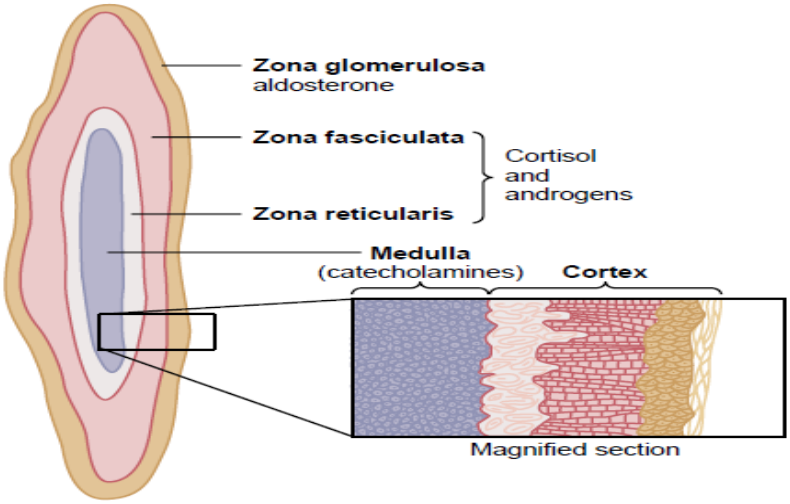
Lecture No.5



Adrenocortical Hormones

The two *adrenal glands* lie at the superior poles of the two kidneys. As each gland is composed of two distinct parts, the *adrenal medulla* and the *adrenal cortex.* The adrenal medulla is functionally related to the sympathetic nervous system; it secretes the hormones *epinephrine* and *norepinephrine* in response to sympathetic stimulation. In turn, these hormones cause almost the same effects as direct stimulation of the sympathetic nerves in all parts of the body. The adrenal cortex secretes an entirely different group of hormones, called *corticosteroids.* These hormones are all synthesized from the steroid cholesterol, and they all have similar chemical formulas. However, slight differences in their molecular structures give them several different but very important functions.

***Corticosteroids Mineralocorticoids, Glucocorticoids, and Androgens*.**

Two major types of adrenocortical hormones, the *mineralocorticoids* and the *glucocorticoids,* are secreted by the adrenal cortex. In addition to these, small amounts of sex hormones are secreted, especially *androgenic hormones,* which exhibit about the same effects in the body as the male sex hormone testosterone. They are normally of only slight importance, although in certain abnormalities of the adrenal cortices, extreme quantities can be secreted and can result in masculinizing effects.

More than 30 steroids have been isolated from the adrenal cortex, but two are of exceptional importance to the normal endocrine function of the human body: *aldosterone,* which is the principal mineralocorticoid, and *cortisol,* which is the principal glucocorticoid.

