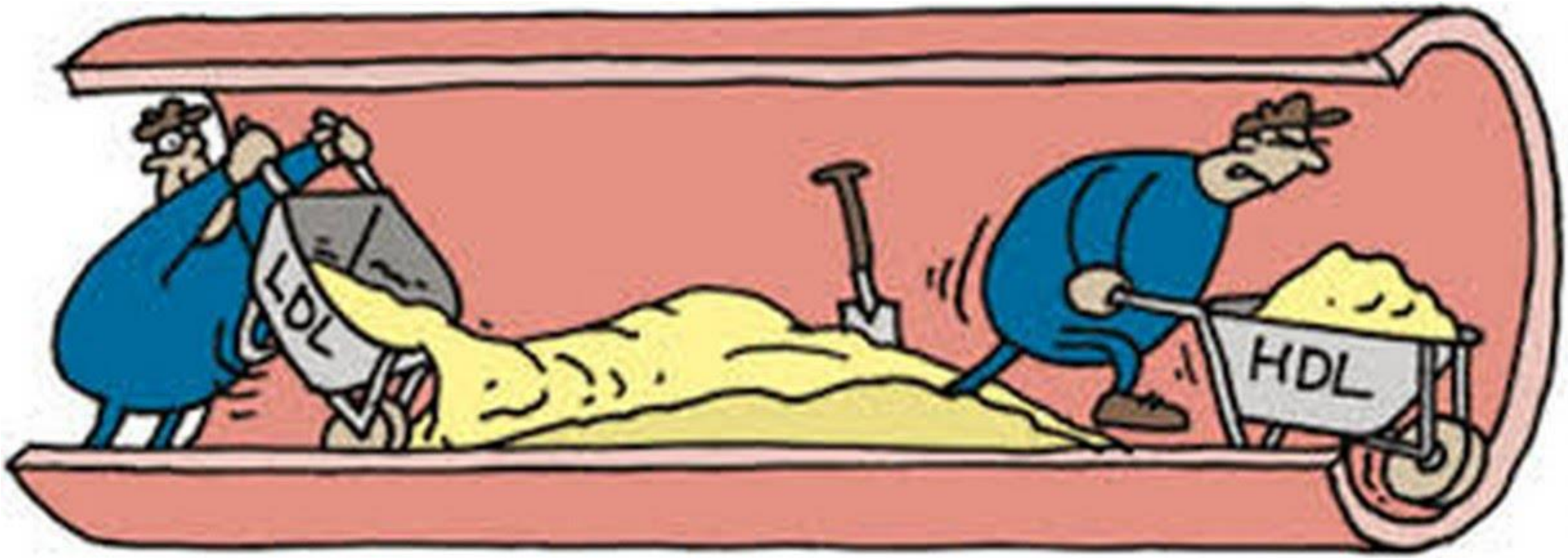
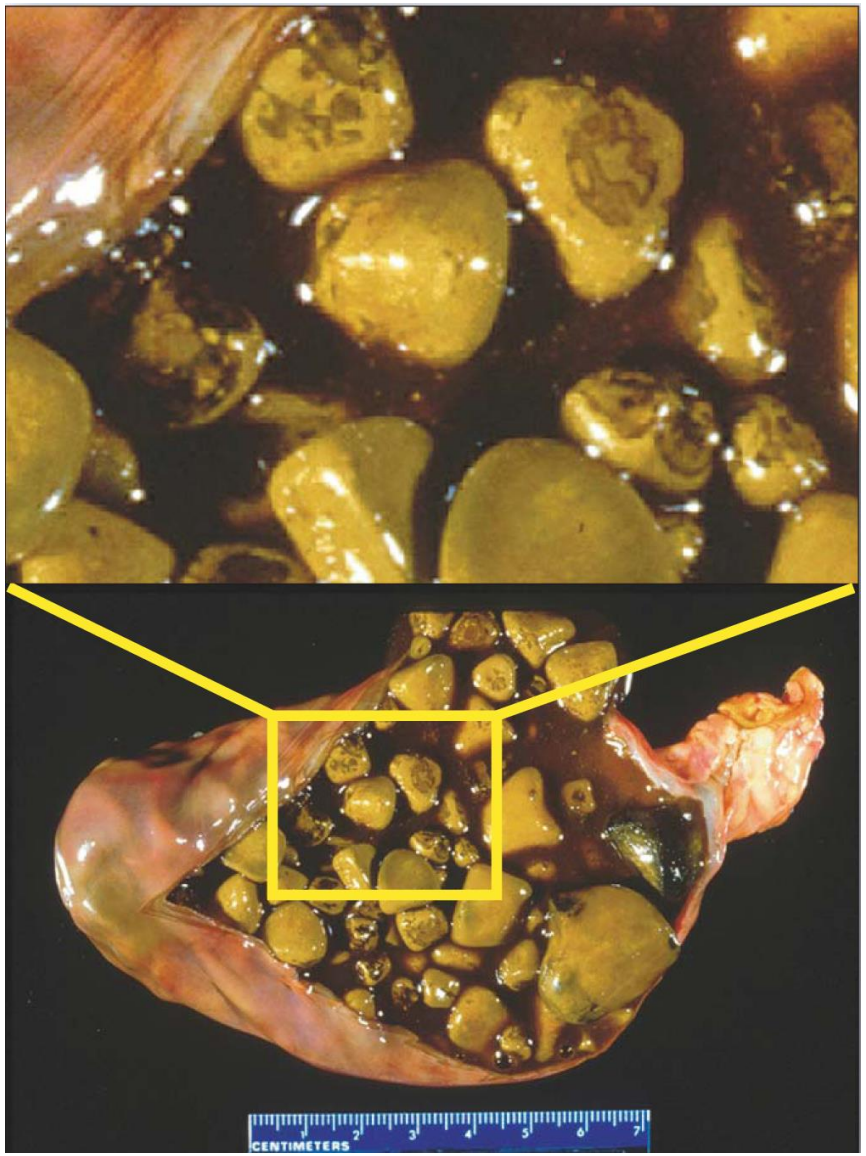


Cholesterol Metabolism

Dr. Diala Abu-Hassan



Cholesterol was isolated from gall bladder stones in 1774

Chole ster ol

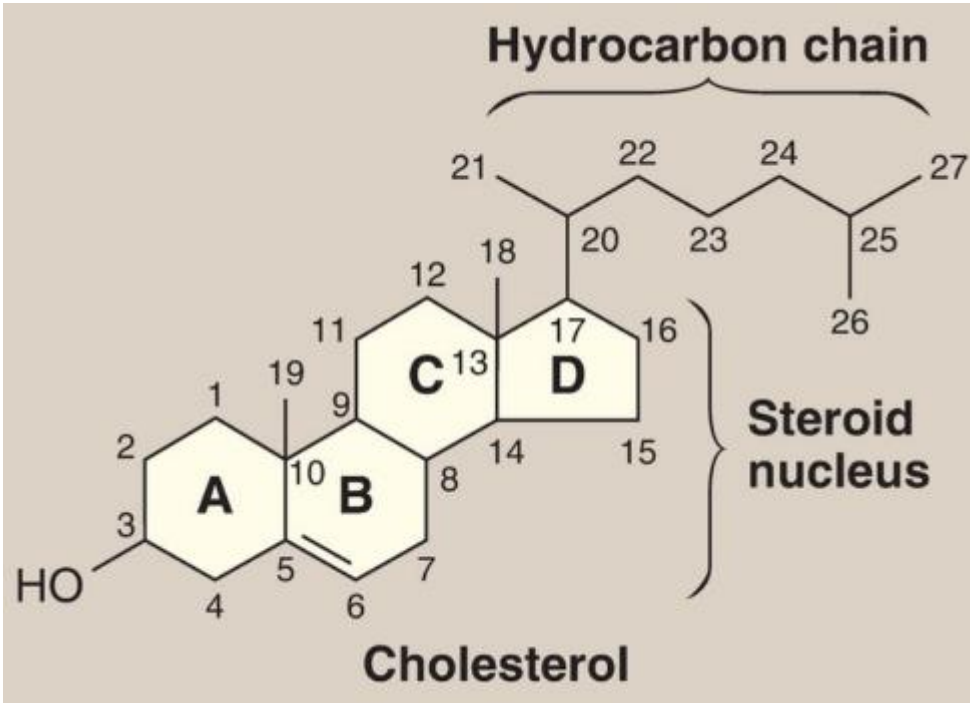
Chole: Bile

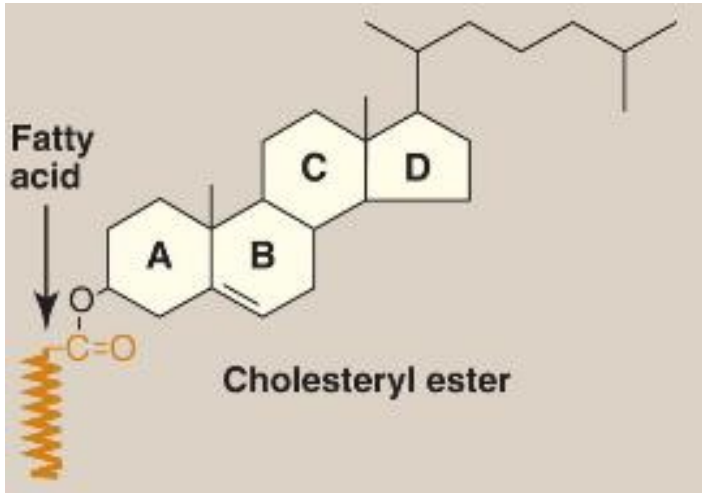
Stereos: solid

ol: alcohol

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.



