Physiology for Medical Students

Endocrine 6

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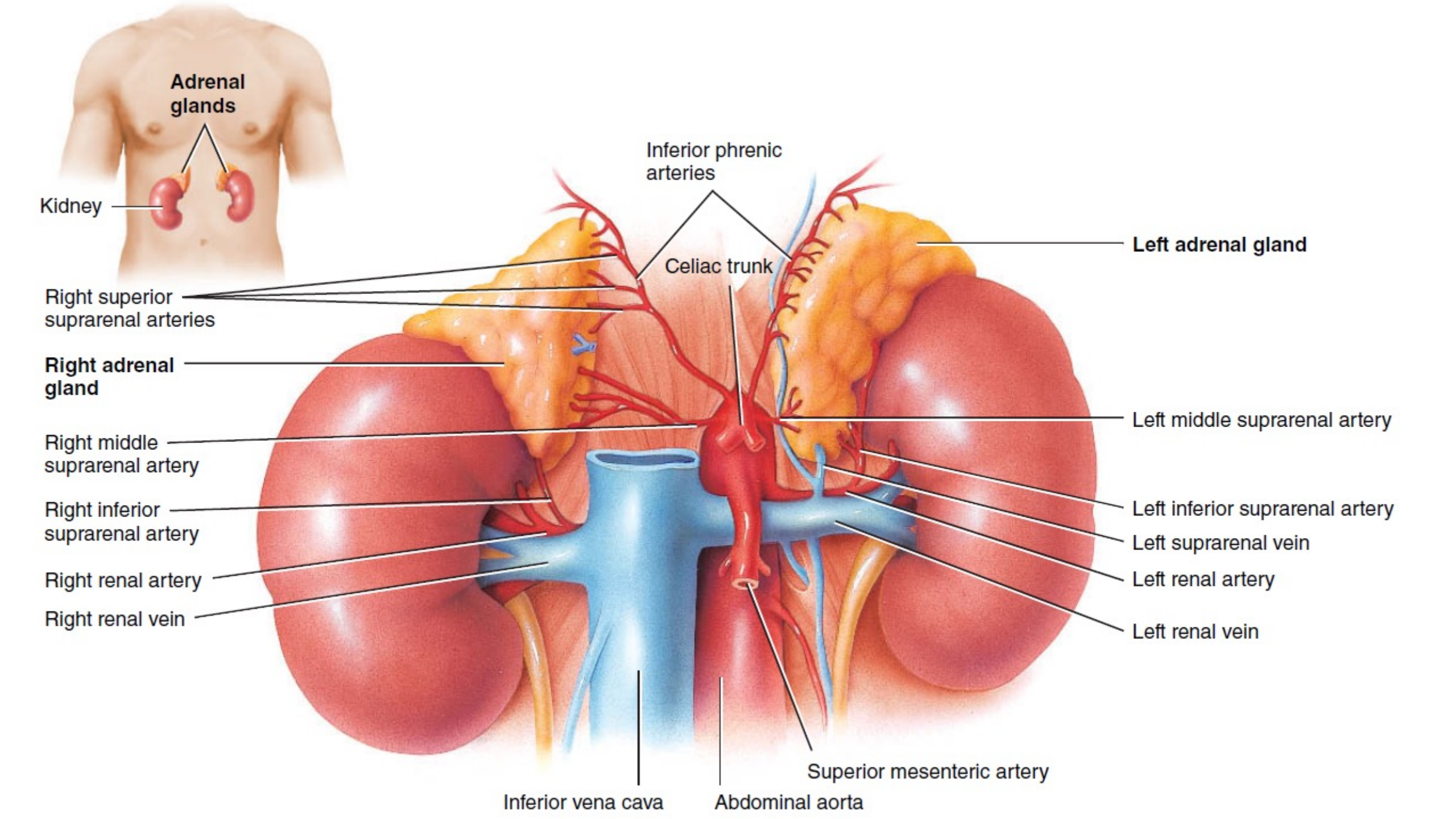
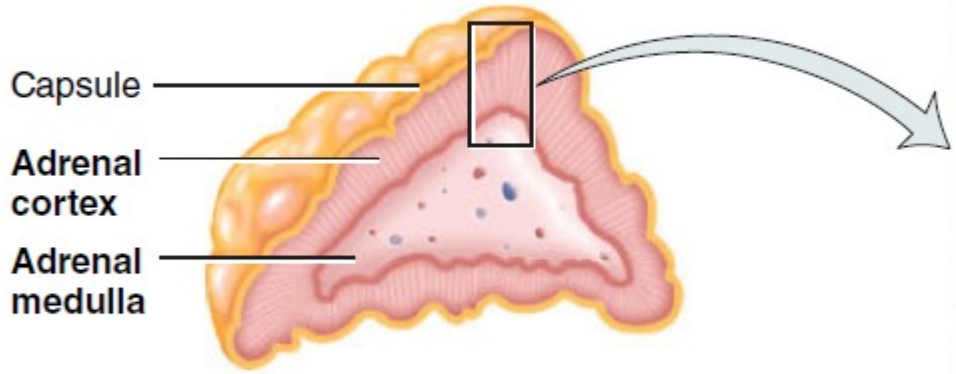
Adrenocortical Hormones

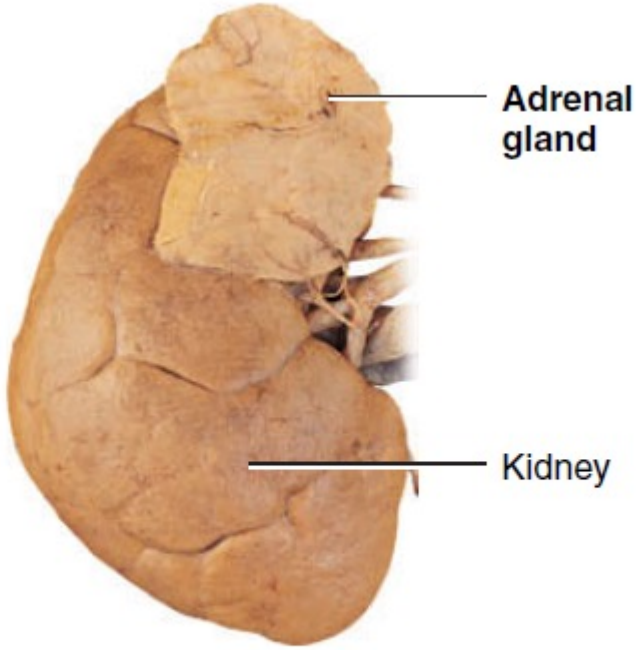
CHAPTER 77


Adrenal glands
Kidney
Inferior phrenic arteries
Celiac trunk
Left adrenal gland
Right superior suprarenal arteries
Right adrenal gland
Left middle suprarenal artery
Right middle suprarenal artery
Left inferior suprarenal artery
Right inferior suprarenal artery
Left suprarenal vein
Right renal artery
Left renal artery
Right renal vein
Left renal vein
Superior mesenteric artery
Inferior vena cava
Abdominal aorta

