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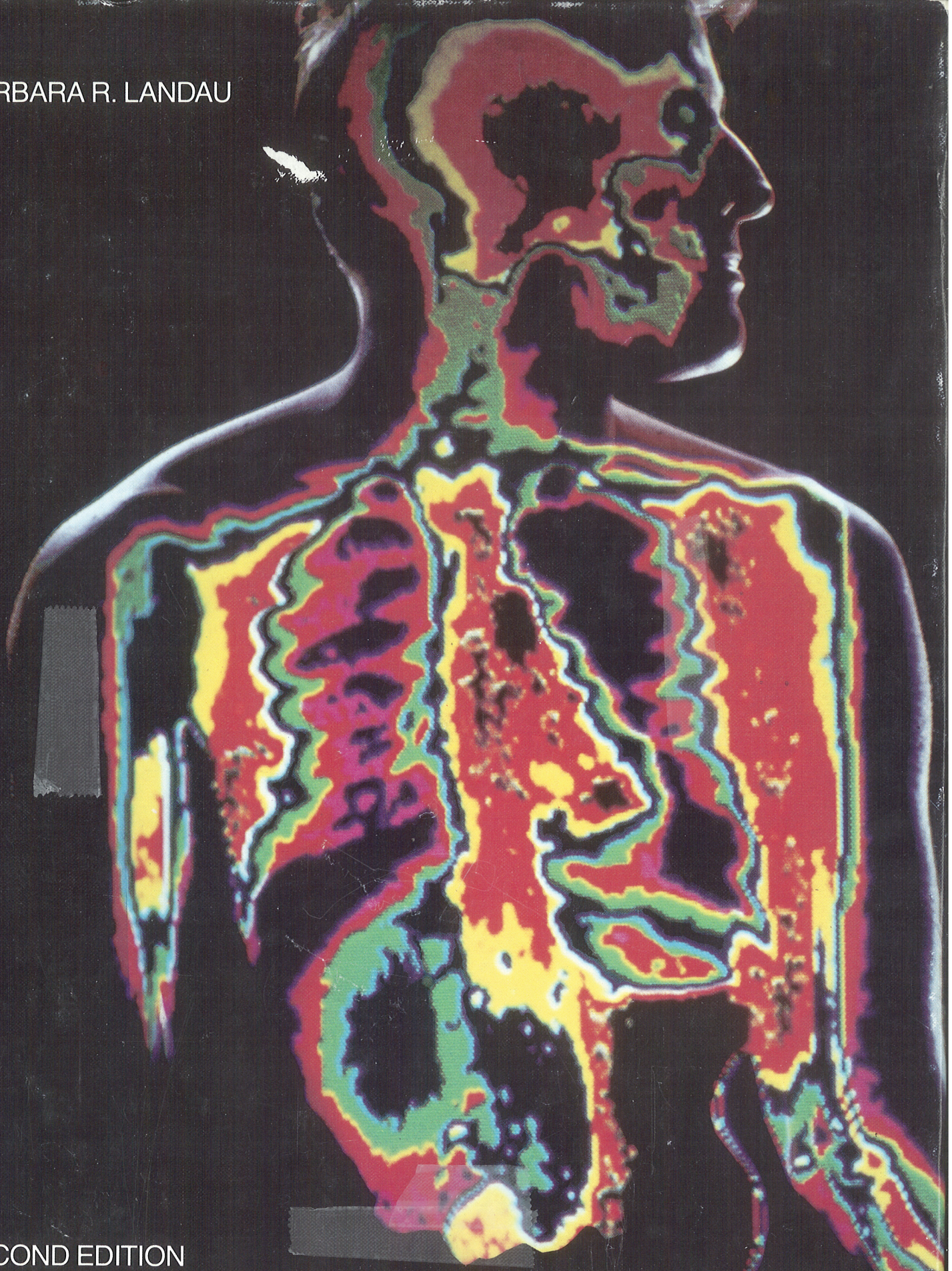

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ESSENTIAL HUMAN ANATOMY AND PHYSIOLOGY

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13

Nature of Hormones and Hormone Action
The Pituitary Gland and Hormone Control
Endocrine Glands and Their Secretions

The Endocrine Glands as a Control System

Preceding chapters have been devoted to the role of the nervous system in the control of body functions. As important as it is, and as widespread as its actions are, the nervous system does not, however, control everything. There is another control system, the endocrine system, whose actions are also vital to our well-being and, indeed, to our very existence.

Most of the body's systems consist of several anatomically connected organs and structures organized to perform important and specific functions for the entire body. The organs of the endocrine system seem to be relatively independent of one another, anatomically and functionally. Though they are not an organ system in the usual sense, the endocrine glands do share a common mode of action: instead of conducting impulses, they secrete hormones which affect many cell functions that are not under neural control. Together the endocrine glands constitute a control system that parallels, but does not duplicate, the nervous system.

In this chapter we discuss how hormones act and examine the characteristics common to all endocrine controls. The individual glands and their hormones are discussed in a rather general way, with the specific details added later in the sections covering the processes that each hormone helps to regulate.

TABLE 13-1 THE ENDOCRINE GLANDS

Pituitary gland (hypophysis)
anterior lobe (adenohypophysis)
posterior lobe (neurohypophysis)
intermediate lobe

Adrenal glands
adrenal medulla
adrenal cortex

Thyroid gland

Parathyroid gland

Pancreatic islands (islets of Langerhans)

Gonads
testis
ovary

Placenta

Digestive tract (stomach, small intestine)

Kidney

Pineal gland (?)

The endocrine system includes the glands listed in Table 13-1. All **endocrine glands** act by secreting their hormones into the bloodstream for distribution throughout the entire body. In contrast, **exocrine glands** such as the salivary glands or sweat glands release their secretions directly (or via a duct) onto the surface of the body (or one of its inward extensions). An endocrine gland is therefore considered to be a specific organ whose bloodborne secretion produces a specific action on an organ (the target organ) at some distance from the gland itself.[1]

NATURE OF HORMONES AND HORMONE ACTION

Hormones affect all types of cells, not just the usual effectors. They do so chiefly by altering a basic cell activity in some way, and this affects the rate of a particular process that may be an essential part of the body economy. The results from hormonal actions are many and varied, but they can be fitted into four broad categories:

1. Hormones help regulate the energy supply, including processes by which the energy is obtained from foodstuffs (or stored reserves). Thus they help control the digestive system, and they are of major importance in regulating metabolism and energy release from foodstuffs after they have been digested and have entered the bloodstream.

2. Hormones help control certain properties of the extracellular fluid (the internal environment). Specifically, they help control the metabolism of water and electrolytes; that is, they determine the fate of much of the sodium, potassium, calcium, phosphorus, and water in the body.

3. Hormones help us cope with adverse conditions or stresses, including such adversities as cold, heat, dehydration, trauma, blood loss, and emotional stress, in terms of withstanding the stress, fighting it, or escaping from it.

4. Hormones help regulate such basic aspects of life as growth, development, and reproduction.

Formation and Transport of Hormones

The chemical nature of many hormones is known, including their molecular structure. Many of those identified are protein derivatives, either *amines*, *peptides*, or *polypeptides*. Amines are small molecules, essentially an amino acid with the carboxyl (acid) group removed and perhaps a small side chain added. Peptides consist of a few amino acids, and polypeptides are longer chains of amino acids. They have many of the properties of proteins, in terms of the kinds of reactions they can enter into, but, of course, they are much smaller molecules.

Protein-related hormones are produced in the manner described in Chapter 2 for general protein synthesis. The short amino acid chains are assembled on ribosomes of rough endoplasmic reticulum and are transported in the ER to the Golgi apparatus where they are packaged into secretion gran-

[1]By this definition, such important chemical regulators as acetylcholine or carbon dioxide are excluded, since acetylcholine is not carried in the blood to a distant site and carbon dioxide is not secreted by a specific organ. They remain chemical regulators, but they are not hormones.

ules to be held until the proper stimulus causes their release from the cell.

The other major group of hormones are *steroids.* These hormones contain the basic steroid nucleus (a specific molecular configuration), so they are all quite similar, but they differ in slight but important specific groups attached at certain sites (see Figure 13–7). One important property of steroids is that they are lipid derivatives so they are fat soluble and thus can diffuse through cell membranes. Steroid hormones are synthesized from cholesterol (a widely distributed steroid) partly in mitochondria and partly in smooth ER. Important steroid hormones are those of the adrenal cortex, ovary, testis, and some of those produced by the placenta.

Since hormones reach their destination by traveling in the bloodstream, much attention has been given to the concentration of hormones in the blood. Many of the advances in endocrinology have come on the heels of better ways to measure the hormone levels in the blood. This is often a difficult problem for, although hormones are potent substances, they are present in very small amounts.[2]

Even knowing the exact concentration of a hormone in the blood does not tell us very much, because hormones do not exert their action in the blood; the blood is merely a transport system for most of them. Hormones in the blood are on their way either *to* some place or *from* some place. The amount of hormone in the blood at any given time depends upon the rate at which it is entering the blood (rate of secretion) and the rate at which it is leaving the blood, either by excretion or inactivation. Many hormones are inactivated in the liver or elsewhere, and many are excreted rather rapidly in the urine. In fact, the half-life (the length of time for one half of a given dose to disappear from the blood) varies from a few minutes to a few hours, and averages only 10–30 minutes.

The fact that hormones are removed so rapidly suggests that in order to maintain a blood level, production must be continual. This is the case, for they are produced continually, but not necessarily at a constant rate. Stimulation of an endocrine gland increases the ongoing rate of production, and inhibition reduces it. The need for continual production is all the more important when one realizes that, with one or two exceptions, we do not store hormones to any great extent. Except for the thyroid hormones, only a one- or two-day supply is on hand.

Most hormones are bound to proteins as they are transported in the blood. It is a reversible condition, and an equilibrium is maintained between the free hormone and the bound hormone:

Free hormone + plasma protein
⇄ Protein-bound hormone
↓
Action

Some hormones are nearly 95 percent bound while others are more nearly half and half. Only the free portion can act, or be acted upon. When some of the free hormone is inactivated or leaves the bloodstream, more is released from the protein and the free/bound equilibrium is maintained. Such binding serves a purpose, for bound hormones are not available to diffuse out of the blood vessel or to be excreted in the urine.

Mechanisms of Hormone Action

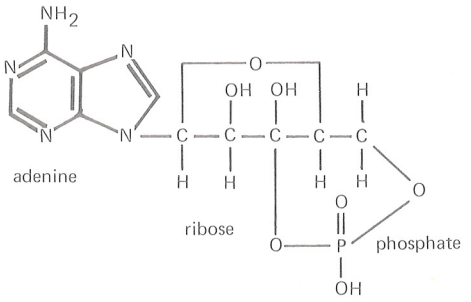
Depending upon how one chooses to classify or count, there may be 40 to 50 different hormones with many different actions, but surprisingly, of those whose mechanism of action is known, all seem to involve only two or three different mechanisms.

[2]Some, such as amines (epinephrine), can be measured directly by chemical analysis. Some are detected by *bioassay,* a method used to measure a hormone when its chemical nature is not known. A bioassay consists of comparing a biological effect (such as the increase in the weight of an organ) of a sample containing an unknown amount of a hormone sample with the effect of a known amount of that hormone. A newer, extremely sensitive method is the *radioimmunoassay,* which makes use of the fact that proteins are bound firmly by specific antibodies. A sample containing an unknown amount of a hormone would interfere with the binding of a known amount of a pure sample. By determining the extent of the interference, the amount of hormone in the unknown sample can be determined. To do so, the pure sample carries a radioactive label, which can be measured very accurately. This method is applicable to protein and to peptide hormones.

As far as is known at present, all hormone actions begin with the combining or binding of the hormone with a specific receptor site of the target cell, in a manner somewhat similar to the binding of transmitter substances at neuromuscular junctions and synapses. Therefore, a hormone can only act on a cell that has receptor sites specifically for that hormone. This is the way in which the hormone "recognizes" its target cell (or vice versa), and it is the mechanism that limits the action of a hormone to certain target cells. The receptors have been described as either fixed receptors or mobile receptors.

