بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Physiology | MID L8

Adrenocortical Hormones

Written by : Mousa Al-Neimat

Layan Abu Haweleh

Reviewed by : NST

Pre-studying Notice

- The professor focuses on what he explicitly says, so don’t worry about all these slides.
- Don’t memorize the steroid cascades in the figures.
- Distinguish different classes and the important enzymes that convert one to another.
- Focus on what is explained in **PURPLE**, but please read and understand everything thoroughly.

Adrenal Glands

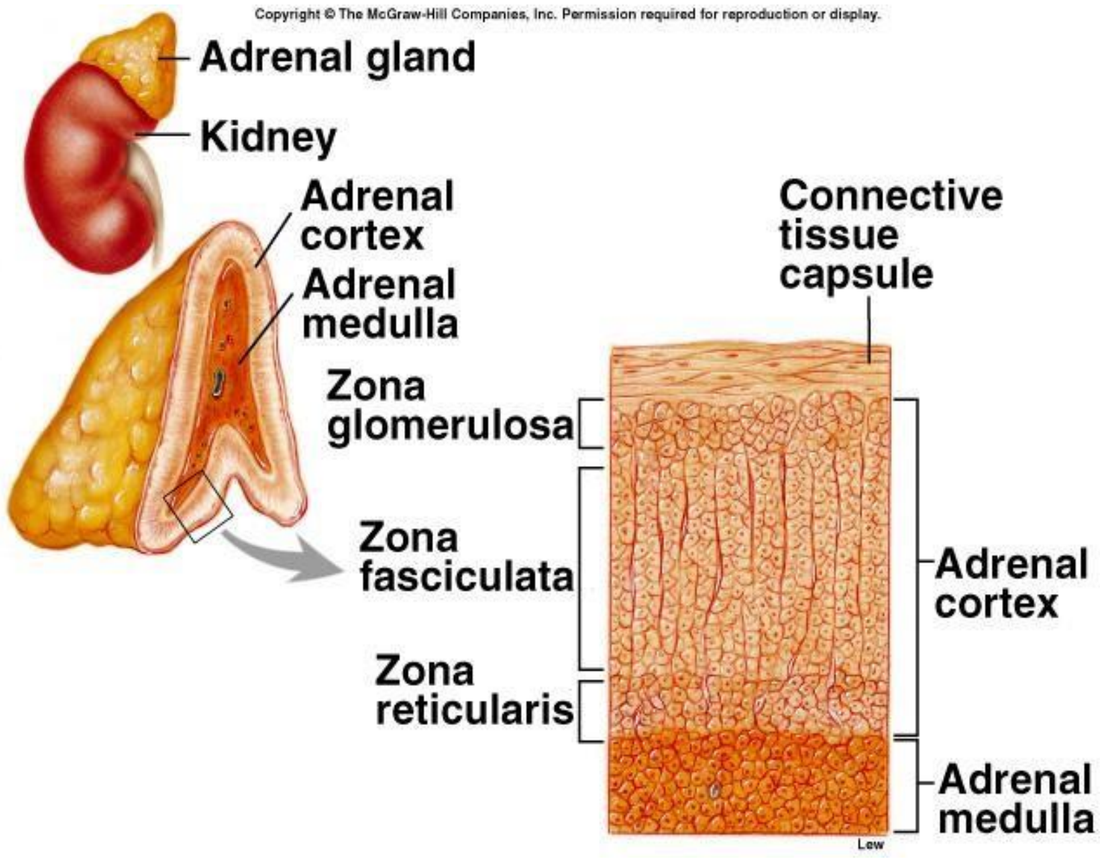
- Paired organs that cap the kidneys (supra-renal glands, above the kidneys).
- Weight 5 gm each.
- Receive **very high blood flow per unit weight, (5 ml/min/gm tissue relatively more than the RBF which is 4 ml/min/g)**.
- Each gland consists of an **outer cortex and inner medulla.**
- Adrenal medulla:
  - Derived from embryonic neural crest ectoderm (same tissue that produces the sympathetic ganglia).
  - Synthesizes and secretes:
  - **Catecholamines (mainly Epi but some NE) or (adrenaline and noradrenaline).**

- The adrenal glands receive significantly more blood than they metabolically need, with approximately blood flow rate **of 5 ml/min/gram of tissue**, compared to the Muscle which receives approximately 0.3 ml/min/g and the **kidney blood flow which is 4ml/min/gram of tissue.** This can be noticed by the small difference of oxygen concentration between the arterial and the venous ends. (more blood flow, less oxygen-carbon dioxide exchange).

Adrenal Glands (continued)

- **Adrenal cortex:**
  - Does **not** receive **neural innervation**.
  - Must be stimulated **hormonally (ACTH).**

- Consists of **3 zones:**
  - Zona glomerulosa.
  - Zona fasciculata.
  - Zona reticularis.
- Secretes **corticosteroids**.



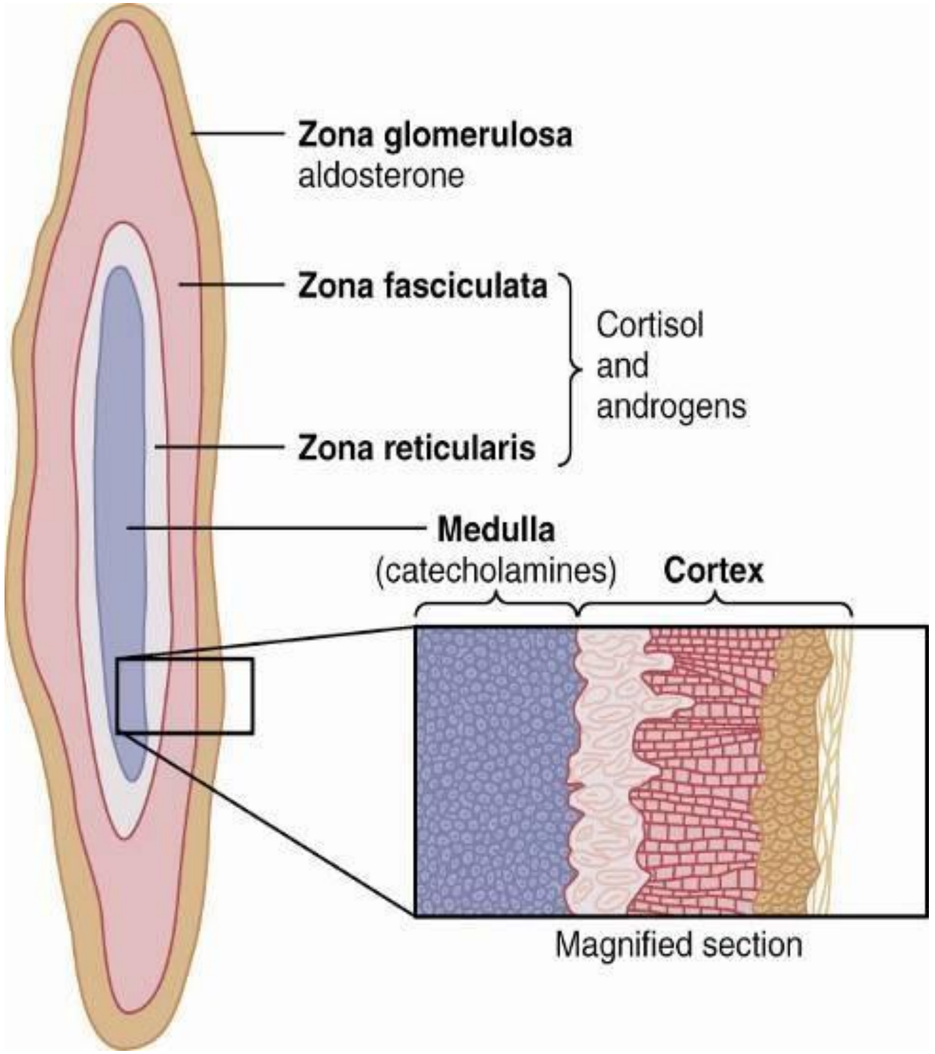
Functions of the Adrenal Cortex

- **Zona glomerulosa: (10-15)%**
  - **Mineralcorticoids (aldosterone):**
    - **Stimulate kidneys to reabsorb Na^+ and secrete K^+.**
- **Zona fasciculata: (75%)**
  - **Glucocorticoids (cortisol):**
  - Inhibit glucose utilization and stimulate gluconeogenesis. Aid in regulating the metabolic functions of the body and in controlling the inflammatory
  - **Essential for survival in stress situations**
- **Zona reticularis (DHEA): (10-15)%**
  - **Sex steroids**: Serve mainly as source of **androgens for women**

Secretion of Adrenocortical Hormones by Different Zones of the Adrenal Cortex

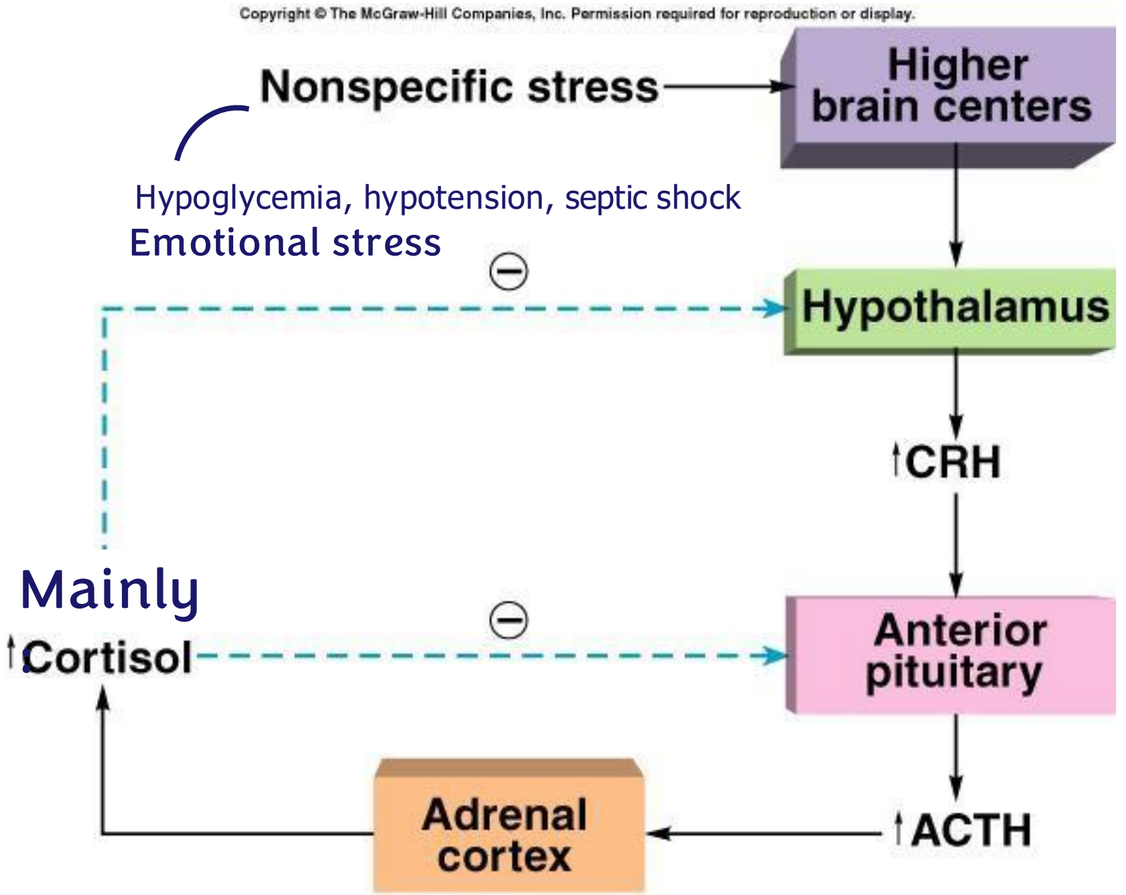
As discussed previously, the adrenal cortex is made of 3 layers:

- **Zona glomerulosa (the outermost layer),** secretes Aldosterone.
- **Zona fasciculata (the middle layer),** secretes cortisol, it is the most stimulated by ACTH.
- **Zona reticularis (premedullary layer),** secretes androgens
- **All theses hormones are considered steroids.**



Stress and the Adrenal Gland

- Non-specific response to stress produces the general adaptation syndrome (GAS) .
- Alarm phase:
  - Adrenal glands activated.
- Stage of resistance:
  - Stage of readjustment.
- Stage of exhaustion:
  - Sickness and/or death if readjustment is not complete.ol;kl;olk,



1. Alarm Phase (Immediate Response)
·First reaction to stress.
·Adrenal glands and sympathetic nervous system are activated.
·Stress hormones increase. (cortisol ↑)
·**Purpose:** Prepare the body for **fight or flight**.
·**Effects:**
- ·↑ Heart rate
- ·↑ Blood pressure
- ·↑ Blood glucose
- ·↑ Alertness

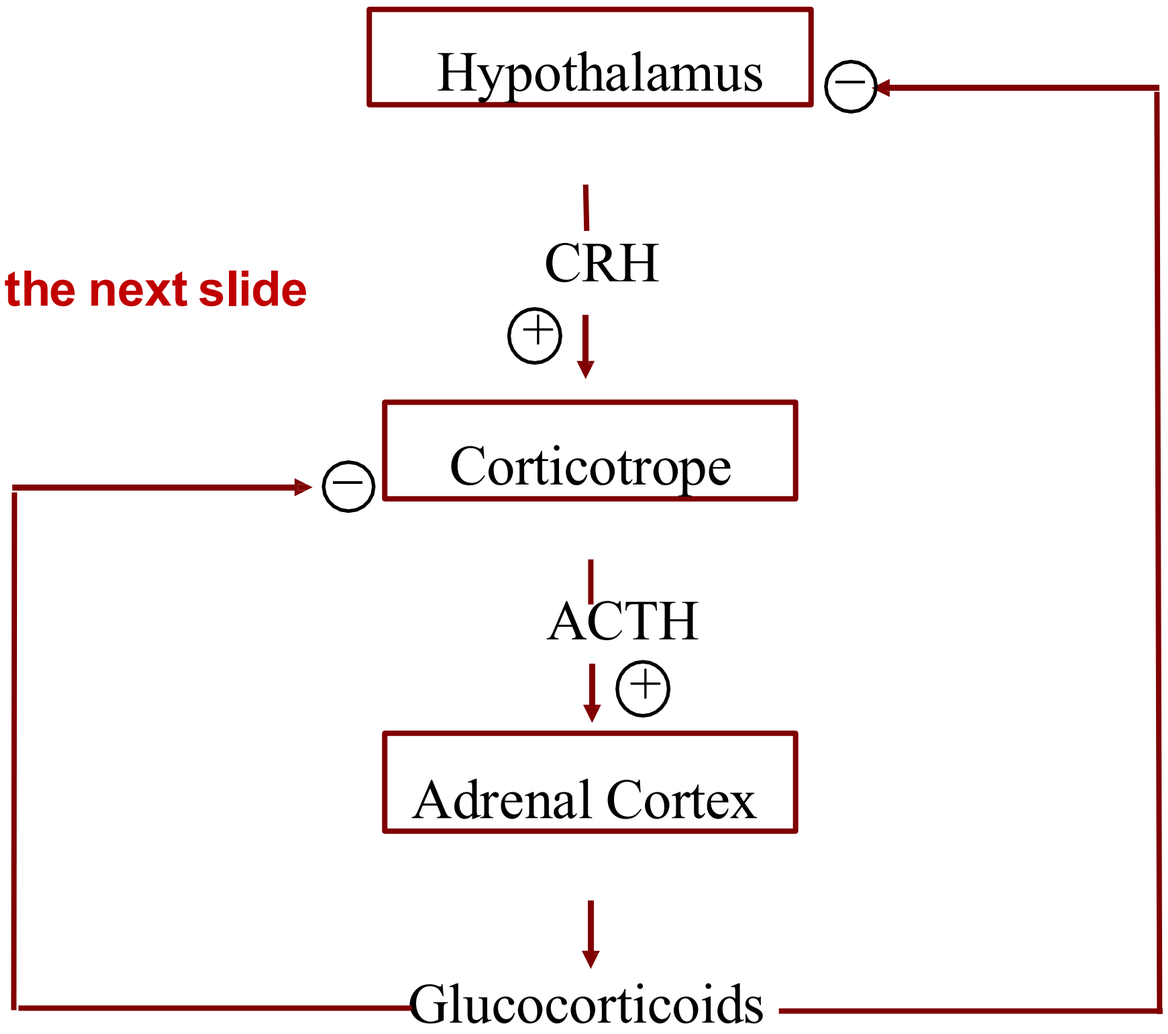
2. Resistance Stage (Adaptation)
Occurs if stress persists.
Body adapts to ongoing stress.
Cortisol remains elevated.
Maintains:
- ·Blood glucose
- ·Blood pressure
- ·Energy supply

Suppresses inflammation.
Purpose: Help the body cope with prolonged stress.

3. Exhaustion Stage
Develops when stress is prolonged (Chronic stress) and adaptation fails.
Body's resources become depleted.
Effects:
- ·Fatigue
- ·Weakened immunity
- ·Weight loss
- ·Organ dysfunction
- ·Severe illness or death if recovery does not occur.

Hypothalamohypophyseal-Adrenal Axis

Discussed in the next slide



ACTH: Regulation, Function, and Clinical Implication

- The hypothalamus secretes **corticotropin-releasing hormone** (CRH), which stimulates the anterior pituitary to release **adrenocorticotropic hormone** (ACTH). **ACTH** then acts on the adrenal cortex to promote the release of cortisol. Elevated **cortisol** levels exert negative feedback on both the hypothalamus and the anterior pituitary, inhibiting further release of **CRH** and **ACTH** to maintain hormonal balance. An underlying condition that leads to no **cortisol** release will lead to higher **ACTH** levels in blood as the negative feedback inhibition by **cortisol** is lost.

- **Adrenocorticotropic hormone** (ACTH) and **melanocyte-stimulating hormone** (MSH) are both derived from the same precursor protein, **proopiomelanocortin** (POMC), in the anterior pituitary. When **POMC** is cleaved, it produces **ACTH** and different forms of **MSH**. At high levels, **ACTH** can stimulate melanocortin receptors, leading to increased melanin production and skin pigmentation.

Role of ACTH and POMC in Adrenal Physiology and Related Disorders

- Adrenocorticotropic hormone (ACTH) is a **byproduct of pro-opiomelanocortin (POMC).**
- POMC is cleaved to produce **both ACTH and melanocyte-stimulating hormone (MSH).**
- This association is **clinically important in Addison disease.**
- In Addison's disease, **increased ACTH leads to elevated MSH activity, which causes hyperpigmentation**. **(See next Slide)**
- ACTH acts on **receptors** located in **the adrenal cortex**, especially in the **zona fasciculata and zona reticularis**.
- These receptors are **G protein-coupled and activate adenylyl cyclase**, which **increases cyclic AMP (cAMP) levels** that serves as a **secondary messenger.**
- The zona **fasciculata** secretes **glucocorticoids**, while the **zona reticularis produces androgens**.
- **Stress stimulates the release of ACTH.**
- **Disorders** involving ACTH can be due to **three mechanisms**:
    1. **Pituitary dysfunction**
    2. **Adrenal dysfunction**
    3. **Ectopic ACTH secretion,** very rare condition (e.g., by lung tumors especially small cell lung carcinoma), these ectopic tissues don't respond to negative feedback by elevated cortisol, for example, an injection of dexamethasone will suppress the secretion of ACTH from the anterior pituitary but won't suppress the secretion of ACTH from an ectopic ACTH secreting tissue.
- The pituitary may be either hypofunctioning (Sheehan syndrome) or hyperfunctioning.
- The adrenal glands can also show hypofunctioning or hyperfunctioning.
- Diseases linked to adrenal dysfunction include Addison disease and Cushing syndrome.

