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Disorders of Adrenal Gland

Adrenal Gland

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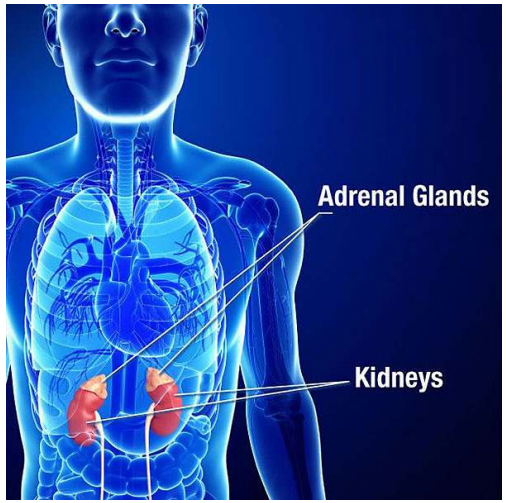
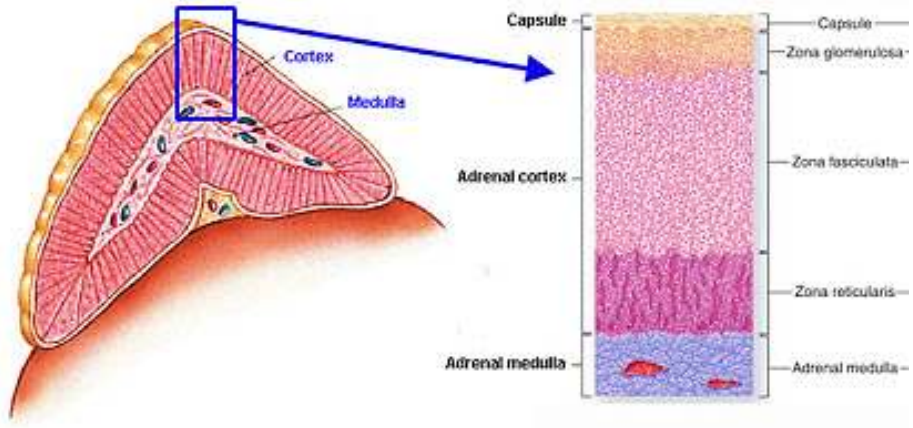
- Adrenal gland, also called **suprarenal gland**, either of **two small triangular** endocrine glands one of which is located **above each kidney.**
- In **humans** each adrenal gland weighs **about 5 grams** (0.18 ounce) and measures about **30 mm (1.2 inches) wide, 50 mm (2 inches) long, and 10 mm (0.4 inch) thick.**
- Each gland consists of two parts: an **inner medulla**, which produces **epinephrine and norepinephrine (adrenaline and noradrenaline),** and **an outer cortex,** which produces **steroid hormones.**
- The gland is surrounded by a **thick connective tissue capsule.**
- Vessels and nerves reach the medulla by way of connective tissue trabeculae which extend from the capsule towards the medulla.
- **Cortex and medulla are two distinct endocrine organs** but they differ in their embryological origin, and their secretions are under different modes of control.





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Location

The adrenal glands are embedded in adipose tissue. It lies in the retro peritoneum above or medial to the upper poles of the kidneys.

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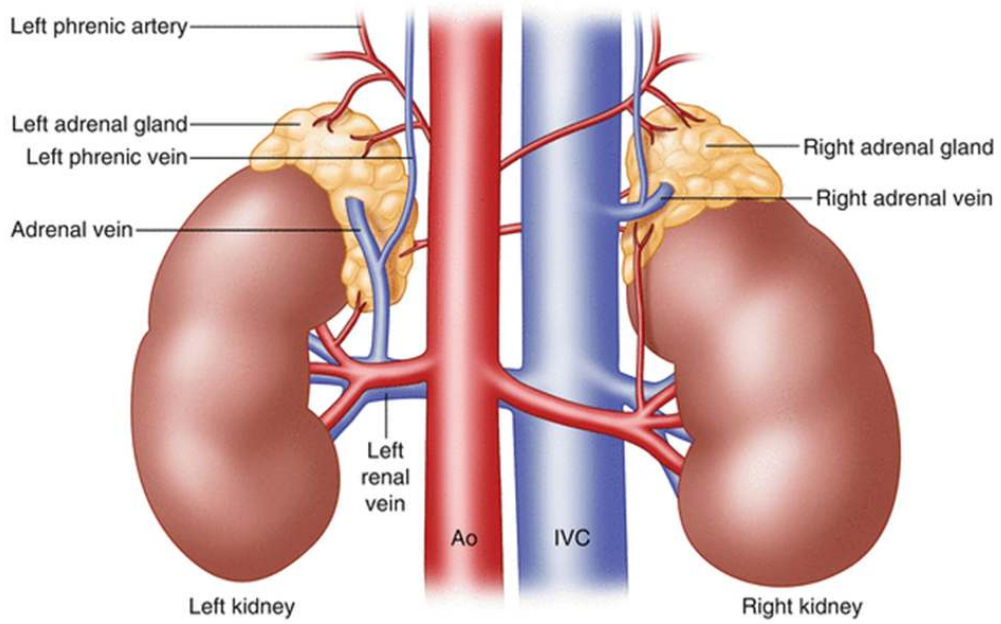
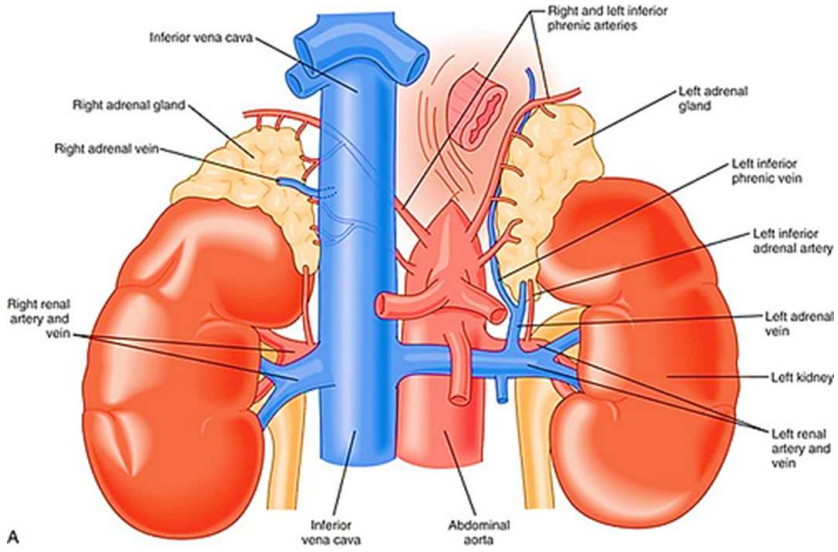


General Anatomy

- **A fibrous capsule surrounds the gland**; the **yellowish outer cortex comprises 90%,** while the **inner medulla about 10%** of the adrenal weight.
- The **cortex is richly vascularized and receives its main arterial supply from inferior phrenic artery, renal arteries and the aorta**. The **right adrenal vein drains into the posterior vena cava**, whereas the **left vein enters the left renal vein.**
- In mammals, the medulla is surrounded by the cortex. In human, the **medulla occupies a central position in the widest part of the gland,** with only small portions extending into the narrower parts. There is no clear demarcation between cortex and medulla.
- The cells of the **adrenal medulla are innervated by preganglionic fibres** of the sympathetic nervous system.
- Some of such fibres reach the wall of the central vein, where they synapse with small autonomic ganglia.
- The **medulla is nourished by some vessels that supply the adrenal cortex**. A few of such vessels penetrate the cortex, passing directly to the medulla.
- Arteries supplying the central vein and cuff of cortical tissue around the central vein also supply the medulla. It would appear that most of the blood supply to the medullary cells is via a portal vascular system arising from the capillaries in the cortex.



