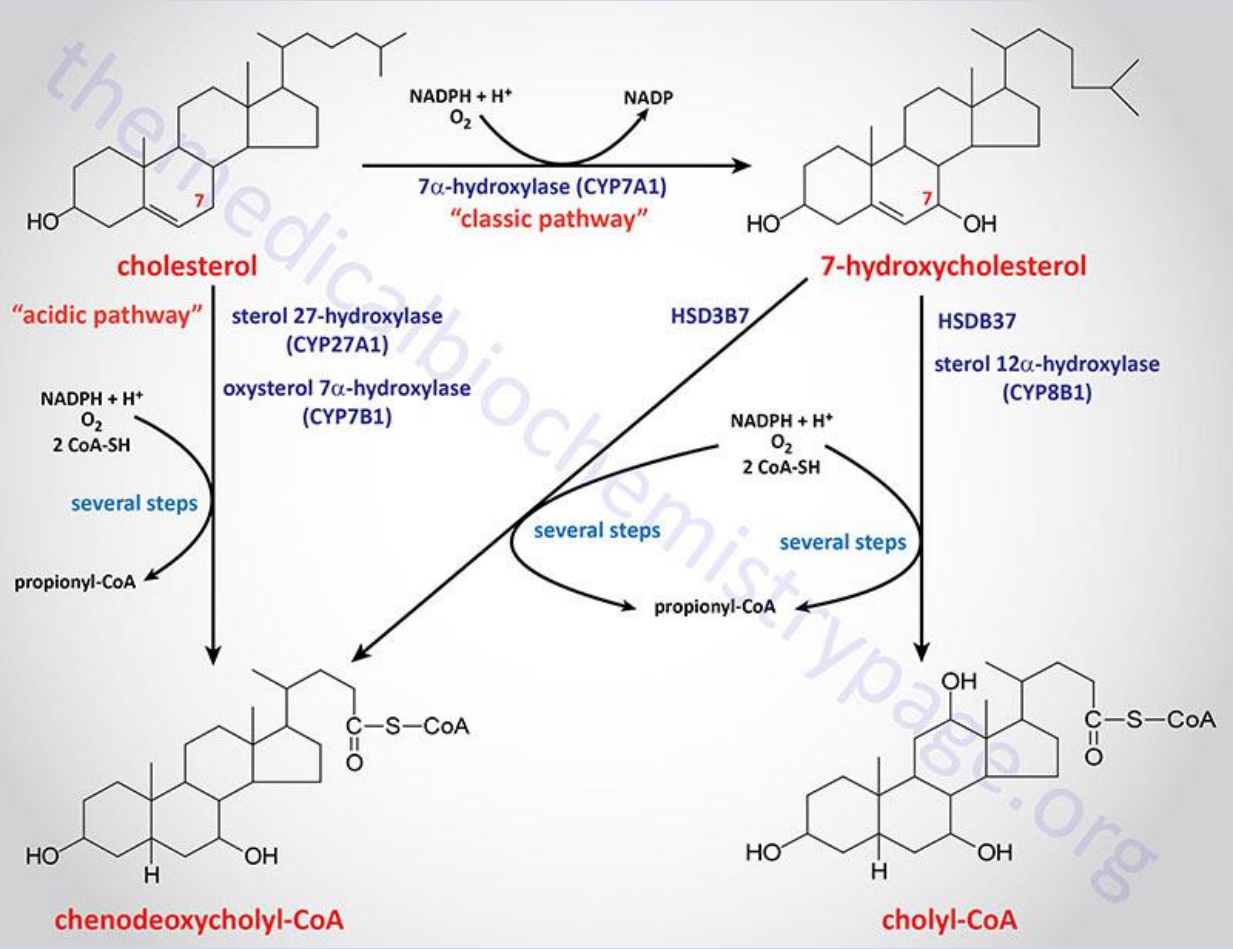
BILE ACIDS



Professor Sameeh Al-Sarayreh
Professor of Medical Biochemistry
Department of Biochemistry and Molecular Biology
Faculty of Medicine, Mutah University

Bile acids

Bile acids are hydroxylated steroids, synthesized in the liver from cholesterol. Peroxisomal enzymes assist in the hepatic biosynthesis of bile acids.

Bile acids are found predominantly in the bile of mammals and other vertebrates. Diverse bile acids are synthesized in the liver.

Bile acids are conjugated with taurine or glycine residues to give anions called bile salts

Bile acid synthesis occurs in liver cells, which synthesize primary bile acids (cholic acid and chenodeoxycholic acid in humans)

Approximately 600 mg of bile salts are synthesized daily to replace bile acids lost in the feces

Classification of bile acids/salts

- Bile acids: primary & secondary.
- Bile acids: conjugated & non-conjugated.
- Bile salts: sodium & potassium salts of bile acids.

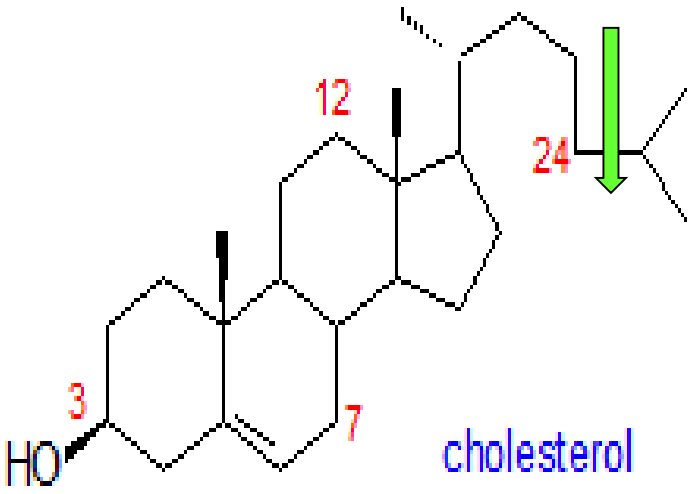
Bile acids: structure

- Bile salts constitute a large family of molecules, composed of a steroid structure with four rings, a side-chain terminating in a carboxylic acid, and the presence of different numbers of hydroxyl groups.

- All bile acids have a 3-hydroxyl group (OH at carbon number 3), derived from the parent molecule, **cholesterol.**

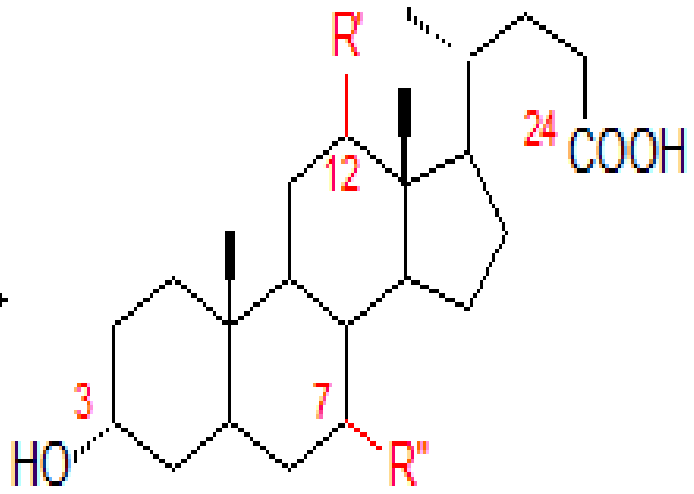
- Bile acids/salts are polar derivatives of cholesterol.
- Bile acids are amphipathic.