The paired **adrenal glands or *suprarenal glands*, one of which lies superior to each kidney in the retroperitoneal space

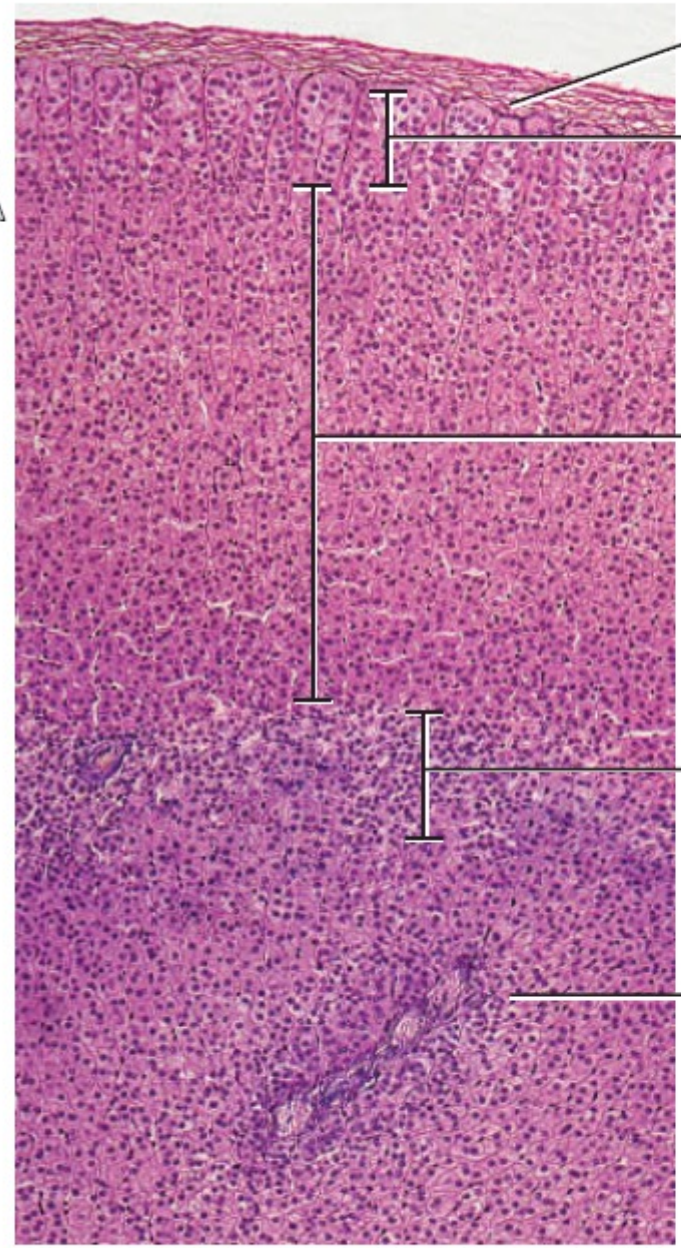


(b) Section through left adrenal gland



Dissection Shawn Miller, Photograph Mark Nielsen

(c) Anterior view of adrenal gland and kidney



Mark Nielsen LM 50x

(d) Subdivisions of the adrenal gland

**During embryonic development, the adrenal glands differentiate into two structurally and functionally distinct
regions: a large, peripherally located **adrenal cortex**, comprising 80–90% of the gland, and a small, centrally located **adrenal medulla**.
** A connective tissue capsule covers the gland.