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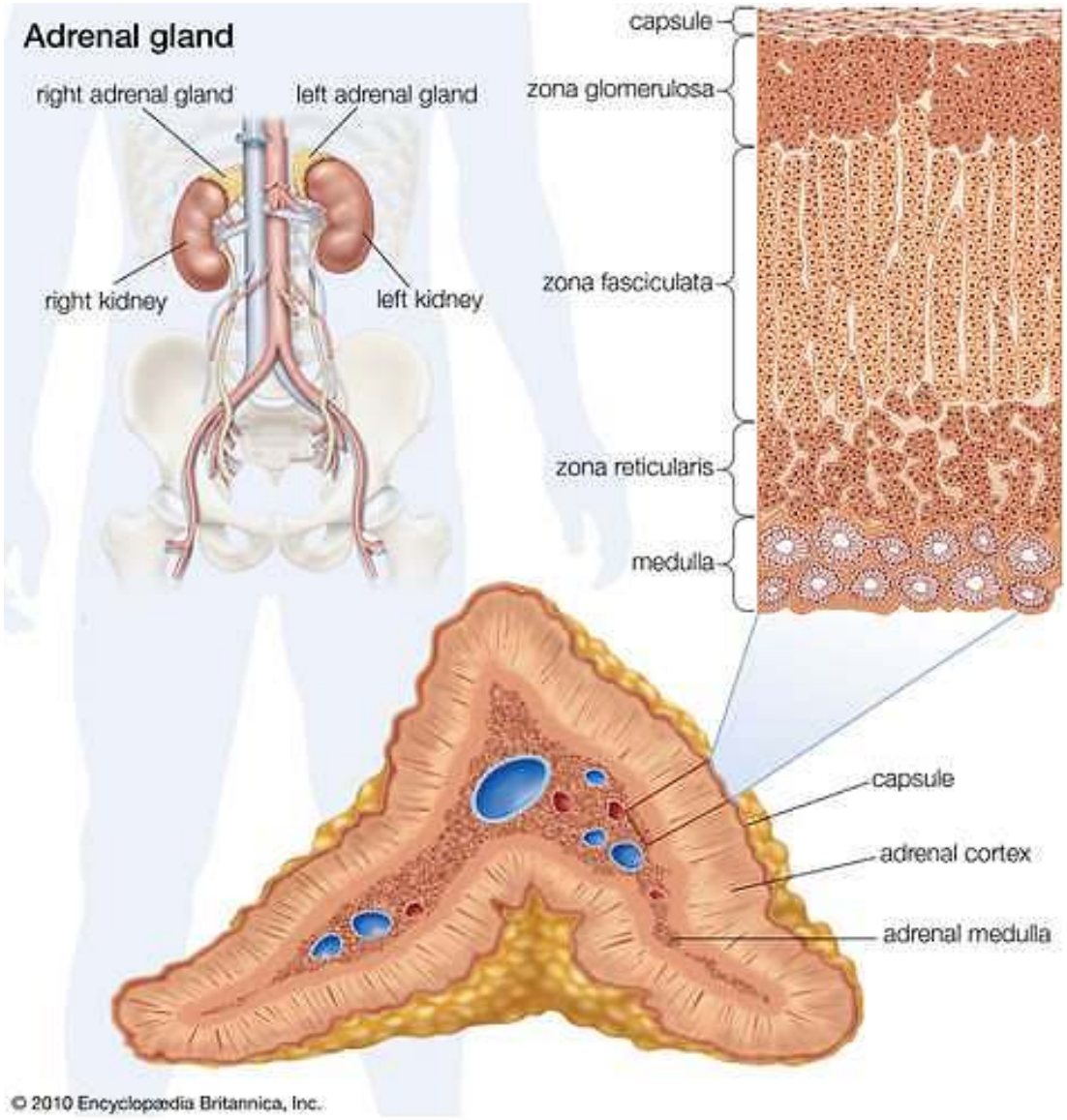
Adrenal gland
right adrenal gland
left adrenal gland
right kidney
left kidney
capsule
zona glomerulosa
zona fasciculata
zona reticularis
medulla
capsule
adrenal cortex
adrenal medulla
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Histology

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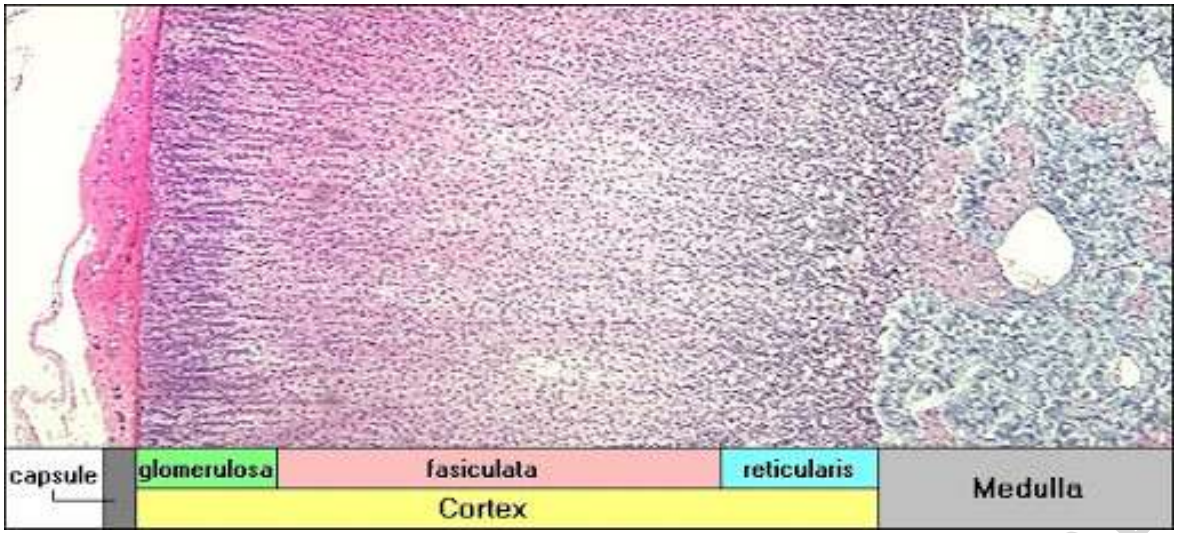

