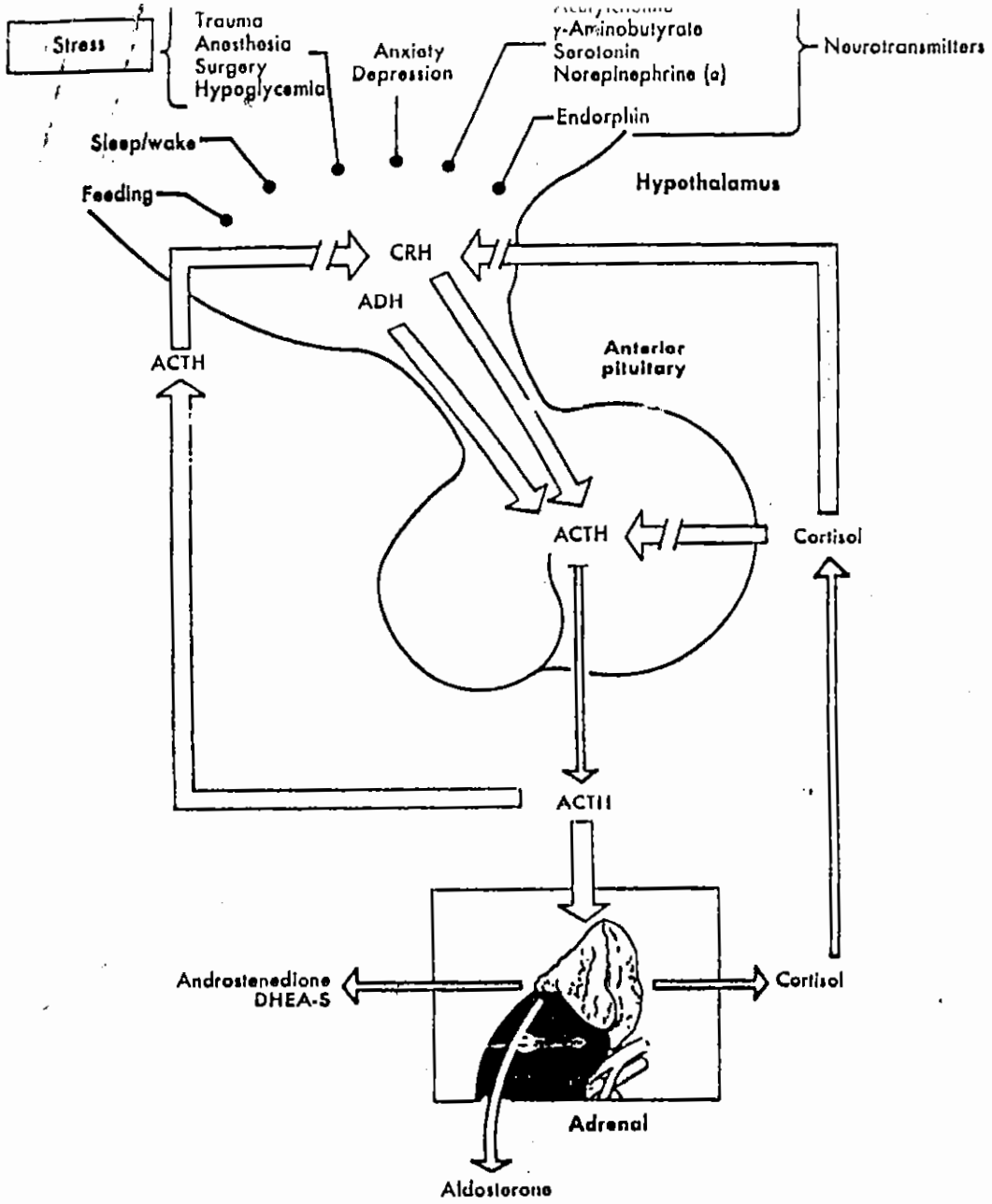


FIGURE 41-3 The regulation of cortisol secretion by the hypothalamic-pituitary-adrenal axis. A variety of inputs to the hypothalamus stimulate corticotropin—releasing hormone *(CRH)* secretion, and in turn adrenocorticotropin *(ACTH)* and cortisol secretion. Cortisol exerts negative feedback at both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

- ACTH secretion responds most strikingly to stressful stimuli, a response that is critical to survival.
- Extraadrenal actions of ACTH: lipolysis and MSH Likeaction

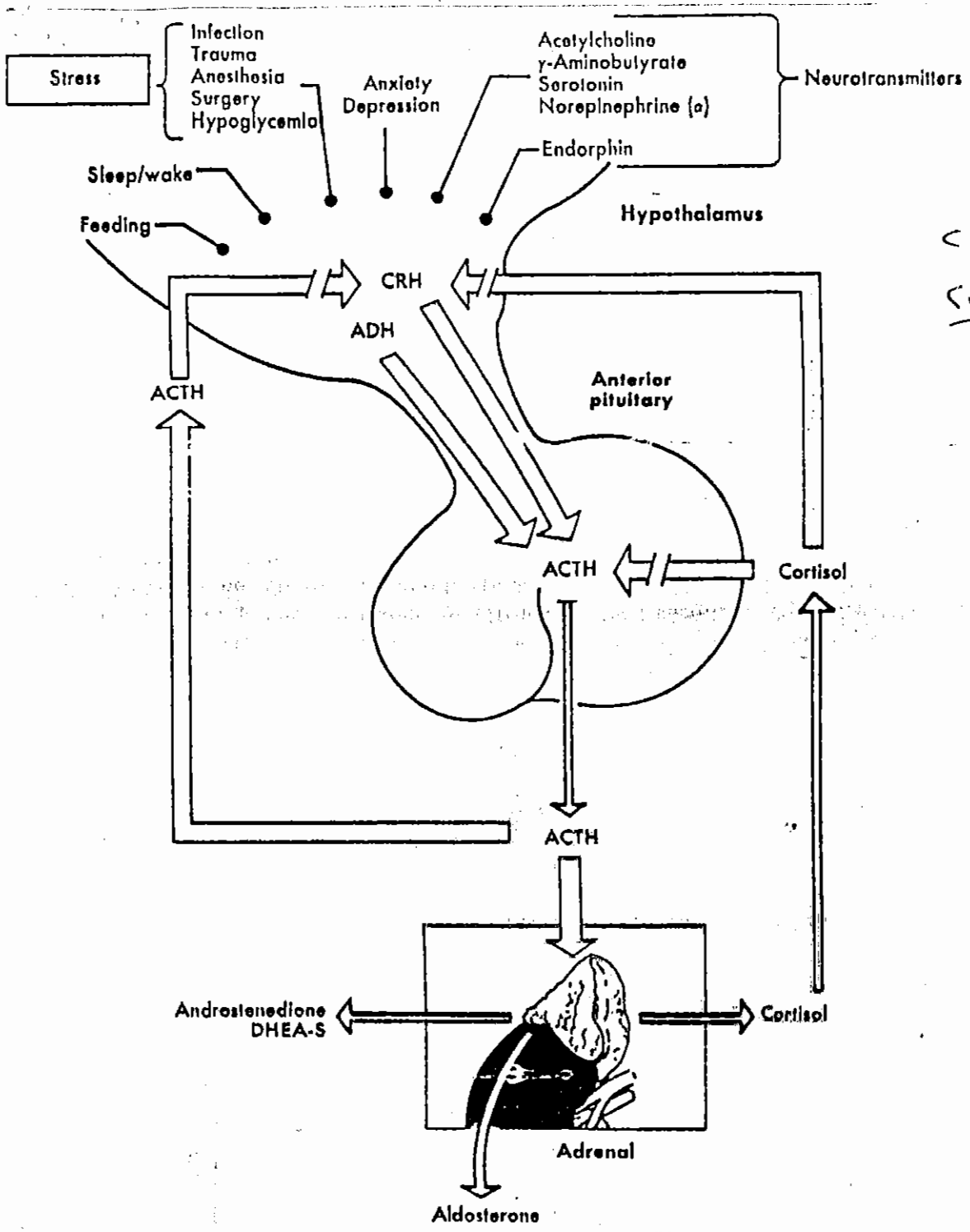


FIGURE 41-3 The regulation of cortisol secretion by the hypothalamic-pituitary-adrenal axis. A variety of inputs to the hypothalamus stimulate corticotropin—releasing hormone *(CRH)* secretion, and in turn adrenocorticotropin *(ACTH)* and cortisol secretion. Cortisol exerts negative feedback at both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

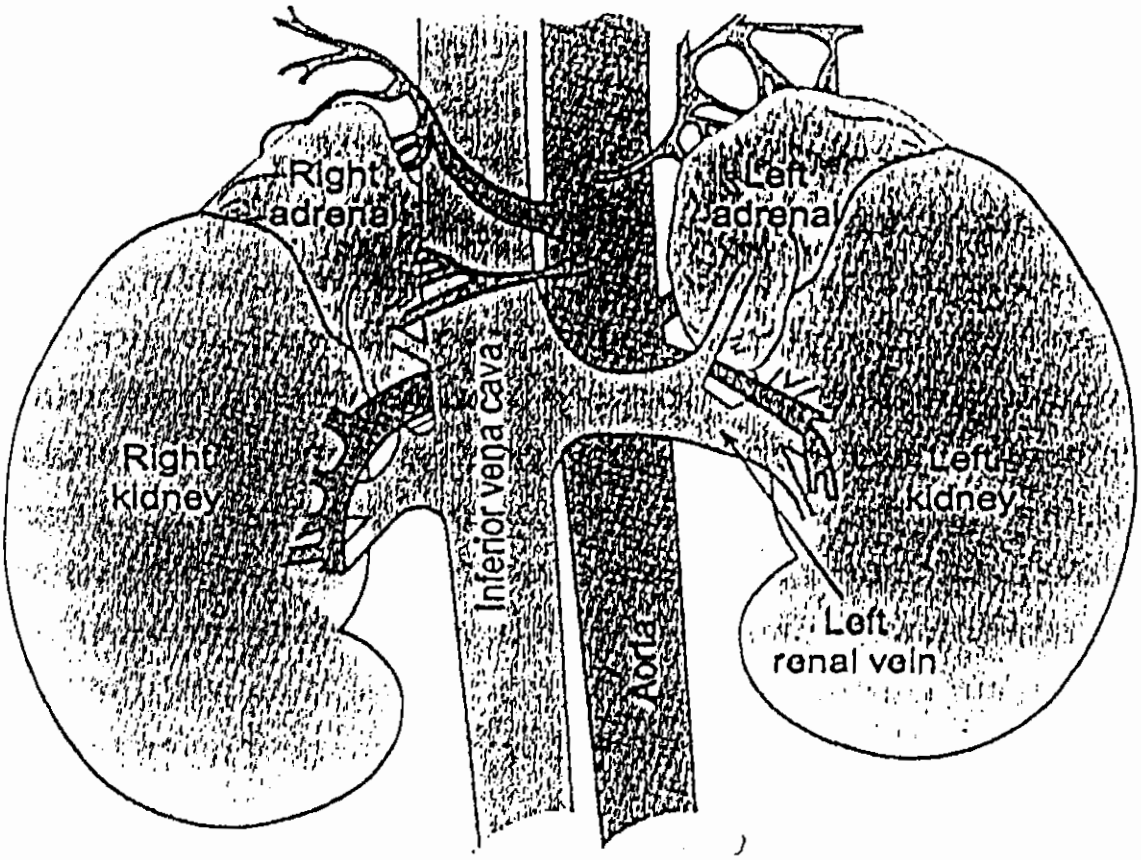


Fig. 12.15 The anatomic location of the adrenal glands and the organization of their blood supply. Note that the arterial supply is via many small arteries which originate from the aorta. The venous drainage is via a large central vein that empties into the inferior vena cava.

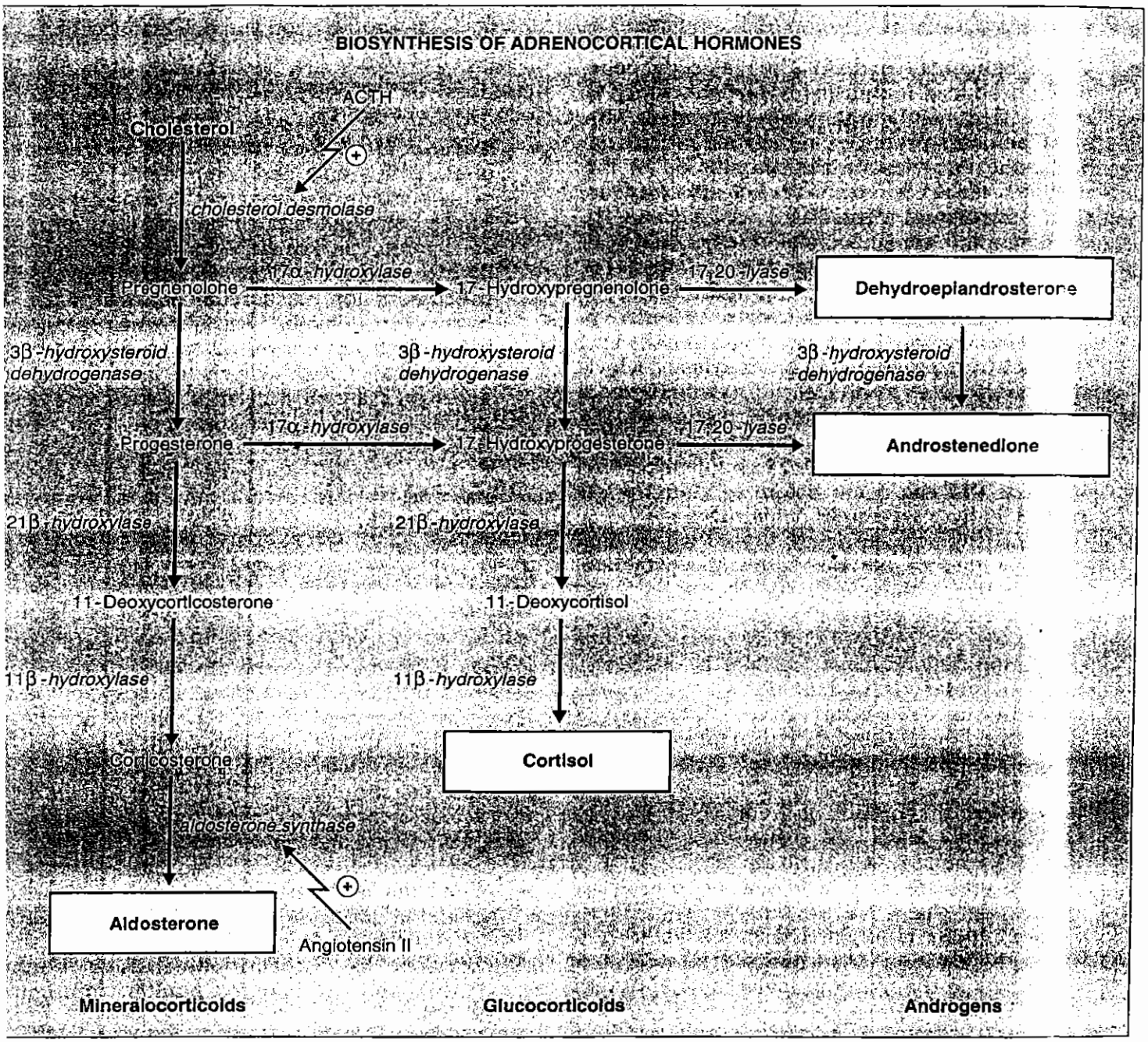
TABLE 19–2 Major Adrenocortical Abnormalities

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 Related to aldosterone deficiency: hyperkalemia; hyponatremia; hypotension (if severe enough, fatal)
Deficient cortisol	Secondary adrenocortical insufficiency	Insufficient ACTH caused by hypothalamic or anterior pituitary failure	

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, adrenocotropic hormone.

Actions of Adrenal Androgens

Females: presence of pubic and axillary hair; libido

Males: same as testosterone

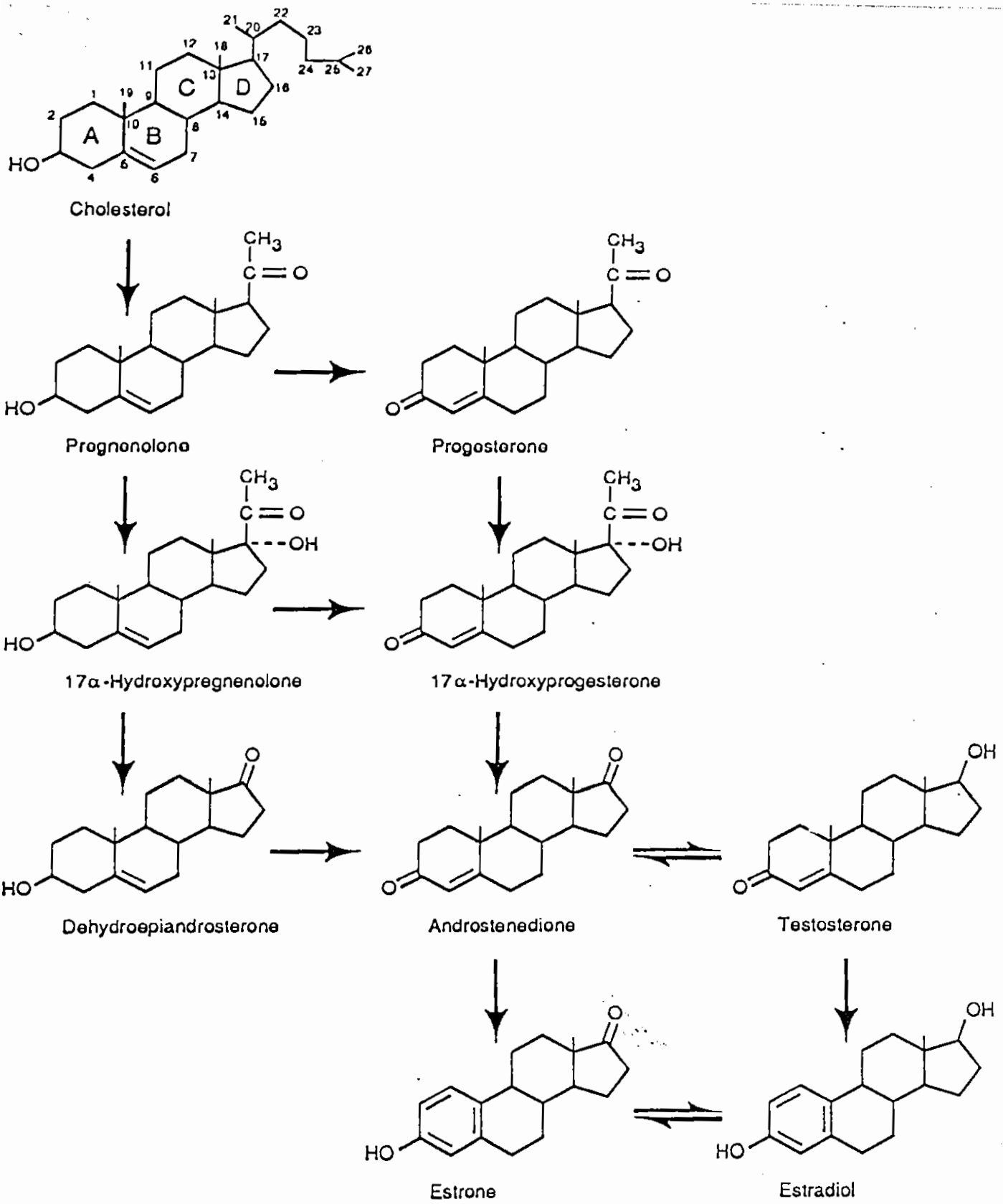


FIGURE 5
Biosynthetic pathway for androgens and estrogens. In the adrenal, the sequence does not usually proceed all the way to testosterone and the estrogens, which are the gonadal hormones. Because the cells of the zona glomerulosa lack 17α-hydroxylase, these reactions can occur only in the inner zones.

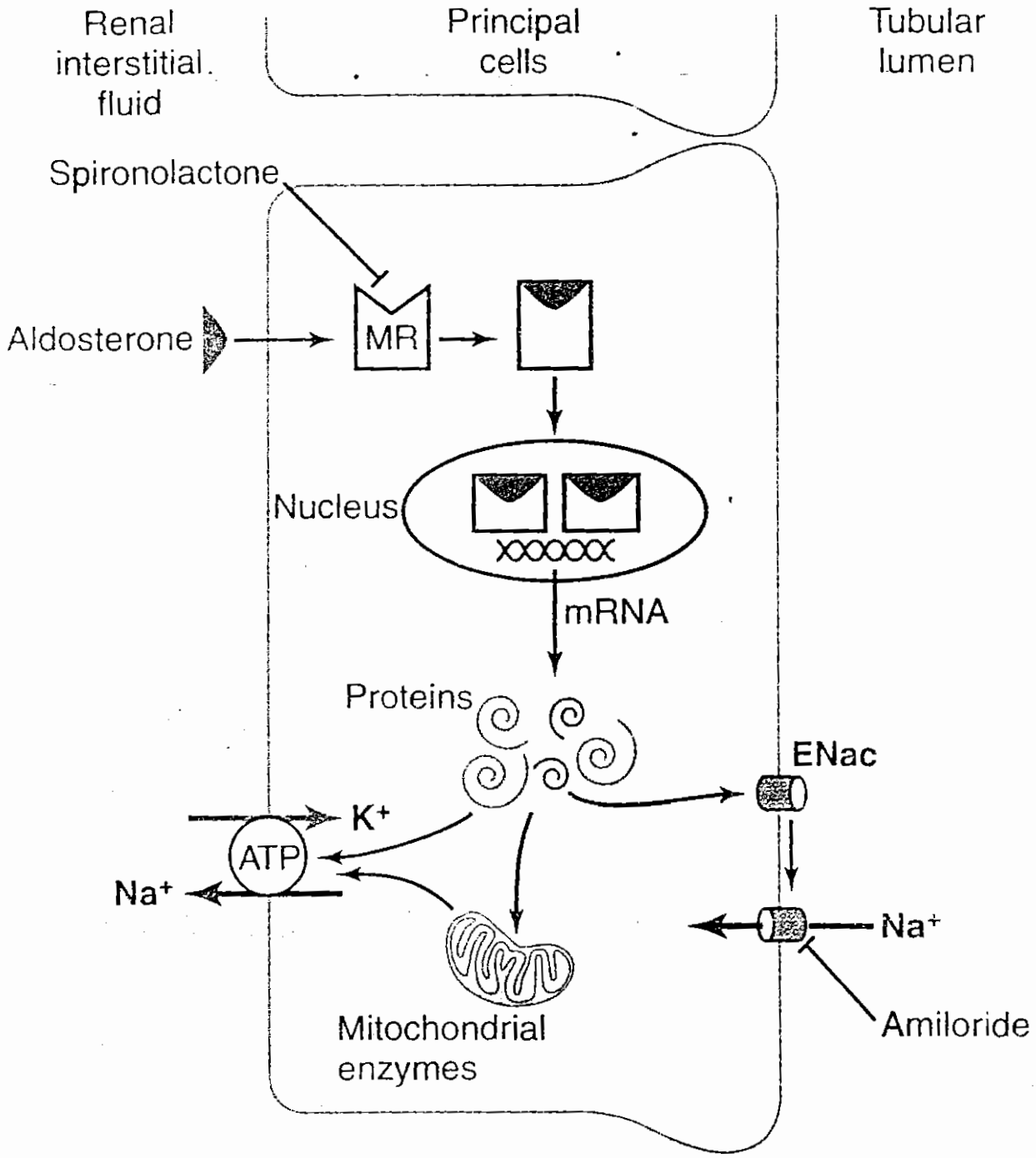


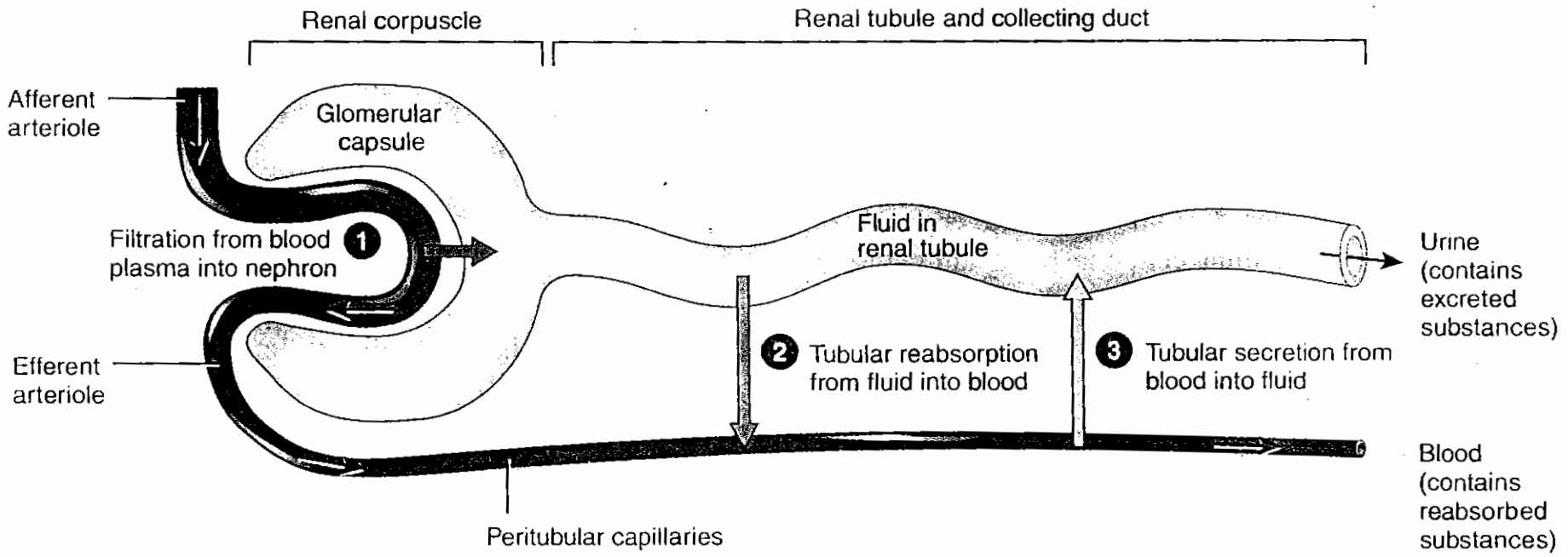
Figure 77-4 Aldosterone-responsive epithelial cell signaling pathways. ENaC, epithelial sodium channel proteins; MR, mineralocorticoid receptor. Activation of the MR by aldosterone can be antagonized with spironolactone. Amiloride is a drug that can be used to block ENaC.

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.

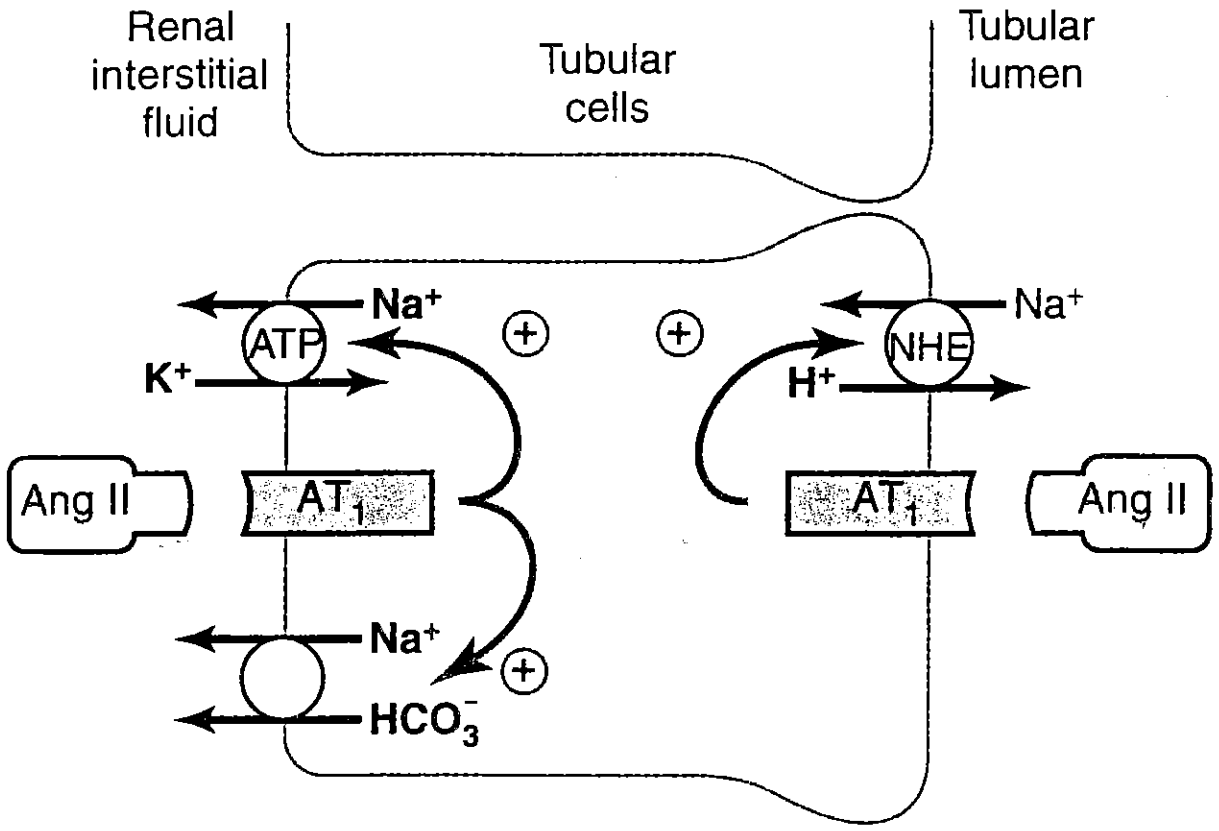
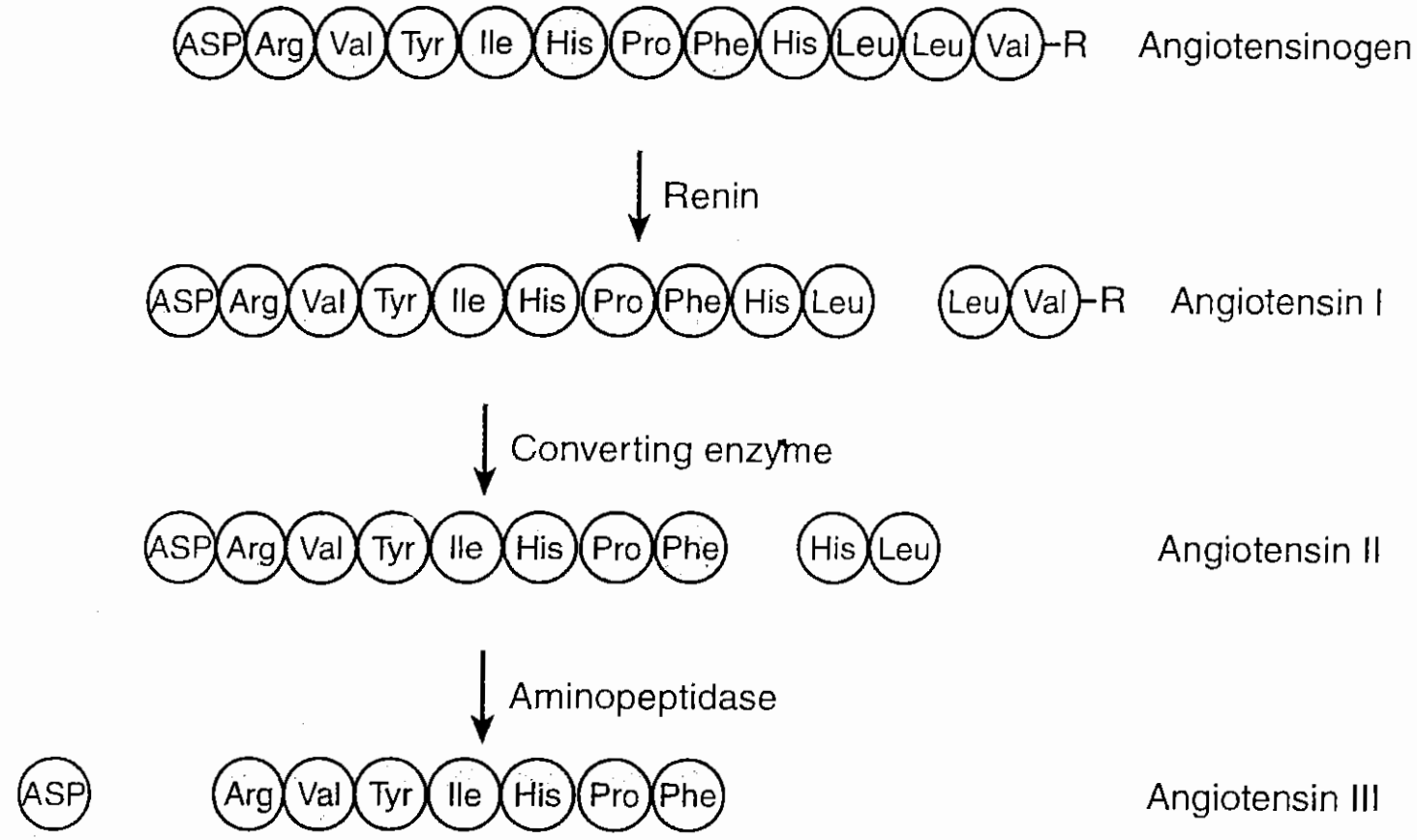


Figure 27-17 Direct effects of angiotensin II (*Ang II*) to increase proximal tubular sodium reabsorption. Ang II stimulates sodium sodium-hydrogen exchange (*NHE*) on the luminal membrane and the sodium-potassium ATPase transporter as well as sodium-bicarbonate co-transport on the basolateral membrane. 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.

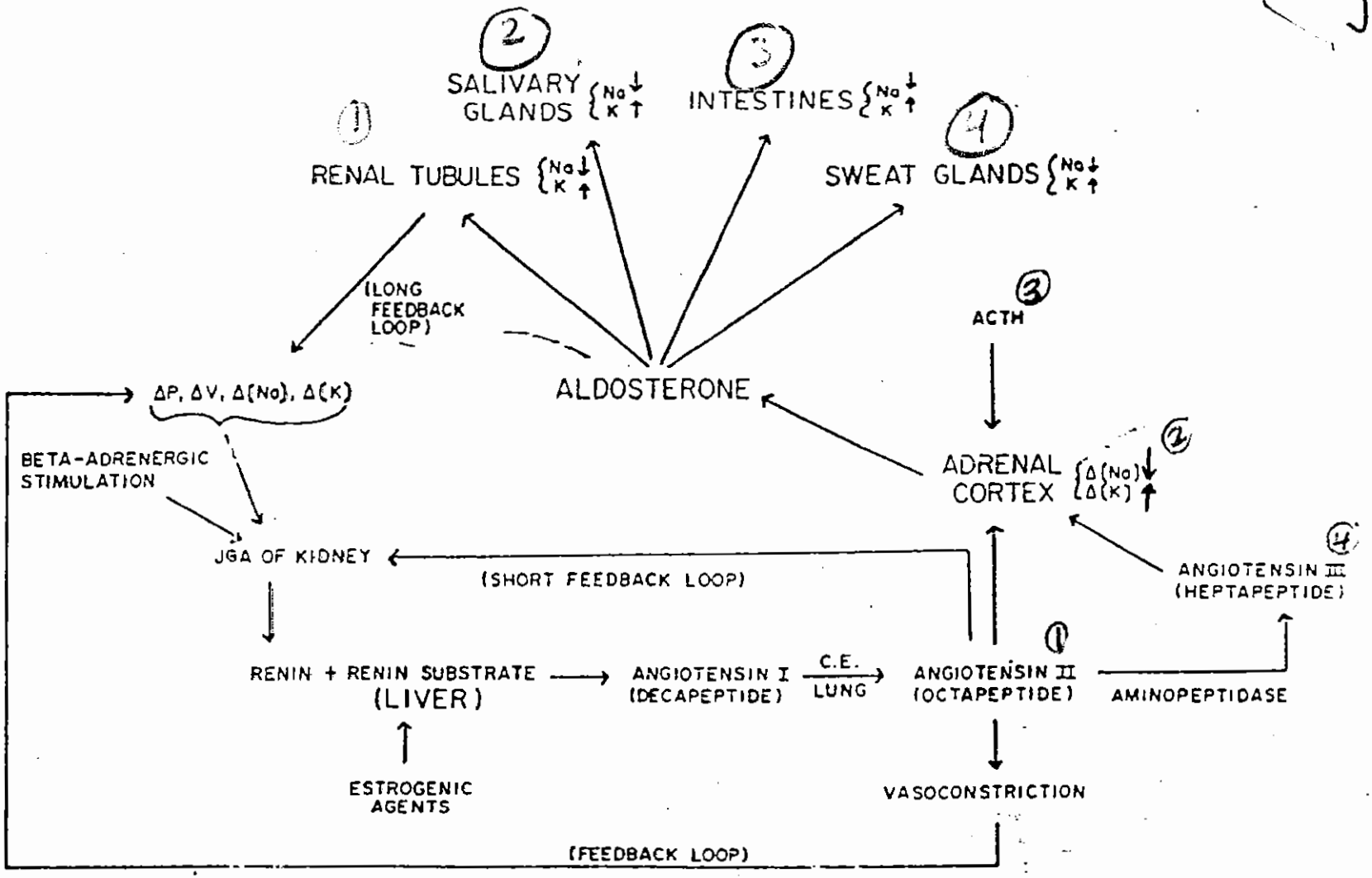


FIGURE 5-18: The physiologic factors controlling aldosterone secretion rate (C.E. = converting enzyme).

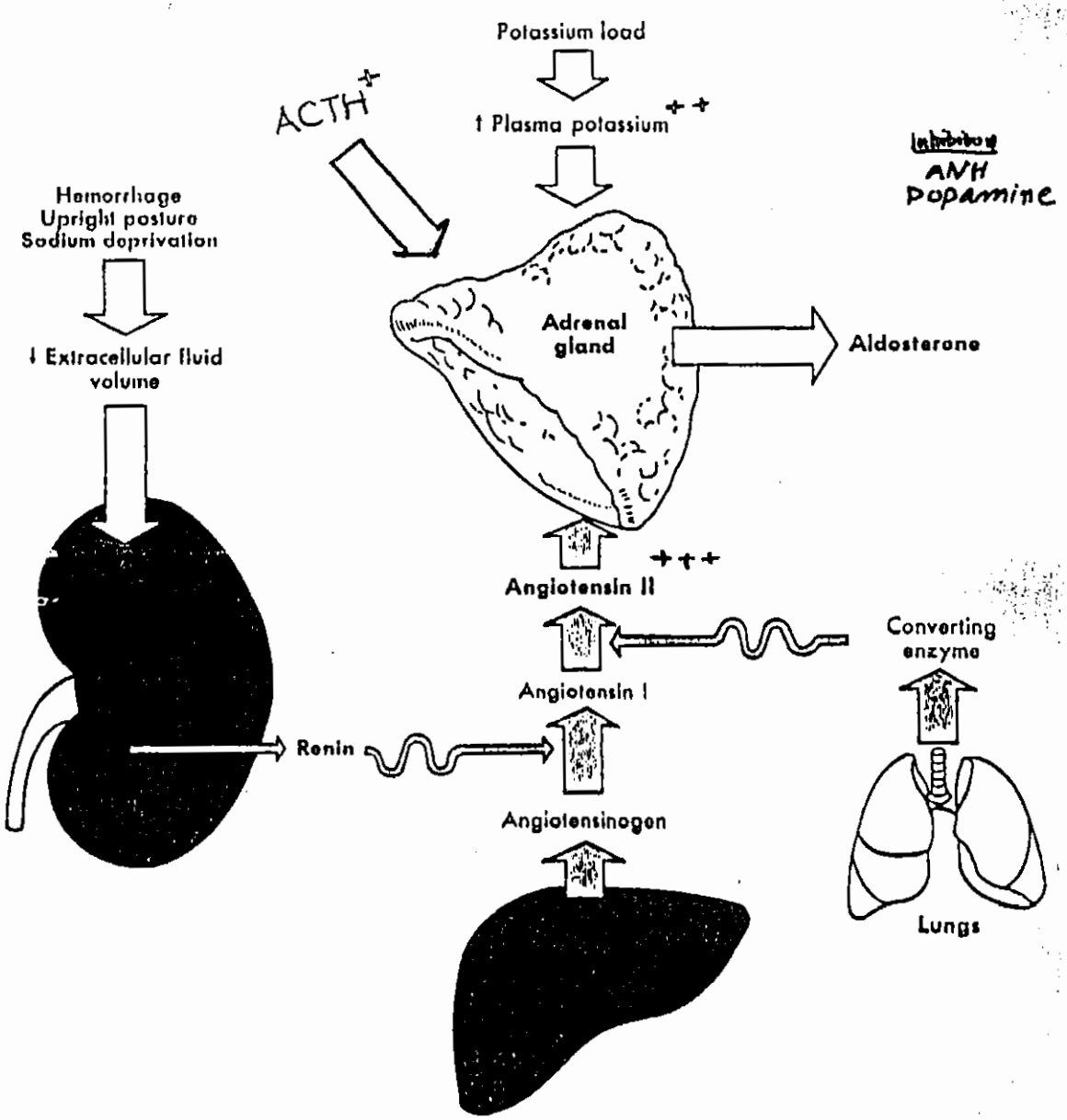


FIGURE 41-8 The regulation of aldosterone secretion. Activation of the renin-angiotensin system in response to hypovolemia is the predominant stimulus to aldosterone production. Elevation of plasma potassium is the other major stimulus.

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.

