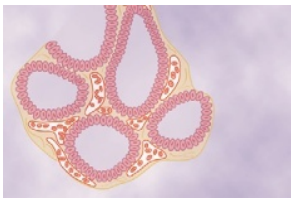
Thyroid Metabolic Hormones



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.

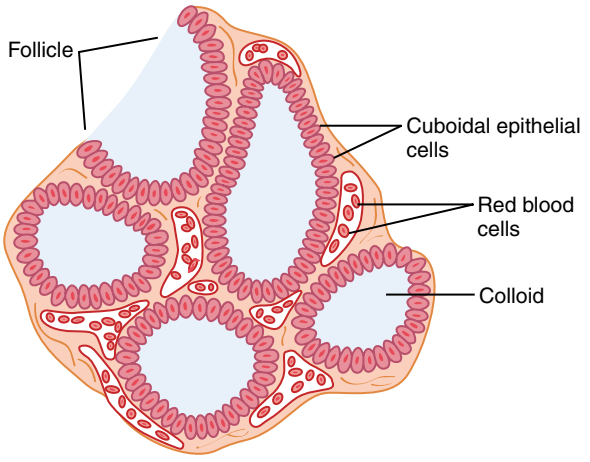


Figure 76-1 Microscopic appearance of the thyroid gland, showing secretion of thyroglobulin into the follicles.

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-transports 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

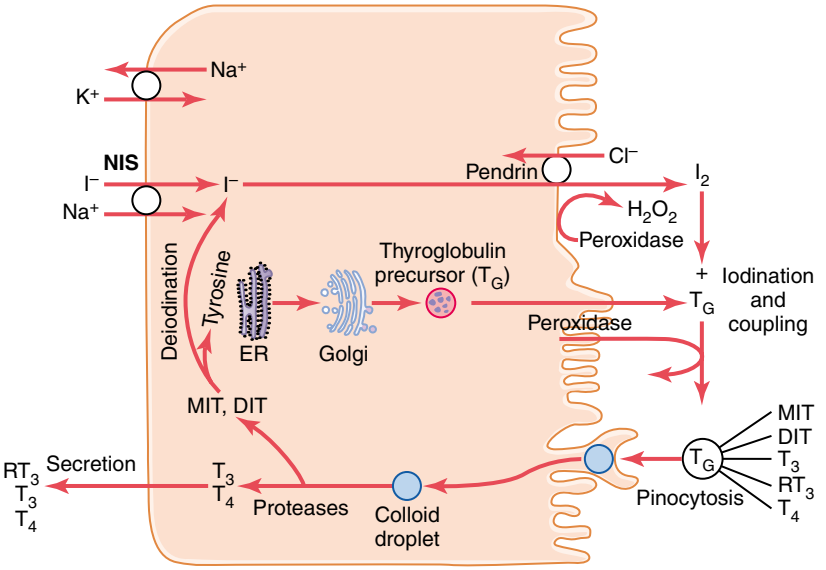


Figure 76-2 Thyroid cellular mechanisms for iodine transport, thyroxine and triiodothyronine formation, and thyroxine and triiodothyronine release into the blood. DIT, diiodotyrosine; MIT, monoiodotyrosine; NIS, sodium-iodide symporter; RT_3, reverse triiodothyronine; T_3, triiodothyronine; T_4, thyroxine;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

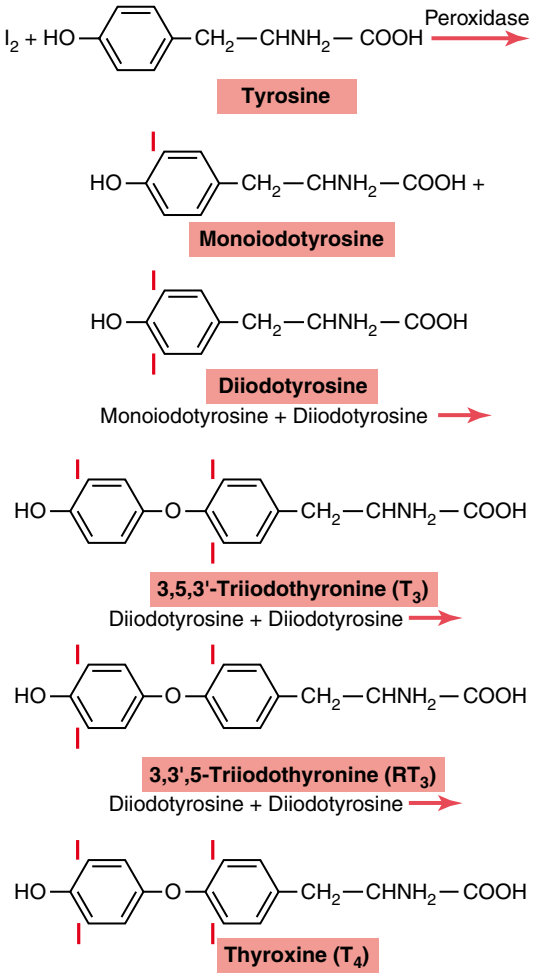


Figure 76-3 Chemistry of thyroxine and triiodothyronine formation.

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.

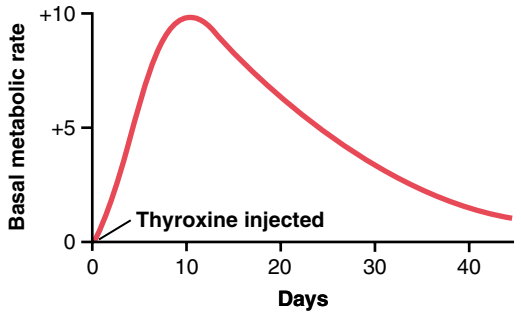


Figure 76-4 Approximate prolonged effect on the basal metabolic rate caused by administering a single large dose of thyroxine.

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.

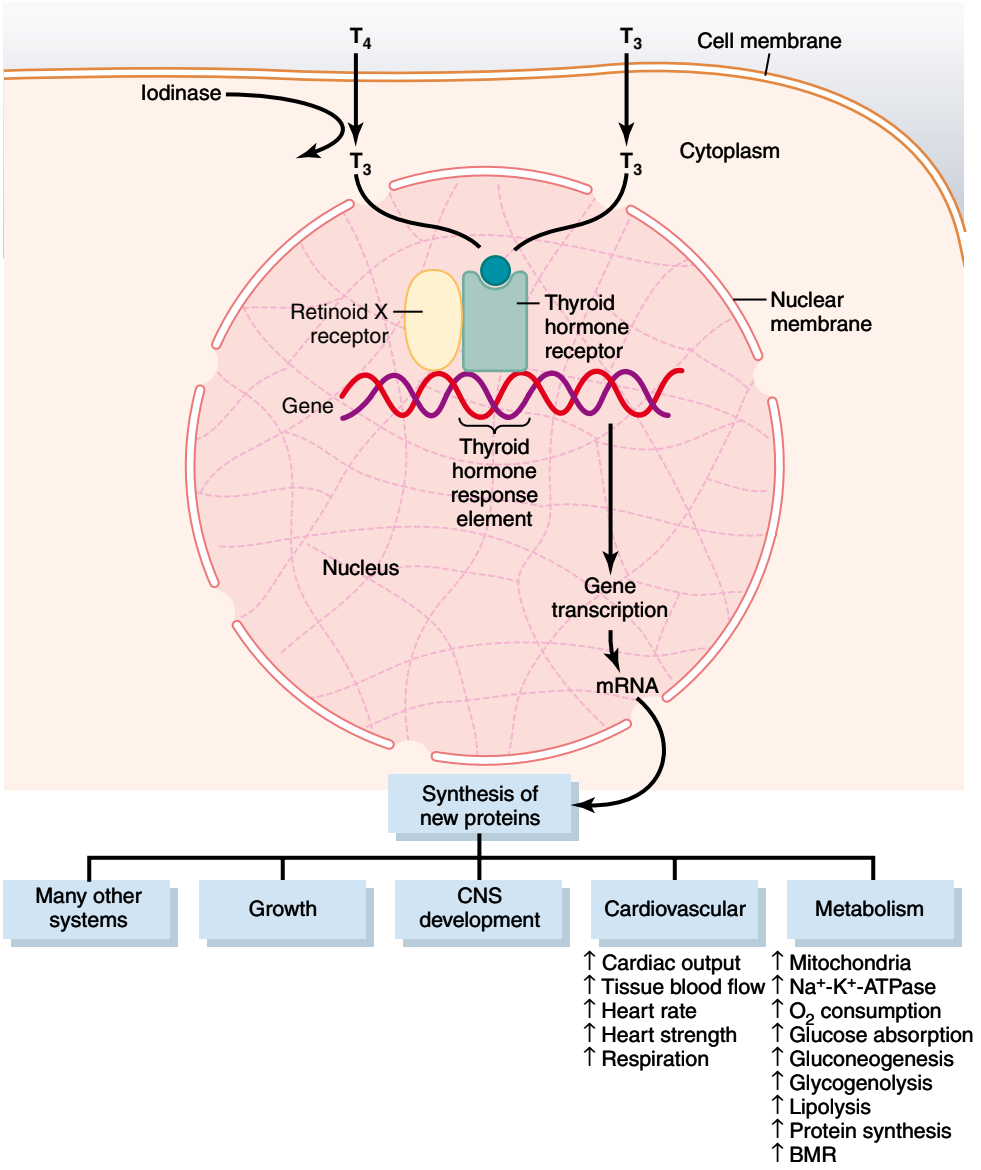


Figure 76-5 Thyroid hormone activation of target cells. Thyroxine (T_4) and triiodothyronine (T_3) readily diffuse through the cell membrane. Much of the T_4 is deiodinated to form T_3, which interacts with the thyroid hormone receptor, bound as a heterodimer with a retinoid X receptor, of the thyroid 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.

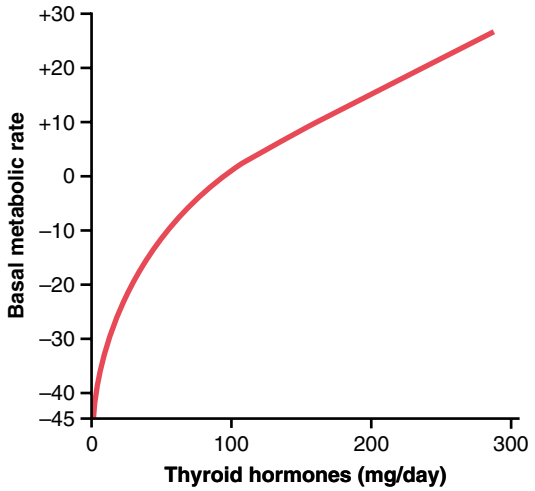


Figure 76-6 Approximate relation of daily rate of thyroid hormone (T_4 and T_3) secretion to the basal metabolic rate.

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 adrenocorticotropic 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-hypophysial 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 hypophysial 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.