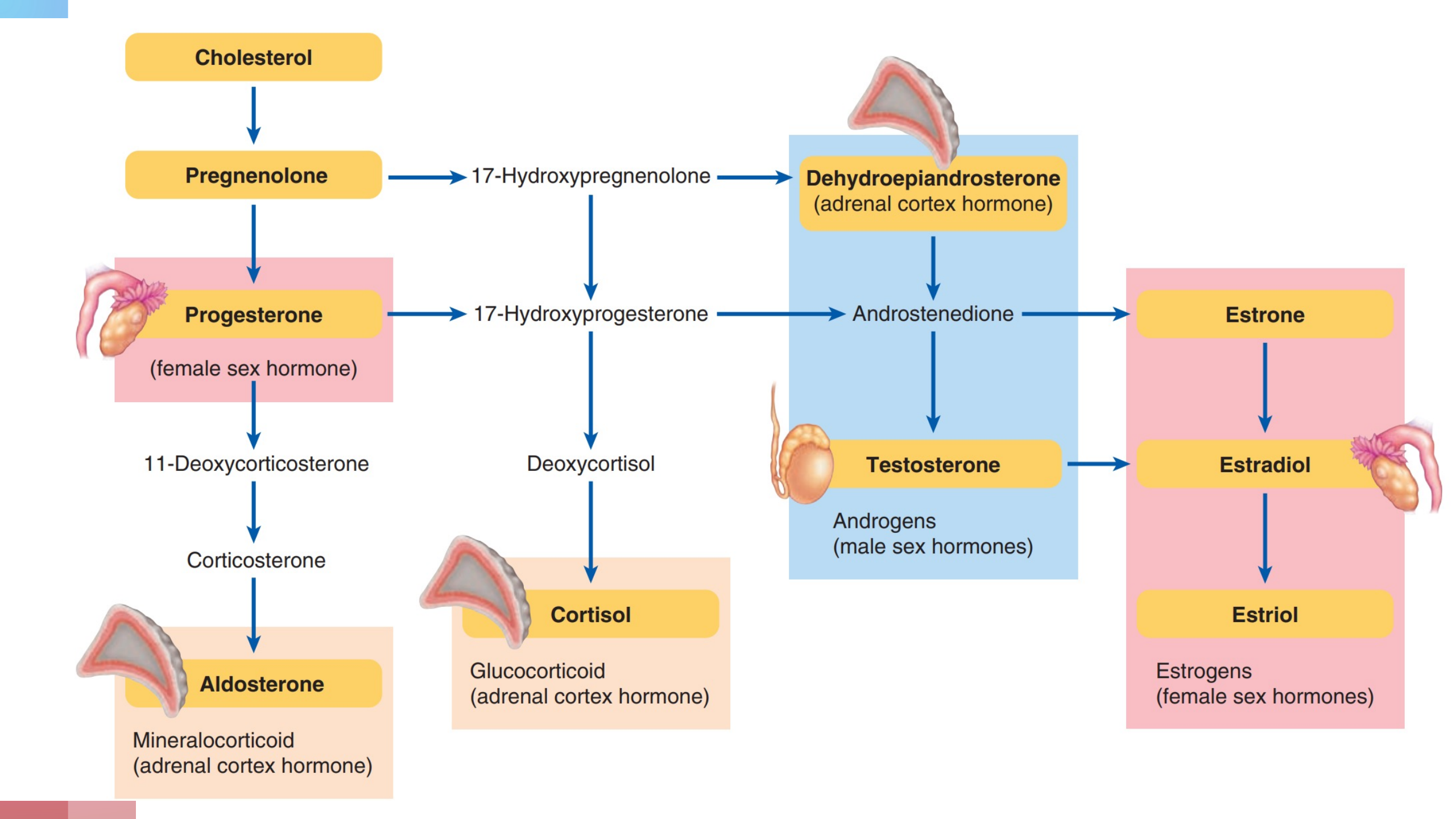
**The adrenal cortex produces steroid hormones that are essential for life. Complete loss of adrenocortical hormones leads to
death due to dehydration and electrolyte imbalances in a few days to a week, unless hormone replacement therapy begins promptly. The adrenal medulla produces three catecholamine hormones—norepinephrine, epinephrine, and a small amount of dopamine.

** The adrenal cortex consists of three layers, or zones: the zona glomerulosa, the outermost layer; the zona fasciculata, the middle and largest portion; and the zona reticularis, the innermost zone.

Adrenal Cortex

- **Corticosteroids: Mineralocorticoids, Glucocorticoids, and Androgens**
- **Zona glomerulosa 15%–>** The outer zone → **mineralocorticoids** → affect mineral homeostasis.
- **Zona fasciculata 75%→** The middle zone (widest) → **glucocorticoids, primarily cortisol** →affect glucose homeostasis.
- **zona reticularis 10%→** the inner zone → **androgens** → steroid hormones that have masculinizing effects.

**all synthesized from the steroid cholesterol
***It is clear from this list that some of these hormones have both glucocorticoid and mineralocorticoid activities.* It is especially significant that cortisol normally has some mineralocorticoid activity, because some syndromes of excess cortisol secretion can cause significant mineralocorticoid effects, along with its much more potent glucocorticoid effects.
**Aldosterone's mineralocorticoid activity is about 3000 times greater than that of cortisol


Cholesterol
Pregnenolone
17-Hydroxypregnenolone
Dehydroepiandrosterone
(adrenal cortex hormone)
Progesterone
(female sex hormone)
17-Hydroxyprogesterone
Androstenedione
Estrone
11-Deoxycorticosterone
Deoxycortisol
Testosterone
Estradiol
Androgens
(male sex hormones)
Corticosterone
Cortisol
Estriol
Aldosterone
Glucocorticoid
(adrenal cortex hormone)
Estrogens
(female sex hormones)
Mineralocorticoid
(adrenal cortex hormone)

** All steroidogenic tissues **first convert cholesterol to pregnenolone**, then modify this common core molecule by stepwise enzymatic reactions to produce active steroid hormones.
** Each steroidogenic tissue has a **complement of enzymes to produce one or several but not all steroid hormones**.
** Slight variations in structure confer different functional capabilities on the various adrenocortical hormones.
** Because the adrenocortical hormones are all lipophilic and immediately **diffuse through the plasma membrane** of the steroidogenic cell into the blood after being synthesized, **controlling the rate of synthesis regulates the rate of secretion**.
** Being lipophilic, the adrenocortical hormones are all carried in the blood extensively bound to plasma proteins. Cortisol is bound mostly to a plasma protein specific for it **called corticosteroid-binding globulin** (transcortin), whereas **aldosterone and dehydroepiandrosterone are largely bound to albumin**

Mineralocorticoids

CHAPTER 77

Aldosterone

- Regulates homeostasis of two mineral ions.
- Promotes Na retention and enhances K elimination.
- Adjusts blood pressure and blood volume.
- Promotes excretion of H+ in the urine; this removal of acids from the body can help prevent acidosis.

The principal site of aldosterone action is on the distal and **collecting tubules** of the kidney, where it promotes Na retention and enhances K elimination.

** The promotion of Na retention by aldosterone secondarily induces osmotic retention of H_2O, expanding the ECF volume (including the plasma volume), which is important in the long-term regulation of blood pressure.