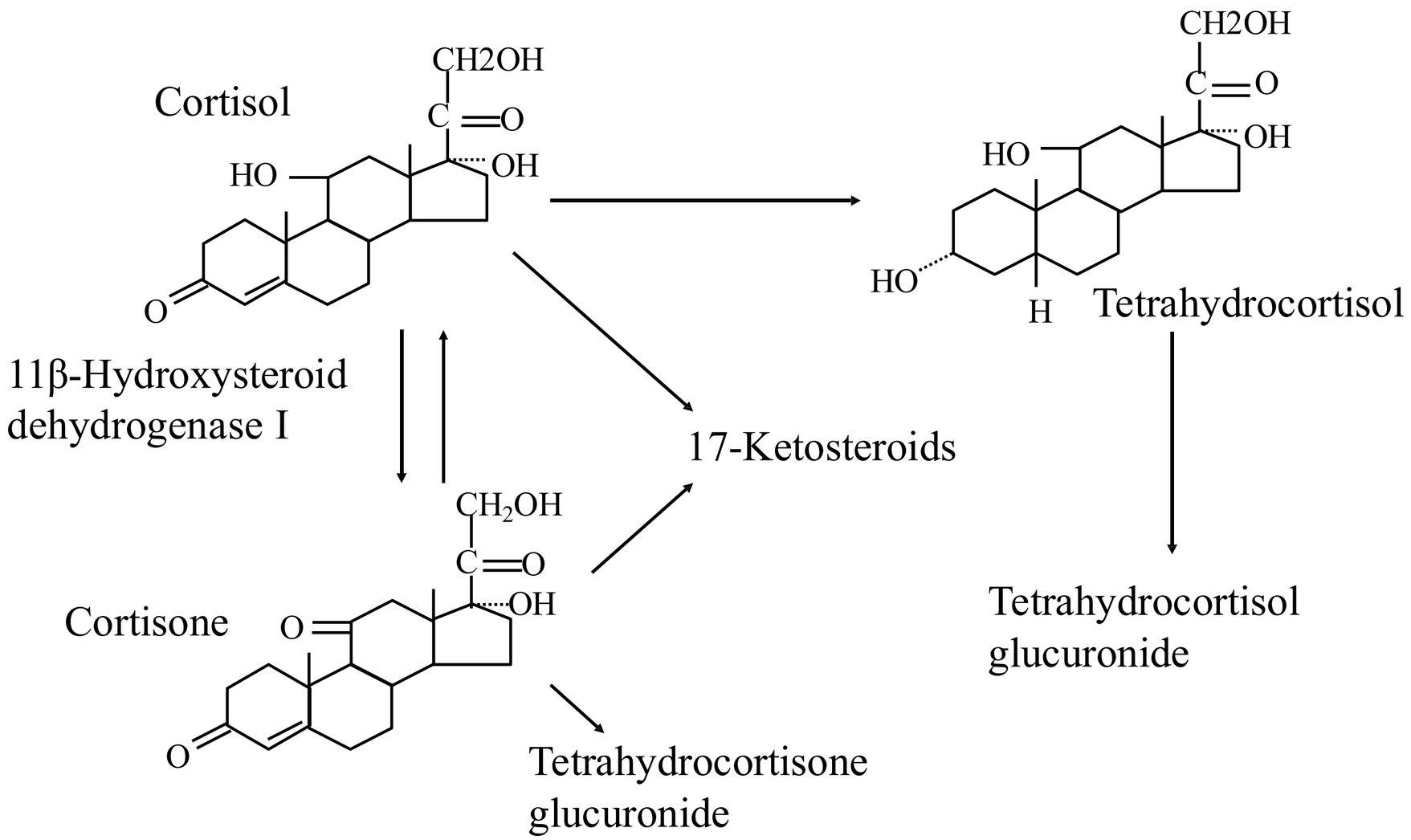
Addison disease (primary adrenal insufficiency)

- If **atrophy affects both adrenal glands** (as in autoimmune adrenal disease), the adrenal cortex stops producing cortisol, or its production decreases significantly. As a result, the **negative feedback inhibition** normally exerted by cortisol on the anterior pituitary is lost. This causes the pituitary gland to increase the synthesis and secretion of **ACTH**. ACTH is produced from the precursor **proopiomelanocortin (POMC)**, which also gives rise to **MSH (melanocyte-stimulating hormone)**. The elevated levels of ACTH and MSH stimulate melanocytes to produce more **melanin**, resulting in **hyperpigmentation** of the skin and mucous membranes.

Cortisone vs. Hydrocortisone: Activation and Use

- Cortisone and hydrocortisone are **not the same**.
- Cortisone is **a *prodrug***, meaning it must be converted into **hydrocortisone** (also called *cortisol*) in the ***liver*** to become **active**.
- **Hydrocortisone is the active form** and is **effective** when used **topically**, while **cortisone** is **less effective on the skin** because it requires **metabolic activation.**

Hepatic Metabolism of Cortisol



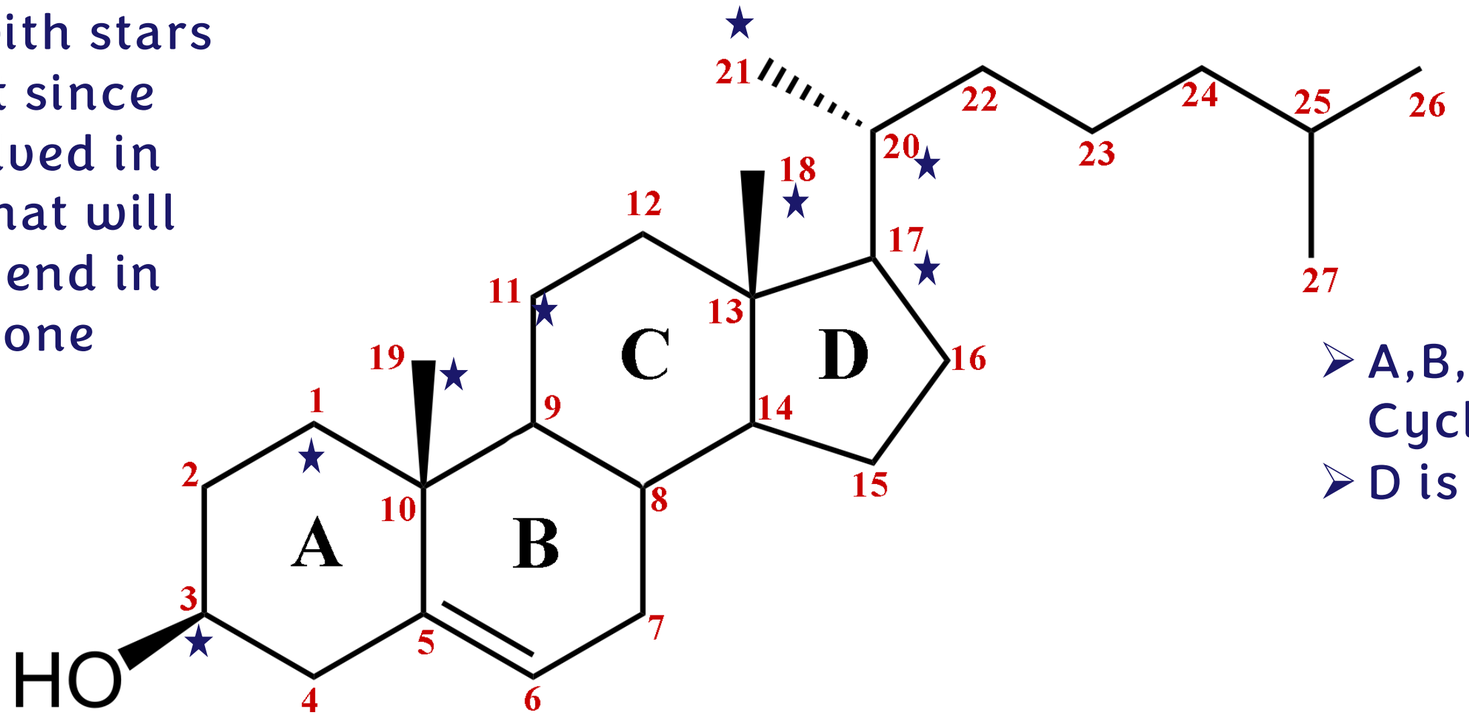
Gonane Structure, Steroidogenesis, and Steroid Terminology

- **Gonane** is the **core steroid nucleus**, a fundamental structural unit found in many steroid compounds, including hormones. It consists of **four fused rings, three cyclohexane rings and one cyclopentane ring**, and contains **17 carbon** atoms. Gonane serves as the parent structure from which **other steroids**, such as androstane and estrane**, are derived.**

- The side-chain cleavage enzyme (SCC), also known as cholesterol desmolase **(this enzyme is activated by ACTH in the 3 zones of the cortex),** is a cytochrome P450 enzyme. This enzyme converts cholesterol into pregnenolone, a key step in steroidogenesis, and plays a critical role in placental progesterone synthesis.

- The word "glucocorticoid" combines glucose, cortex, and steroid, reflecting its function in glucose metabolism, its origin in the adrenal cortex, and its steroidal nature. This same naming principle applies to mineralocorticoids.

- The carbon atoms that are marked with stars are important since they are involved in metabolism that will results in the end in adrenal hormone production.



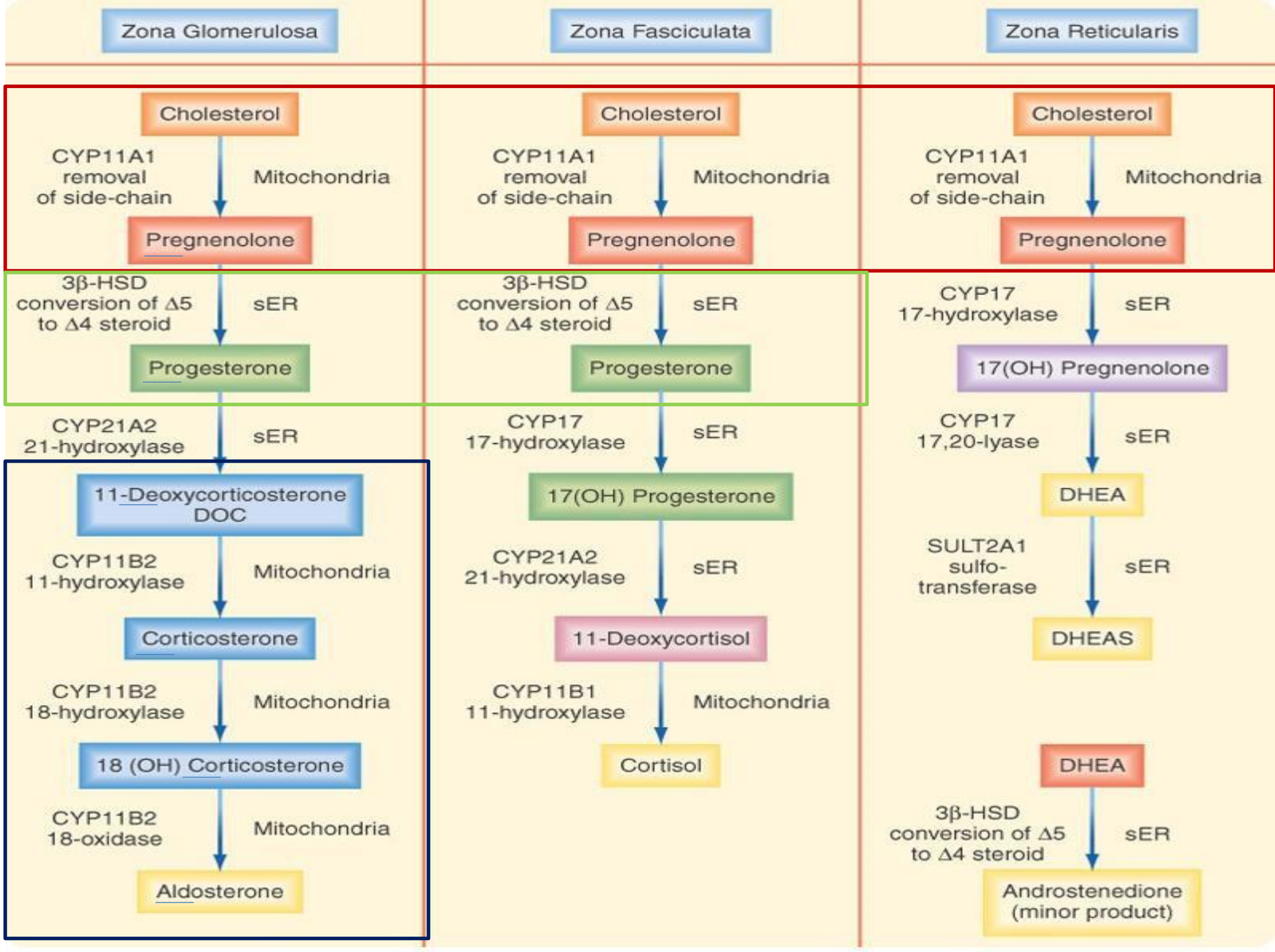
- A,B, and C are Cyclohexane.
- D is Cyclopentane.

- Shown in the figure is the chemical structure of **cholesterol**, a precursor molecule of steroid hormones.
  - Ring changes, double bonds, and functional groups (OH, CHO, ketones) define their class.

- This step is common in the production of all adrenal hormones, The downstream difference in the pathway is what determine the final hormone produced.

Aldosterone synthesis is catalyzed by the enzyme aldosterone synthase (CYP11B2), which carries out the final three steps of aldosterone biosynthesis in the zona glomerulosa of the adrenal cortex.

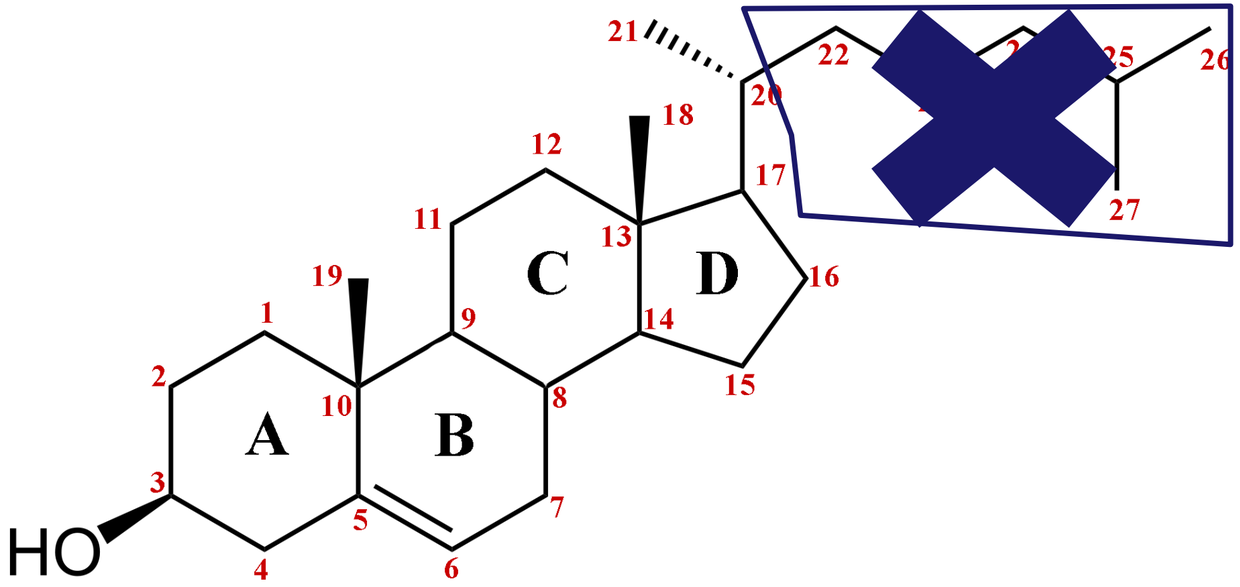
Pre → Pro → D → C → C → A

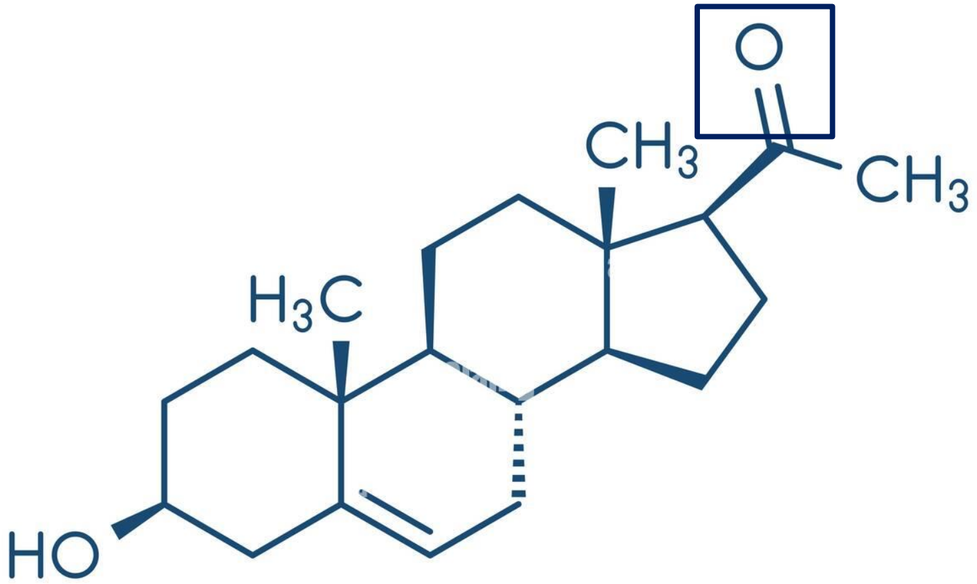


Cholesterol → pregnenolone

This is a common step between all three pathways for different adrenal hormones synthesis

- By Cytochrome P450 Enzyme
  (known as Cholesterol Desmolase)



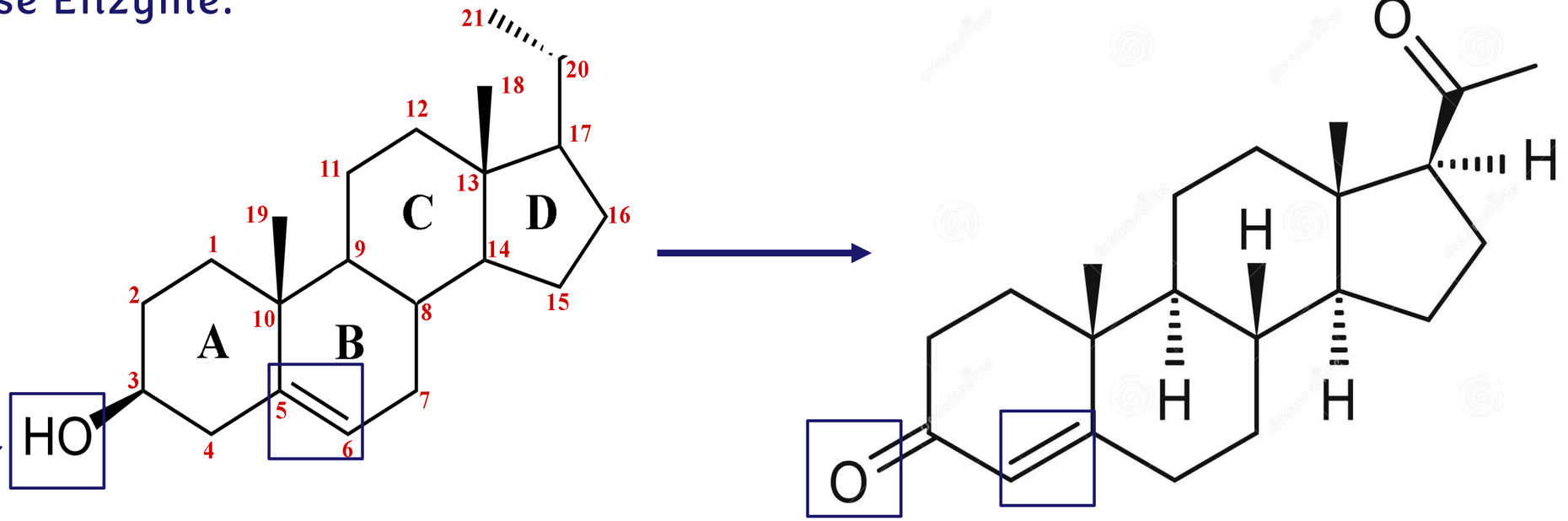


Pregnenolone → Progesterone

This is a common step between Aldosterone synthesis (glomerulosa) and cortisol synthesis (Fasciculata)

- By Hydroxysteroid dehydrogenase Enzyme.

