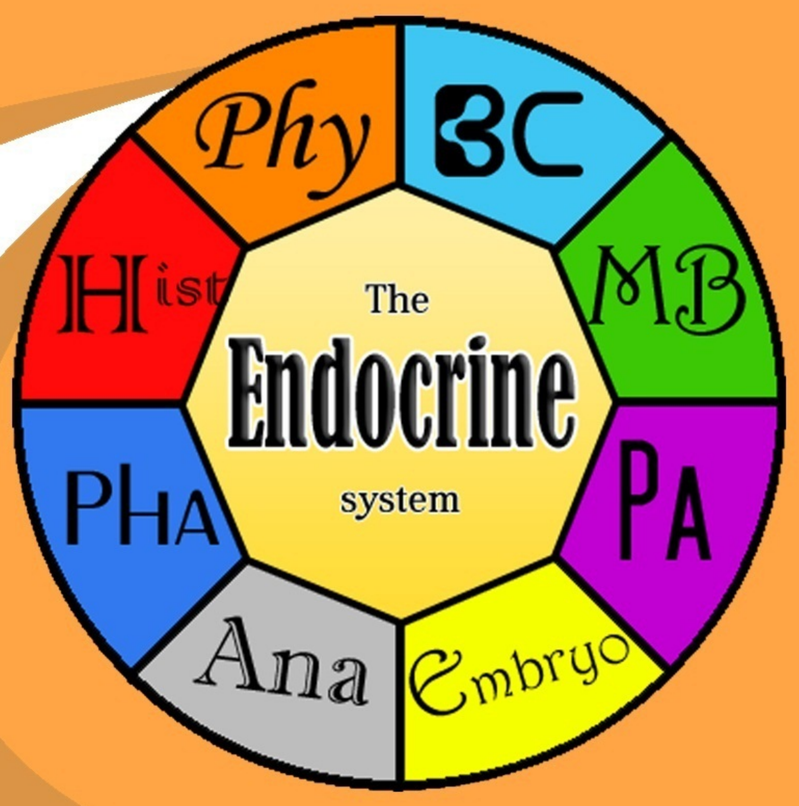
University of Jordan
Faculty of Medicine

Medical Committee
The University of Jordan
2018 2012



Physiology

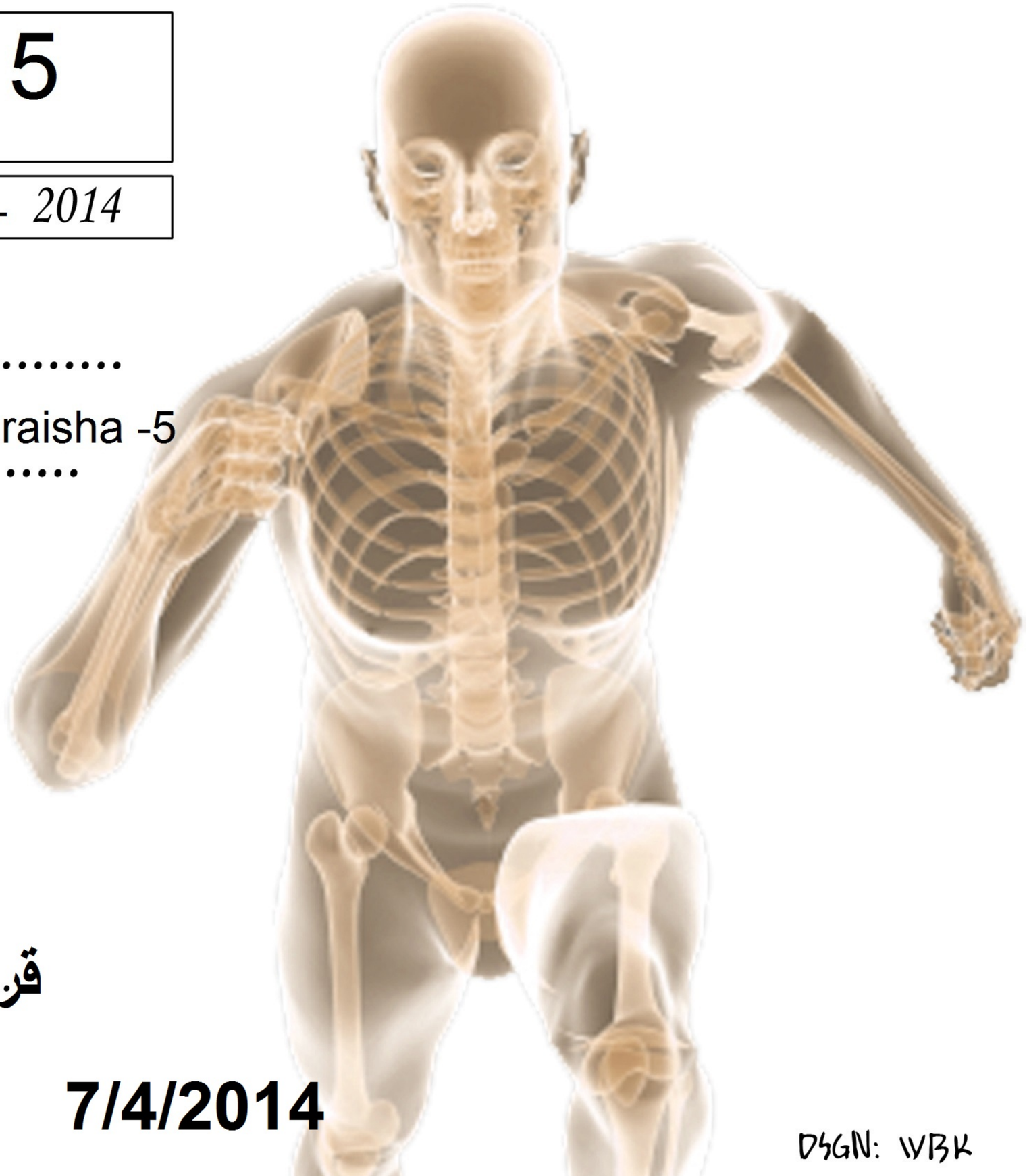
Slides ■
Sheet □
5
6-4- 2014

Title: ADRENAL GLANDS .....

Professor: Dr. Saleem Al-Khraisha -5 .....

Written by:

.....



Price: 45 قرش

7/4/2014

DSGN: WBK

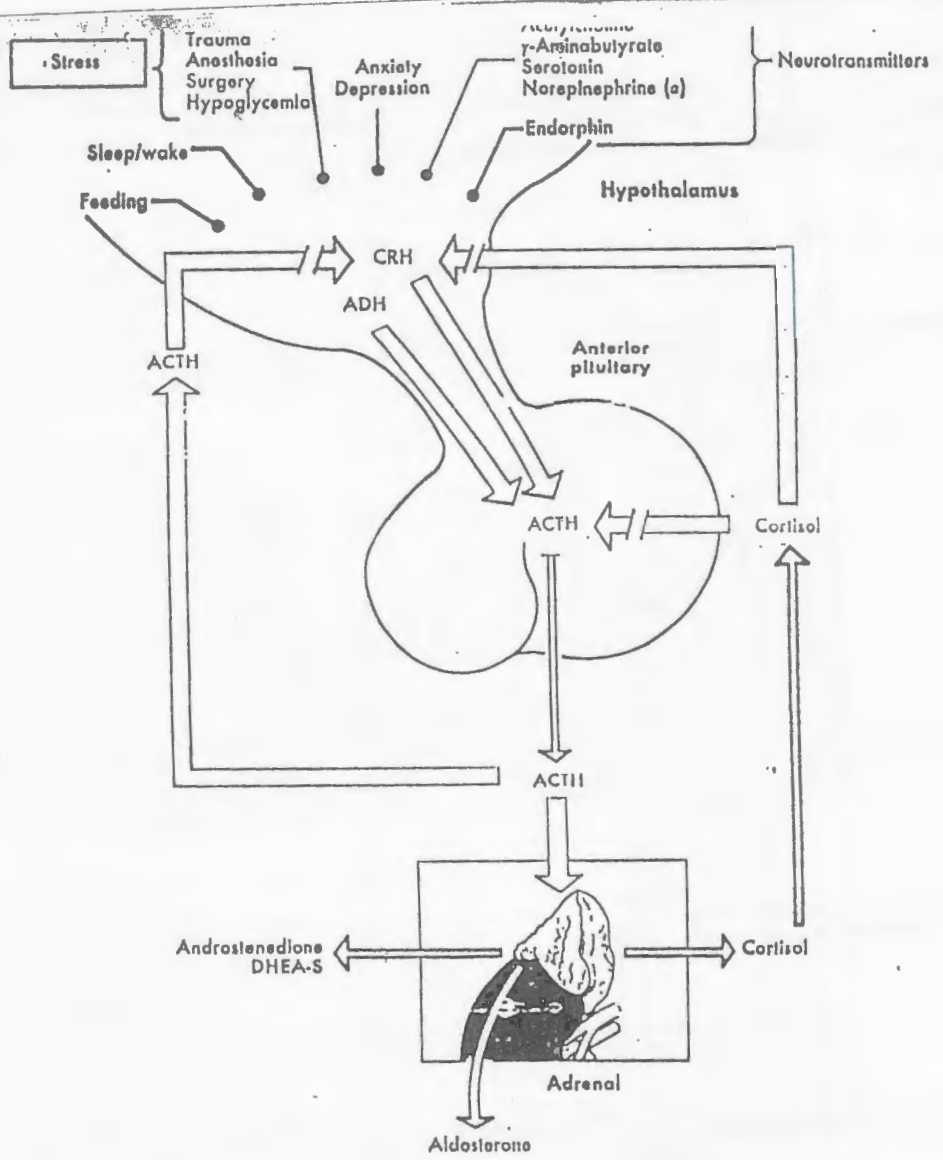


FIGURE 41-3 The regulation of cortisol secretion by the hypothalamic-pituitary-adrenal axis. A variety of inputs to the hypothalamus stimulate corticotropin—releasing hormone *(CRH)* secretion, and in turn adrenocorticotropin *(ACTH)* and cortisol secretion. Cortisol exerts negative feedback at both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

- ACTH is an anterior pituitary polypeptide hormone.
- Regulates the growth and secretion of the adrenal cortex.
- Its most important target gland hormone is cortisol.
- Fetus ACTH synthesis and secretion begin just before the development of the adrenal cortex.
- The regulation of ACTH secretion is among the most complex of all the pituitary hormones.
- 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.

Extra adrenal actions of ACTH: lipolysis and MSH Like action

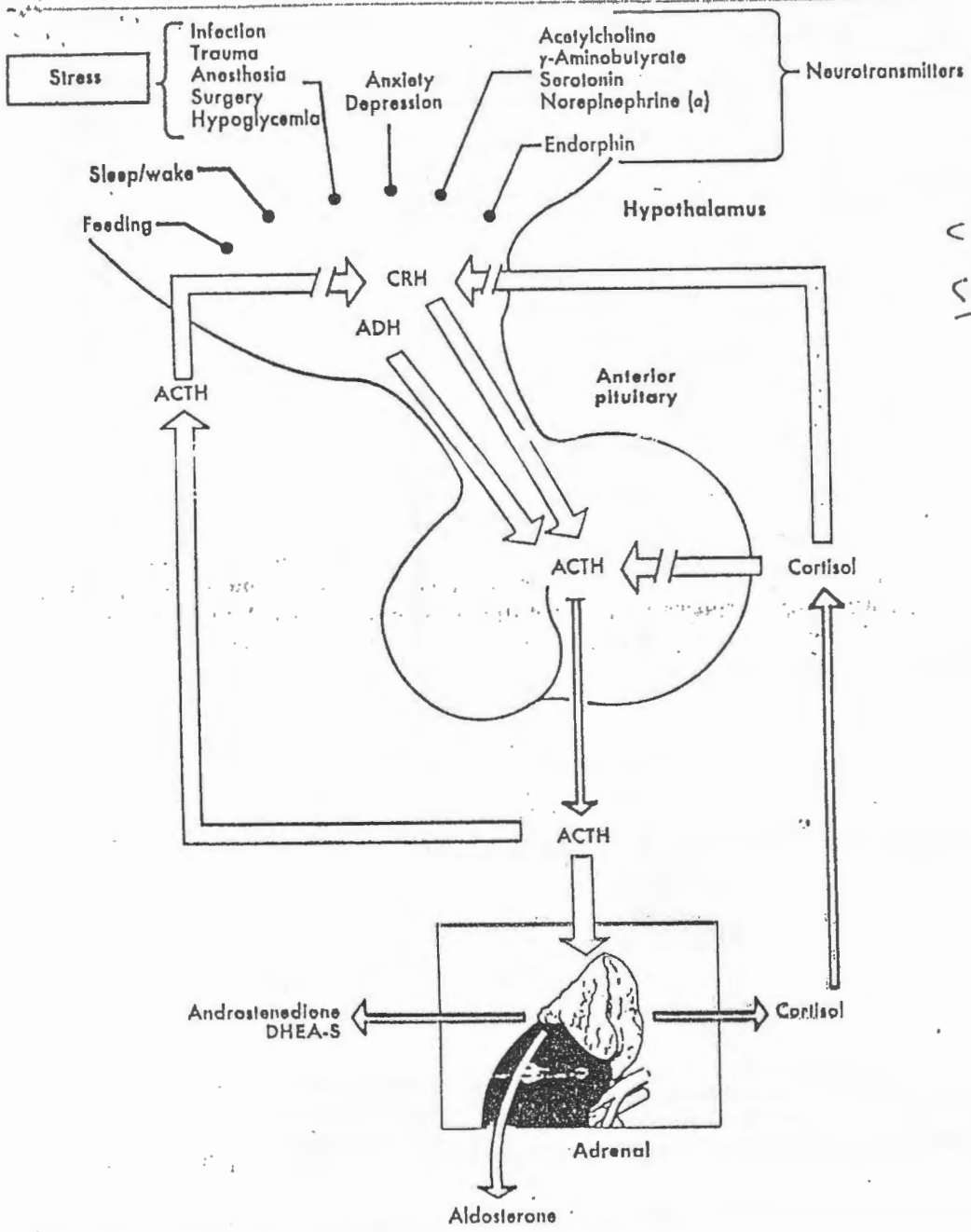


FIGURE 41-3 The regulation of cortisol secretion by the hypothalamic-pituitary-adrenal axis. A variety of inputs to the hypothalamus stimulate corticotropin—releasing hormone *(CRH)* secretion, and in turn adrenocorticotropin *(ACTH)* and cortisol secretion. Cortisol exerts negative feedback at both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

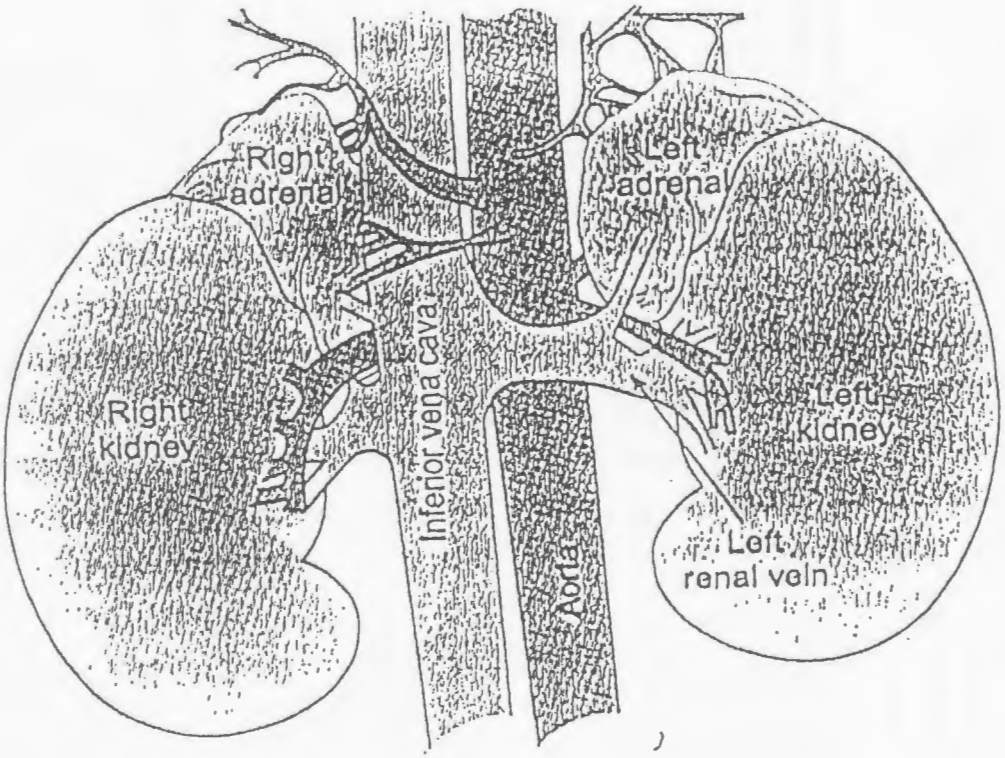


Fig. 12.15 The anatomic location of the adrenal glands and the organization of their blood supply. Note that the arterial supply is via many small arteries which originate from the aorta. The venous drainage is via a large central vein that empties into the inferior vena cava.

