Metabolism of lipids VIII:

Cholesterol

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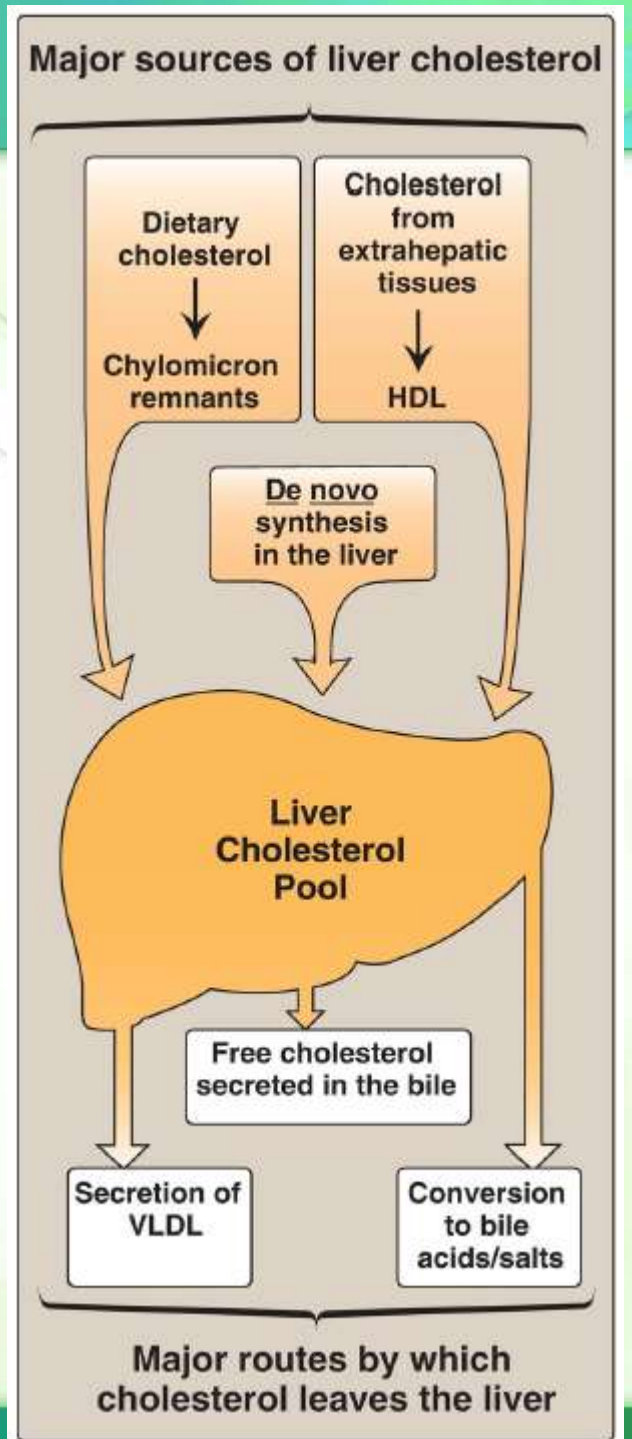
Resources

- This lecture
- Lippincott's Biochemistry, Ch. 17

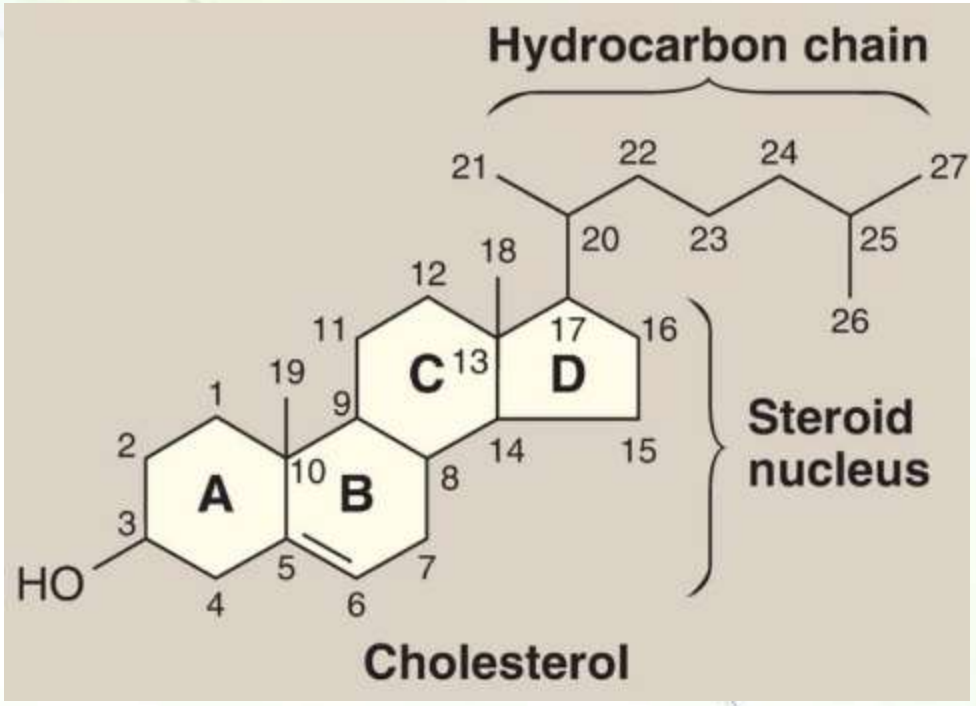
Life of cholesterol

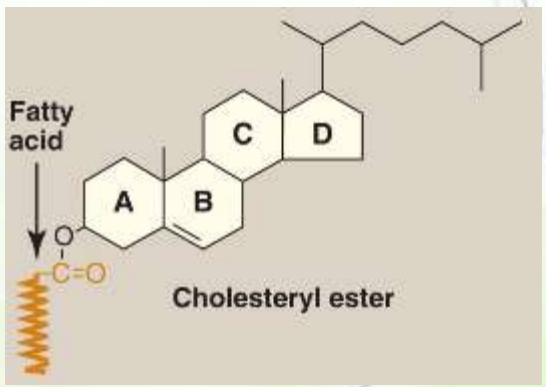
- The balance between cholesterol influx and efflux is not precise, resulting in a gradual deposition of cholesterol in the tissues, particularly in the endothelial linings of blood vessels.



Structure of cholesterol

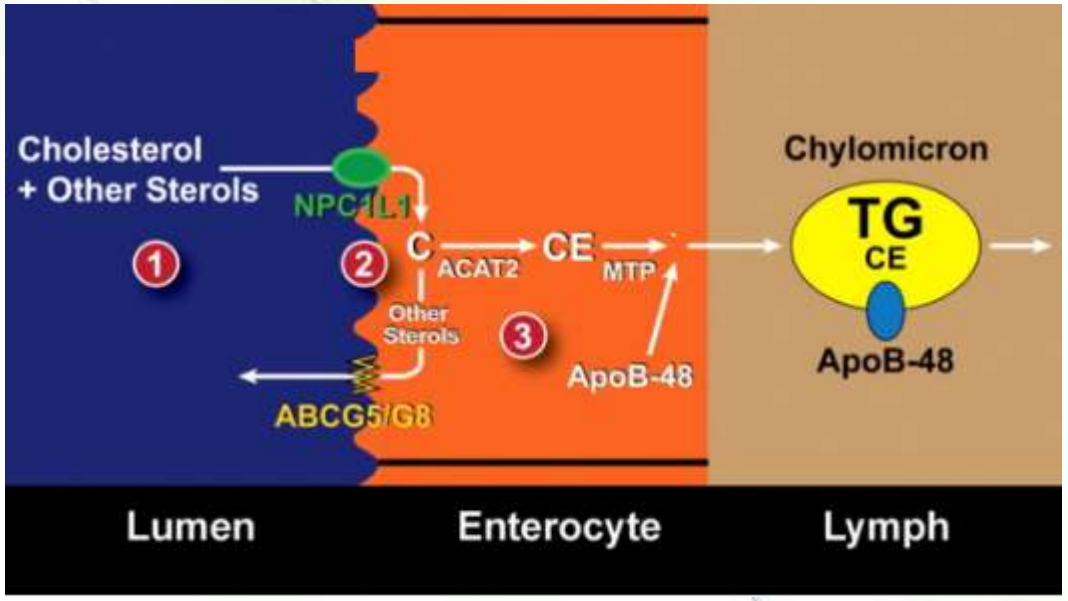
- Cholesterol is a very hydrophobic compound.
- It is a 27-carbon molecule that consists of:
  - Four fused hydrocarbon rings (A–D) of 17 carbons called the steroid nucleus
  - Two methyl groups (C18 and 19)
  - Eight-carbon, branched hydrocarbon chain attached to carbon 17 of the D ring.
    - Ring A has a hydroxyl group at carbon 3.
    - Ring B has a double bond between C5 and c6.
- Most plasma cholesterol is esterified with a fatty acid attached at carbon 3.

