Drug metabolism and Cytochromes P450 & Bile

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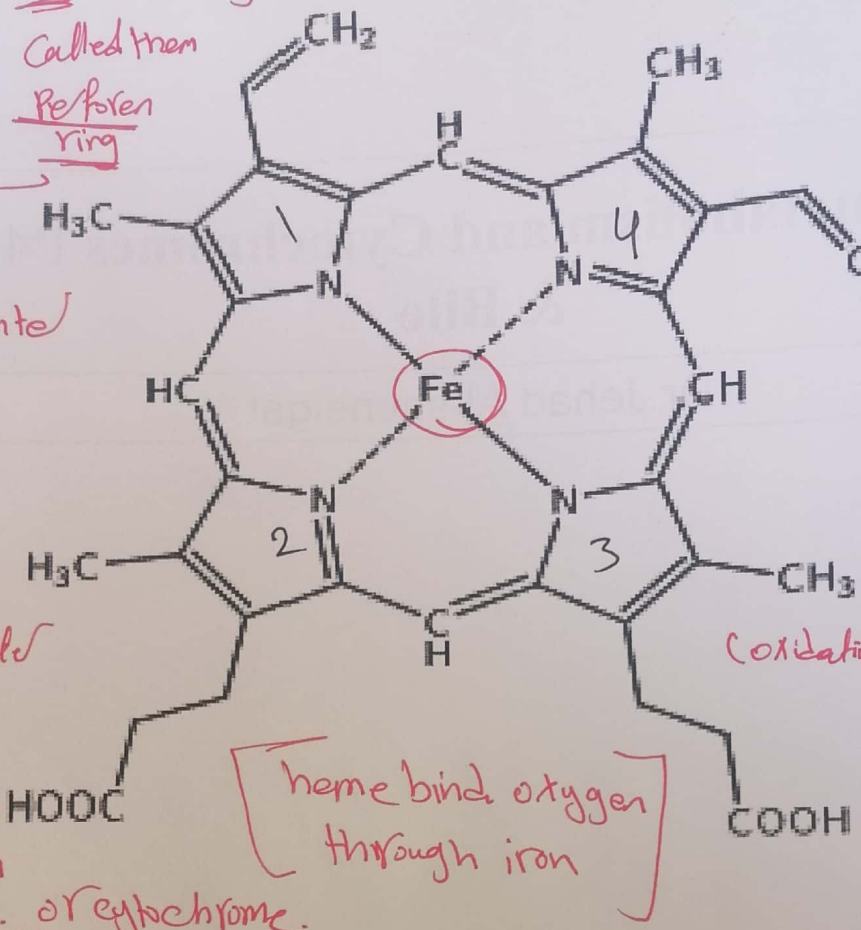
Drug metabolism

- **Cytochromes: are** heme-containing proteins
- Heme is made of a porphyrin ring containing an atom of iron.
- In the electron transport chain, they are involved as carriers of electrons
- The major respiratory cytochromes are classified as a, b, or c, depending on the wavelengths of the spectral absorption peaks.
- Cytochromes are also found in the endoplasmic reticulum eg P450, *b*5
- **Cytochrome P450** family are found associated with the membrane of the smooth endoplasmic reticulum particularly in liver. The cytochrome P450 got its name because when reduced and complexed with carbon monoxide it exhibited a spectral absorbance maximum at 450 nm.
- It uses iron to oxidise molecules to makes them water-soluble and thus easy to dispose out of body. (Oxidation means the addition of oxygen to a molecule or the removal of hydrogen from a molecule)
- The iron acts as an electron carrier, undergoing alternate reduction to the ferrous +2 states and oxidation to the ferric +3 state.

Heme



4 Pe/ol ring
Called them
Pe/porin
ring

When iron
come in center
called
heme

heme has
semi liquid structure
whether in
~~hemoglobin~~
myoglobien
hemoglobin or cytochrome

[heme bind oxygen
through iron]

Fe^{+2} Ferrous
state can bind
oxygen

(oxidation) Fe^{+3} Ferric state
Can not bind oxyg

Drug metabolism reactions can be divided into phase I & phase II

1- Phase I reactions involve oxidation, reduction, hydroxylation, hydrolysis, cyclization or decyclization reactions. Oxidation is the most common phase I reactions and it involves the addition of oxygen or removal of hydrogen by mixed function oxidases in the liver.