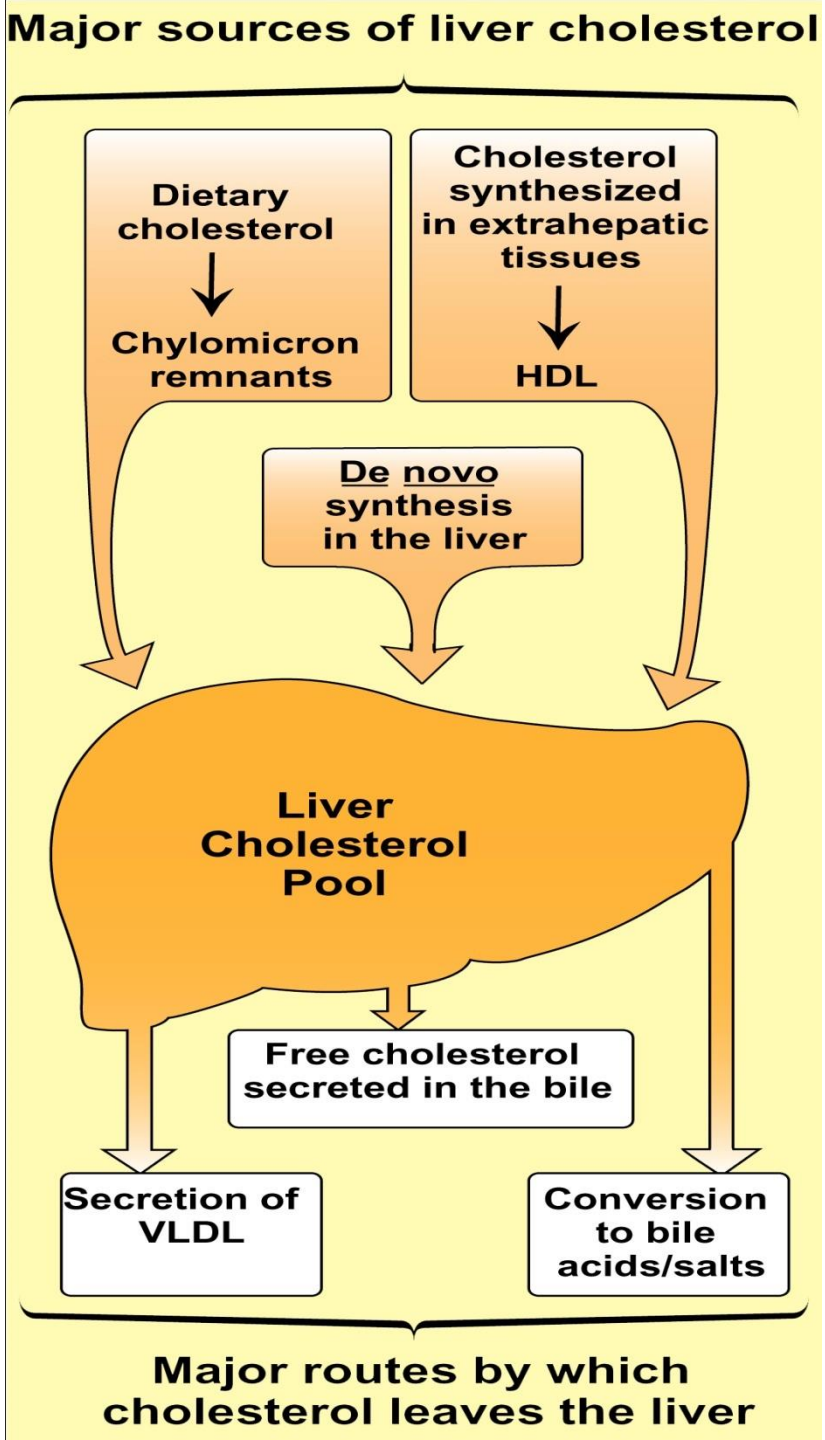


Sources and Elimination of Cholesterol

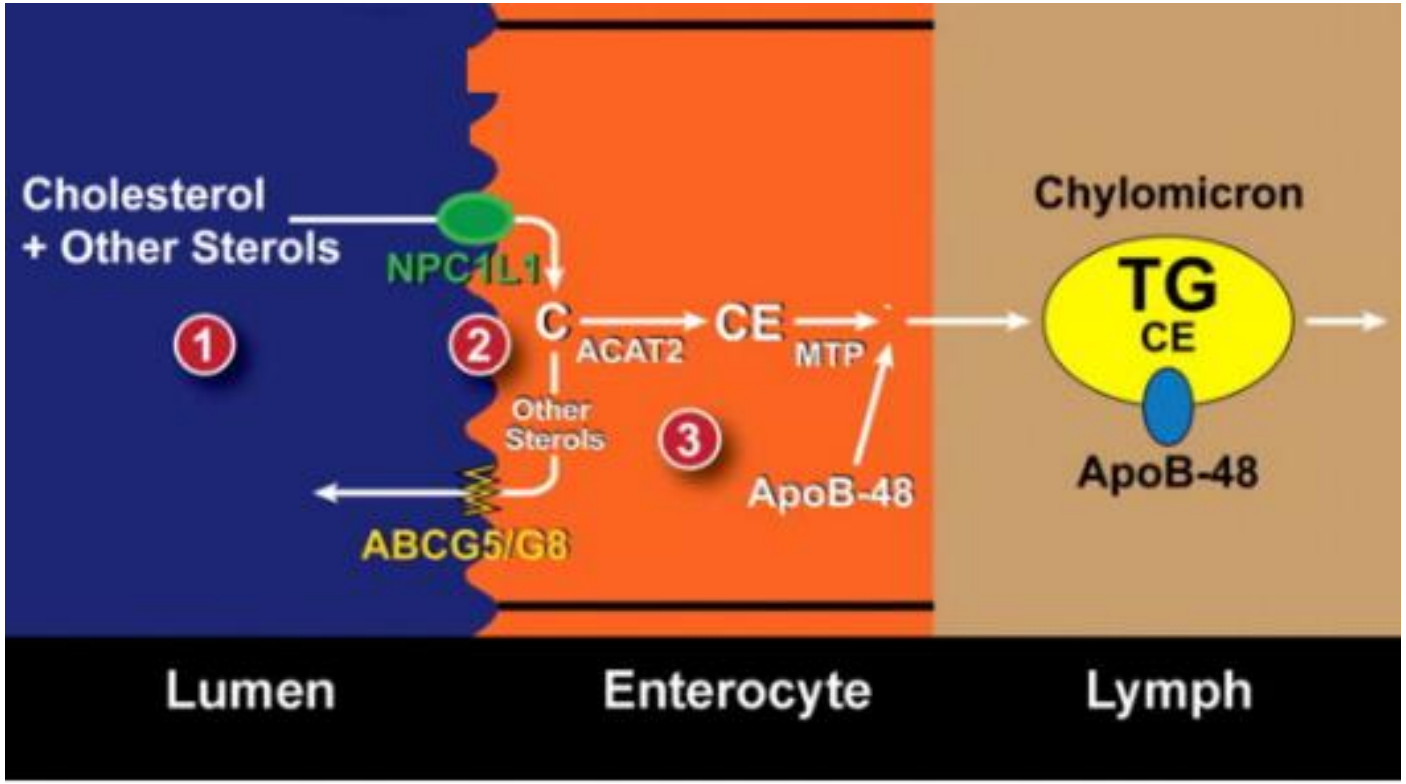
- ✓Synthesis: ≈ 1000 mg

  Liver, Small Intestine, Adrenal Cortex …
- ✓Dietary: ≈ 300 mg
- ✓**Elimination: Via the Bile**