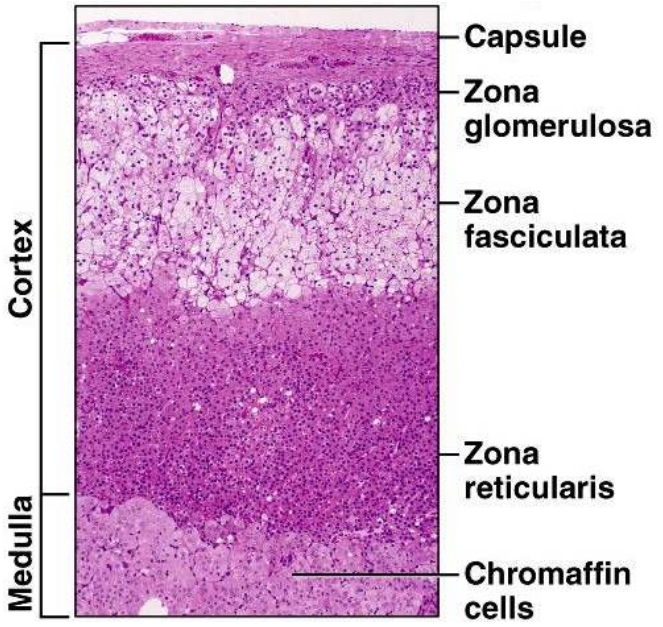

A. Adrenal Cortex

Cells in the adrenal cortex are **arranged into three concentric zones**. However, the boundaries between zones are indistinct.

Adult human adrenal cortex is composed of three concentric zones:

(i) A thin, outer **zona glomerulosa** immediately beneath the capsule;

(ii) A broad, intermediate **zona fasciculata**

(iii) An inner **zona reticularis** adjacent to the medulla

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(i) Zona glomerulosa

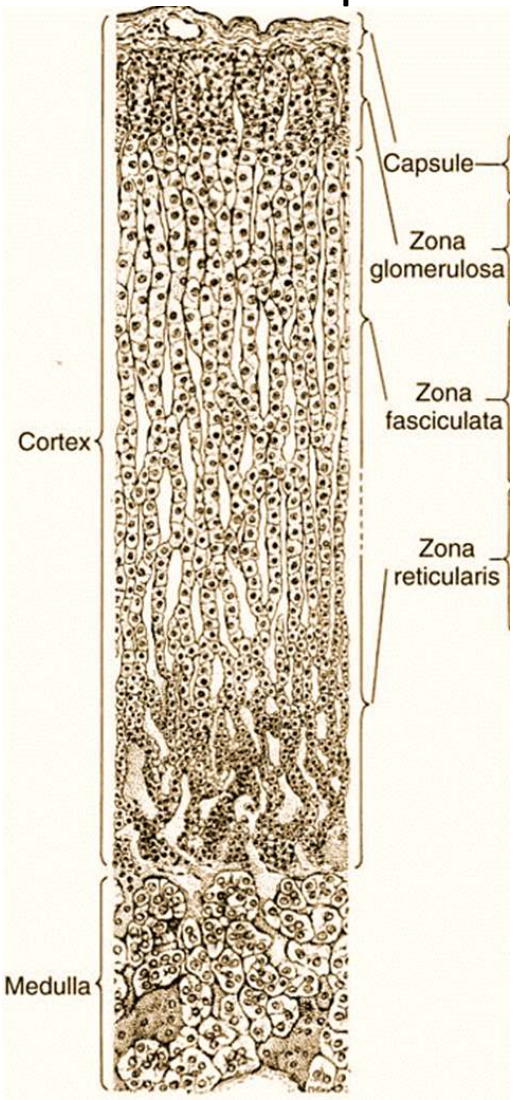
In this outer cortical zone, **columnar epithelial cells** form closely spaced arcades that bear a superficial resemblance to the acini of exocrine glands.

(ii) Zona fasciculata

The middle cortical zone is made up of **pale staining polyhedreal cells arranged in long columns that are oriented radially in relation to the medulla.**

(iii) Zona reticularis

The parallel cell columns of zona fasciculata give way to a three-dimensional network of **anastomosing cell cords in the inner zona reticularis.**



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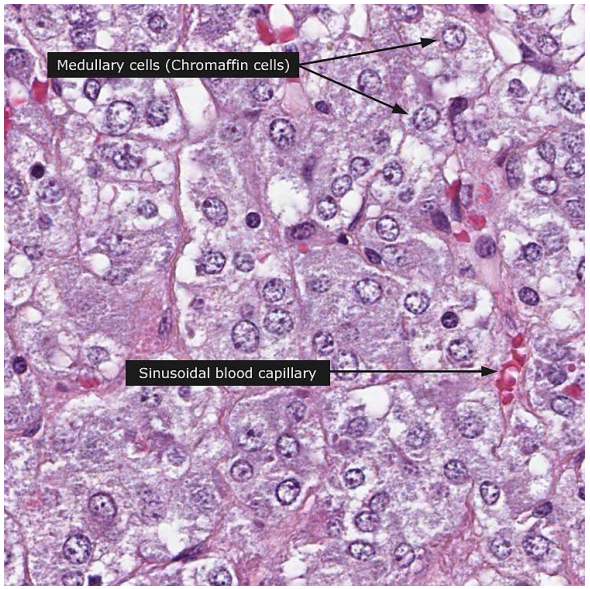
B. Adrenal medulla

- In human, the **boundary between the cortex and medulla of adrenal gland is irregular with some reticularis cords** penetrating a short distance into the medulla.
- In the medulla, **large epitheloid cells are arranged in rounded clusters or short cords** that are in intimate relation to capillaries and venules.
- Such cells and isolated groups of cells in other organs that display this **staining reaction are called chromaffin cells or pheochromocytes (pheo-brown).**
- The **browning of granules with chromium salts is called chromaffin reaction that is due to oxidation and polymerisation of catecholamine present in the granules.**