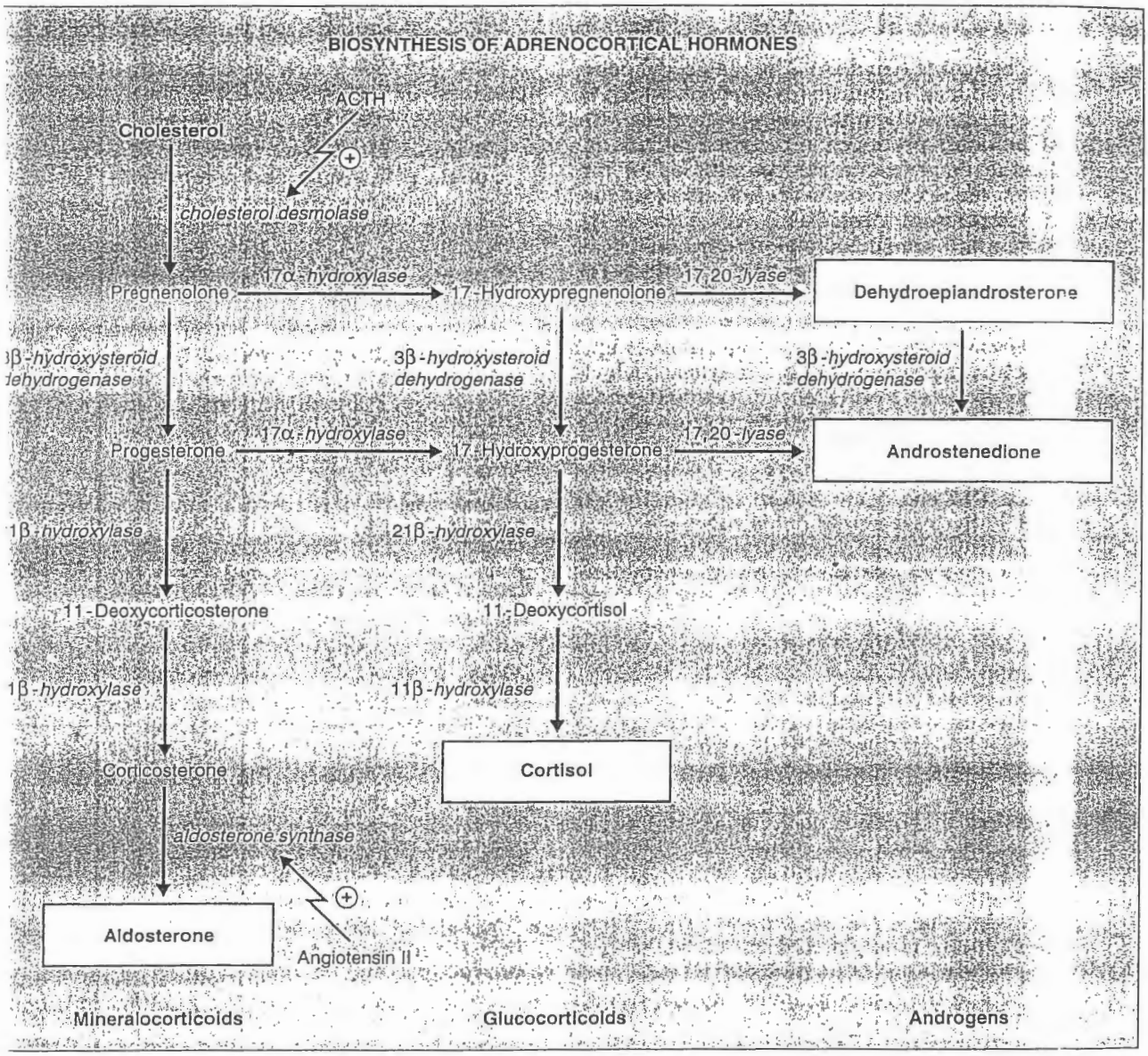
TABLE 19–2 Major Adrenocortical Abnormalities

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

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

Actions of Adrenal Androgens

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



RE 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

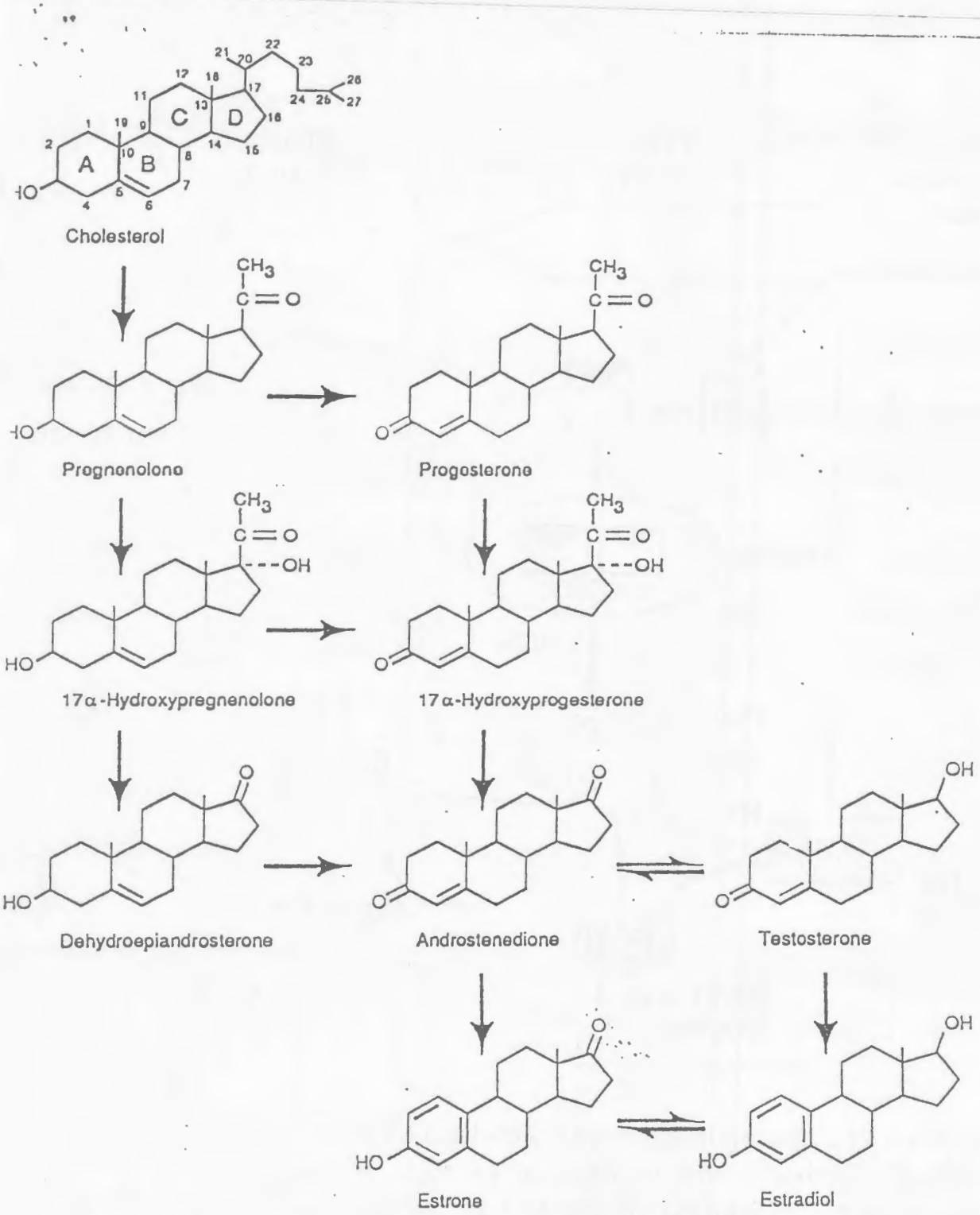


FIGURE 5
Biosynthetic pathway for androgens and estrogens. In the adrenal, the sequence does not usually proceed all the way to testosterone and the estrogens, which are the gonadal hormones. Because the cells of the zona glomerulosa lack 17α-hydroxylase, these reactions can occur only in the inner zones.

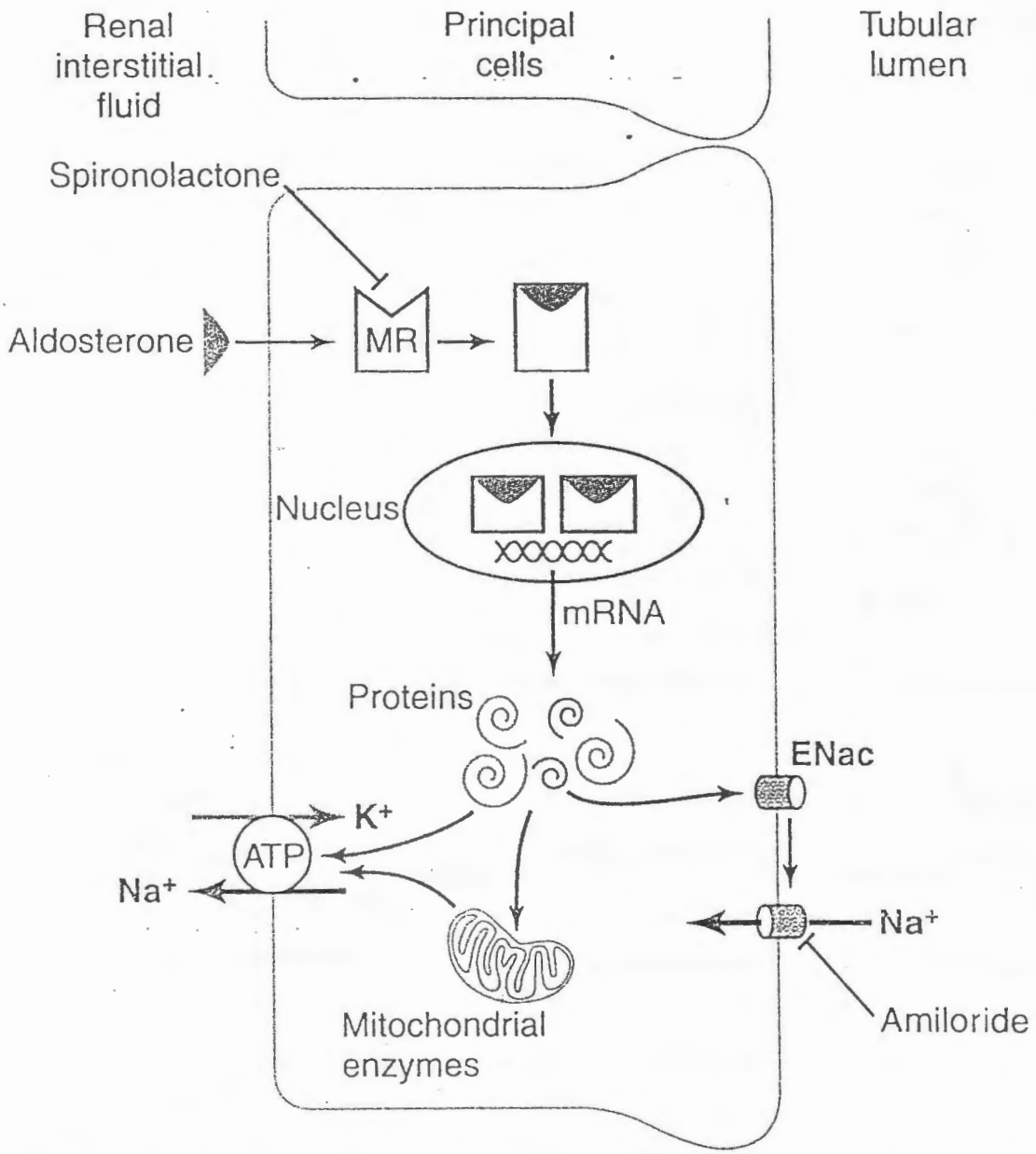


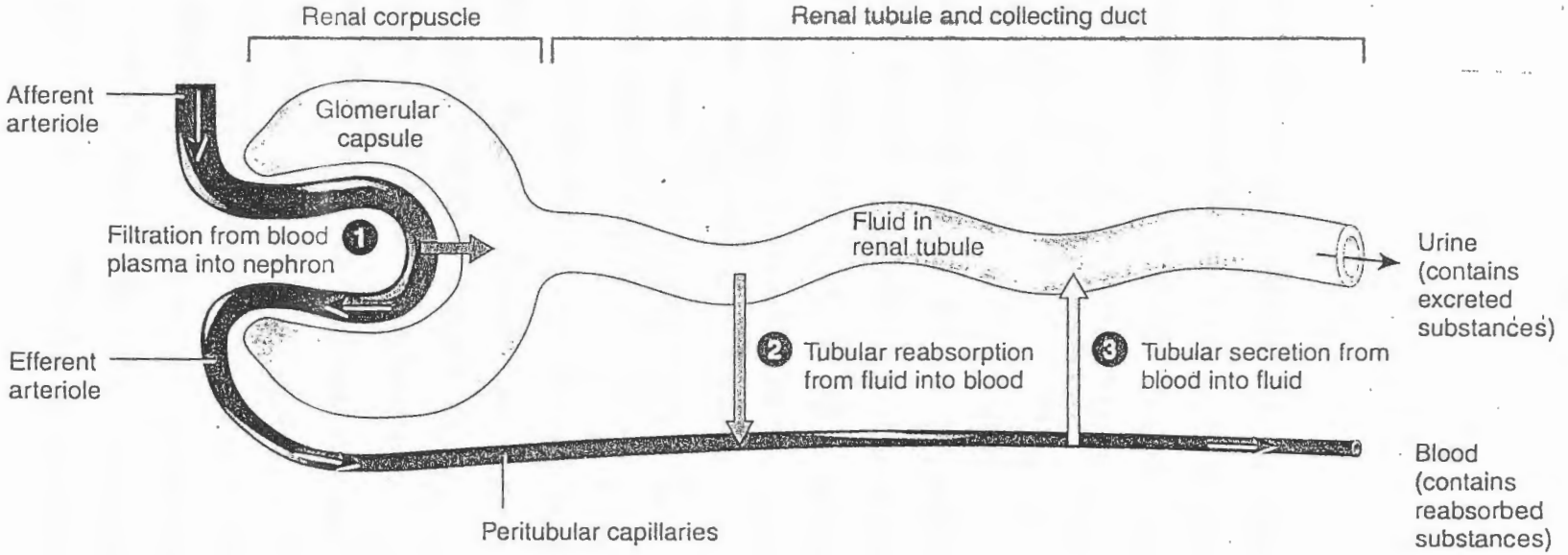
Figure 77-4 Aldosterone-responsive epithelial cell signaling pathways. ENaC, epithelial sodium channel proteins; MR, mineralocorticoid receptor. Activation of the MR by aldosterone can be antagonized with spironolactone. Amiloride is a drug that can be used to block ENaC.

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.