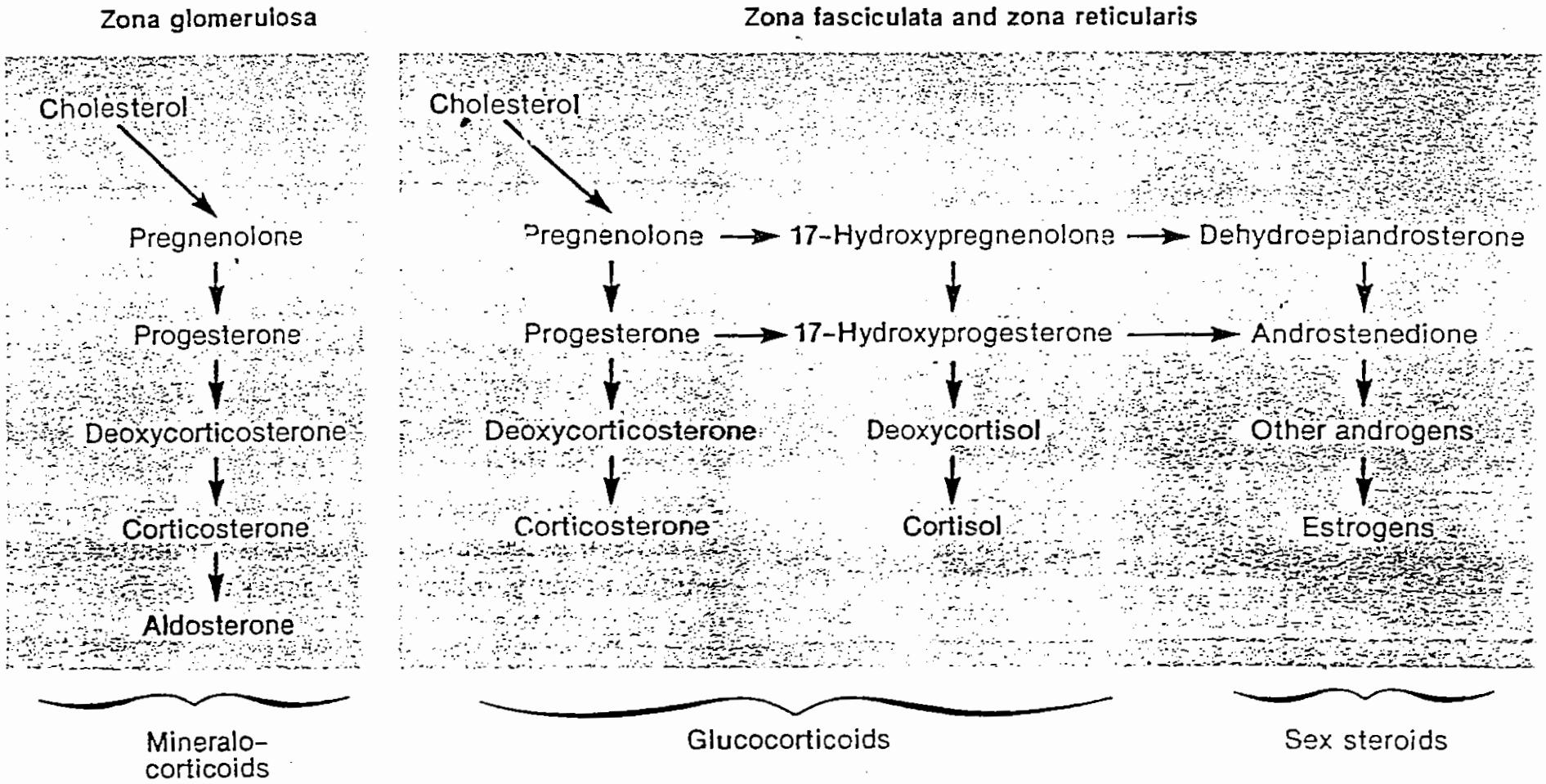


TABLE 5-3: Physiologic Actions of Glucocorticoid Hormones

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		

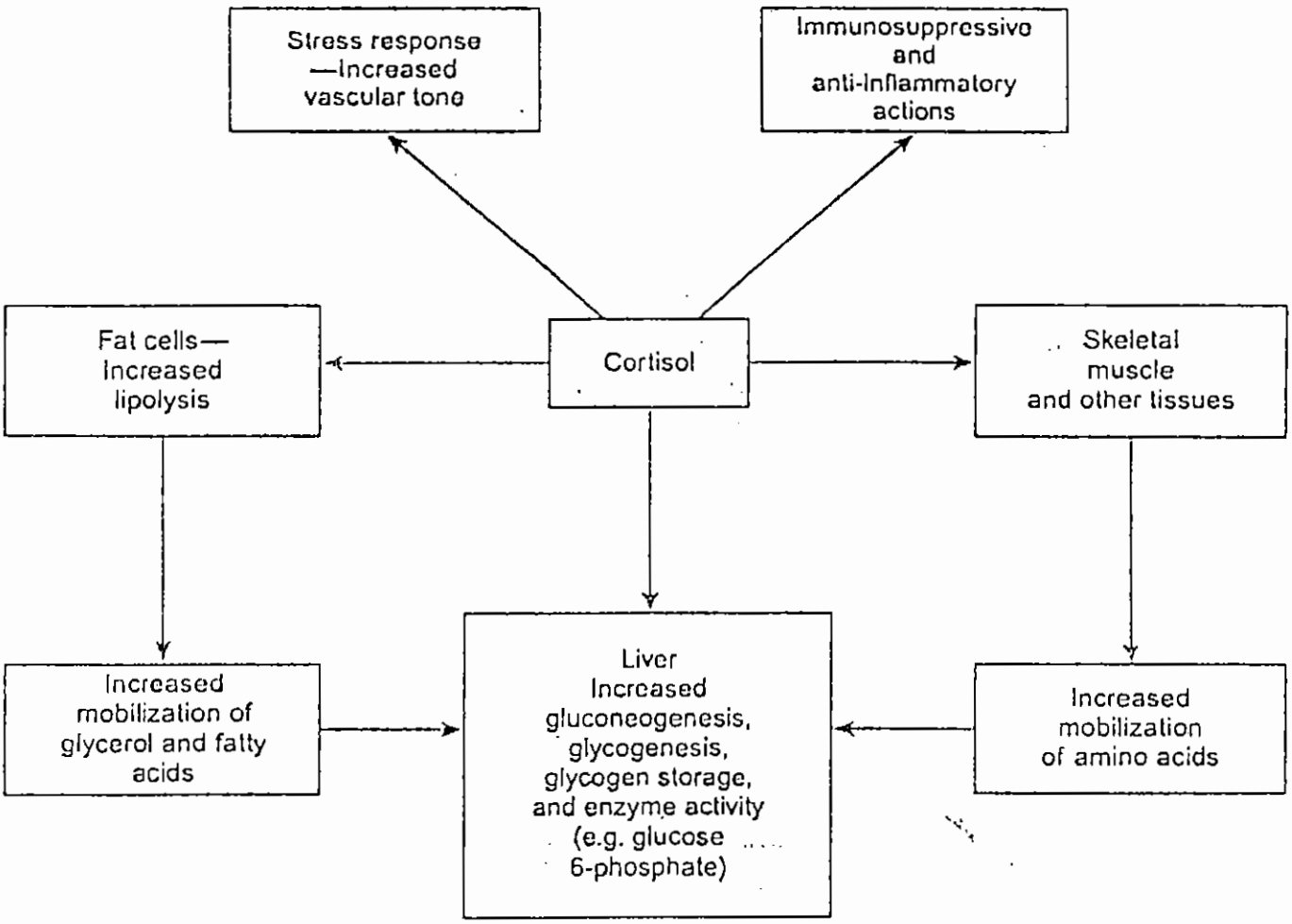


Fig. 12.18 The principal physiological actions of the glucocorticoid hormone, cortisol.

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)

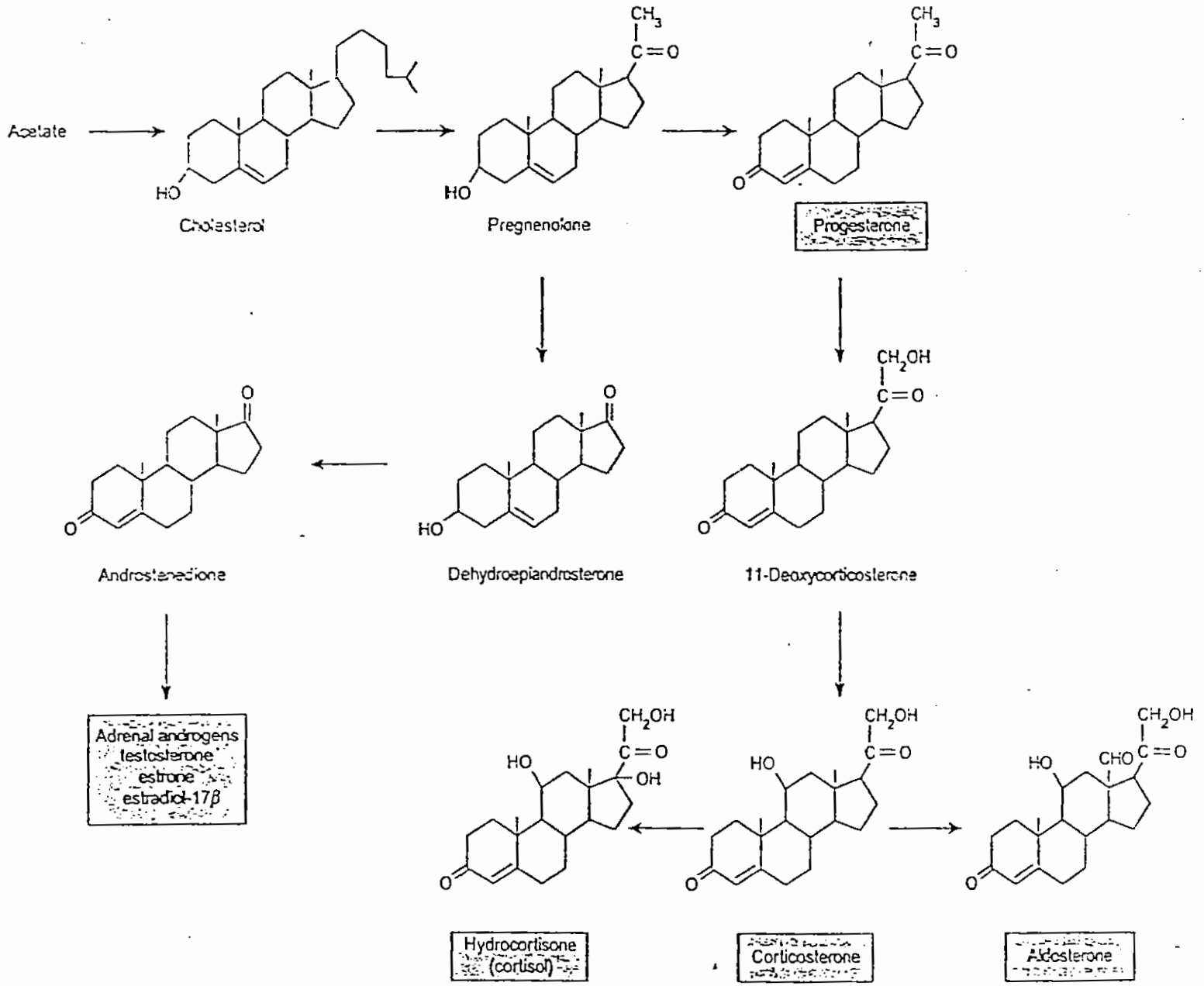


Fig. 12.17 The principal steps in the synthesis of the adrenal steroid hormones from cholesterol. Cortisol is the principal glucocorticoid and aldosterone is the principal mineralocorticoid.

Table 5.4.2 Plasma protein binding of corticosteroids

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

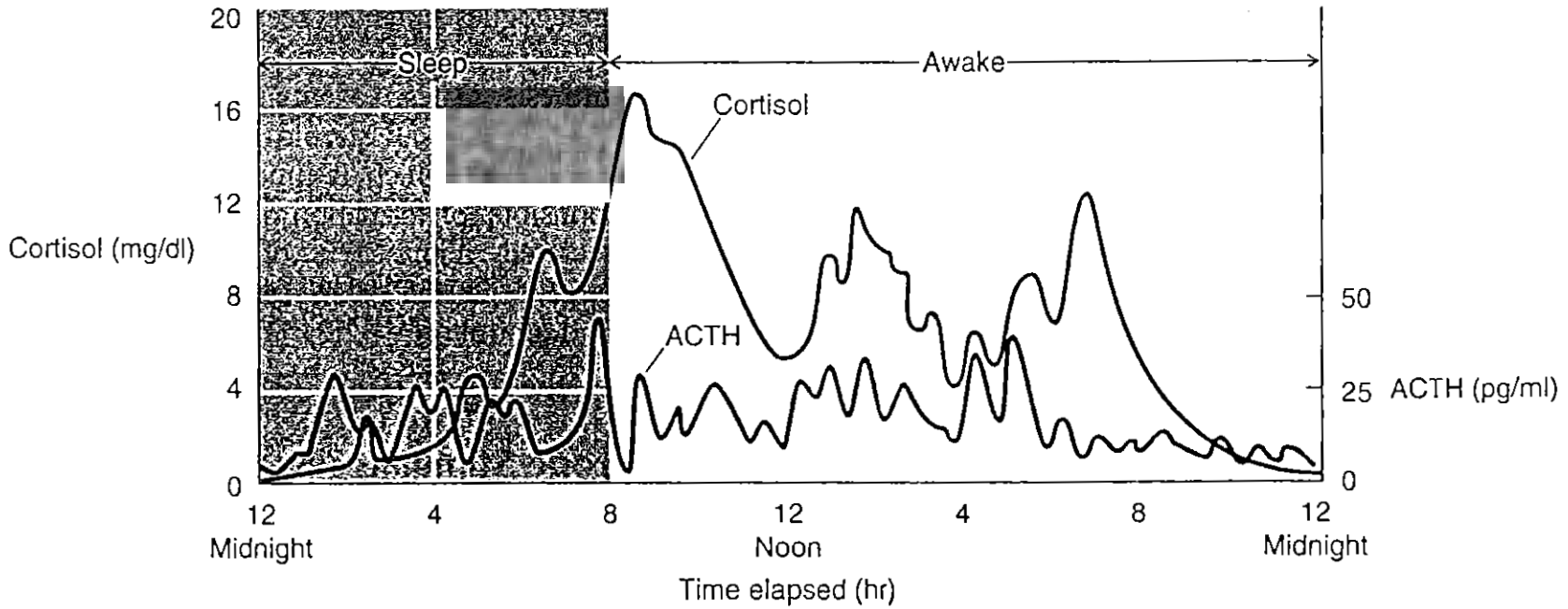


FIGURE 49–5. Rhythm of ACTH and cortisol. The corticotrophs release ACTH in a circadian rhythm, greater in the early morning hours and less late in the afternoon and early evening. Superimposed on the circadian rhythm is the effect on the corticotrophs of the pulsatile secretion of CRH by the hypothalamus. 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.)

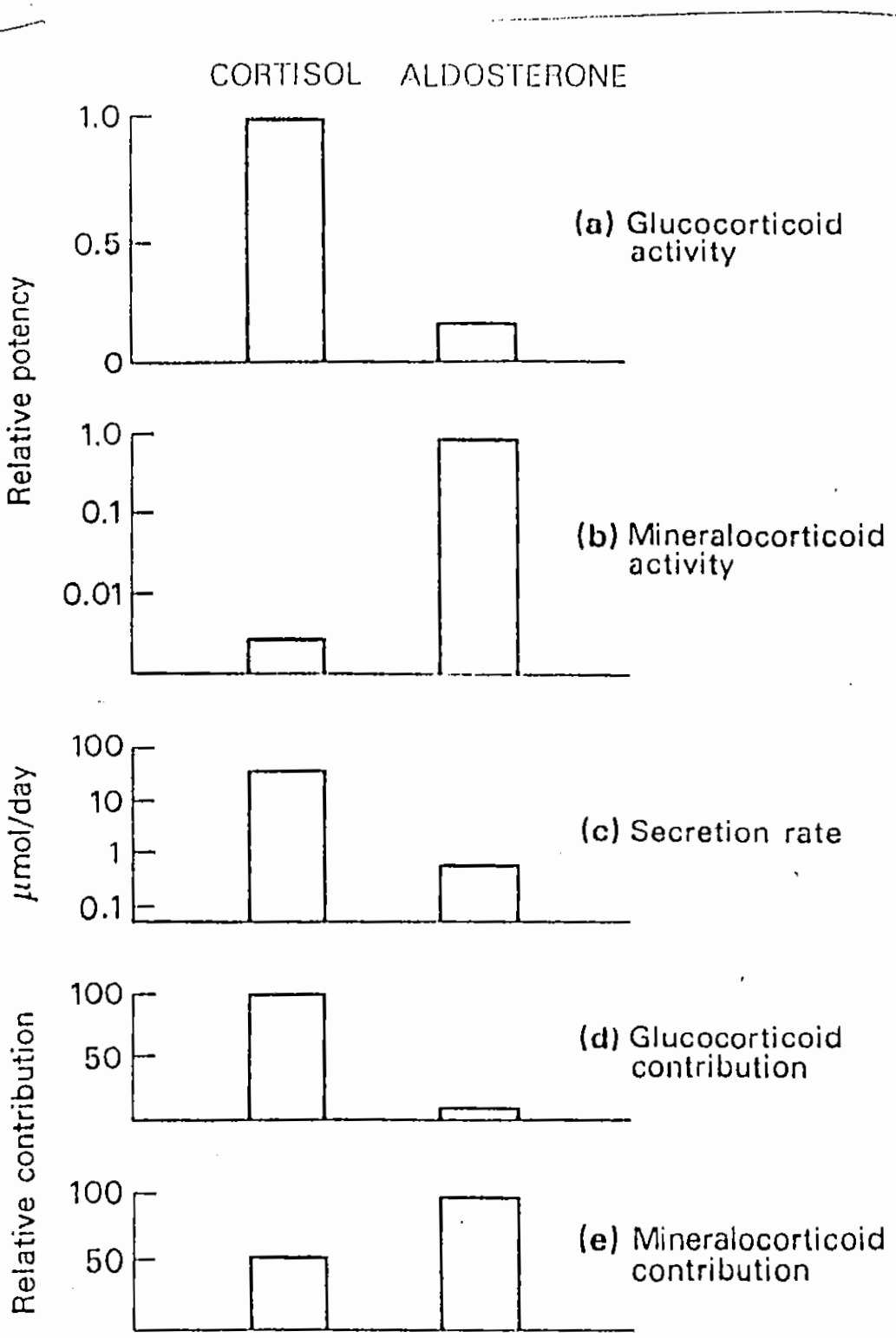


Fig. 3.5 A comparison of cortisol and of aldosterone. Glucocorticoid activity was measured as ability to increase glycogen in the liver: cortisol is very potent in this assay. Mineralocorticoid effects were measured in terms of the ability to reduce the ratio of the excretion of sodium to the excretion 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).

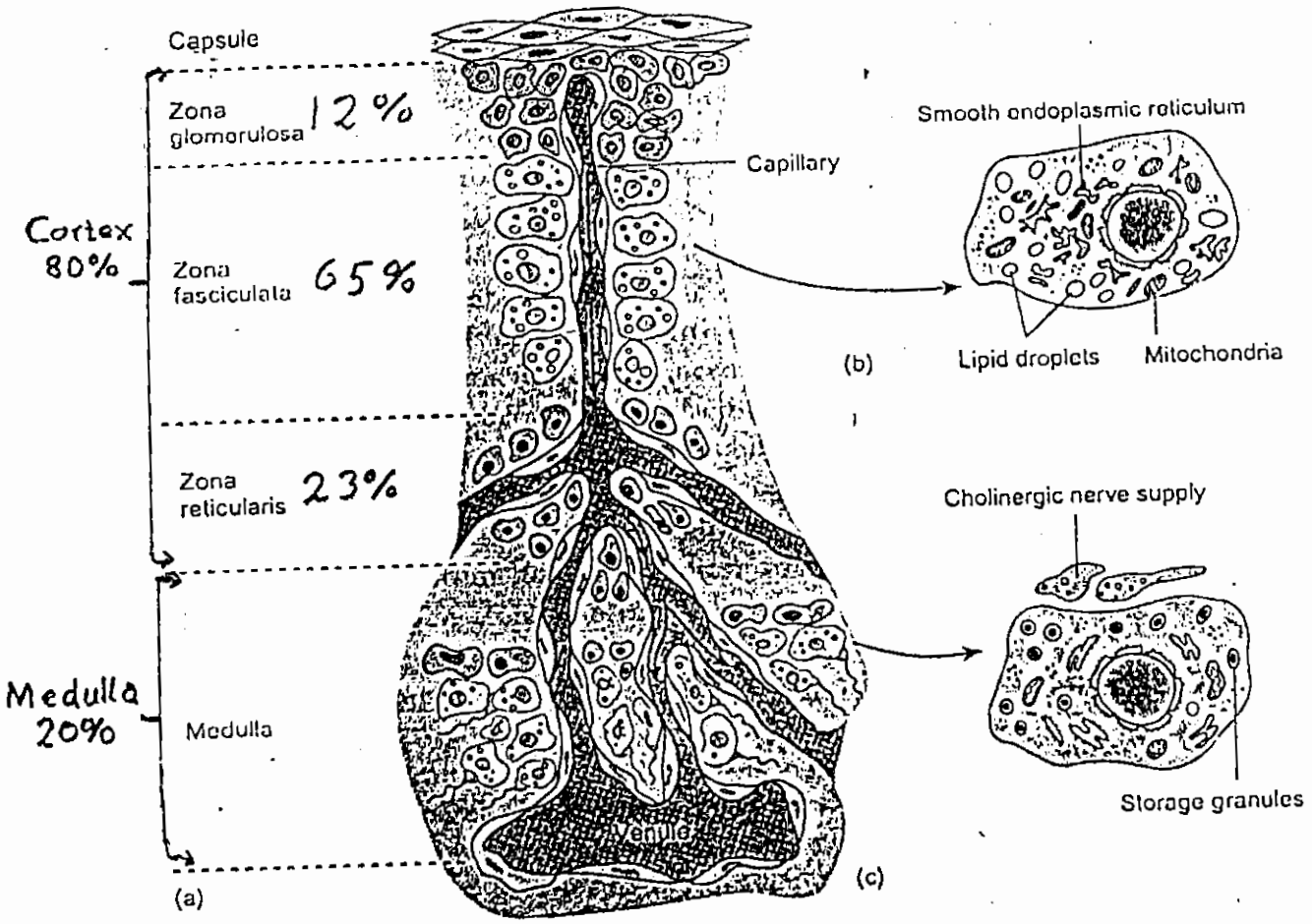


Fig. 12.16 (a) A diagrammatic representation of a section through the cortex and medulla of the adrenal gland. Note the three zones of the adrenal cortex, the cells of which secrete steroid hormones. (b) The appearance of steroid-secreting cells. (c) A single catecholamine-secreting chromaffin cell.

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.

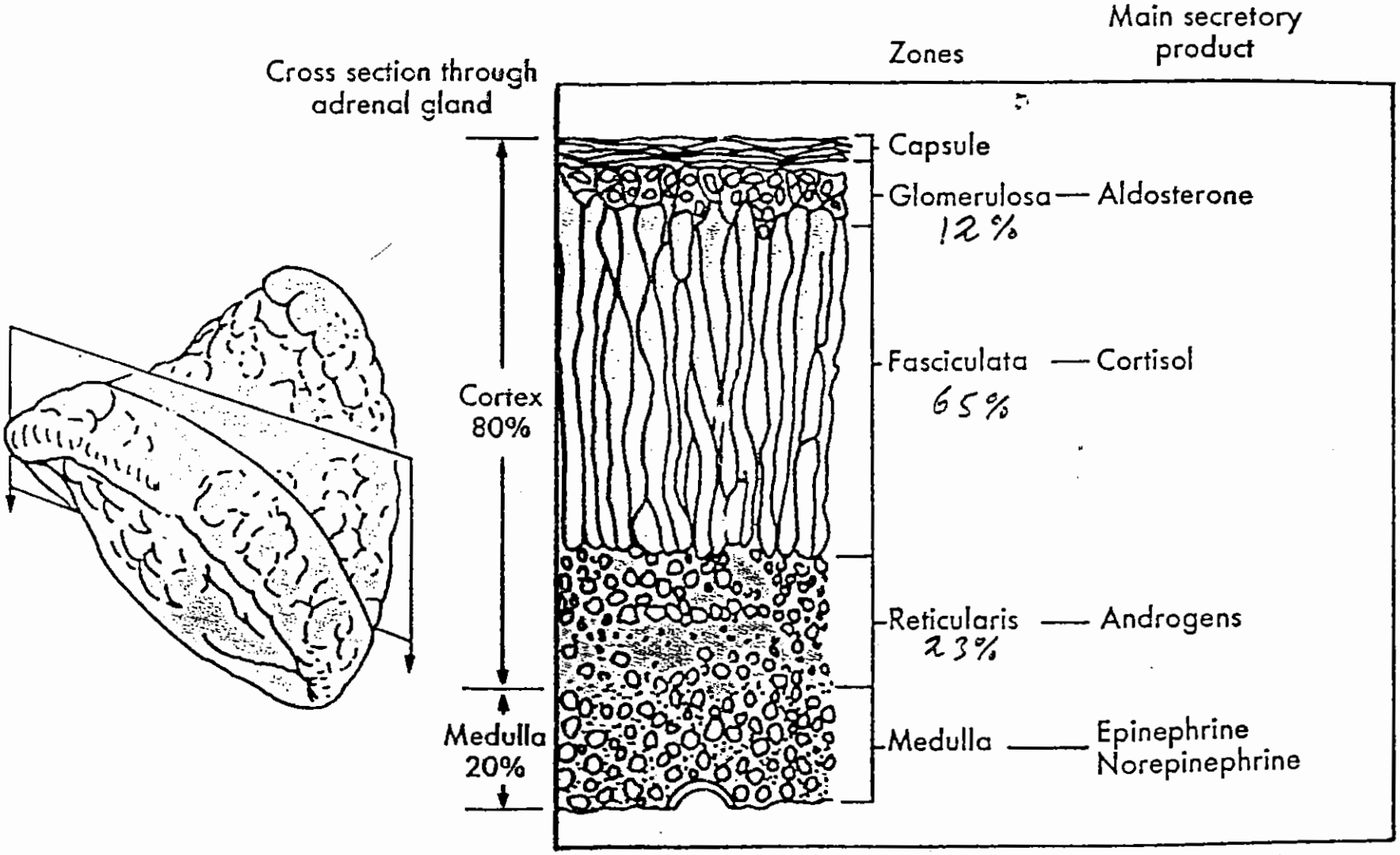


FIGURE 41-1 Schematic representation of the adrenal gland and its main secretory products.

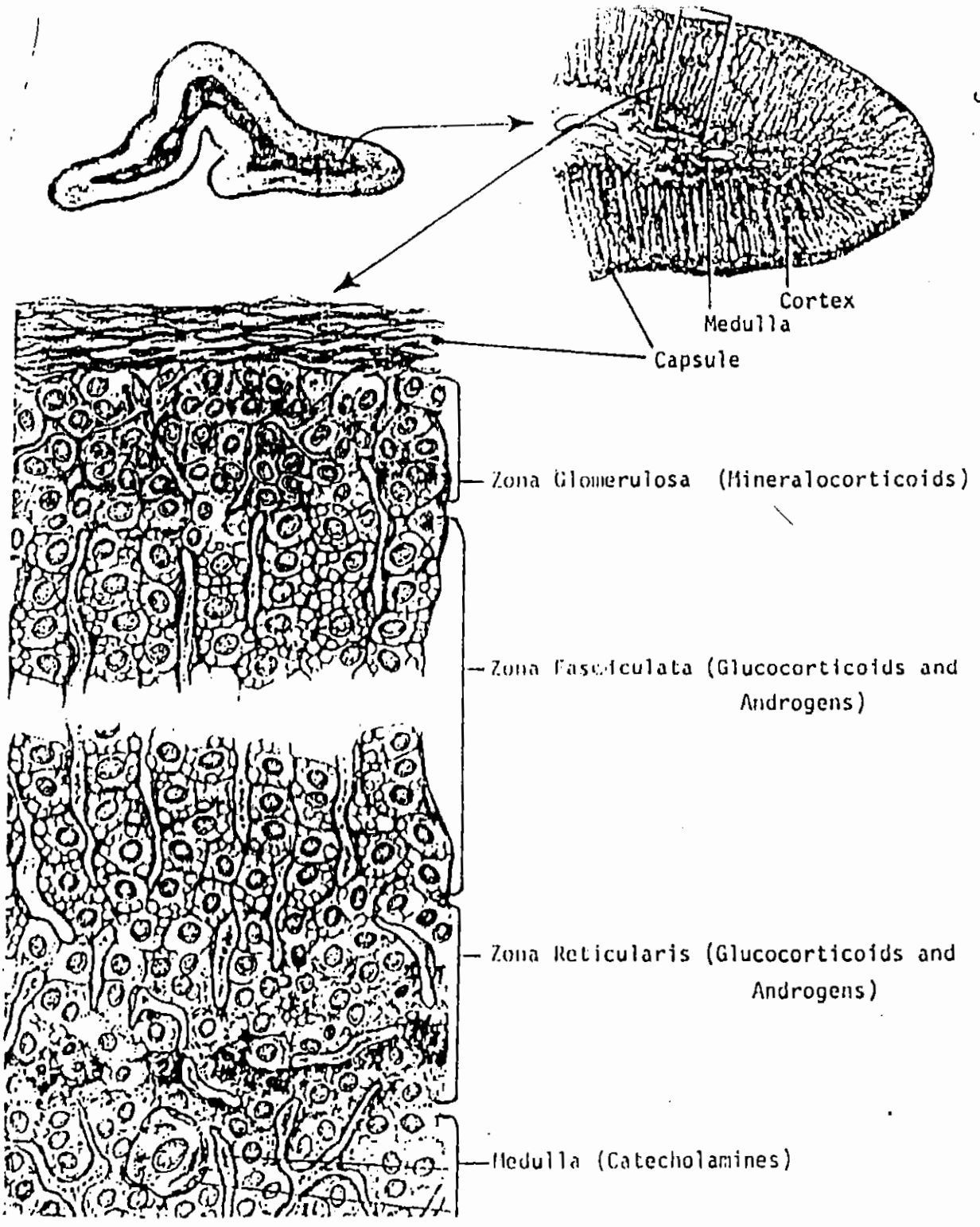


FIGURE 5-1: Cross section through the adrenal, illustrating the major subdivisions and cell layers as well as their hormonal products. (*Adapted from:* Ham and Cormack, 1970.)

" Adrenal Glands "

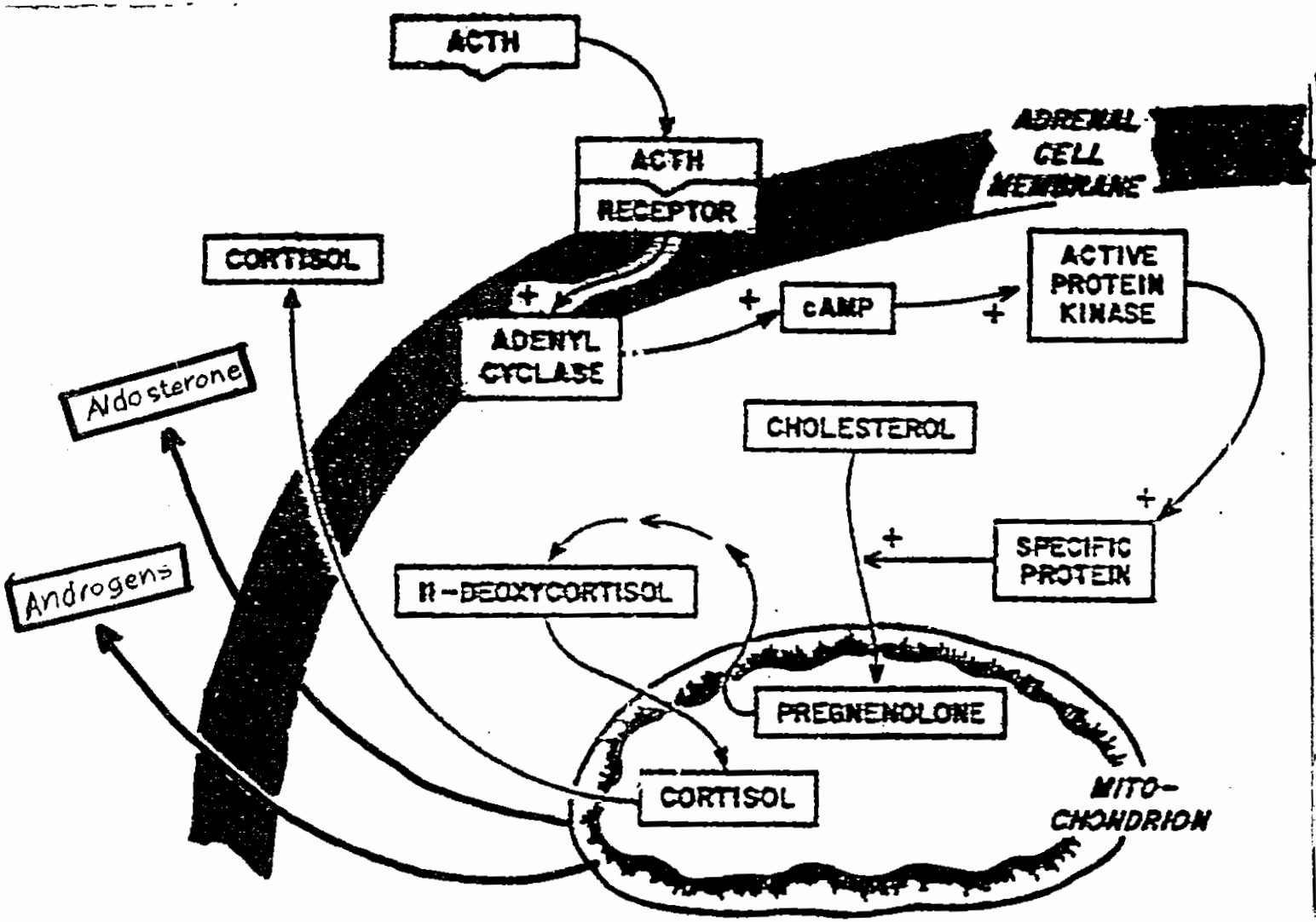
* The adrenal gland is made up of two distinct organs, the adrenal cortex and adrenal medulla, which differ in their histological structure, anatomy, development and functions. Their total weight is 6–10 g.

* 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.



* 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

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

S.K

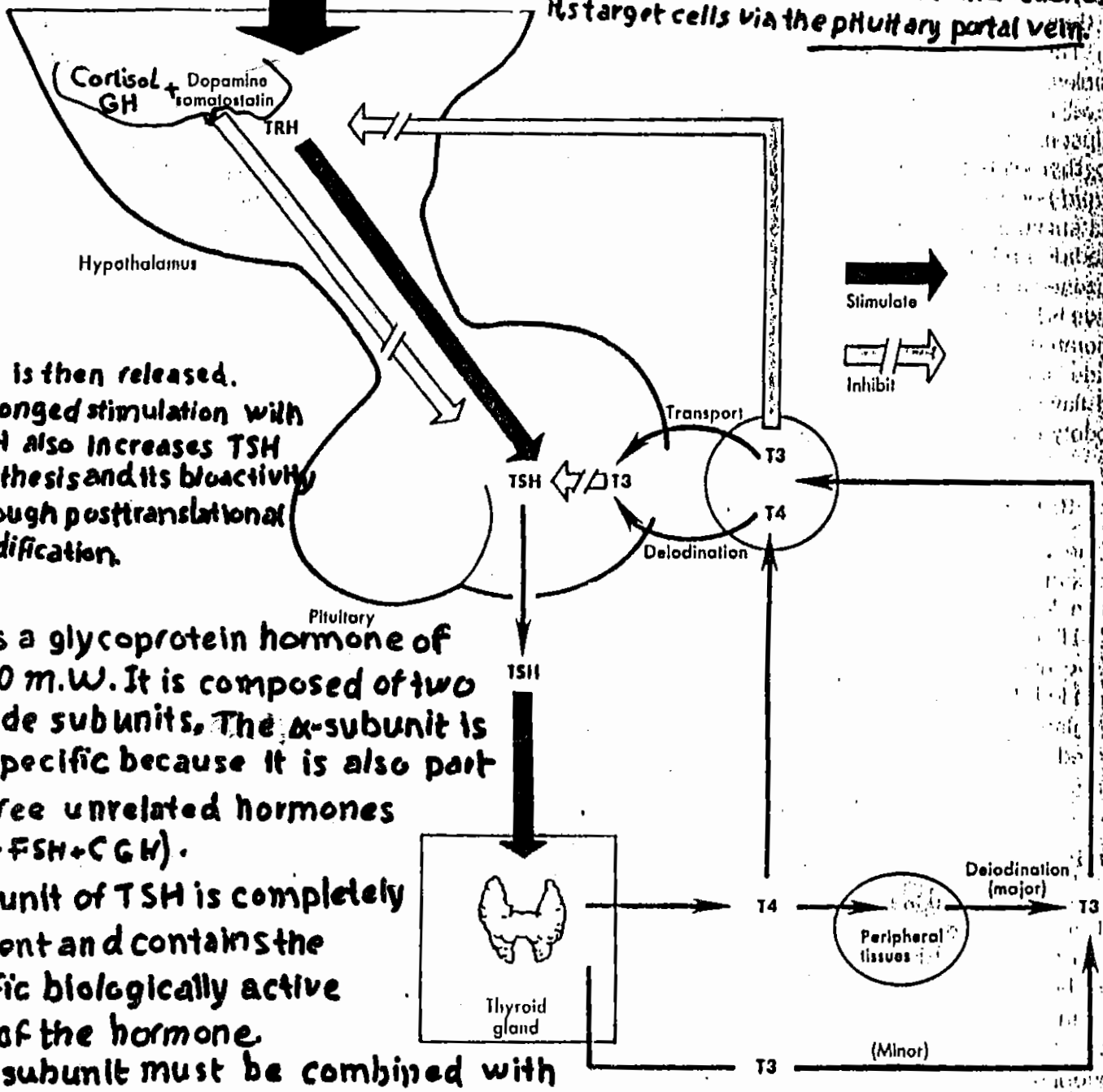


FIGURE 40-4 The hypothalamic–pituitary gland–thyroid gland axis. Thyrotropin-releasing hormone *(TRH)* stimulates thyrotropin *(TSH)* release from the pituitary gland. TSH stimulates T_4 and to a minor degree T_3 secretion by the thyroid gland. T_3 arising from T_4 in peripheral tissues or within the pituitary gland itself blocks the effect of TRH and suppresses TSH release by negative feedback. Dopamine and somatostatin also tonically inhibit TSH release.

① TRH is a tripeptide, its synthesis in the hypothalamus

② TRH is stored in the median eminence and reaches its target cells via the pituitary portal vein.

③ TSH is then released. Prolonged stimulation with TRH also increases TSH synthesis and its bioactivity through posttranslational modification.

SH is a glycoprotein hormone of
B,000 m.W. It is composed of two
eptide subunits. The α-subunit is
ionspecific because it is also part
f three unrelated hormones
(L·H+FSH+CGH).
-subunit of TSH is completely
ifferent and contains the
pecific biologically active
ites of the hormone.
e β-subunit must be combined with
subunit for
H to
nulate
yroid cells.

④ Cortisol and growth hormone reduce TSH secretion probably by stimulating somatostatin release.

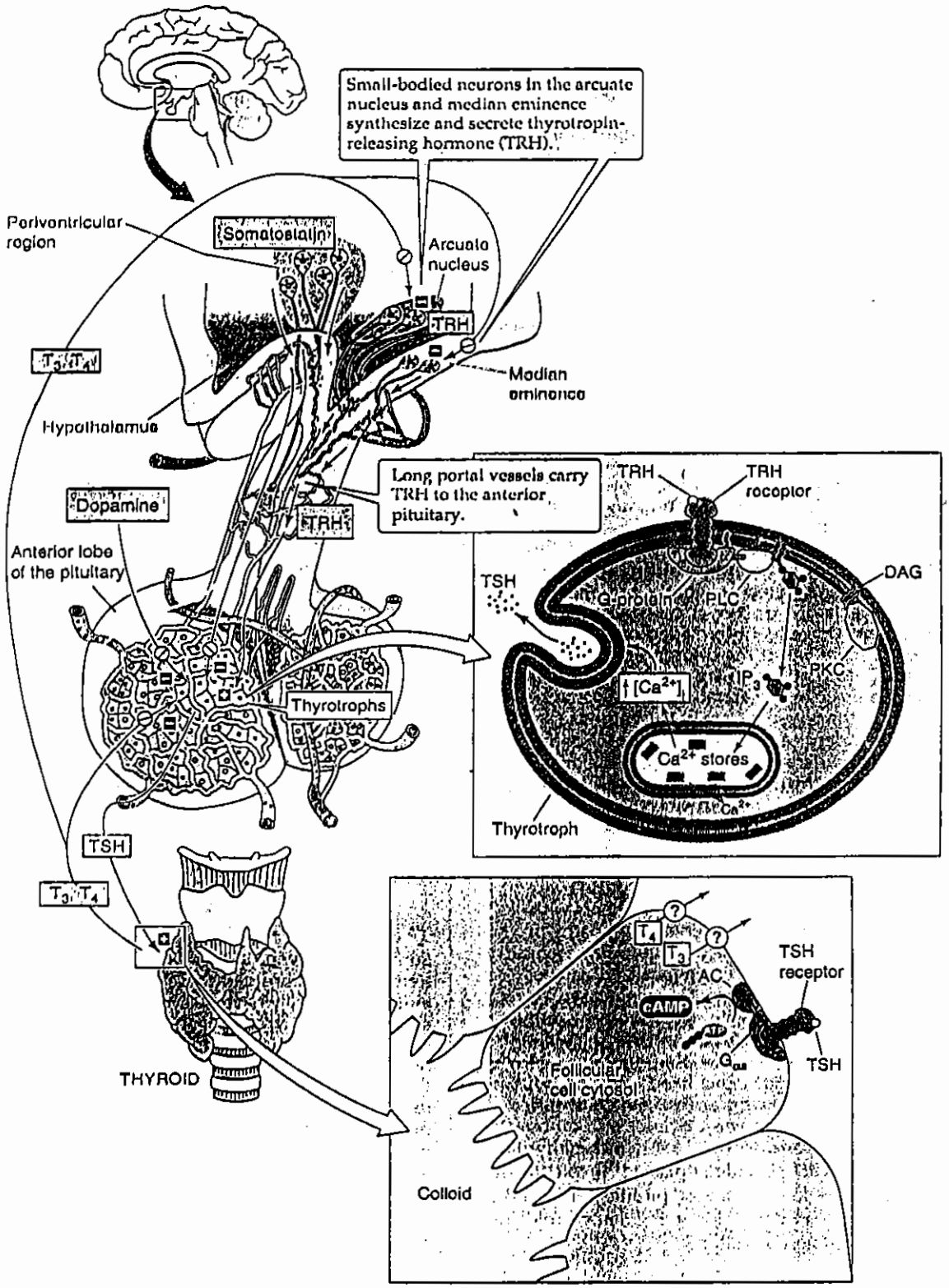


FIGURE 48–9. The hypothalamic-pituitary-thyroid axis. Small-bodied neurons in the arcuate nucleus and median eminence of the hypothalamus secrete thyrotropin-releasing hormone (TRH), a tripeptide that reaches the thyrotrophs in the anterior pituitary via the long portal veins. TRH binds to a G protein–coupled receptor on the thyrotroph membrane, triggering the DAG/IP_3 pathway, leading to protein phosphorylation and raising $[Ca^{2+}]_i$. These pathways stimulate the thyrotrophs to synthesize and release thyrotrophin (or thyroid-stimulating hormone [TSH]), which is a 28-kDa glycoprotein stored in secretory granules. The TSH binds to receptors on the basolateral membrane of thyroid follicular cells, stimulating $G\alpha_s$, which in turn activates adenylyl cyclase and raises $[cAMP]_i$. As outlined in Figure 48–3, TSH stimulates a number of steps in the synthesis and release of T_4 and T_3. Inside the pituitary, the type-2 form of 5′/3′-monodeiodinase converts T_4 to T_3, which negatively feeds back on the thyrotrophs as well as on the TRH-secreting neurons. Somatostatin and dopamine—released by hypothalamic neurons—inhibit TSH release and thus can influence the "set point" at which TSH is released in response to a given amount of T_3 in the pituitary. AC, adenylyl cyclase; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP_3, inositol triphosphate; PKC, protein kinase C; PLC, phospholipase C.

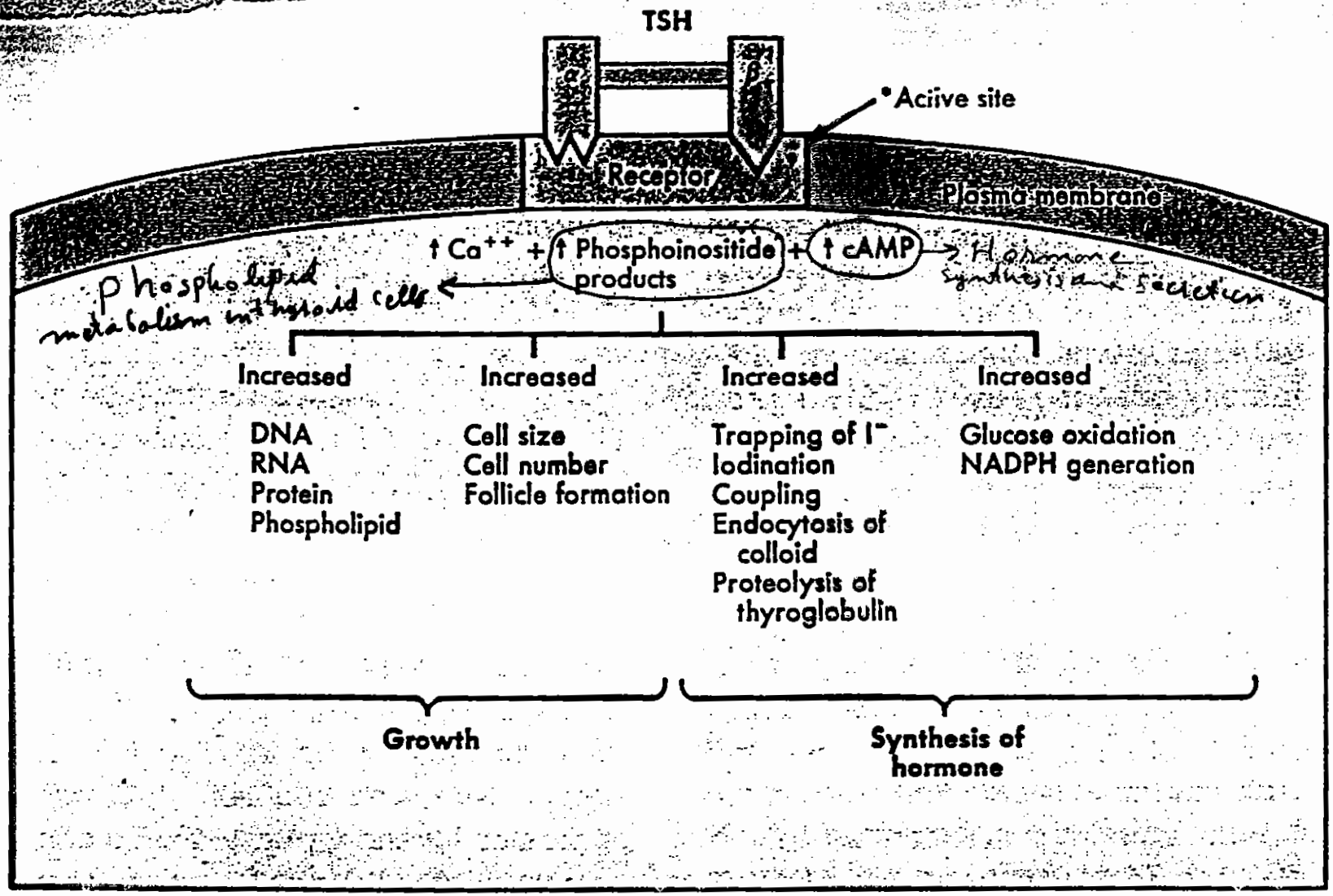


FIGURE 40-5 TSH actions on the thyroid cell. Cyclic adenosine monophosphate *(cAMP)* along with calcium ions *(Ca^{++})* and phosphoinositol products act as second messengers generated by TSH binding to its receptor. All steps in thyroid hormone production, as well as many aspects of thyroid cell metabolism and growth, are stimulated by TSH.