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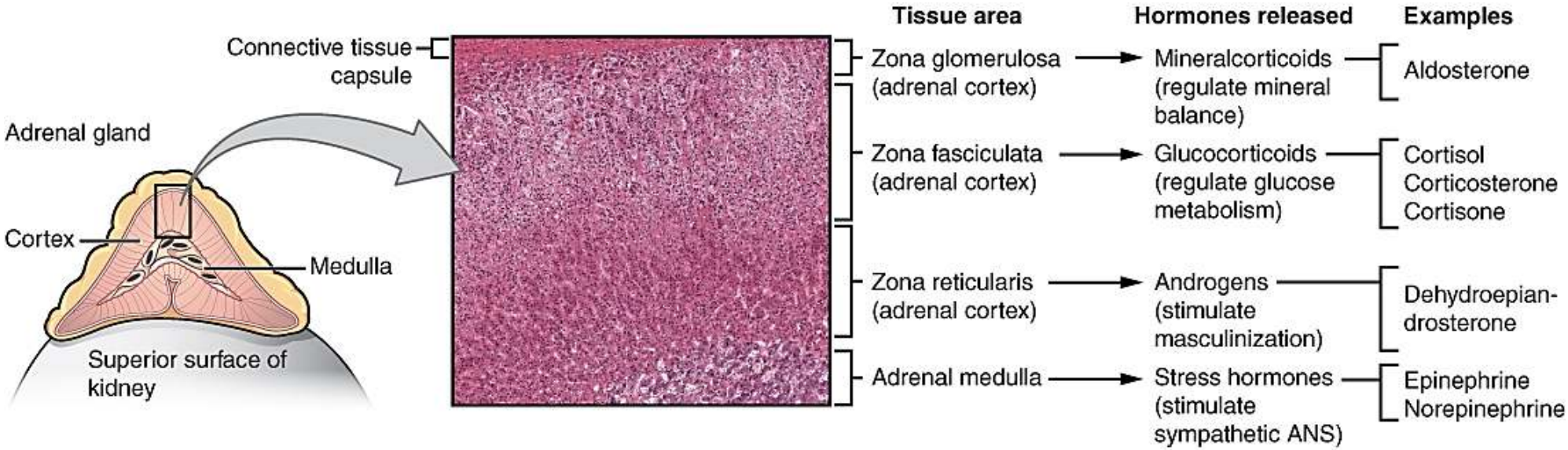
Hormones of Adrenal gland



Cortical Hormones
1. Mineralocorticoids

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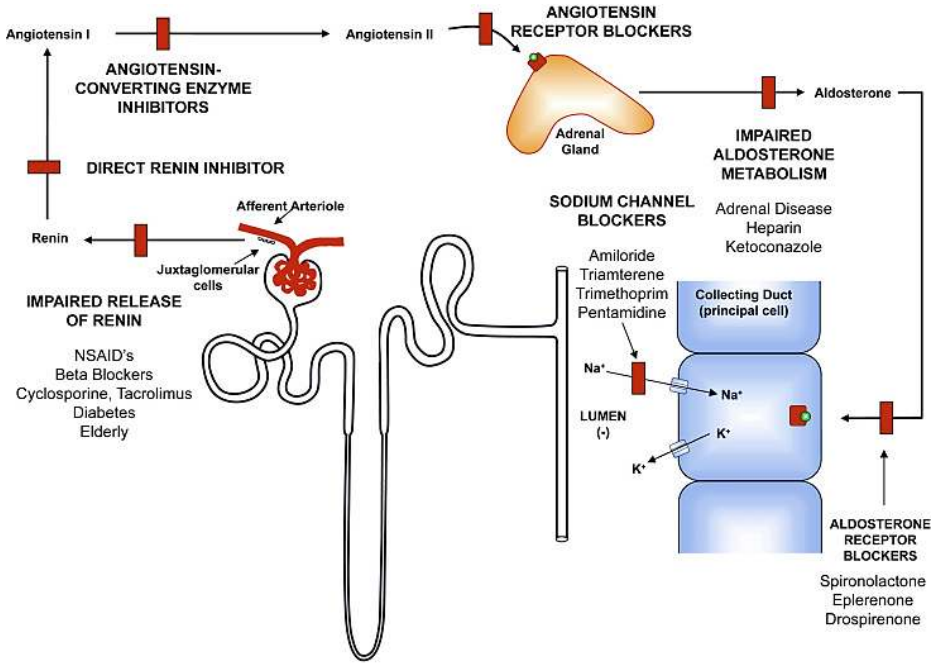

The major target of aldosterone is the distal tubule of the kidney, where it stimulates exchange of sodium and potassium. Three primary physiologic effects of aldosterone result:

1. Increased resorption of sodium: sodium loss in urine is decreased under aldosterone stimulation.

2. Increased resorption of water, with consequent expansion of extracellular fluid volume. This is an osmotic effect directly related to increased resorption of sodium.

3. Increased renal excretion of potassium.

Aldosterone stimulates transcription of the gene encoding the sodium-potassium ATPase, leading to increased numbers of **"sodium pumps" in the basolateral membranes of tubular epithelial cells.** Aldosterone also stimulates expression of a sodium channel which facilitates uptake of sodium from the tubular lumen. **Aldosterone has effects on sweat glands, salivary glands and the colon** which are essentially identical to those seen in the distal tubule of the kidney.

The major net effect is again to **conserve body sodium by stimulating its resorption or, in the case of the colon, absorption from the intestinal lumen.** Conservation of water follows conservation of sodium.

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Cortical Hormones
2. Glucocorticoids

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1. Effects on Metabolism

The name glucocorticoid derives from early observations that these hormones were involved in glucose metabolism. In the fasted state, cortisol stimulates several processes that collectively serve to increase and maintain normal concentrations of glucose in blood. These effects include:

a. Stimulation of gluconeogenesis, particularly in the liver: This pathway results in the synthesis of glucose from non-hexose substrates such as amino acids and lipids and is particularly important in carnivores and certain herbivores. Enhancing the expression of enzymes involved in gluconeogenesis is probably the best known metabolic function of glucocorticoids.

b. Mobilization of amino acids from extrahepatic tissues: These serve as substrates for gluconeogenesis.

c. Inhibition of glucose uptake in muscle and adipose tissue: A mechanism to conserve glucose.

d. Stimulation of fat breakdown in adipose tissue: The fatty acids released by lipolysis are used for production of energy in tissues like muscle, and the released glycerol provide another substrate for gluconeogenesis.

e. **It can reduce intestinal calcium absorption**, which tends to lower the serum calcium. It also increases the urinary calcium excretion.

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2. Effects on Inflammation and Immune Function

Glucocorticoids have potent anti-inflammatory and immunosuppressive properties (by blocking the release of lysosomal hydrolase, by decreasing vascular permeability to prevent extravasation of fluids, decresing the number of circulating monocytes, eosinophils etc.) .

3. Other Effects of Glucocorticoids

- Glucocorticoids have multiple effects on fetal development. An important example is their role in promoting maturation of the lung and production of the surfactant necessary for extrauterine lung function.
- It can influence both leukotype movement and functions.
- It may stimulate cardiac output and increase peripheral vascular tone.
- It can effect water and electrolyte balance.
- Several aspects of cognitive function are known to both stimulate glucocorticoid secretion and be influenced by glucocorticoids. Fear provides an interesting example of this. Fear-inducing stimuli lead to secretion of glucocorticoids from the adrenal gland, and treatment of phobic individuals with glucocorticoids prior to a fear-inducing stimulus can blunt the fear response.