Dehydroxylation



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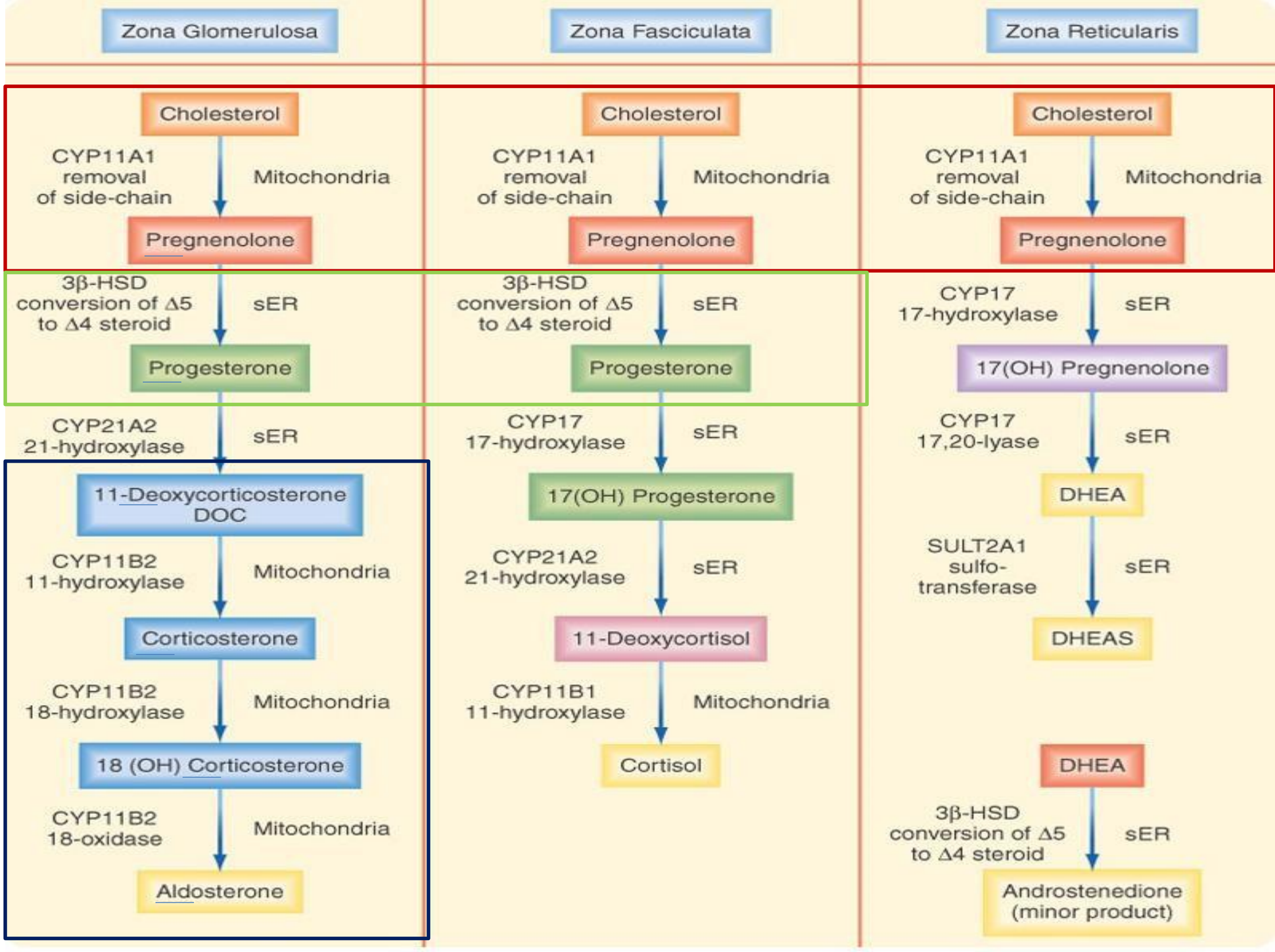
Pre → Pro → D → C → C → A



Explanation of the Diagram

In the Zona Glomerulosa (leftmost column): making Aldosterone

Boxed in **blue**, this pathway has 6 steps after cholesterol:

1) **Pregnenolone → Progesterone**
   - Enzyme: 3β-HSD (3-beta-hydroxysteroid dehydrogenase), converts a Δ5 steroid to a Δ4 steroid
   - Location: sER

2) **Progesterone → 11-Deoxycorticosterone (DOC)**
   - Enzyme: CYP21A2 (21-hydroxylase)
   - Location: sER

3) **DOC → Corticosterone**
   - Enzyme: CYP11B2 (11-hydroxylase activity)
   - Location: mitochondria

4) **Corticosterone → 18(OH) Corticosterone**
   - Enzyme: CYP11B2 (18-hydroxylase activity)
   - Location: mitochondria

5) **18(OH) Corticosterone → Aldosterone**
   - Enzyme: CYP11B2 (18-oxidase/aldosterone synthase activity)
   - Location: mitochondria

the last 3 steps (in the diagram not the nervy text that I have wrote) are all done by the *same enzyme*, CYP11B2 – commonly nicknamed "aldosterone synthase." This enzyme is unique to the zona glomerulosa. No other zone has it, which is exactly why only this zone can produce aldosterone. This is the molecular reason aldosterone production is zone-restricted.

Pre → Pro → D → C → C → A

(Pregnenolone → Progesterone → DOC → Corticosterone → 18-OH Corticosterone → Aldosterone).

Explanation of the Diagram

In the Zona Fasciculata (middle column): making Cortisol

1) **Pregnenolone → Progesterone**
   - Enzyme: 3β-HSD
   - Location: sER

2) **Progesterone → 17(OH) Progesterone**
   - Enzyme: **CYP17** (17-hydroxylase activity)
   - Location: sER

3) **17(OH) Progesterone → 11-Deoxycortisol**
   - Enzyme: CYP21A2 (21-hydroxylase)
   - Location: sER

4) **11-Deoxycortisol → Cortisol**
   - Enzyme: **CYP11B1** (11-hydroxylase)
   - Location: mitochondria

Pre → Pro → 17HydroxyP → D → C

(Pregnenolone → Progesterone → 17(OH)Progesterone → Deoxycortisol → Cortisol.

- Notice this zone has **CYP17, which the glomerulosa lacks — that single enzyme difference is what diverts the pathway away from aldosterone and toward cortisol**. Also note it uses **CYP11B1** (not CYP11B2) **for the final hydroxylation** — a different isoform than the glomerulosa uses, and **CYP11B1 stops at cortisol; it can't do the extra 18-hydroxylation/oxidation steps that CYP11B2 does.**

Explanation of the Diagram

In the Zona Reticularis (rightmost column): making Androgens

1) **Pregnenolone → 17(OH) Pregnenolone**
   - Enzyme: CYP17 (17-hydroxylase activity)
   - Location: sER

2) **17(OH) Pregnenolone → DHEA**
   - Enzyme: CYP17 (**17,20-lyase** activity – same enzyme, different catalytic function)
   - Location: sER

3) **DHEA → DHEAS**
   - Enzyme: SULT2A1 (sulfotransferase – adds a sulfate group)
   - Location: sER
   - ❖ **Note : DHEA can be turned into testosterone in the testis.**
   - ❖ **The problem that arise is that the DHEA, which it's function still hasn't been clearly defined, is the most abundant steroid in our body.**

Pre → Pro → DHEA → DHEAS→ DHEA →A

(Pregnenolone → Progesterone → DHEA → DHEAS → Androstenedione.

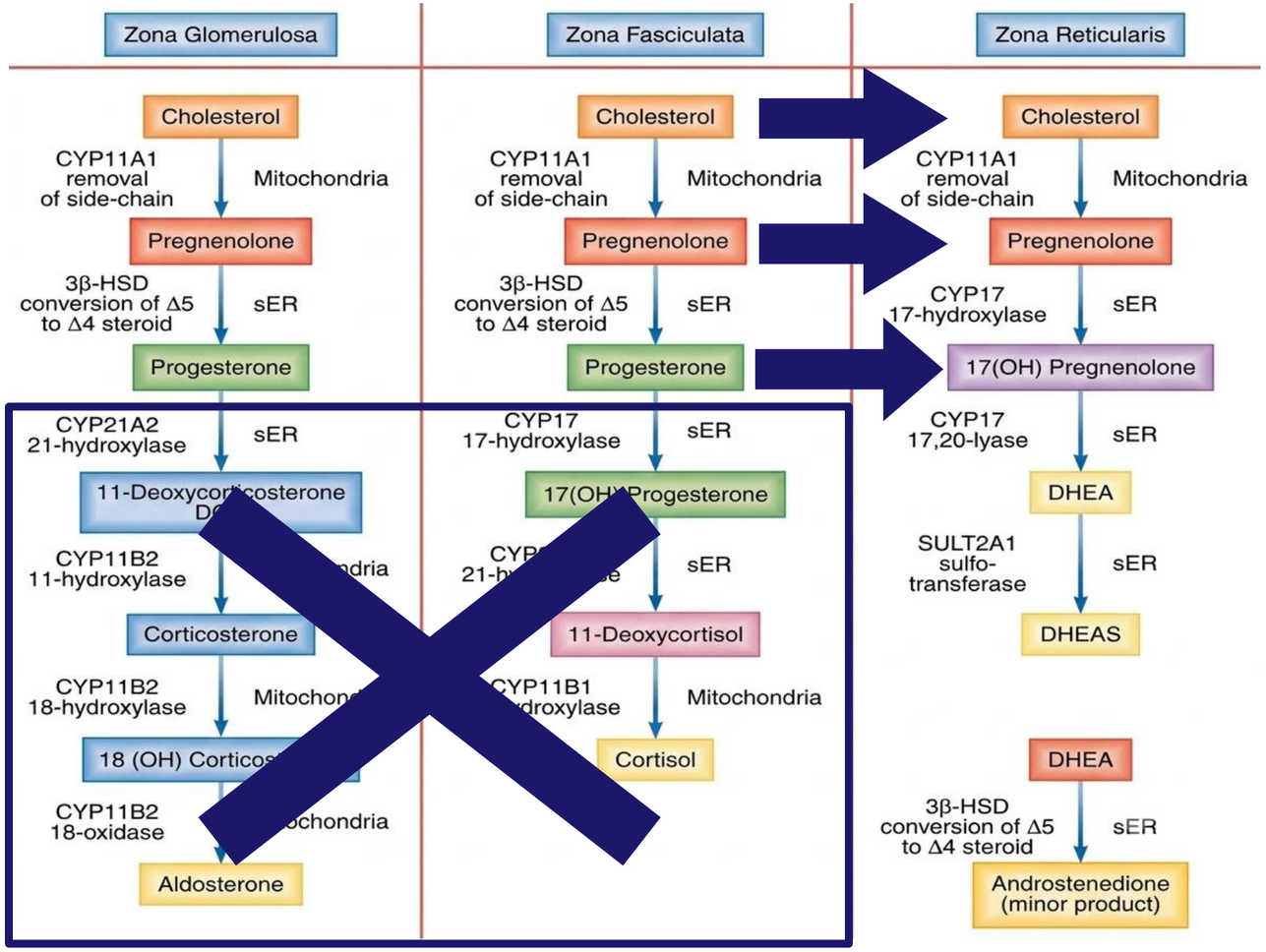
4) **DHEAS → back to DHEA → Androstenedione** (minor product)
   - Enzyme: 3β-HSD
   - Location: sER

This zone has the **highest CYP17 activity**, and critically it has strong **17,20-lyase activity** (the second function of CYP17), which the fasciculata has much less of. **This lyase activity is what strips off the side chain to make DHEA – an androgen precursor. This is why the reticularis is androgen-producing rather than glucocorticoid-producing, even though it also uses CYP17.**

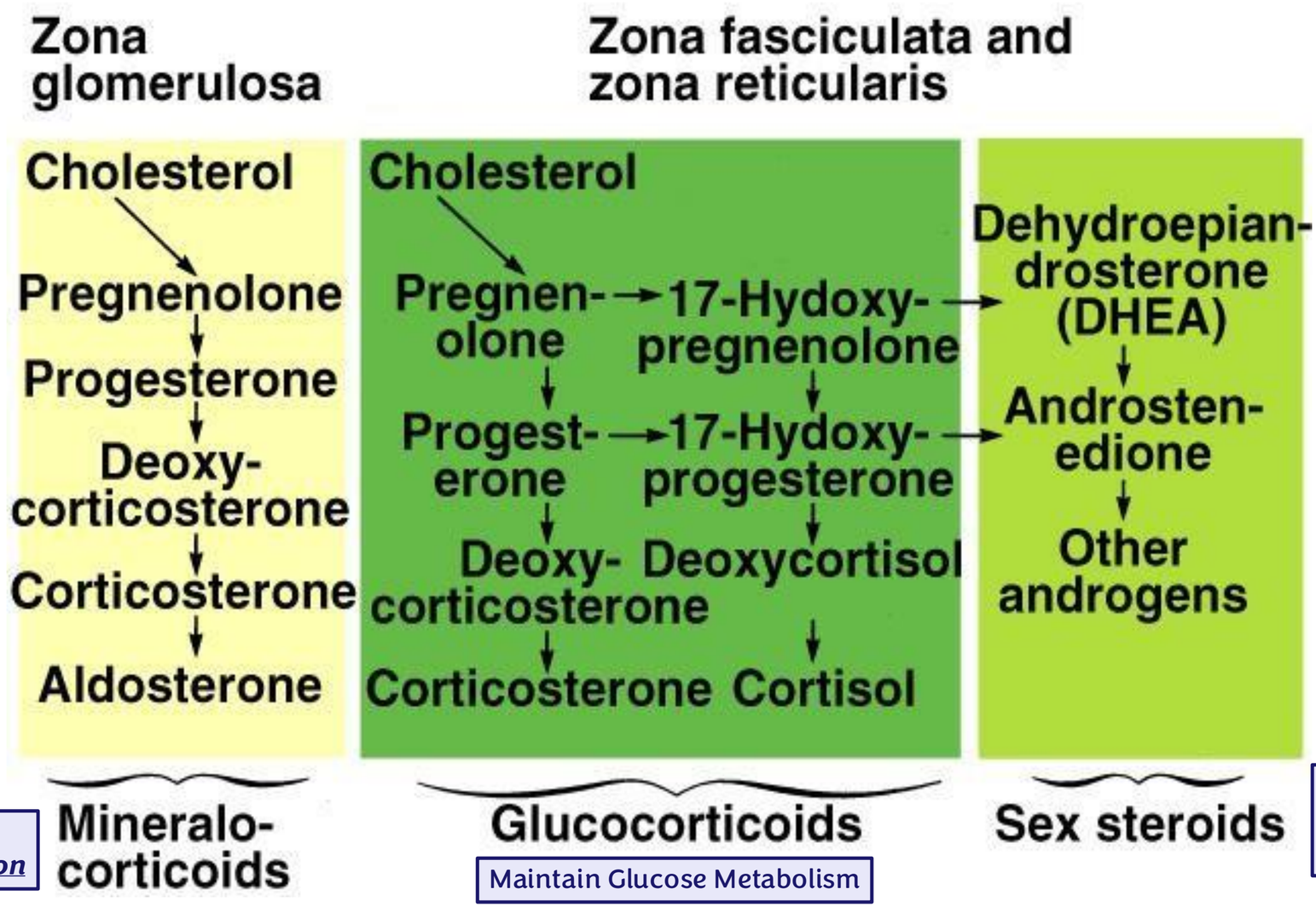
Explanation of the Diagram

- Let's consider a person who is having a deficiency in the **enzyme CYP21A2 (21-Hydroxylase)**, this will result in **inhibition of the production of DOC (Deoxycorticosterone) in the zona glomerulosa and Deoxycortisol in the zona fasiculata pathway.**

- The pathway will be **directed towards the synthesis of Androstenedione** which will result in very high concentrations of DHEA, DHEAS and Androstenedione.



Functions of the Adrenal Cortex



Causes :
Na+ Reabsorbtion / K+ Secretion

Maintain Glucose Metabolism

Causes production of:
Testosterone(Males)/ Estrogen(Females)

Actions of Cortisol

Cortisol has a complex relationship with insulin. Cortisol can inhibit insulin secretion from the pancreas and reduce insulin's effectiveness in facilitating glucose uptake by cells, by desensitization, leading to insulin resistance.

- Glucose metabolism, **it increases blood glucose.**
- Protein metabolism → Amino Acid
- Fat metabolism → Free Fatty acid

} Gluconeogenesis.

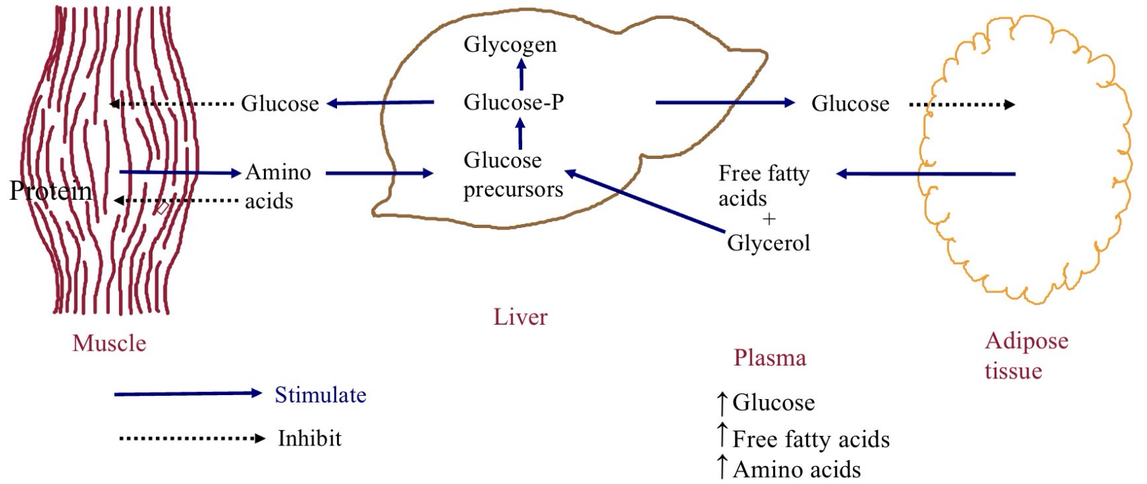
- Used mainly for its : Anti-inflammatory action **through inhibition of cycloxygenase which decreases prostaglandins.**

- Psychic effect
- **Permissive effect,**

Enhancing the actions of epinephrine and norepinephrine by expressing adrenergic receptors on target cells; this leads to remarkable effects in fight-or-flight response, increasing blood glucose (by glycogenolysis) and blood pressure (via alpha-1 receptors on blood vessels).

Metabolic Effects of Cortisol

Focus on the arrows; notice that cortisol breaks down triglycerides and protein (wasted muscle mass, especially proximally), making for increased glucose in the blood and filling glycogen stores to get ready for any need.



- **Cortisol increases blood glucose levels** through several mechanisms.
- The **liver converts amino acids into glucose**, a process called **gluconeogenesis**.
- Cortisol also acts on **skeletal muscle**, causing **protein breakdown**. The released **amino acids** are transported to the liver, where they are converted into glucose through **gluconeogenesis**.