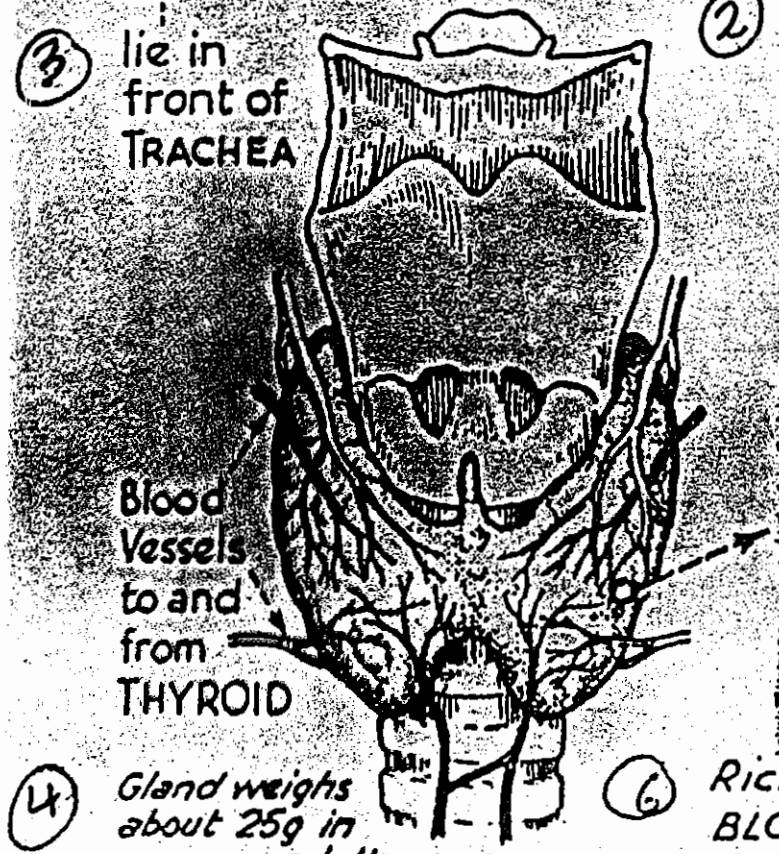
THYROID

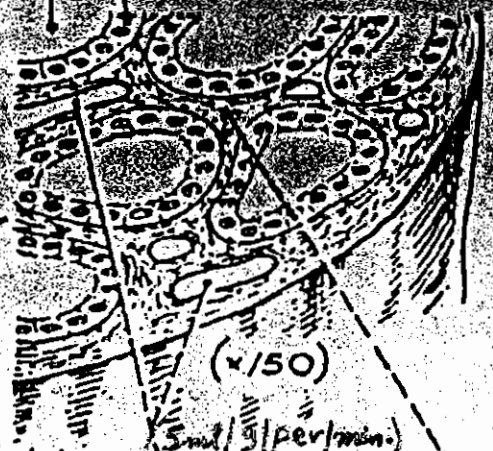
STRUCTURE:

(1) 2 LOBES (joined by ISTHMUS) composed of

(2) FOLLICLES lined by CUBICAL EPITHELIUM (NO DUCTS)

(3) lie in front of TRACHEA





(4) Gland weighs about 25g in adult

(6) Richly supplied with BLOOD CAPILLARIES

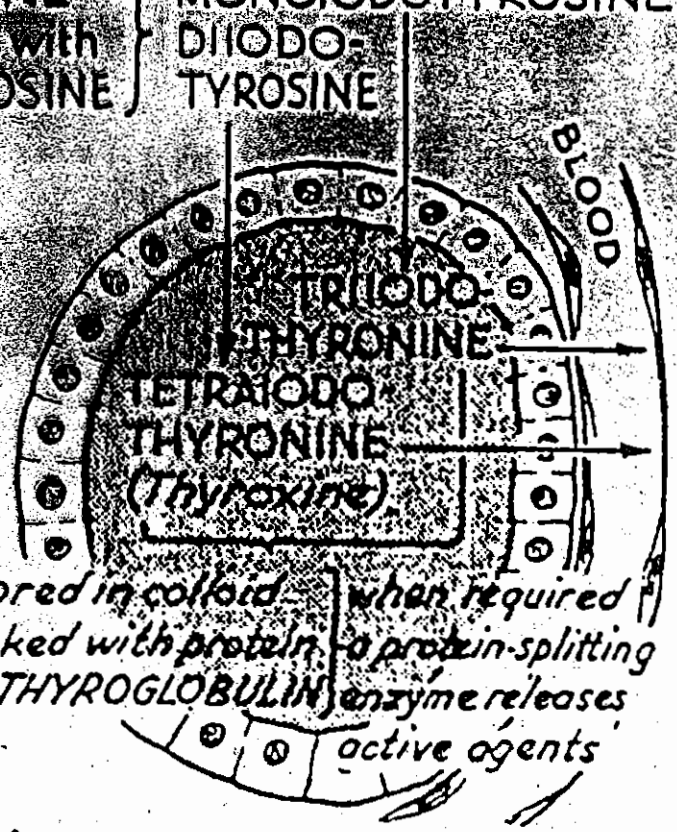
(5) PARAFOLLICULAR or "C" CELLS → Calcitonin ↓ Ca^{++} plasma level

FUNCTION:

CUBICAL EPITHELIUM extracts from the Blood stream (and concentrates) INORGANIC IODIDE

↓

IODINE links with TYROSINE } MONOIODOTYROSINE, DIIODOTYROSINE



Stored in colloid linked with protein as THYROGLOBULIN

when required a protein-splitting enzyme releases active agents

By 12 weeks of human gestation, the gland is capable of synthesizing and secreting thyroid hormones under the stimulus of the fetal hypothalamus and pituitary gland. This entire axis is required for subsequent normal intrauterine development of the central nervous system and skeleton because neither maternal thyroid hormone nor its pituitary stimulating hormone can cross the placenta.

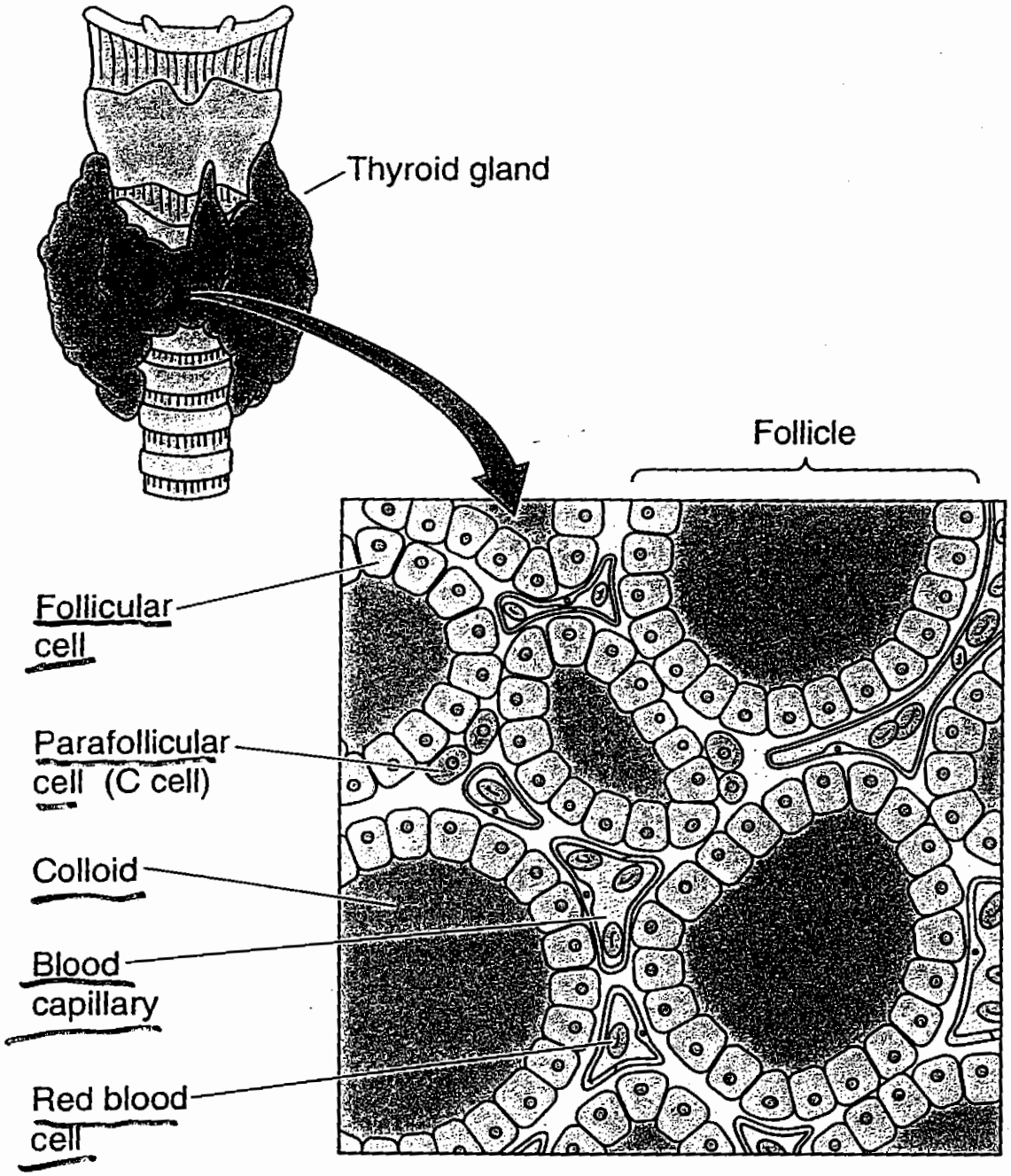


FIGURE 48–1. Structure of the thyroid gland. The thyroid gland is located anterior to the cricoid cartilage in the anterior neck. The gland comprises numerous follicles, which are filled with colloid and lined by follicular cells. These follicular cells are responsible for the trapping of iodine and the synthesis of thyroglobulin, which contains thyroid hormone as part of its primary structure. These cells also secrete thyroglobulin—the major protein of the thyroid colloid—into the lumen of the follicle. The thyroglobulin protein that is stored in the follicular lumen contains numerous iodinated tyrosines and thyronines, which are derivatives of the amino acid tyrosine. On command, the follicular cells take up the thyroglobulin and release the thyroid hormones triiodothyronine (T_3) and thyroxine, or tetraiodothyronine (T_4), into the blood.

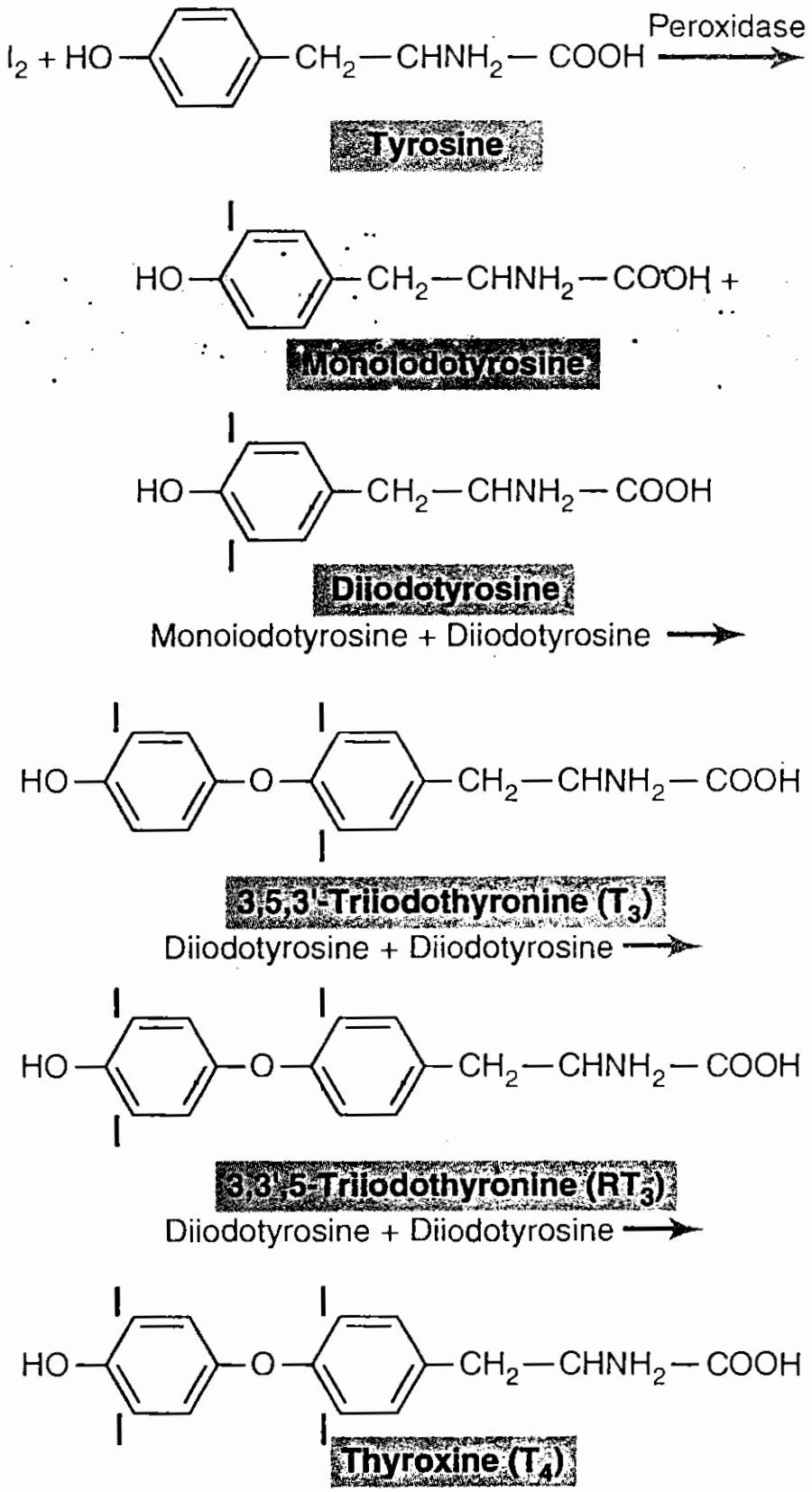


Figure 76-3 Chemistry of thyroxine and triiodothyronine formation.

(1)

Thyroid hormones are unique in that they incorpo-
te an inorganic element, iodine, into an organic
ructure made up of two molecules of the amino acid
rosine. (2) The secretory products of the thyroid gland
e known as iodothyronines (T_4, T_3, rT_3).

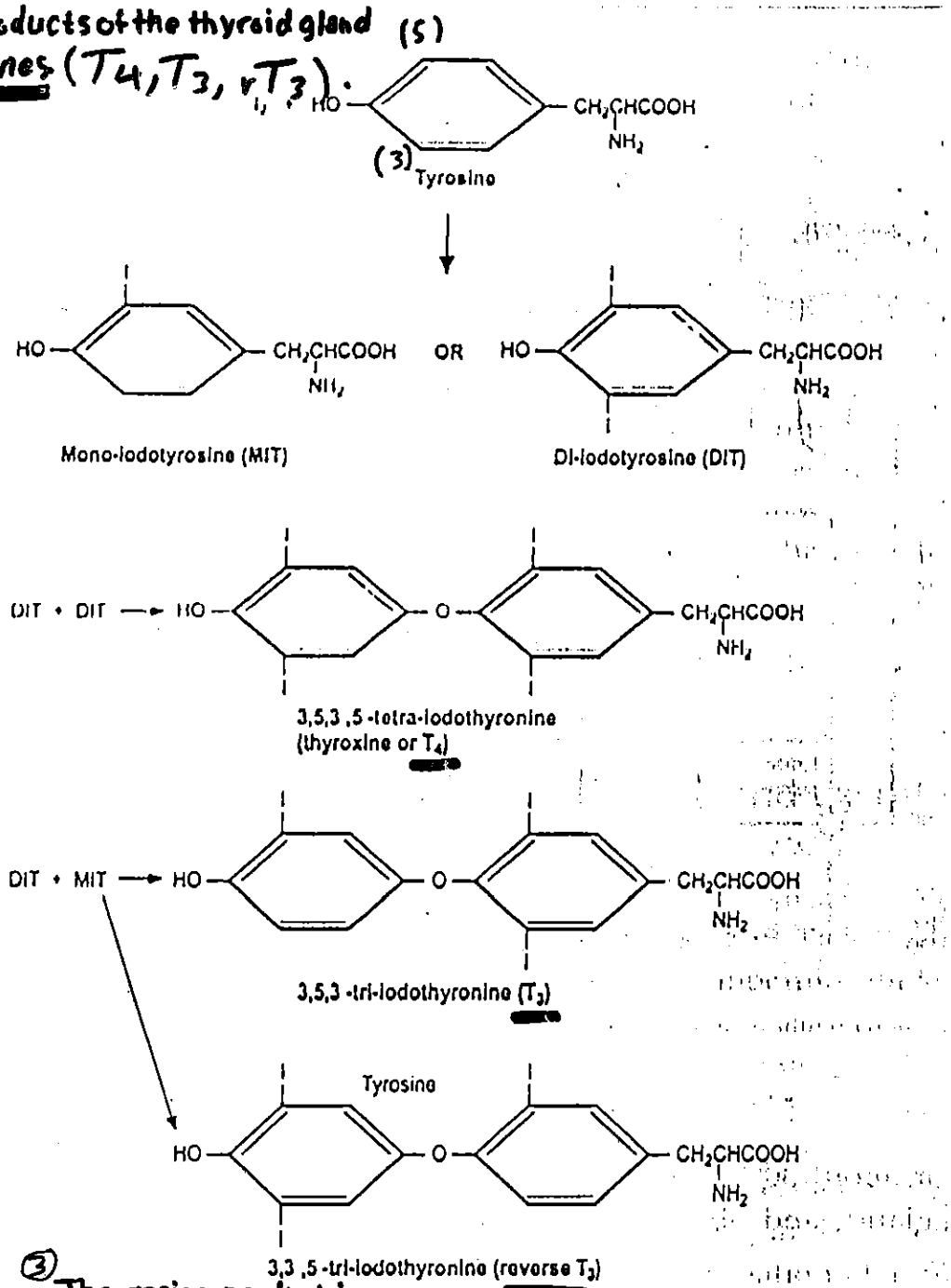
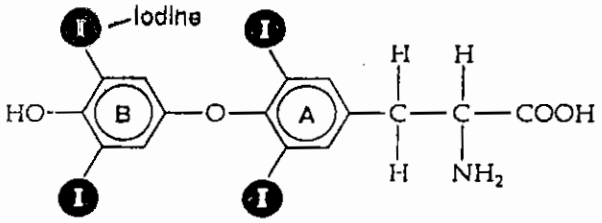


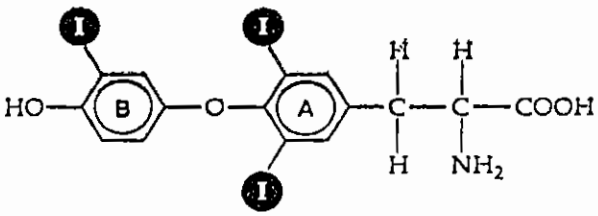
Fig. 5.3.4 Pathway of thyroid hormone synthesis.

(3) The major product is
,3',5'-tetraiodothyronine, known as thyroxine and
erred to as T_4. (4) This molecule functions largely as a
culating prohormone. (5) Secreted in much less quan-
y is 3,5,3'-triiodothyronine, known simply as triio-
thyronine and referred to as T_3. (6) This molecule
hich provides virtually all thyroid hormone activity
target cells, is actually produced mostly in periph-
l tissues from the prohormone T_4. (7) A trivial secre-
y product with no identified hormonal action is
',5'-triiodothyronine. This is known as reverse T_3 or rT_3, because it differs from T_3 only in the
ation of one of the three iodine atoms. This is inactive alternate product of
the prohormone T_4.

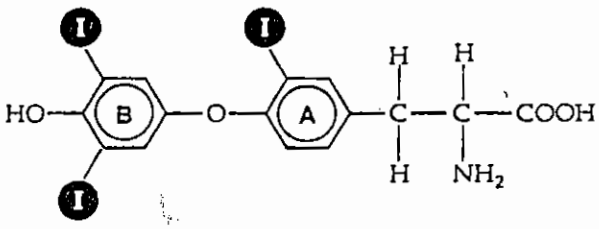
Thyroxine (T_4) (3,5,3',5'-tetraiodo-L-thyronine)



Triiodothyronine (T_3) (3,5,3',-triiodo-L-thyronine)



Reverse T_3 (rT_3) (3,3',5' triiodothyronine)



Peptide backbone of thyroglobulin molecule

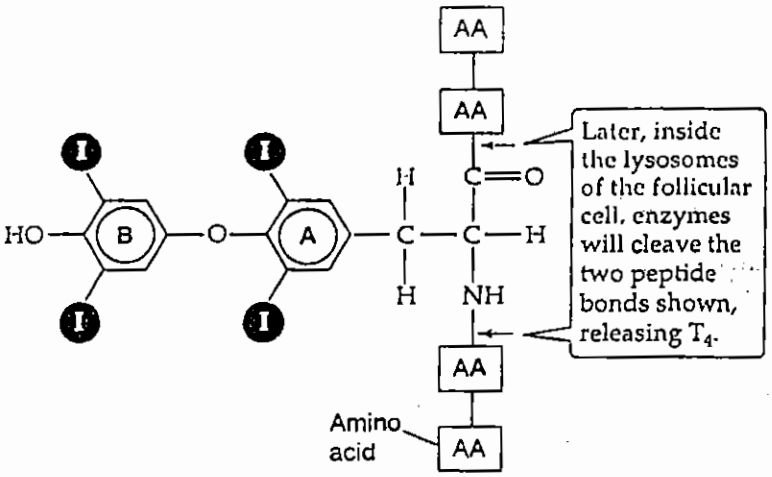


FIGURE 48–2. The structure of thyroxine (T_4), triiodothyronine (T_3), and reverse T_3 (rT_3). T_4, T_3, and rT_3 all are products of the coupling of two iodinated tyrosine derivatives. Only T_4 and T_3 are biologically active, and T_3 is far more active than T_4 because of a higher affinity for thyroid hormone receptors. Reverse T_3 forms as an iodine is removed from the inner benzyl ring (labeled "A") of T_4; rT_3 is present in approximately equal molar amounts with T_3. However, rT_3 is essentially devoid of biologic activity. As shown in the bottom panel, T_4 is part of the peptide backbone of the thyroglobulin molecule, as are T_3 and rT_3. Cleavage of the two indicated peptide bonds would release T_4.

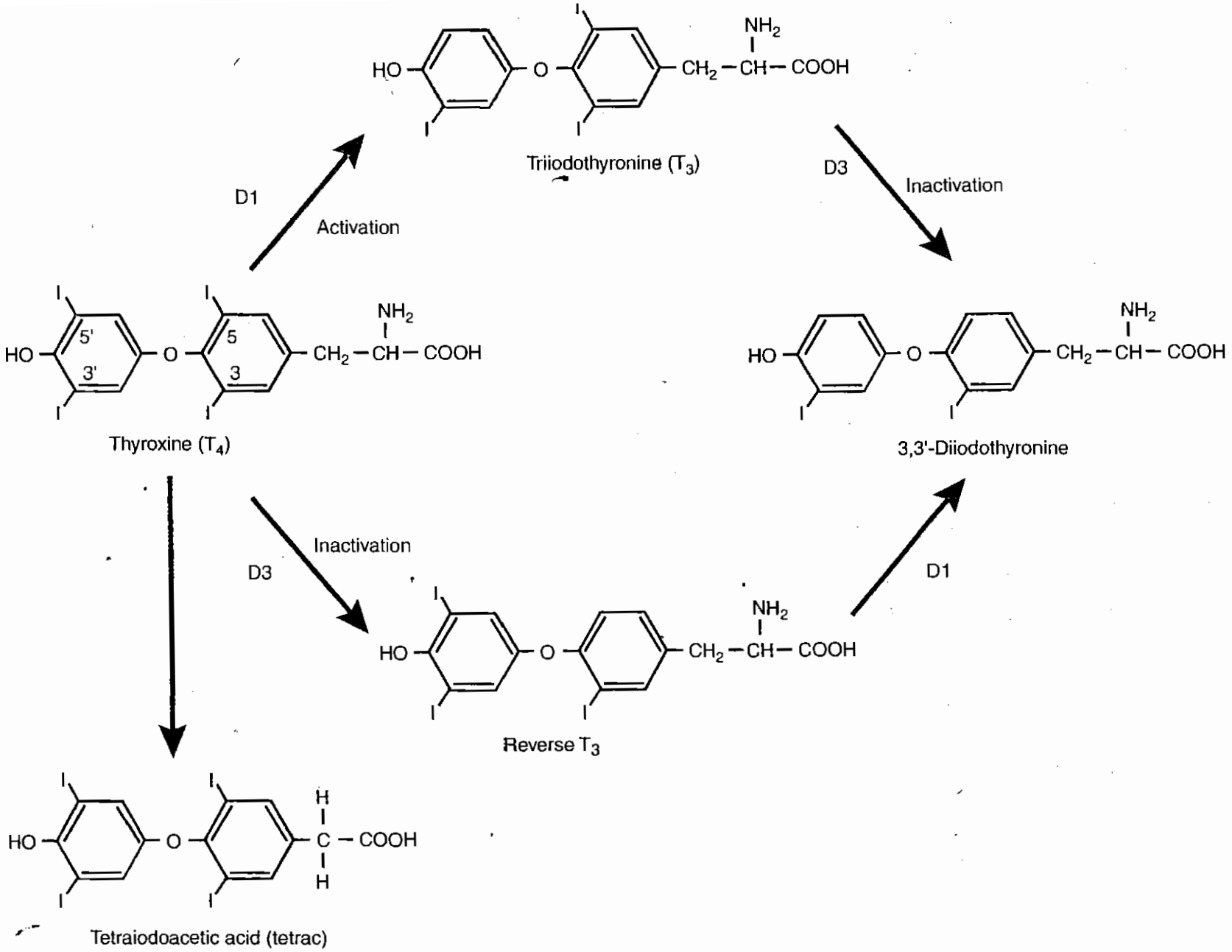


FIGURE 32.4 The metabolism of thyroxine. Deiodinase type 1 (D1) deiodinates thyroxine (T_4) at the 5′ position to form triiodothyronine (T_3), the physiologically active thyroid hormone. Deiodinase type 3 (D3) also enzymatically deiodinates some T_4 at the 5 position to form the inactive metabolite, reverse T_3. T_3 and reverse T_3 undergo additional deiodinations to 3,3′-diiodothyronine before being excreted. A small amount of T_4 is also decarboxylated and deaminated to form the

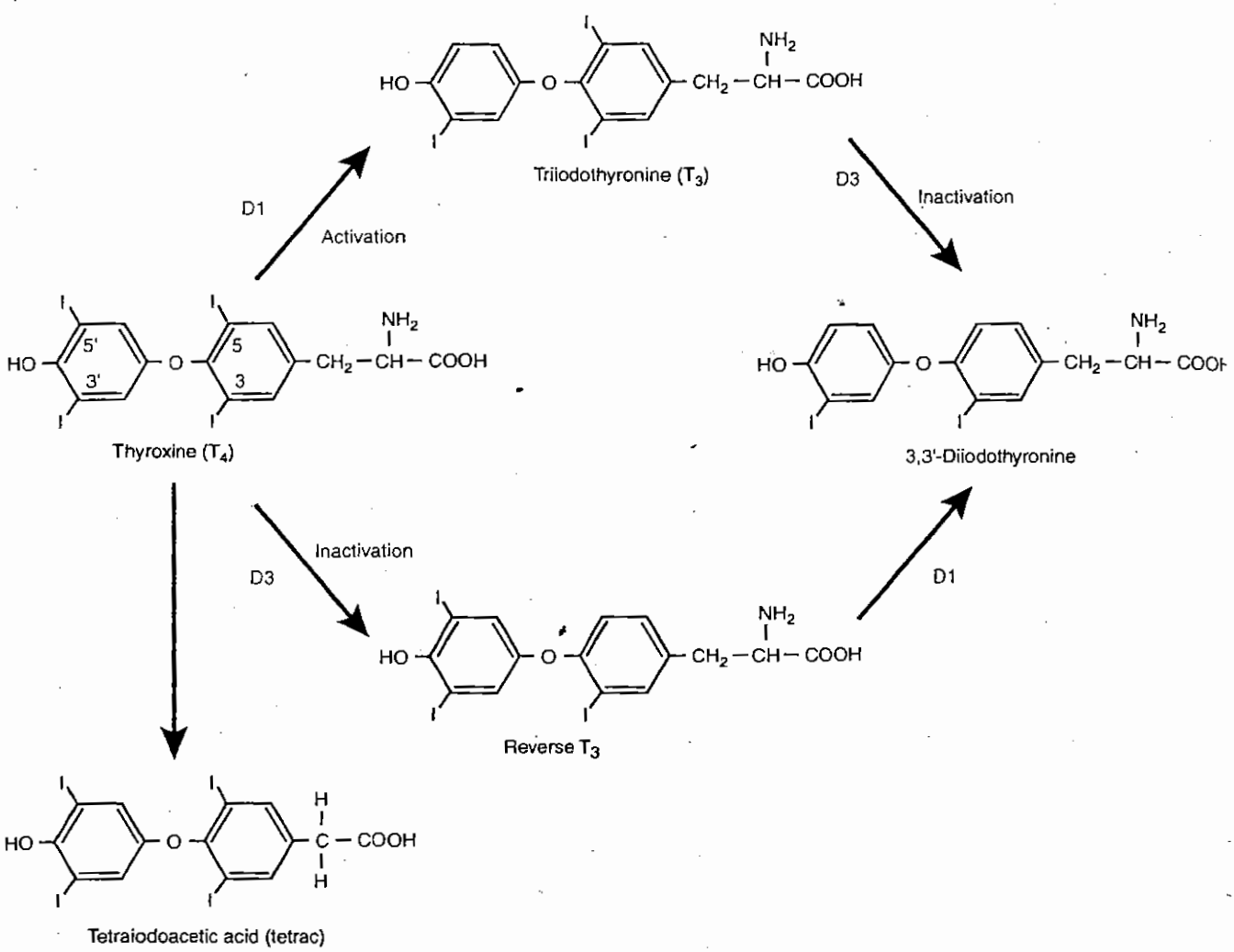
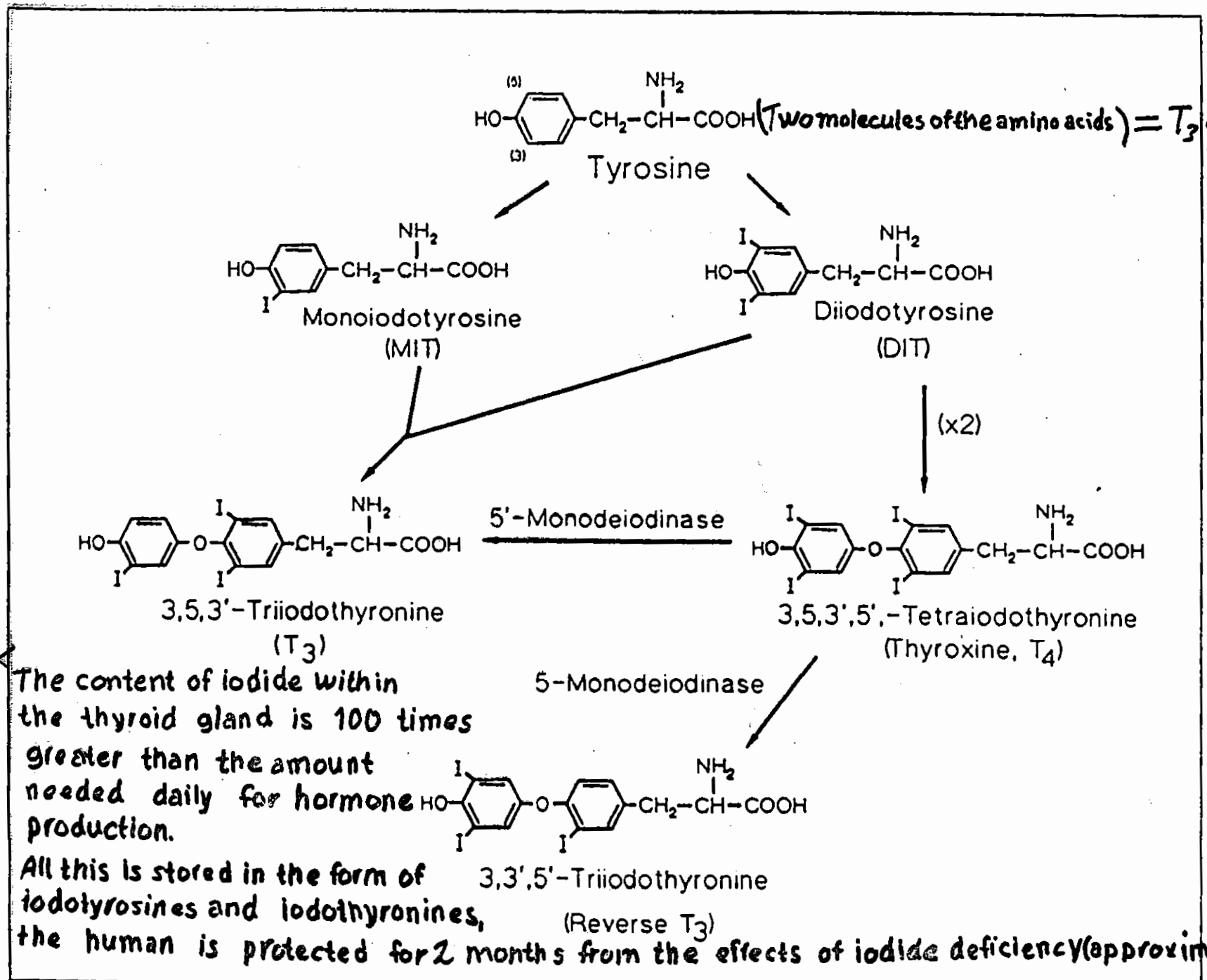


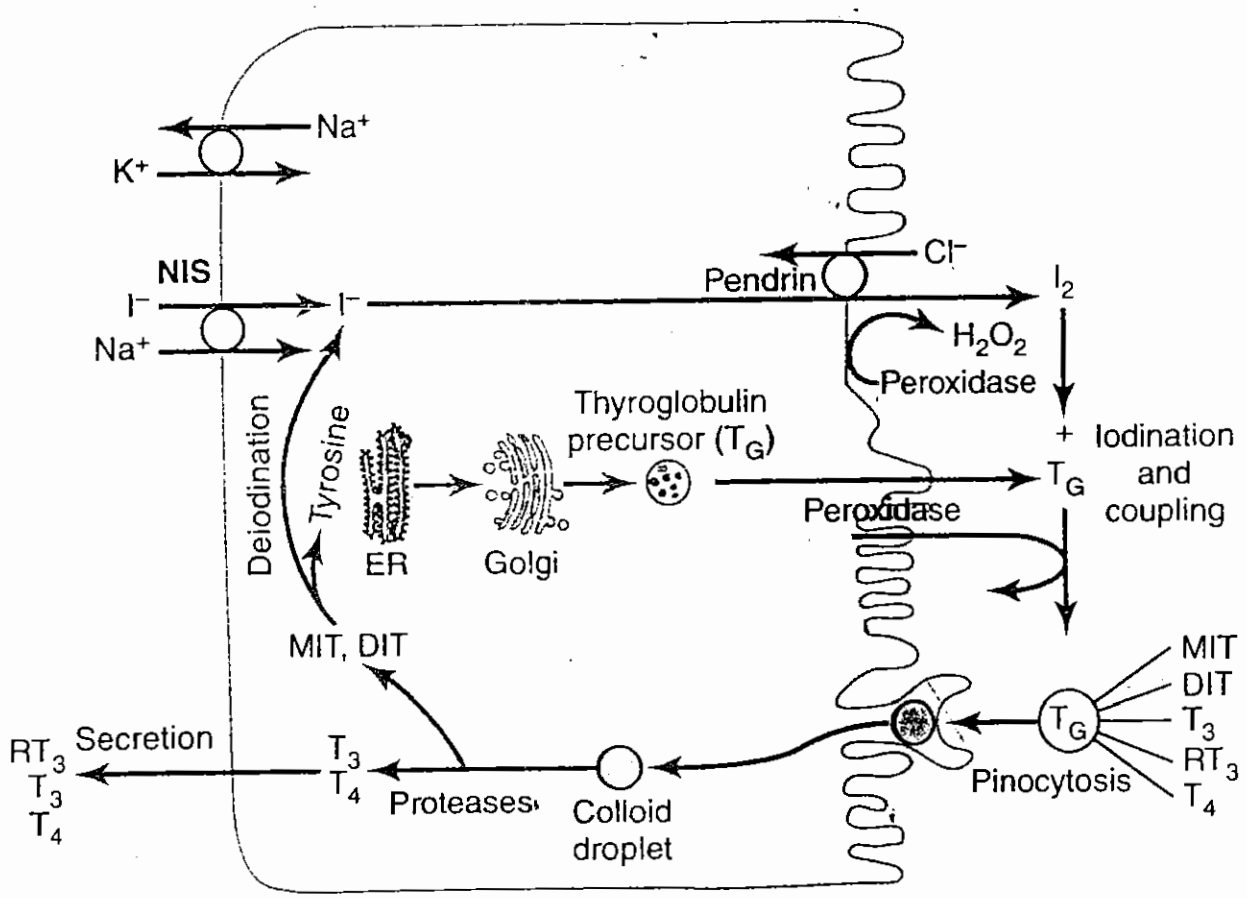
FIGURE 32.4 The metabolism of thyroxine. Deiodinase type 1 (D1) deiodinates thyroxine (T_4) at the 5′ position to form triiodothyronine (T_3), the physiologically active thyroid hormone. Deiodinase type 3 (D3) also enzymatically deiodinates some T_4 at the 5 position to form the inactive metabolite, reverse T_3. T_3 and reverse T_3 undergo additional deiodinations to 3,3′-diiodothyronine before being excreted. A small amount of T_4 is also decarboxylated and deaminated to form the metabolite, tetraiodoacetic acid (tetrac). Tetrac may then be deiodinated before being excreted.



* The content of iodide within the thyroid gland is 100 times greater than the amount needed daily for hormone production.
All this is stored in the form of iodotyrosines and iodothyronines, the human is protected for 2 months from the effects of iodide deficiency (approximately).

Fig. 50-1. Thyroid hormone synthesis and structures of thyroid

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



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

Each molecule of thyroglobulin contains about 70 tyrosine amino acids, and they are the major substrates that combine with iodine to form the thyroid hormones. But only 4 to 8 of these are normally incorporated into thyroid hormones.

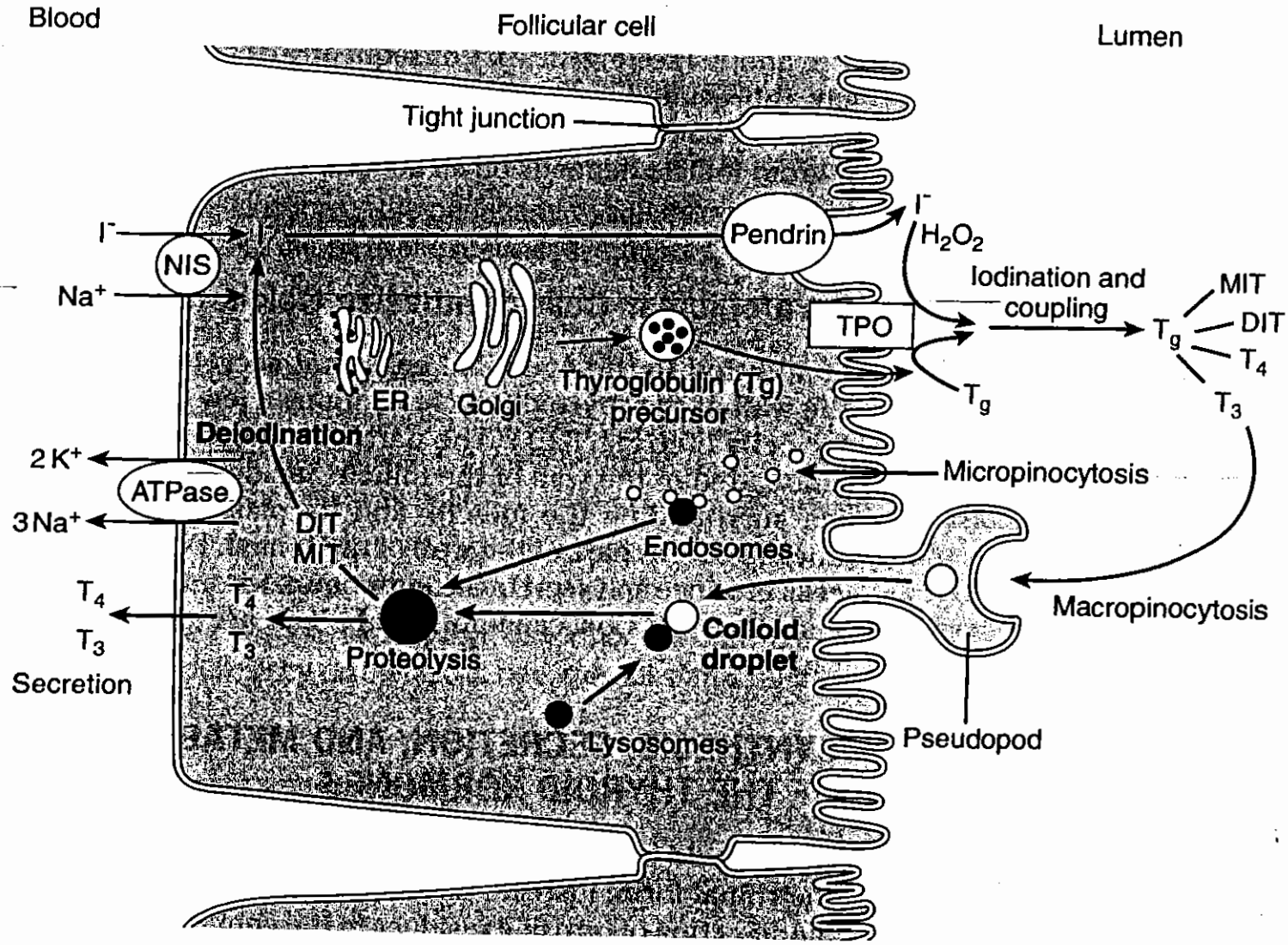


FIGURE 32.3 Thyroid hormone synthesis and secretion. (See text for details.) ATPase, adenosine triphosphatase; DIT, diiodotyrosine; ER, endoplasmic reticulum; MIT, monoiodotyrosine; NIS, sodium iodide symporter; T_3, triiodothyronine; T_4, thyroxine; TPO, thyroid peroxidase. Modified from Larson PR, Davies TF, Schlumberg M-J, Hay ID. Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: Larson PR, Kronenberg HM, Melmed S, Polonsky KS, eds. Williams Textbook of Endocrinology. 10th Ed. Philadelphia: Saunders, 2003.