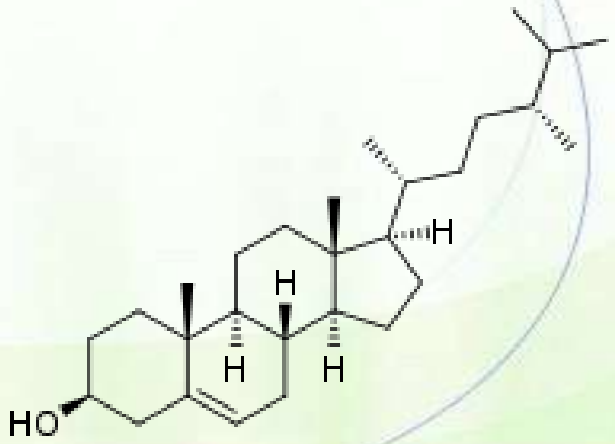




Intestinal absorption of cholesterol

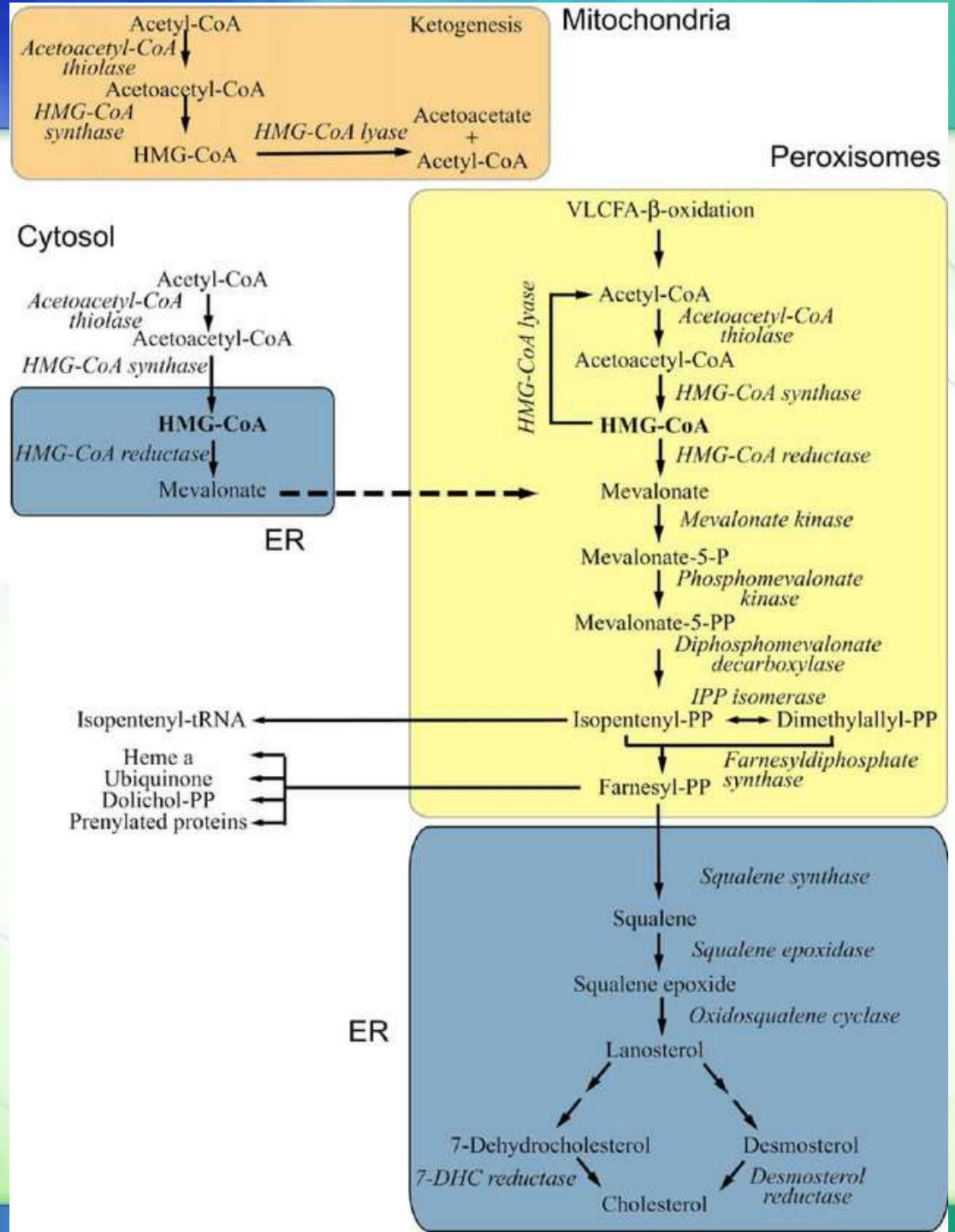
- Intestinal uptake of cholesterol is mediated by the Niemann-Pick C1-like 1 protein, the target of ezetimibe, and pumped out by ABCG5/8.
  - Defects in the efflux transporter (ABCG5/8) result in the rare condition of sitosterolemia.
- Plant sterols (phytosterols) are poorly absorbed by humans (5% vs. 40% for cholesterol) and are actively transported back into the intestinal lumen.
  - Plant sterols reduce the absorption of dietary cholesterol.
    - A dietary strategies to reduce plasma cholesterol levels.





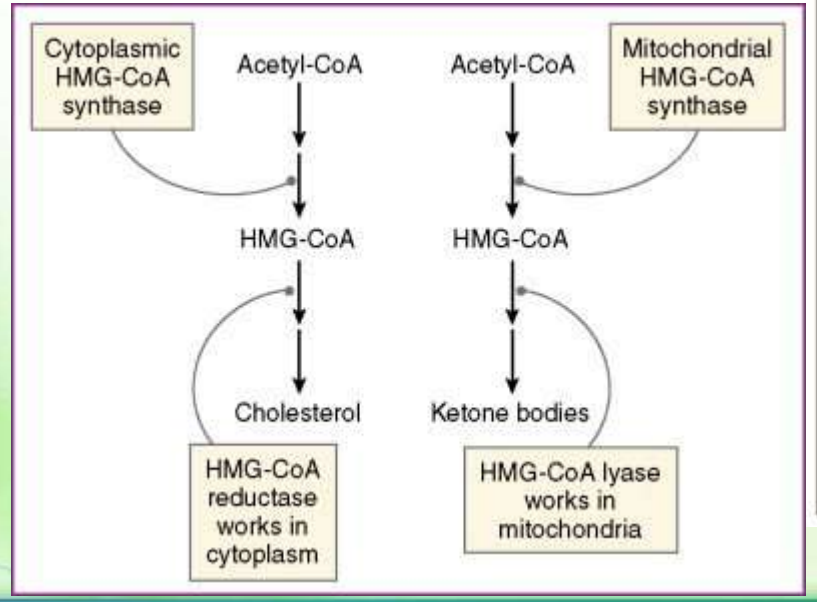
Notes regarding synthesis of cholesterol

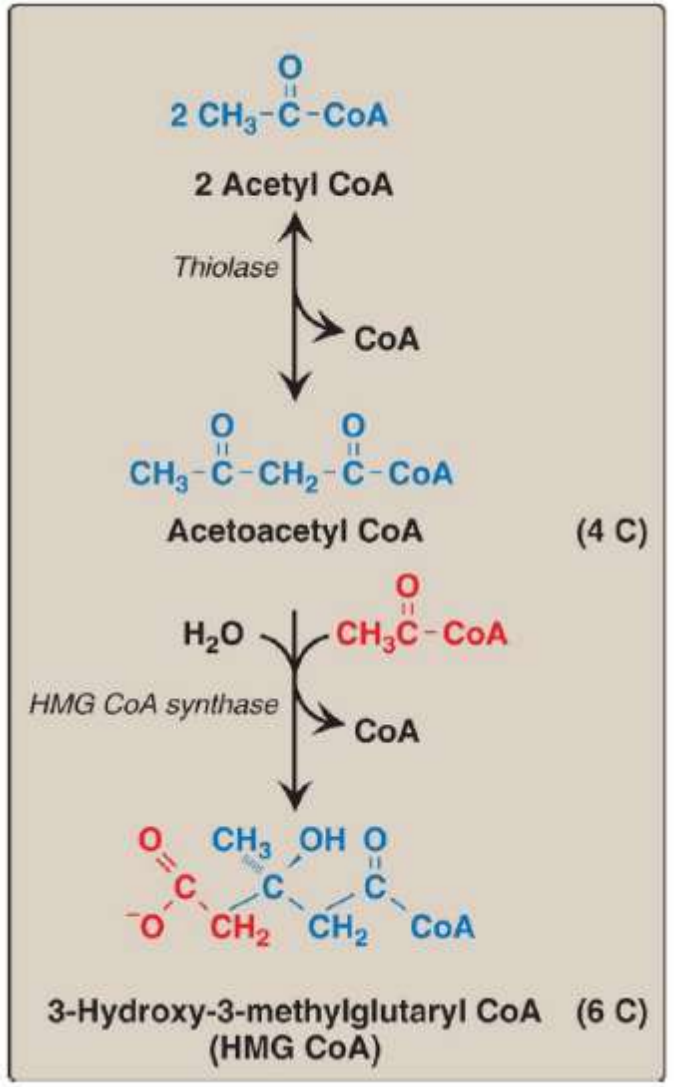
- All the carbon atoms in cholesterol are provided by acetyl coenzyme A (CoA).
- NADPH is the reducing agent.
- The pathway is endergonic, and energy is provided by the hydrolysis of
  - The thioester bond of acetyl CoA
  - ATP
- Synthesis requires enzymes in the cytosol, the membrane of the smooth endoplasmic reticulum (SER), and the peroxisomes.
- The pathway is regulated to balance the rate of cholesterol synthesis/excretion.


Mitochondria
Acetyl-CoA
Ketogenesis
Acetoacetyl-CoA thiolase
Acetoacetyl-CoA
HMG-CoA synthase
HMG-CoA lyase
Acetoacetate + Acetyl-CoA
HMG-CoA
Peroxisomes
Cytosol
VLCFA-β-oxidation
Acetyl-CoA
Acetoacetyl-CoA thiolase
Acetoacetyl-CoA
HMG-CoA synthase
HMG-CoA lyase
HMG-CoA
HMG-CoA reductase
Mevalonate
ER
Mevalonate kinase
Mevalonate-5-P
Phosphomevalonate kinase
Mevalonate-5-PP
Diphosphomevalonate decarboxylase
IPP isomerase
Isopentenyl-tRNA
Isopentenyl-PP
Dimethylallyl-PP
Heme a
Ubiquinone
Dolichol-PP
Prenylated proteins
Farnesyldiphosphate synthase
Farnesyl-PP
Squalene synthase
Squalene
Squalene epoxidase
Squalene epoxide
ER
Oxidosqualene cyclase
Lanosterol
7-Dehydrocholesterol
Desmosterol
7-DHC reductase
Desmosterol reductase
Cholesterol

The first reactions...