Catabolic Effects of Cortisol

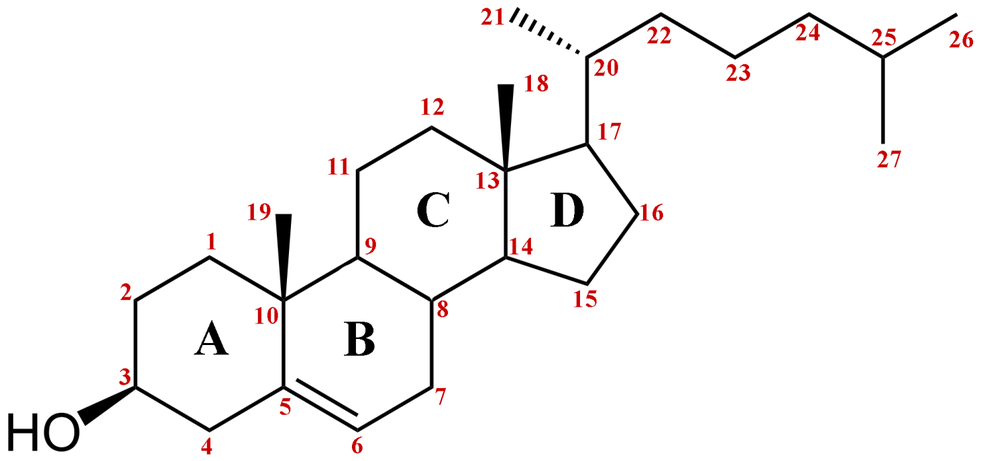
- **In adipose tissue:**
  - **Inhibits glucose uptake**, keeping more glucose in the bloodstream.
  - **Increases lipolysis, releasing fatty acids** which are going to be used as a **source of energy** and **glycerol** which is going to be used in **gluconeogensis**.

- **In skeletal muscle:**
  - **Inhibits glucose uptake.**
  - **Increases protein breakdown**, releasing amino acids.
  - This leads to **muscle weakness**, especially of the **proximal muscles**.
- The amino acids released from muscle are transported to the **liver**, where they are converted into **glucose** via **gluconeogenesis**.
- Some of the newly produced glucose is then converted into **glycogen** and stored in the liver.

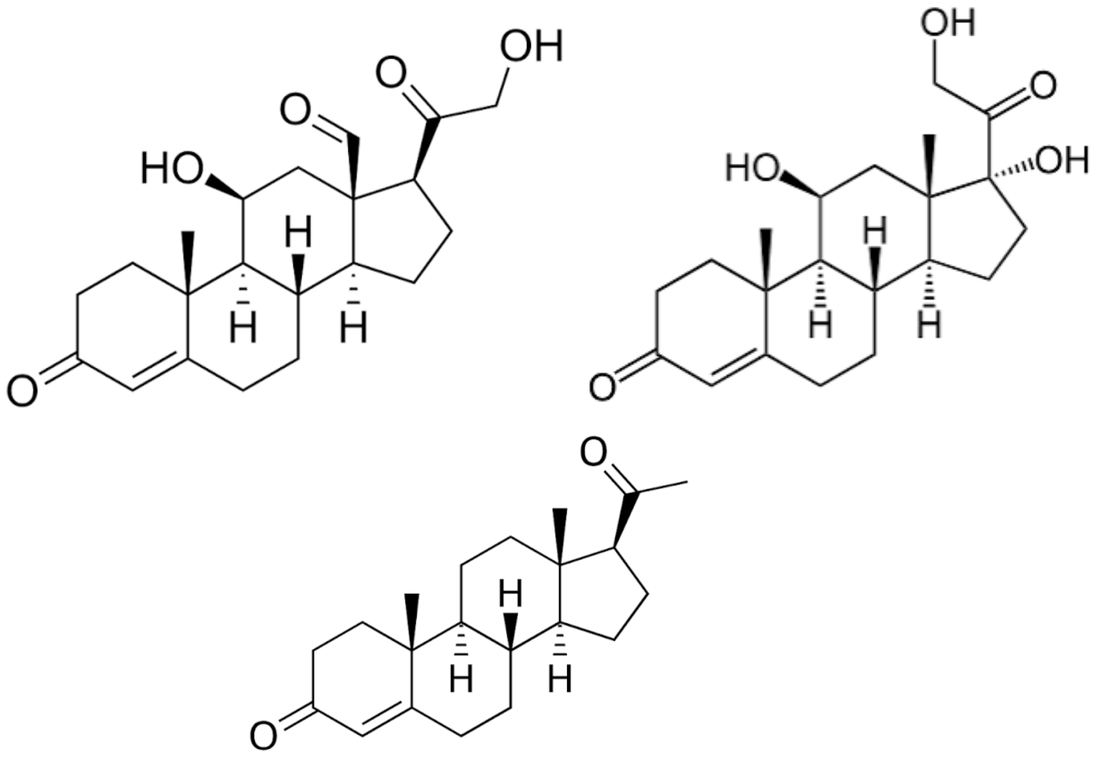
Why is glucose converted into glycogen?

- Although this may seem counterintuitive, during **stress**, **adrenaline (epinephrine)** is released.
- Adrenaline stimulates **glycogenolysis** (breakdown of glycogen into glucose).
- Therefore, cortisol **indirectly increases blood glucose** by promoting glycogen storage, which can later be rapidly broken down by adrenaline during stress.

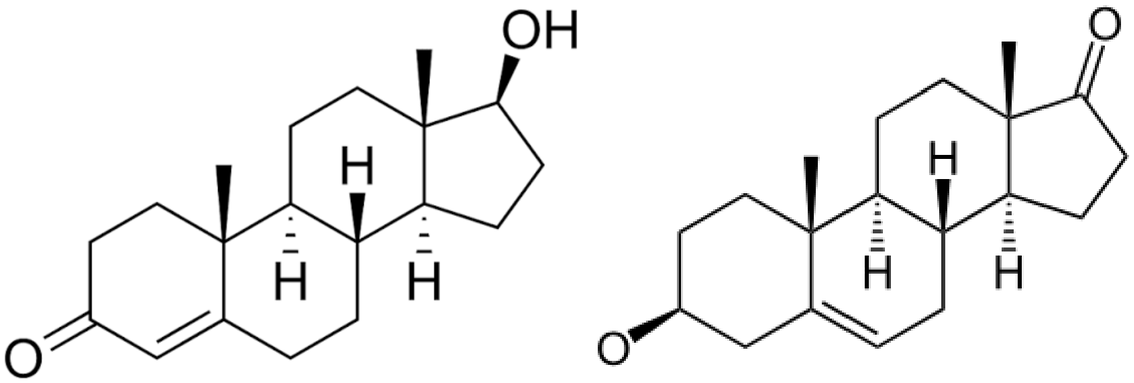
Important Note Regarding Cholesterol



Cholesterol (27 carbon atom)



21 Carbon atom could be **Aldosterone, Progesterone & Cortisol**



19 Carbon atom could be **testosterone, DHEA.**

Important Note Regarding Cholesterol

- steroids in our body are categorized into :

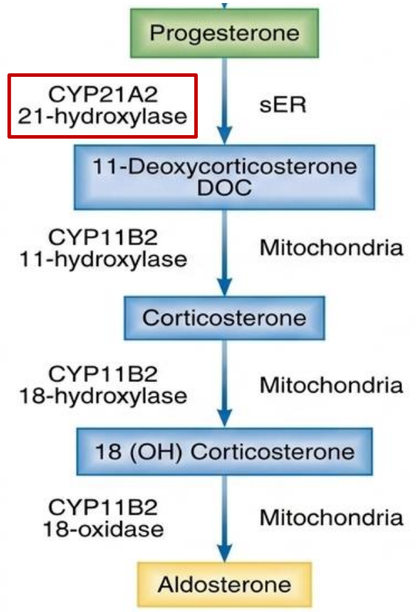
  - **18 carbons steroids such as estrogen**
  - **19 carbons steroids such as testosterone**
  - **21 carbon steroids such as progesterone, aldosterone and cortisol**

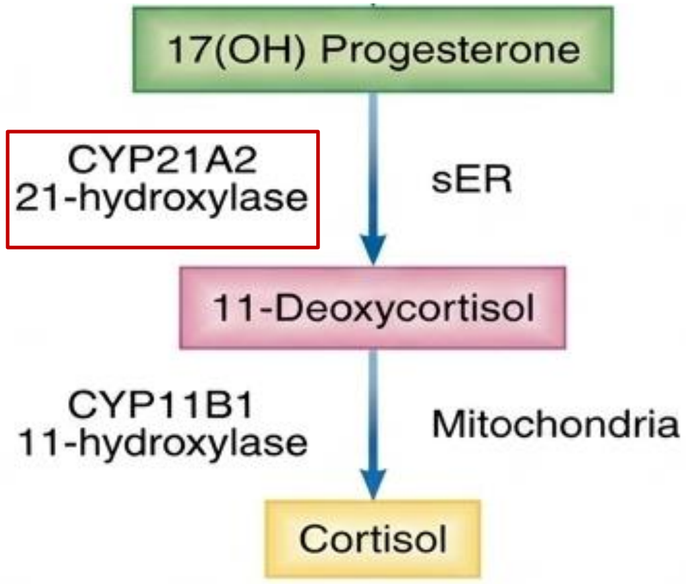
- Steroids with unusual carbon numbers are often synthetic. **An example is dexamethasone**, a synthetic steroid with 22 carbon atoms. It is a drug with a wide range of clinical uses and is **approximately 30 times more potent than cortisol.**

Common Enzyme Deficiencies

- **21-hydroxylase** deficiency accounting **for >90% of cases.**

This condition leads to **deficient production of cortisol and aldosterone.** As a result, **ACTH levels increase due to loss of negative feedback.** Elevated ACTH stimulates **adrenal steroidogenesis, shunting precursors toward DHEA and other androgens.** This causes **adrenal cortex hyperplasia (called congenital adrenal cortex hyperplasia since it is genetic)** and **excess androgen production**, which may manifest as **virilization** in females and **precocious puberty** in males.

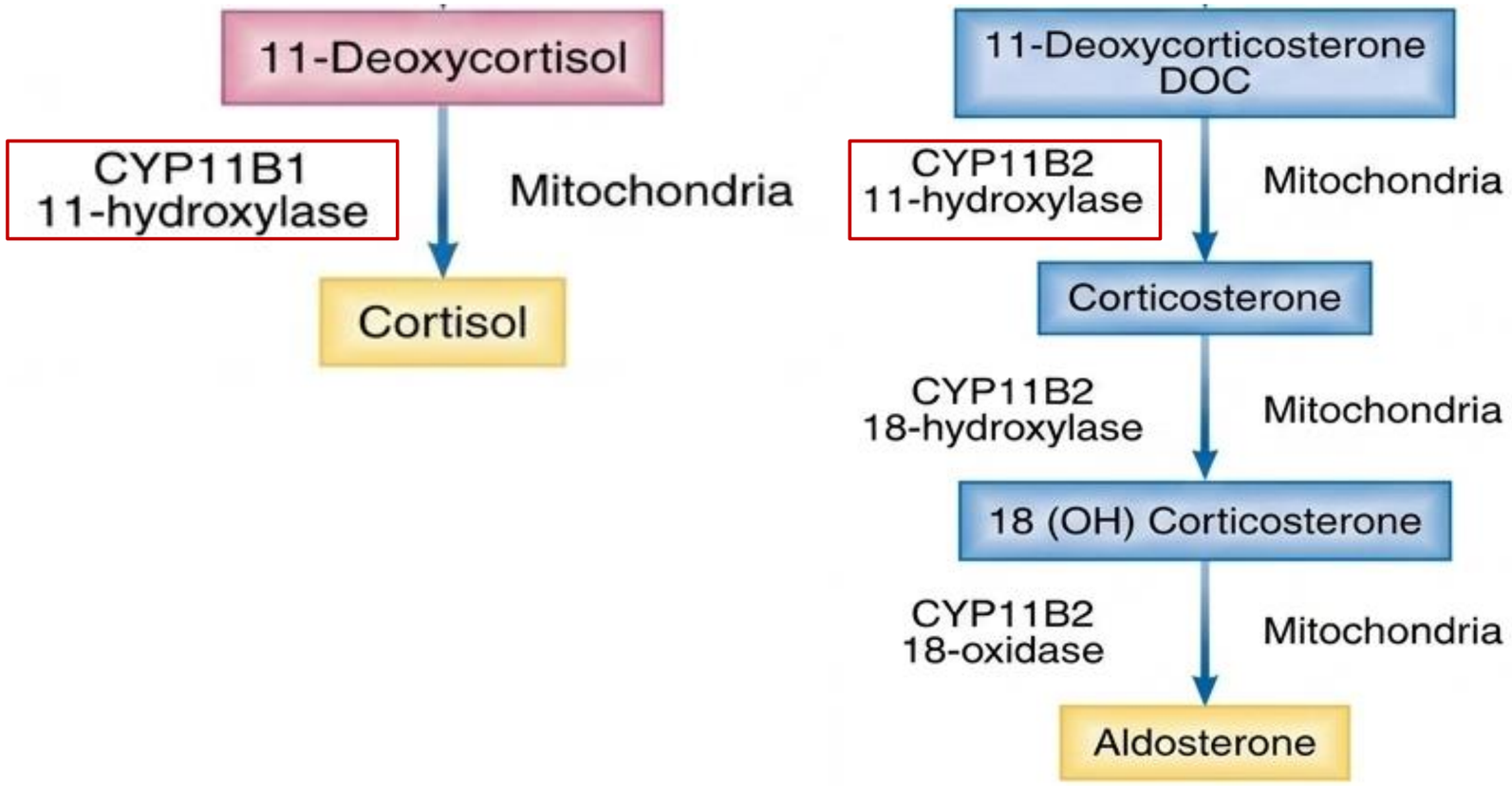




Common Enzyme Deficiencies

- **11-β-hydroxylase** deficiency accounting **for 9% of cases.**

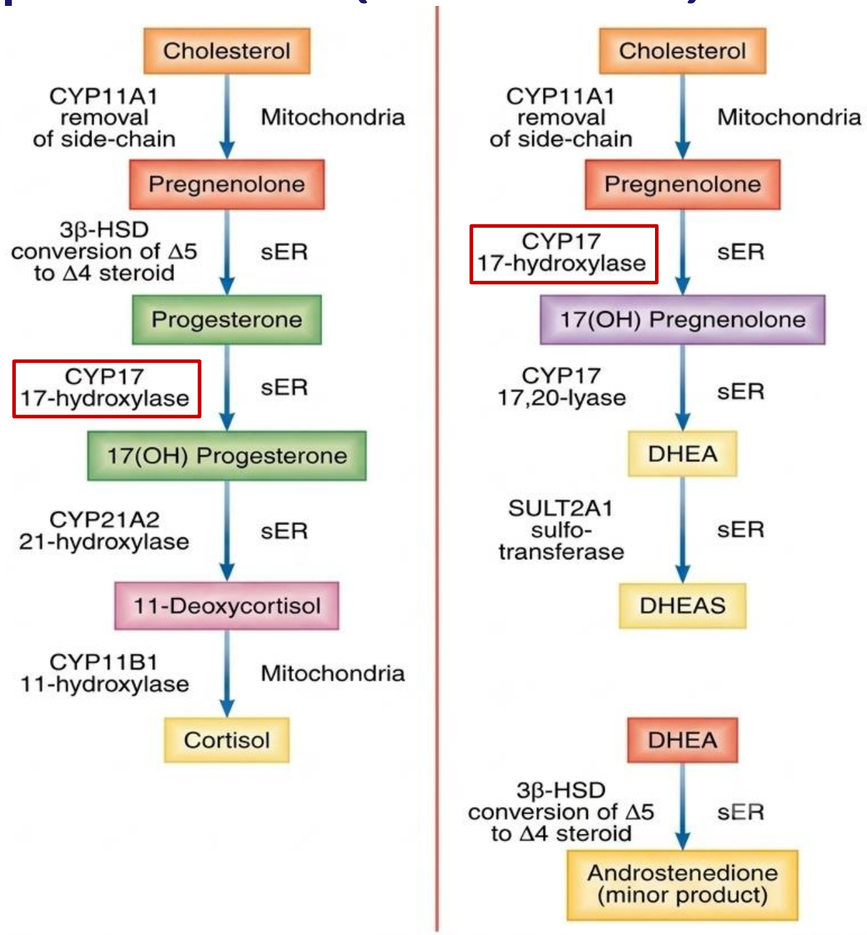
- **Less significant than 21-B-Hydroxylase** deficiency, because DOC can function as a week aldosterone (has mineral corticosteroids activity)
- 1 Aldosterone = 3000 Corticosteroid activity
- 1 DOC = 1 Corticosteroid activity



Common Enzyme Deficiencies

- **17-hydroxylase** deficiency accounting **for 1% of cases.**

The body cannot synthesize cortisol or androgens (see the pathway). This leads to accumulation of aldosterone and thus hypertension (see slide 41).



Stages of Adrenal Cortical Insufficiency

Either hyper-functioning or hypo-functioning.

- **Primary adrenal cortical insufficiency** (Addison's disease)
  - **ACTH levels are elevated** because of **lack** of **feedback inhibition.**
  - Could be due to TB infection of the adrenal gland (not common now), Autoimmune diseases or other causes that leads to adrenal crisis.
- Death can occur due to this case due to :
  1) Decreased reabsorption of Na+ due to aldosterone deficiency.
  2) Being exposed to severe stress.

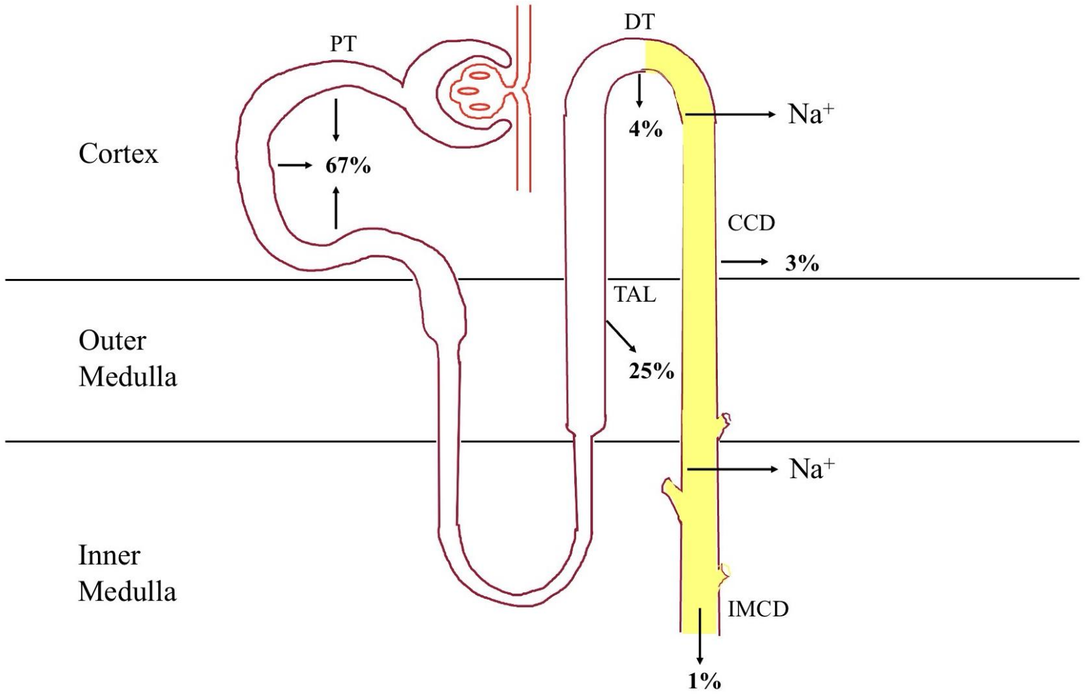
Tubular Effects of Aldosterone

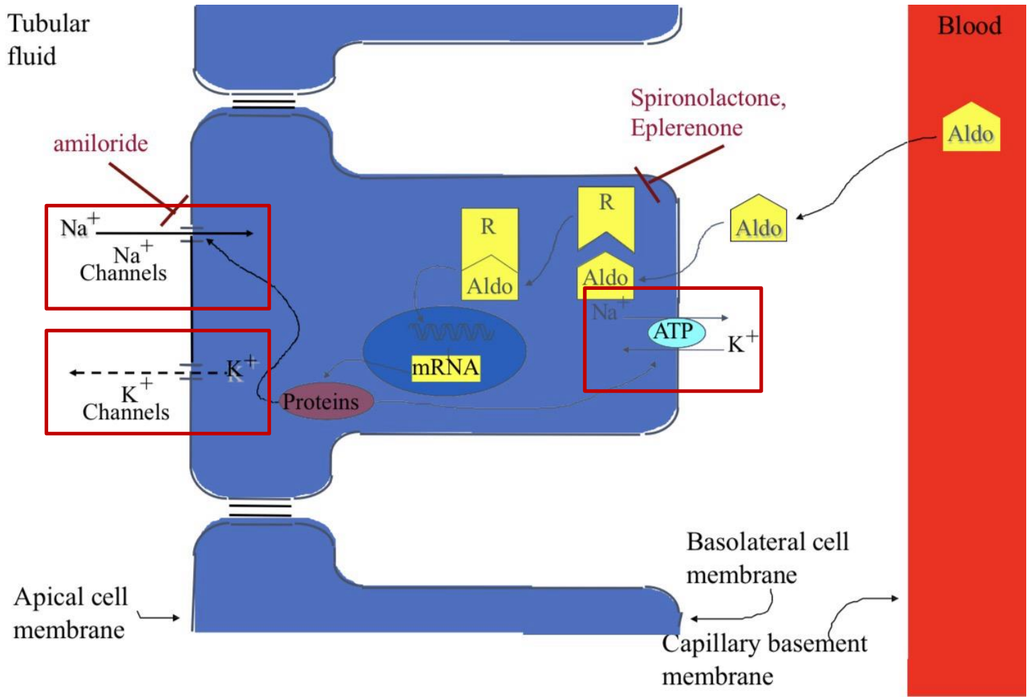
The kidneys contain about **one million nephrons each**, so both kidneys together contain about **two million nephrons**.