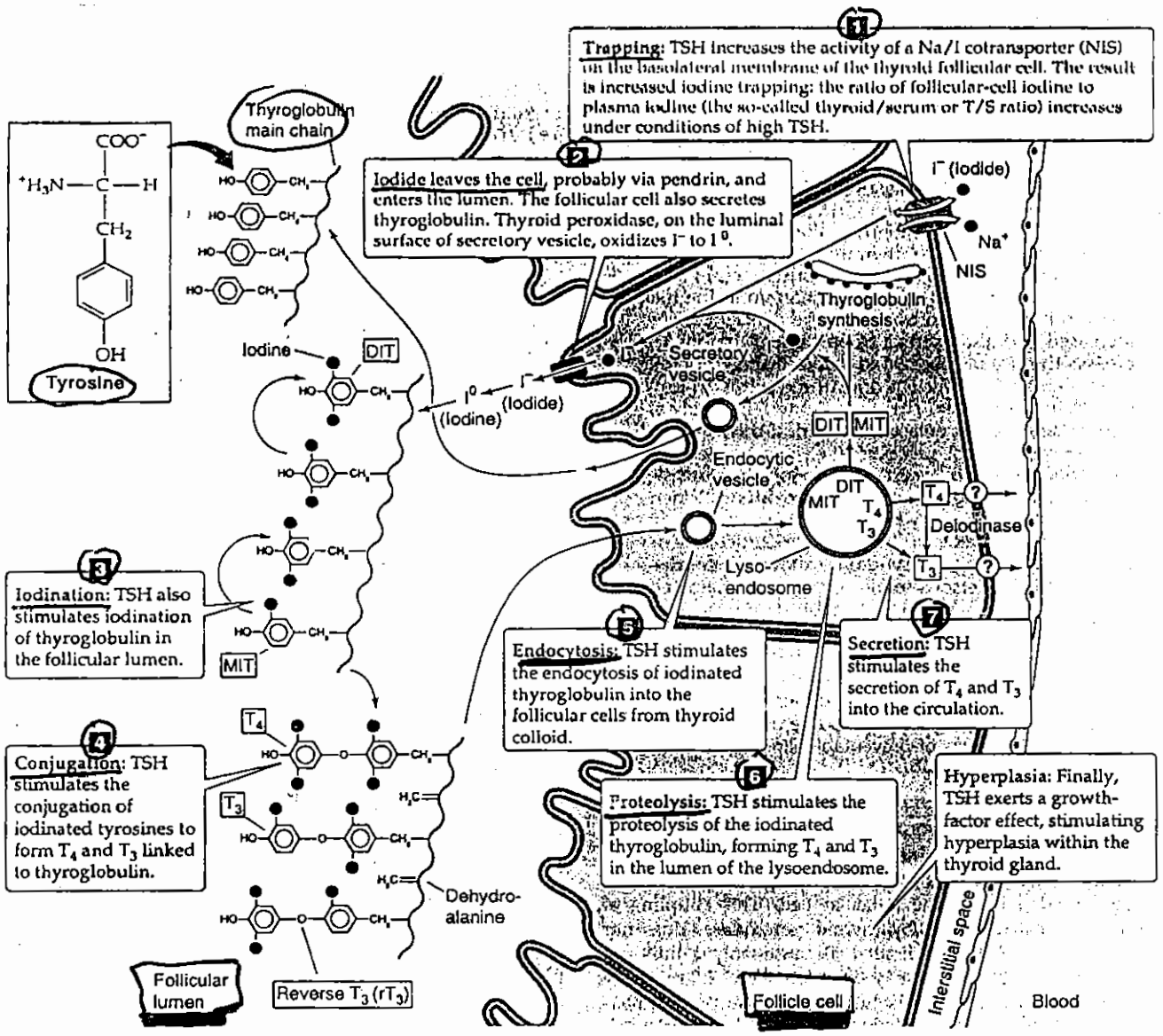
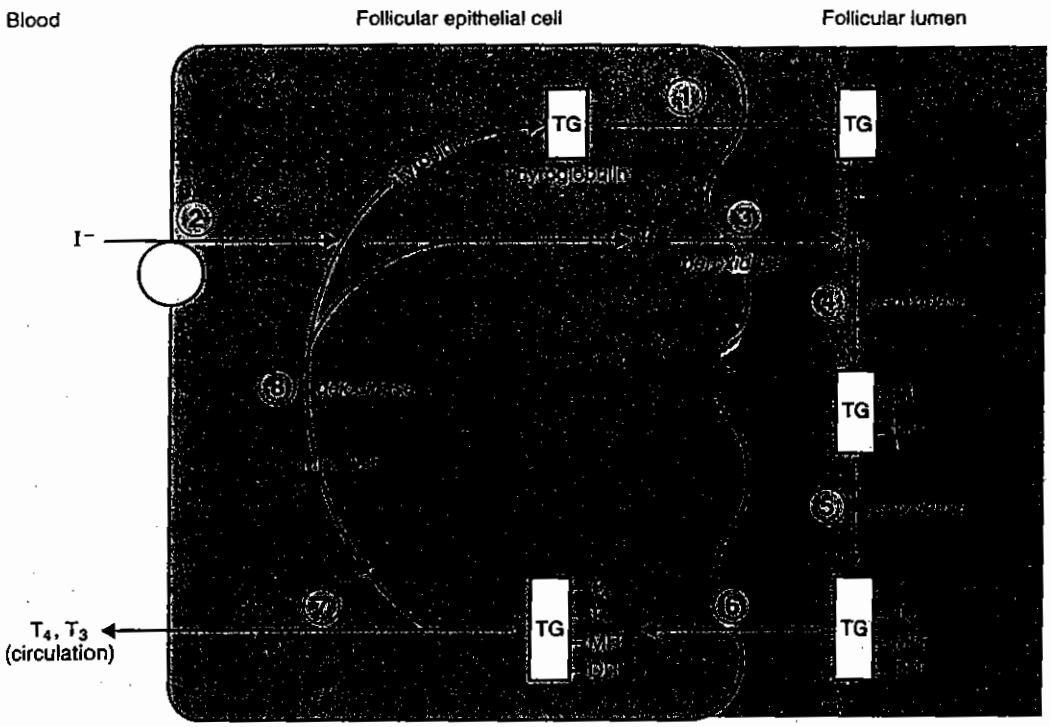


FIGURE 48–3. The follicular cell and its role in the synthesis of thyroxine (T_4) and triiodothyronine (T_3). The synthesis and release of T_4 and T_3 occurs in seven steps. Inside the follicular cell, a deiodinase converts some of the T_4 to T_3. Thyrotropin (or thyroid-stimulating hormone [TSH]) stimulates each of these steps except step 2. In addition, TSH exerts a growth factor or hyperplastic effect on the follicular cells. DIT, diiodotyronine; MIT, monoiodotyronine.



odination and Coupling occur only with tyrosine linked to thyroglobulin.

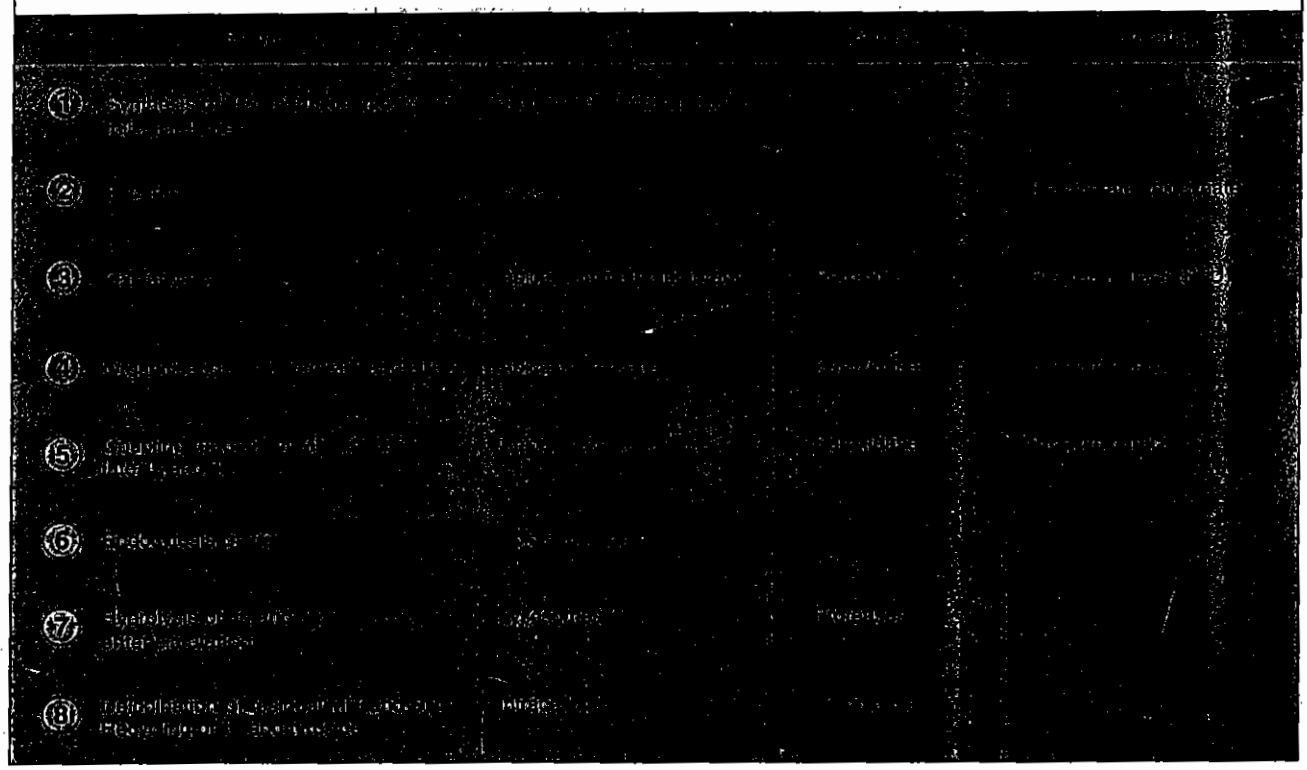


FIGURE 9–16. Steps involved in the synthesis of thyroid hormones in thyroid follicular cells. Circled numbers correspond to steps discussed in the text. DIT, diiodotyrosine; ER, endoplasmic reticulum; MIT, monoiodotyrosine; PTU, propylthiouracil; TG, thyroglobulin; T_3, triiodothyronine; T_4, thyroxine.

Table 53-1 Thyroid hormone turnover

	T_4	T_3	rT_3
Daily production (μg)	90	35	35
From thyroid (%)	100	25	5
From T_4 (%)	—	75	95
Extracellular pool (μg)	850	40	40
Plasma concentration			
Total (μg/dl)	8.0	0.12	0.04
Free (ng/dl)	2.0	0.28	0.20
Half-life (days)	7	1	0.8
Metabolic clearance (L/day)	1	26	77
Fractional turnover per day (%)	10	75	90

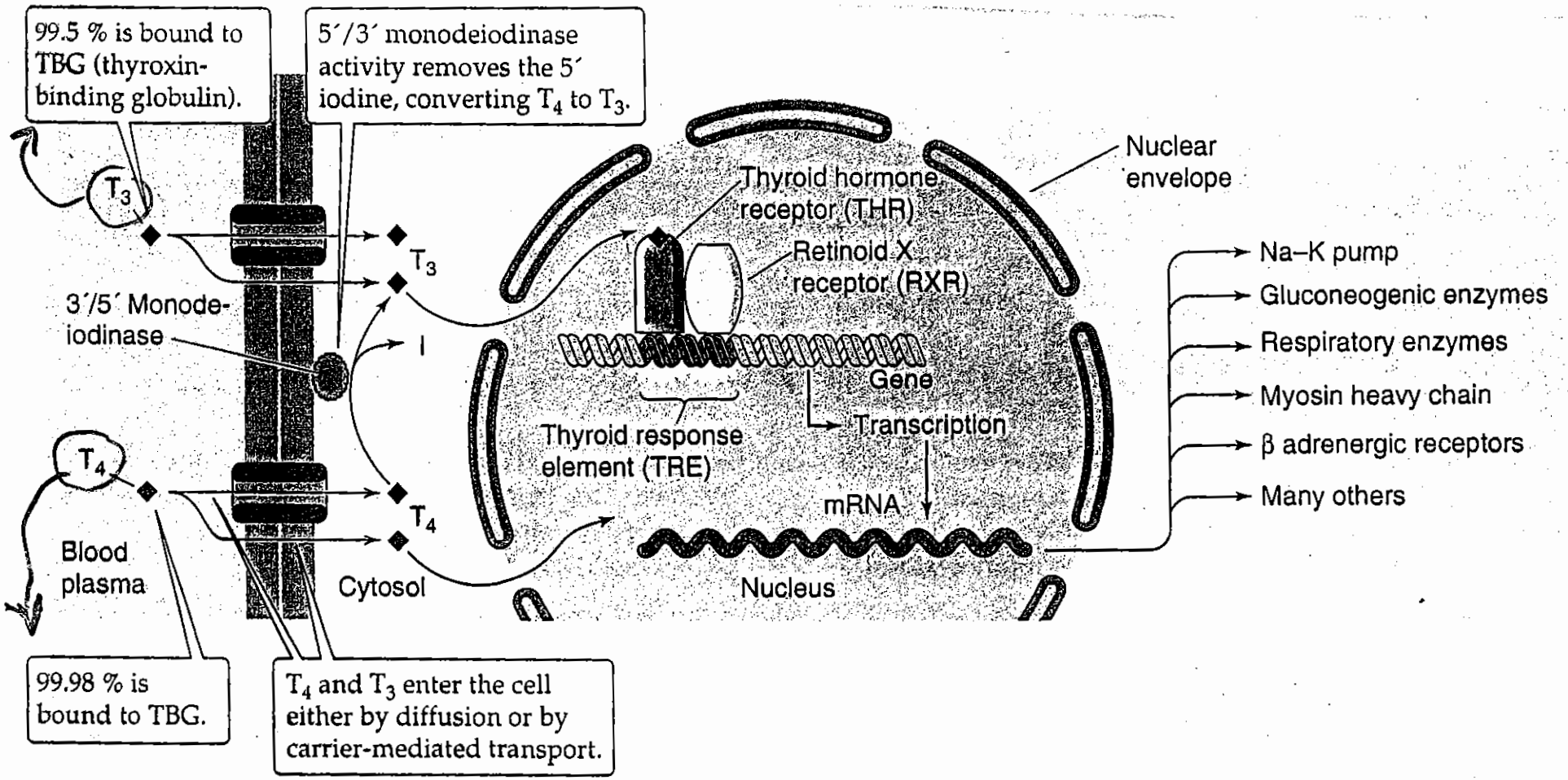


FIGURE 48–5. Action of thyroid hormones on target cells. Free extracellular thyroxine (T_4) and triiodothyronine (T_3) enter the target cell either by diffusion or by carrier-mediated transport. Once the T_4 is inside the cell, a cytoplasmic 5′/3′-monodeiodinase converts much of the T_4 to T_3, so that that cytoplasmic levels of T_4 and T_3 are about equal. Both T_4 and T_3 enter the nucleus. Thyroid hormone receptors bind to DNA at thyroid response elements in the promoter region of genes regulated by thyroid hormones. The binding of T_3 or T_4 to the receptor regulates the transcription of these genes. The receptor preferentially binds T_3. Therefore, of the total thyroid hormone bound to receptor, approximately 90% is T_3. The receptor that binds to the DNA is preferentially a heterodimer of the thyroid hormone receptor and retinoid X receptor. Thyroid hormone promotes the transcription of genes encoding a wide range of proteins. mRNA, messenger RNA.

Table 5.3.2 Approximate normal values for thyroid hormones in the blood

	Total	Percentage free	Absolute concentration free
T_4	100 nmol/l (80 µg/l)	0.03	30 pmol/l (24 ng/l)
T_3	1.8 nmol/l (1.2 µg/l)	0.3	5 pmol/l (0.4 µg/l)

Table 5.3.3 Thyroid hormone binding proteins

	Concentration (μmol/l)	Binding affinity	Actual binding T_4 (%)	Actual binding T_3 (%)
TBG	0.3	Very high	75	75
Albumin	640	Very low	10	25
TBPA	5.0	Low	15	0

TBG = thyronine-binding globulin; TBPA = thyroxine-binding pre-albumin

Two biologic functions can be ascribed to TBG. First:-by creating a circulating reservoir of T_4, it buffers against acute changes in thyroid gland function. Even the sudden addition to the plasma of an entire day's thyroid gland output would cause only a 10% increase in the total T_4 concentration. After removal ofthe gland, it would take nearly 1 week for the plasma T_4 concentration to fall 50%. Second, by binding

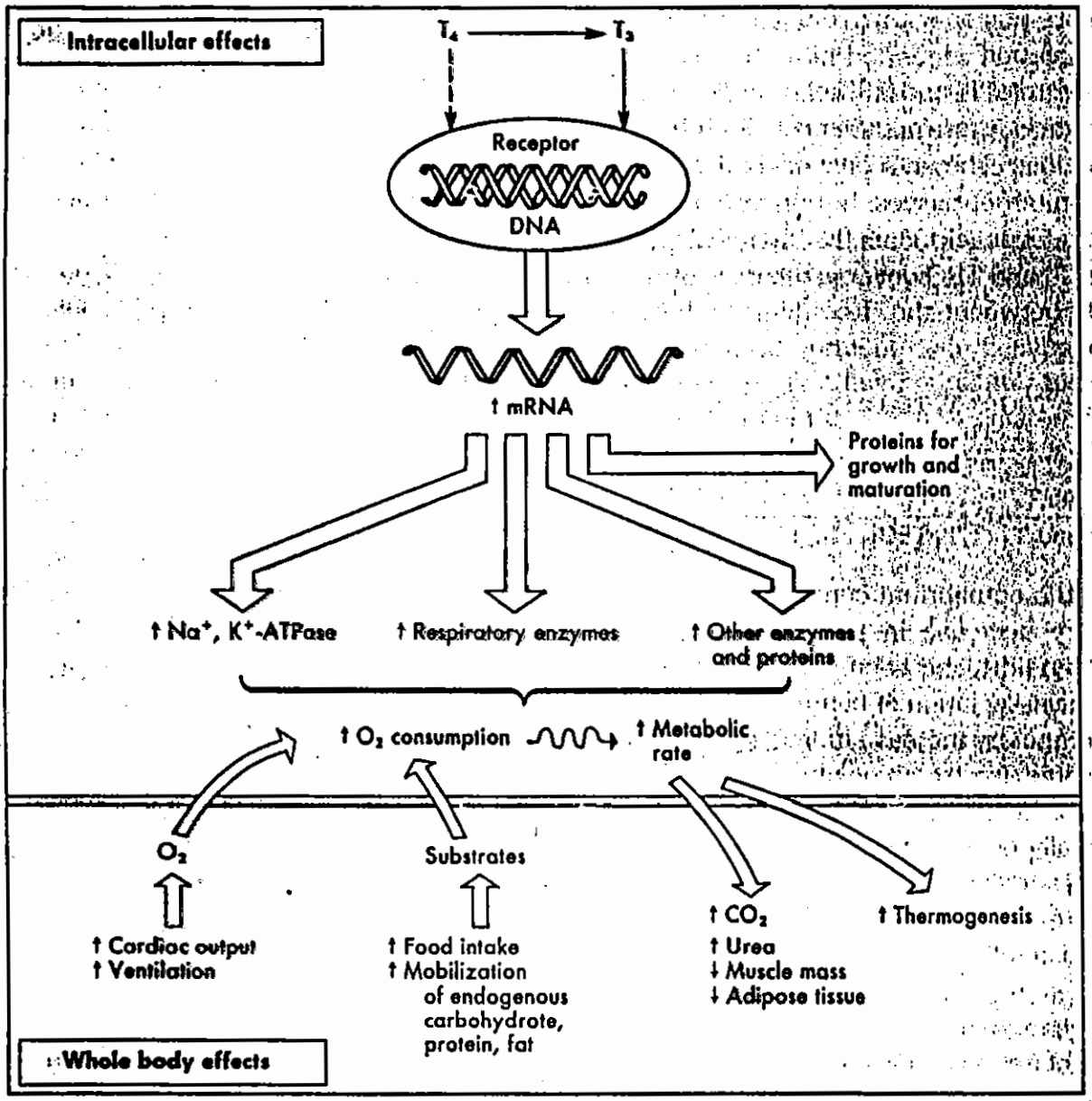


FIGURE 40-6 Overall schema of thyroid hormone effects. The upper portion represents intracellular actions; the lower portion, whole body effects.

TABLE 32.1 The Physiological Actions of Thyroid Hormones

Category	Specific Action
Development of CNS	Inhibit nerve cell replication Stimulate growth of nerve cell bodies Stimulate branching of dendrites Stimulate rate of axon myelinization
Body growth	Stimulate expression of gene for GH in somatotrophs Stimulate synthesis of many structural and enzymatic proteins Promote calcification of bones
Basal energy economy of the body	Regulate basal rates of oxidative phosphorylation, body heat production, and oxygen consumption (thermogenic effect)
Intermediary metabolism	Stimulate synthetic and degradative pathways of carbohydrate, lipid, and protein metabolism
Thyroid-stimulating hormone (TSH) secretion	Inhibit TSH secretion by decreasing sensitivity of thyrotrophs to thyrotropin-releasing hormone (TRH)

CNS, central nervous system; GH, growth hormone.

Table 13–6
Summary of the Effects of Thyroid Hormones

1- Stimulate calorigenesis in most cells
2- Increase cardiac output
    Increase rate of cardiac contractions
    Increase strength of cardiac contractions
3- Increase oxygenation of blood
    Increase rate of breathing
    Increase number of red blood cells in the circulation
4- Effects on carbohydrate metabolism
    Promote glycogen formation in liver
    Increase glucose uptake into adipose and muscle
5- Effects on lipid turnover
    Increased lipid synthesis
    Increased lipid mobilization
    Increased lipid oxidation
6- Effects on protein metabolism
    Stimulate protein synthesis
7- Promote normal growth
    Stimulate growth hormone (GH) secretion
    Promote bone growth
    Promote IGF-I production by liver
8- Promote development and maturation of nervous system
    Promote neural branching
    Promote myelinization of nerves

TABLE 9–8. Factors Affecting Thyroid Hormone Secretion

Stimulatory Factors	Inhibitory Factors
TSH	I^- deficiency
Thyroid-stimulating immunoglobulins	Deiodinase deficiency
Increased TBG levels (e.g., pregnancy)	Excessive I^- intake (Wolff-Chaikoff effect)
	Perchlorate; thiocyanate (inhibit I^- pump)
	Propylthiouracil (inhibits peroxidase enzyme)
	Decreased TBG levels (e.g., liver disease)

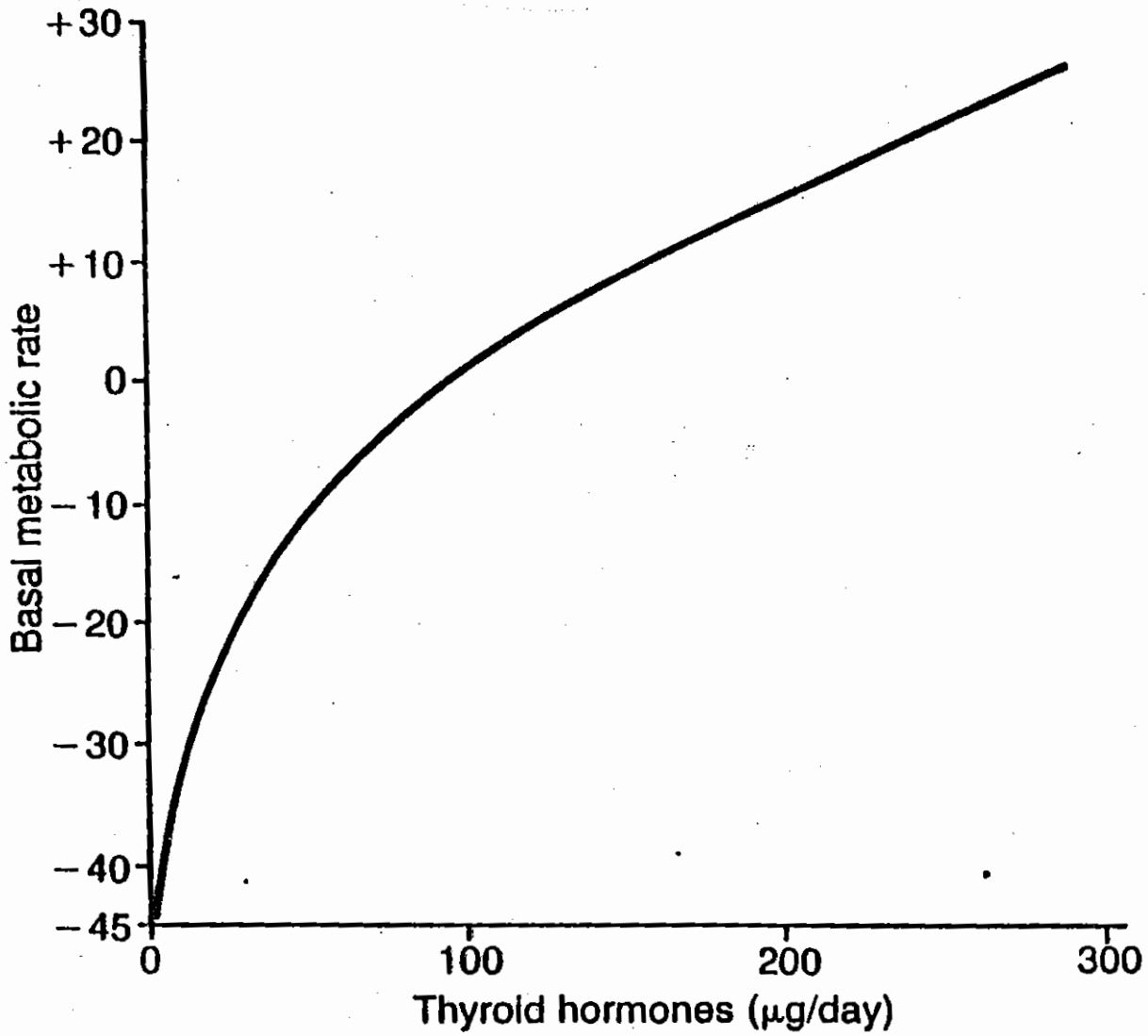


Figure 76–5. Approximate relationship of thyroid hormone (T_4 and T_3) daily rate of secretion to the basal metabolic rate.

Effect on Basal Metabolic Rate. Because thyroid hormone increases metabolism in almost all cells of the body, excessive quantities of the hormone can occasionally increase the basal metabolic rate to as much as 60 to 100 per cent above normal. On the other hand, when no thyroid hormone is produced, the basal metabolic rate falls almost to half normal; that is, the basal metabolic rate becomes −30 to −50, as discussed in Chapter 72. Figure 76–5 shows the approximate relationship between the daily supply of thyroid hormones and the basal metabolic rate. Extreme amounts of the hormones are required to cause very high basal metabolic rates.

* Multiple hormones, including growth hormone (GH), insulin – like growth factors (IGF-I and -II), insulin, thyroid hormones, glucocorticoids, androgens & estrogens contribute to the growth process in humans. Among these , GH & IGF–I have been implicated as the major determinants of growth in normal postuterine life.

* Thyroid hormones are essential in normal amounts for growth; excess does not produce overgrowth as with GH, but causes increase catabolism of proteins & other nutrients.

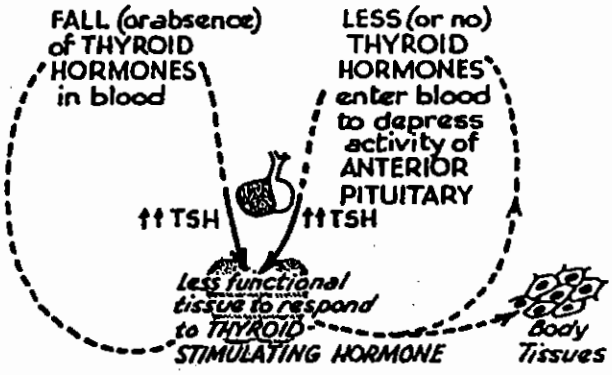
* Thyroxine at normal concentrations has permissive effect on the action of GH on protein synthesis in its absence aminoacids uptake & protin synthesis are not much stimulated.

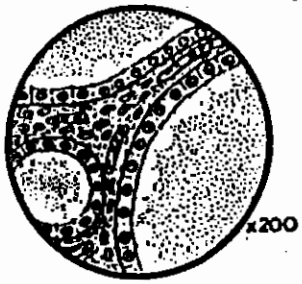
* Reduced thyroid activity in childhood produces dwarfs who are mentally retarded, whereas reduced GH in childhood produces dwarfs with normal intelligence.

Multiple hormones, including growth hormone (GH), insulin-like growth factors (IGF-I and -II), insulin, thyroid hormones, glucocorticoids, androgens, and estrogens contribute to the growth process in humans. Among these, GH and IGF-I have been implicated as the major determinants of growth in normal postuterine life. However, deficiencies (or excesses) of each of the other hormones can seriously affect the normal growth of the musculoskeletal system as well as the growth and maturation of other tissues.

UNDERACTIVITY of THYROID

If the THYROID shows *atrophy* of its secretory cells or is inadequately stimulated by the Anterior Pituitary:-





Insufficient HORMONAL SECRETION released to Blood Stream.

— TISSUE OXIDATIONS are depressed. *ie.* Rate at which cells use energy is reduced.

— The Basal Metabolic Rate falls.

— Less Heat is produced.

— Body Temperature falls (and person feels COLD).

Energy units are stored with water.

— SKIN - Thick, leathery, puffy, yellow (due to circulating carotene).

— Blood cholesterol increases.

— Appetite is reduced; Weight increases.

— Gut movements sluggish → Constipation.

— Heart and Respiratory Rates and Blood Pressure reduced.

— Thought processes slow down → Lethargy; Apathy; Somnolence.

— HAIR - Brittle, sparse, dry.

— Slow, husky voice. Bone marrow suppressed → ANAEMIA.

I. *In the ADULT*

MYXOEDEMA

Protein complexes deposited in skin

SLOWING UP OF ALL BODILY PROCESSES

II. *In the CHILD* — *e.g. congenital absence of the gland*

CRETIN

GROSS DWARFING

- *FAILURE of*
  - *SKELETAL*
  - *SEXUAL*
  - *MENTAL*

} GROWTH and DEVELOPMENT

All "milestones" of babyhood are delayed.

THYROXINE (taken by mouth) restores individuals to normal.

TABLE 9–9. Pathophysiology of Thyroid Hormones

	Hyperthyroidism	Hypothyroidism
Symptoms	Increased basal metabolic rate (BMR) Weight loss Negative nitrogen balance Increased heat production Sweating Increased cardiac output Dyspnea (shortness of breath) Tremor, muscle weakness Exophthalmos Goiter	Decreased basal metabolic rate Weight gain Positive nitrogen balance Decreased heat production Cold sensitivity Decreased cardiac output Hypoventilation Lethargy, mental slowness Drooping eyelids Myxedema Growth retardation Mental retardation (perinatal) Goiter
Causes	Graves' disease (increased thyroid-stimulating immunoglobulins) Thyroid neoplasm Excess TSH secretion Exogenous T_3 or T_4	Thyroiditis (autoimmune or Hashimoto's thyroiditis) Surgery for hyperthyroidism I^- deficiency Congenital (cretinism) Decreased TRH or TSH
TSH levels	Decreased (feedback inhibition of T_3 on the anterior lobe)	Increased (by negative feedback if primary defect is in thyroid gland) Decreased (if defect is in hypothalamus or anterior pituitary)
Treatment	Propylthiouracil (inhibits peroxidase enzyme and thyroid hormone synthesis) Thyroidectomy ^{131}I (destroys thyroid) β-Adrenergic blocking agents (adjunct therapy)	Thyroid hormone replacement therapy

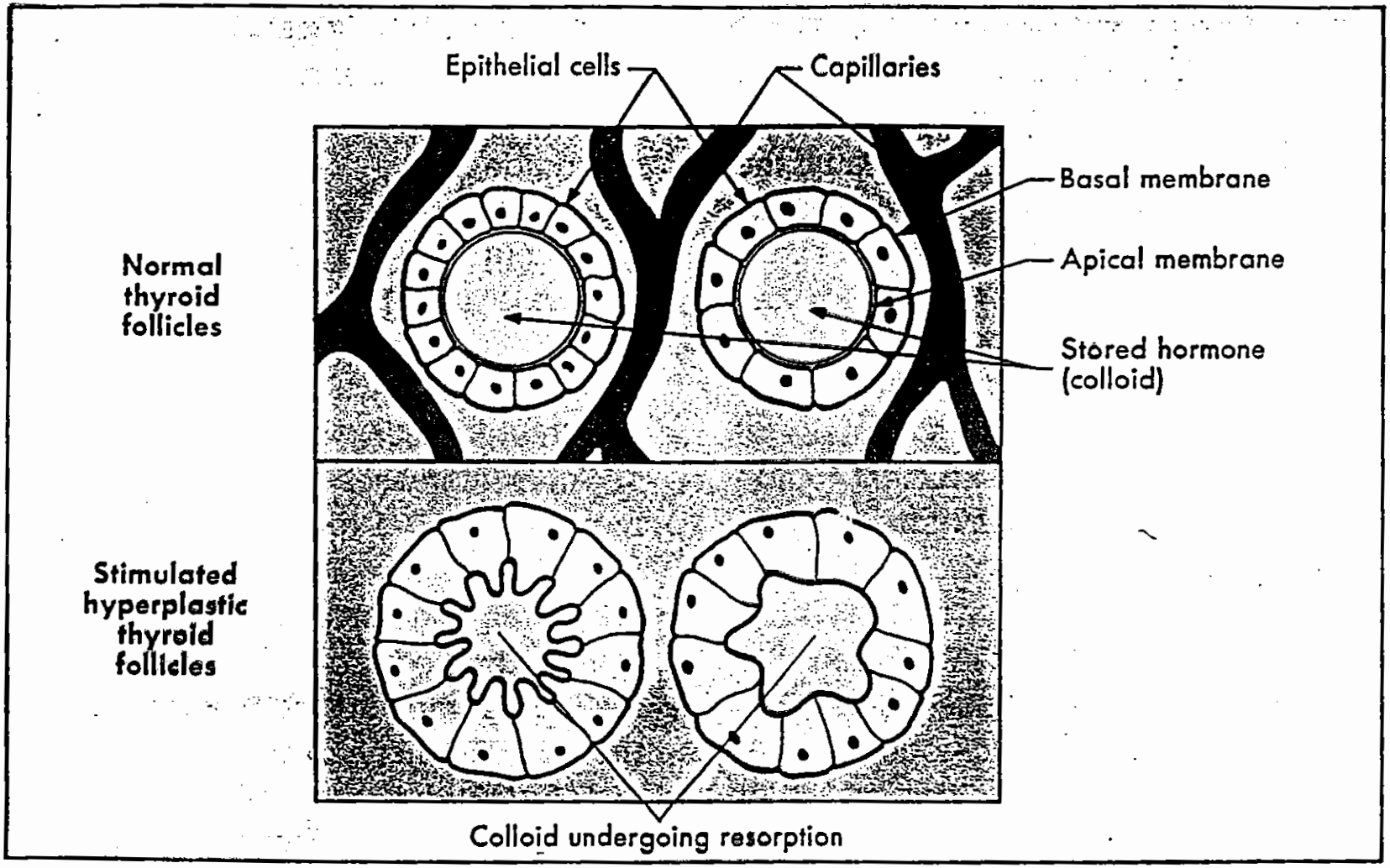


FIGURE 40-1 Schematic representation of the basic thyroid unit. A normal follicle consists of a central core of colloid material surrounded by a single layer of cuboidal cells. When stimulated by thyrotropin, the cells elongate and the central core becomes scalloped because of resorption of the colloid.

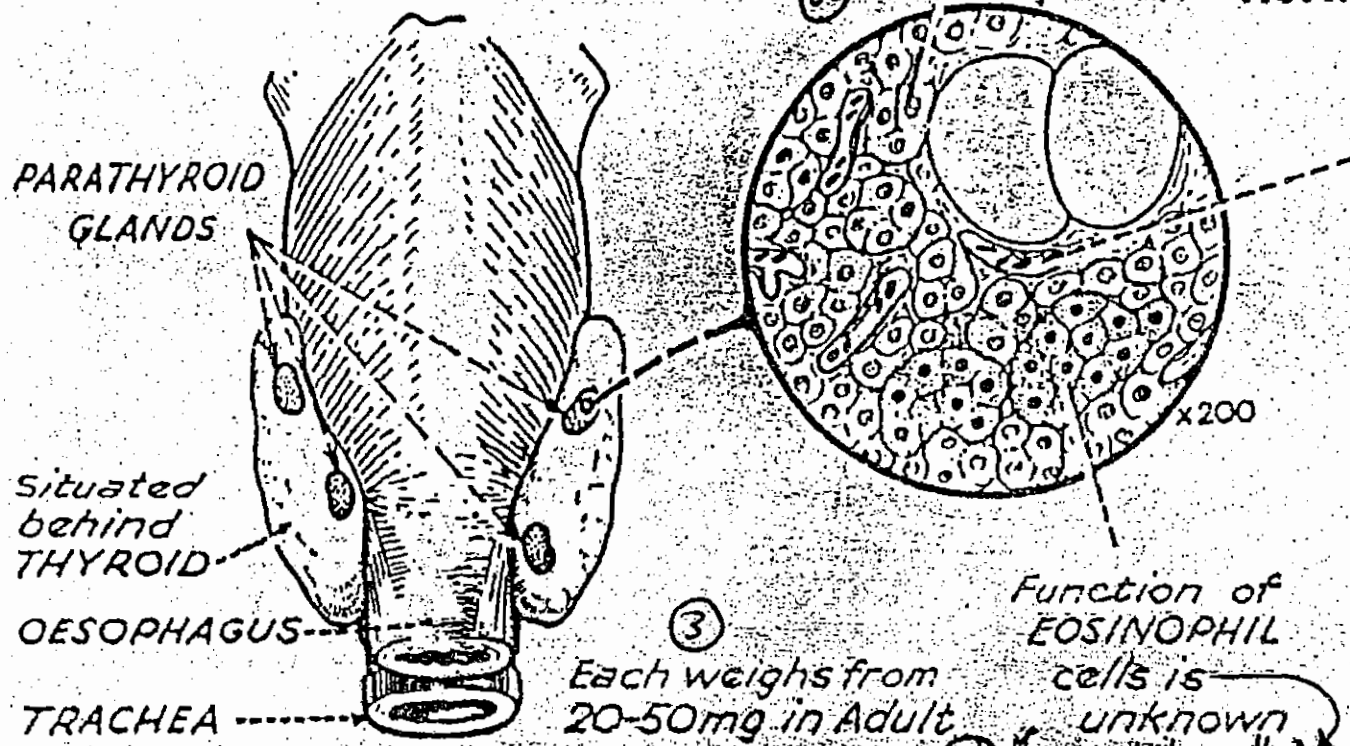
TABLE 15-5 Types of Thyroid Dysfunctions

THYROID DYSFUNCTION	CAUSE	PLASMA CONCENTRATIONS OF RELEVANT HORMONES	GOITER PRESENT?
Hypothyroidism	Primary failure of thyroid gland	↓ T_3 and T_4; ↑ TSH	Yes
	Secondary to hypothalamic or anterior pituitary failure	↓ T_3 and T_4; ↓ TRH and/or ↓ TSH	No
	Lack of dietary iodine	↓ T_3 and T_4; ↑ TSH	Yes
Hyperthyroidism	Abnormal presence of thyroid-stimulating immunoglobulin (TSI) (Grave's disease)	↑ T_3 and T_4; ↓ TSH	Yes
	Secondary to excess hypothalamic or anterior pituitary secretion	↑ T_3 and T_4; ↑ TRH and/or ↑ TSH	Yes
	Hypersecreting thyroid tumor	↑ T_3 and T_4; ↓ TSH	No


MODERATE SIZE
NONTOXIC
DIFFUSE
GOITER
LARGE
DIFFUSE
GOITER
SIMPLE GOITER
F. Netter M.D.
©CIBA
NODULAR
GOITERS

PARATHYROIDS

) FOUR small glands composed of *cords of cells* which secrete Parathyroid Hormone – PARATHORMONE or PTH



(a) (Chief Cells)

CAPILLARIES → GENERAL CIRCULATION → to ALL TISSUES of the body

But not all tissues are sensitive to it.

It plays an important rôle in CALCIUM and PHOSPHATE METABOLISM

③ Each weighs from 20-50mg in Adult

Function of EOSINOPHIL cells is unknown

(b) (Oxyphil cells)

④ PARATHORMONE acts on KIDNEY TUBULES, BONE and on GUT to maintain ionized BLOOD CALCIUM level at 11mg/100ml PLASMA (*necessary for normal neuromuscular excitability*).

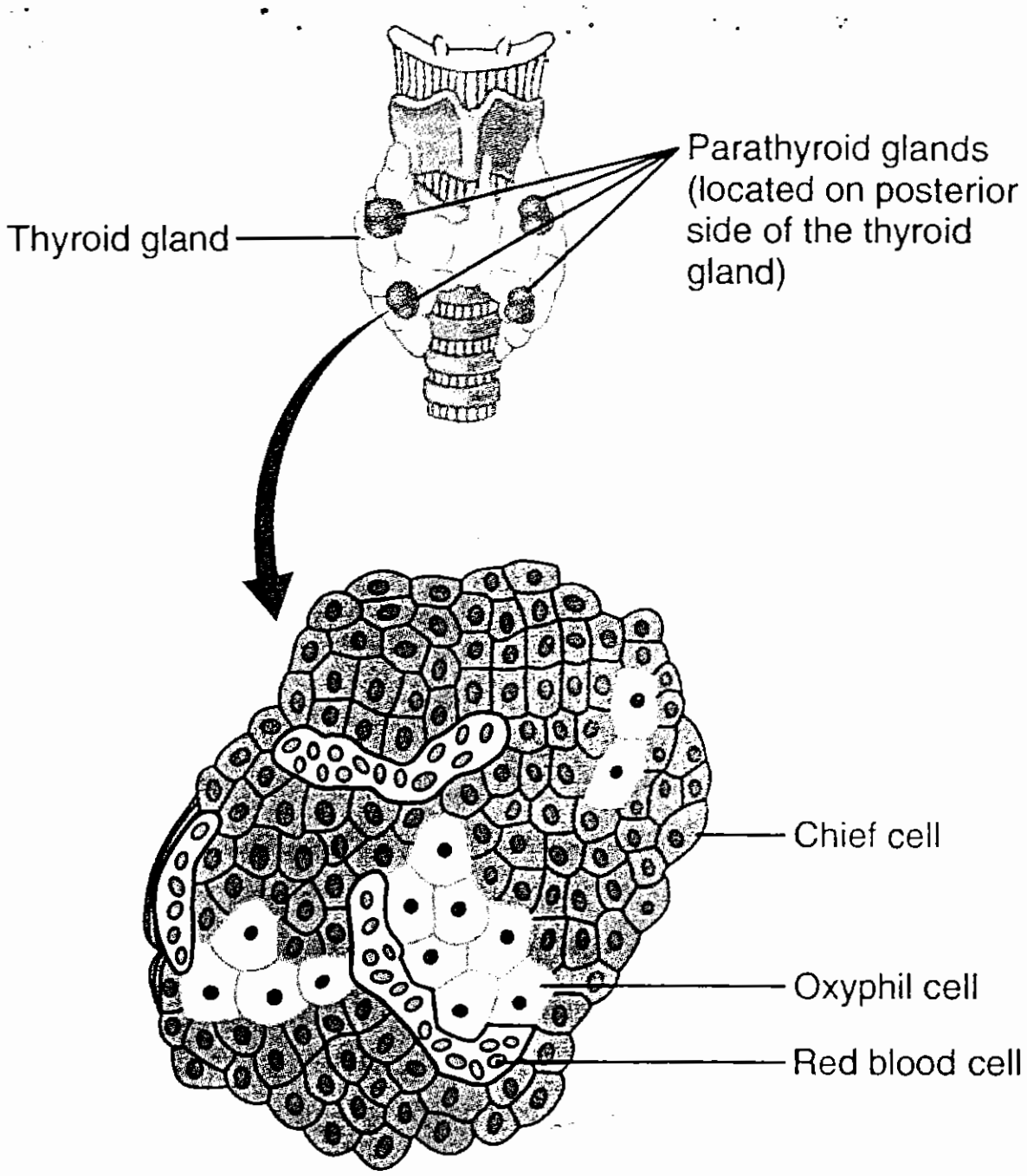


Figure 79-10 The four parathyroid glands lie immediately behind the thyroid gland. Almost all of the parathyroid hormone (PTH) is synthesized and secreted by the chief cells. The function of the oxyphil cells is uncertain, but they may be modified or depleted chief cells that no longer secrete PTH.

1-The parathyroid glands develop at 5-14 weeks of gestation.

2- PTH is a single chain protein (9600 molecular weight) that contains 84 amino acids.

The biologic activity of the hormone resides within a.a.1-34.

3- PTH interacts with receptors on the surface of the target cells increasing the formation of cAMP, IP & diacylglycerol.

4- PTH is free in plasma with half life 25 m.

5- PTH is essential for life, without it Ca++ falls in plasma neuromuscular excitability ↑, tetany & death occurs.

6- The dominant regulator of PTH secretion is the plasma Ca++ level.

7- Ca++ also regulates the size & the number of parathyroid cells.

8- Hypomagnesemia stimulates PTH secretion such as Ca++ but less potent.

9- Arise in plasma phosphate concentration indirectly causes a transient ↑ in PTH secretion.

10- 1,25 $(OH)_2$ -D directly redues PTH secretion.

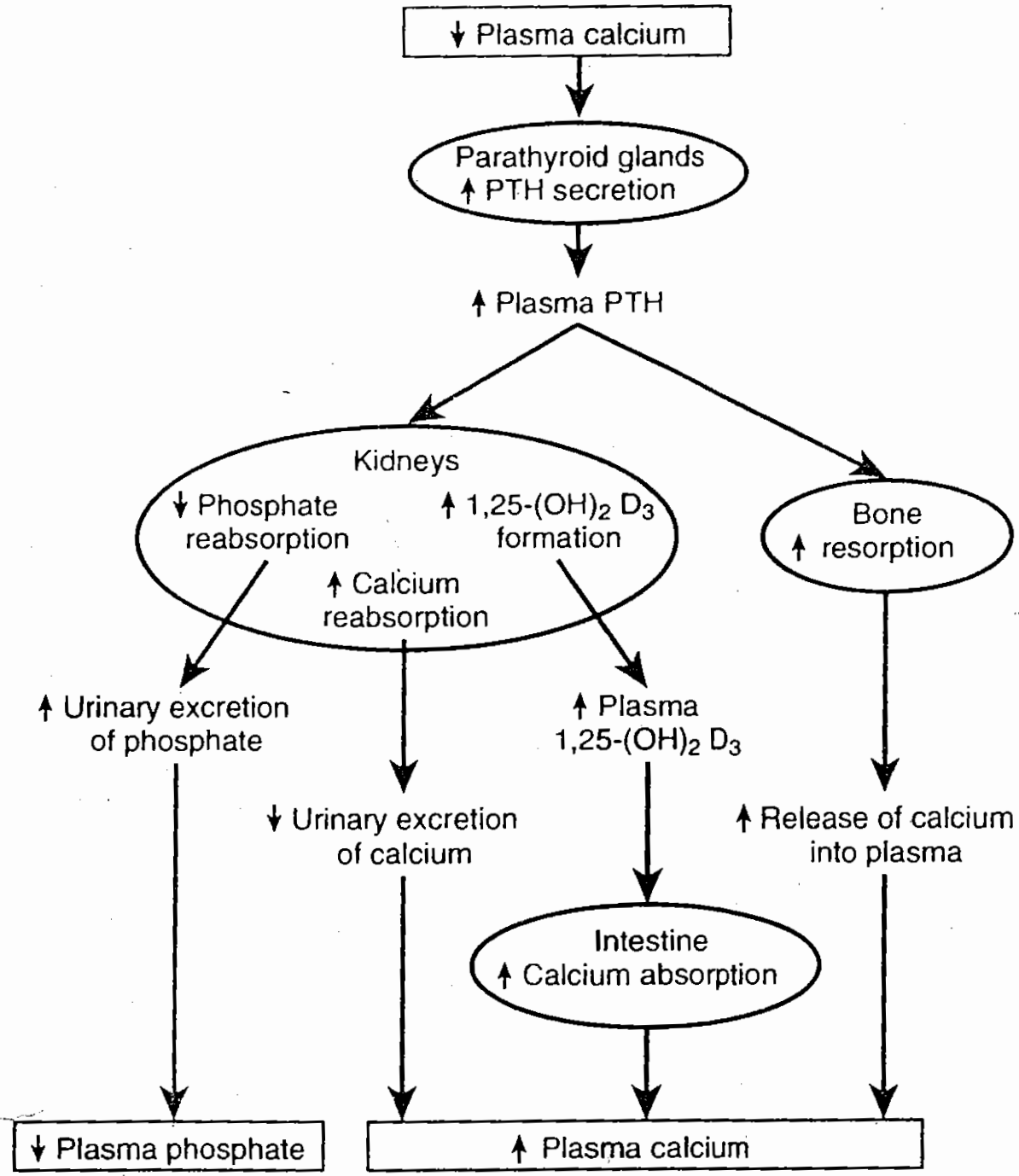


FIGURE 36.7 Effects of parathyroid hormone (PTH) on calcium and phosphate metabolism.

