensations.

As in the male, the sexual sensory signals are transmitted to the sacral segments of the spinal cord through the pudendal nerve and sacral plexus. Once these signals have entered the spinal cord, they are transmitted to the cerebrum. Also, local reflexes integrated in the sacral and lumbar spinal cord are at least partly responsible for some of the reactions in the female sexual organs.

**Female Erection and Lubrication.** Located around the introitus and extending into the clitoris is erectile tissue almost identical to the erectile tissue of the penis. This erectile tissue, like that of the penis, is controlled by the parasympathetic nerves that pass through the *nervi erigentes* from the sacral plexus to the external genitalia. In the early phases of sexual stimulation, parasympathetic signals dilate the arteries of the erectile tissue, probably resulting from release of acetylcholine, nitric oxide, and vasoactive intestinal polypeptide (VIP) at the nerve endings. This allows rapid accumulation of blood in the erectile tissue so that the introitus tightens around the penis; this aids the male greatly in his attainment of sufficient sexual stimulation for ejaculation to occur.

Parasympathetic signals also pass to the bilateral Bartholin glands located beneath the labia minora and cause them to secrete mucus immediately inside the introitus. This mucus is responsible for much of the

lubrication during sexual intercourse, although much is also provided by mucus secreted by the vaginal epithelium and a small amount from the male urethral glands. This lubrication is necessary during intercourse to establish a satisfactory massaging sensation rather than an irritative sensation, which may be provoked by a dry vagina. A massaging sensation constitutes the optimal stimulus for evoking the appropriate reflexes that culminate in both the male and female climaxes.

**Female Orgasm.** When local sexual stimulation reaches maximum intensity, and especially when the local sensations are supported by appropriate psychic conditioning signals from the cerebrum, reflexes are initiated that cause the female orgasm, also called the *female climax*. The female orgasm is analogous to emission and ejaculation in the male, and it may help promote fertilization of the ovum. Indeed, the human female is known to be somewhat more fertile when inseminated by normal sexual intercourse rather than by artificial methods, thus indicating an important function of the female orgasm. Possible reasons for this are as follows.

First, during the orgasm, the perineal muscles of the female contract rhythmically, which results from spinal cord reflexes similar to those that cause ejaculation in the male. It is possible that these reflexes increase uterine and fallopian tube motility during the orgasm, thus helping to transport the sperm upward through the uterus toward the ovum; information on this subject is scanty, however. Also, the orgasm seems to cause dilation of the cervical canal for up to 30 minutes, thus allowing easy transport of the sperm.

Second, in many lower animals, copulation causes the posterior pituitary gland to secrete oxytocin; this effect is probably mediated through the brain amygdaloid nuclei and then through the hypothalamus to the pituitary. The oxytocin causes increased rhythmical contractions of the uterus, which have been postulated to cause increased transport of the sperm. A few sperm have been shown to traverse the entire length of the fallopian tube in the cow in about 5 minutes, a rate at least 10 times as fast as that which the swimming motions of the sperm themselves could possibly achieve. Whether this occurs in the human female is unknown.

In addition to the possible effects of the orgasm on fertilization, the intense sexual sensations that develop during the orgasm also pass to the cerebrum and cause intense muscle tension throughout the body. But after culmination of the sexual act, this gives way during the succeeding minutes to a sense of satisfaction characterized by relaxed peacefulness, an effect called *resolution*.

## Female Fertility

**Fertile Period of Each Sexual Cycle.** The ovum remains viable and capable of being fertilized after it is expelled from the ovary probably no longer than 24 hours. Therefore, sperm must be available soon after ovulation if fertilization

is to take place. A few sperm can remain fertile in the female reproductive tract for up to 5 days. Therefore, for fertilization to take place, intercourse must occur sometime between 4 and 5 days before ovulation up to a few hours after ovulation. Thus, the period of female fertility during each month is short, about 4 to 5 days.

**Rhythm Method of Contraception.** One of the commonly practiced methods of contraception is to avoid intercourse near the time of ovulation. The difficulty with this method of contraception is predicting the exact time of ovulation. Yet the interval from ovulation until the next succeeding onset of menstruation is almost always between 13 and 15 days. Therefore, if the menstrual cycle is regular, with an exact periodicity of 28 days, ovulation usually occurs within 1 day of the 14th day of the cycle. If, in contrast, the periodicity of the cycle is 40 days, ovulation usually occurs within 1 day of the 26th day of the cycle. Finally, if the periodicity of the cycle is 21 days, ovulation usually occurs within 1 day of the seventh day of the cycle. Therefore, it is usually stated that avoidance of intercourse for 4 days before the calculated day of ovulation and 3 days afterward prevents conception. But such a method of contraception can be used only when the periodicity of the menstrual cycle is regular. The failure rate of this method of contraception, resulting in an unintentional pregnancy, may be as high as 20 to 25 percent per year.

**Hormonal Suppression of Fertility—"The Pill."** It has long been known that administration of either estrogen or progesterone, if given in appropriate quantities during the first half of the monthly cycle, can inhibit ovulation. The reason for this is that appropriate administration of either of these hormones can prevent the preovulatory surge of LH secretion by the pituitary gland, which is essential in causing ovulation.

Why the administration of estrogen or progesterone prevents the preovulatory surge of LH secretion is not fully understood. However, experimental work has suggested that immediately before the surge occurs, there is probably a sudden depression of estrogen secretion by the ovarian follicles, and this might be the necessary signal that causes the subsequent feedback effect on the anterior pituitary that leads to the LH surge. The administration of sex hormones (estrogens or progesterone) could prevent the initial ovarian hormonal depression that might be the initiating signal for ovulation.

The challenge in devising methods for the hormonal suppression of ovulation has been in developing appropriate combinations of estrogens and progestins that suppress ovulation but do not cause other, unwanted effects. For instance, too much of either hormone can cause abnormal menstrual bleeding patterns. However, use of certain synthetic progestins in place of progesterone, especially the 19-norsteroids, along with small amounts of estrogens usually prevents ovulation yet allows an almost normal pattern of menstruation. Therefore, almost all "pills" used for the control of fertility consist of some combination of synthetic estrogens and synthetic progestins. The main reason for using synthetic estrogens and progestins is that the *natural* hormones are almost entirely destroyed by the liver within a short time after they are absorbed from the gastrointestinal tract into the portal circulation. However, many of the *synthetic* hormones can resist this destructive propensity of the liver, thus allowing oral administration.

Two of the most commonly used synthetic estrogens are *ethinyl estradiol* and *mestranol*. Among the most commonly used progestins are *norethindrone*, *norethynodrel*, *ethynodiol*, and *norgestrel*. The drug is usually begun in the early stages of the monthly cycle and continued beyond the time that ovulation would normally occur. Then the drug is stopped, allowing menstruation to occur and a new cycle to begin.

The failure rate, resulting in an unintentional pregnancy, for hormonal suppression of fertility using various forms of the "pill" is about 8 to 9 percent per year.

**Abnormal Conditions That Cause Female Sterility.** About 5 to 10 percent of women are infertile. Occasionally, no abnormality can be discovered in the female genital organs, in which case it must be assumed that the infertility is due to either abnormal physiological function of the genital system or abnormal genetic development of the ova themselves.

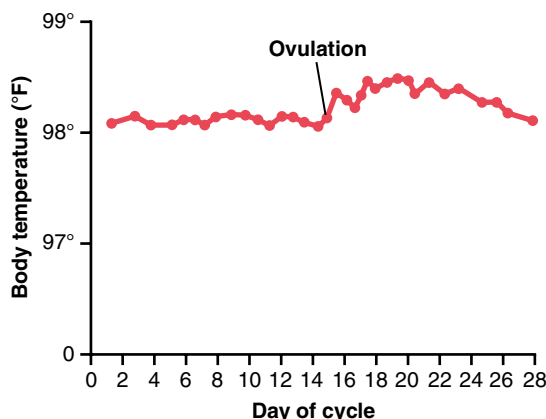
The most common cause of female sterility is failure to ovulate. This can result from hyposecretion of gonadotropic hormones, in which case the intensity of the hormonal stimuli is simply insufficient to cause ovulation, or it can result from abnormal ovaries that do not allow ovulation. For instance, thick ovarian capsules occasionally exist on the outsides of the ovaries, making ovulation difficult.

Because of the high incidence of anovulation in sterile women, special methods are often used to determine whether ovulation occurs. These methods are based mainly on the effects of progesterone on the body because the normal increase in progesterone secretion usually does not occur during the latter half of anovulatory cycles. In the absence of progestational effects, the cycle can be assumed to be anovulatory.

One of these tests is simply to analyze the urine for a surge in pregnanediol, the end product of progesterone metabolism, during the latter half of the sexual cycle; the lack of this substance indicates failure of ovulation. Another common test is for the woman to chart her body temperature throughout the cycle. Secretion of progesterone during the latter half of the cycle raises the body temperature about 0.5°F, with the temperature rise coming abruptly at the time of ovulation. Such a temperature chart, showing the point of ovulation, is illustrated in Figure 81-13.

Lack of ovulation caused by hyposecretion of the pituitary gonadotropic hormones can sometimes be treated by appropriately timed administration of *human chorionic gonadotropin*, a hormone (discussed in Chapter 82) that is extracted from the human placenta. This hormone, although secreted by the placenta, has almost the same effects as LH and is therefore a powerful stimulator of ovulation. However, excess use of this hormone can cause ovulation from many follicles simultaneously; this results in multiple births, an effect that has caused as many as eight babies (stillborn in many cases) to be born to mothers treated for infertility with this hormone.

One of the most common causes of female sterility is *endometriosis*, a common condition in which endometrial tissue almost identical to that of the normal uterine endometrium grows and even menstruates in the pelvic cavity surrounding the uterus, fallopian tubes, and ovaries. Endometriosis causes fibrosis throughout the pelvis, and this fibrosis sometimes so enshrouds the ovaries that an ovum cannot be released into the abdominal cavity. Often, endometriosis occludes the fallopian tubes, either at the fimbriated ends or elsewhere along their extent.



**Figure 81-13** Elevation in body temperature shortly after ovulation.

Another common cause of female infertility is *salpingitis*, that is, *inflammation of the fallopian tubes*; this causes fibrosis in the tubes, thereby occluding them. In the past, such inflammation occurred mainly as a result of gonococcal infection. But with modern therapy, this is becoming a less prevalent cause of female infertility.

Still another cause of infertility is secretion of abnormal mucus by the uterine cervix. Ordinarily, at the time of ovulation, the hormonal environment of estrogen causes the secretion of mucus with special characteristics that allow rapid mobility of sperm into the uterus and actually guide the sperm up along mucous “threads.” Abnormalities of the cervix itself, such as low-grade infection or inflammation, or abnormal hormonal stimulation of the cervix, can lead to a viscous mucous plug that prevents fertilization.

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# Pregnancy and Lactation



In Chapters 80 and 81, the sexual functions of the male and female are described to the point of fertilization of the ovum. If the ovum becomes fertilized, a new sequence of events

called *gestation*, or *pregnancy*, takes place, and the fertilized ovum eventually develops into a full-term fetus. The purpose of this chapter is to discuss the early stages of ovum development after fertilization and then to discuss the physiology of pregnancy. In Chapter 83, some special aspects of fetal and early childhood physiology are discussed.

## Maturation and Fertilization of the Ovum

While still in the ovary, the ovum is in the *primary oocyte* stage. Shortly before it is released from the ovarian follicle, its nucleus divides by meiosis and a *first polar body* is expelled from the nucleus of the oocyte. The primary oocyte then becomes the *secondary oocyte*. In this process, each of the 23 pairs of chromosomes loses one of its partners, which becomes incorporated in a *polar body* that is expelled. This leaves 23 *unpaired* chromosomes in the secondary oocyte. It is at this time that the ovum, still in the secondary oocyte stage, is ovulated into the abdominal cavity. Then, almost immediately, it enters the fimbriated end of one of the fallopian tubes.

**Entry of the Ovum into the Fallopian Tube (Uterine Tube).** When ovulation occurs, the ovum, along with a hundred or more attached granulosa cells that constitute the *corona radiata*, is expelled directly into the peritoneal cavity and must then enter one of the fallopian tubes (also called uterine tubes) to reach the cavity of the uterus. The fimbriated ends of each fallopian tube fall naturally around the ovaries. The inner surfaces of the fimbriated tentacles are lined with ciliated epithelium, and the *cilia* are activated by estrogen from the ovaries, which causes the cilia to beat toward the opening, or *ostium*, of the involved fallopian tube. One can actually

see a slow fluid current flowing toward the ostium. By this means, the ovum enters one of the fallopian tubes.

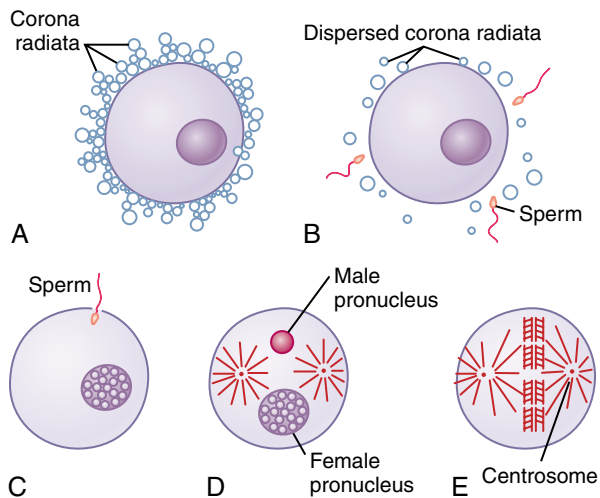
Although one might suspect that many ova fail to enter the fallopian tubes, conception studies suggest that up to 98 percent succeed in this task. Indeed, in some recorded cases, women with one ovary removed and the opposite fallopian tube removed have had several children with relative ease of conception, thus demonstrating that ova can even enter the opposite fallopian tube.

**Fertilization of the Ovum.** After the male ejaculates semen into the vagina during intercourse, a few sperm are transported within 5 to 10 minutes upward from the vagina and through the uterus and fallopian tubes to the *ampullae* of the fallopian tubes near the ovarian ends of the tubes. This transport of the sperm is aided by contractions of the uterus and fallopian tubes stimulated by prostaglandins in the male seminal fluid and also by oxytocin released from the posterior pituitary gland of the female during her orgasm. Of the almost half a billion sperm deposited in the vagina, a few thousand succeed in reaching each ampulla.

Fertilization of the ovum normally takes place in the ampulla of one of the fallopian tubes soon after both the sperm and the ovum enter the ampulla. But before a sperm can enter the ovum, it must first penetrate the multiple layers of granulosa cells attached to the outside of the ovum (the *corona radiata*) and then bind to and penetrate the *zona pellucida* surrounding the ovum. The mechanisms used by the sperm for these purposes are presented in Chapter 80.

Once a sperm has entered the ovum (which is still in the secondary oocyte stage of development), the oocyte divides again to form the *mature ovum* plus a *second polar body* that is expelled. The mature ovum still carries in its nucleus (now called the *female pronucleus*) 23 chromosomes. One of these chromosomes is the female chromosome, known as the *X chromosome*.

In the meantime, the fertilizing sperm has also changed. On entering the ovum, its head swells to form a *male pronucleus*, shown in Figure 82-1D. Later, the 23 unpaired chromosomes of the male pronucleus and the 23 unpaired chromosomes of the female pronucleus align themselves



**Figure 82-1** Fertilization of the ovum. *A*, The mature ovum surrounded by the corona radiata. *B*, Dispersal of the corona radiata. *C*, Entry of the sperm. *D*, Formation of the male and female pronuclei. *E*, Reorganization of a full complement of chromosomes and beginning division of the ovum. (Modified from Arey LB: *Developmental Anatomy: A Textbook and Laboratory Manual of Embryology*, 7th ed. Philadelphia: WB Saunders, 1974.)

to re-form a complete complement of 46 chromosomes (23 pairs) in the *fertilized ovum* (Figure 82-1E).