Biosynthesis of bile acids



cholesterol

1, 2, 3, 4



1, hydroxylation reactions

2, epimerization of the 3β-hydroxyl group

3, saturation of the double bond

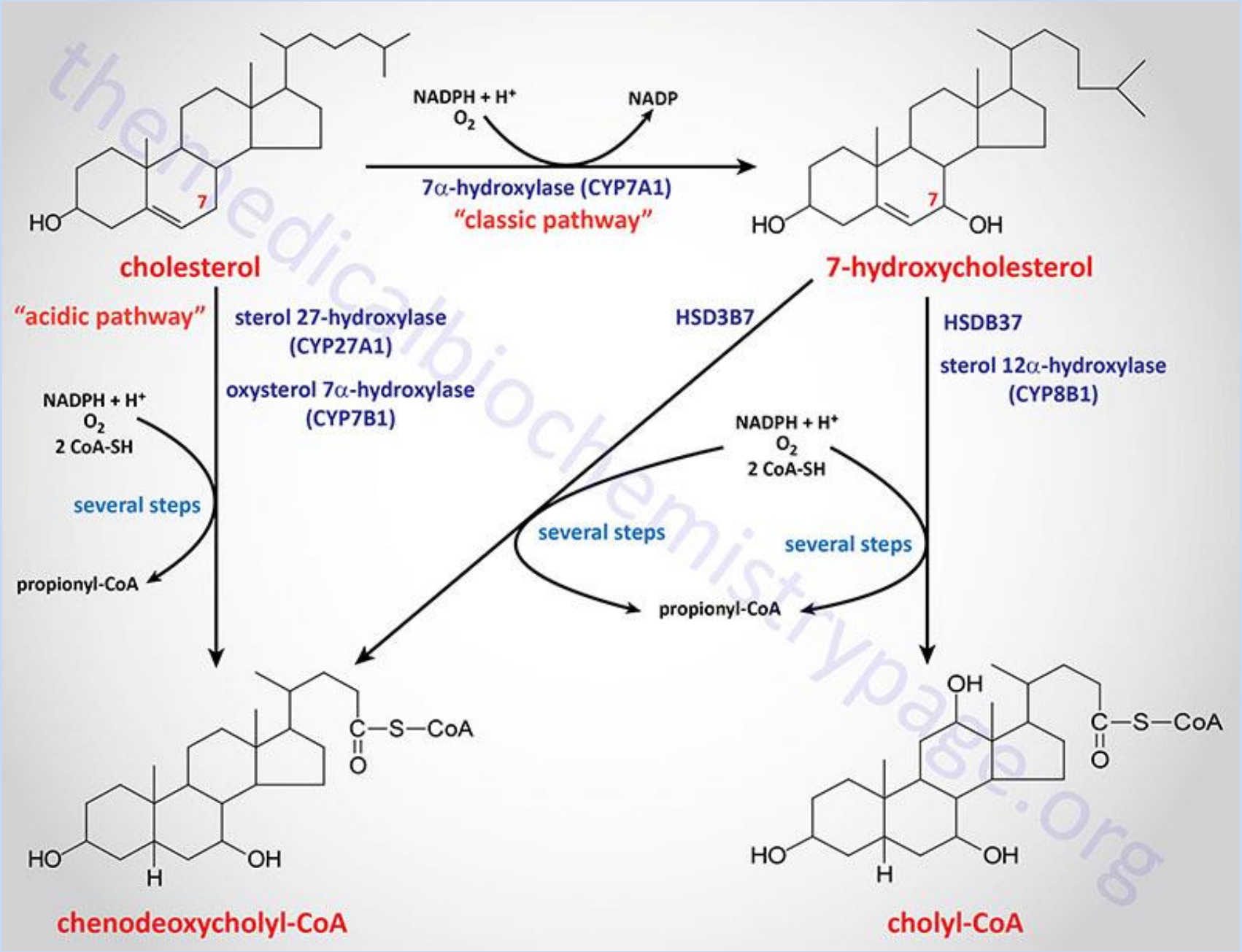
4, side-chain cleavage/oxidation

R' = H, R" = OH, chenodeoxycholic acid

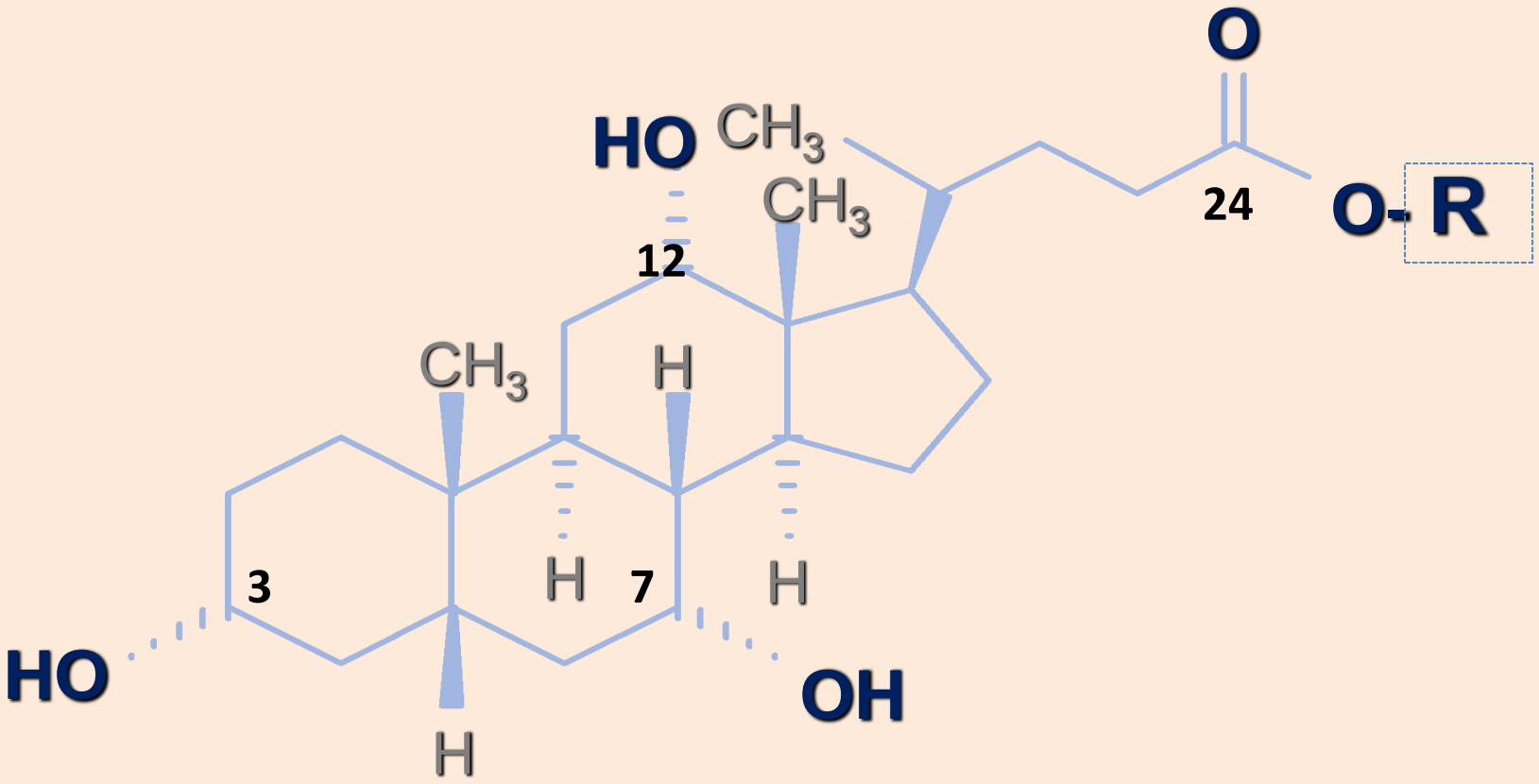
R = OH, R" = OH, cholic acid

R' = OH, R" = H, deoxycholic acid

glycine and taurine conjugates



Bile acids/salts



R= H in non-conjugated bile acids.