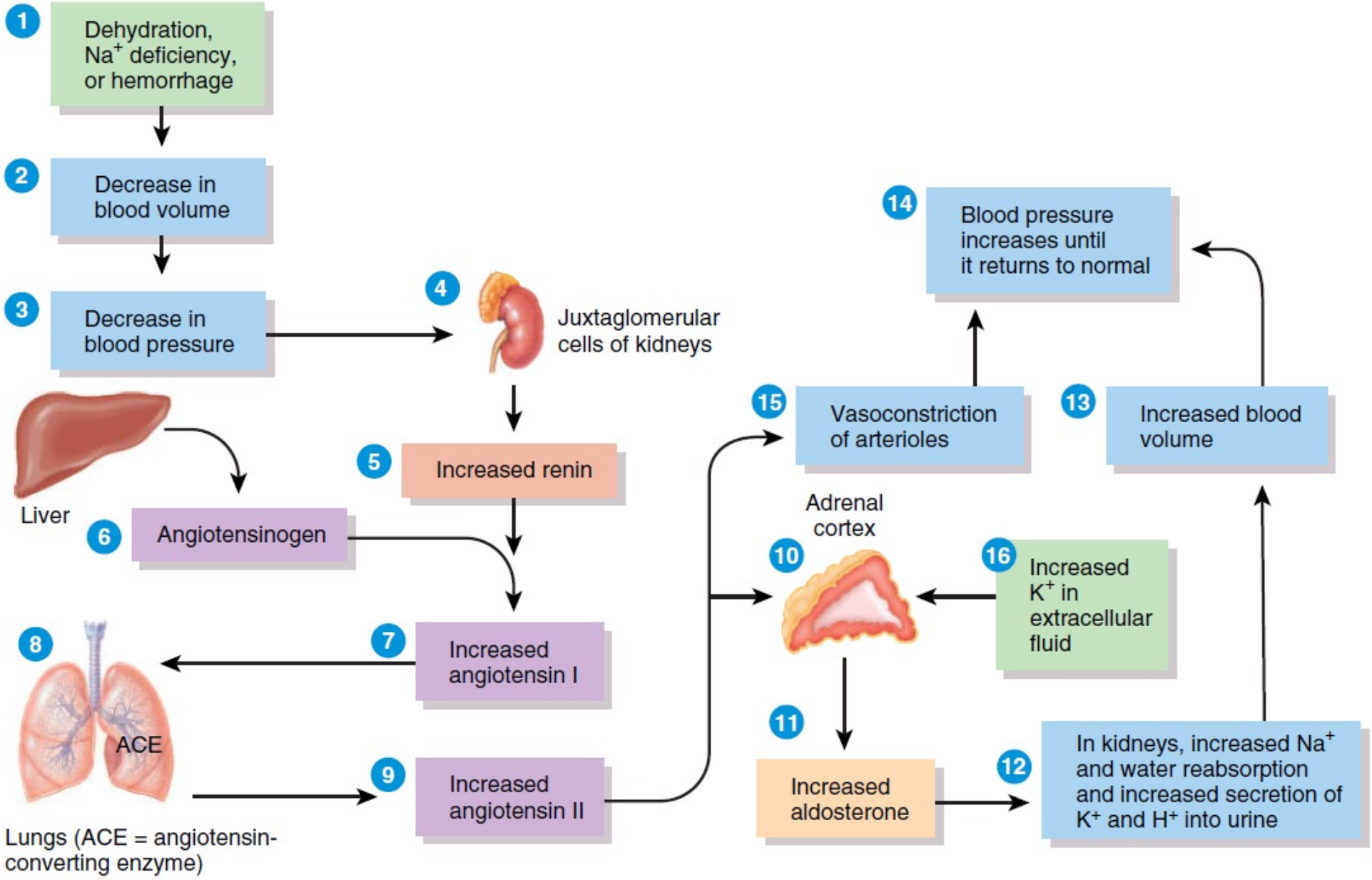
** **Although aldosterone has a potent effect to decrease the rate of sodium excretion by the kidneys, the concentration of sodium in the extracellular fluid often rises only a few milliequivalents. The reason for this is that when sodium is reabsorbed by the tubules, simultaneous osmotic absorption of almost equivalent amounts of water occurs. Also, small increases in extracellular fluid sodium concentration stimulate thirst and increased water intake, if water is available, and increase secretion of antidiuretic hormone, which enhances water reabsorption by the distal and collecting tubules of the kidneys. Therefore, the extracellular fluid volume increases almost as much as the retained sodium, but without much change in sodium concentration.**

** Mineralocorticoids are essential for life. Without aldosterone, a person rapidly dies from circulatory shock because of the marked fall in plasma volume caused by excessive losses of H2O-holding Na.

** Total loss of adrenocortical secretion may cause death within 3 to 14 days unless the person receives extensive salt therapy or injection of mineralocorticoids.

**** Excess aldosterone causes hypokalemia and muscle weakness; aldosterone deficiency causes hyperkalemia and cardiac toxicity.**

Renin–Angiotensin–Aldosterone (RAA)



1 Stimuli that initiate the renin–angiotensin–aldosterone pathway
include dehydration, Na+ deficiency, or hemorrhage.
2 These conditions cause a decrease in blood volume.
3 Decreased blood volume leads to decreased blood pressure.
4 Lowered blood pressure stimulates certain cells of the kidneys, called juxtaglomerular cells, to secrete the enzyme **renin**.
5 The level of renin in the blood increases.
6 Renin converts **angiotensinogen**, a plasma protein produced by the liver, into **angiotensin I**.

7 Blood containing increased levels of angiotensin I circulates in the body.
8 As blood flows through capillaries, particularly those of the lungs, the enzyme **angiotensin-converting enzyme (ACE)** converts angiotensin I into the hormone **angiotensin II**.
9 Blood level of angiotensin II increases.
10 Angiotensin II stimulates the adrenal cortex to secrete aldosterone.
11 Blood containing increased levels of aldosterone circulates to the kidneys.
12 In the kidneys, aldosterone increases reabsorption of Na+, which in turn causes reabsorption of water by osmosis (*principal cells of the collecting tubules*). As a result, less water is lost in the urine. Aldosterone also stimulates the kidneys to increase secretion of K+ and H+ into the urine.

13 With increased water reabsorption by the kidneys, blood volume increases.
14 As blood volume increases, blood pressure increases to normal.
15 Angiotensin II also stimulates contraction of smooth muscle in the
walls of arterioles. The resulting vasoconstriction of the arterioles increases blood pressure and thus helps raise blood pressure to normal.
16 Besides angiotensin II, a second stimulator of aldosterone secretion is an increase in the K+ concentration of blood (or interstitial fluid).

Regulation of Aldosterone Secretion

1.Increased potassium ion concentration in the extracellular fluid greatly *increases* aldosterone secretion.

2.Increased angiotensin II concentration in the extracellular fluid also greatly *increases* aldosterone secretion.

