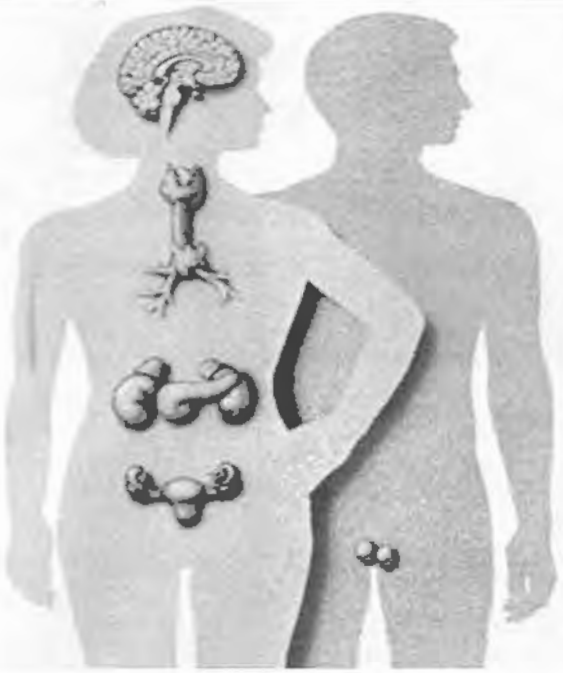
University of Jordan - Faculty of Medicine
(2013-19)

Medical Committee
The University of Jordan

Endocrine System



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Lecture #: 1+2+3

Date: 7/7/2015

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TABLE 1-1 ***Organ Systems: Components and Functions***

System	*Components*	*Functions*
Nervous	Brain, spinal cord, peripheral nerves, ganglia	**Controls activities of other systems**; receives information from the environment; stores memories; initiates and controls behavior
Skeletal	Bone, connective tissue	Support; mineral storage; production of blood cells
Cardiovascular	Heart, blood vessels, red blood cells	Transports nutrients, gases, metabolic end products, and hormones between organ systems
Respiratory	Nose and throat, trachea, bronchi, bronchioles, lungs	Takes up oxygen and releases carbon dioxide to atmosphere; produces sounds; partly responsible for regulating blood acidity
Digestive	Mouth, esophagus, stomach, small and large intestines, salivary glands, liver gall bladder, pancreas	Digestion, food storage, absorption of nutrients; protects against infection
Urinary	Kidneys, ureters, bladder, urethra	Homeostasis of extracellular fluid volume and composition; excretion of waste products
Endocrine	Pituitary, adrenals, thyroid, parathyroids, gonads, pancreas; many other organs secrete hormones in addition to their other functions	Regulation of reproduction, growth, metabolism, energy balance, extracellular fluid composition
Reproductive	Male: testes, associated glands and ducts, penis Female: ovaries, fallopian tubes, uterus, vagina, clitoris, breasts	Reproduction, sexual gratification
Lymphatic	Lymph vessels, lymph nodes	Fluid balance; transport of digested fat; cells of the immune system are also located within it
Immune	Lymphoid tissues, bone marrow, white blood cells, thymus	Resists infection, parasitization, and cancer

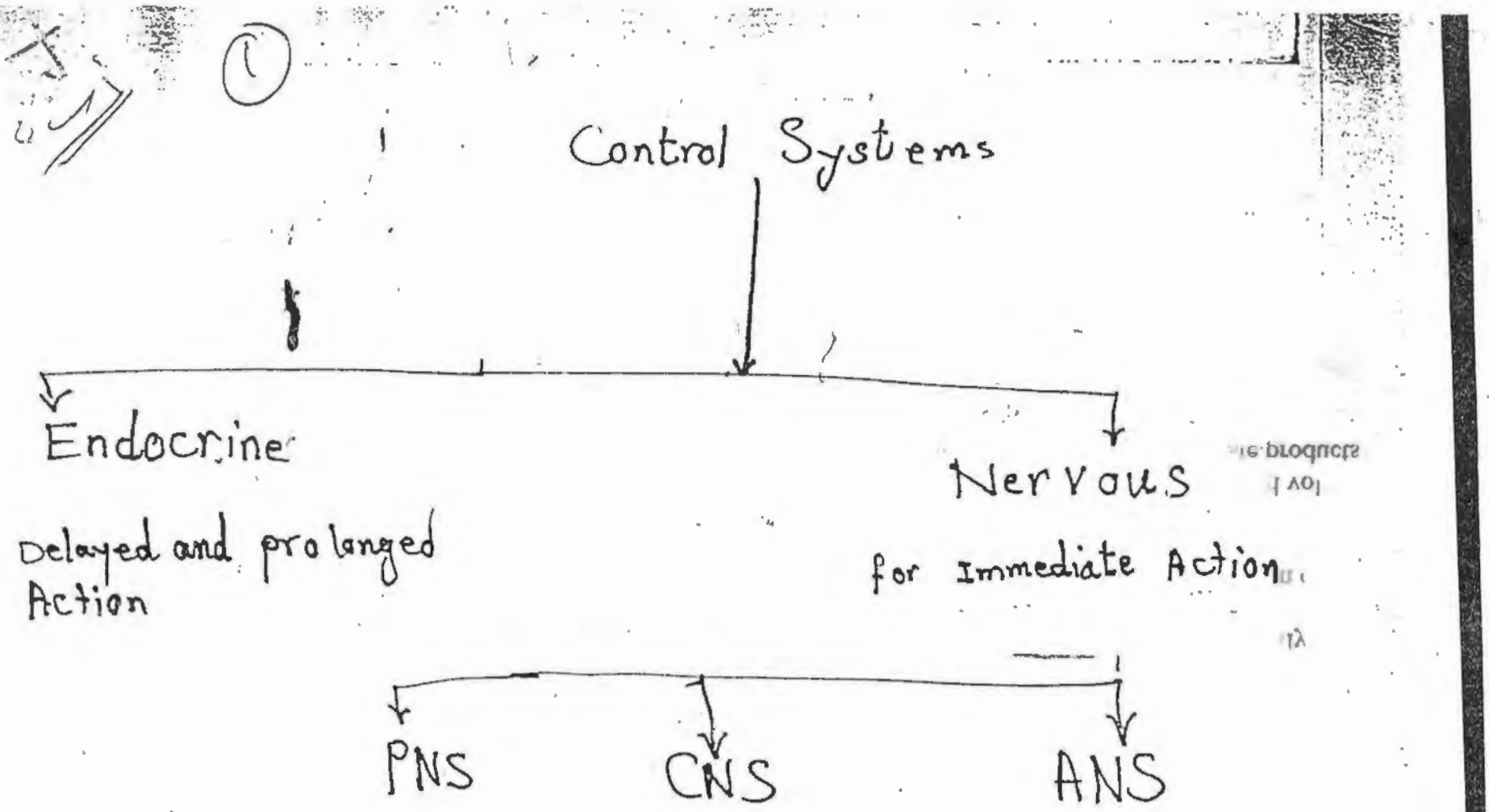
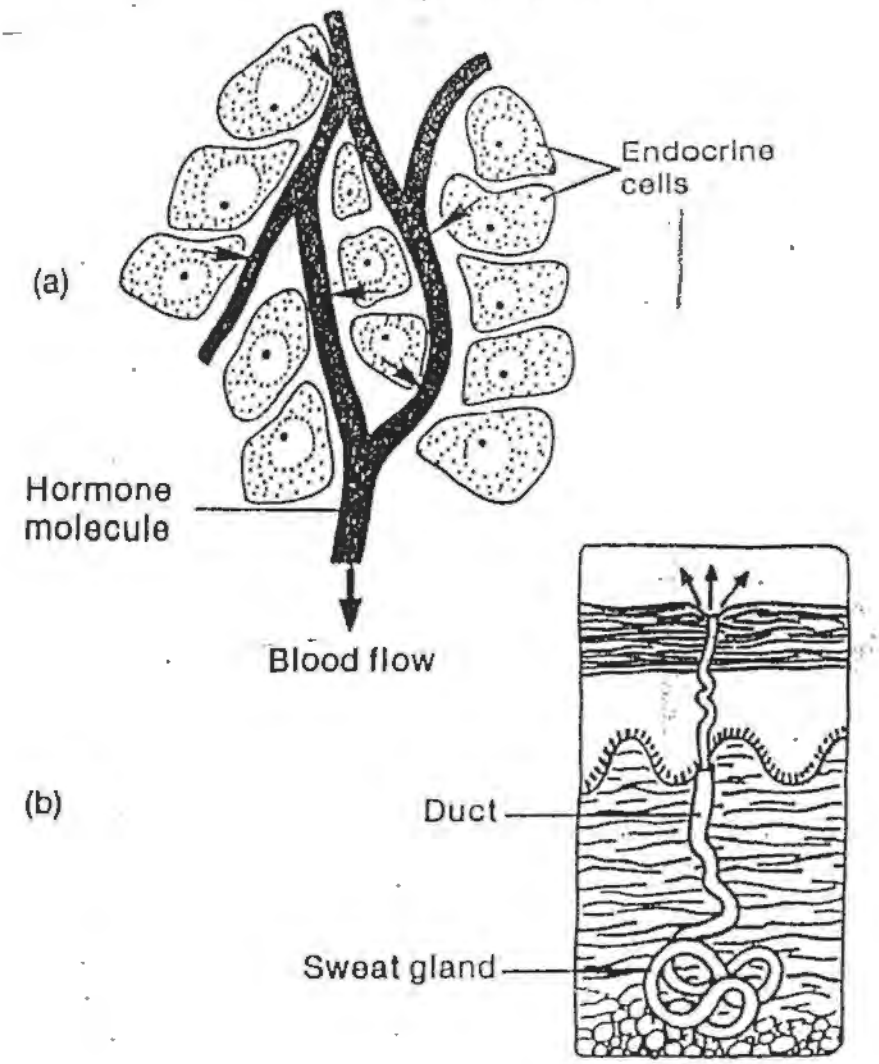

Control Systems
Endocrine
Delayed and prolonged Action
Nervous
for Immediate Action
PNS
CNS
ANS

EXHIBIT 18.1 COMPARISON OF NERVOUS SYSTEM AND ENDOCRINE SYSTEM REGULATION OF HOMEOSTASIS

Characteristic	Nervous System	Endocrine System
Mechanism of control	Neurotransmitters released in response to nerve impulses.	Hormones delivered to tissues throughout the body by the blood.
Cells affected	Muscle cells, gland cells, other neurons.	Virtually all body cells.
Type of action that results	Muscular contraction or glandular secretion.	Changes in metabolic activities.
Time to onset of action	Typically within milliseconds.	Seconds to hours or days.
Duration of action	Generally briefer.	Generally longer.

Endocrine glands, such as (*a*) the thyroid gland, release hormones into body fluids. Exocrine glands, such as (*b*) sweat glands, release their secretions into ducts that lead to body surfaces.



This section focuses on the classic endocrine glands and their hormones.

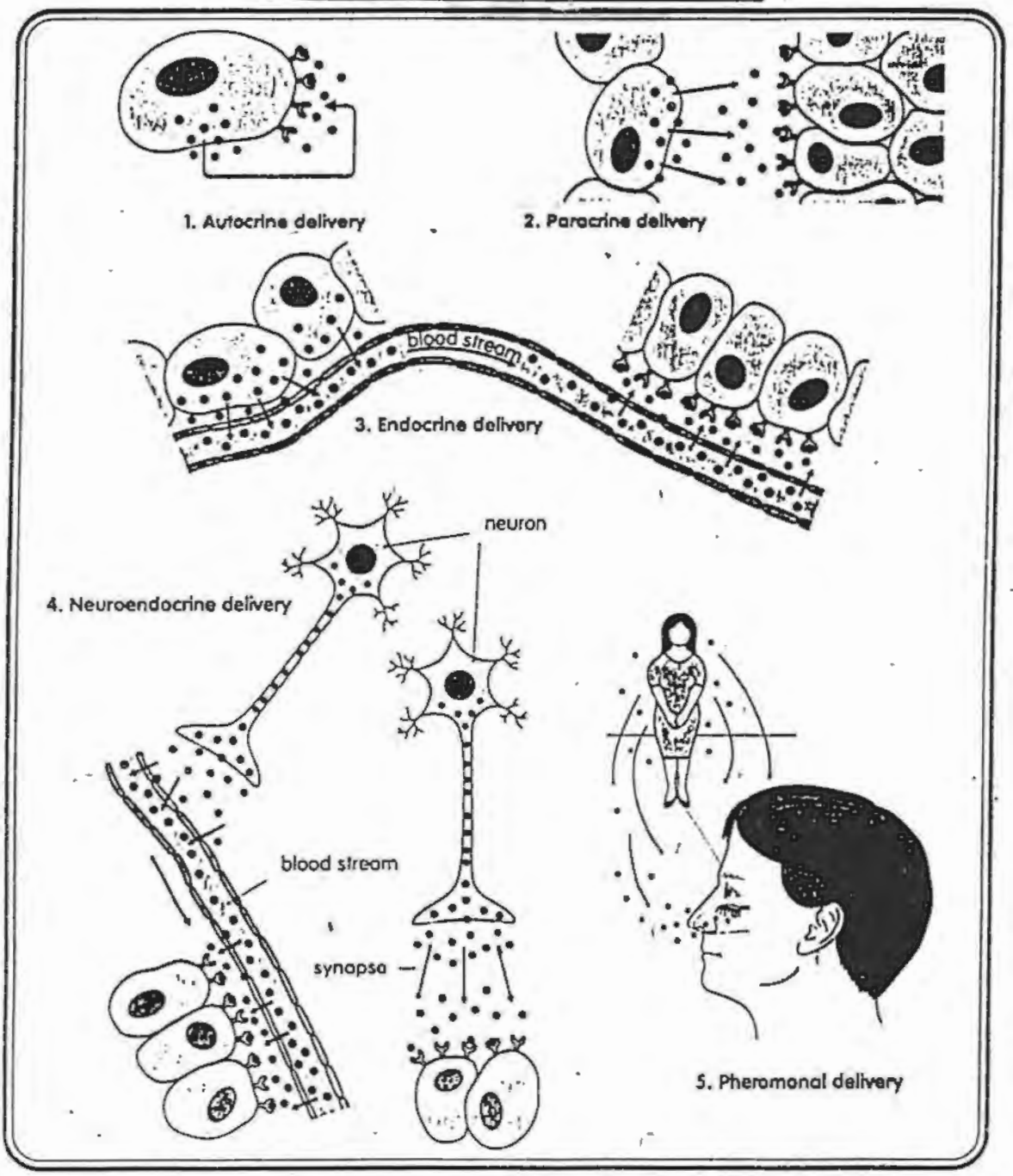
A hormone is chemical substance that is released into the blood in small amounts and that, after delivery by the circulation, elicits a typical physiologic response in other cells.

An endocrine gland is a group of cells that produce and secrete a hormone.

Endocrine glands are also called ductless glands to distinguish them from exocrine glands, which deliver their products through ducts to the outside of the body or the lumen of the gastrointestinal tract.

Fig. 1.3 Mode of delivery of hormones to their target cells:

TYPES OF HORMONE ACTION



Autocrine delivery—chemical message released acts on the cells that synthesized it, e.g. the cytokine prostaglandin E_2 stimulates the myometrial cells that produced it

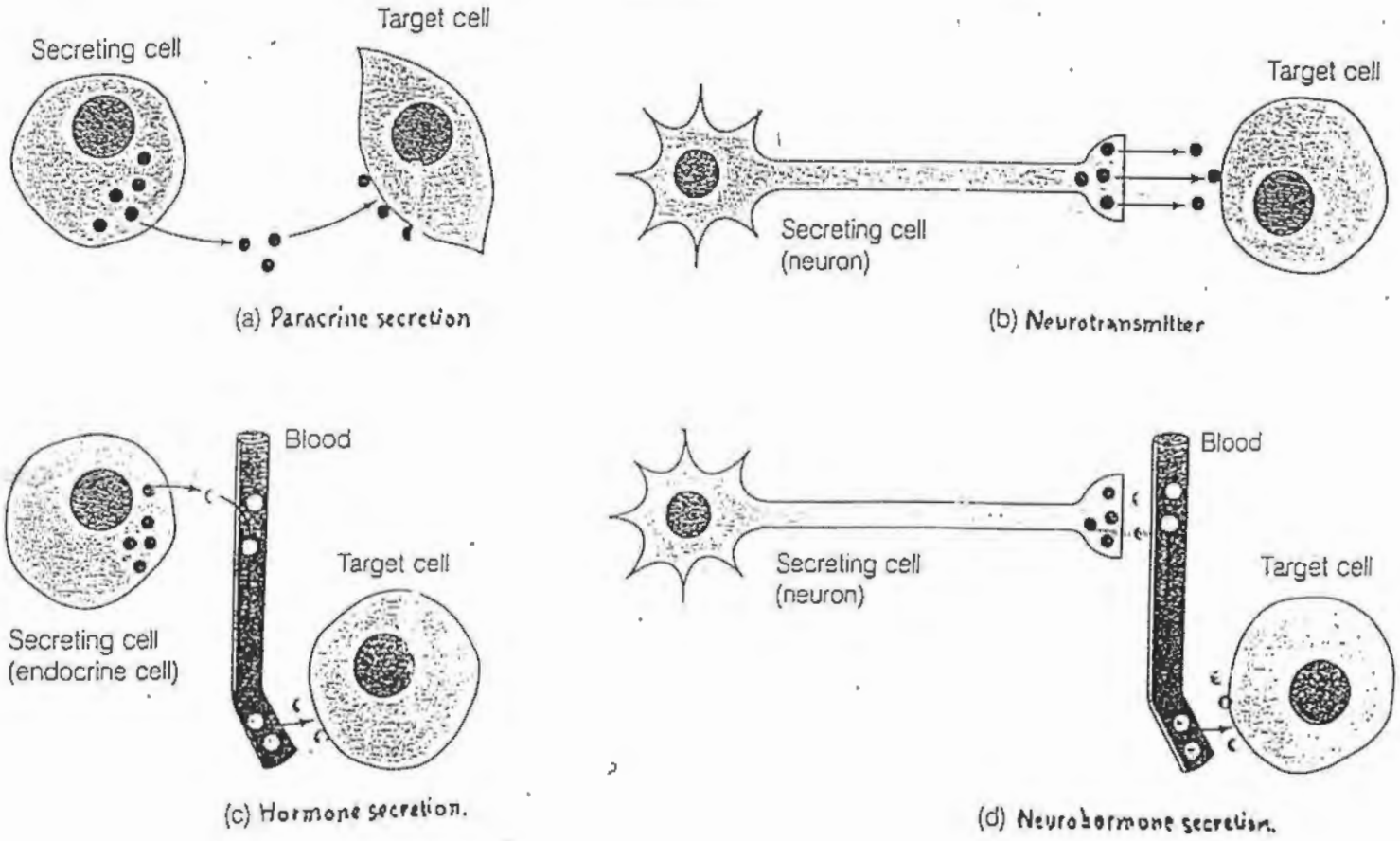
Pheromonal delivery—volatile hormones (classified as pheromones) released into the environment act on olfactory cells in another individual (pheromones, although only found in other species, may be important in controlling human sexual behaviour).

TABLE 35-1. TYPES OF HORMONE ACTION

Endocrine	Hormone synthesized in one location and released into plasma; binds to specific receptor in cells at a distant site to elicit characteristic response. *Example*: The action of thyroid-stimulating hormone from the anterior pituitary gland on the thyroid.
Neuroendocrine	Hormone synthesized in nerve ending and released into extracellular space; interacts with receptors of cells at distant site. *Example*: The action of norepinephrine synthesized in splanchnic nerve ending on the heart.
Neurocrine	Hormone synthesized in neurons and released into extracellular space; binds to receptor in nearby cell and affects its function. *Example*: The action on cardiac muscle cells of norepinephrine synthesized in nerve endings in the heart.
Neurotransmission	Hormone synthesized in neurons and released from nerve endings; crosses synapse and binds to specific receptor in another neuron, affecting its action. *Example*: Release of acetylcholine from preganglionic nerve fibers in sympathetic ganglia and binding to receptor in postganglionic neuron with liberation of norepinephrine.
Paracrine	Hormone synthesized in endocrine cells and released into interstitial space; binds to specific receptor of nearby cell and affects its function. *Example*: Release of somatostatin from islet delta cells and its subsequent action on nearby alpha and beta cells in the same pancreatic islet.
Autocrine	Hormone synthesized in endocrine cells and sometimes released into interstitial space; binds to specific receptor on the cell of origin, thereby autoregulating its function. *Example*: The action of somatostatin on its own secretion.
Exocrine	Hormone synthesized in endocrine cells and released into lumen of gut; binds to cells lining the gut at varying distances from the endocrine cells, thereby affecting their function. *Example*: The release of gastrin by mucosal cells and its action on gastric acid secretion by the stomach.

(Modified from Williams, R.H., Ed.: Textbook of Endocrinology. 6th ed. Philadelphia, W.B. Saunders Co., 1981. p. 998.)

FIGURE 15–1 Types of Intercellular Communication by Chemical Messengers (a) Paracrine secretion. (b) Neurotransmitter secretion. (c) Hormone secretion. (d) Neurohormone secretion.



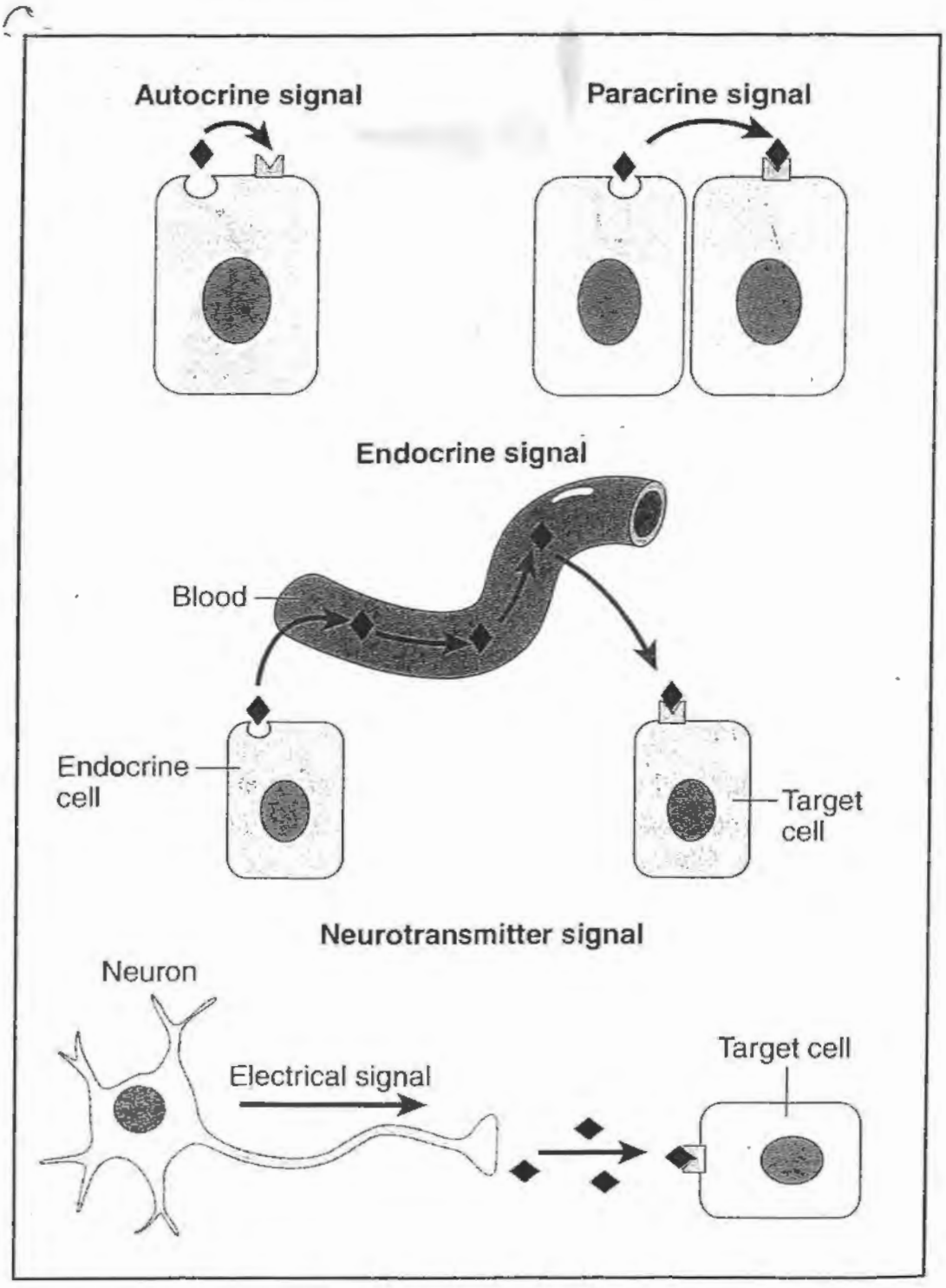


Figure 4-5. Extracellular messengers interact with receptors on the target cell. The distance between the cell secreting the messenger and the target cell containing the receptor is the basis for classifying the action as an autocrine, a paracrine, a neurotransmitter, or an endocrine event.

Pheromones

Substances produced by an animal that act at a distance to produce hormonal, behavioral, or other physiologic changes in another animal of the same species have been called **pheromones.** The sex attractants of certain insects are particularly well-known examples. The odorant pheromones that act via the vomeronasal organ play a prominent role in the sexual and dominance behavior of rodents. In primates, including humans, pheromones also have effects. For example, women who are good friends or roommates tend to synchronize their menstrual cycles, and armpit odor of women has been shown to be capable of modifying the menstrual cycle. Also, infants prefer pads wiped on breast or axillary areas of their own mothers over pads from unfamiliar women.

The following points add to the complexity of the endocrine system:

- A single endocrine gland may produce multiple hormones. The anterior pituitary, for example, secretes six different hormones; each is under different control mechanisms and has different functions, some being tropic and others having nontropic effects.

- A single hormone may be secreted by more than one endocrine gland. For example, the hypothalamus and pancreas both secrete the hormone somatostatin.

Frequently, a single hormone has more than one type of target cell and therefore can induce more than one type of effect. As an example, vasopressin promotes H_2O reabsorption by the kidney tubules as well as vasoconstriction of arterioles throughout the body.

A single target cell may be influenced by more than one hormone. Some cells contain an array of receptors for responding in different ways to different hormones. To illustrate, insulin promotes the conversion of glucose into glycogen within liver cells by stimulating one particular hepatic enzyme, whereas another hormone, glucagon, enhances the degradation of glycogen into glucose within liver cells by activating yet another hepatic enzyme.

- The same chemical messenger may be either a hormone or a neurotransmitter, depending on its source and mode of delivery to the target cell. Norepinephrine, which is secreted as a hormone by the adrenal medulla and released as a neurotransmitter from sympathetic postganglionic nerve fibers, is a prime example.

Some organs are exclusively endocrine in function (they specialize in hormonal secretion alone, the anterior pituitary and thyroid glands being examples), whereas other organs of the endocrine system perform nonendocrine functions in addition to secreting hormones. For example, the testes produce sperm and also secrete the male sex hormone testosterone. Other examples of mixed organs are the ovaries, digestive tract, pancreas, kidneys, and even the brain. In each case except the brain, mixed function occurs because the organ houses nonendocrine tissue plus isolated clusters of endocrine cells that migrated to the organ during embryonic development. The endocrine function of the brain derives from the presence of neurosecretory neurons. There are no endocrine cells as such in the brain.

Physiological effects of hormones on body functions

Body function	Effects of hormones
metabolism	regulate metabolic processes, i.e. the rate of synthesis and degradation of carbohydrates, proteins, and lipids
reproduction	control reproductive processes, including the development of the sex organs, secondary sexual characteristics, gametogenesis, and the menstrual cycle
digestion	control digestive processes, including gut motility and the secretion of digestive enzymes, bile, gastric acid, and bicarbonate
blood circulation	regulate blood pressure by altering cardiac output, vascular constriction, and blood volume via the control of water excretion by the kidneys
transport of substrates to tissues (blood composition)	regulate blood plasma concentrations of glucose, minerals (e.g. sodium, potassium, calcium), gases (oxygen, carbon dioxide), blood cells, water, and hydrogen ions (pH regulation)
defence against pathogens	regulate immune system responses, including leucocyte activation, inflammation, antibody production, and fever
growth	control cell division and differentiation
stress response	regulate the body's response to stress
behaviour	control sexual and social behaviour

Fig. 1.2 Physiological effects of hormones on body functions

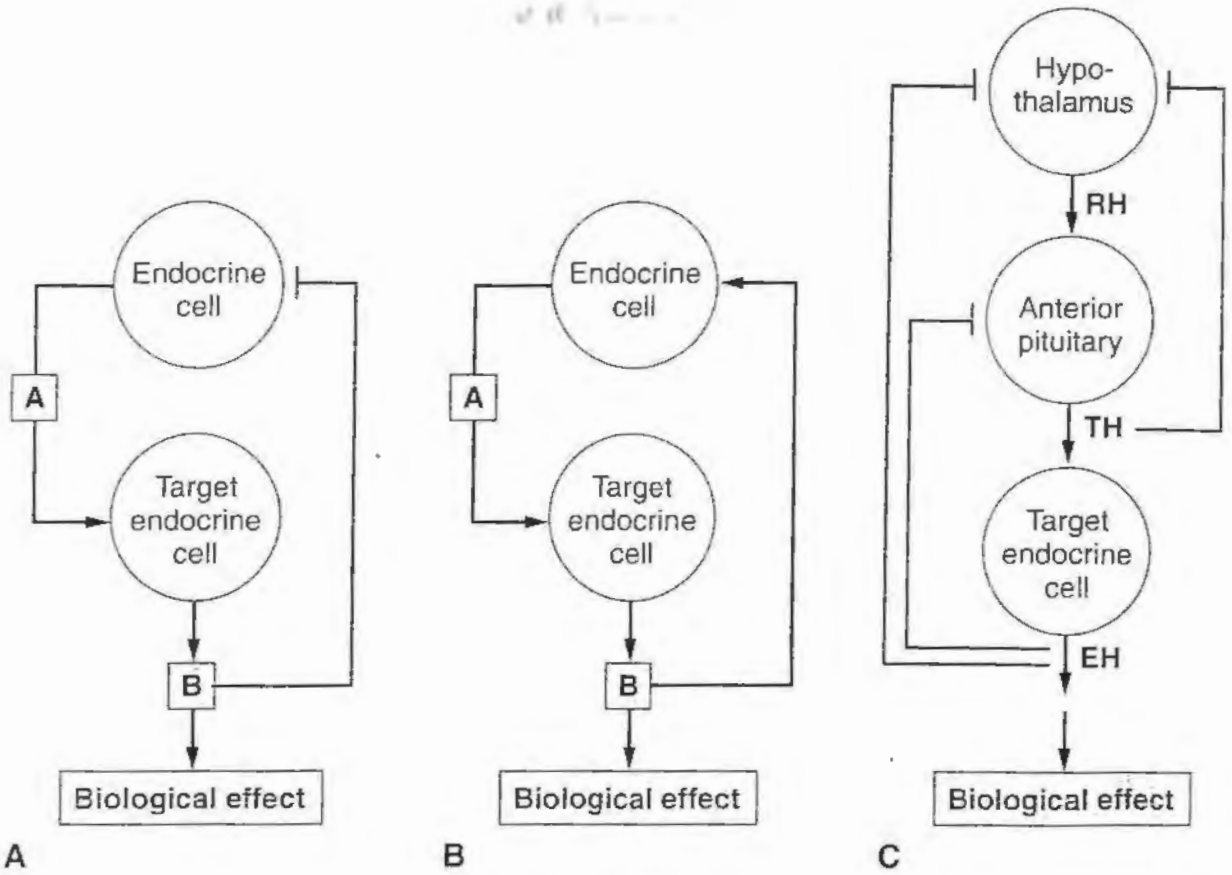


FIGURE 30.2 **Negative, positive, and complex feedback mechanisms in the endocrine system. A**, Negative feedback loop. **B**, Positive feedback loop. **C**, A complex, multilevel feedback loop: the hypothalamic-pituitary-target gland axis. Black lines indicate stimulatory effects; blue lines indicate inhibitory, negative-feedback effects. EH, endocrine cell hormone; RH, releasing hormone; TH, trophic hormone.

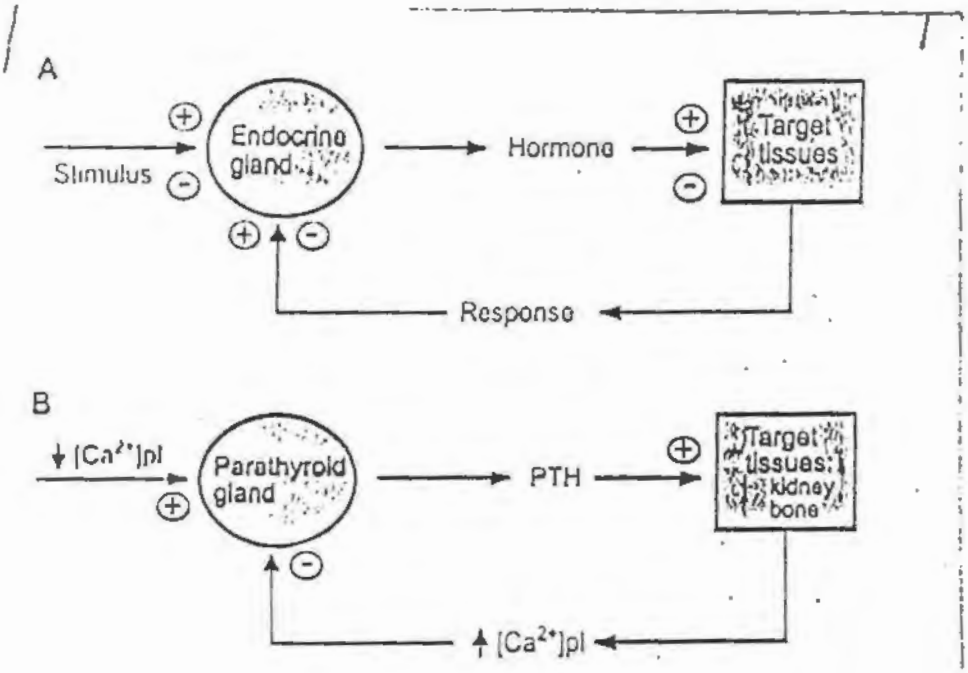


Fig. 5.1.12 Direct negative feedback. A. General principle. B. Example of direct negative feedback using PTH and its effect on plasma calcium.

Regulation of Hormone Secretion

Feedback control

Hormone-hormone
Substrate-hormone
Mineral-hormone

Neural control

(act to evoke or suppress hormone secretion)

Adrenergic
Cholinergic
Dopaminergic
Serotoninergic
Endorphinergic-enkephalinergic

Pain, emotion, sexual excitement, fright, injury and stress all can modulate hormone secretion through neural mechanisms.

Chronotropic control

(Many hormones are secreted in distinct pulses.)