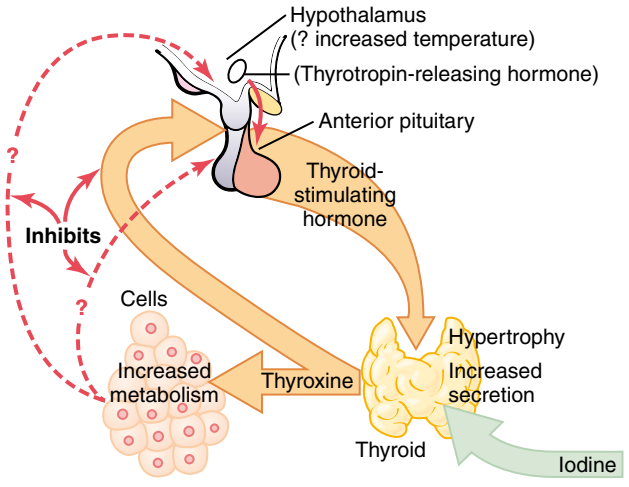


Figure 76-7 Regulation of thyroid secretion.

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.

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 severalfold; 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 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.

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.)

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 foodstuffs 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

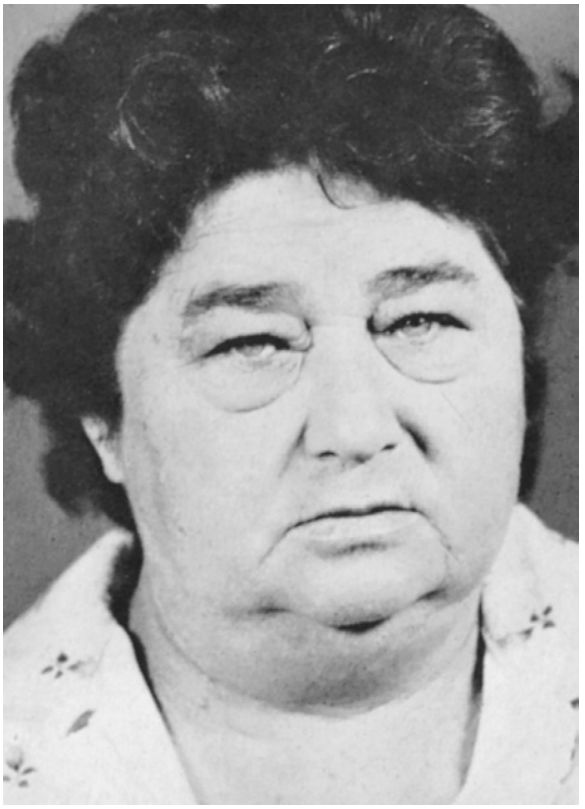


Figure 76-9 Patient with myxedema. (Courtesy Dr. Herbert Langford.)

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 populaces 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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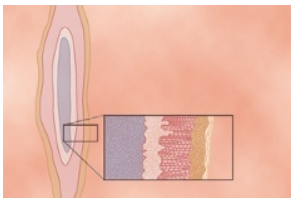
CHAPTER 77

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

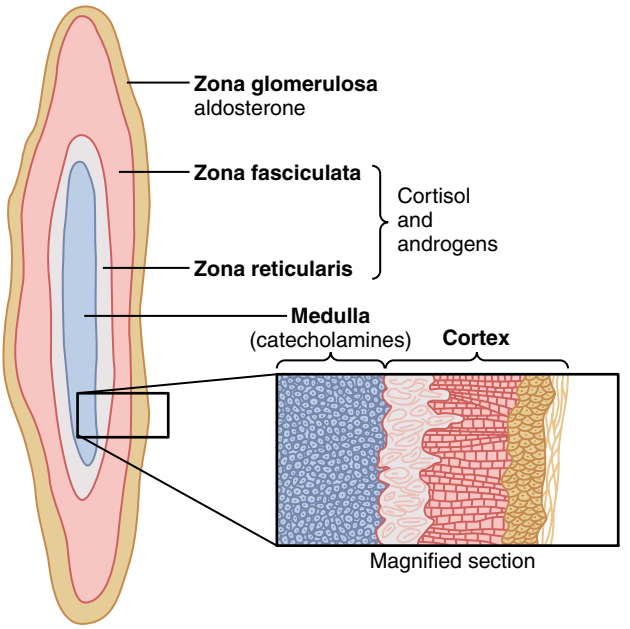


Figure 77-1 Secretion of adrenocortical hormones by the different zones of the adrenal cortex and secretion of catecholamines by the adrenal medulla.

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 *adrenocorticotropic 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)
- 9α-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

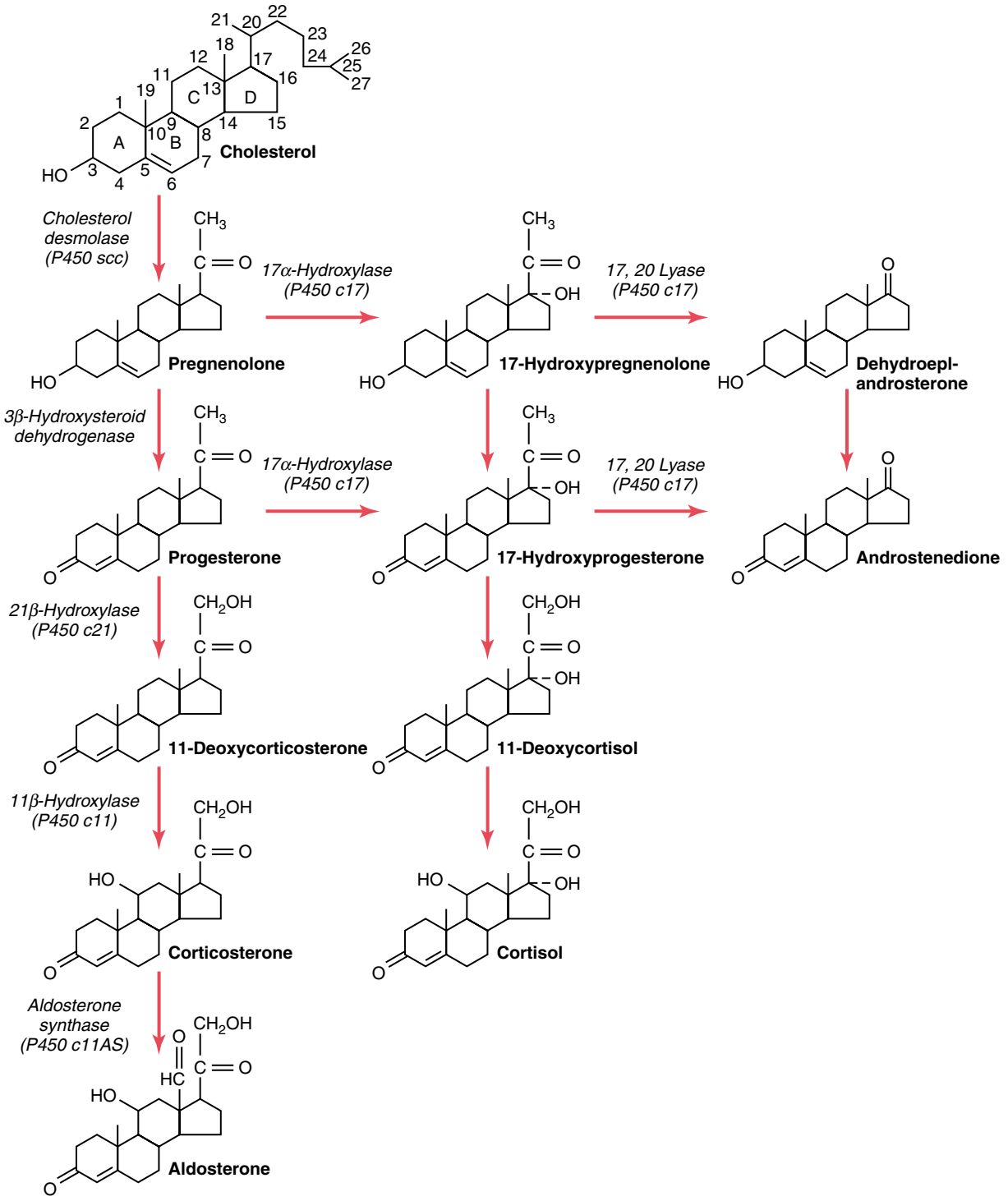


Figure 77-2 Pathways for synthesis of steroid hormones by the adrenal cortex. The enzymes are shown in italics.

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, μg/100 ml)	Average Amount Secreted (mg/24 hr)	Glucocorticoid Activity	Mineralocorticoid Activity
Adrenal Steroids				
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	—	—
Synthetic Steroids				
Cortisone	—	—	0.8	1.0
Prednisolone	—	—	4	0.8
Methylprednisone	—	—	5	—
Dexamethasone	—	—	30	—
9α-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 μg/day (0.15 mg/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 μg/100 ml, and the secretory rate averages 15 to 20 mg/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 11β-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 11β-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 glycyrrhetinic acid, may also cause AME due to its ability to block 11β-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).

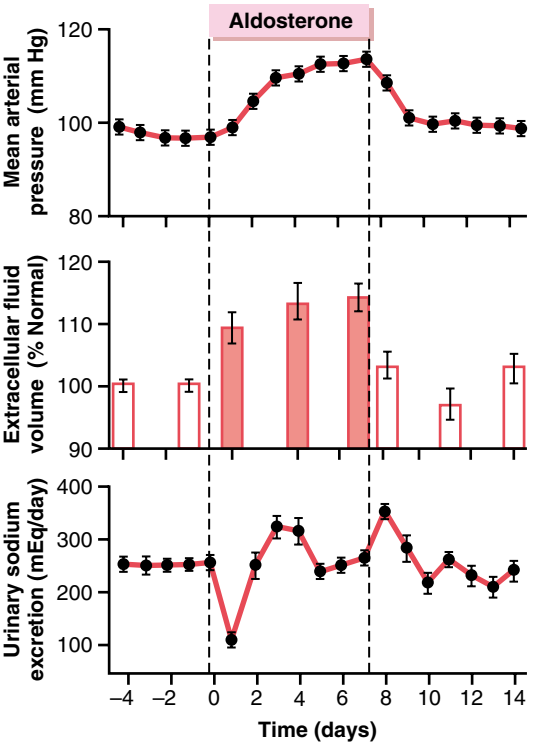


Figure 77-3 Effect of aldosterone infusion on arterial pressure, extracellular fluid volume, and sodium excretion in dogs. Although aldosterone was infused at a rate that raised plasma concentrations to about 20 times normal, note the "escape" from sodium retention on the second day of infusion as arterial 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 I):I183-192, 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 11β-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.

