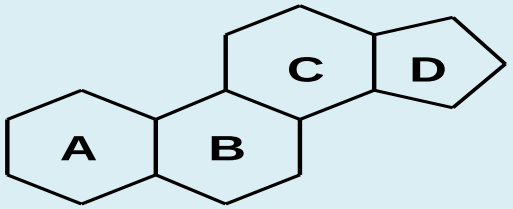
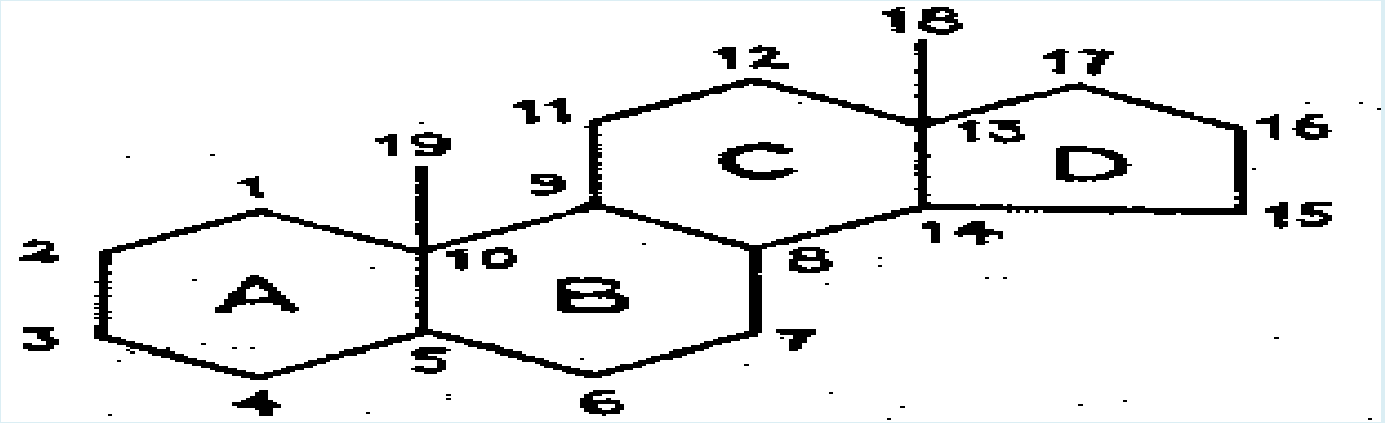
Steroids

- **Steroids are group of plant and animal lipids that have a similar tetracyclic nucleus.**

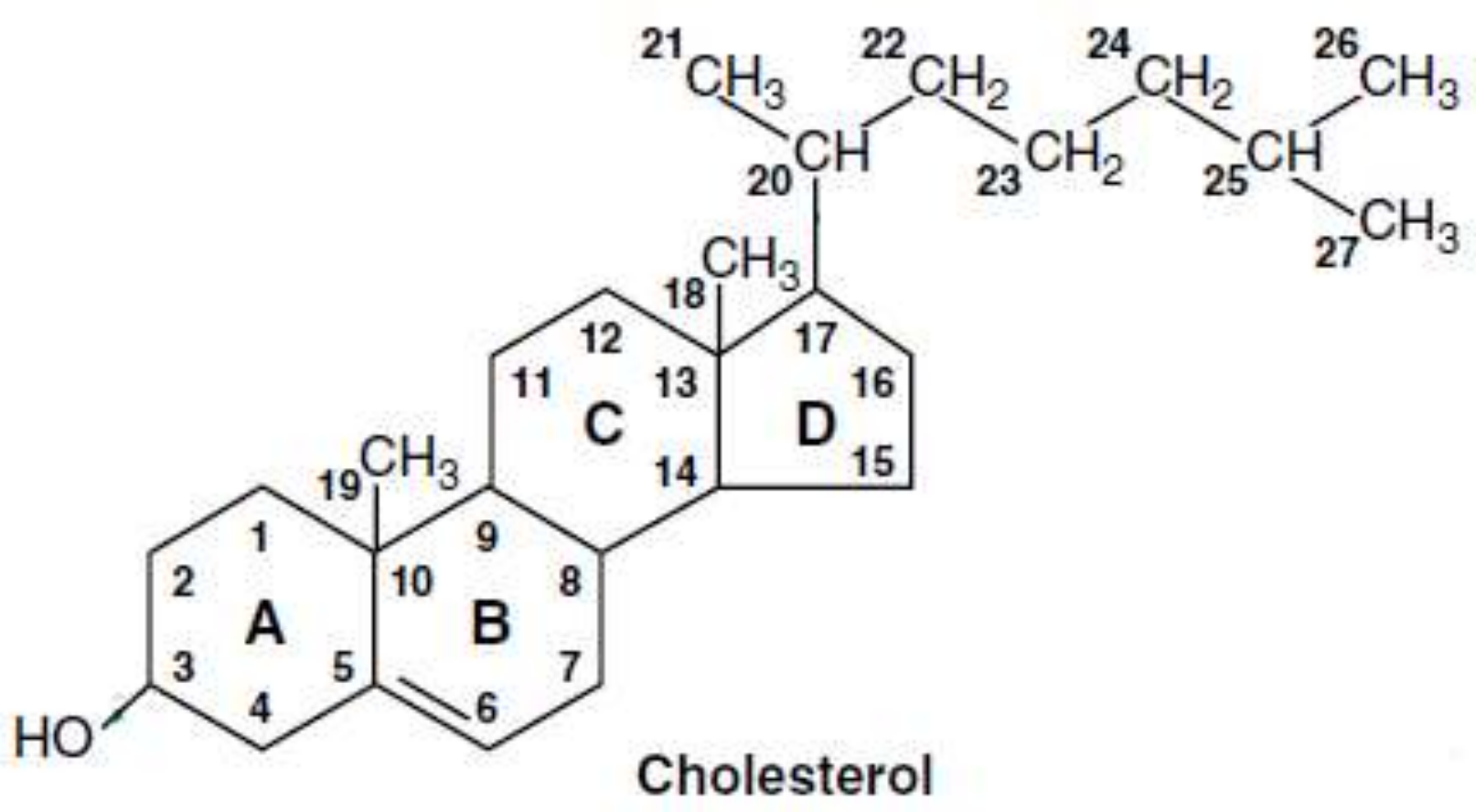


Steroid nucleus:

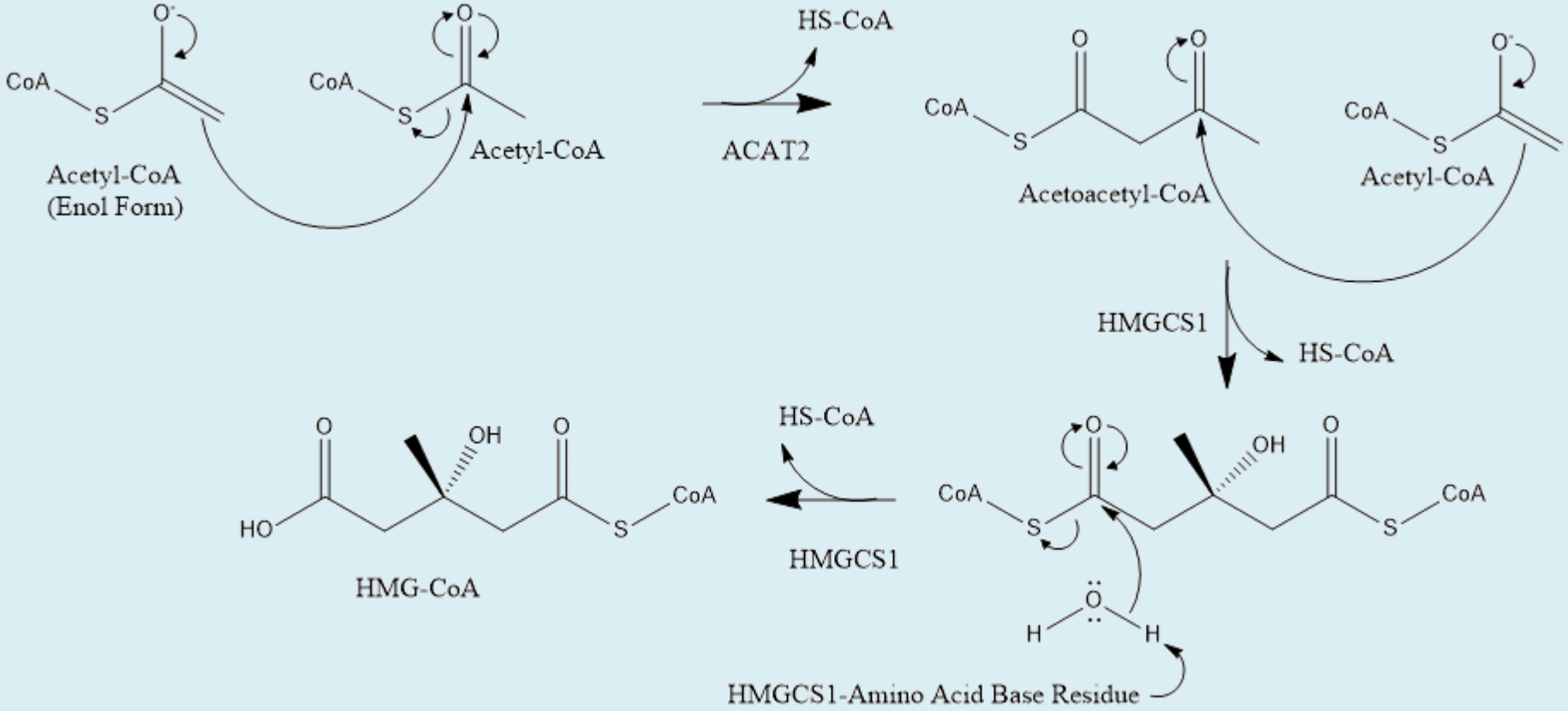
- **So these rings are composed of 17 carbon atoms besides two methyl groups (C_{18}, C_{19}).**
- **There is a methyl group at C_{10} (it makes C 19).**
- **And there is another methyl group at C_{13} (it makes C18).**