❖ Each nephron consists of:
- **Bowman's capsule**
- **Proximal convoluted tubule (PCT)**
- **Loop of Henle**
- Descending limb
- Ascending limb (thin and thick segments)
- **Distal convoluted tubule (DCT)**
  - In the **distal tubule**, each epithelial cell has: A **luminal (apical) side**, facing the tubular lumen.
  - A **basolateral side**, facing the blood capillaries (interstitium).

❖ **Aldosterone** arrives from the bloodstream and enters the epithelial cell.
❖ Because aldosterone is a **steroid hormone**, it is **lipid-soluble** and can cross the cell membrane by **simple diffusion**.
❖ Inside the cell, aldosterone binds to its **intracellular receptor**. The aldosterone-receptor complex then undergoes **translocation** into the nucleus, where it binds to **specific DNA sequences**.
❖ This stimulates **transcription**, producing **mRNA**, which is then translated by **ribosomes** into proteins.

These proteins may include:
- **Sodium (Na^+) channels**
- **Potassium (K^+) channels**
- **Na^+/K^+ ATPase pumps**





Cellular Actions of Aldosterone on Principal Cells of Collecting Tubules

Looking at the diagram:

- Aldosterone comes from the **blood** into the **interstitium**.
  - It easily crosses the cell membrane.
  - It binds to its intracellular receptor.

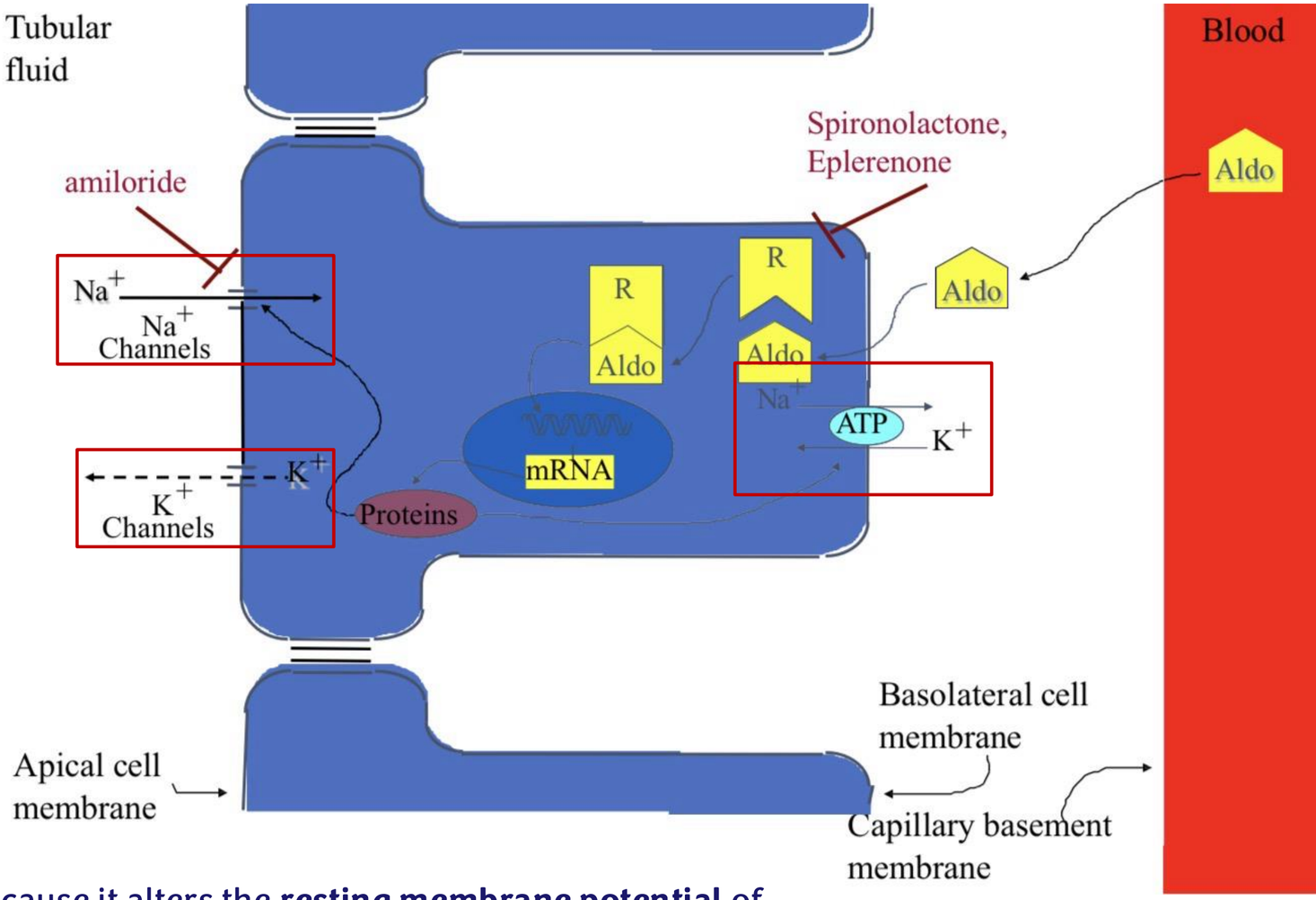
- The hormone–receptor complex enters the nucleus.
- It activates specific DNA sequences.
- DNA is transcribed into **mRNA**.
- mRNA is translated into proteins such as sodium channels, potassium channels, and sodium–potassium pumps.

The diagram also shows the **tubular lumen** on one side and the **interstitium** on the other.
As a result, aldosterone:

- **Increases sodium reabsorption** from the tubular lumen into the blood.
- **Increases potassium secretion** from the blood into the tubular lumen.

Therefore, if aldosterone is absent:

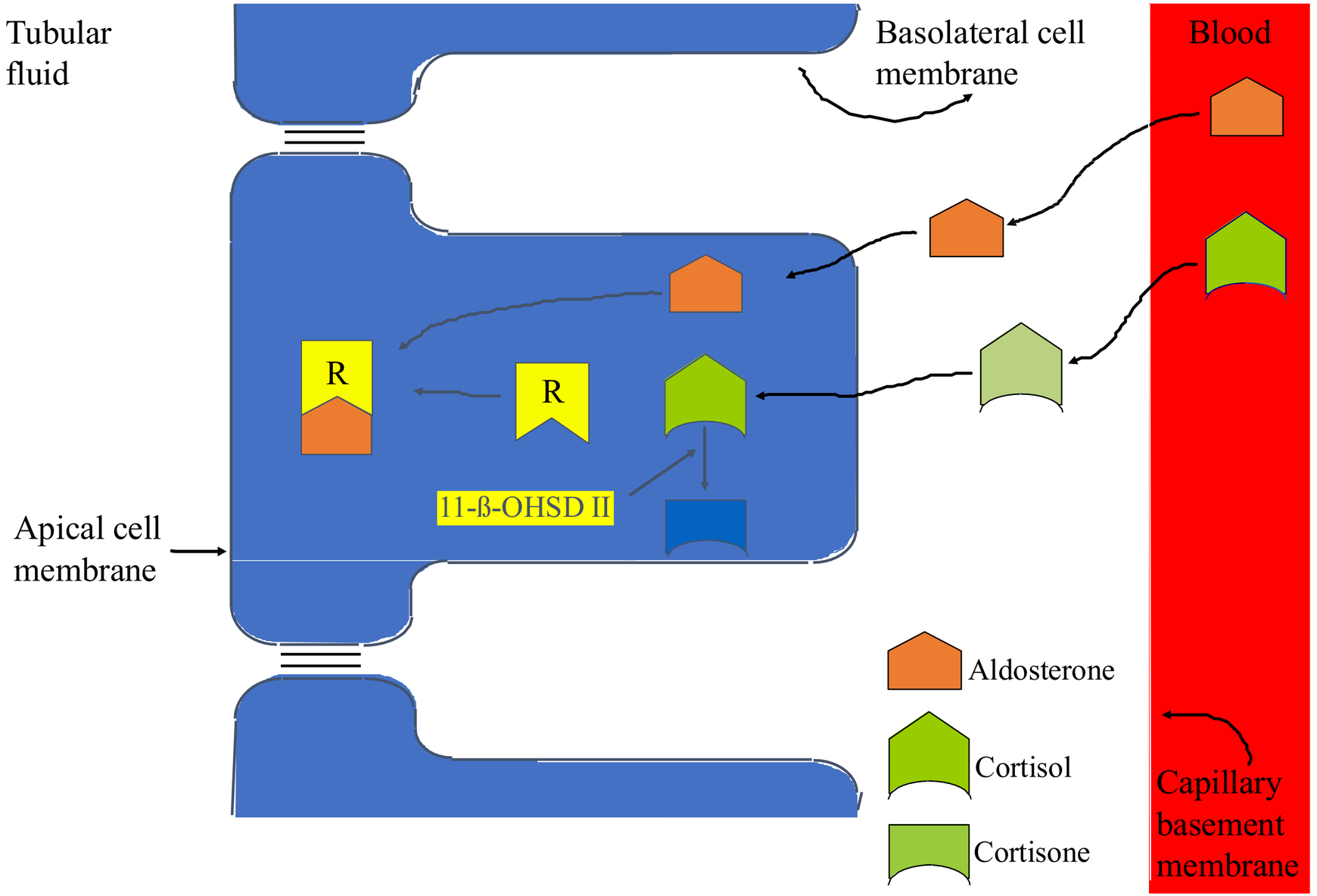
- Sodium is **not reabsorbed**, so excessive amounts are lost in the urine.
- Potassium is **not secreted**, leading to **hyperkalemia**.



Hyperkalemia is very dangerous, especially for the heart, because it alters the **resting membrane potential** of cardiac cells and changes the **excitability of the heart**.

The prof. skipped this.

Mechanism for Aldosterone Specificity in Target Cells



Stages of Adrenal Cortical Insufficiency

- **Secondary adrenal cortical insufficiency**
  - Occurs as a result of **hypopituitarism** (due to the presence of non- functioning tumor)or **because pituitary gland has been surgically removed.**
  - **You can distinguish clinically between primary and secondary adrenal insufficiency by looking at skin and mucus membrane colors :**
    - **Hyperpigmentation → primary since it is elevated ACTH (a combined with elevated MSH).**
    - **Hypopigmentation → No elevation in ACTH (and MSH).**
- **Acute adrenal crisis**
  - Life-threatening situation occurs. Lack of cortisol can cause shock with 20% death rate. (Next Slide)

Stages of Adrenal Cortical Insufficiency

- **Acute adrenal crisis**
  - Life-threatening situation occurs. Lack of cortisol can cause shock with 20% death rate.

➢ Suppose a patient has been receiving **cortisol (glucocorticoid) therapy** for a long time—for example, **six months**—because they have some type of **autoimmune disease**.

➢ Cortisol is a very potent **anti-inflammatory** drug. In some autoimmune diseases, there is no specific cure, so we use **non-specific treatment**, such as corticosteroids, to suppress inflammation.
For example:
- **Glomerulonephritis**
- **Nephrotic syndrome**
- **Systemic lupus erythematosus (SLE)**

In these conditions, corticosteroids often improve the patient's symptoms and reduce inflammation. However, they are **not always a disease-specific or definitive treatment**; they mainly suppress the inflammatory process.

Now imagine that, for some reason, the patient suddenly **stops taking cortisol**.

This is dangerous why?

Stages of Adrenal Cortical Insufficiency

• Acute adrenal crisis

➢ This is dangerous, why ?

- While the patient has been taking exogenous cortisol, the high cortisol level causes **negative feedback** on the hypothalamus and pituitary gland, suppressing the release of: **CRH (corticotropin-releasing hormone)** from the hypothalamus.
- **ACTH (adrenocorticotropic hormone)** from the anterior pituitary.

- As a result, the patient's own hypothalamic–pituitary–adrenal (HPA) axis becomes suppressed.
- If cortisol is stopped **abruptly**, there is: No exogenous cortisol.
- Suppressed CRH.
- Suppressed ACTH.

Therefore, the adrenal glands cannot immediately produce enough endogenous cortisol, and the patient may develop an **acute adrenal crisis**, which is a medical emergency.

The mortality rate can be as high as **20%** if not treated promptly.

For this reason, **corticosteroids should never be stopped suddenly** after long-term therapy.

1. Instead, they must be **tapered gradually** according to a specific protocol: Reduce the dose gradually.
2. Then give the medication on alternate days if appropriate.
3. Continue tapering over several weeks (or longer, depending on the patient).

Stages of Adrenal Cortical Insufficiency

- **Acute adrenal crisis**

➢ This gradual taper (gradual stop of cortisol administration) allows:

- The **pituitary gland** to resume ACTH secretion.
- The **hypothalamus** to resume CRH secretion.
- The adrenal cortex to recover and return to its normal pattern of cortisol production.

Alterations of Adrenal Function

- Disorders of the adrenal cortex
  - Cushing disease
    - Excessive anterior pituitary secretion of ACTH
  - Cushing syndrome
    - Excessive level of cortisol, regardless of cause:
    1. Exogenous (Iatrogenic) – 90% of the time.
    2. Endogenous, such as tumors – less common.

These two disorders involve increased levels of cortisol. However, **Cushing disease** means that the problem resides in the anterior pituitary, where there is hypersecretion of ACTH. **Cushing syndrome**, on the other hand, refers to excessive cortisol regardless of the cause, whether it is exogenous (which accounts for most cases) or endogenous.
As the doctor said, **every disease is a syndrome, but not every syndrome is a disease.** What is meant here is that every person with hypersecretion of ACTH from the pituitary will experience Cushing syndrome. However, not every person with excessive cortisol has a pituitary problem.
The doctor also said that he will not focus much on the distinction between these terms.

Alterations of Adrenal Function

- Disorders of the adrenal cortex
  - Hyperaldosteronism

An aldosterone-secreting tumor

1. **Primary hyperaldosteronism (Conn disease)**

It could be a <u>tumor</u> in the adrenal cortex that increases the secretion of aldosterone. This will lead to excessive reabsorption of sodium and water from the distal tubule, which will eventually result in **hypervolemia** (an increase in blood volume) and **arterial hypertension.**
Since we know that aldosterone also increases the excretion of potassium, these patients will develop **hypokalemia** (low levels of potassium).

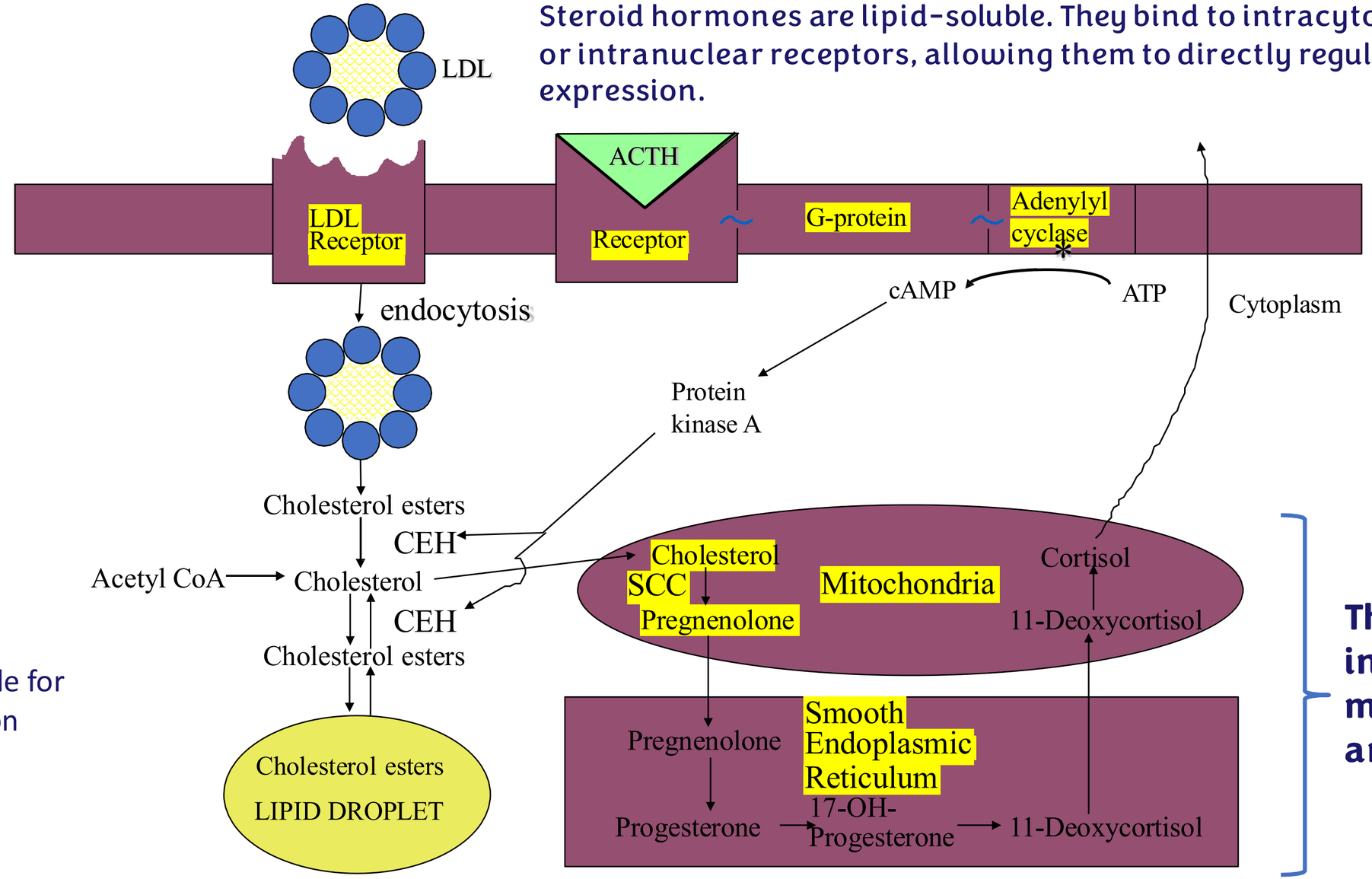
Therefore, if a patient presents with hypertension, you should test their potassium level. If it is low, you should perform imaging, such as a CT scan, to determine the underlying cause.