3.Increased sodium ion concentration in the extracellular fluid *very slightly decreases* aldosterone secretion.

4. Increased atrial natriuretic peptide (ANP), a hormone secreted by the heart when specific cells of the cardiac atria are stretched (see Chapter 28), decreases aldosterone secretion

5.ACTH is necessary for aldosterone secretion but has little effect in controlling the rate of secretion in most physiological condition

Of these factors, ***potassium ion concentration* and **the *renin-angiotensin system*** are by far the most potent in regulating aldosterone secretion.

** In the case of **ACTH**, if even a small amount is secreted by the anterior pituitary gland, it is **usually enough** to permit the adrenal glands to secrete whatever amount of aldosterone is required, but **total absence of ACTH can significantly reduce aldosterone** secretion. Therefore, **ACTH appears to play a "permissive" role in regulation of aldosterone secretion.**

Glucocorticoids

CHAPTER 77

Effects of Cortisol on Carbohydrate Metabolism

- **Stimulation of gluconeogenesis.**
- Decreased glucose utilization by cells (by many tissues, but not the brain)
- Elevated blood glucose concentration and “adrenal diabetes.”

** Cortisol inhibits glucose uptake and use by many tissues, but not the brain, thus sparing glucose for use by the brain, which requires it as a metabolic fuel.
** This increased rate of gluconeogenesis results mainly from direct effects of cortisol on the liver, as well as by antagonizing the effects of insulin.

Effects of Cortisol on Protein Metabolism

- Decreased protein synthesis :
  - ✓ decreased amino acid transport into extrahepatic tissues
  - ✓ depresses formation of RNA
  - ✓ especially in muscle and lymphoid tissue

- Increased catabolism of protein.

(Reduction in Cellular Protein in essentially all body cells except those of the liver)

“” In the presence of great excesses of cortisol, the muscles can become so weak that the person cannot rise from the squatting position. And the immunity functions of the lymphoid tissue can be decreased to a small fraction of normal.

Effects of Cortisol on Protein Metabolism

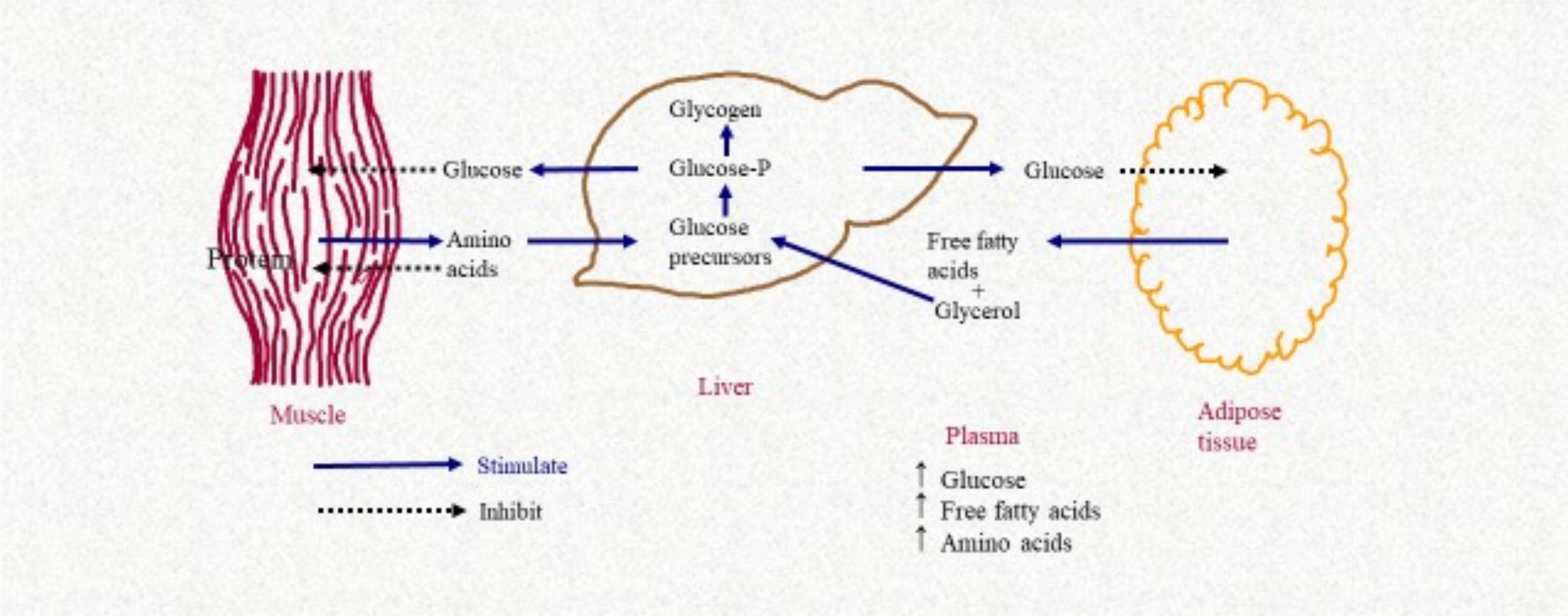
- Degradation of cellular protein in many tissues.
- Increased blood amino acids
- Diminished transport of amino acids into extrahepatic cells, and enhanced transport into hepatic cells.
- increases liver and plasma proteins

It stimulates protein degradation in many tissues, especially muscle. By breaking down a portion of muscle proteins into their constituent amino acids, cortisol increases the blood amino acid concentration. These mobilized amino acids are available for use in gluconeogenesis or wherever else they are needed, such as for repair of damaged tissue or synthesis of new cellular structures.

Effects of Cortisol on Fat Metabolism

- Promotes mobilization of fatty acids from adipose tissue.
- This increases the concentration of free fatty acids in the plasma,
- Increases utilization of fat for energy.
- Important for long-term conservation of body glucose and glycogen.