Oscillating
Pulsatile
Diurnal rhythm
Sleep-wake cycle
Menstrual rhythm
Seasonal rhythm
Developmental rhythm

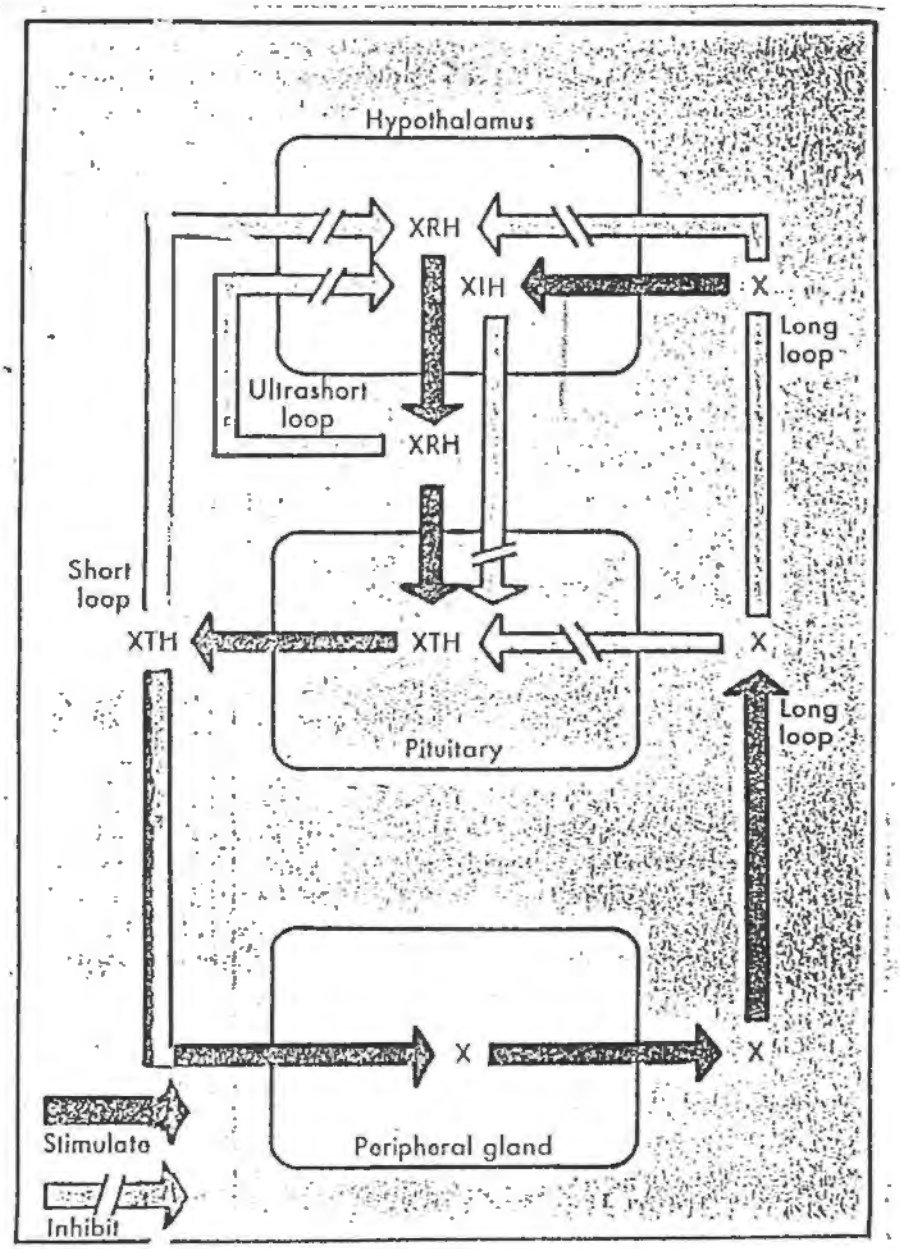


FIGURE 3\ 4 Negative feedback loops regulating hormone secretion in a typical hypothalamus-pituitary-peripheral gland axis. *X*, Peripheral gland hormone; *XTH*, pituitary tropic hormone; *XRH*, hypothalamic releasing hormone; *XIH*, hypothalamic inhibiting hormone.

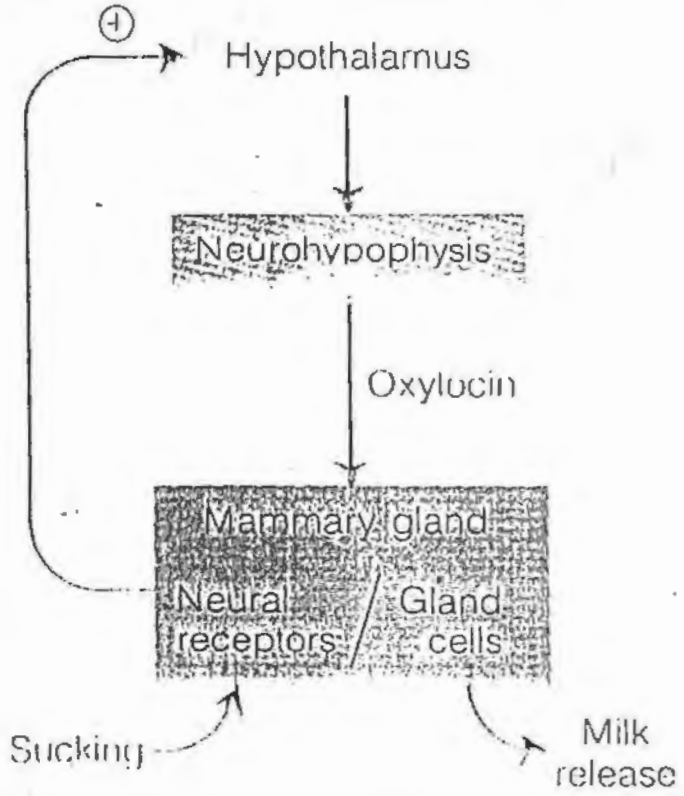


FIGURE 16.12

A neural-hormonal positive feedback loop. The sucking of an infant stimulates receptors in the nipple of the mammary gland. Neural signals travel to the hypothalamus, where they stimulate the release of oxytocin from the neurohypophysis. Oxytocin travels in the blood to the mammary gland and stimulates the release of milk.

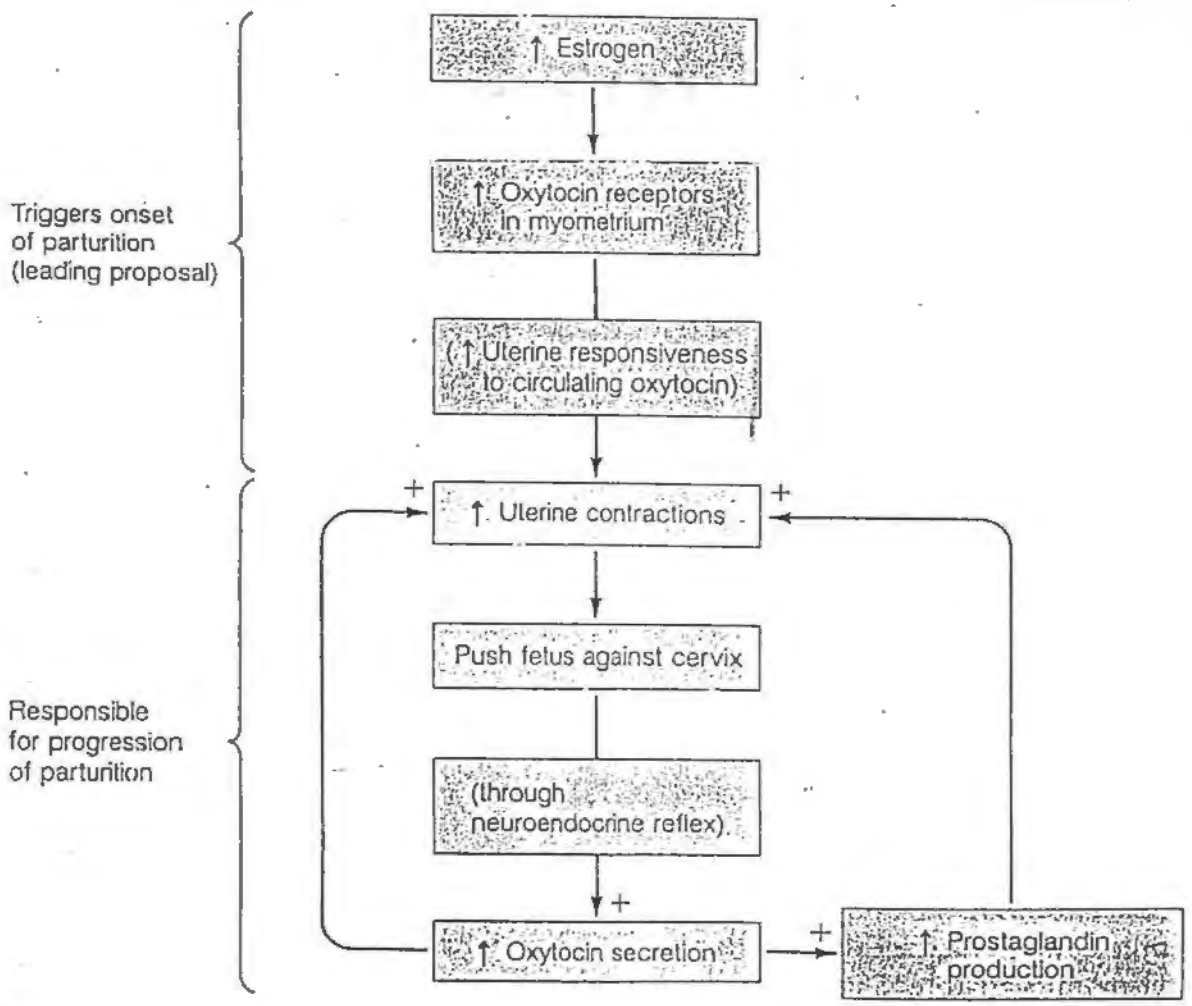


FIGURE 16–22 Positive Hormonal Feedback during Parturition

TABLE 5-4 Structural Categories of Hormones

Structural category	Examples
Proteins	Growth hormone
	Prolactin
	Insulin
	Parathyroid hormone
Glycoproteins	Follicle-stimulating hormone
	Luteinizing hormone
	Thyroid-stimulating hormone
Polypeptides	Thyrotropin-releasing hormone
	Oxytocin
	Antidiuretic hormone
	Calcitonin
	Melanocyte-stimulating hormone
	Adrenocorticotropic hormone
	Hypothalamic hormones
	Somatostatin
Amino acid derivatives	Epinephrine
	Thyroxine
	Melatonin
Steroids	Estrogen
	Progesterone
	Testosterone
	Cortisol

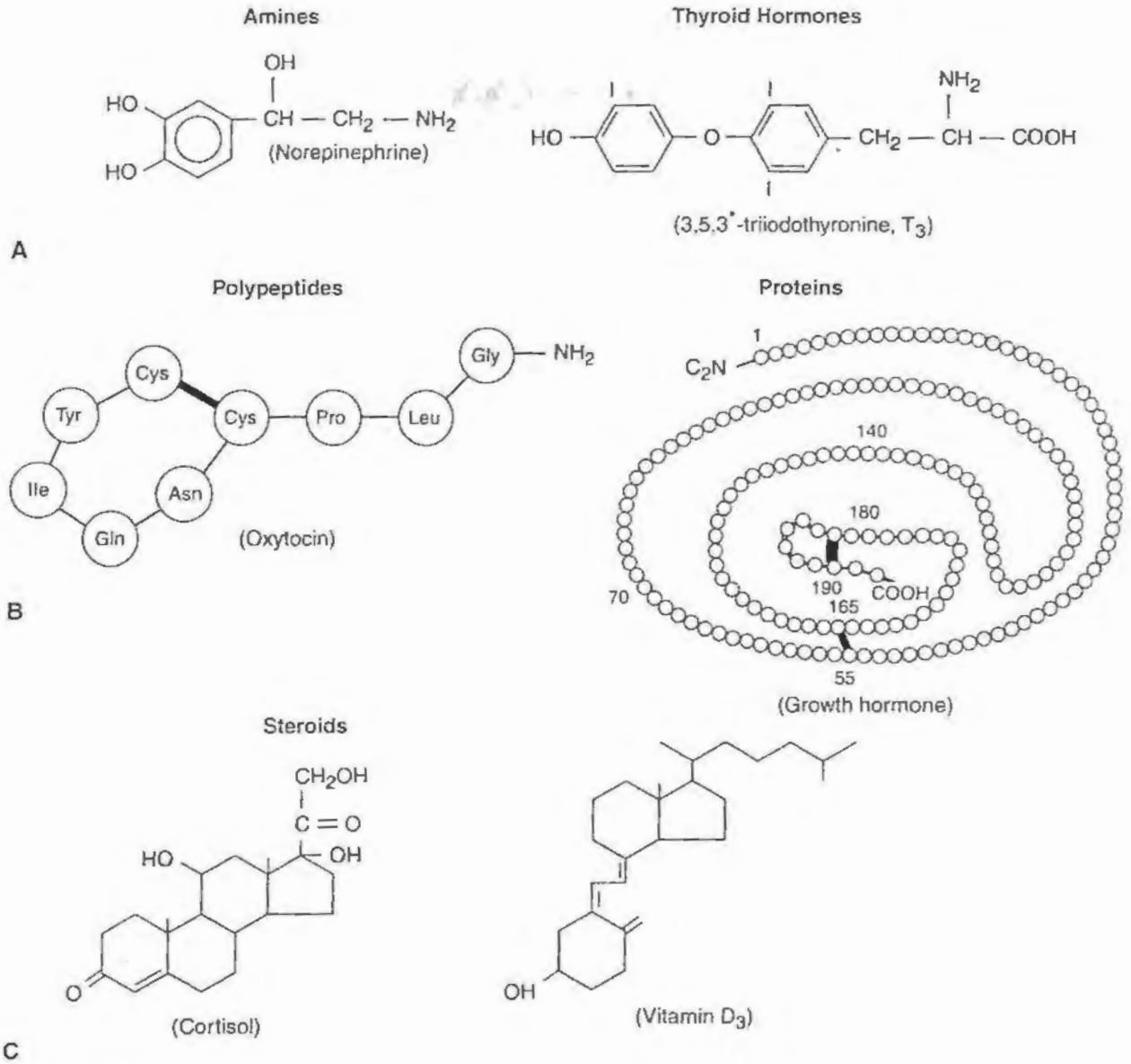


FIGURE 30.3 **Examples of different hormone chemical structures. A**, Amine hormones. **B**, Peptide hormones. **C**, Steroid hormones. (Modified from Griffin JE, Ojeda SR. Textbook of Endocrine Physiology. 4th Ed. Oxford: Oxford University Press, 2000: Fig. 1.1.)

Eicosanoids

Animals fed a fat-free diet fail to grow, develop skin & kidney lesions & become infertile. Adding linolenic, linoleic & arachidonic acids to the diet cures all the deficiency symptoms. These three acids are polyunsaturated fatty acids & because of their action are called **essential fatty acids**.

One of the reasons & possibly the only reason, that essential fatty acids are necessary for health is that they are the precursors of prostaglandins, prostacyclin, thromboxanes, lipoxins, leukotrienes & related compounds. These substances are called **eicosanoids**.

The leukotrienes, thromboxanes, lipoxins & prostaglandins have been called local hormones. They undoubtedly act mainly in the tissues at sites in which they are produced.

TABLE 3 Chemical Nature of the Classic Hormones

Tyrosine Derivatives	Steroids	Peptides (<20 amino acids)	Proteins (>20 amino acids)
Epinephrine	Testosterone	Oxytocin	Insulin
Norepinephrine	Estradiol	Vasopressin	Glucagon
Dopamine	Progesterone	Angiotensin	Adrenocorticotropic hormone
Triiodothyronine	Cortisol	Melanocyte-stimulating hormone	Thyroid-stimulating hormone
Thyroxine	Aldosterone	Somatostatin	Follicle-stimulating hormone
	Vitamin D	Thyrotropin-releasing hormone	Luteinizing hormone
		Gonadotropin-releasing hormone	Growth hormone
			Prolactin
			Corticotropin-releasing hormone
			Growth hormone-releasing hormone
			Parathyroid hormone
			Calcitonin
			Chorionic gonadotropin
			Choriosomatomammotropin

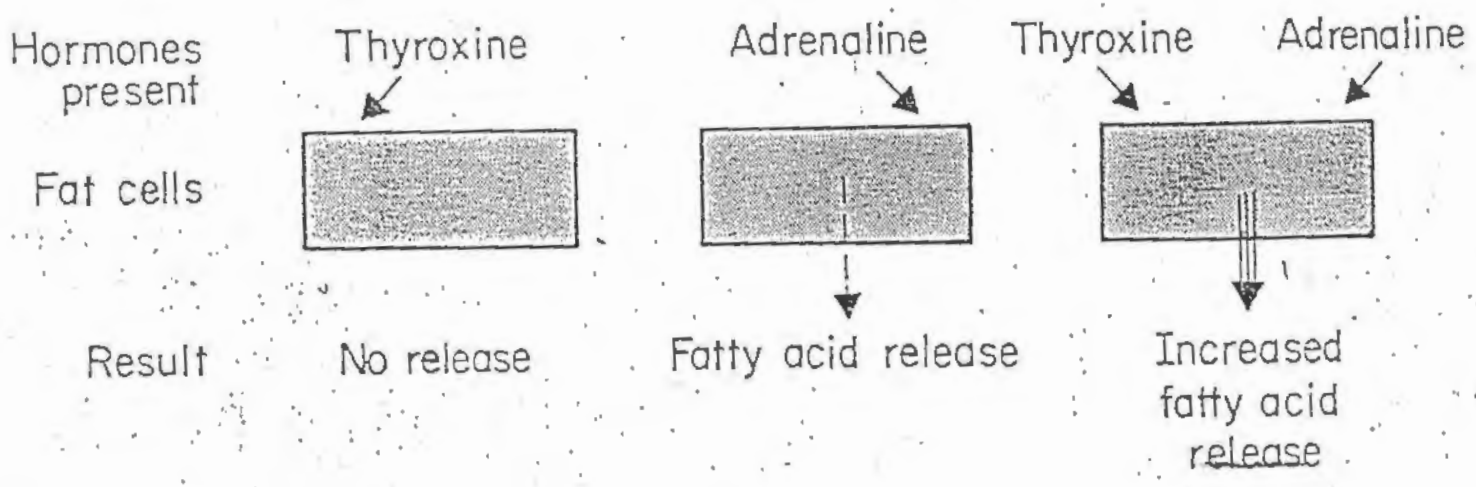


Fig. 11.1 Specific action of one hormone depends on the 'permissive' presence of another.

One type of interaction is referred to as a ***permissive effect.*** In this interaction, the effect of one hormone on a target cell requires a previous or simultaneous exposure to another hormone(s). Such previous exposure enhances the response of a target cell or increases the activity of another hormone. An example of a permissive effect, as noted earlier, is the exposure of the uterus first to estrogens and then to progesterone in order to prepare the organ for implantation.

Another type of hormonal interaction is known as a ***synergistic effect.*** In this situation, the effects of two or more hormones complement each other in such a way that the target cell responds effectively to the sum of the hormones involved. For example, the production and secretion of milk by the mammary glands requires, among others, the synergistic effects of estrogens, progesterone, prolactin (PRL), and oxytocin (OT).

Cells can regulate their receptor number and/or function in several ways. Exposing cells to an excess of hormone for a sustained period of time typically results in a decreased number of receptors for that hormone per cell. This phenomenon is referred to as **down-regulation**. In the case of peptide hormones, which have receptors on cell surfaces, a redistribution of receptors from the cell surface to intracellular sites usually occurs as part of the process of down-regulation. Therefore, there may be fewer total receptors per cell, and a smaller percentage may be available for hormone binding on the cell surface.

upregulation may occur when certain conditions or treatments cause an increase in receptor number compared with normal. Changes in rates of receptor synthesis may also contribute to long-term down-regulation or upregulation.

In addition to changing receptor number, many target cells can regulate receptor function. Chronic exposure of cells to a hormone may cause the cells to become less responsive to subsequent exposure to the hormone by a process termed **desensitization**. If the exposure of cells to a hormone has a desensitizing effect on further action by that same hormone, the effect is termed **homologous desensitization**. If the exposure of cells to one hormone has a desensitizing effect with regard to the action of a different hormone, the effect is termed **heterologous desensitization**.

In addition, some hormones are known to have different effects in several different target tissues. For example, testosterone, the male sex steroid, promotes normal sperm formation in the testes, stimulates growth of the accessory sex glands, such as the prostate and seminal vesicles, and promotes the development of several secondary sex characteristics, such as beard growth and deepening of the voice.

Multiplicity of regulation is also common in the endocrine system. The input of information from several sources allows a highly integrated response to many stimuli, which is of ultimate benefit to the whole animal. For example, several different hormones, including insulin, glucagon, epinephrine, thyroid hormones, and adrenal glucocorticoids, may regulate liver glycogen metabolism.

Most hormones have multiple actions in their target tissues and are, therefore, said to have **pleiotropic** effects. This phenomenon occurs when a single hormone regulates several functions in a target tissue. For example, in skeletal muscle, insulin stimulates glucose uptake, stimulates glycolysis, stimulates glycogenesis, inhibits glycogenolysis, stimulates amino acid uptake, stimulates protein synthesis, and inhibits protein degradation.

TABLE 55–7

HORMONES AFFECTING THE MAMMARY GLAND DURING PREGNANCY AND BREAST-FEEDING

Mammogenic hormones (promote cell proliferation)
- Lobuloalveolar growth
  - Estrogen
  - Growth hormone (IGF-I)
  - Cortisol
  - Prolactin
  - Relaxin?
- Ductal growth
  - Estrogen
  - Growth hormone
  - Cortisol
  - Relaxin

Lactogenic hormones (promote initiation of milk production by alveolar cells)
- Prolactin
- hCS (or hPL)
- Cortisol
- Insulin (IGF-I)
- Thyroid hormones
- Growth hormone?
- Withdrawal of estrogens and progesterone

Galactokinetic hormones (promote contraction of myoepithelial cells, and thus milk ejection)
- Oxytocin
- Vasopressin (1%–20% as powerful as OT)

Galactopoietic hormones (maintain milk production after it has been established)
- Prolactin (primary)
- Cortisol and other metabolic hormones (permissive)

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hCS, human chorionic somatomammotropin; hPL, human placental lactogen; IGF-I, insulin-like growth factor type I; OT, oxytocin.

A final example of a hormonal interaction is an ***antagonistic effect.*** Here, the effect of one hormone on a target cell is opposed by another hormone. An example is calcitonin (CT), which lowers blood calcium level, and parathyroid hormone (PTH), which raises blood calcium level (see Figure 18-14). Another antagonistic situation involves insulin, which lowers blood sugar level, and glucagon, which raises it.

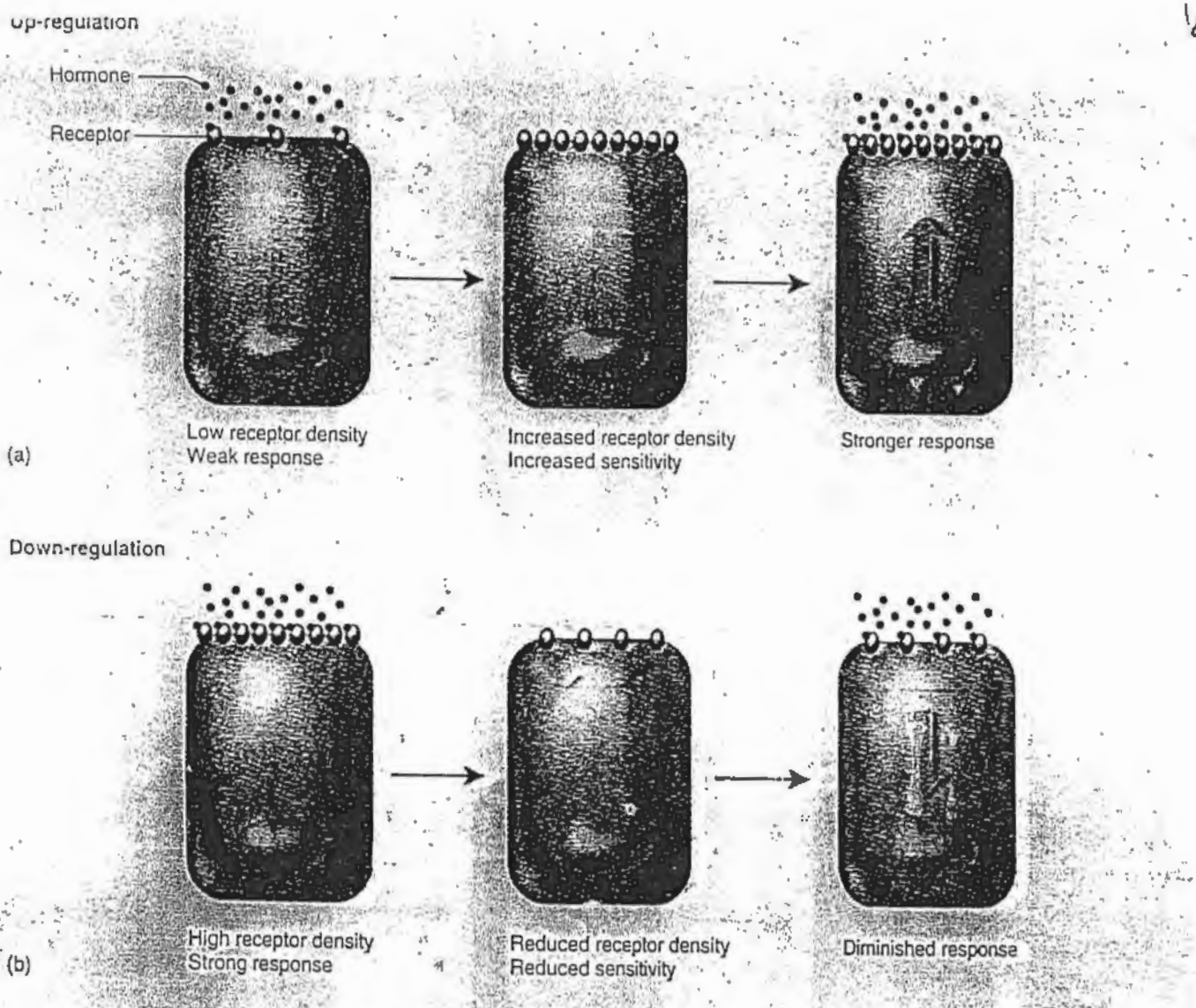


Figure 17.28 Modulation of Target Cell Sensitivity. (*a*) Up-regulation, in which a cell produces more receptors and increases its own sensitivity to a hormone. (*b*) Down-regulation, in which a cell reduces the density of its receptors and lessens its sensitivity to a hormone.

changing the *affinity* of the receptors for the hormone. The greater the number of receptors for a hormone, the greater the maximal response. The higher the affinity of the receptor for the hormone, the greater the likelihood of a response.

A change in the number or in the affinity of receptors is called down-regulation or up-regulation. **Down-regulation** means that the number of receptors or the affinity of the receptors for the hormone has decreased. **Up-regulation** means that the number or the affinity of the receptors has increased. Hormones may down-regulate or up-regulate their own receptors in target tissues and even may regulate receptors for related hormones.

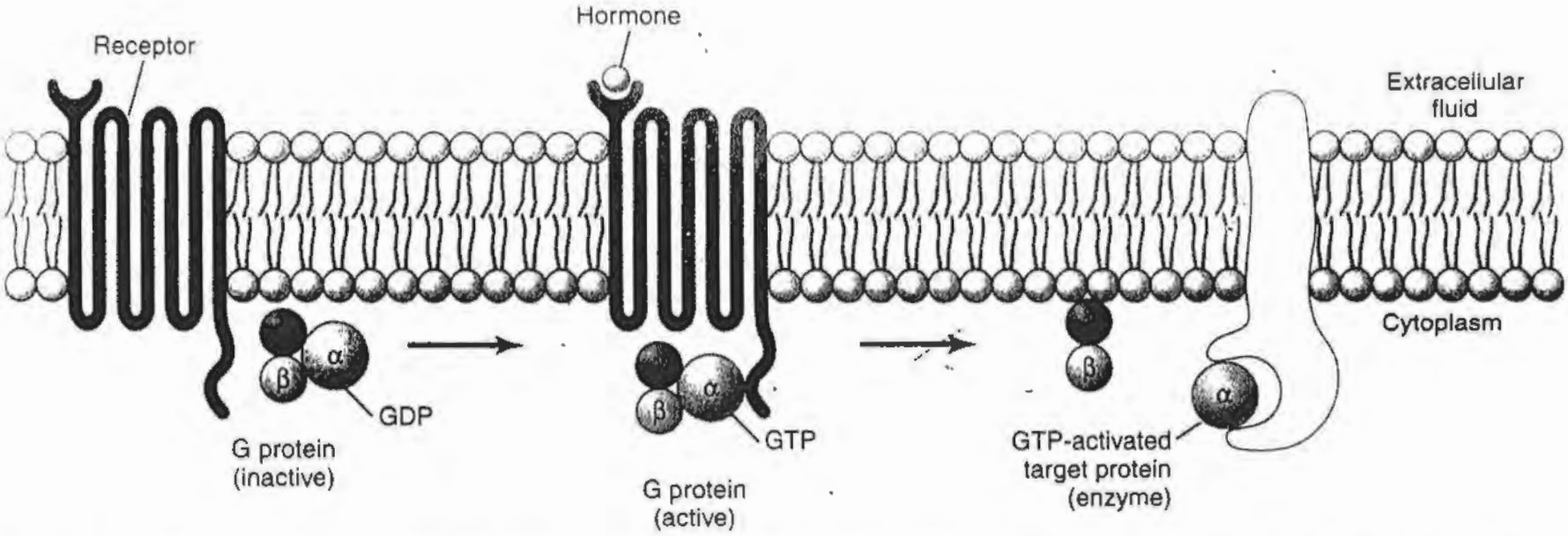


Figure 74-4 Mechanism of activation of a G protein–coupled receptor. When the hormone activates the receptor, the inactive α, β, and γ G protein complex associates with the receptor and is activated, with an exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP). This causes the α subunit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

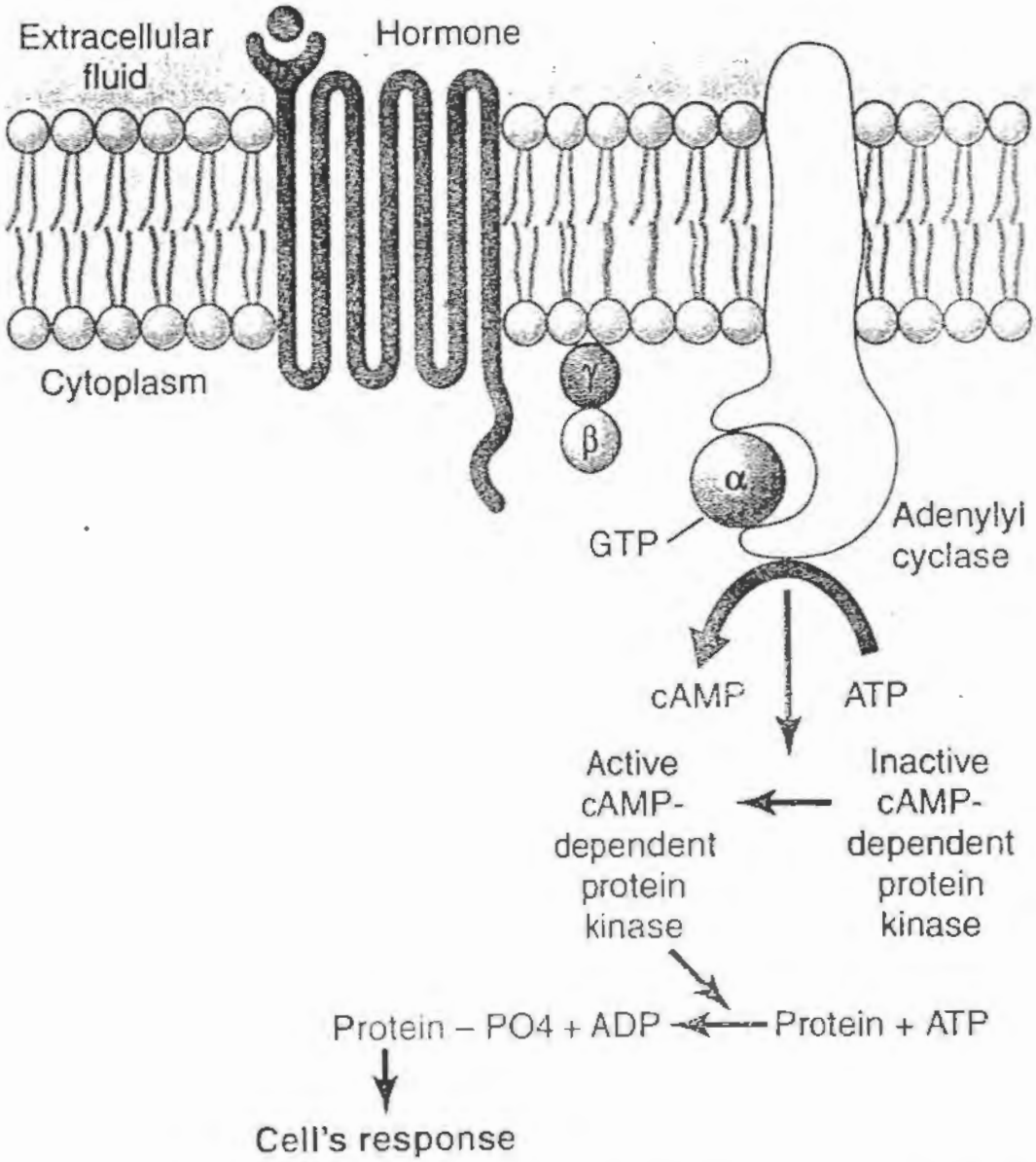


Figure 74-7 Cyclic adenosine monophosphate (cAMP) mechanism by which many hormones exert their control of cell function. ADP, adenosine diphosphate; ATP, adenosine triphosphate.

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

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

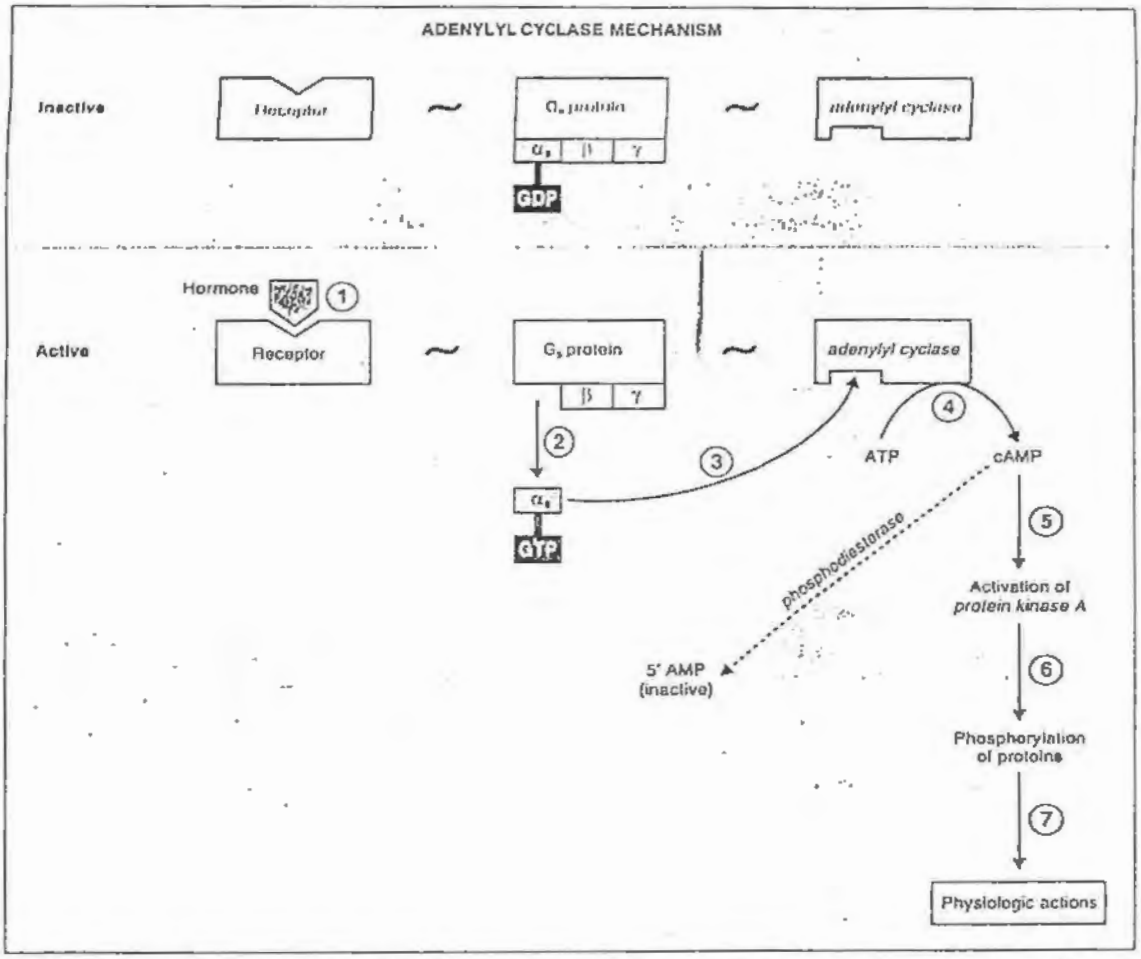


FIGURE 9–5. Steps involved in the adenylyl cyclase (cAMP) mechanism of action. Circled numbers correspond to steps discussed in the text. AMP, adenosine monophosphate; ATP, adenosine triphosphate; GDP, guanosine diphosphate; GTP, guanosine triphosphate.

lyzes the conversion of ATP to cAMP, which serves as the second messenger *(Step 4)*. Although not shown, intrinsic GTPase activity converts GTP back to GDP, and the α_s subunit returns to its inactive state.