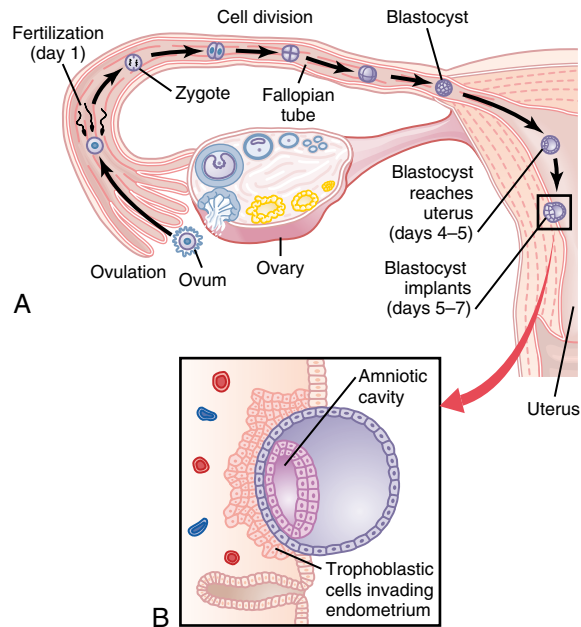
### What Determines the Sex of the Fetus That Is Created?

After formation of the mature sperm, half of these carry in their genome an X chromosome (the female chromosome) and half carry a Y chromosome (the male chromosome). Therefore, if an X chromosome from a sperm combines with an X chromosome from an ovum, giving an XX combination, a female child will be born, as explained in Chapter 80. But if a Y chromosome from a sperm is paired with an X chromosome from an ovum, giving an XY combination, a male child will be born.

### Transport of the Fertilized Ovum in the Fallopian Tube

After fertilization has occurred, an additional 3 to 5 days is normally required for transport of the fertilized ovum through the remainder of the fallopian tube into the cavity of the uterus (Figure 82-2). This transport is effected mainly by a feeble fluid current in the tube resulting from epithelial secretion plus action of the ciliated epithelium that lines the tube; the cilia always beat toward the uterus. Weak contractions of the fallopian tube may also aid the ovum passage.

The fallopian tubes are lined with a rugged, cryptoid surface that impedes passage of the ovum despite the fluid current. Also, the *isthmus* of the fallopian tube (the last 2 centimeters before the tube enters the uterus) remains spastically contracted for about the first 3 days after ovulation. After this time, the rapidly increasing progesterone secreted by the ovarian corpus luteum first promotes



**Figure 82-2** *A*, Ovulation, fertilization of the ovum in the fallopian tube, and implantation of the blastocyst in the uterus. *B*, Action of trophoblast cells in implantation of the blastocyst in the uterine endometrium.

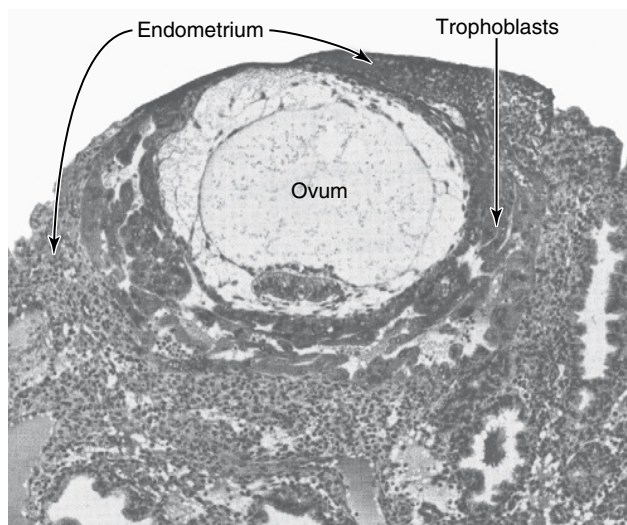
increasing progesterone receptors on the fallopian tube smooth muscle cells; then the progesterone activates the receptors, exerting a tubular relaxing effect that allows entry of the ovum into the uterus.

This delayed transport of the fertilized ovum through the fallopian tube allows several stages of cell division to occur before the dividing ovum—now called a *blastocyst*, with about 100 cells—enters the uterus. During this time, the fallopian tube secretory cells produce large quantities of secretions used for the nutrition of the developing blastocyst.

### Implantation of the Blastocyst in the Uterus

After reaching the uterus, the developing blastocyst usually remains in the uterine cavity an additional 1 to 3 days before it implants in the endometrium; thus, implantation ordinarily occurs on about the fifth to seventh day after ovulation. Before implantation, the blastocyst obtains its nutrition from the uterine endometrial secretions, called “uterine milk.”

Implantation results from the action of *trophoblast cells* that develop over the surface of the blastocyst. These cells secrete proteolytic enzymes that digest and liquefy the adjacent cells of the uterine endometrium. Some of the fluid and nutrients released are actively transported by the same trophoblast cells into the blastocyst, adding more sustenance for growth. Figure 82-3 shows an early implanted human blastocyst, with a small embryo. Once implantation has taken place, the trophoblast cells and other adjacent cells (from the blastocyst and the uterine endometrium) proliferate rapidly, forming the placenta and the various membranes of pregnancy.



**Figure 82-3** Implantation of the early human embryo, showing trophoblastic digestion and invasion of the endometrium. (Courtesy Dr. Arthur Hertig.)

### Early Nutrition of the Embryo

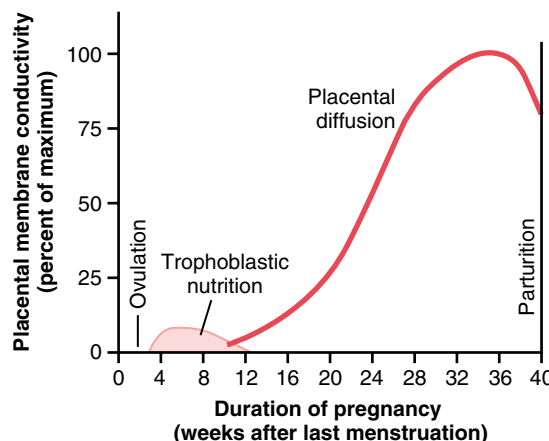
In Chapter 81, we pointed out that the progesterone secreted by the ovarian corpus luteum during the latter half of each monthly sexual cycle has an effect on the uterine endometrium, converting the endometrial stromal cells into large swollen cells containing extra quantities of glycogen, proteins, lipids, and even some minerals necessary for development of the *conceptus* (the embryo and its adjacent parts or associated membranes). Then, when the conceptus implants in the endometrium, the continued secretion of progesterone causes the endometrial cells to swell further and to store even more nutrients. These cells are now called *decidual cells*, and the total mass of cells is called the *decidua*.

As the trophoblast cells invade the decidua, digesting and imbibing it, the stored nutrients in the decidua are used by the embryo for growth and development. During the first week after implantation, this is the only means by which the embryo can obtain nutrients; the embryo continues to obtain at least some of its nutrition in this way for up to 8 weeks, although the placenta also begins to provide nutrition after about the 16th day beyond fertilization (a little more than 1 week after implantation). Figure 82-4 shows this trophoblastic period of nutrition, which gradually gives way to placental nutrition.

### Function of the Placenta

#### Developmental and Physiologic Anatomy of the Placenta

While the trophoblastic cords from the blastocyst are attaching to the uterus, blood capillaries grow into the cords from the vascular system of the newly forming embryo. About 21 days after fertilization, blood also begins to be pumped by the heart of the human embryo. Simultaneously, *blood sinuses* supplied with blood from the mother develop around



**Figure 82-4** Nutrition of the fetus. Most of the early nutrition is due to trophoblastic digestion and absorption of nutrients from the endometrial decidua, and essentially all the later nutrition results from diffusion through the placental membrane.

the outsides of the trophoblastic cords. The trophoblast cells send out more and more projections, which become *placental villi* into which fetal capillaries grow. Thus, the villi, carrying fetal blood, are surrounded by sinuses that contain maternal blood.

The final structure of the placenta is shown in Figure 82-5. Note that the fetus's blood flows through two *umbilical arteries*, then into the capillaries of the villi, and finally back through a single *umbilical vein* into the fetus. At the same time, the mother's blood flows from her *uterine arteries* into large *maternal sinuses* that surround the villi and then back into the *uterine veins* of the mother. The lower part of Figure 82-5 shows the relation between the fetal blood of each fetal placental villus and the blood of the mother surrounding the outsides of the villus in the fully developed placenta.

The total surface area of all the villi of the mature placenta is only a few square meters—many times less than the area of the pulmonary membrane in the lungs. Nevertheless, nutrients and other substances pass through this placental membrane mainly by diffusion in much the same manner that diffusion occurs through the alveolar membranes of the lungs and the capillary membranes elsewhere in the body.

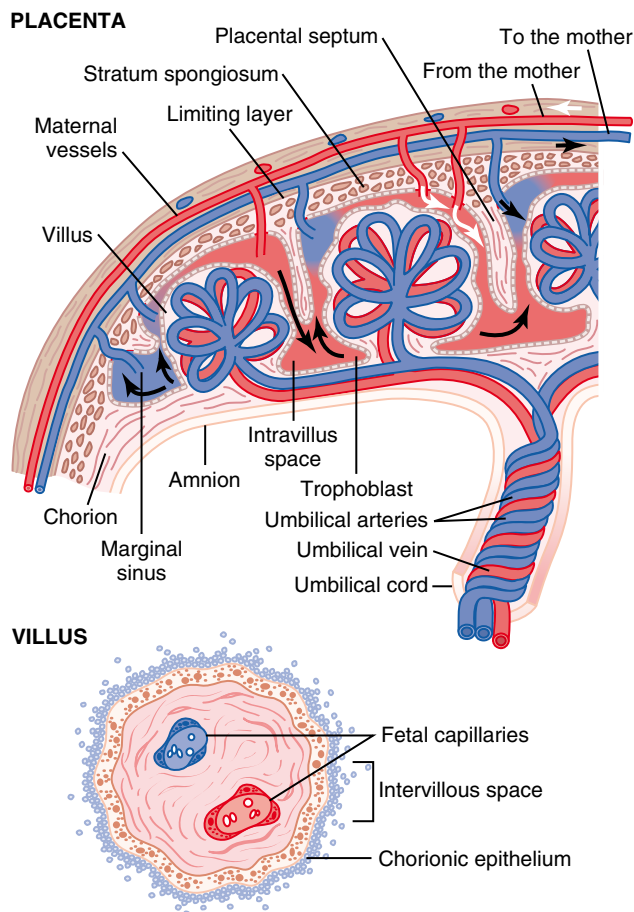
### Placental Permeability and Membrane Diffusion Conductance

The major function of the placenta is to provide for diffusion of foodstuffs and oxygen from the mother's blood into the fetus's blood and diffusion of excretory products from the fetus back into the mother.

In the early months of pregnancy, the placental membrane is still thick because it is not fully developed. Therefore, its permeability is low. Further, the surface area is small because the placenta has not grown significantly. Therefore, the total diffusion conductance is minuscule at first. Conversely, in later pregnancy, the permeability increases because of thinning of the membrane diffusion layers and because the surface area expands many times over, thus giving the tremendous increase in placental diffusion shown in Figure 82-4.

Rarely, “breaks” occur in the placental membrane, which allows fetal blood cells to pass into the mother or,





**Figure 82-5** Above, Organization of the mature placenta. Below, Relation of the fetal blood in the villus capillaries to the mother's blood in the intervillous spaces. (Modified from Gray H, Goss CM: *Anatomy of the Human Body*, 25th ed. Philadelphia: Lea & Febiger, 1948; and from Arey LB: *Developmental Anatomy: A Textbook and Laboratory Manual of Embryology*, 7th ed. Philadelphia: WB Saunders, 1974.)

even less commonly, the mother's cells to pass into the fetus. Fortunately, it is rare for the fetus to bleed severely into the mother's circulation because of a ruptured placental membrane.

**Diffusion of Oxygen Through the Placental Membrane.** Almost the same principles for diffusion of oxygen through the pulmonary membrane (discussed in detail in Chapter 39) are applicable for diffusion of oxygen through the placental membrane. The dissolved oxygen in the blood of the large maternal sinuses passes into the fetal blood by *simple diffusion*, driven by an oxygen pressure gradient from the mother's blood to the fetus's blood. Near the end of pregnancy, the mean  $\text{Po}_2$  of the mother's blood in the placental sinuses is about 50 mm Hg, and the mean  $\text{Po}_2$  in the fetal blood after it becomes oxygenated in the placenta is about 30 mm Hg. Therefore, the mean pressure gradient for diffusion of oxygen through the placental membrane is about 20 mm Hg.

One might wonder how it is possible for a fetus to obtain sufficient oxygen when the fetal blood leaving the placenta has a  $\text{Po}_2$  of only 30 mm Hg. There are three reasons why even this low  $\text{Po}_2$  is capable of allowing the fetal blood to

transport almost as much oxygen to the fetal tissues as is transported by the mother's blood to her tissues.

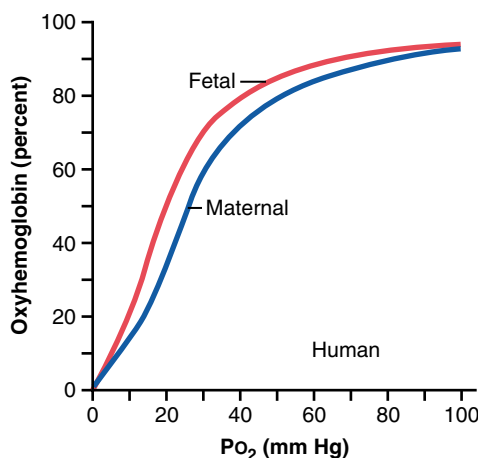
First, the hemoglobin of the fetus is mainly *fetal hemoglobin*, a type of hemoglobin synthesized in the fetus before birth. Figure 82-6 shows the comparative oxygen dissociation curves for maternal hemoglobin and fetal hemoglobin, demonstrating that the curve for fetal hemoglobin is shifted to the left of that for maternal hemoglobin. This means that at the low  $\text{Po}_2$  levels in fetal blood, the fetal hemoglobin can carry 20 to 50 percent more oxygen than maternal hemoglobin can.

Second, the *hemoglobin concentration of fetal blood is about 50 percent greater than that of the mother*; this is an even more important factor in enhancing the amount of oxygen transported to the fetal tissues.

Third, the *Bohr effect*, which is explained in relation to the exchange of carbon dioxide and oxygen in the lung in Chapter 40, provides another mechanism to enhance the transport of oxygen by fetal blood. That is, hemoglobin can carry more oxygen at a low  $\text{PCO}_2$  than it can at a high  $\text{PCO}_2$ . The fetal blood entering the placenta carries large amounts of carbon dioxide, but much of this carbon dioxide diffuses from the fetal blood into the maternal blood. Loss of the carbon dioxide makes the fetal blood more alkaline, whereas the increased carbon dioxide in the maternal blood makes it more acidic.

These changes cause the capacity of fetal blood to combine with oxygen to increase and that of maternal blood to decrease. This forces still more oxygen from the maternal blood, while enhancing oxygen uptake by the fetal blood. Thus, the Bohr shift operates in one direction in the maternal blood and in the other direction in the fetal blood. These two effects make the Bohr shift twice as important here as it is for oxygen exchange in the lungs; therefore, it is called the *double Bohr effect*.

By these three means, the fetus is capable of receiving more than adequate oxygen through the placental



**Figure 82-6** Oxygen-hemoglobin dissociation curves for maternal and fetal blood, showing that fetal blood can carry a greater quantity of oxygen than can maternal blood for a given blood  $\text{Po}_2$ . (Data from Metcalfe J, Moll W, Bartels H: Gas exchange across the placenta. *Fed Proc* 23:775, 1964.)



membrane, despite the fact that the fetal blood leaving the placenta has a  $\text{Po}_2$  of only 30 mm Hg.

The total *diffusing capacity* of the entire placenta for oxygen at term is about 1.2 milliliters of oxygen per minute per millimeter of mercury oxygen pressure difference across the membrane. This compares favorably with that of the lungs of the newborn baby.

**Diffusion of Carbon Dioxide Through the Placental Membrane.** Carbon dioxide is continually formed in the tissues of the fetus in the same way that it is formed in maternal tissues, and the only means for excreting the carbon dioxide from the fetus is through the placenta into the mother's blood. The  $\text{PCO}_2$  of the fetal blood is 2 to 3 mm Hg higher than that of the maternal blood. This small pressure gradient for carbon dioxide across the membrane is more than sufficient to allow adequate diffusion of carbon dioxide because the extreme solubility of carbon dioxide in the placental membrane allows carbon dioxide to diffuse about 20 times as rapidly as oxygen.