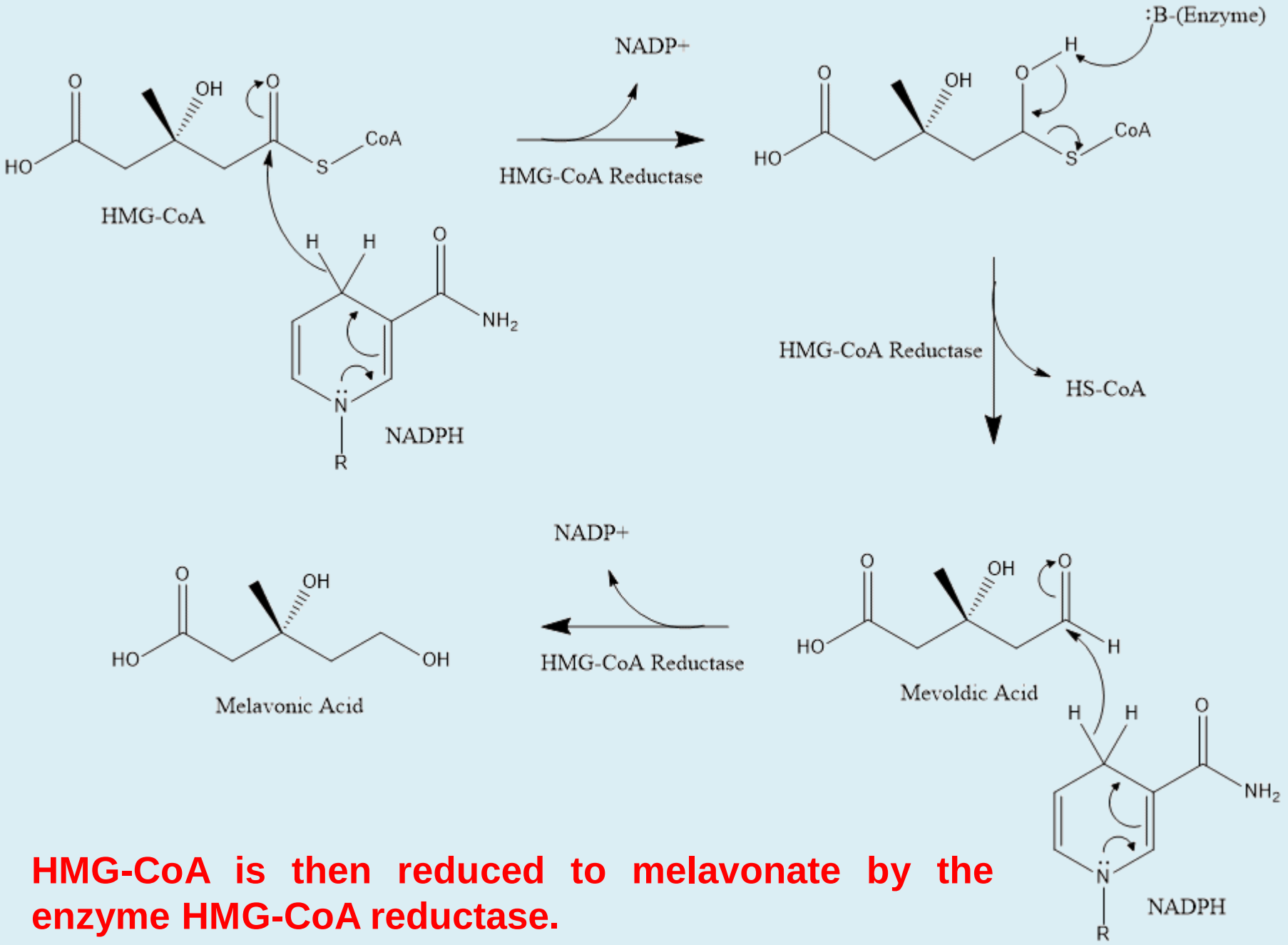
- **Cholesterol consists of**
- **Four fused hydrocarbon rings (A, B, C, and D, called the "steroid nucleus")**
- **Eight-carbon branched hydrocarbon chain attached to C17 of the D ring.**
- **Ring A has a hydroxyl group at C-3, and ring B has a double bond between C-5 and C-6.**



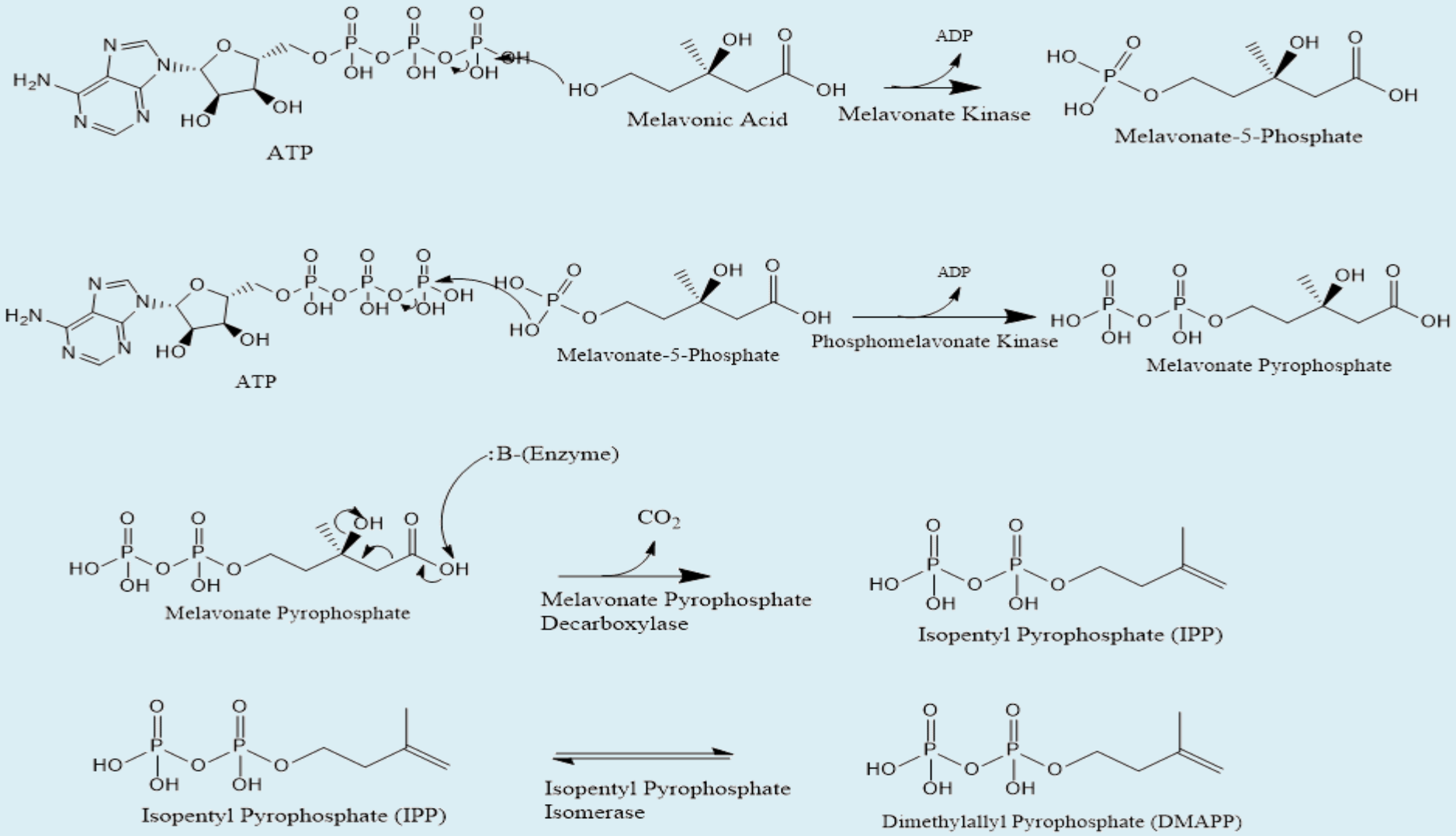
Cholesterol



Synthesis of cholesterol starts with the melavonate pathway where two molecules of acetyl CoA condense to form acetoacetyl-CoA. Then followed by another condensation with acetyl CoA to form 3-hydroxy-3-methylglutaryl CoA (HMG-CoA)