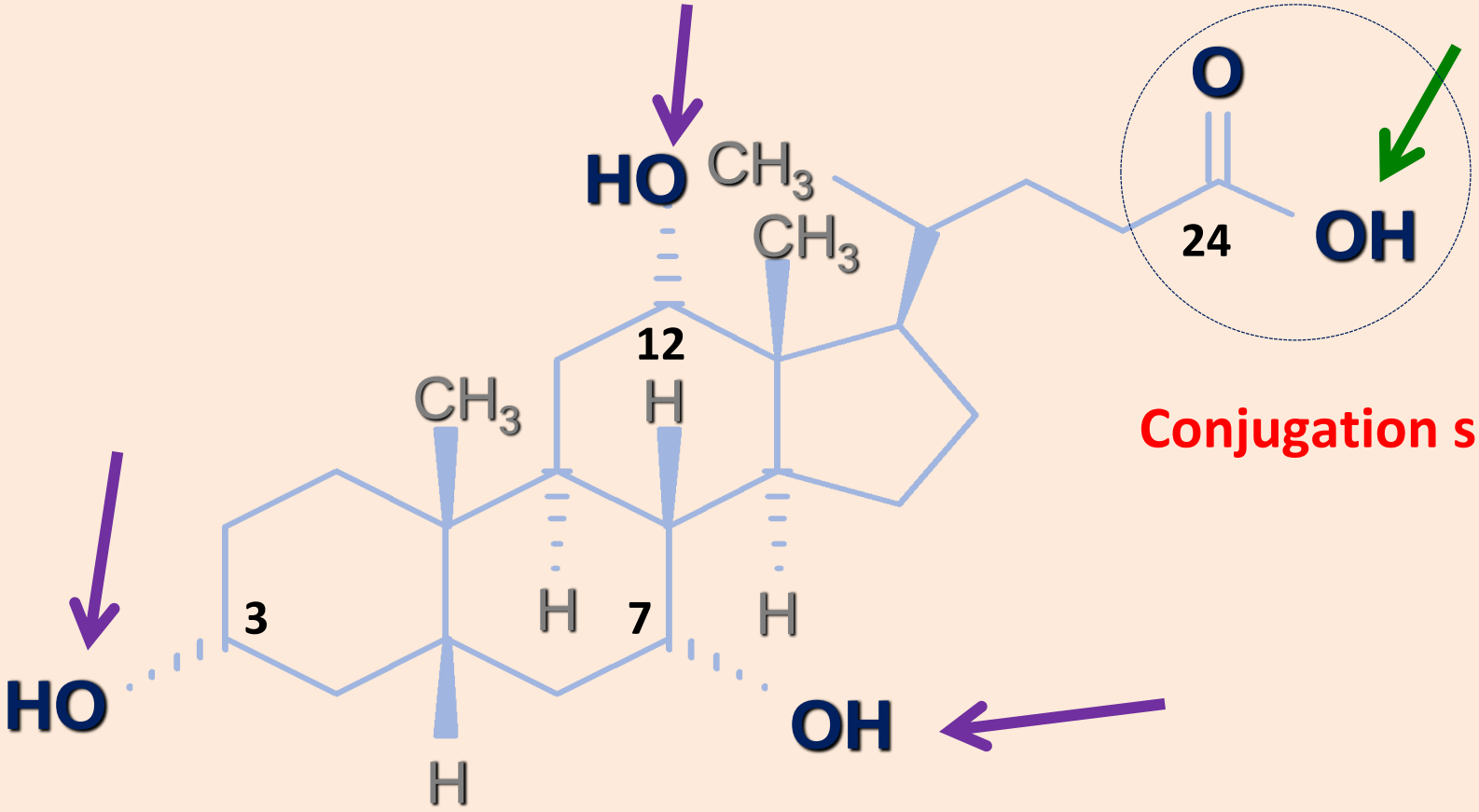
R= Na+/K+ in non-conjugated bile salts.

R= glycine/taurine in conjugated bile acids.

R= Na+/K+ salts of glycine/taurine in conjugated bile salts.

Bile acids: Cholic acid

non-conjugated bile acid



Conjugation site

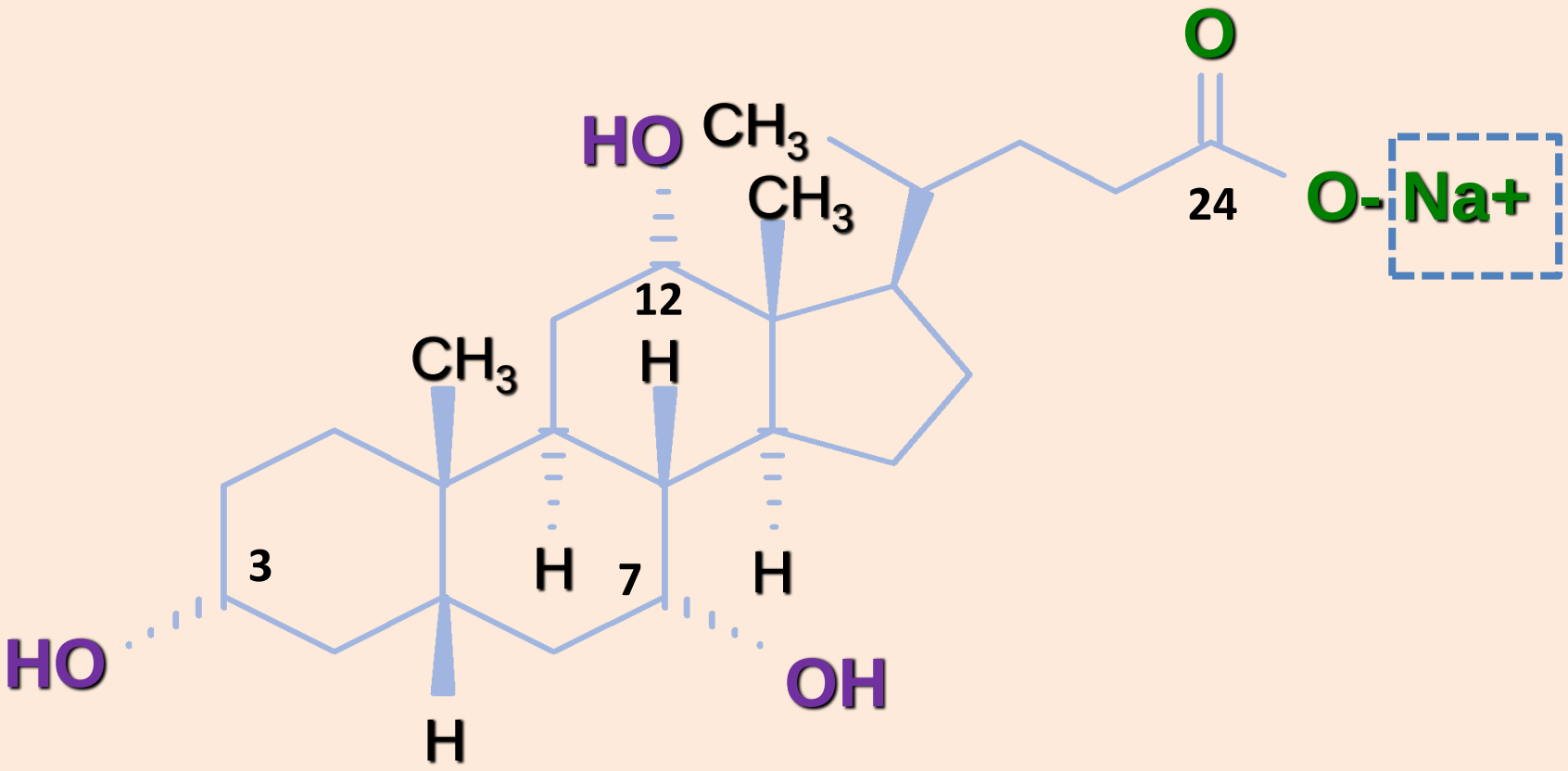
Polar groups are:

- OH groups
- COOH group

Cholic acid is the most common bile acid. It contains 3 OH groups at 3, 7, 12.

Bile salts: Sodium Cholate

(non-conjugated bile salt)



Conjugation

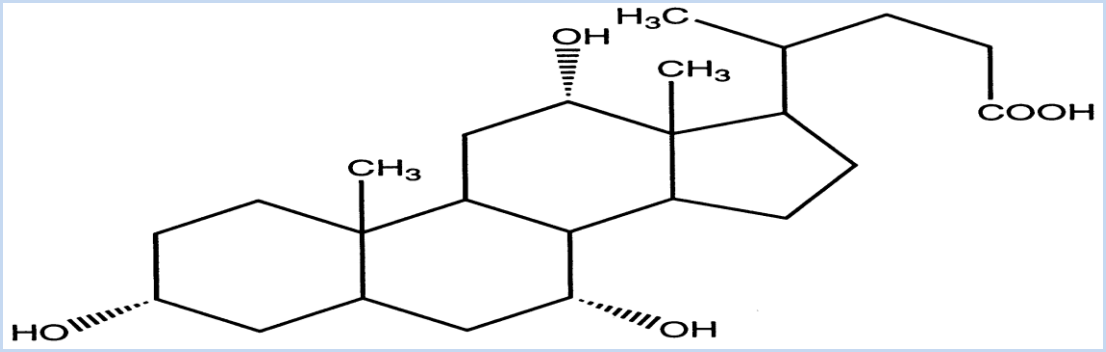
- **Prior to secreting any of the four bile acids (primary and secondary), liver cells conjugate them with one of two amino acids, glycine or taurine, to form a total of 8 possible conjugated bile acids.**