**Diffusion of Foodstuffs Through the Placental Membrane.** Other metabolic substrates needed by the fetus diffuse into the fetal blood in the same manner as oxygen does. For instance, in the late stages of pregnancy, the fetus often uses as much glucose as the entire body of the mother uses. To provide this much glucose, the trophoblast cells lining the placental villi provide for *facilitated diffusion* of glucose through the placental membrane. That is, the glucose is transported by carrier molecules in the trophoblast cells of the membrane. Even so, the glucose level in fetal blood is 20 to 30 percent lower than that in maternal blood.

Because of the high solubility of fatty acids in cell membranes, these also diffuse from the maternal blood into the fetal blood, but more slowly than glucose, so that glucose is used more easily by the fetus for nutrition. Also, such substances as ketone bodies and potassium, sodium, and chloride ions diffuse with relative ease from the maternal blood into the fetal blood.

**Excretion of Waste Products Through the Placental Membrane.** In the same manner that carbon dioxide diffuses from the fetal blood into the maternal blood, other excretory products formed in the fetus also diffuse through

the placental membrane into the maternal blood and are then excreted along with the excretory products of the mother. These include especially the *nonprotein nitrogens* such as *urea*, *uric acid*, and *creatinine*. The level of urea in fetal blood is only slightly greater than that in maternal blood because urea diffuses through the placental membrane with great ease. However, creatinine, which does not diffuse as easily, has a fetal blood concentration considerably higher than that in the mother's blood. Therefore, excretion from the fetus depends mainly, if not entirely, on the diffusion gradients across the placental membrane and its permeability. Because there are higher concentrations of the excretory products in the fetal blood than in the maternal blood, there is continual diffusion of these substances from the fetal blood to the maternal blood.

### Hormonal Factors in Pregnancy

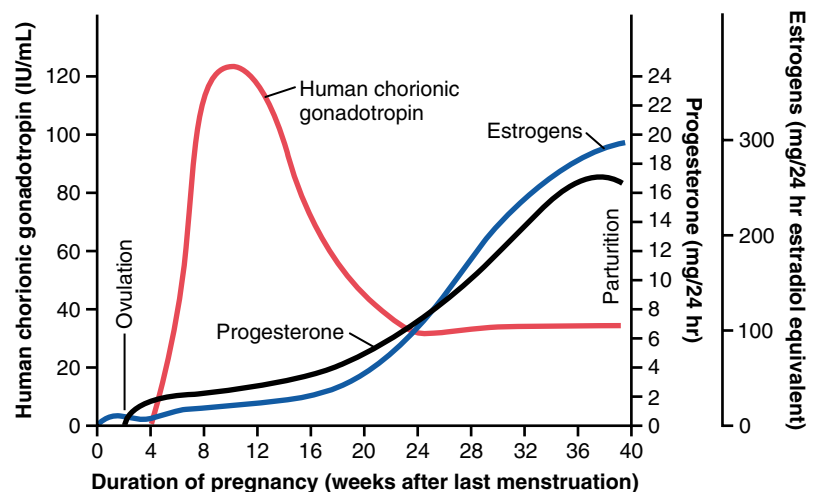
In pregnancy, the placenta forms especially large quantities of *human chorionic gonadotropin*, *estrogens*, *progesterone*, and *human chorionic somatomammotropin*, the first three of which, and probably the fourth as well, are all essential to a normal pregnancy.

#### Human Chorionic Gonadotropin Causes Persistence of the Corpus Luteum and Prevents Menstruation

Menstruation normally occurs in a nonpregnant woman about 14 days after ovulation, at which time most of the endometrium of the uterus sloughs away from the uterine wall and is expelled to the exterior. If this should happen after an ovum has implanted, the pregnancy would terminate. However, this is prevented by the secretion of human chorionic gonadotropin by the newly developing embryonic tissues in the following manner.

Coincidental with the development of the trophoblast cells from the early fertilized ovum, the hormone *human chorionic gonadotropin* is secreted by the syncytial trophoblast cells into the fluids of the mother, as shown in Figure 82-7. The secretion of this hormone can first be

**Figure 82-7** Rates of secretion of estrogens and progesterone, and concentration of human chorionic gonadotropin at different stages of pregnancy.



measured in the blood 8 to 9 days after ovulation, shortly after the blastocyst implants in the endometrium. Then the rate of secretion rises rapidly to reach a maximum at about 10 to 12 weeks of pregnancy and decreases back to a lower value by 16 to 20 weeks. It continues at this elevated level for the remainder of pregnancy.

**Function of Human Chorionic Gonadotropin.** Human chorionic gonadotropin is a glycoprotein having a molecular weight of about 39,000 and much the same molecular structure and function as luteinizing hormone secreted by the pituitary gland. By far, its most important function is to prevent involution of the corpus luteum at the end of the monthly female sexual cycle. Instead, it causes the corpus luteum to secrete even larger quantities of its sex hormones—progesterone and estrogens—for the next few months. These sex hormones prevent menstruation and cause the endometrium to continue to grow and store large amounts of nutrients rather than being shed in the menstruum. As a result, the *decidua-like cells* that develop in the endometrium during the normal female sexual cycle become actual *decidual cells*—greatly swollen and nutritious—at about the time that the blastocyst implants.

Under the influence of human chorionic gonadotropin, the corpus luteum in the mother's ovary grows to about twice its initial size by a month or so after pregnancy begins. Its continued secretion of estrogens and progesterone maintains the decidual nature of the uterine endometrium, which is necessary for the early development of the fetus.

If the corpus luteum is removed before approximately the seventh week of pregnancy, spontaneous abortion almost always occurs, sometimes even up to the 12th week. After that time, the placenta secretes sufficient quantities of progesterone and estrogens to maintain pregnancy for the remainder of the gestation period. The corpus luteum involutes slowly after the 13th to 17th week of gestation.

**Effect of Human Chorionic Gonadotropin on the Fetal Testes.** Human chorionic gonadotropin also exerts an *interstitial cell*—stimulating effect on the testes of the male fetus, resulting in the production of testosterone in male fetuses until the time of birth. This small secretion of testosterone during gestation is what causes the fetus to grow male sex organs instead of female organs. Near the end of pregnancy, the testosterone secreted by the fetal testes also causes the testes to descend into the scrotum.

### Secretion of Estrogens by the Placenta

The placenta, like the corpus luteum, secretes both estrogens and progesterone. Histochemical and physiological studies show that these two hormones, like most other placental hormones, are secreted by the *syncytial trophoblast* cells of the placenta.

Figure 82-7 shows that toward the end of pregnancy, the daily production of placental estrogens increases to about 30 times the mother's normal level of production. However, the secretion of estrogens by the placenta is quite

different from secretion by the ovaries. Most important, the estrogens secreted by the placenta are not synthesized *de novo* from basic substrates in the placenta. Instead, they are formed almost entirely from androgenic steroid compounds, *dehydroepiandrosterone* and *16-hydroxy-dehydroepiandrosterone*, which are formed both in the mother's adrenal glands and in the adrenal glands of the fetus. These weak androgens are transported by the blood to the placenta and converted by the trophoblast cells into estradiol, estrone, and estriol. (The cortices of the fetal adrenal glands are extremely large, and about 80 percent consists of a so-called *fetal zone*, the primary function of which seems to be to secrete dehydroepiandrosterone during pregnancy.)

**Function of Estrogen in Pregnancy.** In the discussions of estrogens in Chapter 81, we pointed out that these hormones exert mainly a proliferative function on most reproductive and associated organs of the mother. During pregnancy, the extreme quantities of estrogens cause (1) enlargement of the mother's uterus, (2) enlargement of the mother's breasts and growth of the breast ductal structure, and (3) enlargement of the mother's female external genitalia.

The estrogens also relax the pelvic ligaments of the mother, so the sacroiliac joints become relatively limber and the symphysis pubis becomes elastic. These changes allow easier passage of the fetus through the birth canal. There is much reason to believe that estrogens also affect many general aspects of fetal development during pregnancy, for example, by affecting the rate of cell reproduction in the early embryo.

### Secretion of Progesterone by the Placenta

Progesterone is also essential for a successful pregnancy—in fact, it is just as important as estrogen. In addition to being secreted in moderate quantities by the corpus luteum at the beginning of pregnancy, it is secreted later in tremendous quantities by the placenta, averaging about a 10-fold increase during the course of pregnancy, as shown in Figure 82-7.

The special effects of progesterone that are essential for the normal progression of pregnancy are as follows:

1. Progesterone causes decidual cells to develop in the uterine endometrium, and these cells play an important role in the nutrition of the early embryo.
2. Progesterone decreases the contractility of the pregnant uterus, thus preventing uterine contractions from causing spontaneous abortion.
3. Progesterone contributes to the development of the conceptus even before implantation because it specifically increases the secretions of the mother's fallopian tubes and uterus to provide appropriate nutritive matter for the developing *morula* (the spherical mass of 16 to 32 blastomeres formed before the blastula) and *blastocyst*. There is also reason to believe that

progesterone affects cell cleavage in the early developing embryo.

4. The progesterone secreted during pregnancy helps the estrogen prepare the mother's breasts for lactation, which is discussed later in this chapter.

### Human Chorionic Somatomammotropin

A more recently discovered placental hormone is called *human chorionic somatomammotropin*. It is a protein with a molecular weight of about 22,000, and it begins to be secreted by the placenta at about the fifth week of pregnancy. Secretion of this hormone increases progressively throughout the remainder of pregnancy in direct proportion to the weight of the placenta. Although the functions of chorionic somatomammotropin are uncertain, it is secreted in quantities several times greater than all the other pregnancy hormones combined. It has several possible important effects.

First, when administered to several types of lower animals, human chorionic somatomammotropin causes at least partial development of the animal's breasts and in some instances causes lactation. Because this was the first function of the hormone discovered, it was first named *human placental lactogen* and was believed to have functions similar to those of prolactin. However, attempts to promote lactation in humans with its use have not been successful.

Second, this hormone has weak actions similar to those of growth hormone, causing the formation of protein tissues in the same way that growth hormone does. It also has a chemical structure similar to that of growth hormone, but 100 times as much human chorionic somatomammotropin as growth hormone is required to promote growth.

Third, human chorionic somatomammotropin causes decreased insulin sensitivity and decreased utilization of glucose in the mother, thereby making larger quantities of glucose available to the fetus. Because glucose is the major substrate used by the fetus to energize its growth, the possible importance of such a hormonal effect is obvious. Further, the hormone promotes the release of free fatty acids from the fat stores of the mother, thus providing this alternative source of energy for the mother's metabolism during pregnancy. Therefore, it appears that human chorionic somatomammotropin is a general metabolic hormone that has specific nutritional implications for both the mother and the fetus.

### Other Hormonal Factors in Pregnancy

Almost all the nonsexual endocrine glands of the mother also react markedly to pregnancy. This results mainly from the increased metabolic load on the mother but also, to some extent, from the effects of placental hormones on the pituitary and other glands. Some of the most notable effects are the following.

**Pituitary Secretion.** The anterior pituitary gland of the mother enlarges at least 50 percent during pregnancy and

increases its production of *corticotropin*, *thyrotropin*, and *prolactin*. Conversely, pituitary secretion of follicle-stimulating hormone and luteinizing hormone is almost totally suppressed as a result of the inhibitory effects of estrogens and progesterone from the placenta.

**Increased Corticosteroid Secretion.** The rate of adrenocortical secretion of the *glucocorticoids* is moderately increased throughout pregnancy. It is possible that these glucocorticoids help mobilize amino acids from the mother's tissues so that these can be used for synthesis of tissues in the fetus.

Pregnant women usually have about a twofold increase in the secretion of *aldosterone*, reaching a peak at the end of gestation. This, along with the actions of estrogens, causes a tendency for even a normal pregnant woman to reabsorb excess sodium from her renal tubules and, therefore, to retain fluid, occasionally leading to *pregnancy-induced hypertension*.

**Increased Thyroid Gland Secretion.** The mother's thyroid gland ordinarily enlarges up to 50 percent during pregnancy and increases its production of thyroxine a corresponding amount. The increased thyroxine production is caused at least partly by a thyrotropic effect of *human chorionic gonadotropin* secreted by the placenta and by small quantities of a specific thyroid-stimulating hormone, *human chorionic thyrotropin*, also secreted by the placenta.

**Increased Parathyroid Gland Secretion.** The mother's parathyroid glands usually enlarge during pregnancy; this is especially true if the mother is on a calcium-deficient diet. Enlargement of these glands causes calcium absorption from the mother's bones, thereby maintaining normal calcium ion concentration in the mother's extracellular fluid even while the fetus removes calcium to ossify its own bones. This secretion of parathyroid hormone is even more intensified during lactation after the baby's birth because the growing baby requires many times more calcium than the fetus does.

**Secretion of "Relaxin" by the Ovaries and Placenta.** Another substance besides the estrogens and progesterone, a hormone called *relaxin*, is secreted by the corpus luteum of the ovary and by placental tissues. Its secretion is increased by a stimulating effect of human chorionic gonadotropin at the same time that the corpus luteum and the placenta secrete large quantities of estrogens and progesterone.

Relaxin is a 48-amino acid polypeptide having a molecular weight of about 9000. This hormone, when injected, causes relaxation of the ligaments of the symphysis pubis in the estrous rat and guinea pig. This effect is weak or possibly even absent in pregnant women. Instead, this role is probably played mainly by the estrogens, which also cause relaxation of the pelvic ligaments. It has also been claimed that relaxin softens the cervix of the pregnant woman at the time of delivery.

### Response of the Mother's Body to Pregnancy

Most apparent among the many reactions of the mother to the fetus and to the excessive hormones of pregnancy is the increased size of the various sexual organs. For instance, the uterus increases from about 50 grams to 1100 grams, and the breasts approximately double in size. At the same time, the vagina enlarges and the introitus opens more widely.

Also, the various hormones can cause marked changes in a pregnant woman's appearance, sometimes resulting in the development of edema, acne, and masculine or acromegalic features.

### Weight Gain in the Pregnant Woman

The average weight gain during pregnancy is about 25 to 35 pounds, with most of this gain occurring during the last two trimesters. Of this, about 8 pounds is fetus and 4 pounds is amniotic fluid, placenta, and fetal membranes. The uterus increases about 3 pounds and the breasts another 2 pounds, still leaving an average weight increase of 8 to 18 pounds. About 5 pounds of this is extra fluid in the blood and extracellular fluid, and the remaining 3 to 13 pounds is generally fat accumulation. The extra fluid is excreted in the urine during the first few days after birth, that is, after loss of the fluid-retaining hormones from the placenta.

During pregnancy, a woman often has a greatly increased desire for food, partly as a result of removal of food substrates from the mother's blood by the fetus and partly because of hormonal factors. Without appropriate prenatal control of diet, the mother's weight gain can be as great as 75 pounds instead of the usual 25 to 35 pounds.

### Metabolism During Pregnancy

As a consequence of the increased secretion of many hormones during pregnancy, including thyroxine, adrenocortical hormones, and the sex hormones, the basal metabolic rate of the pregnant woman increases about 15 percent during the latter half of pregnancy. As a result, she frequently has sensations of becoming overheated. Also, owing to the extra load that she is carrying, greater amounts of energy than normal must be expended for muscle activity.

### Nutrition During Pregnancy

By far the greatest growth of the fetus occurs during the last trimester of pregnancy; its weight almost doubles during the last 2 months of pregnancy. Ordinarily, the mother does not absorb sufficient protein, calcium, phosphates, and iron from her diet during the last months of pregnancy to supply these extra needs of the fetus. However, anticipating these extra needs, the mother's body has already been storing these substances—some in the placenta, but most in the normal storage depots of the mother.

If appropriate nutritional elements are not present in a pregnant woman's diet, a number of maternal deficiencies can occur, especially in calcium, phosphates, iron, and the vitamins. For example, the fetus needs about 375 milligrams of iron to form its blood, and the mother needs an additional 600 milligrams to form her own extra blood. The normal store of nonhemoglobin iron in the mother at the outset of pregnancy is often only 100 milligrams and almost never more than 700 milligrams. Therefore, without sufficient iron in her food, a pregnant woman usually develops *hypochromic anemia*. Also, it is especially important that she receive vitamin D, because although the total quantity of calcium used by the fetus is small, calcium is normally poorly absorbed by the mother's gastrointestinal tract without vitamin D. Finally, shortly before birth of the baby, vitamin K is often added to the mother's diet so that the baby will have sufficient prothrombin to prevent hemorrhage, particularly brain hemorrhage, caused by the birth process.