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Cortical Hormones
3. Adrenal Androgen

- Adrenal androgens (AAs), normally secreted by the fetal adrenal zone and the zona reticularis of the adrenal cortex, are steroid hormones with weak androgenic activity. They include dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione (A4), androstenediol (A5) and 11β-hydroxyandrostenedione (11βOHA4).
- In males, physiological effects are negligible. However, in boys, it causes premature penile enlargement and early development of secondary sexual characteristics.
- **In females**, its overproduction results in some **abnormalities manifested by acne, hirsutism and virilization.** In later case, an **involution of female secondary sexual characters and development of male secondary sex characters.**

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Medullary Hormones

Functions of adrenalin and noradrenalin

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Physiological activities	*Epinephrine*	*Nor-epinephrine*
1. Eosinophil count	Increased	No effect
2. Cardiac output	Increased	Slightly decreased or no effect
3. Heart rate	Increased	Decreased
4. Diastolic pressure	No effect	Increased
5. Blood vessel diameter	Vasodilation	Vasoconstriction
6. Blood sugar level	Increased	Slightly increased
7. Blood lactate	Increased	Slightly increased or no change
8. Glycogenolysis	Decreased	Increased
9. Total peripheral resistance	Decreased	Increased
10. Uterine muscle contraction	Strongly inhibition	Weak inhibition
11. On CNS	Decreased	No change
12. Skeletal muscle	100% increase	Unaltered or decreased

- The **"fight or flight" response** of the sympathetic nervous system is a direct result of the multisystem action of catecholamines.
- Secretion from the adrenal medulla **proceeding the activation of the sympathetic nervous system functions to regulate blood pressure** by contracting the smooth muscle in the vasculature (via alpha-1 receptors).
- The **adrenergic receptors linked to blood vessels have an especially high affinity for norepinephrine relative to the other amines.**
- Further musculoskeletal actions of catecholamines include **enhanced contractility of cardiac muscle (via beta-1 receptors), contraction of the pupillary dilator (via alpha-1 receptors), piloerection (via alpha-1 receptors), and relaxation of smooth muscle in the gastrointestinal tract, urinary tract, and bronchioles (via beta-2 receptors).**
- **Both epinephrine and norepinephrine modulate metabolism to increase blood glucose levels by stimulating glycogenolysis in the liver (via beta-2 receptors), increased glucagon secretion (via beta-2 receptors) and decreased insulin secretion (via alpha-2 receptors) from the pancreas, and lipolysis in adipose tissue (via beta-3 receptors).**
- **Epinephrine also inhibits release of mediators from mast cells and basophils** in type I hypersensitivity reactions.

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Functions of Epinephrine

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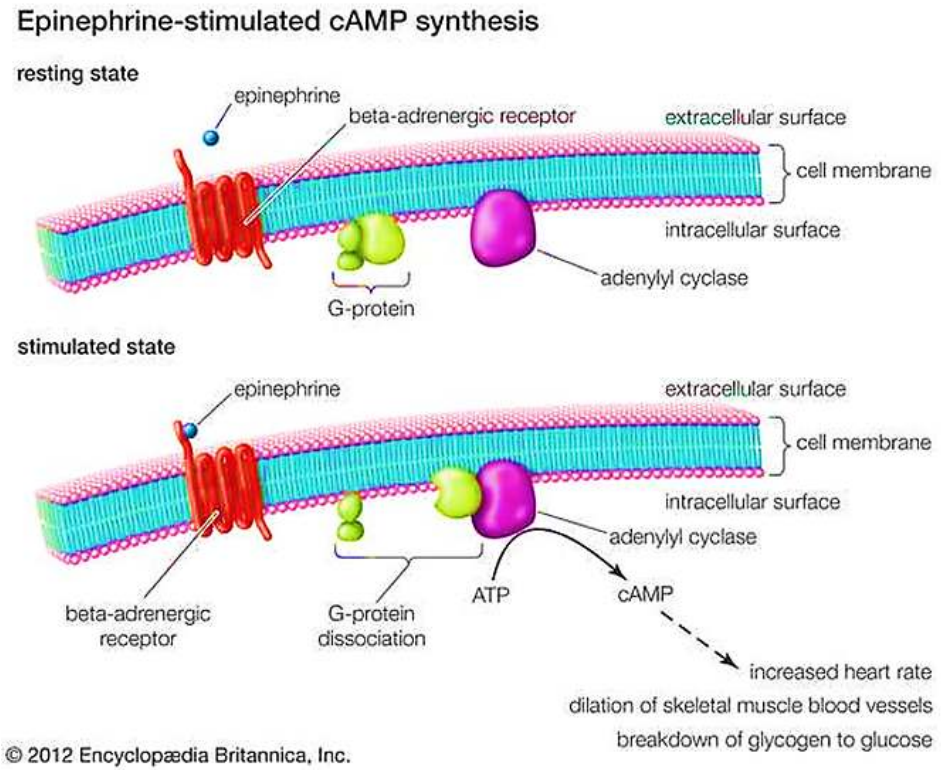

- When the brain **perceives danger, the amygdala triggers the hypothalamus to activate the autonomic nervous system.**
- **Signals from the autonomic nervous system stimulate the adrenal gland to start pumping epinephrine into the bloodstream**. People often refer to this surge of epinephrine as an adrenaline rush or the fight or flight response.
- Epinephrine **affects the heart, lungs, muscles, and blood vessels.** Its release into the bloodstream brings about several physiological changes, such as:
- **increased heart rate and blood flow**
- **faster breathing**
- **raised blood sugar levels**
- **increased strength and physical performance**

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Function of Norepinephrine

- The adrenal **medulla produces norepinephrine in response to low blood pressure and stress.**
- Norepinephrine **promotes vasoconstriction,** which is a narrowing of the blood vessels, and this increases blood pressure.
- Like epinephrine, norepinephrine **also increases the heart rate and blood sugar levels.**