Alterations of Adrenal function

- **Secondary hyperaldosteronism: excess renin production due to** various conditions, including:
  - renal artery stenosis, decreasing renal perfusion
  - left heart failure,
  - liver failure,
  - cor pulmonale,
  - pregnancy,
  - renin-secreting tumor etc.

Steroid Hormone Synthesis and Secretion: Cholesterol Side-Chain Cleavage Pathway

Remember that ACTH is water-soluble. It binds to a specific cell surface receptor and uses cAMP as a second messenger. Steroid hormones are lipid-soluble. They bind to intracytoplasmic or intranuclear receptors, allowing them to directly regulate gene expression.



Go to the next slide for further explanation

The pathway includes both mitochondria and SER.

This image illustrates steroid hormone synthesis and secretion with regard to cortisol.

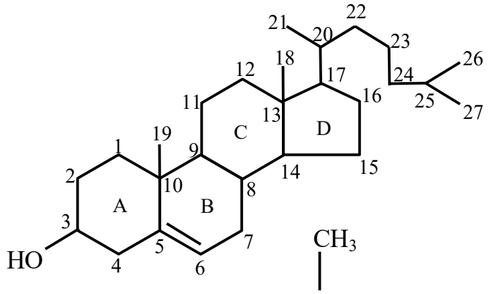
First, **cholesterol** enters the cell through LDL. It then enters the mitochondria, where **side-chain cleavage** occurs, producing **pregnenolone**. Pregnenolone then moves to the smooth endoplasmic reticulum (SER), where 3β-hydroxysteroid dehydrogenase converts it into **progesterone**. Progesterone is then converted into **17-hydroxyprogesterone,** which is further converted into **deoxycortisol.** Deoxycortisol re-enters the mitochondria, where it is converted into the final product, **cortisol**, which exits the cell by diffusion.

ACTH, through the cyclic AMP (cAMP) pathway, increases the activity of desmolase, the enzyme that catalyzes the first step. ACTH also increases the activity of aldosterone synthase.
A very important point to note is that the true negative feedback on ACTH secretion comes only from cortisol, not from aldosterone. Aldosterone does not exert negative feedback on ACTH secretion. Therefore, the **hypothalamic-pituitary-adrenal (HPA) axis is regulated through cortisol only.**

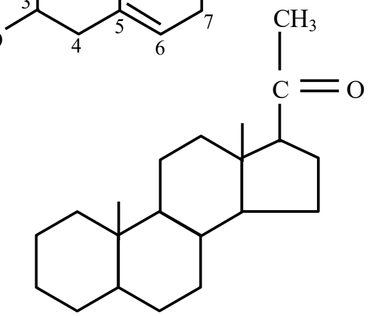
Basic Structure of Adrenocortical & Gonadal Steroids

Already discussed

Cholesterol
(27 carbons)

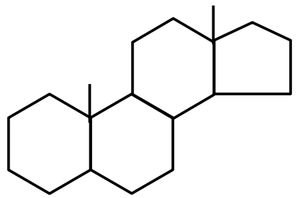


Pregnane derivatives
(21 carbons)



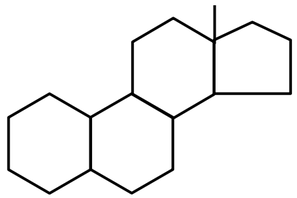
→ Progesterone
Corticoids

Androstane derivatives
(19 carbons)



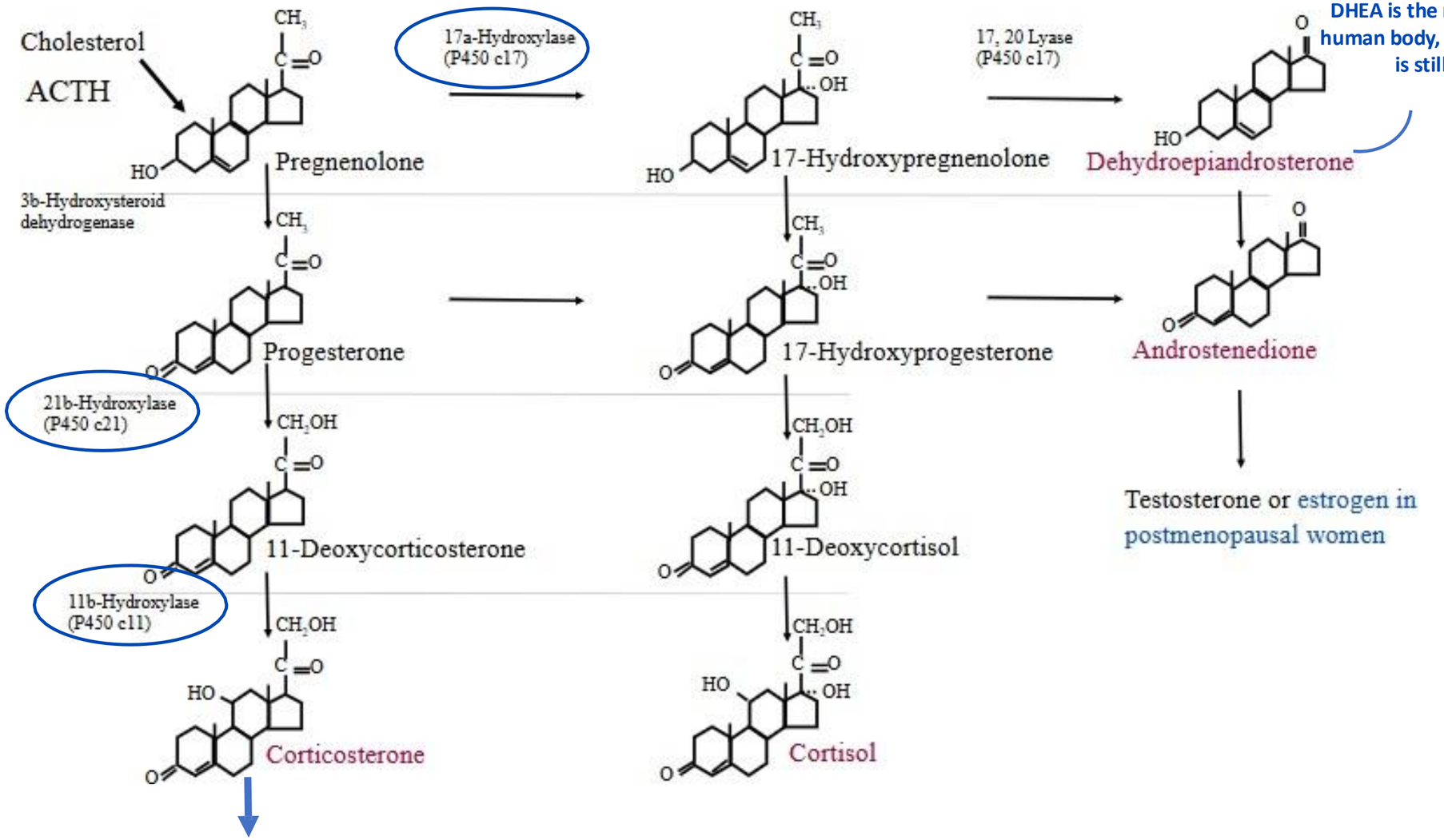
→ Androgens

Estrane derivatives
(18 carbons)



→ Estrogens

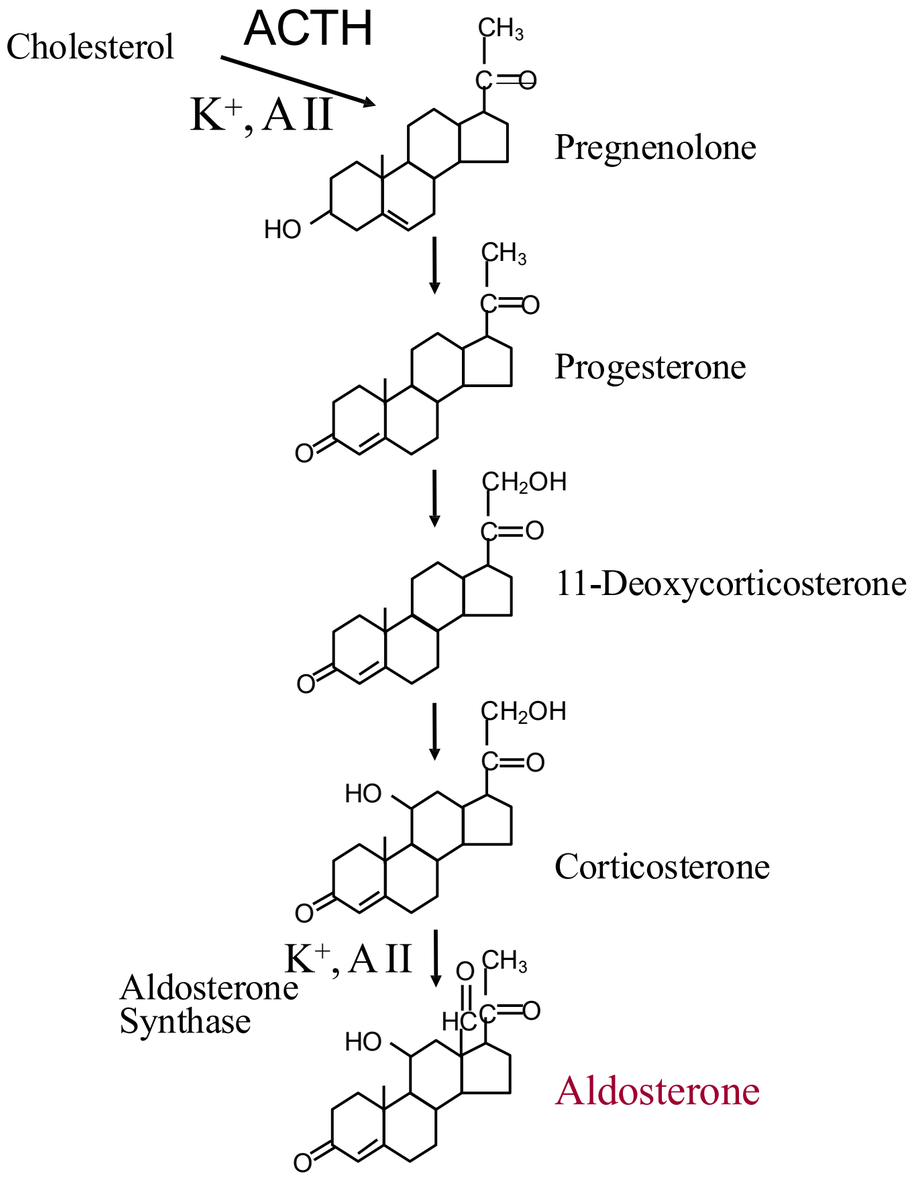
Hormone Biosynthesis in the Zona Fasciculata & Reticularis



DHEA is the most abundant steroid in the human body, although its physiological role is still not well understood.

This pathway ends with the synthesis of aldosterone.

Hormone Biosynthesis in the Zona Glomerulosa



Corticosteroids & Their Relative Glucocorticoid & Mineralocorticoid Activities Compared to Cortisol

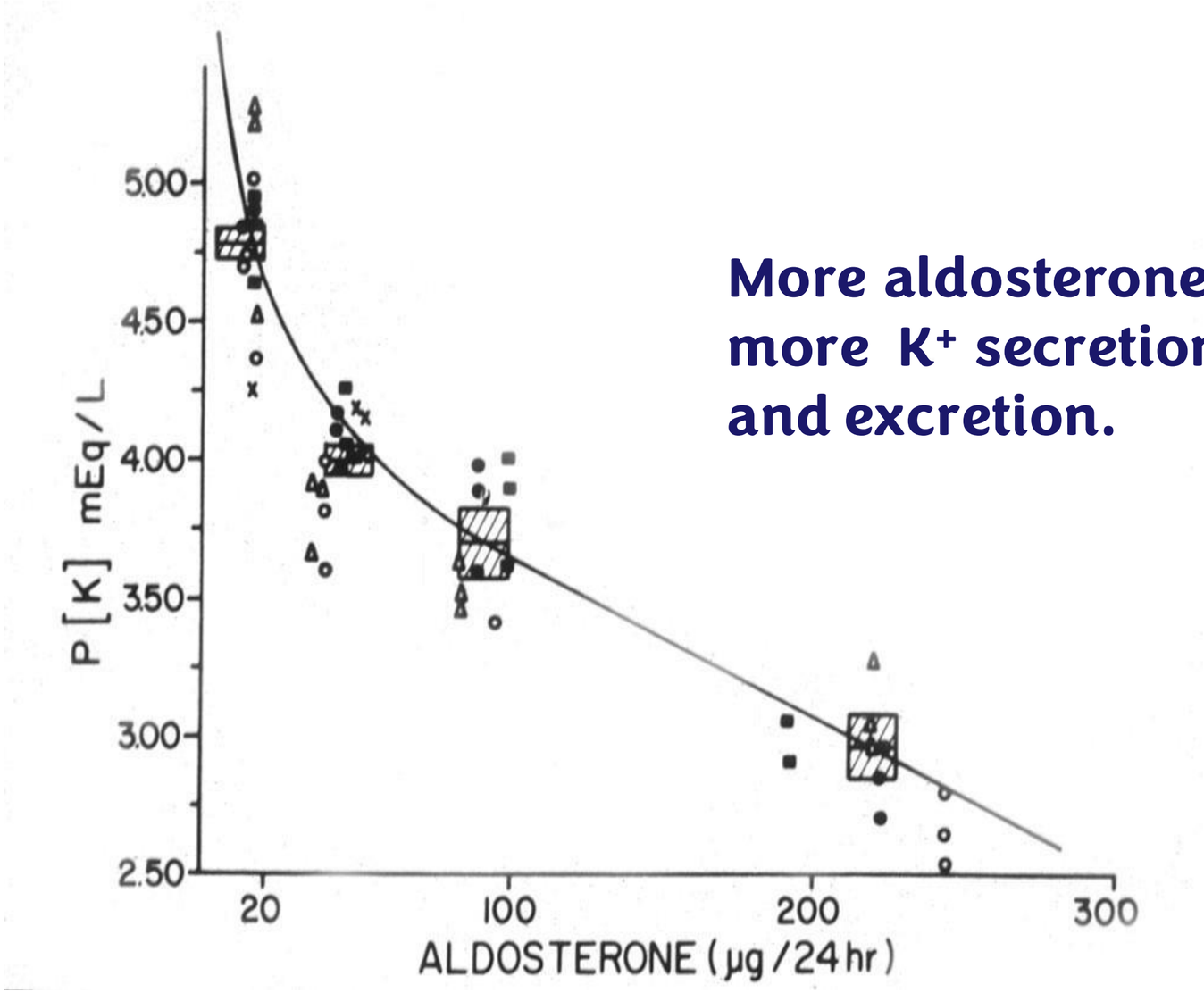
Steroids	Average Plasma Concentration (free and bound, µg/100 ml)	Average Amount Secreted (mg/24 hr)	Glucocorticoid Activity	Mineralocorticoid Activity
Adrenal Steroids (naturally occurring)				
Cortisol	12	15	1	1
Corticosterone	0.4	3	0.3	15.0
Aldosterone	0.006	0.15	0.3	3000
Deoxycorticosterone	0.006	0.2	0.2	**100 (decent)**
Dehydroepiandrosterone	**175 (highest)**	**20 (highest)**	—	—
Synthetic Steroids				
Cortisone	—	—	0.7	1.0
Prednisolone	—	—	4	0.8
Methylprednisone	—	—	5	—
Dexamethasone	—	—	**30 (potent)**	—
9α-fluorocortisol	—	—	10	125

Table 77-1, Guyton & Hall

Regarding last slide

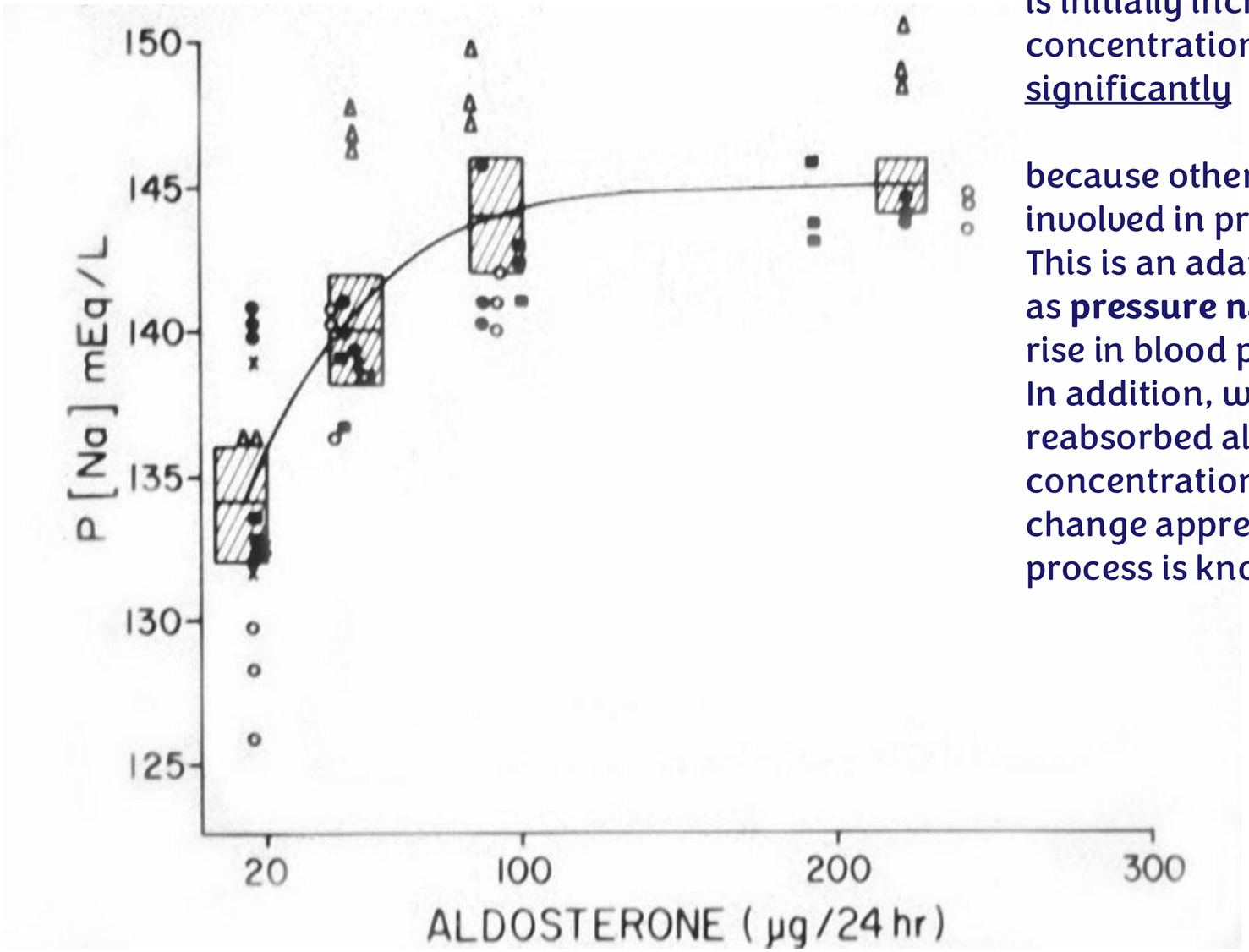
Recall that **cortisone** is the inactive form that is converted into its active form in the liver. **Cortisol** is also known as hydrocortisone.
Notice the distinction: **natural vs. synthetic.**
DHEA is the most abundant.
Regarding DHEA, some theories suggest that it could be the only source of estrogen in postmenopausal females. It is also believed to play a role in female libido.
Aldosterone is the strongest mineralocorticoid (3000), nevertheless deoxycorticosterone (100) can prevent hypotension if aldosterone synthesis is impaired.
The numbers in the two columns at the right are in **reference to the cortisol activity.**
Synthetic steroids, such as prednisolone and dexamethasone are commonly prescribed.
Regarding dexamethasone, it is a 22-carbon steroid. (As we discussed, remember that only 18-, 19-, and 21-carbon steroids are naturally occurring). Dexamethasone is used as an anti-inflammatory agent and is approximately **30 times** more potent than cortisol. Therefore, it should be prescribed in low doses.
Regarding **fludrocortisone**, it is used to treat aldosterone deficiency.