Fixed Receptors For hormones that bind to **fixed receptors,** the receptors are on the outer surface of the cell membrane. The hormone binds there and never enters the cell. The hormone-receptor combination serves to activate an enzyme that is also in the cell membrane, but presumably on its inner surface (Figure 13–1A). This enzyme, **adenyl cyclase,** acts upon adenosine triphosphate (ATP) in the cell cytoplasm, converting it to a cyclic form, **cyclic AMP (cAMP):**

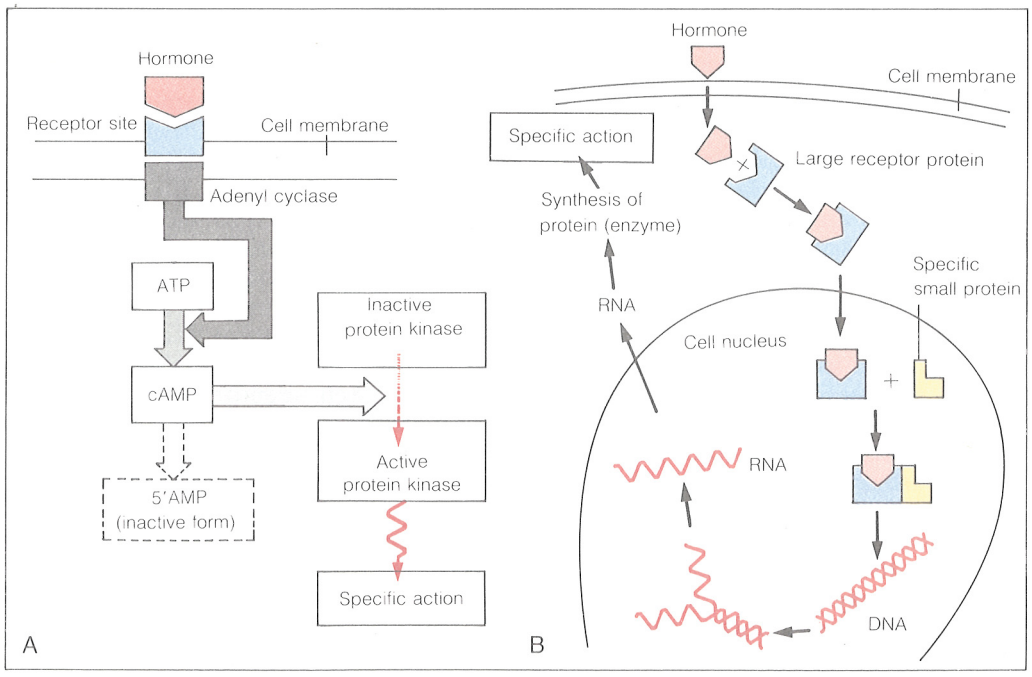
cAMP—Cyclic Adenosine 3′ 5′ Monophosphate



Cyclic AMP is inactivated rather quickly, but before that happens, cAMP causes an action which, in most if not all cases, is the activation of a **protein kinase.** Protein kinase describes a class of enzymes that activates another enzyme by transfering phosphate (from ATP) to it. The action that occurs when a protein kinase is activated depends upon the action of the enzyme it activates. Therefore, the effect of a hormone (which is specific) depends upon the action of a particular protein kinase (which is also specific). The link between them is the adenyl cyclase and cyclic AMP, and they are the same in many hormone actions.

Because cAMP is inactivated rather quickly, more hormone is needed and

FIGURE 13–1 Mechanisms of hormone action. A. Fixed receptor model. B. Mobile receptor model.



more cAMP must be produced to continue the action (in much the same way that additional packets of acetylcholine must be continually released if a muscle contraction is to be maintained). Epinephrine is one of about a dozen hormones known to act by way of cAMP. In fact, studies on how epinephrine causes glucose to be released from the liver led to the discovery of the role of adenyl cyclase and cAMP in the first place. Cyclic AMP is sometimes called the "second messenger," the hormone being the "first messenger."

Mobile Receptors **Mobile receptors** are involved in the action of steroid hormones. Recall that as lipid substances, steroids can pass through the cell membrane. The receptor site for steroid hormones is in the cytoplasm of the cell, and they diffuse into the cell and bind to the site (Figure 13–1B). The hormone-receptor combination then moves into the nucleus of the cell where it combines with a smaller protein which enables it to have an action on the DNA of the nucleus. The DNA of a particular gene unwinds leading to the synthesis of mRNA that carries the code for a particular protein. The mRNA moves to the cytoplasm, and that protein is synthesized at the ribosomes. The new protein is generally an enzyme to catalyze a particular reaction.

In either case, the varied effects of a hormone, whether brought about by fixed or mobile receptors, result in the presence of more active enzymes, thus accelerating (or blocking) a particular cellular reaction, which we describe as the action of that hormone.

Other Possible Mechanisms of Action A third mode of action involves an alteration in the properties of the cell membrane, so as to increase the permeability of the membrane to a specific substance. One of the best-known examples is the hormone insulin, which increases the rate of entry of glucose into the cells. Some hormones that act in this way do so by way of cAMP, but others do not and their mechanism of action is not understood.

A final possible mechanism of action has been postulated. It is not understood yet, but it could explain the fact that some hormones alter the effectiveness of another hormone. It is suggested that the action may come about by an effect on the receptor sites. If hormone A destroys receptors for hormone B, or occupies them leaving no place for hormone B to bind, the effectiveness of hormone B will be greatly reduced. Some hormones have what is called a *permissive action.* They do not bring about a particular effect by themselves, but their presence is necessary for another hormone to be fully effective. One possible explanation (there are others) might be that the permissive action of hormone A could have a favorable effect on the binding sites for hormone B.

Prostaglandins and Hormone Actions Prostaglandins are among the most confusing substances we will encounter in the body! The confusion begins with their name. Prostaglandins were first discovered in semen, the secretion of the male reproductive tract, and were presumably produced by the prostate gland, hence the name. It turned out that the seminal vesicles are the chief source of prostaglandins in semen, but the name has stuck. Prostaglandins are not hormones, but they are often considered with them (partly for lack of a better category), and their actions are related to hormone action in several ways.

Prostaglandins are synthesized by most, if not all, cells of the body. There are more than a dozen different prostaglandins, differing only slightly in their molecular configuration (and in some actions). They are all derivatives of a 20-carbon fatty acid and are therefore lipid-soluble and able to diffuse through cell membranes. Prostaglandins are extremely potent substances, but are present in very small amounts, more so in some tissues or at certain times. They are present in the blood, probably entering by diffusion rather than actually being secreted into it, but they are rapidly inactivated, especially in the lungs, liver, and kidney.

Prostaglandins are almost as

widely distributed as ATP, but their actions are so varied that it is almost impossible to find a common thread among them. Since they are produced by virtually all cells, and since their actions seem to be local (that is, within "diffusing distance" rather than requiring a transport medium), it is assumed that they exert their effects locally—in the cell or its immediate vicinity. They have actions on some part of nearly every organ system, but their actions on the reproductive, cardiovascular, and digestive systems seem to have received the most attention. One of their actions, for example, is to inhibit smooth muscle in blood vessels, which dilates the vessels and reduces the blood pressure. But they also cause contraction of other smooth muscle, such as in the digestive tract and uterus. These and other actions have prompted investigations into their possible value for a number of applications ranging from treatment of high blood pressure to inducing labor.

When all the effects of the prostaglandins are tabulated, it is noted that most if not all actions are those in which cAMP is involved. Prostaglandins increase the content of cAMP in most cases, but there are a few tissues in which they decrease the amount of cAMP. By altering the formation of cAMP in cells the prostaglandins can affect the response of those cells to a hormone whose action involves cAMP. Prostaglandins may turn out to be local modulators of cAMP-induced reactions. It remains to be seen what controls the production of the prostaglandins.

Control of Hormone Secretion

The rate of secretion of an endocrine gland is regulated by neural and/or chemical means. A number of endocrine glands are innervated by autonomic fibers, chiefly parasympathetic, but for the most part these nerves exert only secondary control. Cutting the nerve does not have much effect on the secretion of the gland, and stimulation may only raise the level of secretion slightly.

One endocrine gland, however, receives an important nerve supply. That is the adrenal medulla, which receives sympathetic innervation by a preganglionic neuron, and secretion by the adrenal medulla is part of the response of the sympathetic nervous system. (Recall that epinephrine, the hormone produced by the adrenal medulla, resembles norepinephrine, the sympathetic postganglionic transmitter, both chemically and in the action produced.) In addition, the release of hormones from the posterior lobe of the pituitary gland is directly controlled by neurons from the brain in a unique manner, to be discussed below.

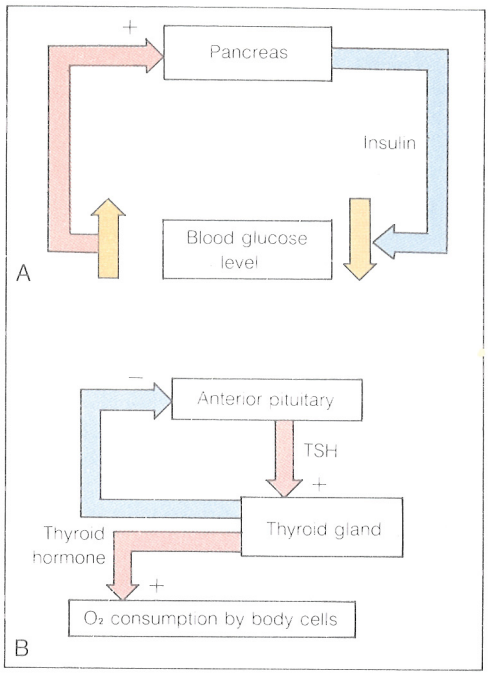


FIGURE 13–2
Negative feedback control of hormone secretion. A. Direct action, as in control of insulin secretion by the blood glucose level. B. Indirect action, as in control of thyroid hormone secretion by its effect upon secretion of thyroid stimulating hormone (TSH) by the anterior pituitary.

The major control of endocrine glands is chemical in nature. It is exerted by what is known as a **negative feedback mechanism.** The simplest form is a direct feedback such as in the control of the secretion of insulin. The overall effect of insulin is to lower the blood glucose level. Elevation of the blood glucose concentration causes increased production of insulin, which causes glucose to leave the blood and enter cells. As the level of glucose in the blood falls, there is less stimulation of the pancreas, insulin secretion declines, and the blood glucose level begins to rise once more (Figure 13–2A). When

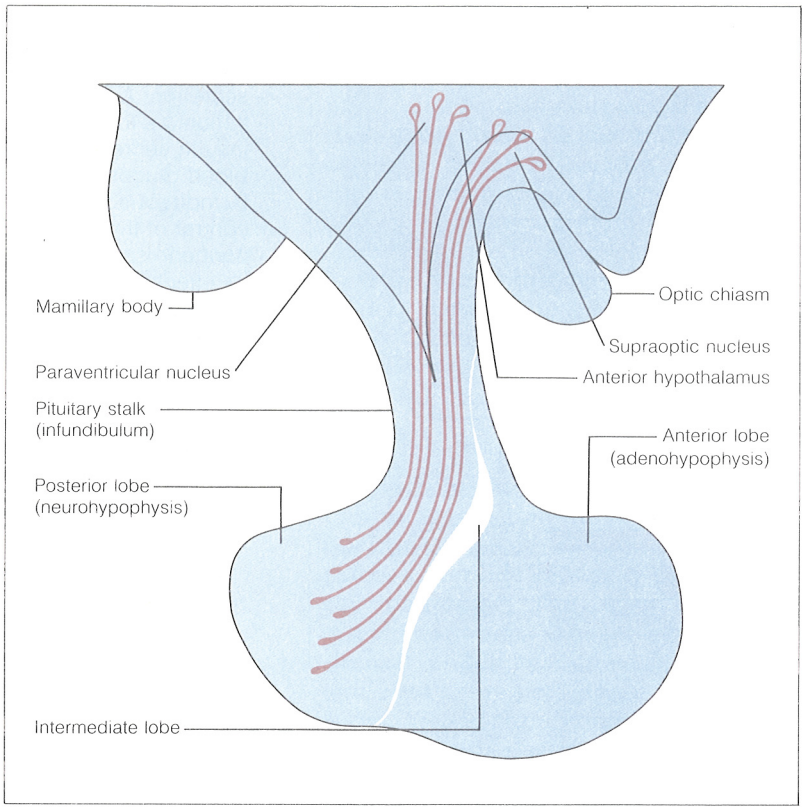


FIGURE 13–3 The pituitary gland and its innervation.

blood glucose is made to fluctuate by other factors (such as eating or exercise), the secretion of insulin is adjusted to reduce the magnitude of the fluctuations of glucose concentration. Negative feedback mechanisms are designed to maintain the status quo, to prevent change or, if change occurs, to bring things back to "normal." Thus, negative feedback is a homeostatic mechanism.

Several endocrine glands are controlled by a more indirect version of the same mechanism, as illustrated by the thyroid gland (Figure 13–2B). Thyroid secretion is stimulated by a hormone from the anterior pituitary known appropriately as the **thyroid-stimulating hormone (TSH).** A high level of thyroid hormone in the blood inhibits the pituitary secretion of TSH, which results in less stimulus for secretion of the thyroid hormone. Soon there is less of the latter to inhibit the production of TSH, and as TSH rises, the thyroid gland secretes more of its hormone.

The implication of the pituitary gland in the control of endocrine secretion is a rather complex subject that requires further consideration for two reasons. First, the anterior pituitary gland produces hormones that stimulate secretion by other endocrine glands, and it is regulated by the secretions of those glands (by negative feedback). Second, the pituitary is an important link between the nervous system and the endocrine system.

THE PITUITARY GLAND AND HORMONE CONTROL

The pituitary gland occupies a unique position among endocrine glands because of its role in the control of secretion by other endocrine glands. It also has a unique association with the nervous system—part of it (the neurohypophysis) is actually part of the diencephalon. The anterior portion (adenohypophysis) also has close ties with the brain. These connections regulate secretion by the pituitary, and therefore also the secretion by those glands controlled by the anterior pituitary. Because the pituitary gland has a special role in the overall regulation of hormone secretion, it is considered in some detail at this time.

Anatomy of the Pituitary Gland

The pituitary gland **(hypophysis),** safely hidden in the sella turcica of the sphenoid bone (see Figure 10–3), is three essentially separate glands, the anterior, posterior, and intermediate lobes (Figure 13–3). The **posterior lobe,** or **neurohypophysis,** is an outgrowth of the brain. It is connected directly to the brain by the **pituitary stalk** *(infundibulum),* and a tiny extension of the third ventricle of the brain can often be traced into the stalk and into the neurohypophysis itself. The posterior lobe contains relatively few cells and does not look much like glandular tissue. The **anterior lobe,** or **adenohypophysis,** develops embryologically as an isolated outgrowth of the primitive gut and migrates toward the neurohypophysis; it has a glandular appearance, with cords of several types of cells inter-

spersed with networks of vascular sinusoids. The **intermediate lobe** arises where the anterior and posterior portions of the developing pituitary come into contact with one another.