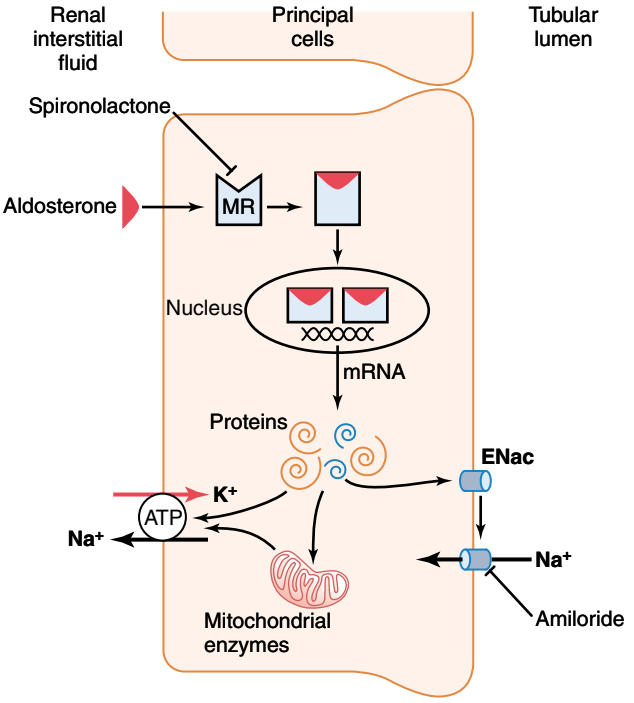


Figure 77-4 Aldosterone-responsive epithelial cell signaling pathways. ENaC, epithelial sodium channel proteins; MR, mineralocorticoid receptor. Activation of the MR by aldosterone can be antagonized with spironolactone. Amiloride is a drug that can be used to block ENaC.

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

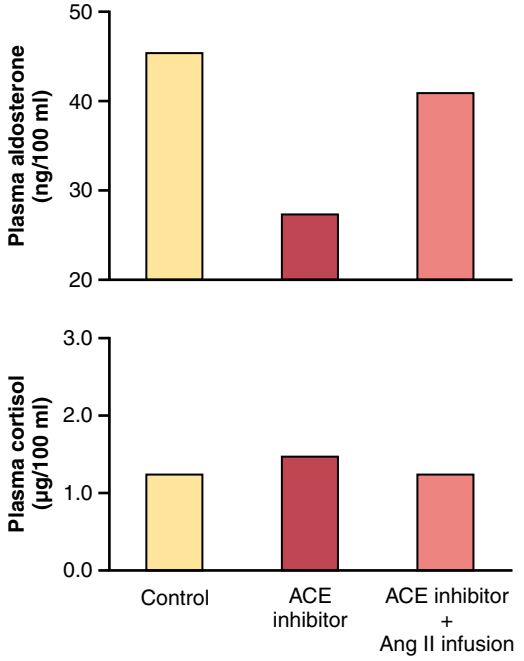


Figure 77-5 Effects of treating sodium-depleted dogs with an angiotensin-converting enzyme (ACE) inhibitor for 7 days to block formation of angiotensin II (Ang II) and of infusing exogenous Ang II to restore plasma Ang II levels after ACE inhibition. Note that blocking Ang II formation reduced plasma 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^+. 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 α-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

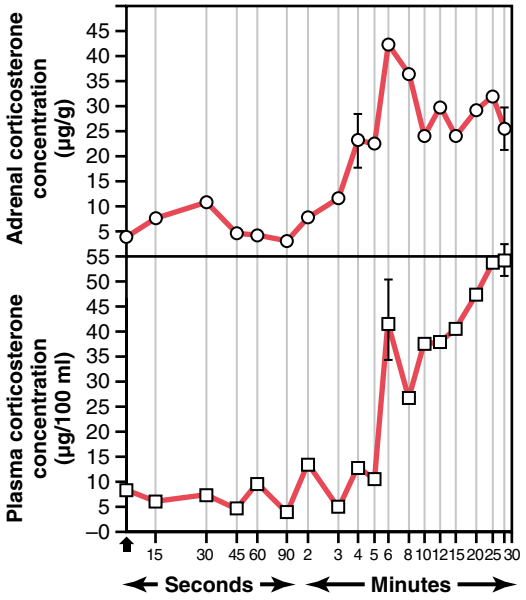


Figure 77-6 Rapid reaction of the adrenal cortex of a rat to stress caused by fracture of the tibia and fibula at time zero. (In the rat, corticosterone is secreted in place of cortisol.) (Courtesy Drs. Guillemin, Dear, and Lipscomb.)

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 Adrenocorticotropic 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 hypophysial 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 hypophysial 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

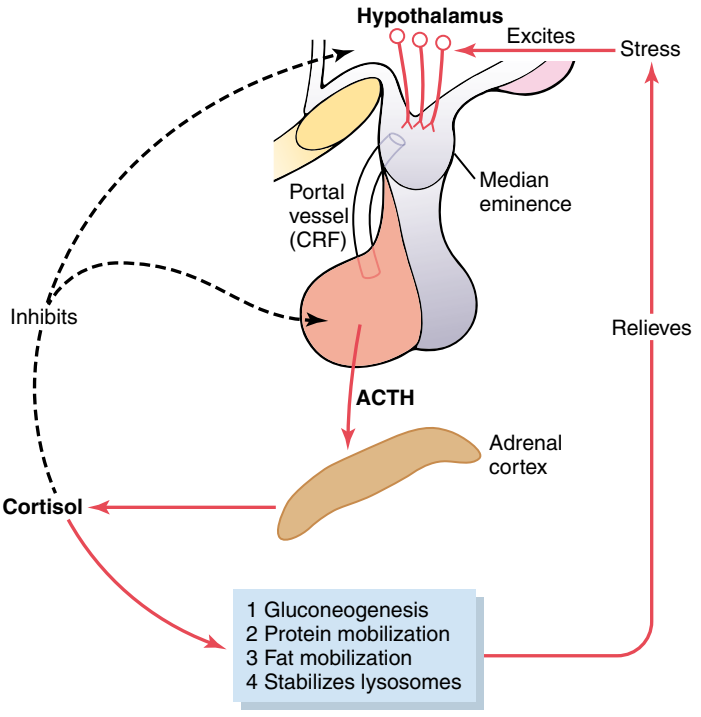


Figure 77-7 Mechanism for regulation of glucocorticoid secretion. ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor.

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.

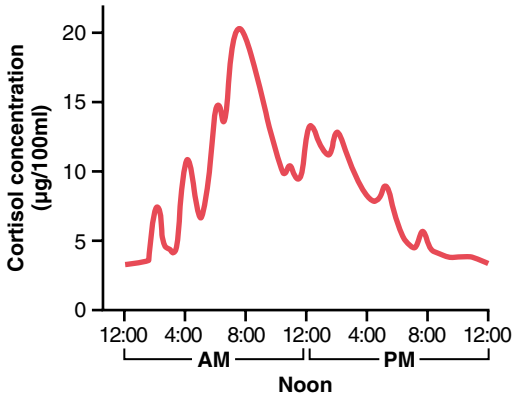


Figure 77-8 Typical pattern of cortisol concentration during the day. Note the oscillations in secretion as well as a daily secretory surge an hour or so after awaking in the morning.

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 preprohormone 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),

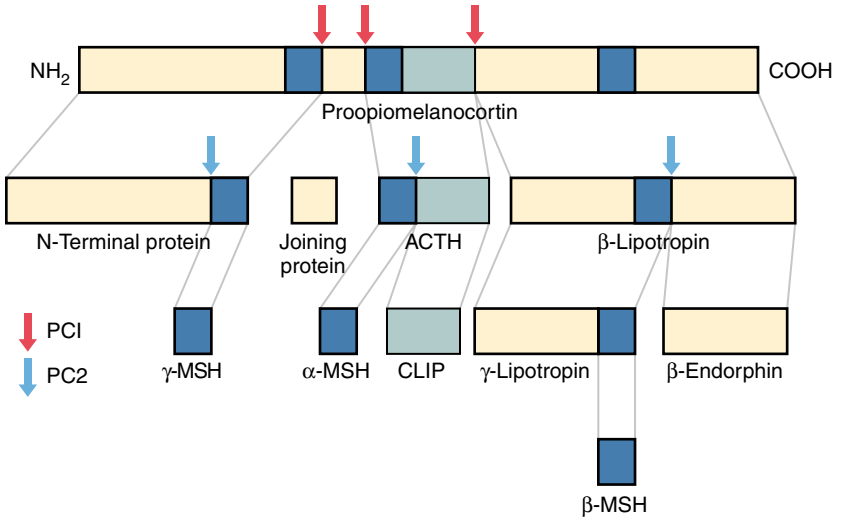


Figure 77-9 Proopiomelanocortin (POMC) processing by prohormone convertase 1 (PC1, *red arrows*) and PC 2 (*blue arrows*). Tissue-specific expression of these two enzymes results in different peptides produced in various tissues. The anterior pituitary expresses PC1, resulting in formation of N-terminal peptide, joining peptide, ACTH, and β-lipotropin. Expression of PC2 within the hypothalamus leads to the production of α-, β-, and γ-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 β-lipotropin. In the hypothalamus, the expression of PC2 leads to the production of α-, β-, and γ-MSH and β-endorphin but not ACTH. As discussed in Chapter 71, α-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

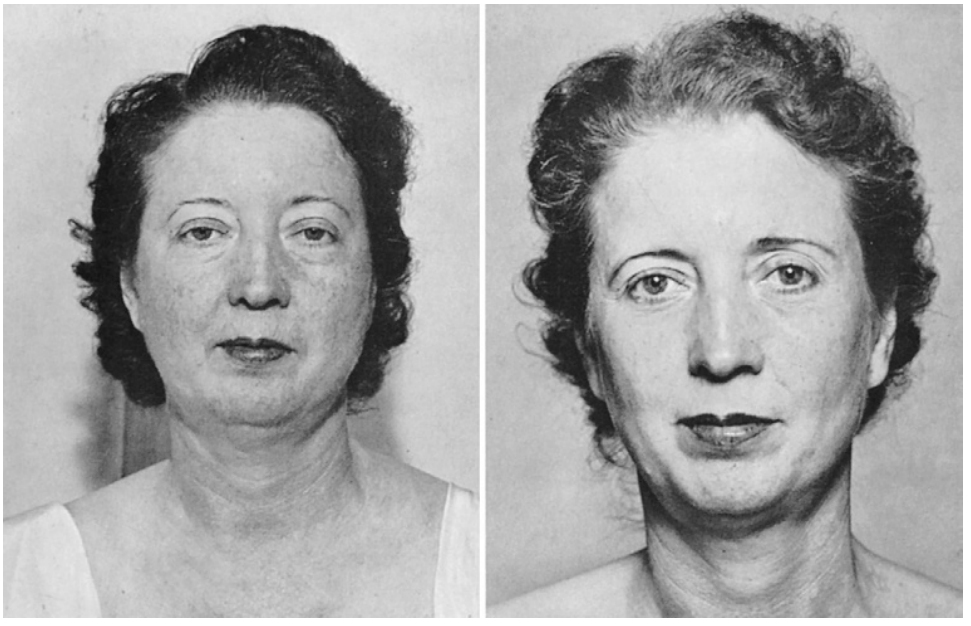


Figure 77-10 A person with Cushing's syndrome before (*left*) and after (*right*) subtotal adrenalectomy. (Courtesy Dr. Leonard Posey.)