### Changes in the Maternal Circulatory System During Pregnancy

**Blood Flow Through the Placenta, and Maternal Cardiac Output Increases During Pregnancy.** About 625 milliliters of blood flows through the maternal circulation of the placenta each minute during the last month of pregnancy. This, plus the general increase in the mother's metabolism, increases the mother's cardiac output to 30 to 40 percent above normal by the 27th week of pregnancy; then, for reasons unexplained, the cardiac output falls to only a little above normal during the last 8 weeks of pregnancy, despite the high uterine blood flow.

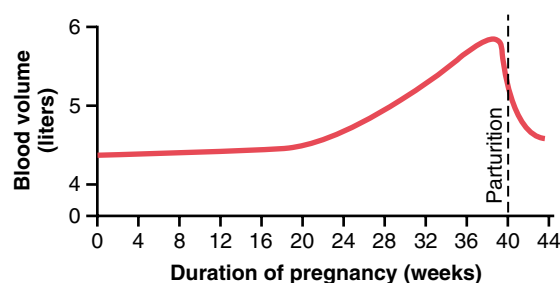
**Maternal Blood Volume Increases During Pregnancy.** The maternal blood volume shortly before term is about 30 percent above normal. This increase occurs mainly during the latter half of pregnancy, as shown by the curve of Figure 82-8. The cause of the increased volume is likely due, at least in part, to aldosterone and estrogens, which are greatly increased in pregnancy, and to increased fluid retention by the kidneys. Also, the bone marrow becomes increasingly active and produces extra red blood cells to go with the excess fluid volume. Therefore, at the time of birth of the baby, the mother has about 1 to 2 liters of extra blood in her circulatory system. Only about one fourth of this amount is normally lost through bleeding during delivery of the baby, thereby allowing a considerable safety factor for the mother.

### Maternal Respiration Increases During Pregnancy

Because of the increased basal metabolic rate of a pregnant woman and because of her greater size, the total amount of oxygen used by the mother shortly before birth of the baby is about 20 percent above normal and a commensurate amount of carbon dioxide is formed. These effects cause the mother's minute ventilation to increase. It is also believed that the high levels of progesterone during pregnancy increase the minute ventilation even more, because progesterone increases the respiratory center's sensitivity to carbon dioxide. The net result is an increase in minute ventilation of about 50 percent and a decrease in arterial  $PCO_2$  to several millimeters of mercury below that in a nonpregnant woman. Simultaneously, the growing uterus presses upward against the abdominal contents, which press upward against the diaphragm, so the total excursion of the diaphragm is decreased. Consequently, the respiratory rate is increased to maintain the extra ventilation.

### Maternal Kidney Function During Pregnancy

The rate of urine formation by a pregnant woman is usually slightly increased because of increased fluid intake and increased load of excretory products. But in addition, several special alterations of kidney function occur.



**Figure 82-8** Effect of pregnancy to increase the mother's blood volume.



First, the renal tubules' reabsorptive capacity for sodium, chloride, and water is increased as much as 50 percent as a consequence of increased production of salt and water retaining hormones, especially steroid hormones by the placenta and adrenal cortex.

Second, the renal blood flow and glomerular filtration rate increase up to 50 percent during normal pregnancy due to renal vasodilation. Although the mechanisms that cause renal vasodilation in pregnancy are still unclear, some studies suggest that increased levels of nitric oxide or the ovarian hormone relaxin may contribute to these changes. The increased glomerular filtration rate likely occurs, at least in part, as a compensation for increased tubular reabsorption of salt and water. Thus, the *normal* pregnant woman ordinarily accumulates only about 5 pounds of extra water and salt.

#### Amniotic Fluid and Its Formation

Normally, the volume of *amniotic fluid* (the fluid inside the uterus in which the fetus floats) is between 500 milliliters and 1 liter, but it can be only a few milliliters or as much as several liters. Isotope studies of the rate of formation of amniotic fluid show that, on average, the water in amniotic fluid is replaced once every 3 hours and the electrolytes sodium and potassium are replaced an average of once every 15 hours. A large portion of the fluid is derived from renal excretion by the fetus. Likewise, a certain amount of absorption occurs by way of the gastrointestinal tract and lungs of the fetus. However, even after in utero death of a fetus, some turnover of the amniotic fluid is still present, which indicates that some of the fluid is formed and absorbed directly through the amniotic membranes.

#### Preeclampsia and Eclampsia

About 5 percent of all pregnant women experience a rapid rise in arterial blood pressure to hypertensive levels during the last few months of pregnancy. This is also associated with leakage of large amounts of protein into the urine. This condition is called *preeclampsia* or *toxemia of pregnancy*. It is often characterized by excess salt and water retention by the mother's kidneys and by weight gain and development of edema and hypertension in the mother. In addition, there is impaired function of the vascular endothelium and arterial spasm occurs in many parts of the mother's body, most significantly in the kidneys, brain, and liver. Both the renal blood flow and the glomerular filtration rate are decreased, which is exactly opposite to the changes that occur in the normal pregnant woman. The renal effects also include thickened glomerular tufts that contain a protein deposit in the basement membranes.

Various attempts have been made to prove that preeclampsia is caused by excessive secretion of placental or adrenal hormones, but proof of a hormonal basis is still lacking. Another theory is that preeclampsia results from some type of autoimmunity or allergy in the mother caused by the presence of the fetus. In support of this, the acute symptoms usually disappear within a few days after birth of the baby.

There is also evidence that preeclampsia is initiated by *insufficient blood supply to the placenta*, resulting in the placenta's release of substances that cause widespread dysfunction of the maternal vascular endothelium. During normal placental development, the trophoblasts invade the arterioles of the uterine endometrium and completely remodel the maternal arterioles into large blood vessels with low resistance to blood flow. In patients with preeclampsia, the maternal arterioles fail to undergo these adaptive changes, for reasons that are still unclear, and there is insuf-

ficient blood supply to the placenta. This, in turn, causes the placenta to release various substances that enter the mother's circulation and cause impaired vascular endothelial function, decreased blood flow to the kidneys, excess salt and water retention, and increased blood pressure.

Although the factors that link reduced placental blood supply with maternal endothelial dysfunction are still uncertain, some experimental studies suggest a role for increased levels of *inflammatory cytokines* such as *tumor necrosis factor- $\alpha$*  and *interleukin-6*. Placental factors that impede angiogenesis (blood vessel growth) have also been shown to contribute to increased inflammatory cytokines and preeclampsia. For example, the antiangiogenic proteins *soluble fms-related tyrosine kinase 1* (s-Flt1) and *soluble endoglin* are increased in the blood of women with preeclampsia. These substances are released by the placenta into the maternal circulation in response to ischemia and hypoxia of the placenta. Soluble endoglin and s-Flt1 have multiple effects that may impair function of the maternal vascular endothelium and result in hypertension, proteinuria, and the other systemic manifestations of preeclampsia. However, the precise role of the various factors released from the ischemic placenta in causing the multiple cardiovascular and renal abnormalities in women with preeclampsia is still uncertain.

*Eclampsia* is an extreme degree of preeclampsia, characterized by vascular spasm throughout the body; clonic seizures in the mother, sometimes followed by coma; greatly decreased kidney output; malfunction of the liver; often extreme hypertension; and a generalized toxic condition of the body. It usually occurs shortly before birth of the baby. Without treatment, a high percentage of eclamptic mothers die. However, with optimal and immediate use of rapidly acting vasodilating drugs to reduce the arterial pressure to normal, followed by immediate termination of pregnancy—by cesarean section if necessary—the mortality even in eclamptic mothers has been reduced to 1 percent or less.

## Parturition

### Increased Uterine Excitability Near Term

*Parturition* means birth of the baby. Toward the end of pregnancy, the uterus becomes progressively more excitable, until finally it develops such strong rhythmical contractions that the baby is expelled. The exact cause of the increased activity of the uterus is not known, but at least two major categories of effects lead up to the intense contractions responsible for parturition: (1) progressive hormonal changes that cause increased excitability of the uterine musculature and (2) progressive mechanical changes.

### Hormonal Factors That Increase Uterine Contractility

**Increased Ratio of Estrogens to Progesterone.** Progesterone inhibits uterine contractility during pregnancy, thereby helping to prevent expulsion of the fetus. Conversely, estrogens have a definite tendency to increase the degree of uterine contractility, partly because estrogens increase the number of gap junctions between the adjacent uterine smooth muscle cells, but also because

of other poorly understood effects. Both progesterone and estrogen are secreted in progressively greater quantities throughout most of pregnancy, but from the seventh month onward, estrogen secretion continues to increase while progesterone secretion remains constant or perhaps even decreases slightly. Therefore, it has been postulated that the *estrogen-to-progesterone ratio* increases sufficiently toward the end of pregnancy to be at least partly responsible for the increased contractility of the uterus.

#### Oxytocin Causes Contraction of the Uterus.

Oxytocin is a hormone secreted by the neurohypophysis that specifically causes uterine contraction (see Chapter 75). There are four reasons to believe that oxytocin might be important in increasing the contractility of the uterus near term: (1) The uterine muscle increases its oxytocin receptors and, therefore, increases its responsiveness to a given dose of oxytocin during the latter few months of pregnancy. (2) The rate of oxytocin secretion by the neurohypophysis is considerably increased at the time of labor. (3) Although hypophysectomized animals can still deliver their young at term, labor is prolonged. (4) Experiments in animals indicate that irritation or stretching of the uterine cervix, as occurs during labor, can cause a neurogenic reflex through the paraventricular and supraoptic nuclei of the hypothalamus that causes the posterior pituitary gland (the neurohypophysis) to increase its secretion of oxytocin.

**Effect of Fetal Hormones on the Uterus.** The fetus's pituitary gland secretes increasing quantities of oxytocin, which might play a role in exciting the uterus. Also, the fetus's adrenal glands secrete large quantities of cortisol, another possible uterine stimulant. In addition, the fetal membranes release prostaglandins in high concentration at the time of labor. These, too, can increase the intensity of uterine contractions.

### Mechanical Factors That Increase Uterine Contractility

**Stretch of the Uterine Musculature.** Simply stretching smooth muscle organs usually increases their contractility. Further, intermittent stretch, as occurs repeatedly in the uterus because of fetal movements, can also elicit smooth muscle contraction. Note especially that twins are born, on average, *19 days* earlier than a single child, which emphasizes the importance of mechanical stretch in eliciting uterine contractions.

**Stretch or Irritation of the Cervix.** There is reason to believe that stretching or irritating the uterine cervix is particularly important in eliciting uterine contractions. For instance, the obstetrician frequently induces labor by rupturing the membranes so that the head of the baby stretches the cervix more forcefully than usual or irritates it in other ways.

The mechanism by which cervical irritation excites the body of the uterus is not known. It has been suggested that stretching or irritation of nerves in the cervix initiates reflexes to the body of the uterus, but the effect could

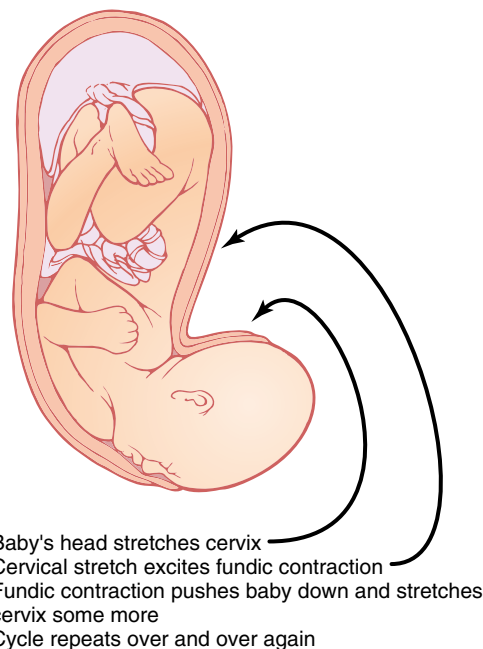
also result simply from myogenic transmission of signals from the cervix to the body of the uterus.

### Onset of Labor—A Positive Feedback Mechanism for Its Initiation

During most of the months of pregnancy, the uterus undergoes periodic episodes of weak and slow rhythmic contractions called *Braxton Hicks contractions*. These contractions become progressively stronger toward the end of pregnancy; then they change suddenly, within hours, to become exceptionally strong contractions that start stretching the cervix and later force the baby through the birth canal, thereby causing parturition. This process is called *labor*, and the strong contractions that result in final parturition are called *labor contractions*.

We do not know what suddenly changes the slow, weak rhythmicity of the uterus into strong labor contractions. However, on the basis of experience with other types of physiological control systems, a theory has been proposed for explaining the onset of labor. The *positive feedback* theory suggests that stretching of the cervix by the fetus's head finally becomes great enough to elicit a strong reflex increase in contractility of the uterine body. This pushes the baby forward, which stretches the cervix more and initiates more positive feedback to the uterine body. Thus, the process repeats until the baby is expelled. This theory is shown in Figure 82-9, and the observations supporting it are the following.

First, labor contractions obey all the principles of positive feedback. That is, once the strength of uterine contraction becomes greater than a critical value, each contraction leads to subsequent contractions that become stronger and stronger until maximum effect is achieved. Referring to the discussion in Chapter 1 of positive



**Figure 82-9** Theory for the onset of intensely strong contractions during labor.

feedback in control systems, one can see that this is the precise nature of all positive feedback mechanisms when the feedback gain becomes greater than a critical value.

Second, two known types of positive feedback increase uterine contractions during labor: (1) Stretching of the cervix causes the entire body of the uterus to contract, and this contraction stretches the cervix even more because of the downward thrust of the baby's head. (2) Cervical stretching also causes the pituitary gland to secrete oxytocin, which is another means for increasing uterine contractility.

To summarize, we can assume that multiple factors increase the contractility of the uterus toward the end of pregnancy. Eventually a uterine contraction becomes strong enough to irritate the uterus, especially at the cervix, and this increases uterine contractility still more because of positive feedback, resulting in a second uterine contraction stronger than the first, a third stronger than the second, and so forth. Once these contractions become strong enough to cause this type of feedback, with each succeeding contraction greater than the preceding one, the process proceeds to completion—all *because positive feedback initiates a vicious circle when the gain of the feedback is greater than a critical level*.

One might ask about the many instances of false labor, in which the contractions become stronger and stronger and then fade away. Remember that for a vicious circle to continue, *each* new cycle of the positive feedback must be stronger than the previous one. If at any time after labor starts some contractions fail to re-excite the uterus sufficiently, the positive feedback could go into a retrograde decline and the labor contractions would fade away.

### Abdominal Muscle Contractions During Labor

Once uterine contractions become strong during labor, pain signals originate both from the uterus and from the birth canal. These signals, in addition to causing suffering, elicit neurogenic reflexes in the spinal cord to the abdominal muscles, causing intense contractions of these muscles. The abdominal contractions add greatly to the force that causes expulsion of the baby.

#### Mechanics of Parturition

The uterine contractions during labor begin mainly at the top of the uterine fundus and spread downward over the body of the uterus. Also, the intensity of contraction is great in the top and body of the uterus but weak in the lower segment of the uterus adjacent to the cervix. Therefore, each uterine contraction tends to force the baby downward toward the cervix.

In the early part of labor, the contractions might occur only once every 30 minutes. As labor progresses, the contractions finally appear as often as once every 1 to 3 minutes and the intensity of contraction increases greatly, with only a short period of relaxation between contractions. The combined contractions of the uterine and abdominal musculature during delivery of the baby cause a downward force on the fetus of about 25 pounds during each strong contraction.

It is fortunate that the contractions of labor occur intermittently, because strong contractions impede or sometimes even stop blood flow through the placenta and

would cause death of the fetus if the contractions were continuous. Indeed, overuse of various uterine stimulants, such as oxytocin, can cause uterine spasm rather than rhythmical contractions and can lead to death of the fetus.

In more than 95 percent of births, the head is the first part of the baby to be expelled, and in most of the remaining instances, the buttocks are presented first. When the baby enters the birth canal with the buttocks or feet first, this is called a *breech* presentation.