The neurohypophysis receives a prominent nerve supply in the several short fiber tracts that enter it by way of the pituitary stalk. These bundles arise in specific nuclei of the hypothalamus where the neurons have their cell bodies, and end near capillaries in the posterior lobe. Despite many persistent attempts to demonstrate secretory nerves, the adenohypophysis has no known innervation other than a few autonomic fibers to the blood vessels.

The posterior lobe receives its blood supply from tiny branches of the internal carotid artery (Figure 13–4). Arteries for the anterior lobe first form a network of capillary loops in the inferior portion of the hypothalamus. These capillaries then converge to form the several vessels of the **hypophyseal portal system** that descend along the stalk and drain into the sinusoidal capillaries in the adenohypophysis. Blood reaching the anterior lobe has therefore already passed through one capillary bed in the nearby hypothalamus.

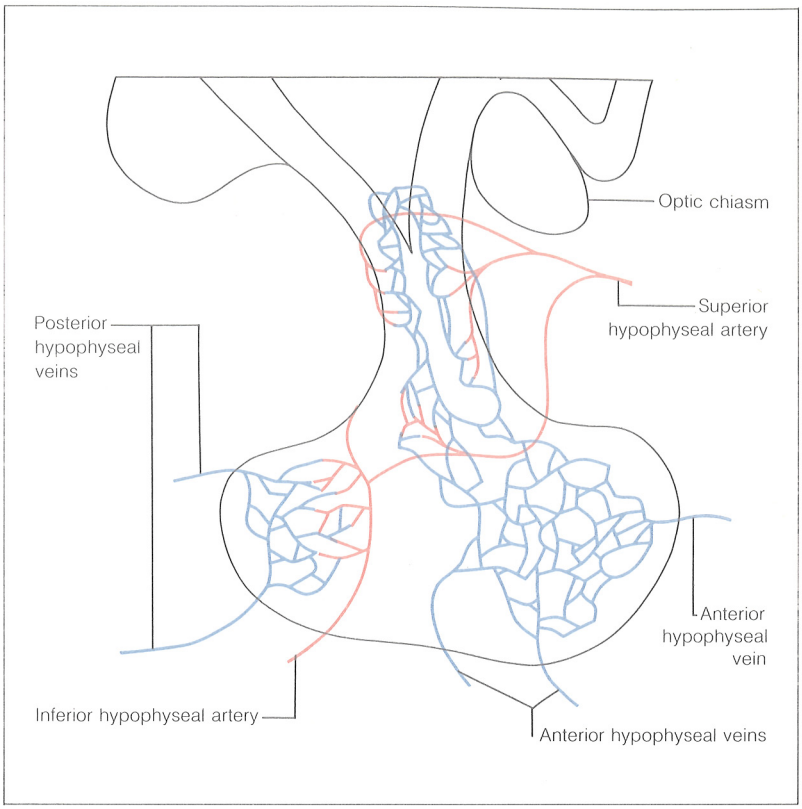


FIGURE 13–4 The blood supply of the pituitary.

The hormones secreted by the pituitary gland and their main actions are shown in Table 13–2. Over the years, other "factors" or "principles" have been attributed to the anterior lobe, but these effects are now generally believed to belong to the known pituitary hormones. Of those produced by the anterior pituitary, only the *growth hormone* and *prolactin* (in humans) do not have another endocrine gland as their target organ. FSH and LH, the gonadotropins, affect the gonads (ovary and testis), but they do much more than stimulate hormone secretion by the gonads. Prolactin has sometimes been considered to be a gonadotropin because in female rodents (especially the much-studied laboratory rat) it affects the gonad (luteotropic action), but this action is lacking in humans.

Control of Pituitary Secretion

Because the adenohypophysis controls the activity of several other endocrine glands, it has often been called the "master" gland. It is not, however, really in decisive control of the "lesser" glands; it relays messages, and it is itself controlled by the hypothalamus, which secretes minute amounts of specific substances called **releasing hormones** into the blood of the hypophyseal portal system. Upon reaching the anterior pituitary, each releasing hormone causes secretion of one of the anterior lobe hormones (Figure 13–5).

Releasing hormones that have been identified include a *growth hormone-releasing hormone (GRH)*, a *prolactin-releasing hormone (PRF)*, a *thyrotropin-releasing hormone (TRF)*, a *corticotropin-releasing hormone (CRF)*, a *follicle-stimulating hormone-releasing hormone (FRH)*, and a *luteinizing hormone-releasing hormone (LRH)*, although there is some question as to whether FRH and LRH are actually two different substances. There is also a hormone that inhibits the release of growth hormone (*GIH* or *somatostatin*) and prolactin *(PIH)*. There may also be a releasing hormone for melanocyte-stimulating hormone (MSH) produced

TABLE 13-2 THE PITUITARY HORMONES AND THEIR ACTIONS

Hormone	Other Names	Major Action
Adenohypophysis		
Growth hormone	GH; somatotropin, somatotropic hormone	stimulates growth of body
Thyroid-stimulating hormone	TSH; thyrotropin	stimulates thyroid growth and secretion
Adrenocorticotropic hormone	ACTH; corticotropin	stimulates growth and secretion by adrenal cortex
Follicle-stimulating hormone	FSH; gonadotropin	stimulates growth of ovarian follicle in female and spermatogenesis in male
Luteinizing hormone	LH; interstitial cell-stimulating hormone, ICSH; gonadotropin	stimulates ovulation, formation of corpus luteum, and hormone secretion in female; stimulates secretion by interstitial cells in male
Prolactin	lactogenic hormone, luteotropic hormone, LTH	stimulates secretion of milk; maintains corpus luteum in female rodents
Neurohypophysis		
Antidiuretic hormone	ADH; vasopressin	promotes water reabsorption from collecting tubule of kidney
Oxytocin	—	stimulates milk ejection, and contraction of pregnant uterus
Intermediate lobe		
Melanocyte-stimulating hormone	MSH; melanotropin, intermedin	expands melanophores (changes skin color); no known function in humans

by the intermediate lobe. One wonders if there is any significance to the fact that inhibitory hormones exist for the hormones whose target organ is not another endocrine gland.

A rather different arrangement exists for the neurohypophysis. The neurons in the fiber tracts that run from the hypothalamus to the posterior lobe release substances from their terminals upon stimulation, but the nerve endings are near capillaries in the posterior lobe. These capillaries are not part of the hypophyseal portal system, and the substances entering them are carried throughout the body. The hormones of the posterior pituitary are actually produced by neurons whose cell bodies are in the hypothalamus. Since so-called posterior lobe hormones are released from it, but not produced by it, one may rightfully question whether the posterior lobe is, in fact, an endocrine gland.

The arrangement by which the hypothalamus exerts control over the pituitary gland is not as unique as it might seem. We have seen that all nerve fibers produce their actions by releasing a chemical, which we call a transmitter, from their terminals when they are stimulated. The hypothalamic neurons do the same. The difference is that they release their "transmitter substances" near capillaries instead of postjunctional membranes. In the posterior lobe the substances are released near and enter capillaries of the general circulation of distribution throughout the body; the substances are called *hormones*. Other hypothalamic fibers release their "transmitter" near capillaries of the hypophyseal portal system to be carried to the anterior and intermediate lobes where they diffuse into the interstitial fluid and act on the pituitary cells; these substances are called *releasing hormones*. Each kind of releasing hormone "recognizes" the cell that produces "its" hormone because the membrane of that cell has receptor binding sites for that releasing hor-

mone. The releasing hormone then binds to it and triggers the sequence of events for which that cell is programmed. The hormone produced as a result is released from the pituitary cell, enters the bloodstream, and is carried to the target organs.

Hypothalamic control of pituitary function is the means by which the nervous system exerts control over many hormonal systems. The nervous system has a much more highly developed sensing mechanism, and the hypothalamus, in a sense, gives the endocrine system a "digest" of the sensory information obtained by the nervous system. This information ensures that endocrine responses are appropriate to internal and external conditions. The hypothalamic connections explain the effects of stresses (emotional and otherwise) upon a number of hormonally controlled processes.

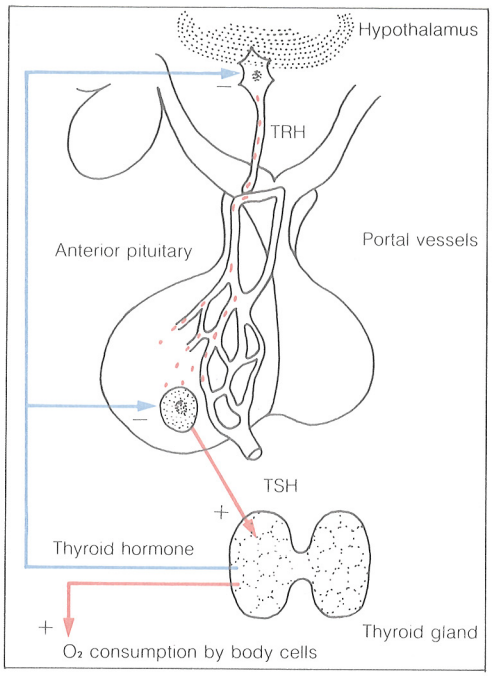


FIGURE 13–5 Control of hormone secretion by hypothalamic releasing hormones.

Neural Versus Hormonal Control

Most of the activities of the body are in response to a stimulus, with controls built into the system to ensure its effectiveness. A control system for stimulus-response behavior requires the following elements:

1 A mechanism to produce a response (the efferent and effector).
2 A mechanism to detect or monitor conditions (receptor and afferent).
3 A mechanism to bring the two together in order to assess and evaluate incoming information and to determine the appropriate response (a center).

We have two systems by which responses can be directed, the nervous system and the endocrine system. The nervous system sends messages from one place to another in the form of action potentials which travel along nerve fibers that extend from here to there. The action is exerted by the release of small packets of chemicals (transmitters) at the neuroeffector junction. The endocrine system sends messages in the form of chemicals (hormones) released into the bloodstream to be carried from here to there. They exert their action at some distant target organ.

The nervous system has all the required elements of a control system. It has a well-developed efferent system. It can get messages to all sorts of effectors (excitable cells) to produce a response that may be brief and instant or continuous, precise and localized, or generalized and widespread. The nervous system has a well-developed array of monitors and sensors, which includes receptors on the body surface that provide information about the external environment, and receptors in skeletal muscle and viscera that tell about conditions inside the body. The nervous system has marvelous centers to integrate all this information and to send out directions. The centers are organized in a hierarchy of command with the minimal elements for a simple response (a stretch reflex) on the spinal cord level. Centers in the brainstem exert control over the cord centers, and centers above that (cerebellum, basal ganglia) exert a higher level of control, while areas of the cerebral cortex exert control over all of those below.

The endocrine system, on the other

hand, has a good efferent component, but lacks a true integrating center of its own. It also does not have a very good mechanism for sensing and monitoring the environment, either external or internal. There is no means for providing information about what is happening "out there," except for the negative feedback mechanism, which is limited in scope.

Further contrasts are apparent if we consider characteristics of the responses produced by the two control systems. We tend to think of neural responses as rapid and quick, as in a knee jerk, while the endocrine response is slower and with a longer latency and more prolonged action. Perhaps it would be better to make comparisons in a different way, so as to show the two systems less as opposite or antagonistic systems. This may be generalizing too much, but it might contribute some perspective to your overall view.

Consider the somatic nervous system. It involves responses to changes in the external environment. The stimuli come from outside the body, applied to the body surface or to visual or auditory receptors that detect changes at a distance. The response is of the "body." Skeletal muscle, as the effector, brings about movement of parts, primarily the limbs, resulting in movement of the body. The response is quick (measured in milliseconds to seconds), usually brief and precise, and well localized.

Consider the autonomic nervous system. It involves primarily responses to changes in the internal environment (pressure of the blood, distension of the stomach or urinary bladder). The responses are carried out by smooth muscle, cardiac muscle, and glands of certain organ systems and bring about adjustments that tend to support and maintain homeostasis. The responses are of longer latency, slower and more prolonged, being measured in seconds and minutes.

Consider the endocrine system. Here we see a system that responds to metabolic needs, involving stimuli such as changing levels of substances in the blood (glucose, calcium, etc.). The responses are carried out at the cellular level and involve metabolic functions, such as increased synthesis of a particular enzyme, changes in the permeability of a cell membrane to a substance (glucose), or activation of some enzyme. These responses are generally of still longer latency and are slower, more prolonged actions. They are measured for the most part in minutes and hours.

The nervous system and endocrine system should not be considered as two opposing systems, but rather as elements of a continuous spectrum of control with considerable overlap between the various parts. The autonomic nervous system seems to be a link between neural and hormonal controls through its association with the hypothalamus, and with the adrenal medulla and its secretion of epinephrine which has both neural and endocrine functions.

There are certain reflexes, known as *neuroendocrine reflexes*, in which the receptor and afferent are neural and the efferent limb is hormonal. Such mechanisms are involved in control of one of the hormones released from the posterior pituitary (see below). And finally, the nervous system, which has the better sensory system and better integrative centers, directs and coordinates much of the endocrine function through the action of hypothalamic releasing hormones[3] on the anterior pituitary and its endocrine target organs.

ENDOCRINE GLANDS AND THEIR SECRETIONS

The remainder of this chapter is devoted to the individual endocrine glands and the hormones they produce. The discussion of the action of these secretions and their significance, however, will be more in the nature of an introduction than a complete coverage. Hormones affect the actions of specific cells that carry out specific processes of

[3]Evidence is accumulating that the releasing hormones may have other actions. Some have been found in other parts of the nervous system and may be synaptic transmitters, and at least one (GIH), which has been found in other organs, has some effect on the digestive system.

the individual organ systems, and you cannot fully understand the hormone actions until you have some understanding of the organ systems. The actions of most of the hormones identified here are discussed more fully in the chapters that follow, as part of the regulation of a particular organ system.