  Cholesterol, Bile Salts



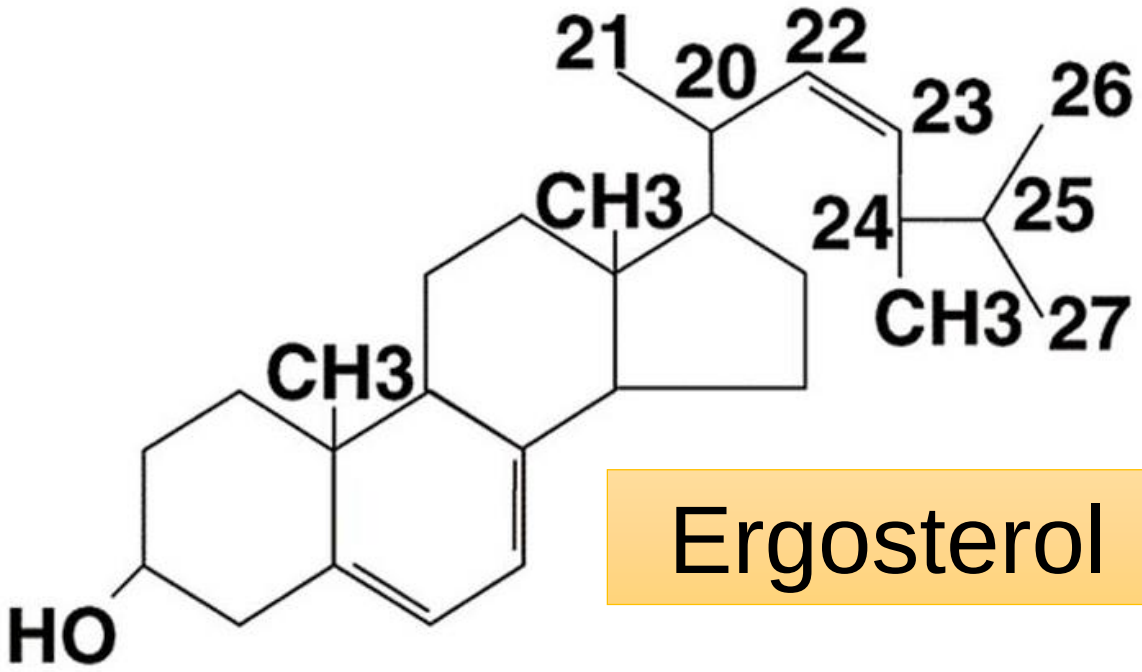
Intestinal absorption of cholesterol



- 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 increasing the risk of MI.

Plant sterols

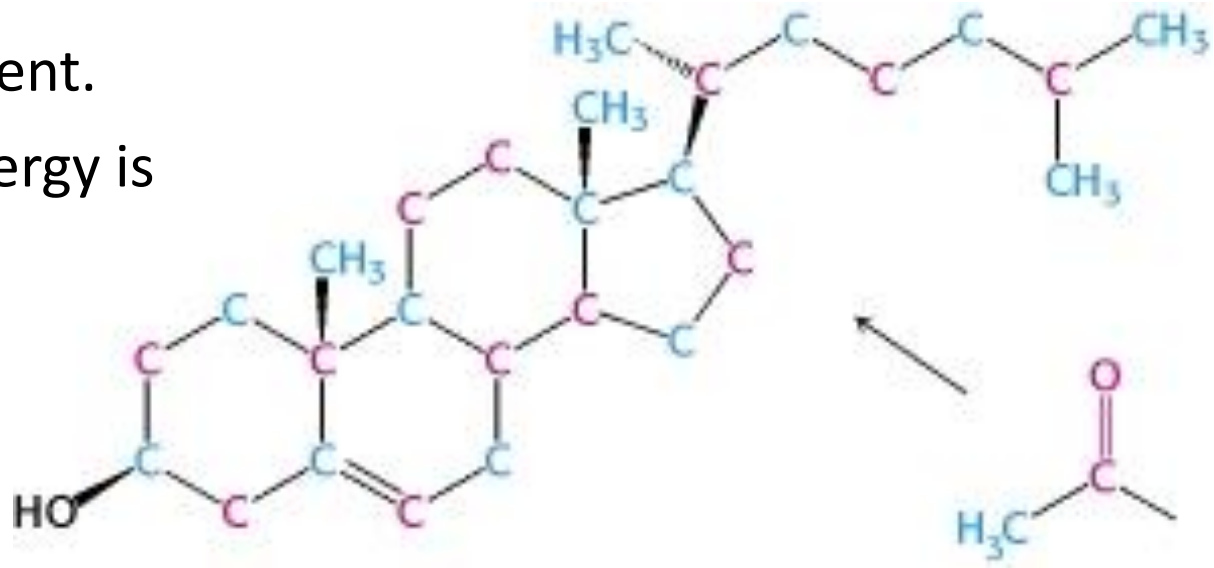
- Plants manufacture phytosterols (substance chemically similar to cholesterol produced within plants
- They compete with cholesterol for absorption in the intestinal tract, thus potentially reducing cholesterol absorption
- Plant sterols (phytosterols) are poorly absorbed by humans (5% vs. 40% for cholesterol) 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 (an important protective mechanism).



Ergosterol

Cholesterol Synthesis Requires

- **Carbon source**: All the carbon atoms in cholesterol are provided by acetyl coenzyme A (CoA).
- **Reducing power**: NADPH is the reducing agent.
- **Energy**: The pathway is endergonic, and energy is provided by the hydrolysis of
  - The thioester bond of acetyl CoA
  - ATP
- **O_2**
- 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.



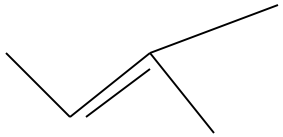
Stages in Cholesterol Synthesis

Acetyl CoA (C2)

↓

Mevalonate (C6)

↓



Isoprene Units (C5)

↓

Squalene (C30)

↓

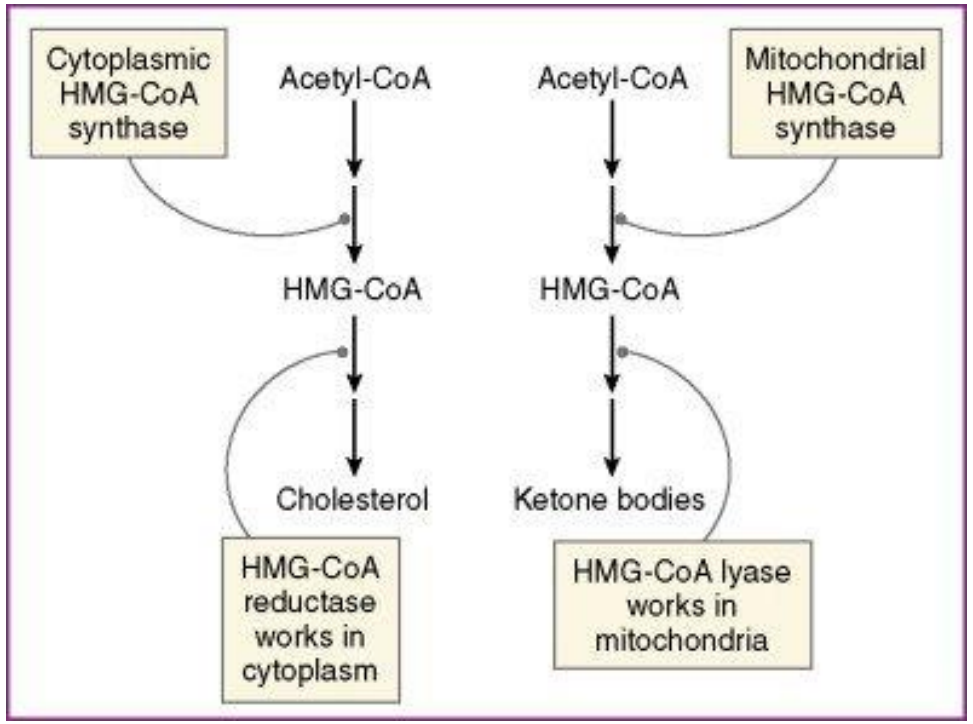
Lanosterol (C30)