The head acts as a wedge to open the structures of the birth canal as the fetus is forced downward. The first major obstruction to expulsion of the fetus is the uterine cervix. Toward the end of pregnancy, the cervix becomes soft, which allows it to stretch when labor contractions begin in the uterus. The so-called *first stage of labor* is a period of progressive cervical dilation, lasting until the cervical opening is as large as the head of the fetus. This stage usually lasts for 8 to 24 hours in the first pregnancy but often only a few minutes after many pregnancies.

Once the cervix has dilated fully, the fetal membranes usually rupture and the amniotic fluid is lost suddenly through the vagina. Then the fetus's head moves rapidly into the birth canal, and with additional force from above, it continues to wedge its way through the canal until delivery is effected. This is called the *second stage of labor*, and it may last from as little as 1 minute after many pregnancies to 30 minutes or more in the first pregnancy.

### Separation and Delivery of the Placenta

For 10 to 45 minutes after birth of the baby, the uterus continues to contract to a smaller and smaller size, which causes a *shearing* effect between the walls of the uterus and the placenta, thus separating the placenta from its implantation site. Separation of the placenta opens the placental sinuses and causes bleeding. The amount of bleeding is limited to an average of 350 milliliters by the following mechanism: The smooth muscle fibers of the uterine musculature are arranged in figures of eight around the blood vessels as the vessels pass through the uterine wall. Therefore, contraction of the uterus after delivery of the baby constricts the vessels that had previously supplied blood to the placenta. In addition, it is believed that vasoconstrictor prostaglandins formed at the placental separation site cause additional blood vessel spasm.

### Labor Pains

With each uterine contraction, the mother experiences considerable pain. The cramping pain in early labor is probably caused mainly by hypoxia of the uterine muscle resulting from compression of the blood vessels in the uterus. This pain is not felt when the visceral sensory *hypogastric nerves*, which carry the visceral sensory fibers leading from the uterus, have been sectioned.

However, during the second stage of labor, when the fetus is being expelled through the birth canal, much more severe pain is caused by cervical stretching, perineal stretching, and stretching or tearing of structures in the vaginal canal itself. This pain is conducted to the mother's spinal cord and brain by somatic nerves instead of by the visceral sensory nerves.

### Involution of the Uterus After Parturition

During the first 4 to 5 weeks after parturition, the uterus involutes. Its weight becomes less than half its immediate postpartum weight within 1 week, and in 4 weeks, if the



mother lactates, the uterus may become as small as it was before pregnancy. This effect of lactation results from the suppression of pituitary gonadotropin and ovarian hormone secretion during the first few months of lactation, as discussed later. During early involution of the uterus, the placental site on the endometrial surface autolyzes, causing a vaginal discharge known as “lochia,” which is first bloody and then serous in nature, continuing for a total of about 10 days. After this time, the endometrial surface becomes re-epithelialized and ready for normal, nongravid sex life again.

## Lactation

### Development of the Breasts

The breasts, shown in Figure 82-10, begin to develop at puberty. This development is stimulated by the estrogens of the monthly female sexual cycle; estrogens stimulate

growth of the breasts' *mammary glands* plus the deposition of fat to give the breasts mass. In addition, far greater growth occurs during the high-estrogen state of pregnancy, and only then does the glandular tissue become completely developed for the production of milk.

**Estrogens Stimulate Growth of the Ductal System of the Breasts.** All through pregnancy, the large quantities of estrogens secreted by the placenta cause the ductal system of the breasts to grow and branch. Simultaneously, the stroma of the breasts increases in quantity, and large quantities of fat are laid down in the stroma.

Also important for growth of the ductal system are at least four other hormones: *growth hormone*, *prolactin*, the *adrenal glucocorticoids*, and *insulin*. Each of these is known to play at least some role in protein metabolism, which presumably explains their function in the development of the breasts.

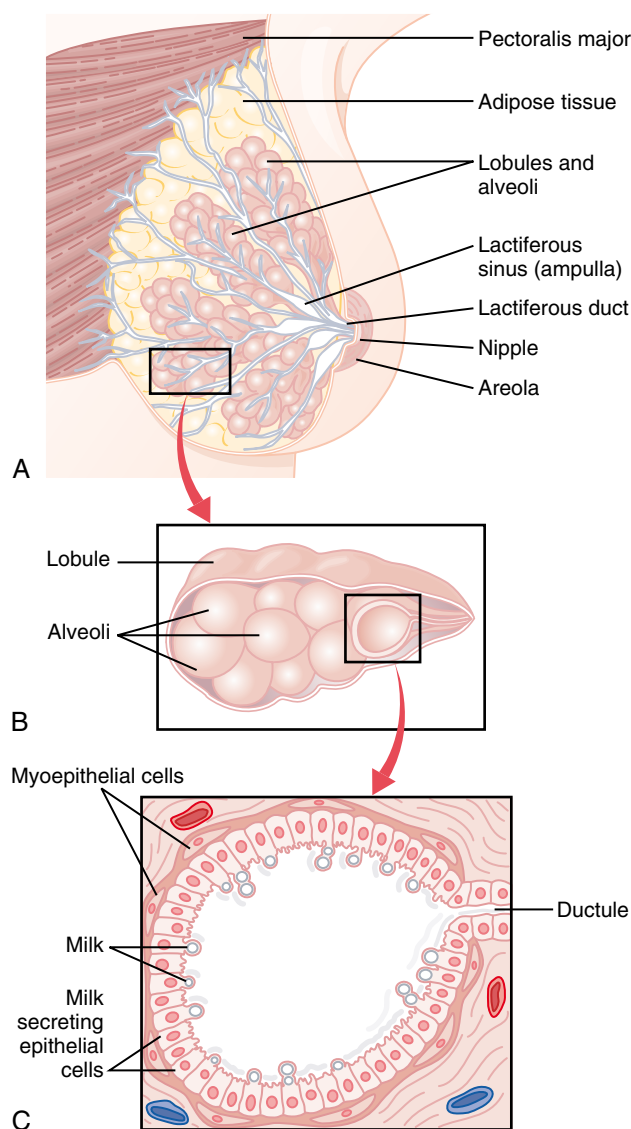
**Progesterone Is Required for Full Development of the Lobule-Alveolar System.** Final development of the breasts into milk-secreting organs also requires *progesterone*. Once the ductal system has developed, progesterone—acting synergistically with estrogen, as well as with the other hormones just mentioned—causes additional growth of the breast lobules, with budding of alveoli and development of secretory characteristics in the cells of the alveoli. These changes are analogous to the secretory effects of progesterone on the endometrium of the uterus during the latter half of the female menstrual cycle.

### Prolactin Promotes Lactation

Although estrogen and progesterone are essential for the physical development of the breasts during pregnancy, a specific effect of both these hormones is to inhibit *the actual secretion of milk*. Conversely, the hormone *prolactin* has exactly the opposite effect on milk secretion—promoting it. This hormone is secreted by the mother's anterior pituitary gland, and its concentration in her blood rises steadily from the fifth week of pregnancy until birth of the baby, at which time it has risen to 10 to 20 times the normal nonpregnant level. This high level of prolactin at the end of pregnancy is shown in Figure 82-11.

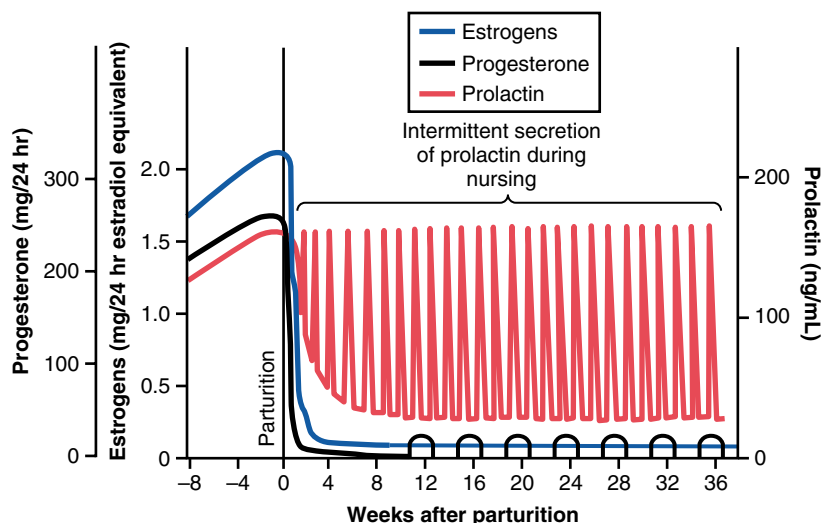
In addition, the placenta secretes large quantities of *human chorionic somatomammotropin*, which probably has lactogenic properties, thus supporting the prolactin from the mother's pituitary during pregnancy. Even so, because of the suppressive effects of estrogen and progesterone, no more than a few milliliters of fluid are secreted each day until after the baby is born. The fluid secreted during the last few days before and the first few days after parturition is called *colostrum*; it contains essentially the same concentrations of proteins and lactose as milk, but it has almost no fat and its maximum rate of production is about 1/100 the subsequent rate of milk production.

Immediately after the baby is born, the sudden loss of both estrogen and progesterone secretion from the



**Figure 82-10** The breast and its secretory lobules, alveoli, and lactiferous ducts (milk ducts) that constitute its mammary gland (A). The enlargements show a lobule (B) and milk-secreting cells of an alveolus (C).





**Figure 82-11** Changes in rates of secretion of estrogens, progesterone, and prolactin for 8 weeks before parturition and 36 weeks thereafter. Note especially the decrease of prolactin secretion back to basal levels within a few weeks after parturition, but also the intermittent periods of marked prolactin secretion (for about 1 hour at a time) during and after periods of nursing.

placenta allows the lactogenic effect of prolactin from the mother's pituitary gland to assume its natural milk-promoting role, and over the next 1 to 7 days, the breasts begin to secrete copious quantities of milk instead of colostrum. This secretion of milk requires an adequate background secretion of most of the mother's other hormones as well, but most important are *growth hormone*, *cortisol*, *parathyroid hormone*, and *insulin*. These hormones are necessary to provide the amino acids, fatty acids, glucose, and calcium required for milk formation.

After birth of the baby, the *basal level* of prolactin secretion returns to the nonpregnant level over the next few weeks, as shown in Figure 82-11. However, each time the mother nurses her baby, nervous signals from the nipples to the hypothalamus cause a 10- to 20-fold surge in prolactin secretion that lasts for about 1 hour, which is also shown in Figure 82-11. This prolactin acts on the mother's breasts to keep the mammary glands secreting milk into the alveoli for the subsequent nursing periods. If this prolactin surge is absent or blocked as a result of hypothalamic or pituitary damage or if nursing does not continue, the breasts lose their ability to produce milk within 1 week or so. However, milk production can continue for several years if the child continues to suckle, although the rate of milk formation normally decreases considerably after 7 to 9 months.

**Hypothalamus Secretes Prolactin Inhibitory Hormone.** The hypothalamus plays an essential role in controlling prolactin secretion, as it does for almost all the other anterior pituitary hormones. However, this control is different in one aspect: The hypothalamus mainly *stimulates* production of all the other hormones, but it mainly *inhibits* prolactin production. Consequently, damage to the hypothalamus or blockage of the hypothalamic-hypophyseal portal system often increases prolactin secretion while it depresses secretion of the other anterior pituitary hormones.

Therefore, it is believed that anterior pituitary secretion of prolactin is controlled either entirely or almost entirely

by an inhibitory factor formed in the hypothalamus and transported through the hypothalamic-hypophyseal portal system to the anterior pituitary gland. This factor is called *prolactin inhibitory hormone*. It is almost certainly the same as the catecholamine *dopamine*, which is known to be secreted by the arcuate nuclei of the hypothalamus and can decrease prolactin secretion as much as 10-fold.

**Suppression of the Female Ovarian Cycles in Nursing Mothers for Many Months After Delivery.** In most nursing mothers, the ovarian cycle (and ovulation) does not resume until a few weeks after cessation of nursing. The reason seems to be that the same nervous signals from the breasts to the hypothalamus that cause prolactin secretion during suckling—either because of the nervous signals themselves or because of a subsequent effect of increased prolactin—inhibit secretion of gonadotropin-releasing hormone by the hypothalamus. This, in turn, suppresses formation of the pituitary gonadotropic hormones—luteinizing hormone and follicle-stimulating hormone. However, after several months of lactation, in some mothers, especially in those who nurse their babies only some of the time, the pituitary begins to secrete sufficient gonadotropic hormones to reinstate the monthly sexual cycle, even though nursing continues.

### Ejection (or "Let-Down") Process in Milk Secretion—Function of Oxytocin

Milk is secreted continuously into the alveoli of the breasts, but it does not flow easily from the alveoli into the ductal system and, therefore, does not continually leak from the breast nipples. Instead, the milk must be *ejected* from the alveoli into the ducts before the baby can obtain it. This is caused by a combined neurogenic and hormonal reflex that involves the posterior pituitary hormone *oxytocin*, as follows.

When the baby suckles, it receives virtually no milk for the first half minute or so. Sensory impulses must first be transmitted through somatic nerves from the nipples to

the mother's spinal cord and then to her hypothalamus, where they cause nerve signals that promote *oxytocin* secretion at the same time that they cause prolactin secretion. The oxytocin is carried in the blood to the breasts, where it causes *myoepithelial cells* (which surround the outer walls of the alveoli) to contract, thereby expressing the milk from the alveoli into the ducts at a pressure of +10 to 20 mm Hg. Then the baby's suckling becomes effective in removing the milk. Thus, within 30 seconds to 1 minute after a baby begins to suckle, milk begins to flow. This process is called *milk ejection* or *milk let-down*.

Suckling on one breast causes milk flow not only in that breast but also in the opposite breast. It is especially interesting that fondling of the baby by the mother or hearing the baby crying often gives enough of an emotional signal to the hypothalamus to cause milk ejection.

**Inhibition of Milk Ejection.** A particular problem in nursing a baby comes from the fact that many psychogenic factors or even generalized sympathetic nervous system stimulation throughout the mother's body can inhibit oxytocin secretion and consequently depress milk ejection. For this reason, many mothers must have an undisturbed period of adjustment after childbirth if they are to be successful in nursing their babies.

### Milk Composition and the Metabolic Drain on the Mother Caused by Lactation

Table 82-1 lists the contents of human milk and cow's milk. The concentration of lactose in human milk is about 50 percent greater than in cow's milk, but the concentration of protein in cow's milk is ordinarily two or more times greater than in human milk. Finally, only one third as much ash, which contains calcium and other minerals, is found in human milk compared with cow's milk.

At the height of lactation in the human mother, 1.5 liters of milk may be formed each day (and even more if the mother has twins). With this degree of lactation, great quantities of energy are drained from the mother; approximately 650 to 750 kilocalories per liter (or 19 to 22 kilocalories per ounce) are contained in breast milk, although the composition and caloric content of the milk depends on the mother's diet and other factors such as the fullness of the breasts. Large amounts of metabolic sub-

strates are also lost from the mother. For instance, about 50 grams of fat enter the milk each day, as well as about 100 grams of lactose, which must be derived by conversion from the mother's glucose. Also, 2 to 3 grams of calcium phosphate may be lost each day; unless the mother is drinking large quantities of milk and has an adequate intake of vitamin D, the output of calcium and phosphate by the lactating mammae will often be much greater than the intake of these substances. To supply the needed calcium and phosphate, the parathyroid glands enlarge greatly and the bones become progressively decalcified. The mother's bone decalcification is usually not a big problem during pregnancy, but it can become more important during lactation.

**Antibodies and Other Anti-infectious Agents in Milk.** Not only does milk provide the newborn baby with needed nutrients, but it also provides important protection against infection. For instance, multiple types of *antibodies* and other anti-infectious agents are secreted in milk along with the nutrients. Also, several different types of white blood cells are secreted, including both *neutrophils* and *macrophages*, some of which are especially lethal to bacteria that could cause deadly infections in newborn babies. Particularly important are antibodies and macrophages that destroy *Escherichia coli* bacteria, which often cause lethal diarrhea in newborns.

When cow's milk is used to supply nutrition for the baby in place of mother's milk, the protective agents in it are usually of little value because they are normally destroyed within minutes in the internal environment of the human being.