~~detoxification~~
detoxification
From hydrophobic
to hydrophilic

2- Metabolites that are not sufficiently polar may undergo phase II metabolism which involves Sulfation (SO_4^{-2}), Methylation (example methylation process helps convert the toxic amino acid (homocysteine) into a beneficial amino acid (methionine), Glucuronidation (D-Glucuronic Acid is a sugar acid formed by the oxidation of the C-6 carbon of

hydrophobic → phydrophilic
Soluble in water So kidny can excelt them with urine

Xenobiotic or waste metabolite in the diet or peripheral circulation	Phase I reactions	Primary metabolite	Phase II reactions	Secondary metabolite, suitable for excretion
	Reduction Oxidation Hydroxylation Hydrolysis		Conjugation Sulfation Methylation Glucuronidation	

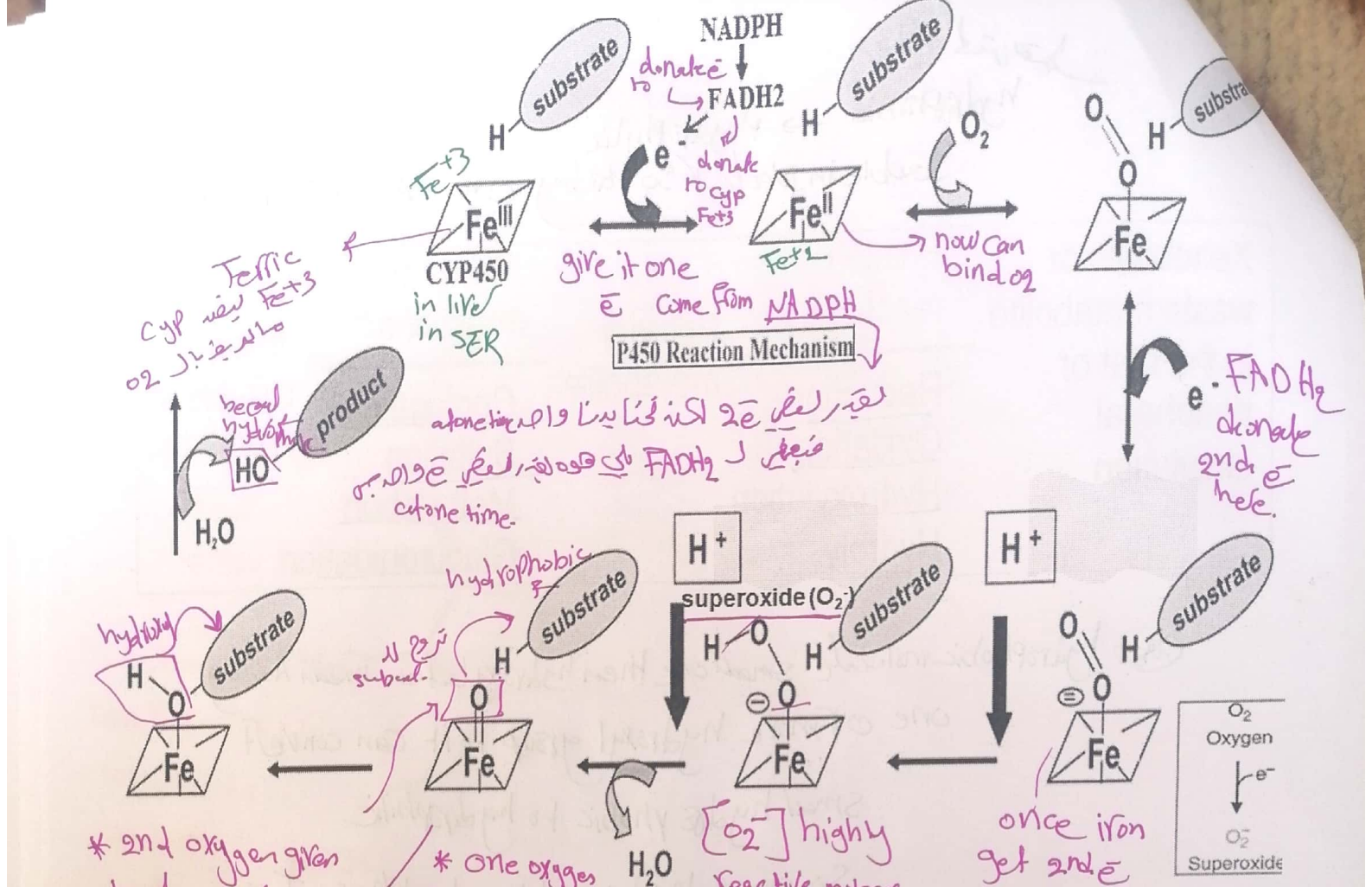
hydrophobic molecule small one then hydroxylation mean Adding one or more hydroxyl group to it can convert small hydrophobic to hydrophilic
So small hydrophobic mole phase I is enough to convert