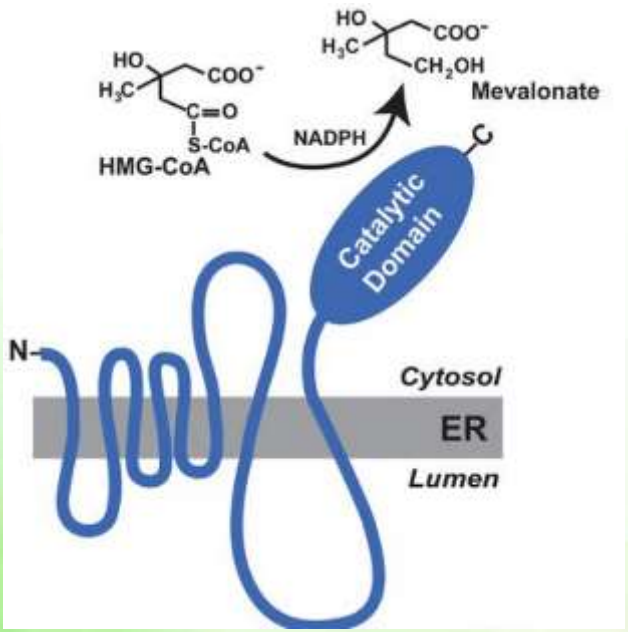
- Similar to the synthesis of ketone bodies.
- Liver parenchymal cells contain two isoenzymes of the HMG CoA synthase.
  - A cytosolic enzyme participates in cholesterol synthesis.
  - A mitochondrial enzyme functions in the pathway for ketone body synthesis.

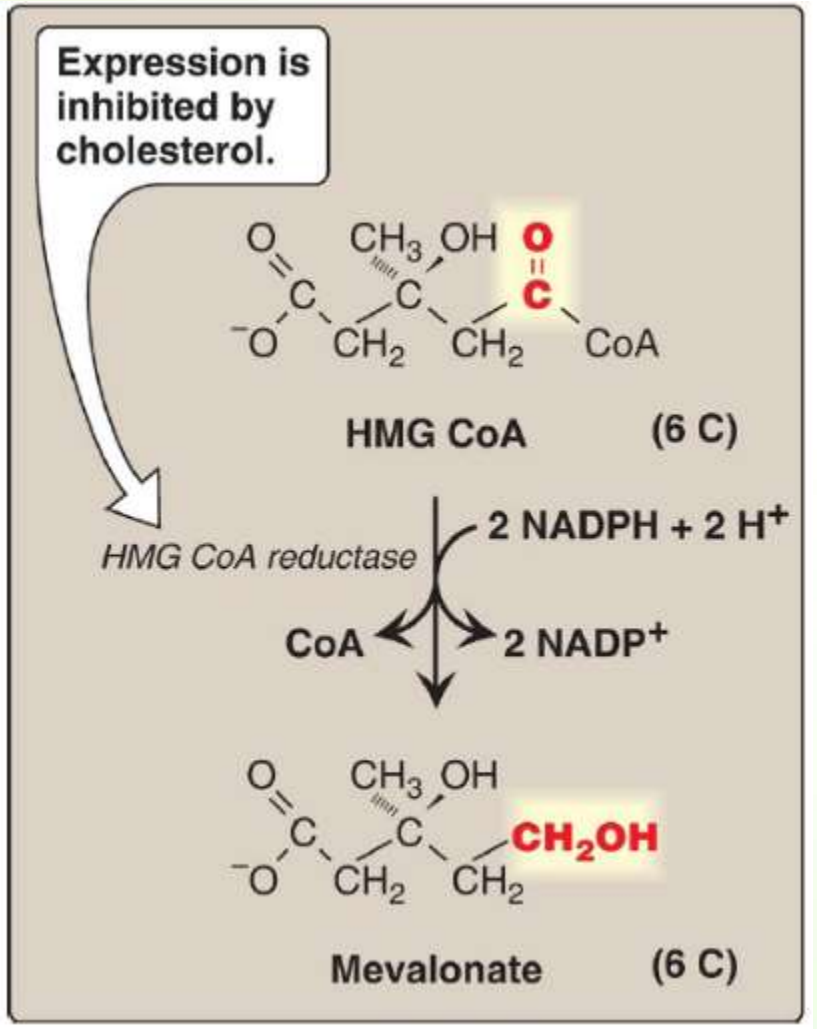




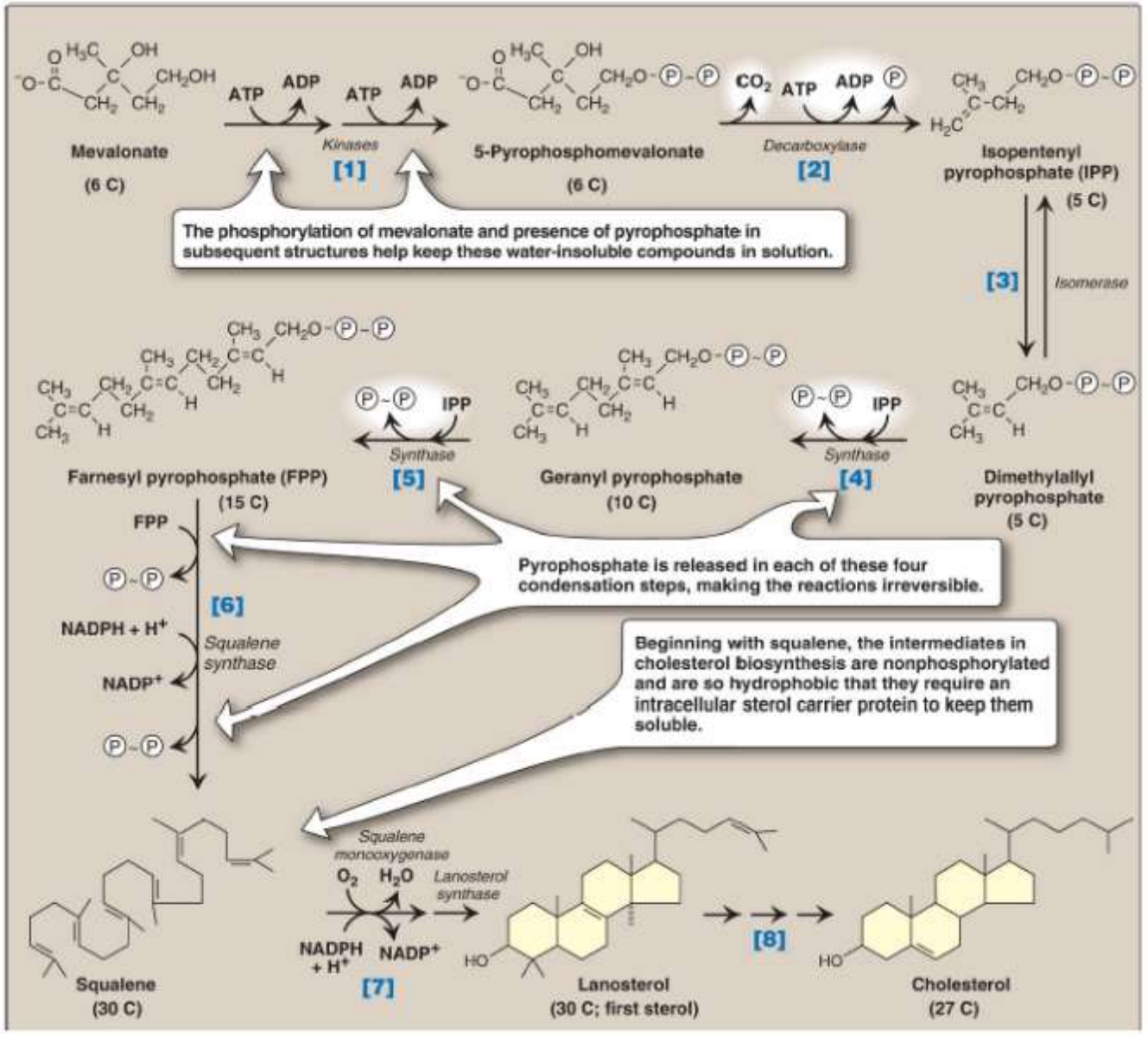
Synthesis of mevalonate

- HMG CoA is reduced to mevalonate by HMG CoA reductase.
  - The reaction is rate-limiting and a committed step.
  - Two molecules of NADPH are oxidized.
  - CoA is released making the reaction irreversible.
- HMG CoA reductase is an integral membrane protein of the SER, with its catalytic domain projecting into the cytosol.