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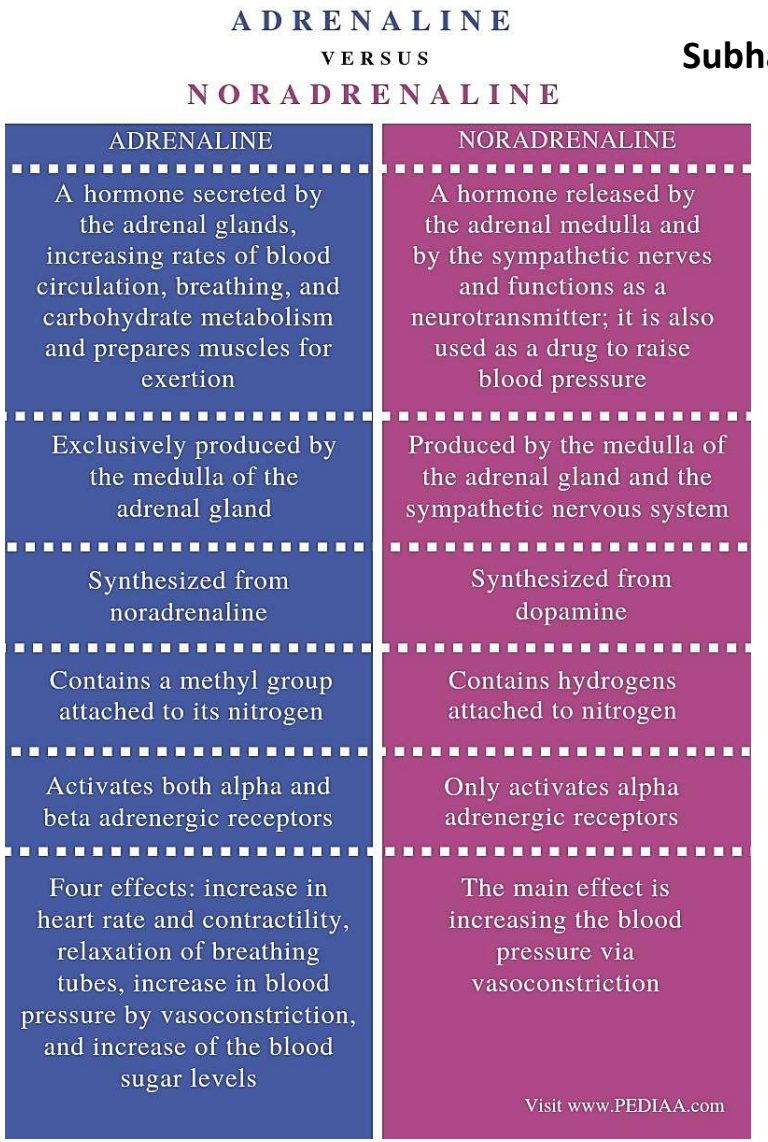

Disorders

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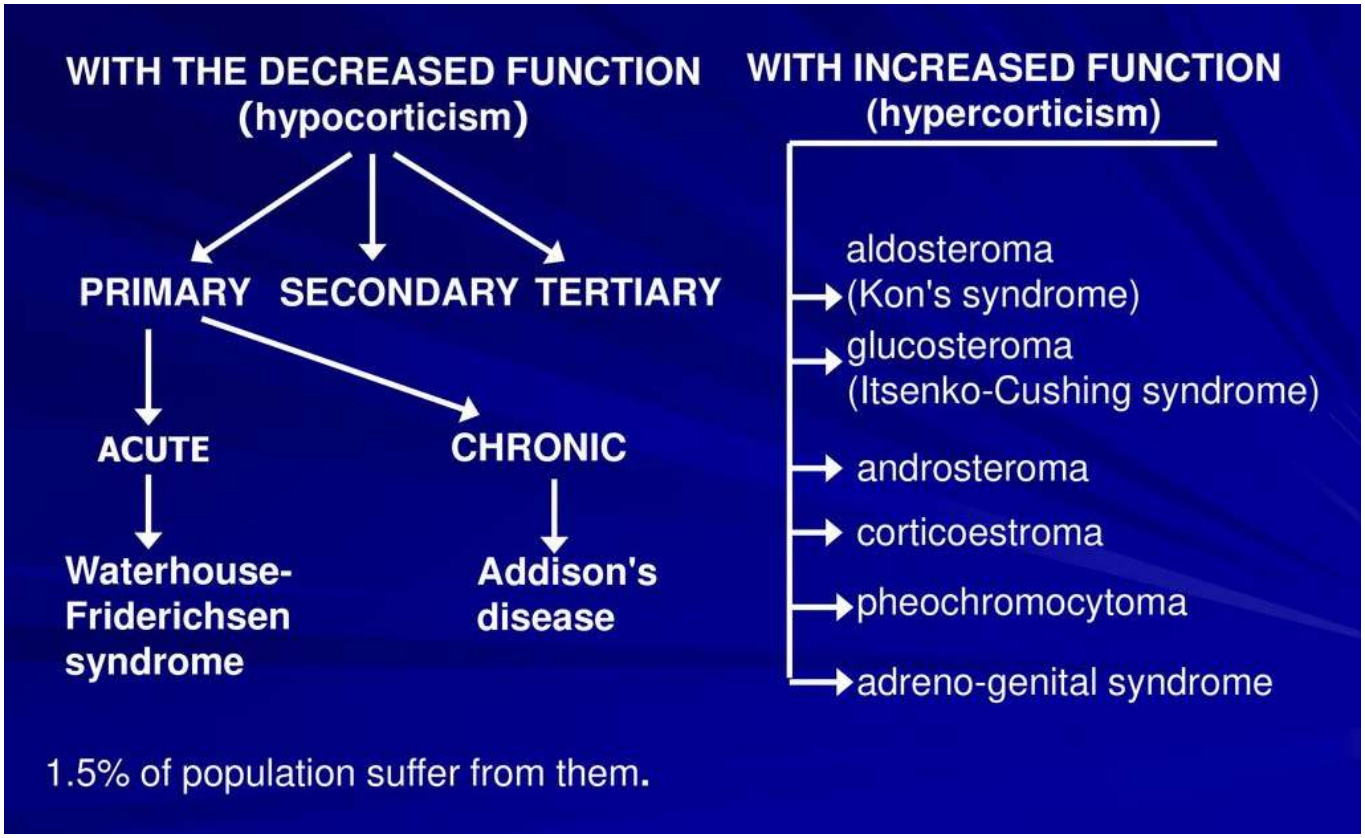

The primary adrecortical insufficiency (Addison's Disease)

- **The primary adrecortical insufficiency** of the adrenal cortex leads to **Addison's disease,** hypocorticism, bronzed disease. It was first described by Tomas Addison in 1855.
- Addison's disease is serious chronic disease, **caused by partial or absolute abnormality of hormonal function of the adrenal cortex**.
- **Major causes:** Autoimmune (80%), Tuberculosis (20%).
- **Rare cases:** Idiopathic atrophy of adrenal cortex (antigens to mitochondrion and microsomal fraction), adrenal glands haemorrhage, amyloidosis, syphilis.
- The **pathogenesis** and development of clinical symptoms under Addison's disease are **atrophy or dystrophy of adrenal cortex, aldosterone is absent or significant decreased 17-ketosteroids are absent or significant decreased cortisol is absent or significant decreased clinical symptoms, hypotension, absence of pubic hair growth, muscle atrophy, pigmentation, weakness, asthenia, achlorhydria, anorexia.**
- **Cortisol deficiency:** weakness, fatigue, nausea, hypotension, hypoglycaemia.
- **Mineralocorticoid deficiency:** dehydration, hypotension, hyperkalemia, lymphocytosis, hypoglycaemia.