hydrophobic molecule large Adding few hydroxyl group to it will not converting to hydrophobic so large hydrophobic molecule need phase II reaction
So need phase I / II to be hydrophilic

P450 Oxidation mechanism

hydroxilation Add OH hydroxyl group.

detoxification :-
converting from hydrophobic to hydrophilic because our body can excelted it with urine.



Nomenclature of P450

CYTOCHROME P450

CYP **3** **A** **4**

- CYP — Family
- 3 — Subfamily
- A — Specific isoform
- 4 — Sequenced A.A different but catalyze same reaction

P denotes the cytochrome P450, the 3 denotes bfamily, and the 4 denotes the specific isozyme nary structure but catalyze the same reaction).

hydroxyl group Added to hydrophobic molecul converting it to hydrophilic

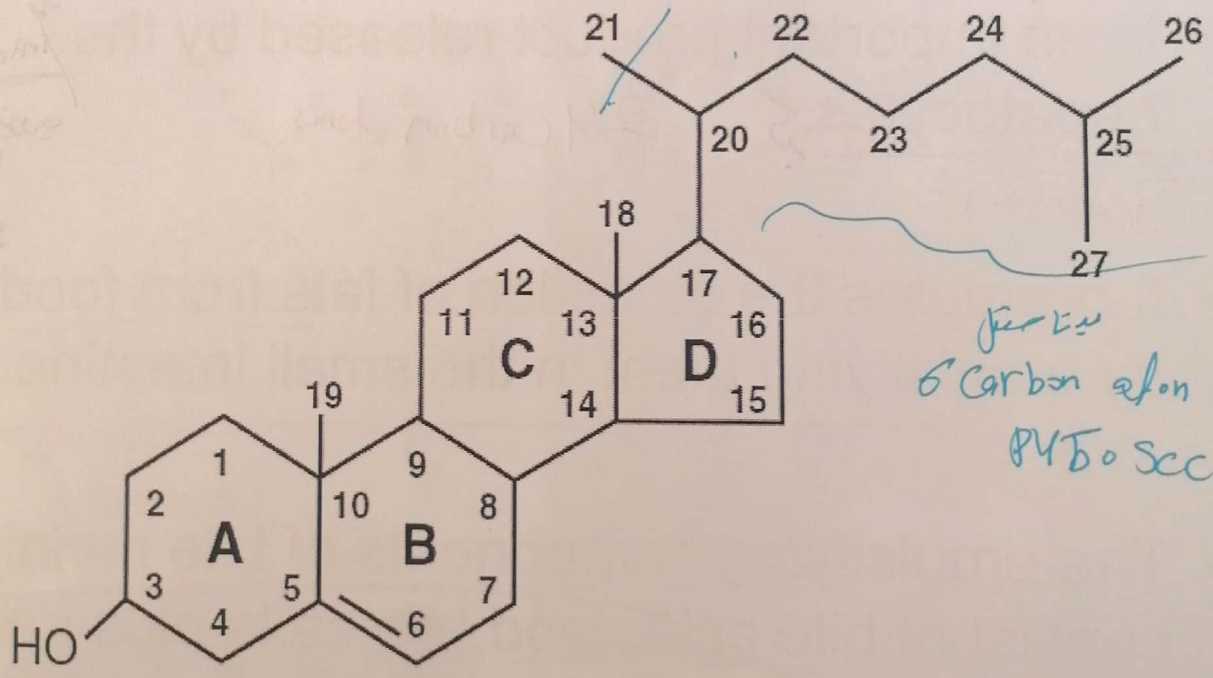
Substrate with H so it hydrophobic molecule