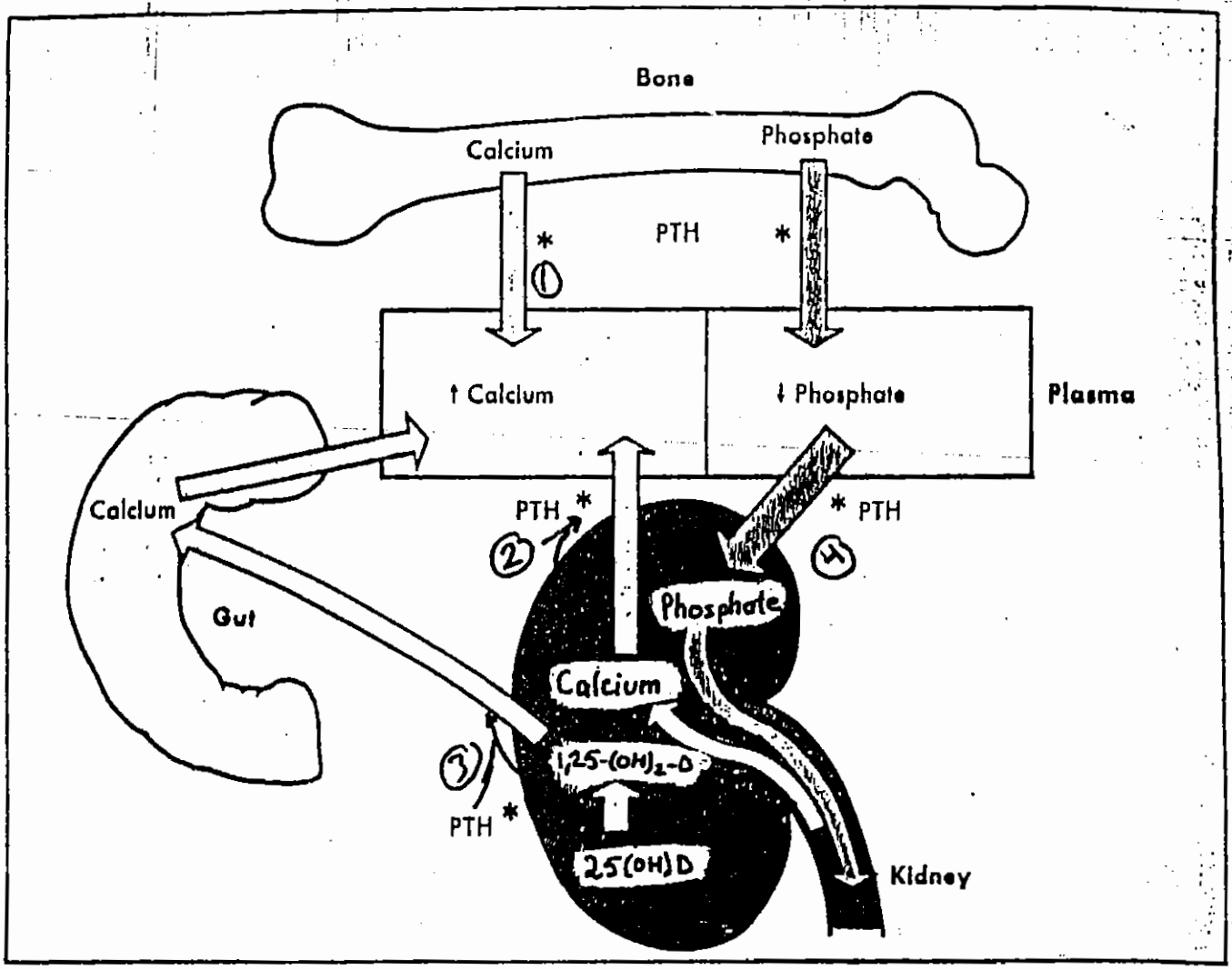
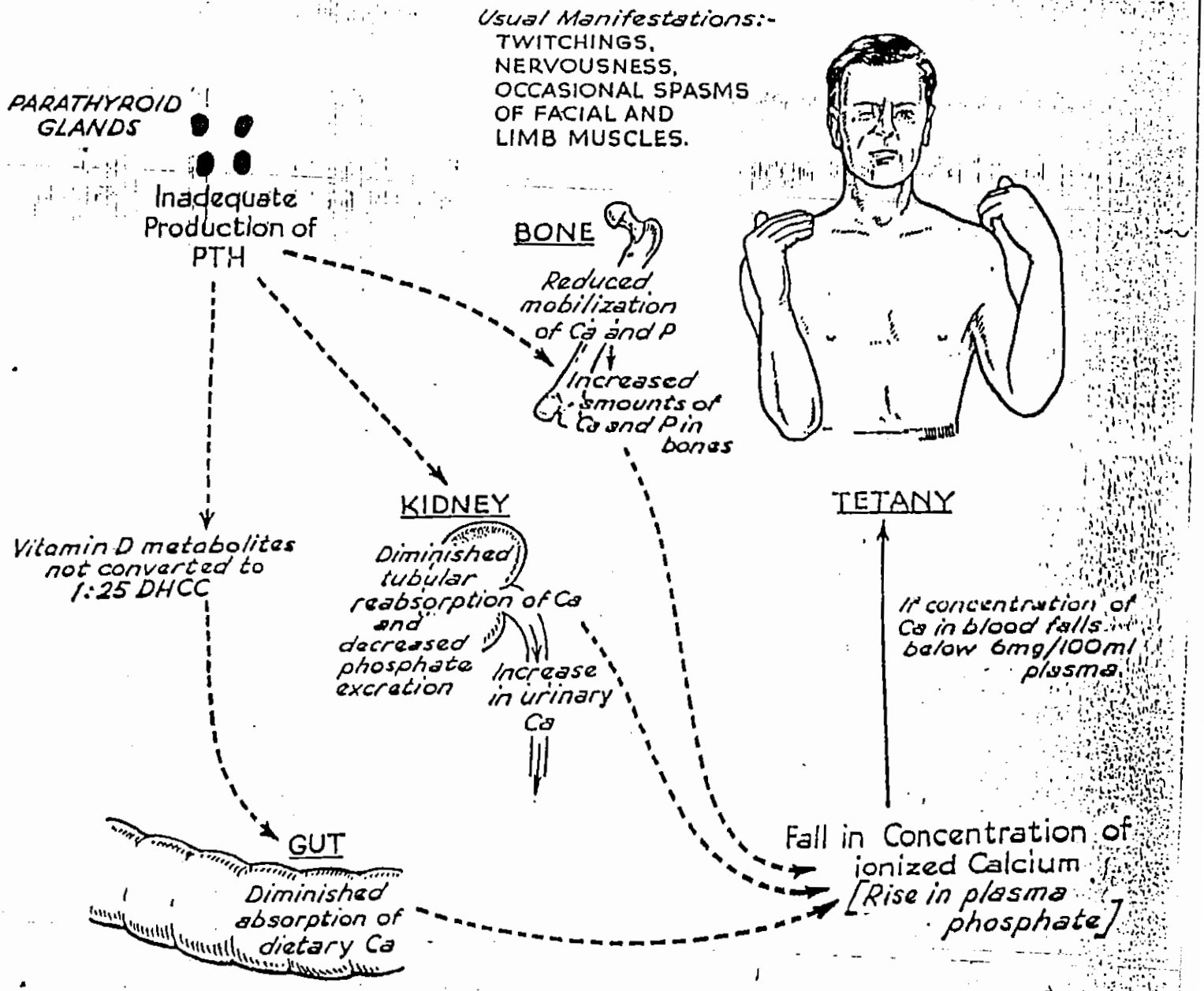


FIGURE 38-7 Overview of parathyroid hormone *(PTH)* actions. PTH acts directly on bone and kidney to increase calcium influx into plasma. By stimulating $1,25\text{-}(OH)_2\text{-}D$ synthesis, PTH indirectly also increases calcium absorption from the gut. Thus plasma calcium level increases. In contrast, PTH inhibits renal tubular resorption of phosphate, thereby increasing urinary phosphate excretion. This effect quantitatively offsets entry of phosphate from bone and gut. Therefore plasma phosphate level decreases.

UNDERACTIVITY of PARATHYROIDS

Atrophy or removal of Parathyroid tissue causes a fall in BLOOD CALCIUM level and increased excitability of Neuromuscular tissue. This leads to severe convulsive disorder – TETANY.



[Note the inverse relationship between plasma calcium and inorganic phosphate]

Symptoms are relieved by injection of Calcium, large doses of a Vit.D compound and Parathormone.

OVERACTIVITY of PARATHYROIDS

Overactivity of the Parathyroids *(due often to tumour)* leads to rise in BLOOD CALCIUM level and eventually to OSTEITIS FIBROSA CYSTICA.

(After case by ASHHURST.)

OSTEITIS FIBROSA CYSTICA

PARATHYROID GLANDS

Overproduction of PTH

BONE

Greatly increased mobilization of Ca and P

Excess amounts of Ca and P are withdrawn from stores in bones

Eventual Softening and deformity of bones

KIDNEY

Greatly increased tubular reabsorption of Ca and tubular secretion of P

Great loss of P in Urine

↑ 1:25 DHCC

GUT

Great increase in absorption of dietary Ca

Great increase in Concentration of Ca in Blood

(Plasma Ca may be over 16mg/100ml → Increased Viscosity of Plasma.)

Deposition of Calcium in Unusual Sites e.g. Kidney.

Signs of Toxicity

(nausea, vomiting, loss of appetite, etc.)

The increased level of blood calcium eventually leads to excessive loss of CALCIUM in URINE (in spite of ↑ reabsorption) and also of WATER since the salt is excreted in solution. POLYURIA and THIRST result.

Excision of the overactive Parathyroid tissue abolishes syndrome.

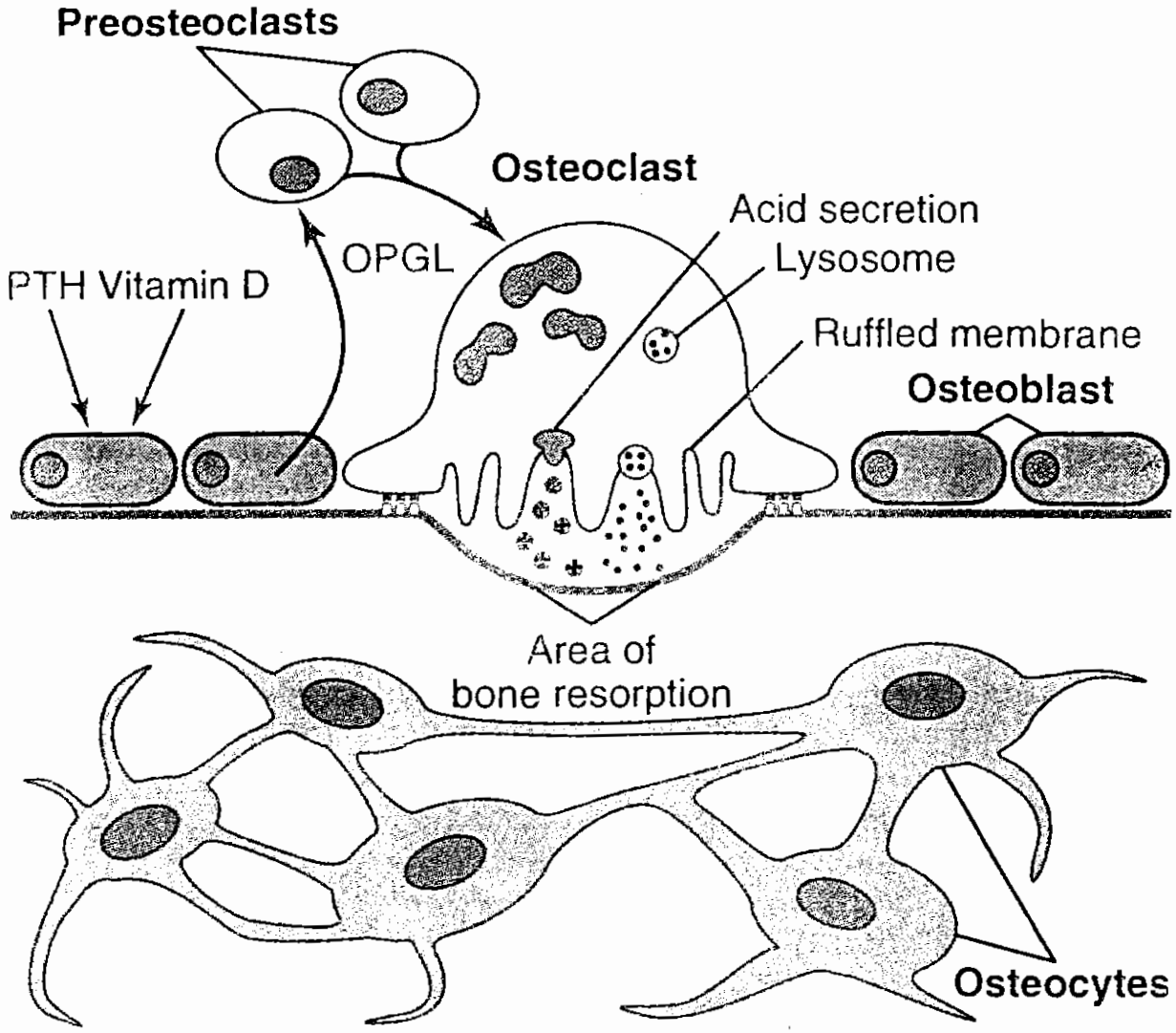


Figure 79-5 Bone resorption by osteoclasts. Parathyroid hormone (PTH) binds to receptors on osteoblasts, causing them to release osteoprotegerin ligand (OPGL), which binds to receptors on preosteoclast cells. This causes the cells to differentiate into mature osteoclasts. The osteoclasts then develop a ruffled border and release enzymes from lysosomes, as well as acids that promote bone resorption. Osteocytes are osteoblasts that have become encased in bone matrix during bone tissue production; the osteocytes form a system of interconnected cells that spreads all through the bone.

Vitamin D

Vitamin D, in conjunction with PTH, is the second major regulatory hormone for Ca^{2+} and phosphate metabolism. The roles of PTH and vitamin D can be distinguished as follows. The role of *PTH* is to maintain the plasma Ca^{2+} concentration, and its actions are coordinated to increase the ionized Ca^{2+} concentration toward normal. The role of *vitamin D* is to promote mineralization of new bone, and its actions are coordinated to increase *both* Ca^{2+} and phosphate concentrations in plasma so that these elements can be deposited in new bone mineral.

- **Bone.** In bone, 1,25-dihydroxycholecalciferol acts synergistically with PTH to stimulate osteoclast activity and bone resorption. This action may seem paradoxical, since the overall action of 1,25-dihydroxycholecalciferol is to promote bone mineralization. However, mineralized "old" bone is resorbed to provide more Ca^{2+} and phosphate to ECF so that "new" bone can be mineralized (bone remodeling).

Vitamin D & its Metabolism

1. Vitamin D, is a major regulator of calcium & phosphate metabolism.

2. Vitamin D is a hormone in the sense that it is synthesized in the body, although not by an endocrine gland; after further processing, it is transported via the circulation to act on target cells.

3. It is a vitamin in the sense that when it cannot be synthesized in sufficient quantities, it must be ingested in minimal amounts for health to be maintained.

4. Deficiency of vitamin D causes failure of bone mineralization & results in the classic disease of rickets in children & softening of the bones (osteomalacia) in adults.

5. The sterol structure of the synthesized form of vitamin D (D_3) differs slightly from the form usually ingested (D_2).

6. Vitamins D_3 & D_2 are essentially prohormones that undergo identical processing that converts them to molecules with identical qualitative & quantitative actions.

7. Once vitamin D enters the circulation from the skin or the gut, it is concentrated in the liver. There it is hydroxylated to 25-OH-D. this molecule is transported to the kidney where it undergoes alternative fates.

8. 24,25-$(OH)_2$-D is only 1/20th as potent as 1,25-$(OH)_2$-D & mainly serves to dispose of excess vitamin D.

9. Vitamin D, 25-OH-D & 1,25-$(OH)_2$-D circulate bound to a protein carrier. 1,25-$(OH)_2$-D has by far the lowest concentration & the shortest half-life of the three.

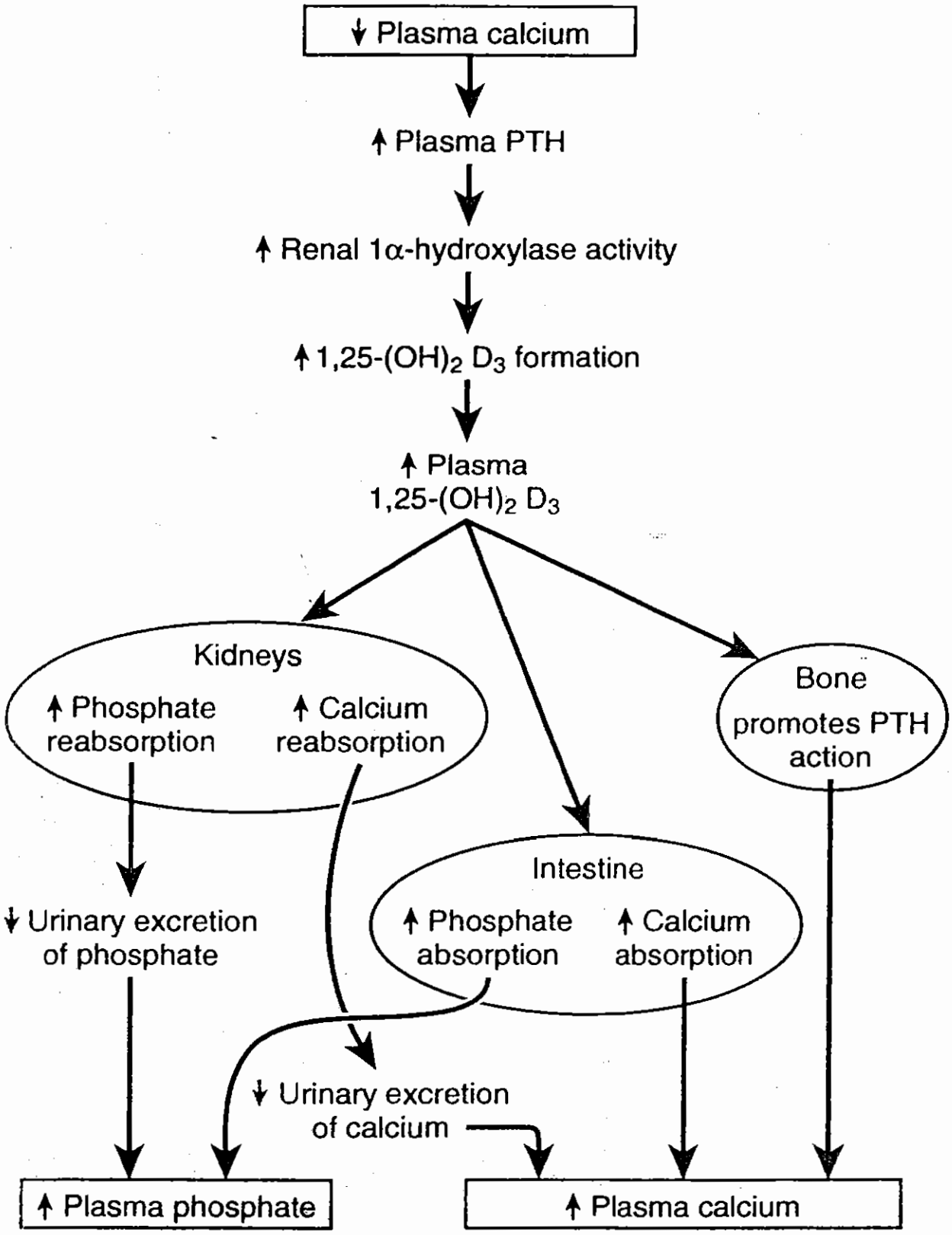


FIGURE 36.9 **Effects of 1,25-dihydroxycholecalciferol [1,25-$(OH)_2$ D_3] on calcium and phosphate metabolism.**

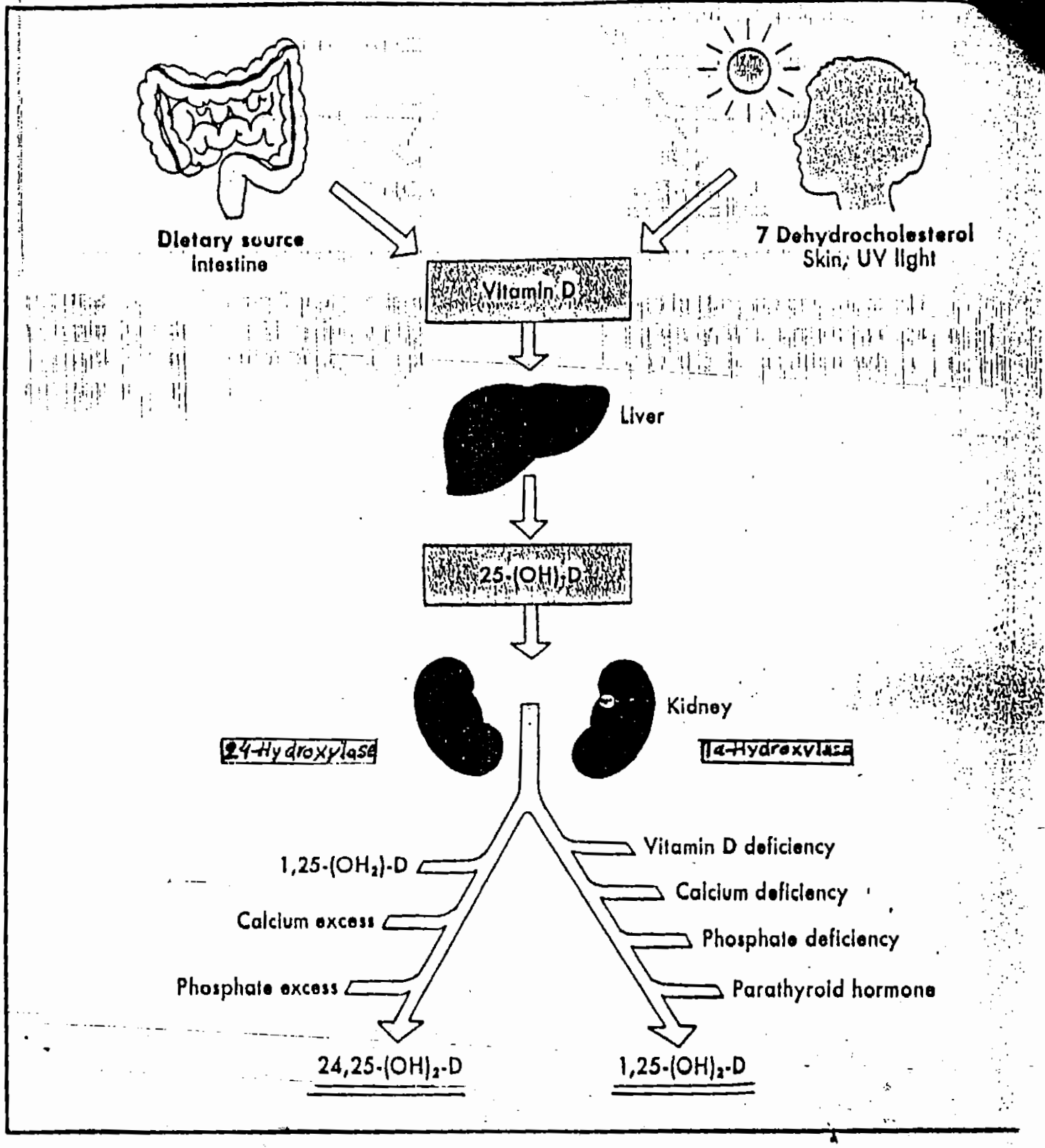


FIGURE 38-5 Vitamin D metabolism. Whether synthesized in the skin or absorbed from the d vitamin D undergoes 25 hydroxylation in the liver. In the kidney, it is further hydroxylated in 1 position when more biological activity is required or in the 24 position when less biol activity is required.

TABLE 51-2. Vitamin D metabolism in humans

	Plasma concentration (μg/L)	*Plasma half-life (days)*	*Estimated production rate (μg/day)*
$1.25\text{-}(OH)_2\text{-}D_3$	0.03	1 to 3	1
$24,25\text{-}(OH)_2\text{-}D_3$	2	15 to 40	1
$25\text{-}OH\text{-}D_3$	20	5 to 20	10

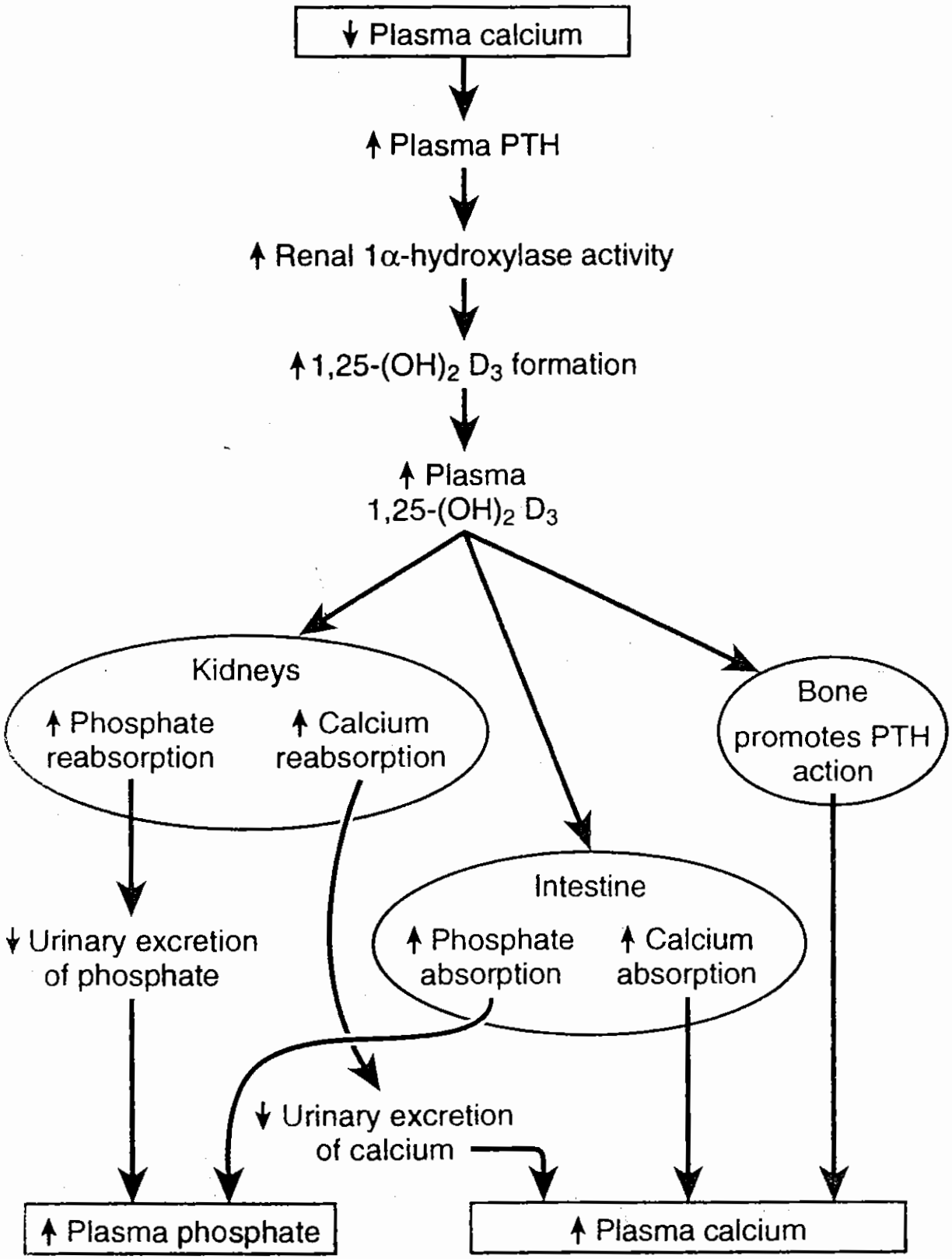


FIGURE 36.9 Effects of 1,25-dihydroxycholecalciferol [1,25-$(OH)_2$ D_3] on calcium and phosphate metabolism.

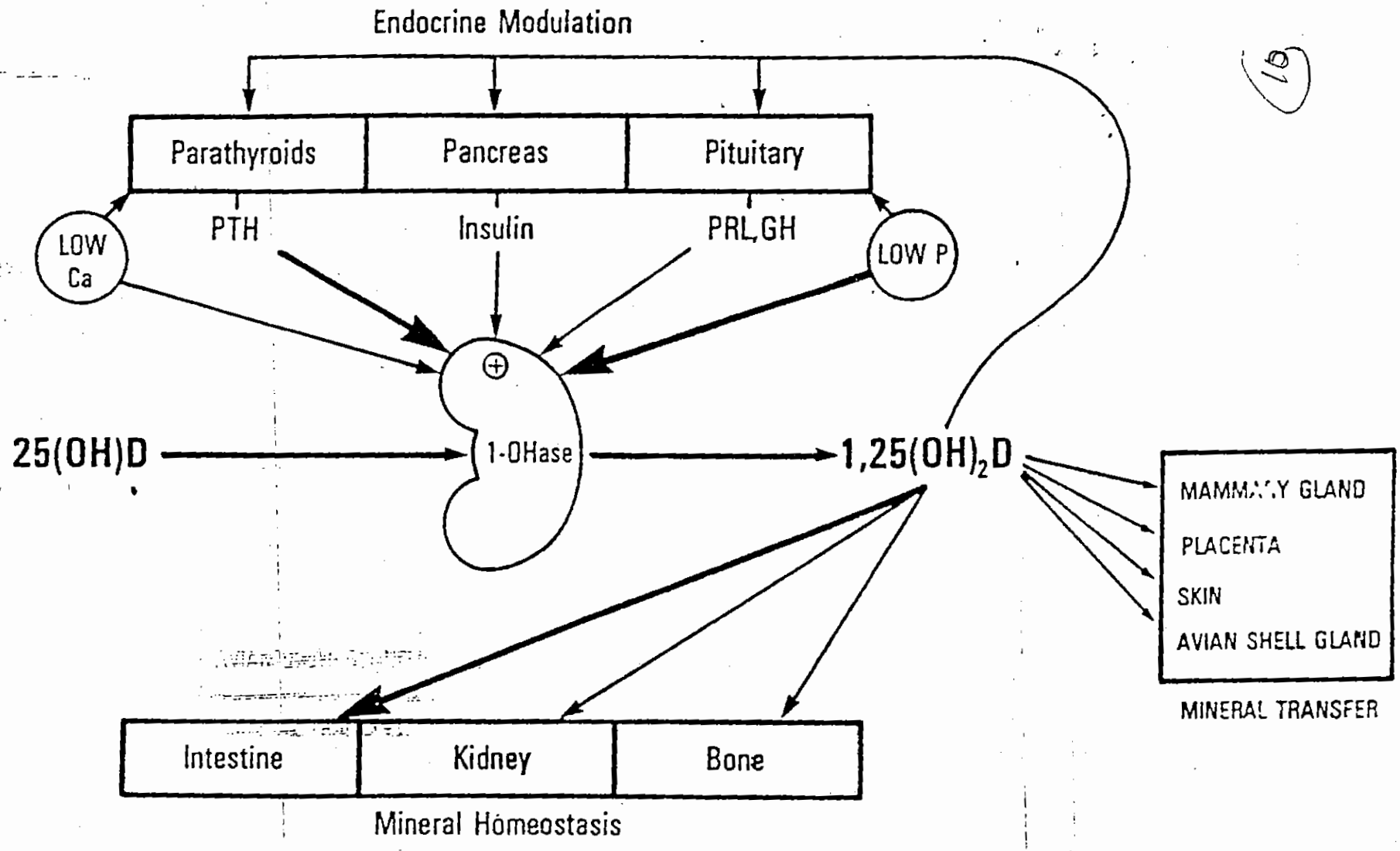


Figure 8.41. Function and regulation of 1,25-$(OH)_2D$. (From Haussler and McCain, 1977.)

Table 7.5 Causes of deficiency of 1:25-dihydroxycalciferol

Failure to synthesize cholecalciferol in the skin (this occurs in dark-skinned people in a temperature climate)
Dietary deficiency of cholecalciferol (relatively unimportant)
Failure to hydroxylate cholecalciferol in the 25 position (this occurs in chronic liver disease; hepatic osteodystrophy)
Rapid metabolism of cholecalciferol and its active metabolites (this occurs when hepatic enzymes are induced and is seen in patients taking anticonvulsants)
Failure to hydroxylate 25-cholecalciferol in the 1 position (this occurs in patients with chronic renal failure; renal osteodystrophy)

Table 27–1
Some of the Physiological Actions of Calcium

1. Required for the maintenance of normal sodium permeability in nerves
2. Involved in triggering the release of acetylcholine from nerve endings at the neuromuscular junction
3. Involved in excitation-contraction coupling in muscle cells
4. Serves as an intracellular signal for some hormones
5. Required by some enzymes for normal activity
6. Required for blood clotting to occur normally
7. Required for protein secretion
8. Constituent of bone

Table 21–1. Distribution (mmol/L) of calcium in normal human plasma.

Diffusible		1.34
Ionized (Ca^{2+})	1.18	
Complexed to HCO_3^-, citrate, etc	0.16	
Nondiffusible (protein-bound)		1.16
Bound to albumin	0.92	
Bound to globulin	0.24	
Total plasma calcium		2.50

⊛ Ionized Ca^{++} concentration, depends on blood pH. Alkalosis increases the protein-bou and decreases the ionized Ca^{++} concentration, whereas acidosis has the opposite eff. ect.

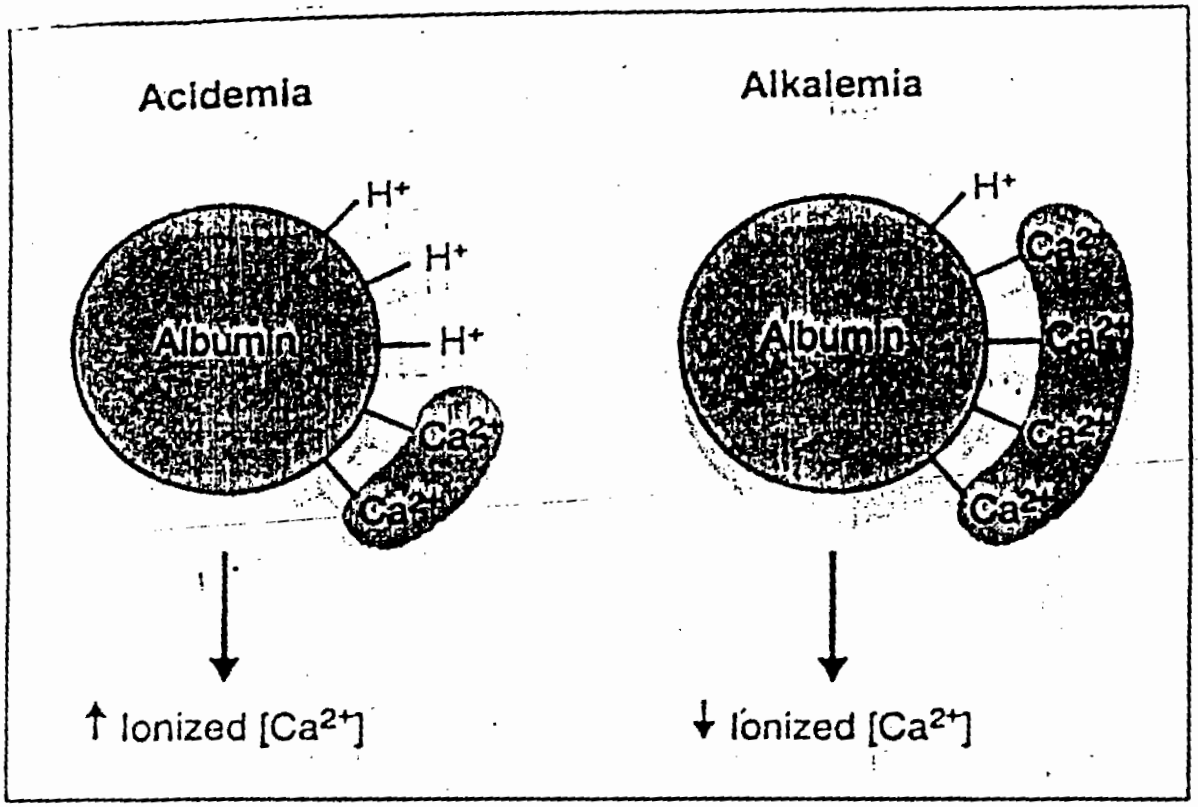


FIGURE 9–32. Effects of acid-base disturbances on plasma protein-binding of Ca^{2+} and the ionized Ca^{2+} concentration in blood.

Table 27–4
Major Inorganic Constituents of Bone

Constituent	Total Body Content Present in Bone (%)
Calcium	99
Phosphate	85
Carbonate	80
Magnesium	50
Sodium	35
Water	9

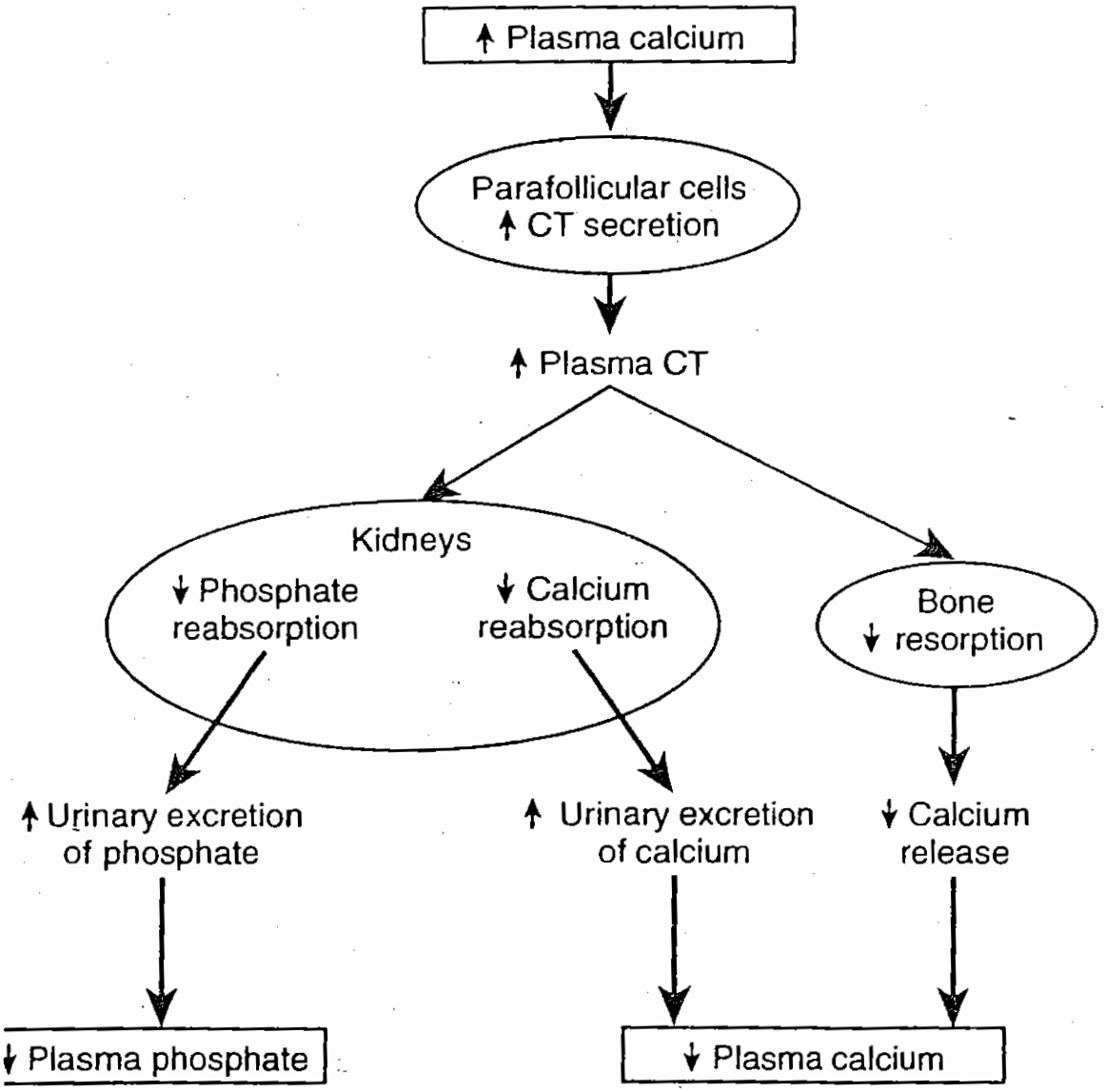


FIGURE 36.8 **Effects of calcitonin (CT) on calcium and phosphate metabolism.**

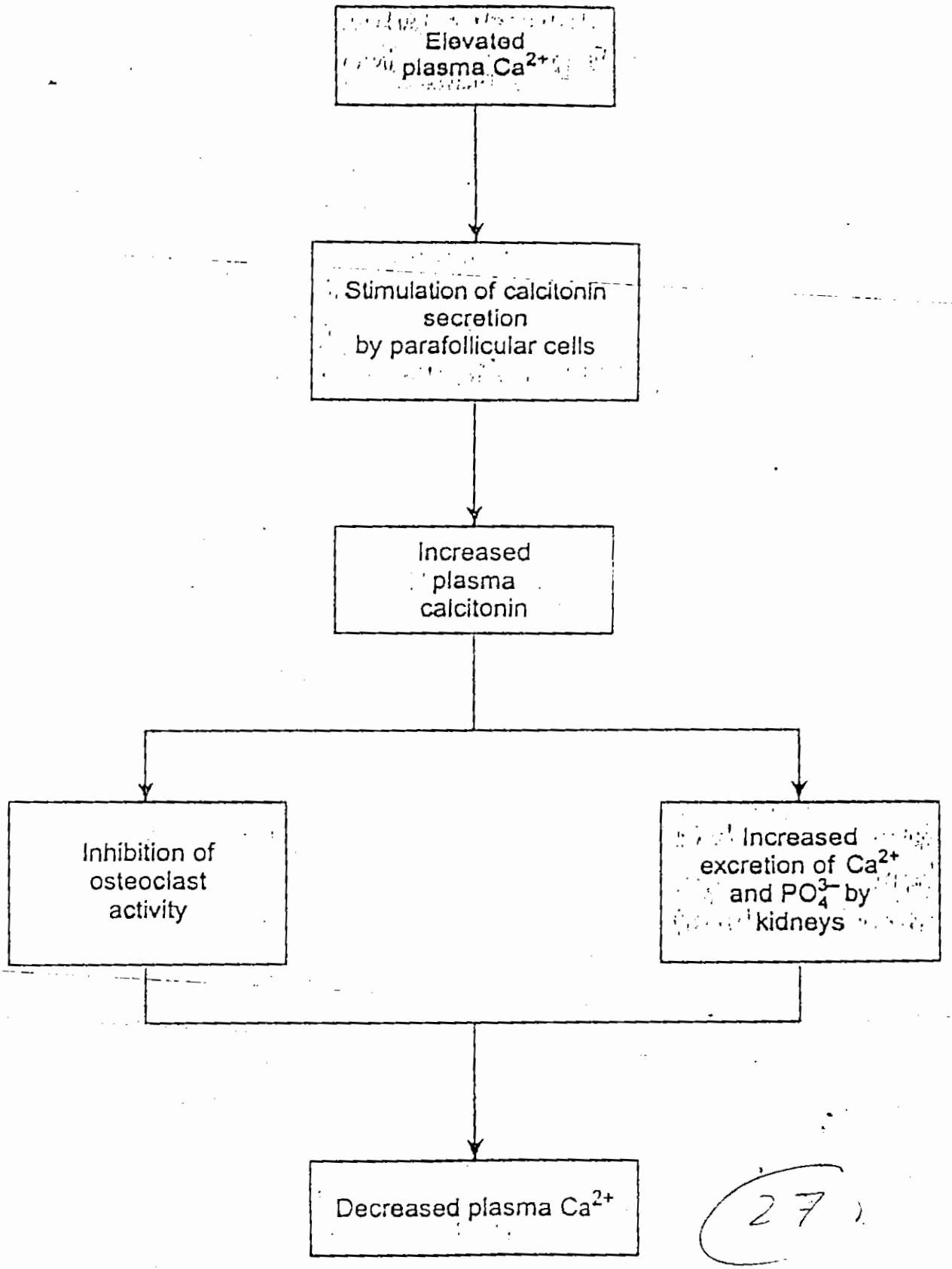


Fig. 12.26 The principal actions of calcitonin and the factors thought to regulate its secretion.