The Pituitary Gland

The anatomy and control of the pituitary gland have been described in earlier sections, and some of its hormones have been mentioned. At this time we need only consider those hormones and their actions.

Adenohypophysis The action of most of the hormones of the adenohypophysis is very simple—they stimulate secretion by their target organs. Some have other actions as well, and these will be discussed with their target organs.

The target organ for the **growth hormone,** however, is not another endocrine gland. As indicated by its other name, **somatotropin,** it stimulates many parts of the body, although its major effects are on the metabolic reactions of skeletal muscle and on developing bone. In the latter case, it increases the rate of cell division among cartilage cells in the growing bones, which increases cartilage growth in the epiphyses of long bones and delays the completion of ossification. By postponing the final closure of the epiphyses the bone is able to grow for a longer period of time and attain a greater length. Besides helping cartilage formation in bone, growth hormone also has a positive effect on synthesis of the organic component of bone, which is related to its effect on protein metabolism.

In all tissues, but especially in skeletal muscle, growth hormone has several actions that favor protein anabolism, that is, the use of amino acids to form protein rather than for energy or formation of glucose or fat. This leads to an increase in the amount of structural protein and to a general increase in muscle mass. Such use of amino acids is aided by other actions of the hormone, because growth hormone also causes mobilization of fat from storage, releasing more fatty acids into the circulation, and it raises the blood glucose level by causing the release of glucose from the liver. The way in which these metabolic actions fit into the total body economy will be made more apparent in Chapter 24.

Although the pituitary gland is not essential for life, an animal deprived of it (by *hypophysectomy*) has serious problems, due largely to absence of the adenohypophysis. Target organs that depend upon the drive of the pituitary tropic hormones tend to atrophy, and there is a reduction both of their hormone secretion and of their other functions. Most of the symptoms of hypophysectomy (removal of the gland) can be traced to the resulting *hypofunction* of the various target organs. Since several of the hormones of the pituitary and its target organs have important effects on metabolism, the hypophysectomized animal is susceptible to many things because it cannot properly adjust its metabolic processes. Similarly, *hyperfunction* of the pituitary shows up largely as increased activity of the target organs. Pituitary malfunction usually involves all the pituitary hormones, but selective malfunction is most likely to involve growth hormone.

Hyposecretion of growth hormone in a young child results in an individual of small stature, the **pituitary dwarf** or midget. Such people are well proportioned, but they are small. They are usually of normal mentality, but hyposecretion by other pituitary target organs, particularly the thyroid and adrenal cortex, may cause other problems. Also, the pituitary dwarf often fails to attain sexual maturity or fertility because of insufficient gonadotropin to cause development of the gonads.

Hypersecretion of growth hormone during the growth years, before ossification is completed, produces a condition known as **gigantism,** in which the individual is tall but has the musculature appropriate to the large frame. If the secretion of growth hormone becomes excessive only after the epiphyses have closed, there is no increase in the length of the long bones; instead there is a thickening of certain bones.

The lower jaw grows and the brows become prominent, giving a characteristic and striking facial appearance. The hands and feet become enlarged and there are changes within the bone tissue. This condition is known as **acromegaly.**

Thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH) cause secretion of the thyroid and certain adrenal cortical hormones, respectively. The effects of malfunction are those of hypo- or hypersecretion of the target organ and are discussed with those organs. Likewise, gonadotropin and prolactin are discussed with the reproductive systems whose function they help control.

Neurohypophysis Two hormones known to be released from the neurohypophysis are the **antidiuretic hormone (ADH)** and **oxytocin.** They have almost identical chemical structures, each one being composed of nine amino acids, seven of which are the same. They are released from the neurohypophysis by stimulation of the nerve fibers from the hypothalamus rather than by releasing factors. As stated above, hormones released from the neurohypophysis are synthesized in the nuclei of the hypothalamus (ADH in the supraoptic nucleus and oxytocin in the paraventricular nucleus), from which the nerve fibers arise (see Figure 13–3). The hormones migrate down the nerve fibers as secretory granules and accumulate at the nerve endings near blood vessels in the neurohypophysis.

Antidiuretic hormone is released when receptors in the hypothalamus *(osmoreceptors)* detect an increase in the osmotic pressure of the plasma of the blood flowing through them, as might occur when you are dehydrated. A decrease in the plasma osmotic pressure inhibits the release of ADH. The hormone acts almost exclusively on cells of certain ducts of the urine-producing apparatus of the kidney (collecting ducts). The fluid in these ducts is destined to be excreted from the body as urine. By themselves, they are not permeable to water, and nearly all of the fluid passing through the ducts is excreted. ADH increases the amount of cAMP in the cells; this increases their permeability to water. Therefore, in the presence of ADH, much of the water in the ducts is transferred through these cells and is returned to the blood (reabsorption). ADH thus reduces the volume of urine excreted but makes it more concentrated. A lack of ADH causes *diabetes insipidus,* a disease characterized by excretion of excessive amounts of very dilute urine (see Chapter 28).

In large amounts (*pharmacological* rather than *physiological* doses), ADH causes constriction of blood vessels which raises blood pressure. This effect is not very prominent in humans, but in some species it is important, and it is the basis for the other name for ADH, *vasopressin.*

Oxytocin has two actions, both upon reproductive structures: the mammary glands and the uterus. (It has no known function in the male, although it is secreted.) Once the mammary glands have been primed by the actions of several other hormones, which cause development of a duct system and secretory apparatus within the gland, oxytocin causes ejection of the milk by a neuroendocrine reflex. The suckling infant stimulates touch receptors in the nipple whose afferent fibers have connections with the hypothalamus and lead to oxytocin release. After a short latency, milk is ejected from the alveoli in the mammary gland.

The second action of oxytocin is upon the smooth muscle of the uterus. During pregnancy the uterine musculature becomes progressively more sensitive to oxytocin until, in late pregnancy, strong uterine contractions can be elicited by very small amounts of oxytocin. It is doubtful that oxytocin plays an important part in the induction of labor, but it is released during the course of labor. The mechanism seems to be another neuroendocrine reflex, this one apparently initiated by stimulation of receptors in the lower part of the uterus (the cervix) as the fetus passes along the birth canal. Pituitary extracts containing oxytocin are sometimes administered to induce labor, but this must be done with great care, since extremely powerful uterine contractions may result.

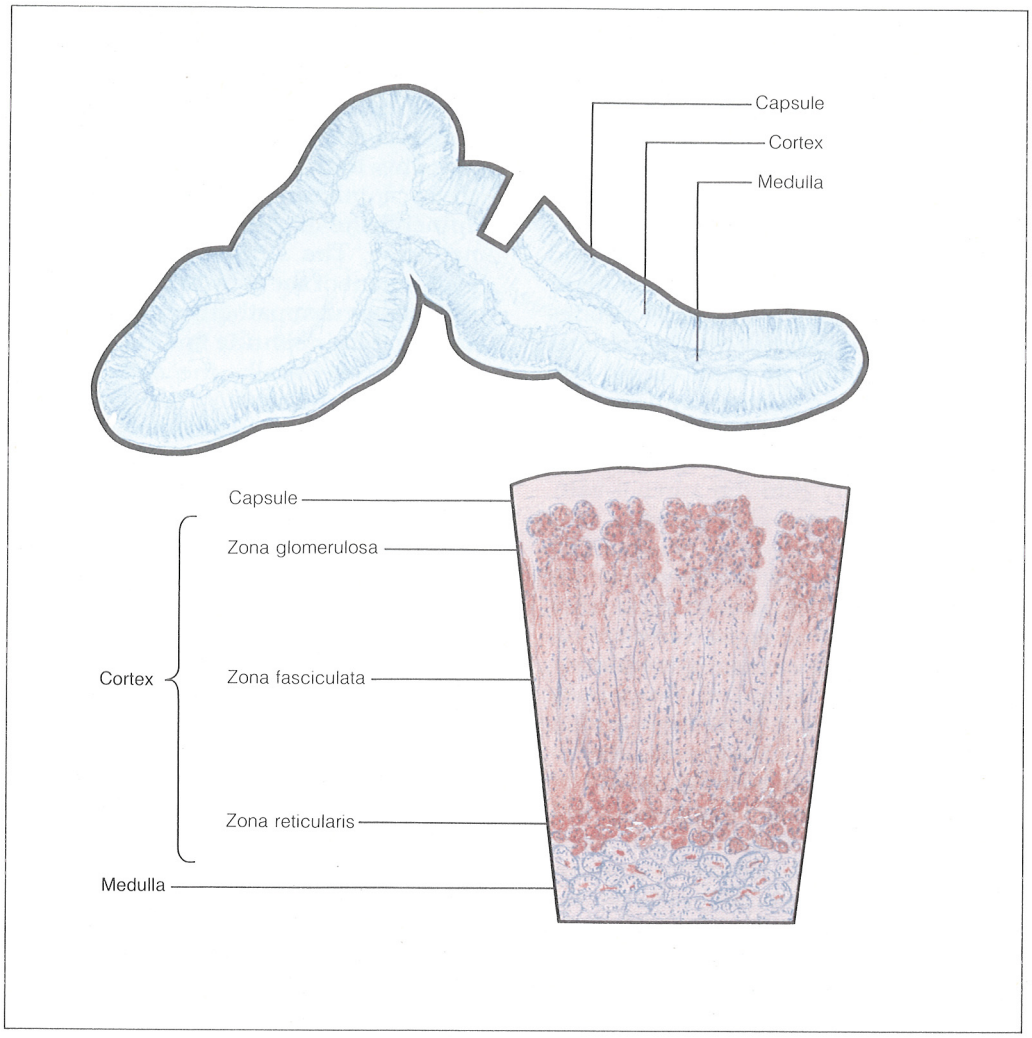


FIGURE 13–6 Structure of the adrenal gland.

Intermediate Lobe The skin of amphibians, fish, and reptiles contains melanocytes whose melanin pigment granules can move about within the cytoplasm. When the melanin granules are congregated around the nucleus they are less visible and the skin appears light, but when they are dispersed throughout the cytoplasm the skin looks dark. In these species, the hormone of the intermediate lobe, **melanocyte-stimulating hormone (MSH),** causes dispersion of the pigment granules and darkens the skin. The mechanism is probably a neuroendocrine reflex. Receptors in the retina of the eye have connections with the hypothalamus, which may either cause or inhibit the release of MSH. There is an MSH-RFH as well as nerve fibers to the intermediate lobe. This response does not occur in mammals, since the melanocyte granules cannot move. MSH therefore has no known effect in mammals, although there is some evidence of its involvement in certain conditions of hyperpigmentation in humans.

Adrenal Glands

Because of their location atop the kidneys, the adrenal glands are also known as the **suprarenal glands.** Like the pituitary, each adrenal gland consists of separate entities, an outer **adrenal cortex** and an inner **adrenal medulla** (see Figure 13–6). The two are

very different glands in terms of their embryological origins, their controlling mechanisms, the hormones they produce, and the processes these hormones affect.

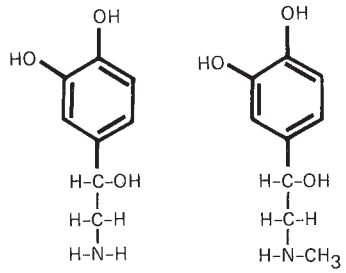
Anatomy of Adrenal Glands The adrenal gland receives a greater blood flow per gram of tissue than any other organ in the body. The adrenal arteries enter the gland through the capsule that encloses it. Some of them break into capillaries in the cortex, while others pass directly to the medulla, but all vessels eventually drain through the medulla and empty into the adrenal vein, which thus drains both cortex and medulla.

The adrenal cortex develops near the kidney and remains in close association with it. Its characteristic three layers include the **zona glomerulosa,** whose cells are arranged in globular clumps (glomeruli), a thicker middle **zona fasciculata,** whose cells are arranged in long parallel cords separated by sinusoids (small venous sinuses), and the innermost and relatively narrow **zona reticularis.** The latter zone lies adjacent to the adrenal medulla, but there is no sharp line of demarcation between them, even though they are different organs. The adrenal cortex does not receive a nerve supply other than to its blood vessels.

The smaller adrenal medulla develops from neural tissue, but early in fetal life it migrates laterally until it comes to be embedded in cortical tissue. It is composed of irregularly interconnecting cords of cells interspersed with capillaries and venules. It has been likened to a sympathetic ganglion whose neurons have lost their axons, since it is innervated by sympathetic preganglionic neurons, and its secretion is very similar to the transmitter released by sympathetic postganglionic fibers.

Adrenal Medulla The anatomical tie between the adrenal medulla and the sympathetic nervous system is further reflected in their functions. Medullary secretion is governed by sympathetic neurons and is an important part of sympathetic discharge. The adrenal medulla, like the rest of the sympathetic nervous system, is not essential to life, but it is important to the ability of the organism to meet emergencies.

The human adrenal medulla secretes a mixture of about 80 percent epinephrine and 20 percent norepinephrine. The latter is also the chief component of the transmitter substance released by sympathetic postganglionic endings. Epinephrine and norepinephrine are chemically the same, except that epinephrine has an extra CH_3 (methyl) group.[4] They belong to a class of compounds known as the **catecholamines,** and are frequently referred to by this name because they are often found together, and because many analytical tests cannot distinguish between them. For the most part, the actions of epinephrine and norepinephrine are similar to one another and to those of the sympathetic nervous system. The differences between them are in part quantitative and in part due to the fact that epinephrine, as a true hormone, is widely distributed throughout the body, while the action of norepinephrine is more restricted to the immediate vicinity of the adrenergic (sympathetic postganglionic) nerve endings. Once released, both epinephrine and norepinephrine have a very short half-life.