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 *metyrapone, 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 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.

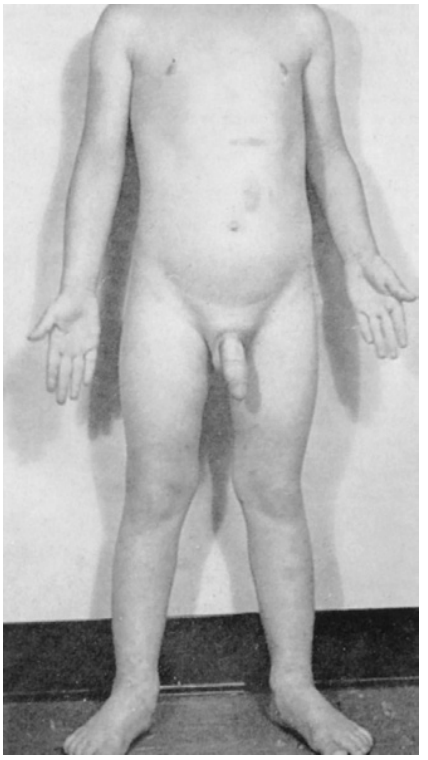


Figure 77-11 Adrenogenital syndrome in a 4-year-old boy. (Courtesy Dr. Leonard Posey.)

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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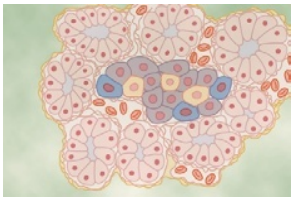
CHAPTER 78

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

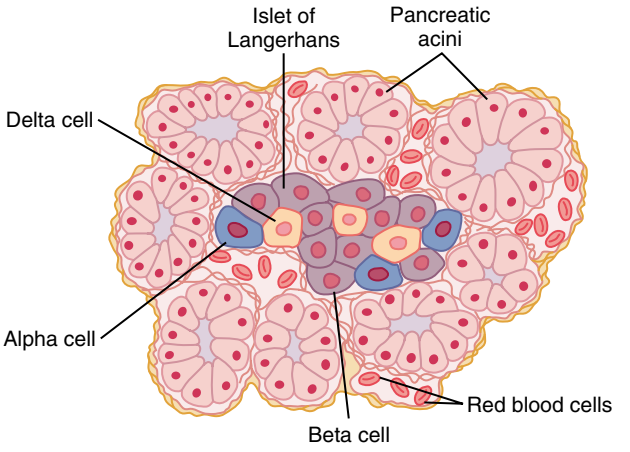


Figure 78-1 Physiologic anatomy of an islet of Langerhans in the pancreas.

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.

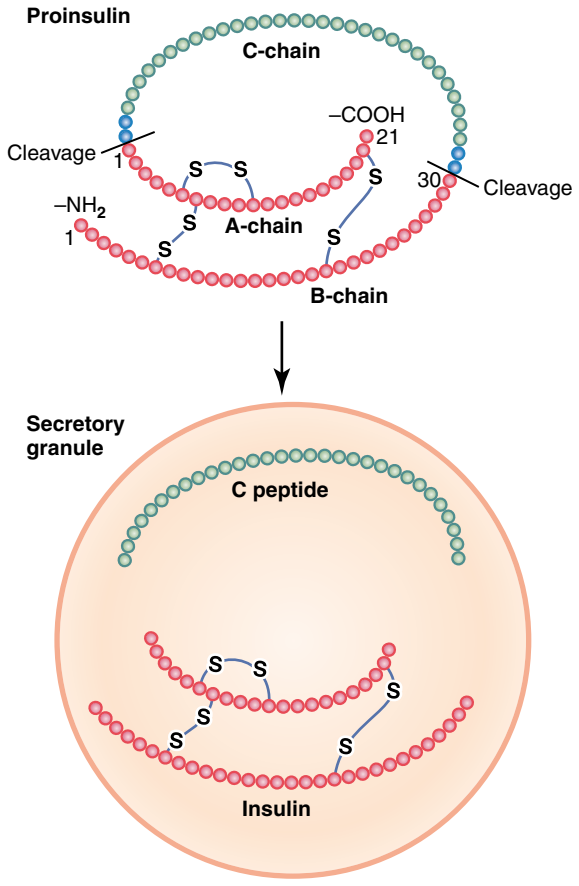


Figure 78-2 Schematic of the human proinsulin molecule, which is cleaved in the Golgi apparatus of the pancreatic beta cells to form connecting peptide (C peptide), and insulin, which is composed of the A and B chains connected by disulfide bonds. The C peptide and insulin are packaged in granules and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

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

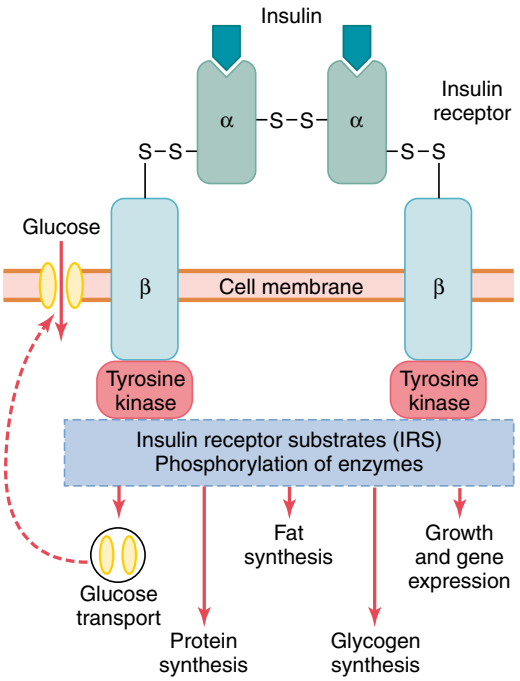


Figure 78-3 Schematic of the insulin receptor. Insulin binds to the α-subunit of its receptor, which causes autophosphorylation of the β-subunit receptor, which in turn induces tyrosine kinase activity. The receptor tyrosine kinase activity begins a cascade of cell phosphorylation that increases or decreases 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

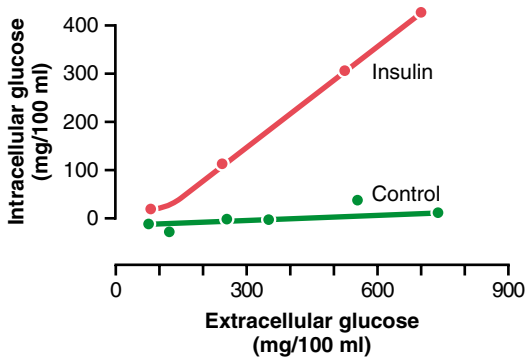


Figure 78-4 Effect of insulin in enhancing the concentration of glucose inside muscle cells. Note that in the absence of insulin (control), the intracellular glucose concentration remains near zero, despite high extracellular glucose concentrations. (Data from Eisenstein AB: The Biochemical Aspects of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

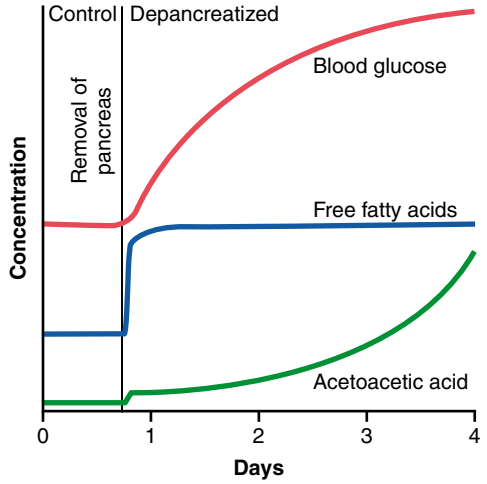


Figure 78-5 Effect of removing the pancreas on the approximate concentrations of blood glucose, plasma free fatty acids, and acetoacetic acid.

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 β-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 β-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

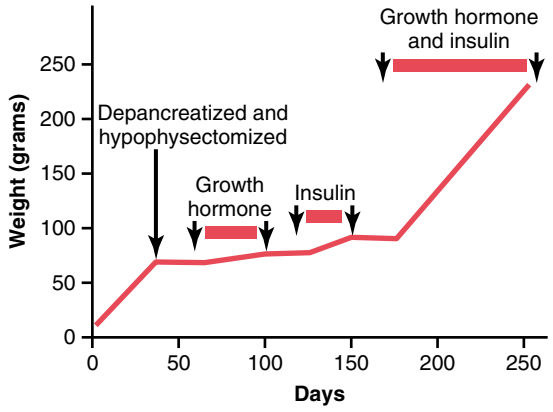


Figure 78-6 Effect of growth hormone, insulin, and growth hormone plus insulin on growth in a depancreatized and hypophysectomized rat.

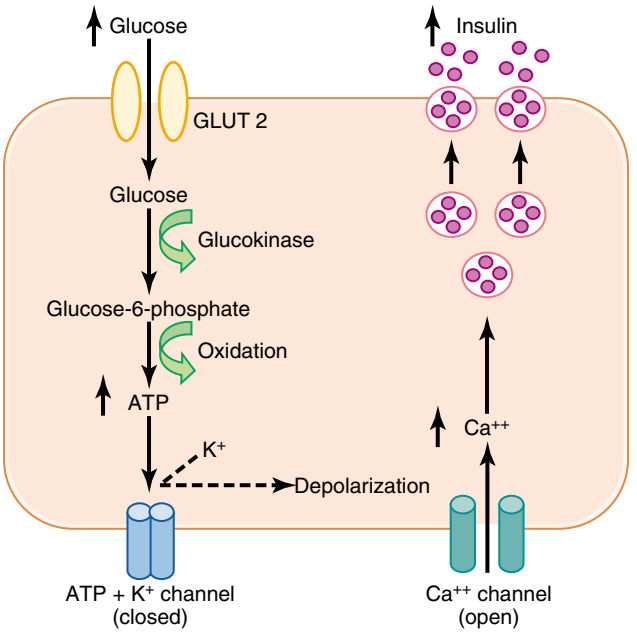


Figure 78-7 Basic mechanisms of glucose stimulation of insulin secretion by beta cells of the pancreas. GLUT, glucose transporter.

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 α-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)	α-Adrenergic activity Leptin
Glucagon, growth hormone, cortisol	
Parasympathetic stimulation; acetylcholine	
β-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 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.