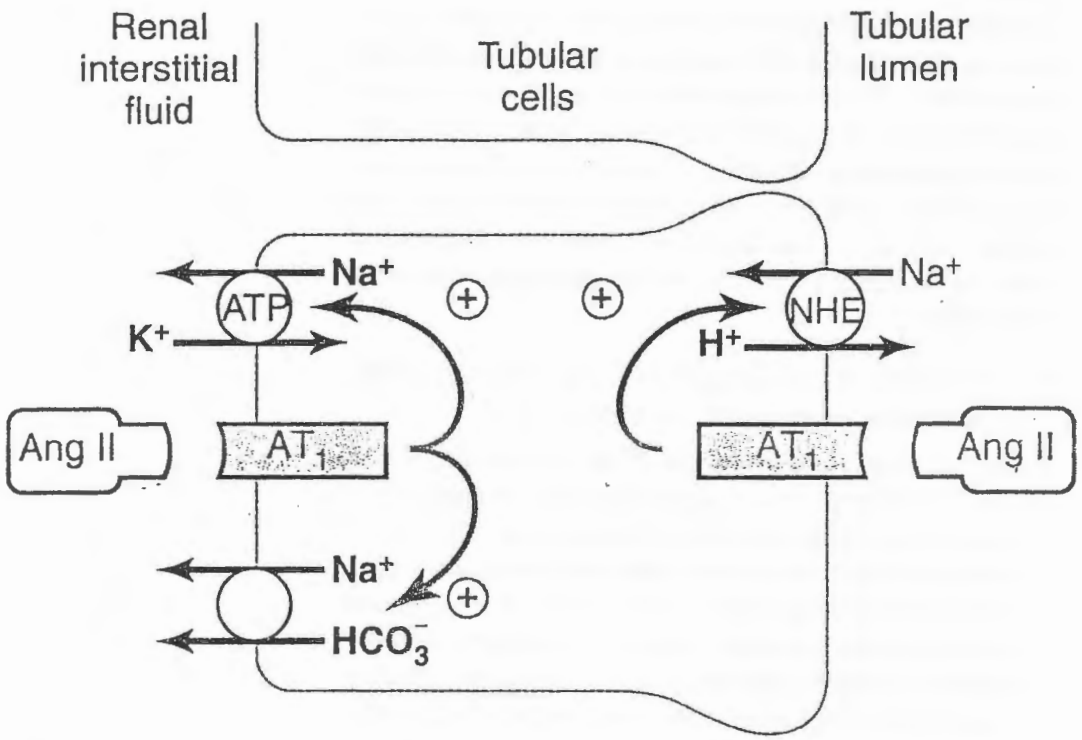
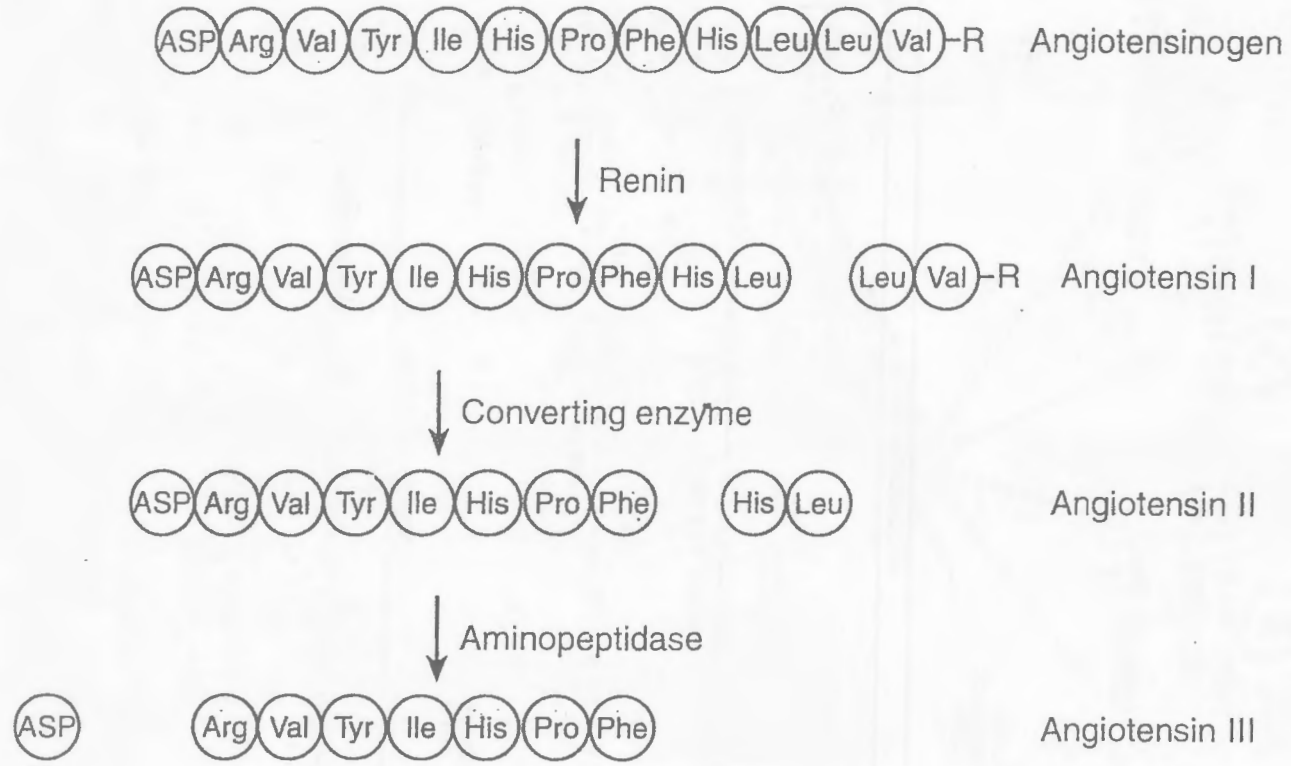


Figure 27-17 Direct effects of angiotensin II (*Ang II*) to increase proximal tubular sodium reabsorption. Ang II stimulates sodium sodium-hydrogen exchange (*NHE*) on the luminal membrane and the sodium-potassium ATPase transporter as well as sodium-bicarbonate co-transport on the basolateral membrane.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

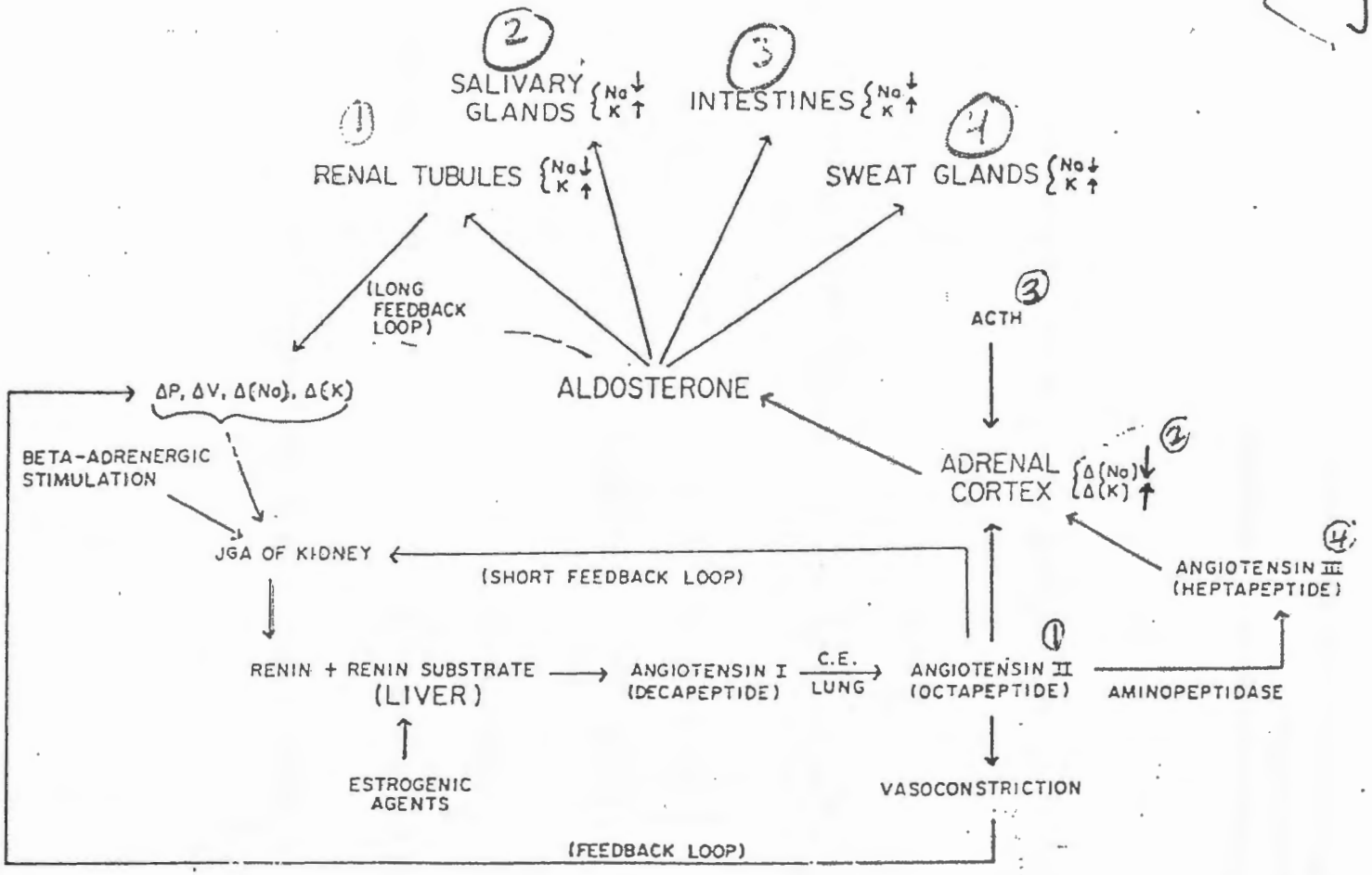


FIGURE 5-18: The physiologic factors controlling aldosterone secretion rate (C.E. = converting enzyme).

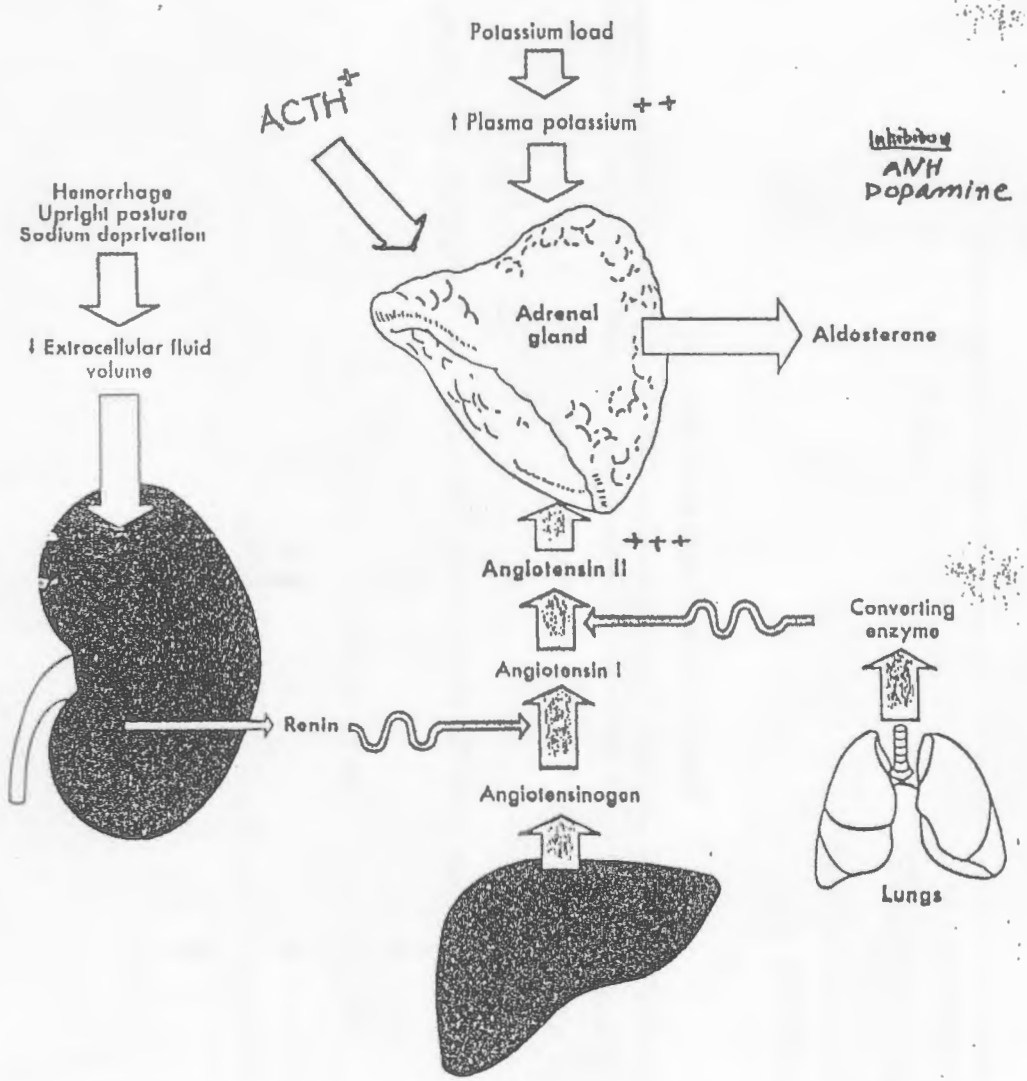


FIGURE 41-8 The regulation of aldosterone secretion. Activation of the renin-angiotensin system in response to hypovolemia is the predominant stimulus to aldosterone production. Elevation of plasma potassium is the other major stimulus.

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.