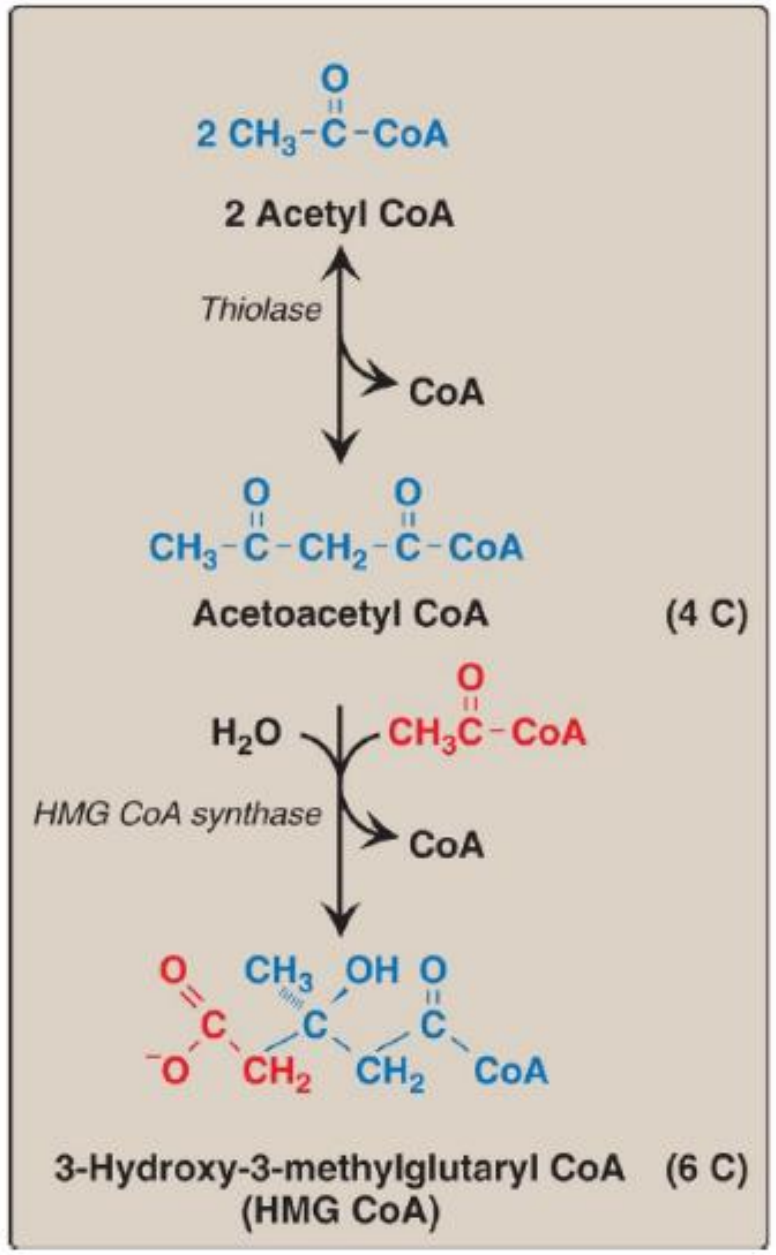
↓

Cholesterol (C27)

Cholesterol synthesis, the first reactions in the cytosol…

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

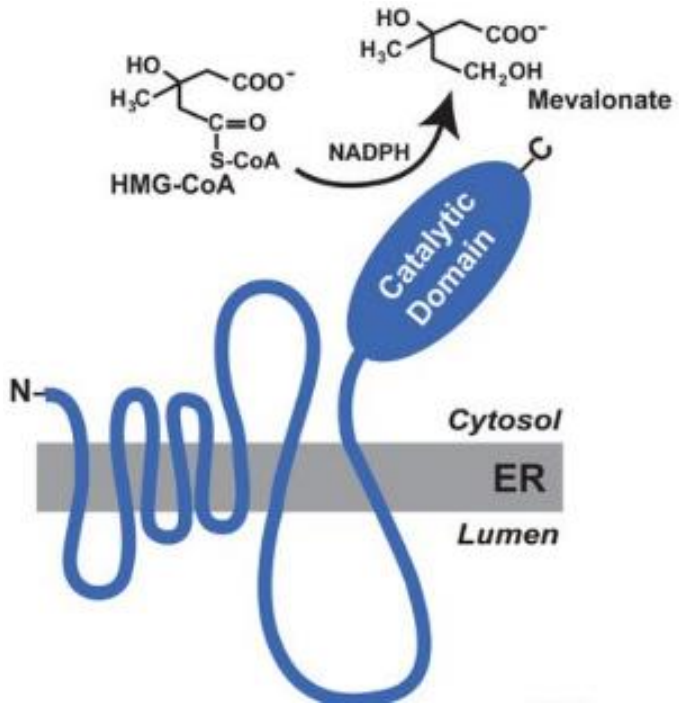


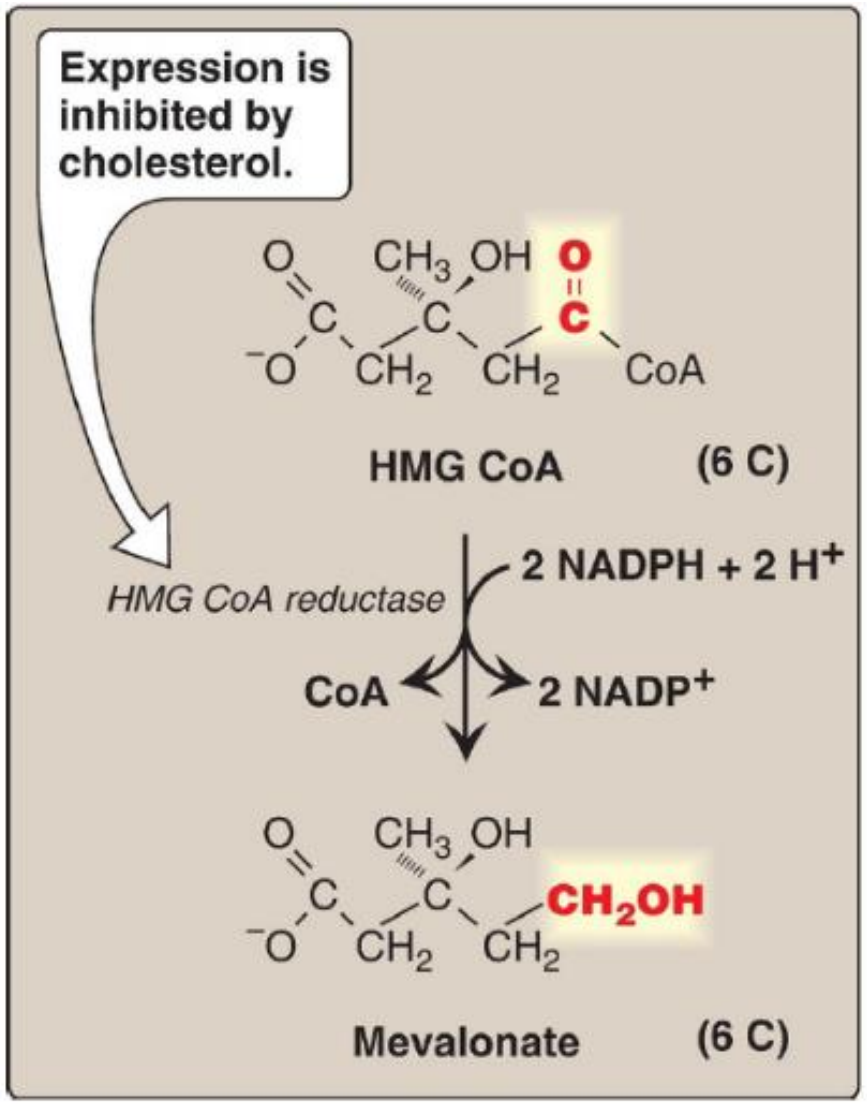


Cholesterol synthesis , synthesis of mevalonate

- HMG CoA is reduced to mevalonate by HMG CoA reductase.
  - A rate-limiting reaction and a committed step.
  - Two molecules of NADPH are oxidized.
  - CoA is released making the reaction irreversible.

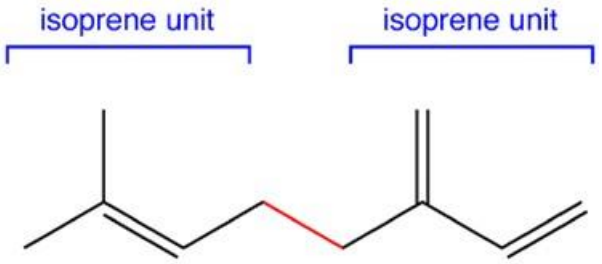
- HMG CoA reductase is an integral membrane protein of the **SER**, with its catalytic domain projecting into the cytosol.