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**Table 82-1** Composition of Milk

Constituent	Human Milk (%)	Cow's Milk (%)
Water	88.5	87.0
Fat	3.3	3.5
Lactose	6.8	4.8
Casein	0.9	2.7
Lactalbumin and other proteins	0.4	0.7
Ash	0.2	0.7

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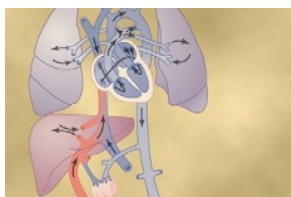
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# Fetal and Neonatal Physiology



A complete discussion of fetal development, functioning of the child immediately after birth, and growth and development through the early years of life lies within the province of formal courses in obstetrics and pediatrics. However, many

physiologic principles are peculiar to the infant and this chapter discusses the more important of these.

## Growth and Functional Development of the Fetus

Initial development of the placenta and fetal membranes occurs far more rapidly than development of the fetus. In fact, during the first 2 to 3 weeks after implantation of the blastocyst, the fetus remains almost microscopic, but thereafter, as shown in Figure 83-1, the length of the fetus increases almost in proportion to age. At 12 weeks, the length is about 10 centimeters; at 20 weeks, 25 centimeters; and at term (40 weeks), 53 centimeters (about 21 inches). Because the weight of the fetus is approximately proportional to the cube of length, the weight increases almost in proportion to the cube of the age of the fetus.

Note in Figure 83-1 that the weight remains minuscule during the first 12 weeks and reaches 1 pound only at 23 weeks (5½ months) of gestation. Then, during the last trimester of pregnancy, the fetus gains rapidly, so 2 months before birth, the weight averages 3 pounds, 1 month before birth 4.5 pounds, and at birth 7 pounds—the final birth weight varying from as low as 4.5 pounds to as high as 11 pounds in normal infants with normal gestational periods.

## Development of the Organ Systems

Within 1 month after fertilization of the ovum, the gross characteristics of all the different organs of the fetus have already begun to develop, and during the next 2 to 3 months, most of the details of the different organs are established. Beyond month 4, the organs of the fetus are grossly the same as those of the neonate. However, cellular development in each organ is usually far from complete and requires the full remaining 5 months of pregnancy for complete development. Even at birth, certain structures, particularly in the nervous system,

the kidneys, and the liver, lack full development, as discussed in more detail later in the chapter.

**Circulatory System.** The human heart begins beating during the fourth week after fertilization, contracting at a rate of about 65 beats/min. This increases steadily to about 140 beats/min immediately before birth.

**Formation of Blood Cells.** Nucleated red blood cells begin to be formed in the yolk sac and mesothelial layers of the placenta at about the third week of fetal development. This is followed 1 week later (at 4 to 5 weeks) by formation of non-nucleated red blood cells by the fetal mesenchyme and also by the endothelium of the fetal blood vessels. Then, at 6 weeks, the liver begins to form blood cells, and in the third month, the spleen and other lymphoid tissues of the body begin forming blood cells. Finally, from the third month on, the bone marrow gradually becomes the principal source of the red blood cells, as well as most of the white blood cells, except for continued lymphocyte and plasma cell production in lymphoid tissue.

**Respiratory System.** Respiration cannot occur during fetal life because there is no air to breathe in the amniotic cavity. However, attempted respiratory movements do take place beginning at the end of the first trimester of pregnancy. Tactile stimuli and fetal asphyxia especially cause these attempted respiratory movements.

During the last 3 to 4 months of pregnancy, the respiratory movements of the fetus are mainly inhibited, for reasons unknown, and the lungs remain almost completely deflated. The inhibition of respiration during the later months of fetal life prevents filling of the lungs with fluid and debris from the

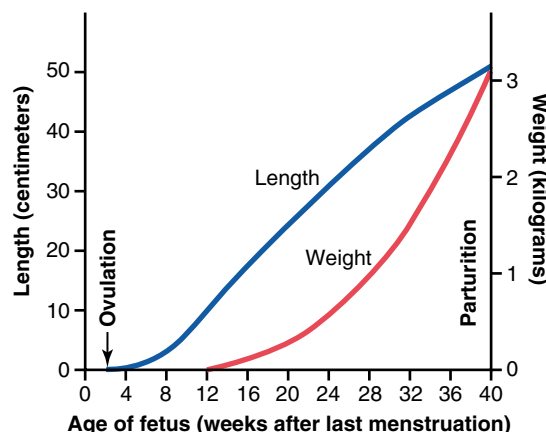


Figure 83-1 Growth of the fetus.

*meconium* excreted by the fetus's gastrointestinal tract into the amniotic fluid. Also, small amounts of fluid are secreted into the lungs by the alveolar epithelium up until the moment of birth, thus keeping only clean fluid in the lungs.

**Nervous System.** Most of the reflexes of the fetus that involve the spinal cord and even the brain stem are present by the third to fourth months of pregnancy. However, those nervous system functions that involve the cerebral cortex are still only in the early stages of development even at birth. Indeed, myelination of some major tracts of the brain becomes complete only after about 1 year of postnatal life.

**Gastrointestinal Tract.** By midpregnancy the fetus begins to ingest and absorb large quantities of amniotic fluid, and during the last 2 to 3 months, gastrointestinal function approaches that of the normal neonate. By that time, small quantities of *meconium* are continually formed in the gastrointestinal tract and excreted from the anus into the amniotic fluid. Meconium is composed partly of residue from swallowed amniotic fluid and partly of *mucus*, epithelial cells, and other residues of excretory products from the gastrointestinal mucosa and glands.

**Kidneys.** The fetal kidneys begin to excrete urine during the second trimester pregnancy, and fetal urine accounts for about 70 to 80 percent of the amniotic fluid. Abnormal kidney development or severe impairment of kidney function in the fetus greatly reduces the formation of amniotic fluid (*oligohydramnios*) and can lead to fetal death.

Although the fetal kidneys form urine, the renal control systems for regulating fetal extracellular fluid volume and electrolyte balances, and especially acid-base balance, are almost nonexistent until late fetal life and do not reach full development until a few months after birth.

**Fetal Metabolism.** The fetus uses mainly glucose for energy, and the fetus has a high capability to store fat and protein, much if not most of the fat being synthesized from glucose rather than being absorbed directly from the mother's blood. In addition to these generalities, there are special problems of fetal metabolism in relation to calcium, phosphate, iron, and some vitamins.

**Metabolism of Calcium and Phosphate.** Figure 83-2 shows the rates of calcium and phosphate accumulation in the fetus, demonstrating that about 22.5 grams of calcium and 13.5 grams of phosphorus are accumulated in the aver-

age fetus during gestation. About one half of these accumulate during the last 4 weeks of gestation, which is coincident with the period of rapid ossification of the fetal bones and with the period of rapid weight gain of the fetus.

During the earlier part of fetal life, the bones are relatively unossified and have mainly a cartilaginous matrix. Indeed, x-ray films ordinarily do not show any ossification until after the fourth month of pregnancy.

Note especially that the total amounts of calcium and phosphate needed by the fetus during gestation represent only about 2 percent of the quantities of these substances in the mother's bones. Therefore, this is a minimal drain from the mother. Much greater drain occurs after birth during lactation.

**Accumulation of Iron.** Figure 83-2 also shows that iron accumulates in the fetus even more rapidly than calcium and phosphate. Most of the iron is in the form of hemoglobin, which begins to be formed as early as the third week after fertilization of the ovum.

Small amounts of iron are concentrated in the mother's uterine prostegational endometrium even before implantation of the ovum; this iron is ingested into the embryo by the trophoblastic cells and is used to form the very early red blood cells. About one third of the iron in a fully developed fetus is normally stored in the liver. This iron can then be used for several months after birth by the neonate for formation of additional hemoglobin.

**Utilization and Storage of Vitamins.** The fetus needs vitamins equally as much as the adult and in some instances to a far greater extent. In general, the vitamins function the same in the fetus as in the adult, as discussed in Chapter 71. Special functions of several vitamins should be mentioned, however.

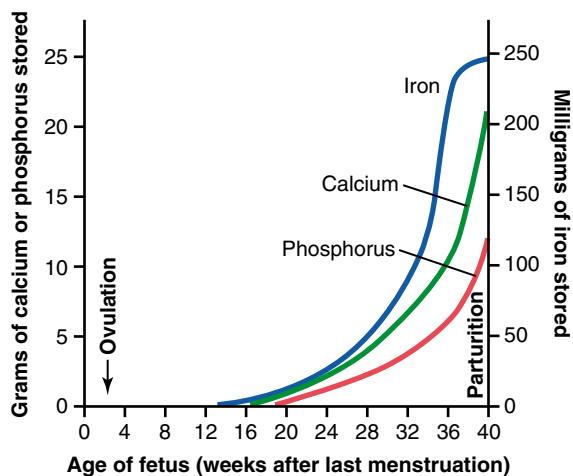
The B vitamins, especially vitamin B<sub>12</sub> and folic acid, are necessary for formation of red blood cells and nervous tissue, as well as for overall growth of the fetus.

Vitamin C is necessary for appropriate formation of intercellular substances, especially the bone matrix and fibers of connective tissue.

Vitamin D is necessary for normal bone growth in the fetus, but even more important, the mother needs it for adequate absorption of calcium from her gastrointestinal tract. If the mother has plenty of vitamin D in her body fluids, large quantities of the vitamin will be stored by the fetal liver to be used by the neonate for several months after birth.

Vitamin E, although the mechanisms of its functions are not entirely clear, is necessary for normal development of the early embryo. In its absence in laboratory animals, spontaneous abortion usually occurs at an early stage of pregnancy.

Vitamin K is used by the fetal liver for formation of Factor VII, prothrombin, and several other blood coagulation factors. When vitamin K is insufficient in the mother, Factor VII and prothrombin become deficient in the fetus and the mother. Because most vitamin K is formed by bacterial action in the mother's colon, the neonate has no adequate source of vitamin K for the first week or so of life after birth until normal colonic bacterial flora become established in the newborn infant. Therefore, prenatal storage in the fetal liver of at least small amounts of vitamin K derived from the mother is helpful in preventing fetal hemorrhage, particularly hemorrhage in the brain when the head is traumatized by squeezing through the birth canal.



**Figure 83-2** Iron, calcium, and phosphorus storage in the fetus at different stages of gestation.

## Adjustments of the Infant to Extrauterine Life

### Onset of Breathing

The most obvious effect of birth on the baby is loss of the placental connection with the mother and, therefore, loss of this means of metabolic support. One of the most important immediate adjustments required of the infant is to begin breathing.

**Cause of Breathing at Birth.** After normal delivery from a mother who has not been depressed by anesthetics, the child ordinarily begins to breathe within seconds and has a normal respiratory rhythm within less than 1 minute after birth. The promptness with which the fetus begins to breathe indicates that breathing is initiated by sudden exposure to the exterior world, probably resulting from (1) a slightly asphyxiated state incident to the birth process, but also from (2) sensory impulses that originate in the suddenly cooled skin. In an infant who does not breathe immediately, the body becomes progressively more hypoxic and hypercapnic, which provides additional stimulus to the respiratory center and usually causes breathing within an additional minute after birth.

**Delayed or Abnormal Breathing at Birth—Danger of Hypoxia.** If the mother has been depressed by a general anesthetic during delivery, which at least partially anesthetizes the fetus as well, the onset of respiration is likely to be delayed for several minutes, thus demonstrating the importance of using as little anesthesia as feasible. Also, many infants who have had head trauma during delivery or who undergo prolonged delivery are slow to breathe or sometimes do not breathe at all. This can result from two possible effects: First, in a few infants, intracranial hemorrhage or brain contusion causes a concussion syndrome with a greatly depressed respiratory center. Second, and probably much more important, prolonged fetal hypoxia during delivery can cause serious depression of the respiratory center.

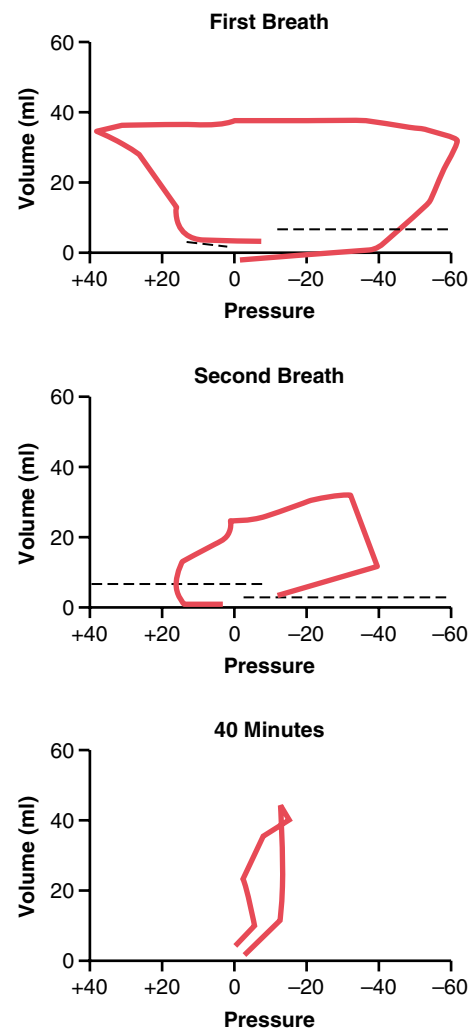
Hypoxia frequently occurs during delivery because of (1) compression of the umbilical cord; (2) premature separation of the placenta; (3) excessive contraction of the uterus, which can cut off the mother's blood flow to the placenta; or (4) excessive anesthesia of the mother, which depresses oxygenation even of her blood.

**Degree of Hypoxia That an Infant Can Tolerate.** In an adult, failure to breathe for only 4 minutes often causes death, but a neonate often survives as long as 10 minutes of failure to breathe after birth. Permanent and serious brain impairment often ensues if breathing is delayed more than 8 to 10 minutes. Indeed, actual lesions develop mainly in the thalamus, in the inferior colliculi, and in other brain stem areas, thus permanently affecting many of the motor functions of the body.

**Expansion of the Lungs at Birth.** At birth, the walls of the alveoli are at first collapsed because of the surface tension of the viscid fluid that fills them. More than 25 mm Hg of negative inspiratory pressure in the lungs is usually required to oppose the effects of this surface tension and to open the alveoli for the first time. But once the alveoli do open, further respiration can be effected with relatively weak respiratory movements. Fortunately, the first inspirations of the normal neonate are extremely powerful, usually capable of creating as much as 60 mm Hg negative pressure in the intrapleural space.

Figure 83-3 shows the tremendous negative intrapleural pressures required to open the lungs at the onset of breathing. At the top is shown the pressure-volume curve ("compliance" curve) for the first breath after birth. Observe, first, the lower part of the curve *beginning at the zero pressure point* and moving to the right. The curve shows that the volume of air in the lungs remains almost exactly zero until the negative pressure has reached  $-40$  centimeters water ( $-30$  mm Hg). Then, as the negative pressure increases to  $-60$  centimeters of water, about 40 milliliters of air enters the lungs. To deflate the lungs, considerable positive pressure, about  $+40$  centimeters of water, is required because of viscous resistance offered by the fluid in the bronchioles.

Note that the second breath is much easier, with far less negative and positive pressures required. Breathing does not become completely normal until about 40 minutes after birth, as shown by the third compliance curve, the shape of which compares favorably with that for the normal adult, as shown in Chapter 38.



**Figure 83-3** Pressure-volume curves of the lungs ("compliance" curves) of a neonate immediately after birth, showing the extreme forces required for breathing during the first two breaths of life and development of a nearly normal compliance curve within 40 minutes after birth. (Redrawn from Smith CA: The first breath. *Sci Am* 209:32, 1963, © 1963 by Scientific American, Inc. All rights reserved.)

**Respiratory Distress Syndrome Caused When Surfactant Secretion Is Deficient.** A small number of infants, especially premature infants and infants born of diabetic mothers, develop severe respiratory distress in the early hours to the first several days after birth, and some die within the next day or so. The alveoli of these infants at death contain large quantities of proteinaceous fluid, almost as if pure plasma had leaked out of the capillaries into the alveoli. The fluid also contains desquamated alveolar epithelial cells. This condition is called *hyaline membrane disease* because microscopic slides of the lung show the material filling the alveoli to look like a hyaline membrane.