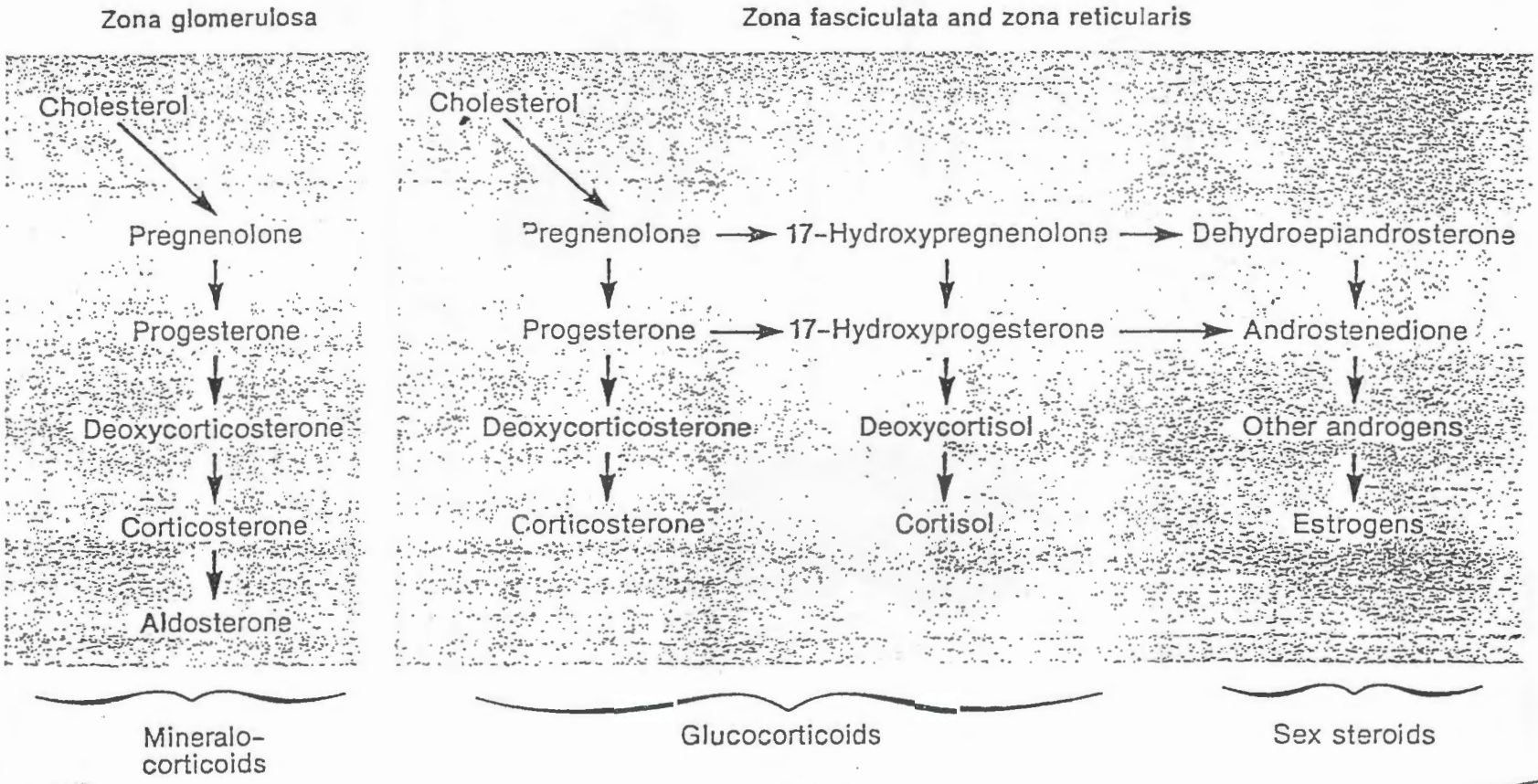


TABLE 5-3: Physiologic Actions of Glucocorticoid Hormones

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		

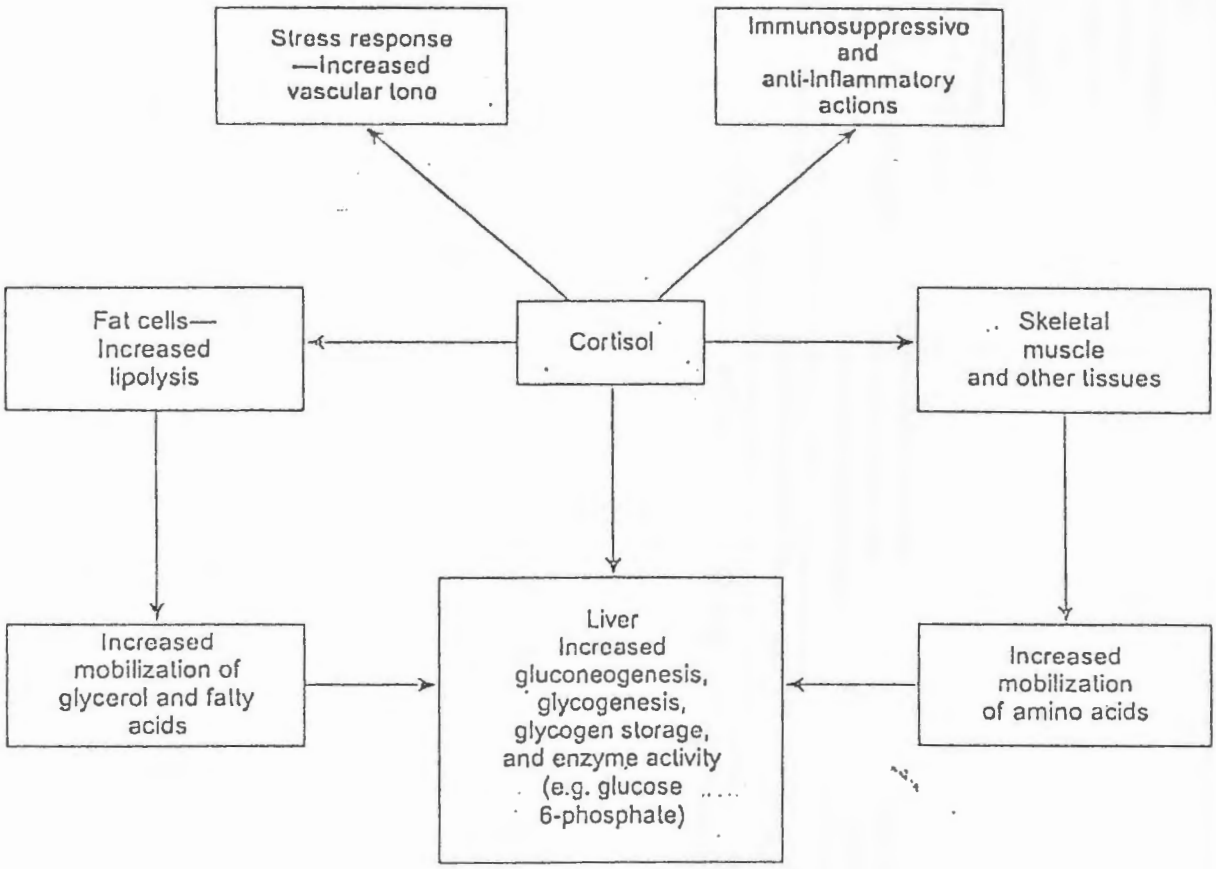


Fig. 12.18 The principal physiological actions of the glucocorticoid hormone, cortisol.

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)

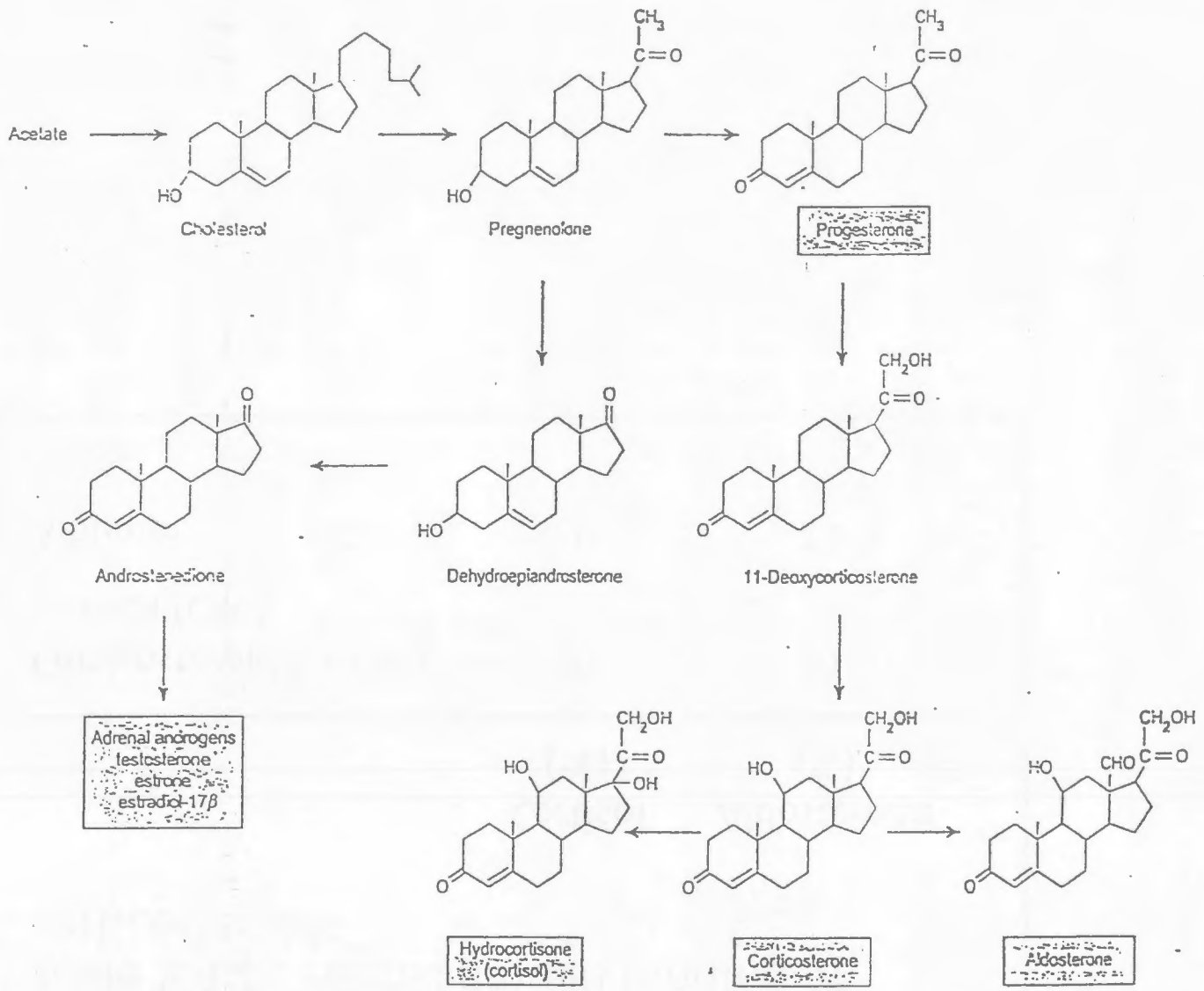


Fig. 12.17 The principal steps in the synthesis of the adrenal steroid hormones from cholesterol. Cortisol is the principal glucocorticoid and aldosterone is the principal mineralocorticoid.

Table 5.4.2 Plasma protein binding of corticosteroids

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

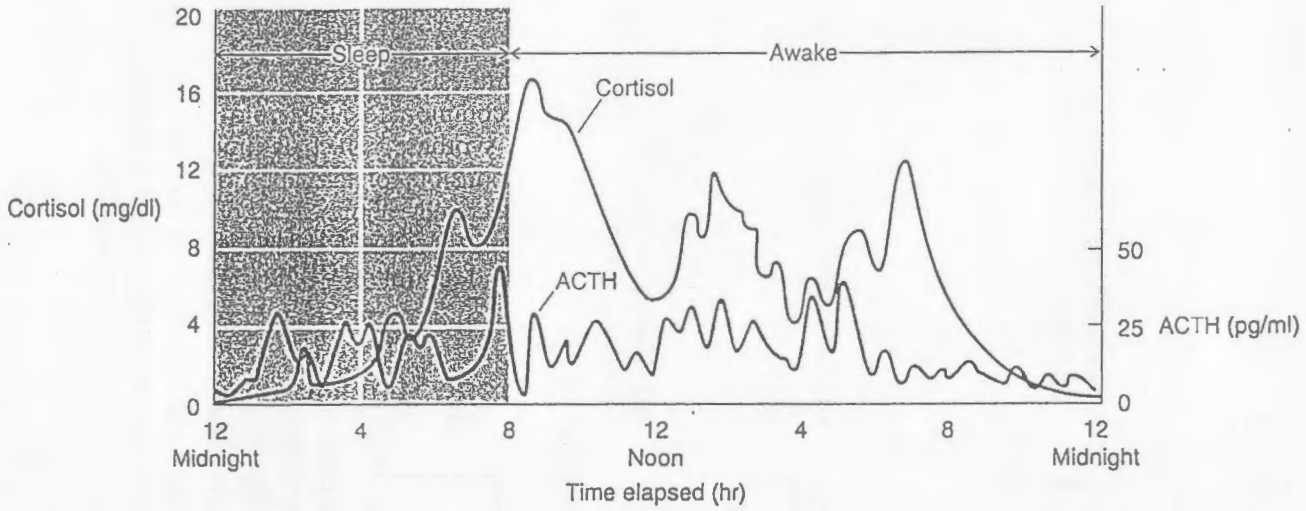


FIGURE 49–5. Rhythm of ACTH and cortisol. The corticotrophs release ACTH in a circadian rhythm, greater in the early morning hours and less late in the afternoon and early evening. Superimposed on the circadian rhythm is the effect on the corticotrophs of the pulsatile secretion of CRH by the hypothalamus.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

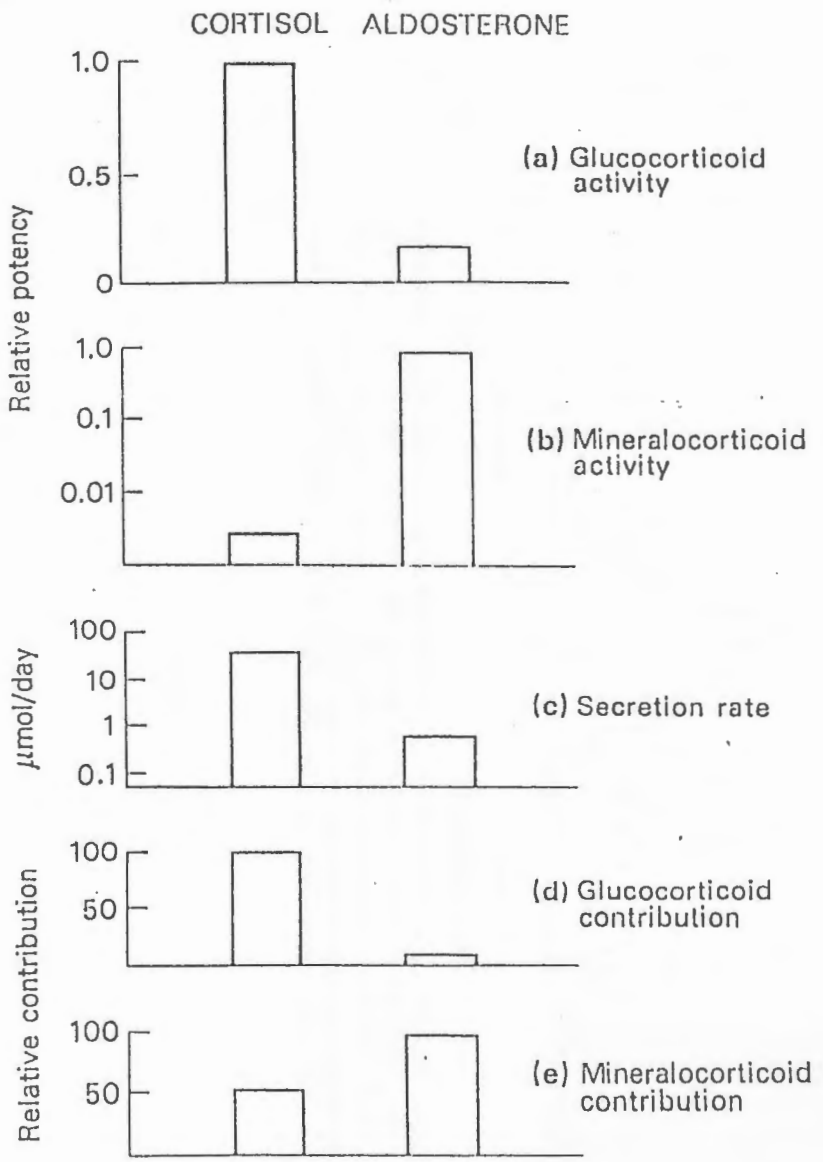


Fig. 3.5 A comparison of cortisol and of aldosterone. Glucocorticoid activity was measured as ability to increase glycogen in the liver: cortisol is very potent in this assay. Mineralocorticoid effects were measured in terms of the ability to reduce the ratio of the excretion of sodium to the excretion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

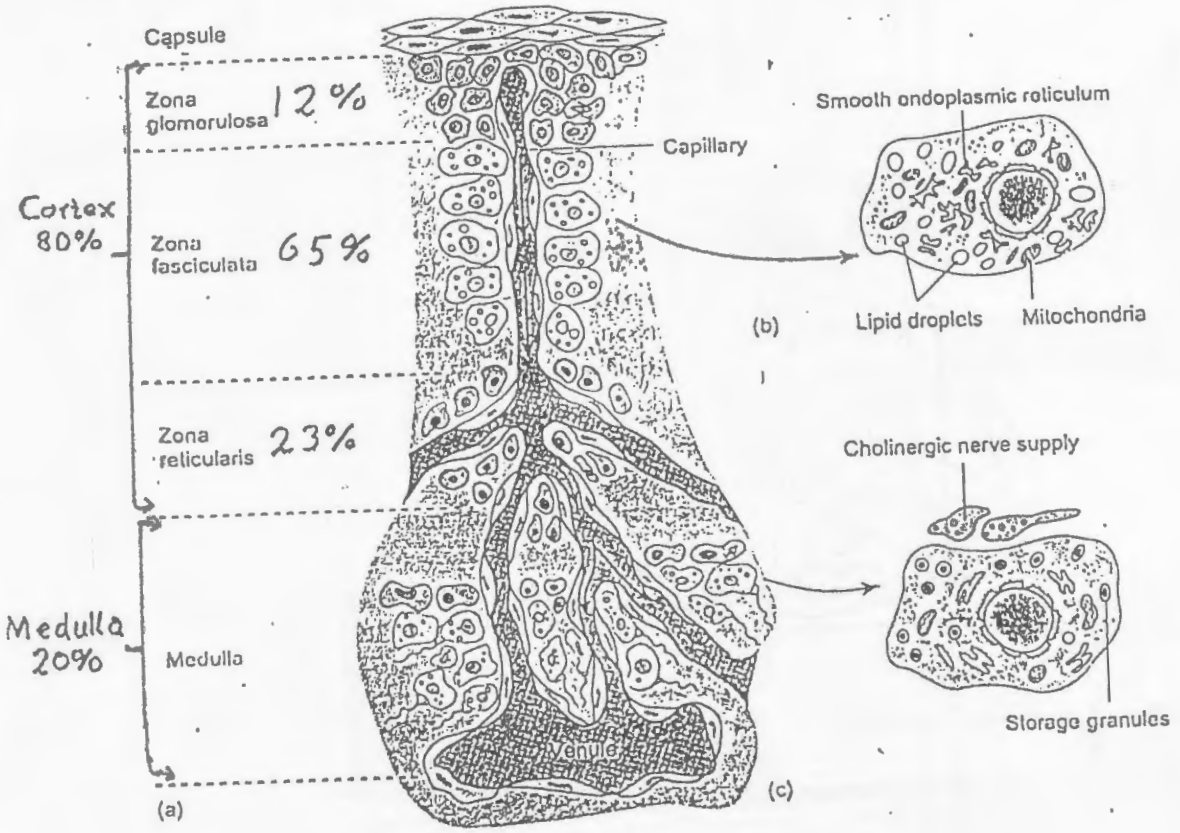


Fig. 12.16 (a) A diagrammatic representation of a section through the cortex and medulla of the adrenal gland. Note the three zones of the adrenal cortex, the cells of which secrete steroid hormones. (b) The appearance of steroid-secreting cells. (c) A single catecholamine-secreting chromaffin cell.