Substrate with OH hydroxyl so it hydrophilic molecule

- **Role of cytochromes P- 450 in the metabolism of Steroid hormones**
- Cholesterol is the precursor of all steroid hormones.

- Steroid hormones contain 21 or fewer carbon atoms, whereas cholesterol contains 27.

- The first stage in the synthesis of steroid hormones is the removal of a six-carbon unit from the side chain of cholesterol to form pregnenolone. The removal is accomplished by Cytochrome $P450_{SCC}$ (desmolase) that cleaves the bond ($P450_{SCC}$ is Cholesterol Side-Chain Cleavage Enzyme).
- Desmolase that include $P450_{SCC}$ is found in the mitochondria of tissues that synthesize steroids (mainly the adrenal glands and gonads)
- Other steroid hormones are produced from progesterone by reactions that involve members of the P450 family.



Cholesterol (C_{27})

Few points on CYP & Drugs

- Different people have different activity of CYP due to genetic variation (polymorphism) that result in higher or lower expression of CYP than normal.
- This can lead to differences in drug metabolism: poor metabolizer, normal metabolizer or ultra drug metabolizer.
- Some of drugs intermediates are toxic specially if accumulated at high concentrations so if a patient is a high drug metabolizer this may lead to patient toxicity
- Some drugs are given for special purposes that inhibit P450 enzymes to prolong the activity of some other drugs
- Some drugs that have a narrow range of effective dose before they become toxic might be overdosed in a poor metabolizer.
- Poorer P450 substrates drugs would last longer in the body before elimination, which is desirable for some drugs
- CYP may lead to making some drugs ineffective while activating others.

Bile

- Is an important product released by the hepatocytes.
- It promotes the digestion of fats from food by emulsifying them in the small intestine.
- The emulsifying components of bile mainly consist of bile acids and bile salts plus free cholesterol.

- **A. Bile acids and bile salts**
- Bile acids are steroids (cholesterol) consisting of 24 C atoms carrying one carboxyl group and several hydroxyl groups.
- Cholic acid and chenodeoxycholic acid are the most important primary bile acids.
- Cytochrome P450 in the sER is involved in many of the steps.

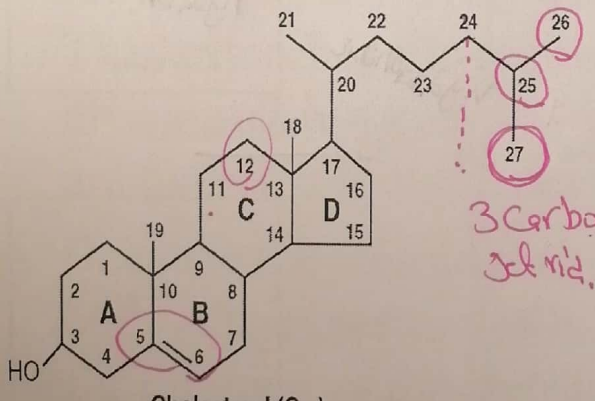
Formation of bile acid

1- Cholesterol double bond is removed.