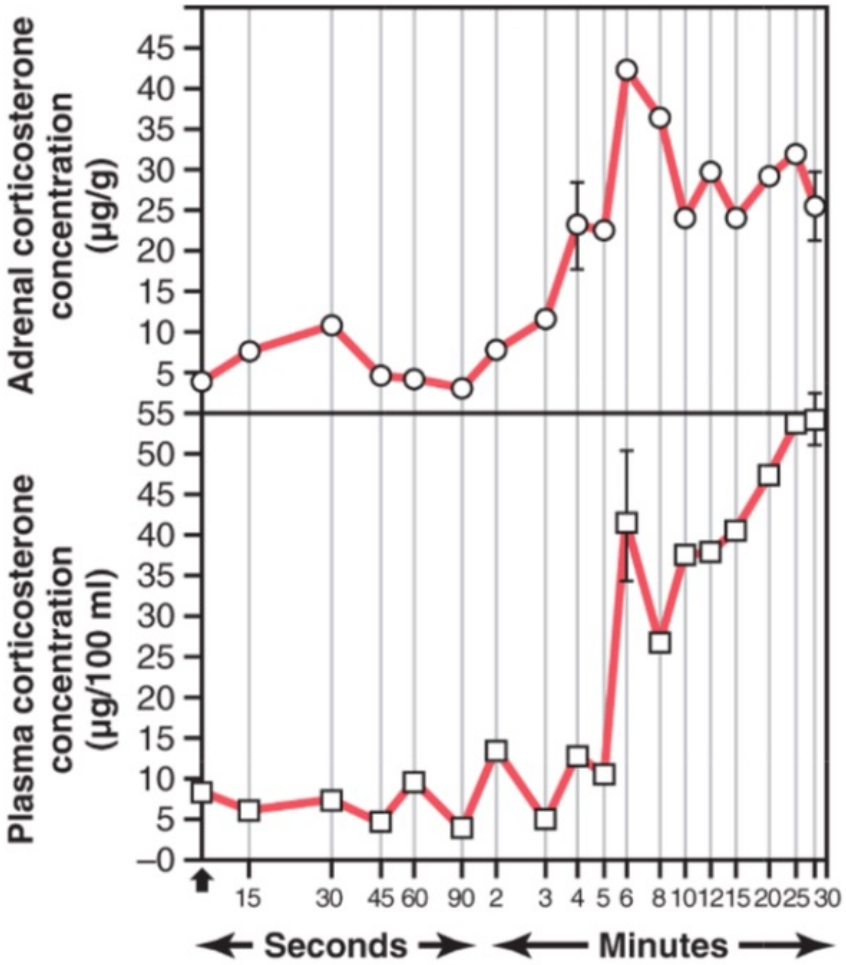
Metabolic Effects of Cortisol



The overall effect of cortisol’s metabolic actions is to increase the concentration of blood glucose at the expense of protein and fat stores

Cortisol Is Important in Stress adaptation

- Rapid reaction of the adrenal cortex of a rat to stress caused by fracture of the tibia and fibula at time zero.
- Increased six-fold in a rat within 4 to 20 min.



A cortisol-induced shift away from protein and fat stores in favor of expanded carbohydrate stores and increased availability of blood glucose would help protect the brain from malnutrition during the imposed fasting period. Also, the amino acids liberated by protein degradation would provide a supply of building blocks for tissue repair if physical injury occurred.

** All this is mainly supposition and is supported only by the fact that cortisol usually does not mobilize the basic functional proteins of the cells, such as the muscle contractile proteins and the proteins of neurons, until almost all other proteins have been released. This preferential effect of cortisol in mobilizing labile proteins could make amino acids available to needy cells to synthesize substances essential to life.

Anti-Inflammatory Effects of High Levels of Cortisol

- When large amounts of cortisol are secreted or injected into a person, the glucocorticoid has two basic anti-inflammatory effects:
- (1) it can block the early stages of the inflammation process before noticeable inflammation even begins, or
- (2) if inflammation has already begun, it causes rapid resolution of the inflammation and increased rapidity of healing.

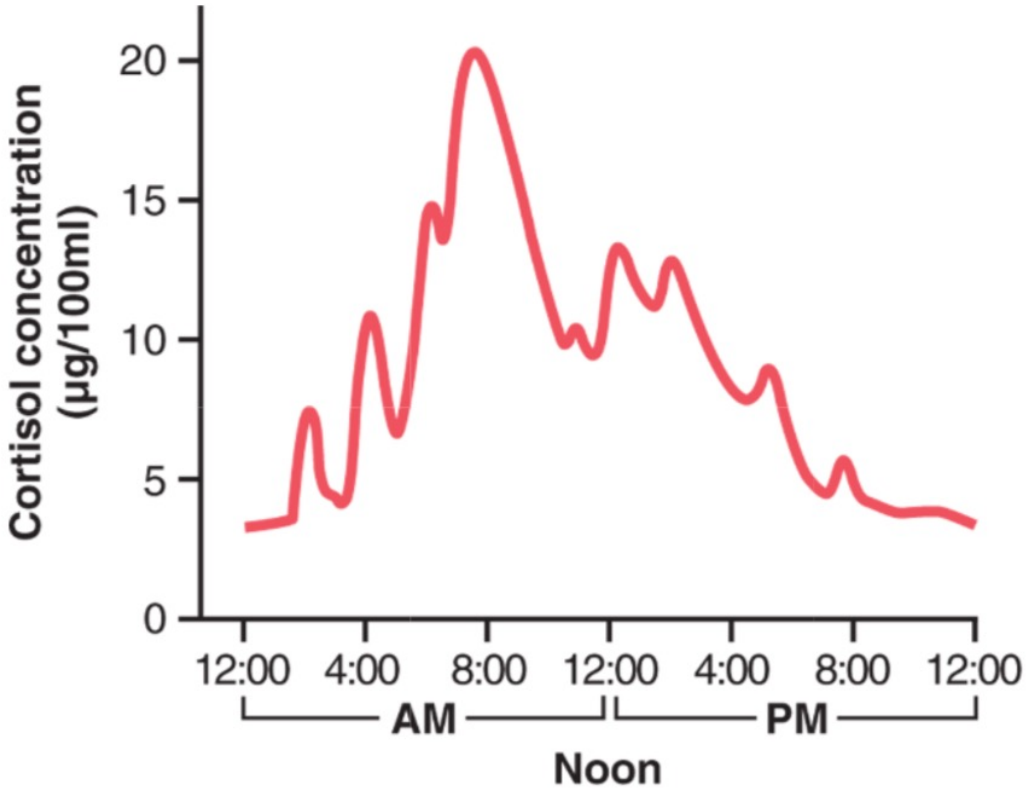
** When stress is accompanied by tissue injury, inflammatory and immune responses accompany the stress response. Cortisol exerts anti-inflammatory and immunosuppressive effects to help hold these immune system responses in a check-and-balance fashion.