Norepinephrine Epinephrine

[4]They are synthesized from the amino acid phenylalanine, to which the two hydroxyl (OH^-) groups are added, forming *dihydroxyphenylalanine (DOPA).* Removal of the carboxyl group ($COOH^-$) leaves *dopamine,* and addition of another OH^- gives *norepinephrine,* while addition of a methyl group yields *epinephrine.*

Dopamine is probably a transmitter in its own right. It is present in high concentrations in certain parts of the brain. Dopamine is the substance that is in low concentration in the basal ganglia of patients with Parkinson's disease. DOPA is the substance that relieves the symptoms in some of these patients.

Both epinephrine and norepinephrine increase the heart rate, but epinephrine has a greater effect. Epinephrine also causes the cardiac muscle to shorten faster and contract more forcefully. It therefore can cause a marked increase in the amount of blood pumped by the heart (the cardiac output).

Norepinephrine and epinephrine are both effective constrictors of the blood vessels of the skin and viscera, which receive important sympathetic innervation. This action increases the resistance to the flow of blood and raises the blood pressure. Epinephrine, however, is a dilator of skeletal muscle blood vessels (where the role of the sympathetic innervation is still unsettled), and because so much of the body's mass is muscle, the overall effect of epinephrine may be a fall in total resistance and a consequent slight fall in pressure. These effects on blood pressure are also influenced by the response of the heart. The cardiovascular effects of the catecholamines are also discussed in Chapters 15, 17, and 18.

Epinephrine has greater effects on metabolic processes than norepinephrine, such as raising the blood glucose level by causing its release from the liver. However, both facilitate the use of glucose by skeletal muscle and other tissues, raise the metabolic rate and heat production, and stimulate the central nervous system.

Epinephrine and norepinephrine, like other hormones, must first bind with a receptor on the target cell. Observations that certain drugs would block some of the actions of the catecholamines, but not others, led to the discovery that there are two kinds of receptors to which they may bind. They have been designated *alpha* and *beta receptors.* In general, binding with alpha receptors leads to constriction of blood vessels (and elevation of blood pressure), while binding to beta receptors leads to increased rate and force of the heartbeat as well as metabolic and other effects. Beta receptors activate adenyl cyclase resulting in the formation of cAMP. Drugs that block actions mediated by the alpha receptors have been helpful in treating certain types of hypertension (high blood pressure).

There are no particular problems due to hyposecretion of the adrenal medulla, and only rarely may a tumor cause hypersecretion of epinephrine. The symptoms of this condition can readily be predicted.

Adrenal Cortex The adrenal cortex is essential to life, and its removal is fatal within about a week unless certain hormones are administered. This fact has been known for a long time, but it was not until shortly after World War II that the substances produced by this gland were isolated, identified, and made available for use.

Approximately forty compounds have been isolated from the adrenal cortex. About a fourth of them are biologically active, but in humans only three or four are actually secreted by the gland in significant amounts. The other compounds are all chemically related and many are intermediates in the synthesis or degradation of the secreted hormones.

All of these substances belong to a class of compounds known as the **steroids.** The steroids, which include male and female sex hormones, bile acids, vitamin D, and cholesterol, are a special group of lipids characterized by the presence of the "steroid nucleus," a four-ring framework (Figure 13–7). For convenience, each carbon is numbered, and individual steroids are described by the sidechains attached to certain carbon atoms.

The adrenal cortical steroids are synthesized from cholesterol and differ only slightly in their molecular configurations. They are divided into the following three groups principally on the basis of their major actions:

1 The **mineralocorticoids** primarily affect electrolyte metabolism.
2 The **glucocorticoids,** named for their effect on glucose metabolism, also importantly affect protein and fat metabolism.
3 The **androgens** have male sex hormone activity.

In general, glucocorticoid activity has been associated with the presence of oxygen (as =O or —OH) at C11 (the eleventh carbon atom), and mineralo-

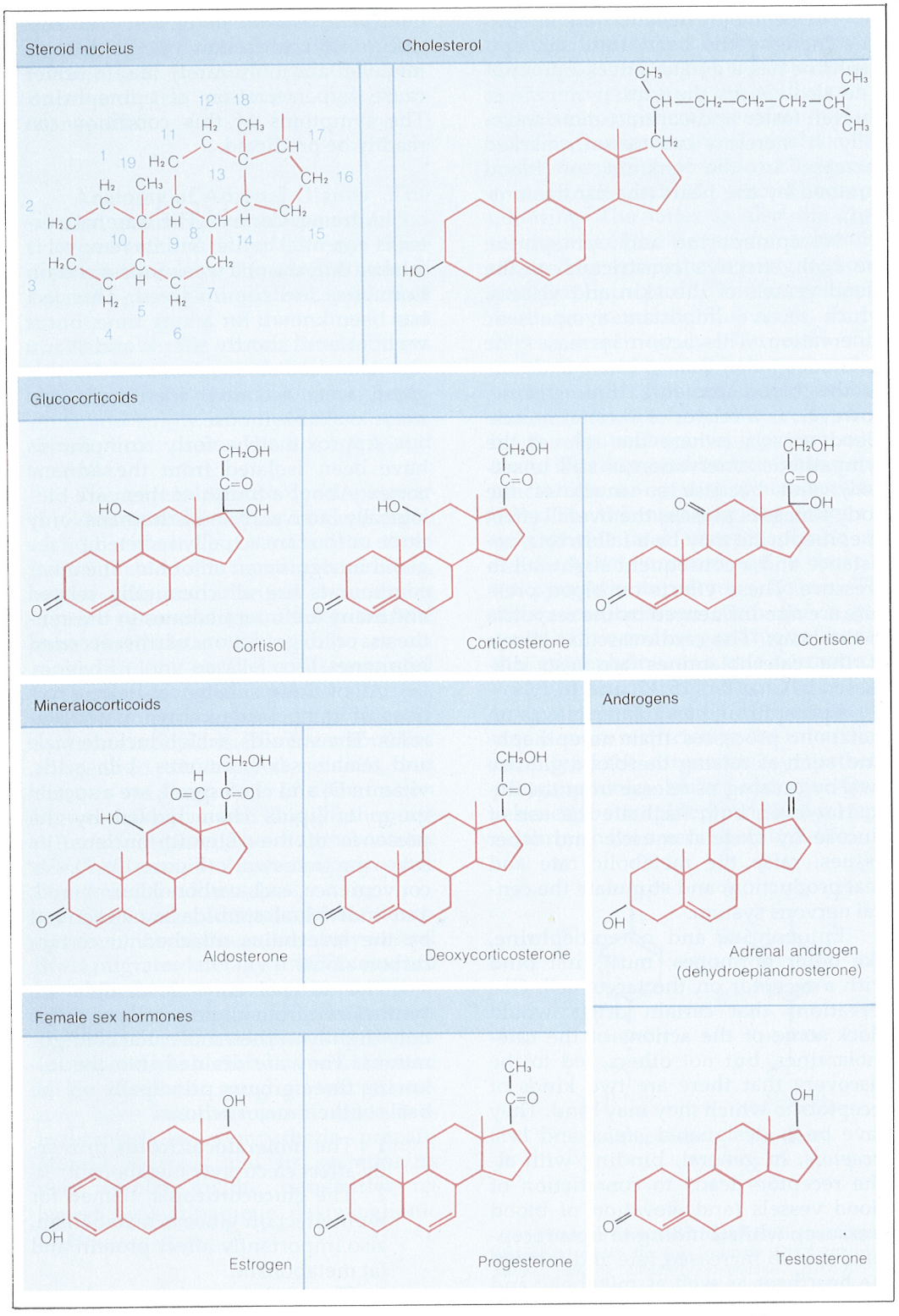


FIGURE 13–7 The steroid nucleus and some biologically important steroids.

corticoid activity with steroids lacking oxygen at that site. Mineralocorticoids and glucocorticoids have 21 carbons, but steroids with androgenic activity tend to have only 19 carbons. These "rules" are not, however, hard and fast, since aldosterone, the most potent mineralocorticoid, has an —OH at C11. Aldosterone also has some glucocorticoid activity as well, and this overlapping of actions is actually typical of most of the adrenal cortical steroids; their actions are not one *or* the other, but varying degrees of both. Certain chemical configurations enhance or impair particular actions, and knowledge of these structure-activity relationships has been applied by organic chemists in the search for synthetic compounds with the desired actions, but without undesirable side-effects.

As steroids, the adrenal cortical hormones act in the nucleus of the target cell. They increase formation of the RNA needed for synthesis of the enzymes that carry out the specific actions attributed to the steroid homones.

Mineralocorticoids. The two important mineralocorticoids are **aldosterone,** which is effective in extremely small amounts and is the most important physiologically, and **deoxycorticosterone,** which is much less potent. Deoxycorticosterone is not produced by the adrenal cortex in significant amounts, but because it can be synthesized easily and inexpensively, it is often used clinically (as deoxycorticosterone acetate, DOCA, DCA) when mineralocorticoid treatment is called for.

Aldosterone is secreted only by the zona glomerulosa, and it is produced continuously, for unlike the rest of the adrenal cortex, it does not depend upon the pituitary command (ACTH) for secretion to occur. ACTH is not totally ineffective, however, since it can cause an increase in the rate of aldosterone secretion. In the absence of ACTH, the aldosterone secretion in response to stressful stimuli is greatly reduced, but the zona glomerulosa does not atrophy.

The rate of aldosterone secretion is influenced by many conditions, including blood volume, plasma electrolyte concentration, and certain types of stress, but its major control is apparently the renin-angiotensin mechanism described in Chapter 28. The angiotensin II produced in response to renin release is an important stimulus to aldosterone secretion. All the necessary stimuli for this mechanism are not completely understood, but renin release is known to follow both reduction in blood flow to the kidney and reduction in sodium transport in the kidney. Low sodium and increased potassium in the plasma are also known to increase aldosterone production, but whether directly or through the renin-angiotensin mechanism is unclear. At any rate, aldosterone secretion is increased when blood volume and pressure are down or when the electrolyte content is disturbed. The resulting secretion of aldosterone then brings about adjustments that help relieve these situations.

The mineralocorticoids, in general, and aldosterone in particular, reduce the amount of sodium lost in the urine. Sodium is actively transported from the urine across the kidney cells and is returned to the bloodstream. The reabsorption of sodium secondarily increases reabsorption of chloride and, by diffusion and osmosis, water. Aldosterone helps retain sodium by reducing its content in sweat, saliva, and gastric juice. Mineralocorticoids also increase the loss of potassium in the urine by reducing its reabsorption.

In the absence of mineralocorticoids, sodium reabsorption is reduced. Although the excretion of sodium causes some increase in water excretion, the sodium loss is greater, and the extracellular fluids become slightly hypotonic. Water then tends to enter the cells and the extracellular fluid volume (including plasma) is further reduced. This causes circulatory problems, beginning with a fall in blood pressure that reduces the flow of blood to all organs, including the kidney. The ability of the kidney to excrete wastes is impaired and waste concentration in the blood rises. Continued lack of mineralocorticoids eventually leads to circulatory collapse and death. The adrenal cortex is essential to life, chiefly because of the mineralocorticoids.

Glucocorticoids. The glucocorticoids are concerned with metabolism of

protein, fat, and carbohydrate. Metabolic effects are associated with steroids that have an oxygen at C11, and the most potent have oxygen at C17 as well. The most important glucocorticoids produced by the human adrenal cortex are **cortisol** and **corticosterone** (see Figure 13–7), with cortisol being produced in much greater amounts. **Cortisone** is not actually secreted by the gland, but it is biologically active and commercial preparations are widely used for conditions that respond to glucocorticoid therapy.

The actions of glucocorticoids on the three major foodstuffs are so interrelated that it is difficult to determine which are primary actions and which are secondary. The glucocorticoids tend to elevate the blood glucose level by increasing *protein catabolism,* which raises the amount of amino acids available for conversion to glucose. They also mobilize fat in adipose tissues, thus increasing the free fatty acids in the blood, and they interfere with the utilization of glucose in the tissues, especially in skeletal muscle. An important, though poorly understood, action of the glucocorticoids is their "permissive action." There are a number of metabolic reactions which the glucocorticoids do not cause, but which will not occur in their absence.

The glucocorticoids have several specific actions that do not appear to be direct results of their metabolic effects. One of these is to maintain *vascular reactivity,* since without glucocorticoids the blood vessels are unable to respond to circulating epinephrine or to norepinephrine liberated by sympathetic nerve fibers. This inability undoubtedly contributes to the circulatory difficulties encountered in adrenal insufficiency.

Glucocorticoids (primarily cortisone) are often administered in massive (pharmacological) doses because at very high levels they inhibit the *inflammatory reaction.* The inflammatory reaction is the normal response of cells to tissue injury (see Chapter 14), and typically includes three phases:

1 local swelling, redness, and pain due to dilation of blood vessels and movement of fluid from blood vessels into the tissue spaces of the injured area;
2 invasion of the area by macrophages from the blood (some white blood cells are phagocytes) and from surrounding tissues;
3 increased synthesis of connective tissue, which walls off the injured area and is the first step in repair of the injured tissue.

Glucocorticoids exert an inhibitory action on all three phases of the inflammatory reaction. They are believed to inhibit the local release of some of the substances that cause dilation of the blood vessels, thereby reducing the accumulation of fluid in the affected area. Part of the normal inflammatory reaction is due to the action of hydrolytic enzymes (similar to enzymes in the digestive tract) released from the lysosomes of injured cells, including overworked phagocytes. Glucocorticoids are believed to stabilize the membranes of the lysosomes and thus prevent the release of these enzymes and the breakdown they cause. Fibroblasts produce the collagen fibers and ground substance that surround and wall off the inflamed area and begin the repair process. Glucocorticoids inhibit the fibroblasts, which slows the process of healing and tissue repair.