➢ **Glycine= $NH_2-CH_2-COO^-$**

➢ **Taurine = $NH_2-CH_2-CH_2-SO_3^-$**

- **Conjugated bile acids are almost always in their deprotonated (A-) form in the duodenum, which makes them much more water soluble thus, able to emulsify fats.**

Bile Acid Conjugation



Cholic acid

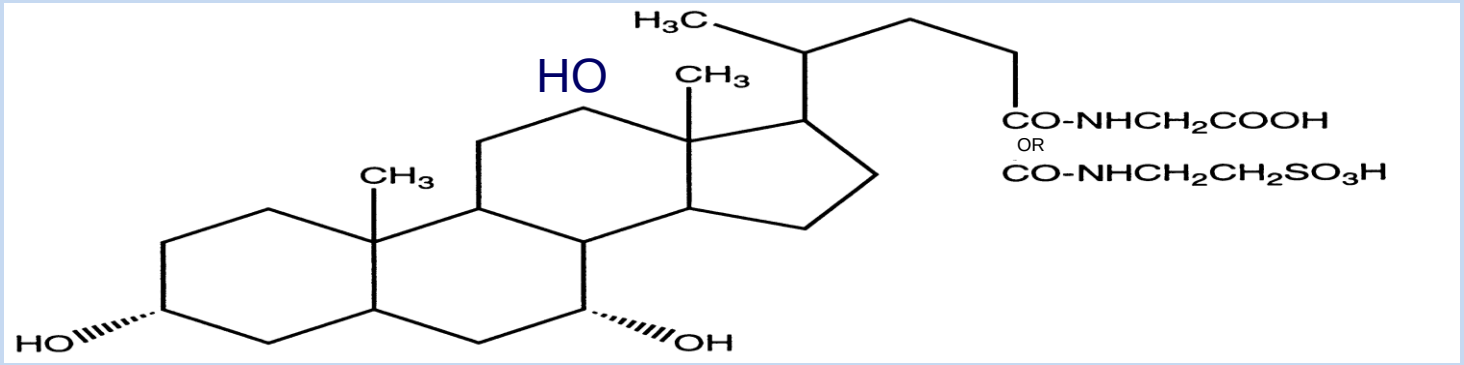
Bile Acids

+

Glycine

OR

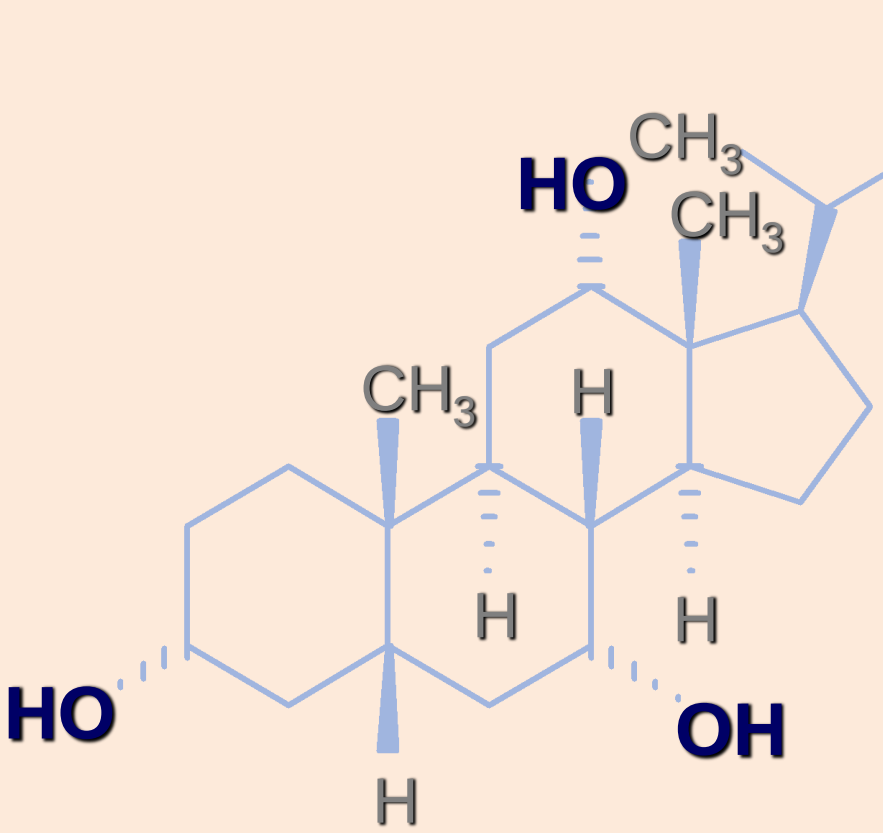
Taurine



Glycocholic acid Or Taurocholic acid

Bile salts: Sodium taurocholate

(conjugated bile salt)



or
NH-CH2-COO-Na
(sodium glycocholate)

Biosynthesis of bile acids & Enterohepatic circulation

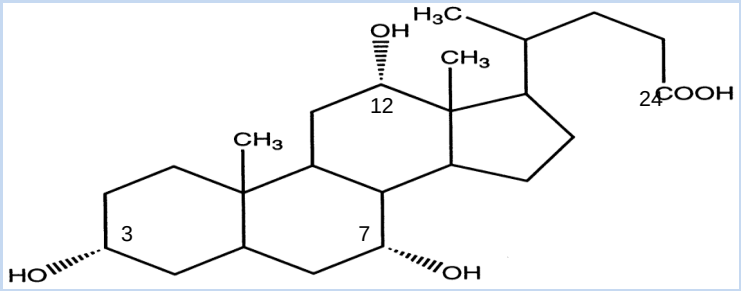
- Bile acid synthesis occurs in liver cells which synthesize primary bile acids in humans from cholesterol.
- Bile acids are stored in the gallbladder and are cycled between the intestines and liver via the enterohepatic circulation.

- When these bile acids are secreted into the lumen of the intestine, bacterial partial dehydroxylation (OH at carbon 7) forms the secondary bile acids.
- Cholic acid is converted into deoxycholic acid and chenodeoxycholic acid is converted into lithocholic acid.

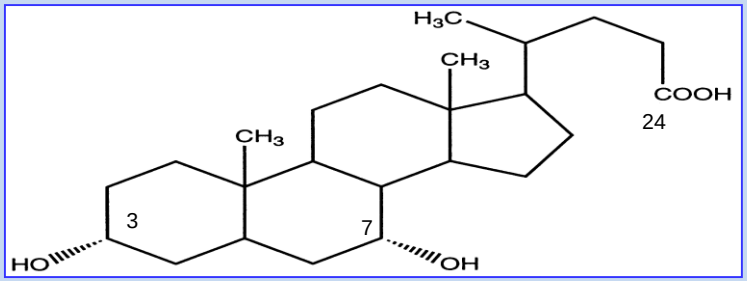
- All these bile acids can be taken back up into the blood stream (~ 95%), return to the liver, and be re-secreted in a process known as enterohepatic circulation. ~5% are excreted in faeces.

Primary and secondary bile acids

Primary Bile Acids



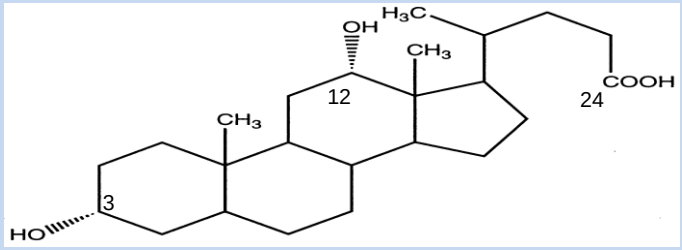
Cholic acid
(3 OH groups)



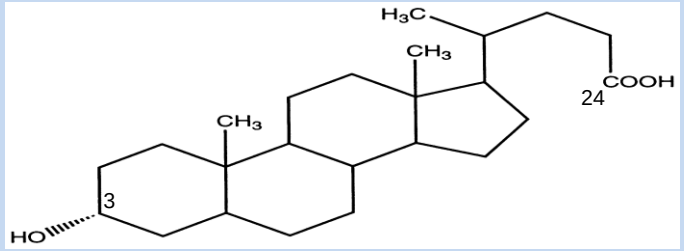
Chenodeoxycholic acid
(2 OH groups)