HMG-CoA is then reduced to melavonate by the enzyme HMG-CoA reductase.



Melavonate is finally converted to isopentenyl pyrophosphate (IPP) through two phosphorylation steps and one decarboxylation step that requires ATP

Cholesterol Sources

1. **It is formed in the body from acetyl CoA. Most of the cholesterol is synthesized by the liver.**
2. **It is present in diet: egg yolk, meat, liver and brain.**

Biomedical importance:

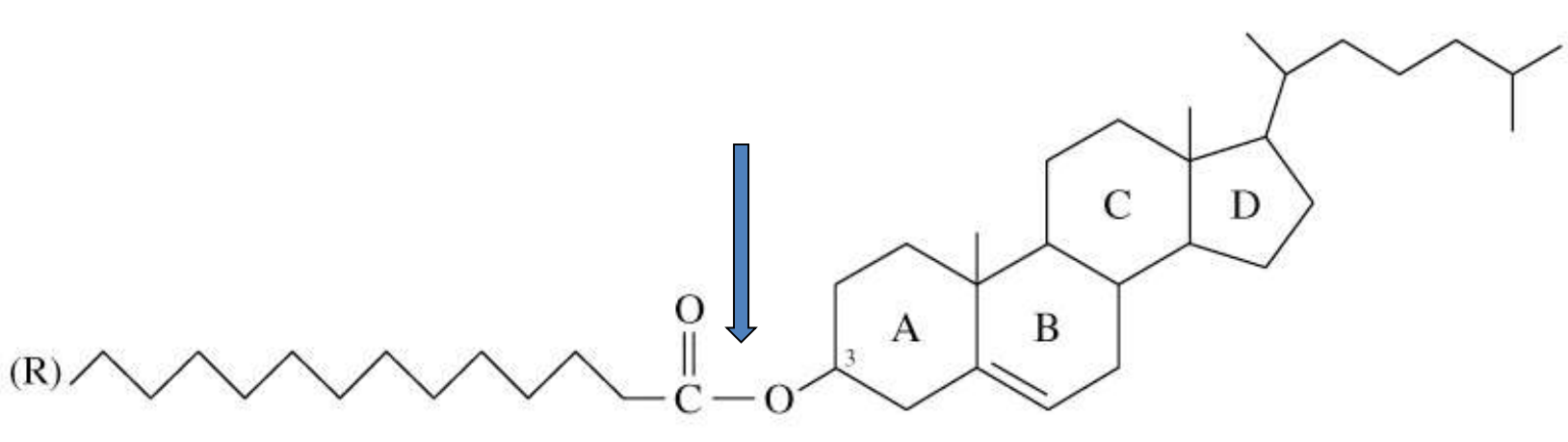
1- **It is the main sterol in human body (Nervous tissue, brain, suprarenal gland, and in bile, ,,).**

2- **It is present in blood (normal level 150-200 mg / dl).**

3- **It is often found as cholesterol ester (in combination with fatty acids). The fatty acid is attached to the hydroxyl group e.g. Cholesteryl oleate or linoleate.**

Cholesterol esters (CE)

- Cholesterol is converted to cholesteryl esters for cell **storage** or **transport** in blood
- Fatty acid is esterified to C-3 OH of cholesterol
- Cholesterol esters are **very water insoluble (hydrophobic)** and must be complexed with phospholipids or amphipathic proteins for transport



Biomedical importance:

4- It is a major constituent of the **plasma membrane.**The fused ring system makes cholesterol less flexible than most other lipids.

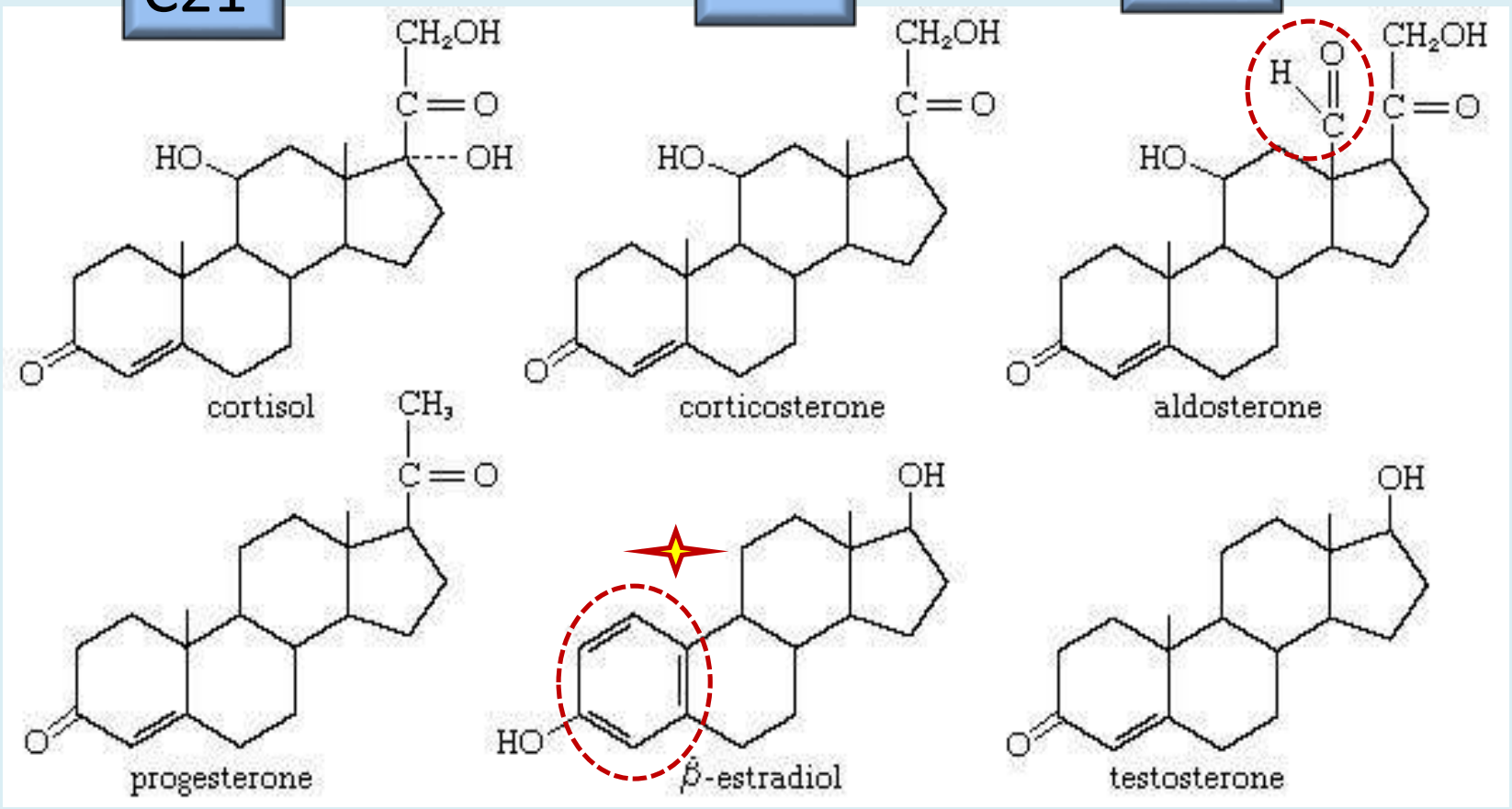
5- It is the precursor of:

- **Sex hormones**
- **Cortical hormones**
- **Vitamin D**
- **Bile acids**.