Aldosterone-Plasma [K] Relationships



More aldosterone, more K^+ secretion and excretion.

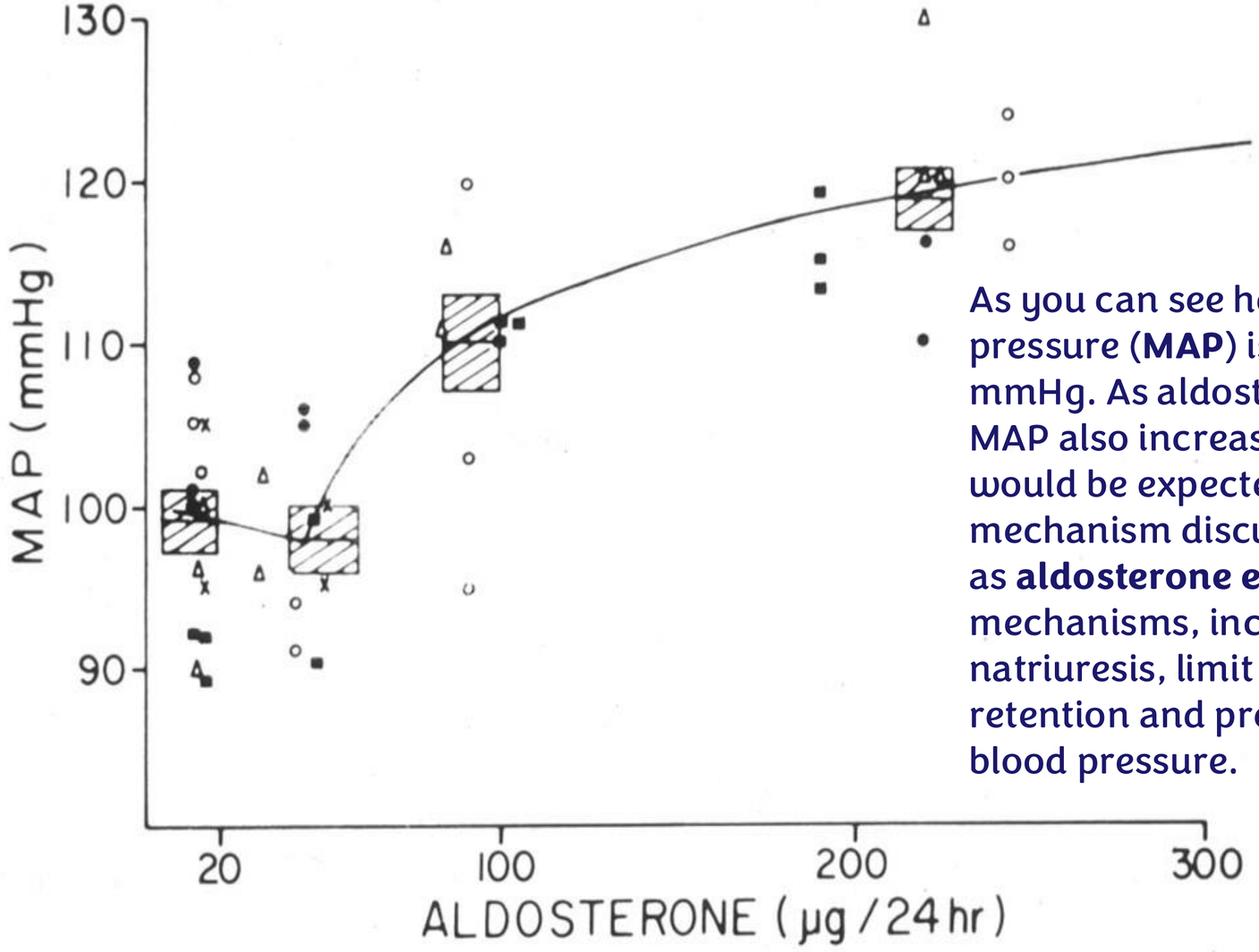
Aldosterone-Plasma [Na] Relationships



The **normal** sodium concentration is approximately **140** mEq/L. If aldosterone is initially increased, the sodium concentration <u>will not change significantly</u>

because other mechanisms become involved in promoting sodium excretion. This is an adaptive mechanism known as **pressure natriuresis,** which limits the rise in blood pressure.
In addition, we know that sodium is reabsorbed along with water, so its concentration in the blood does not change appreciably. This entire adaptive process is known as **aldosterone escape**.

Aldosterone-MAP Relationships

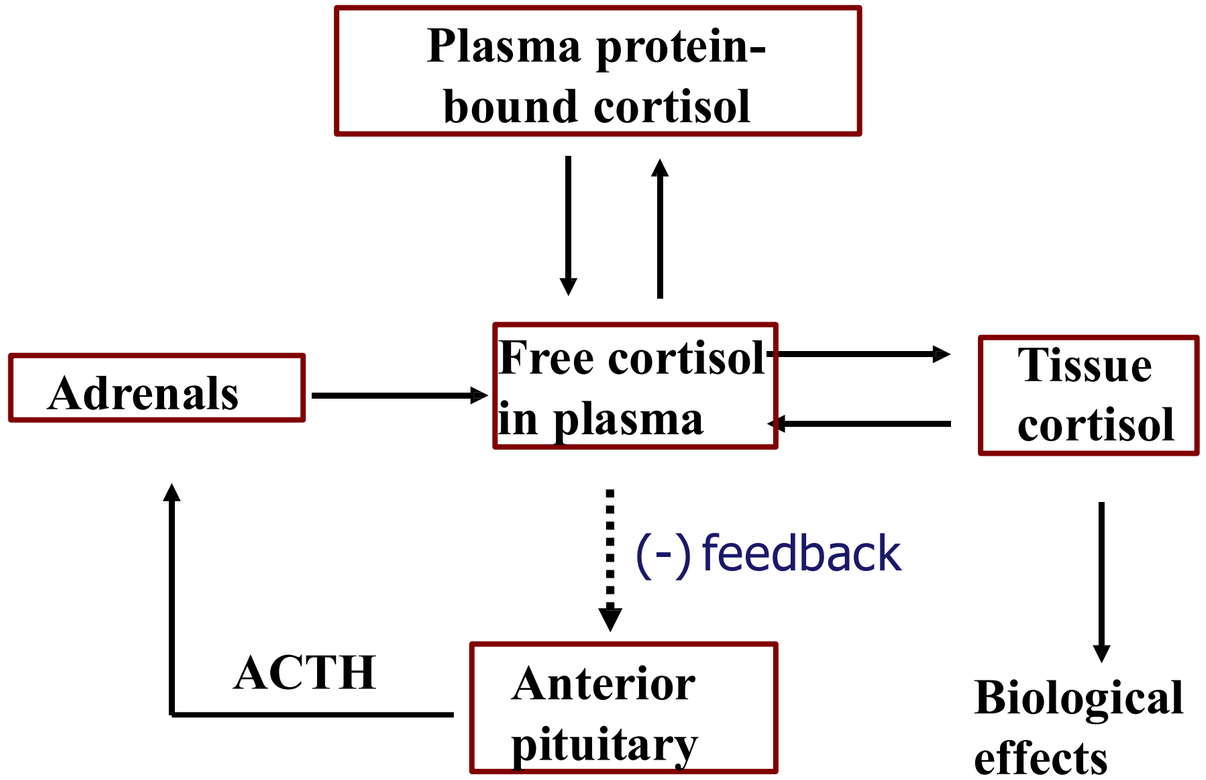


As you can see here, the mean arterial pressure (**MAP**) is normally about **100** mmHg. As aldosterone levels increase, the MAP also increases, but not as much as would be expected. This is due to the same mechanism discussed above, known as **aldosterone escape,** in which adaptive mechanisms, including pressure natriuresis, limit further sodium and water retention and prevent a marked rise in blood pressure.

Circulating Transport Proteins

Transport Protein	Principle Hormone Transported
Specific	
Corticosteroid binding globulin (CBG, transcortin) – **main carrier for both aldosterone and cortisol**	
Nonspecific	
Albumin **(about 25% only)**	
And 4% is free	

Interrelationships Between Free & Bound Cortisol



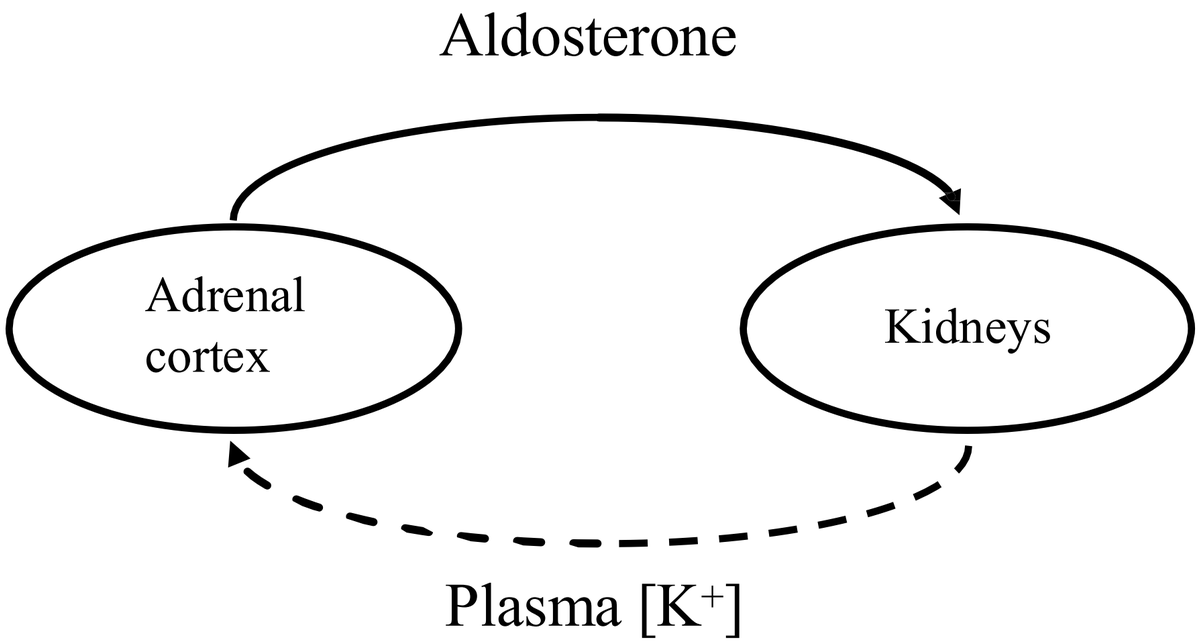
Regulation of Aldosterone Secretion

- **Increased plasma K^+**
- **ANG II;**
- **ACTH;** ACTH does not have a significant effect on aldosterone secretion.

Hyperkalemia is the strongest stimulus for aldosterone secretion. The **second major** stimulus is angiotensin II, which is part of the renin-angiotensin-aldosterone system (RAAS).

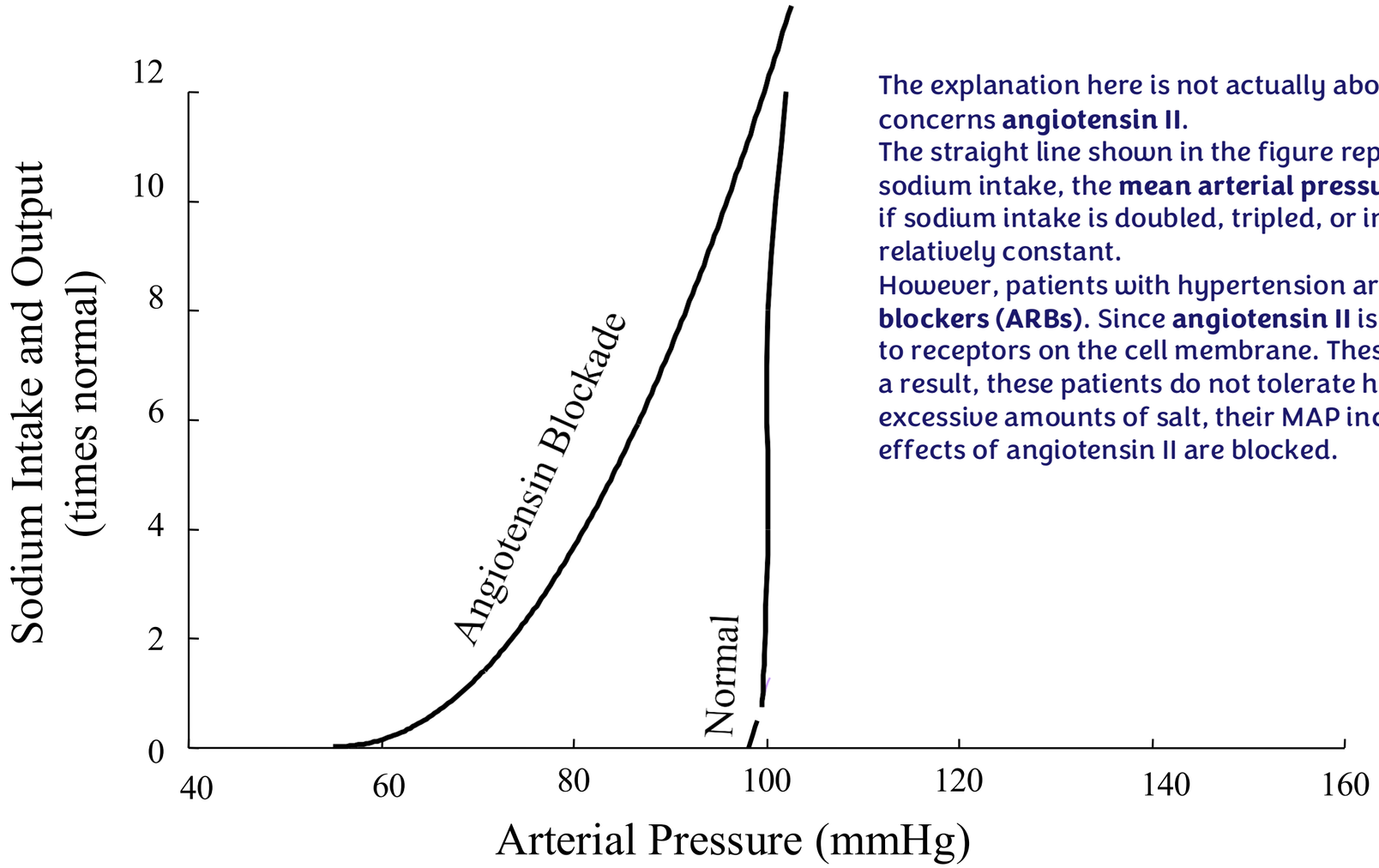
Let's briefly discuss this system. If someone experiences bleeding, the blood volume decreases, leading to a reduction in cardiac output. This, in turn, decreases renal blood flow (RBF). The reduced renal blood flow stimulates specialized cells in the kidney to secrete renin, a peptide enzyme. Eventually, this leads to the formation of angiotensin II, which has four main functions. However, we will only discuss the function that stimulates aldosterone secretion, ultimately helping to restore blood pressure to normal.

Aldosterone & Plasma [K] Regulation



Hyperkalemia is a trigger for aldosterone secretion.

RAS & Regulation of Arterial Pressure



The explanation here is not actually about the adrenal gland; rather, it concerns **angiotensin II**.
The straight line shown in the figure represents the normal situation. With a normal sodium intake, the **mean arterial pressure (MAP)** remains normal. Surprisingly, even if sodium intake is doubled, tripled, or increased several-fold, the MAP remains relatively constant.
However, patients with hypertension are often treated with **angiotensin II receptor blockers (ARBs)**. Since **angiotensin II** is an octapeptide, it exerts its effects by binding to receptors on the cell membrane. These drugs block the action of angiotensin II. As a result, these patients do not tolerate high salt intake well. Whenever they consume excessive amounts of salt, their MAP increases because the normal compensatory effects of angiotensin II are blocked.

The prof. skipped this.

ACTH & Aldosterone Secretion

- Permissive effect
- Acute effect
- No chronic effect

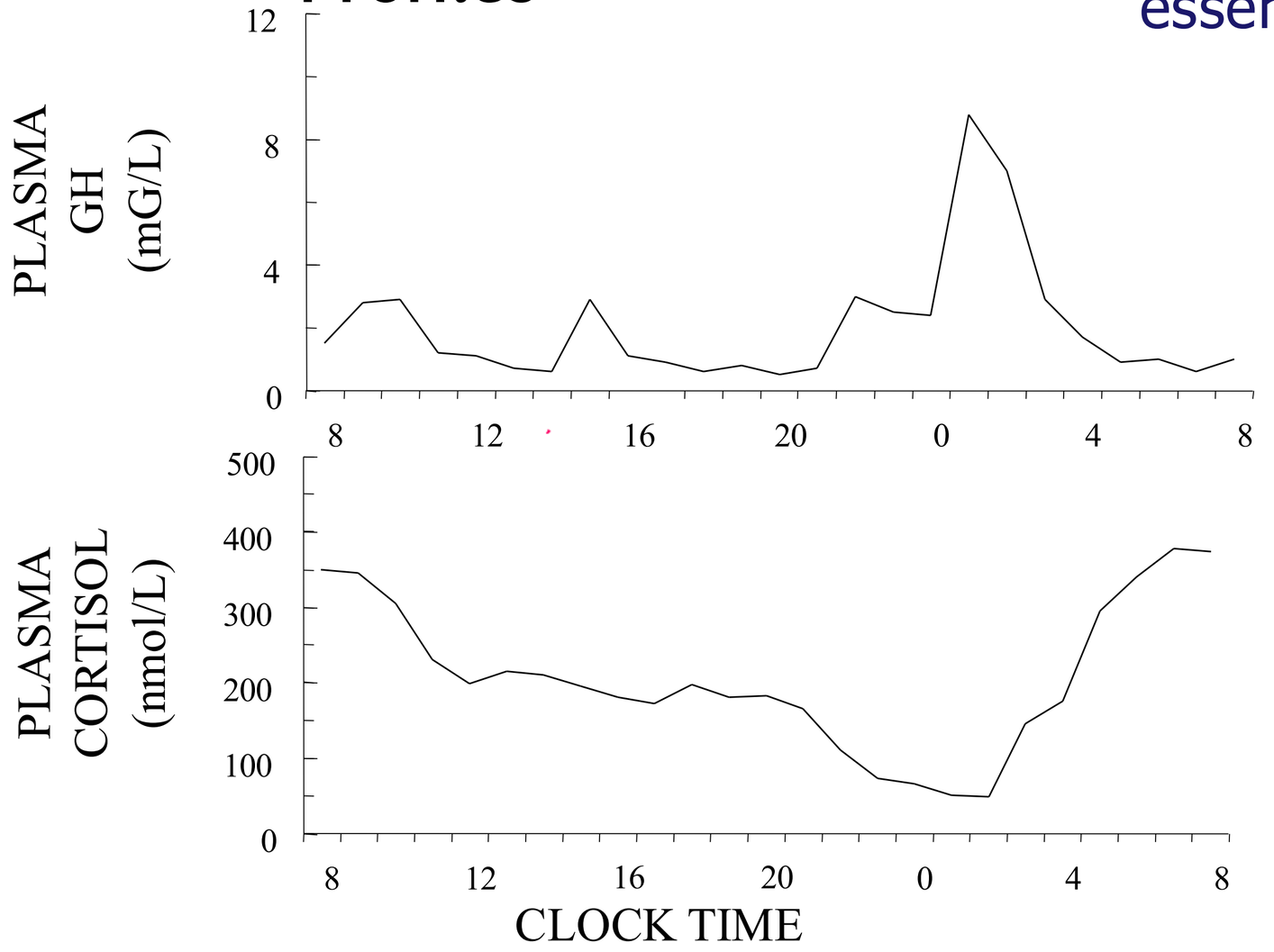
Regulation of Cortisol Secretion

- ACTH

Hormone Secretion Profiles

Night sleep is essential for growth.