3. **cAMP, via a series of steps involving activation of protein kinase A,** phosphorylates intracellular proteins *(Steps 5 and 6)*. These phosphorylated proteins then execute the final physiologic actions *(Step 7)*.

4. Intracellular cAMP is degraded to an inactive metabolite, 5′ AMP, by the enzyme phosphodiesterase, thereby turning off the action of the second messenger.

Phospholipase C Mechanism

Hormones that utilize the phospholipase C (IP_3/Ca^{2+}) mechanism also are listed in Table 9–3. The mechanism involves binding of hormone to a receptor, coupling via a G_q or G_i protein, and activation or inhibition of phospholipase C. Intracellular levels of IP_3 and Ca^{2+} are either increased or decreased, producing the final physiologic actions. The steps in the phospholipase C (IP_3/Ca^{2+}) mechanism are shown in Figure 9–6. A hormone that utilizes a G_q protein is shown.

The receptor-G_q-phospholipase C complex is imbedded in the cell membrane. With no hormone bound to the receptor, the α_q subunit binds GDP. In this configuration, the G_q protein is inactive. When

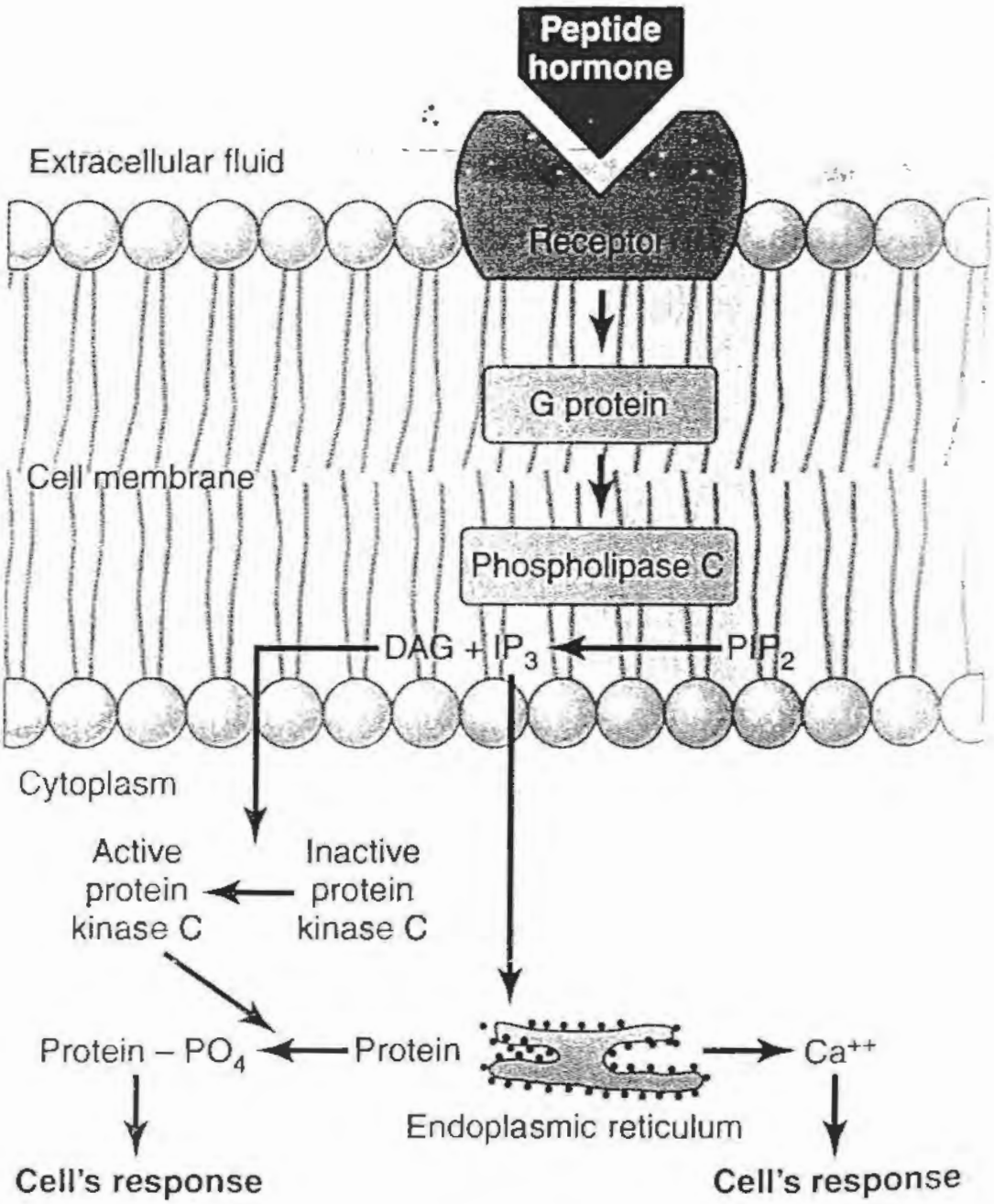


Figure 74-8 The cell membrane phospholipid second messenger system by which some hormones exert their control of cell function. DAG, diacylglycerol; IP_3, inositol triphosphate; PIP_2, phosphatidylinositol biphosphate.

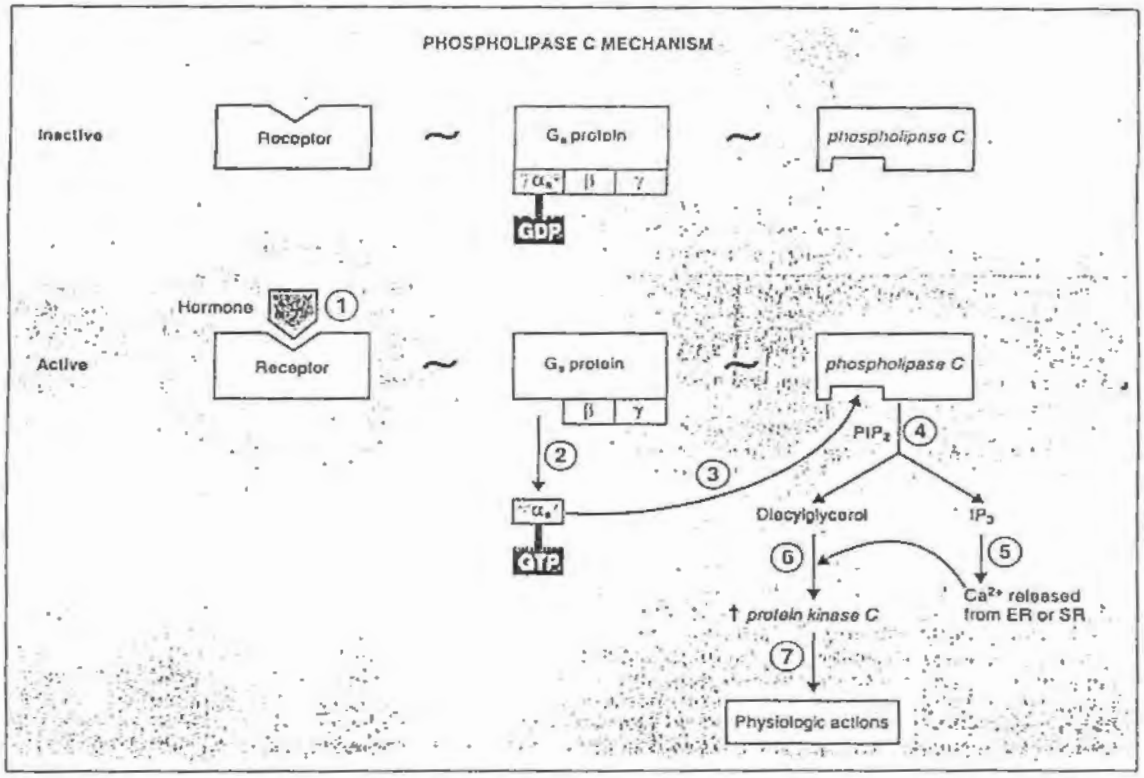


FIGURE 9–6. Steps involved in the phospholipase C (IP_3/Ca^{2+}) mechanism of action. Circled numbers correspond to steps discussed in the text. ER, endoplasmic reticulum; GDP, guanosine diphosphate; GTP, guanosine triphosphate; IP_3, inositol 1,4,5-triphosphate; PIP_2, phosphatidylinositol 4,5-diphosphate; SR, sarcoplasmic reticulum.

the hormone binds to the receptor, G_s is activated, which activates phospholipase C, in the following *steps*.

1. Hormone binds to its receptor in the cell membrane, producing a conformational change in the α_s subunit *(Step 1)*. GDP is released from the α_s subunit, is replaced by GTP, and the α_s subunit detaches from the G_s protein *(Step 2)*.

2. The α_s-GTP complex migrates within the cell membrane and binds to and activates phospholipase C *(Step 3)*. Activated phospholipase C catalyzes the liberation of diacylglycerol and IP_3 from phosphatidylinositol 4,5-diphosphate (PIP_2), a membrane phospholipid *(Step 4)*. The IP_3 generated causes the release of Ca^{2+} from intracellular stores in the endoplasmic or sarcoplasmic reticulum, resulting in an increase in intracellular Ca^{2+} concentration *(Step 5)*.

3. Together, Ca^{2+} and diacylglycerol activate protein kinase C *(Step 6)*, which phosphorylates proteins and produces the final physiologic actions *(Step 7)*.

Steroid and Thyroid Hormone Mechanism

Steroid hormones and thyroid hormones have the same mechanism of action. In contrast to the adenylyl cyclase and phospholipase C mechanisms, which involve cell membrane receptors and the generation of intracellular second messengers, the steroid hormone mechanism involves nuclear receptors, DNA transcription, and synthesis of new proteins. In further contrast to peptide hormones, which act quickly on their target cells (within minutes), steroid hormones act slowly (taking hours).

The *steps* in the steroid hormone mechanism are shown in Figure 9–7 and described as follows.

1. The steroid hormone diffuses across the cell membrane into the cytoplasm (not shown) and then across the nuclear membrane *(Step 1)*. In the nucleus, the hormone binds to a nuclear receptor at a site near the C terminus of a receptor protein. Once the hormone is bound, a conformational change occurs, activating the receptor. The conformational change includes moving blocking proteins out of the way and exposing the DNA-binding domain of the

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

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

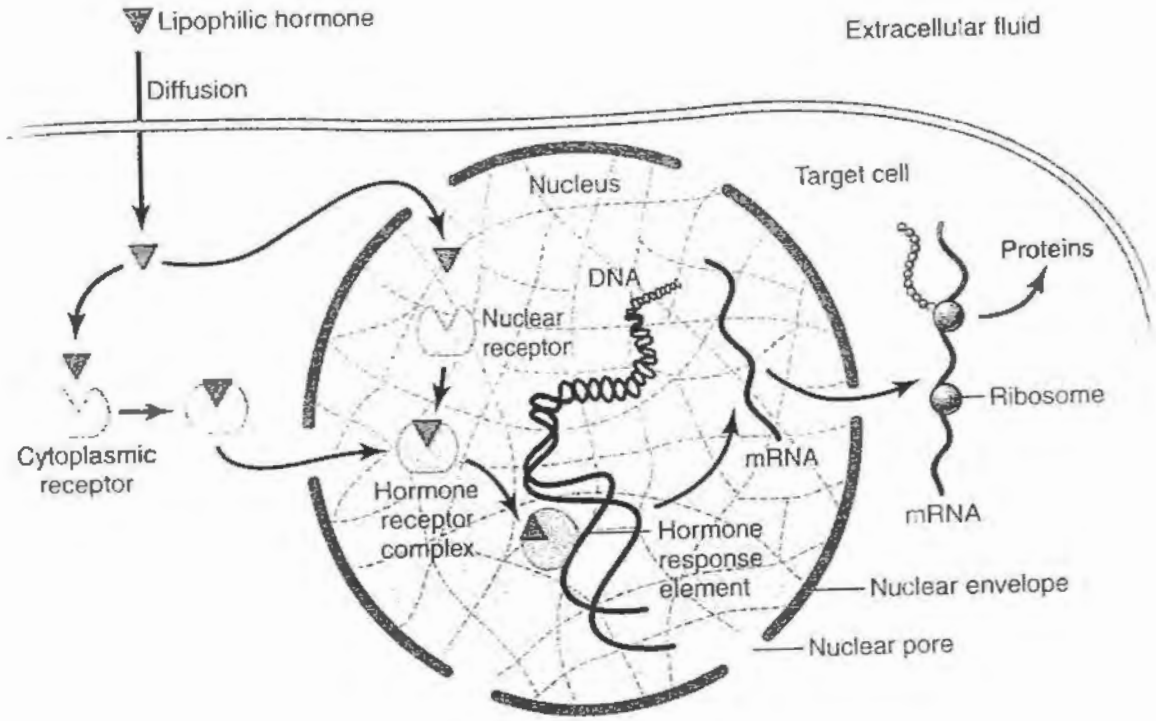


Figure 74-6 Mechanisms of interaction of lipophilic hormones, such as steroids, with intracellular receptors in target cells. After the hormone binds to the receptor in the cytoplasm or in the nucleus, the hormone-receptor complex binds to the hormone response element (promoter) on the DNA. This either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

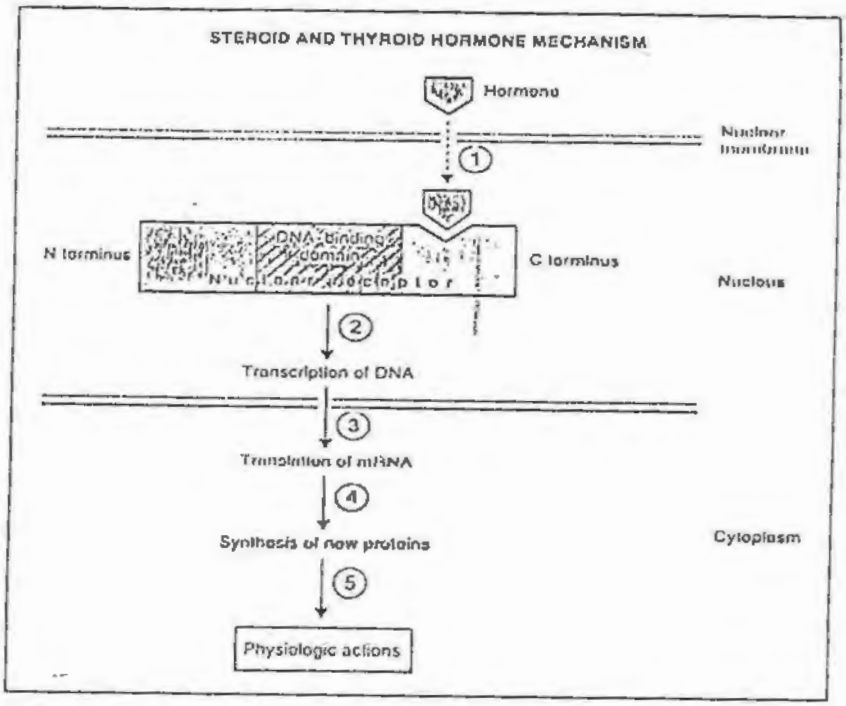


FIGURE 9–7. Steps involved in the steroid hormone mechanism of action. Circled numbers correspond to steps discussed in the text. DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid.

receptor. The exposed DNA-binding domain now binds DNA, beginning the transcription process to generate new mRNA *(Step 2)*.

2. The mechanism continues in the cytoplasm, where mRNA is translated *(Step 3)* and new proteins are synthesized *(Step 4)*. The nature of the new proteins is specific to the hormone and accounts for the specificity of the hormone's physiologic actions *(Step 5)*. For example, 1,25-dihydroxycholecalciferol induces the synthesis of a Ca^{2+}-binding protein, which aids in the absorption of Ca^{2+} from the gastrointestinal tract; aldosterone induces the synthesis of Na^+ channels in renal principal cells, which aids in the reabsorption of Na^+ in the kidney; and thyroid hormones induce the synthesis of Na^+-K^+ ATPase, which increases O_2 consumption and metabolic rate. Each hormone induces the synthesis of different proteins and has very different physiologic actions, depending on the nature of that protein.

It is important to visualize the anatomic relationships between the hypothalamus and the pituitary, since these relationships underlie the functional connections between the glands.

The pituitary gland, which also is called the hypophysis, consists of a posterior lobe and an anterior lobe. The posterior lobe (or posterior pituitary) is also called the neurohypophysis. The anterior lobe (or anterior pituitary) is also called the adenohypophysis. The hypothalamus is connected to the pituitary gland by a thin stalk called the infundibulum. Functionally, the hypothalamus controls the pituitary gland by both neural and hormonal mechanisms (Figure 9–8).

MECHANISMS OF HORMONE ACTION AND SECOND MESSENGERS

Hormone actions on target cells begin when the hormone binds to a membrane receptor, forming a hormone-receptor complex. In many hormonal systems, the hormone-receptor complex is coupled to effector proteins by guanosine triphosphate (GTP)-binding proteins (G proteins). The effector proteins usually are enzymes, either adenylyl cyclase or phospholipase C. When the effector proteins are activated, a second messenger, either cAMP or IP_3 (inositol 1,4,5-triphosphate), is produced, which amplifies the original hormonal signal and then orchestrates the physiologic actions.

The three major mechanisms of hormone action on target cells are the adenylyl cyclase mechanism, in which cAMP is the second messenger; the phospholipase C mechanism, in which IP_3/Ca^{2+} is the second messenger; and the steroid hormone mechanism. In addition, insulin and insulin-like growth factors (IGF) act on their target cells by a tyrosine kinase mechanism. Finally, several hormones activate guanylate cyclase, in which cyclic guanosine monophosphate (cyclic GMP, cGMP) is the second messenger. The three major mechanisms of hormone action are discussed in this section; the tyrosine kinase mechanism is discussed in the section on insulin. The mechanisms of action of the major hormones are summarized in Table 9–3.

G Proteins

G proteins are discussed in Chapter 2 in the context of autonomic receptors. Briefly, G proteins are a family of membrane-bound proteins that couple hormone receptors to effector enzymes (e.g., adenylyl cyclase). Thus, G proteins serve as "molecular switches" that decide whether the hormone action can proceed.

At the molecular level, G proteins are heterotrimeric (i.e., having three subunits) serpentine proteins that span the cell membrane seven times, winding like a "snake." The three subunits are designated as alpha (α), beta (β), and gamma (γ). The α subunit can bind either guanosine diphosphate (GDP) or GTP, and it contains GTPase activity. When GDP is bound to the α subunit, the G protein is inactive; when GTP is bound, the G protein is active and can perform its coupling function.

G proteins can be either stimulatory or inhibitory and are called, accordingly, G_s or G_i. Stimulatory or inhibitory activity resides in the α subunit, which are called α_s or α_i.

In summary, when GTP is bound to the α_s subunit of a G_s protein, the G_s protein *stimulates* the effector enzyme (e.g., adenylyl cyclase). When GTP is bound to the α_i subunit of a G_i protein, the G_i protein *inhibits* the effector enzyme.

Adenylyl Cyclase Mechanism

The adenylyl cyclase/cAMP mechanism is utilized by many hormonal systems (see Table 9–3). This mechanism involves binding of a hormone to a receptor, coupling by a G_s or G_i protein, and then activation or inhibition of adenylyl cyclase, leading to increases or decreases in intracellular cAMP. cAMP, the second messenger, then amplifies the hormonal signal to produce the final physiologic actions.

The steps in the adenylyl cyclase/cAMP mechanism are shown in Figure 9–5. In this example, the hormone utilizes a G_s protein (rather than a G_i protein). The receptor-G_s-adenylyl cyclase complex is imbedded in the cell membrane. When no hormone is bound to the receptor, the α_s subunit of the G_s protein binds GDP. In this configuration, the G_s protein is inactive. When hormone binds to its receptor, the G_s protein is activated, and the following steps occur.

1. Hormone binds to its receptor in the cell membrane, producing a conformational change in the α_s subunit *(Step 1)*, which produces two changes: GDP is released from the α_s subunit and is replaced by GTP, and the α_s subunit detaches from the G_s protein *(Step 2)*.

2. The α_s-GTP complex migrates within the cell membrane and binds to and activates adenylyl cyclase *(Step 3)*. Activated adenylyl cyclase cata-

TABLE 9–3. Mechanisms of Hormone Action

Adenylyl Cyclase Mechanism (cAMP)	Phospholipase C Mechanism (IP_3/Ca^{2+})	Steroid Hormone Mechanism	Tyrosine Kinase Mechanism	Guanylate Cyclase Mechanism (cGMP)
CTH	GnRH	Glucocorticoids	Insulin	Atrial natriuretic hormone
H	TRH	Estrogen	IGF-1	Endothelial-derived relaxing factor (EDRF)
SH	GHRH	Progesterone		Nitric oxide (NO)
SH	Angiotensin II	Testosterone		
DH (V_2 receptor)	ADH (V_1 receptor)	Aldosterone		
CG	Oxytocin	1,25-Dihydroxycholecalciferol		
ISH	α Receptors	Thyroid hormones		
RH				
alcitonin				
TH				
lucagon				
β_1 and β_2 receptors				

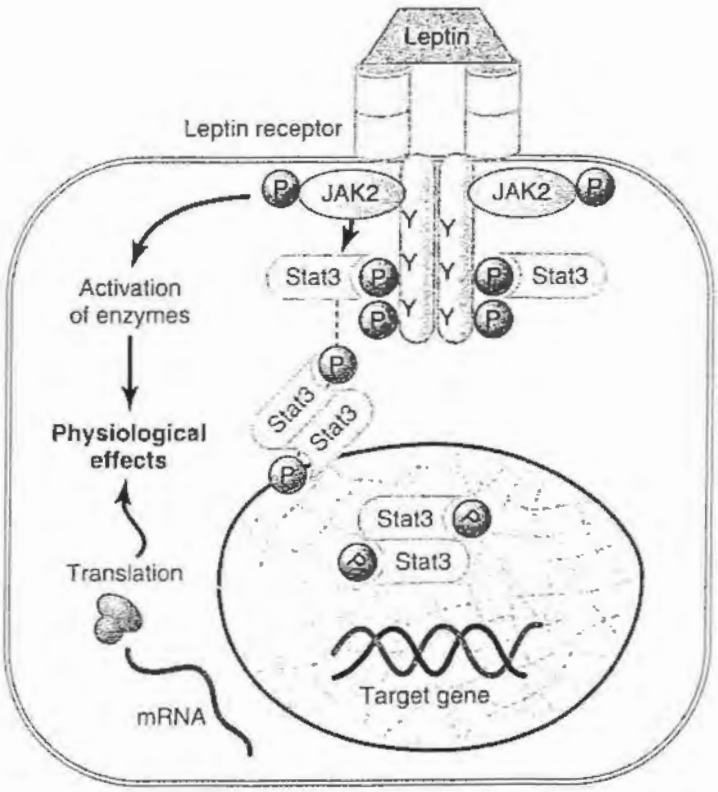


Figure 74-5 An enzyme-linked receptor—the leptin receptor. The receptor exists as a homodimer (two identical parts), and leptin binds to the extracellular part of the receptor, causing phosphorylation and activation of the intracellular associated janus kinase 2 (JAK2). This causes phosphorylation of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

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

One example of an enzyme-linked receptor is the *leptin receptor* (Figure 74-5). Leptin is a hormone secreted by fat cells and has many physiological effects, but it is especially important in regulating appetite and energy balance, as discussed in Chapter 71. The lep-

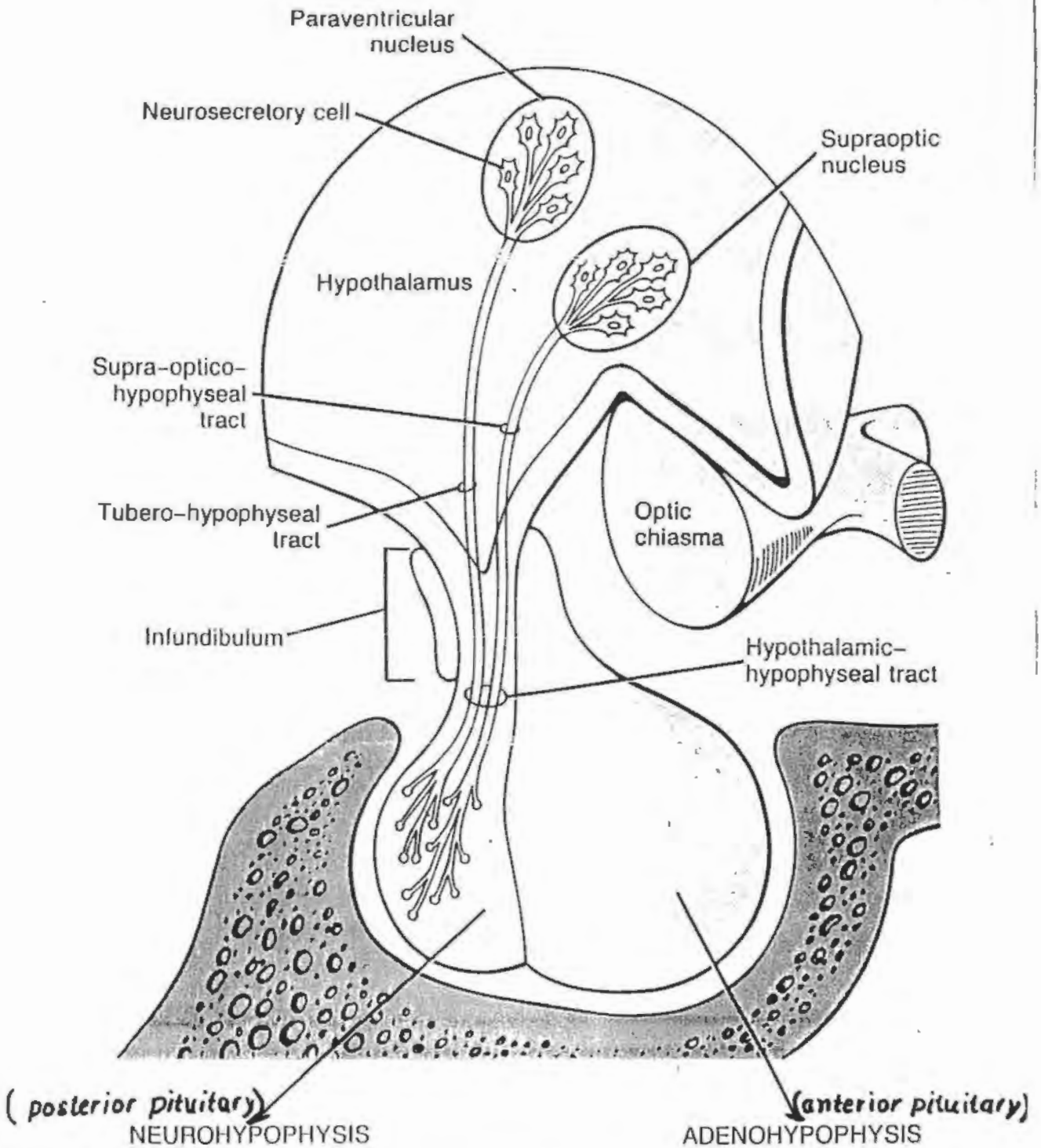


Figure 16-8
Tortora/Anagnostakos: Principles of Anatomy and Physiology, 5/e

The Pituitary GLAND

(hypophysis)

small gland—about 1 cm in diameter and 0.5 to 1 gram in weight—that lies in the sella turcica at the base of the brain.

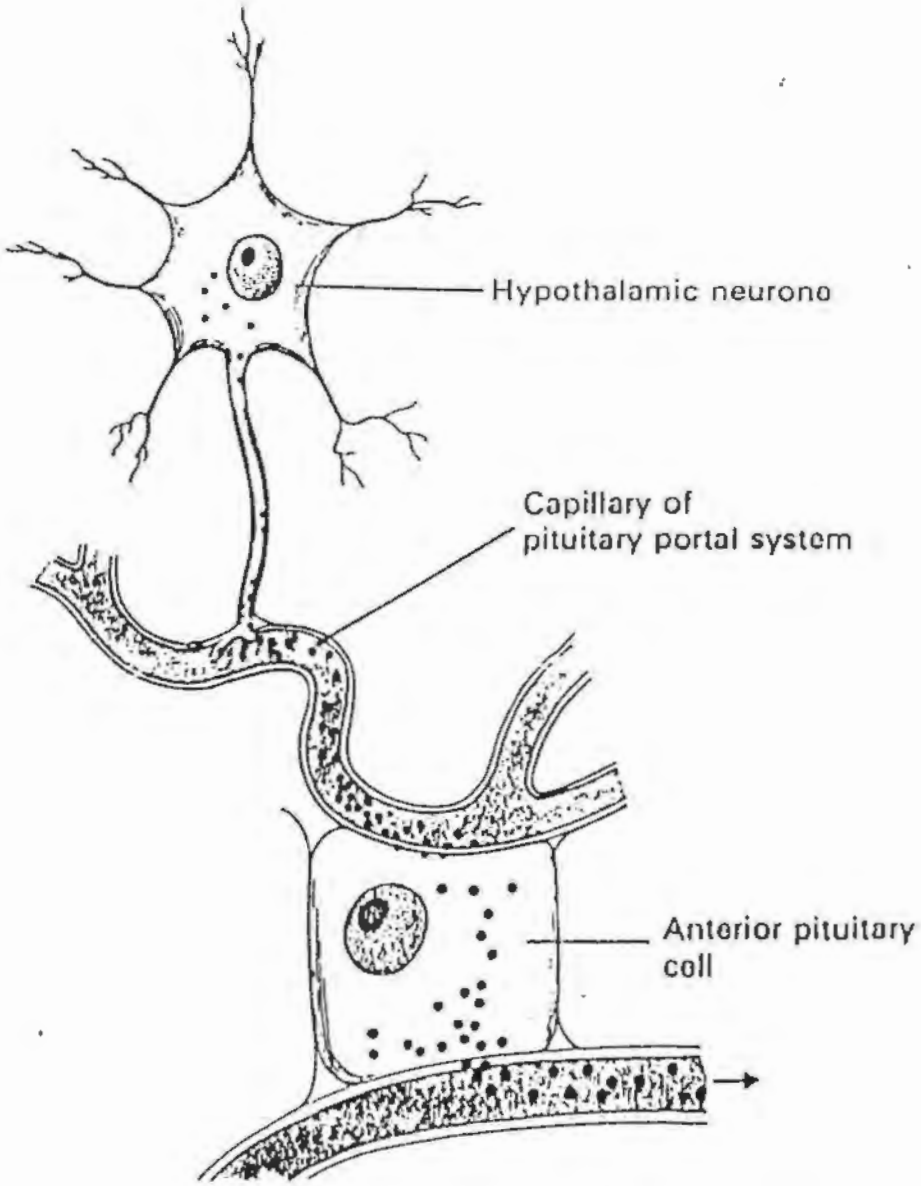


Fig. 28.5 Relationship between hypothalamic neurones and anterior pituitary cells. (*From* R. Guillemin & R. Burgus (1972) *Scientific American* 227 (5) 24–33.)

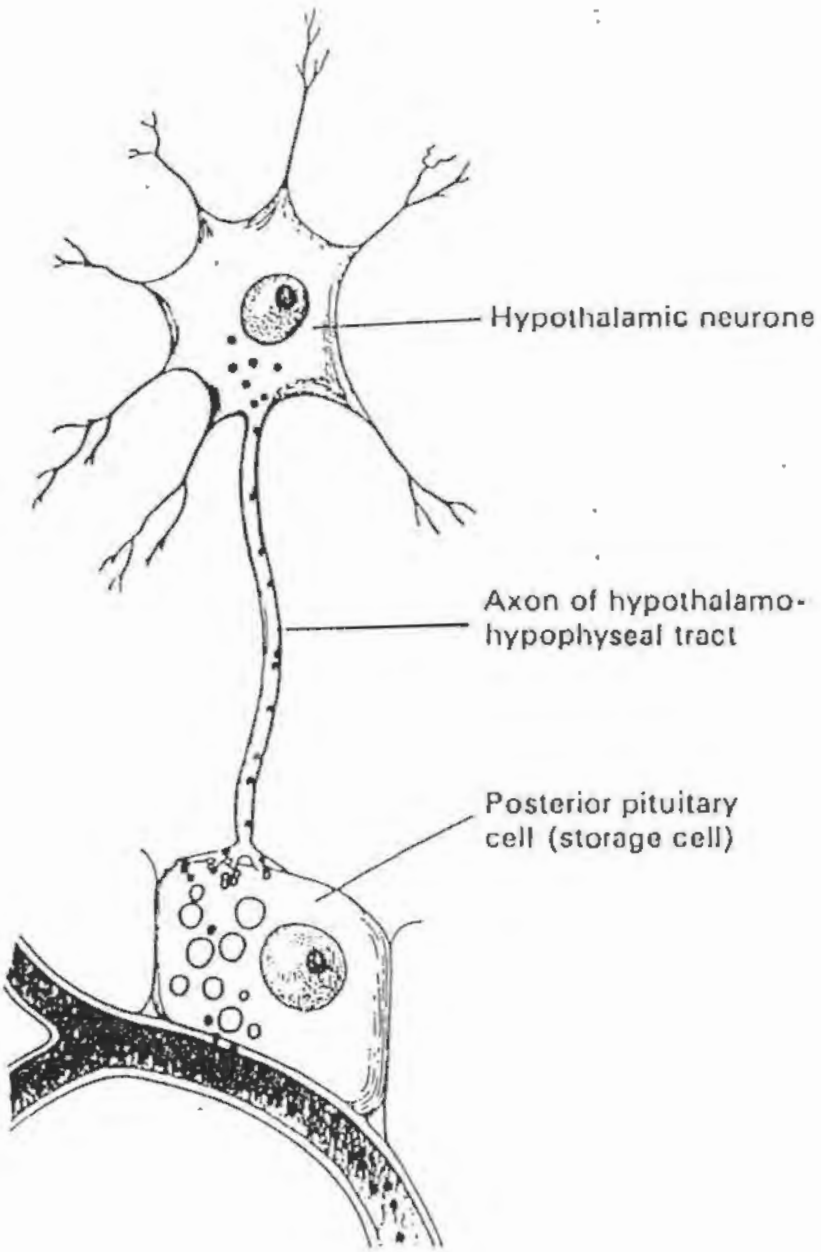


Fig. 28.8 Role of the posterior pituitary cells in the storage of the hormones oxytocin and ADH elaborated by hypothalamic neurones (*From* R. Guillemin & R. Burgus (1972) *Scientific American* 227 (5) 24–33).