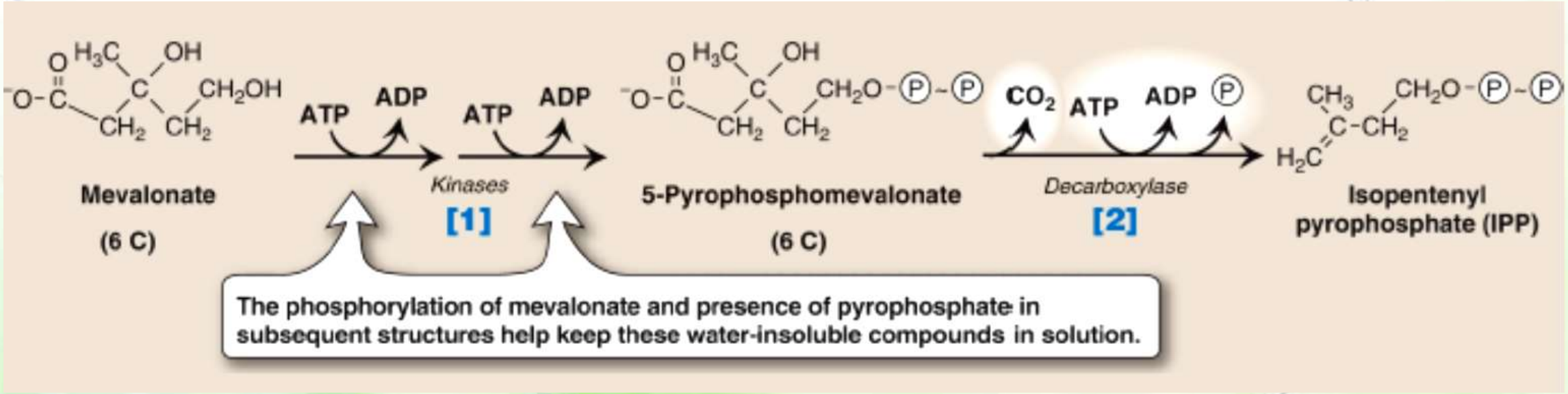




Synthesis of cholesterol

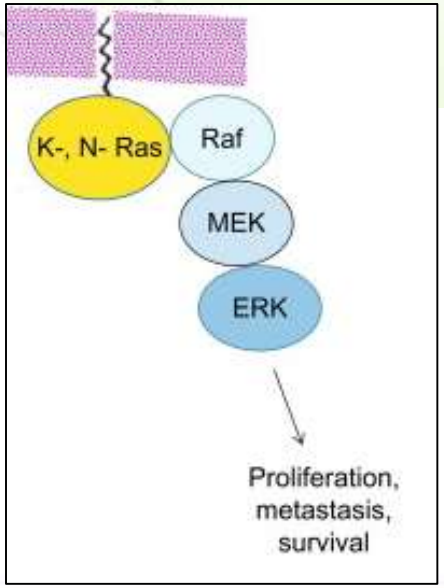


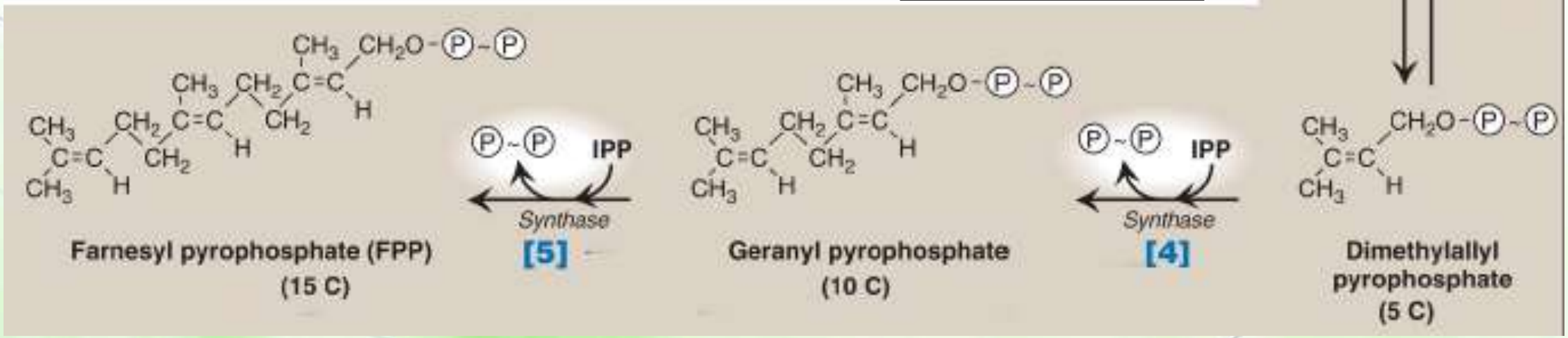
- [1] Mevalonate is activated by transferring 2 phosphate groups from ATP.
- [2] A five-carbon isoprene unit, isopentenyl pyrophosphate (IPP), is formed by the decarboxylation of 5-pyrophosphomevalonate.
  - The reaction requires ATP.
  - IPP is the precursor of a family of molecules with diverse functions, the isoprenoids.
    - Cholesterol is a sterol isoprenoid.
    - Nonsterol isoprenoids include ubiquinone (or, coenzyme Q).



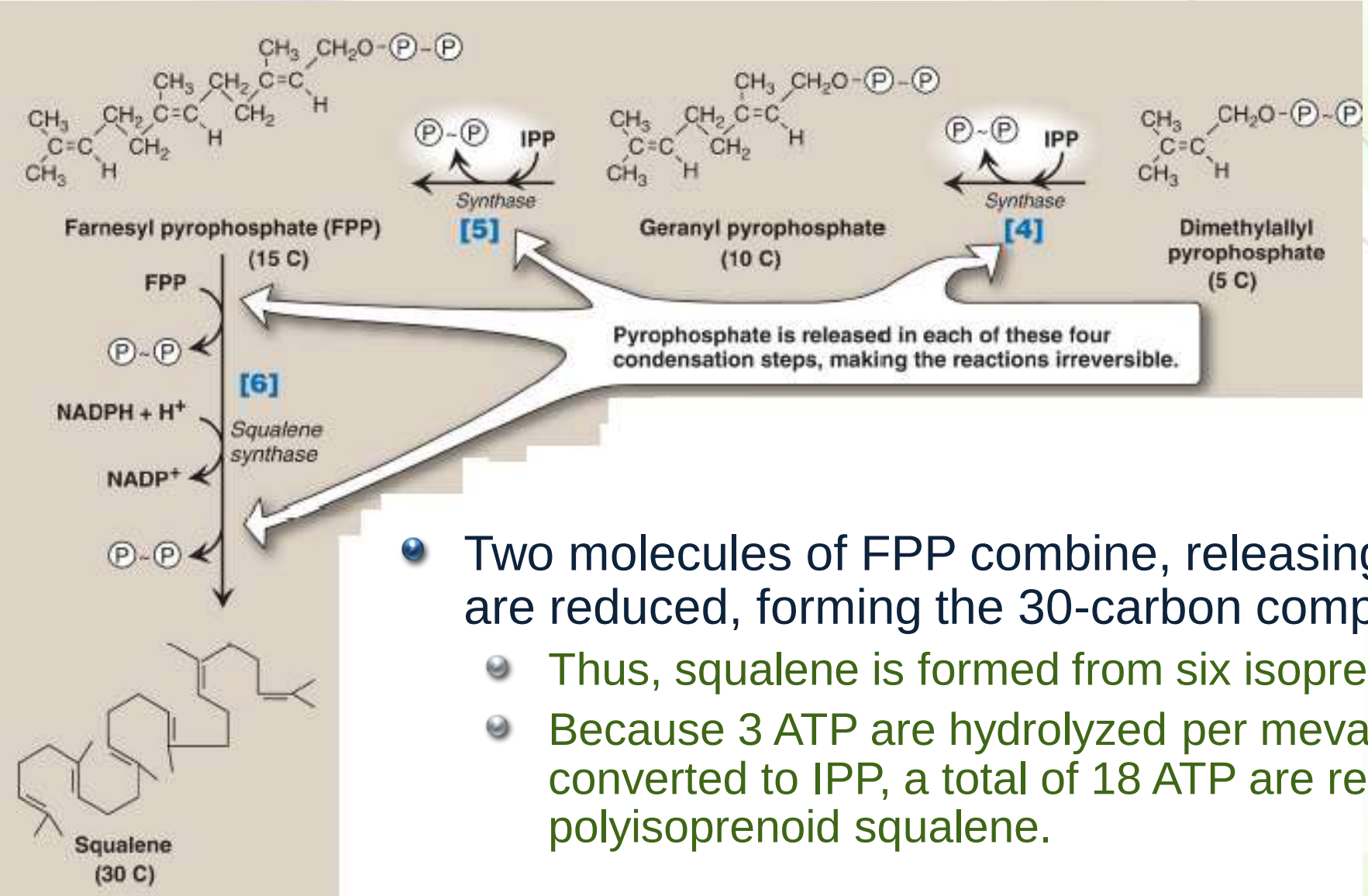
From 5 to 15

- [3] IPP is isomerized to 3,3-dimethylallyl pyrophosphate (DPP).
- [4] IPP and DPP condense to form 10-carbon geranyl pyrophosphate (GPP).
- [5] A second molecule of IPP then condenses with GPP to form 15-carbon farnesyl pyrophosphate (FPP).
  - Covalent attachment of farnesyl to proteins, a process known as prenylation, is one mechanism for anchoring proteins (for example, Ras) to the inner face of plasma membranes.