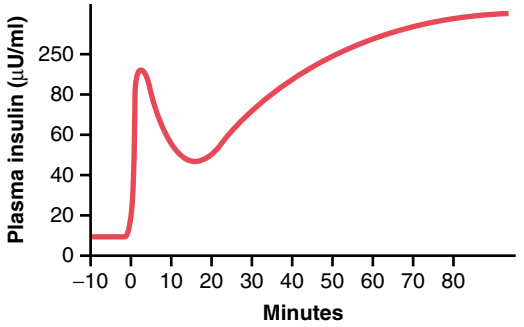


Figure 78-8 Increase in plasma insulin concentration after a sudden increase in blood glucose to two to three times the normal range. Note an initial rapid surge in insulin concentration and then a delayed but higher and continuing increase in concentration beginning 15 to 20 minutes later.

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

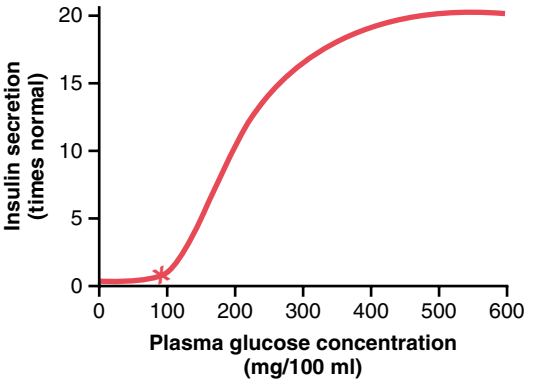


Figure 78-9 Approximate insulin secretion at different plasma glucose levels.

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 insulinotrophic 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

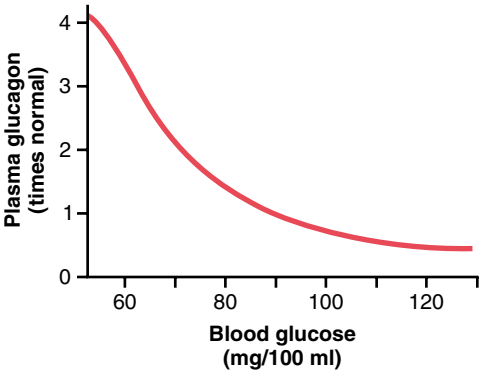


Figure 78-10 Approximate plasma glucagon concentration at different blood glucose levels.

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 β-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 β-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.

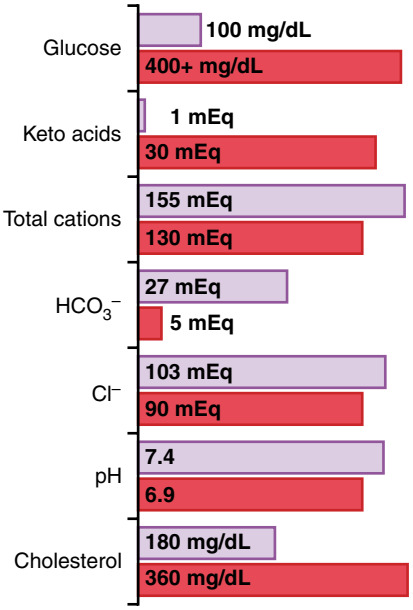


Figure 78-11 Changes in blood constituents in diabetic coma, showing normal values (*lavender bars*) and diabetic coma values (*red bars*).

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 γ (PPARγ)
• 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

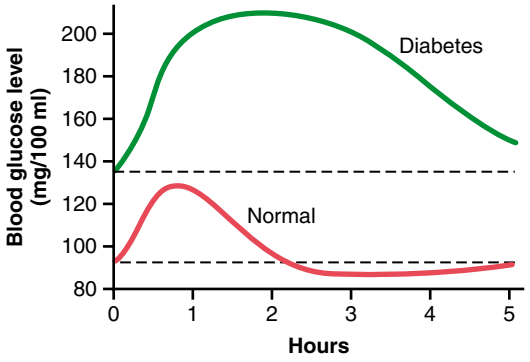


Figure 78-12 Glucose tolerance curve in a normal person and in a person with diabetes.

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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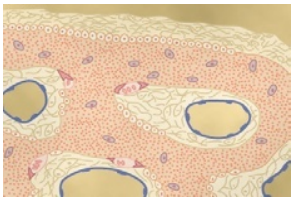
CHAPTER 79

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: $HPO_4^=$ and $H_2PO_4^-$. The concentration of $HPO_4^=$ is about 1.05 mmol/L, and the concentration of $H_2PO_4^-$ 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 $H_2PO_4^-$ and a decrease in $HPO_4^=$, 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 $HPO_4^=$ and $H_2PO_4^-$ 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

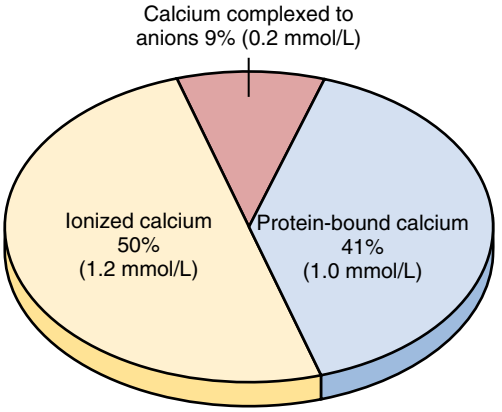


Figure 79-1 Distribution of ionized calcium (Ca^{++}), diffusible but un-ionized calcium complexed to anions, and nondiffusible protein-bound calcium in blood plasma.

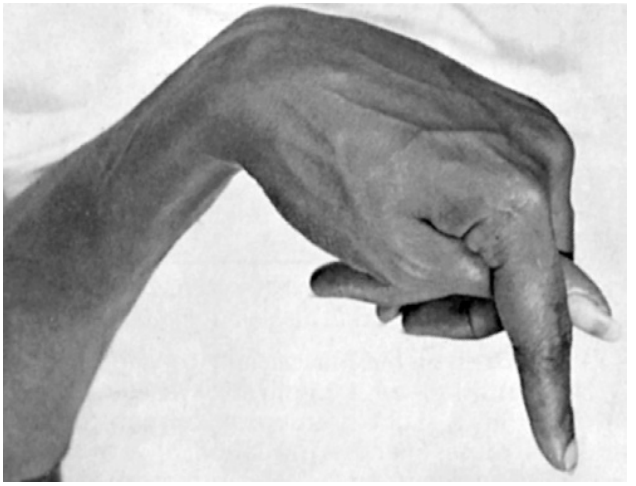


Figure 79-2 Hypocalcemic tetany in the hand, called *carpopedal spasm*.

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 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).

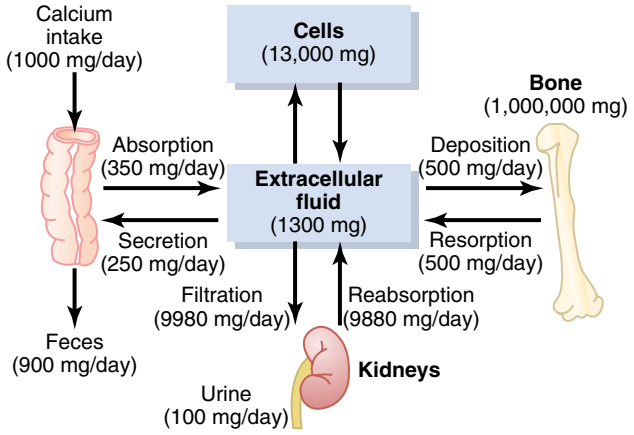


Figure 79-3 Overview of calcium exchange between different tissue compartments in a person ingesting 1000 mg of calcium per day. Note that most of the ingested calcium is normally eliminated in the feces, although the kidneys have the capacity to excrete large amounts by reducing tubular reabsorption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

$$Ca_{10}(PO_4)_6(OH)_2$$

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 (noncrystalline), a mixture of salts such as $CaHPO_4 \cdot 2H_2O$, $Ca_3(PO_4)_2 \cdot 3H_2O$, 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 $CaHPO_4$ 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 dissoluting 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 a ruffled border and release enzymes and acids that promote bone resorption.

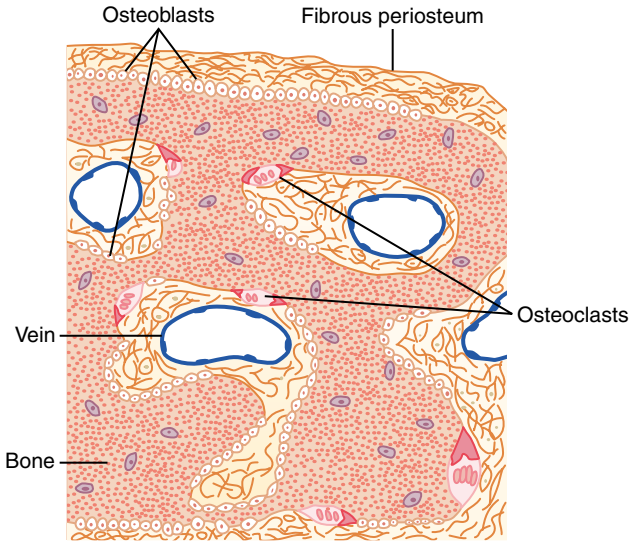


Figure 79-4 Osteoblastic and osteoclastic activity in the same bone.

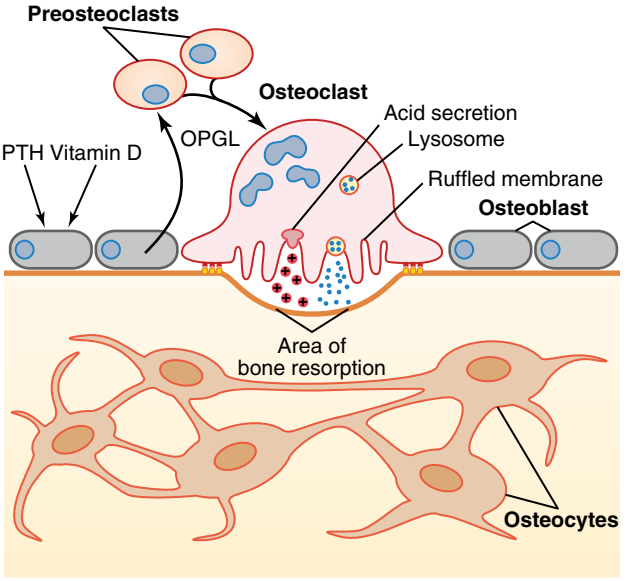


Figure 79-5 Bone resorption by osteoclasts. Parathyroid hormone (PTH) binds to receptors on osteoblasts, causing them to release osteoprotegerin ligand (OPGL), which binds to receptors on preosteoclast cells. This causes the cells to differentiate into mature osteoclasts. The osteoclasts then develop 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.