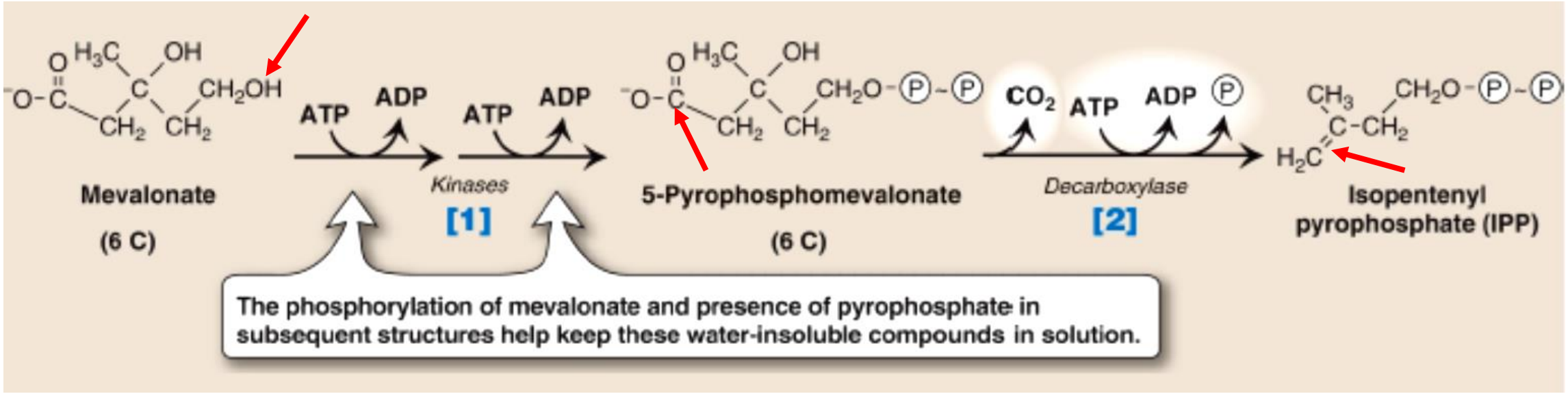




Synthesis of cholesterol-Isoprene unit (5Cs) in Peroxisomes

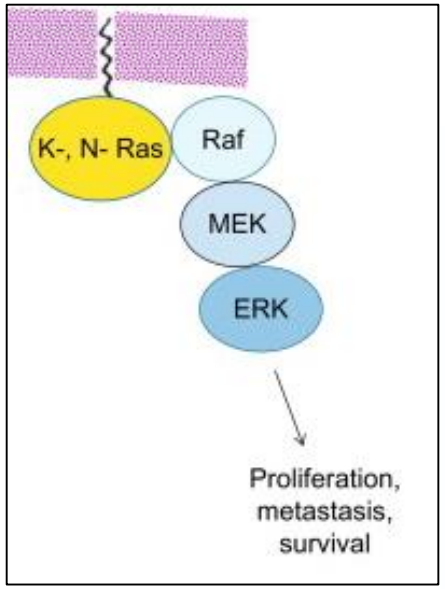
- Mevalonate is transported to the peroxisome
- [1] Mevalonate is activated by transferring 2 phosphate groups from ATP.
- [2] A five-carbon isoprene unit, isopentenyl pyrophosphate (IPP), is formed by the decarboxylation of 5-pyrophosphomevalonate.
  - The reactions require ATP.
  - IPP is the precursor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

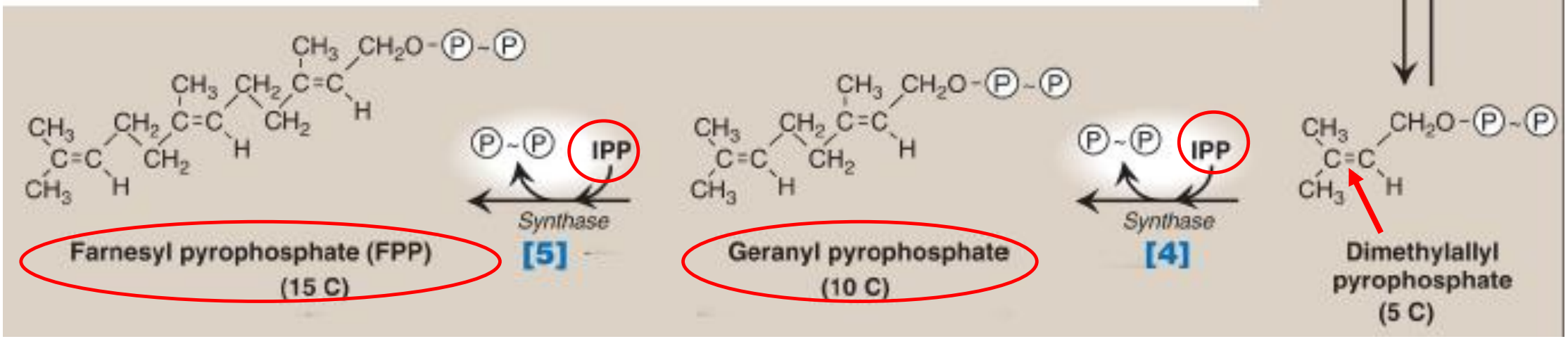




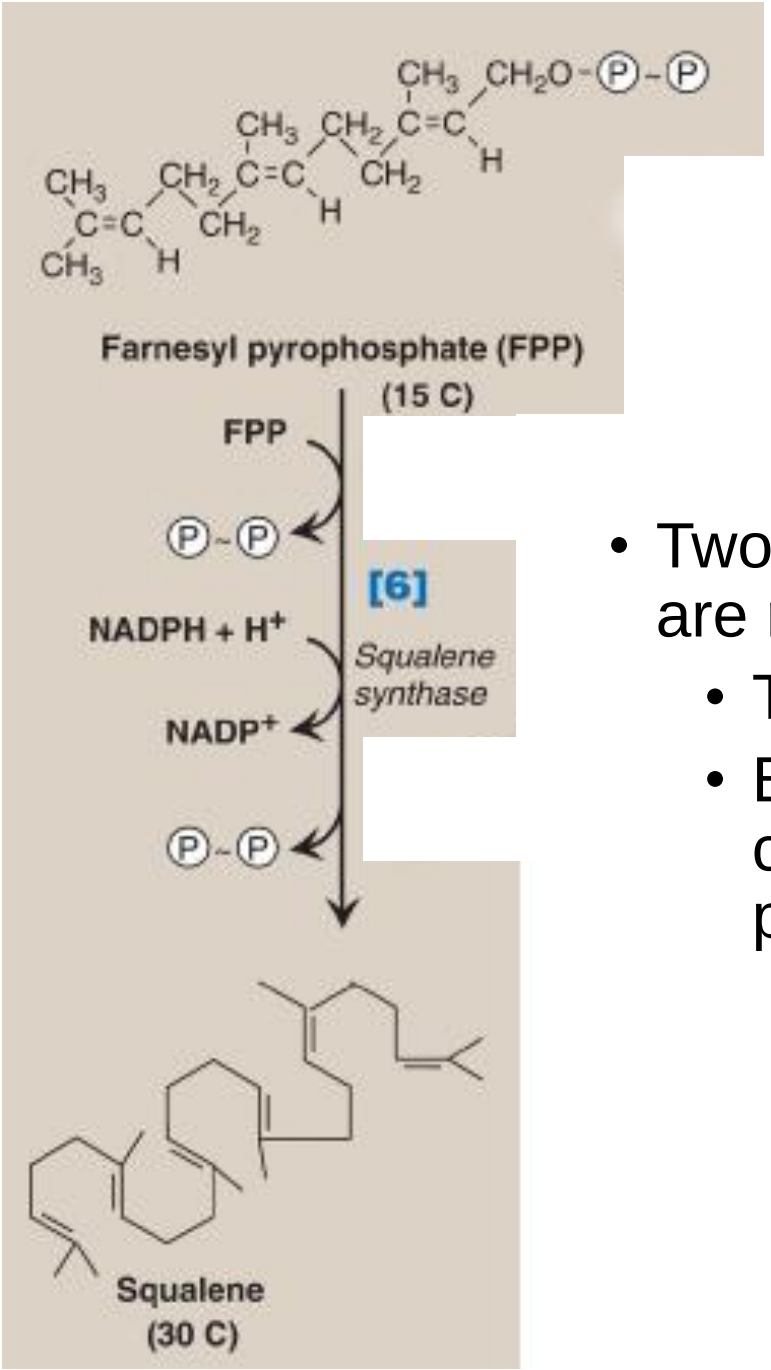
Synthesis of cholesterol- From 5 to 15 Cs in the Peroxisome

- [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.