Synthesis and Secretion of Adrenocortical Hormones

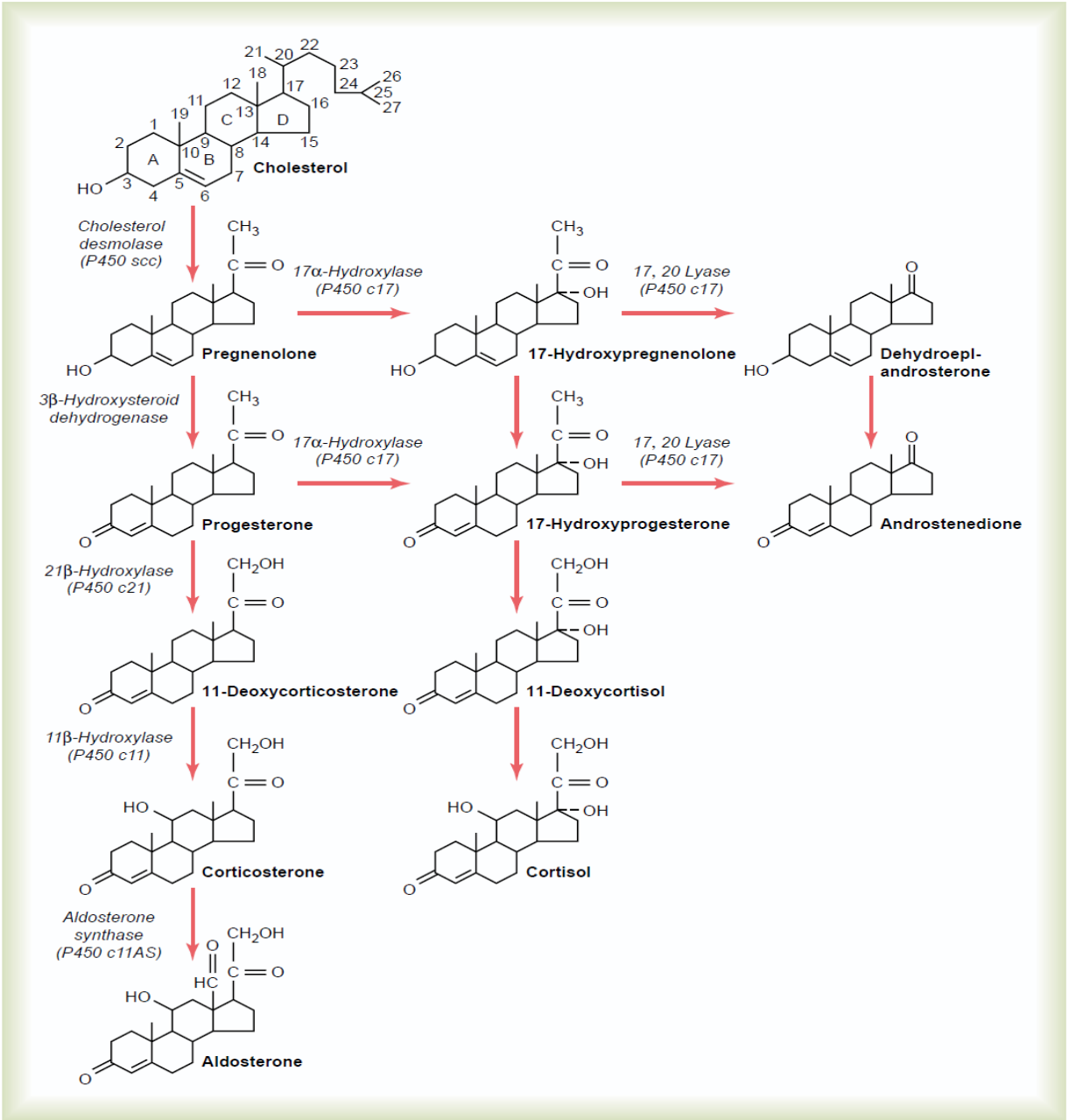
***The Adrenal Cortex Has Three Distinct Layers*.**

1. The *zona glomerulosa,* a thin layer of cells that lies just underneath the capsule. These cells are the only ones in the adrenal gland capable of secreting significant amounts of *aldosterone* because they contain the enzyme *aldosterone synthase,* which is necessary for synthesis of aldosterone. The secretion of these cells is controlled mainly by the extracellular fluid concentrations of *angiotensin II* and *potassium,* both of which stimulate aldosterone secretion.
2. The *zona fasciculata,* the middle and widest layer and secretes the glucocorticoids *cortisol* and *corticosterone,* as well as small amounts of *adrenal androgens* and *estrogens.* The secretion of these cells is controlled in large part by the hypothalamic-pituitary axis via *adrenocorticotropic hormone (ACTH).*
3. The *zona reticularis,* the deep layer of the cortex, secretes the adrenal androgens *dehydroepiandrosterone (DHEA)* and *androstenedione,* as well as small amounts of estrogens and some glucocorticoids.ACTH also regulates secretion of these cells, although other factors such as *cortical androgen-stimulating hormone,* released from the pituitary, may also be involved.

Adrenocortical Hormones Are Steroids Derived from Cholesterol.