Because they suppress the inflammatory reaction, the glucocorticoids are effective in alleviating the symptoms of the so-called *collagen diseases,* such as rheumatoid arthritis. But they also interfere with wound healing in these patients (as after surgery). Furthermore, the absence of the inflammatory response may mask the presence of dangerous infection and allow it to spread unchecked.

The glucocorticoids also have beneficial effects on certain allergic reactions because of some of their anti-inflammatory effects.

The glucocorticoids are believed to be secreted chiefly by the middle layer of the adrenal cortex, the zona fasciculata. Secretion is the result of stimulation by ACTH from the adenohypophysis, and this portion of the adrenal cortex is quite dependent upon ACTH. Without it the cells atrophy and fail to secrete adequate amounts of hormone. Circulating glucocorticoids inhibit the release of ACTH, probably by direct action upon the pituitary gland and upon

hypothalamic production of the corticotropin-releasing hormone (CRH).

ACTH secretion is increased by a number of stimuli commonly considered stressful. They probably increase the secretion of CRH. Such diverse factors as trauma, infection, hemorrhage, exposure to cold, heavy muscular exercise, and such psychological traumas as fear, pain, and noise all quickly increase ACTH production, often enough to elicit a maximum secretion of glucocorticoids. The ability to respond to stress situations with an increase in glucocorticoids seems to be essential for the "nonspecific systemic reactions" that enable the body to survive long exposure to such stresses. Many of these stresses also cause a response of the sympathetic nervous system, and it is probable that part of the role of the glucocorticoids is related to this. Glucocorticoids are needed for the catecholamines to be fully effective, since they maintain the vascular reactivity that is so much a part of the catecholamine effects, and they enhance the fatty acid mobilizing action. Since sympathectomized animals can tolerate stress, the glucocorticoids must also have other important roles that are not yet understood.

Androgens. The adrenal cortex also produces steroids with sex hormone activity. The actions of these C19 steroids are predominantly those of male sex hormones (androgens), but there is probably some secretion of female sex hormones as well. Both are secreted by males and females under the stimulus of ACTH rather than of gonadotropins. In normal amounts these androgens have no known physiological function, but symptoms may occur when they are produced in abnormally high amounts. Androgens cause development of male characteristics, and when adrenal androgen secretion is excessive in young males, it may bring about an early puberty. The effects are less apparent in adult males. If adrenal androgen secretion is elevated in the female, the effect is masculinization, commonly including a receding hairline and facial hair. The actions of the sex hormones are further discussed in Chapters 29 and 30.

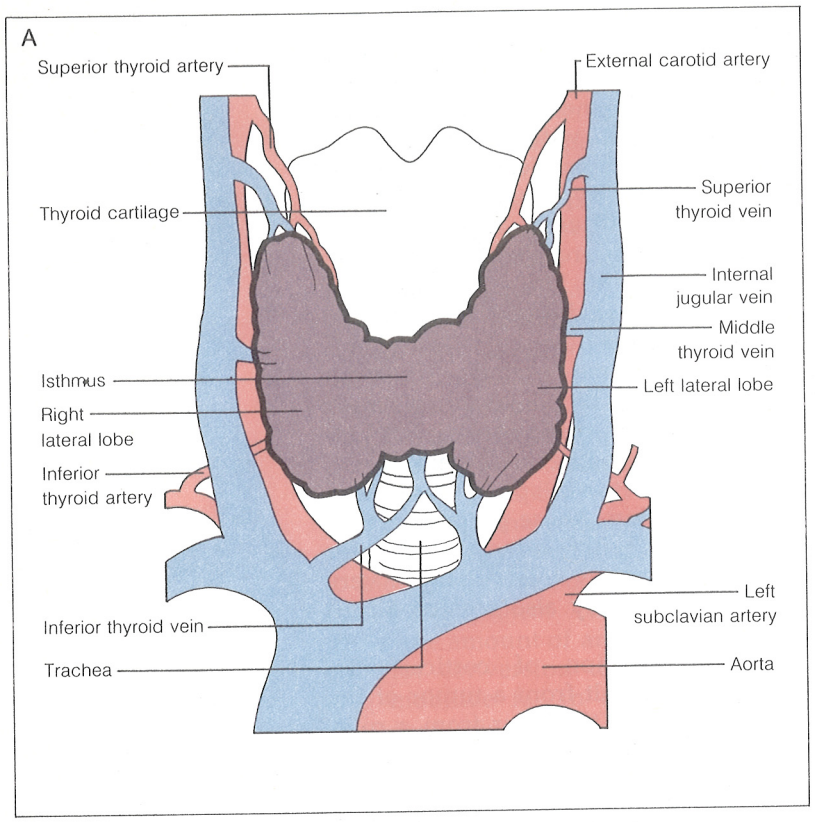
Abnormal secretion of adrenal cortical hormones. Removal of the adrenal glands *(adrenalectomy)* eliminates the source of both medullary and cortical hormones and, without replacement therapy, results in death. In humans adrenal cortical hypofunction is known as **Addison's disease.** The most conspicuous effects are the electrolyte disturbances due to lack of aldosterone, leading to reduced blood pressure and the related cardiovascular problems. Other symptoms include muscular weakness, low blood sugar (glucose), gastrointestinal disturbances, including loss of appetite and weight loss, and a progressive spotty pigmentation of the skin. These patients can be maintained with mineralocorticoids (DOCA), but they tolerate stress very poorly unless they also receive glucocorticoids.

Hypersecretion of cortical hormones may result from a tumor of the adrenal cortical tissue or from a pituitary malfunction. **Cushing's disease** is an example of the effects of excessive production of ACTH. The disease is characterized by obesity of the face, neck, and trunk, but *not* of the extremities. The skin is usually thin and the muscles weak, due to protein catabolism, and wounds heal poorly. There is high blood sugar, a certain amount of salt retention, frequently hypertension, and sometimes *hirsutism* (excessive hairiness). Many of these symptoms also occur as side effects of treatment with large doses of glucocorticoids (cortisone) or ACTH, but disappear once the treatment is discontinued.

Thyroid Gland

Anatomy of the Thyroid Gland The thyroid gland is an H-shaped organ located in the neck; it sits astride the trachea at its junction with the larynx (Figure 13–8). Two lobes, one on either side of the trachea, are joined by a narrow band of tissue, the *isthmus.* The thyroid has a blood supply second only to that of the adrenal glands, but its nerve supply is meager, mostly to the blood vessels.

The microscopic structure of the thyroid gland is unique. It consists of numerous closely-packed spheres, or



Courtesy Carolina Biological Supply Company

FIGURE 13–8 A. Gross anatomy of the thyroid gland. B. Photomicrograph of the thyroid gland.

follicles, formed of a single layer of cuboidal epithelial cells. These are the major secretory cells of the gland. The follicles contain a homogeneous protein substance called **colloid.** Interspersed between the follicles are small clusters of rather clear cells, often called **C-cells,** which also have a secretory function. Also between the follicles are numerous blood and lymph vessels, as well as the connective tissue necessary to support the gland.

Thyroid Hormones The function of the thyroid follicle is to produce, store, and release **thyroxin** and **tri-iodothyronine,** the major thyroid hormones. The cells that make up the follicle are responsible for the production of the thyroid hormones, but the actual synthesis occurs in the colloid of the follicle. The follicle cells are the source of the necessary enzymes, and they also produce the protein found in the colloid, which is known as **thyroglobulin.** The thyroid gland is unique in that the hormone produced in the follicles is stored there until it is needed, when it is transported across the follicle cells and released into the circulation.

To make the hormone, however, the cells require iodine, which occurs in the blood as *iodide* (I^-). Cells obtain it by actively pumping it from the blood into their cytoplasm, from which it diffuses into the colloid and is oxidized to "active iodine." This trapping process is so effective that nearly half the iodine in the body is in this small gland.[5]

The basis for the hormone molecules is the amino acid *tyrosine* (Figure 13–9). It is bound to the thyroglobulin

[5]The ability to trap iodine is the basis for one method of treating certain hyperthyroid conditions. Radioactive iodine (^{131}I) is administered in doses so small that only in the thyroid gland, which traps it so efficiently, is the concentration of radioactive iodine great enough to destroy any tissue. This permits tumors to be destroyed without surgery.

in the colloid in such a way that the ring portion of its molecule protrudes. Iodine becomes attached to the tyrosine ring at one or two sites to form mono-iodotyrosine (MIT) or di-iodotyrosine (DIT). These molecules are condensed to form tri-iodothyronine (T_3) or tetra-iodothyronine (T_4). The latter, T_4, is the chief hormone of the thyroid gland, thyroxin. These iodinated compounds are stored within the follicle, bound to the thyroglobulin (Figure 13–10).

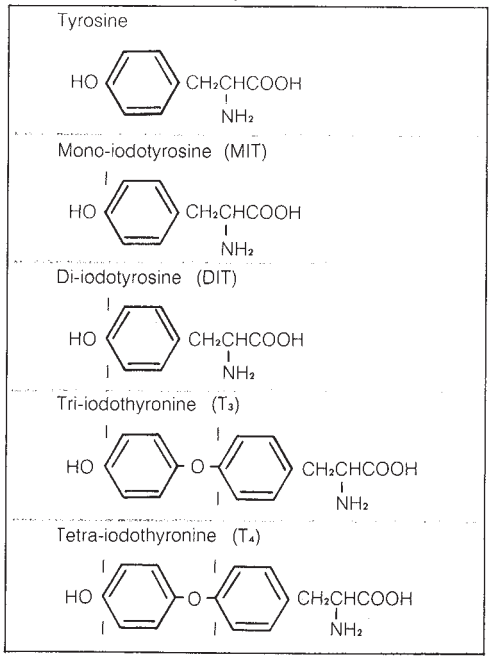
Release of the hormone into the bloodstream involves transporting it across the follicle cell. The follicle cell takes a "bite" of the edge of the adjacent colloid substance, ingesting thyroglobulin in a process much like phagocytosis. The thyroglobulin, with iodinated compounds still attached, now lies in a vesicle in the thyroid cell. The membrane of the vesicle merges with that of a lysosome, whose enzymes break off the iodine compounds. T_3 and T_4 are released into the bloodstream as thyroid hormones, but the iodine is removed from MIT and DIT and all of these components are recycled back into the colloid.

The thyroid gland also produces another hormone, **calcitonin.** It is not produced by follicle cells, but rather by the C-cells which lie between follicles. Calcitonin acts to lower the calcium level in the blood. Its role is discussed with the parathyroid glands whose secretions are most important in calcium metabolism (below).

Action of thyroid hormones. The specific effects of thyroxin and T3 on several organ systems can usually be traced to their more general effects, an increase in the oxygen consumption and metabolic rate of nearly all cells. The major action appears to be exerted on the mitochondria, since the cells of hyperthyroid animals have a larger number of mitochondria. It has been suggested that thyroxin stimulates the mechanism for forming mitochondria. The mitochondria contain the enzymes for breaking down fatty acids, for the citric acid cycle and the hydrogen transport system, and it is here that the energy released by oxidation is used to form ATP. It has been suggested—and disputed—that thyroid hormones cause more energy to be released by oxidation, but that less of it is used to form ATP and more is released as heat. Thyroid hormones do seem to increase RNA synthesis and hence protein formation, but this does not completely explain their effect.

Regulation of thyroid secretion. Thyroid secretion—the trapping of iodine and hormone synthesis and release—is increased by the thyroid-stimulating hormone (*thyrotropin,* TSH) from the adenohypophysis. Thyrotropin is in turn controlled by the thyrotropin-releasing hormone (TRH) from the hypothalamus, and TSH and TRH are both inhibited by circulating thyroxin and T_3. Other controlling factors are those that influence the release of TRH. Continued cold and various neural stimuli, including stress of various types, increase it, while thyroxin, T_3, and a warm environment inhibit it (the effects of temperature are beneficial, in view of the effect of thyroxin on heat production). In addition, several chemical agents can reduce thyroxin secretion by blocking synthesis at one stage or another.

FIGURE 13–9 Compounds important in thyroid hormone synthesis.



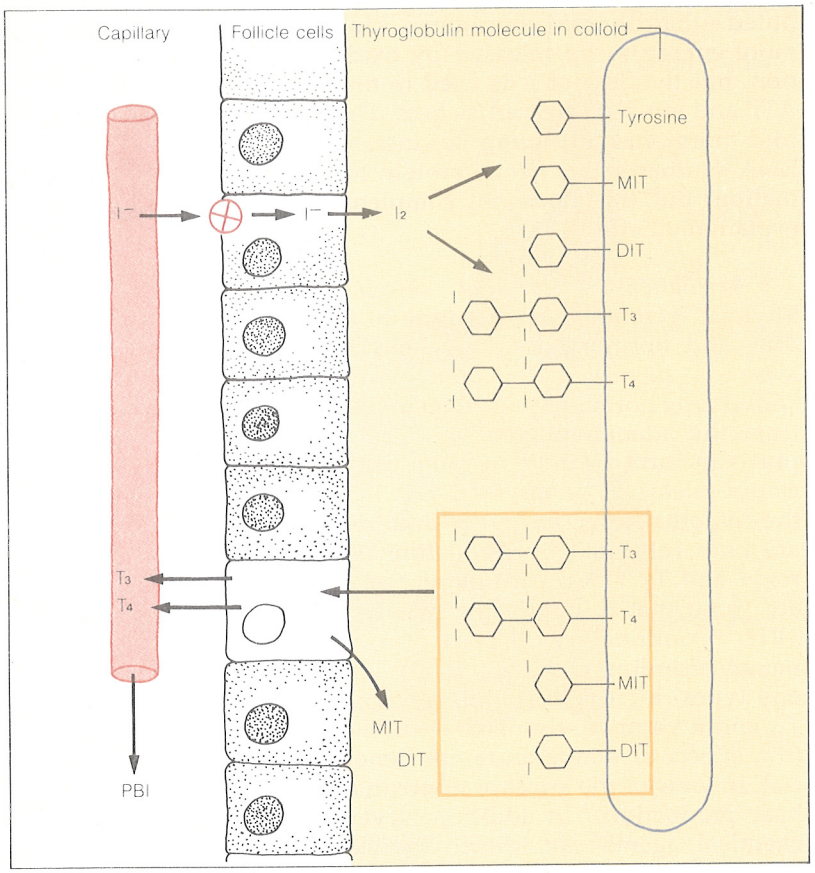


FIGURE 13–10 Synthesis of thyroid hormones.