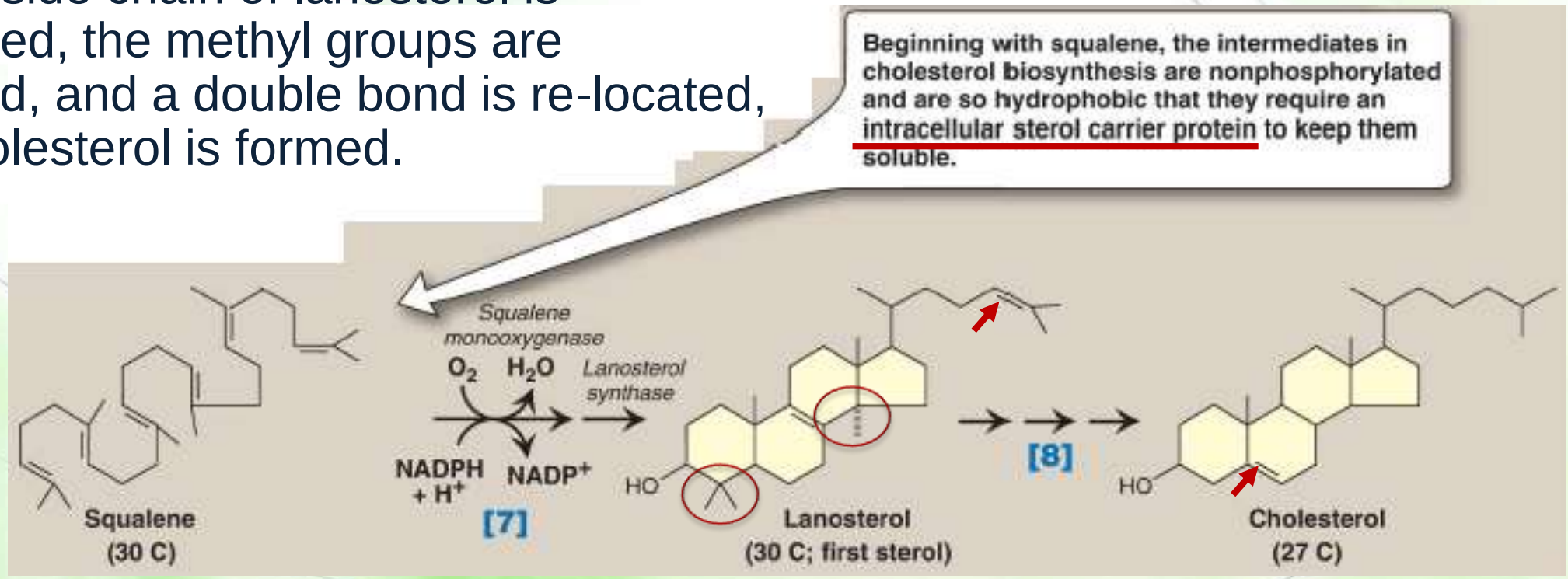
The synthesis of squalene



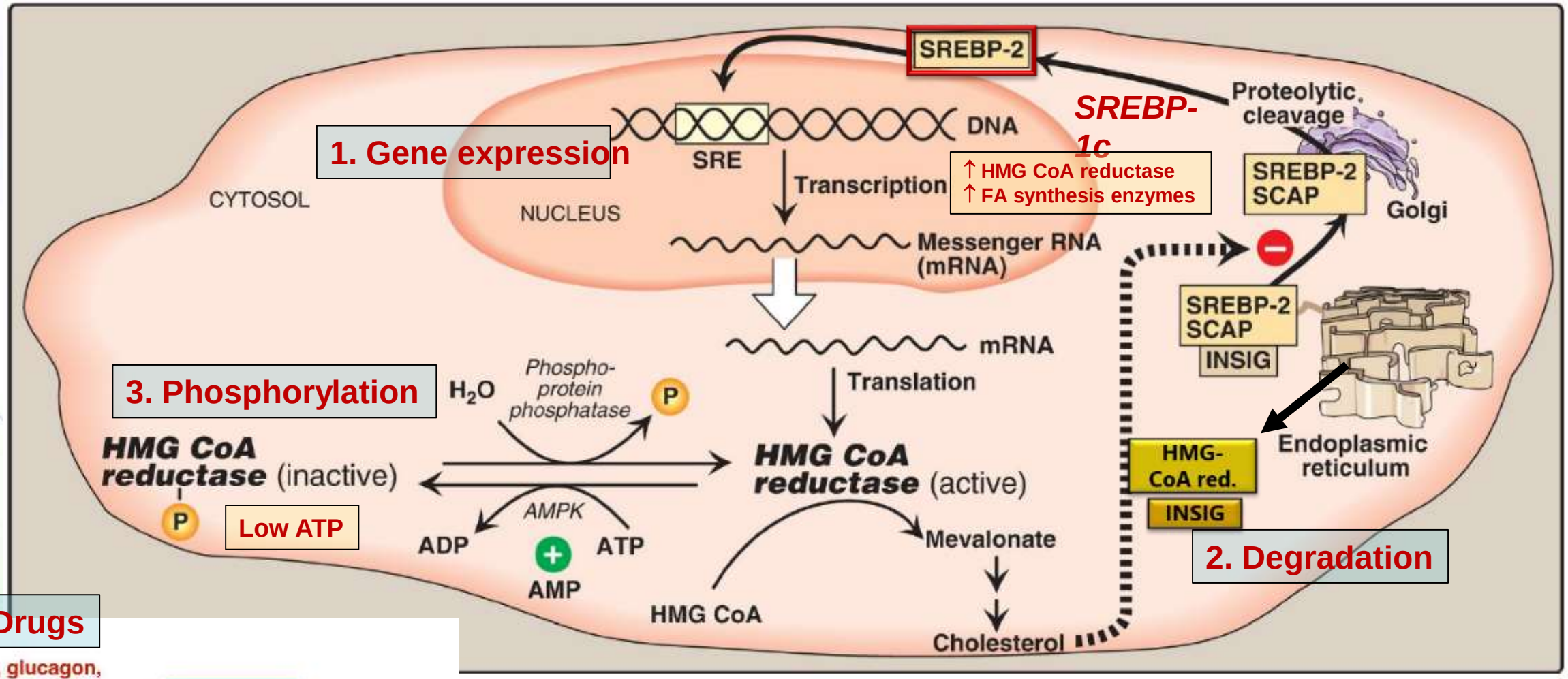
- Two molecules of FPP combine, releasing pyrophosphate, and are reduced, forming the 30-carbon compound squalene.
  - Thus, squalene is formed from six isoprenoid units.
  - Because 3 ATP are hydrolyzed per mevalonate residue converted to IPP, a total of 18 ATP are required to make the polyisoprenoid squalene.

And finally...

- [7] Squalene is converted to the sterol lanosterol by SER-associated enzymes that use molecular oxygen (O2) and NADPH.
  - The hydroxylation of linear squalene triggers the cyclization of the structure to lanosterol.
- [8] The side chain of lanosterol is shortened, the methyl groups are removed, and a double bond is re-located, and cholesterol is formed.