All human steroid hormones, including those produced by the adrenal cortex, are synthesized from cholesterol. Although the cells of the adrenal cortex can synthesize de novo small amounts of cholesterol from acetate, approximately 80 per cent of the cholesterol used for steroid synthesis is provided by low-density lipoproteins (LDL) in the circulating plasma .The LDLs, which have high concentrations of cholesterol, diffuse from the plasma into the interstitial fluid and attach to specific receptors contained in structures called *coated pits* on the adrenocortical cell membranes. The coated pits are then internalized by *endocytosis,* forming vesicles that eventually fuse with cell lysosomes and release cholesterol that can be used to synthesize adrenal steroid hormones. Transport of cholesterol into the adrenal cells is regulated by feedback mechanisms that can markedly alter the amount available for steroid synthesis. For example, ACTH, which stimulates adrenal steroid synthesis, increases the number of adrenocortical cell receptors for LDL, as well as the activity of enzymes that liberate cholesterol from LDL. Once the cholesterol enters the cell, it is delivered to the mitochondria, where it is cleaved by the enzyme *cholesterol desmolase* to form *pregnenolone;* this is the rate-limiting step in the eventual formation of adrenal steroids. In all three zones of the adrenal cortex, this initial step in steroid synthesis is

stimulated by the different factors that control secretion of the major hormone products aldosterone and cortisol. For example, both ACTH, which stimulates cortisol secretion, and angiotensin II, which stimulates aldosterone secretion, increase the conversion of cholesterol to pregnenolone.



***Adrenocortical Hormones Are Metabolized in the Liver*.**

The adrenal steroids are degraded mainly in the liver and conjugated especially to *glucuronic acid* and, to a lesser extent, sulfates. These substances are inactive and do not have mineralocorticoid or glucocorticoid activity. About 25 per cent of these conjugates are excreted in the bile and then in the feces.The remaining conjugates formed by the liver enter the circulation but are not bound to plasma proteins, are highly soluble in the plasma, and are therefore filtered readily by the kidneys and excreted in the urine. Diseases of the liver markedly depress the rate of inactivation of adrenocortical hormones, and kidney diseases reduce the excretion of the inactive conjugates. The normal concentration of aldosterone in blood is about 6 nanograms (6 billionths of a gram) per 100 ml, and the average secretory rate is approximately 150 μg/day (0.15 mg/day). The concentration of cortisol in the blood averages 12 μg/100 ml, and the secretory rate averages 15 to 20 mg/day.

Functions of the Mineralocorticoids- Aldosterone

Total loss of adrenocortical secretion usually causes death within 3 days to 2 weeks unless the person receives extensive salt therapy or injection of mineralocorticoids . without mineralocorticoids, potassium ion concentration of the extracellular fluid rises markedly, sodium and chloride are rapidly lost from the body, and the total extracellular fluid volume and blood volume become greatly reduced. The person soon develops, diminished cardiac output, which progresses to a shocklike state, followed by death. This entire sequence can be prevented by the administration of aldosterone or some other mineralocorticoid. Therefore, the mineralocorticoids are said to be the acute “lifesaving” portion of the adrenocortical hormones.

1-Aldosterone Increases Renal Tubular Reabsorption of Sodium and Secretion of Potassium.

2- Excess Aldosterone Increases Extracellular Fluid Volume and Arterial Pressure but Has Only a Small Effect on Plasma Sodium Concentration.

3-Excess Aldosterone Causes Hypokalemia and Muscle Weakness; Too Little Aldosterone Causes Hyperkalemia and Cardiac Toxicity

4-Excess Aldosterone Increases Tubular Hydrogen Ion Secretion, and Causes Mild Alkalosis**.**

Aldosterone Stimulates Sodium and Potassium Transport in Sweat Glands, Salivary Glands, and Intestinal Epithelial Cells

Aldosterone has almost the same effects on sweat glands and salivary glands as it has on the renal tubules. Both these glands form a primary secretion that contains large quantities of sodium chloride, but much of

the sodium chloride, on passing through the excretory ducts, is reabsorbed, whereas potassium and bicarbonate ions are secreted. Aldosterone greatly increases the reabsorption of sodium chloride and the secretion of potassium by the ducts. The effect on the sweat glands is important to conserve body salt in hot environments, and the effect on the salivary glands is necessary to conserve salt when excessive quantities of saliva are lost. Aldosterone also greatly enhances sodium absorption by the intestines, especially in the colon, which prevents loss of sodium in the stools. Conversely, in the absence of aldosterone, sodium absorption can be poor, leading to failure to absorb chloride and other anions and water as well. The unabsorbed sodium chloride and water then lead to diarrhea, with further loss of salt from the body.