A characteristic finding in respiratory distress syndrome is failure of the respiratory epithelium to secrete adequate quantities of *surfactant*, a substance normally secreted into the alveoli that decreases the surface tension of the alveolar fluid, therefore allowing the alveoli to open easily during inspiration. The surfactant-secreting cells (type II alveolar epithelial cells) do not begin to secrete surfactant until the last 1 to 3 months of gestation. Therefore, many premature babies and a few full-term babies are born without the capability to secrete sufficient surfactant, which causes both a collapse tendency of the alveoli and development of pulmonary edema. The role of surfactant in preventing these effects is discussed in Chapter 37.

### Circulatory Readjustments at Birth

Equally as essential as the onset of breathing at birth are immediate circulatory adjustments that allow adequate blood flow through the lungs. Also, circulatory adjustments during the first few hours of life cause more and more blood flow through the baby's liver, which up to this point has had little blood flow. To describe these readjustments, we must first consider the anatomical structure of the fetal circulation.

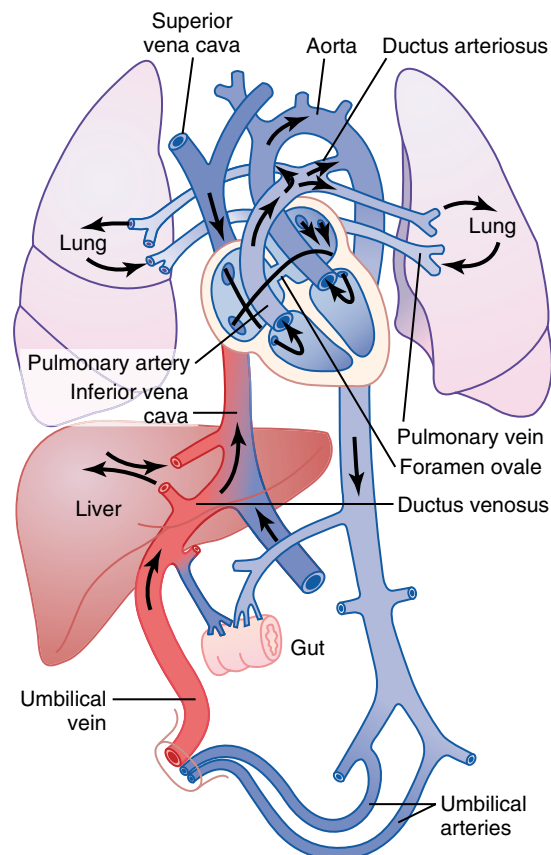
#### Specific Anatomical Structure of the Fetal Circulation.

Because the lungs are mainly nonfunctional during fetal life and because the liver is only partially functional, it is not necessary for the fetal heart to pump much blood through either the lungs or the liver. However, the fetal heart must pump large quantities of blood through the placenta. Therefore, special anatomical arrangements cause the fetal circulatory system to operate much differently from that of the newborn baby.

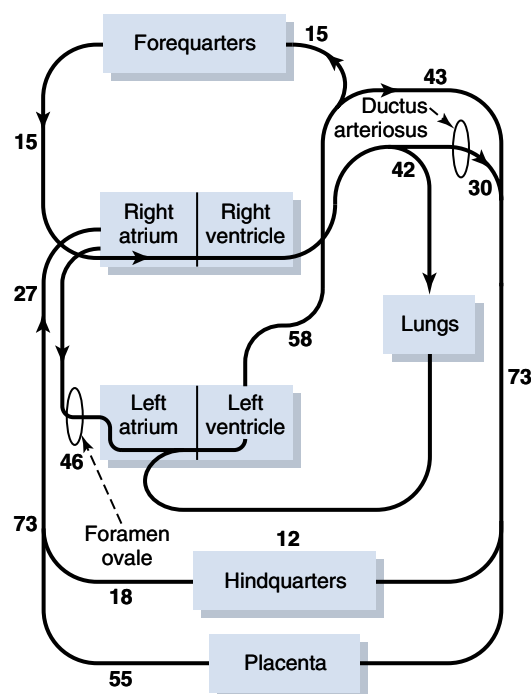
First, as shown in Figure 83-4, blood returning from the placenta through the umbilical vein passes through the *ductus venosus*, mainly bypassing the liver. Then most of the blood entering the right atrium from the inferior vena cava is directed in a straight pathway across the posterior aspect of the right atrium and through the *foramen ovale* directly into the left atrium. Thus, the well-oxygenated blood from the placenta enters mainly the left side of the heart, rather than the right side, and is pumped by the left ventricle mainly into the arteries of the head and forelimbs.

The blood entering the right atrium from the superior vena cava is directed downward through the tricuspid valve into the right ventricle. This blood is mainly deoxygenated blood from the head region of the fetus. It is pumped by the right ventricle into the pulmonary artery and then mainly through the *ductus arteriosus* into the descending aorta, then through the two umbilical arteries into the placenta, where the deoxygenated blood becomes oxygenated.

Figure 83-5 gives the relative percentages of the total blood pumped by the heart that pass through the different vascular



**Figure 83-4** Organization of the fetal circulation. (Modified from Arey LB: *Developmental Anatomy: A Textbook and Laboratory Manual of Embryology*, 7th ed. Philadelphia: WB Saunders, 1974.)



**Figure 83-5** Diagram of the fetal circulatory system, showing relative distribution of blood flow to the different vascular areas. The numerals represent the percentage of the total output from both sides of the heart that pass through each particular area.



circuits of the fetus. This figure shows that 55 percent of all the blood goes through the placenta, leaving only 45 percent to pass through all the tissues of the fetus. Furthermore, during fetal life, only 12 percent of the blood flows through the lungs; immediately after birth, virtually all the blood flows through the lungs.

**Changes in the Fetal Circulation at Birth.** The basic changes in the fetal circulation at birth are discussed in Chapter 23 in relation to congenital anomalies of the ductus arteriosus and foramen ovale that persist throughout life in a few persons. Briefly, these changes are the following.

**Decreased Pulmonary and Increased Systemic Vascular Resistances at Birth.** The primary changes in the circulation at birth are, first, loss of the tremendous blood flow through the placenta, which approximately doubles the systemic vascular resistance at birth. This increases the aortic pressure, as well as the pressures in the left ventricle and left atrium.

Second, the *pulmonary vascular resistance greatly decreases* as a result of expansion of the lungs. In the unexpanded fetal lungs, the blood vessels are compressed because of the small volume of the lungs. Immediately on expansion, these vessels are no longer compressed and the resistance to blood flow decreases severalfold. Also, in fetal life, the hypoxia of the lungs causes considerable tonic vasoconstriction of the lung blood vessels, but vasodilation takes place when aeration of the lungs eliminates the hypoxia. All these changes together reduce the resistance to blood flow through the lungs as much as fivefold, which *reduces the pulmonary arterial pressure, right ventricular pressure, and right atrial pressure.*

**Closure of the Foramen Ovale.** The *low right atrial pressure* and the *high left atrial pressure* that occur secondarily to the changes in pulmonary and systemic resistances at birth cause blood now to attempt to flow backward through the foramen ovale; that is, from the left atrium into the right atrium, rather than in the other direction, as occurred during fetal life. Consequently, the small valve that lies over the foramen ovale on the left side of the atrial septum closes over this opening, thereby preventing further flow through the foramen ovale.

In two thirds of all people, the valve becomes adherent over the foramen ovale within a few months to a few years and forms a permanent closure. But even if permanent closure does not occur, the left atrial pressure throughout life normally remains 2 to 4 mm Hg greater than the right atrial pressure and the backpressure keeps the valve closed.

**Closure of the Ductus Arteriosus.** The ductus arteriosus also closes, but for different reasons. First, the increased systemic resistance elevates the aortic pressure while the decreased pulmonary resistance reduces the pulmonary arterial pressure. As a consequence, after birth, blood begins to flow backward from the aorta into the pulmonary artery through the ductus arteriosus, rather than in the other direction, as in fetal life. However, after only a few hours, the muscle wall of the ductus arteriosus constricts markedly and within 1 to 8 days, the constriction is usually sufficient to stop all blood flow. This is called *functional closure* of the ductus arteriosus. Then, during the next 1 to 4 months, the ductus arteriosus ordinarily becomes anatomically occluded by growth of fibrous tissue into its lumen.

The cause of ductus arteriosus closure relates to the increased oxygenation of the blood flowing through the ductus. In fetal life the  $\text{PO}_2$  of the ductus blood is only 15 to

20 mm Hg, but it increases to about 100 mm Hg within a few hours after birth. Furthermore, many experiments have shown that the degree of contraction of the smooth muscle in the ductus wall is highly related to this availability of oxygen.

In one of several thousand infants, the ductus fails to close, resulting in a *patent ductus arteriosus*, the consequences of which are discussed in Chapter 23. The failure of closure has been postulated to result from excessive ductus dilation caused by vasodilating prostaglandins in the ductus wall. In fact, administration of the drug *indomethacin*, which blocks synthesis of prostaglandins, often leads to closure.

**Closure of the Ductus Venosus.** In fetal life the portal blood from the fetus's abdomen joins the blood from the umbilical vein, and these together pass by way of the *ductus venosus* directly into the vena cava immediately below the heart but above the liver, thus bypassing the liver.

Immediately after birth, blood flow through the umbilical vein ceases, but most of the portal blood still flows through the ductus venosus, with only a small amount passing through the channels of the liver. However, within 1 to 3 hours the muscle wall of the ductus venosus contracts strongly and closes this avenue of flow. As a consequence, the portal venous pressure rises from near 0 to 6 to 10 mm Hg, which is enough to force portal venous blood flow through the liver sinuses. Although the ductus venosus rarely fails to close, we know almost nothing about what causes the closure.

### Nutrition of the Neonate

Before birth, the fetus derives almost all its energy from glucose obtained from the mother's blood. After birth, the amount of glucose stored in the infant's body in the form of liver and muscle glycogen is sufficient to supply the infant's needs for only a few hours. The liver of the neonate is still far from functionally adequate at birth, which prevents significant gluconeogenesis. Therefore, the infant's blood glucose concentration frequently falls the first day to as low as 30 to 40 mg/dl of plasma, less than half the normal value. Fortunately, however, appropriate mechanisms are available for the infant to use its stored fats and proteins for metabolism until mother's milk can be provided 2 to 3 days later.

Special problems are also frequently associated with getting an adequate fluid supply to the neonate because the infant's rate of body fluid turnover averages seven times that of an adult, and the mother's milk supply requires several days to develop. Ordinarily, the infant's weight decreases 5 to 10 percent and sometimes as much as 20 percent within the first 2 to 3 days of life. Most of this weight loss is loss of fluid rather than of body solids.

### Special Functional Problems in the Neonate

An important characteristic of the neonate is instability of the various hormonal and neurogenic control systems. This results partly from immature development of the different organs of the body and partly from the fact that the control systems simply have not become adjusted to the new way of life.

### Respiratory System

The normal rate of respiration in a neonate is about 40 breaths per minute, and tidal air with each breath averages 16 milliliters. This gives a total minute respiratory volume of 640 ml/min, which is about twice as great in relation to the body weight as that of an adult. *The functional residual capacity of the infant's lungs is only one-half that of an adult in relation to body weight.* This difference causes excessive cyclical increases and decreases in the newborn baby's blood gas concentrations if the respiratory rate becomes slowed because it is the residual air in the lungs that smoothes out the blood gas variations.

### Circulation

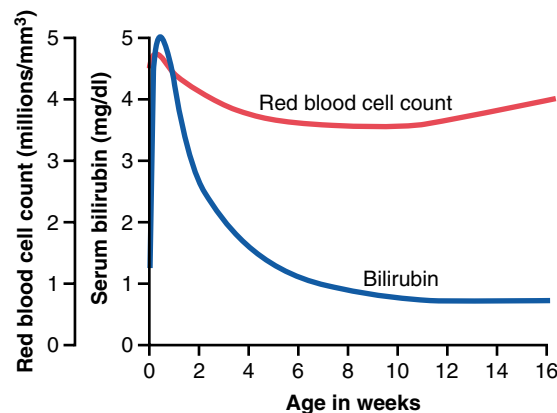
**Blood Volume.** The blood volume of a neonate immediately after birth averages about 300 milliliters, but if the infant is left attached to the placenta for a few minutes after birth or if the umbilical cord is stripped to force blood out of its vessels into the baby, an additional 75 milliliters of blood enters the infant, to make a total of 375 milliliters. Then, during the ensuing few hours, fluid is lost into the neonate's tissue spaces from this blood, which increases the hematocrit but returns the blood volume once again to the normal value of about 300 milliliters. Some pediatricians believe that this extra blood volume caused by stripping the umbilical cord can lead to mild pulmonary edema with some degree of respiratory distress, but the extra red blood cells are often valuable to the infant.

**Cardiac Output.** The cardiac output of the neonate averages 500 ml/min, which, like respiration and body metabolism, is about twice as much in relation to body weight as in the adult. Occasionally a child is born with an especially low cardiac output caused by hemorrhage of much of its blood volume from the placenta at birth.

**Arterial Pressure.** The arterial pressure during the first day after birth averages about 70 mm Hg systolic and 50 mm Hg diastolic; this increases slowly during the next several months to about 90/60. Then there is a much slower rise during the subsequent years until the adult pressure of 115/70 is attained at adolescence.

**Blood Characteristics.** The red blood cell count in the neonate averages about 4 million per cubic millimeter. If blood is stripped from the cord into the infant, the red blood cell count rises an additional 0.5 to 0.75 million during the first few hours of life, giving a red blood cell count of about 4.75 million per cubic millimeter, as shown in Figure 83-6. Subsequent to this, however, few new red blood cells are formed in the infant during the first few weeks of life, presumably because the hypoxic stimulus of fetal life is no longer present to stimulate red cell production. Thus, as shown in Figure 83-6, the average red blood cell count falls to less than 4 million per cubic millimeter by about 6 to 8 weeks of age. From that time on, increasing activity by the baby provides the appropriate stimulus for returning the red blood cell count to normal within another 2 to 3 months. Immediately after birth, the white blood cell count of the neonate is about 45,000 per cubic millimeter, which is about five times as great as that of the normal adult.

**Neonatal Jaundice and Erythroblastosis Fetalis.** Bilirubin formed in the fetus can cross the placenta into the mother and be excreted through the liver of the mother, but immediately after birth, the only means for ridding the neonate of bilirubin is through the neonate's own liver, which



**Figure 83-6** Changes in the red blood cell count and in serum bilirubin concentration during the first 16 weeks of life, showing physiological anemia at 6 to 12 weeks of life and physiological hyperbilirubinemia during the first 2 weeks of life.

for the first week or so of life functions poorly and is incapable of conjugating significant quantities of bilirubin with glucuronic acid for excretion into the bile. Consequently, the plasma bilirubin concentration rises from a normal value of less than 1 mg/dl to an average of 5 mg/dl during the first 3 days of life and then gradually falls back to normal as the liver becomes functional. This effect, called *physiological hyperbilirubinemia*, is shown in Figure 83-6, and it is associated with mild *jaundice* (yellowness) of the infant's skin and especially of the sclerae of its eyes for a week or two.

However, by far the most important abnormal cause of serious neonatal jaundice is *erythroblastosis fetalis*, which is discussed in detail in Chapter 32 in relation to Rh factor incompatibility between the fetus and mother. Briefly, the *erythroblastic baby* inherits Rh-positive red cells from the father, while the mother is Rh negative. The mother then becomes immunized against the Rh-positive factor (a protein) in the fetus's blood cells, and her antibodies destroy fetal red cells, releasing extreme quantities of bilirubin into the fetus's plasma and often causing fetal death for lack of adequate red cells. Before the advent of modern obstetrical therapeutics, this condition occurred either mildly or seriously in 1 of every 50 to 100 neonates.

### Fluid Balance, Acid-Base Balance, and Renal Function

The rate of fluid intake and fluid excretion in the newborn infant is seven times as great in relation to weight as in the adult, which means that even a slight percentage alteration of fluid intake or fluid output can cause rapidly developing abnormalities.