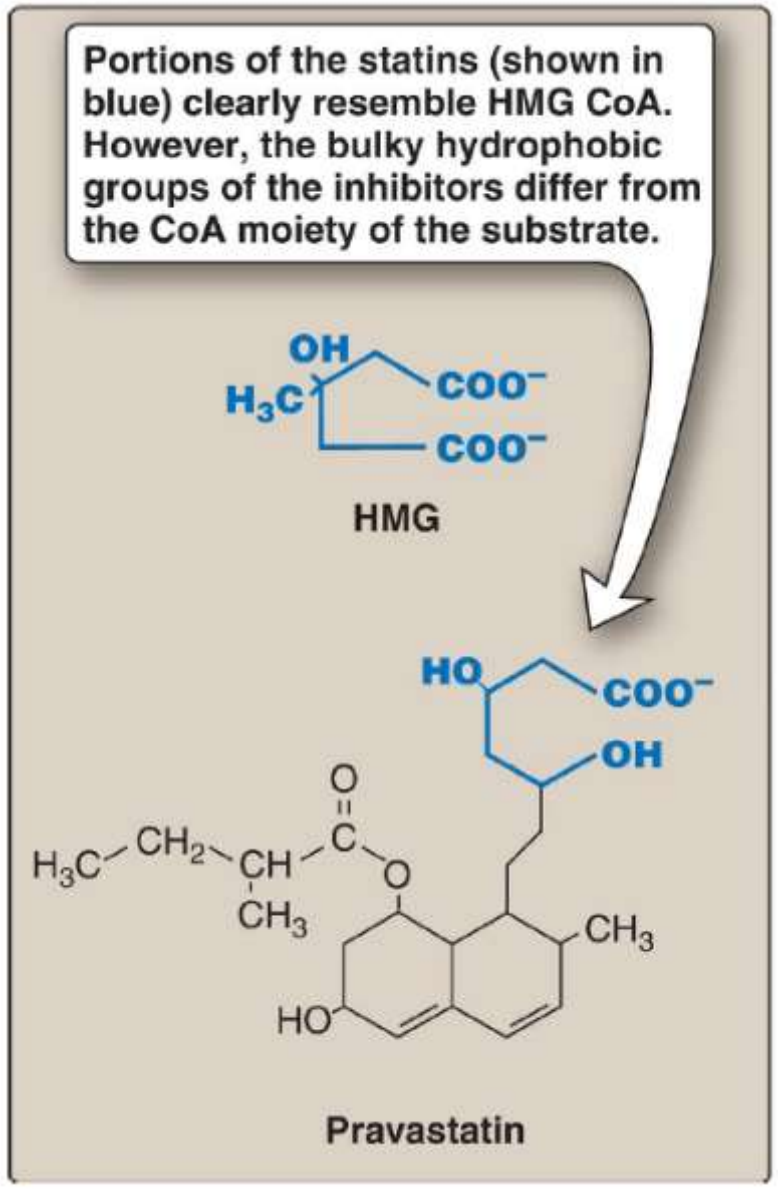


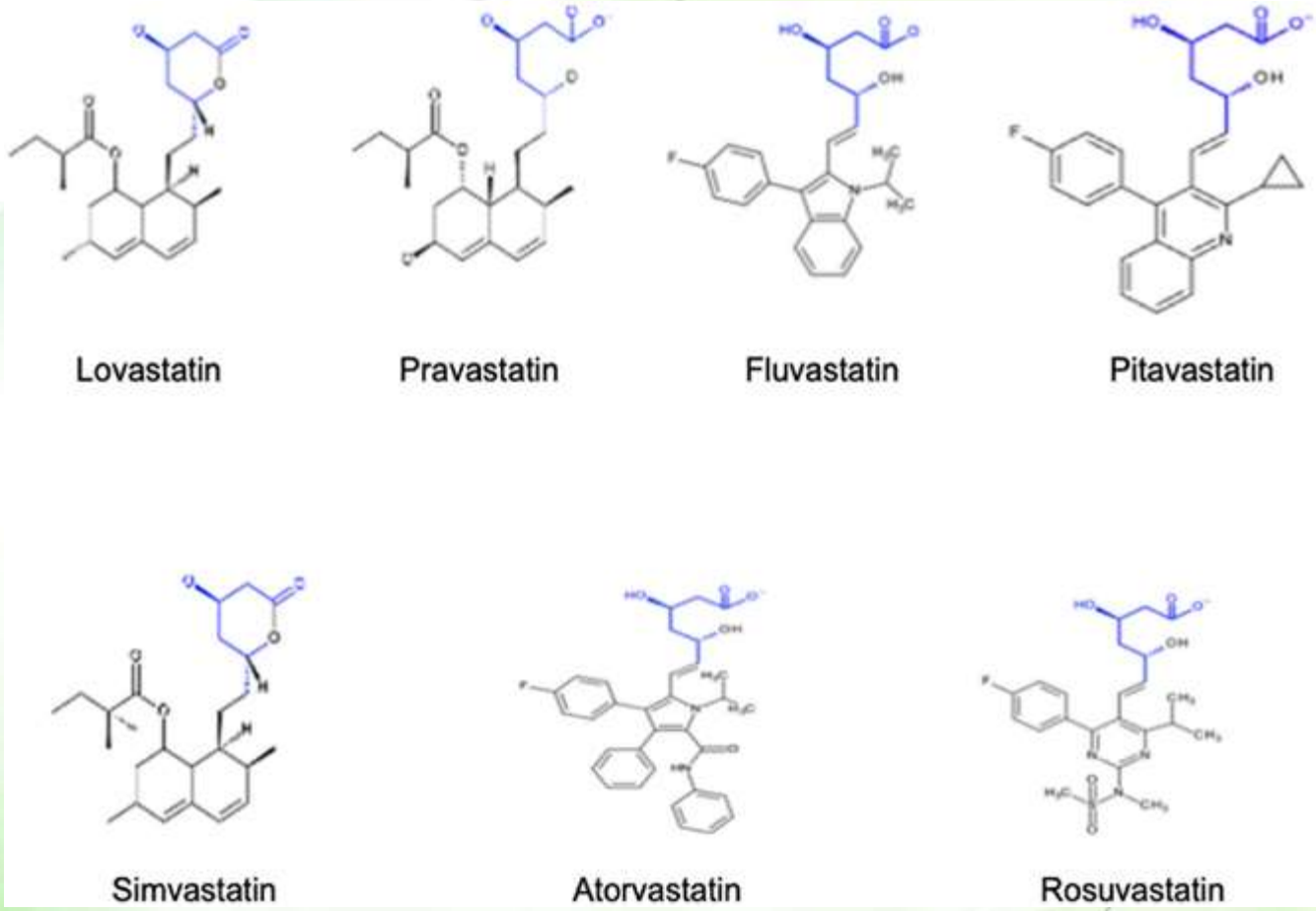
Regulation of cholesterol synthesis



SRE: Sterol regulatory element
SREBP: SRE binding protein
SCAP: SREBP cleavage–activating protein
INSIG : Insulin-induced gene

Statins


Portions of the statins (shown in blue) clearly resemble HMG CoA. However, the bulky hydrophobic groups of the inhibitors differ from the CoA moiety of the substrate.
OH
H3C
COO−
COO−
HMG
HO
COO−
OH
H3C
CH2
CH
C
O
CH3
O
CH3
HO
Pravastatin


Lovastatin
Pravastatin
Fluvastatin
Pitavastatin
Simvastatin
Atorvastatin
Rosuvastatin

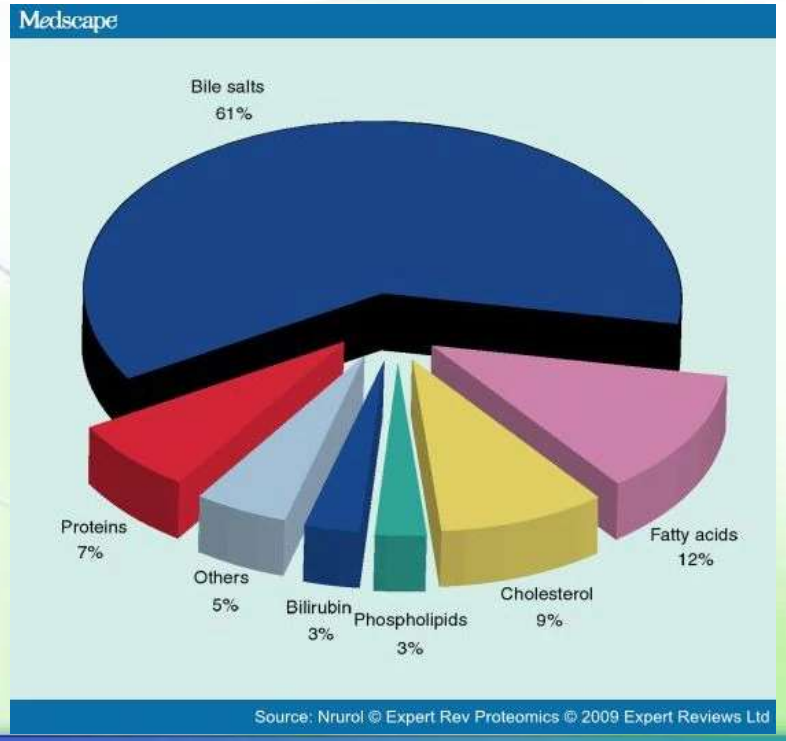
Elimination of cholesterol

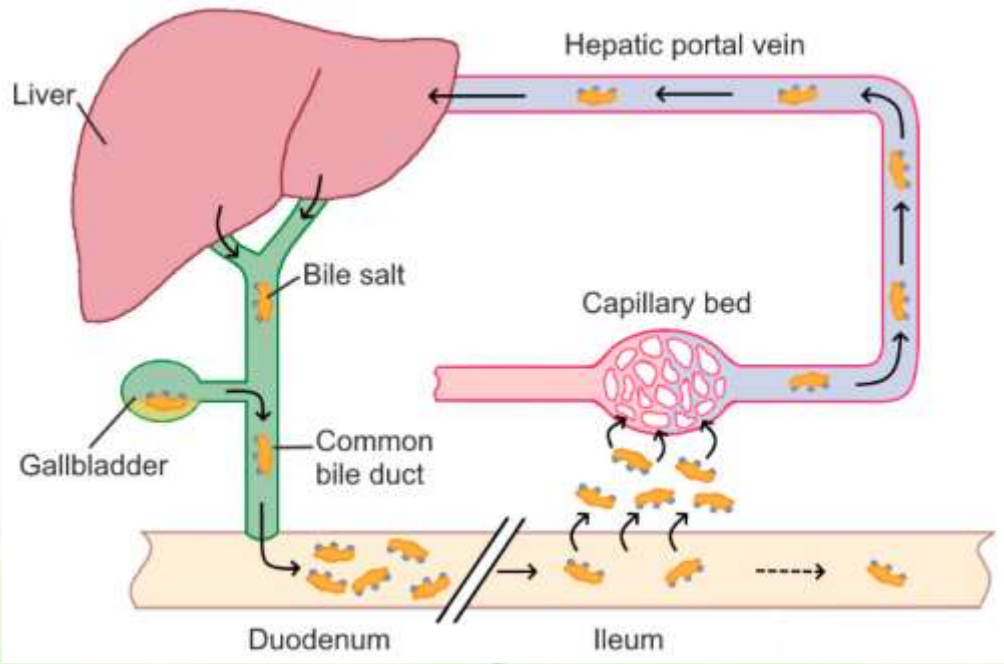
- The intact steroid nucleus is eliminated from the body by:
  - conversion to bile acids and bile salts, a small percentage of which is excreted in the feces.
  - secretion of cholesterol into the bile, which transports it to the intestine for elimination.

- *Note: The terms bile acid and bile salt are frequently used interchangeably.*

What is bile?

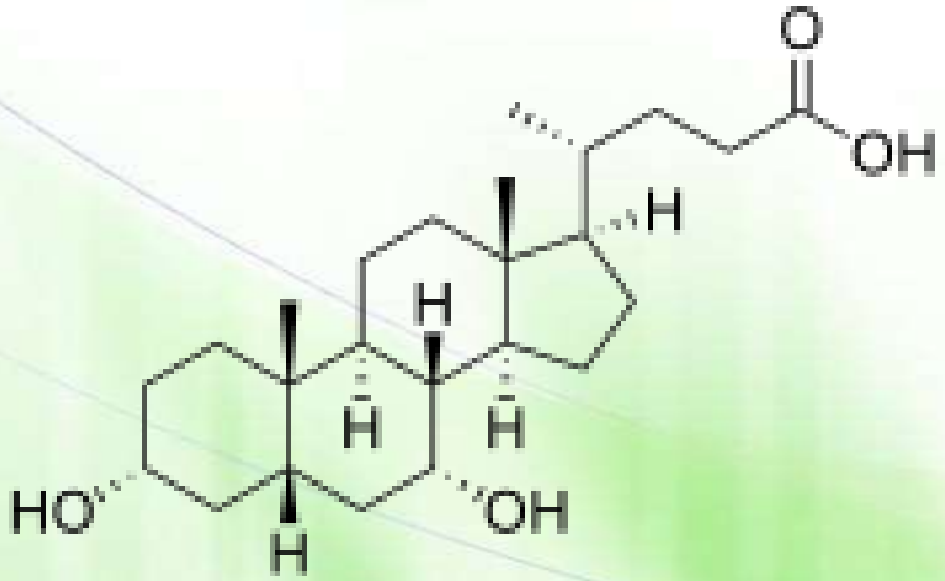
- Bile consists of a watery mixture of organic and inorganic compounds.
  - Phosphatidylcholine (PC) and conjugated bile salts are the most important organic components of bile.
- Bile can either pass directly from the liver, *where it is synthesized*, into the duodenum through the common bile duct, or be stored in the gallbladder.