Functions of the Glucocorticoids

Even though mineralocorticoids can save the life of an acutely adrenalectomized animal, the animal still is far from normal. Instead, its metabolic systems for utilization of proteins, carbohydrates, and fats remain considerably deranged. Furthermore, the animal cannot resist different types of physical or even mental stress, and minor illnesses such as respiratory tract infections can lead to death. Therefore, the glucocorticoids have functions just as important to the long-continued life of the animal as those of the mineralocorticoids. They are explained in the following sections. At least 95 per cent of the glucocorticoid activity of the adrenocortical secretions results from the secretion of *cortisol*, known also as *hydrocortisone*. In addition to this, a small but significant amount of glucocorticoid activity is provided by *corticosterone*.

Elevated Blood Glucose Concentration and "Adrenal Diabetes."

Both the increased rate of gluconeogenesis and the moderate reduction in the rate of glucose utilization by the cells cause the blood glucose concentrations to rise. The rise in blood glucose in turn stimulates secretion of insulin. The increased plasma levels of insulin, however, are not as effective in maintaining plasma glucose as they are under normal conditions. For reasons that are not entirely clear, high levels of glucocorticoid reduce the sensitivity of many tissues, especially skeletal muscle and adipose tissue, to the stimulatory effects of insulin on glucose uptake and utilization. One possible explanation is that high levels of fatty acids, caused by the effect of glucocorticoids to mobilize lipids from fat depots, may impair insulin's actions on the tissues. In this way, excess secretion of glucocorticoids may produce disturbances of carbohydrate metabolism very similar to those found in patients with excess levels of growth hormone .The increase in blood glucose concentration is

occasionally great enough (50 per cent or more above normal) that the condition is called *adrenal diabetes.* Administration of insulin lowers the blood glucose concentration only a moderate amount in adrenaldiabetes-not nearly as much as it does in pancreatic diabetes-because the tissues are resistant to the effects of insulin.

Obesity Caused by Excess Cortisol.

Despite the fact that cortisol can cause a moderate degree of fatty acid mobilization from adipose tissue, many people with excess cortisol secretion develop a peculiar type of obesity, with excess deposition of fat in the chest and head regions of the body, giving a buffalo-like torso and a rounded "moon face." Although the cause is unknown, it has been suggested that this obesity results from excess stimulation of food intake, with fat being generated in some tissues of the body more rapidly than it is mobilized and oxidized.

Anti-inflammatory Effects of High Levels of Cortisol

When tissues are damaged by trauma, by infection with bacteria, or in other ways, they almost always become "inflamed." In some conditions, such as in rheumatoid arthritis, the inflammation is more damaging than the trauma or disease itself. The administration of large amounts of cortisol can usually block this inflammation or even reverse many of its effects once it has begun.

There are five main stages of inflammation:

(1)release from the damaged tissue cells of chemical substances that activate the inflammation processchemicals such as histamine, bradykinin, proteolytic enzymes, prostaglandins, and leukotrienes;

(2) an increase in blood flow in the inflamed area caused by some of the released products from the tissues, an effect called *erythema;*

(3) leakage of large quantities of almost pure plasma out of the capillaries into the damaged areas because of increased capillary permeability, followed by clotting of the tissue fluid, thus causing a *nonpitting type of edema;*

(4) infiltration of the area by leukocytes; and

(5) after days or weeks, ingrowth of fibrous tissue that often helps in the healing process. When large amounts of cortisol are secreted or injected into a person, the cortisol has two basic *anti-inflammatory effects:* (A) it can block the early stages of the inflammation process before inflammation even begins, or (B) if inflammation has already begun, it causes rapid resolution of the inflammation and increased rapidity of healing.