6- High levels of cholesterol in blood will lead to its precipitation in the wall of blood vessels **"atherosclerosis".** Also high levels of blood cholesterol may lead to stones in gall bladder **(gall stone).**

- **Cholesterol is the precursor of all five classes of steroid hormones:**
- **Glucocorticoids:** 21 carbons (eg; Cortisol)
- **Mineralcorticoids:** 21 carbons (eg; Aldosterone)
- **Progestins:** 21 carbons (eg; Progesterone)
- **Androgens:** 19 carbons (eg; Testosterone)
- **Estrogens:** 18 carbons (eg; Estradiol)

Steroid hormones: chemical structure



Steroid hormones: Characteristics

- **Steroid hormones: produced in the *adrenal cortex*, *testis*, *ovary*, and *some peripheral tissues* (adipose tissue, the brain).**

- **All steroids are lipid soluble and thus are freely permeable to membranes so are not stored in cells.**

- **Steroid hormones are not water soluble so have to be carried in the blood complexed to specific binding globulins.**

➢ ***Corticosteroid binding globulin* carries cortisol**

➢ ***Sex steroid binding globulin* carries testosterone and estradiol.**

How does the synthesis of steroids differ from that of peptide hormones?

- While peptide hormones are encoded by specific genes, steroid hormones are synthesized from the enzymatic modification of cholesterol.
- Thus, there is **no gene** which encodes ex, aldosterone.
- ***As a result*:**

  - There are far fewer different types of steroid hormones than peptide hormones.
  - Steroid structures are the same from species to species.
  - The **regulation of steroidogenesis** involves control of the enzymes which modify cholesterol into the steroid hormone of interest.
- Steroid hormones are slower acting and have longer half-life than peptide hormones.

Steroid hormones: mechanism of action

- Enzymes which produce steroid hormones from cholesterol are located in mitochondria and smooth endoplasmic reticulum (ER).

Functions of steroid hormones:

- Steroid hormones play important roles in:
  - carbohydrates regulation (glucocorticoids)
  - minerals balance (mineralocorticoids)
  - reproductive functions (gonadal steroids)

- Steroids also play roles in inflammatory responses, stress responses, bone metabolism, cardiovascular fitness, behavior, cognition, and mood.

Steroid hormones: function

Product	Functions
Progesterone	prepares uterus lining for implantation of ovum
Glucocorticoids (cortisol) (produced in adrenal cortex)	promote gluconeogenesis; favor breakdown of fat and protein (fuel mobilization); anti-inflammatory
Mineralocorticoids (aldosterone) (produced in adrenal glands)	maintains blood volume and blood pressure by increasing sodium reabsorption by kidney
Androgens (testosterone) (produced in testis primarily)	development of male secondary sex characteristics; prevents bone resorption
Estrogen (produced in ovaries primarily but also in adipose cells of males and females)	development of female secondary sex characteristics; prevents bone resorption; increase HDL & dec.LDL

- **All mammalian steroid hormones are formed from Cholesterol via Pregnenolone.**
- **Steroidogenic enzymes:**

Common name	"Old" name	Current name
Side-chain cleavage enzyme; desmolase	$P450_{SCC}$	CYP11A1
3 beta-hydroxysteroid dehydrogenase	3 β-HSD	3 β-HSD
17 alpha-hydroxylase/17,20 lyase	$P450_{C17}$	CYP17
21-hydroxylase	$P450_{C21}$	CYP21A2
11 beta-hydroxylase	$P450_{C11}$	CYP11B1
Aldosterone synthase	$P450_{C11AS}$	CYP11B2
Aromatase	$P450_{aro}$	CYP19

Steroidogenesis:

- **All mammalian steroid hormones are formed from Cholesterol via Pregnenolone.**
- **The first step is the conversion of cholesterol to pregnenolone, which occurs in the *mitochondria*.**

- **This reaction is carried out by the enzyme, *cytochrome P450 side chain cleavage* (P450scc). (also called desmolase, or CYP11A1). Carbons 20 and 22 are sequentially oxidized followed by oxidative cleavage of the bond between them.**

- **This is a rate limiting, nonreversible enzymatic step in the initiation of steroid biosynthesis.**

- **Adrenal Steroidogenesis formation of pregnenolone**

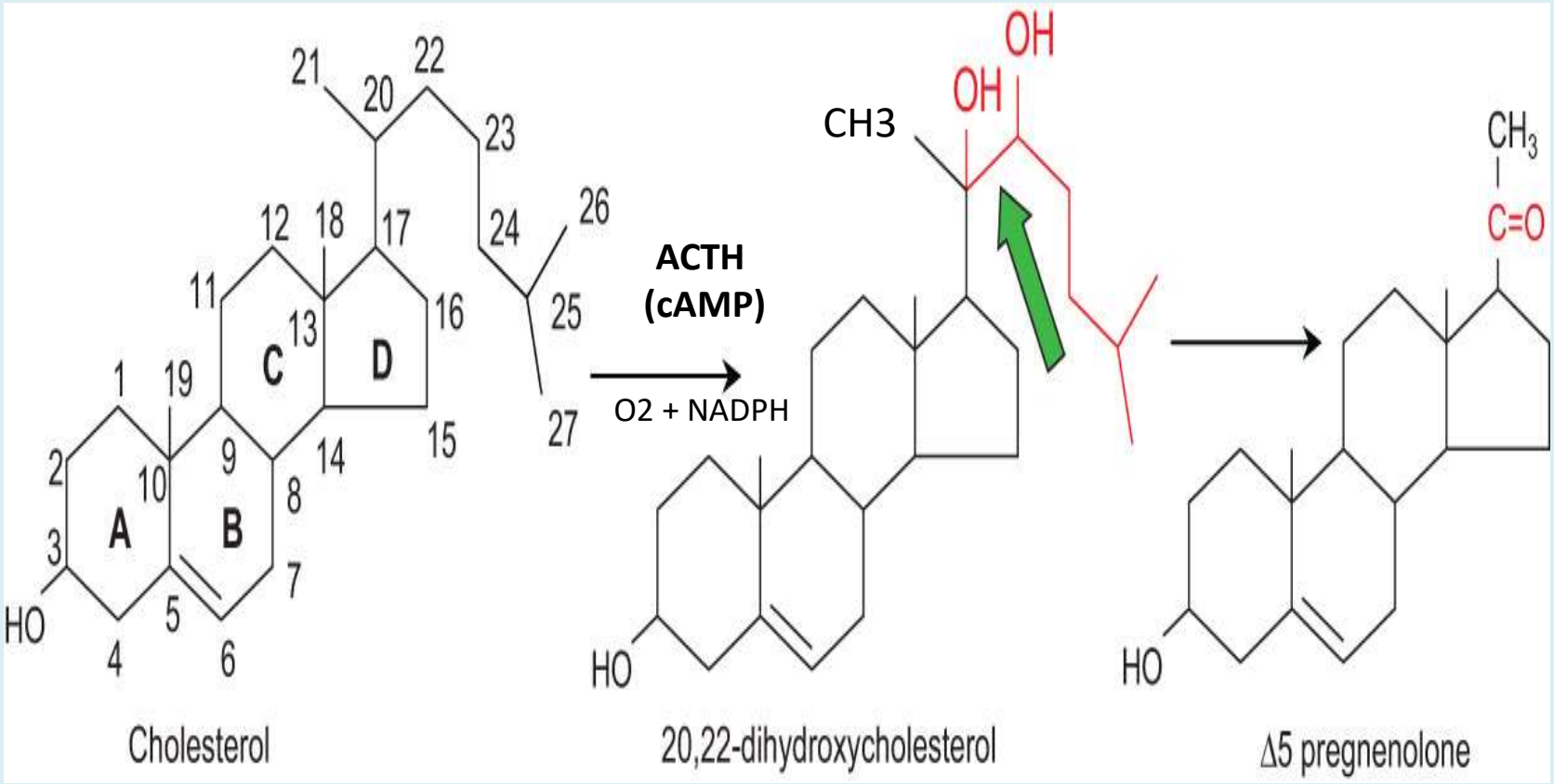
- **Cholesterol in the adrenal is esterified and stored in cytoplasmic lipid droplets.**

- **Upon stimulation of the adrenal by adrenocorticotropic hormone (ACTH), an esterase is activated, and cholesterol is transported into the mitochondrion by ACTH-dependent steroidogenic acute regulatory (StAR) protein**

- **Cytochrome P450 side chain cleavage enzyme (P450scc) converts cholesterol to pregnenolone in the inner mitochondrial membrane by**

1- Hydroxylations, first at C22 and then at C20

2- Side chain cleavage, removal of the six-carbon fragment isocaproaldehyde, to give the 21-carbon steroid.