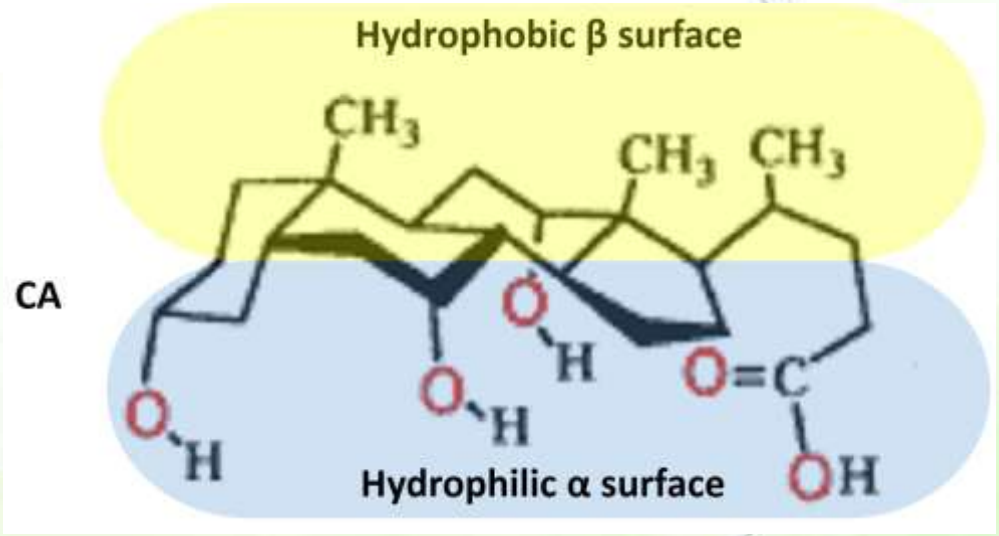




Structure and protonation states

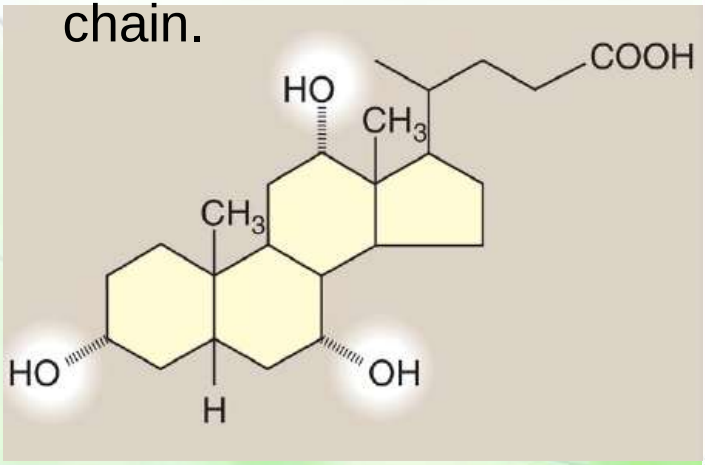
- The bile acids contain 24 carbons, with two or three hydroxyl groups and a side chain that terminates in a carboxyl group.
- The carboxyl group has a pKa of ~6.
  - In the duodenum (pH ~6), 50% exist as bile acids (protonated) and 50% exists as bile salts (deprotonated).

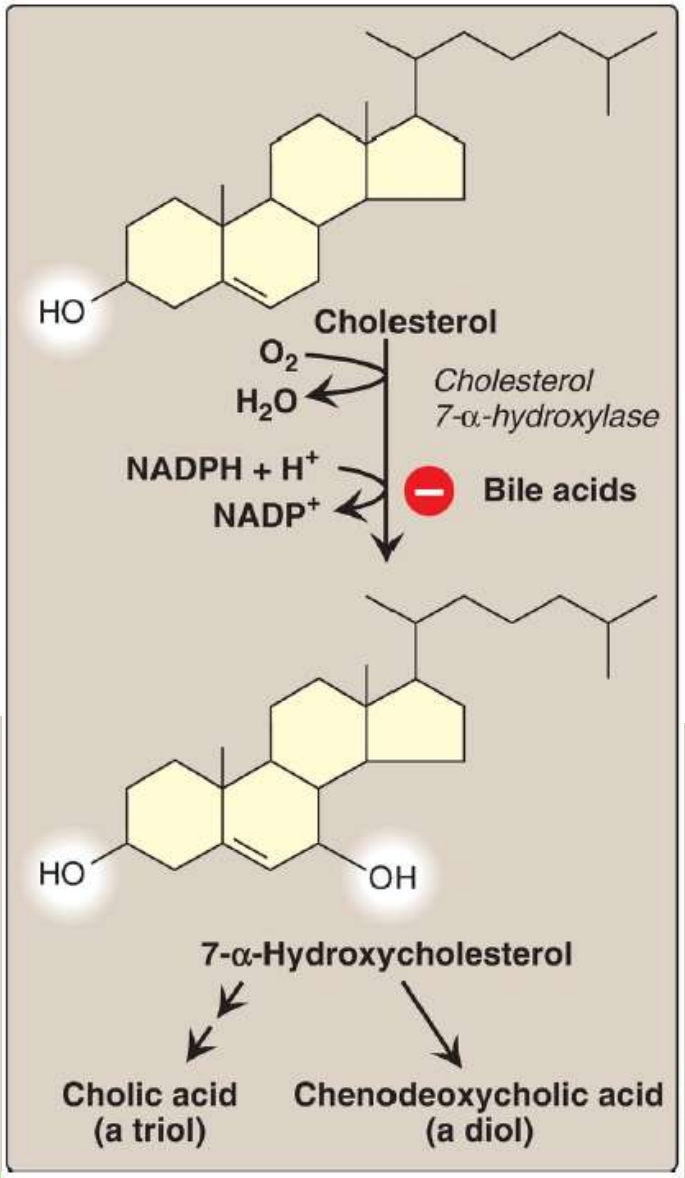




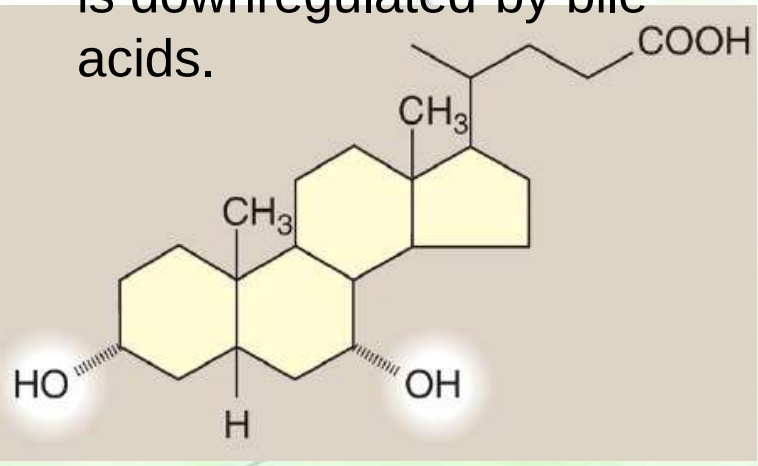
Synthesis of primary bile acids

1. Hydroxyl groups are inserted.
2. The double bond of the cholesterol B ring is reduced.
3. The hydrocarbon chain is shortened by three carbons.
4. Introducing a carboxyl group at the end of the chain.



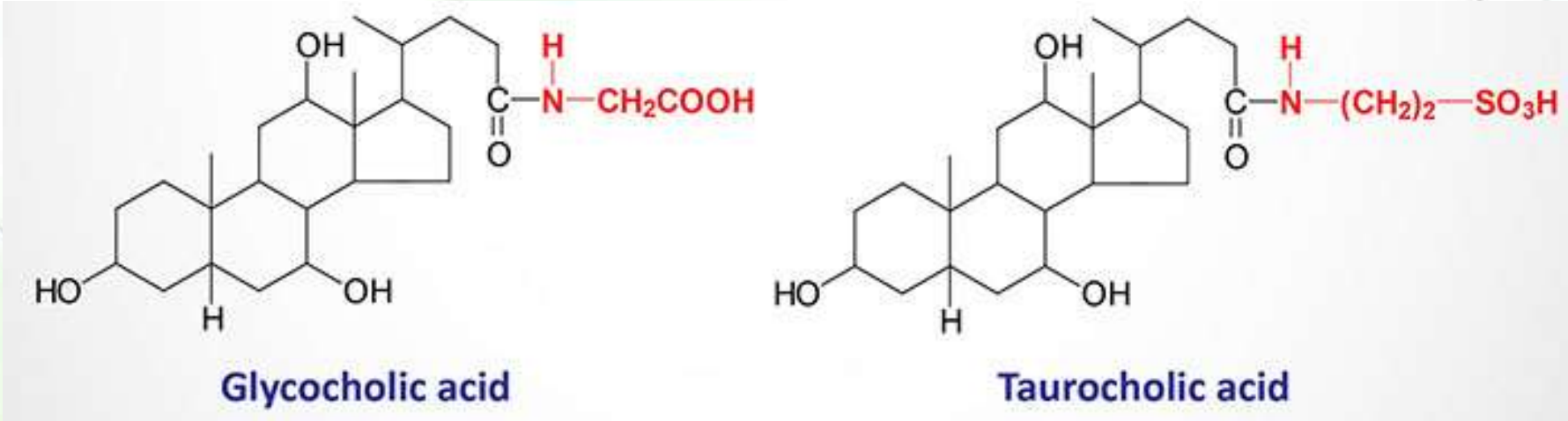


- The rate-limiting step is catalyzed by *7-α-hydroxylase*, a SER-associated *cytochrome P450 monooxygenase* found only in liver.
- Expression of the enzyme is downregulated by bile acids.