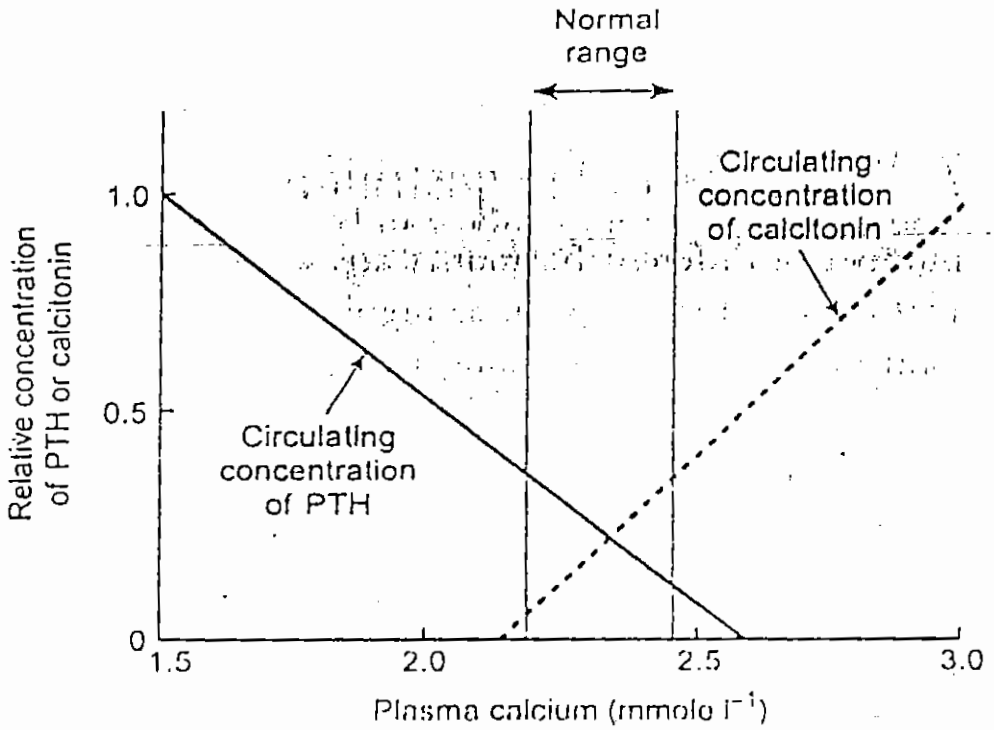


Fig. 12.25 The relationship between the plasma calcium concentration and the secretion of both parathyroid hormone and calcitonin. As calcium rises, the secretion of parathyroid hormone falls while that of calcitonin rises.

Calcitonin

1. Calcitonin, a straight-chain peptide of 32 amino acids, has a molecular weight of 3400.
2. The biologically active core of the molecule probably resides in its central region.
3. Calcitonin is secreted by thyroid parafollicular cells known as "C" cells.
4. Calcitonin, (CT), decreases plasma calcium levels by antagonizing the actions of PTH on bone.
5. Calcitonin is also present in nervous tissue, where it may function as a neuromodulator.
6. The major stimulus to CT secretion is a rise in plasma calcium concentration.
7. The hypocalcemic action is caused by inhibition both of osteocytic osteolysis & osteoclastic bone resorption particularly when these are stimulated by PTH.
8. However, with respect to phosphate, it has the same net effect as PTH; that is, CT decreases plasma phosphate concentration & increases urinary phosphate excretion slightly.
9. The importance of CT in humans is controversial CT deficiency does not lead to hypercalcemia & CT hypersecretion does not produce hypocalcemia. It may be that abnormal CT secretion is easily compensated for by adjustment in PTH & vitamin D levels.
10. Is degraded within the liver & kidney, after half-life of 30-60 minutes.

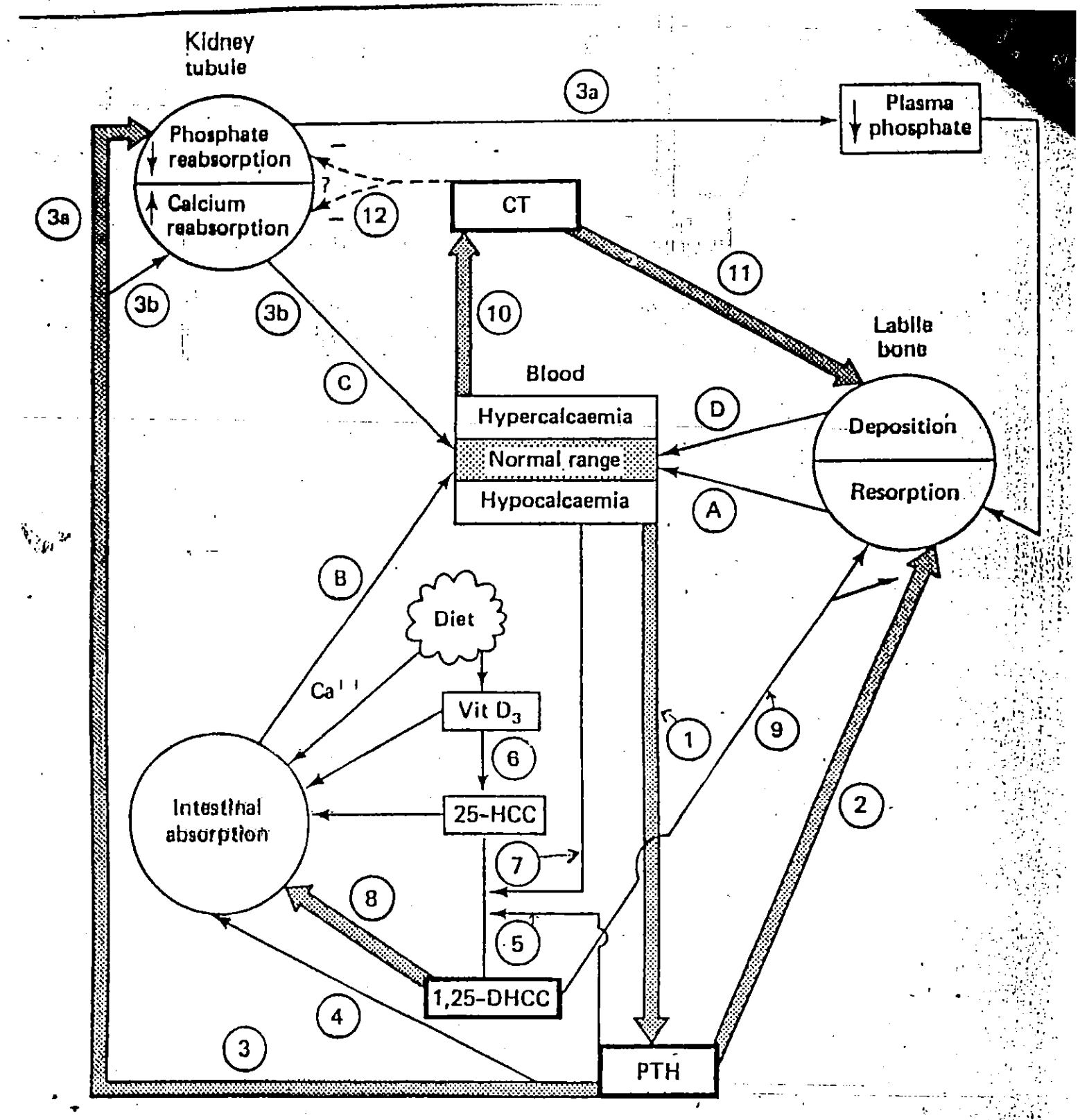


Fig. 12.7 A diagram to illustrate the interactions of parathormone, calcitonin and vitamin D_3 and its derivatives in calcium homeostasis.

① Ca^{++}, PO_4^{---} and Mg^{++} homeostasis are essential for health and life. A complex system acts to maintain normal body contents and ECF levels of these minerals in the face of environmental (e.g., diet) and internal (e.g., pregnancy) changes.

② The key elements in the system are:-
Ⓐ- vit. D. Ⓑ- PTH. Ⓒ- calcitonin. Ⓓ- other hormones

③ The G.I.T, the kidneys, the skeleton, the skin and the liver are involved in the homeostatic regulation.

Table 21–2. Factors that affect bone formation and calcium metabolism.

Parathyroid hormone
1,25-Dihydroxycholecalciferol
Calcitonin
Glucocorticoids
Growth hormone and somatomedins
Thyroid hormones
Estrogens
Insulin
IGF-I
Epidermal growth factor
Fibroblast growth factor
Platelet-derived growth factor
Prostaglandin E_2
Osteoclast activating factor

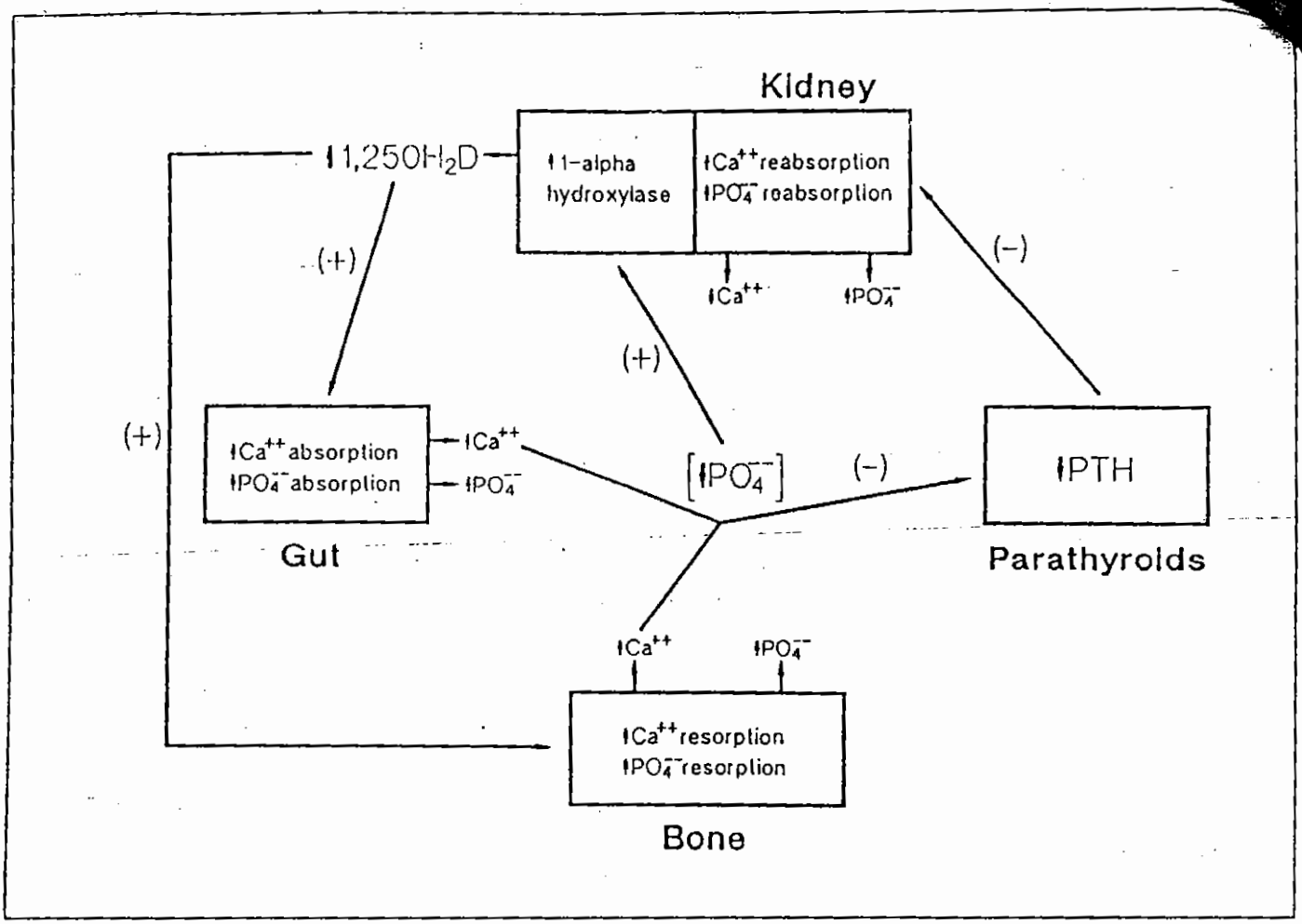


Fig. 51-3. Integrated phosphate homeostasis. The responses to marked decreases of serum phosphate concentrations are shown; opposite responses occur to marked increases. (+ = stimulation; − = inhibition; *PTH* = parathyroid hormone.)

Table 27-2
Some of the Physiological Actions of Phosphate

1. Functions as part of the intracellular buffer system
2. Important constituent of a variety of macromolecules, such as nucleic acids, phospholipids, metabolic intermediates, and phosphoproteins
3. Constituent of bone

نقص فيتامين «دي» يؤدي لمخاطر بالقلب لدى الشباب

اظهرت دراسة جديدة ان المراهقين الذين يعانون من نقص في الفيتامين دي يواجهون خطرا اكبر بالاصابة بمشاكل في القلب والسكري وارتفاع الضغط ونسبة السكر في الدم.

وتظهر الدراسة كذلك ان المراهقين البيض لديهم معدل من الفيتامين دي اكثر بمرتين تقريبا من الشباب السود واكثر بنسبة ٣٠٪ من المراهقين الاميركيين من اصل مكسيكي.

وقال روبرت اكيل الرئيس السابق لجمعية ''اميركان هارت'' ان هذه ''المعطيات حول الفيتامين دي عند الشباب تثير مخاوف حول الخيارات الغذائية وحول الوقت الذي يمضونه في الشمس''.

وينتج جسم الانسان الفيتامين دي من خلال التعرض لاشعة الشمس وهذا الفيتامين موجود ايضا في اغذية مثل الحليب والسمك والبيض. ويساعد الفيتامين دي في امتصاص الكالسيوم وابقاء مستوى مناسب من الفوسفور والكالسيوم في الدم.

والفيتامين دي يتحلل في الدهون لذا فان الاشخاص الذين يعانون من زيادة في الوزن او من البدانة عند مستوى البطن لديهم مستويات غير كافية من هذه الفيتامين. والمراهقون الذين لديهم مستويات متدنية جدا من الفيتامين دي يواجهون خطر الاصابة بمجموعة من المشاكل في القلب والسكري ومستوى منخفض من الكوليسترول اربع مرات اكثر من الاشخاص الاخرين.

اما خطر الاصابة بارتفاع ضغط الدم فيترفع ٢،٣٦ مرة ونسبة السكر في الدم ٢،٥٤ مرة.

وحللت الدراسة التي عرضت خلال المؤتمر السنوي ل ''اميركان هارت اسوسييشن'' معطيات عن ٣٥٧٧ مراهقا.

اف ب

Osteomalacia

Osteomalacia is rickets in adults and is frequently called "adult rickets."

Normal adults rarely have a serious *dietary* deficiency of vitamin D or calcium because large quantities of calcium are not needed for bone growth as in children. However, a serious deficiency of both vitamin D and calcium occasionally occurs as a result of steatorrhea (failure to absorb fat), for vitamin D is fat-soluble, and calcium tends to form insoluble soaps with fat; consequently, in steatorrhea both vitamin D and calcium tend to pass into the feces. Under these conditions an adult occasionally has such poor calcium and phosphate absorption that adult rickets can occur, though this almost never proceeds to the stage of tetany—but very often is a cause of severe bone disability.

TABLE 36.3 Causes of Osteomalacia and Rickets

Inadequate availability of vitamin D	Dietary deficiency or lack of exposure to sunlight
	Fat-soluble vitamin malabsorption
Defects in metabolic activation of vitamin D	25-Hydroxylation (liver)
	Liver disease
	Certain anticonvulsants, such as phenobarbital
	1-Hydroxylation (kidney)
	Renal failure
	Hypoparathyroidism
	Certain anticonvulsants
Impaired action of 1,25-dihydroxycholecalciferol on target tissues	1,25-Dihydroxycholecalciferol receptor defects
	Uremia

RICKETS

Rickets occurs mainly in children as a result of calcium or phosphate deficiency in the extracellular fluid. Yet, ordinarily rickets is due to lack of vitamin D, rather than a dietary lack of calcium or phosphate. If the child is properly exposed to sunlight, the 7-dehydrocholesterol in the skin becomes activated by the ultraviolet rays and forms vitamin D_3, which prevents rickets by promoting calcium and phosphate absorption from the intestines, as discussed earlier in the chapter.

Children who remain indoors through the winter in general do not receive adequate quantities of vitamin D without some supplementary therapy in the diet. Rickets tends to occur especially in the spring months because vitamin D formed during the preceding summer is stored in the liver and is still available for use during the early winter months. Also, calcium and phosphate absorption from the bones can prevent clinical signs of rickets for the first few months of vitamin D deficiency.

OSTEOPOROSIS

Osteoporosis, the most common of all bone diseases in adults and especially in old age, is a different disease from osteomalacia and rickets, for it results from diminished organic matrix rather than abnormal bone calcification. Usually, in osteoporosis the osteoblastic activity in the bone is less than normal, and consequently the rate of bone deposition is depressed. But occasionally, as in hyperparathyroidism, the cause of the diminished bone is excess osteoclastic activity.

CAUSES OF OSTEOPOROSIS ARE:

1) Lack of physical stress on the bones because of inactivity.
2) Malnutrition to the extent that sufficient protein matrix cannot be formed.
3) Lack of vitamin C,
4) Postmenopausal lack of estrogen secretion.
5) Old age, in which many of the protein anabolic functions are poor .
6) Cushing's disease, because massive quantities of glucocorticoids cause decreased deposition of protein.
7) Acromegaly, possibly because of lack of sec hormones, excess of adrenocortical hormnes, and often lack of insulin because of the diabetogenic effect of growth hormone.

Hypocalcemic Tetany

Hypocalcemic tetany is the involuntary tetanic contraction of skeletal muscles that occurs when the extracellular Ca^{2+} concentration falls to about 40 percent of its normal value. This may seem surprising, because we have seen that Ca^{2+} is required for excitation–contraction coupling. However, recall that this Ca^{2+} is sarcoplasmic reticulum Ca^{2+}, not extracellular Ca^{2+}. The effect of changes in extracellular Ca^{2+} is exerted not on the sarcoplasmic reticulum Ca^{2+} but directly on the plasma membrane. Low extracellular Ca^{2+} (**hypocalcemia**) increases the opening of Na^+ channels in excitable membranes, leading to membrane depolarization and the spontaneous firing of action potentials. This causes the increased muscle contractions, which are similar to muscular cramping. Chapter 11 discusses the mechanisms controlling the extracellular concentration of calcium ions.

Calcium plays a key role in nerve and muscle function, enzyme function, and mineral balance in bone.

Calcium affects nerve and muscle excitability, neuro-
ransmitter release from axon terminals, and excitation–
contraction coupling in muscle cells. It serves as a second
or third messenger in several intracellular signal trans-
luction pathways. Some enzymes use calcium as a cofac-
or, including some in the blood-clotting cascade. Finally,
calcium is a major constituent of bone. Of all these roles,
he one that demands the most careful regulation of
plasma calcium is the effect of calcium on nerve excit-
bility. Calcium affects the sodium permeability of nerve
nembranes, which influences the ease with which action
potentials are triggered. Low plasma calcium (**hypocal-
cemia**) can lead to the generation of spontaneous action
potentials in nerves. When motor neurons are affected,
etany of the muscles of the motor unit may occur; this
ondition is called **hypocalcemic tetany**.

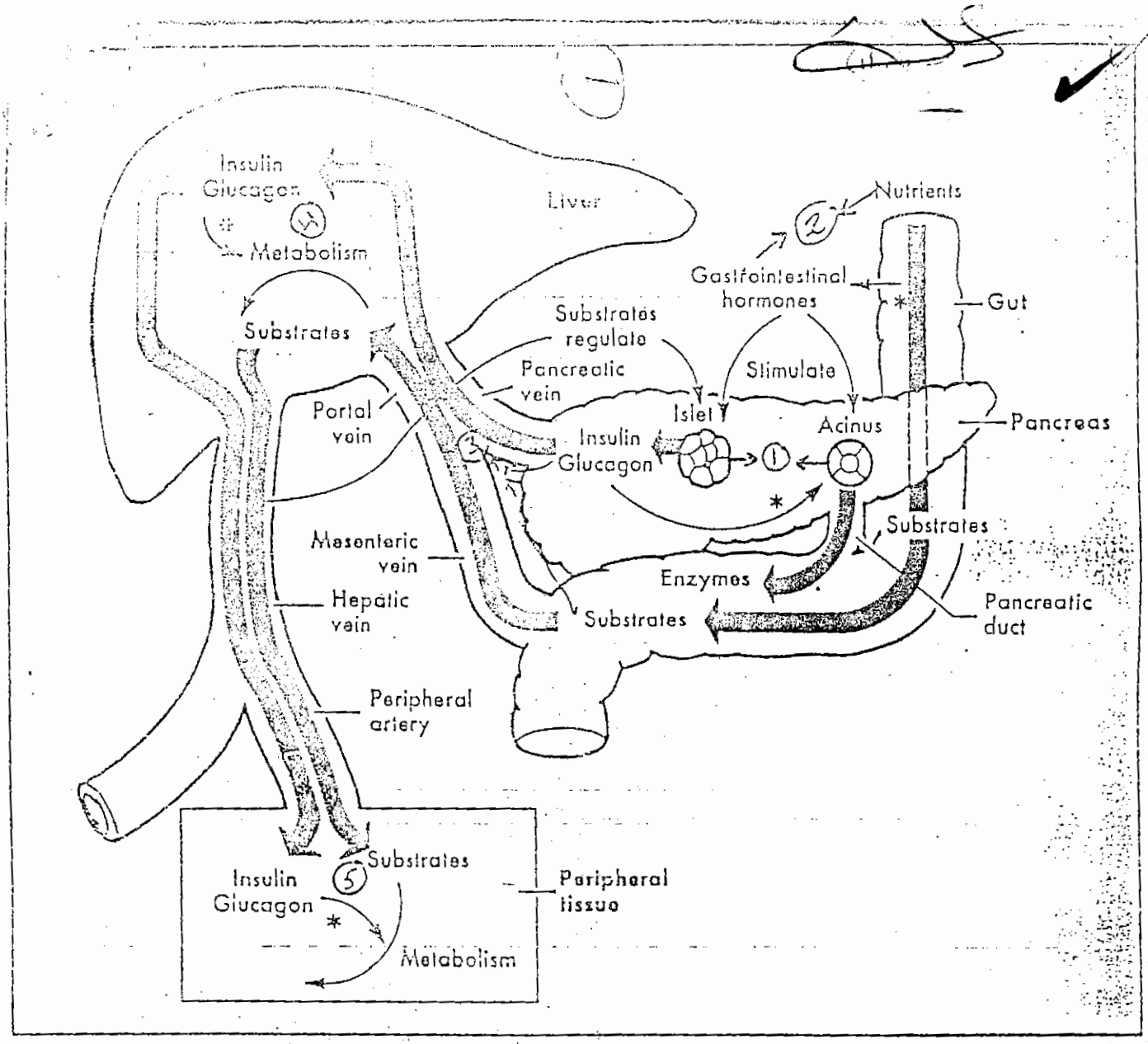


FIGURE 37-1 A schematic view of the pivotal location of the pancreatic islets. Secretion of the islet hormones insulin and glucagon is coordinated with secretion of exocrine pancreatic enzymes. Both are stimulated by entry of nutrients into the gastrointestinal tract and by gastrointestinal hormones. Islet hormones are secreted into the portal vein and thereby reach the liver with the substrate products of nutrient digestion. Within the liver they affect the metabolism of the ingested substrates. Islet hormones that pass through the liver with substrates affect disposition of these substrates by peripheral tissues. In turn these substrates feed back on the pancreatic islets to modulate the secretion of insulin and glucagon.

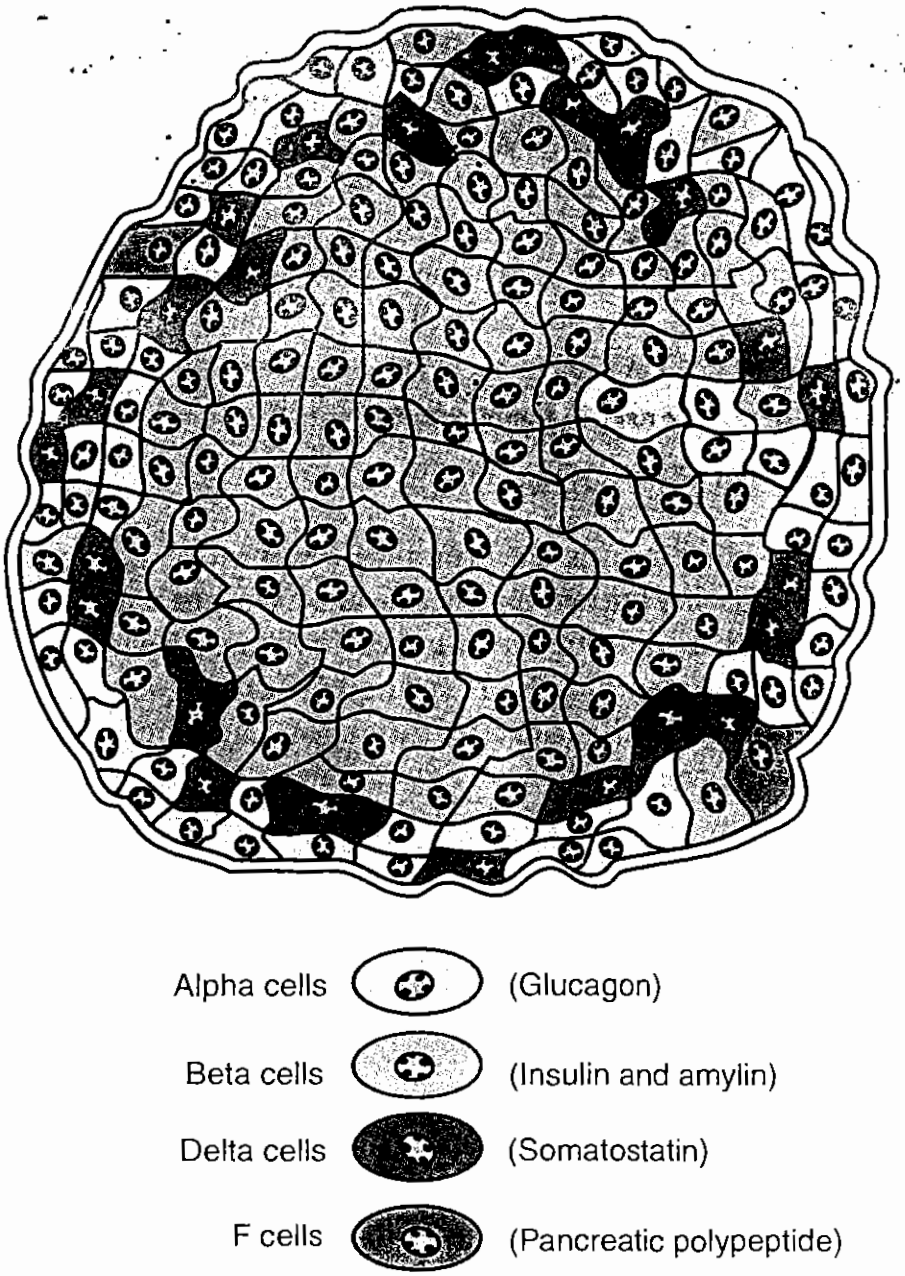


FIGURE 34.1 Major cell types in a typical islet of Langerhans. Note the distinct anatomic arrangement of the various cell types. (Modified from Orci L, Unger RH. Functional subdivision of islets of Langerhans and possible role of D cells. Lancet 1975;2:1243–1244.)

Amylin is a 37–amino acid peptide that is almost exclusively expressed within pancreatic beta cells, where it is copackaged with insulin in secretory granules. Preclinical data indicate that amylin acts as a neuroendocrine hormone that complements the actions of insulin in postprandial glucose homeostasis via several mechanisms. These include a suppression of postprandial glucagon secretion and a slowing of the rate at which nutrients are delivered from the stomach to the small intestine for absorption.

Table 19–1. Cell types in pancreatic islets of Langerhans.

Cell Types	Approximate % of Islet Mass	Secretory Products
A cell (α)	20%	Glucagon, proglucagon
B cell (β)	75%	Insulin, C peptide, proinsulin
D cell (δ)	3–5%	Somatostatin
F cell (PP cell)	< 2%	Pancreatic polypeptide

(10)

Pancreatic islets of Langerhans comprise 1% to 2% of the mass of pancreas and are scatered throughout the organ

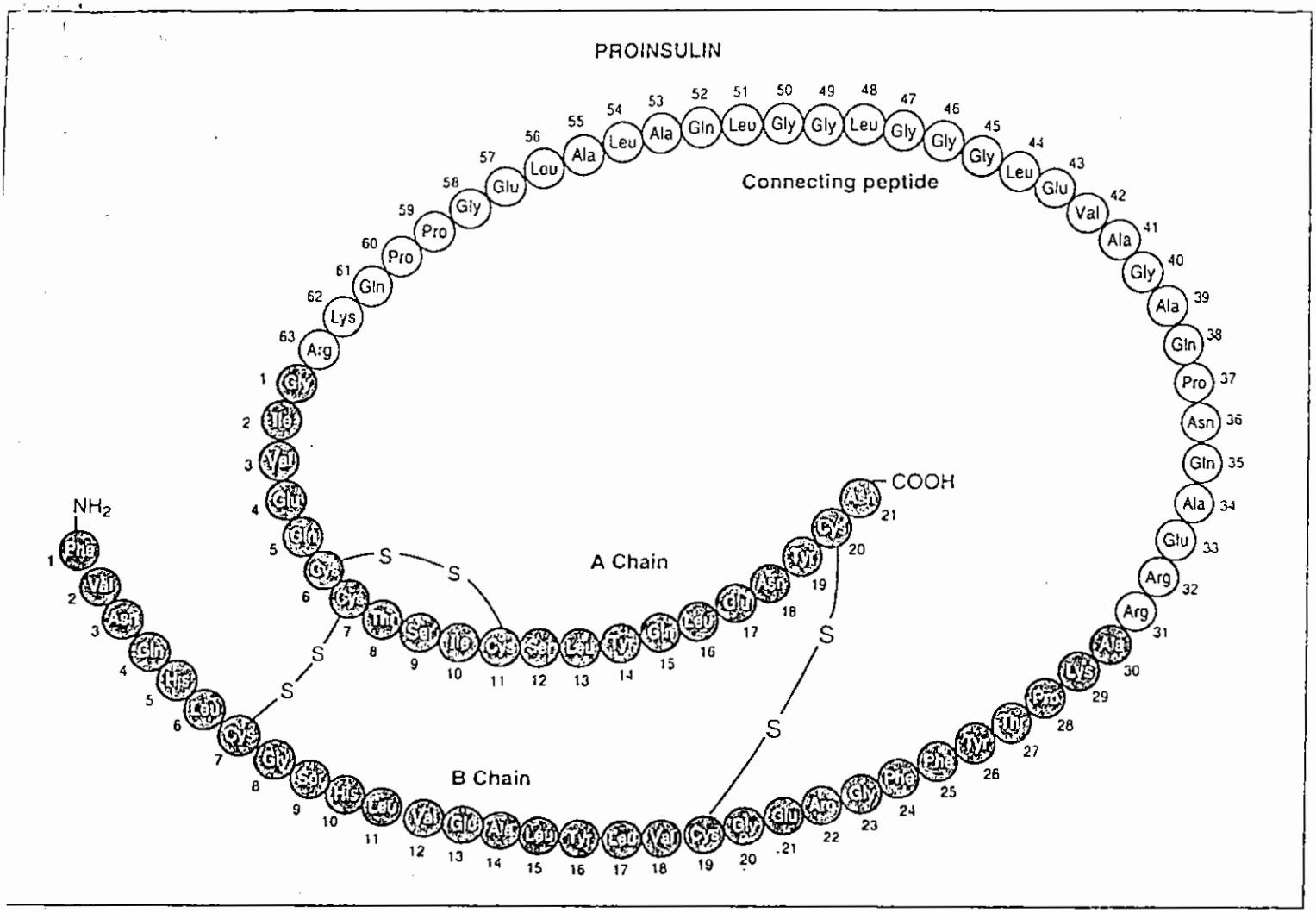


FIGURE 9–26. Structure of porcine proinsulin. The connecting peptide (C peptide) is cleaved to form insulin. (Modified with permission from W. N. Shaw and R. R. Chance. Effect of porcine proinsulin in vitro on adipose tissue and diaphragm of the normal rat. Diabetes 17:737, 1968.)

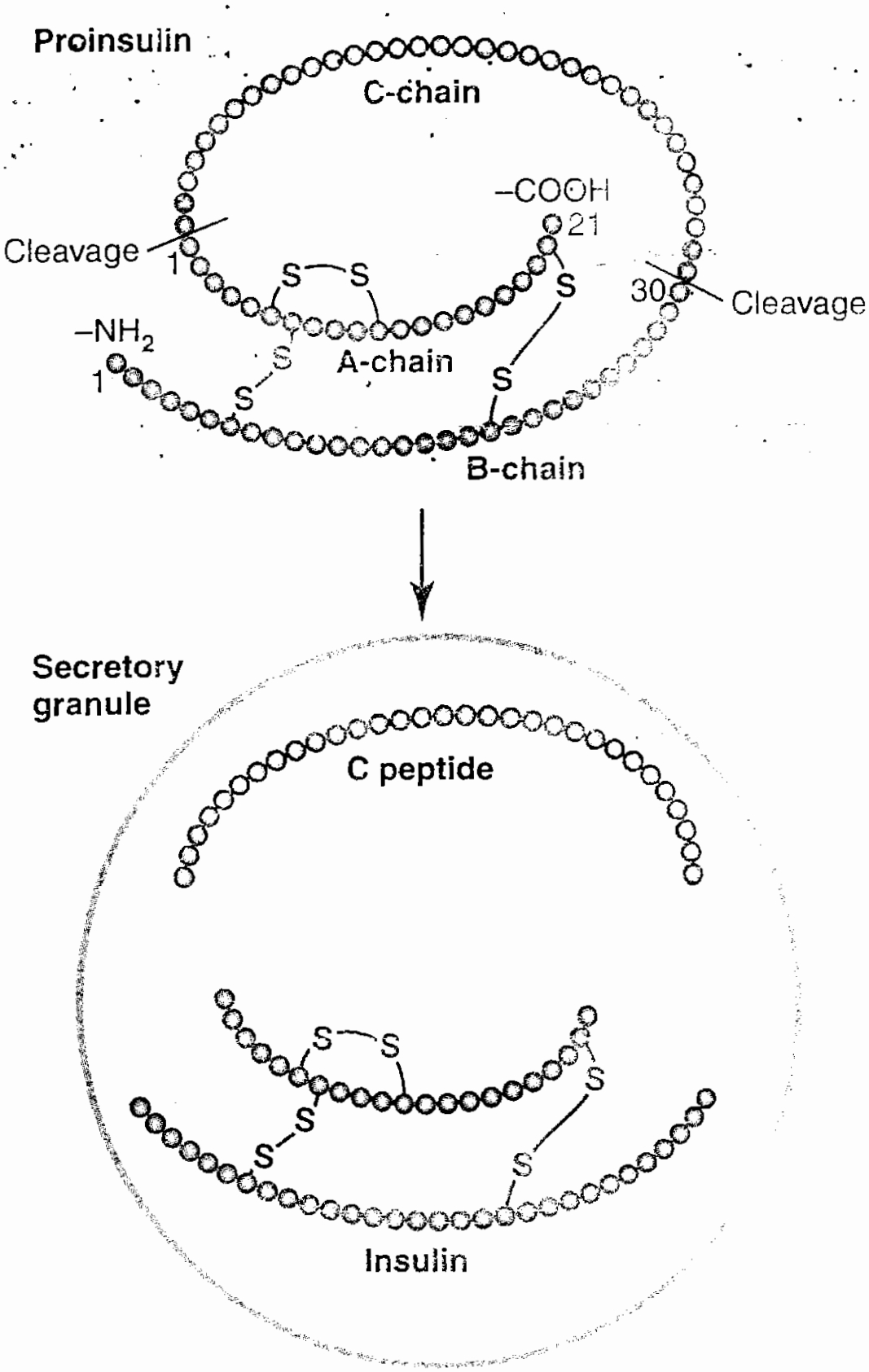


Figure 78-2 Schematic of the human proinsulin molecule, which is cleaved in the Golgi apparatus of the pancreatic beta cells to form connecting peptide (C peptide), and insulin, which is composed of the A and B chains connected by disulfide bonds. The C peptide and insulin are packaged in granules and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

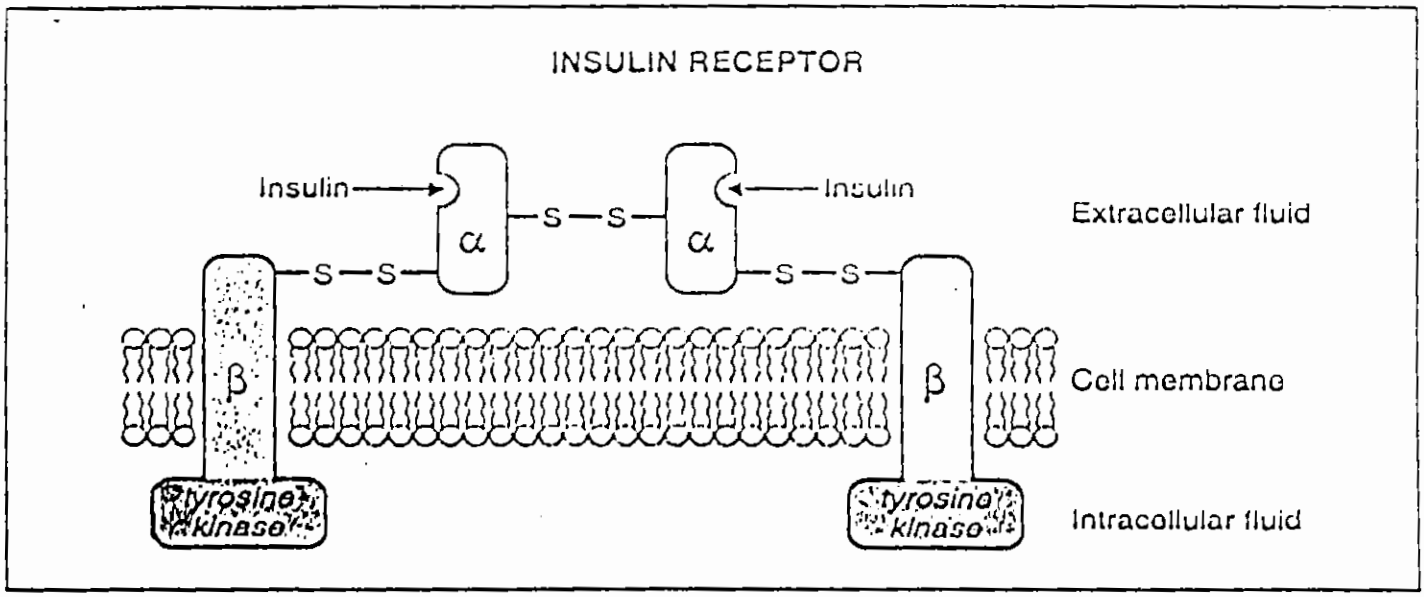


FIGURE 9–28. Structure of the insulin receptor. The two α subunits are connected by disulfide bonds; each α subunit is connected to a β subunit by a disulfide bond. The β subunits have tyrosine kinase activity.

Insulin receptors are found on many different cells in the body, including cells in which insulin does not increase glucose uptake. The receptor is made up of 2 α and 2 β glycoprotein subunits. The subunits are linked to each other and to β subunits by disulfide bonds. The α subunits bind insulin and are extracellular, whereas the β subunits span the membrane. The intracellular ends of the β subunits have tyrosine kinase activity. Binding of insulin triggers the tyrosine kinase activity of the β subunits, producing autophoisphorylation of the β subunits on tyrosine residues. This autophosphorylation in necessary for insulin to exert its biologic effects.

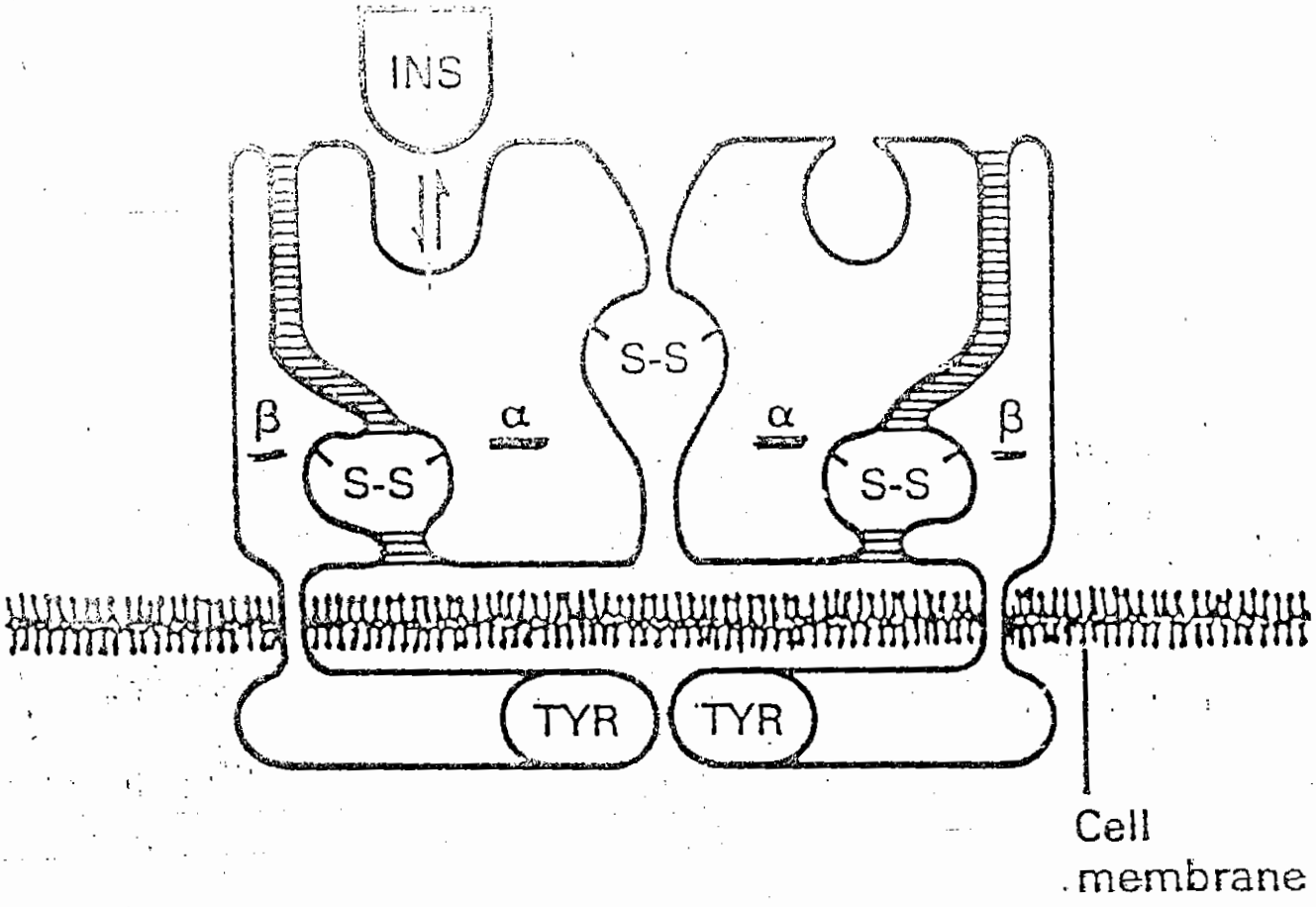


Figure 19-5. Diagrammatic representation of the structure of the insulin receptor. The receptor is a tetrameric protein made up of 2 α and 2 β subunits joined by disulfide (—S—S—) bonds. Insulin (INS) binds to the α subunits and this triggers autophosphorylation of the tyrosine kinase portions of the β subunits inside the cell. The autophosphorylation in turn triggers the rest of the multiple and extensive effects of insulin (Modified from Andersen AS: Reception and transmission *Nature* 1989;**337:**12.)