Synthesis of cholesterol- the synthesis of squalene in the SER



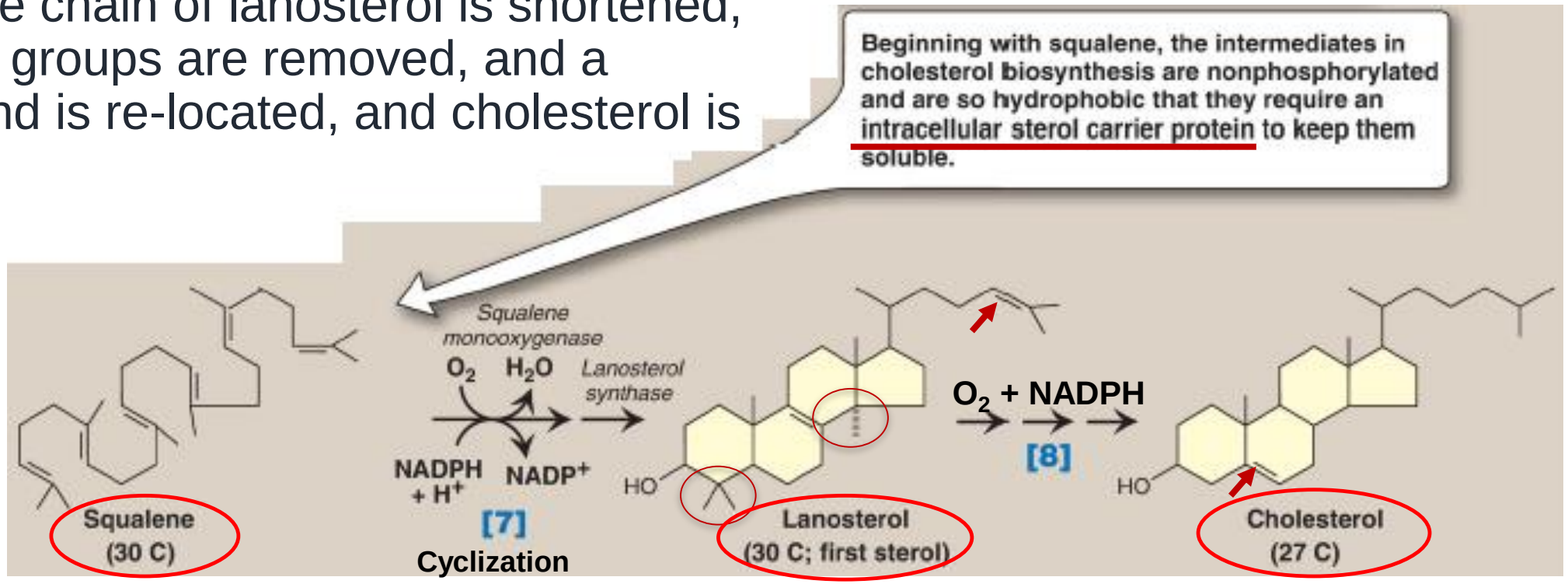
- Two molecules of FPP combine, releasing pyrophosphate, and are reduced, forming the 30-carbon compound squalene.
  - Thus, squalene is formed from six isoprenoid units.
  - Because 3 ATP are hydrolyzed per mevalonate residue converted to IPP, a total of 18 ATP are required to make the polyisoprenoid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

Synthesis of cholesterol- final steps in the SER

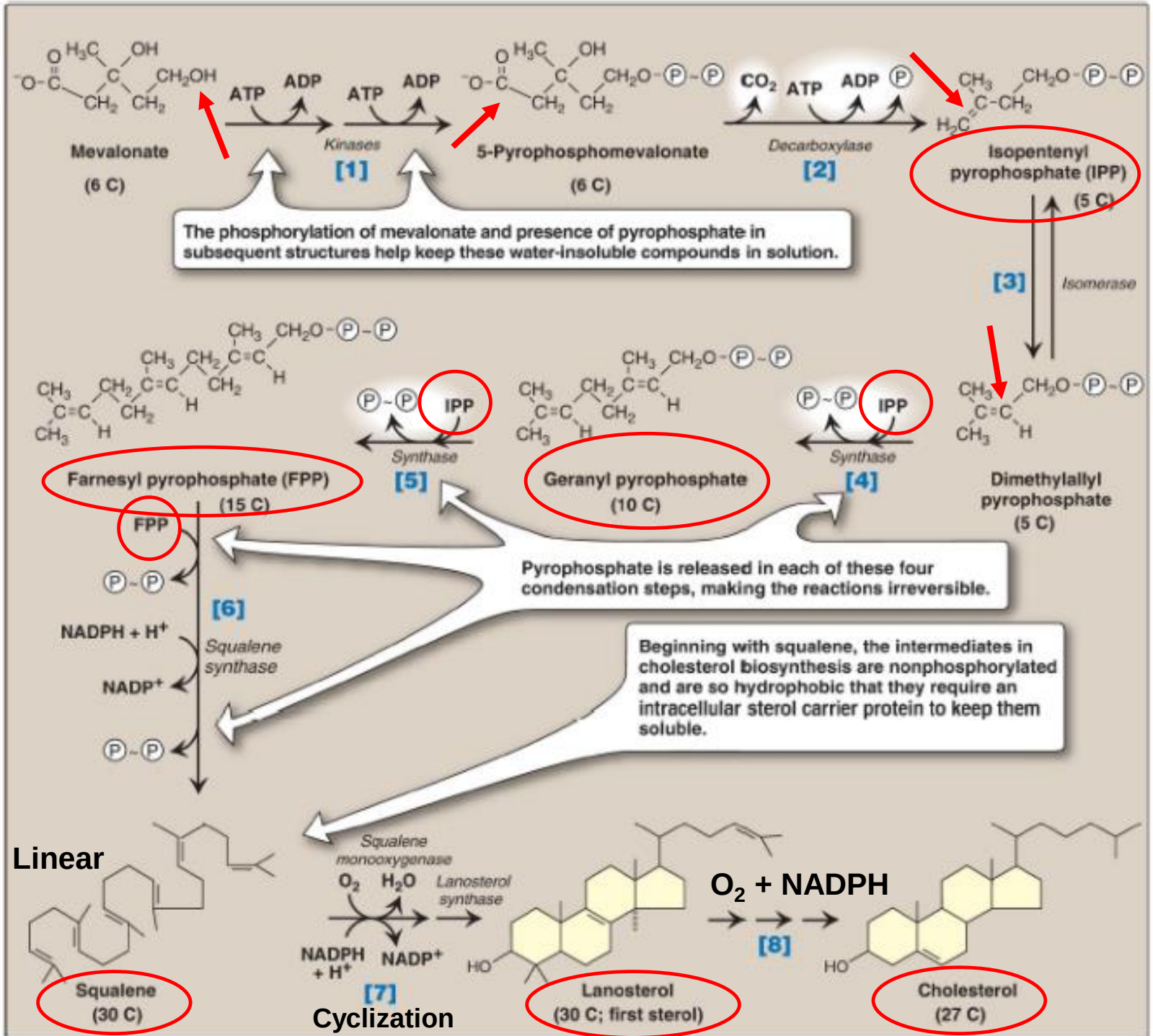
[7] Squalene is converted to the sterol lanosterol by **SER**-associated enzymes that use molecular oxygen (O2) and NADPH.

- 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.