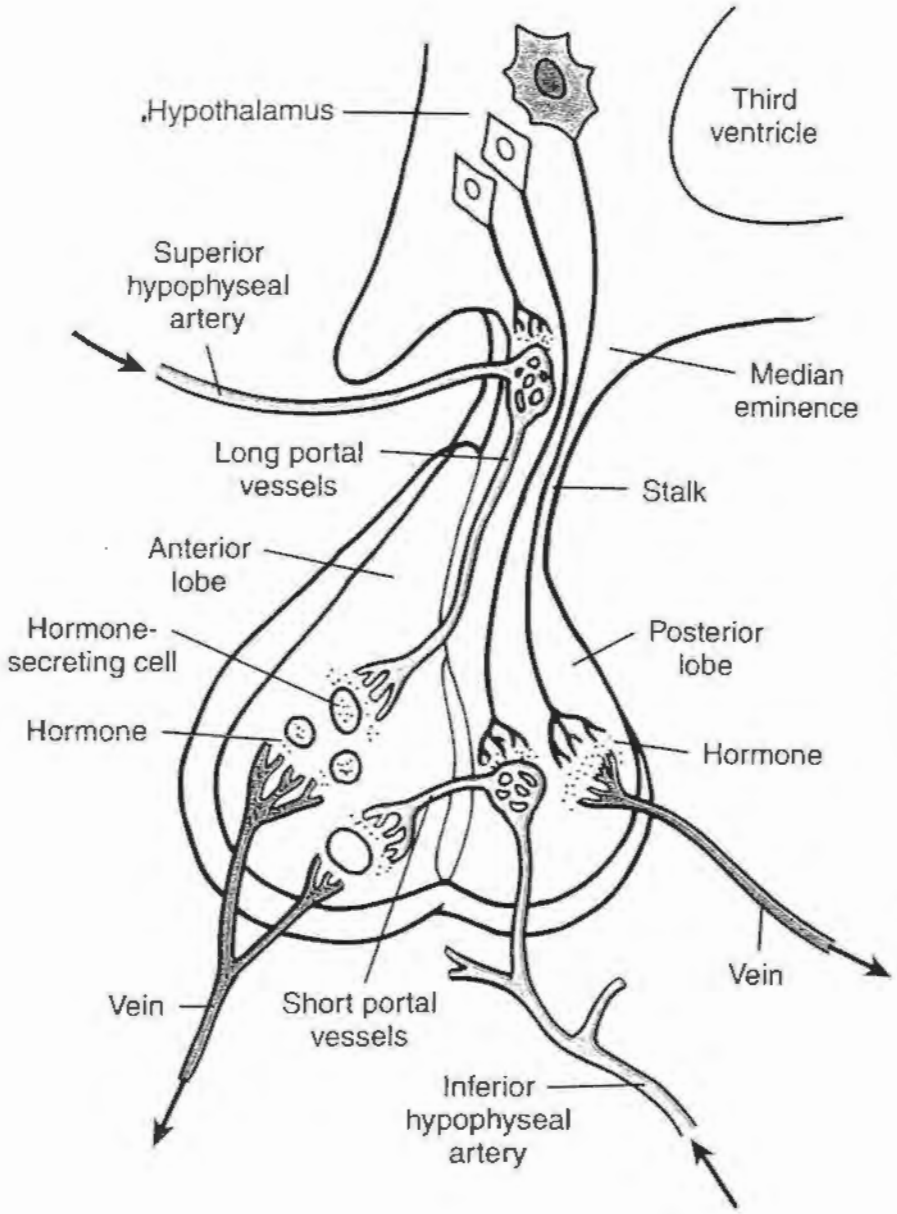


FIGURE 31.2 The blood supply to the anterior pituitary. This illustration shows the relationship of the pituitary blood supply to hypothalamic magnocellular neurons and to hypothalamic neurosecretory cells that produce releasing hormones. The magnocellular neuron (larger, dark blue cell body) releases AVP or oxytocin at its axon terminals into capillaries that give rise to the venous drainage of the posterior lobe. The neurons with smaller, light blue cell bodies are secreting releasing factors into capillary networks that give rise to the long and short hypophyseal portal vessels, respectively. Releasing hormones are shown reaching the hormone-secreting cells of the anterior lobe via the portal vessels.

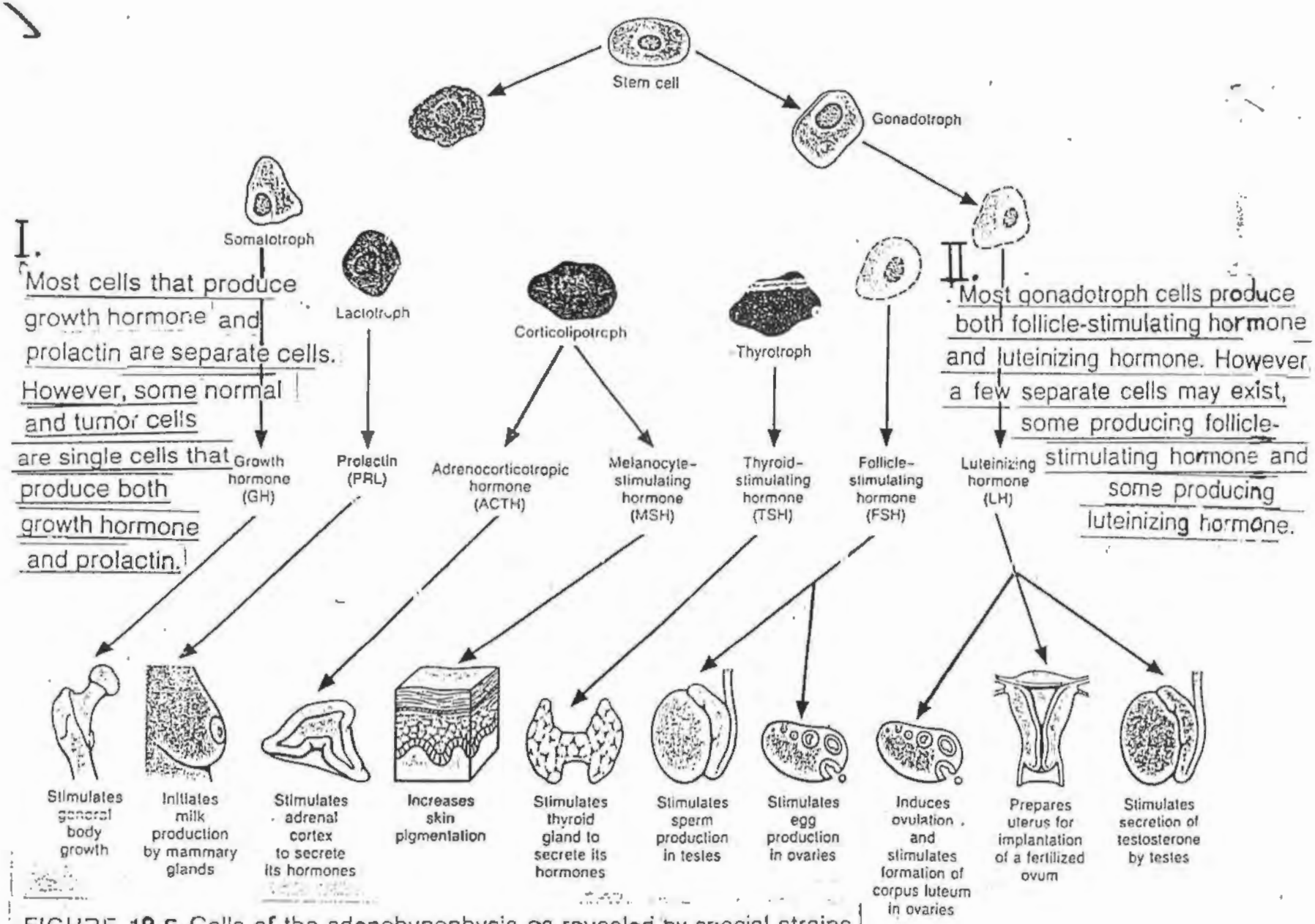


FIGURE 18-6 Cells of the adenohypophysis as revealed by special strains.

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

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

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

IGF, insulin-like growth factor.

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

Specific Areas in the Hypothalamus Control Secretion of Specific Hypothalamic Releasing and Inhibitory Hormones. All or most of the hypothalamic hormones are secreted at nerve endings in the median eminence before being transported to the anterior pituitary gland. Electrical stimulation of this region excites these nerve endings and, therefore, causes release of essentially all the hypothalamic hormones. However, the neuronal cell bodies that give rise to these median eminence nerve endings are located in other discrete areas of the hypothalamus or in closely related areas of the basal brain.

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

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

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

For most of the anterior pituitary hormones, it is the releasing hormones that are important, but for prolactin, a hypothalamic inhibitory hormone probably exerts more control.

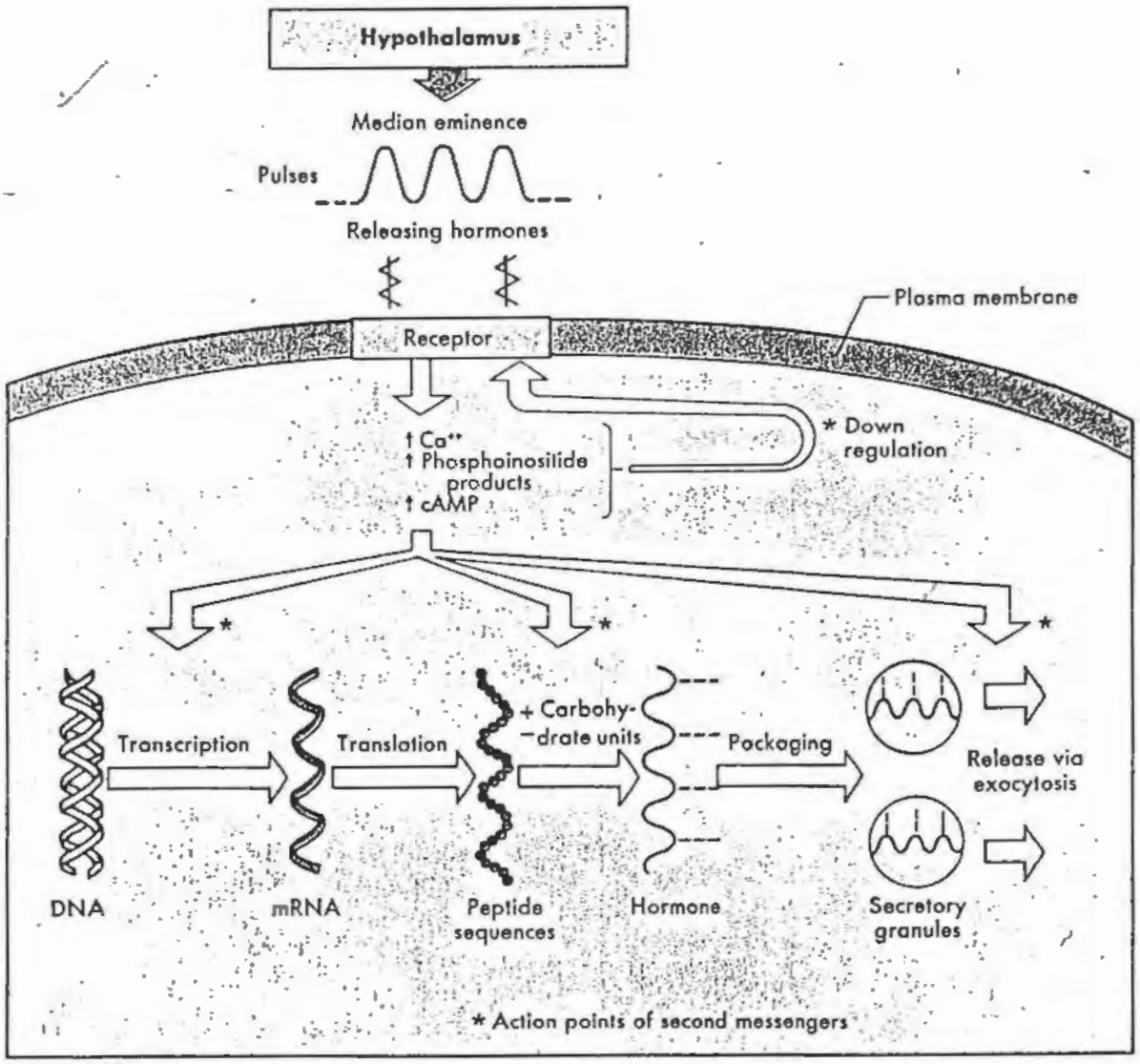


FIGURE 39-3 The action of hypothalamic releasing or inhibiting hormones on anterior pituitary cells. Characteristically the neurohormones are released in pulses, bind to plasma membrane receptors, and act through calcium ions *(Ca^{++})* and other second messengers. They regulate gene expression, posttranslational processes, and secretion of anterior pituitary tropic hormones. cAMP, Cyclic adenosine monophate; *DNA*, deoxyribonucleic acid; mRNA, messenger ribonucleic acid.

Vasopressin & Oxytocin

In most mammals, the hormones secreted by the posterior pituitary gland are **arginine vasopressin** (AVP) and **oxytocin.** In hippopotami and most pigs, arginine in the vasopressin molecule is replaced by lysine to form **lysine vasopressin.** The posterior pituitaries of some species of pigs and marsupials contain a mixture of arginine and lysine vasopressin. The posterior lobe hormones are nonapeptides with a disulfide ring at one end (Figure 14–10).

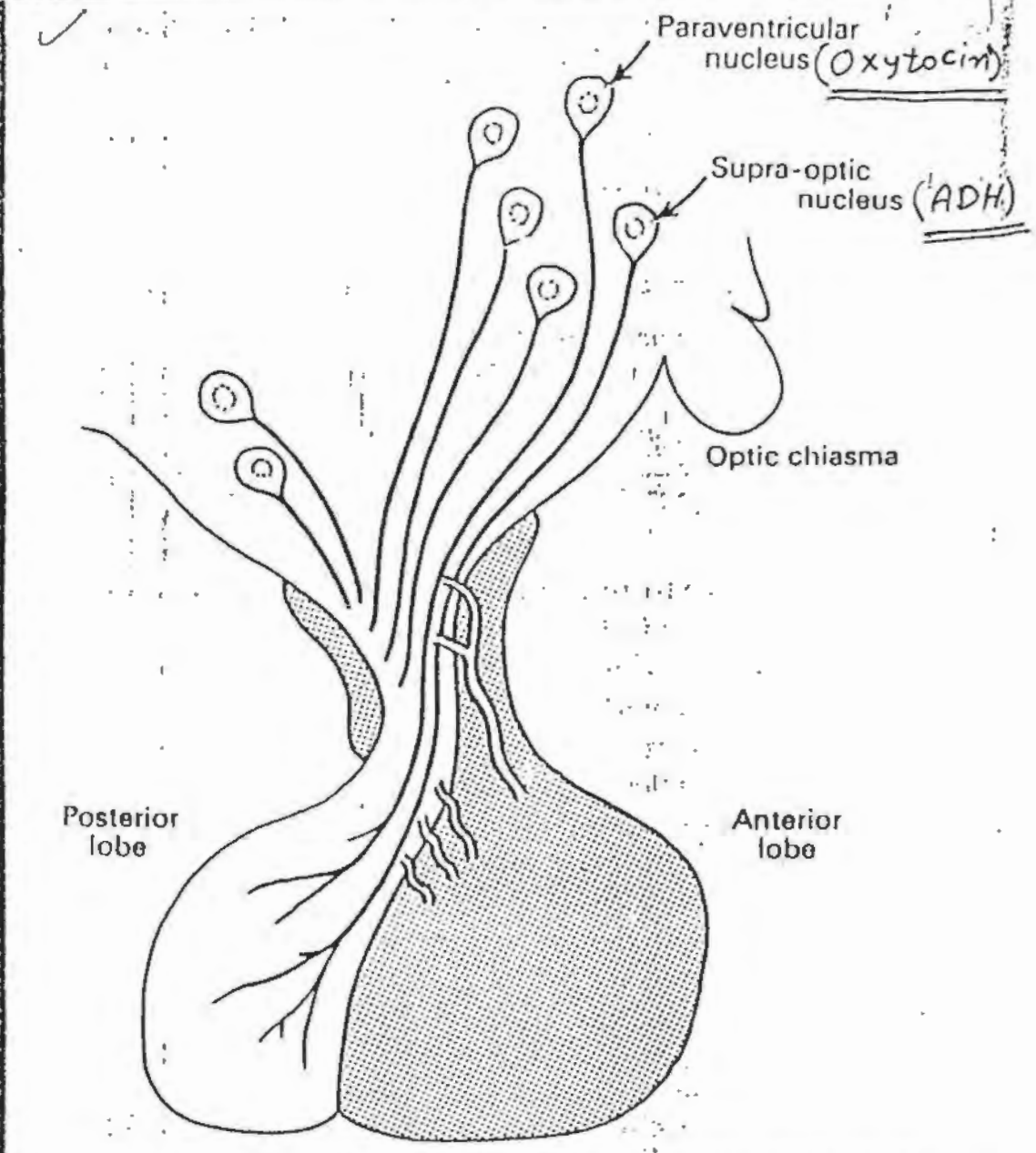


Fig. 28.7 The tracts from the hypothalamus to the pituitary. The paraventricular nucleus and the supra-optic nucleus are thought to be responsible for the elaboration of oxytocin and ADH respectively. The other tracts terminate in the capillary plexus shown in Figure 28.4 and carry the hypothalamic hormones which control the release of the hormones of the anterior pituitary.

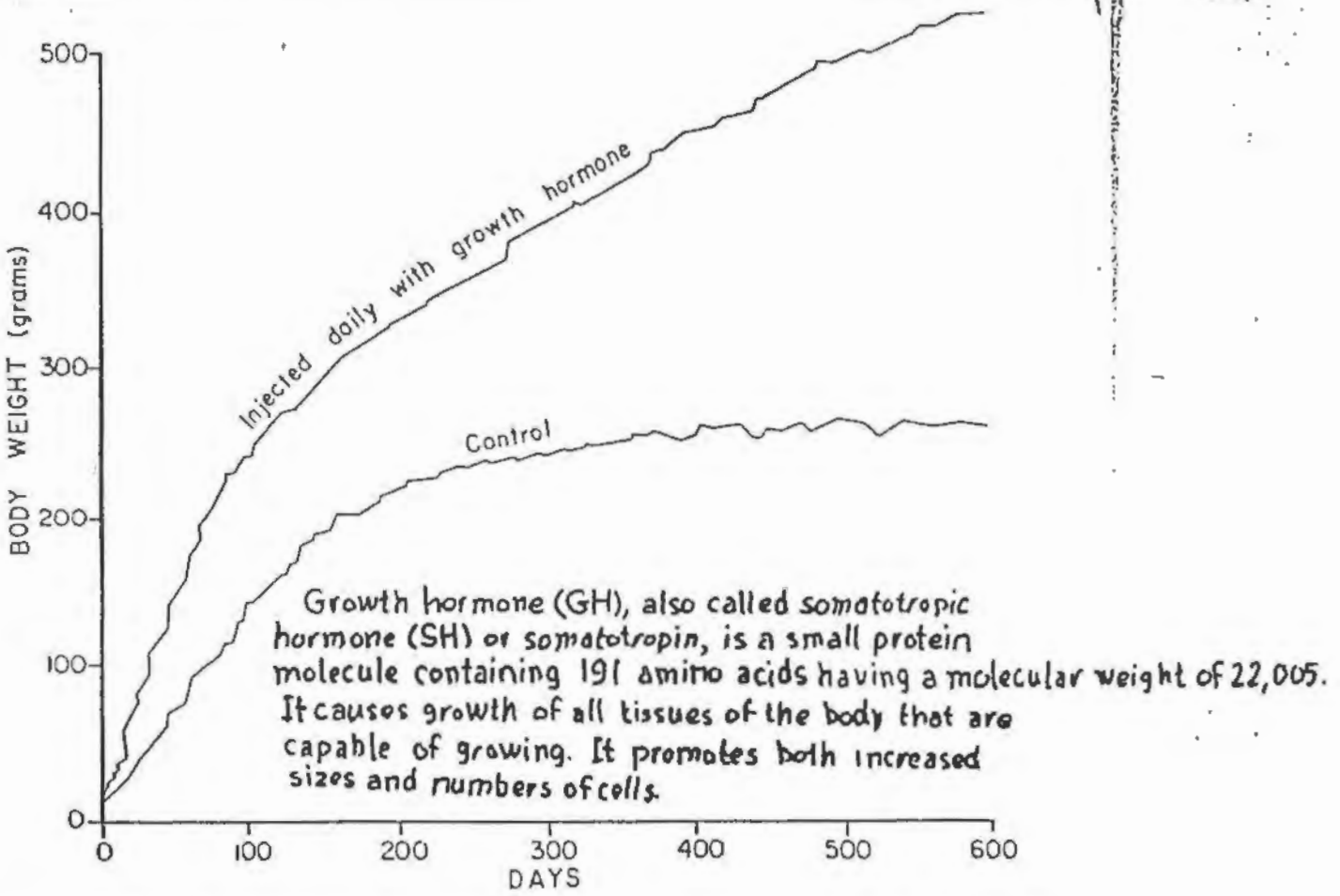
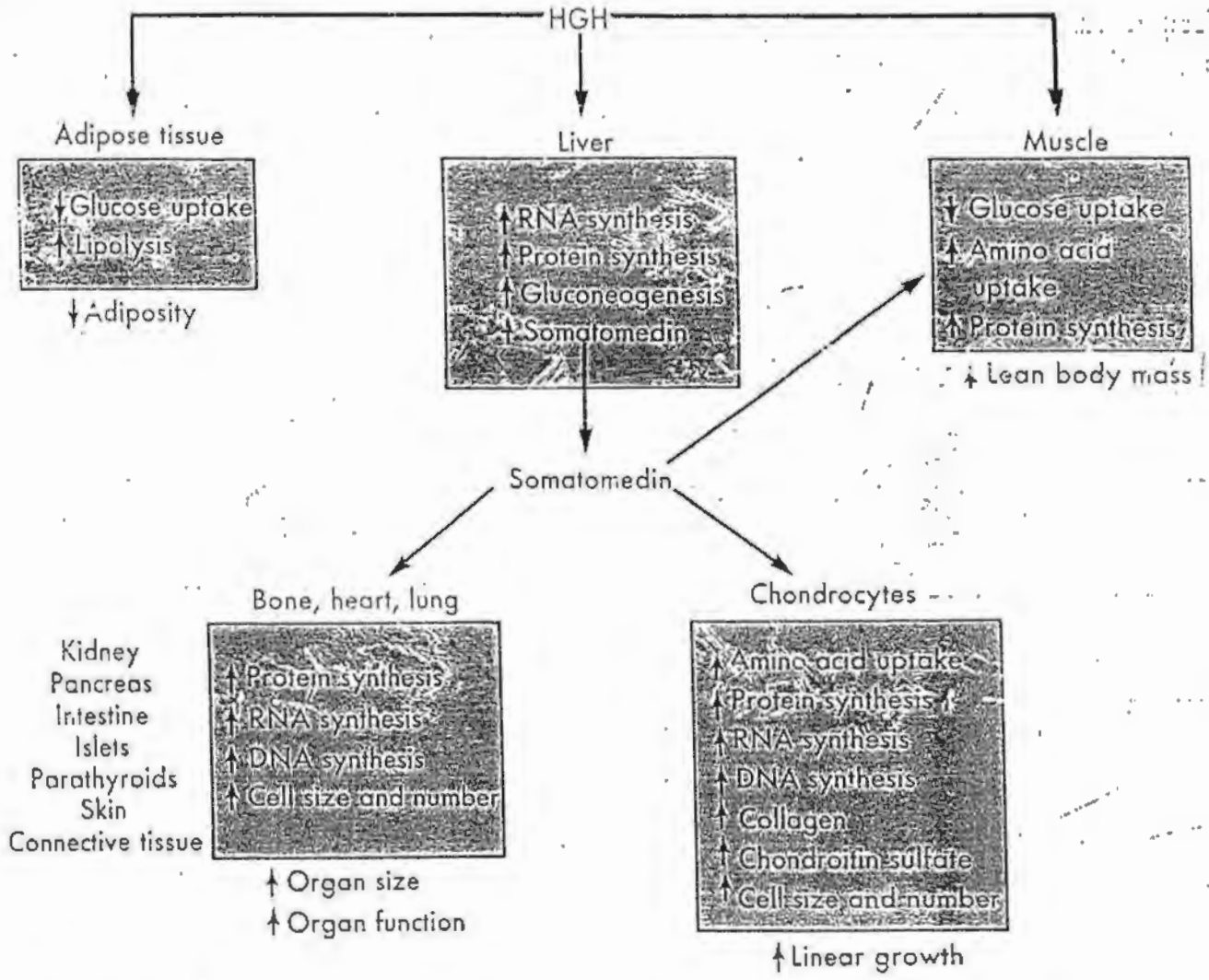


Figure 75–4. Comparison of weight gain of a rat injected daily with growth hormone with that of a normal rat.



■ Fig. 48-21 Biological actions of GH. The effects on linear growth, organ size, and lean body mass are mediated by somatomedin produced in the liver.

EFFECT OF GH IN ENHANCING FAT UTILISATION, FOR ENERGY:

1) INCREASES THE RELEASE OF FATTY ACIDS FROM THE ADIPOSE TISSUE.
2) FATTY ACIDS CONCENTRATION INCREASES IN BODY FLUIDS.
3) IT ENHANCES THE CONVERSION OF FATTY ACIDS INTO ACETYL- C O A., WITH THE SUBSEQUENT UTILISATION FOR ENERGY.
4) IN THIS CASE SPARE THE PROTEIN
5) UNDER THE EFFECT OF GH THE MOBILISATION OF FAT REQUIRES MINUTES TO HOURS, WHERE AS PROTEIN SYNTHESIS CAN BEGIN IN MINUTES.
6) UNDER THE EXCESSIVE OF GH GREAT AMOUNT OF FAT MOBILISED, THEREFORE A LOT OF ACETOACETIC ACIDS ARE FORMED BY THE LIVER AND RELEASED INTO THE BODY FLUIDS, THUS CAUSING (KETOSIS). WHICH IS CALLED "KETOGENIC EFFECT" OF GH.

DIABETOGENIC EFFECT OF GH.

1) WE HAVE ALREADY MENTIONED THAT GH INCREASES BLOOD GLUCOSE CONCENTRATION.

2) IN ADDITION GH MAY HAVE A DIRECT EFFECT ON BETA-CELLS.

3) IN THESE CASES PANCREAS OVER STIMULATED AND THE CELLS FINALLY, BURN OUT.

4) WHEN THIS OCCURS THE PERSON DEVELOPS DIABETES MELLITUS.

5) THEREFORE IS SAID GH HAS DIABETOGENIC EFFECT.

Diabetogenic Effects of Other Anterior Pituitary Hormones. Growth hormone is not the only anterior pituitary hormone that increases the blood glucose concentration. At least three others can do the same: adrenocorticotropin, thyroid-stimulating hormone, and prolactin. Especially important is adrenocorticotropin, which increases the rate of cortisol secretion by the adrenal cortex. Cortisol then increases the blood glucose concentration by increasing the rate of gluconeogenesis. This effect, quantitatively, is probably equally as diabetogenic as the effect of growth hormone.

1) TSH
2) Prolactin
3) ACTH^{+++}
↓
Cortisol
↓
gluconeogenesis

Growth hormone is secreted in a pulsatile pattern, increasing and decreasing. The precise mechanisms that control secretion of growth hormone are not fully understood, but several factors related to a person's state of nutrition or stress are known to stimulate secretion:

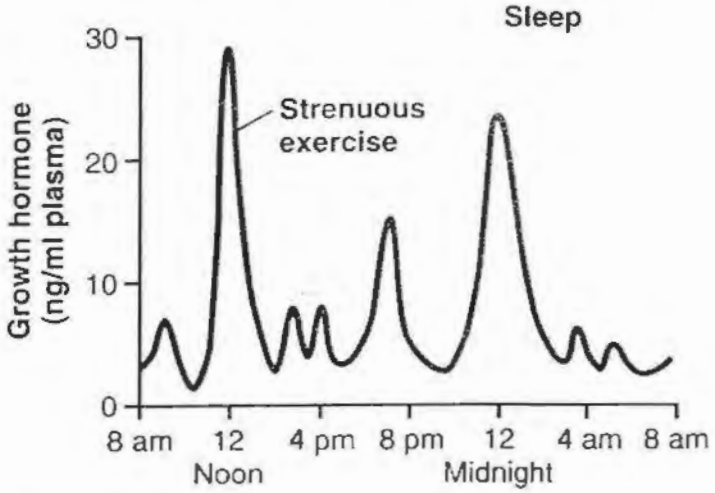


Figure 75-6 Typical variations in growth hormone secretion throughout the day, demonstrating the especially powerful effect of strenuous exercise and also the high rate of growth hormone secretion that occurs during the first few hours of deep sleep.

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

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

● *ghrelin,* a hormone secreted by the stomach before meals.

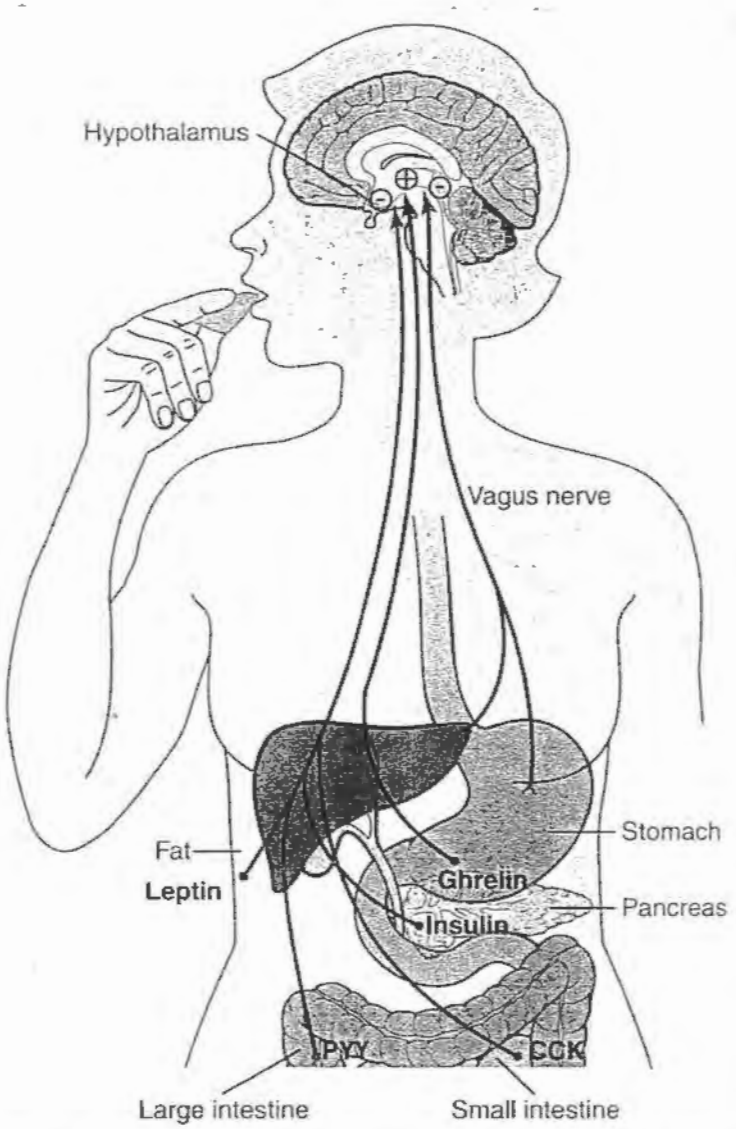
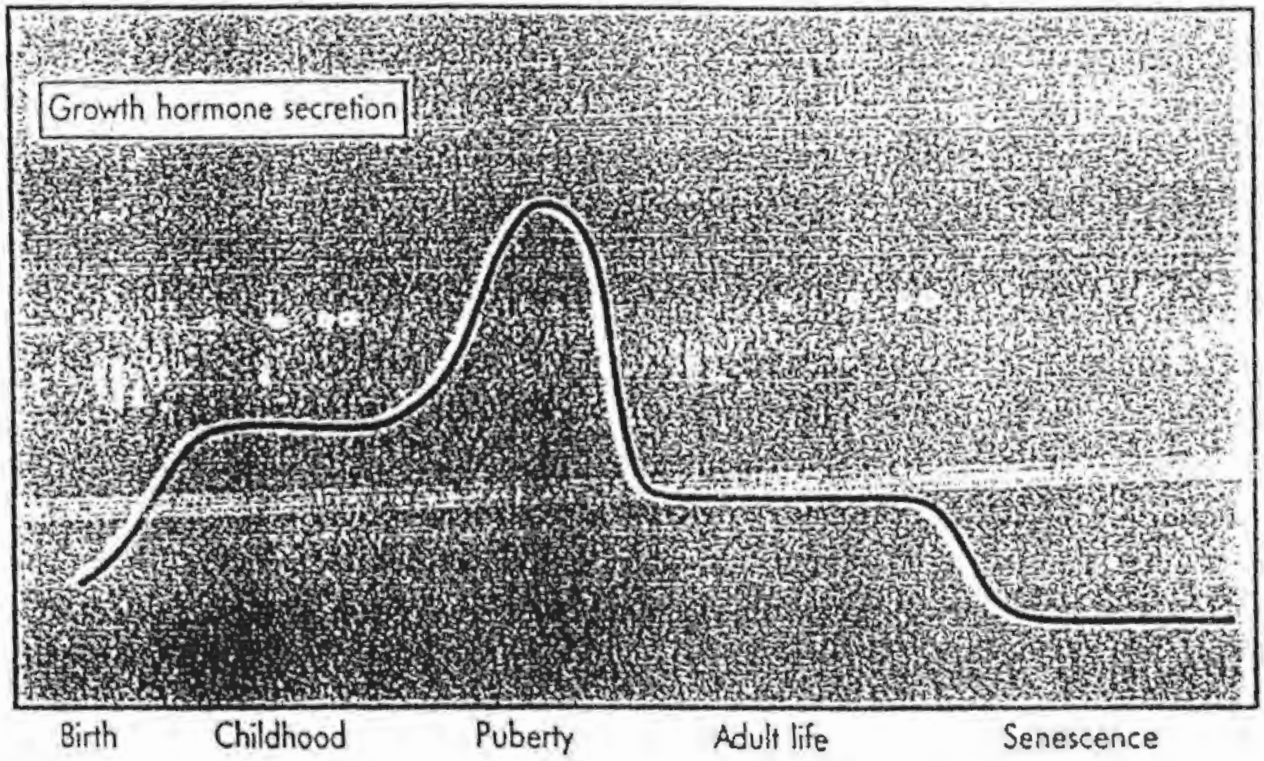
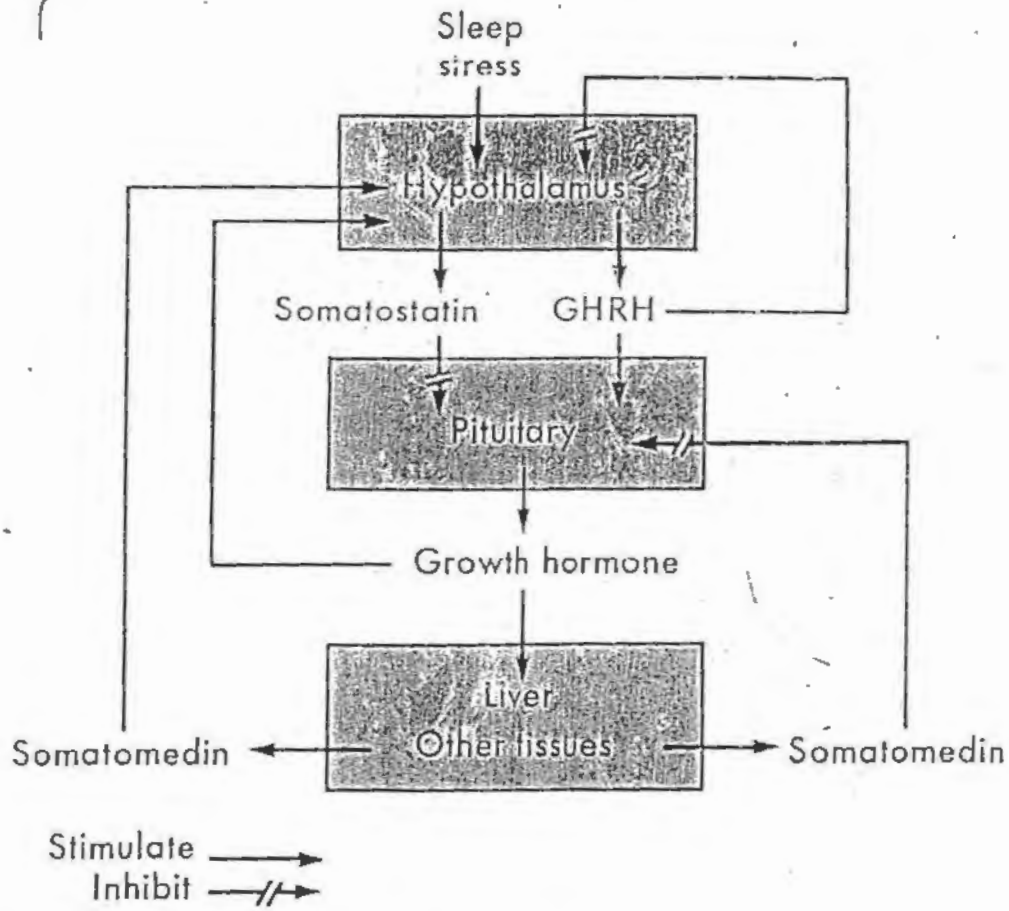


Figure 71-1 Feedback mechanisms for control of food intake. Stretch receptors in the stomach activate sensory afferent pathways in the vagus nerve and inhibit food intake. Peptide YY (*PYY*), cholecystokinin (*CCK*), and insulin are gastrointestinal hormones that are released by the ingestion of food and suppress further feeding. Ghrelin is released by the stomach, especially during fasting, and stimulates appetite. Leptin is a hormone produced in increasing amounts by fat cells as they increase in size; it inhibits food intake.