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.

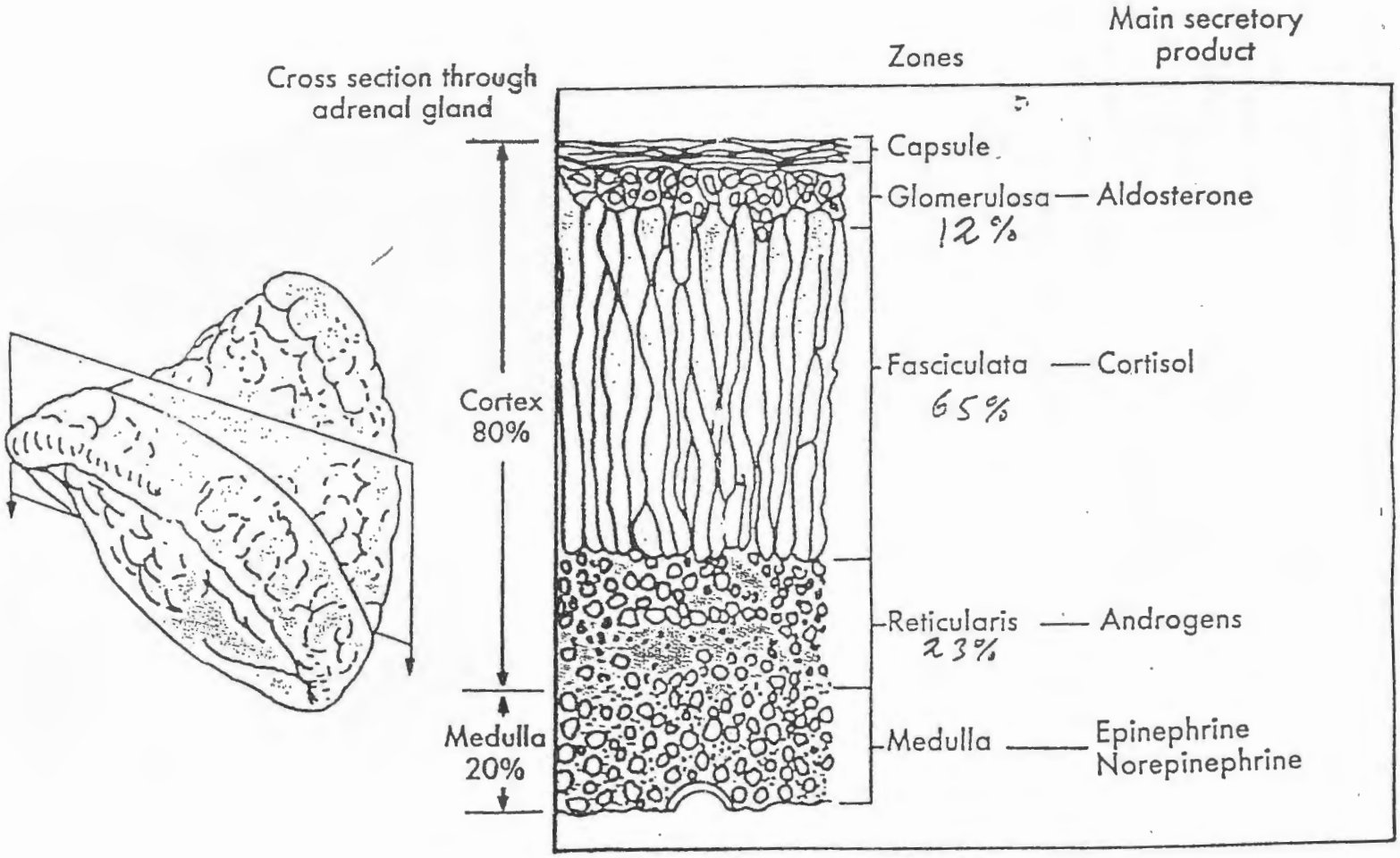


FIGURE 41-1 Schematic representation of the adrenal gland and its main secretory products.

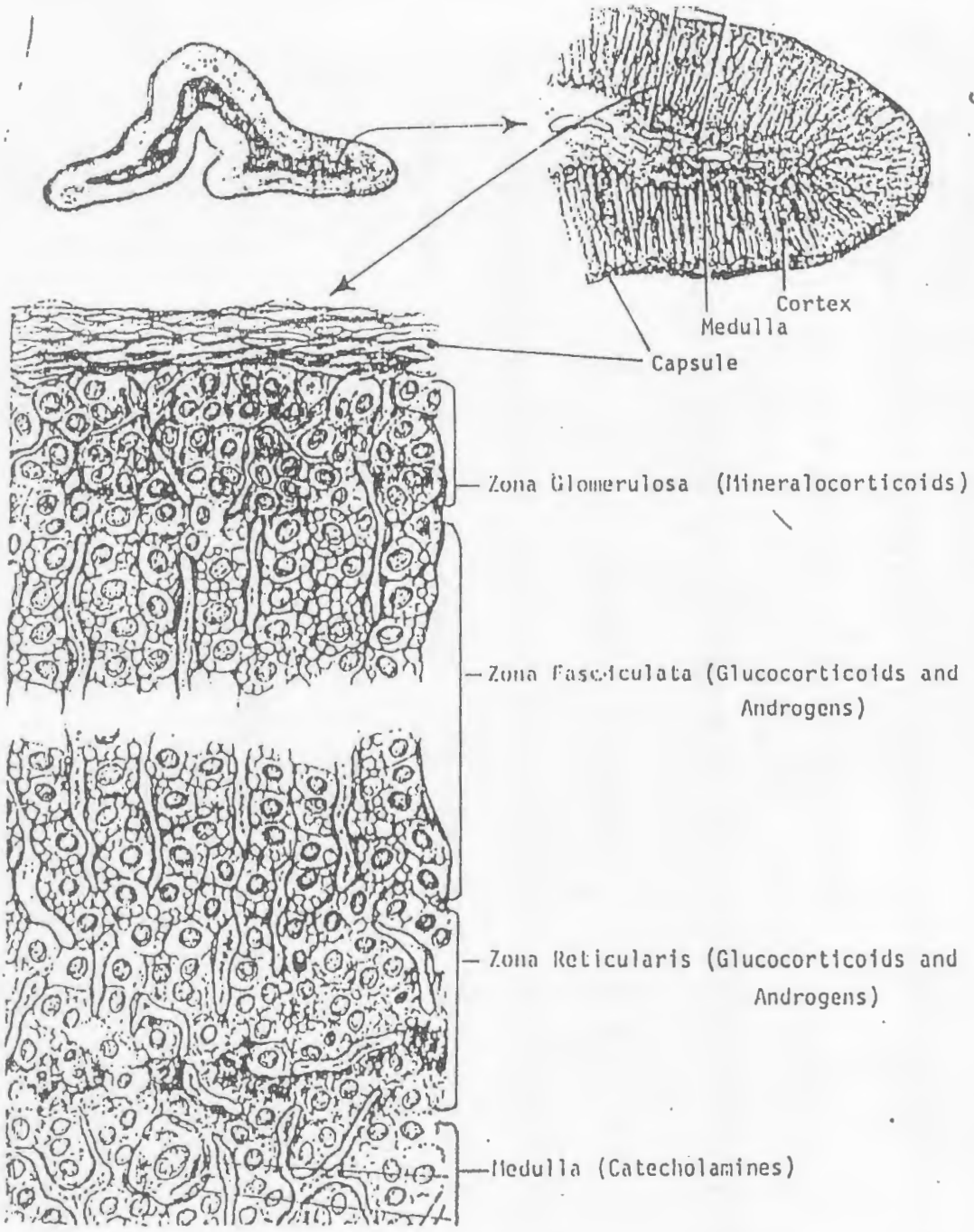


FIGURE 5-1: Cross section through the adrenal, illustrating the major subdivisions and cell layers as well as their hormonal products. (*Adapted from:* Ham and Cormack, 1979.)

" Adrenal Glands "

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

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

a). Controls Na, k and H_2O metabolism.

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

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

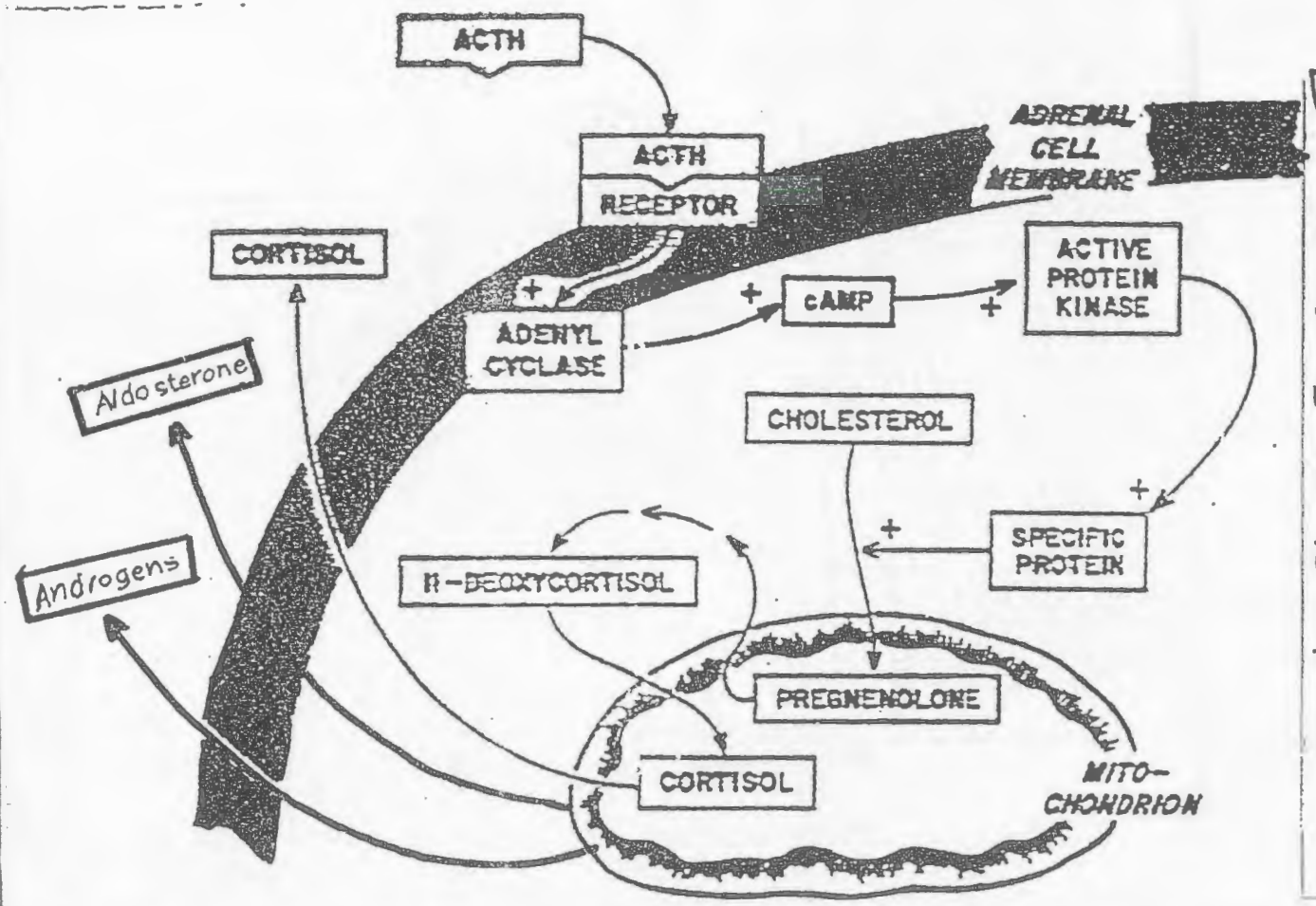


Fig 10–10.—Simplified scheme of stimulation of cortisol synthesis and secretion by ACTH. Note importance of mitochondrion.

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

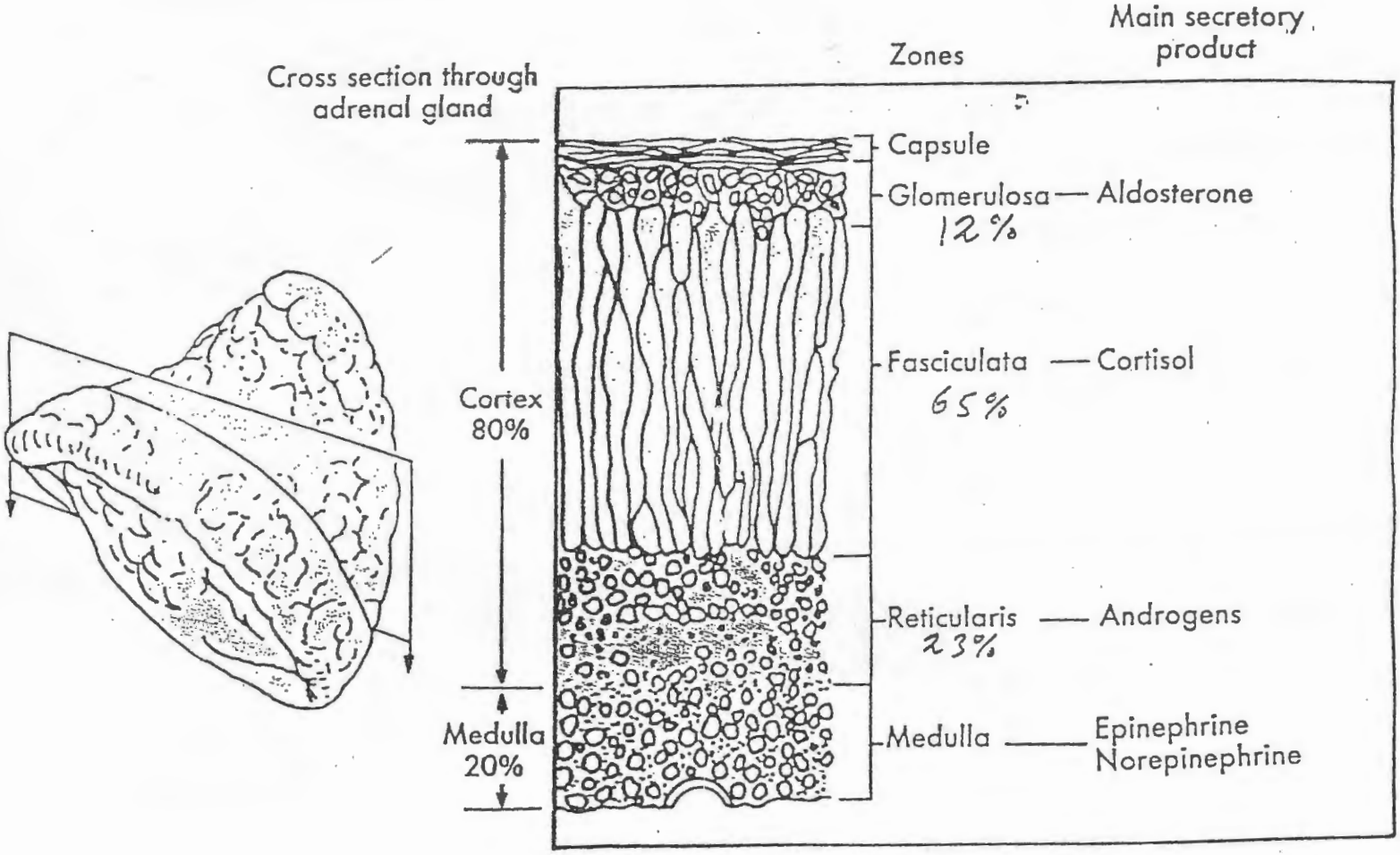


FIGURE 41-1 Schematic representation of the adrenal gland and its main secretory products.