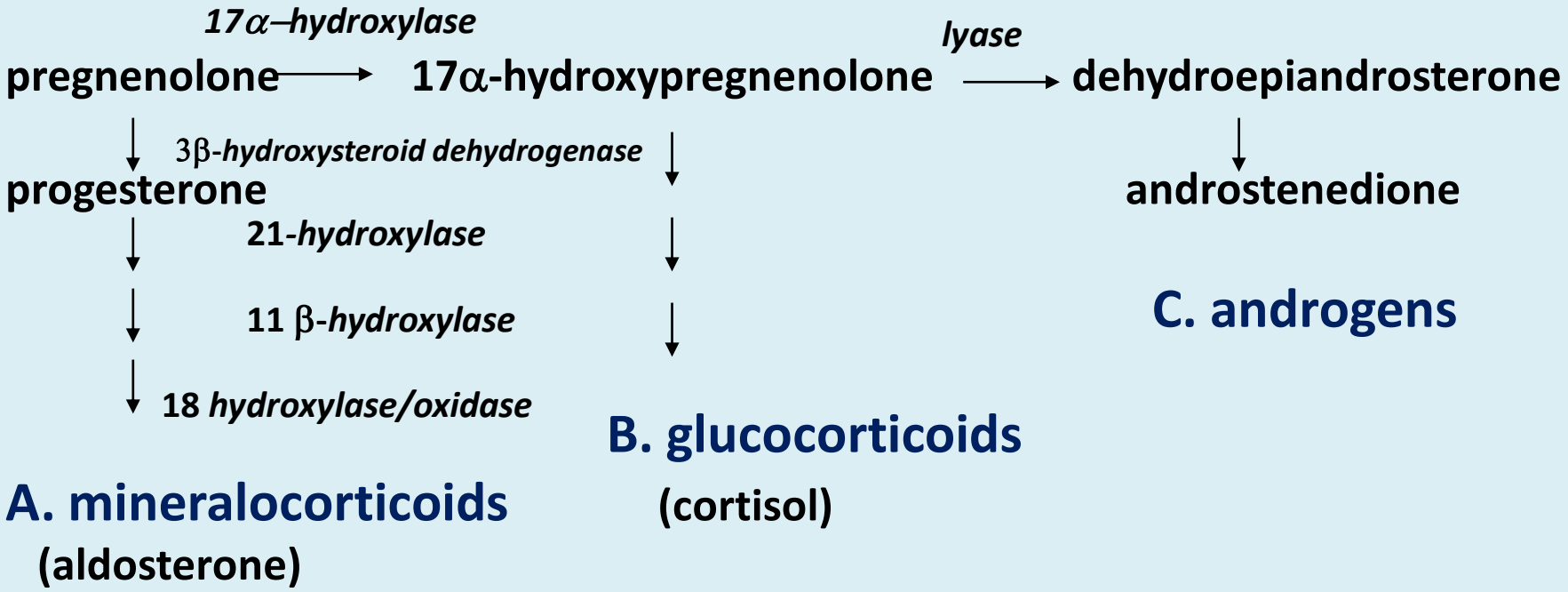


+ isocaproaldehyde (6C)

Conversion of cholesterol to pregnenolone

Adrenal Steroidogenesis

- **Next, pregnenolone can be converted *(in smooth ER)* into three different pathways, depending upon whether the cell wants to make mineralcorticoids, glucocorticoids, or androgens.**



What determines which pathway is taken?

- **Each step of the pathway is regulated by a specific enzyme. For ex., 18- hydroxylase and hydroxysteroid dehydrogenases, which are required for aldosterone synthesis are found only in the zona glomerulosa cells, so that the biosynthesis of this mineralocorticoid is confined to this region.**

- **Different zones of the adrenal cortex have *different relative activities of enzymes*, resulting in different chemical reactions taking place.**

- **Adrenal steroid biosynthesis involves the shuttling of precursors between mitochondria and the ER**

1. Mineralocorticoids: biosynthesis

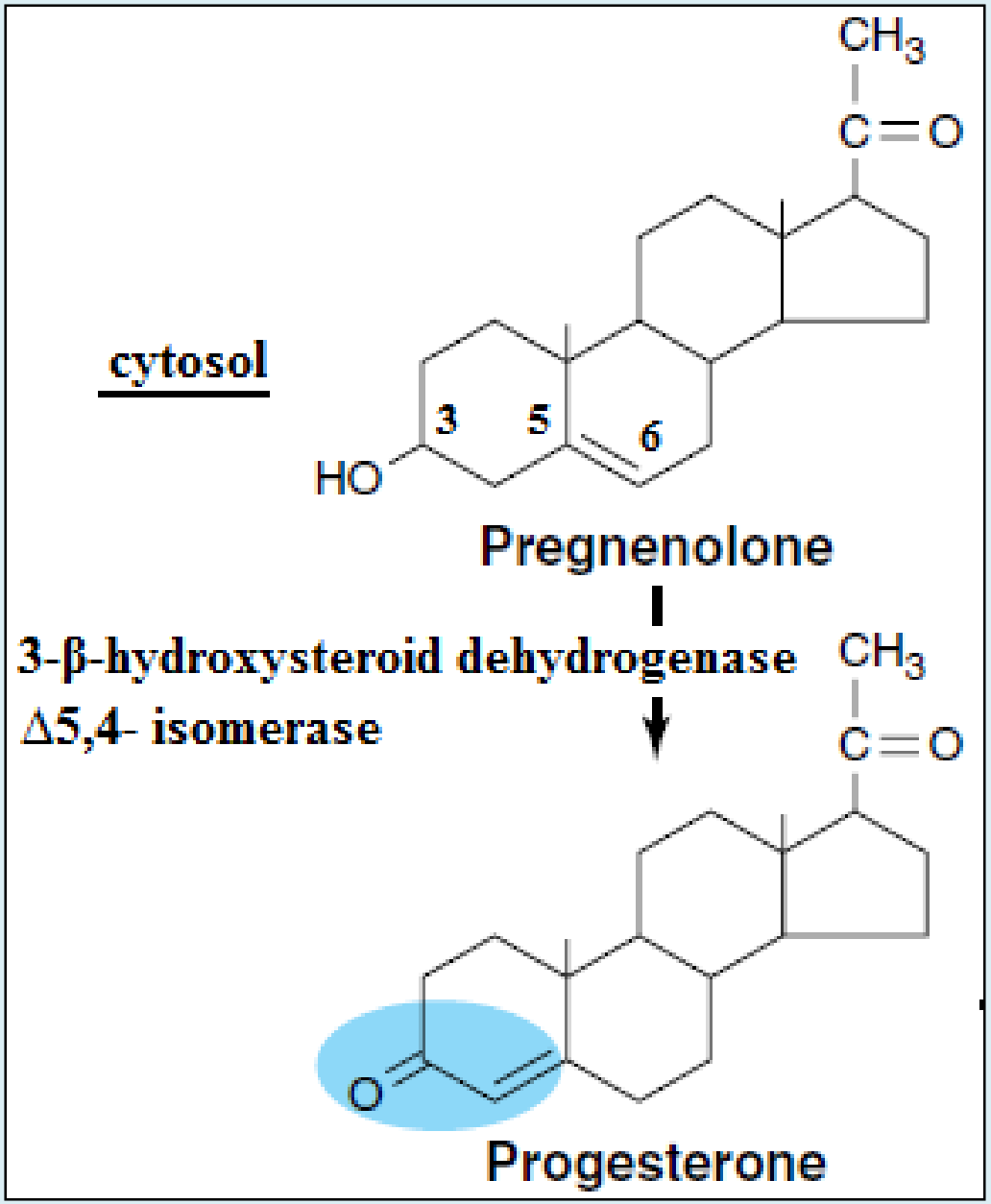
- **Occurs in Zona glomerulosa [ZG].**
- **All mammalian steroid hormones are formed from cholesterol via pregnenolone**
- **Biosynthesis of mineralocorticoids:**
- **Pregnenolone is converted to progesterone by *3β-hydroxysteroid DH (3 β -OHSD) and $\Delta^{4,5}$- isomerase***
- **Progesterone is *hydroxylated at C21* to form 11-deoxycorticosterone (DOC). DOC is an active (Na+-retaining) mineralocorticoid**
- **Next *hydroxylation is at C11* producing corticosterone**
- ***18-Hydroxylase* acts on corticosterone to form aldosterone**

Progesterone

is synthesized in two steps:

1- The 3-hydroxyl group of pregnenolone is oxidized to 3- keto group by 3-β-hydroxysteroid dehydrogenase.