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Addisonian crisis

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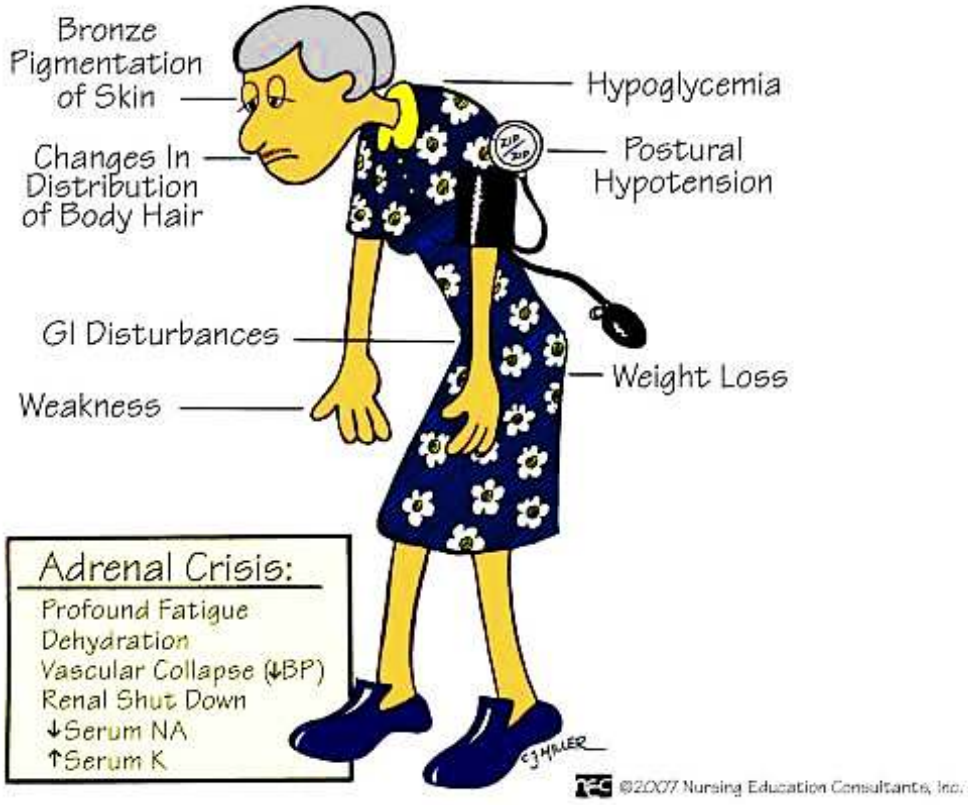
An Addisonian crisis is a serious medical condition caused by the body's inability to produce a sufficient amount of cortisol. An Addisonian crisis is also known as an acute adrenal crisis.



The secondary adrenal insufficiency

- **The secondary adrenal insufficiency** may result due to ACTH deficiency which , in turn, results from exogenous glucocorticoid therapy. However, pituitary and hypothalamic tumors may be the most common causes of naturally occurring pituitary hypo secretion.
- ACTH hypo secretion leads to decreased synthesis of cortisol and androgen secretion.
- At this stage, there is not only decreased ACTH responsiveness to stress but also decreased adrenal responsiveness to acute stimulation with exogenous ACTH.
- Hypoglycemia is occasionally present. Acute decompensation with severe hypotension or shock unresponsiveness to vassopressors may result.

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Hyper secretion of Adrenal hormones (Cushing's Syndrome)

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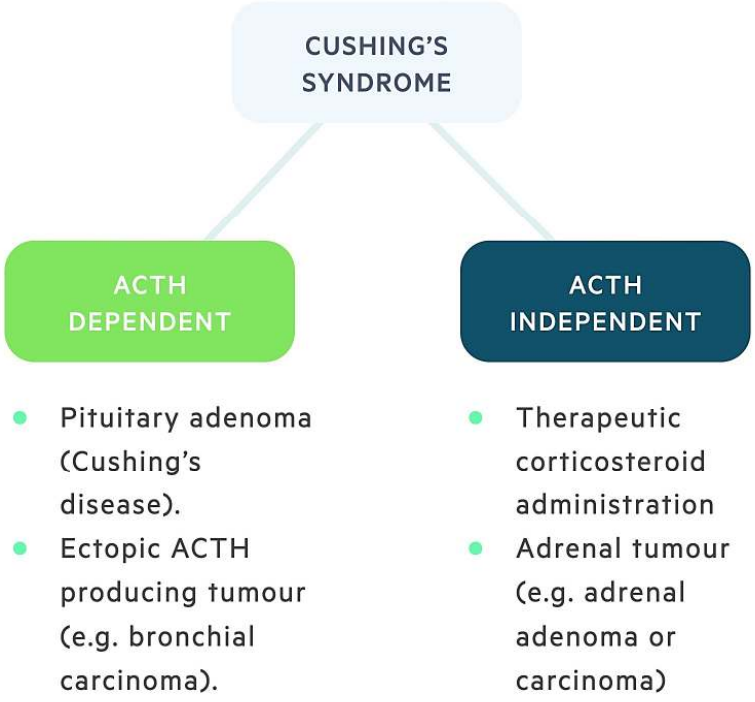
- Cushing's syndrome is a disorder that occurs when your body makes too much of the hormone cortisol over a long period of time.



Common signs and symptoms of Cushing syndrome

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- Weight gain and fatty tissue deposits, particularly around the midsection and upper back, in the face (moon face), and between the shoulders (buffalo hump)
- Pink or purple stretch marks (striae) on the skin of the abdomen, thighs, breasts and arms.
- Thinning, fragile skin that bruises easily.
- Slow healing of cuts, insect bites and infections.
- Acne.

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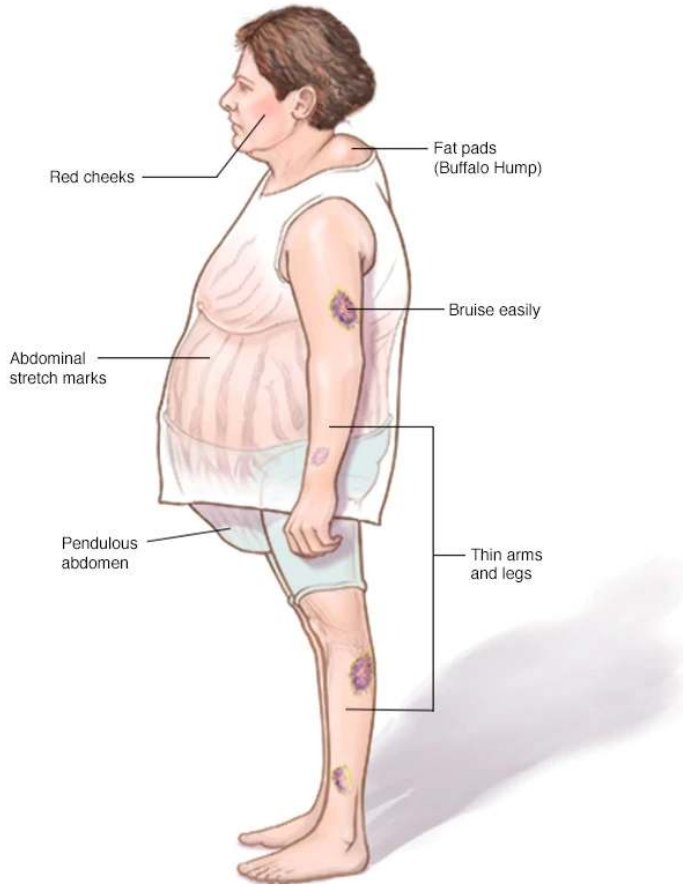

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Ectopic Cushing's syndrome

- Ectopic Cushing syndrome is a form of Cushing syndrome in which **a tumor outside the pituitary gland produces a hormone called** adrenocorticotropic hormone (ACTH).
- ACTH and cortisol hypersecretion is randomly episodic.
- Hyperpigmentation is common.