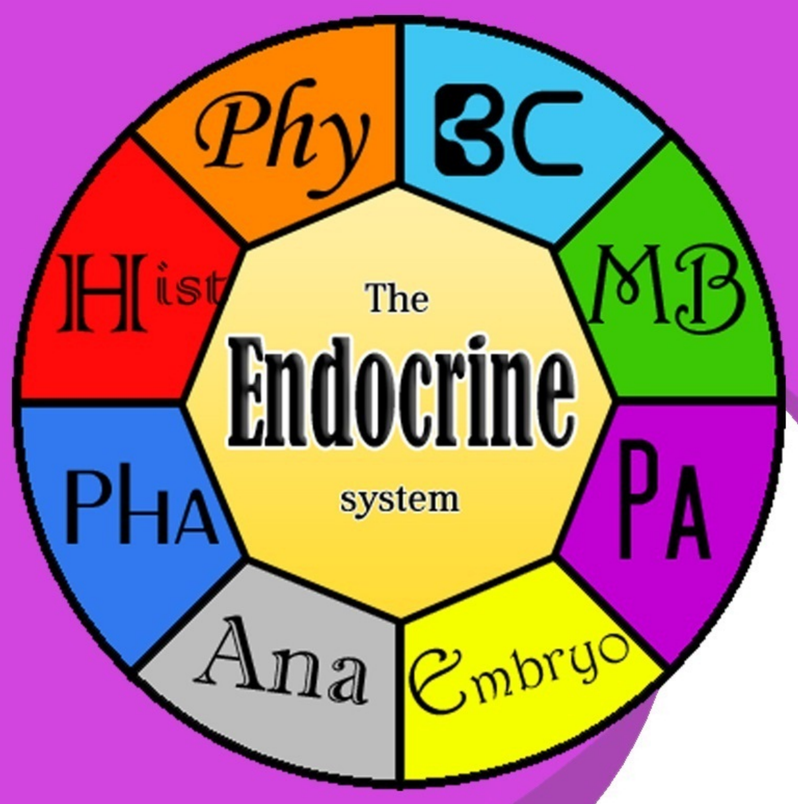
Treating Hypertension by Attacking the Renin-Angiotensin-Aldosterone Axis

Because the renin-angiotensin-aldosterone axis plays an important role in maintaining extracellular volume and arterial pressure, pharmacologists have sought ways to disrupt this system to treat hypertension. Several agents acting on different parts of the axis are available. **Spironolactone** is a diuretic that directly antagonizes the effects of aldosterone on the renal tubule. It is a weak diuretic, but it is particularly useful in treating patients with ascites. For patients with hypertension or congestive heart failure, it is usually added to one of the more common thiazide diuretics (see Chapter 35) to prevent K^+ wasting.

→ ACE inhibitors have been available for many years and are among the safest and best-tolerated of all antihypertensive medications. The first to be marketed in the United States was captopril, but many others, with longer half-lives that allow once-daily administration, are now available. These drugs also improve the quality of life and survival of patients with heart failure. More recently, drugs have been developed that specifically block the AT_1 receptor. These drugs offer a good alternative for those patients who cannot tolerate ACE inhibitors, usually because of a chronic cough, the most common side effect of these drugs.

University of Jordan
Faculty of Medicine

2018 2012
Medical Committee
The University of Jordan



PATHOLOGY

Slides
Sheet

3-4

6-4- 2014

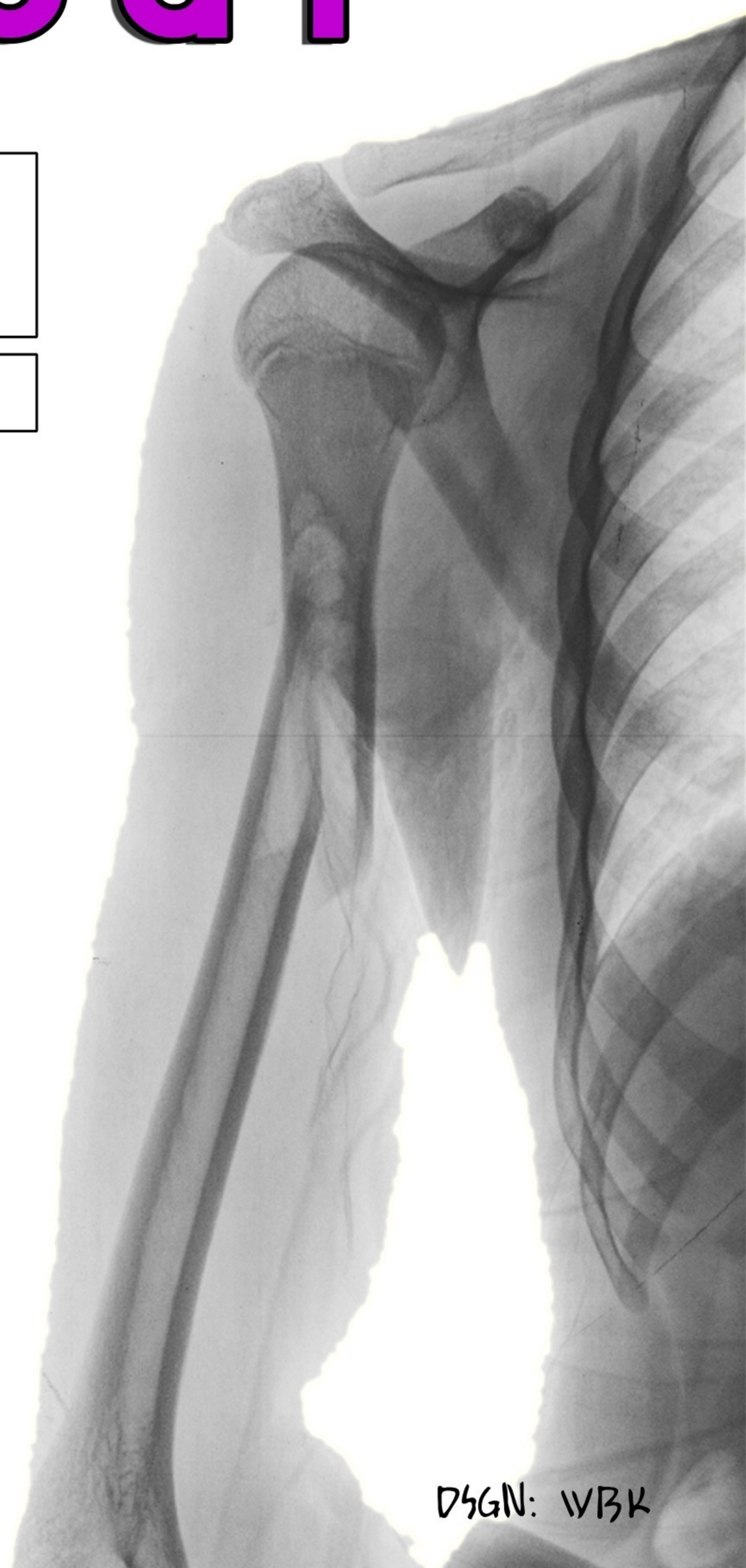
TITLE: PAPILLARY ADENOMA ...

PROFESSOR: Dr. Fatima Al-Obeidat -3,4

WRITTEN BY:

PRICE: 30 قرش

7/4/2014



DSGN: WBK

University of Jordan
MD Class of 2018
groups/Docotrs2012
www.msg18.weebly.com

B. Environmental Factors.

a. The major risk factor to papillary thyroid cancer is exposure to ionizing radiation, during the first 2 decades of life.

b. Deficiency of dietary iodine:

- Is linked with a higher frequency of follicular carcinomas.

1. **Papillary Carcinoma :**

- Is most the most common form
- accounts for the majority of thyroid carcinomas associated with previous exposure to ionizing radiation.
- The most common thyroid cancer in children
- May occur at any age,

Gross: Either solitary or multifocal lesions

Microscopically

1. The nuclei of papillary carcinoma cells

a.are optically clear nuclei, or "Orphan Annie eye" nuclei.

b. Have pseudoinclusions)

2. A papillary architecture is common

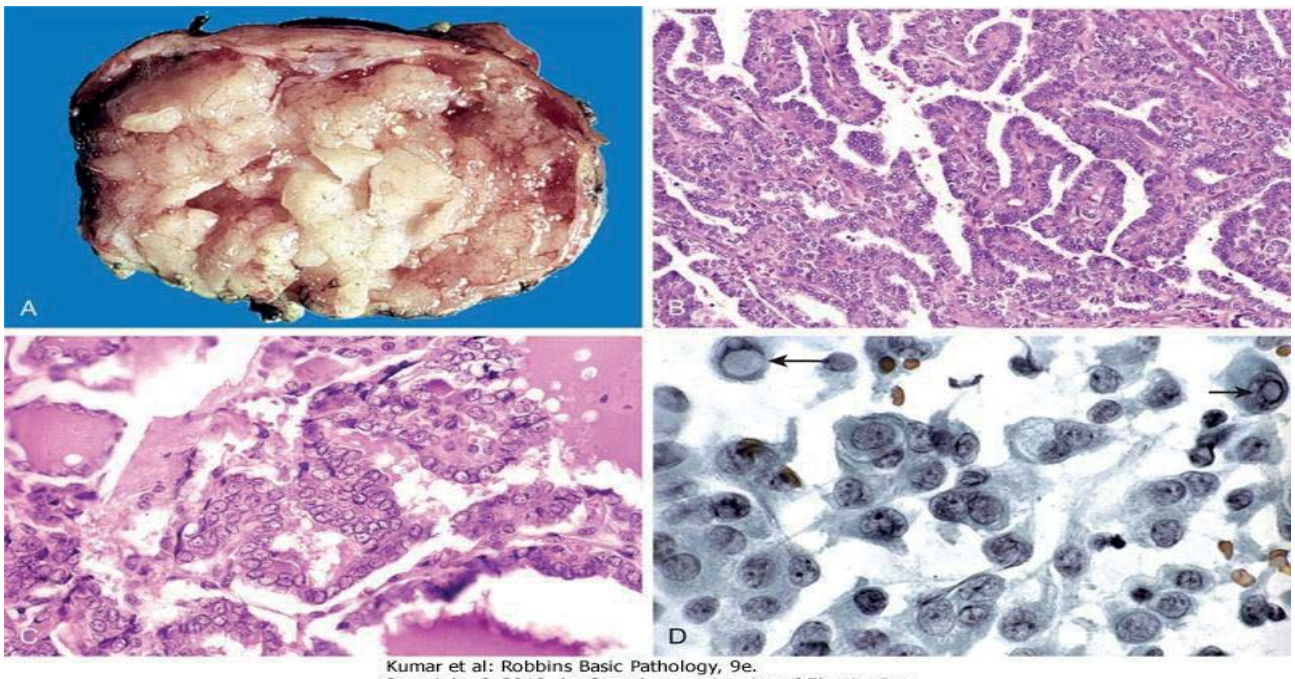
3. Concentrically calcified structures(psammoma bodies)

4. Foci of lymphatic permeation by tumor cells are present, with metastases to cervical lymph nodes in half of cases.

5. but invasion of blood vessels is uncommon

Variants: The most common is follicular variant associated with a lower incidence of lymph node metastases and extrathyroidal extension than that for conventional type

Papillary carcinoma



Kumar et al: Robbins Basic Pathology, 9e.
Copyright © 2013 by Saunders, an imprint of Elsevier Inc.

Clinical Features of papillary carcinomas

a. Are nonfunctional tumors manifest as painless mass in the neck, either within the thyroid or as metastasis in a cervical lymph node

b. Are indolent lesions, with 10-year survival rates of 95%.

c. The presence of isolated cervical nodal metastases does not have a influence on good prognosis of these lesions.

.

d. In a minority of patients, hematogenous metastases are present at the time of diagnosis, most commonly to lung

- The bad prognostic factors are:

a. Tumors arising in patients older than 60

b. The presence of extrathyroidal extension

c. Presence of distant metastases (stage)

2. Follicular Carcinoma :

-- More common in women and in areas with dietary iodine deficiency (accounting for 25% to 40% of thyroid cancers in these regions).

- The peak incidence between the ages of 40 and 60 years

Pathologically It may be

a. Widely invasive, infiltrating the thyroid parenchymaand extrathyroidal soft tissues, or

b. Minimally invasive that may be impossible to distinguish from follicular adenomas on gross examination and

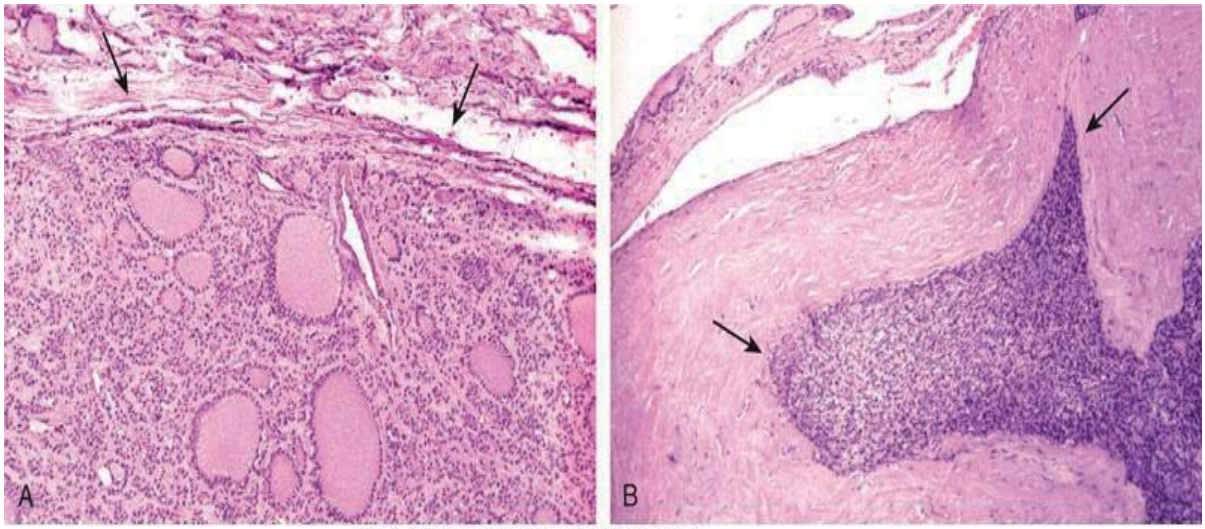
.

and/or vascular invasion to differentiate it from follicular adenoma

Clinical Features

- Manifest frequently as solitary *cold thyroid nodule.*
- Tend to metastasize through h*ematogenous routes* to lungs, bone, and liver but uncommon regional nodal metastases are uncommon .
- Half of patients with widely invasive carcinomas succumb to their disease within 10 years,
- less than 10% of patients with minimally invasive follicular carcinomas die within the same time span.

Follicular carcinoma



Kumar et al: Robbins Basic Pathology, 9e.
Copyright © 2013 by Saunders, an imprint of Elsevier Inc.

- Are treated with surgical excision.
- Because better-differentiated lesions may be stimulated by TSH, patients usually are placed on a thyroid hormone regimen after surgery to suppress endogenous TSH.

.

3. Anaplastic Carcinoma

- Are undifferentiated tumors of the thyroid epithelium, with mean age of 65 years.
- They are aggressive, with a mortality rate of 100%.
- Approximately 1/4th of patients have a past history a well-differentiated carcinoma, and harbor a well-differentiated tumor in the resected specimen
- Metastases to distant sites are common, but death occurs in less than 1 year as a result of aggressive local growth which compromise of vital structures in the neck.

4. Medullary Carcinoma

- Are neuroendocrine neoplasms.
- Secrete calcitonin, the measurement of which plays an important role in the diagnosis and postoperative follow-up evaluation of patients.
- In some cases, the tumor cells elaborate , serotonin, and vasoactive intestinal peptide (VIP)
- Are sporadic in about 70% of cases
- 30% are *familial* cases

a. Occurring in the setting of MEN syndrome 2A or 2B, have been reported in younger patients, including children

b. or familial medullary thyroid carcinoma without an associated MEN syndrome

Note: Both familial and sporadic forms demonstrate activating *RET* mutations.

- Sporadic medullary carcinomas, as well as familial cases without an associated MEN syndrome, occur in adults , with a peak incidence in the fifth and sixth decades.

. MORPHOLOGY

- Multicentricity is particularly common in familial cases.