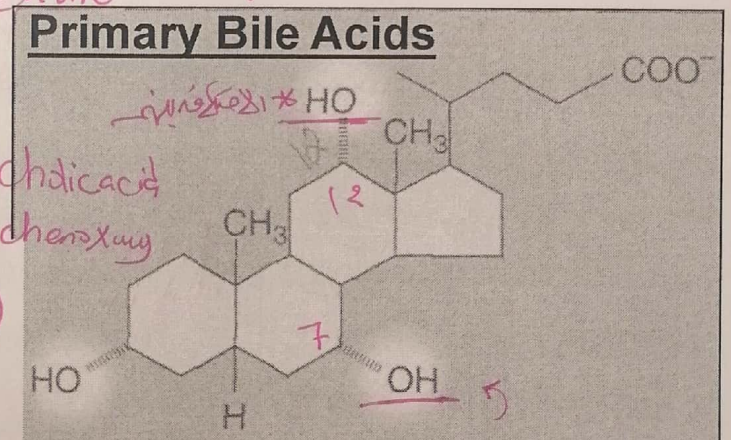
2- Monooxygenases then introduce one or two additional OH groups into steroid ring (to atoms 7, 12 in Cholic acid and atom 7 to chenodeoxycholic acid)

3- The side chain is shortened by three C atoms, and the terminal C atom is oxidized to a carboxylate group.

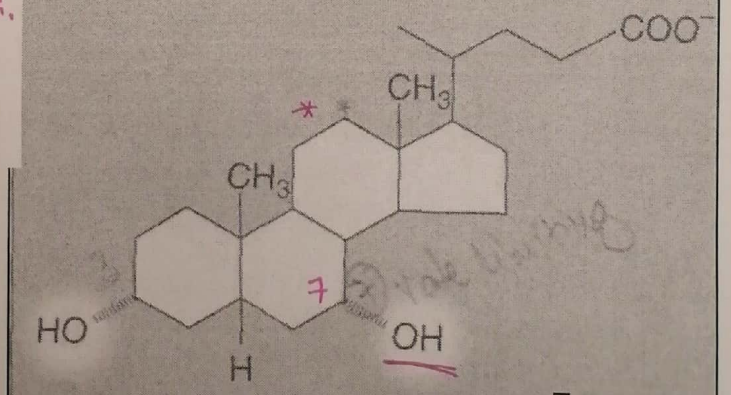
4- During bile acid synthesis it is important that A and B rings is altered from *trans* to *cis* so the hydrophilic groups in the bile acids lie on one side of the molecule.



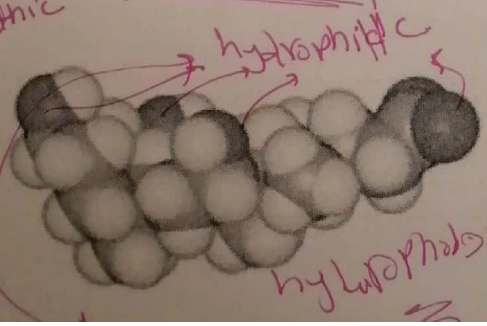
Cholesterol (C_{27})



Cholic acid (24C)