7-dehydroxylation by gut bacteria

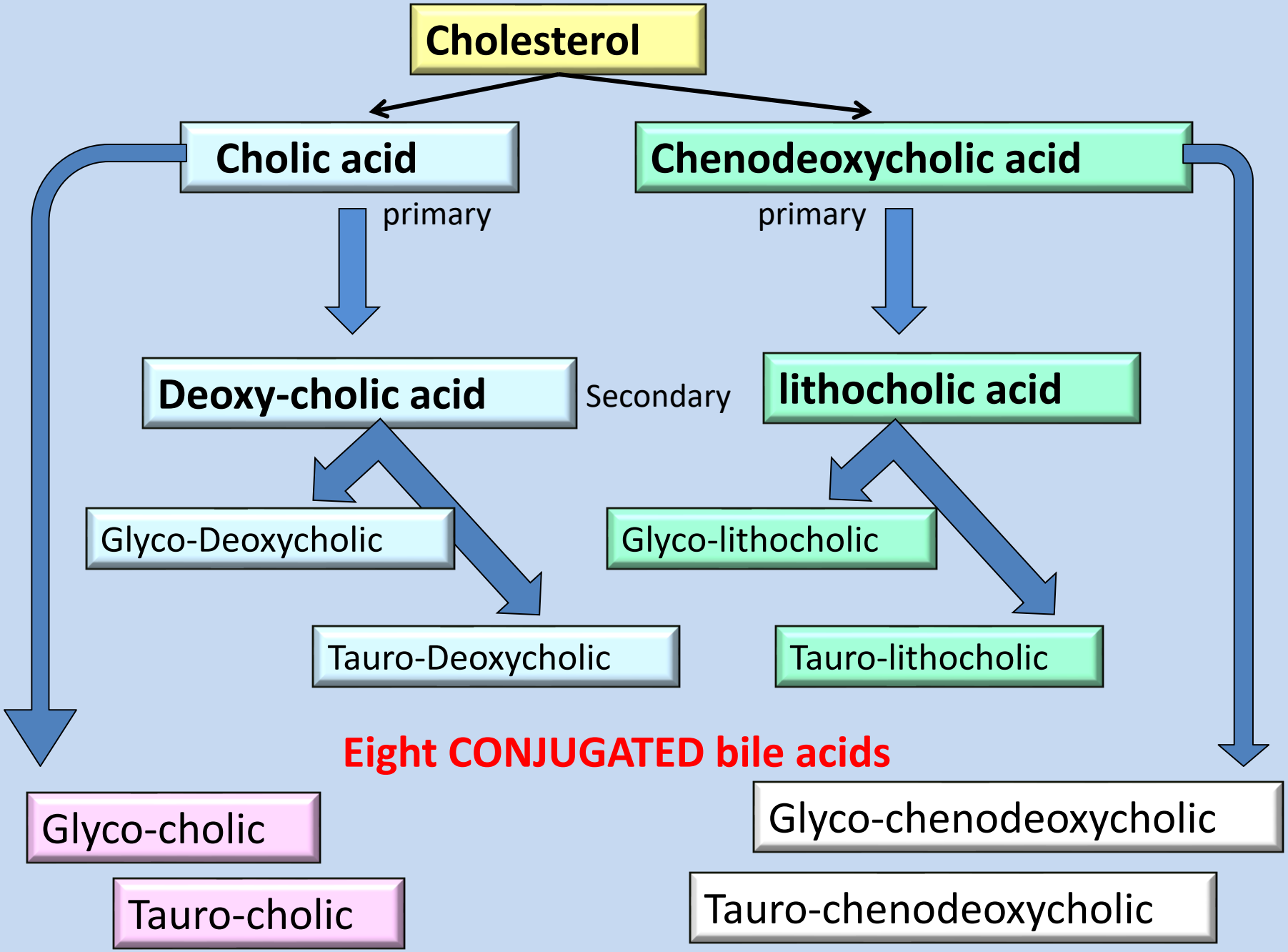
Secondary Bile Acids



Deoxycholic acid
(2 OH groups)



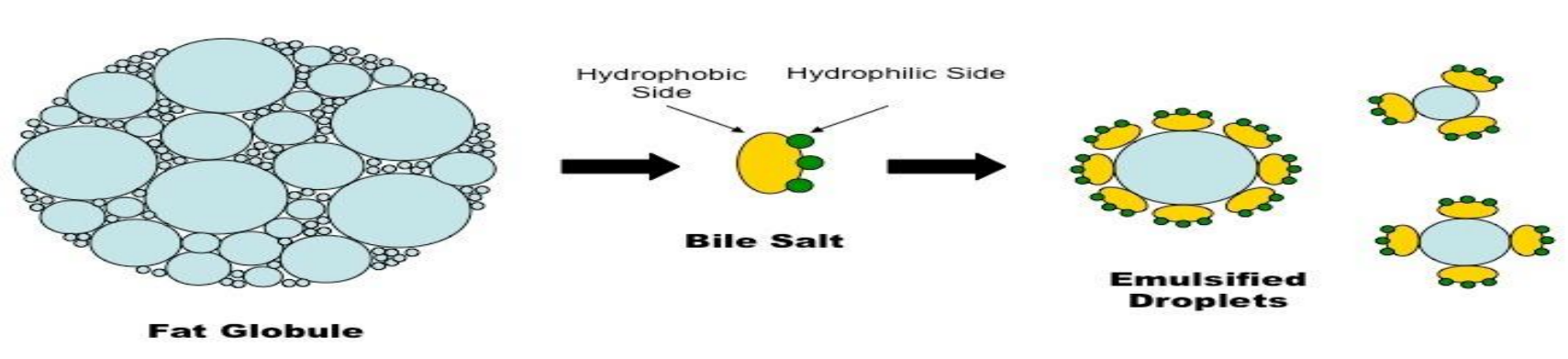
Lithocholic acid
(1 OH group)


Cholesterol
Cholic acid
primary
Chenodeoxycholic acid
primary
Deoxy-cholic acid
Secondary
lithocholic acid
Glyco-Deoxycholic
Glyco-lithocholic
Tauro-Deoxycholic
Tauro-lithocholic
Eight CONJUGATED bile acids
Glyco-cholic
Glyco-chenodeoxycholic
Tauro-cholic
Tauro-chenodeoxycholic

Functions of bile acids/salts

1. The main function of bile acids is to act as powerful detergents or emulsifying agents in the intestines to aid the digestion and absorption of ***fatty acids***, ***monoacylglycerols***, ***fat-soluble vitamins*** and other fatty products.

- As amphipathic molecules, conjugated bile salts sit at the lipid/water interface to form micelles and can solubilize lipids.
- Bile acid-containing micelles aid lipases to digest lipids.



Functions of bile acids/salts

2. Prevent the precipitation of cholesterol in bile.

3. This is the major pathway for the removal of cholesterol from the body as ~ 5% of bile acids is lost into the faeces.

4. bile acids act as signaling molecules.

- **They have an influence on the metabolism of lipids and of glucose.**

Clinical significance of bile salts

Hyperlipidemia:

- As bile acids are made from endogenous cholesterol, disruption of the enterohepatic circulation of bile acids will lower cholesterol.

- Bile acid sequestrants bind bile acids in the gut, preventing reabsorption. In so doing, more endogenous cholesterol is shunted into the production of bile acids, thereby lowering cholesterol levels. The sequestered bile acids are then excreted in the faeces.

Cholestasis

- Structural or functional abnormalities of the biliary system result in an increase in bile acids in the blood. Bile acids are related to the itching.