2- The Δ^5 double bond is isomerized to a Δ^4 double bond by $\Delta^{4,5}$-isomerase.



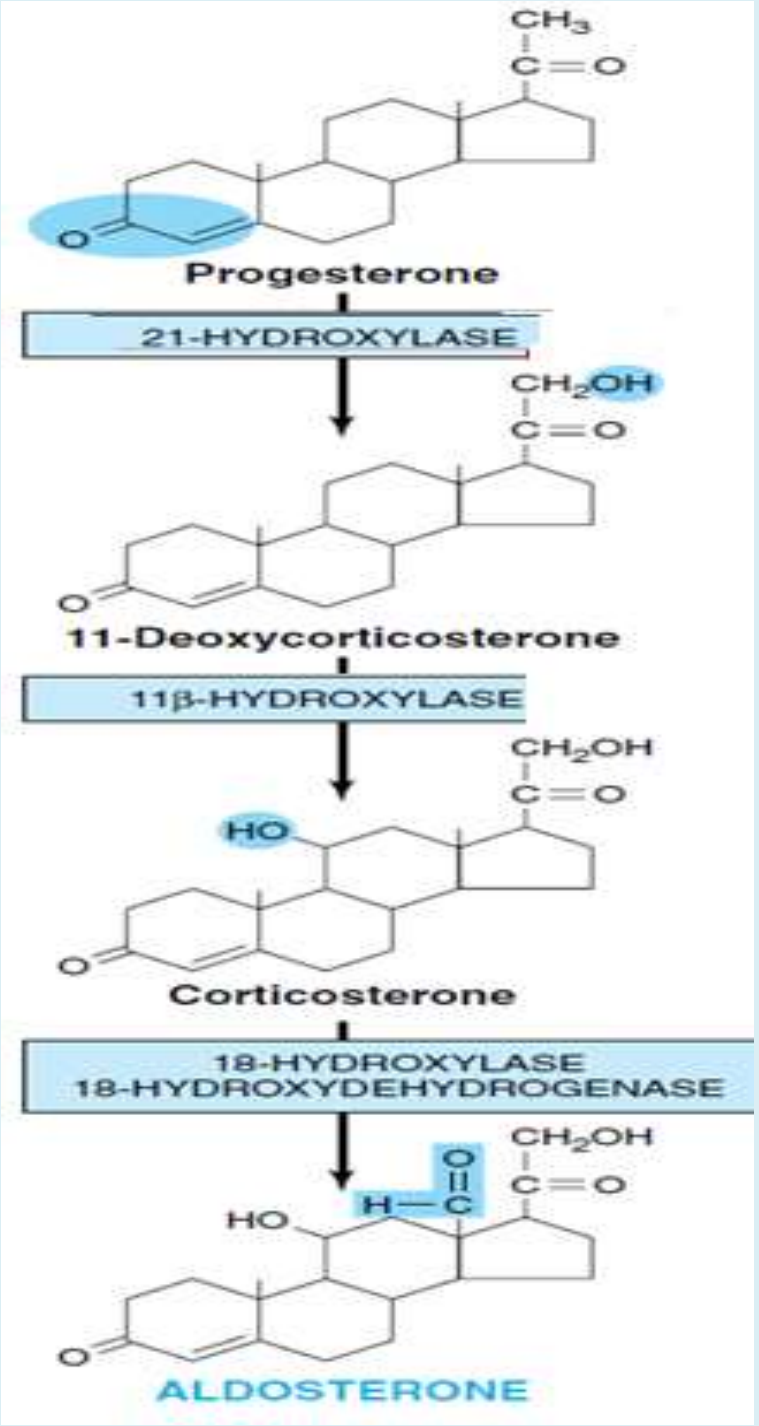
Aldosterone

(mineralocorticoid)

1- Hydroxylation of progesterone at C-21 by 21-hydroxylase.

2- The resulting deoxycorticosterone is hydroxylated at C-11 by 11β-hydroxylase.

3- The oxidation of the C-18 to an aldehyde then yields aldosterone by:
18-hydroxylase and 18-hydroxysteroid dehydrogenase.



2. Glucocorticoids: biosynthesis

- **Occurs in the Zona fasiculata [ZF] and Zona reticularis [ZR] of adrenal cortex.**
- **All mammalian steroid hormones are formed from cholesterol via pregnenolone**
- **Biosynthesis of glucocorticoids (A & B pathways):**

❖ A. Pathway:

- **Pregnenolone is converted to progesterone by *3β-hydroxysteroid DH (3 β -OHSD) and $\Delta^{4,5}$- isomerase***
- **Progesterone is *hydroxylated at C21* to form 11-deoxycorticosterone (DOC).**
- **Next *hydroxylation is at C11* producing Corticosterone. (it has glucocorticoid & weak mineralocorticoid action).**

B. Pathway:

- ***17α-Hydroxylase*** **acts upon either progesterone or pregnenolone to form 17 α - hydroxyprogesterone and/or 17 α -hydroxypregnenolone.**

- **17 α -hydroxyprogesterone is *hydroxylated at C21* to form 11-deoxycortisol.**

- **11-deoxycortisol is then *hydroxylated at C11* to form Cortisol.**

Glucocorticoid: biosynthesis

- **Cortisol is the most potent natural glucocorticoid hormone in humans.**
- **Cortisol release is primarily under *ACTH.***
- **3 hydroxylases are needed for cortisol synthesis on position:**

➢ **C17 by 17alpha-hydroxylase, (acts rapidly; present in ER)**

➢ **C21 by 21-hydroxylase, (acts rapidly; present in ER)**

➢ **C11 by 11-hydroxylase, (acts slowly; present in mitochondria).**

- **If C 11 is hydroxylated first, the action of 17alpha-hydroxylase is impeded and mineralocorticoid pathway is followed (forming corticosterone or aldosterone depending on the cell type).**