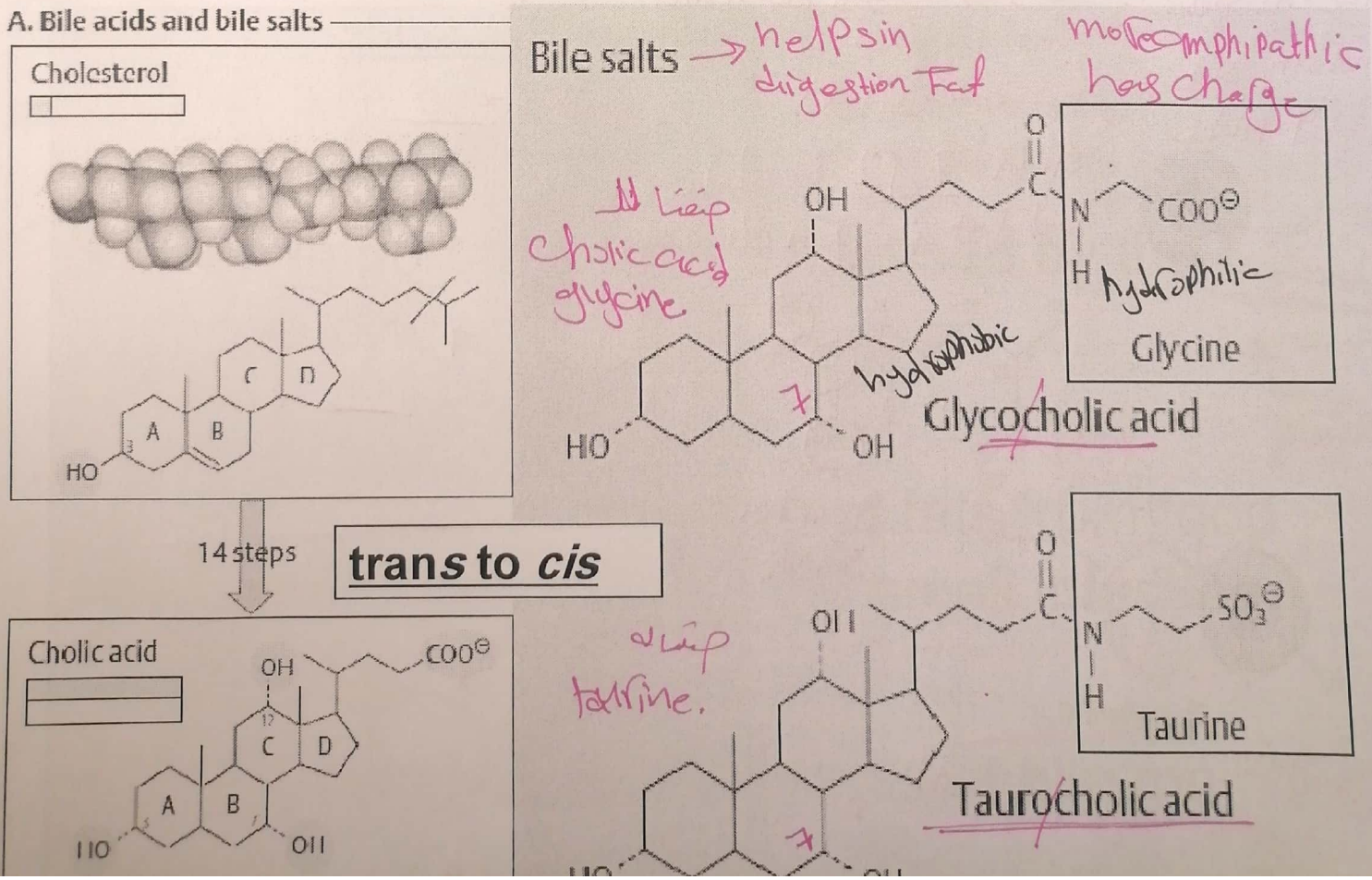


Chenodeoxycholic acid



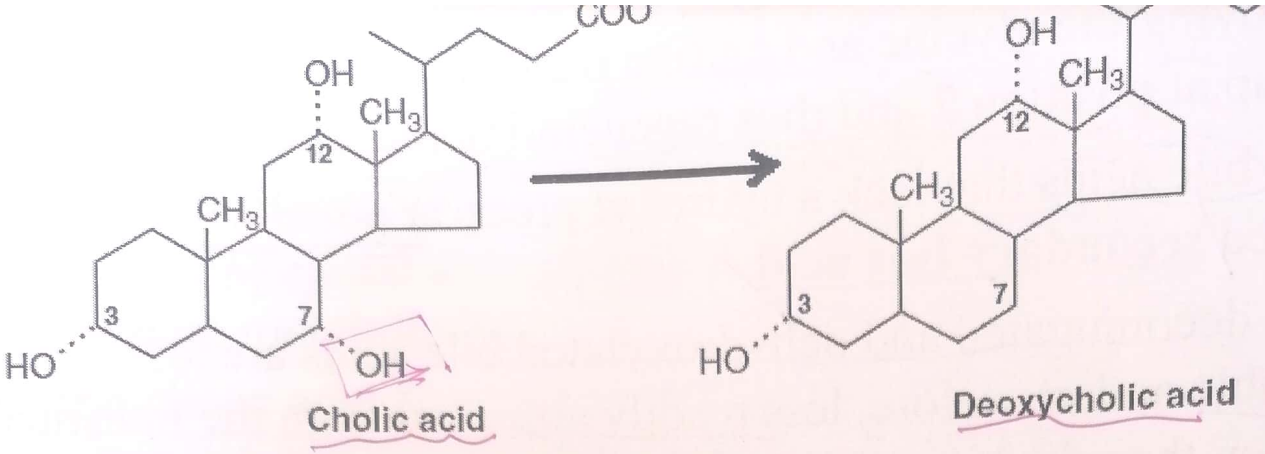
- **Conversion of bile acid to bile salt**
- Cholic acid and chenodeoxycholic acid, known as **primary bile acids.**
- They are activated with coenzyme A
- Then conjugated with glycine or taurine (an end-product of cysteine metabolism).
- The cholic acid conjugates with glycine and taurine are called the **conjugated bile acids** or **bile salts**.