**Treatment for all these diseases are characterized by severe local inflammation, and the harmful effects on the body are caused mainly by the inflammation itself and not by other aspects of the disease: rheumatoid arthritis, rheumatic fever, and acute glomerulonephritis.

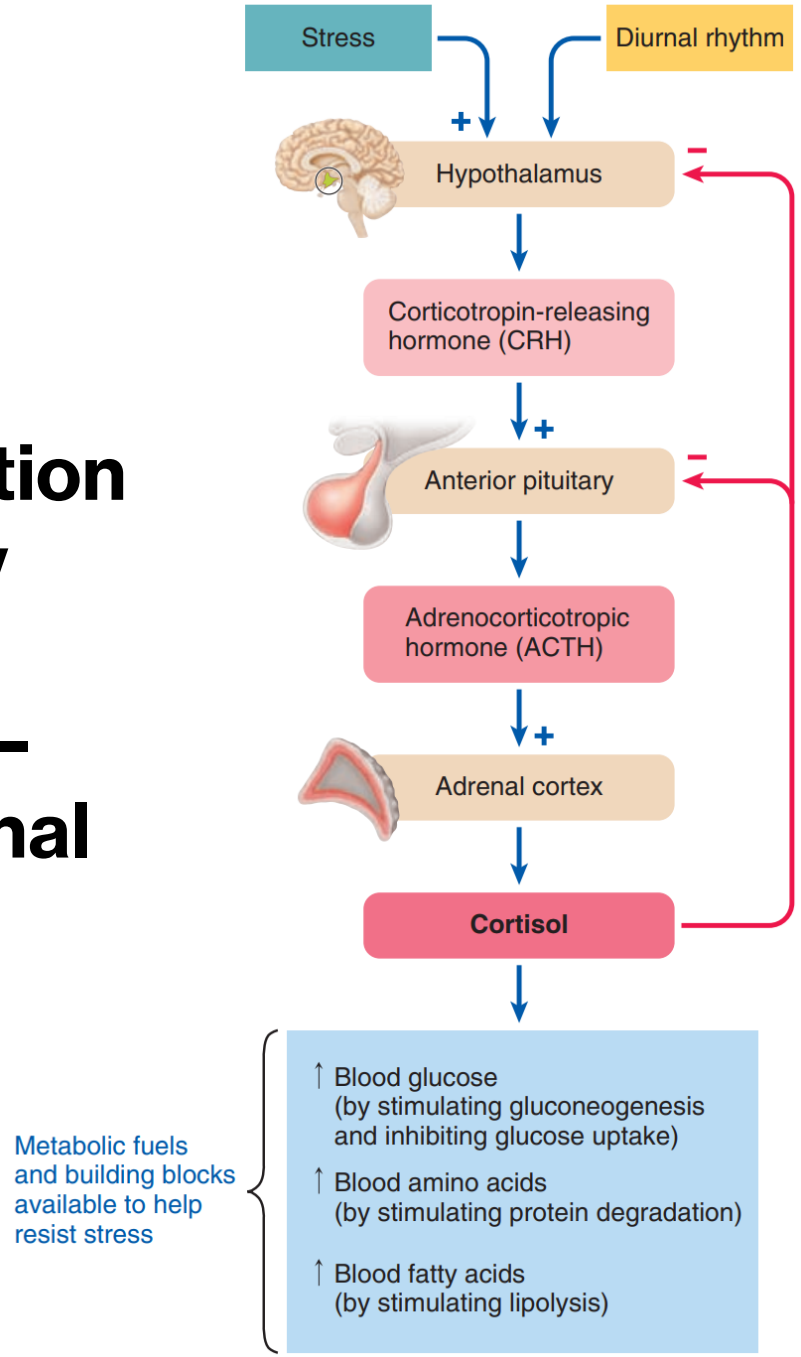
** allergic disorders (reducing inflammation and release of inflammatory products, can be lifesaving)
** and in preventing organ transplant rejections.

Circadian Rhythm of Glucocorticoid Secretion

- The secretory rates of ACTH, and cortisol are high in the early morning but low in the late evening.
- Surge an hour or so after awaking in the morning.
- Therefore, measurements of blood cortisol levels are meaningful only when expressed in terms of the time in the cycle at which the measurements are made.



Cortisol secretion is regulated by the hypothalamus–pituitary–adrenal cortex axis



** The negative-feedback system for cortisol maintains the level of cortisol secretion relatively constant around the set point. Superimposed on the basic negative-feedback control system are two additional factors that influence plasma cortisol concentrations by changing the set point: diurnal rhythm and stress, both of which act on the hypothalamus to vary the secretion rate of CRH.

** Long-term stimulation of the adrenal cortex by ACTH not only increases secretory activity but also causes hypertrophy and proliferation of the adrenocortical cells, especially in the zona fasciculata and zona reticularis, where cortisol and the androgens are secreted.

**Prolonged suppression of this axis can lead to irreversible atrophy (shrinkage) of the cortisol-secreting cells of the adrenal gland and thus to permanent inability of the body to produce its own cortisol.

Adrenal Androgens

CHAPTER 77

Adrenal Androgen

- The adrenal cortex secretes both male and female sex hormones in both sexes
- The most important of which is **D**e**H**ydro**E**pi**A**ndrosterone (DHEA)
- Continually secreted by the adrenal cortex, especially during fetal life.
- Part of the early development of the male sex organ during childhood.
- DHEA governs androgen-dependent processes in the female such as growth of pubic and axillary hair, enhancement of the pubertal growth spurt, and development and maintenance of the female sex drive.