Ghrelin—a Gastrointestinal Hormone—Increases Feeding. *Ghrelin* is a hormone released mainly by the oxyntic cells of the stomach but also, to a much less extent, by the intestine. Blood levels of ghrelin rise during fasting, peak just before eating, and then fall rapidly after a meal, suggesting a possible role in stimulating feeding. Also, administration of ghrelin increases food intake in experimental animals, further supporting the possibility that it may be an orexigenic hormone. However, its physiologic role in humans is still uncertain.



■ Fig. 48-19 Lifetime pattern of growth hormone (GH) secretion. GH levels are higher in children than adults with a peak period during puberty. GH secretion declines with aging.



■ **Fig. 48-20** Regulation of growth hormone (GH) secretion. The hypothalamic peptide (GHRH) stimulates growth hormone release, whereas the hypothalamic peptide somatostatin inhibits it. Negative feedback is by the peripheral mediator of HGH action: somatomedin. Negative feedback occurs both via somatomedin inhibition of GHRH action and by somatomedin stimulation of somatostatin release. HGH inhibits its own secretion by short-loop feedback. In addition GHRH inhibits its own release via ultra short-loop feedback. In both of these cases the negative feedback is, probably via increasing somatostatin release.

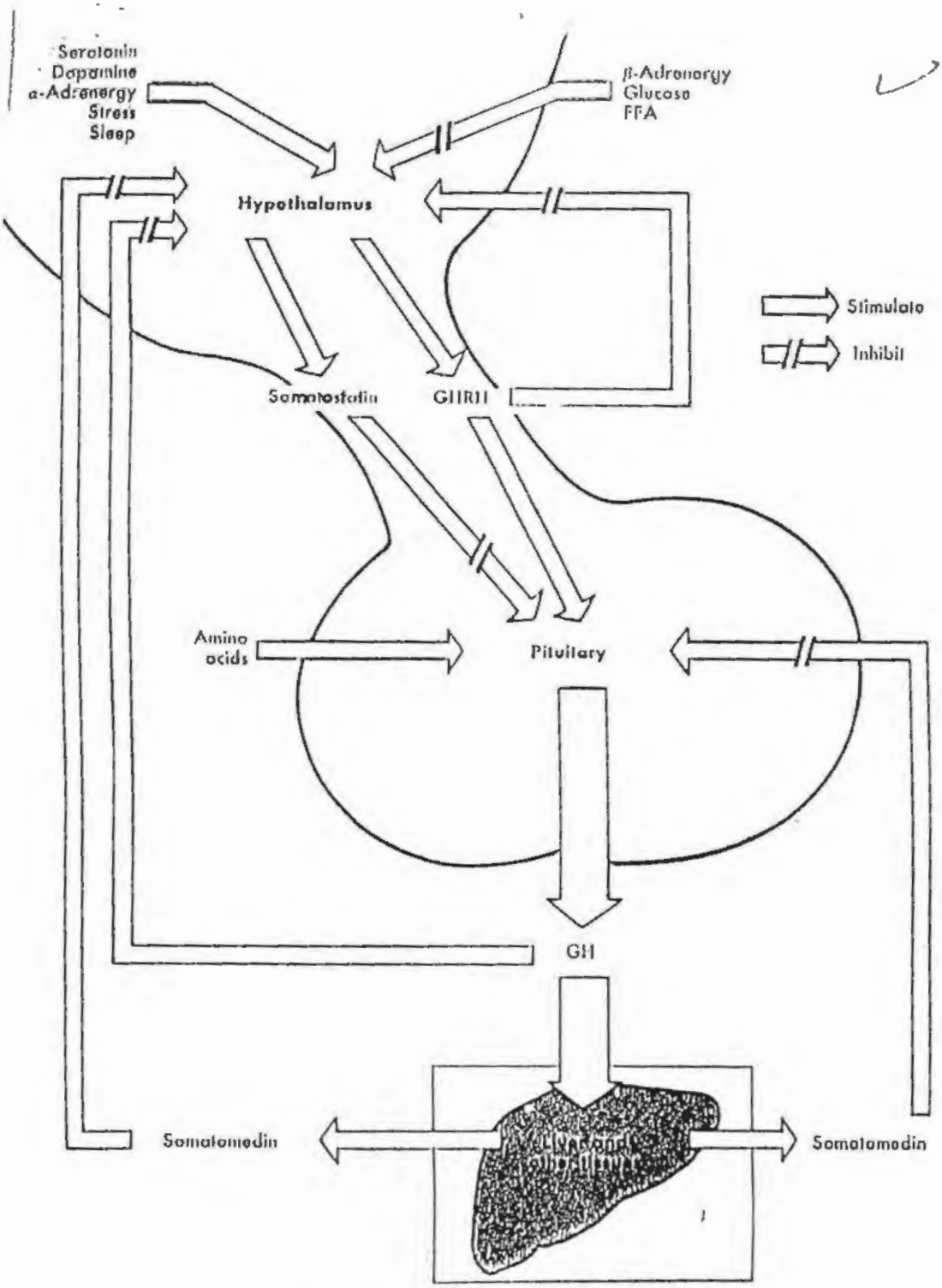
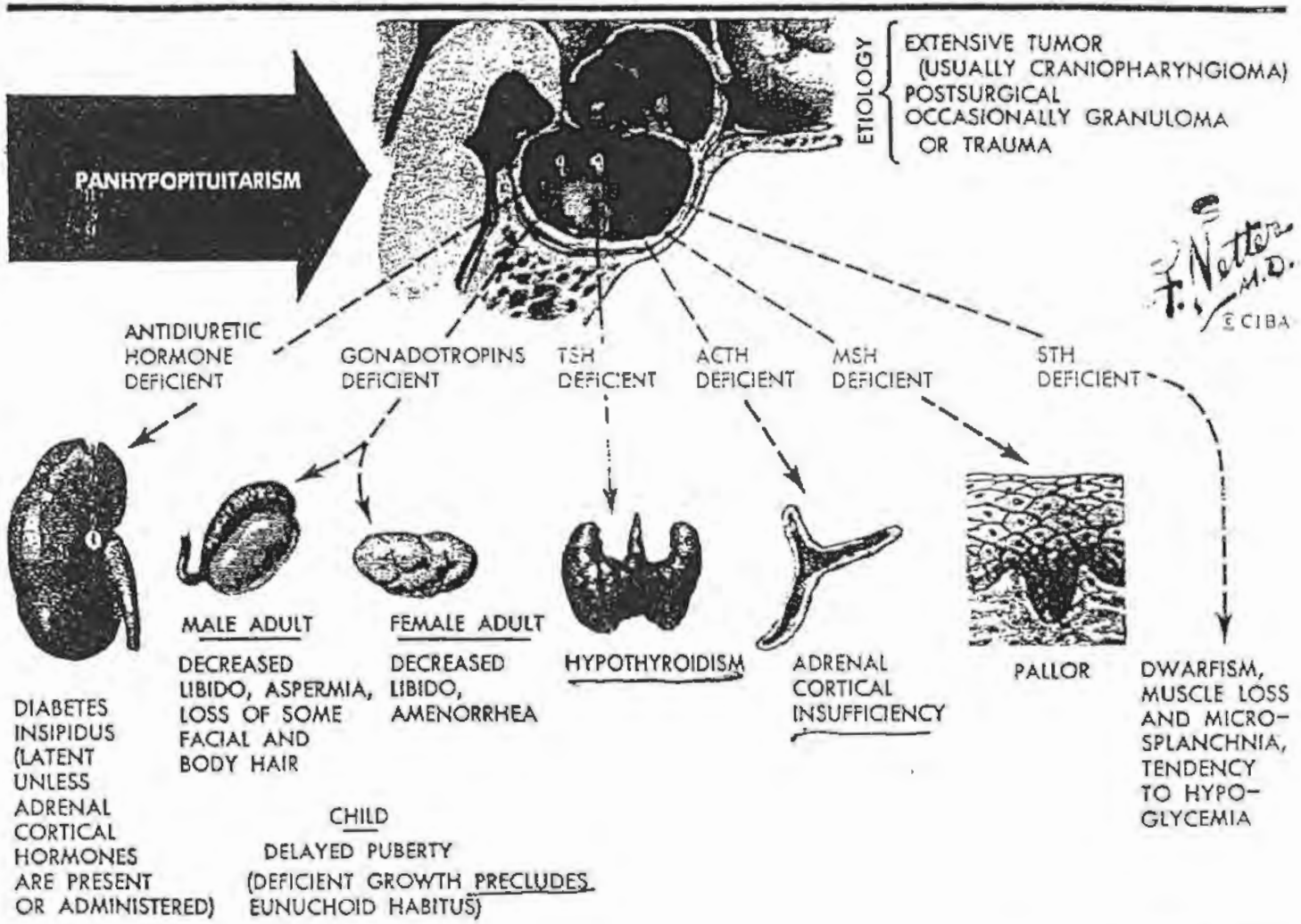
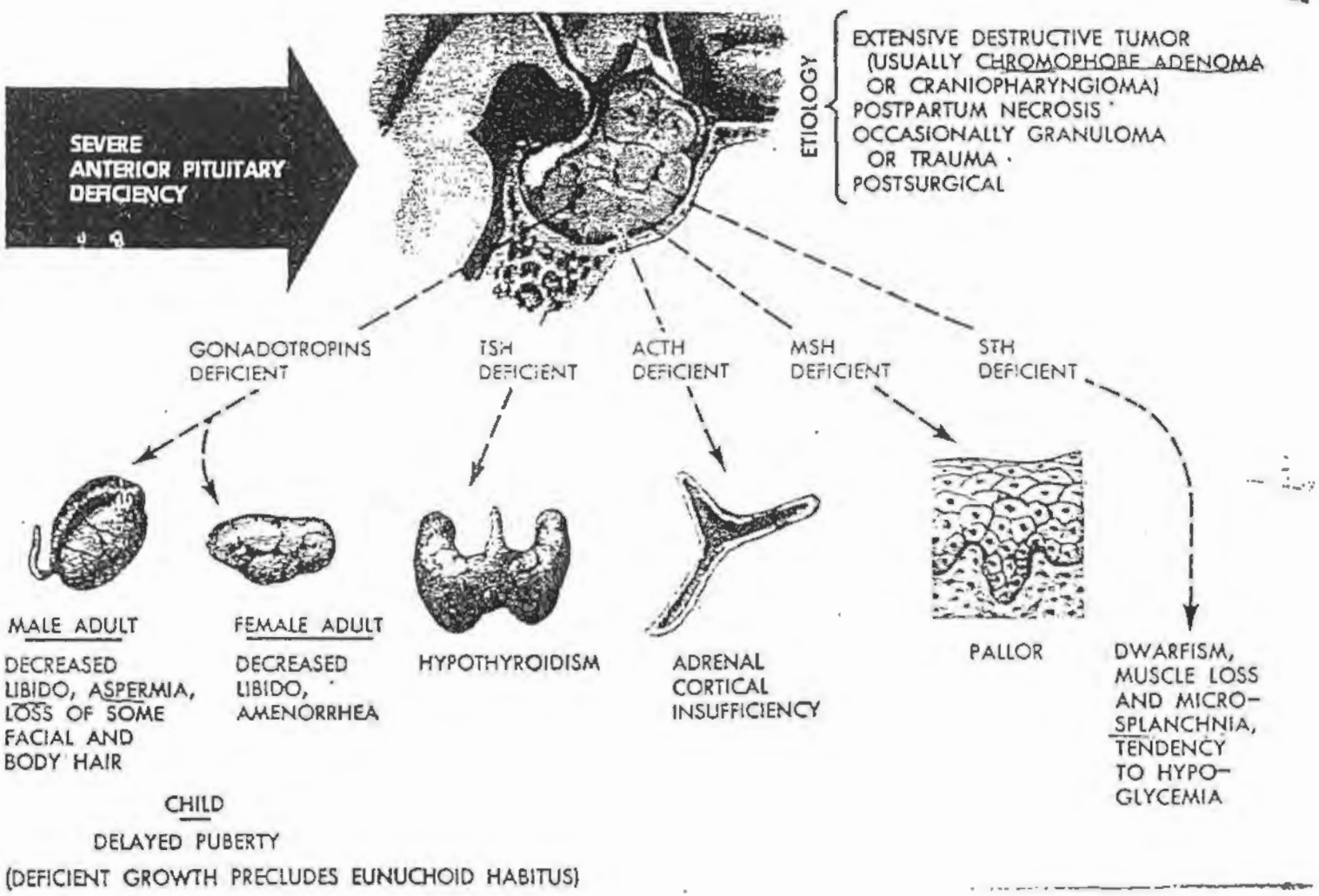


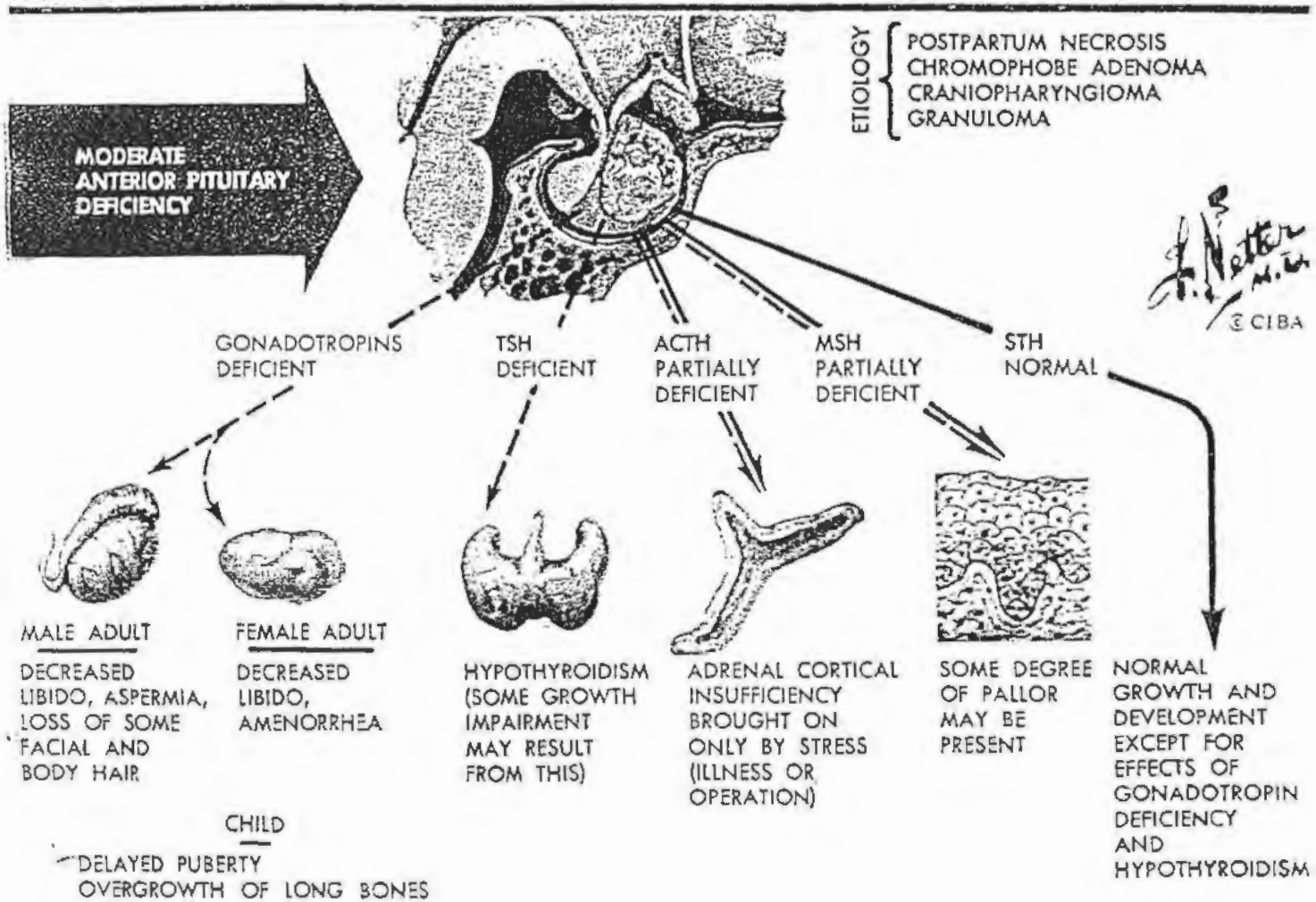
FIGURE 39-10 Regulation of GH secretion. Note both a direct stimulatory and a direct inhibitory influence from the hypothalamus. Negative feedback by the peripheral product is exerted at the hypothalamic and the pituitary level. *GHRH*, Growth hormone-releasing hormone; *FFA*, free fatty acids.

EFFECTS OF HYPOPHYSECTOMY. Several notable morphological and functional alterations result from total hypophysectomy in the young animal. These are as follows:

1. Failure of the gonads to mature, with resultant infantile sexual development and sterility because of lack of LH and FSH.
2. Atrophy of the thyroid gland and the characteristics of thyroid insufficiency because of lack of TSH.
3. Atrophy of the adrenal cortex and signs of hypoadrenalism without salt loss because of ACTH deficiency.
4. Cessation of growth, failure to attain an adult stature, a decided tendency toward hypoglycemia, hypersensitivity to insulin, and a loss of body nitrogen accompanied by diminished fat catabolism because of lack of STH.


PANHYPOPITUITARISM
ETIOLOGY
EXTENSIVE TUMOR (USUALLY CRANIOPHARYNGIOMA)
POSTSURGICAL
OCCASIONALLY GRANULOMA OR TRAUMA
F. Netter M.D.
CIBA
ANTIDIURETIC HORMONE DEFICIENT
GONADOTROPINS DEFICIENT
TSH DEFICIENT
ACTH DEFICIENT
MSH DEFICIENT
STH DEFICIENT
MALE ADULT
FEMALE ADULT
DECREASED LIBIDO, ASPERMIA, LOSS OF SOME FACIAL AND BODY HAIR
DECREASED LIBIDO, AMENORRHEA
HYPOTHYROIDISM
ADRENAL CORTICAL INSUFFICIENCY
PALLOR
DWARFISM, MUSCLE LOSS AND MICRO-SPLANCHNIA, TENDENCY TO HYPO-GLYCEMIA
DIABETES INSIPIDUS (LATENT UNLESS ADRENAL CORTICAL HORMONES ARE PRESENT OR ADMINISTERED)
CHILD
DELAYED PUBERTY
(DEFICIENT GROWTH PRECLUDES EUNUCHOID HABITUS)


SEVERE
ANTERIOR PITUITARY
DEFICIENCY
ETIOLOGY
EXTENSIVE DESTRUCTIVE TUMOR
(USUALLY CHROMOPHOBE ADENOMA
OR CRANIOPHARYNGIOMA)
POSTPARTUM NECROSIS
OCCASIONALLY GRANULOMA
OR TRAUMA
POSTSURGICAL
GONADOTROPINS
DEFICIENT
TSH
DEFICIENT
ACTH
DEFICIENT
MSH
DEFICIENT
STH
DEFICIENT
MALE ADULT
DECREASED
LIBIDO, ASPERMIA,
LOSS OF SOME
FACIAL AND
BODY HAIR
FEMALE ADULT
DECREASED
LIBIDO,
AMENORRHEA
HYPOTHYROIDISM
ADRENAL
CORTICAL
INSUFFICIENCY
PALLOR
DWARFISM,
MUSCLE LOSS
AND MICRO-
SPLANCHNIA,
TENDENCY
TO HYPO-
GLYCEMIA
CHILD
DELAYED PUBERTY
(DEFICIENT GROWTH PRECLUDES EUNUCHOID HABITUS)


MODERATE ANTERIOR PITUITARY DEFICIENCY
ETIOLOGY
POSTPARTUM NECROSIS
CHROMOPHOBE ADENOMA
CRANIOPHARYNGIOMA
GRANULOMA
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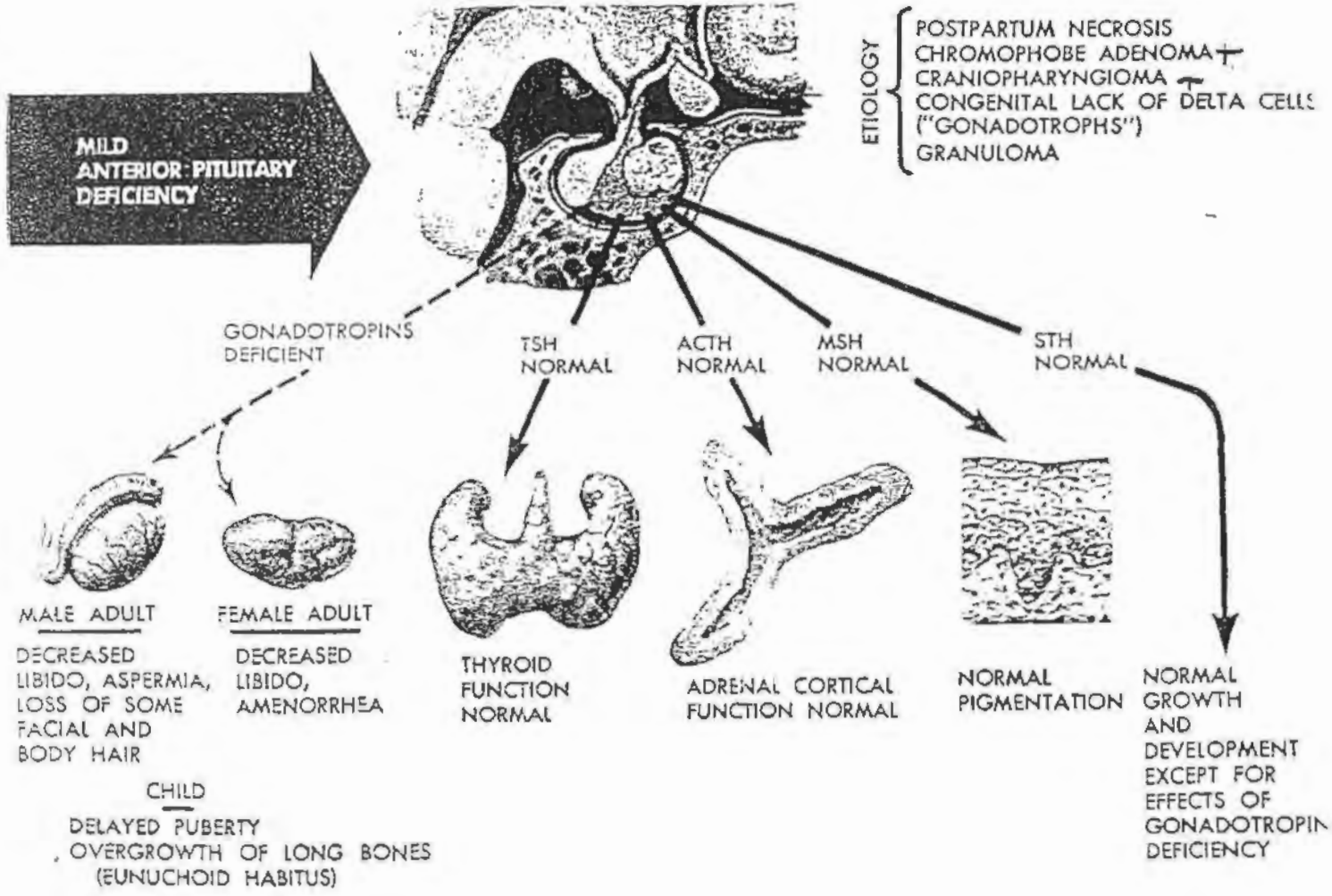
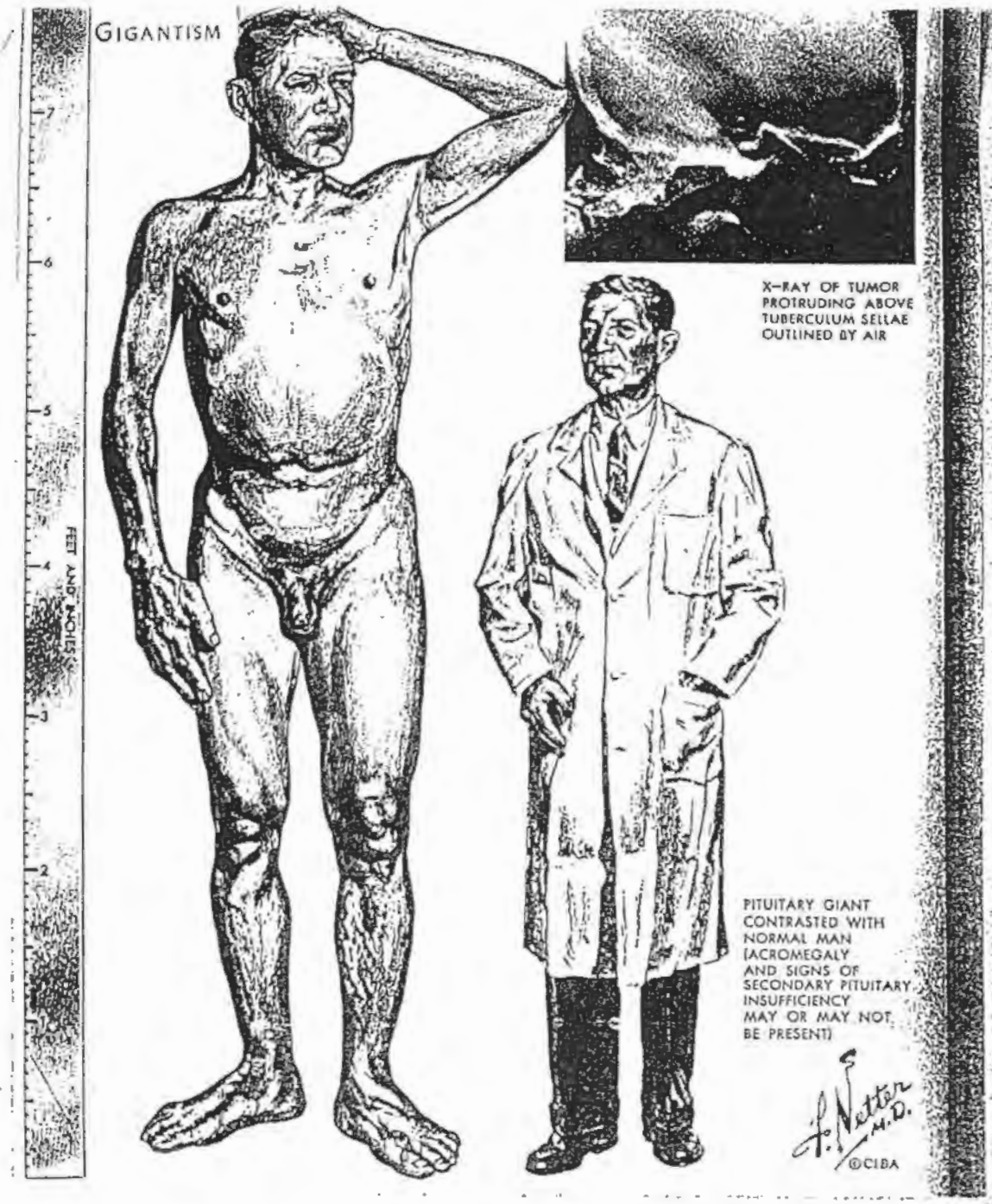
© CIBA
GONADOTROPINS DEFICIENT
TSH DEFICIENT
ACTH PARTIALLY DEFICIENT
MSH PARTIALLY DEFICIENT
STH NORMAL
MALE ADULT
DECREASED LIBIDO, ASPERMIA, LOSS OF SOME FACIAL AND BODY HAIR
FEMALE ADULT
DECREASED LIBIDO, AMENORRHEA
CHILD
DELAYED PUBERTY
OVERGROWTH OF LONG BONES (EUNUCHOID HABITUS)
HYPOTHYROIDISM (SOME GROWTH IMPAIRMENT MAY RESULT FROM THIS)
ADRENAL CORTICAL INSUFFICIENCY BROUGHT ON ONLY BY STRESS (ILLNESS OR OPERATION)
SOME DEGREE OF PALLOR MAY BE PRESENT
NORMAL GROWTH AND DEVELOPMENT EXCEPT FOR EFFECTS OF GONADOTROPIN DEFICIENCY AND HYPOTHYROIDISM


MILD
ANTERIOR PITUITARY
DEFICIENCY
ETIOLOGY
POSTPARTUM NECROSIS
CHROMOPHOBE ADENOMA
CRANIOPHARYNGIOMA
CONGENITAL LACK OF DELTA CELLS
("GONADOTROPHS")
GRANULOMA
GONADOTROPINS
DEFICIENT
TSH
NORMAL
ACTH
NORMAL
MSH
NORMAL
STH
NORMAL
MALE ADULT
DECREASED
LIBIDO, ASPERMIA,
LOSS OF SOME
FACIAL AND
BODY HAIR
FEMALE ADULT
DECREASED
LIBIDO,
AMENORRHEA
CHILD
DELAYED PUBERTY
OVERGROWTH OF LONG BONES
(EUNUCHOID HABITUS)
THYROID
FUNCTION
NORMAL
ADRENAL CORTICAL
FUNCTION NORMAL
NORMAL
PIGMENTATION
NORMAL
GROWTH
AND
DEVELOPMENT
EXCEPT FOR
EFFECTS OF
GONADOTROPIN
DEFICIENCY

Giantism (Gigantism):- If G.H. producing cells tumour occurs before adolescence, all body tissues will grow rapidly including the bones, because the epiphyses of the long bones have not fused with the shafts.

1- Their heights 8-9 feet
2- The giants have hyperglycemia, 10% develop diabetes mellitus.
3- If the giants remain without treatment will develop pan-hyp.

GIGANTISM

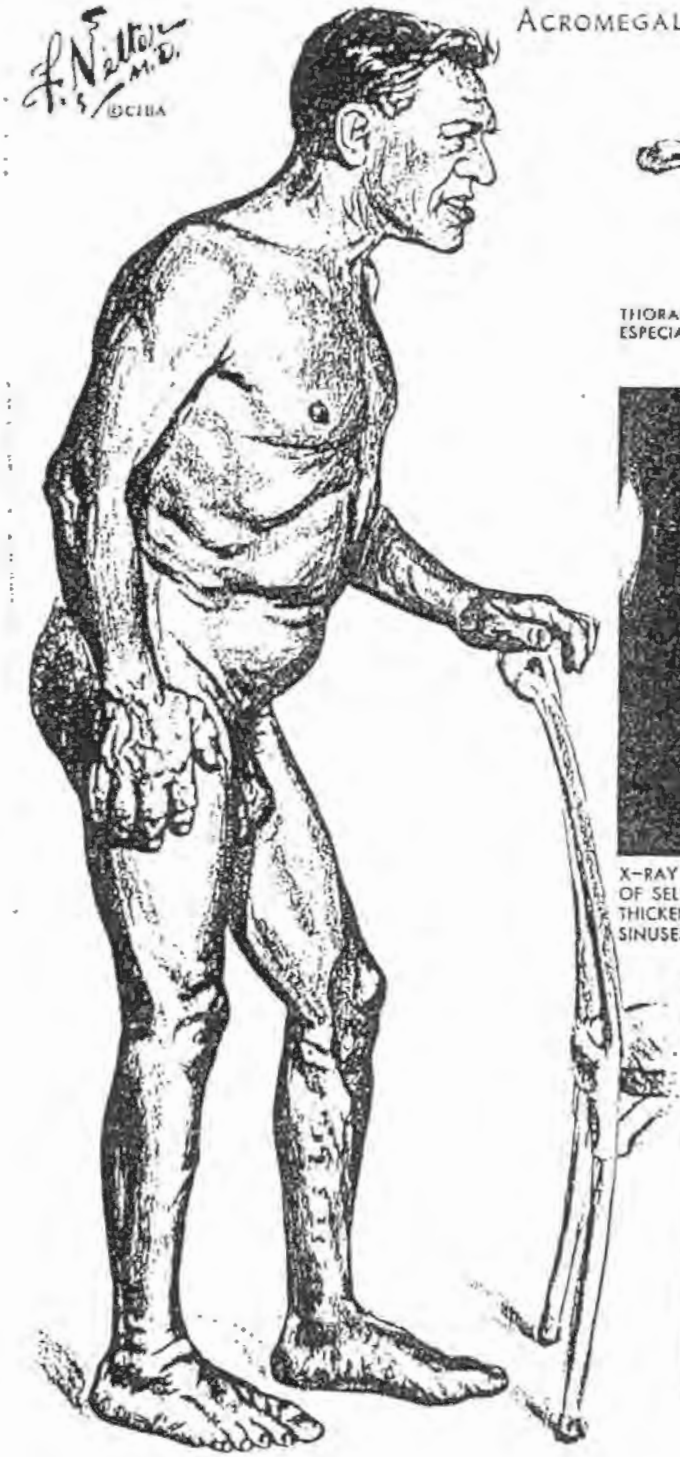

FEET AND INCHES
X-RAY OF TUMOR PROTRUDING ABOVE TUBERCULUM SELLAE OUTLINED BY AIR
PITUITARY GIANT CONTRASTED WITH NORMAL MAN (ACROMEGALY AND SIGNS OF SECONDARY PITUITARY INSUFFICIENCY MAY OR MAY NOT BE PRESENT)
F. Netter M.D.
©CIBA

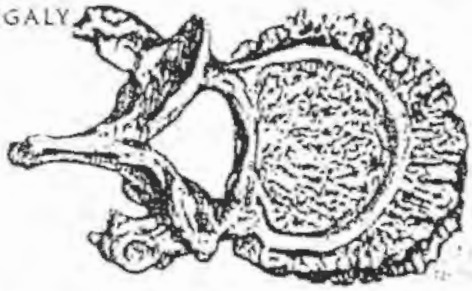
Acromegaly:- If tumour occurs after adolescence, after the fusion of the long bones. The person can not grow taller, but the soft tissues can continue growing and the bones can grow in thickness.

1- Enlargment marked in the small bones of the hands and feet and also the craniums, nose, forehead, supra orbital ridges, the lower jaw bones and the portions of the vertebrae.

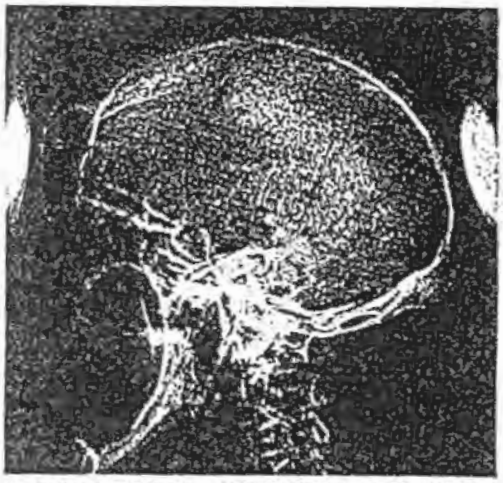
2- Finally, many soft tissues or organs like liver, tongue, kidneys became greatly enlarged.