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

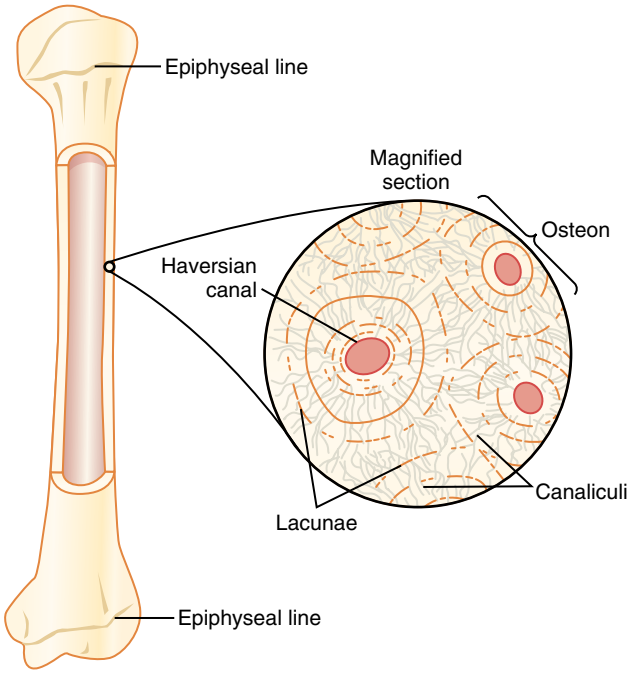


Figure 79-6 Structure of bone.

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 nonathletes. 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 $1,25(OH)_2D_3$. 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 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 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

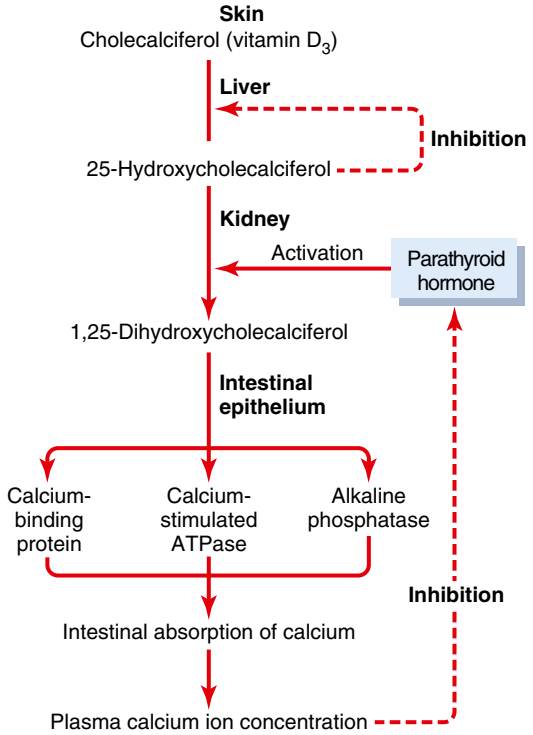


Figure 79-7 Activation of vitamin D_3 to form 1,25-dihydroxycholecalciferol and the role of vitamin D in controlling the plasma calcium concentration.

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_3 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_3 is altered over a wide range.

Second, this controlled conversion of vitamin D_3 to 25-hydroxycholecalciferol conserves the vitamin D 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

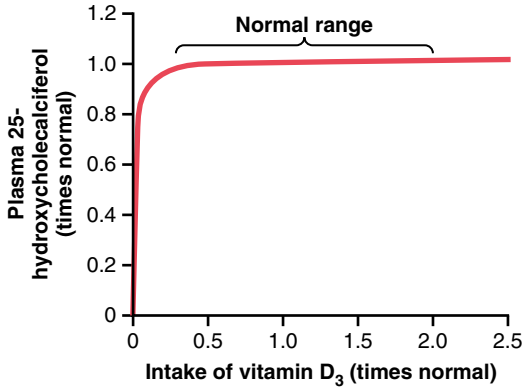


Figure 79-8 Effect of increasing vitamin D_3 intake on the plasma concentration of 25-hydroxycholecalciferol. This figure shows that increases in vitamin D intake, up to 2.5 times normal, have little effect on the final quantity of activated vitamin D that is formed. Deficiency of activated vitamin D occurs only at very low levels of vitamin D intake.

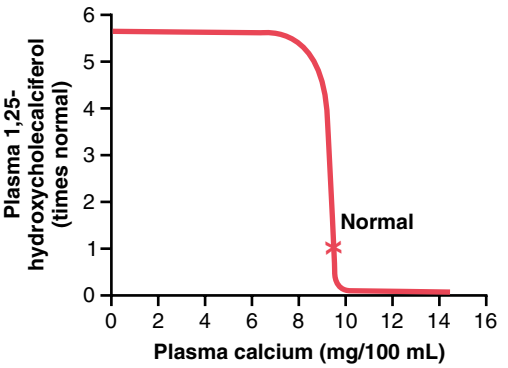


Figure 79-9 Effect of plasma calcium concentration on the plasma concentration of 1,25-dihydroxycholecalciferol. This figure shows that a slight decrease in calcium concentration below normal causes increased formation of activated vitamin D, which in turn leads to greatly increased absorption of calcium 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 hormone'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.

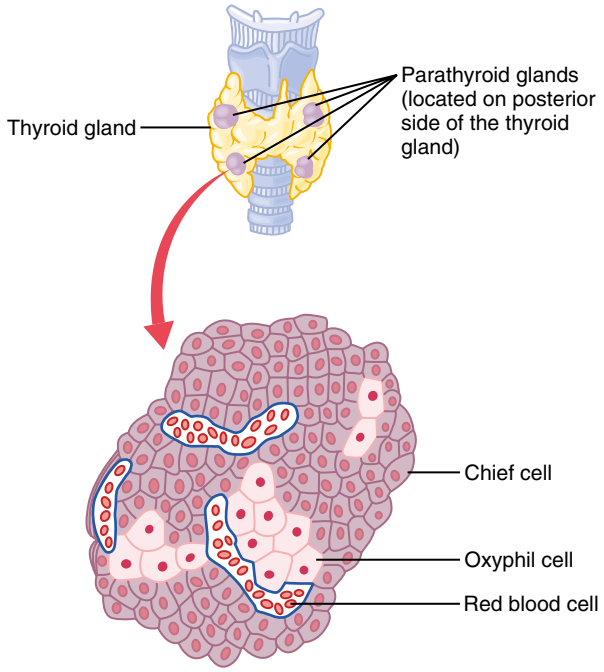


Figure 79-10 The four parathyroid glands lie immediately behind the thyroid gland. Almost all of the parathyroid hormone (PTH) is synthesized and secreted by the chief cells. The function of the oxyphil cells is uncertain, but they may be modified or depleted chief cells that no longer secrete PTH.

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

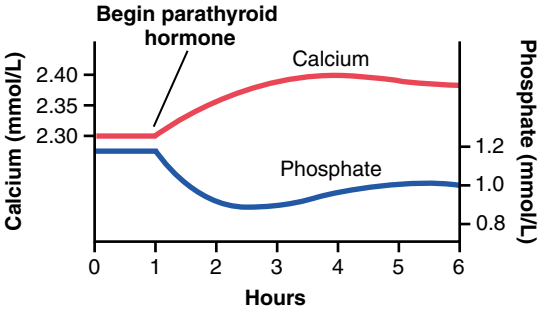


Figure 79-11 Approximate changes in calcium and phosphate concentrations during the first 5 hours of parathyroid hormone infusion at a moderate rate.

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.

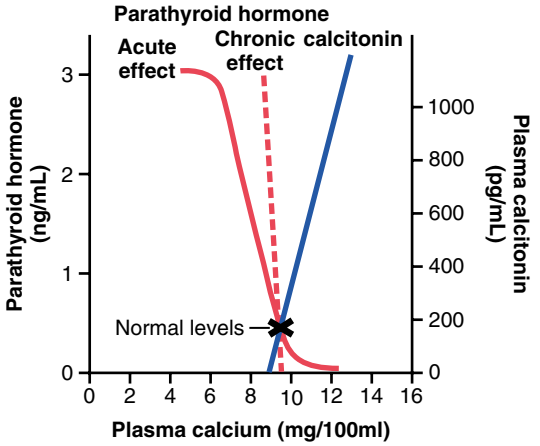


Figure 79-12 Approximate effect of plasma calcium concentration on the plasma concentrations of parathyroid hormone and calcitonin. Note especially that long-term, chronic changes in calcium concentration of only a few percentage points can cause as much as 100 percent change in parathyroid hormone concentration.

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

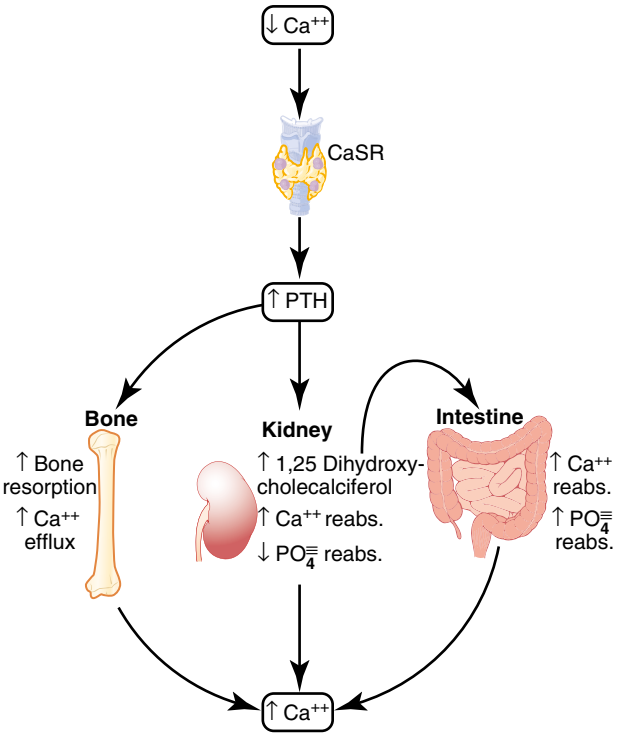


Figure 79-13 Summary of effects of parathyroid hormone (PTH) on bone, the kidneys, and the intestine in response to decreased extracellular fluid calcium ion concentration. CaSR, calcium sensing receptor.

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 $CaHPO_4$ 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 ($CaHPO_4$) 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 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

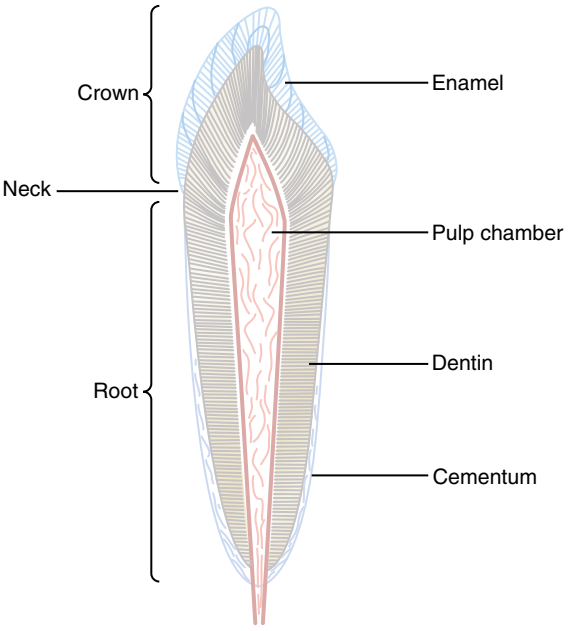


Figure 79-14 Functional parts of a tooth.