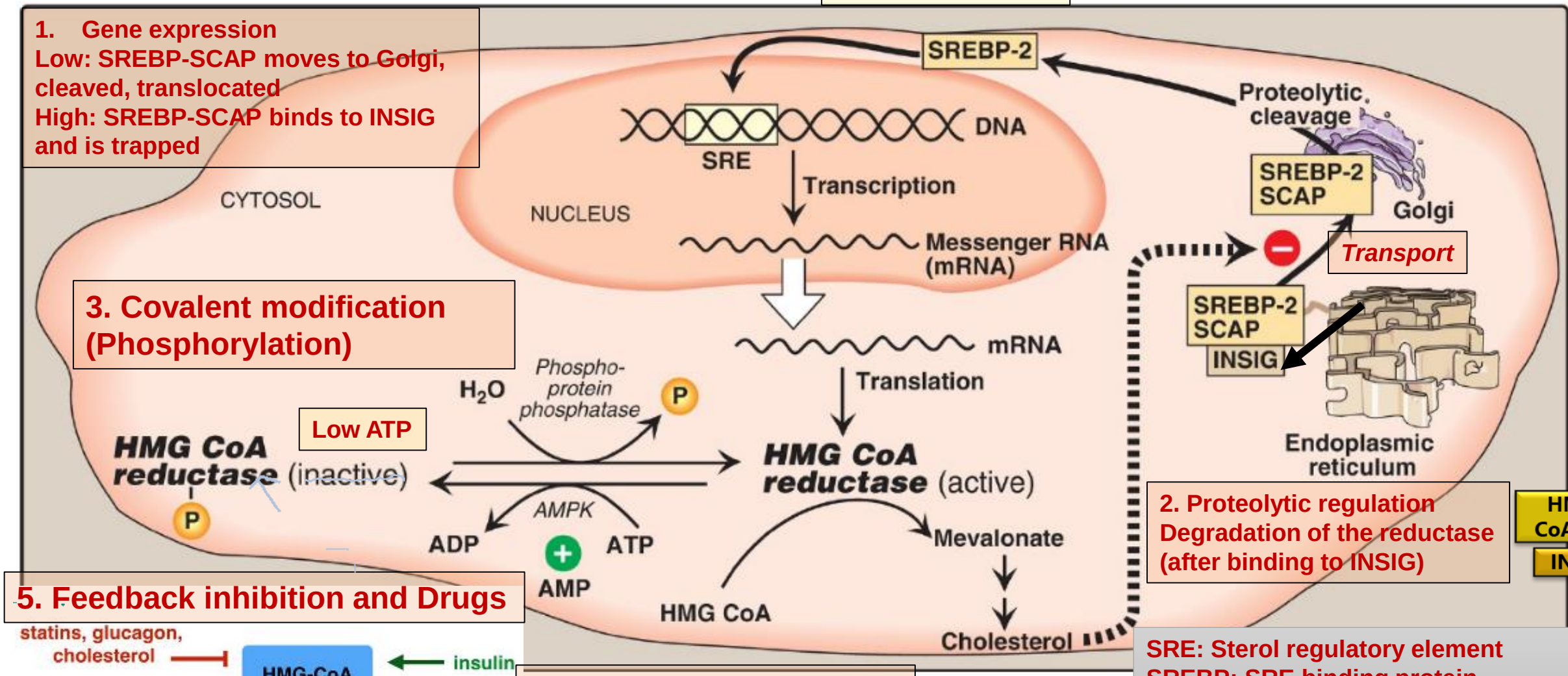
Synthesis of cholesterol



Regulation of cholesterol synthesis

↑ HMG CoA reductase
↑ FA synthesis enzymes

1. Gene expression
Low: SREBP-SCAP moves to Golgi, cleaved, translocated
High: SREBP-SCAP binds to INSIG and is trapped



3. Covalent modification (Phosphorylation)

2. Proteolytic regulation
Degradation of the reductase (after binding to INSIG)

HMG-CoA red.
INSIG

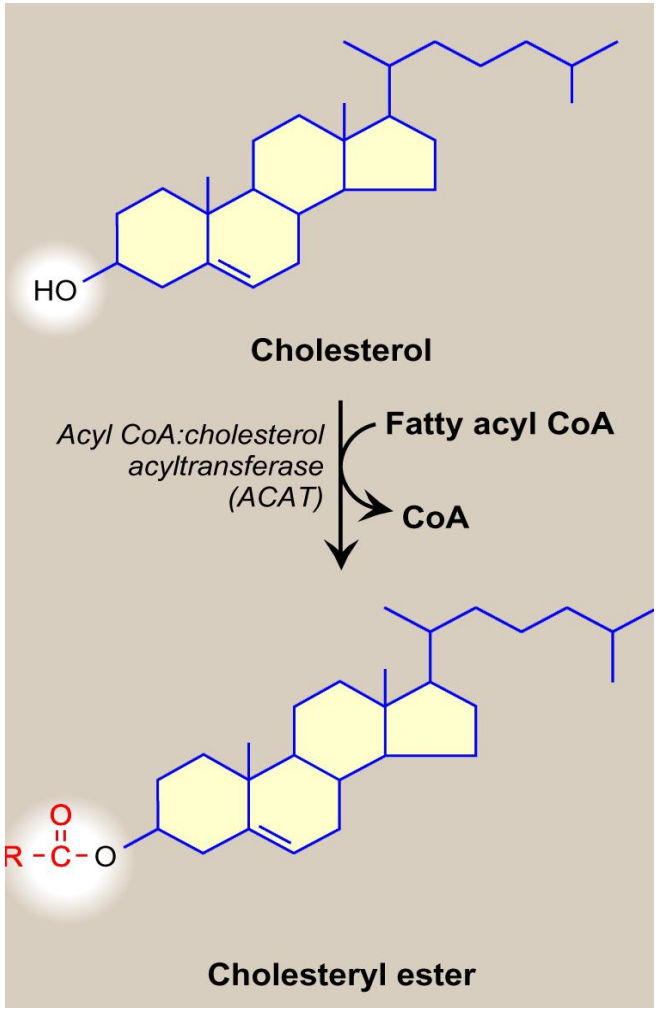
5. Feedback inhibition and Drugs

statins, glucagon, cholesterol ⊣ HMG-CoA reductase ← insulin

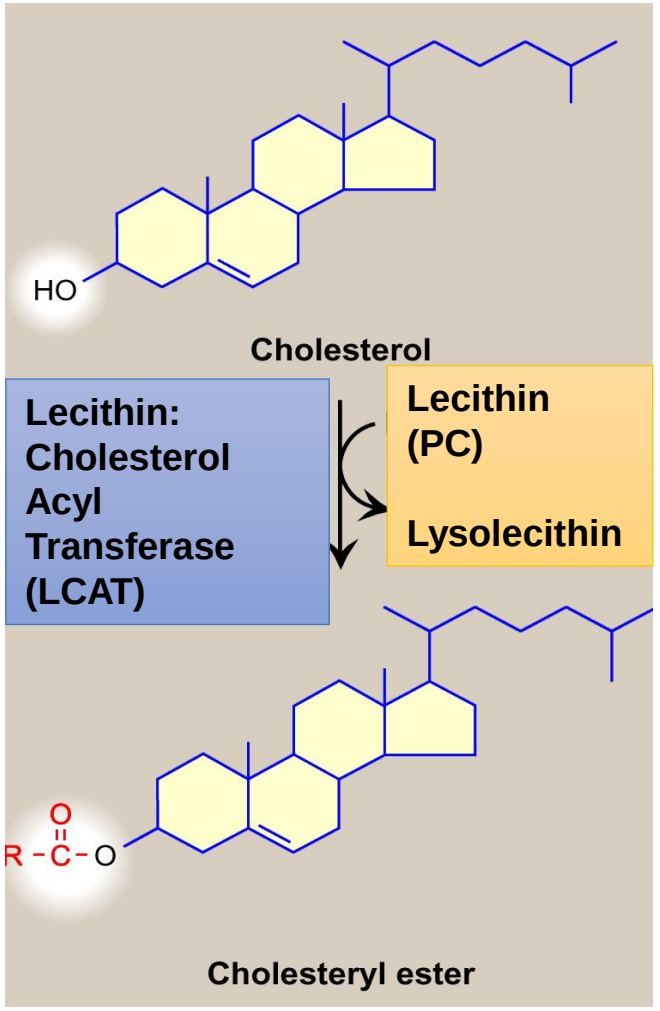
4. Hormonal regulation
(through phosphatase and PKA)

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

Esterification of Cholesterol



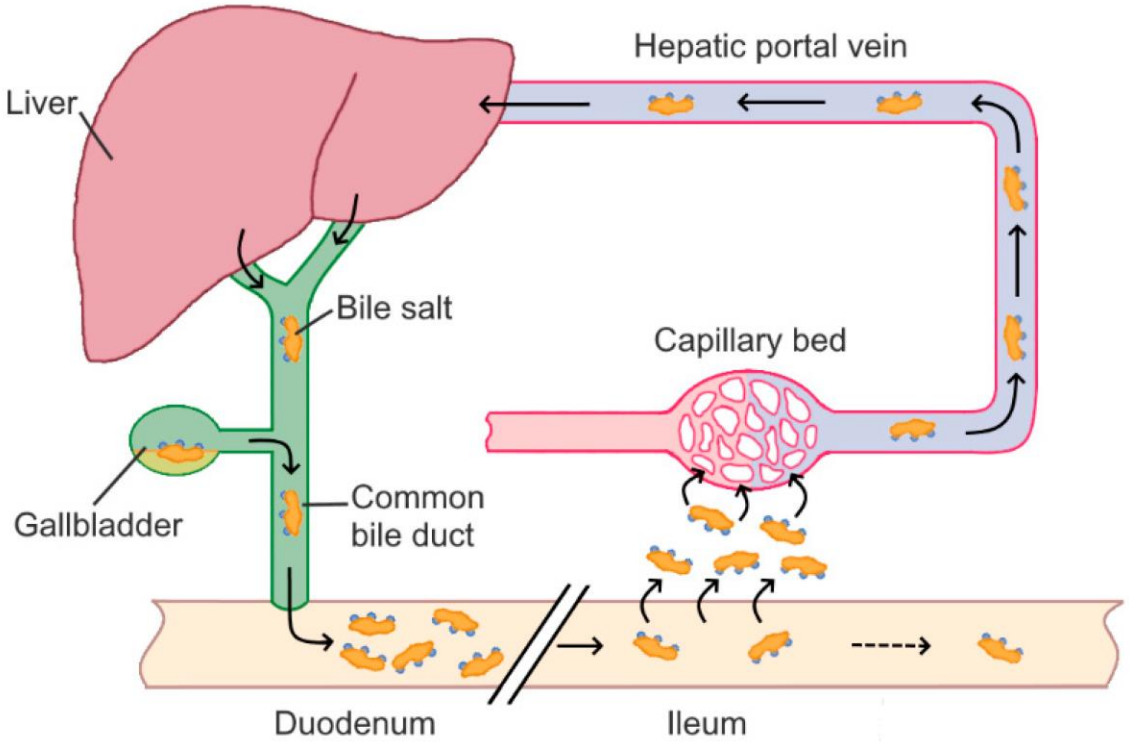
Esterification of cholesterol in the cells