ACROMEGALY

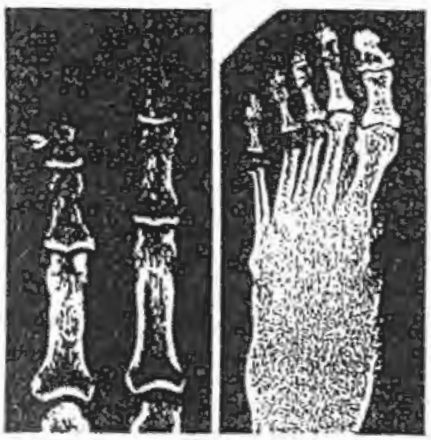




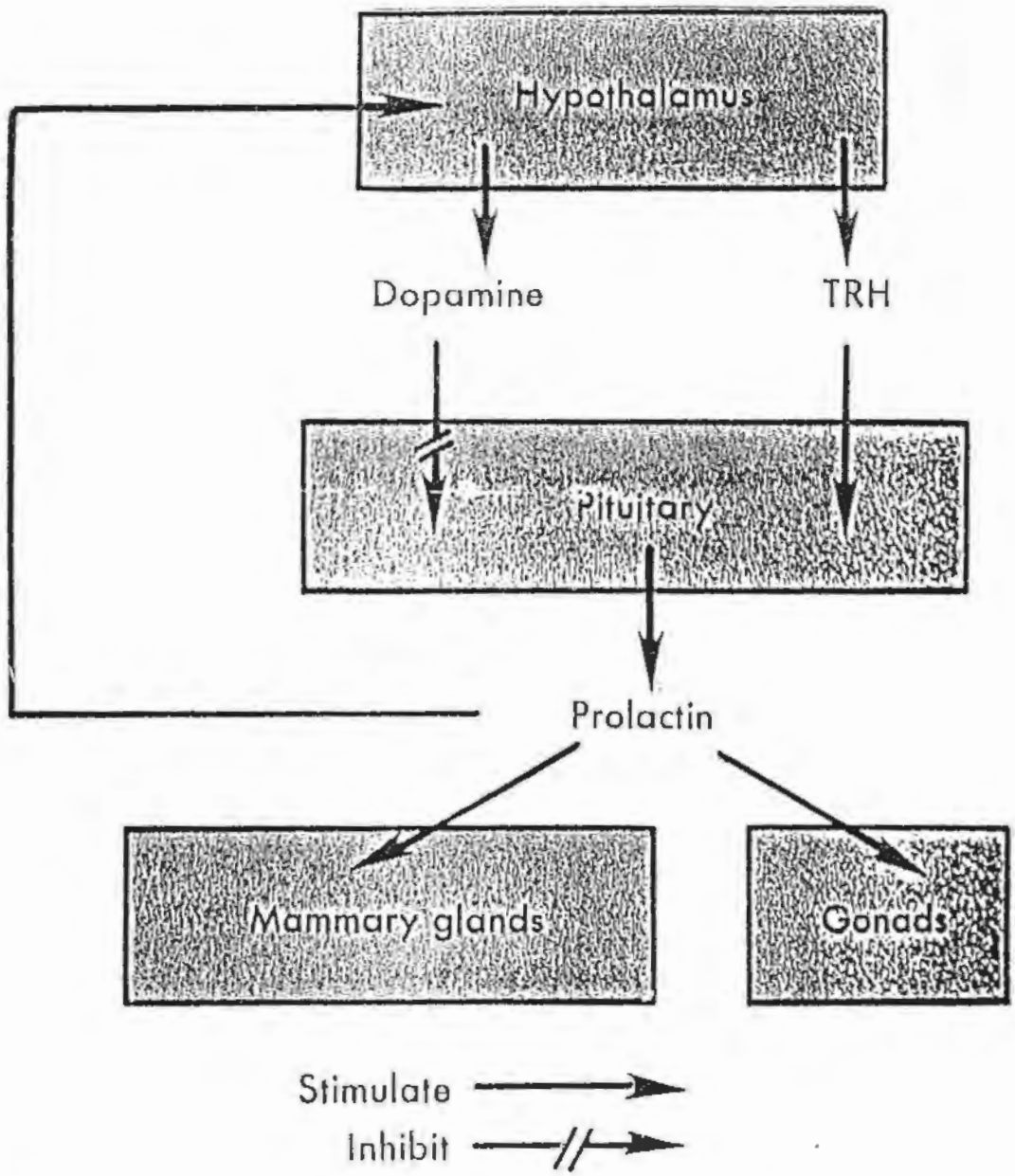
THORACIC VERTEBRA IN ACROMEGALY: HYPEROSTOSIS, ESPECIALLY MARKED ON ANTERIOR ASPECT



X-RAY OF SKULL IN ACROMEGALY: ENLARGEMENT OF SELLA TURCICA, WITH OCCIPITAL PROTUBERANCE, THICKENING OF CRANIAL BONES, ENLARGEMENT OF SINUSES AND OF MANDIBLE



TUFTING OF PHALANGES IN HANDS AND NARROWING OF PHALANGES IN FEET



■ **Fig. 52-25.** Regulation of prolactin secretion. The predominant mode of hypothalamic regulation is tonic inhibition via dopamine. Although TRH stimulates prolactin release, its physiological role is uncertain, and evidence suggests another hypothalamic peptide may be more physiologically important. Prolactin exerts short-loop feedback on its own secretion by stimulating production of the hypothalamic inhibitor, dopamine.

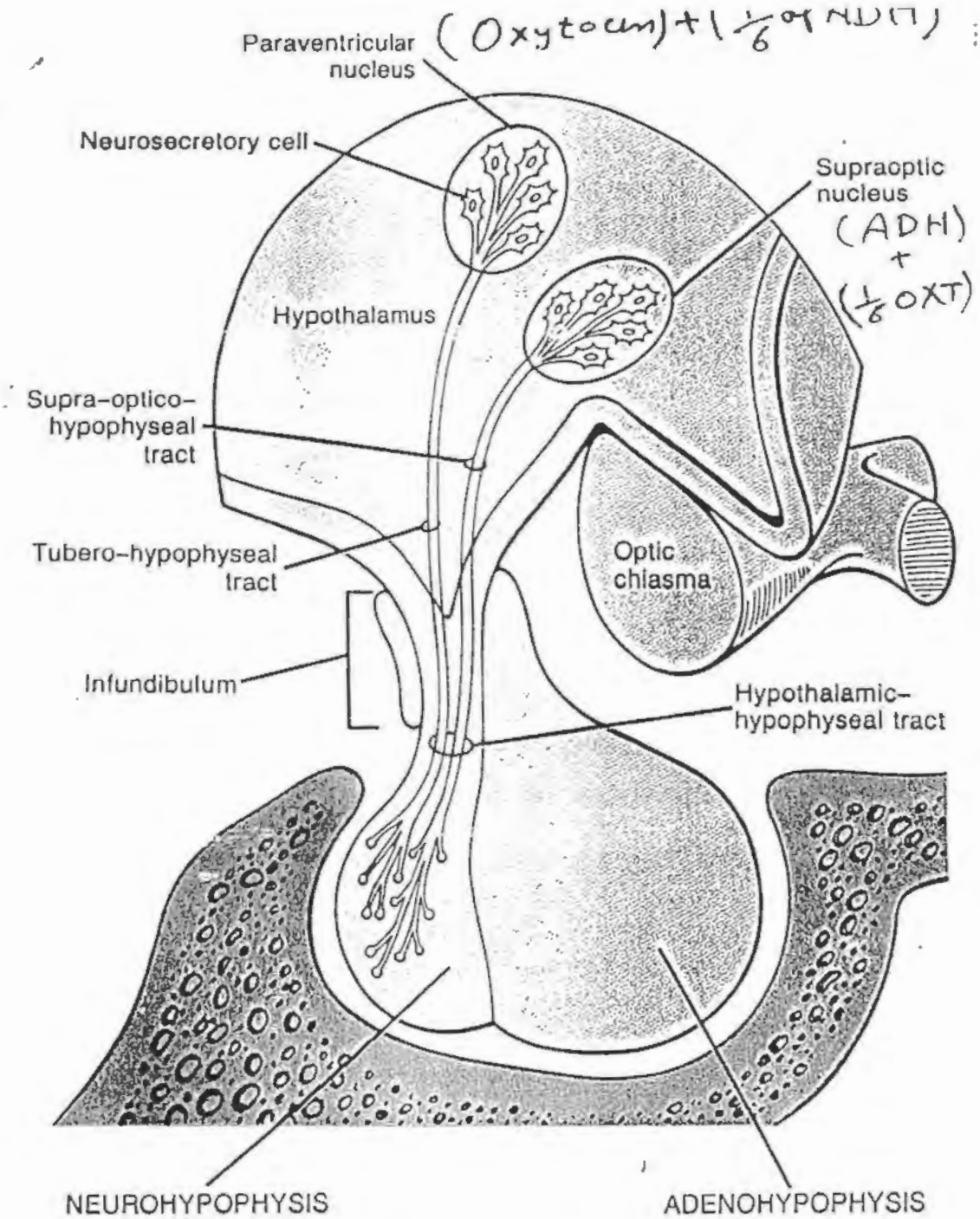


Figure 10-8
Tortora/Anagnostakos: Principles of Anatomy and Physiology, 5/e

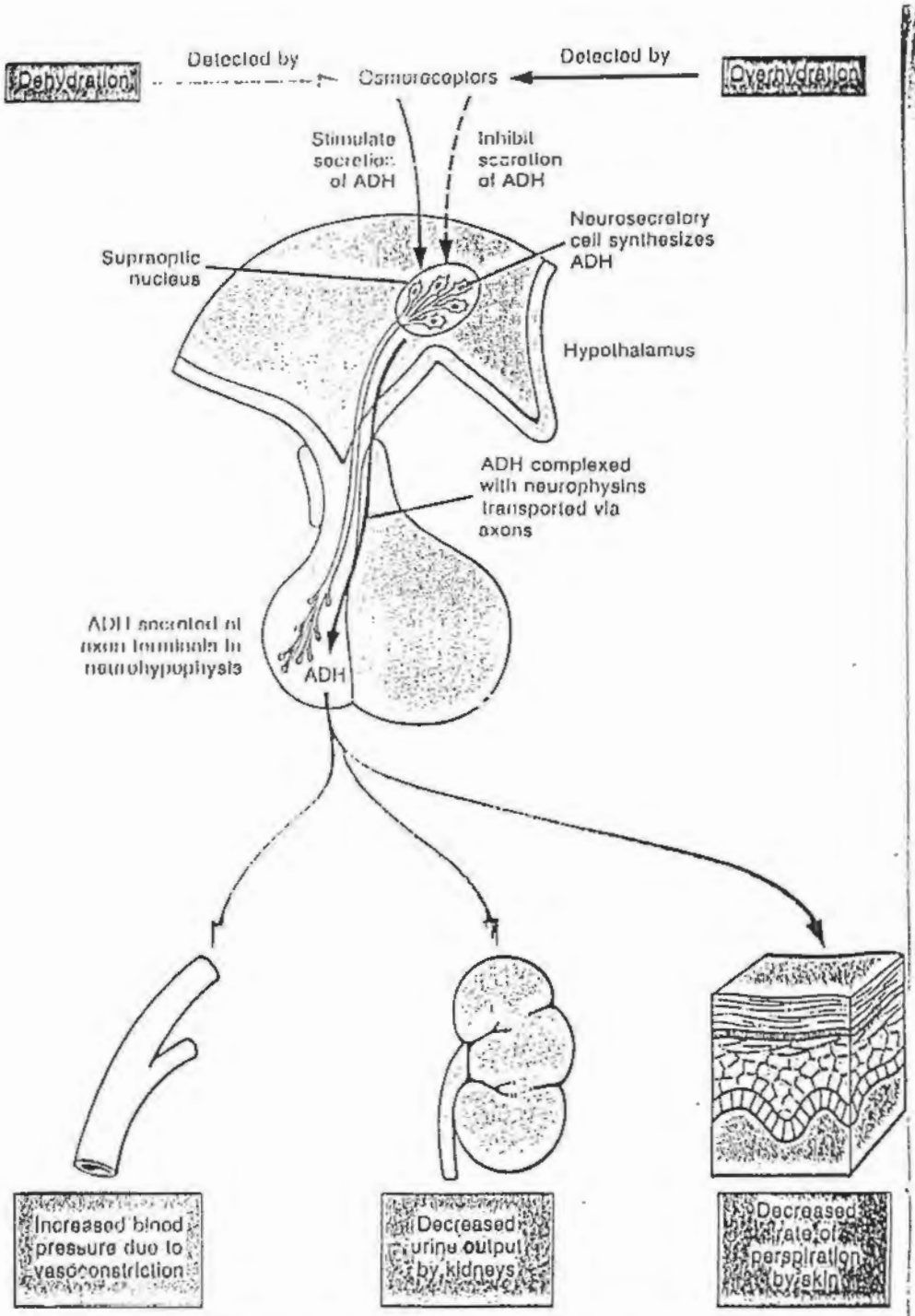


FIGURE 18-10 Regulation of the secretion of antidiuretic hormone (ADH).

Vasopressin & Oxytocin

In most mammals, the hormones secreted by the posterior pituitary gland are **arginine vasopressin (AVP)** and **oxytocin.** In hippopotami and most pigs, arginine in the vasopressin molecule is replaced by lysine to form **lysine vasopressin.** The posterior pituitaries of some species of pigs and marsupials contain a mixture of arginine and lysine vasopressin. The posterior lobe hormones are nonapeptides with a disulfide ring at one end (Figure 14–10).

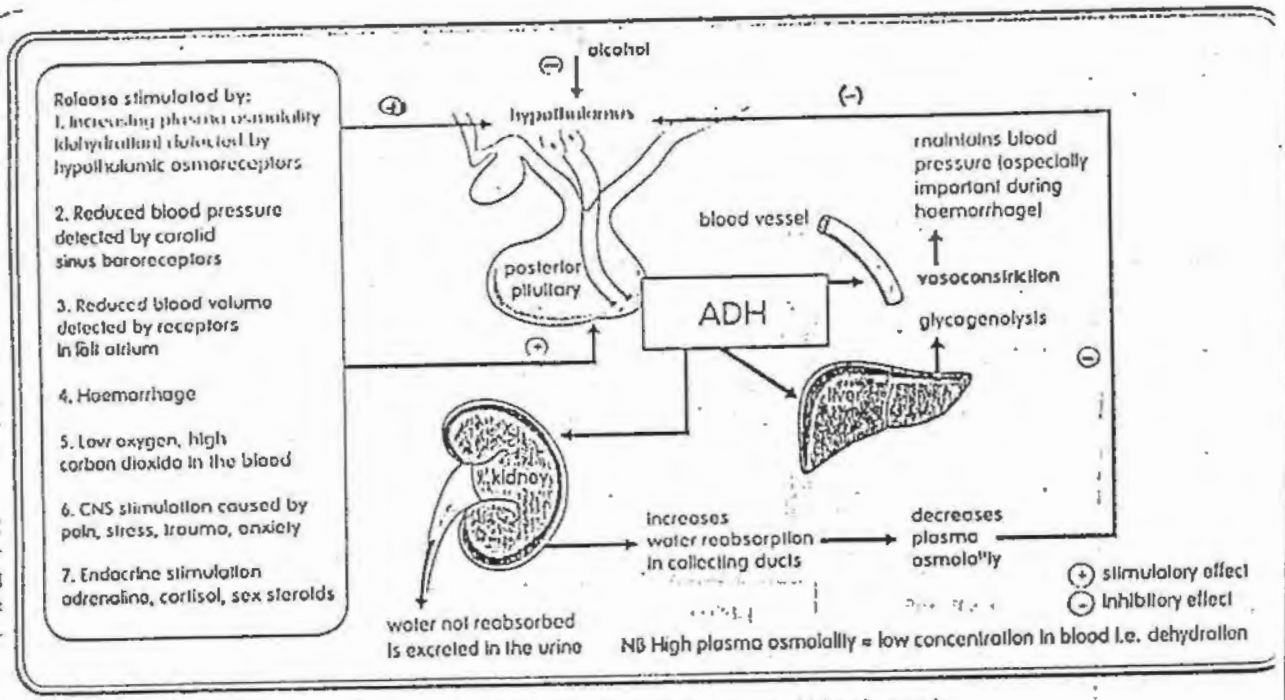


Fig. 7.5 The control of ADH secretion and its actions on the kidney, liver, and blood vessels.

Fig. 30–4. Factors that regulate the secreton of ADH by the hypothalamoneurohypophyseal system (HNS). + = stimulation and − = inhibition.

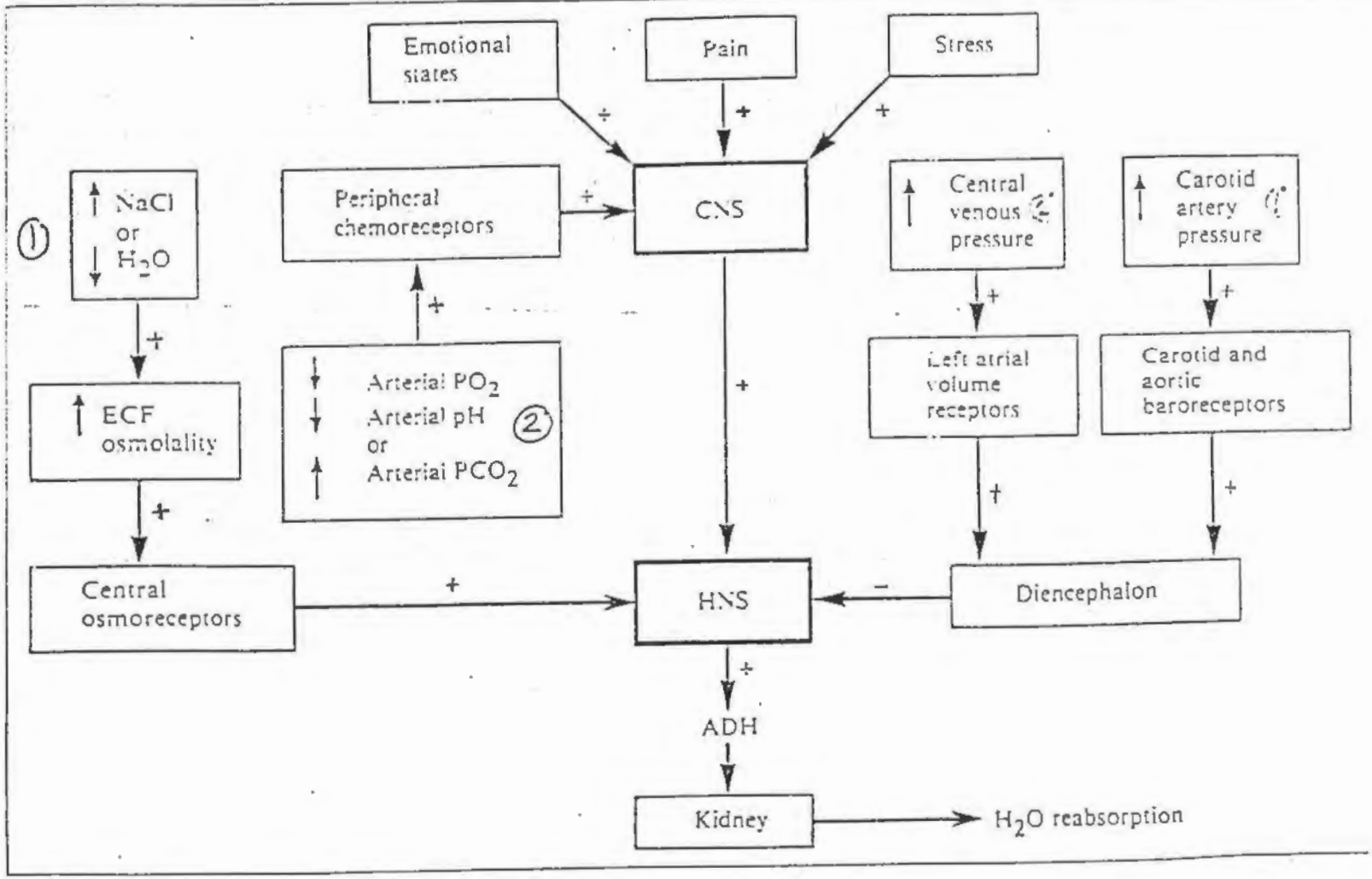
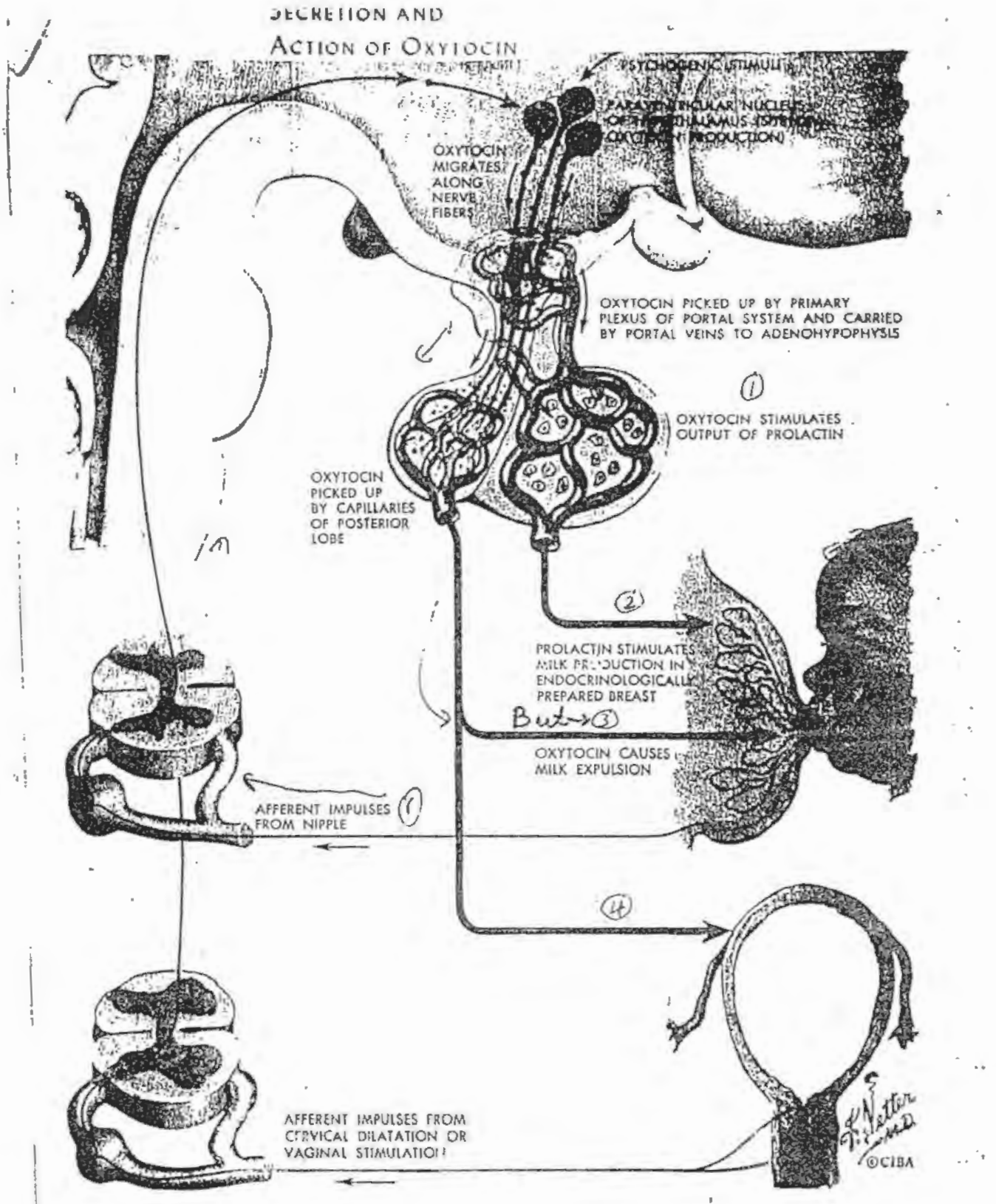


TABLE 9–6. Factors Affecting ADH Secretion

Stimulatory Factors	Inhibitory Factors
Increased serum osmolarity	Decreased serum osmolarity
Decreased ECF volume	Ethanol
Pain	α-Adrenergic agonists
Nausea	Atrial natriuretic peptide (ANP)
Hypoglycemia	
Nicotine	
Opiates	
Antineoplastic drugs	


SECRETION AND
ACTION OF OXYTOCIN
PSYCHOGENIC STIMULI
OXYTOCIN MIGRATES ALONG NERVE FIBERS
OXYTOCIN PICKED UP BY PRIMARY PLEXUS OF PORTAL SYSTEM AND CARRIED BY PORTAL VEINS TO ADENOHYPOPHYSIS
1
OXYTOCIN STIMULATES OUTPUT OF PROLACTIN
OXYTOCIN PICKED UP BY CAPILLARIES OF POSTERIOR LOBE
2
PROLACTIN STIMULATES MILK PRODUCTION IN ENDOCRINOLOGICALLY PREPARED BREAST
But→3
OXYTOCIN CAUSES MILK EXPULSION
AFFERENT IMPULSES FROM NIPPLE
4
AFFERENT IMPULSES FROM CERVICAL DILATATION OR VAGINAL STIMULATION
©CIBA

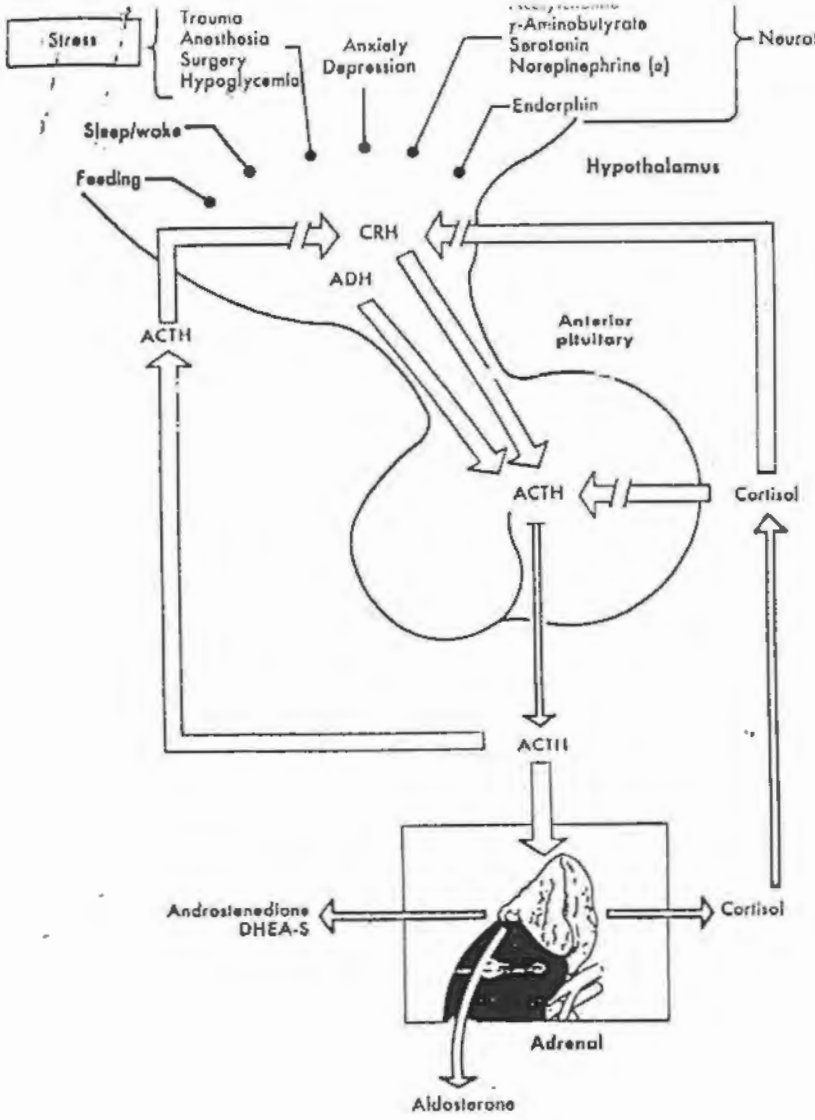


FIGURE 41-3 The regulation of cortisol secretion by the hypothalamic-pituitary-adrenal axis. A variety of inputs to the hypothalamus stimulate corticotropin—releasing hormone *(CRH)* secretion, and in turn adrenocorticotropin *(ACTH)* and cortisol secretion. Cortisol exerts negative feedback at both the hypothalamic and the pituitary levels. *ADH*, Antidiuretic hormone; *DHEA-S*, dehydroepiandrosterone sulfate.

1- ACTH is an anterior pituitary polypeptide hormone.
2- Regulatesthe growth and secretion of the adrenal cortex.
3- Its most important target gland hormone is cortisol.
4- Fetus ACTH synthesis and secretion beginjust before the development of the adrenal cortex.
5- The regulation of ACTH secretion is among the most complex of all the pituitary hormones.
6- Although the mechanisms for each form of control are not completely clear, the CRH is the important mediator. ADH also exhibits corticotropin-releasing activity
7- ACTH secretion responds most strikingly to stressful stimuli, a response that is critical to survival.
8- Extraadrenal actions of ACTH: lipolysis and MSH Like action

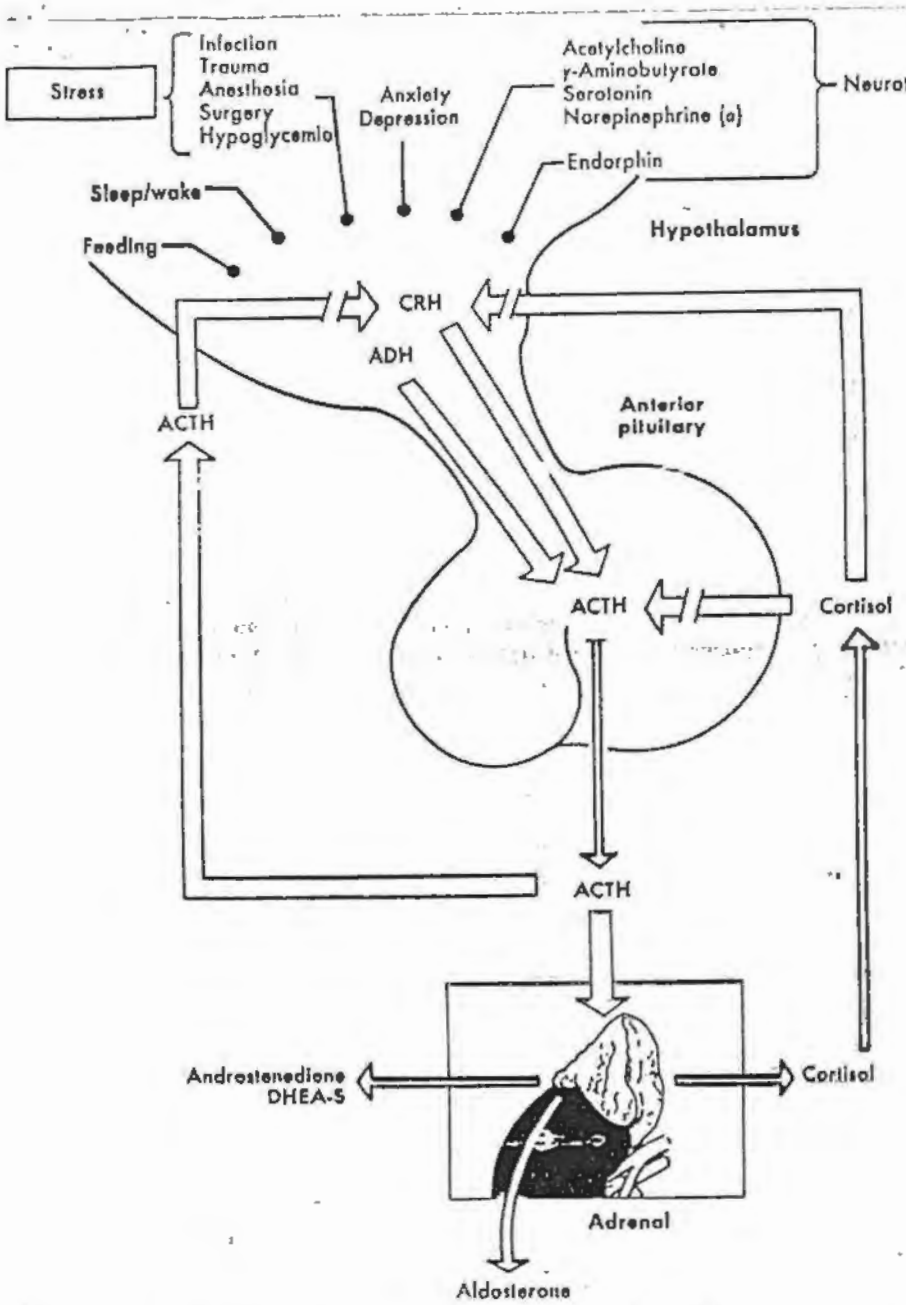


FIGURE 41-3 The regulation of cortisol secretion by the hypothalamic-pituitary-adrenal axis. A variety of inputs to the hypothalamus stimulate corticotropin—releasing hormone *(CRH)* secretion, and in turn adrenocorticotropin *(ACTH)* and cortisol secretion. Cortisol exerts negative feedback at both the hypothalamic and the pituitary levels. *ADH*, Antidiuretic hormone; *DHEA-S*, dehydroepiandrosterone sulfate.

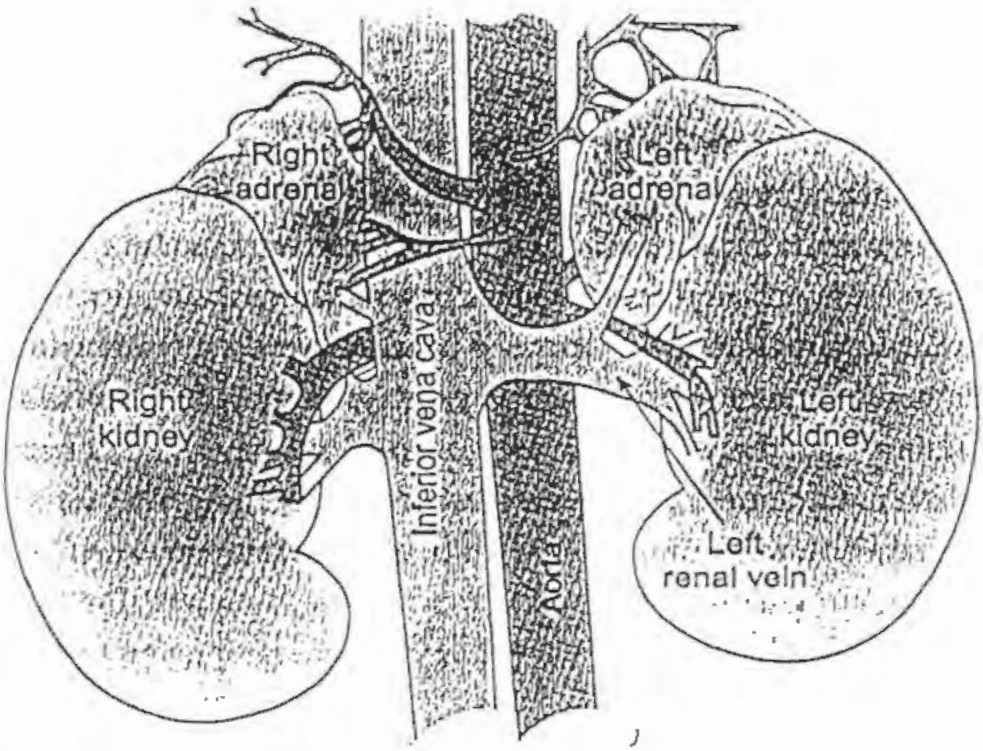


Fig. 12.15 The anatomic location of the adrenal glands and the organization of their blood supply. Note that the arterial supply is via many small arteries which originate from the aorta. The venous drainage is via a large central vein that empties into the inferior vena cava.