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 79-15*A* 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 79-15*B.*

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

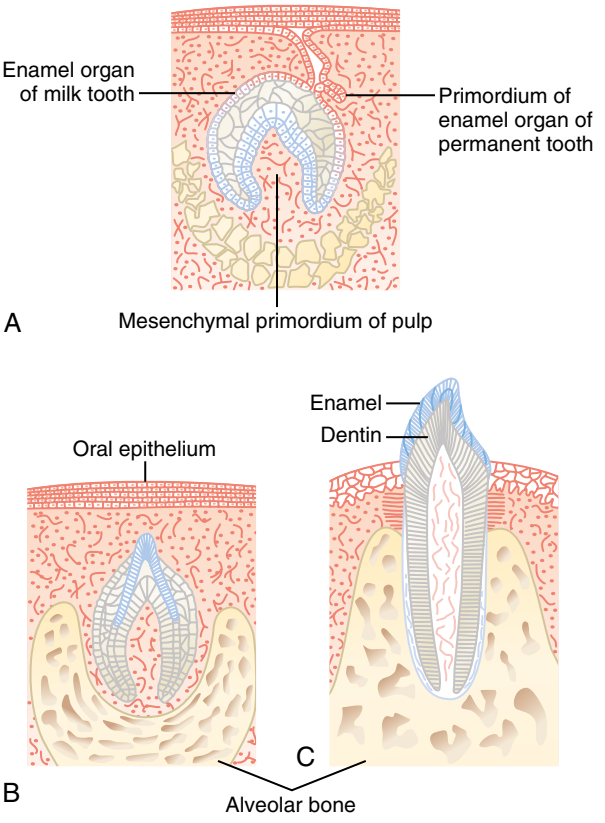


Figure 79-15 *A*, Primordial tooth organ. *B*, Developing tooth. *C*, Erupting tooth.

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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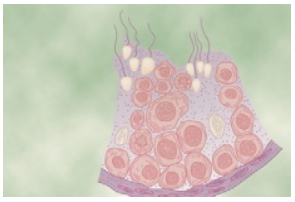
CHAPTER 80

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 80-1*A* shows the various portions of the male reproductive system, and Figure 80-1*B* 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 80-2*A*). 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 80-2*B.*

Steps of Spermatogenesis

Spermatogenesis occurs in the seminiferous tubules during active sexual life as the result of stimulation by anterior

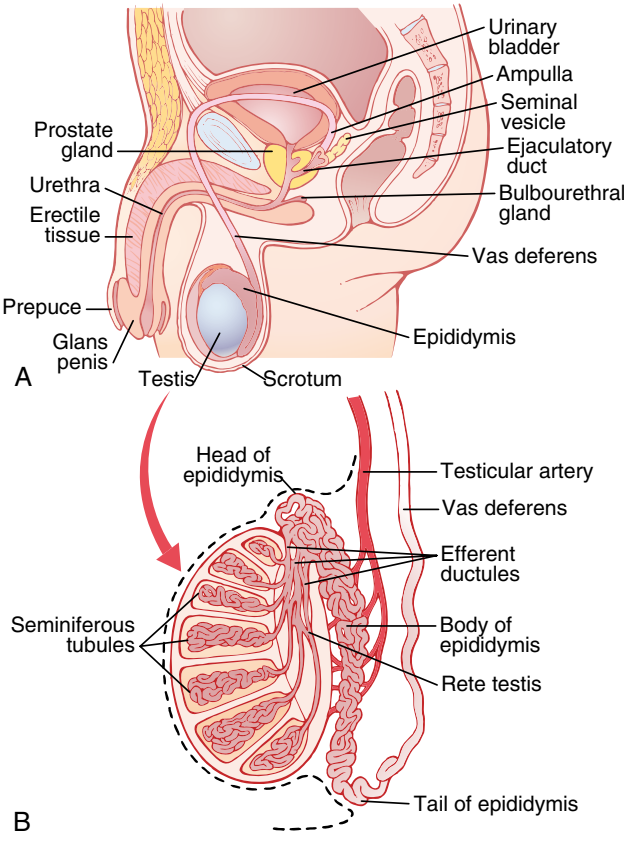


Figure 80-1 *A,* Male reproduction system. (Modified from Bloom V, Fawcett DW: Textbook of Histology, 10th ed. Philadelphia: WB Saunders, 1975.) *B,* Internal structure of the testis and relation of the testis to the epididymis. (Redrawn from Guyton AC: Anatomy and Physiology. Philadelphia: Saunders College Publishing, 1985.)

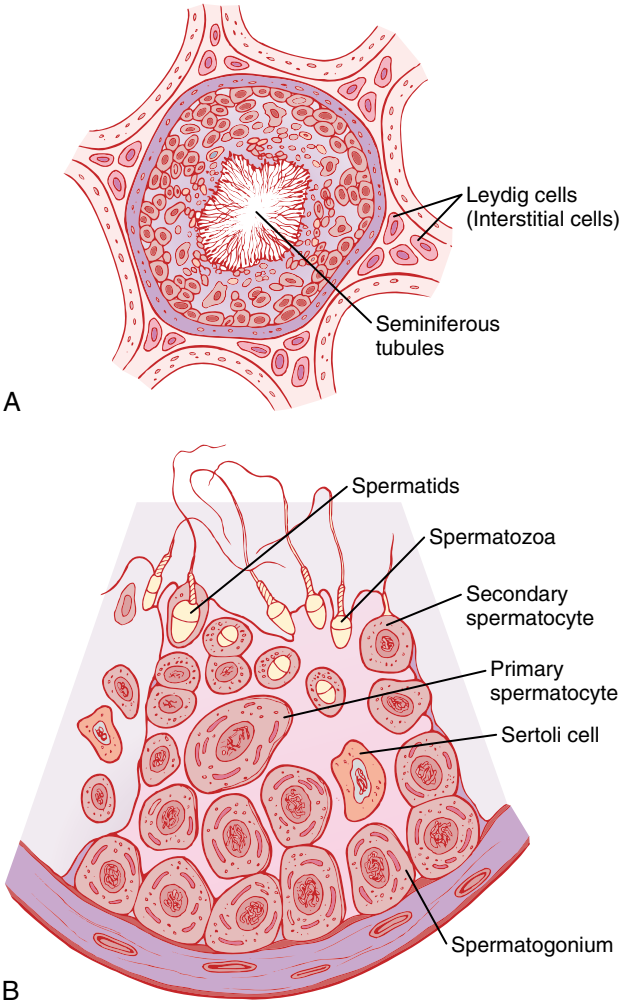


Figure 80-2 *A,* Cross section of a seminiferous tubule. *B,* Stages in the development of sperm from spermatogonia.

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

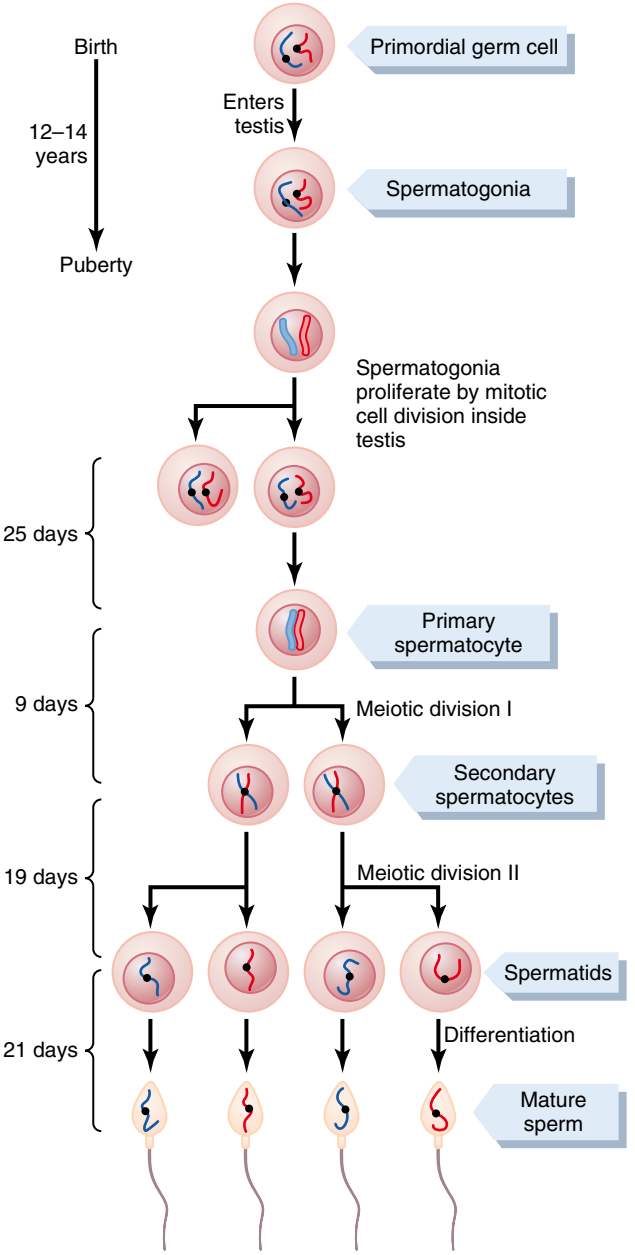


Figure 80-3 Cell divisions during spermatogenesis. During embryonic development the primordial germ cells migrate to the testis, where they become spermatogonia. At puberty (usually 12 to 14 years after birth), the spermatogonia proliferate rapidly by mitosis. Some begin meiosis to become primary spermatocytes 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*).

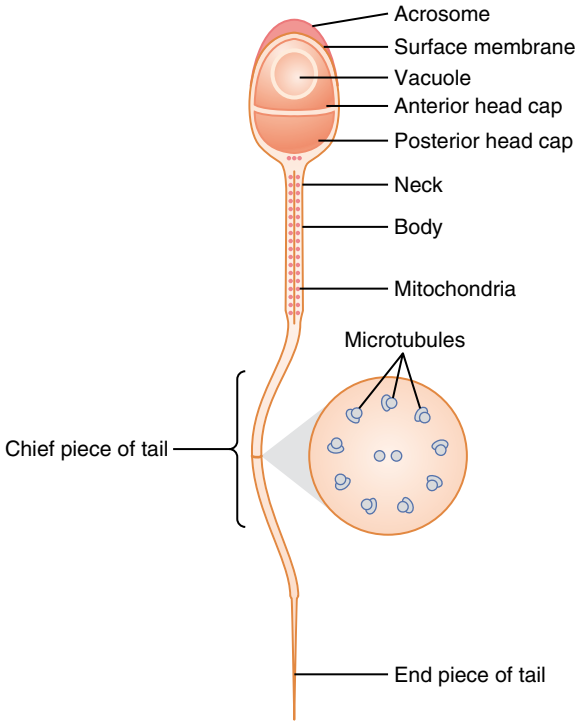


Figure 80-4 Structure of the human spermatozoon.