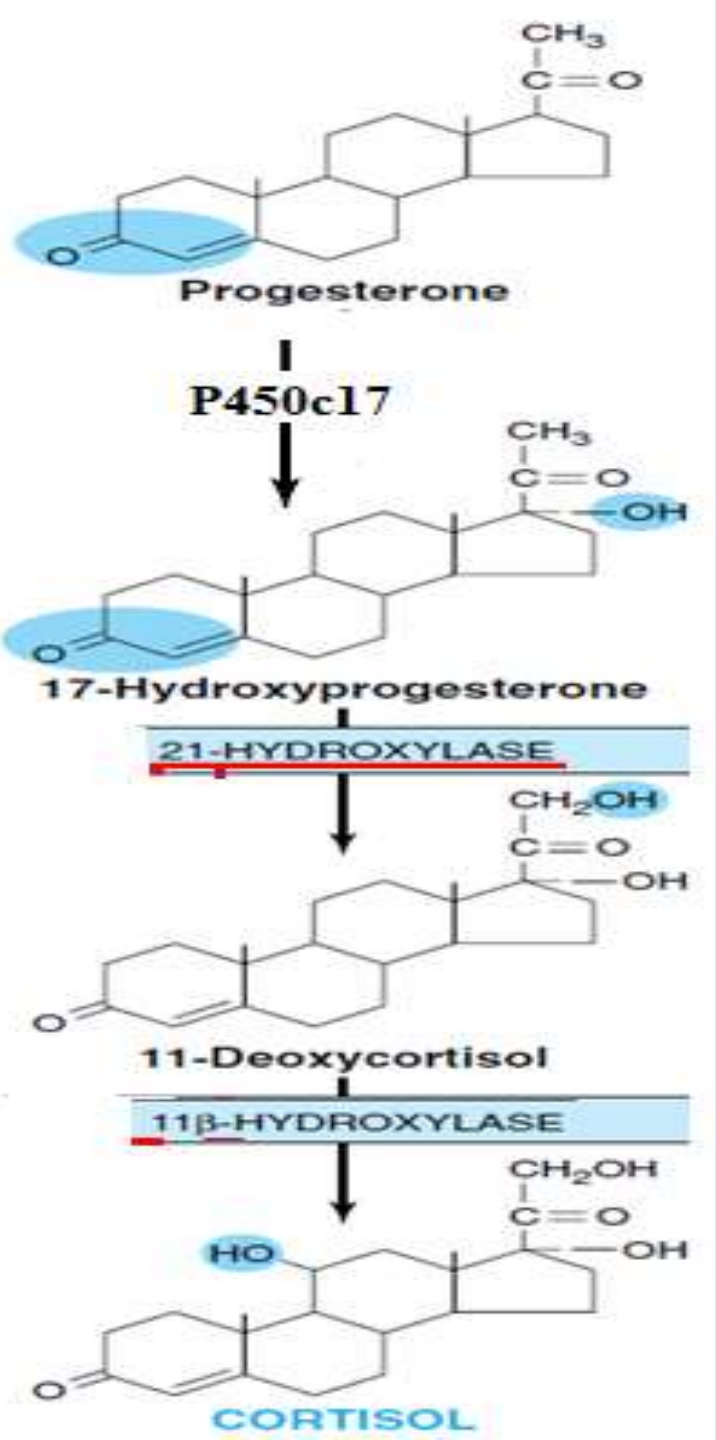
Cortisol

The major glucocorticoid, is synthesized from progesterone by hydroxylation's of

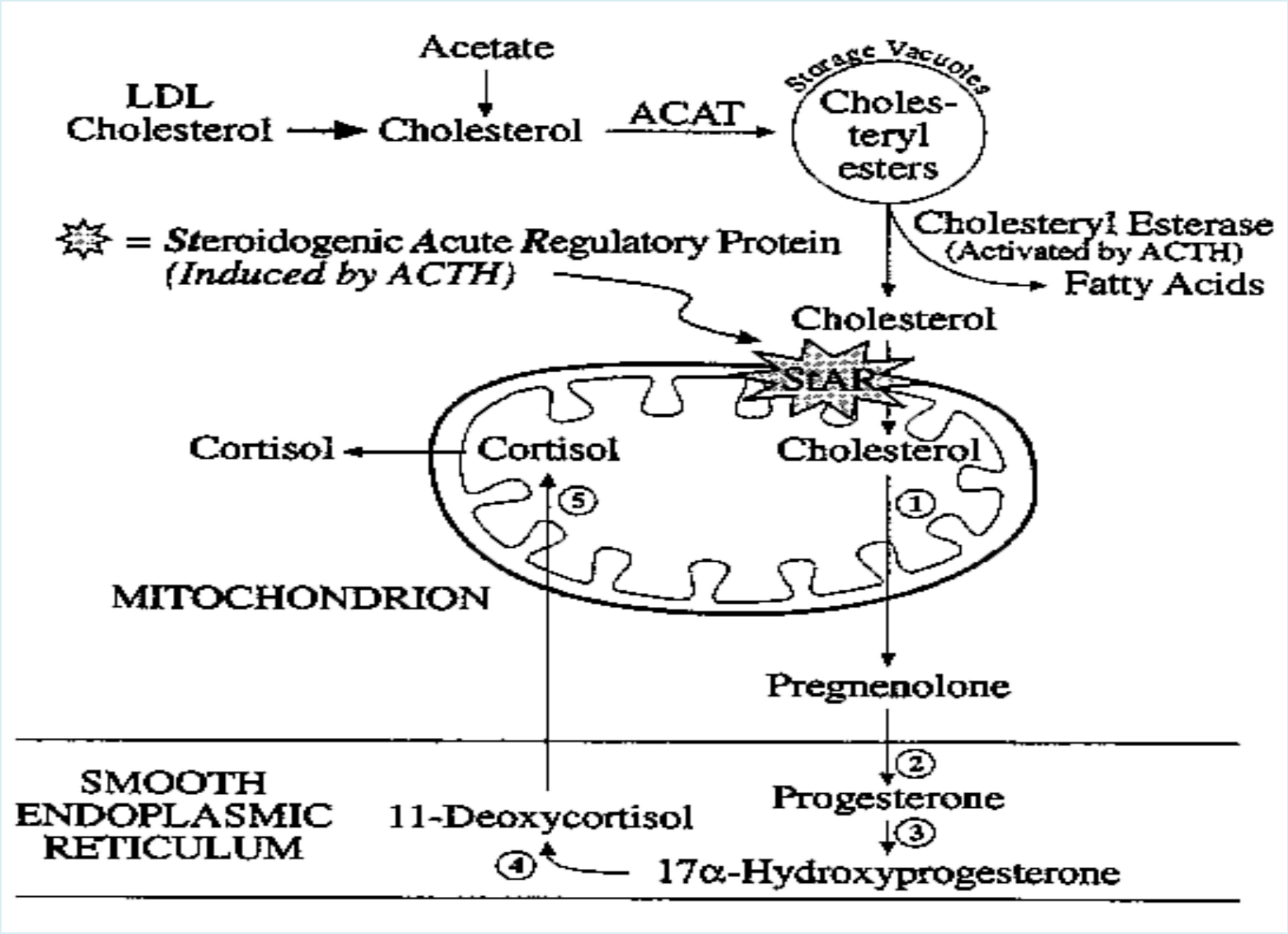
C-17 by P450c17

C-21 by 21-hydroxylase

C-11 by 11β-hydroxylase



Adrenal steroid biosynthesis involves the shuttling of precursors between mitochondria and ER



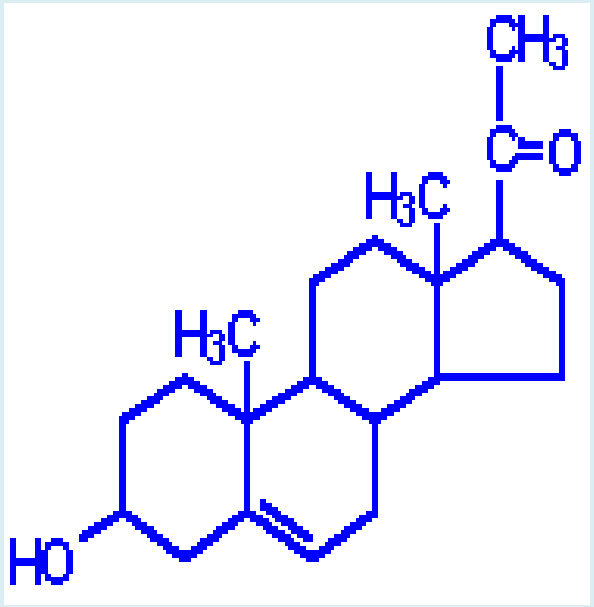
3. Adrenal androgens: biosynthesis

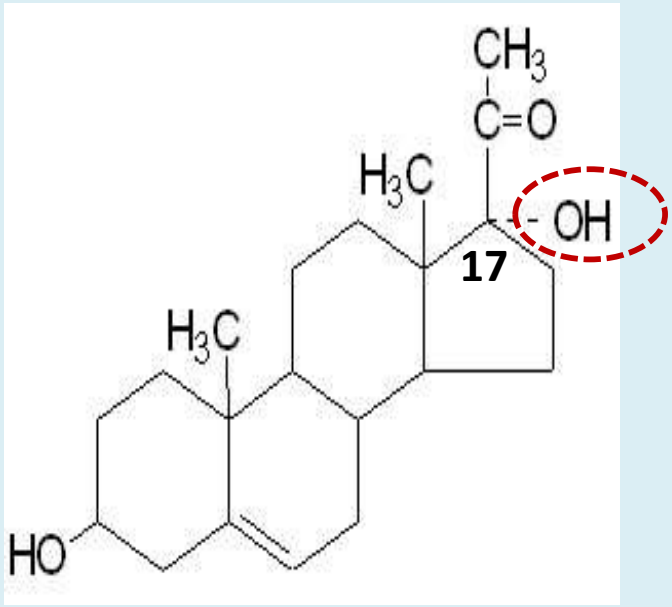
- **Produced in the *zona reticularis [ZR].***
- **The major androgen produced by adrenal cortex is dehydroepiandrosterone (DHEA).**
- **Most of 17-hydroxy pregnenolone follows glucocorticoid pathway.**
- **Few of 17-hydroxy pregnenolone follows androgen pathway.**
- **17alpha-hydroxylase + 17, 20 lyase = dual-function protein.**
- **Lyase activity is important in both adrenals and gonads. Lyase acts exclusively on 17-hydroxy containing molecules.**