Clinical significance of bile salts

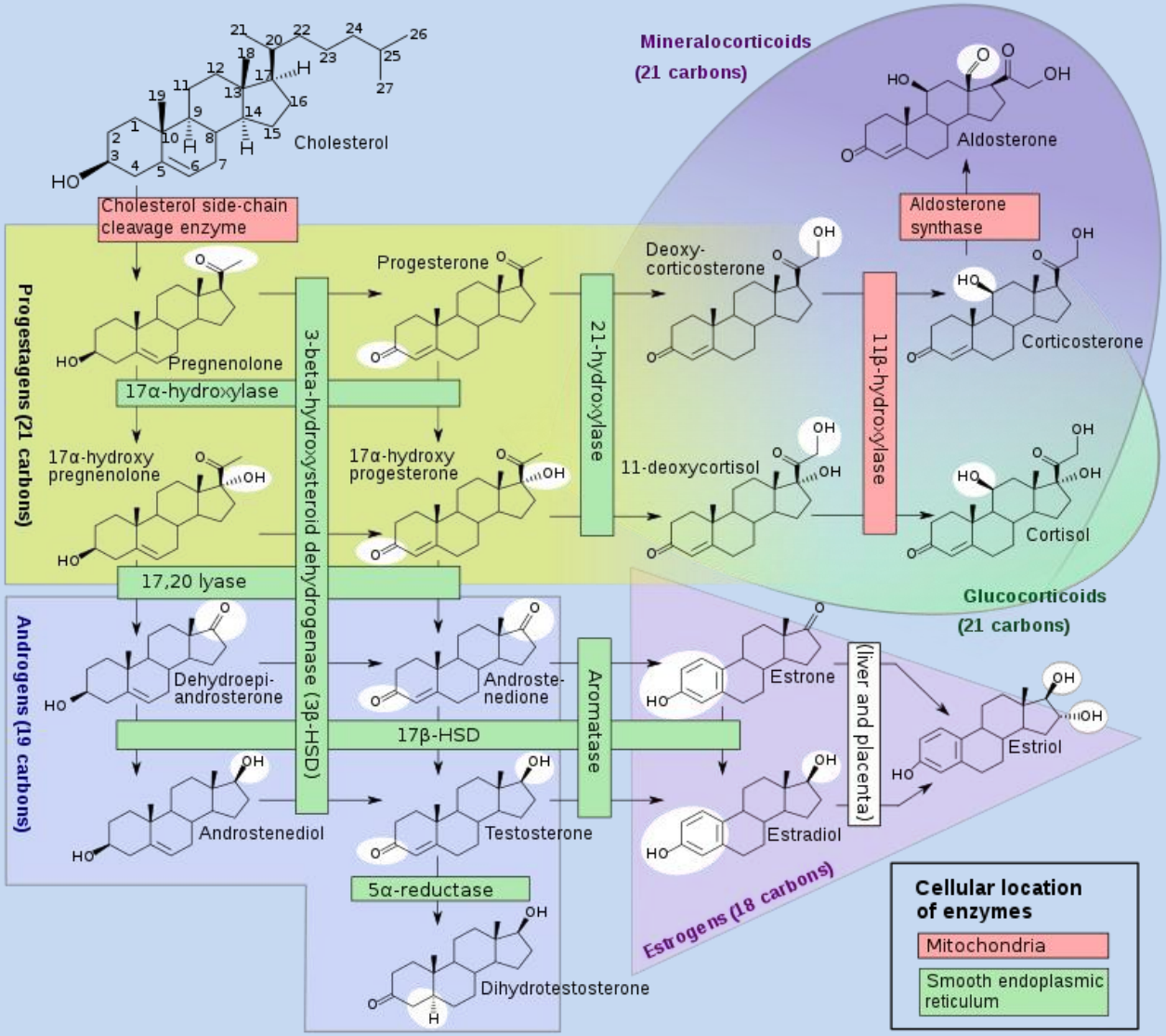
Colon cancer

- **At high concentrations, bile acids are toxic and their presence is relevant to colon cancer.**

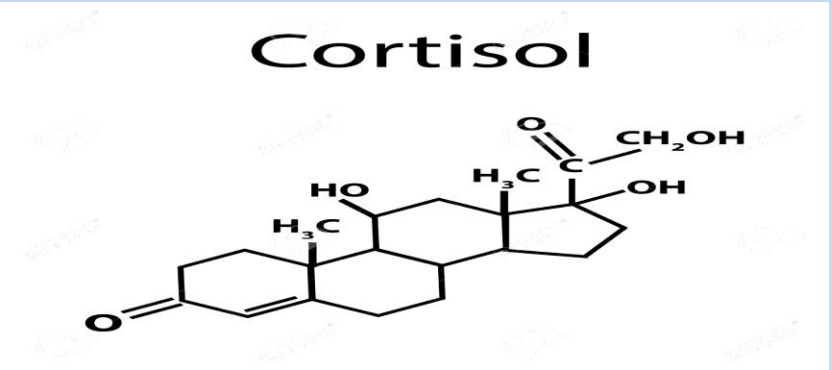
Gallstones:

- **Lower concentrations of Bile acids or Phospholipids in bile reduce cholesterol solubility and lead to microcrystal formation.**
- **Oral therapy with chenodeoxycholic acid has been used to dissolve cholesterol gallstones.**

Steroid Hormones



Corticosteroids:



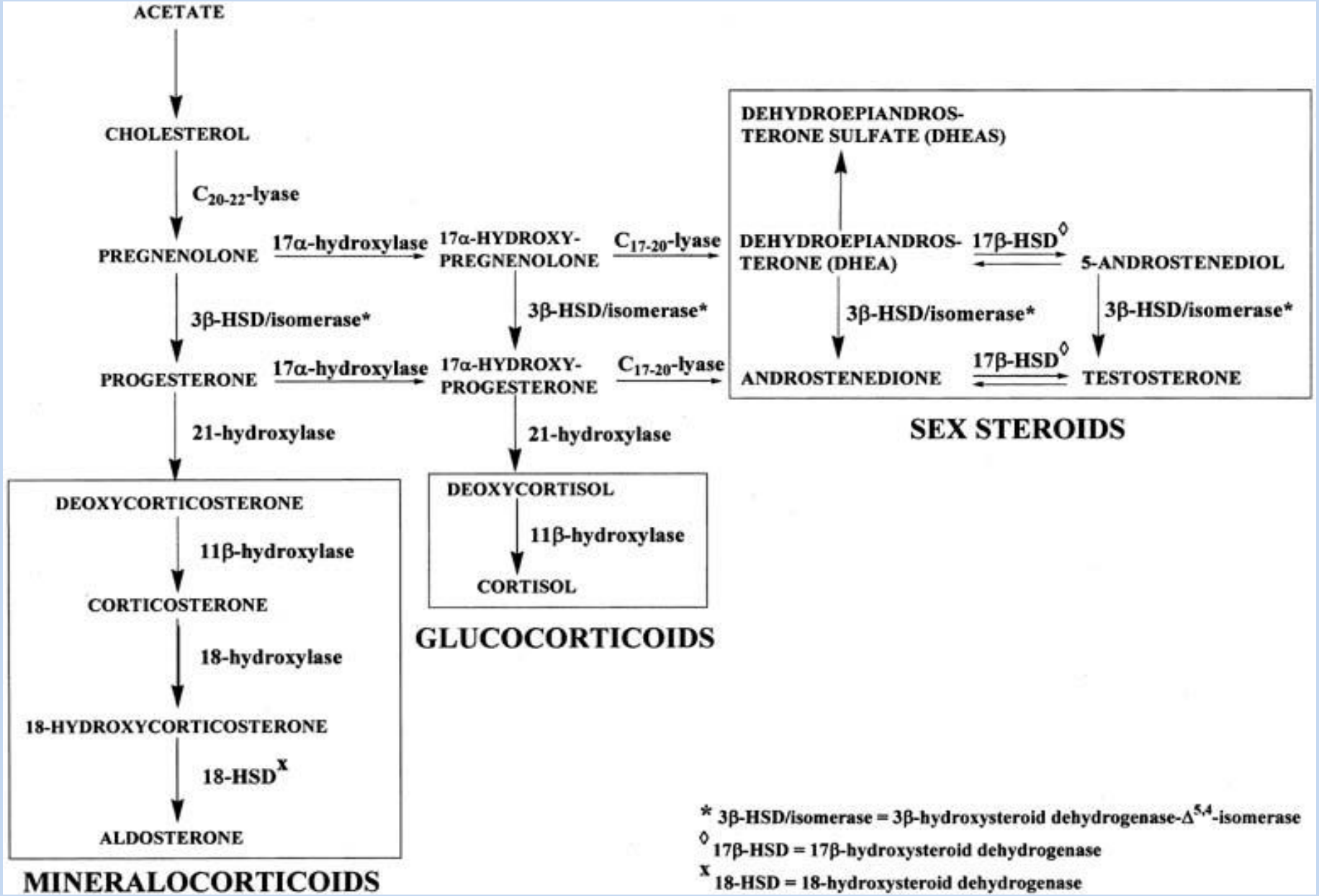
Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex of vertebrates.

Two main classes of corticosteroids, glucocorticoids and mineralocorticoids, are involved in a wide range of physiological processes, including stress response, immune response, and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behaviour.