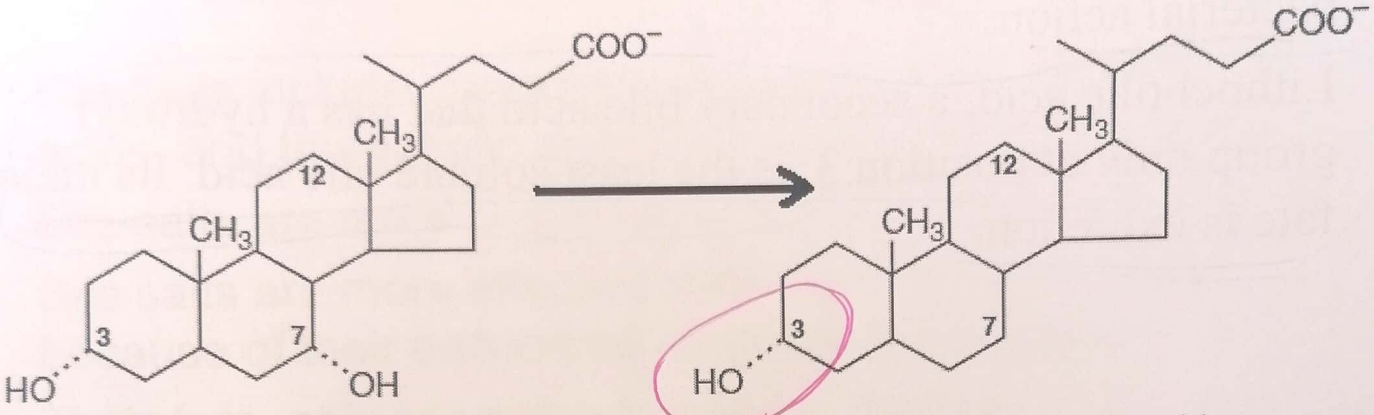
- Bile salts include glycocholic and glycochenodeoxycholic acids, and taurocholic and taurochenodeoxycholic acids
- Bile salts are more amphipathic than the primary products.
- Bile salts are more effective detergents than bile acids because of their **enhanced amphipathic nature.**
- Therefore, only bile salt are found in the bile.



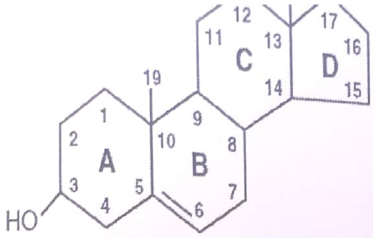
- **Bacteria in the intestine**
- Intestinal bacteria deconjugate and dehydroxylate the bile salts, removing the glycine and taurine residues and the hydroxyl group at position 7 and thus regenerating bile acid.
- The bile acids that lack a hydroxyl group at position 7 are called **secondary bile acid**.
- The deconjugated and dehydroxylated bile acids are less soluble and, therefore, less readily absorbed from the intestinal lumen than the bile acids that have not been subjected to bacterial action.
- Lithocholic acid, a secondary bile acid that has a hydroxyl group only at position 3, is the least soluble bile acid. Its major fate is excretion.

- Greater than 95% of the bile acids are reabsorbed in the ileum and return to the liver via the enterohepatic circulation (via the portal vein). The bile acids are recycled by the liver, which secretes them into the bile. This enterohepatic recirculation of bile salts is extremely efficient. Less than 5% of the bile acid entering the gut are excreted in the feces each day.
- Because the steroid nucleus cannot be degraded in the body, the excretion of bile acid serves as a major route for removal of the steroid nucleus and, thus, of cholesterol from the body.