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,

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°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 dissolute these granulosa cell layers, and then it must penetrate though 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 specifically 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.

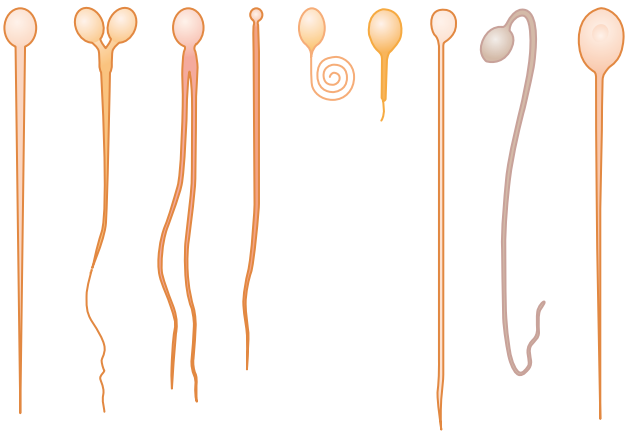


Figure 80-5 Abnormal infertile sperm, compared with a normal sperm on the right.

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.

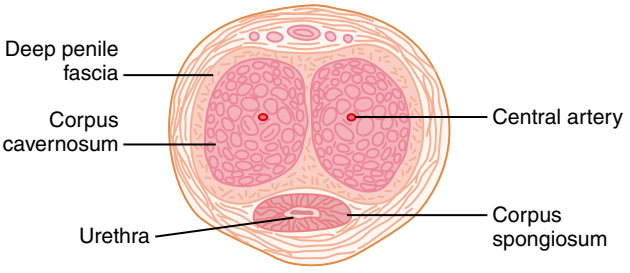


Figure 80-6 Erectile tissue of the penis.

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

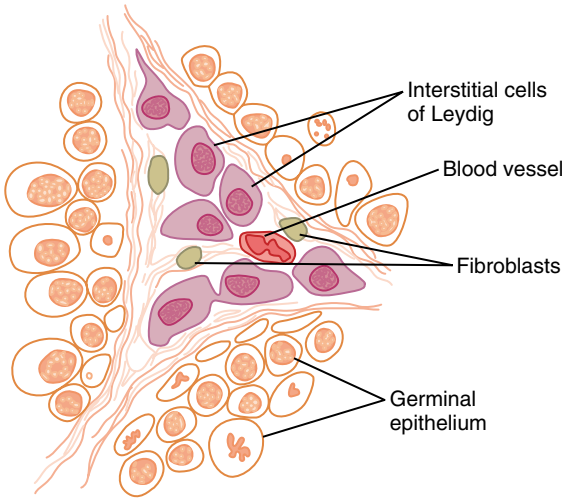


Figure 80-7 Interstitial cells of Leydig, the cells that secrete testosterone, located in the interstices between the seminiferous tubules.

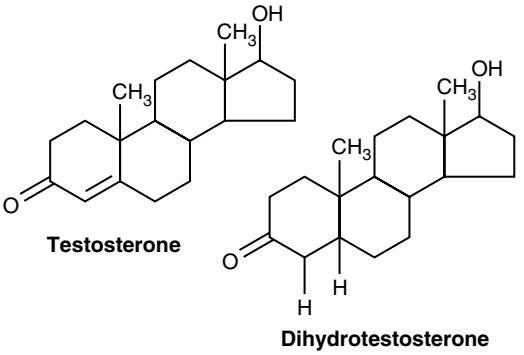


Figure 80-8 Testosterone and dihydrotestosterone.

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* 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 androstanediol 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.

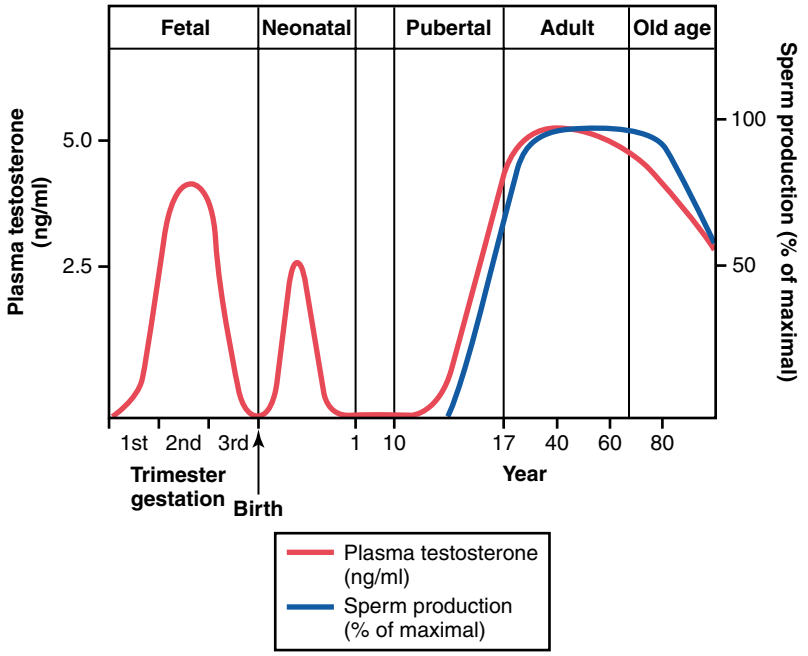


Figure 80-9 The different stages of male sexual function as reflected by average plasma testosterone concentrations (*red line*) and sperm production (*blue line*) at different ages. (Modified from Griffin JF, Wilson JD: The testis. In: Bondy PK, Rosenberg LE [eds]: Metabolic Control and Disease, 8th 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 5α-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 steroidal 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-hypophysial portal vascular system. Then the GnRH is transported to the anterior pituitary gland in the hypophysial 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.*

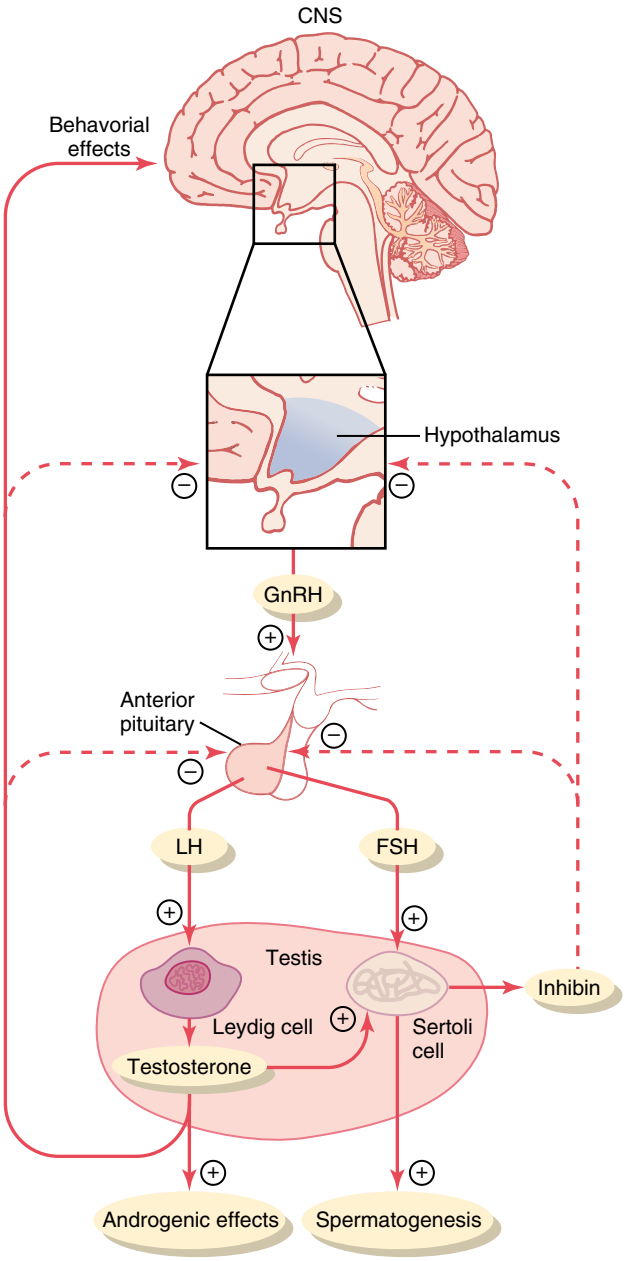


Figure 80-10 Feedback regulation of the hypothalamic-pituitary-testicular axis in males. Stimulatory effects are shown by ⊕ and negative feedback inhibitory effects are shown by ⊖. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

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.*

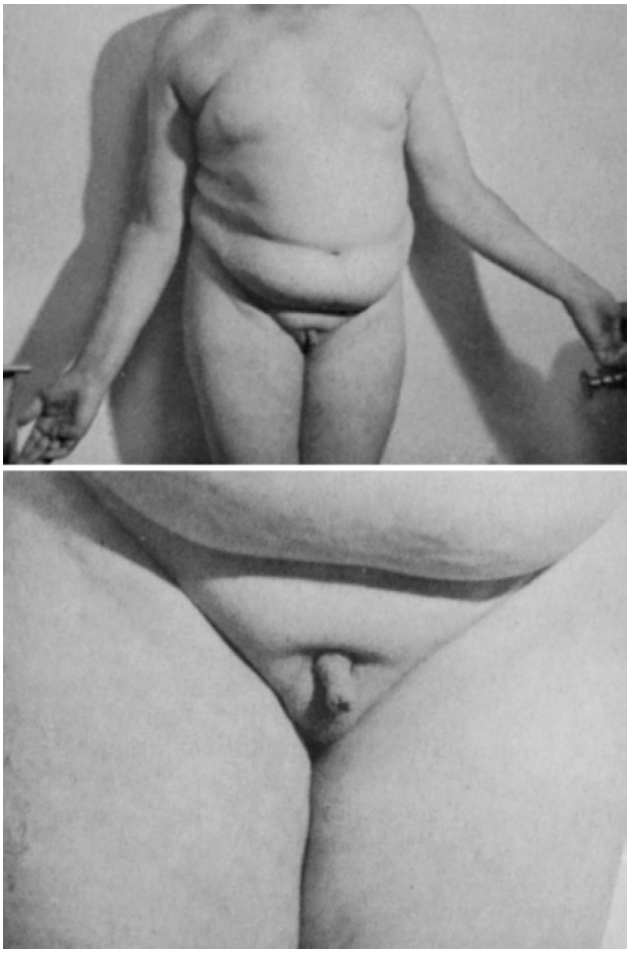


Figure 80-11 Adiposogenital syndrome in an adolescent male. Note the obesity and childlike sexual organs. (Courtesy Dr. Leonard Posey.)

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 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 suprachiasmal 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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