It should be noted that TSH release alone may not result in an increased hormone secretion. The gland must also have sufficient iodine. If it does not, the stimulated gland will appear histologically active (that is, the cells will hypertrophy), but no hormone will be forthcoming.

Abnormal secretion of thyroid hormones. The symptoms of thyroid hypofunction are almost entirely the direct result of the reduced metabolic rate. Afflicted individuals have a diminished rate of oxygen consumption and the body temperature, blood pressure, and heart rate may be reduced. They are mentally and physically sluggish and do not tolerate cold very well. Their hair tends to be coarse, dry, and rather sparse, and their faces appear bloated and puffy due to an accumulation of protein and fluid in the subcutaneous tissues. This last symptom provides the name of the condition in the adult: **myxedema.**

In addition to the above symptoms, the hypothyroid child suffers from arrested growth and development and may be mentally retarded. Such a condition is known as **cretinism,** and the patient is a *cretin.* Both myxedema and cretinism can be remedied by the administration of thyroid hormone. Since both T_3 and thyroxin are relatively small molecules, and can be absorbed from the digestive tract, they can be given orally.

Hyperthyroid persons have increased basal metabolic rates. They use more oxygen and produce more heat and eat more food, while nevertheless losing weight. They are jumpy, irritable, and cannot tolerate heat. Their skin is warm due to dilation of cutaneous blood vessels, and the rate and pumping action of the heart are increased. In severe cases *(thyrotoxicosis),* many of the important symptoms are those of an overloaded cardiovascular system.

Hyperthyroid conditions may be due to a tumor of the thyroid gland *(toxic goiter),* in which case treatment may be surgical removal, destruction of part of the gland by radioactive iodine, or the use of antithyroid drugs to block hormone synthesis. Hyperthyroid symptoms may also be due to excessive stimulation of the gland *(exophthalmic goiter).* It is due to production of an abnormal protein that causes hypertrophy and increased thyroid secretion, but it is not inhibited by the negative feedback of T_3 and T_4. This substance also causes the accumulation of fluid in the soft tissues behind the eyes, which, in turn, causes the eyeballs to protrude *(exophthalmos).* The eyelids are opened widely, and the individual appears to be staring.

Goiter is the term referring to an enlarged thyroid gland. It may reflect either a hypo- or a hyperthyroid condition. *Simple goiter* is often due to an iodine deficiency that reduces hormone output. TSH production is then not inhibited, and the gland responds to the continual stimulation by hypertrophy as it "tries harder." The growth of the gland, by increasing the iodine-trapping tissue, may enable it to produce enough hormone so that the only sign is the increased size of the gland—and it may become very large. If it cannot produce enough hormone, symptoms

Focus

Addison's Disease

The adrenal cortex produces a number of hormones essential to the normal functioning of the body. When something goes wrong with this organ, the effects can therefore be serious and far-reaching. Hypersecretion of the adrenal cortical hormones, caused by an adrenal tumor or excessive pituitary secretion of ACTH, causes the disorder known as Cushing's disease. Hyposecretion, caused by a lack of ACTH, atrophy of the adrenal cortex, or damage to the adrenal cortex, causes Addison's disease, which was first described over one hundred years ago, before any of the hormones were known.

Addison's disease is marked by two kinds of symptoms because both mineralocorticoids (including aldosterone) and glucocorticoids (including cortisol) are in short supply. The lack of mineralocorticoids increases the excretion of sodium and water; as a result, blood volume and blood pressure fall. The lack of glucocorticoids leads to depletion of glycogen stores—they are not adequately replenished because synthesis of glucose from amino acids is impaired. This causes a tendency to hypoglycemia, an increased sensitivity to insulin, and a lack of physical energy. Without cortisol's negative feedback action, there is increased release of melanocyte stimulating hormone (MSH), as well as ACTH. The MSH causes an increase in skin pigmentation, especially in portions of the body exposed to light, pressure, or friction. The lack of glucocorticoids, which are also involved in the body's response to injury, infection, and other forms of stress, decreases the body's ability to adapt and defend itself.

A person with a severe case of Addison's disease may be listless and apathetic, have a small heart with a weak beat, and have very low blood pressure. The metabolic rate and body temperature may be low, and the body is slow to recover from damage and overexertion. Fortunately such cases are not common. More often the symptoms are less severe, owing to a relative lack rather than near or total absence of adrenal cortical hormones. Most individuals can manage quite well on replacement therapy consisting of drugs with mineralocorticoid and with glucocorticoid actions. Synthetic drugs are usually used rather than the natural hormones because they are less expensive. Salt intake usually has to be increased as well, in order to replace the sodium lost in urination. Since these hormone actions are necessary for a person's well-being, it is essential to continue the medication for life; and in times of stress, the dose, particularly of glucocorticoids, must be increased.

of hypothyroidism appear. The disease was formerly quite common in inland areas where the iodine content of the soil (and food) is low, but availability of iodized salt has largely eliminated this problem. Hyperthyroid conditions also produce goiter, since the gland is enlarged due to a tumor or excessive stimulation.

Parathyroid Glands

For many years it was believed that the thyroid gland was essential to life, since when it was removed, the patient died. However, it is now known that death resulted from the inadvertent removal of the parathyroids during the *thyroidectomy*. Two or three of these tiny glands are embedded in the dorsal surface of each lobe of the thyroid gland. They produce **parathormone,** which is necessary to maintain the calcium level of the blood. Thus, the parathyroid gland is essential to life.

Calcium Metabolism The body contains about 1200 g of calcium Ca^{++}, more than any other cation, and about 99 percent of it is in the bones and teeth. The remaining 1 percent is in the extracellular fluid and soft tissues, but only a small part of that, less than 1 g, is in the blood. The calcium in the blood, about 10 mg per 100 ml of blood, exists as a roughly fifty-fifty equilibrium between diffusible calcium and calcium bound to a plasma protein, with the diffusible calcium being the active portion.

The level of calcium in the blood must be maintained within a very narrow range (10 ± 1 mg percent), since calcium is essential for normal contraction of cardiac and skeletal muscle, for normal nerve function, and for blood coagulation. Too much or too little calcium causes serious difficulties. Too high a level of calcium in the blood depresses muscle excitability and causes cardiac irregularities. Too little raises the excitability of both nerve and muscle and results in muscle twitches, which may develop into convulsions and tetany (tonic spasms), particularly of the muscles of the limbs and larynx. If low enough, the end result will be asphyxiation from laryngeal spasm.

The 99 percent of the body's calcium that is in the hard tissues serves as a storage depot. Some of it is readily exchangeable, and bone is continually resorbed and rebuilt as its calcium repeatedly departs and returns. Calcium enters the body (and the blood) from the digestive tract and leaves by excretion from the kidney. While the level of calcium in the blood is the resultant of all processes by which it enters and leaves the blood, it is determined primarily by the shift of calcium to and from bone. Because the bone content is so great, a slight change in bone calcium can make an extremely great change in the blood calcium level.

Parathormone The natural equilibrium between the reactions shown in Figure 13–11 is such that without parathormone the serum calcium levels off at about 7 mg percent (instead of 10 mg percent), which is low enough to produce signs of tetany. The effect of parathormone is to cause more calcium to be absorbed from the digestive tract (and hence less to be lost in the feces) and less to be excreted in the urine. More calcium is removed from the urine being formed in the kidney, and is returned to the bloodstream (a process known as *reabsorption*). Its major action, however, is to raise blood calcium by removing calcium from the bone, perhaps by stimulating the osteoclasts, the cells important in bone resorption. One could therefore summarize the action of parathormone on calcium as increased *absorption* from the gut, increased *reabsorption* in the kidney, and increased *resorption* from bone.

Parathormone also affects phosphorus, whose metabolism is closely associated with that of calcium. The mineral in bone is a complex salt composed mostly of calcium and phosphate. When calcium is withdrawn from bone, the level of phosphate in the blood is therefore also raised. The fact that the calcium and phosphate levels usually vary in opposite directions is explained by noting that the solubility of calcium phosphate depends upon the product of calcium and phosphate ion concentrations in the blood. When this

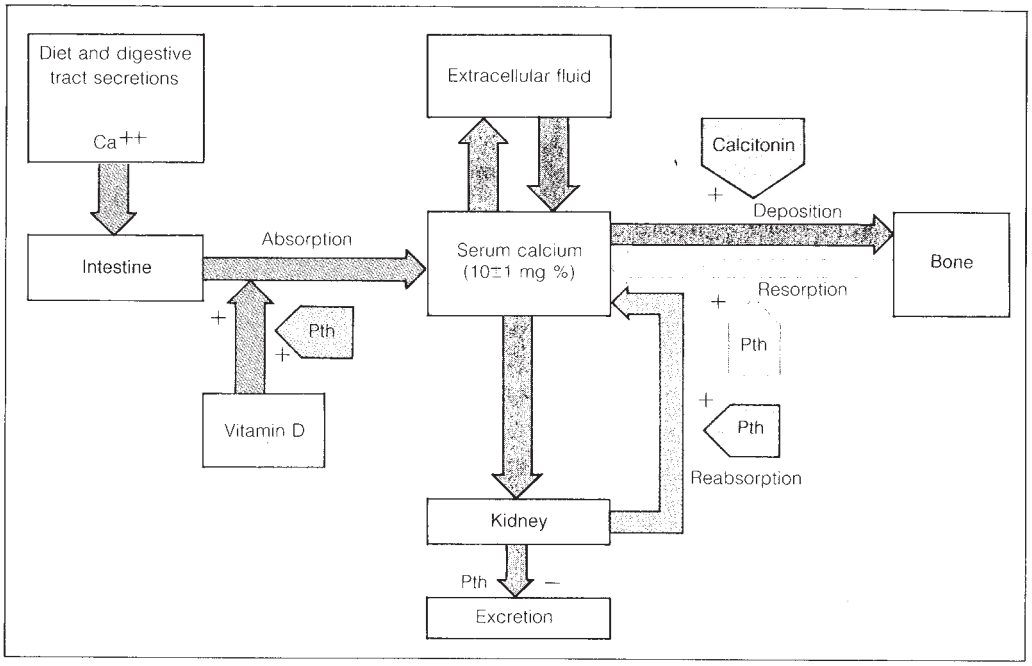


FIGURE 13–11 Hormonal regulation of serum calcium levels. (Pth = parathormone)

product increases, less calcium phosphate can remain in solution and it precipitates out; when it falls, the solubility is greater and more calcium phosphate can remain in solution in the blood. Parathormone keeps the product low, since it reduces the level of phosphate in the blood by increasing the renal excretion of phosphate, which is necessary if more calcium is to be withdrawn from the bone.

There is no evidence of pituitary or hypothalamic involvement in the control of parathormone secretion. The only determining factor appears to be the level of free calcium in the blood; a fall elicits an increase in parathormone secretion, followed by a rise in blood calcium, which in turn depresses parathormone secretion.

Hypo- or hyperfunction of the parathyroid gland is rare. Hypofunction may occur as a result of thyroid surgery and is indicated by signs of tetany, which can often be controlled by administration of calcium and vitamin D (see below). Hyperfunction may eventually cause bone diseases due to excessive removal of calcium from the bone, and calcium-containing kidney stones are common due to the high level of calcium in the blood.

Calcitonin In the early 1960s, a disorder marked by excess calcium in the blood *(hypercalcemia)* was traced to a hormone other than parathormone. This new hormone was called **calcitonin** until it was found to be produced by the thyroid gland and renamed thyrocalcitonin. Since then, cells that produce it have been found in the parathyroid and thymus glands as well, so it is known as calcitonin once more. Calcitonin is secreted when the level of calcium in the blood is elevated, especially in young individuals. Its action is primarily to prevent the resorption of bone and therefore to lower the blood calcium level by counteracting one of the actions of parathormone.

Vitamin D A discussion of calcium and its metabolism is hardly complete without mentioning the role of vitamin D. For many years this vitamin has been highly regarded as a preventive against *rickets,* a disease in which the bones do not calcify properly. The beneficial effect of vitamin D is an increased deposition of mineral in the bones, thanks in part to improved absorption of calcium from the intestine. Without vitamin D, so little cal-

cium and phosphate are absorbed that there is not enough available for normal calcification of the bones. When calcium absorption is improved with vitamin D, calcification becomes normal once more.

The term *vitamin D* covers several closely related steroid compounds. Vitamin D can be ingested in the diet, but it can also be formed from a steroid present in the skin by the action of ultraviolet light from the sun. The compound is converted to its active form by actions first in the liver and then in the kidney. Since the compound is produced in the body, and transported by the blood to a distant site, it is sometimes considered to be a hormone.