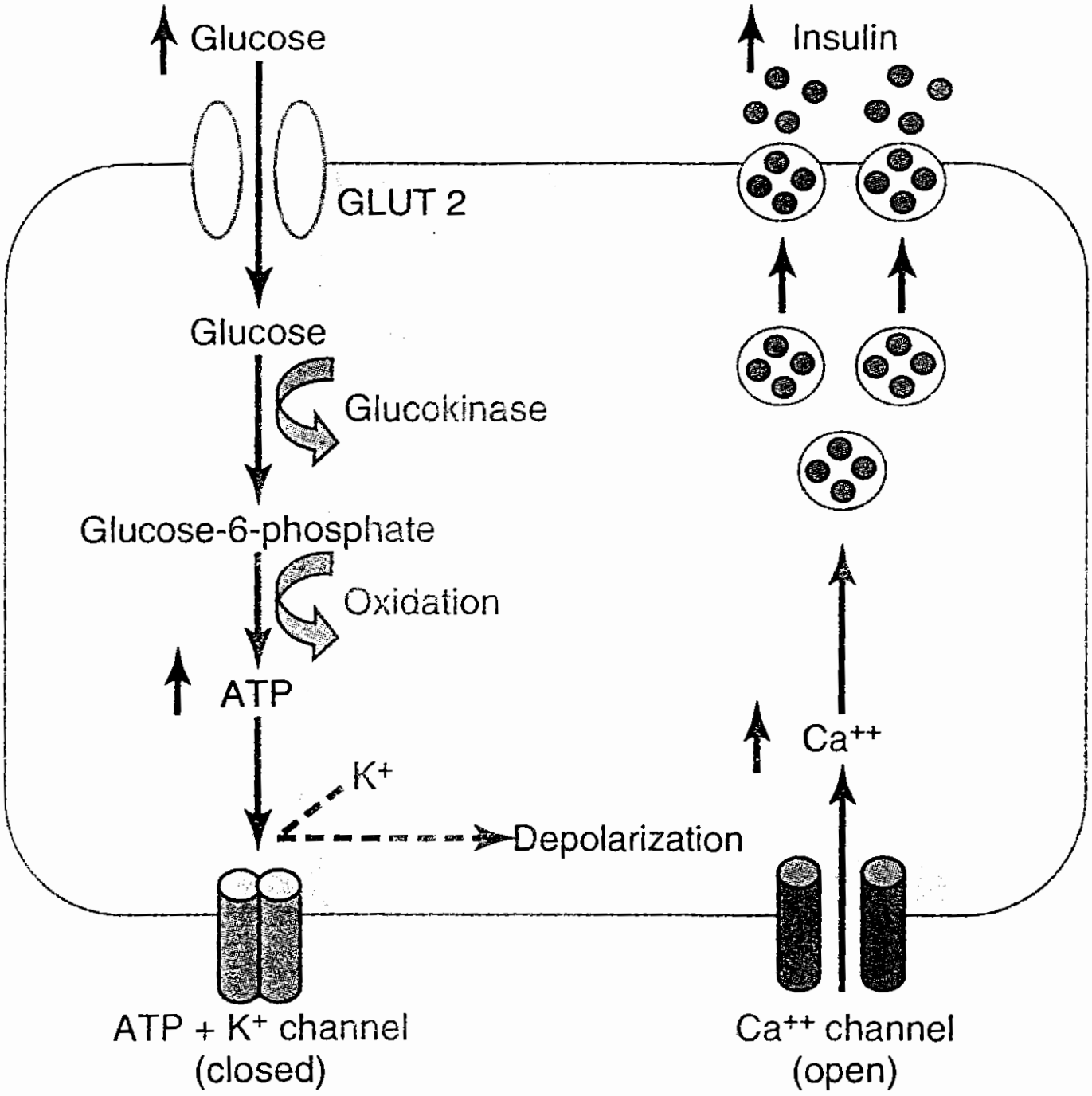


Figure 78-7 Basic mechanisms of glucose stimulation of insulin secretion by beta cells of the pancreas. GLUT, glucose transporter.

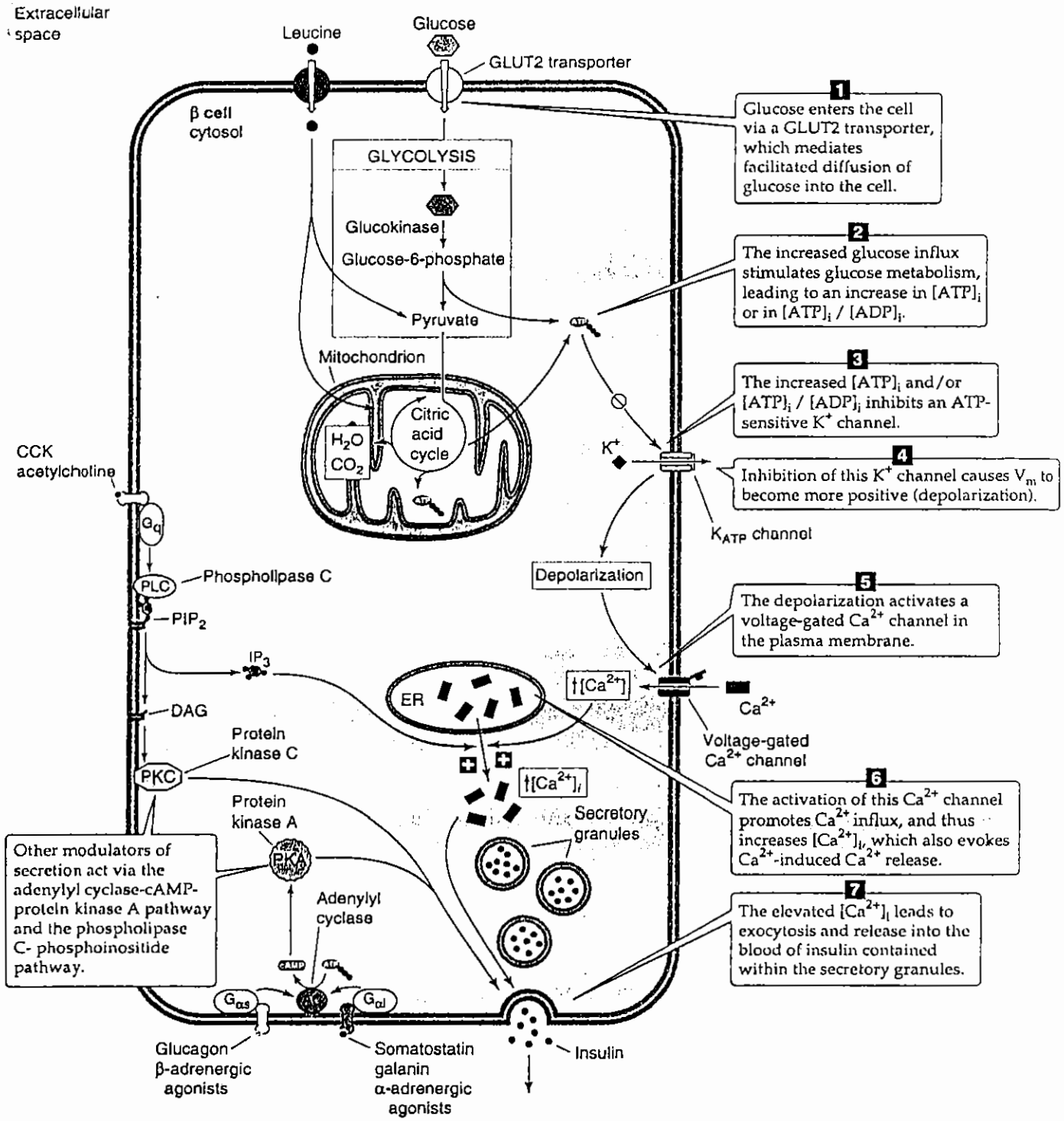


FIGURE 50–4. Mechanism of insulin secretion by the pancreatic β cell. Increased levels of extracellular glucose trigger the β cell to secrete insulin in the seven steps outlined in this figure. Metabolizable sugars (e.g., galactose and mannose) and certain amino acids (e.g., arginine and leucine) can also stimulate the fusion of vesicles that contain previously synthesized insulin. In addition to these fuel sources, certain hormones (e.g., glucagon, somatostatin, CCK) can also modulate insulin secretion. ADP, adenosine diphosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; CCK, cholecystokinin; DAG, diacylglycerol; ER, endoplasmic reticulum; IP_3, inositol 1,4,5-triphosphate; PIP_2, phosphatidylinositol 4,5-biphosphate; PKA, protein kinase A; PLC, phospholipase C.

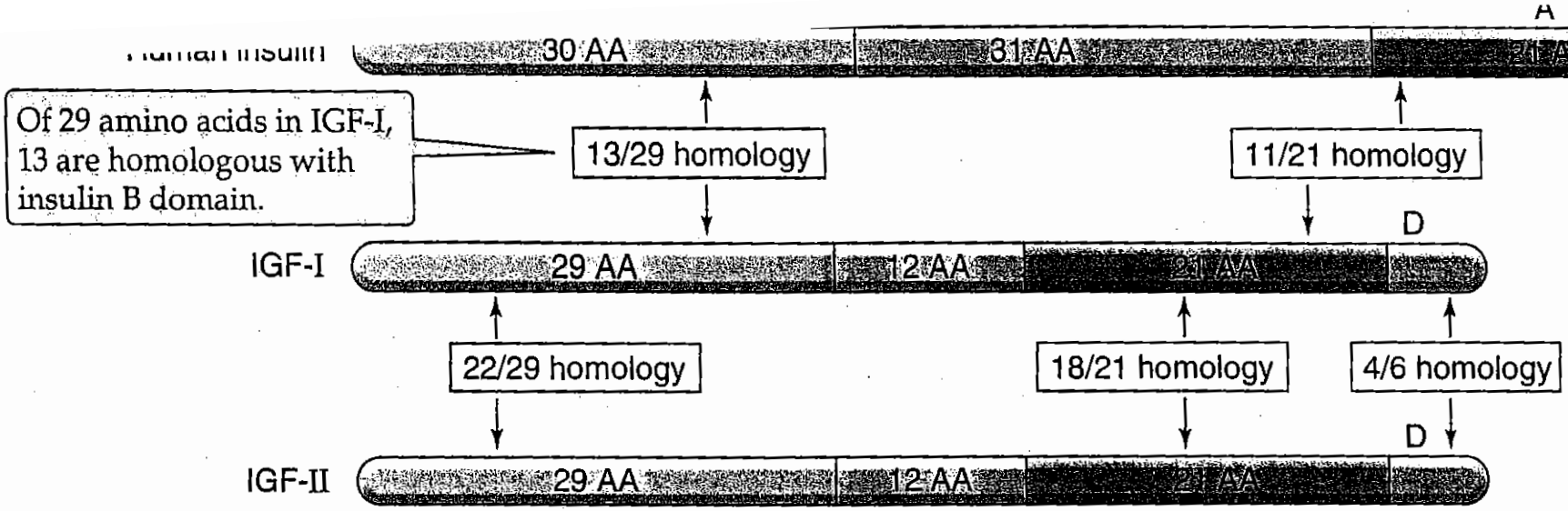


FIGURE 47–5. Structure of the insulin-like growth factors (IGFs). Insulin, IGF-I, and IGF-II share three domains (A, B, and C), which share a high degree of amino acid sequence homology. The C region is cleaved from insulin (as the C peptide) during processing, but is not cleaved from either IGF-I or IGF-II. In addition, IGF-I and IGF-II also have a short D domain.

Insulin-Like Growth Factor I, Which Interacts with a Receptor Similar to the Insulin Receptor, Is the Principal Mediator of the Growth-Promoting Action of Growth Hormone

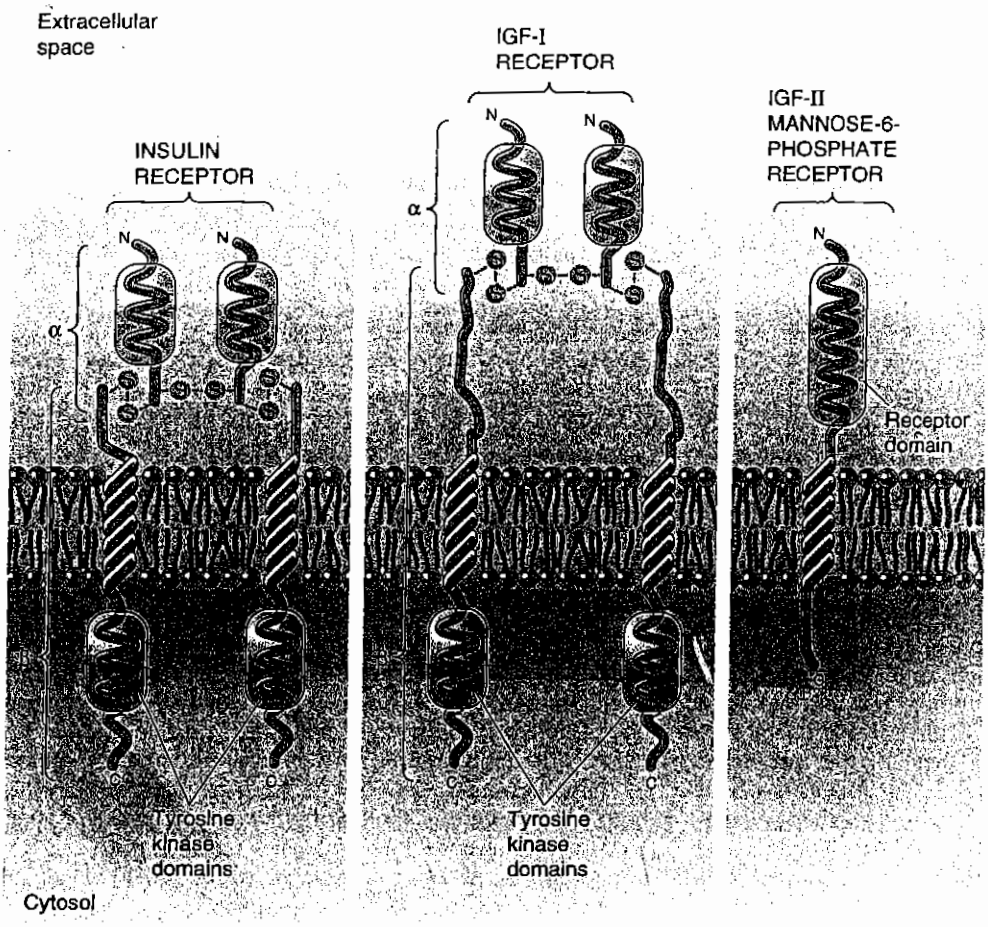


FIGURE 47–6. Comparison of insulin, insulin-like growth factor (IGF)-I, and IGF-II receptors. Both the insulin and IGF-I receptors are heterotetramers joined by disulfide bonds. For both, the cytoplasmic portion of the β subunits have tyrosine kinase domains as well as autophosphorylation sites. The IGF-II receptor (also called mannose-6-phosphate [M6P] receptor) is a single polypeptide chain with no kinase domain.

Insulin-Like Growth Factor II Has Actions Similar to Those of Insulin-Like Growth Factor I, but Is Less Dependent on Growth Hormone

The physiology of IGF-II differs from that of IGF-I in a number of important respects. First, as noted earlier, the synthesis of IGF-II depends less on circulating GH than that of IGF-I. In pituitary dwarfism secondary to GH deficiency, the circulating concentration of IGF-I is decreased, but that of IGF-II is not. In states of excessive GH secretion, plasma IGF-I is reliably elevated, whereas plasma IGF-II is not.

Although IGF-II also binds to the IGF-I receptor, it preferentially binds to its own so-called IGF-II receptor. This IGF-II receptor consists of a single-chain polypeptide and is structurally very distinct from the IGF-I receptor (see Fig. 47–6). The IGF-II receptor lacks a tyrosine-kinase domain and does not undergo autophosphorylation in response to the binding of either IGF-II or IGF-I. The IGF-II receptor also binds mannose-6-phosphate (M6P), but at a site different from that for IGF-II binding, and the receptor's physiological role appears to be in processing mannosylated proteins by targeting them for lysosomal degradation. Thus, the term "IGF-II receptor" is somewhat of a misnomer; the IGF-II receptor's role in the physiological action of IGF-II is not clear.

Despite these differences, IGF-II does share with IGF-I (and also with insulin) the ability to promote tissue growth and cause acute hypoglycemia. These properties appear to be due to IGF-II's structural similarity to proinsulin and its ability to bind to the IGF-I-receptor.

Insulin and glucagon provide short-term regulation of plasma glucose levels

Other hormones involved in the regulation of plasma glucose

Insulin and glucagon play a pivotal role in the fine regulation of plasma glucose levels—indeed, insulin is the only hormone capable of lowering plasma glucose, and glucagon is the most important hyperglycemic hormone. Nevertheless, a number of other agents also contribute to the maintenance of a stable blood glucose, as well as mobilizing glucose when necessary. These hormones include adrenal corticosteroids, growth hormone, the catecholamines, and the thyroid hormones.

TABLE 18-4 SUMMARY OF GLUCOSE-COUNTERREGULATORY CONTROLS*

	Glucagon	Epinephrine	Cortisol	Growth hormone
a - Glycogenolysis	X	X		
a - Gluconeogenesis	X	X	X	X
b - Lipolysis	–	X	X	X
c - Inhibition of glucose uptake	–	–	X	X

*All the processes listed on the left—glycogenolysis, gluconeogenesis, lipolysis, and inhibition of glucose uptake—are opposed to insulin's actions and are stimulated by one or more of the glucose-counterregulatory hormones in the table. An X indicates that the hormone stimulates the process; no X indicates that the hormone has no major physiological effect on the process. Epinephrine stimulates glycogenolysis in both liver and skeletal muscle, whereas glucagon does so only in liver.

To a great extent insulin may be viewed as the "hormone of plenty." Its secretion and plasma concentration are increased during the absorptive period and decreased during postabsorption, and these changes are adequate to cause most of the metabolic changes associated with these periods. In addition, opposed in various ways to insulin's effects are the actions of four major glucose-counterregulatory controls—glucagon, epinephrine and the sympathetic nerves to the liver and adipose tissue, cortisol, and growth hormone (Table 18-4). Glucagon and the sympathetic nervous system are activated during the postabsorptive period (or in any other situation with hypoglycemia) and definitely play roles in preventing hypoglycemia, glucagon being the more important. The rates of secretion of cortisol and growth hormone are not usually coupled to the absorptive-postabsorptive pattern; nevertheless, their presence in the blood at basal concentrations is necessary for normal adjustment of lipid and carbohydrate metabolism to the postabsorptive period, and excessive amounts of either hormone cause abnormally elevated plasma glucose concentrations.

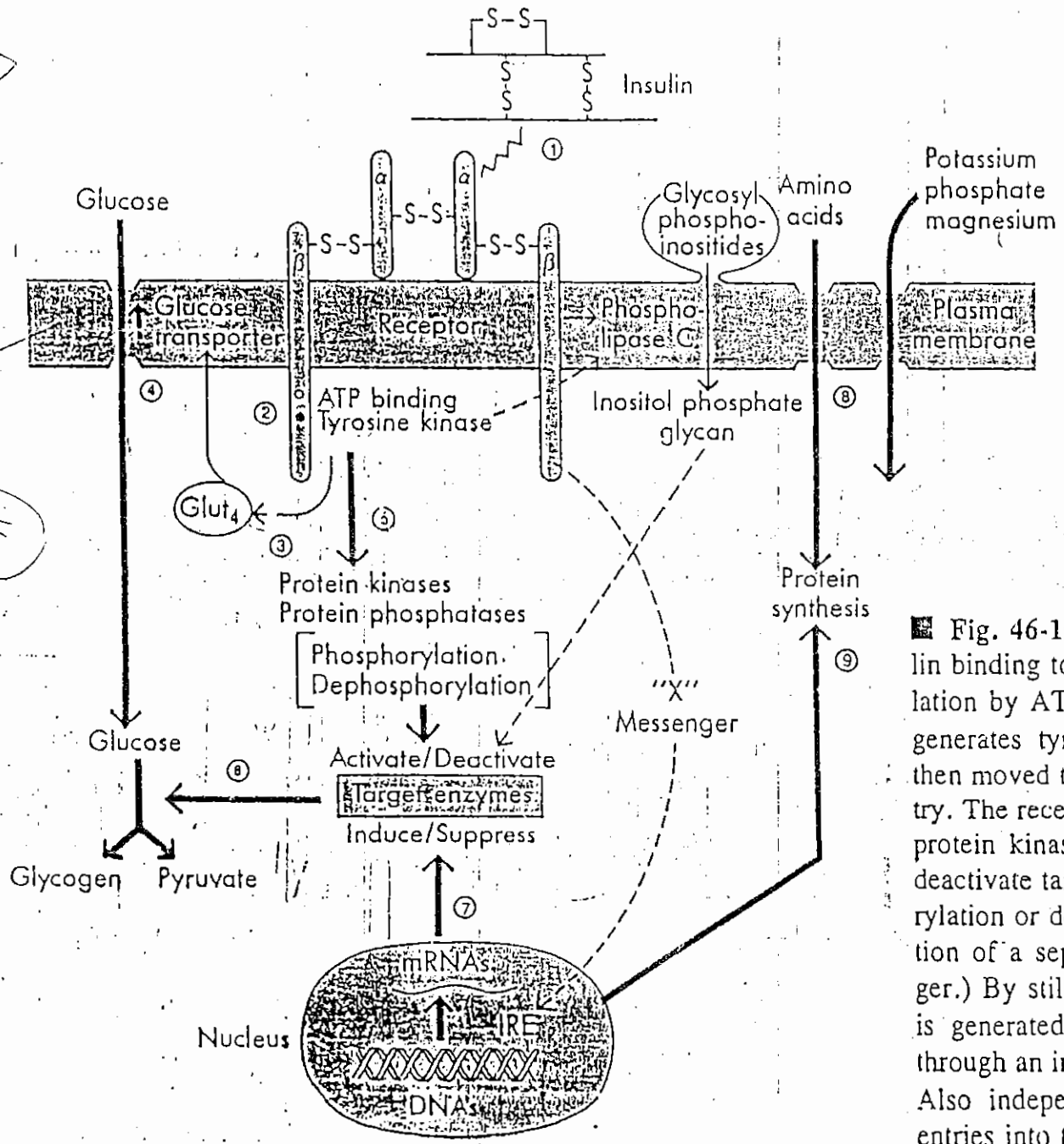


Fig. 46-10 Mechanisms of insulin action on cells. Insulin binding to α-subunit of its receptor causes autophosphorylation by ATP of an intracellular β-subunit receptor site that generates tyrosine kinase activity. Glucose transporters are then moved to the plasma membrane and facilitate glucose entry. The receptor tyrosine kinase is presumed to phosphorylate protein kinases and phosphatases, which in turn activate or deactivate target enzymes of glucose metabolism by phosphorylation or dephosphorylation. (This may be aided by generation of a separate inositol phosphate glycan second messenger.) By still undefined mechanisms, a transcription factor(s) is generated that stimulates or represses gene transcription through an insulin response element (IRE) in DNA molecules. Also independently potassium, magnesium, and phosphate entries into the cell are facilitated.

Table 23.13 Principal actions of insulin on cells

I. *Membrane effects*

Uptake of glucose increased

Uptake of amino acids increased

Uptake of fatty acids increased

Uptake of Mg^{2+} and K^{+} increased

II. *Metabolic effects*

Increased synthesis of DNA and RNA

Increased protein synthesis

Increased synthesis of glycogen (in liver and muscle)

Increased synthesis of triglycerides (in adipose tissue)

Increased synthesis of cholesterol (in liver and gut)

Increased fatty acid synthesis (in liver)

Decreased protein breakdown (in muscle)

Decreased glycogenolysis (in liver)

Decreased gluconeogenesis (in liver and kidney)

Decreased ketone production (in liver)

Decreased triglyceride breakdown (in adipose tissue)

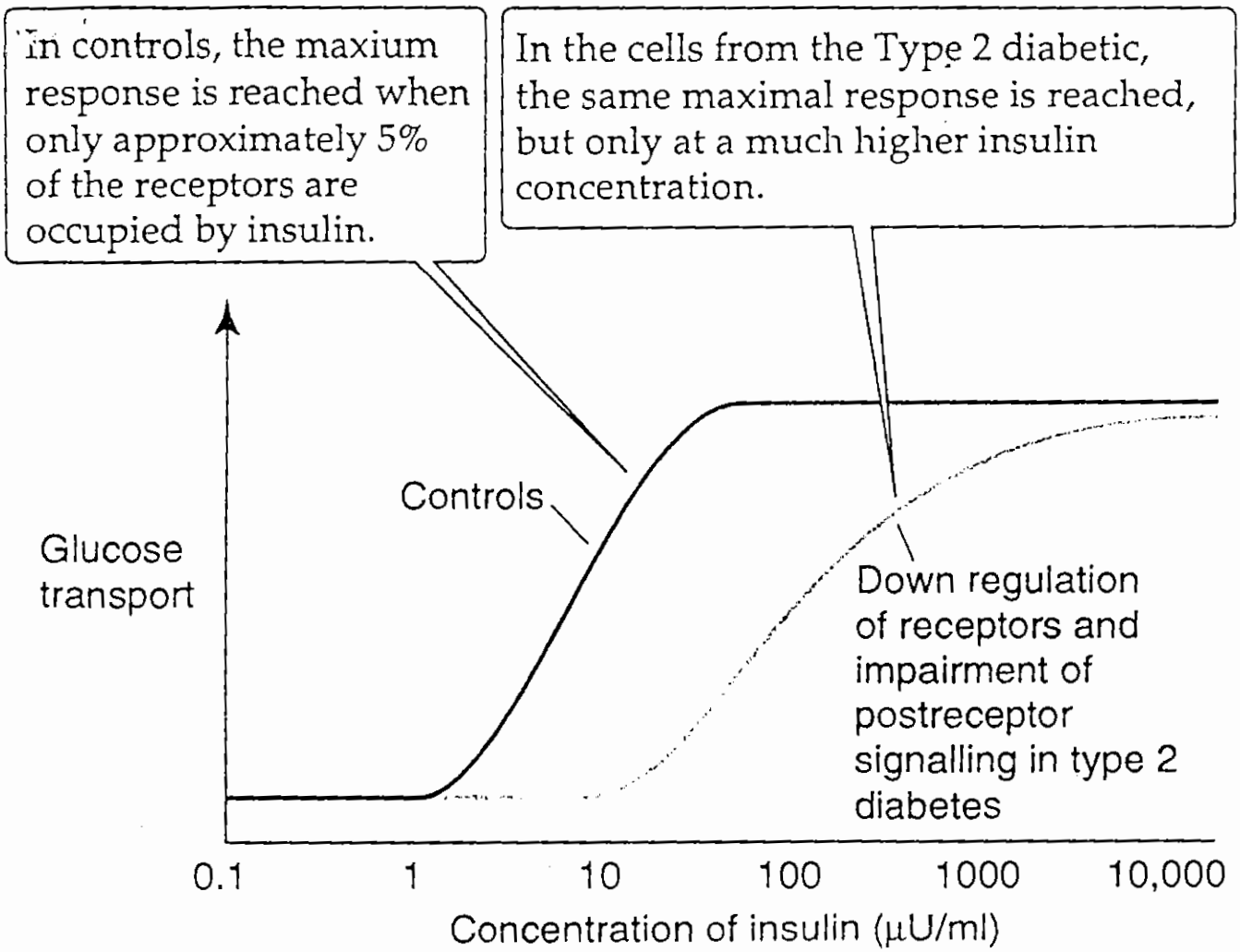


FIGURE 50–7. Response to insulin of normal and "downregulated" adipocytes.

Table 7.6
Biological effects of insulin

A. On carbohydrate metabolism
   1. Reduces rate of release of glucose from liver
      a. by inhibiting glycogenolysis.
      b. by stimulating glycogen synthesis.
      c. by stimulating glucose uptake.
      d. by stimulating glycolysis.
      e. by indirectly inhibiting gluconeogenesis via inhibition of fatty acid mobilization from adipose tissue.
   2. Increases rate of uptake of glucose into all insulin-sensitive tissues, notably muscle and adipose tissue
      a. directly, by stimulating glucose transport across the plasma membrane.
      b. indirectly, by reducing plasma-free fatty acid levels.

B. On lipid metabolism
   1. Reduces rate of release of free fatty acids from adipose tissue.
   2. Stimulates de novo fatty acid synthesis and also conversion of fatty acids to triglycerides in liver.

C. On protein metabolism
   1. Stimulates transport of free amino acids across the plasma membrane in liver and muscle.
   2. Stimulates protein biosynthesis and reduces release of amino acid from muscle.

D. On ion transport

E. On growth and development

Table 19–5. Principal actions of insulin.

Adipose tissue
1. Increased glucose entry
2. Increased fatty acid synthesis
3. Increased glycerol phosphate synthesis
4. Increased triglyceride deposition
5. Activation of lipoprotein lipase
6. Inhibition of hormone-sensitive lipase
7. Increased K^+ uptake

Muscle
1. Increased glucose entry
2. Increased glycogen synthesis
3. Increased amino acid uptake
4. Increased protein synthesis in ribosomes
5. Decreased protein catabolism
6. Decreased release of gluconeogenic amino acids
7. Increased ketone uptake
8. Increased K^+ uptake

Liver
1. Decreased ketogenesis
2. Increased protein synthesis
3. Increased lipid synthesis
4. Decreased glucose output due to decreased gluconeogenesis and increased glycogen synthesis

General
1. Increased cell growth

Table 19–3. Effect of insulin on glucose uptake in tissues in which it has been investigated.

Tissues in which insulin facilitates glucose uptake
Skeletal muscle
Cardiac muscle
Smooth muscle
Adipose tissue
Leukocytes
Crystalline lens of the eye
Pituitary
Fibroblasts
Mammary gland
Aorta
A cells of pancreatic islets
Tissues in which insulin does not facilitate glucose uptake
Brain (except probably part of hypothalamus)
Kidney tubules
Intestinal mucosa
Red blood cells

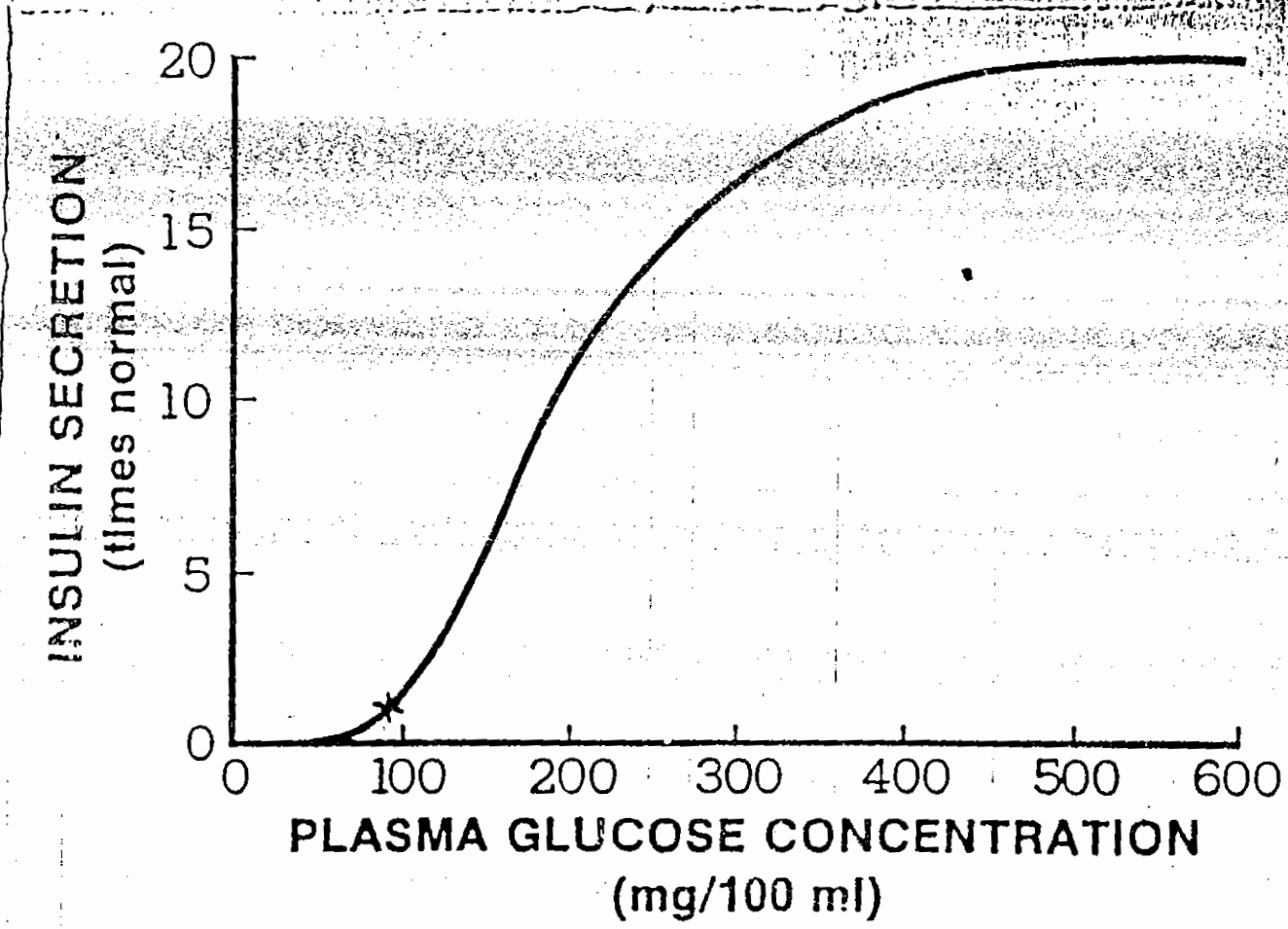


Figure 78–8. Approximate increase in insulin secretion at different plasma glucose levels.

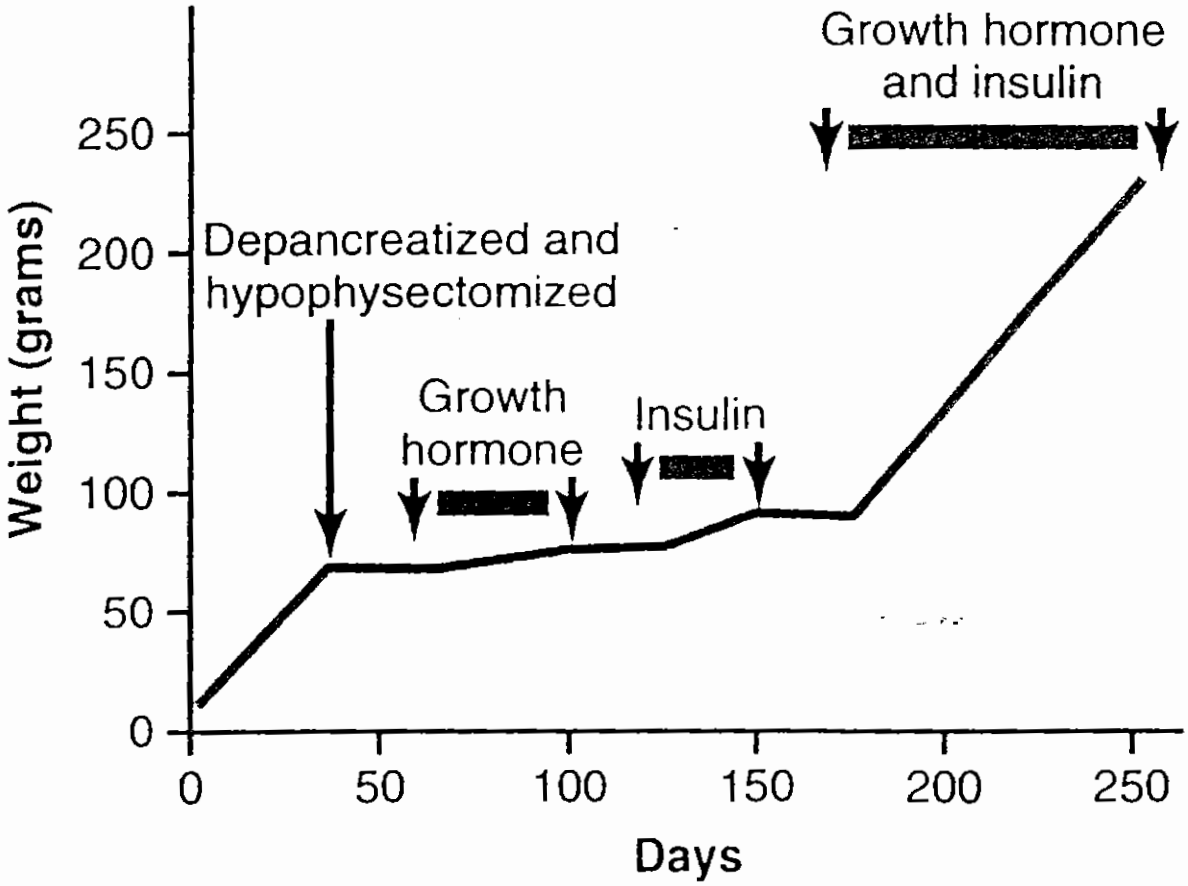


Figure 78-6 Effect of growth hormone, insulin, and growth hormone plus insulin on growth in a depancreatized and hypophysectomized rat.

Insulin and Growth Hormone Interact Synergistically to Promote Growth.

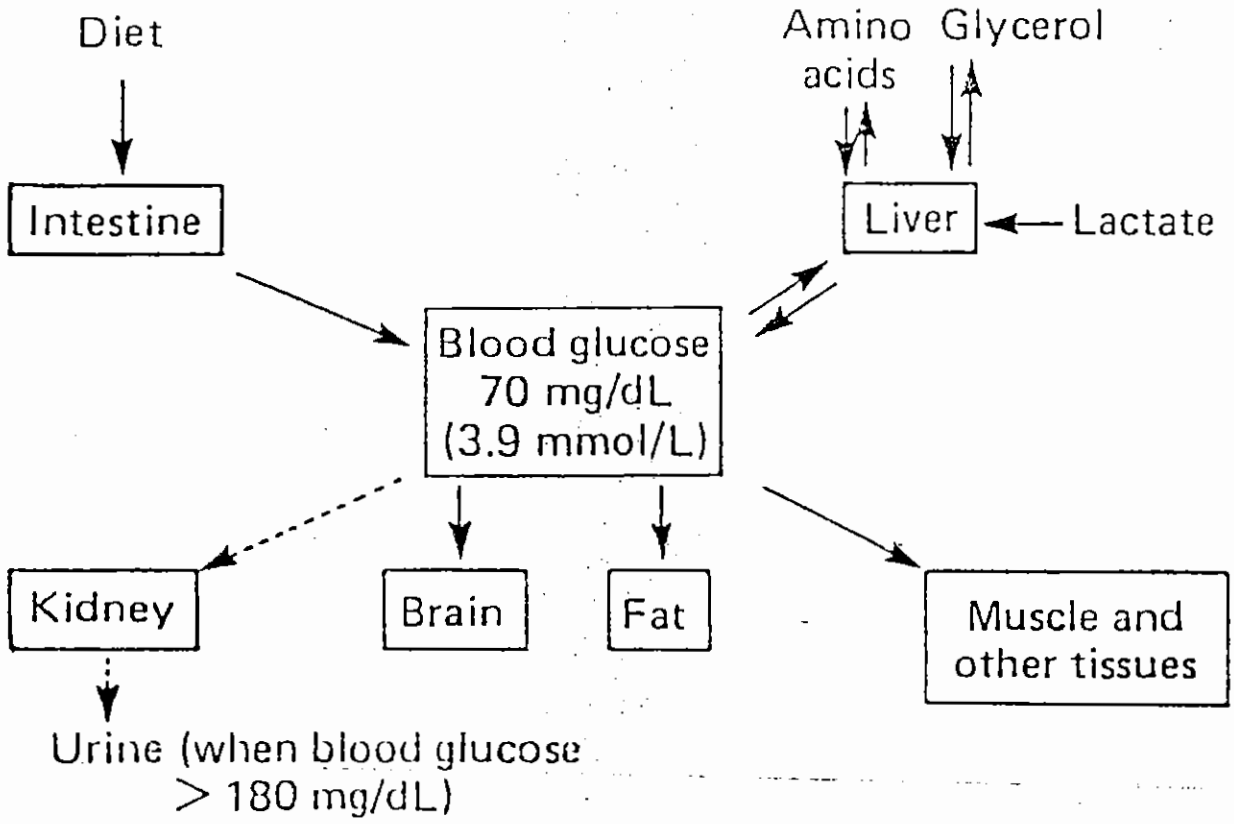


Figure 17–14. Blood glucose homeostasis, illustrating the glucostatic function of the liver.

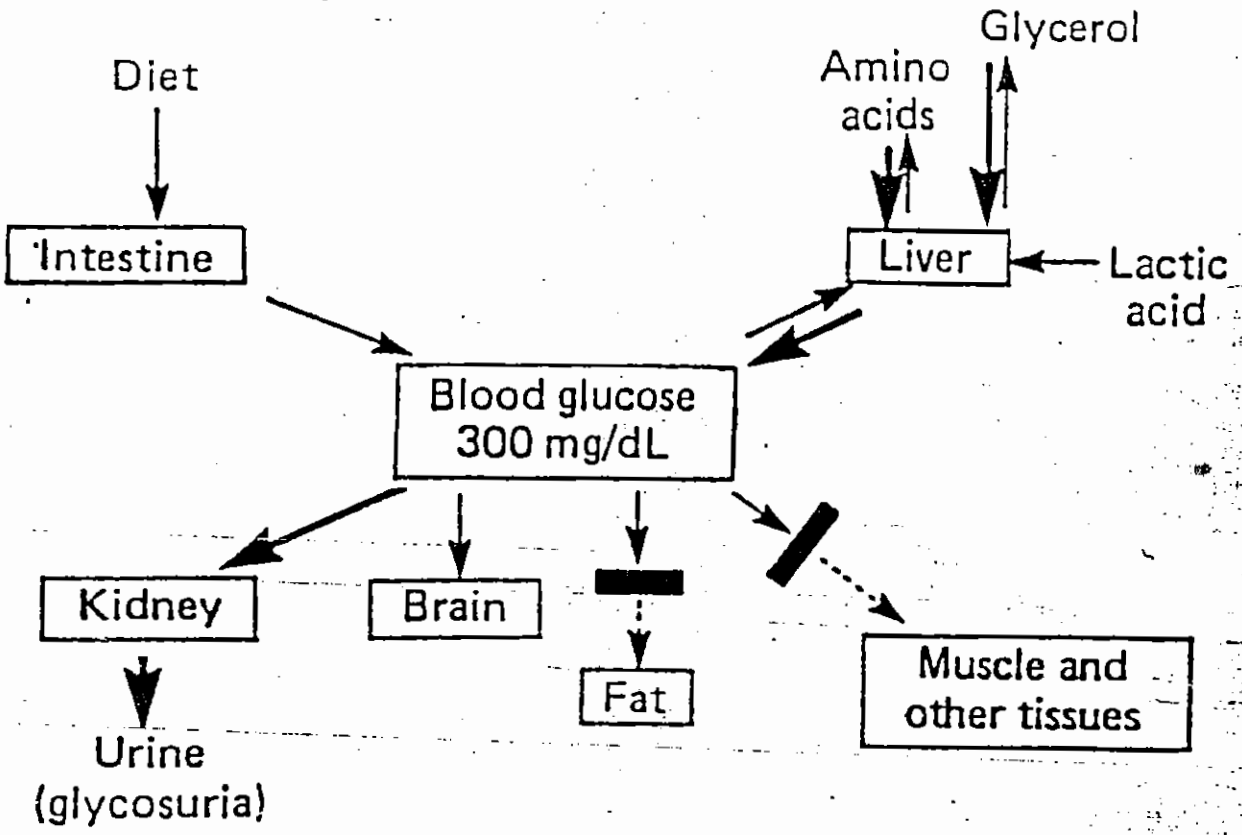


Figure 19–7. Disordered blood glucose homeostasis in insulin deficiency. Compare with Fig 17–14. The heavy arrows indicate reactions that are accentuated. The rectangles across arrows indicate reactions that are blocked.