The rate of metabolism in the infant is also twice as great in relation to body mass as in the adult, which means that twice as much acid is normally formed, creating a tendency toward acidosis in the infant. Functional development of the kidneys is not complete until the end of about the first month of life. For instance, the kidneys of the neonate can concentrate urine to only 1.5 times the osmolality of the plasma, whereas the adult can concentrate the urine to three to four times the plasma osmolality. Therefore, considering the immaturity of the kidneys, together with the marked fluid turnover in the infant and rapid formation of acid, one can readily understand that among the most important problems of infancy are acidosis, dehydration, and, more rarely, overhydration.

### Liver Function

During the first few days of life, liver function in the neonate may be quite deficient, as evidenced by the following effects:

1. The liver of the neonate conjugates bilirubin with glucuronic acid poorly and therefore excretes bilirubin only slightly during the first few days of life.
2. The liver of the neonate is deficient in forming plasma proteins, so the plasma protein concentration falls during the first weeks of life to 15 to 20 percent less than that for older children. Occasionally the protein concentration falls so low that the infant develops hypoproteinemic edema.
3. The gluconeogenesis function of the liver is particularly deficient. As a result, the blood glucose level of the unfed neonate falls to about 30 to 40 mg/dl (about 40 percent of normal) and the infant must depend mainly on its stored fats for energy until sufficient feeding can occur.
4. The liver of the neonate usually also forms too little of the blood factors needed for normal blood coagulation.

### Digestion, Absorption, and Metabolism of Energy Foods; and Nutrition

In general, the ability of the neonate to digest, absorb, and metabolize foods is no different from that of the older child, with the following three exceptions.

First, *secretion of pancreatic amylase in the neonate is deficient*, so the neonate uses starches less adequately than do older children.

Second, *absorption of fats from the gastrointestinal tract is somewhat less than that in the older child*. Consequently, milk with a high fat content, such as cow's milk, is frequently inadequately absorbed.

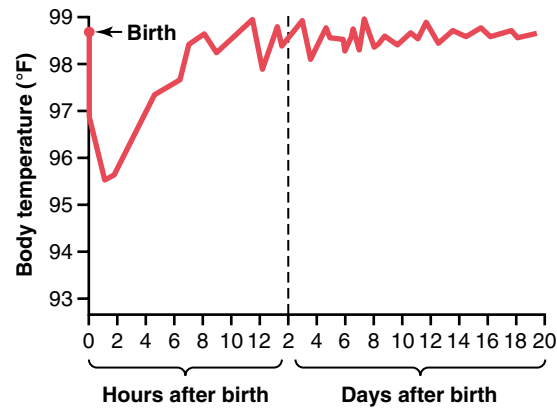
Third, because the liver functions imperfectly during at least the first week of life, *the glucose concentration in the blood is unstable and low*.

The neonate is especially capable of synthesizing and storing proteins. Indeed, with an adequate diet, up to 90 percent of the ingested amino acids is used for formation of body proteins. This is a much higher percentage than in adults.

**Increased Metabolic Rate and Poor Body Temperature Regulation.** The normal metabolic rate of the neonate in relation to body weight is about twice that of the adult, which accounts also for the twice as great cardiac output and twice as great minute respiratory volume in relation to body weight in the infant.

Because the body surface area is large in relation to body mass, heat is readily lost from the body. As a result, the body temperature of the neonate, particularly of premature infants, falls easily. Figure 83-7 shows that the body temperature of even a normal infant often falls several degrees during the first few hours after birth but returns to normal in 7 to 10 hours. Still, the body temperature regulatory mechanisms remain poor during the early days of life, allowing marked deviations in temperature, which are also shown in Figure 83-7.

**Nutritional Needs During the Early Weeks of Life.** At birth, a neonate is usually in complete nutritional balance, provided the mother has had an adequate diet. Furthermore, function of the gastrointestinal system is usually more than adequate to digest and assimilate all the nutritional needs of the infant if appropriate nutrients are provided in the diet.



**Figure 83-7** Fall in body temperature of the neonate immediately after birth, and instability of body temperature during the first few days of life.

However, three specific problems do occur in the early nutrition of the infant.

**Need for Calcium and Vitamin D.** The neonate is in a stage of rapid ossification of its bones at birth, so a ready supply of calcium throughout infancy is necessary. This is ordinarily supplied adequately by the usual diet of milk. Yet absorption of calcium by the gastrointestinal tract is poor in the absence of vitamin D. Therefore, the vitamin D–deficient infant can develop severe rickets in only a few weeks. This is particularly true in premature babies because their gastrointestinal tracts absorb calcium even less effectively than those of normal infants.

**Necessity for Iron in the Diet.** If the mother has had adequate amounts of iron in her diet, the liver of the infant usually has stored enough iron to keep forming blood cells for 4 to 6 months after birth. But if the mother has had insufficient iron in her diet, severe anemia is likely to occur in the infant after about 3 months of life. To prevent this possibility, early feeding of the infant with egg yolk, which contains reasonably large quantities of iron, or the administration of iron in some other form is desirable by the second or third month of life.

**Vitamin C Deficiency in Infants.** Ascorbic acid (vitamin C) is not stored in significant quantities in the fetal tissues, yet it is required for proper formation of cartilage, bone, and other intercellular structures of the infant. Furthermore, milk provides only small supplies of ascorbic acid, especially cow's milk, which has only one fourth as much as human milk. For this reason, orange juice or other sources of ascorbic acid are often prescribed by the third week of life.

### Immunity

The neonate inherits much immunity from the mother because many protein antibodies diffuse from the mother's blood through the placenta into the fetus. However, the neonate does not form antibodies of its own to a significant extent. By the end of the first month, the baby's gamma globulins, which contain the antibodies, have decreased to less than half the original level, with a corresponding decrease in immunity. Thereafter, the baby's own immunity system begins to form antibodies and the gamma globulin concentration returns essentially to normal by the age of 12 to 20 months.

Despite the decrease in gamma globulins soon after birth, the antibodies inherited from the mother protect the infant for about 6 months against most major childhood infectious diseases, including diphtheria, measles, and polio. Therefore, immunization against these diseases before 6 months is usually unnecessary. Conversely, the inherited antibodies against whooping cough are normally insufficient to protect the neonate; therefore, for full safety, the infant requires immunization against this disease within the first month or so of life.

**Allergy.** The newborn infant is seldom subject to allergy. Several months later, however, when the infant's own antibodies first begin to form, extreme allergic states can develop, often resulting in serious eczema, gastrointestinal abnormalities, and even anaphylaxis. As the child grows older and still higher degrees of immunity develop, these allergic manifestations usually disappear. This relation of immunity to allergy is discussed in Chapter 34.

### Endocrine Problems

Ordinarily, the endocrine system of the infant is highly developed at birth, and the infant seldom exhibits any immediate endocrine abnormalities. However, there are special instances in which the endocrinology of infancy is important:

1. If a pregnant mother bearing a female child is treated with an androgenic hormone or if an androgenic tumor develops during pregnancy, the child will be born with a high degree of masculinization of her sexual organs, thus resulting in a type of *hermaphroditism*.
2. The sex hormones secreted by the placenta and by the mother's glands during pregnancy occasionally cause the neonate's breasts to form milk during the first days of life. Sometimes the breasts then become inflamed, or infectious mastitis develops.
3. An infant born of an untreated diabetic mother will have considerable hypertrophy and hyperfunction of the islets of Langerhans in the pancreas. As a consequence, the infant's blood glucose concentration may fall to lower than 20 mg/dl shortly after birth. Fortunately, however, in the neonate, unlike in the adult, insulin shock or coma from this low level of blood glucose concentration only rarely develops.

Maternal type II diabetes is the most common cause of large babies. Type II diabetes in the mother is associated with resistance to the metabolic effects of insulin and compensatory increases in plasma insulin concentration. The high levels of insulin are believed to stimulate fetal growth and contribute to increased birth weight. Increased supply of glucose and other nutrients to the fetus may also contribute to increased fetal growth. However, most of the increased fetal weight is due to increased body fat; there is usually little increase in body length, although the size of some organs may be increased (*organomegaly*).

In the mother with uncontrolled type I diabetes (caused by lack of insulin secretion), fetal growth may be stunted because of metabolic deficits in the mother and growth and tissue maturation of the neonate are often impaired. Also, there is a high rate of intrauterine mortality. Among the fetuses that do come to term, there is still a high mortality rate. Two thirds of the infants who die succumb to *respiratory distress syndrome*, described earlier in the chapter.

4. Occasionally a child is born with hypofunctional adrenal cortices, often resulting from *agenesis* of the adrenal glands or *exhaustion atrophy*, which can occur when the adrenal glands have been vastly overstimulated.
5. If a pregnant woman has hyperthyroidism or is treated with excess thyroid hormone, the infant is likely to be born with a temporarily hyposecreting thyroid gland. Conversely, if before pregnancy a woman had had her thyroid gland removed, her pituitary gland may secrete great quantities of thyrotropin during gestation and the child might be born with temporary hyperthyroidism.
6. In a fetus lacking thyroid hormone secretion, the bones grow poorly and there is mental retardation. This causes the condition called *cretin dwarfism*, discussed in Chapter 76.

### Special Problems of Prematurity

All the problems in neonatal life just noted are severely exacerbated in prematurity. They can be categorized under the following two headings: (1) immaturity of certain organ systems and (2) instability of the different homeostatic control systems. Because of these effects, a premature baby seldom lives if it is born more than 3 months before term.

#### Immature Development of the Premature Infant

Almost all the organ systems of the body are immature in the premature infant and require particular attention if the life of the premature baby is to be saved.

**Respiration.** The respiratory system is especially likely to be underdeveloped in the premature infant. The vital capacity and the functional residual capacity of the lungs are especially small in relation to the size of the infant. Also, surfactant secretion is depressed or absent. As a consequence, *respiratory distress syndrome* is a common cause of death. Also, the low functional residual capacity in the premature infant is often associated with periodic breathing of the Cheyne-Stokes type.

**Gastrointestinal Function.** Another major problem of the premature infant is to ingest and absorb adequate food. If the infant is more than 2 months premature, the digestive and absorptive systems are almost always inadequate. The absorption of fat is so poor that the premature infant must have a low-fat diet. Furthermore, the premature infant has unusual difficulty in absorbing calcium and, therefore, can develop severe rickets before the difficulty is recognized. For this reason, special attention must be paid to adequate calcium and vitamin D intake.

**Function of Other Organs.** Immaturity of other organ systems that frequently causes serious difficulties in the premature infant includes (1) immaturity of the liver, which results in poor intermediary metabolism and often a bleeding tendency as a result of poor formation of coagulation factors; (2) immaturity of the kidneys, which are particularly deficient in their ability to rid the body of acids, thereby predisposing to acidosis and to serious fluid balance abnormalities; (3) immaturity of the blood-forming mechanism of the bone marrow, which allows rapid development of anemia; and (4) depressed formation of gamma globulin by the lymphoid system, which often leads to serious infection.



### Instability of the Homeostatic Control Systems in the Premature Infant

Immaturity of the different organ systems in the premature infant creates a high degree of instability in the homeostatic mechanisms of the body. For instance, the acid-base balance can vary tremendously, particularly when the rate of food intake varies from time to time. Likewise, the blood protein concentration is usually low because of immature liver development, often leading to *hypoproteinemic edema*. And inability of the infant to regulate its calcium ion concentration may bring on hypocalcemic tetany. Also, the blood glucose concentration can vary between the extremely wide limits of 20 to more than 100 mg/dl, depending principally on the regularity of feeding. It is no wonder, then, with these extreme variations in the internal environment of the premature infant, that mortality is high if a baby is born 3 or more months prematurely.

**Instability of Body Temperature.** One of the particular problems of the premature infant is inability to maintain normal body temperature. Its temperature tends to approach that of its surroundings. At normal room temperature, the infant's temperature may stabilize in the low 90's or even in the 80's°F. Statistical studies show that a body temperature maintained below 96°F (35.5°C) is associated with a particularly high incidence of death, which explains the almost mandatory use of the incubator in treatment of prematurity.

### Danger of Blindness Caused by Excess Oxygen Therapy in the Premature Infant

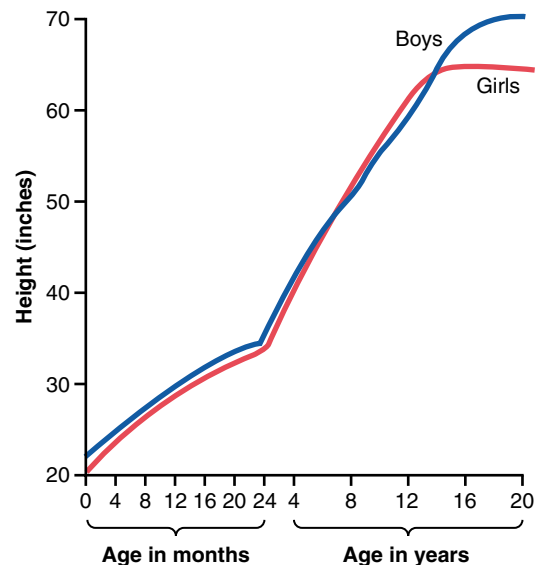
Because premature infants frequently develop respiratory distress, oxygen therapy has often been used in treating prematurity. However, it has been discovered that use of excess oxygen in treating premature infants, especially in early prematurity, can lead to blindness. The reason is that too much oxygen stops the growth of new blood vessels in the retina. Then when oxygen therapy is stopped, the blood vessels try to make up for lost time and burst forth with a great mass of vessels growing all through the vitreous humor, blocking light from the pupil to the retina. And later, the vessels are replaced with a mass of fibrous tissue where the eye's clear vitreous humor should be.

This condition is known as *retrolental fibroplasias* and causes permanent blindness. For this reason, it is particularly important to avoid treatment of premature infants with high concentrations of respiratory oxygen. Physiologic studies indicate that the premature infant is usually safe with up to 40 percent oxygen in the air breathed, but some child physiologists believe that complete safety can be achieved only at normal oxygen concentration in the air that is breathed.

### Growth and Development of the Child

The major physiologic problems of the child beyond the neonatal period are related to special metabolic needs for growth, which have been fully covered in the sections of this book on metabolism and endocrinology.

Figure 83-8 shows the changes in heights of boys and girls from the time of birth until the age of 20 years. Note especially that these parallel each other almost exactly until the end of the first decade of life. Between the ages of 11 and 13 years, the female estrogens begin to be formed and cause rapid growth in height but early uniting of the epiphyses

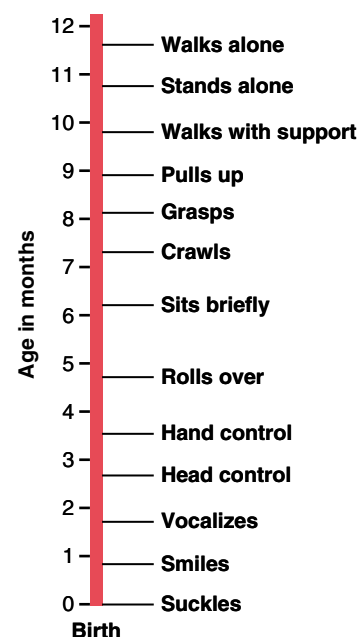


**Figure 83-8** Average height of boys and girls from infancy to 20 years of age.

of the long bones at about the 14th to 16th year of life, so growth in height then ceases. This contrasts with the effect of testosterone in the male, which causes extra growth at a slightly later age—mainly between ages 13 and 17 years. The male, however, undergoes more prolonged growth because of delayed uniting of the epiphyses, so his final height is considerably greater than that of the female.

### Behavioral Growth

Behavioral growth is principally a problem of maturity of the nervous system. It is difficult to dissociate maturity of the anatomical structures of the nervous system from maturity caused by training. Anatomical studies show that certain major tracts in the central nervous system are not completely myelinated until the end of the first year of life. For this reason, it is frequently stated that the nervous system is not



**Figure 83-9** Behavioral development of the infant during the first year of life.

fully functional at birth. The brain cortex and its associated functions, such as vision, seem to require several months after birth for final functional development to occur.

At birth, the infant brain mass is only 26 percent of the adult brain mass and 55 percent at 1 year, but it reaches almost adult proportions by the end of the second year. This is also associated with closure of the fontanelles and sutures of the skull, which allows only 20 percent additional growth of the brain beyond the first 2 years of life. Figure 83-9 shows a normal progress chart for the infant during the first year of life. Comparison of this chart with the baby's actual development is used for clinical assessment of mental and behavioral growth.

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