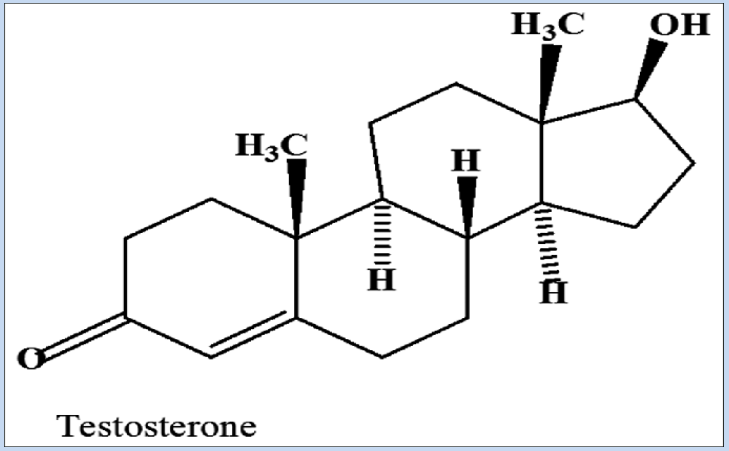
Some common naturally occurring steroid hormones are cortisol, corticosterone, cortisone and aldosterone.

The main corticosteroids produced by the adrenal cortex are cortisol and aldosterone.

Pathway of Corticosteroids biosynthesis



Male sex hormones:
Testosterone



Testosterone

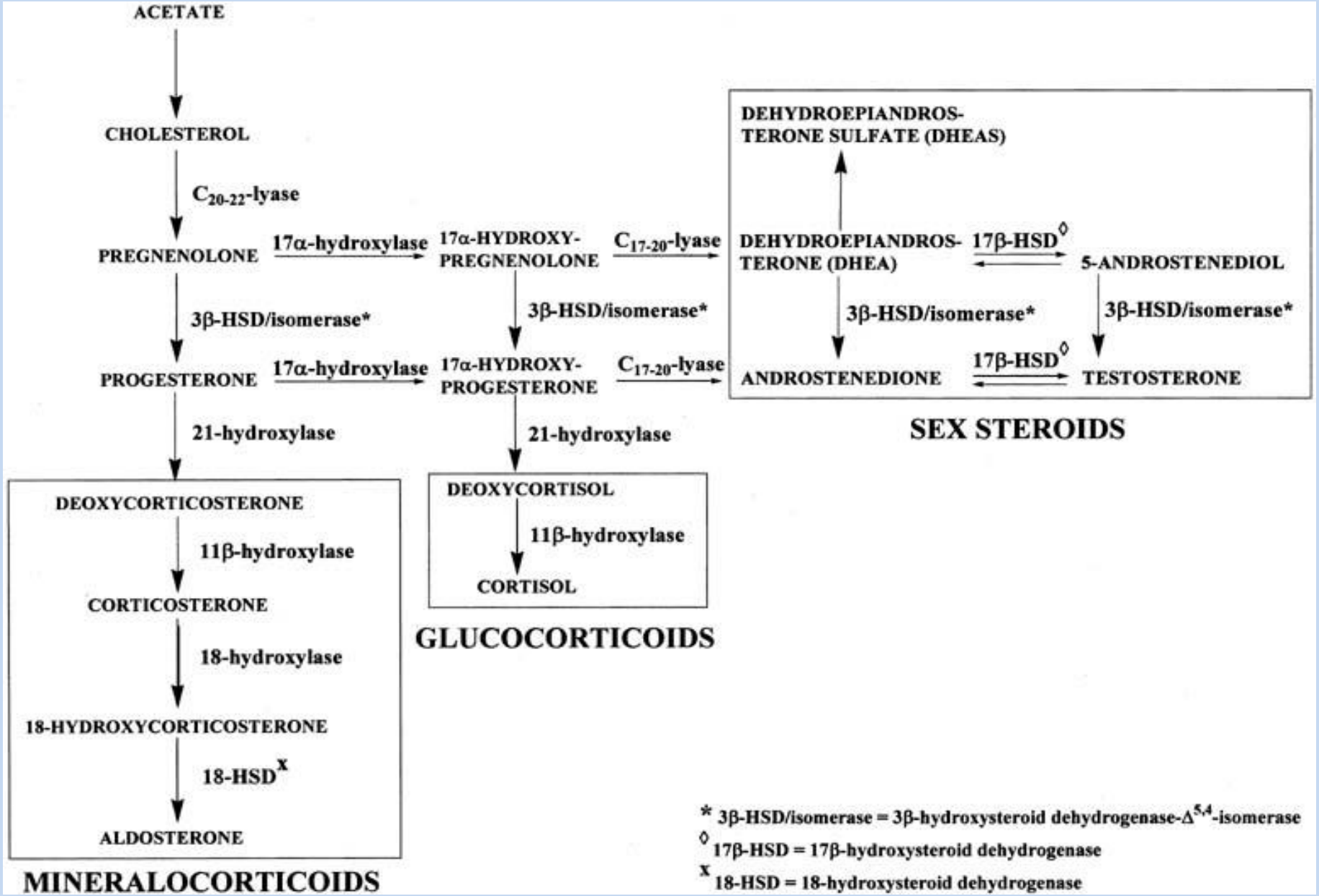
Testosterone is a hormone found in humans, as well as in animals. The testicles primarily make testosterone in men. Women's ovaries also make testosterone, though in much smaller amounts.

The production of testosterone starts to increase significantly during puberty, and begins to dip after age 30 or so.

Testosterone is most often associated with sex drive, and plays a vital role in sperm production.

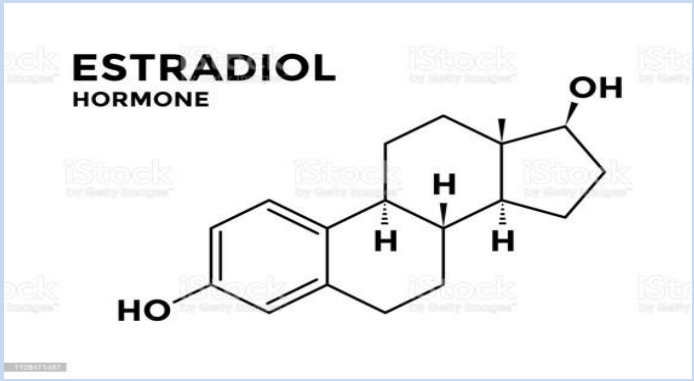
A man's testosterone levels can also affect his mood.

Pathway of testesterone biosynthesis



Female sex hormones:

Estradiol

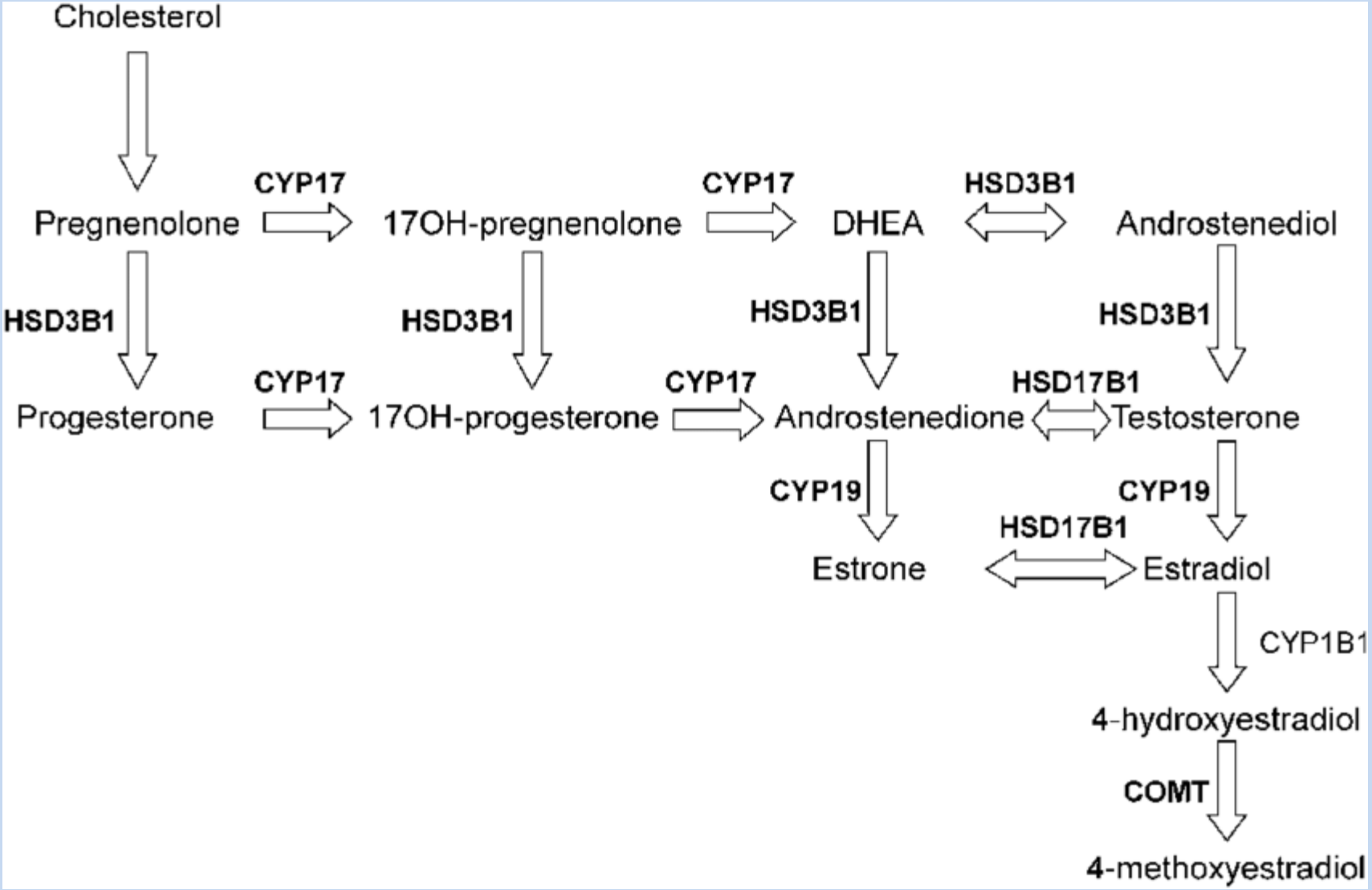


Estradiol , also spelled oestradiol, is an estrogen steroid hormone and the major female sex hormone.

Estradiol is responsible for the development of female secondary sexual characteristics such as the breasts, widening of the hips, and a female-associated pattern of fat distribution

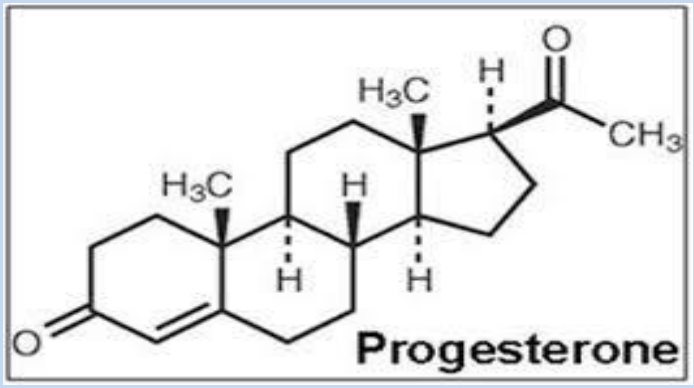
It is important in the development and maintenance of female reproductive tissues such as the mammary glands, uterus, and vagina during puberty, adulthood, and pregnancy.

Pathway of estradiol biosynthesis



Female sex hormones:

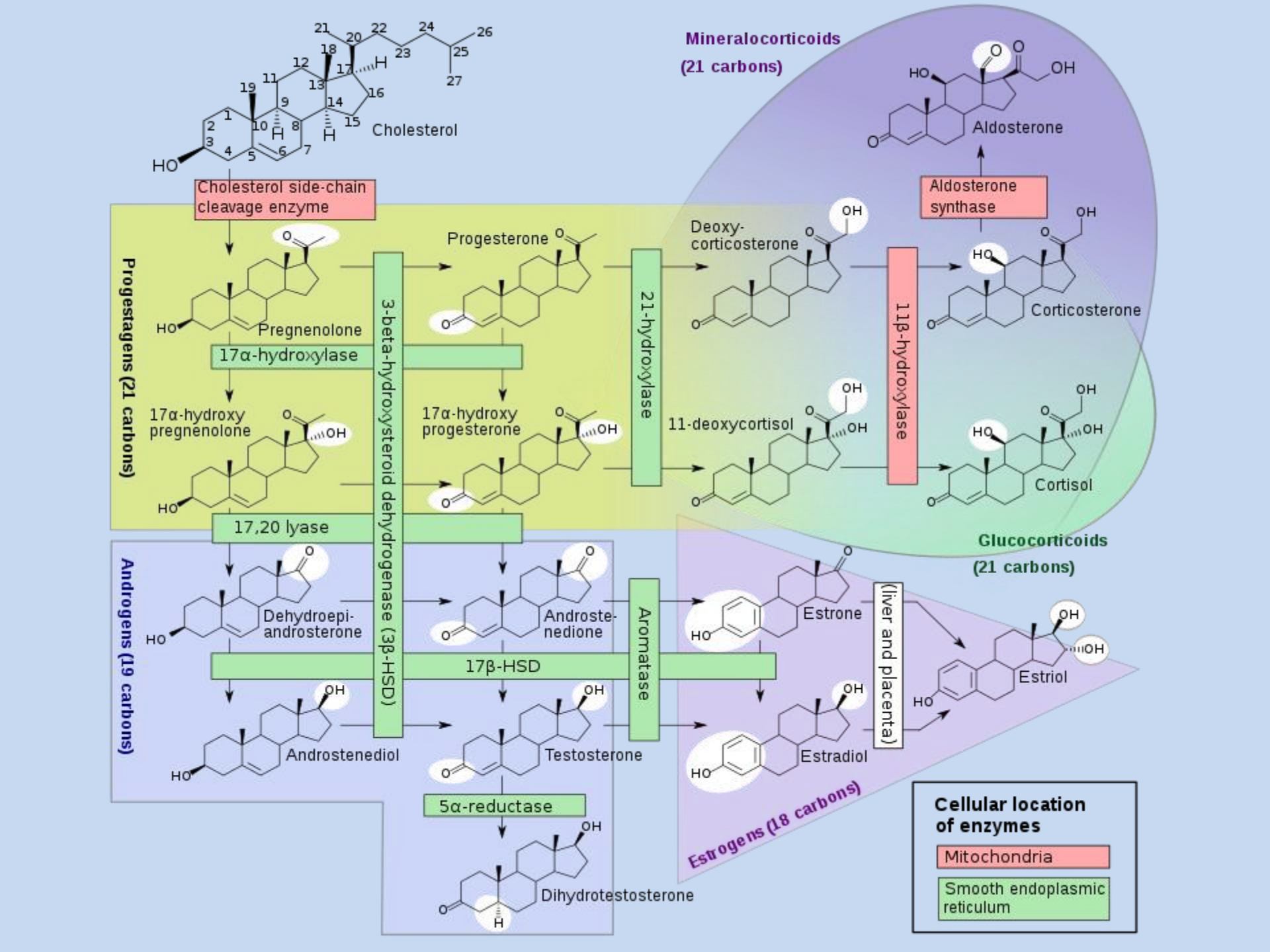
Progesterone



Progesterone is an endogenous steroid and progestogen sex hormone involved in the menstrual cycle, pregnancy, and embryogenesis of humans and other species.

Progesterone has a variety of important functions in the body.

It is also a crucial metabolic intermediate in the production of other endogenous steroids, including the sex hormones and the corticosteroids, and plays an important role in brain function as a neurosteroid


Cholesterol
Cholesterol side-chain cleavage enzyme
Progestagens (21 carbons)
Pregnenolone
Progesterone
17α-hydroxylase
17α-hydroxy pregnenolone
17α-hydroxy progesterone
17,20 lyase
3-beta-hydroxysteroid dehydrogenase (3β-HSD)
21-hydroxylase
Deoxy-corticosterone
11-deoxycortisol
11β-hydroxylase
Corticosterone
Cortisol
Aldosterone synthase
Aldosterone
Mineralocorticoids (21 carbons)
Glucocorticoids (21 carbons)
Androgens (19 carbons)
Dehydroepi-androsterone
Androste-nedione
17β-HSD
Androstenediol
Testosterone
5α-reductase
Dihydrotestosterone
Aromatase
Estrogens (18 carbons)
Estrone
Estradiol
(liver and placenta)
Estriol
Cellular location of enzymes
Mitochondria
Smooth endoplasmic reticulum