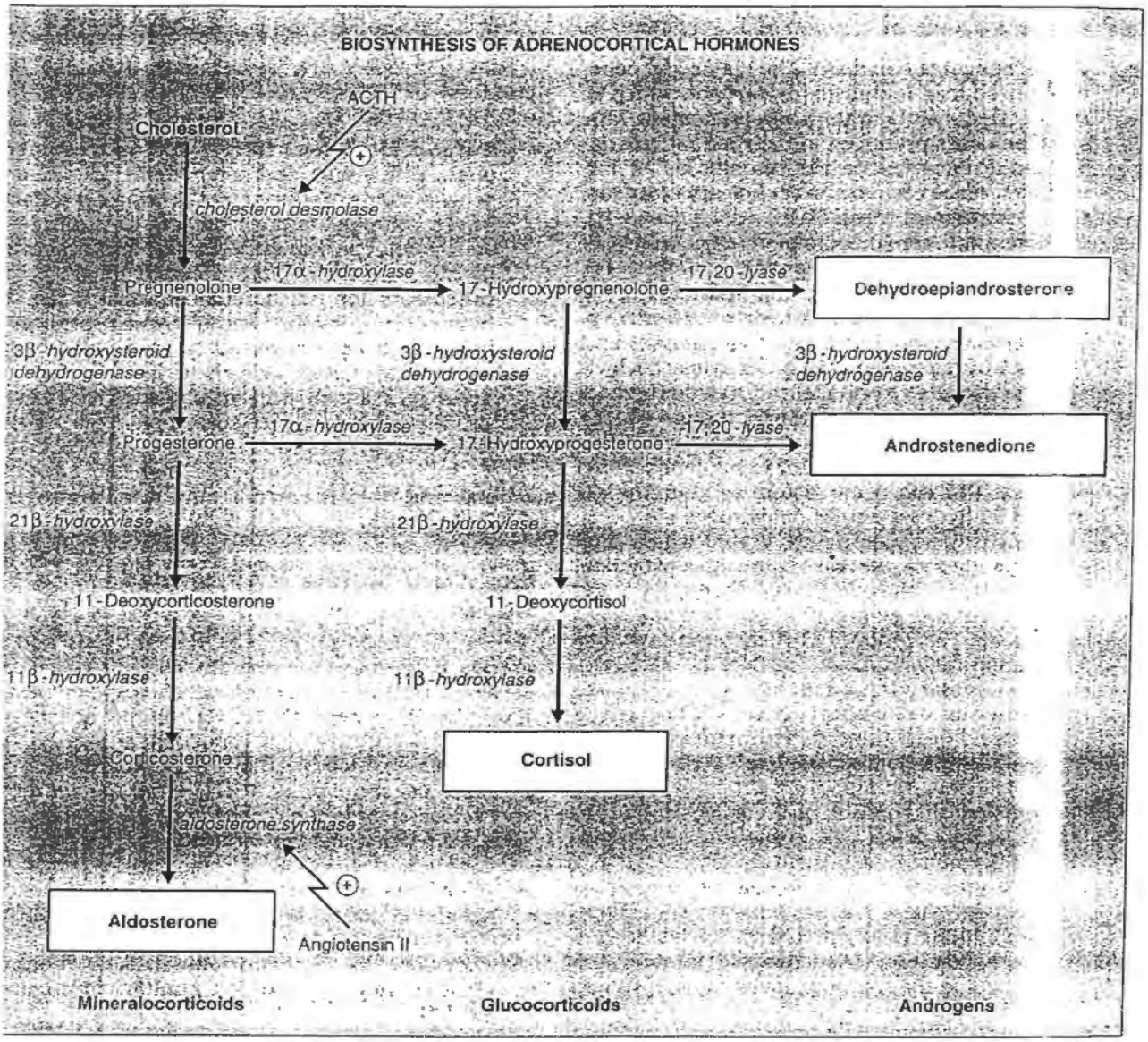
TABLE 19–2 Major Adrenocortical Abnormalities

ABNORMALITY	CONDITION	CAUSE	SYMPTOMS
Excess aldosterone	Conn's syndrome (primary hyperaldosteronism)	Hypersecreting tumor of zona glomerulosa	Hypernatremia; hypokalemia; hypertension
	Secondary hyperaldosteronism	Inappropriately high activity of renin-angiotensin system	
Excess cortisol	Cushing's syndrome	Excess CRH and/or ACTH caused by hypothalmic or anterior pituitary disease; hypersecreting tumor of inner layers of adrenal cortex; ACTH-secreting tumor in lung	Glucose excess; protein shortage; abnormal fat distribution
Excess androgen	Adrenogenital syndrome	Lack of enzyme in cortisol pathway	Inappropriate masculinization in all but adult males
Deficient cortisol and aldosterone	Addison's disease (primary adrenocortical insufficiency)	Destruction or idiopathic atrophy of adrenal cortex	Related to cortisol deficiency: poor response to stress; hypoglycemia; lack of permissiveness for many metabolic activities
Deficient cortisol	Secondary adrenocortical insufficiency	Insufficient ACTH caused by hypothalamic or anterior pituitary failure	Related to aldosterone deficiency: hyperkalemia; hyponatremia; hypotension (if severe enough, fatal)

Adrenal androgens (DHEA and androstenedione). DHEA and androstenedione are androgenic steroids produced by the **zona reticularis.** These compounds have only weak androgenic activity, but in the testes, they are converted to testosterone, a more potent androgen. The precursors for the adrenal androgens are 17-hydroxypregnenolone and 17-hydroxyprogesterone, which are converted to androgens by removal of the C20,21 side chain. In males, adrenal androgens are of little significance; the testes produce their own testosterone from cholesterol and do not require the adrenal precursors . In females, however, the adrenal cortex is the major source of androgenic compounds.

Actions of Adrenal Androgens

Females: presence of pubic and axillary hair; libido
Males: same as testosterone



URE 9–21. **Biosynthetic pathways for glucocorticoids, mineralocorticoids, and androgens in the adrenal cortex.** ACTH, adrenocorticotropic hormone.

Actions of Adrenal Androgens

- Females: presence of pubic and axillary hair; libido
- Males: same as testosterone

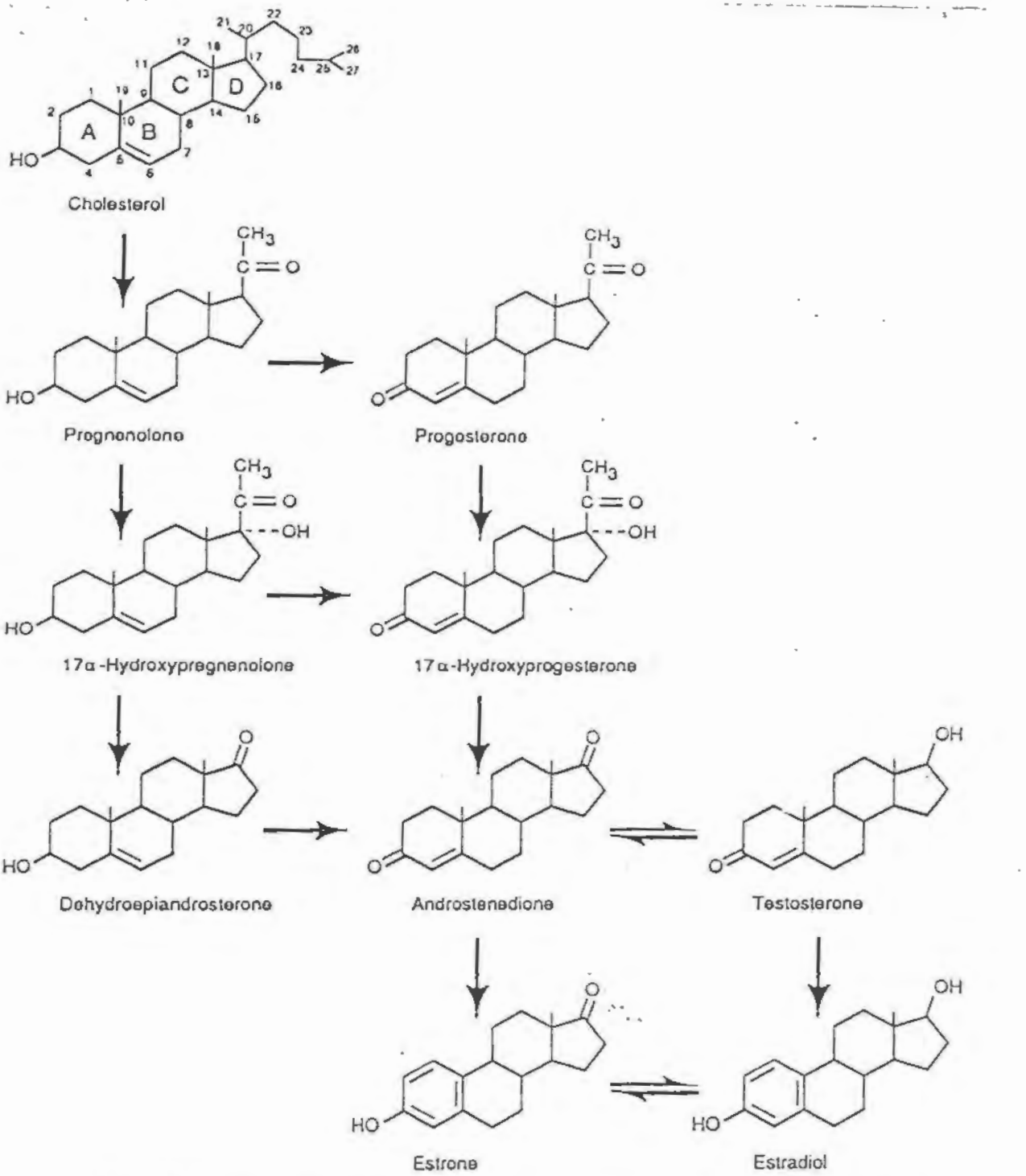


FIGURE 5
Biosynthetic pathway for androgens and estrogens. In the adrenal, the sequence does not usually proceed all the way to testosterone and the estrogens, which are the gonadal hormones. Because the cells of the zona glomerulosa lack 17α-hydroxylase, these reactions can occur only in the inner zones.

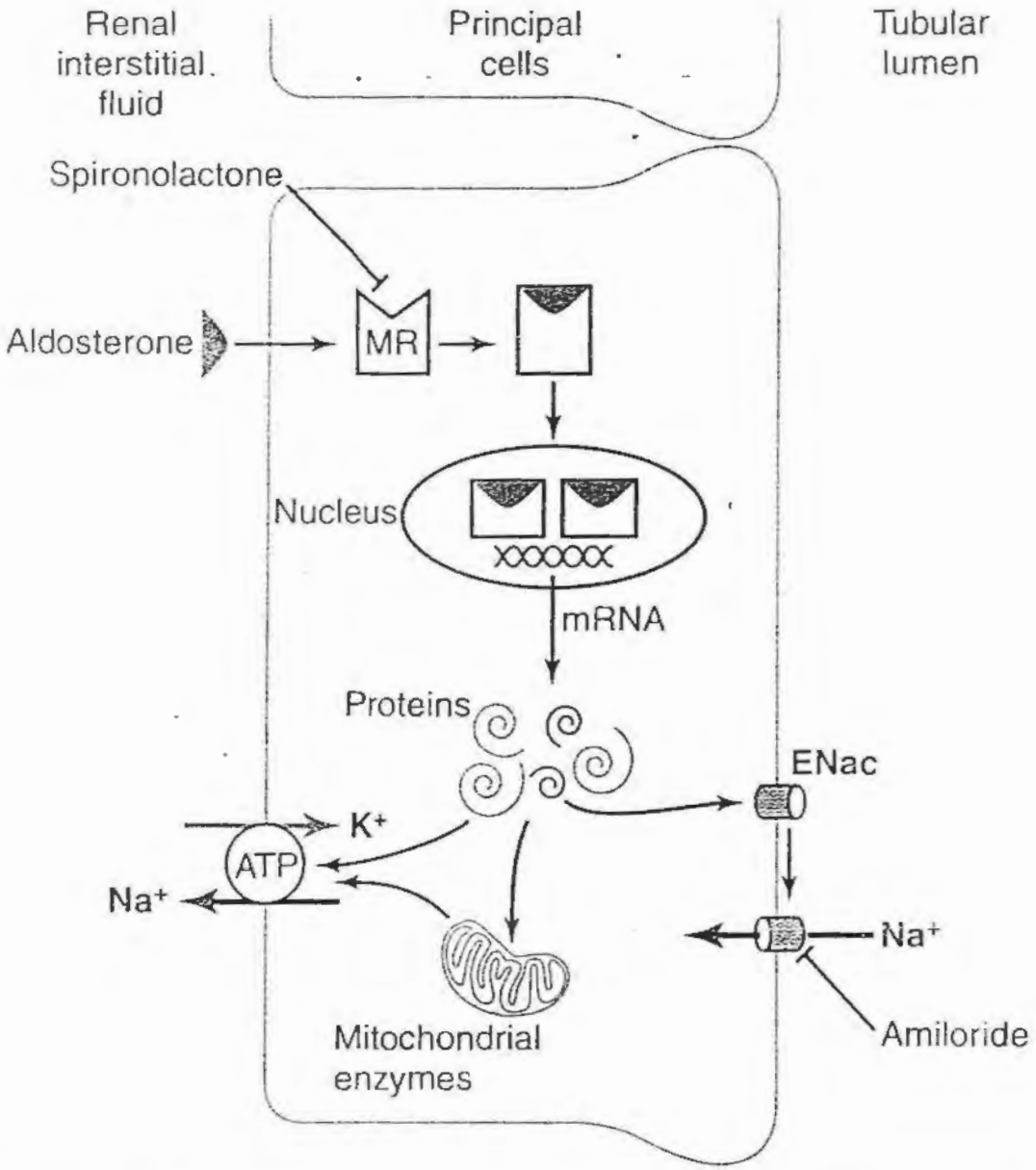


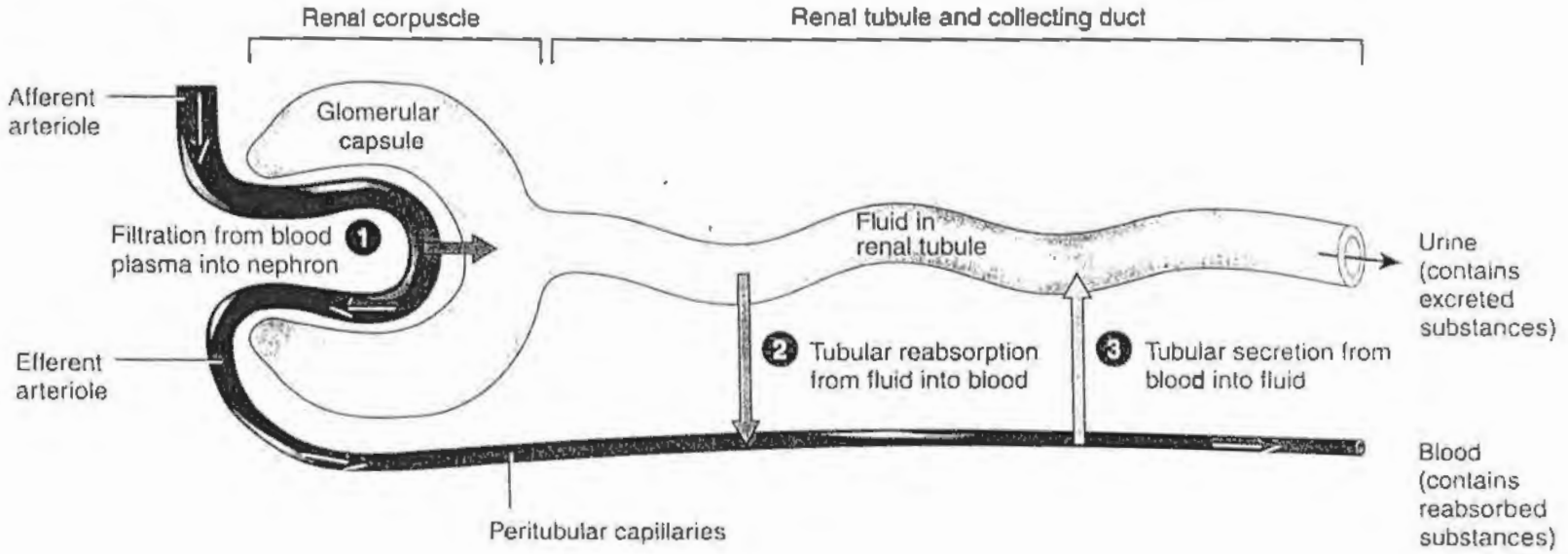
Figure 77-4 Aldosterone-responsive epithelial cell signaling pathways. ENaC, epithelial sodium channel proteins; MR, mineralocorticoid receptor. Activation of the MR by aldosterone can be antagonized with spironolactone. Amiloride is a drug that can be used to block ENaC.

The most important stimuli for aldosterone are (1) increased extracellular potassium concentration and (2) increased angiotensin II levels, which typically occur in conditions associated with sodium and volume depletion or low blood pressure. The increased secretion of aldosterone associated with these conditions causes renal sodium and water retention, helping to increase extracellular fluid volume and restore blood pressure toward normal.

In the absence of aldosterone, as occurs with adrenal destruction or malfunction *(Addison's disease),* there is marked loss of sodium from the body and accumulation of potassium. Conversely, excess aldosterone secretion, as occurs in patients with adrenal tumors *(Conn's syndrome),* is associated with sodium retention and decreased plasma potassium concentration due, in part, to excessive potassium secretion by the kidneys. Although day-to-day regulation of sodium balance can be maintained as long as minimal levels of aldosterone are present, the inability to appropriately adjust aldosterone secretion greatly impairs the regulation of renal potassium excretion and potassium concentration of the body fluids. Thus, aldosterone is even more important as a regulator of potassium concentration than it is for sodium concentration.

Figure 26.7 Relation of a nephron's structure to its three basic functions: glomerular filtration, tubular reabsorption, and tubular secretion. Excreted substances remain in the urine and subsequently leave the body. For any substance S, excretion rate of S = filtration rate of S − reabsorption rate of S + secretion rate of S.

⑥ Glomerular filtration occurs in the renal corpuscle; tubular reabsorption and tubular secretion occur all along the renal tubule and collecting duct.



Angiotensin II Increases Sodium and Water Reabsorption. Angiotensin II is perhaps the body's most powerful sodium-retaining hormone. As discussed in Chapter 19, angiotensin II formation increases in circumstances associated with low blood pressure and/or low extracellular fluid volume, such as during hemorrhage or loss of salt and water from the body fluids by excessive sweating or severe diarrhea. The increased formation of angiotensin II helps to return blood pressure and extracellular volume toward normal by increasing sodium and water reabsorption from the renal tubules through three main effects:

1. *Angiotensin II stimulates aldosterone secretion,* which in turn increases sodium reabsorption.
2. *Angiotensin II constricts the efferent arterioles,* which has two effects on peritubular capillary dynamics that increase sodium and water reabsorption. First, efferent arteriolar constriction reduces peritubular capillary hydrostatic pressure, which increases net tubular reabsorption, especially from the proximal tubules. Second, efferent arteriolar constriction, by reducing renal blood flow, raises filtration fraction in the glomerulus and increases the concentration of proteins and the colloid osmotic pressure in the peritubular capillaries; this increases the reabsorptive force at the peritubular capillaries and raises tubular reabsorption of sodium and water.
3. *Angiotensin II directly stimulates sodium reabsorption in the proximal tubules, the loops of Henle, the distal tubules, and the collecting tubules.* One of the direct effects of angiotensin II is to stimulate the sodium-potassium ATPase pump on the tubular epithelial cell basolateral membrane. A second effect is to stimulate sodium-hydrogen exchange in the luminal membrane, especially in the proximal tubule. A third effect of angiotensin II is to stimulate sodium-bicarbonate co-transport in the basolateral membrane (Figure 27-17).

Thus, angiotensin II stimulates sodium transport across both the luminal and the basolateral surfaces of the epithelial cell membrane in most renal tubular segments. These multiple actions of angiotensin II cause marked sodium and water retention by the kidneys when angiotensin II levels are increased and play a critical role in permitting the body to adapt to wide variations in sodium intake without large changes in extracellular fluid volume and blood pressure.

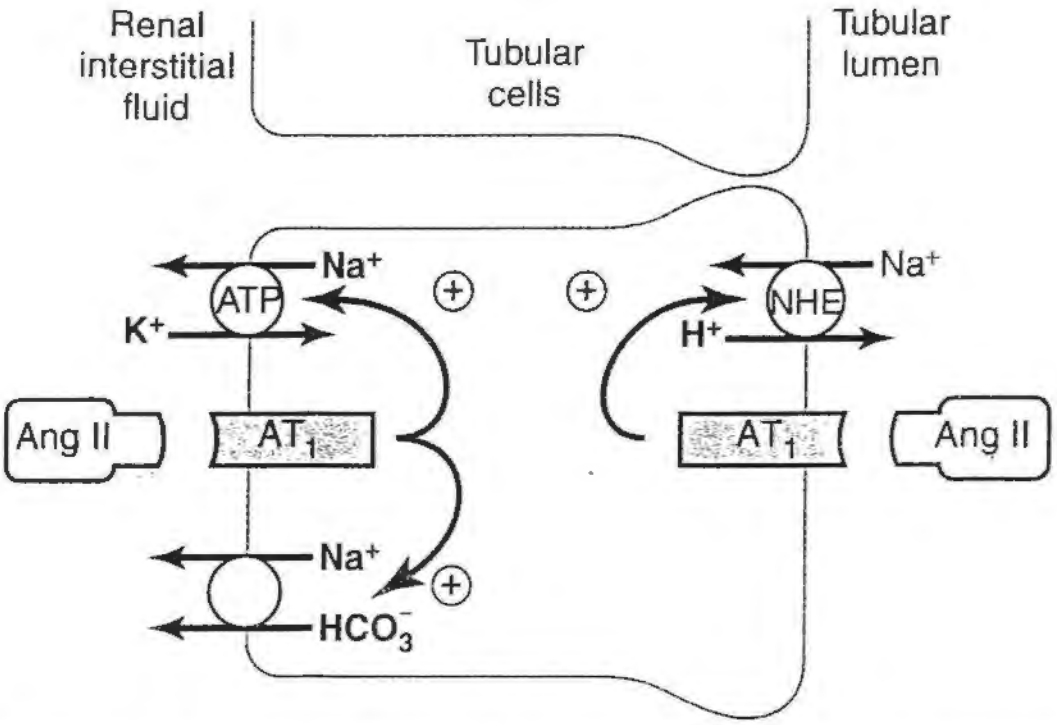
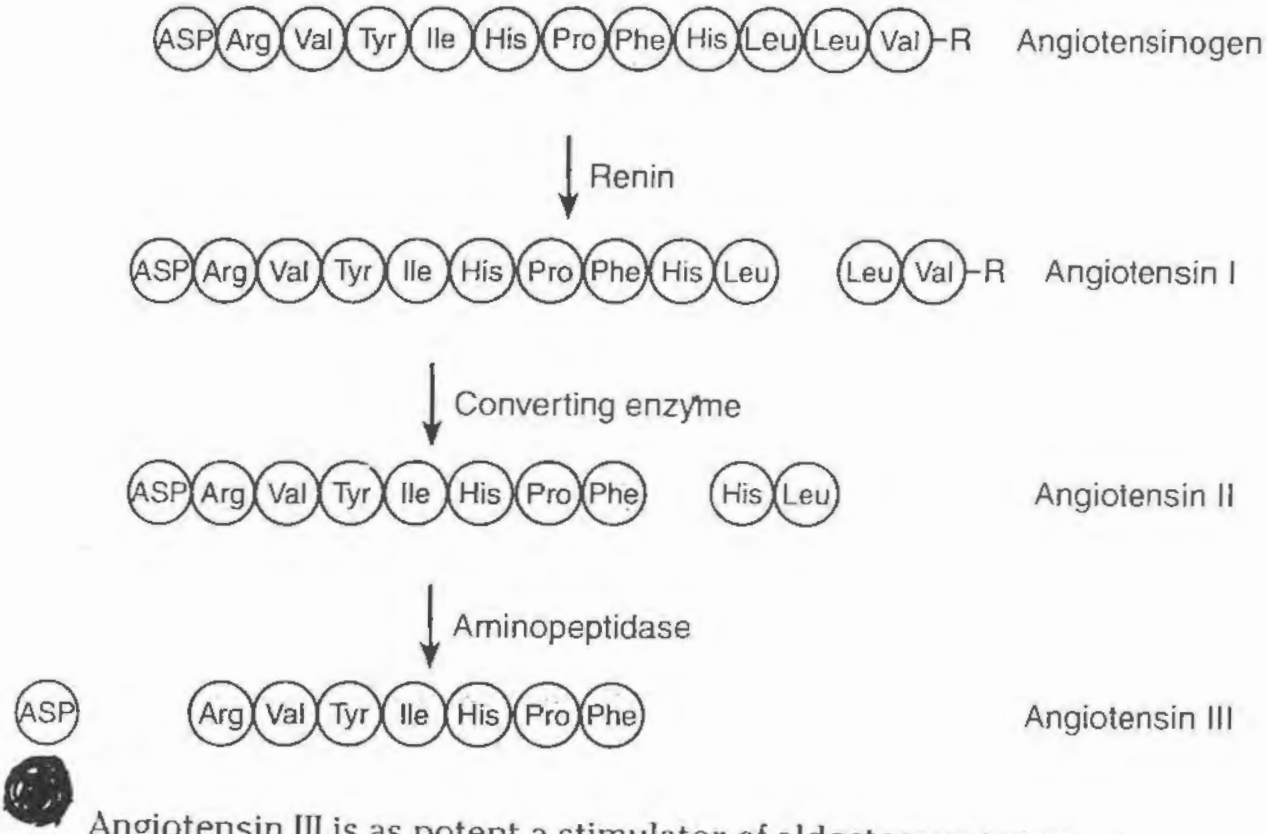


Figure 27-17 Direct effects of angiotensin II (*Ang II*) to increase proximal tubular sodium reabsorption. Ang II stimulates sodium sodium-hydrogen exchange (*NHE*) on the luminal membrane and the sodium-potassium ATPase transporter as well as sodium-bicarbonate co-transport on the basolateral membrane. These same effects of Ang II likely occur in several other parts of the renal tubule, including the loop of Henle, distal tubule, and collecting tubule.

FIGURE 33.8 **The formation of angiotensins I, II, and III from angiotensinogen.**



Angiotensin III is as potent a stimulator of aldosterone secretion as angiotensin II.

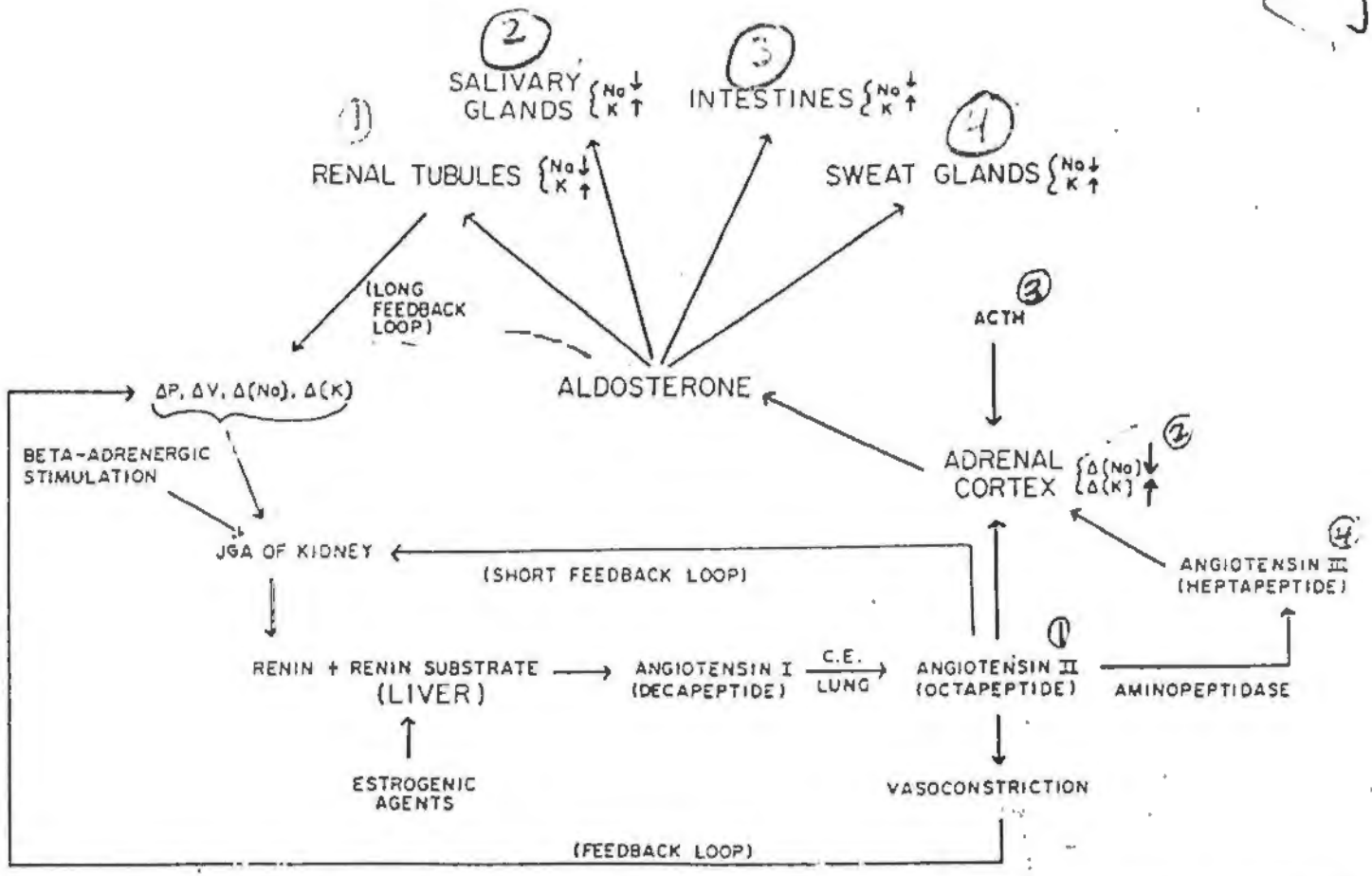


FIGURE 5-18: The physiologic factors controlling aldosterone secretion rate (C.E. = converting enzyme).

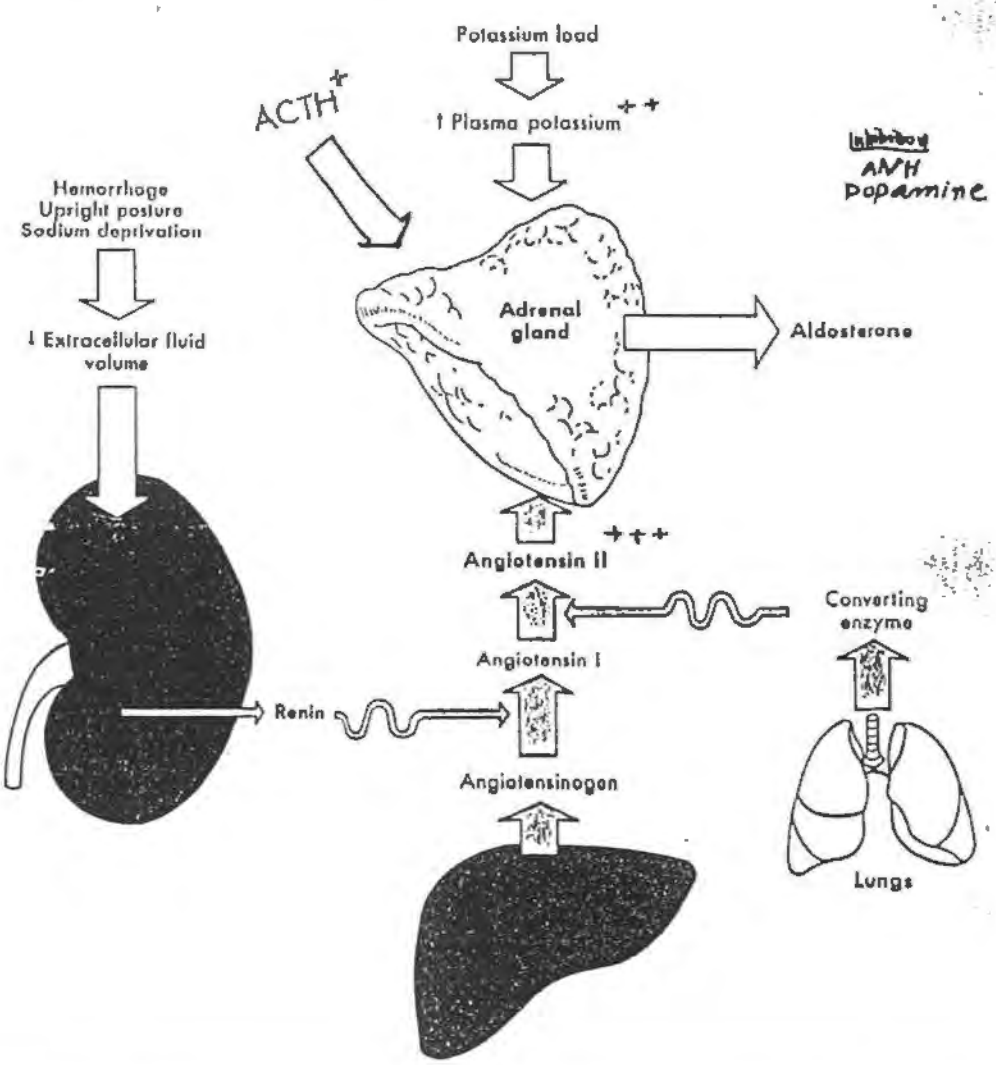


FIGURE 41-8 The regulation of aldosterone secretion. Activation of the renin-angiotensin system in response to hypovolemia is the predominant stimulus to aldosterone production. Elevation of plasma potassium is the other major stimulus.

Figure 11.15. Simplified pathways for the synthesis of steroid hormones in the adrenal cortex. The adrenal cortex produces steroids that regulate Na^+ and K^+ balance (mineralocorticoids), steroids that regulate glucose balance (glucocorticoids), and small amounts of sex steroid hormones.

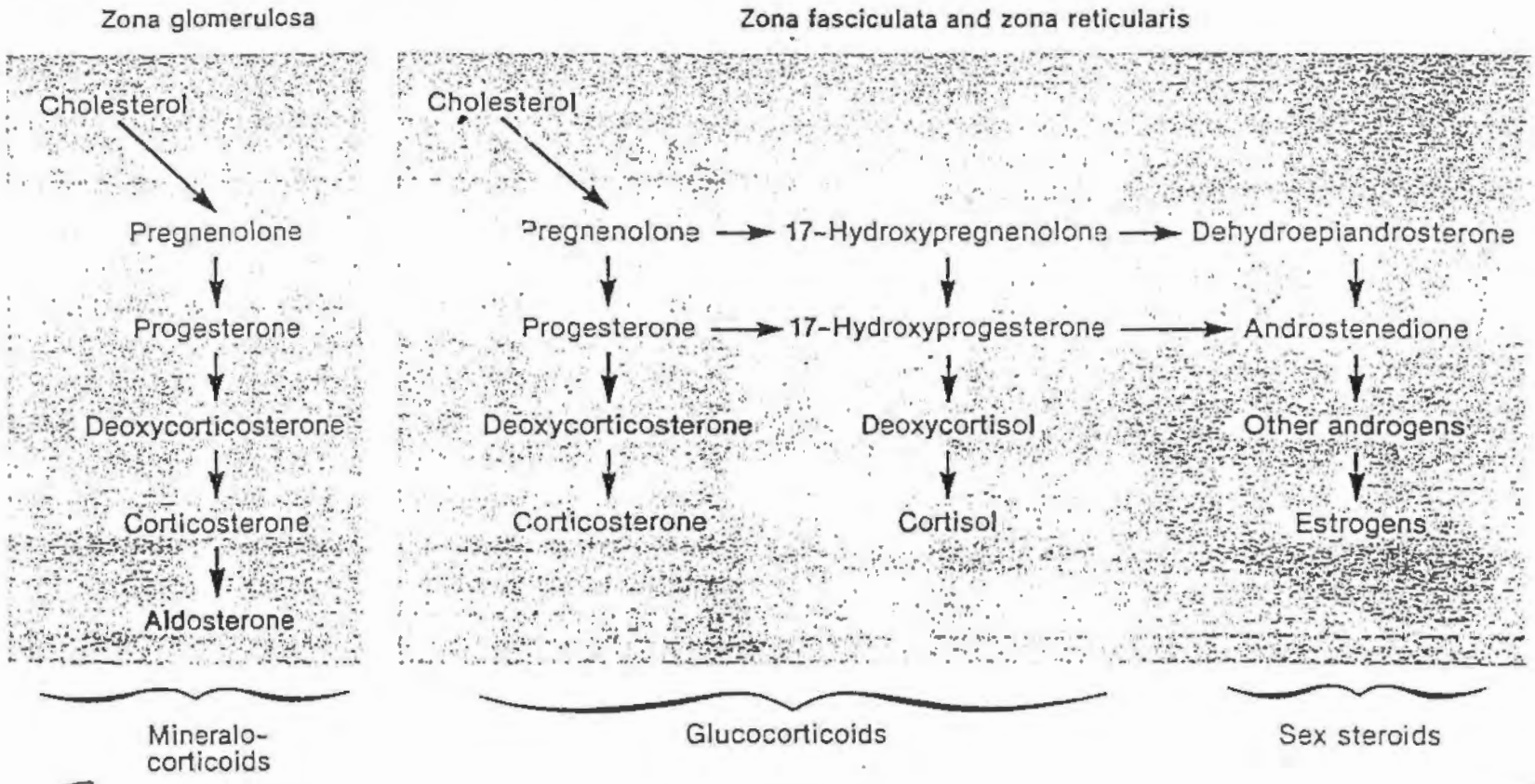


TABLE 5-3: Physiologic Actions of Glucocorticoid Hormones

1. *Carbohydrate Metabolism:* stimulates gluconeogenesis; increases glycogen content in liver and glucose concentrations in blood; may also decrease peripheral utilization of glucose.
2. *Protein Metabolism:* induces marked losses of nitrogen in urine as protein is catabolized to form glucose.
3. *Fat Metabolism:* increases total body fat at the expense of protein; leads to centripetal redistribution of fat.
4. *Water Metabolism:* enhances water diuresis by preserving the rate of glomerular filtration.
5. *Hematologic Effects:* decreases lymphocytes, basophils, and eosinophils; increases neutrophils; total white blood cell count rises slightly; red blood cell count rises.
6. *Central Nervous System Effects:* may control threshold for electrical excitability of the brain; psychiatric disturbances are common with both lack and excess of cortisol.
7. *Gastrointestinal Effects:* production of gastric acid increases and pepsin decreases; the tendency for peptic ulcer formation increases with increasing concentration of cortisol in plasma.
8. *Bone Metabolism:* high levels inhibit formation of protein matrix of bone; this may lead to demineralization of the bone and osteoporosis.
9. *Cardiovascular System:* maintains sensitivity to pressor effects of catecholamines.
10. *Mesenchymal System:* alters connective tissue response to injury, namely, decreased hyperemia, exudation, and cellular infiltration. This illustrates the antiinflammatory action of glucocorticoid hormones.
11. *Immunologic Effects:* high concentrations of glucocorticoids in blood lyse fixed plasma cells and lymphocytes, thereby decreasing antibody production.