Conjugation

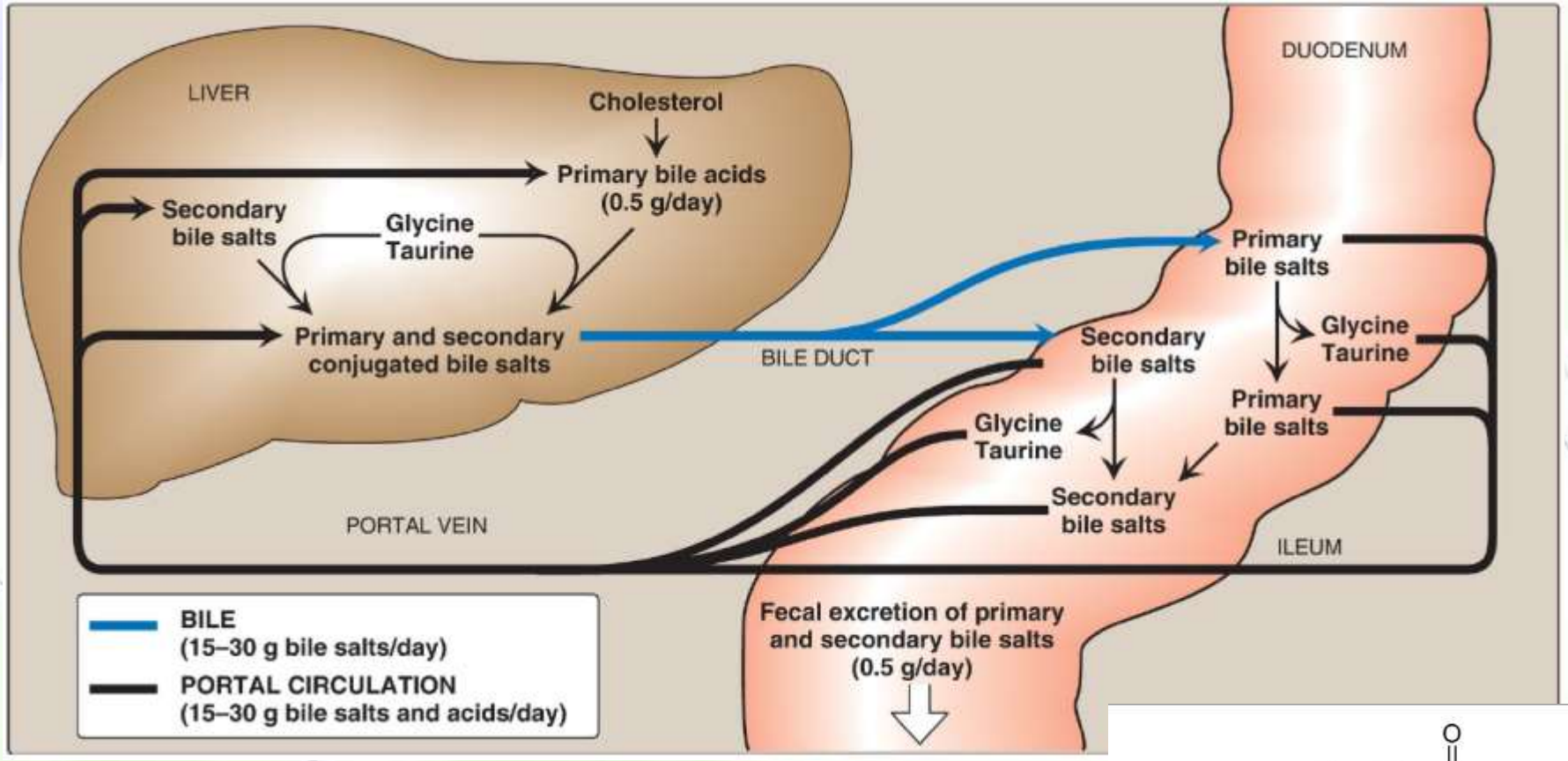
- In the liver, they are conjugated to either glycine or taurine (an end product of cysteine metabolism) forming more amphipathic and ionized compounds, better emulsifiers, and the only ones found in bile.
- The ratio of the glycine to taurine forms in the bile is ~3/1.



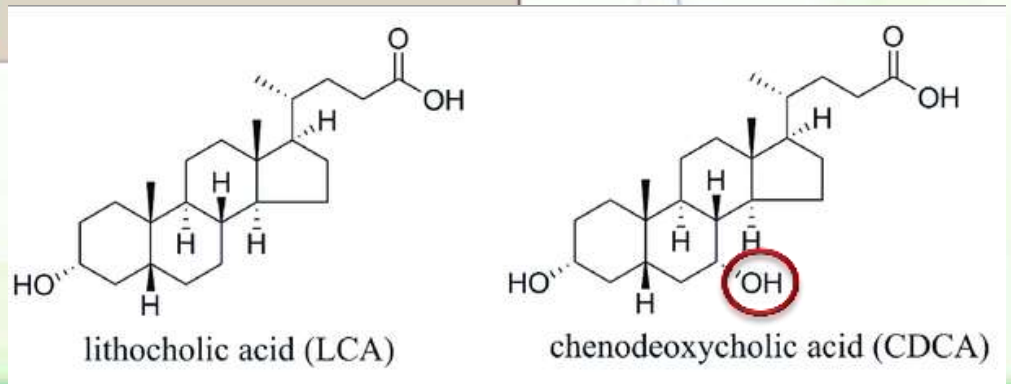
Glycocholic acid
OR Glycochenodeoxycholic acid

Taurocholic acid
OR Taurochenodeoxycholic acid

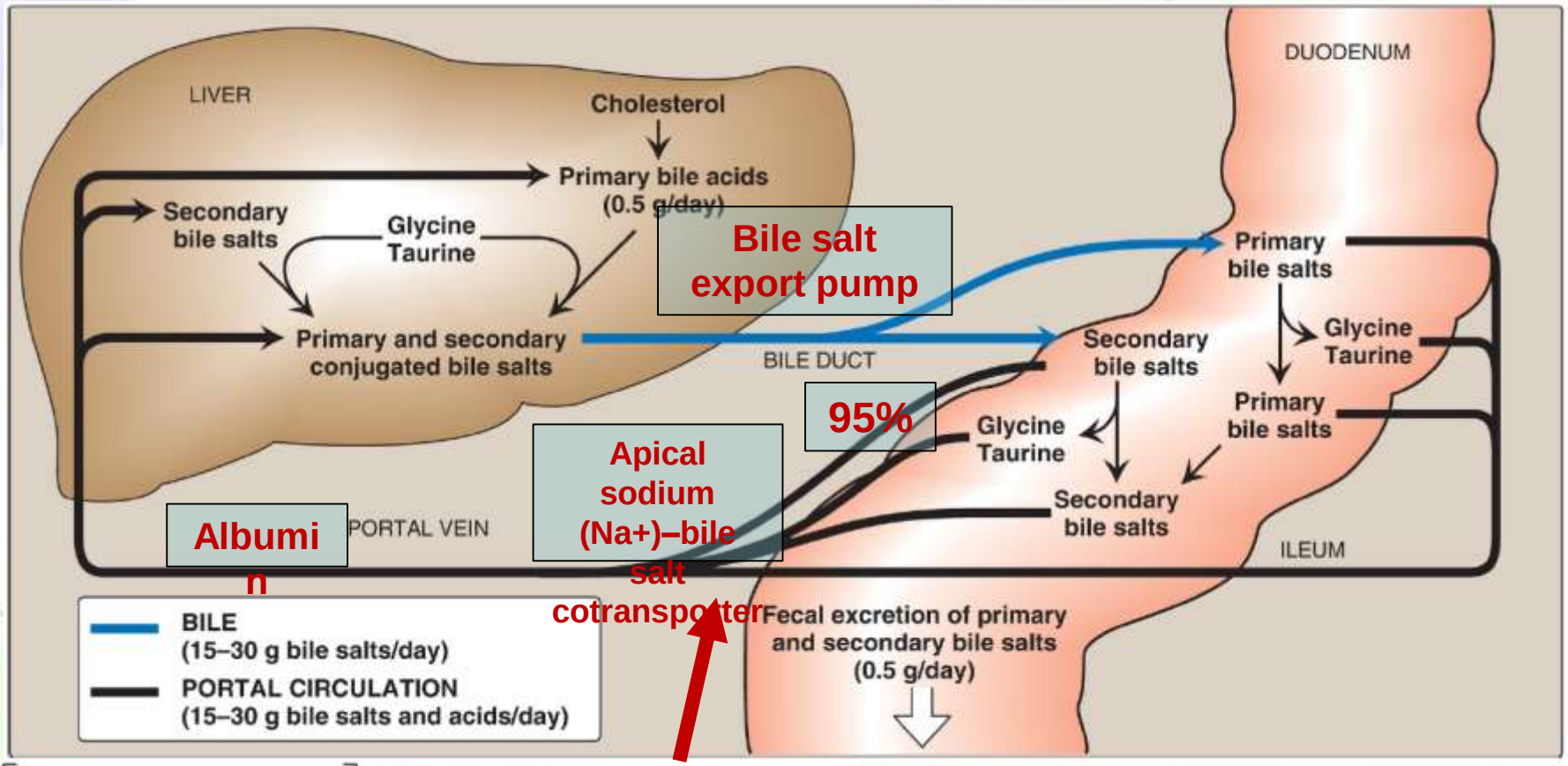
Bacterial actions

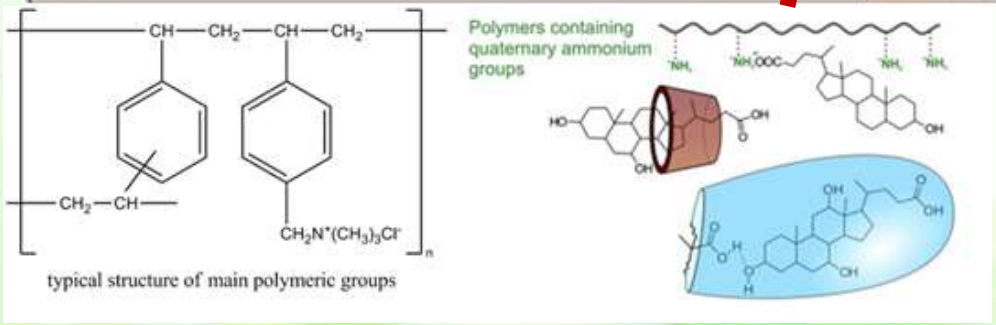


Primary bile acids: cholic acid and chenodeoxycholic acid
Secondary bile acids: deoxycholic acid and lithocholic acid



Enterohepatic circulation





Bile acid sequestrants, such as cholestyramine, bind bile salts in the gut and prevent their reabsorption, thereby promoting their excretion.

Bile salt deficiency: Cholelithiasis

- ↑Cholesterol or ↓bile acids → insolubility → gallbladder stones (cholelithiasis)
- Treatment: cholecystectomy
  - Alternatively: oral administration of chenodeoxycholic acid results in a gradual (months to years) dissolution of the gallstones.