** The testes' primary androgen product is the potent testosterone, but the most abundant adrenal androgen is the weaker DHEA. (Testosterone exerts about 100 times greater "androgenicity" than DHEA.)
** ACTH controls adrenal androgen secretion.
** Adrenal androgens feed back outside the hypothalamus–pituitary–adrenal axis. Instead of inhibiting CRH, DHEA inhibits gonadotropin-releasing hormone, just as testicular androgens do.

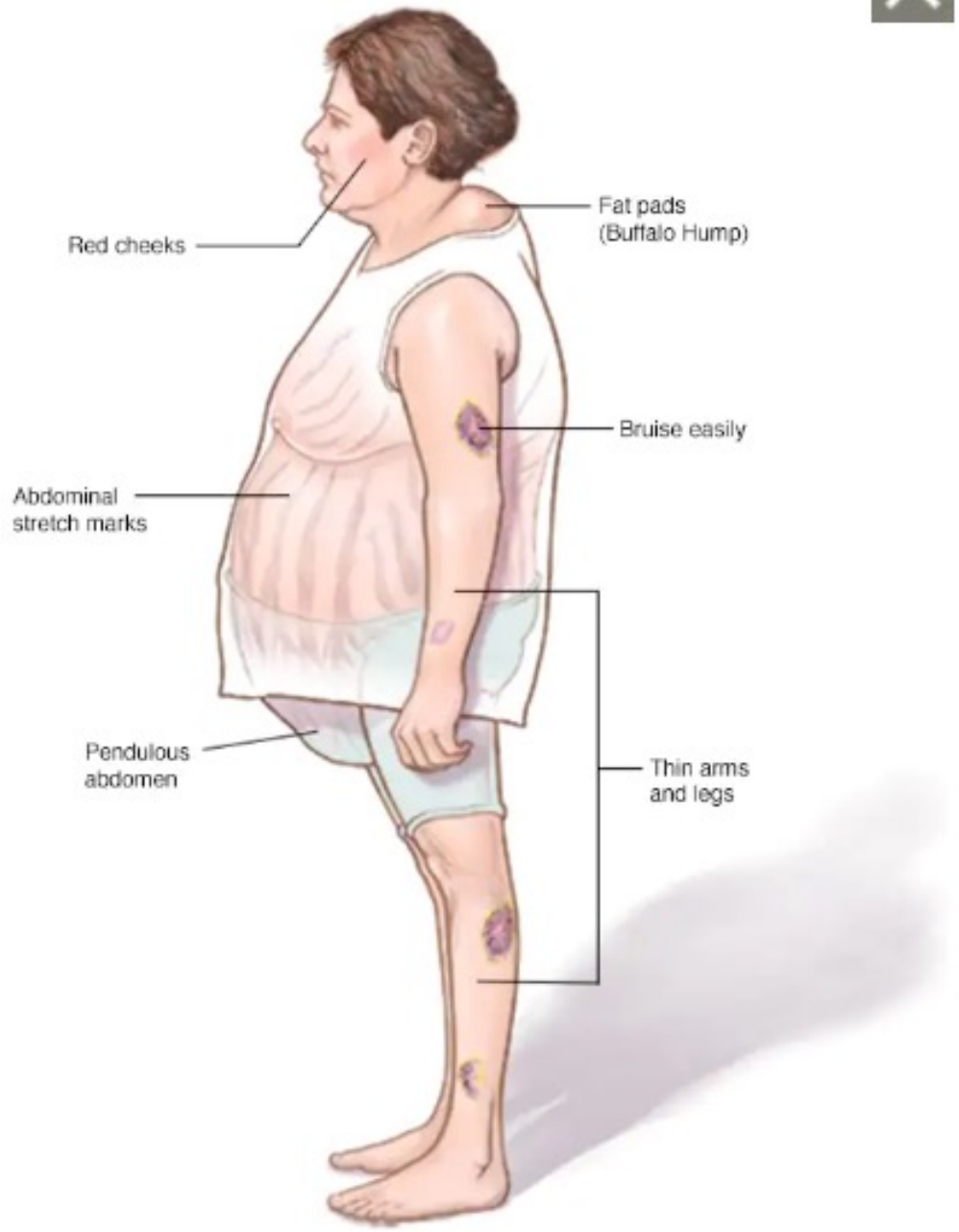
ACTH Activates Adrenocortical Cells to Produce Steroids

- ACTH control the initial conversion of cholesterol to pregnenolone.
- This initial conversion is the “rate-limiting” step for all the adrenocortical hormones, which explains why ACTH is normally necessary for any adrenocortical hormones to be formed.
- Long-term stimulation of the adrenal cortex by ACTH not only increases secretory activity but also causes hypertrophy and proliferation of the adrenocortical cells, especially in the zona fasciculata and zona reticularis.

Cushing’s Syndrome

CHAPTER 77

Signs and Symptoms



**Many of the abnormalities of Cushing's syndrome can be ascribed to abnormal amounts of cortisol, but excess secretion of androgens may also cause important effects.

Signs and Symptoms

- Increased blood glucose concentration.
- Increased Protein catabolism →
- The loss of protein from the muscles → weakness.
- The loss of protein synthesis in the lymphoid tissues → suppressed immune system
- Decreased collagen fibers in the subcutaneous tissue →subcutaneous tissues tear easily, resulting in development of large purplish striae where they have torn apart.
- Decreased protein deposition in the bones → osteoporosis with consequent weakness of the bones.

Signs and Symptoms

- Mobilization of fat from the lower part of the body, with concomitant extra deposition of fat in the thoracic and upper abdominal regions, giving rise to a buffalo torso.
- The excess secretion of steroids also leads to an edematous appearance of the face, and the androgenic potency of some of the hormones sometimes causes acne and hirsutism (excess growth of facial hair). “moon face”.
- 80% of patients have hypertension.

Adrenal Medulla

CHAPTER 77

Adrenal medulla

- The adrenal medulla consists of modified postganglionic sympathetic neurons called chromaffin cells because of their staining.
- Unlike ordinary postganglionic sympathetic neurons, chromaffin cells do not have axonal fibers that terminate on effector organs.
- On stimulation by the preganglionic fiber the chromaffin cells release their chemical transmitter directly into the blood.
- Adrenomedullary catecholamine output, epinephrine accounts for 80% and norepinephrine for 20%