Vitamin D's action seems to be to increase the synthesis of protein involved in the active transport of calcium in the intestine, and probably other cells as well.

Pancreas

The pancreas lies on the posterior wall of the abdominal cavity inferior to the stomach (see Figure 22–9). It is both an exocrine and an endocrine gland. Its exocrine function, the secretion of important digestive enzymes, is discussed in Chapter 23, and its anatomy in Chapter 22. The endocrine function is performed by small isolated clumps of tissue, the **pancreatic islands** or **islets of Langerhans,** scattered throughout the substance of the gland. The cells of these islands are arranged in irregular cords with numerous interspersed capillaries, and they consist of two main types of cells: The alpha cells are believed to secrete **glucagon,** while the more numerous beta cells produce **insulin.** A few delta cells are present, and they produce *somatostatin* (another name for the growth hormone-releasing hormone, GH-RH, of the hypothalamus).

Insulin Insulin is associated primarily with carbohydrate metabolism and blood glucose regulation, although it has important effects on fat and protein metabolism. A number of other hormones contribute to regulation of the same processes, and their actions must be taken into account when considering the actions of insulin. These actions are discussed in Chapter 24.

Insulin is *hypoglycemic.* That is, it enhances those reactions that lower the blood glucose level and inhibits those that raise it. This is largely due to the fact that insulin increases the entry of glucose into cells. Insulin stands alone in this regard, since most of the other metabolic hormones are *hyperglycemic.* Because it enables glucose to enter cells more readily, insulin facilitates all metabolic reactions of glucose, including glycogen formation and use of glucose. These reactions are particularly important in skeletal muscle, where much of the glucose is used.

Insulin has effects on fat metabolism which are almost as important as those upon glucose metabolism, and which indirectly tend to lower the blood glucose. It increases the formation of fat and its storage in adipose tissue and, by increasing glucose entry into cells (including adipose cells), more glucose is available for conversion to and storage as fat.

Insulin also increases the transport of amino acids into cells, with a consequent increase in protein synthesis and reduced protein catabolism. The actions of insulin favor removal of glucose, amino acids, and fatty acids from the blood; they are anabolic, for they lead to synthesis of glycogen, fatty acids and fats, and protein.

A lack of insulin causes a disease known as *diabetes mellitus,* in which there are many metabolic disturbances. The most characteristic is the accumulation of glucose in the bloodstream *(hyperglycemia)* because it cannot enter the cells readily. The hyperglycemia leads to the excretion of glucose in the urine. The role of insulin and the other "metabolic" hormones are discussed in more detail in Chapter 24.

Glucagon Glucagon is a polypeptide produced by the alpha cells of the pancreatic islands. Glucagon's action is exerted mainly on the liver, because it is rapidly inactivated there and reaches the general circulation in reduced amounts. The polypeptide's actions favor energy release; it increases

the breakdown of fats, which raises the supply of fatty acids that can be used as a source of energy. But more importantly, glucagon is the most potent agent known for increasing the breakdown of glycogen in the liver, which it does by activating an enzyme necessary for the reaction. The glycogen breakdown yields more glucose which is released into the circulation. It is interesting to note that epinephrine causes a similar breakdown of glycogen in the liver as well as in skeletal muscle, and that epinephrine also causes the release of fatty acids from fat stores.

Secretion of Pancreatic Hormones

The secretion of insulin is controlled primarily by the glucose content of the blood to the pancreas, since an elevation of the blood glucose level acts directly and promptly to increase the production and release of insulin. When blood glucose falls, insulin secretion also falls. The pituitary has no known effect, but epinephrine, glucagon (the other pancreatic hormone), and secretin and pancreozymin (hormones that increase the exocrine secretion of the pancreas) all increase insulin secretion to some extent. Several drugs have similar effects, and in those cases of diabetes in which the pancreatic islands are functional but simply do not produce enough insulin, these drugs can be used to drive the insulin-producing beta cells. This is an advantage, as these agents can be taken orally; they are the so-called "oral insulins." Unfortunately, they are ineffective in any patient whose pancreas cannot secrete insulin.

The secretion of glucagon also depends largely upon the blood glucose level, except that glucagon secretion is increased by hypoglycemia and diminished by hyperglycemia. Stimulation of sympathetic nerves to the pancreas increases glucagon release, and so do several "stressful" stimuli.

Gonads

The hormones produced by the gonads are the so-called sex hormones. They have important roles in reproduction and in the development and maintenance of the sex characteristics. These hormones and the pituitary gonadotropins that control them are discussed in Chapters 29 and 30 on reproduction. The hormones produced by the placenta during pregnancy will also be discussed in that section.

The Pineal and Other Endocrine Glands

The pineal has been called a mere *vestigial* remnant, a controller of aldosterone secretion, an antagonist of ACTH, and an inhibitor of puberty and of growth, but to date its function in mammals remains unknown. The primary reason for considering it an endocrine gland is precisely that it has no known function. It has therefore been assumed that it must produce an unidentified hormone of unknown action. There is some evidence that in rats it serves as some sort of connection between the retina of the eye and various endocrine glands, thus relating the diurnal rhythm of some glands to the photoperiod (periods of light and darkness). There are nerve connections with the retina, and the indication is that light causes a hormonelike substance to be released by the pineal gland. It should be added, however, that there is also evidence which contradicts this.

Several other hormones, such as those produced by the organs of the digestive tract (gastrin, secretin, pancreozymin-cholecystokinin) and by the kidney (erythropoietin and renin) are discussed in later chapters.

CHAPTER 13 SUMMARY

The endocrine glands secrete into the bloodstream specific substances (hormones) which have a specific effect on some distant organ (target organ).

Hormones secreted by the endocrine glands, their major controls and actions, are listed in the table below. Some of these hormones are not discussed in this chapter, but are covered in later chapters and are included here for completeness.

TABLE 13-3 THE ENDOCRINE GLANDS AND THEIR SECRETIONS

Endocrine Glands and Hormones	Main Stimulus for Secretion	Major Actions
Pituitary gland (hypophysis)		
Anterior lobe (adenohypophysis)		
growth hormone	growth hormone-releasing hormone (GRH); inhibited by inhibitory hormone (GIH)	stimulates body growth, protein anabolism, and other metabolic effects; stimulates growth of epiphyseal cartilage of long bones.
thyroid-stimulating hormone (TSH)	thyrotropin-releasing hormone (TRH)	stimulates growth and secretion by thyroid gland
adrenocorticotropic hormone (ACTH)	corticotropin-releasing hormone (CRH)	stimulates growth and secretion by adrenal cortex, especially secretion of glucocorticoids
follicle-stimulating hormone (FSH)	follicle-stimulating hormone-releasing hormone (FRH)	stimulates growth and development of ovarian follicle in female; stimulates spermatogenesis in male
luteinizing hormone (LH) or interstitial cell-stimulating hormone (ICSH)	luteinizing hormone-releasing hormone (LRH)	stimulates ovulation, formation of corpus luteum and secretion of estrogen and progesterone in female; stimulates secretion of testosterone by interstitial cells in male
prolactin	prolactin-releasing hormone (PRH); inhibited by prolactin inhibitory hormone (PIF)	stimulates secretion by mammary glands
Posterior lobe (neurohypophysis)		
antidiuretic hormone (ADH)	increased osmotic pressure of plasma via hypothalamic osmoreceptors	decreases volume of urine excreted, increases volume of water reabsorbed in kidney
oxytocin	neuroendocrine reflexes initiated by stimulation of receptors in uterus and mammary glands	causes contraction of smooth muscle of uterus and ejection of milk from mammary glands
Adrenal medulla		
epinephrine and norepinephrine	sympathetic nervous system	same actions as sympathetic nervous system (sympathomimetic); metabolic actions, including increased blood level of glucose and release of fatty acids into bloodstream
Adrenal cortex		
glucocorticoids (cortisol)	ACTH	metabolic actions, including protein catabolism, increased levels of glucose and fatty acids in blood; aids in withstanding stress; suppresses inflammatory reaction
mineralocorticoids (aldosterone)	renin-angiotensin mechanism, also ACTH	decreases sodium excretion by kidney, increases retention of sodium; increases excretion of potassium, decreases retention
androgens	ACTH	no significant effects at normal levels
Thyroid gland		
thyroxin and triiodothyronine (T_3)	TSH	increases oxygen consumption and metabolic rate of all cells
calcitonin	increased calcium in blood	lowers calcium in blood, causes calcium deposition in bone
Parathyroid gland		
parathormone	decreased calcium in blood	raises calcium in blood, causes increased absorption from digestive tract, withdrawal from bone, and decreases excretion; increases excretion of phosphate

Endocrine Glands and Hormones	Main Stimulus for Secretion	Major Actions
Pancreatic Islands		
insulin	increased blood glucose level, and other metabolic stimuli	decreases blood glucose levels, increases entry of glucose into cells; metabolic actions include storage of fat and synthesis of protein
glucagon	decreased blood glucose level and other metabolic stimuli	raises blood glucose level, breakdown of glycogen; causes release of fatty acids into bloodstream
Gonads		
Testis		
testosterone	ICSH	stimulates growth and development of male sex organs and sex characteristics; aids spermatogenesis
Ovary		
estrogen	LH	stimulates growth and development of female sex organs and sex characteristics
progesterone	LH	stimulates further development and differentiation of sex organs
relaxin	—	loosens (relaxes) pubic symphysis and aids in dilation of cervix of uterus at end of pregnancy
Placenta		
human chorionic gonadotropin	—	maintains corpus luteum and stimulates it to secrete estrogen and progesterone in early pregnancy
estrogen, progesterone	—	stimulates continued growth and development of sex organs, especially endometrium, during pregnancy
Digestive tract		
Stomach		
gastrin	vagus nerve, and presence of certain substances in stomach	causes secretion of hydrochloric acid and digestive enzyme (pepsin) by lining of stomach
Small intestine (duodenum)		
cholecystokinin-pancreozymin (CCK)	protein digestion products and fat in duodenum	causes secretion of digestive enzymes by exocrine pancreas; causes contraction of gall bladder
secretin	acid (low pH) in duodenum	causes secretion of high-bicarbonate fluid by exocrine pancreas
Kidney		
erythropoietin	hypoxia (low oxygen) in blood to kidney	increases rate of production of red blood cells by bone marrow
renin	decreased blood pressure and blood flow to kidney; decreased sodium transport in kidney	activates angiotensin, which causes constriction of blood vessels and increases blood pressure; increases secretion of aldosterone

Hormones help control processes associated with regulation of metabolism and energy supply, regulation of the extracellular fluid, responses to stress, and with growth, development, and reproduction.

Most hormones are derived from amino acids, as amines or peptides, or are *steroids*. Most are rapidly inactivated and/or excreted and must, therefore, be produced continually.

Many hormones affect target cells without entering them. The hormone "recognizes" and binds a specific *fixed receptor* on the surface of the target cell membrane. This activates adenyl cyclase, an enzyme in the membrane which causes formation of cAMP from

ATP in the cell. The cAMP then activates a specific enzyme in the cell to bring about the hormone's action. Steroid hormones diffuse into the cell to find the receptor *(mobile receptor)*. The receptor-hormone complex moves to the cell nucleus and causes formation of the RNA needed to direct synthesis of a particular protein—the enzyme needed to catalyze a certain reaction. Some hormones act by altering the permeability of the cell membrane to a specific substance.

Some endocrine glands are controlled by the nervous system, but most are controlled by a negative feedback mechanism in which an increase in blood concentration of the hormone inhibits its production by the endocrine gland. The anterior lobe of the pituitary gland *(adenohypophysis)* is important in regulating secretion of many endocrine glands because it produces several hormones whose target organ is another endocrine gland. The adenohypophysis also has direct connections with the hypothalamus by way of the hypophyseal portal system. The blood supply to the anterior lobe passes through a capillary bed in the hypothalamus before reaching the adenohypophysis. Neurons that arise in various hypothalamic nuclei release chemicals (neurotransmitters) near these capillaries, and the neurosecretions are carried to the adenohypophysis where they stimulate secretion of the pituitary hormones. There is a specific neurosecretion, or releasing hormone, for each hormone of the adenohypophysis, plus inhibitory hormones for two of them. The negative feedback control of the target organs of the pituitary hormones is exerted both at the pituitary gland and at the hypothalamus.

The posterior lobe of the pituitary *(neurohypophysis)* receives nerve fibers that arise in hypothalamic nuclei. These fibers release their secretions—ADH and oxytocin, which are synthesized in the hypothalamus—into the bloodstream in the neurohypophysis and become the hormones of the posterior lobe; the neurohypophysis itself does not produce the hormones.

STUDY QUESTIONS

1 In what ways are hormonal and neural actions alike? In what ways are they different?

2 How do hormones exert their actions on cells? Explain the fixed receptor and mobile receptor models for hormone action.

3 What is the hypophyseal portal system? What is its significance?

4 What is meant by negative feedback control?

5 How does the production and release of thyroid hormone differ from that of other hormones?

6 What is the general effect of thyroid hormones? Based on this, what symptoms would you expect to find in a hyperthyroid condition?

7 Compare and contrast the actions of epinephrine and norepinephrine. How do these compare with the actions of the sympathetic nervous system?

8 Do the metabolic actions of growth hormone and glucocorticoids augment or interfere with one another? Explain.

9 What processes determine the calcium level in the blood? How does parathormone affect these processes?

10 What effect does insulin have upon blood glucose level? What processes does it alter to bring about the effect?

11 What effect does insulin have upon fat metabolism?

12 Absence of which hormones is fatal? What controls the secretion of these hormones?