3. Adrenal androgens:

Pregnenolone → **17(OH) pregnenolone**

17α-hydroxylase

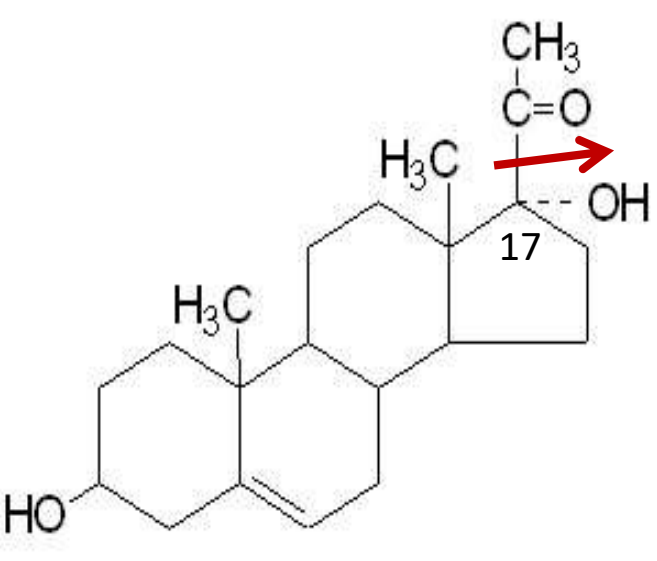


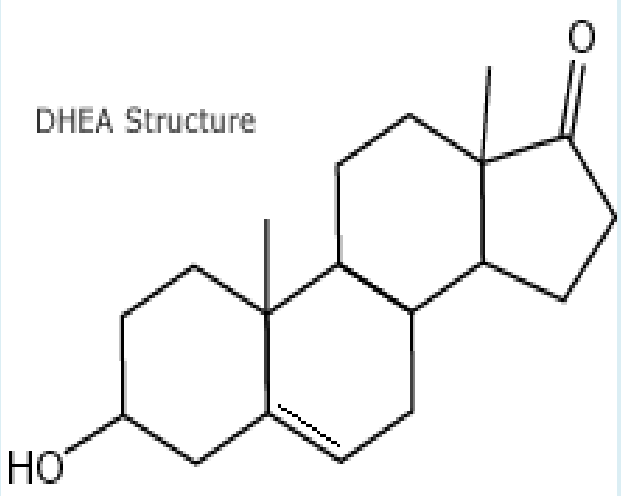


3. Adrenal androgens:

17 (OH) pregnenolone → **Dehydroepiandrosterone (DHEA)**

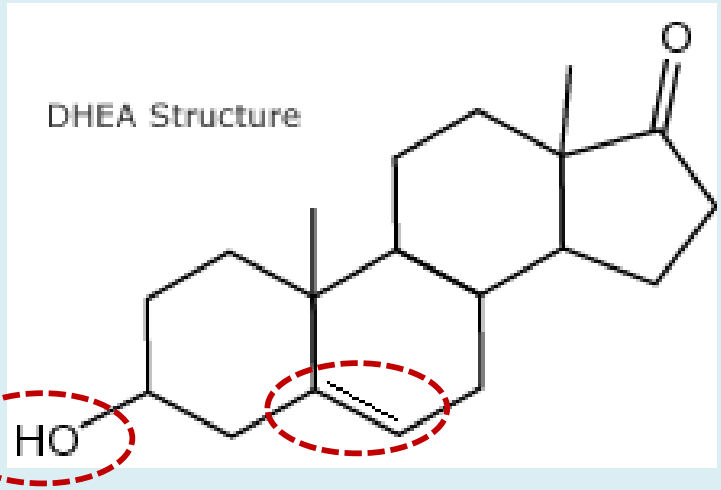
17,20 lyase





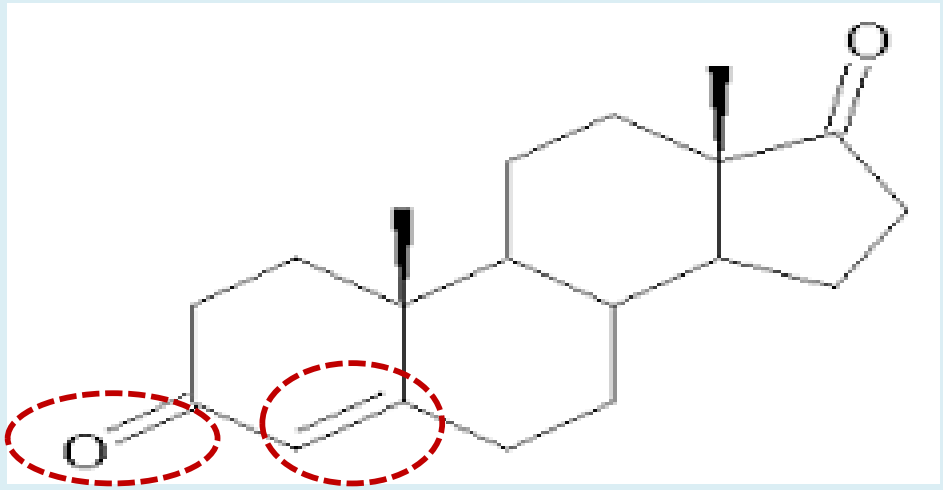
3. Adrenal androgens:

- **Dehydroepiandrosterone**

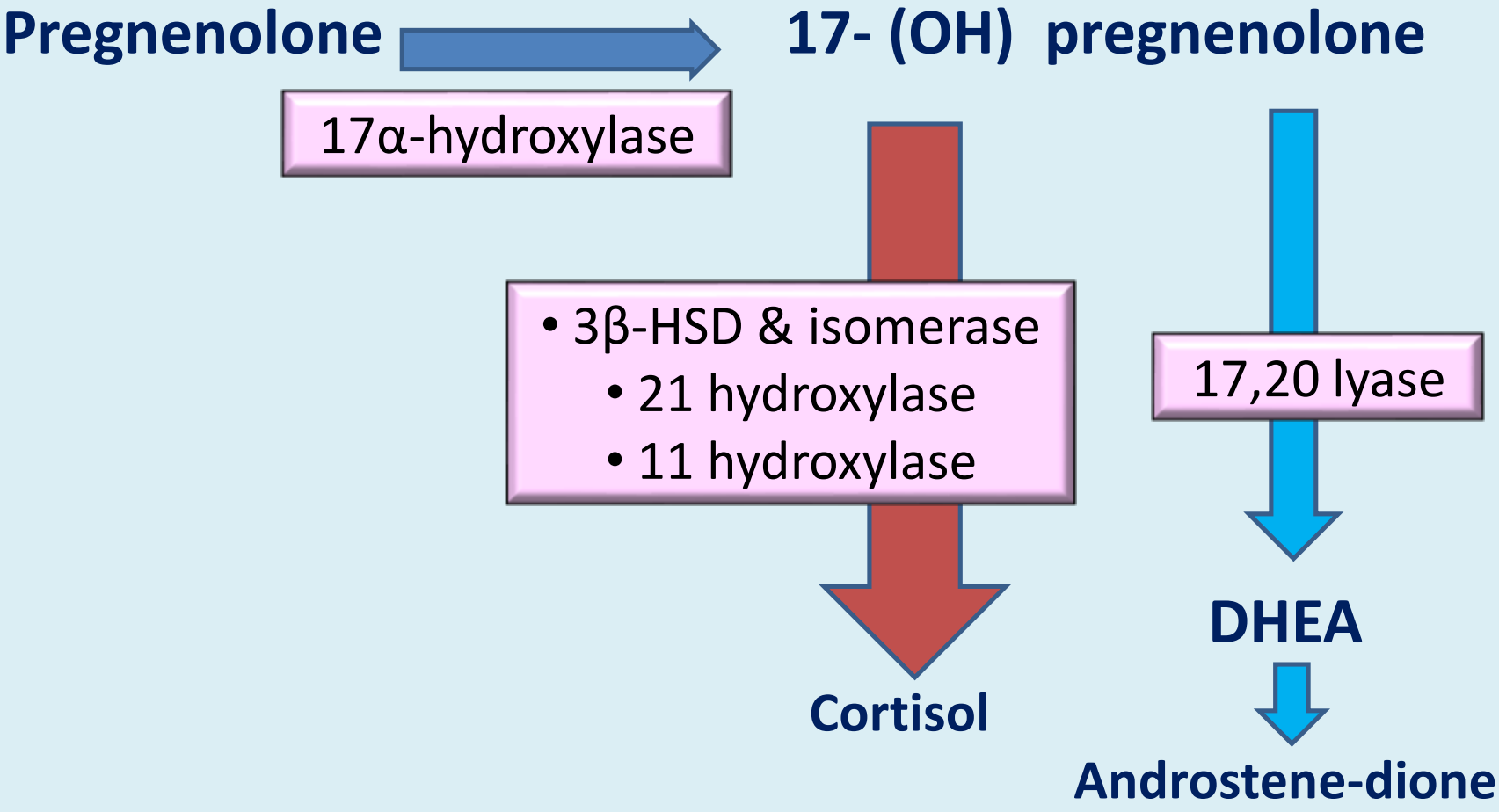


3β (OH)steroid dehydrogenase &
Δ5-4 isomerase

- **Androstene-dione**



3. Adrenal androgens:



Steroid synthesis: overall