On microscopic examination,

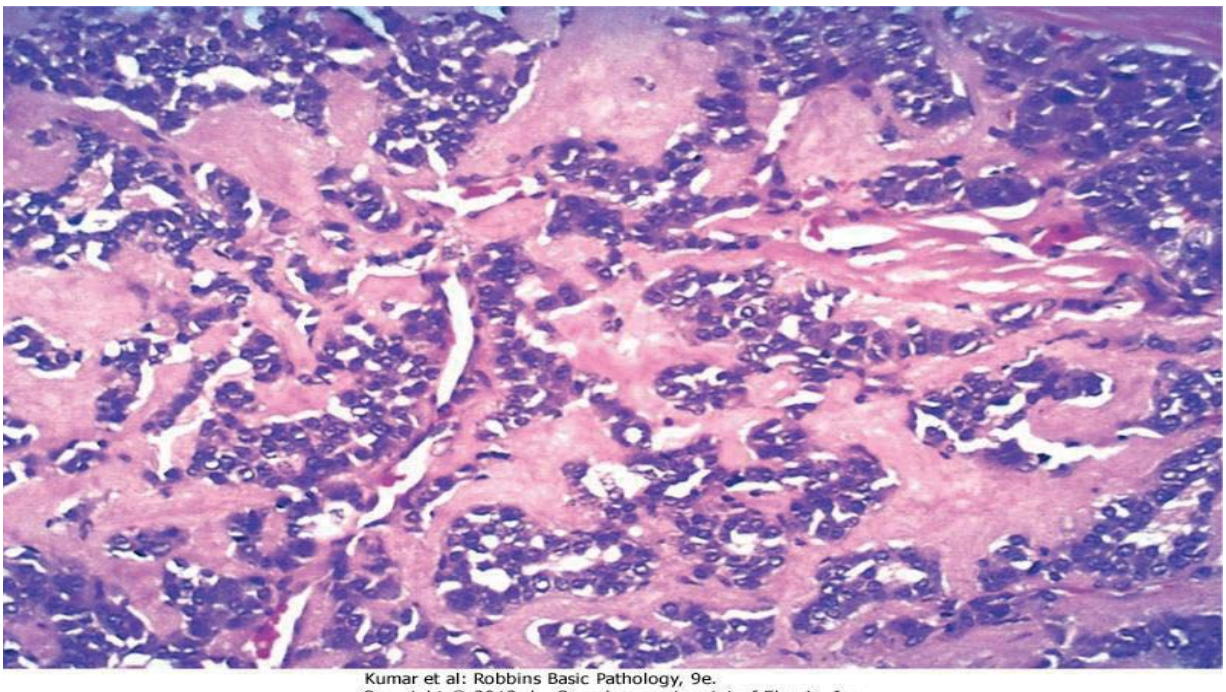
- The tumor cells may form nests, trabeculae, and even follicles.
- Amyloid deposits, derived from calcitonin molecules, are present in the adjacent stroma in many cases
- Calcitonin is readily demonstrable both within the cytoplasm of the tumor cells or amyloid

- Familial cases are characterized by the presence of multicentric C cell hyperplasia in the surrounding thyroid parenchyma, a feature usually absent in sporadic lesions.
- And these foci are believed to represent the precursor lesions from which medullary carcinomas arise

Clinical Features

- The sporadic cases manifests most often as a mass in the neck, sometimes associated with dysphagia or hoarseness.

Medullary carcinoma



Kumar et al: Robbins Basic Pathology, 9e.
Copyright © 2013 by Saunders, an imprint of Elsevier Inc.

- In some instances, the initial manifestations are caused by the secretion of a peptide hormone (e.g., diarrhea caused by the secretion of VIP).
- Screening of the patient's relatives for elevated calcitonin levels or *RET* mutations permits early detection of tumors in familial cases
- All members of MEN-2 kindreds carrying *RET* mutations are offered prophylactic thyroidectomies to prevent the development of medullary carcinomas

- Often, the only finding in the resected thyroid of these asymptomatic carriers is the presence of C cell hyperplasia or small (<1 cm) *micromedullary* carcinomas.

II. Parathyroid gland

I. HYPERPARATHYROIDISM : 3 categories

a. Primary Hyperparathyroidism

- Is a common disorder and important cause of hypercalcemia
- There has been an increase in the detection of cases as a result of the routine inclusion of serum calcium assays in testing for a variety of clinical conditions

Causes of primary hyperparathyrpoidism

1. Parathyroid adenoma (85% to 95%)
2. Primary parathyroid hyperplasia-5% to 10%.
3. Parathyroid carcinoma-(1%)

Genetic changes in parathyroid adenoma

1. Cyclin D1 is overexpressed in 40% of adenomas,
2. MEN1 mutations: About 20% to 30% of parathyroid tumors not associated with the MEN-1 syndrome have mutations in both copies of the *MEN1* gene

Primary hyperparathyroidism

- is a disease of adults and is much more common in women than in men.
- *The most common manifestation is an increase in serum calcium and i*s the most common cause of *clinically silent hypercalcemia.*
- The most common cause of clinically apparent hypercalcemia in adults is

a. paraneoplastic syndromes associated with *malignancy*

b. and bone metastases

Lab findings

a- In persons with hypercalcemia caused by parathyroid hyperfunction, serum PTH is inappropriately elevated

b. in hypercalcemia due to non parathyroid diseases, serum PTH is low to undetectable

c. Hypophosphatemia

d. Increased urinary excretion of calcium and phosphate

Clinical Manifestations :

- Traditionally has been associated with a constellation of symptoms "painful bones, renal stones, abdominal groans, psychic moans.“

1. Pain was at one time a prominent manifestation of primary hyperparathyroidism and is secondary to

a. Fractures of bones

b. and resulting from renal stones

c. Pancreatitis and gall stones

d. Peptic ulcer

Note;

- Because serum calcium is now routinely assessed in the most patients who need blood tests for other conditions, clinically silent hyperparathyroidism is detected early.
- Hence, many of the classic clinical manifestations, , are seen much less frequently .

2. *Gastrointestinal disturbances,* including constipation, nausea, peptic ulcers, pancreatitis, and gallstones

3. CNS alterations, - depression, lethargy, and seizures

4. Neuromuscular abnormalities,- weakness and hypotonia

5. Polyuria and secondary polydipsia

Morphology pf parathyroid adenoma

- lies in close proximity to the thyroid gland or in an ectopic site (the mediastinum)

b. Invested by a capsule

c. is almost invariably confined to single gland

d. and the remaining glands are somewhat shrunken, as a result of feedback inhibition by elevated serum calcium

d. . Most parathyroid adenomas weigh between 0.5 and 5 g.

On microscopic examination, parathyroid adenomas

a- Are composed predominantly of chief cells

b- A few nests of larger oxyphil cells also are also present.

c- A rim of compressed, non-neoplastic tissue, separated by a fibrous capsule, is visible at the edge of the adenoma.

d- Cells with pleomorphic nuclei may be seen (endocrine atypia) and must not be taken as a sign of malignancy.

e. Mitotic figures are rare

f. with inconspicuous adipose tissue

2. Parathyroid hyperplasia

- Is a multiglandular process
- In some cases, however, enlargement may be grossly apparent in only one or two glands, complicating the distinction between hyperplasia and adenoma.
- The combined weight of all glands rarely exceeds 1.0 g .

3. Parathyroid carcinomas :

a. Affects one gland

b.- Consist of irregular nodules that sometimes exceed 10 g in weight

c. A a dense, fibrous capsule encloses the mass.

Note

- The diagnosis of carcinoma based on cytologic detail is unreliable, and invasion of tissues and metastasis are the only definitive criteria
- Local recurrence occurs in one third of cases,
- More distant dissemination occurs in another third

I. Skeletal changes in primary hyperparathyroidism

a. Osteitis fibrosa cystica characterized by

1. Increased osteoclastic activity, resulting in erosion of bone and mobilization of calcium salts, mainly in the metaphyses of long tubular bones.
2. Bone resorption is accompanied by increased osteoblastic activity and the formation of new bone
3. In more severe cases the cortex is grossly thinned
4. The marrow contains increased amounts of fibroustissue accompanied by hemorrhage and cysts

b. Brown tumors of hyperparathyroidism

- Aggregates of osteoclasts,,and hemorrhage occasionally form masses that may be mistaken for neoplasms

II. Kidney changes

a. PTH-induced hypercalcemia favors the formation of urinary tract stones (nephrolithiasis) s

b. Calcification of the renal interstitium (nephrocalcinosis)

III. Metastatic calcification may be seen in the stomach, lungs, myocardium, and blood vessels.

b. Secondary Hyperparathyroidism

- Is caused by any condition causing a chronic decrease in the serum calcium level, because low serum calcium leads to compensatory overactivity of the parathyroids.

- *Renal failure is the most common cause*

1. Chronic renal insufficiency causes decreased phosphate excretion, which in turn results in hyperphosphatemia. and the elevated serumphosphate levels depress serum calcium levels and so stimulate parathyroid gland activity

2. Loss of renal substances reduces the availability of α_1-hydroxylase enzyme necessary for the synthesis of the active form of vitamin D, which in turn reduces intestinal absorption of calcium

Gross-

- The parathyroid glands are hyperplastic and called secondary hyperplasia.

Clinically

a- Are dominated by those related to chronic renal failure

b.- Bone abnormalities (*renal osteodystrophy*) are less severe than those seen in primary type

c.- Serum calcium remains near normal because compensatory increase in PTH levels sustains serum calcium.

d- The metastatic calcification of blood vessels (secondary to hyperphosphatemia) occasionally may result in significant ischemic damage to skin and other organs-a process sometimes referred to as *calciphylaxis*

c. Tertiary hyperparathyroidism

- In a minority of patients, parathyroid activity may become autonomous and excessive, with resultant hypercalcemia-a process termed ***t***ertiary hyperparathyroidism
- Parathyroidectomy may be necessary to control the hyperparathyroidism in such patients

HYPOPARATHYROIDISM:

The major causes are:.

a. Surgically induced hypoparathyroidism:

- Inadvertent removal of parathyroids during thyroidectomy.

b. Congenital absence:

- This occurs in conjunction with thymic aplasia (Di George syndrome) and cardiac defects

c. Autoimmune hypoparathyroidism :

- This is a hereditary polyglandular deficiency

syndrome arising from autoantibodies to multiple endocrine organs(parathyroid, thyroid, adrenals, and pancreas).

Clinical manifestations

- **A**re secondary to hypocalcemia and include:

a. Increased neuromuscular irritability (tingling, muscle spasms, facial grimacing, and sustained carpopedal spasm or tetany),

b. Cardiac arrhythmias, and, on occasion, increased

c. Seizures.

The Adrenal gland

I. Adrerenocortical Hyperfunction (Hyperadrenalism)

1. Hypercortisolism (Cushing Syndrome)

- In clinical practice, most cases are caused by the administration of exogenous glucocorticoids (Iatrogenic)
- The remaining cases are endogenous and caused by one of the following

A. Primary hypothalamic-pituitary diseases associated with hypersecretion of ACTH (Cushing disease)

- Accounts for 70% of cases of spontaneous, endogenous Cushing syndrome .

- Occurs most frequently during young adulthood (the 20s and 30s) and mainly affecting women

Causes of Cushing disease

a. *ACTH-producing microadenoma (most common)*

b. C*orticotroph cell hyperplasia* which may be:

a. Primary

b. secondary to excessive ACTH release by a hypothalamic (CRH)-producing tumor

- The adrenal glands in Cushing disease show bilateral nodular cortical hyperplasia secondary to the elevated levels of ACTH ("ACTH-dependent" Cushing syndrome).
- The cortical hyperplasia, in turn, is responsible for the hypercortisolism

B. Primary adrenal hyperplasia and neoplasms

- Are responsible for about 10% to 20% of cases of endogenous Cushing syndrome and this form is called *ACTH-independent Cushing syndrome,* or adrenal Cushing syndrome and its biochemical hallmark is elevated levels of cortisol with low serum levels of ACTH
- In most cases, adrenal Cushing syndrome is caused by a unilateral adrenocortical neoplasm, which may be either benign (adenoma) or malignant (carcinoma).

- **Note**-
- The overwhelming majority of adrenal hyperplasia are ACTH-dependent, and primary cortical hyperplasia of the adrenal cortices is a rare cause of Cushing syndrome

***C. Secretion of ectopic ACTH* by nonpituitary tumors**

- Accounts for about 10% of cases of Cushing syndrome mostly caused by *small cell carcinoma of the lung*,
- The adrenal glands undergo bilateral hyperplasia due to elevated ACTH, but the rapid downhill course of patients with these cancers cuts short the adrenal enlargement

MORPHOLOGY of the pituitary in Cushing syndrome

Crooke hyaline change :

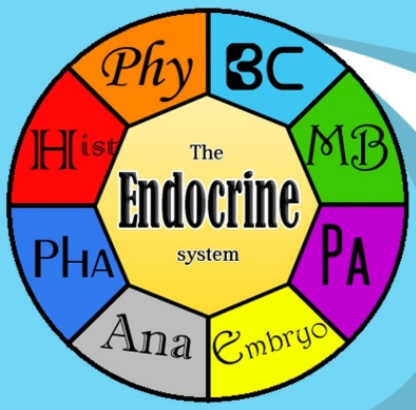
- Results from high levels of glucocorticoids, and in this condition, the normal basophilic cytoplasm of the ACTH-producing cells is replaced by homogeneous slightly basophilic material
- This alteration is the result of the accumulation of intermediate keratin filaments in the cytoplasm.

Changes in adrenal in cases of Cushing syndrome:

1) **Cortical atrophy** :

- If the syndrome results from exogenous glucocorticoids ,suppression of endogenous ACTH results in bilateral cortical atrophy, due to a lack of stimulation of the zona fasciculata and reticularis by ACTH,
- The zona glomerulosa is of normal thickness because it functions independently of ACTH

University of Jordan
Faculty of Medicine



Medical Committee
The University of Jordan

BIOCHEMISTRY

☐ SLIDES
■ SHEET

4

31st Mar. 2014

TITLE: EICOSANOIDS

PROFESSOR: Dr. Faisal Al-Khateeb -4

WRITTEN BY: Alaa' Al-Shqeirat

PRICE: 15 قرش

2014/4/7

MD University of Jordan Class of 2018
groups/Docotrs2012
www.msg18.weebly.com

DSGN: WBK

Before start talking about today's lecture let's revise some points of JAKs (janus kinases)

1*.they are a family of intracellular , non-receptor tyrosine kinases*

2*. they transmit signals via JAK-STAT pathway*

3*.for Growth hormone , JAK 2 is the tyrosine kinase that's associated with its receptor, (the association of JAK2 with the receptor is not covalent , and is increased by the phosphorylation of the receptor)*

Now we will talk about other kinds of receptors in which tyrosine kinase is an integral part of them (the receptor itself is a tyrosine kinase)

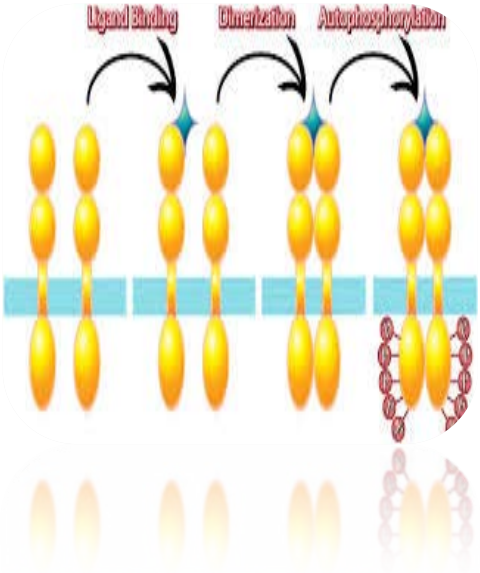
1. EGF (Epidermal growth factor)receptor :

a.**EGF**, is a hormone that is required for growth and development of skin and derma

b. it was discovered accidently

c.it,(the receptor), is monomeric (inactive)

d.EGF binding leads to dimerization of receptor then autophosphorylation , in which each monomer phosphorylates the other (cross phosphorylation),and now the receptor is activated and leads to activation of target proteins.



2.insulin receptor

a.insulin receptor composed of four subunits of (**2alpha & 2 beta**)subunits

b. each alpha subunit and beta subunit make what so called (alpha-beta pair), and the result is dimer of 2 (alpha-beta pairs)

c.these pairs are bounded together via disulfide bridge

d.thus , the receptor itself is a dimer (not monomer as EGF receptor), even when insulin is not bound

e. binding of insulin will lead to activation of integral tyrosine kinase

f. so , dimerization is important(but not sufficient) for activation of the receptor.

Do these receptors transfer information across the membrane in the same way ??

The question was answered by synthesizing a gene that encoded a chemeric of receptors (mixture of receptors), in which the extracellular part came from insulin receptor , and the membrane-spanning and cytosolic part came from EGF receptor . The striking result was that the binding of insulin induced tyrosine kinase activity , as evidenced by rapid autophosphorylation .Hence ,the insulin receptor and the EGF receptor employ a common mechanism of signal transmission across the plasma membrane.

Note that the chemeric receptor is inactive until the binding of insulin .