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All the previous symptoms but.....

- Ectopic dominated by :
  - **Hypokalemic alkalosis (dominant feature)**
  - Fluid retention
  - HTN
  - Glucose intolerance
  - Steroid psychosis
- Absence of other features may be explained by more sudden onset by acquired ACTH from tumor.

Adrenal Tumors

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Malignant Adrenal Tumors

- **Adrenocortical cancer:** These tumors originate in the cortex of the adrenal gland. Adrenocortical cancer is rare, affecting only about 300 to 500 people each year in the United States. There are two main types of adrenocortical cancer:
- **Functioning** tumors are the most common type and account for about 70% of adrenal cancers. These tumors make hormones, such as cortisol, androgens or aldosterone.
- **Non-functioning** tumors do not produce hormones.
- **Malignant adrenal pheochromocytoma:** This cancer begins in the medulla. It is extremely rare, with only about 800 cases are diagnosed each year in the United States.
- **Malignant paragangliomas:** These tumors may begin inside or outside the adrenal gland.

Benign Adrenal Tumors

- **Adenomas:** A type of non-cancerous tumor.
- **Benign pheochromocytomas**
- **Benign paragangliomas**

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Adrenal Tumor Risk Factors

Certain inherited disorders can increase your risk of having an adrenal disease. These include:

- Li-Fraumeni syndrome
- Multiple Endocrine Neoplasia type 2 (MEN2)
- Von Hippel-Lindau disease (VHL)
- Neurofibromatosis type 1, also known as von Recklinghausen's disease
- Paraganglioma syndrome, a condition where tumors form in structures called paraganglia
- Beckwith-Wiedemann syndrome, a type of overgrowth syndrome

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Primary Aldosteronism (Conn's Syndrome)

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- Primary aldosteronism (also called Conn's syndrome) is a **rare condition caused by overproduction of the hormone aldosterone** that controls sodium and potassium in the blood.
- The condition is treated with medications and lifestyle changes to control blood pressure, and in some cases surgery.
- Primary aldosteronism usually **manifests with high blood pressure and low potassium levels in the blood.** Left unchecked, high blood pressure raises your risk for complications including heart attack and stroke, while low potassium can cause heart rhythm irregularities. Electrolyte imbalances and prolonged high blood pressure increase your risk for serious complications, including: Heart attack or heart failure, Irregular heartbeat, Kidney failure, Stroke, Temporary paralysis or the inability to move.
- In some cases, primary aldosteronism results from **benign, or noncancerous, tumors in one or both adrenal glands.**
- Rarely, primary aldosteronism occurs because of an **inherited disorder.** In extremely rare cases, cancerous tumors in one or both adrenal glands cause primary aldosteronism .
- Anyone can develop primary aldosteronism. But it's more likely to be present if you have:

i. Low blood potassium levels (hypokalemia).
ii. High blood pressure starting before age 30.
iii. High blood pressure requiring three or more medications to manage.
iv. An adrenal mass.

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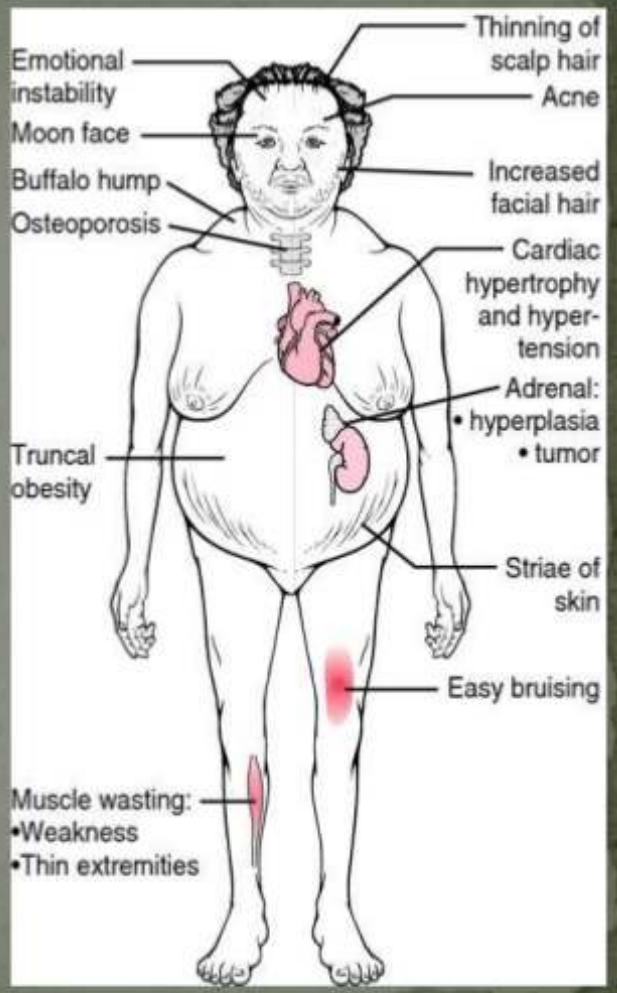
Symptoms

- Frequent urination
- Increased thirst
- Weakness and fatigue
- Headache
- Muscle cramps
- Tingling in fingers
- Temporary paralysis
- Heart palpitations
- Hypertension (high blood pressure)



Hirsutism and Virilism

- Hirsutism is the medical term that refers to the presence of excessive terminal (coarse) hair in androgen-sensitive areas of the female body (upper lip, chin, chest, back, abdomen, arms, and thighs).
- Virilization is more extensive than hirsutism with additional evidence of masculinization (male pattern baldness, excessive facial hair, usually on your cheeks, chin, and upper lip, deepening of your voice, small breasts, enlarged clitoris, irregular menstrual cycles, increased sex drive.

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Pheochromocytoma

- A pheochromocytoma is a rare, usually noncancerous (benign) tumor that develops in an adrenal gland (**tumor derived from chromaffin cells**).
- Pheochromocytoma may **occur as a single tumor or as more than one growth.** It usually develops in the center (medulla) of one or both adrenal glands. In rare cases, a pheochromocytoma occurs outside the adrenal gland. When it does, it is usually somewhere else in the abdomen.
- Very few pheochromocytomas are cancerous.
- The tumors may occur at any age, but they are most common from early to mid-adulthood.
- In few instances, the condition may also be seen among family members (hereditary).

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