Opposite to each other



Growth hormone is secreted primarily at night whereas **cortisol** secretion is highest in the early morning, around **6:00-8:00 a.m.** It then gradually declines throughout the rest of the day. This pattern of hormone secretion is known as the **diurnal** or **circadian rhythm** of secretion.

Pathophysiology of the Adrenal Cortex

- **Cushing's syndrome**
- **Cushing's disease**
- Addison's disease
- Conn's syndrome
- Apparent mineralocorticoid excess
- Congenital adrenal hyperplasia
  - 21 β - Hydroxylase deficiency
  - 11 β - Hydroxylase deficiency

Causes of Cushing's Syndrome

- Adrenal hyperplasia, recall 21-hydroxylase deficiency
  - ↑ Pituitary ACTH

    hypothalamic dysfunction
    pituitary tumors (Cushing's disease)

  - Nonpituitary tumors (ectopic)

    ACTH
    CRH

- Adrenal neoplasia
  - Adenoma
  - Carcinoma

- Iatrogenic: Most common

The doctor didn't explain but he said read it alone

Signs & Symptoms in Cushing's Syndrome

Sign or Symptom	Per Cent of Patients
Central Obesity*	97
Increased body weight	94
Fatigability & weakness	87
Hypertension	82
Hirsuitism*	80
Amenorrhea*	77
Cutaneous striae*	67
Personality changes	66
Ecchymoses*	65
Proximal myopathy*	62
Edema	62

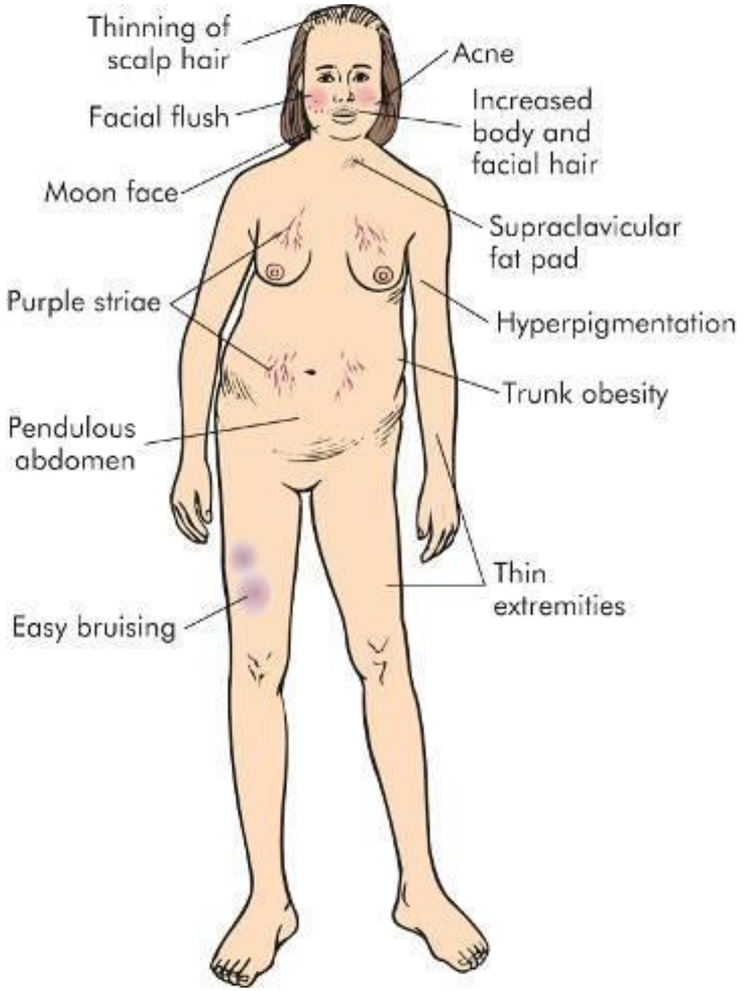
Clinical features of Cushing syndrome (excess cortisol):

- **Redistribution of fat:** Fat is redistributed to the **abdomen** and the **back of the neck/between the shoulders (buffalo hump)**.
- **Weak proximal muscles:** Proximal muscle weakness occurs because cortisol is **catabolic**, causing protein breakdown in muscles.
- **Bone fragility (osteoporosis):** Cortisol decreases collagen and bone formation, leading to **fragile bones and osteoporosis**.
- **Hypertension and diabetes:** Hypertension develops due to the effects of cortisol on blood vessels, while diabetes occurs because of its **anti-insulin action**, with eventual **β-cell burnout**.
- **Effects on androgens:** Excess cortisol, particularly in ACTH-dependent cases, increases adrenal androgen production.causing hirsuitism
- **Skin striae:** Reduced collagen synthesis leads to **thin skin** and **purple striae (stretch marks)**.
- **Depression:** Chronic excess cortisol can eventually lead to **depression and other mood changes**.

+Buffalo hump and moon face (because fat deposit in cheeks)

* More specific for Cushing's syndrome

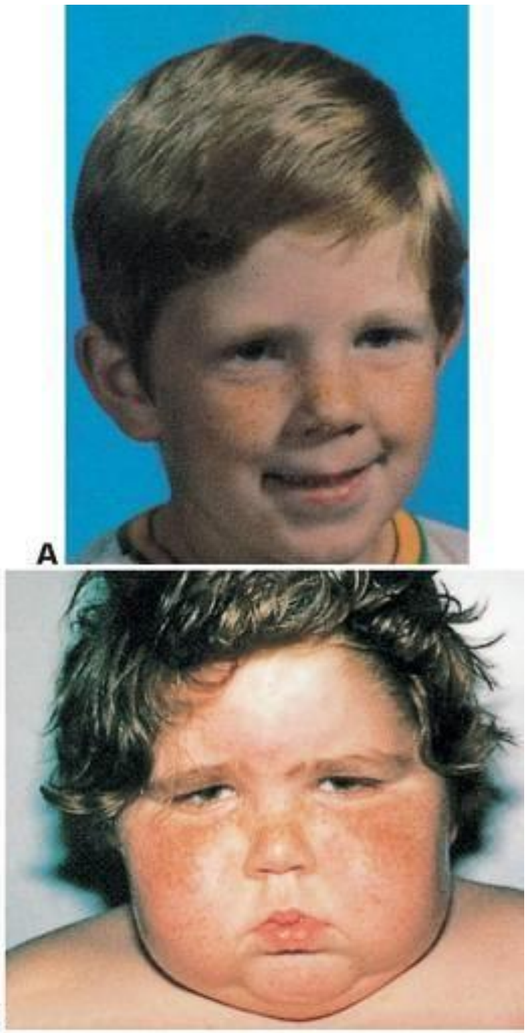
Cushing Disease



Central obesity and thin extremities

Cushing Disease

Normal.



From Zitelli BJ, Davis HW. Atlas of pediatric physical diagnosis, ed 3. London, 1997, Gower.

Moon face

The prof. skipped this.

Treatment of Cushing's Disease

- ↓ ACTH production
  - Hypophysectomy
  - Radiation
- ↓ Adrenocortical cortisol secretion
  - Bilateral adrenalectomy
  - Medical adrenalectomy (metyrapone, aminoglutethimide, ketoconazole)

The prof. skipped this.

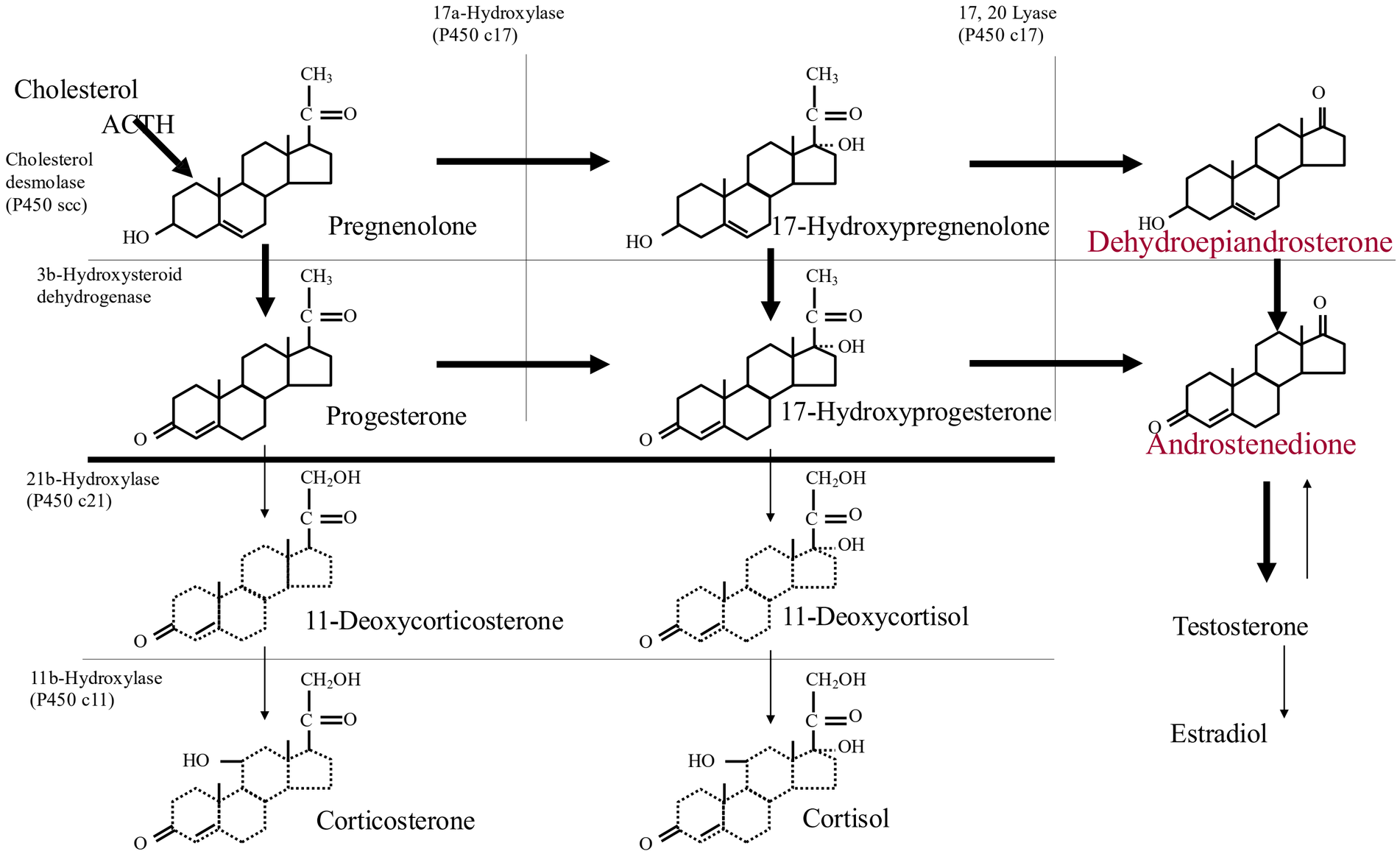
Causes of Adrenal Insufficiency

- Primary adrenal insufficiency
  - Destruction of gland
    - Idiopathic atrophy - autoimmune
    - Infectious - tuberculous
    - Surgery
    - Hemorrhage
  - Metabolic
    - Congenital adrenal hyperplasia
- Secondary adrenal insufficiency
  - Hypothalamic-pituitary disease
  - Suppression of HPA - exogenous steroids

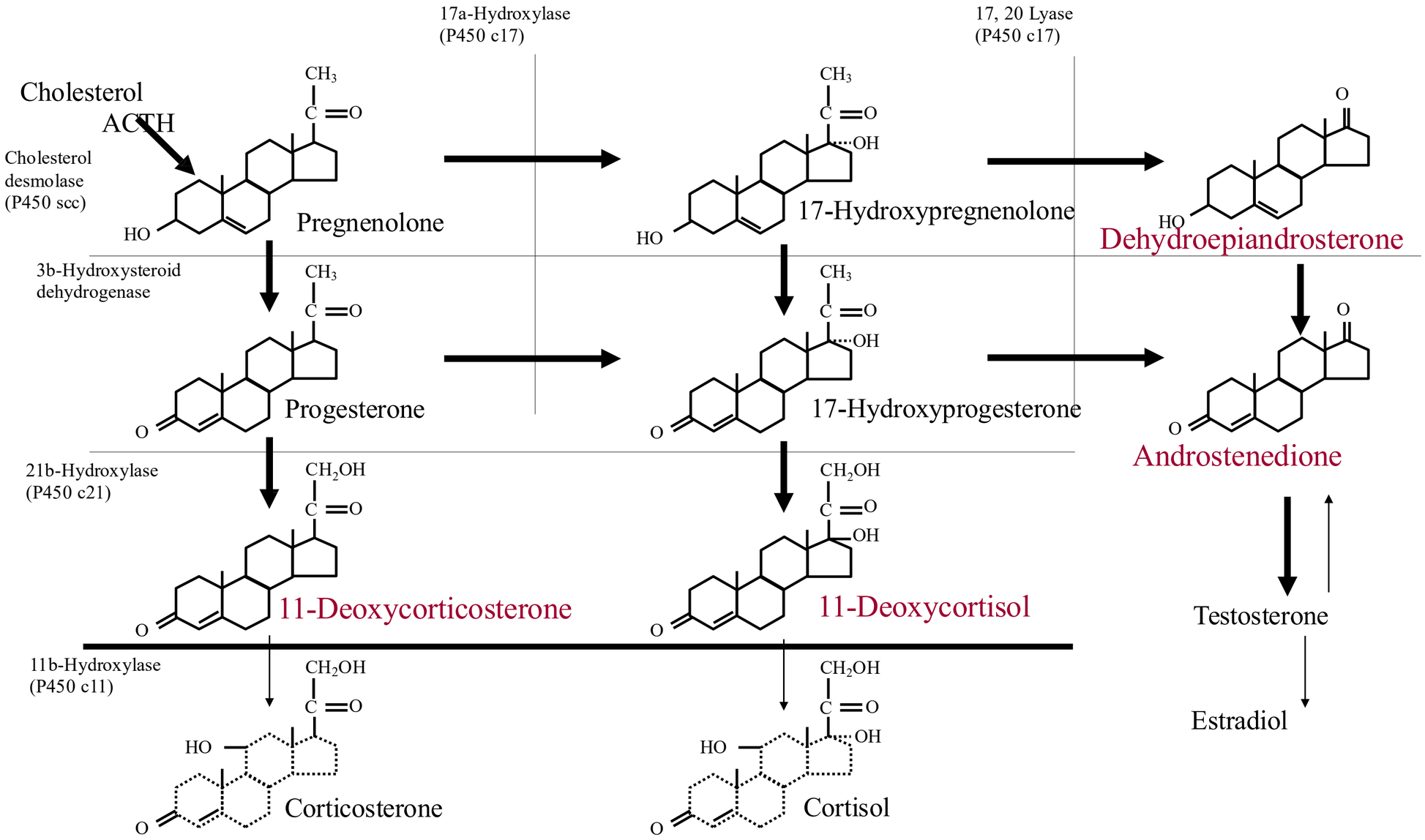
Signs & Symptoms in Adrenal insufficiency

Sign or Symptom	Per Cent of Patients
Weakness	99
Pigmentation of skin(high MSH level)	98
Weight loss	97
Anorexia, nausea, & vomiting	90
Hypotension	87
Pigmentation of mucus membranes	82
Abdominal pain	34
Diarrhea	20
Syncope	16

Congenital Adrenal Hyperplasia: 21β-Hydroxylase Deficiency



Congenital Adrenal Hyperplasia: 11β-Hydroxylase Deficiency

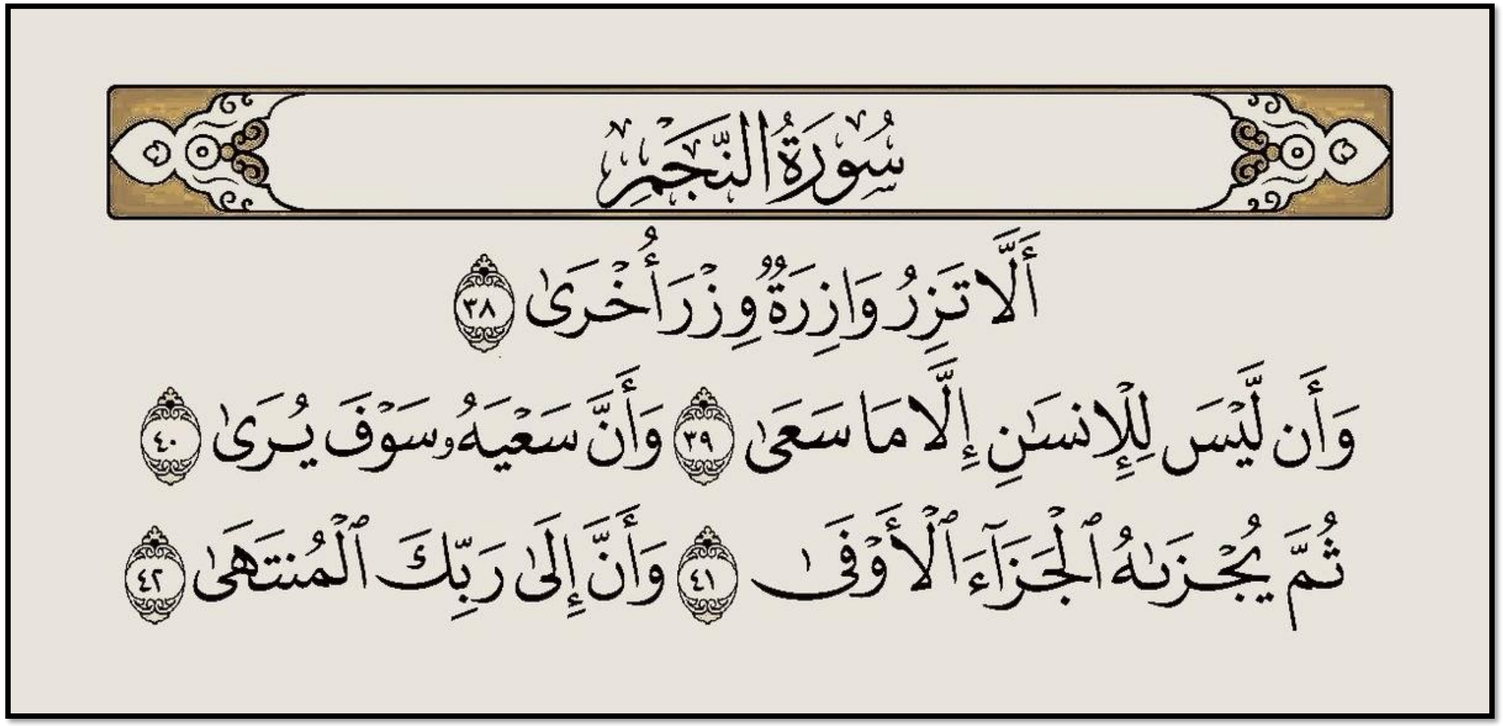


موديفايدالفريقالعلميعمبدرس

Physiology Quiz 8

2/8 Awaits!

رسالة من الفريق العلمي:



For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			