Epidermal growth factor signaling pathway

Phosphorylation of receptors leads to activation of subsequent proteins , these proteins act sequentially to mediate the effect of growth factor, and the proteins participate in EGF signaling are :

1. GRB2 2. SOS 3. RAS

Now ,Read the following points to understand the signaling pathway

1. first, binding of EGF hormone to its receptor leads to autophosphorylation of the receptor (as we mentioned previously),then GRB2 protein come and through its SH2 domain bind to phosphorylated tyrosine residue

2. this protein (GRB2) , also has 2 SH3 domains that bind to SOS protein, so it's activated

3.the binding of SOS allow another protein called RAS to come and bind to it,(RAS is a guanine binding protein , it binds GDP , but once binds to SOS , it exchanges GDP with GTP and become activated).

4.then , it leads to activation of specific protein kinases.

RAS PROTEIN

1. it's a monomeric protein (not a trimer as ordinary G proteins)

2.exist in 2 forms (GDP-inactive,GTP-active)

3.smaller than G protein (resembles the alpha subunit of G protein in structure & mechanism

4.is a member of small G protein family, and also it includes several groups or subfamilies.

5.has GTPase activity

6.it has a major role in growth,differentiation,cellular transport and motility.

DEFECTS IN SIGNALING PATHWAY CAN LEAD TO CANCER AND OTHER DISEASES

*cancer is characterized by uncontrolled growth, one of the causes is that the regulatory or signaling pathways are continuously turned on without stopping and by that will progressively stimulate the growth & differentiation of cells ,leading to cancer

*certain viruses can cause cancer

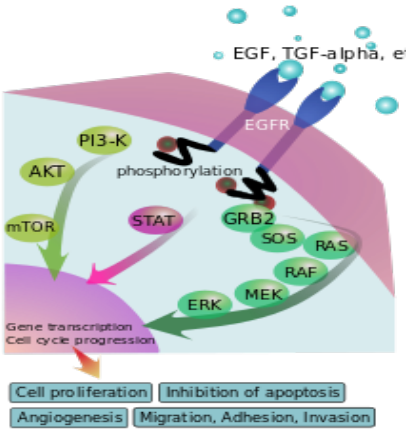
*OR can be associated with defect in signal transduction proteins ; failure of signal transduction process

1/One of the viruses that cause cancer is <u>ROUS SARCOMA VIRUS ,</u> that cause sarcoma in chickens.

How do it causes sarcoma ???

1.**Rous sarcoma virus** contains an oncogene called **v-src** ,the host form of that oncogene is called proto-oncogene **c-src.**

2. it has been shown that these tumor viruses picked up their oncogenes by incorporating normal host genes into their genomes , then



undergo some mutations that lead to changes in that gene and subsequent cancer .
a.the normal host **c-src** gene encodes a tyrosine kinase protein, its structure is composed of SH2 , SH3 domains and protein kinase domain

note that there is a minimal difference between c-src & v-src in a way that cause v –src always active (we will talk about that)

b.when SRC is inactive ,**1**. the phosphorylated tyrosine group interacts with SH2 domain , and **2**. SH3 domain interacts with poly-proline sequence on protein kinase domain, maintaining the inactive unit tightly bound
c.as we mentioned some mutations lead to conversion of proto-oncogen into oncogen that are continuously active (because the tyrosine residues are not phosphorylated , and by that no interaction will occur with SH2 domain to mediate the inactive form)
d.thus ,the presence of this oncogene leads to continuous signal transduction of growth factor and subsequent uncontrolled growth .
the oncogene is trapped in the on position in three ways:
1-SH2 displacement.
2-SH3 displacement.
3- dephosphorylation.
Protein kinase inhibitors are used in such cases of cancer.

2/Impaired GTPase activity can lead to cancer in humans
1.In mammalian cells there are 3 RAS proteins .
2. Mutations will lead to loss ability to hydrolyze GTP .
3.by that , the RAS is locked in ' ON' position and lead to continuous stimulation of growth .

Cholera & whooping cough are due to altered G-protein activity,how?

1. the cholera is a bacterial disease that causes dehydration and diarrhea, and can lead to death as well.
2. the vibrio cholera do not enter the cells.
3.the disease of cholera arises from cholera toxin that causes the toxic manifestations by the following mechanism
*first , cholera toxin is a protein composed of 2 functional subunits
a.***B subunit*** , binds to GM1 gangliosides of the intestinal epithelium
b. ***A subunit*** (catalytic subunit) , which enter the cell,and catalyzes the covalent modification of G-alpha subunit protein by attachment of ADP-ribose **(derived from NAD**)to an arginine residue of G-alpha- s protein
c. this modification leads to stabilization of GTP-bound form of G-alpha s
d. the activated G protein then activates protein kinase A.
e. chloride channels will open continuously , and chloride will diffuse (along with sodium) to the lumen , and water will follow them (osmosis).
f.large amount of water will lost leading to dehydration .

EICOSANOIDS

Eicosanoids are 20 carbon signal molecules that play an important role in inflammation response and in platelet aggregation

1.composed of several classes ;(**prostaglandins, thromboxanes** and **leukotrienes**).
Prostaglandin name was originated because it was discovered for the first time in prostate secretions.

2.produced in almost all tissues

3.they act locally (not carried by circulation) , and affect neighboring cells(paracrine effect) and cells that produce them(autocrine effect).

4.they produce wide range of responses in target cells.

5.they are very potent (although they found in very low concentration).

6.not stored (produced and released immediately).

7.they have short half life.

8. different classes have opposite effects .

Functions of prostaglandins and thromoxanes

The doctor will not ask about them , but you have to know that they have contrary functions.

PGI2, PGE2, PGD2 ('2' is related to number of double bonds in the structure) have the following functions

1. vasodilation

2. increase cAMP

3.decrease platelet, leukocyte aggregation

4.decrease lymphocyte migration

PGF2alpha

1. vasoconstriction

2.bronchoconstriction

3.smooth muscle contration

Thromboxanes

1. vasoconstriction

2. Induce platelet aggregation

3.increase lymphocyte proliferation

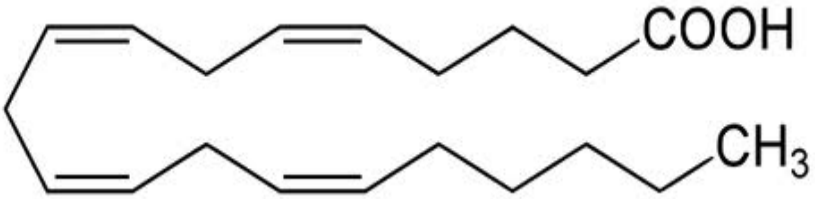
4.bronchoconstriction

Structures of eicosanoids

It's important to be able to recognize the structure of different classes of eicosanoids and differentiate between them .

1.Arachidonic acid : considered as the parent compound in the synthesis of eicosanoids , it's a 20 carbon molecule with 4 double bonds. (look at the

picture below)

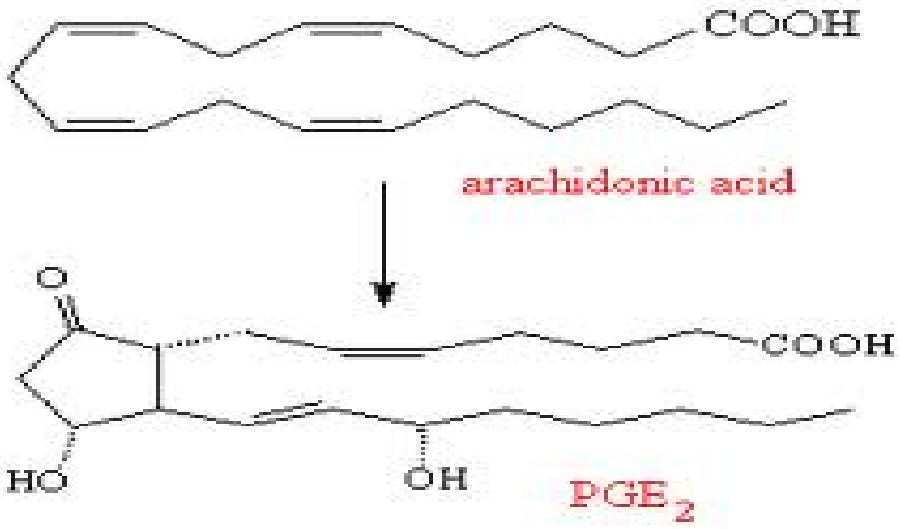


2.prostaglandins:

1. consist of five-membered ring , and 2 side chains ; one contains 7 carbons and the other contains 8 carbon

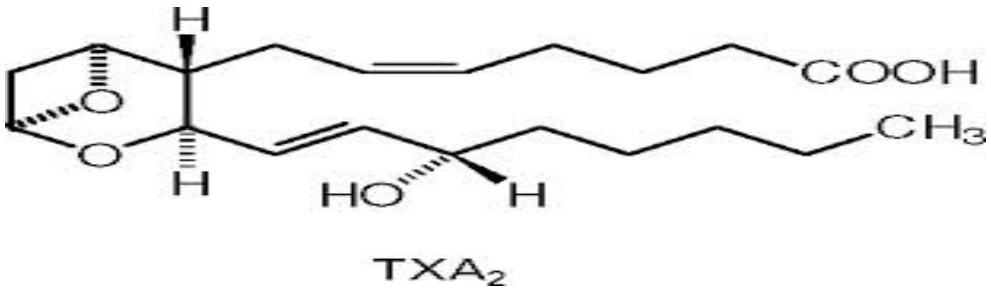
2. have several subclasses (structures are not required).

3. prostaglandin names include numbers such as , PGE2,PGF2 …etc,they are related to number of double bonds.



3.Thromboxanes

1. composed of six –membered ring , one of the atoms that participate in formation of the ring is **oxygen**

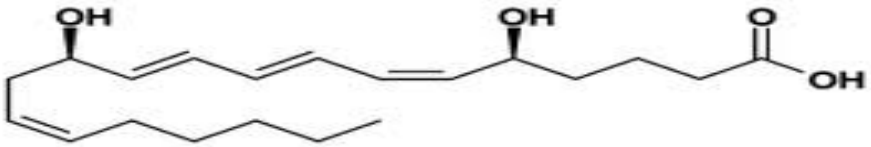


4. leukotrienes:

1 .Leuko**triene** means it contains three conjugated double bonds

2. contain no ring in their structures

3 .several subclasses , one of them **LTB4** , which contains 4 double bonds **.**



Leukotriene B4

*functional groups on the cyclopentane ring determain PG classes (PGA, PGD, PGG…etc).*not required to distinguish between PG classes though.
*PG names include numbers… what are these numbers? They are the numbers of the double bonds.
PGE2: has 2 double bonds. Also PGF2, PGI2 and TXA2.
LTA4: the total number of double bonds is four!

Overview of eicosanoid synthesis

1.As you know the dietary linoleic acid can be converted in the body to Arachidonic acid by elongation and further desaturation.
2. then Arachidonic acid is usually incorporated in the membrane phospholipids (in the inner leaflet of membrane at position 2 in glycerol phospholipids)
3. phospholipase A2 hydrolyze phospholipids at position 2 lead to release of Arachidonic acid (**This step is the rate limiting step in eicosanoid synthesis).**
4.once released different enzymes will act on it to synthesize different eicosanoids (**what makes Arachidonic acid to be converted to prostaglandin, or leukotriens or other eicosanoids ? different and specific enzymes for each class of eicosanoids)**
5. the primary products are :

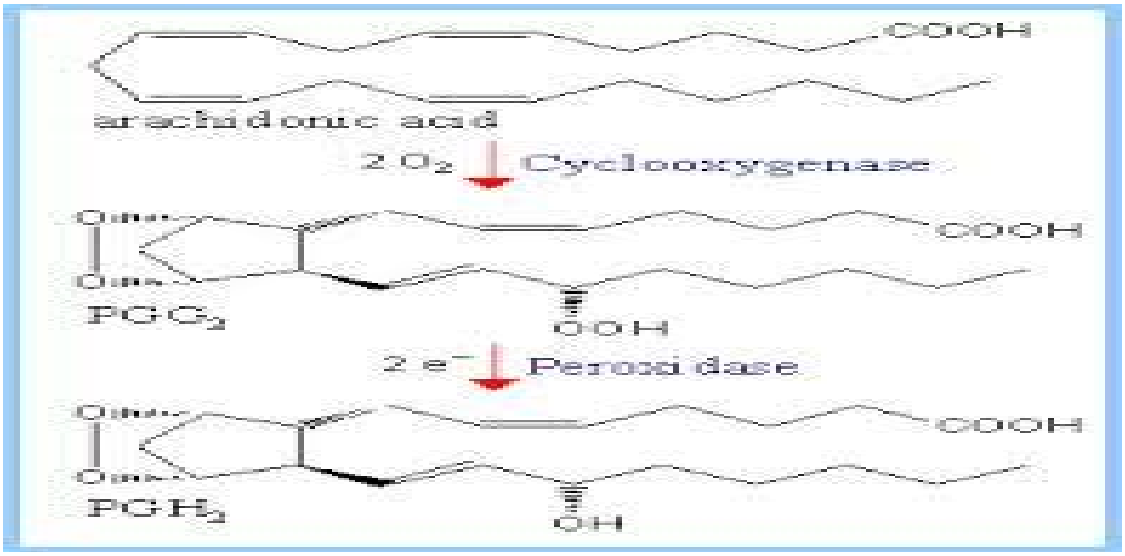
a. PGH2 (parent compound that lead to synthesis of **Thromboxanes**,prostacyclin, and **other prostaglandins**)
b. leukotrienes
c. HETE (hydroxy eicosa tetra enoic acid)

synthesis of PGH2 from Arachidonic acid

1. Arachidonic acid undergo closure of ring between carbon 8 & carbon 12, by cyclooxygenase enzyme and leads to formation of peroxide (OOH) on carbon 15 . The prostaglandin now is **PGG2**

Cyclooxygenase complex is an enzyme complex with two catalytic activities ; cyclooxygenase activity and peroxidase activity .

2. peroxidase enzyme then convert (OOH) group into (OH) group , by the help of reduced glutathione (2 GSH). The prostaglandin now is **PGH2**.



Eicosanoids can be synthesized from other polyunsaturated fatty acid

1. they can be synthesized from any fatty acid containing 20 carbons
2.so fatty acids of 20 carbons with

a. 3 double bonds like Eicosatrienoic acid

b. 4 double bonds as Eicosatetraenoic acid (arachidonic acid)

c.or 5 double bonds(Eicosapentaneoic acid : omega-3 fatty acids)

can synthesize eicosanoids

Now , the product of these 20 carbon fatty acids can be predicted by their number of double bonds

for example:

1. Eicosatetraenoic acid (or arachidonic) contain 4 double bonds , the product will be of 2 double bonds (substract by 2) , for example **PGE2**, **PGF2alpha (4→2)**

2. Eicosatrienoic acid (omega-6) : the products are for example **PGE1 (3→1)**

3.Eicosapentaenoic acid : **PGE3 (5→3)**

Now , which one of these fatty acids (eicosa-pentenoic acid or eicosa-tetraenoic acid) is better to be taken as dietary habits for good health and lifestyle???

the answer is **eicosa-pentaenoic acid ,**because it will produce eicosanoids of 3 double bonds , such as **TxB3 ,** that inhibits platelet aggregation , while **eicosa-tetraenoic acid ,** will produce **TxB2** , that stimulates platelet aggregation.

This explains why myocardial infarction is low in some populations (in east Asia , because they depend on sea food for their diet (rich in omega-3 fatty acids , like eicosa-pentaenoic acids)

Because prostaglandins are implicated in the inflammatory response, sometimes we need to inhibit their synthesis to decrease inflammation

1.Steroidal anti-inflammatory agents : inhibit phospholipase A2 ,and thus inhibit prostaglandin synthesis.

2. NSAIDS (non-steroidal anti-inflammatory drugs) include:

a. Aspirin (acetylsalicylate) : it transfers its acetyl group to cyclooxygenase enzyme, inhibiting it.

b. Ibuprofen : it binds irreversibly to the enzyme ,inhibiting it.

Cyclooxygenase exists in two forms

1. COX 1 : Constitutive ; same concentration all the time , and is produced in cells of gastric mucosa, kidneys and platelets

2. COX 2: inducible , only produced in response to inflammatory stimuli , produced by monocytes, macrophages ,and smooth muscles

This provide us with the benefit to give selective COX-2 inhibitors for long term treatment , because if we give general inhibitor of COX it will inhibit COX-1 in addition to COX-2 , and lead to development of ulcer

Some people take Baby Aspirin (100mg) , every day , why ?

1. it's anti-platelet (inhibits platelet aggregation)

2. it inhibits the production of TxB2

3. It's taken in low dose , because all what you need is to inhibit platelet cells , which are semi-dead cells having no nucleus and no protein synthesis, once inhibiting the enzyme(irreversibly), they can't produce another enzyme molecules .

THE END