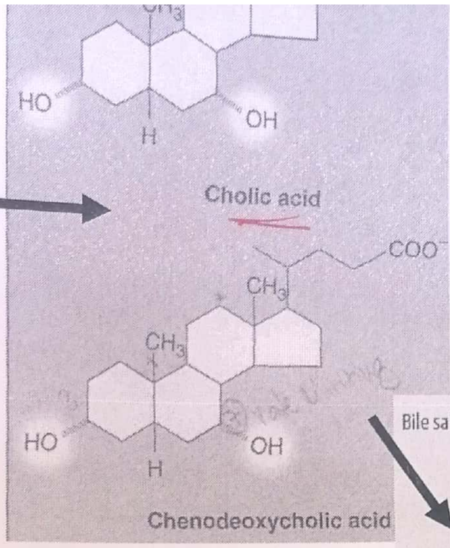


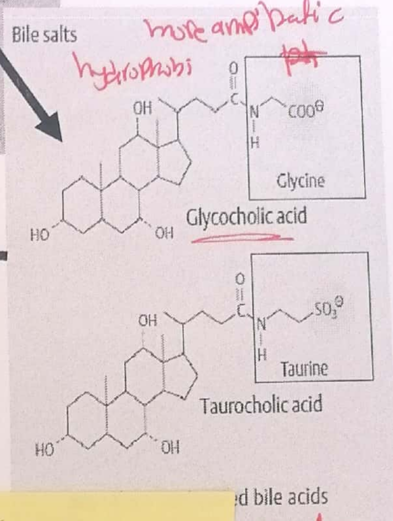


- **Mechanism of action of bile salts**
- Triglycerides are not soluble in water they aggregate into large droplet in the small intestine lumen.
- Bile salt adsorb on the surface of fat droplet, that is the lipid soluble part of the bile salt dissolves in the fat droplet leaving the charged water soluble part projecting from the surface of the droplet.
- Intestinal mixing movement break up large fat droplet into smaller ones. These small droplets would quickly come together were it not for the bile salt adsorbing on their surface and creating a shell of water-soluble negatively charged groups on the surface of each little droplet.
- Because like charges repel these negatively charged groups on the droplet surface cause the fat droplet to repel each other and prevent their come together in to large droplet and thus produces emulsion that increases the surface area available for lipase action.

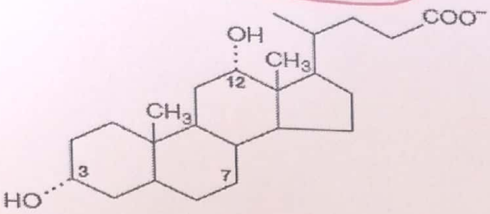


Cholesterol (C_{27})





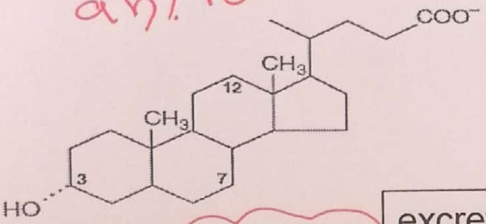
Secondary bile acid



Deoxycholic acid

95% reabsorb

تحول ال Colon



Lithocholic acid excreted

Deoxy chendio colon

5% most hydrophobic one.

① large Fat حركة الأمعاء تحول ال ⟶ small Fat droplet

bile salt عبارة عن شغل ال

⟶ 2 sides ⟶ hydrophobic
⟶ hydrophilic

droplet Fat ⟶ hydrophobic
hydrophobic side of Fat bind with it.
other side [hydrophilic [glycine Taurine] يكون برا ال Fat drop

② What prevent small drops from rejoing to make large drops ⟶ bile salt binds to small drops by hydrophobic side thus [hydrophilic side] glycin/turine out of drop ⟶ negative charge

③ (-) charge so semilar charge repulsion each other (تتنافر) بالتالي ما ترجع ترتبط مع بعض

بنسميها [emulsification of fat]

bile salt بتعمل