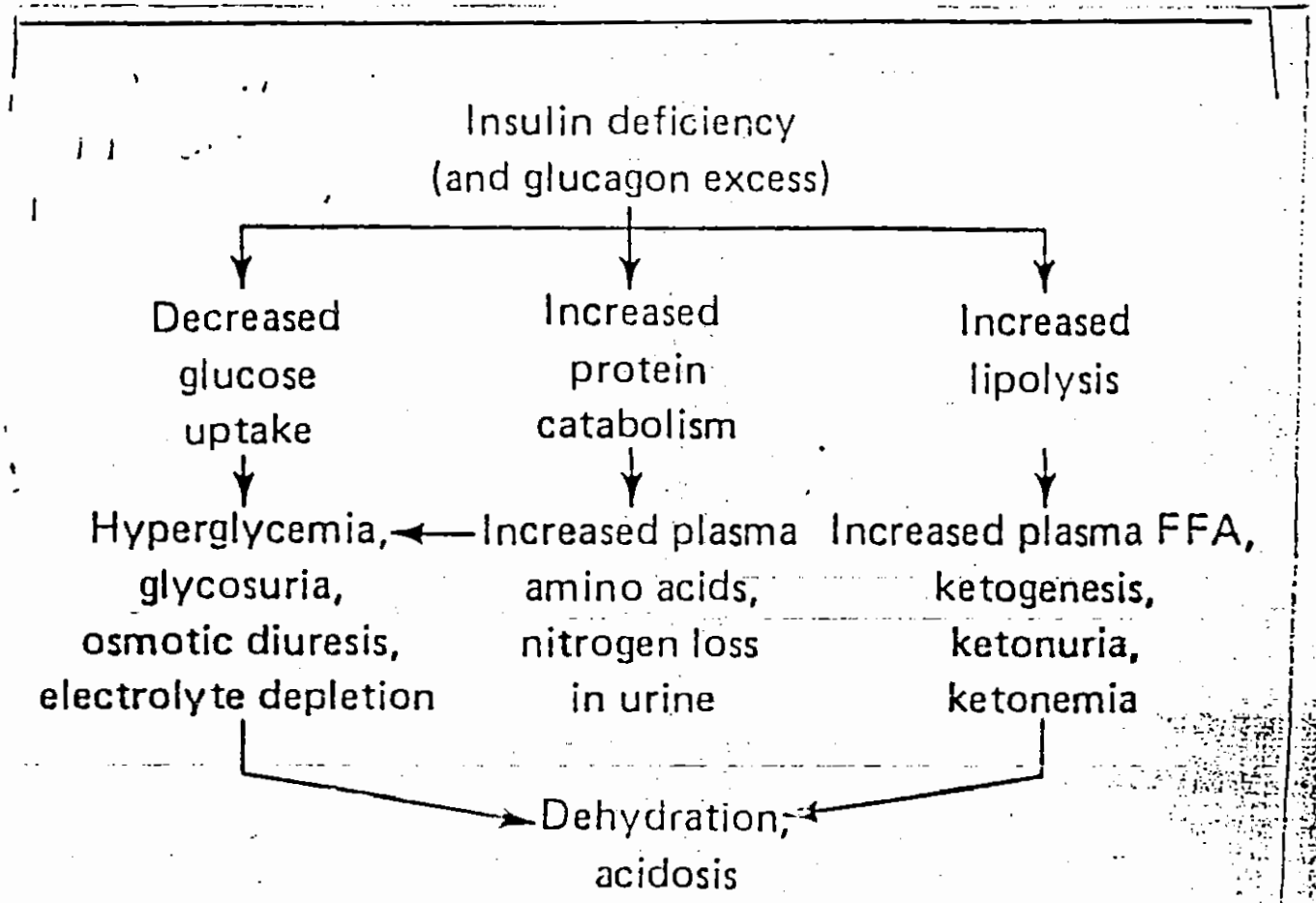


Figure 19–10. Effects of insulin deficiency. (Courtesy of RJ Havel.)

Table 19-3. Types of human diabetes mellitus.

Type	Other Names
Type I	Insulin-dependent diabetes (IDDM). Juvenile diabetes. Ketosis-prone diabetes.
Type II	Non-insulin-dependent diabetes (NIDDM). Maturity-onset diabetes. Ketosis-resistant diabetes.
Diabetes associated with other conditions	Examples include diabetes due to pancreatoectomy or pancreatic disease; diabetes due to defective forms of insulin or insulin receptors; and diabetes in patients with Cushing's syndrome, acromogaly, or other endocrine diseases.

Table 19–10. Types of human diabetes mellitus.

Type	Other Names
Type I	Insulin-dependent diabetes (IDDM). Juvenile diabetes. Ketosis-prone diabetes.

Type I diabetes mellitus, or insulin-dependent diabetes mellitus (IDDM), was formerly known as juvenile-onset diabetes.(1) Type I diabetes develops suddenly, usually before the age of 15 years, and often reflects pathology of the β islet cells resulting from viral infection or an autoimmune response.(2) Type I diabetics totally lack insulin activity, and their disease is extremely difficult to control.(3) Insulin injections must be given several times daily to manage ketosis and, to a lesser extent, hyperglycemia. Because of the early onset of their disease, type I diabetics typically exhibit long-term vascular and neural problems.(4) Complications resulting from vascular problems include atherosclerosis, strokes, heart attacks, gangrene, and blindness; consequences of neuropathies include loss of sensation, impaired bladder function, and impotence.

Type II	Non-insulin-dependent diabetes (NIDDM). Maturity-onset diabetes. Ketosis-resistant diabetes.

Type II diabetes, or non-insulin-dependent diabetes mellitus (NIDDM) was formerly called mature-onset diabetes because it occurs mostly after the age of 40 years and is increasingly common with age. Heredity or a familial predisposition is particularly striking in this diabetic group; if an identical twin has type II diabetes mellitus, the probability that the other twin will have the disease is 100%. Although most type II diabetics produce insulin, the amount is inadequate or there is some abnormality of the insulin receptors. Type II diabetics are almost always overweight and account for over 90% of the known cases of diabetes mellitus. Ketosis is not a major problem for this group, and in many cases the symptoms can be managed solely by diet and exercise. Weight control is very important, because obesity alone causes the insulin receptors to become less sensitive to insulin.

Diabetes associated with other conditions	Examples include diabetes due to pancreatoectomy or pancreatic disease; diabetes due to defective forms of insulin or insulin receptors; and diabetes in patients with Cushing's syndrome, acromogaly, or other endocrine diseases.

①The number or the affinity, or both, of insulin receptors is affected by insulin and other hormones, exercise, food, and other factors②Exposure to increased amounts of insulin decreases receptor concentration (down regulation), and exposure to decreased insulin increases the affinity of the receptors.③The number of receptors per cell is increased in starvation and decreased in obesity and acromegaly. ④The affinity of the receptors is increased in adrenal insufficiency and decreased by excess glucocorticoids

Obesity

Obesity is the most common and most expensive nutritional problem in the USA. A convenient and reliable indicator of body fat is the **body mass index** (BMI), which is the body weight (in kilograms) divided by the square of the height (in meters). Values above 25 are abnormal. Individuals with values of 25–30 are overweight, and those with values > 30 are obese. In the USA, 55% of the population are overweight and 22% are obese. The incidence of obesity is also increasing in other countries. Indeed, the Worldwatch Institute has estimated that although starvation continues to be a problem in many parts of the world, the number of overweight people in the world is now as great as the number of underfed.

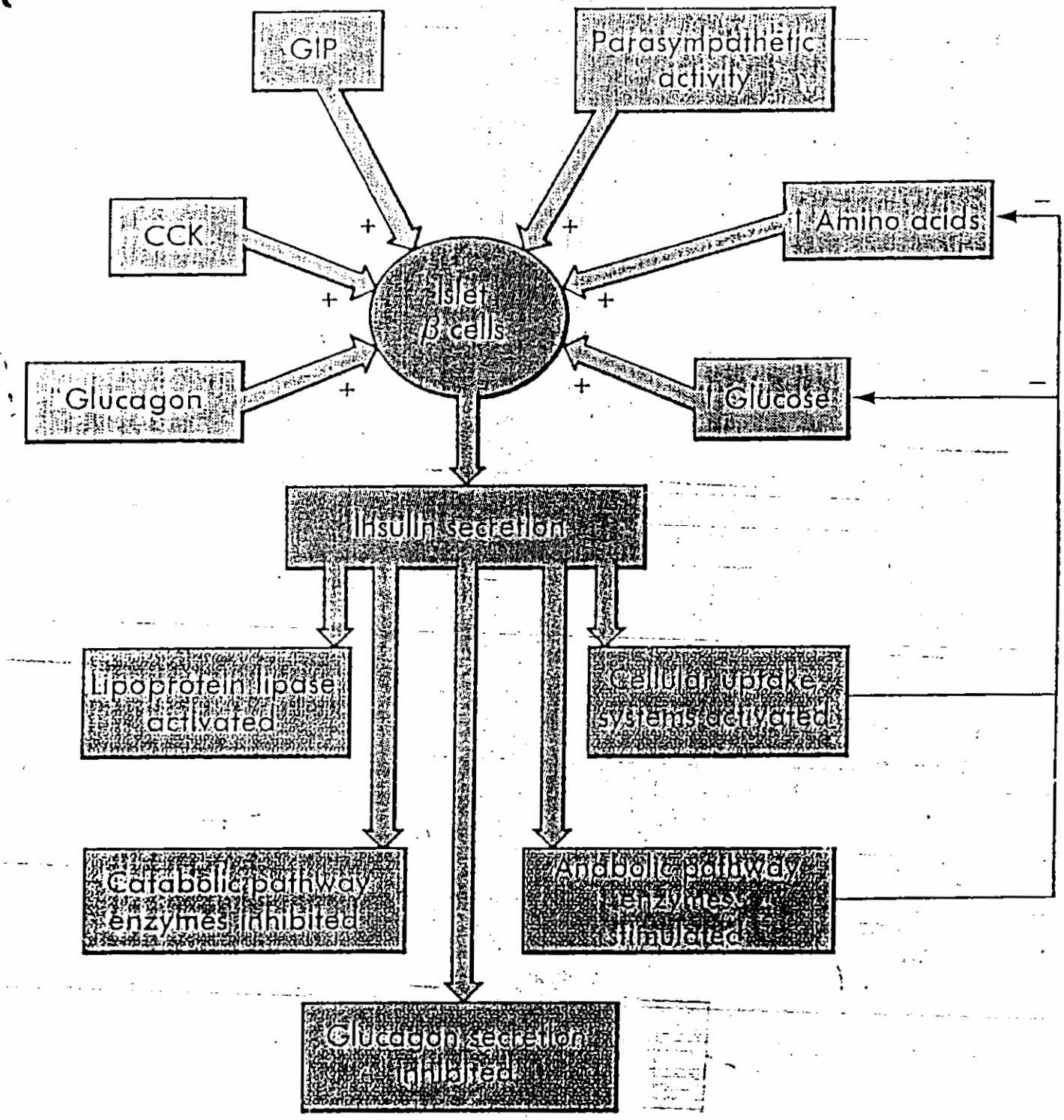


FIGURE 23-2
Inputs to beta cells and effects of insulin, including negative feedback on glucose and amino-acid levels.

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

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

⊛Glucagon is a single peptide of 29 a.a. with m.w of 3500. Biologic activity resides in 1–6 a.a.

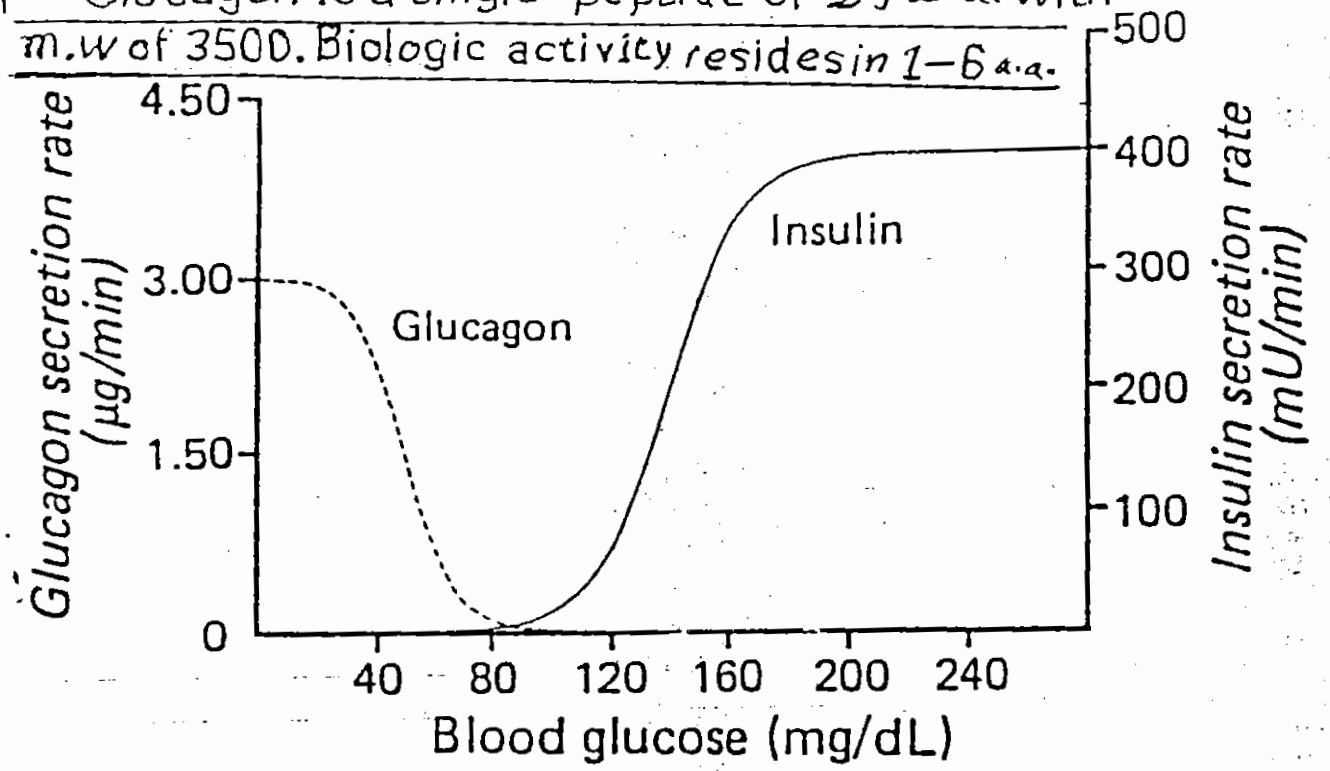


Figure 19–12. Mean rates of insulin and glucagon delivery from an artificial pancreas at various blood glucose levels. The device was programmed to establish and maintain normal blood glucose in insulin-requiring diabetic humans, and the values for hormone output approximate the output of the normal human pancreas. The shape of the insulin curve also resembles the insulin response of incubated B cells to graded concentrations of glucose. (Reproduced, with permission, from Marliss EB et al: Normalization of glycemia in diabetics during meals with insulin and glucagon delivery by the artificial pancreas. *Diabetes* 1977;26:663.)

Table 7.7
Factors influencing glucagon release

Stimulation	Inhibition
Amino acids	Glucose
Gastrointestinal polypeptide hormones	Insulin
Catecholamines (exercise)	Free fatty acids
Growth hormone	
Glucocorticoids	

Action of glucagon on target tissues

It has been established that glucagon is capable of producing the following actions.

1. Glycogenolysis in the liver.
2. Inhibition of glycogen synthesis in the liver.
3. Gluconeogenesis in the liver.
4. Lipolysis in adipose tissue.
5. Stimulation of insulin release from β cells.
6. Stimulation of catecholamine release.
7. A positive inotropic effect on the heart.

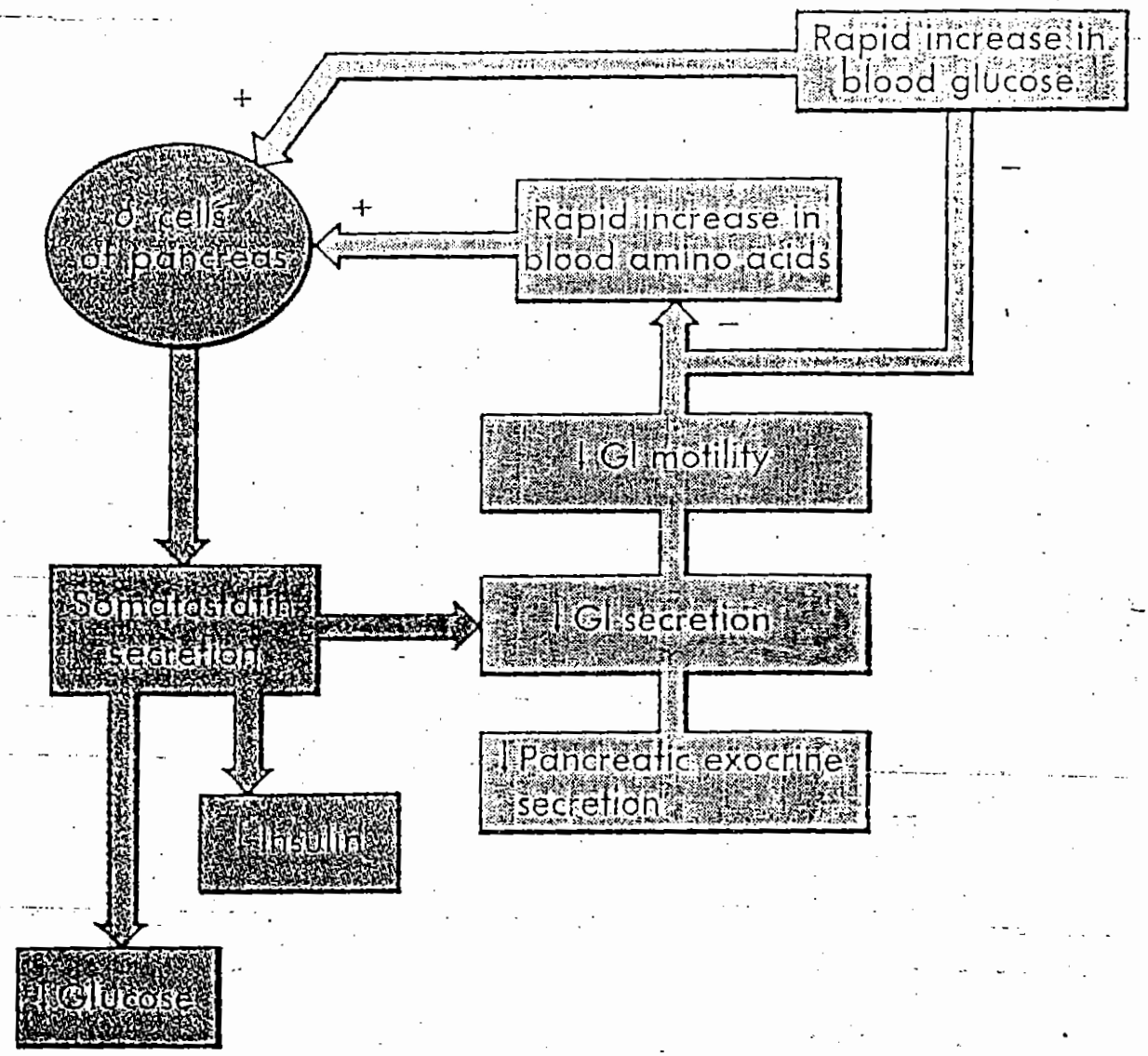


FIGURE 23-7

Inputs to delta cells and effects of somatostatin, including negative feedback, which reduces entry of glucose and amino acids into the circulation.

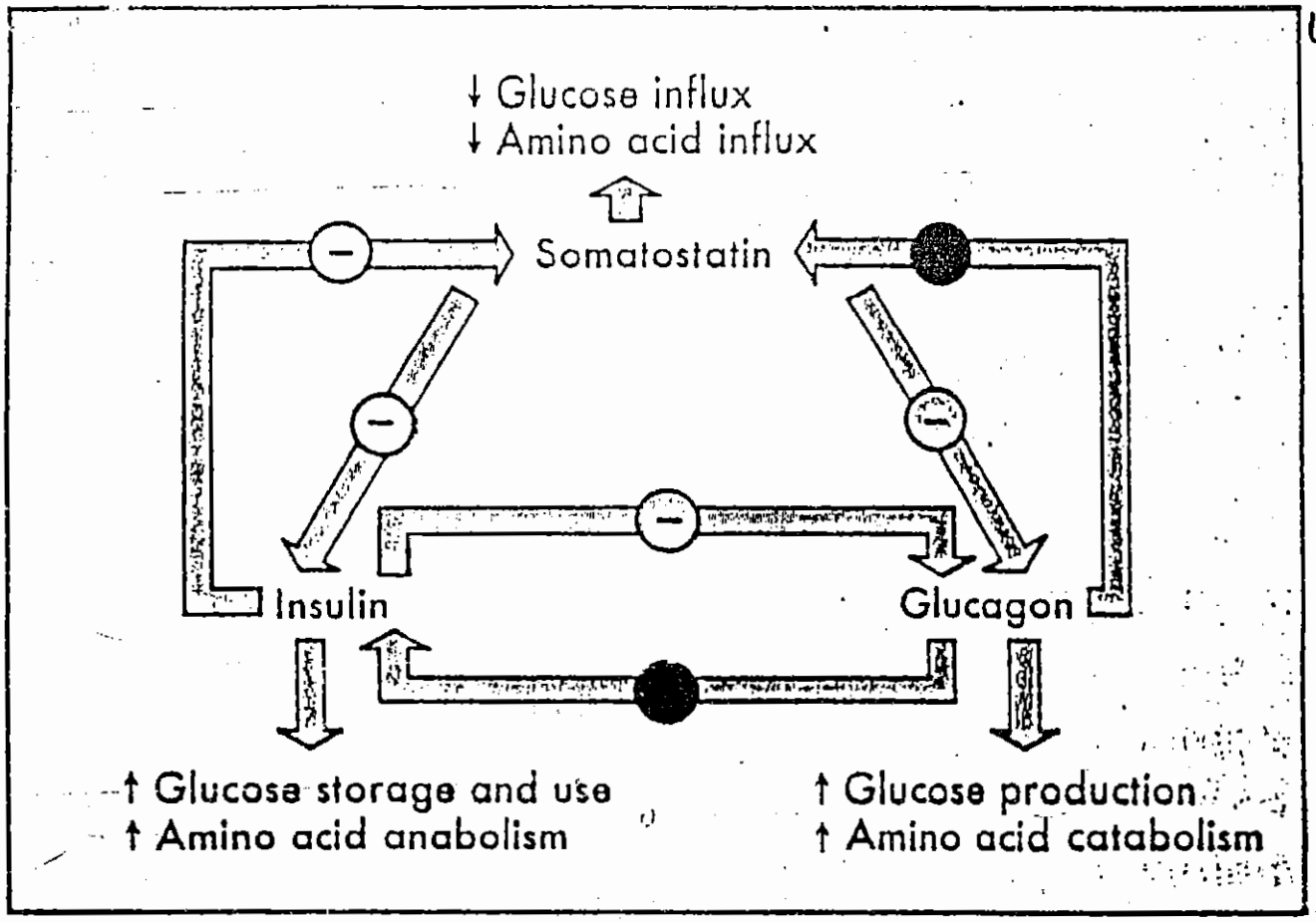


FIGURE 37-8 The interrelationships between somatostatin, insulin, and glucagon effects on each other's secretions and their effects on glucose and amino acid metabolism. (Modified from Unger RH et al. Reproduced with permission from the *Annual Review of Physiology,* volume 40. Copyright © 1978 by Annual Reviews, Inc.)

Cholecystokinin-Pancreozymin

It was formerly thought that a hormone called cholecystokinin produced contraction of the gallbladder whereas a separate hormone called pancreozymin increased the secretion of pancreatic juice rich in enzymes. It is now clear that a single hormone secreted by cells in the mucosa of the upper small intestine has both activities, and the hormone has therefore been named **cholecystokinin-pancreozymin.** It is also called **CCK-PZ** or, most commonly, **CCK.**

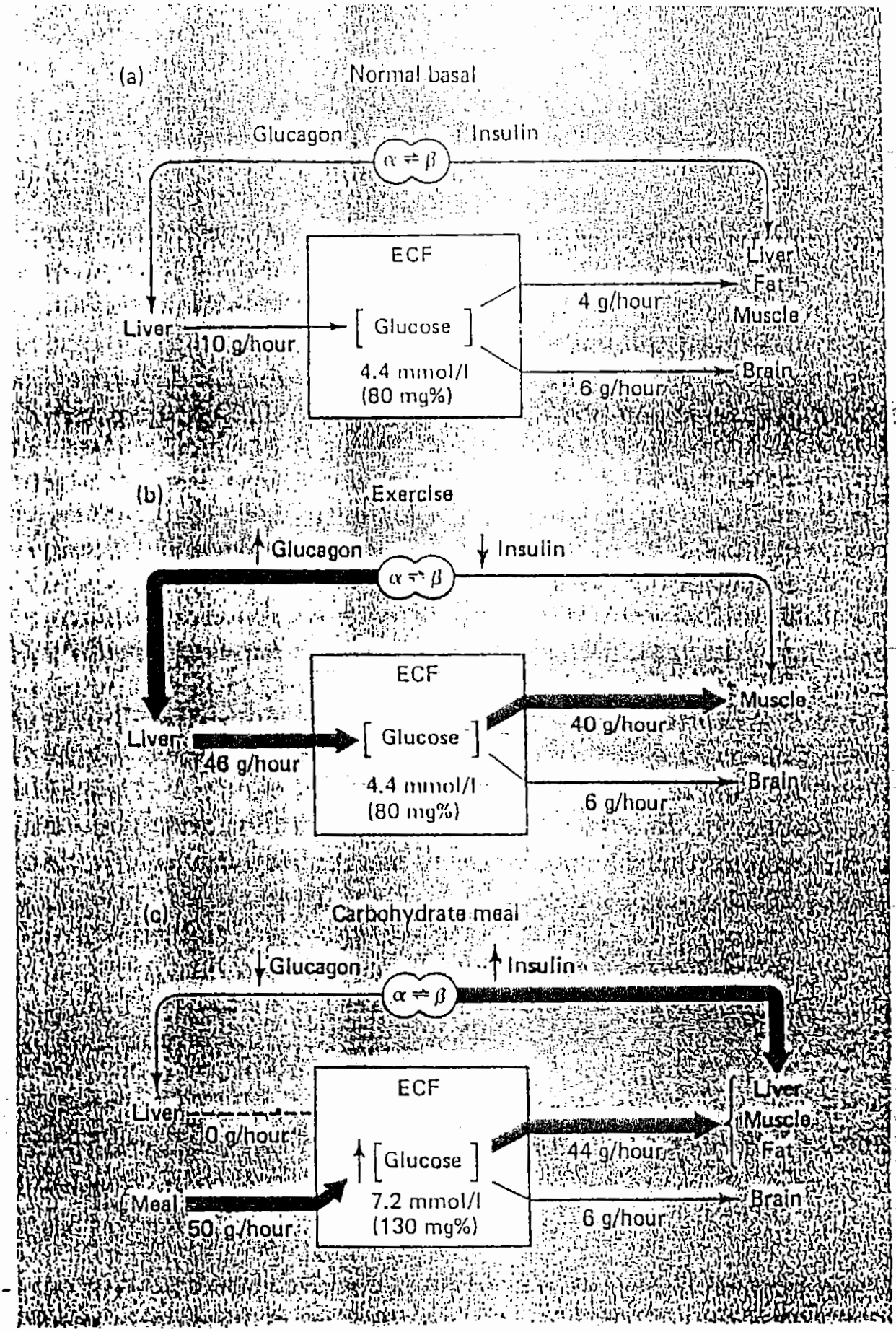


Fig. 4.7 A diagrammatic representation of the patterns of glucagon and insulin release at rest (**A**), during exercise (**B**) and following a meal of carbohydrate (**C**) and the consequential changes in glucagon distribution. (From Unger, R. H. (1976) Diabetes **25**, 136.)

TABLE 35.2 Factors Regulating Glucagon Secretion From the Pancreas

Stimulatory agents or conditions	Hypoglycemia
	Amino acids
	Acetylcholine
	Norepinephrine
	Epinephrine
Inhibitory agents or conditions	Fatty acids
	Somatostatin
	Insulin

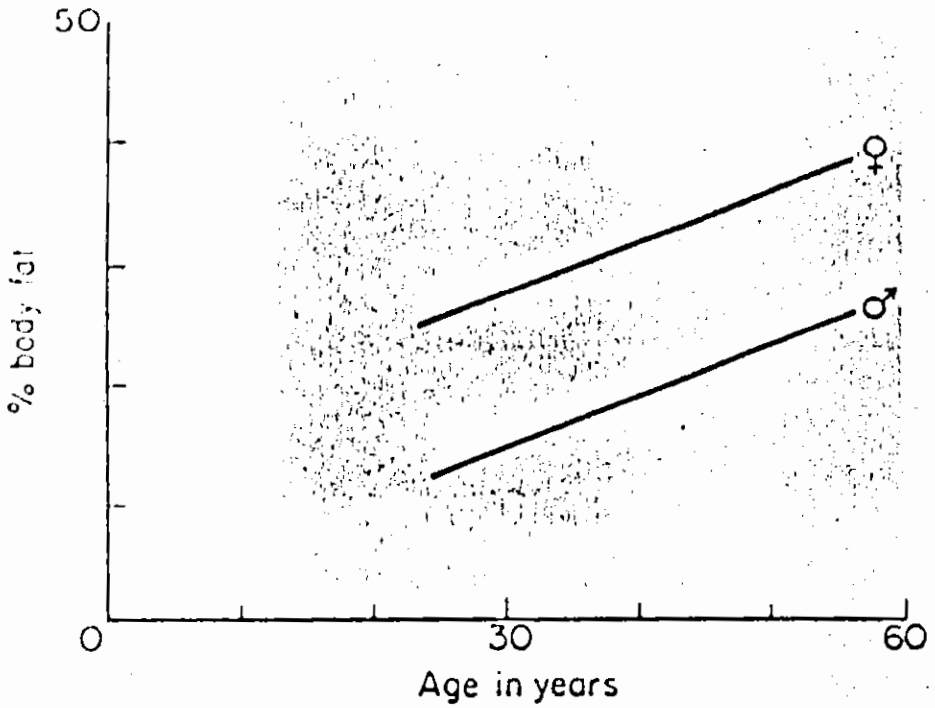
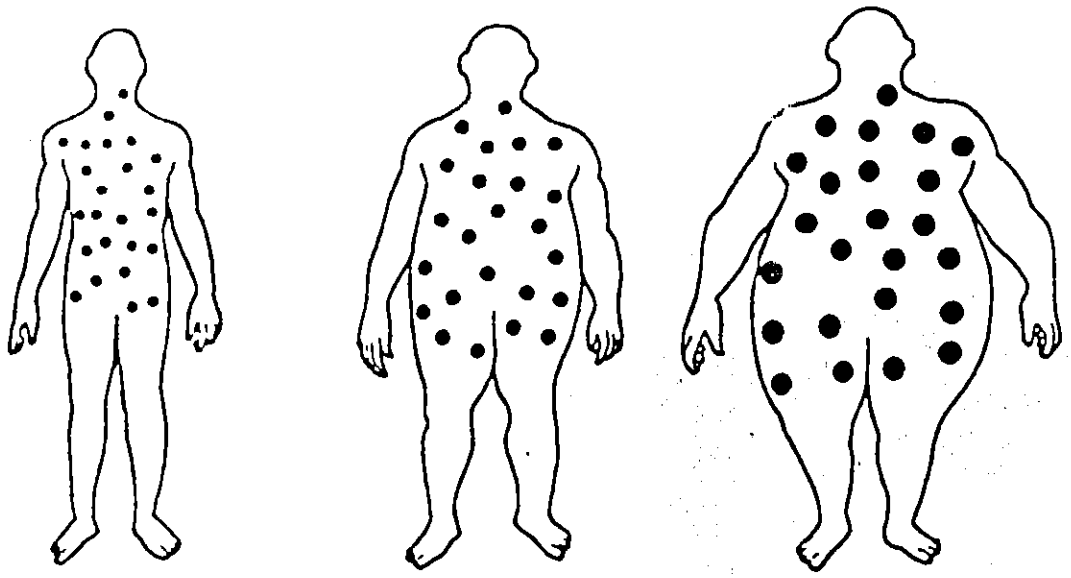


Fig. 6.21 Body fat at different ages in males and females.

Obesity—body weight more than 20% above some desirable standard due to an excessive accumulation of adipose tissue—affects one-third of the adult population in the United States. (An athlete may be *overweight* due to higher-than-normal amounts of muscle tissue without being obese.) Even moderate obesity is hazardous to health; it is implicated as a risk factor in cardiovascular disease, hypertension, pulmonary disease, non-insulin-dependent diabetes mellitus, arthritis, certain cancers (breast, uterus, and colon), varicose veins, and gallbladder disease. Also, loss of body fat in obese individuals has been shown to elevate HDL cholesterol, the type associated with prevention of cardiovascular disease.



Body weight	165 lb	227 lb	328 lb
Fat cell size	0.2 μg/cell	0.6 μg/cell	0.9 μg/cell
Fat cell number	75 billion	75 billion	75 billion

Fig. 6.22 In obesity the number of fat cells (the number is determined in infancy) stays constant, but the fat content of each increases (after Stollerman).

TABLE 78-2

Clinical Characteristics of Patients with Type I and Type II Diabetes Mellitus

Feature	Type I	Type II
Age at onset	Usually <20 years	Usually >40 years
Body mass	Low (wasted) to normal	Obese
Plasma insulin	Low or absent	Normal to high
Plasma glucagon	High, can be suppressed	High, resistant to suppression
Plasma glucose	Increased	Increased
Insulin sensitivity	Normal	Reduced
Therapy	Insulin	Weight loss, thiazolidinediones, metformin, sulfonylureas, insulin

*Insulin-dependent diabetes (IDDM)
Juvenile diabetes.

*Non-insulin-dependent diabetes (NIDDM).
Maturity-onset diabetes.

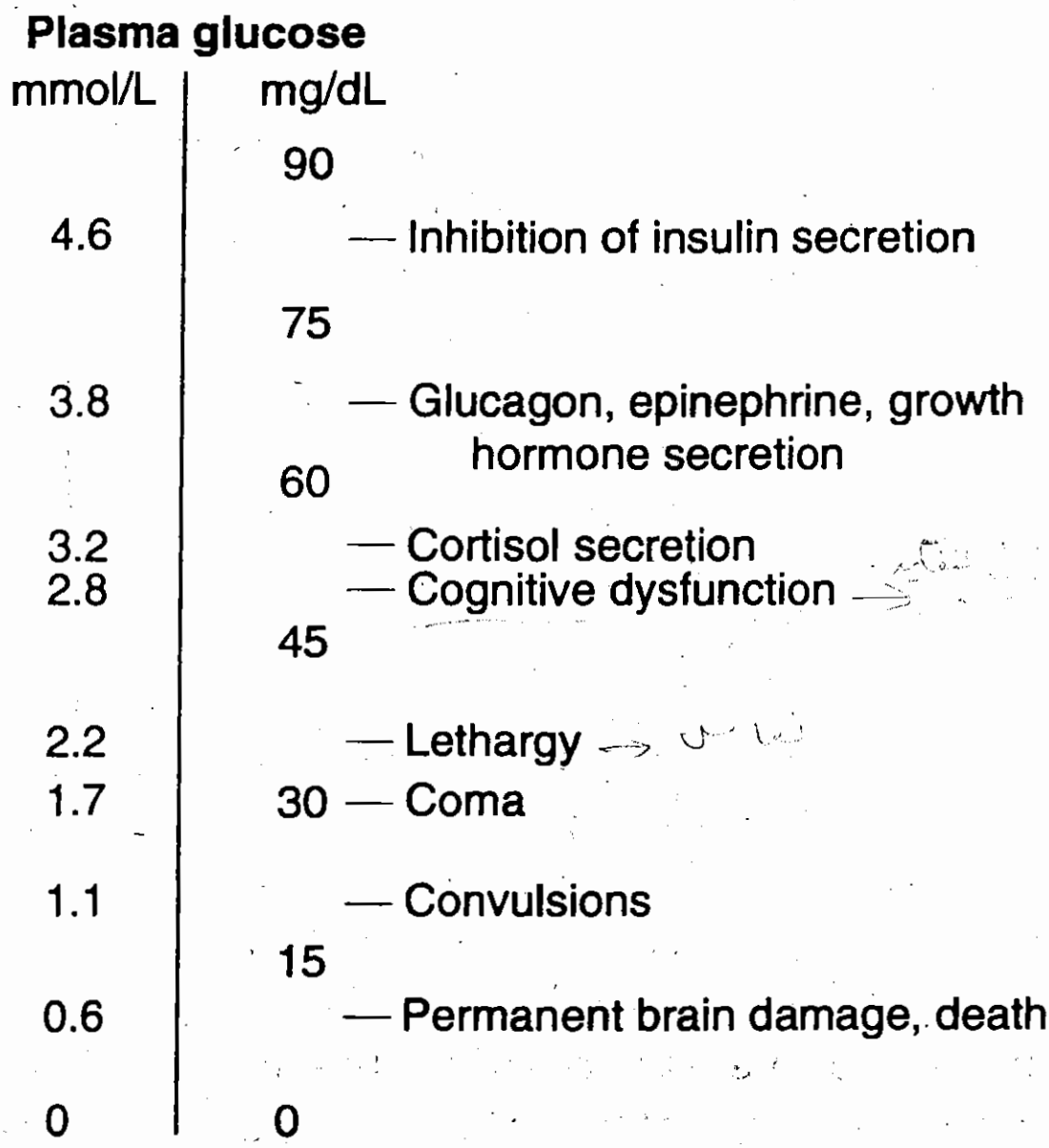


Figure 19–11. Plasma glucose levels in arterialized venous blood at which various effects of hypoglycemia appear.

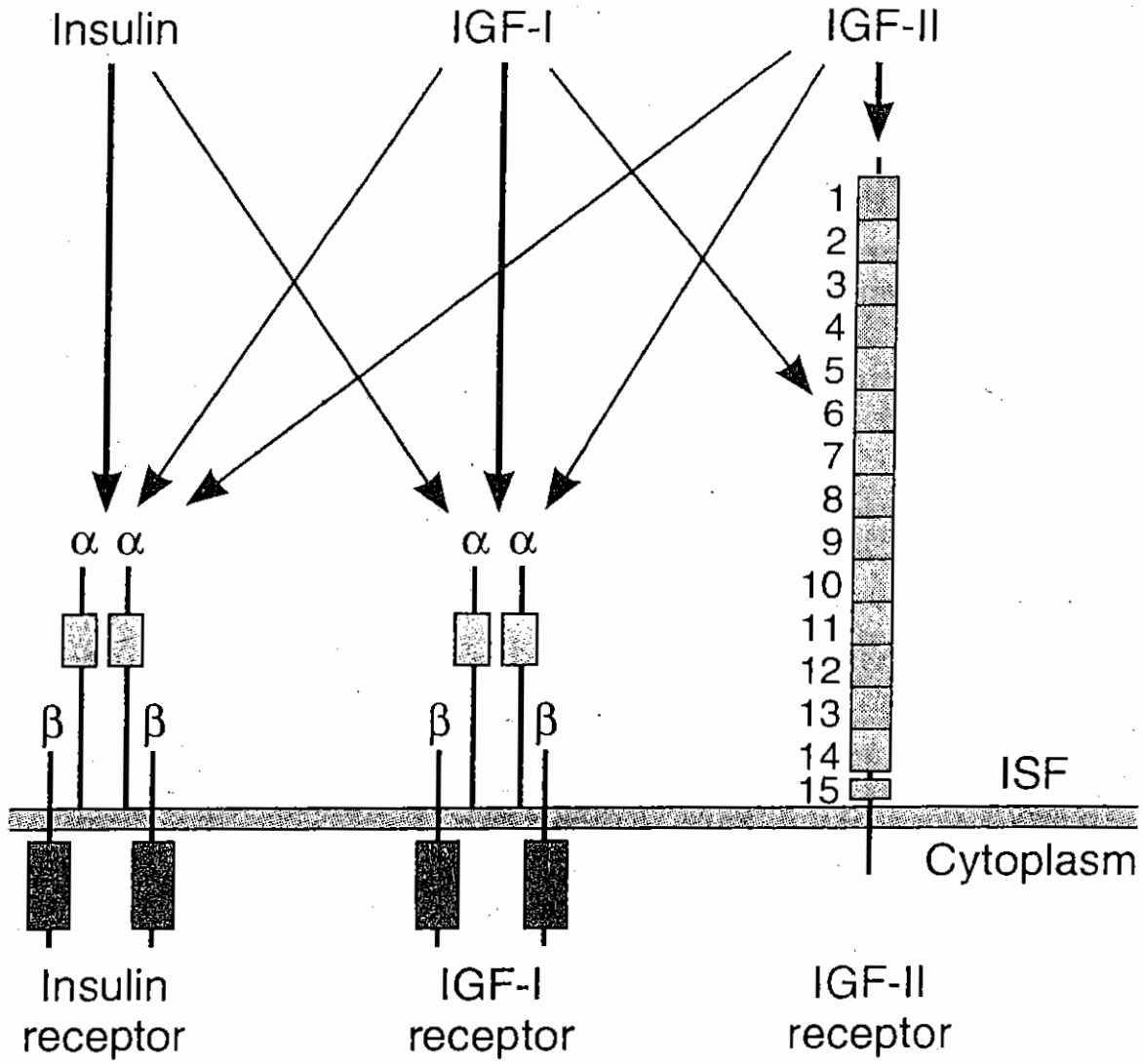


Figure 19–6. Insulin, IGF-I, and IGF-II receptors. Each hormone binds primarily to its own receptor, but insulin also binds to the IGF-I receptor, and IGF-I and IGF-II bind to all three. The dark-colored boxes are intracellular tyrosine kinase domains. Note the marked similarity between the insulin receptor and the IGF-I receptor; also note the 15 repeat sequences in the extracellular portion of the IGF-II receptor.

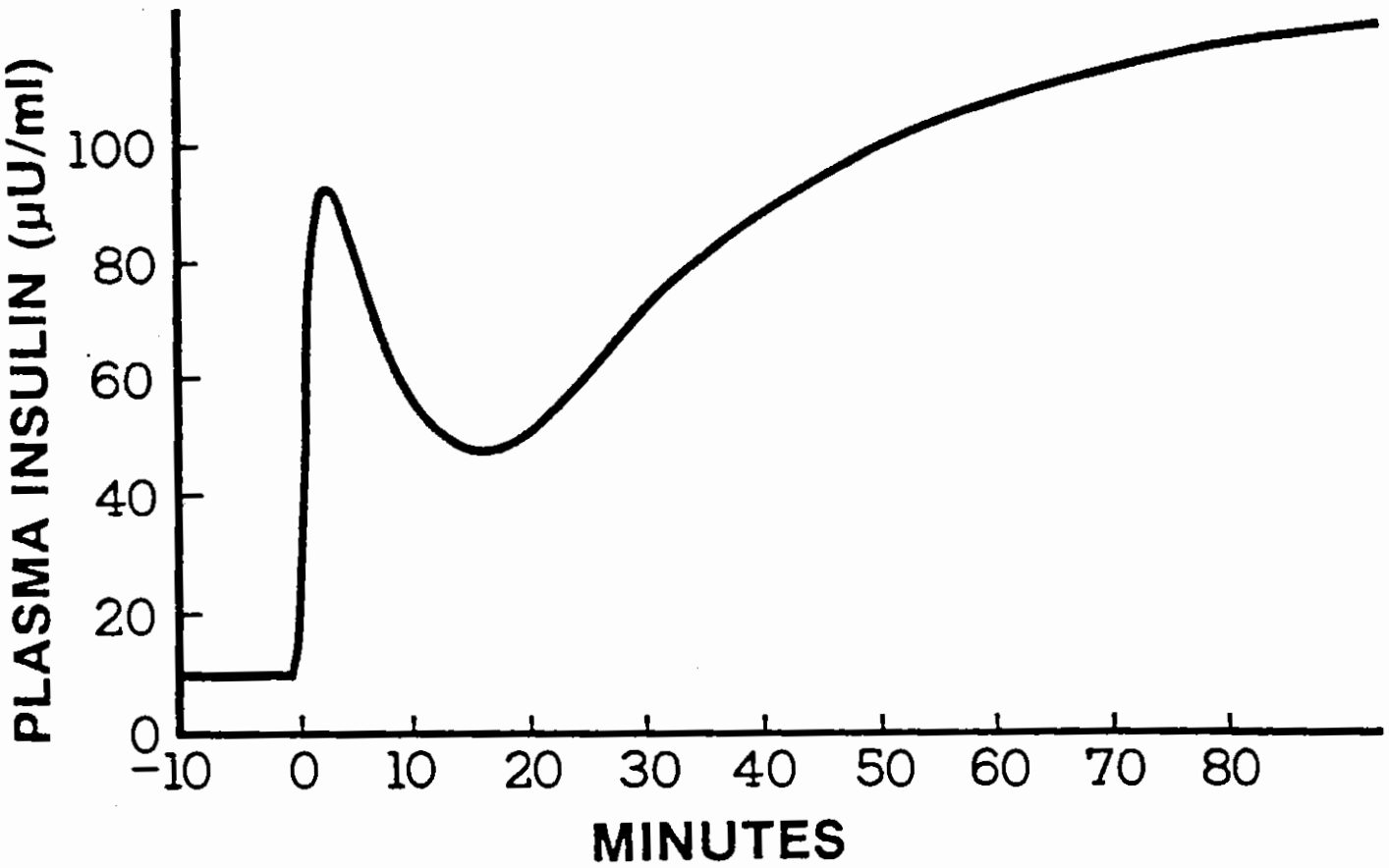


Figure 78–7. Increase in plasma insulin concentration following a sudden increase in blood glucose to two to three times the normal range. Note an initial rapid surge in insulin concentration and then a delayed but higher and continuing increase in concentration beginning 15 to 20 minutes later.