Role of the fetal cortex. *In vitro* studies of primate adrenals and estimation of steroids in umbilical venous blood showed that the fetal adrenal is capable of steroid production at an early stage of gestation. Glucocorticoids in the fetus are involved in a number of important processes:

1 Production of surfactant from type II cells of the alveoli of the lung—a lack of which leads to the respiratory distress syndrome in newborn infants.
2 Development of hypothalamic function and of the thyroid-pituitary axis.
3 The sequential changes of placental structure and in the ionic composition of amniotic and allantoic fluids during development.
4 They are most important in the initiation of the endocrine changes of the fetus and mother which are responsible for parturition.
5 The development of hepatic enzymes, including those involved in gluconeogenesis.
6 Induction of thymic involution.

TABLE 9–11. Actions of Adrenocortical Steroids

Actions of Glucocorticoids	Actions of Mineralocorticoids	Actions of Adrenal Androgens
Increase gluconeogenesis	Increase Na^+ reabsorption	Females: presence of pubic and axillary hair; libido
Increase proteolysis (catabolic)	Increase K^+ secretion	Males: same as testosterone
Increase lipolysis	Increase H^+ secretion	
Decrease glucose utilization		
Decrease insulin sensitivity		
Anti-inflammatory		
Immunosuppression		
Maintain vascular responsiveness to catecholamines		
Inhibit bone formation		
Increase GFR		
Decrease REM sleep		

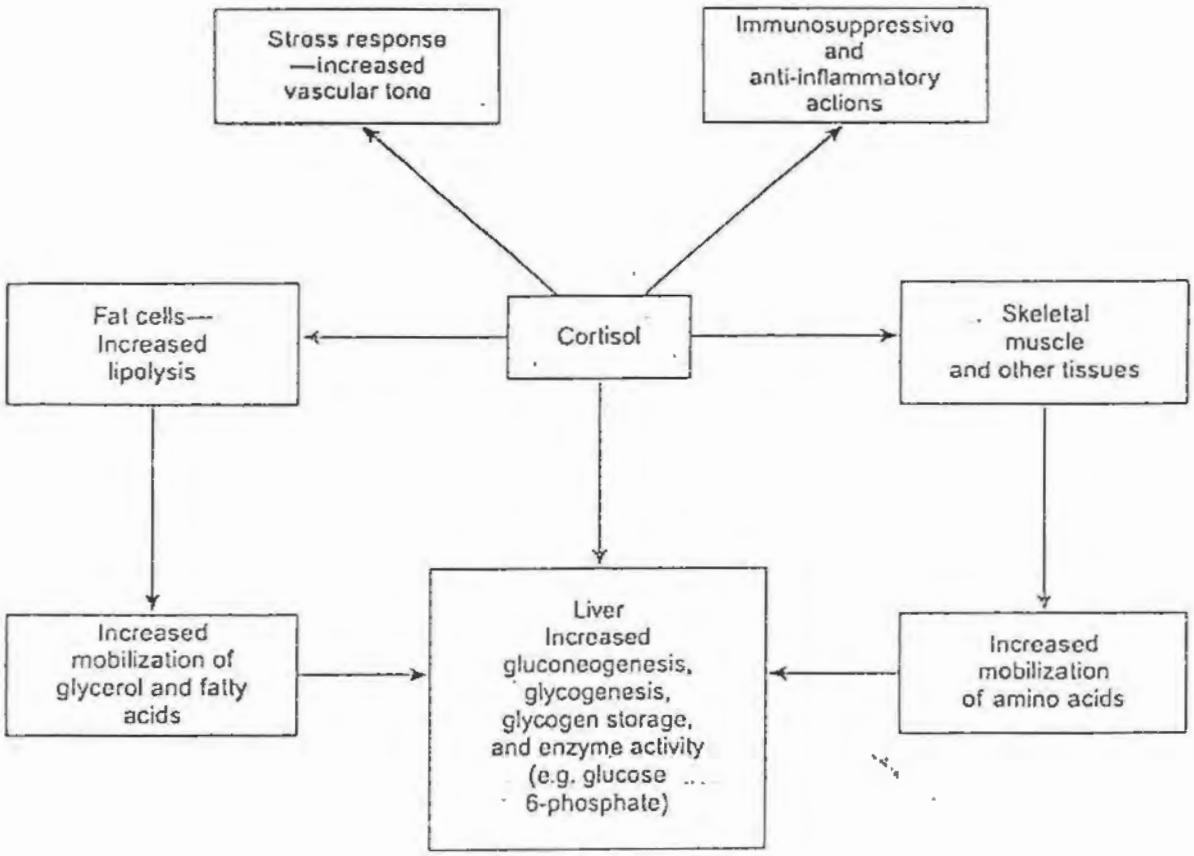


Fig. 12.18 The principal physiological actions of the glucocorticoid hormone, cortisol.

TABLE 1 Some Effects of Glucocorticoids

Tissue	Effects
Central nervous system	Taste, hearing, and smell ↑ in acuity with adrenal cortical insufficiency and ↓ in Cushing's disease
	↓ Corticotropin-releasing hormone (see text)
	↓ ADH secretion
Cardiovascular system	Maintain sensitivity to epinephrine and norepinephrine
	↑ Sensitivity to vasoconstrictor agents
	Maintain microcirculation
Gastrointestinal tract	↑ Gastric acid secretion
	↓ Gastric mucosal cell proliferation
Liver	↑ Gluconeogenesis
Lungs	↑ Maturation and surfactant production during fetal development
Pituitary	↓ ACTH secretion (acute) and synthesis (chronic)
Kidney	↑ GFR
	Needed to excrete dilute urine
Bone	↑ Resorption
	↓ Formation
Muscle	↓ Fatigue (probably secondary to cardiovascular actions)
	↑ Protein catabolism
	↓ Glucose oxidation
	↓ Insulin sensitivity
	↓ Protein synthesis
Immune system (see text)	↓ Mass of thymus and lymph nodes
	↓ Blood concentrations of eosinophils, basophils, and lymphocytes
	↓ Cellular immunity
Connective tissue	↓ Activity of fibroblasts
	↓ Collagen synthesis

ADH, antidiuretic hormone; ACTH, adrenocorticotropic hormone; GFR, glomerular filtration rate.

Glucocorticoids

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

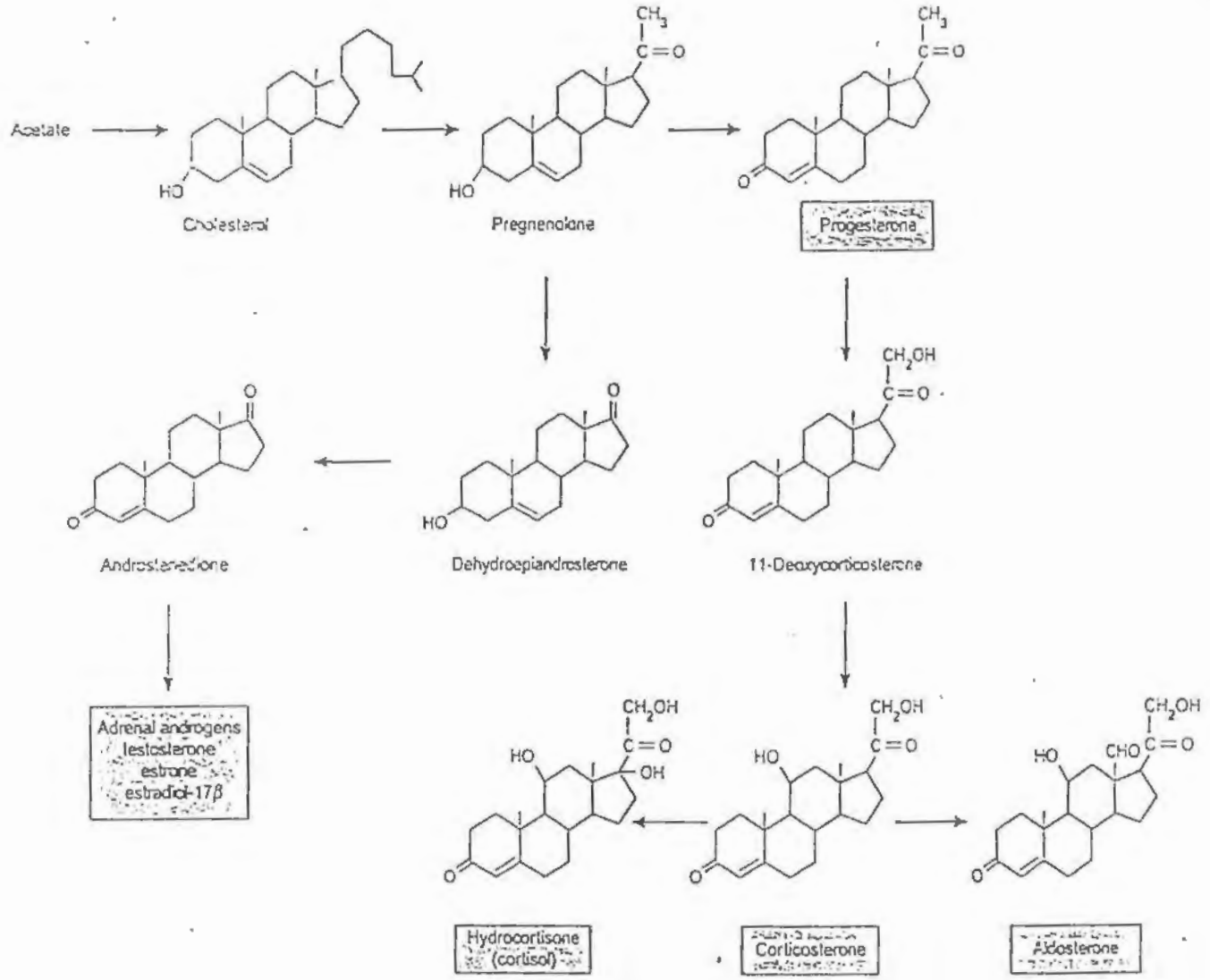


Fig. 12.17 The principal steps in the synthesis of the adrenal steroid hormones from cholesterol. Cortisol is the principal glucocorticoid and aldosterone is the principal mineralocorticoid.

Table 5.4.2 Plasma protein binding of corticosteroids

	Cortisol (%)	Aldosterone (%)
Corticosteroid-binding protein (CBG)	90	20
Albumin	6	40

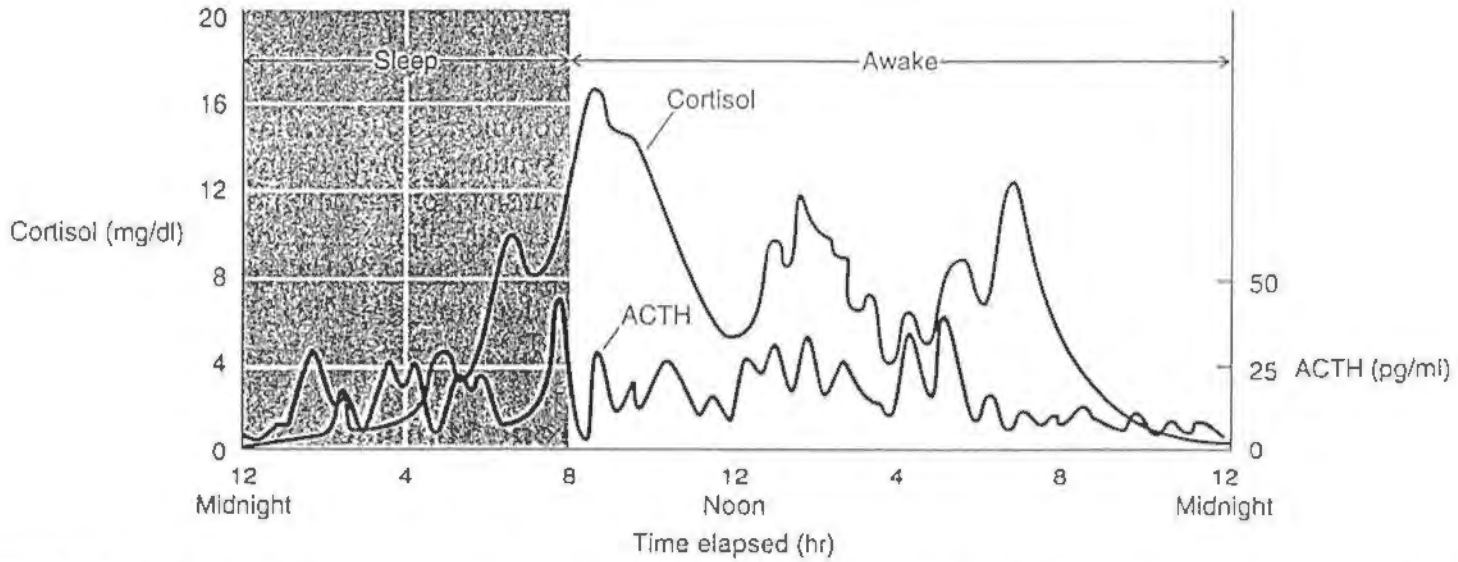


FIGURE 49–5. Rhythm of ACTH and cortisol. The corticotrophs release ACTH in a circadian rhythm, greater in the early morning hours and less late in the afternoon and early evening. Superimposed on the circadian rhythm is the effect on the corticotrophs of the pulsatile secretion of CRH by the hypothalamus. Thus, ACTH levels exhibit both circadian and pulsatile behavior. Notice that, although both ACTH and cortisol are secreted episodically, the duration of the ACTH bursts is briefer, reflecting the shorter half-life of ACTH in plasma. ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone. (Data from Wilson JD et al: Williams Textbook of Endocrinology. Philadelphia, WB Saunders, 1998.)

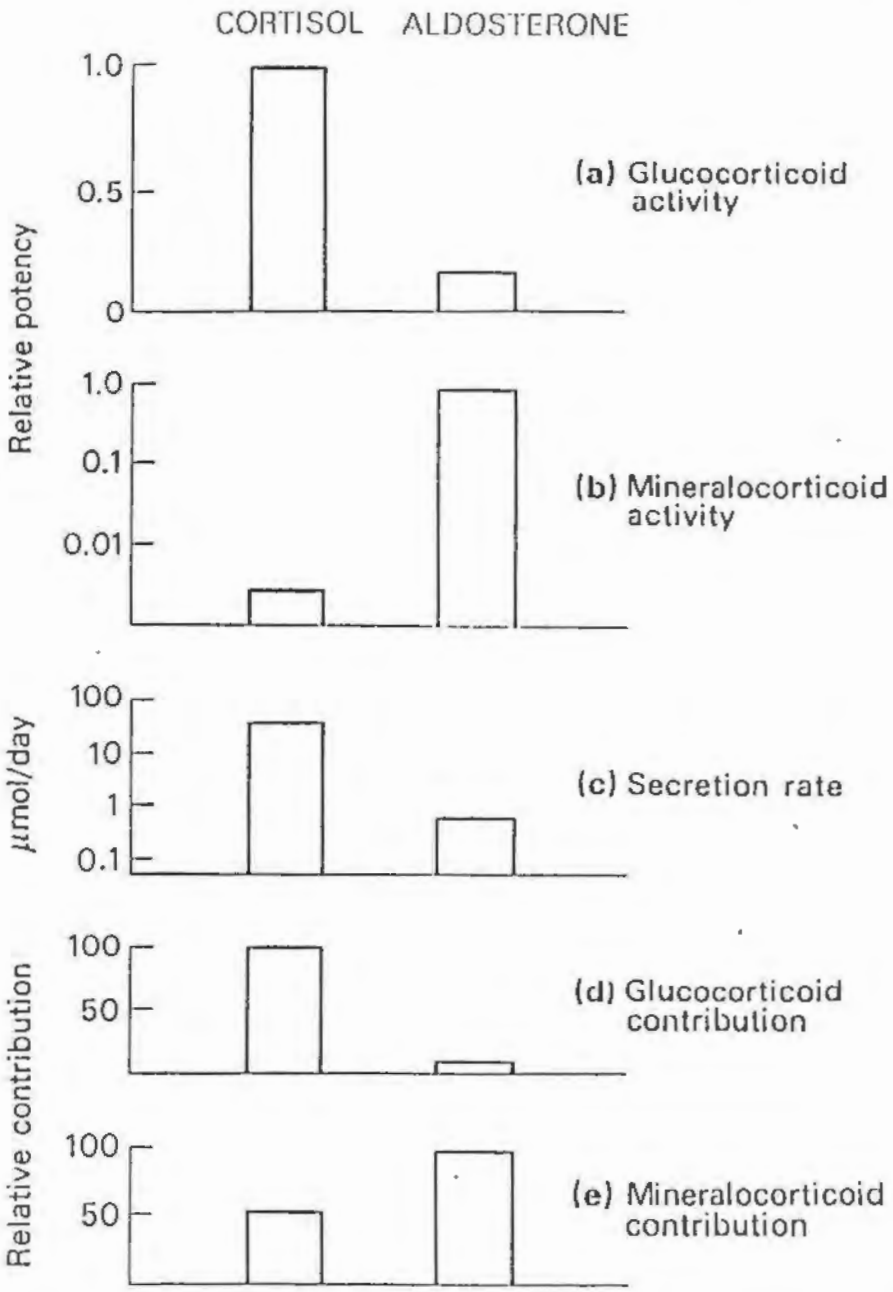


Fig. 3.5 A comparison of cortisol and of aldosterone. Glucocorticoid activity was measured as ability to increase glycogen in the liver: cortisol is very potent in this assay. Mineralocorticoid effects were measured in terms of the ability to reduce the ratio of the excretion of sodium to the excretion of potassium in urine; aldosterone is much more potent. However, since the rate of secretion of cortisol is much higher, it can have significant mineralocorticoid effects (see d and e).

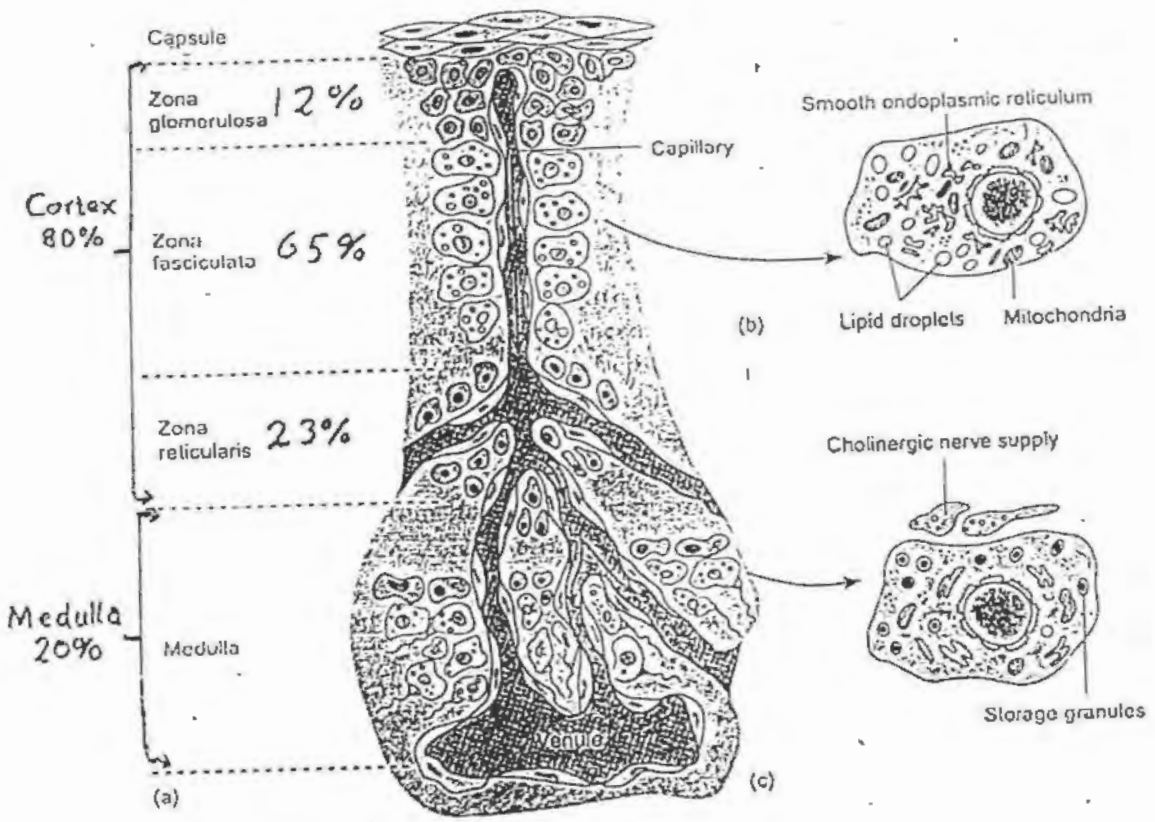


Fig. 12.16 (a) A diagrammatic representation of a section through the cortex and medulla of the adrenal gland. Note the three zones of the adrenal cortex, the cells of which secrete steroid hormones. (b) The appearance of steroid-secreting cells. (c) A single catecholamine-secreting chromaffin cell.

The adrenal cortex

There are three morphologically distinct zones of cells within the adrenal cortex (Fig. 12.16). These are the outer *zona glomerulosa* (occupying around 10 per cent of the adrenal cortex), the *zona fasciculata* (around 75 per cent), and the *zona reticularis*, which lies closest to the adrenal medulla. The zona reticularis does not differentiate fully until between 6 and 8 years of age. In the adult gland, the cells of the glomerulosa continually migrate down through the zona fasciculata to the zona reticularis, changing their secretory pattern as they go. The purpose of this migration is not clear.

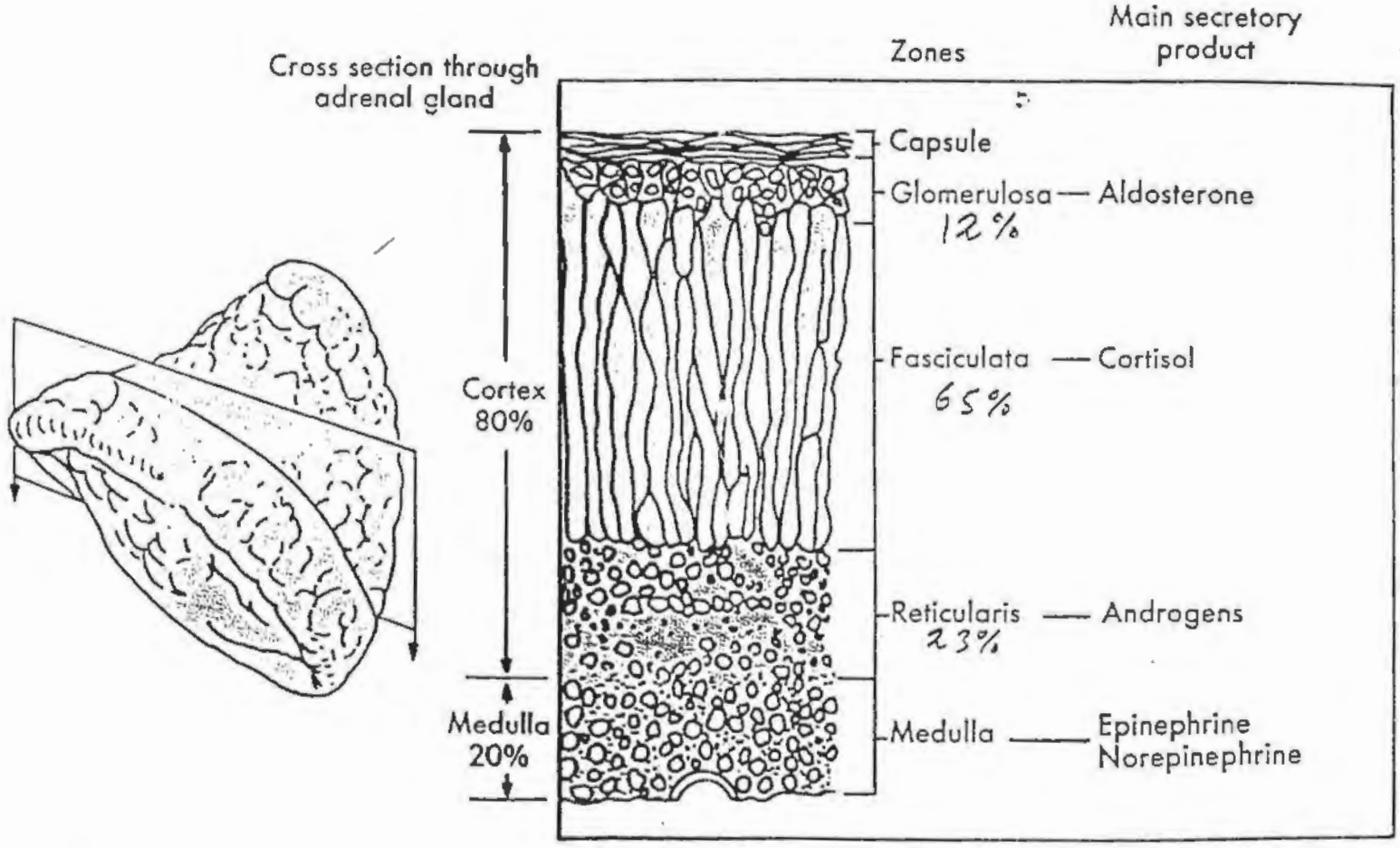


FIGURE 41-1 Schematic representation of the adrenal gland and its main secretory products.

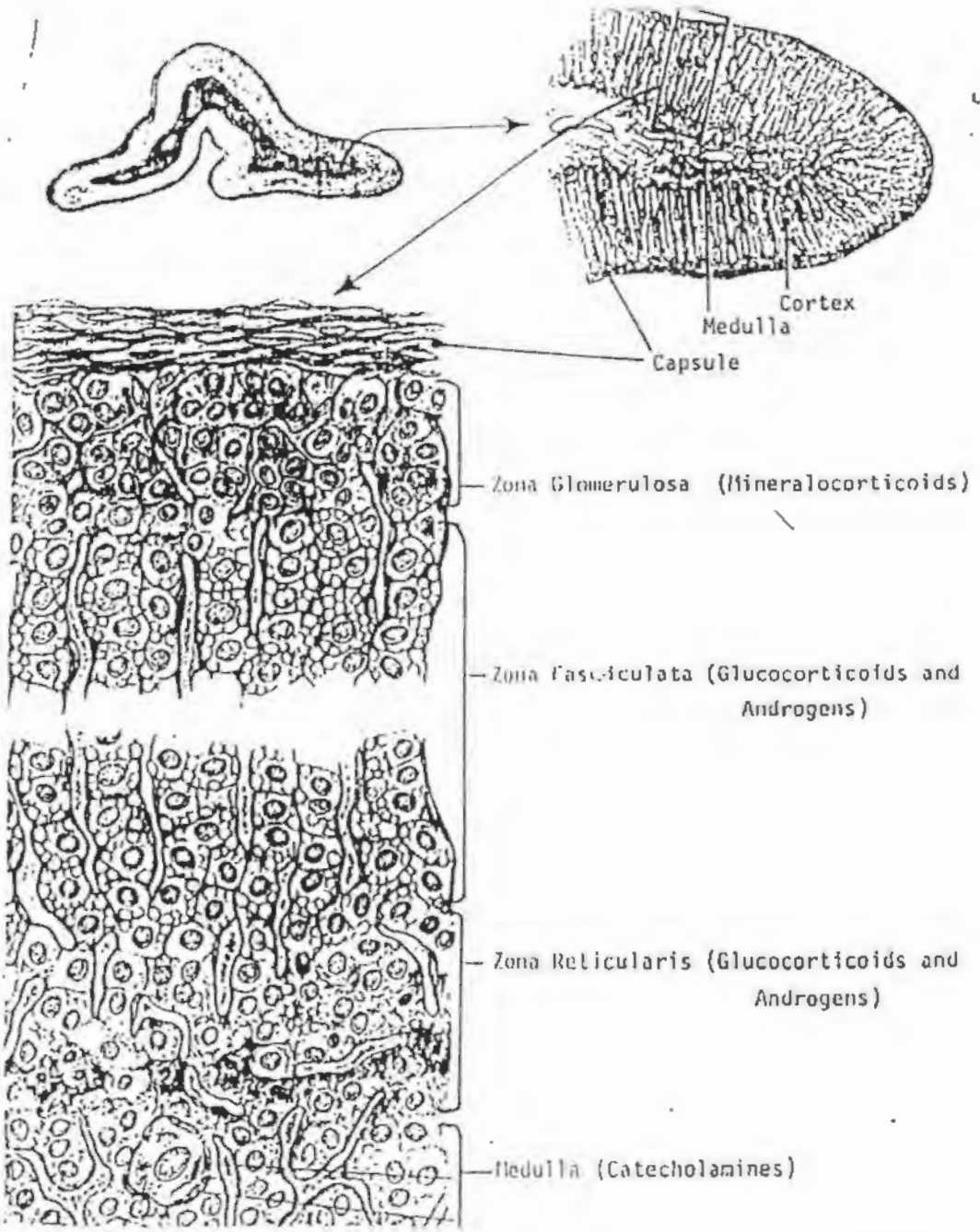


FIGURE 5-1: Cross section through the adrenal, illustrating the major subdivisions and cell layers as well as their hormonal products. [*Adopted from*: Hum and Cormack, 1070.]

" Adrenal Glands "

* The adrenal gland is made up of two distinct organs, the adrenal cortex and adrenal medulla, which differ in their histological structure, anatomy, development and functions. Their total weight is 6–10 g.

* The adrenal cortex is essential to life, because it:

a). Controls Na, k and H_2O metabolism.

b). Controls carbohydrate, fat and ptn. metabolism and mobilisation for energy.

c). participates in responses to stresses of various kinds.

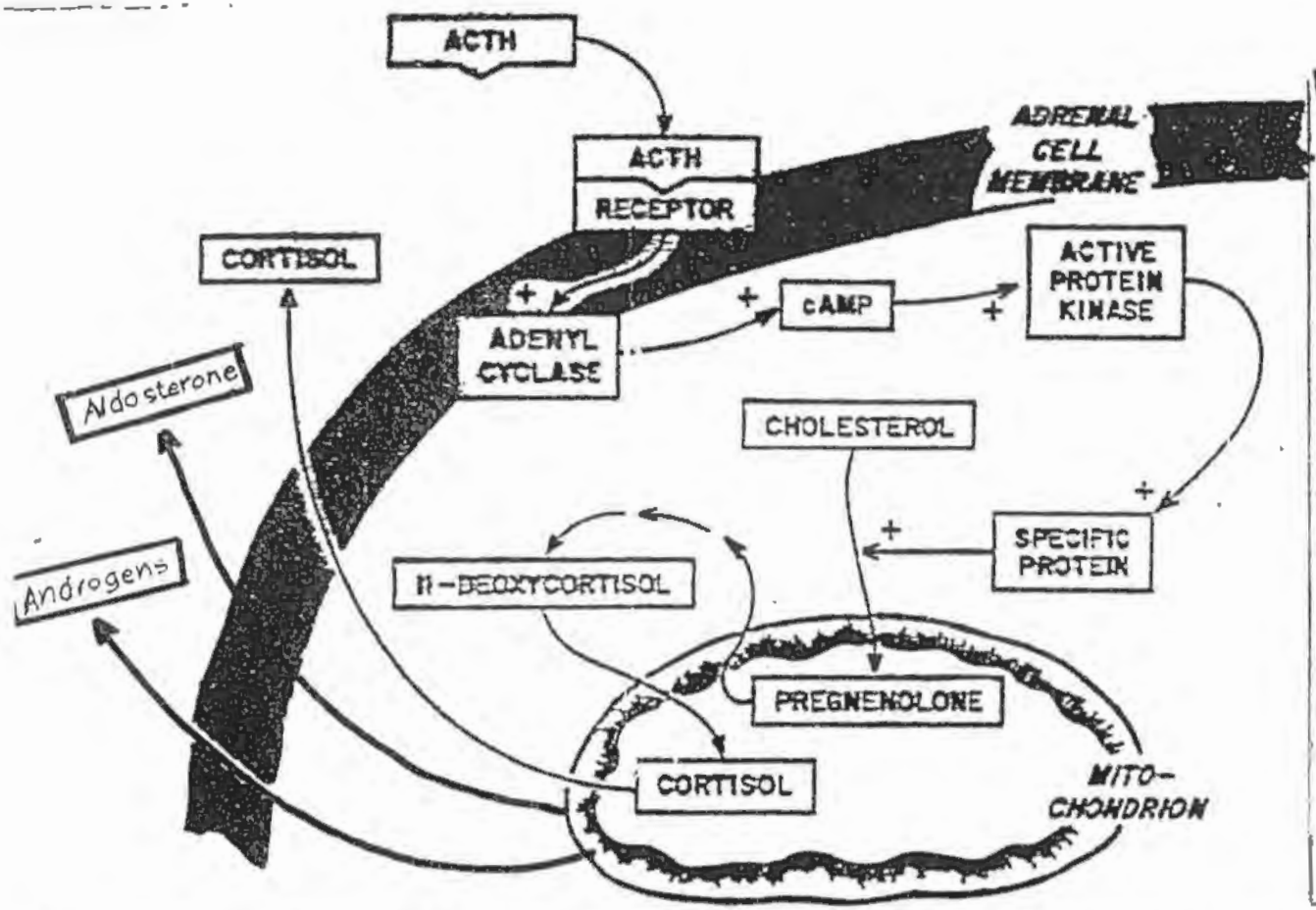


Fig 10–10.—Simplified scheme of stimulation of cortisol synthesis and secretion by ACTH. Note importance of mitochondrion.

* The Most Important of All The ACTH-Stimulated Steps for Controlling Adrenocortical Secretion Is Activation of The Enzyme Desmolase, Which Causes Initial Conversion of Cholesterol to Pregnenolone