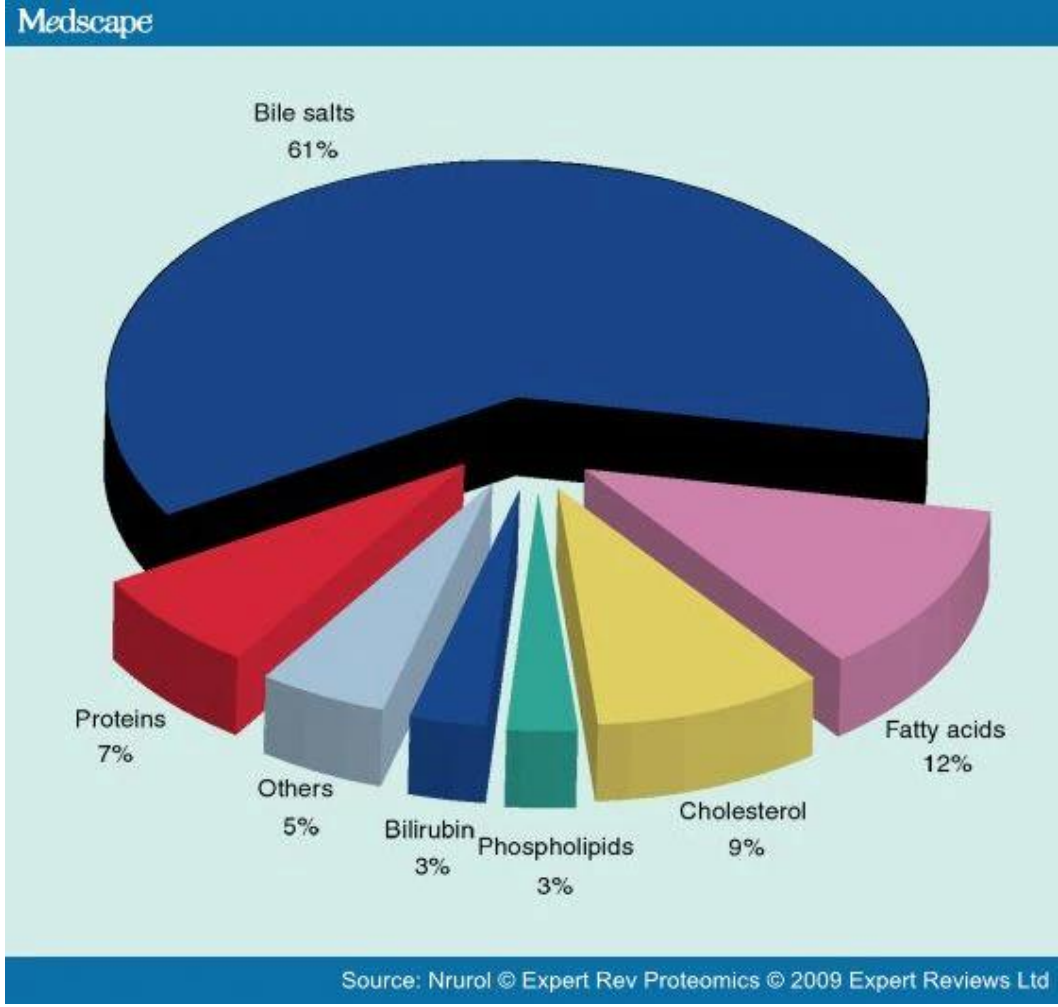


Esterification of cholesterol in the plasma

The use of cholesterol to make bile

- Bile consists of a watery mixture of organic and inorganic compounds.
  - PC and conjugated bile salts are the most important organic components of bile.

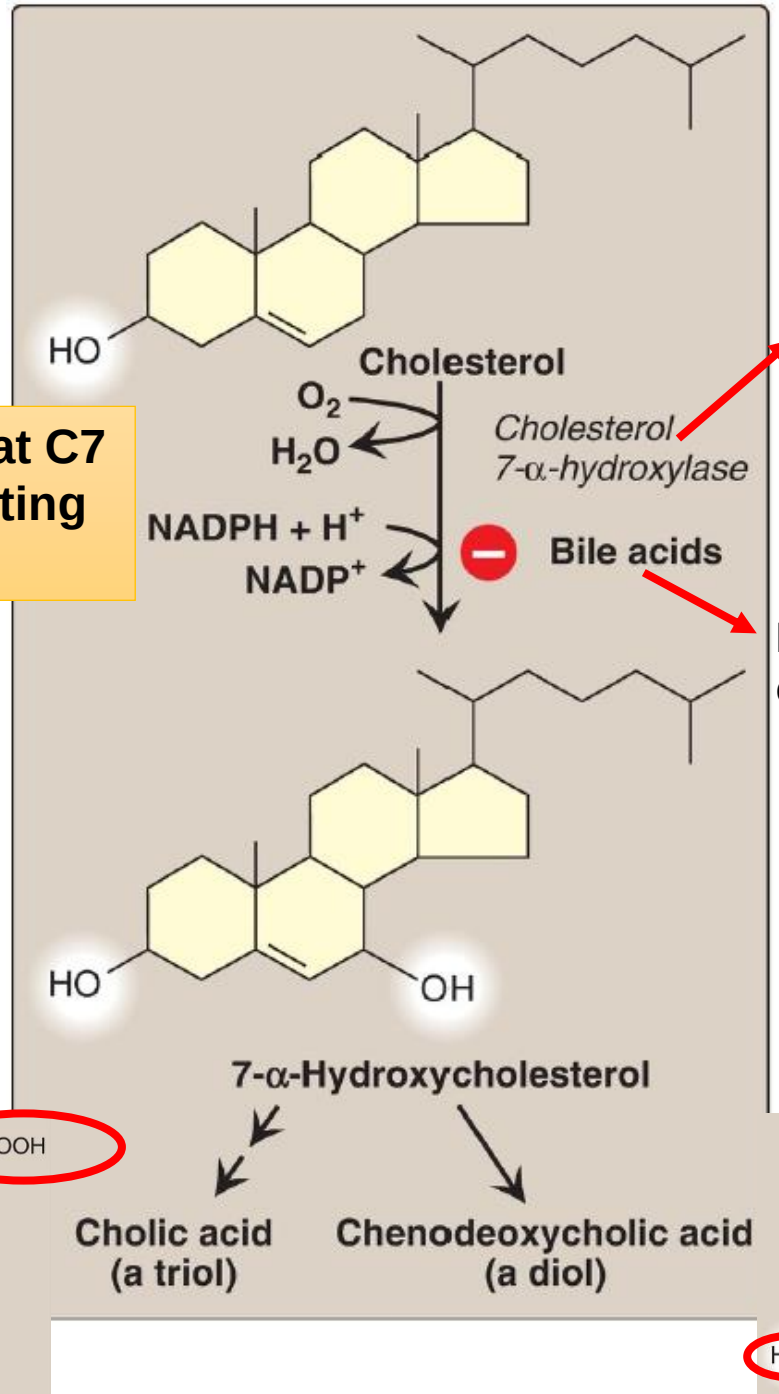




- Bile can either pass directly from the liver, where it is synthesized, into the duodenum through the common bile duct, or be stored in the gallbladder.

Synthesis of Bile Acids and Salts

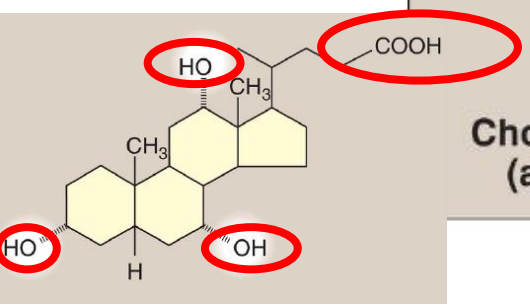
Hydroxylation at C7 is the rate-limiting Step

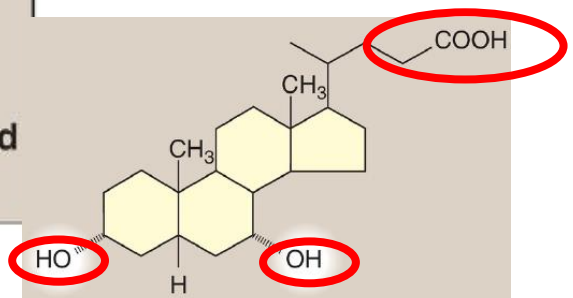


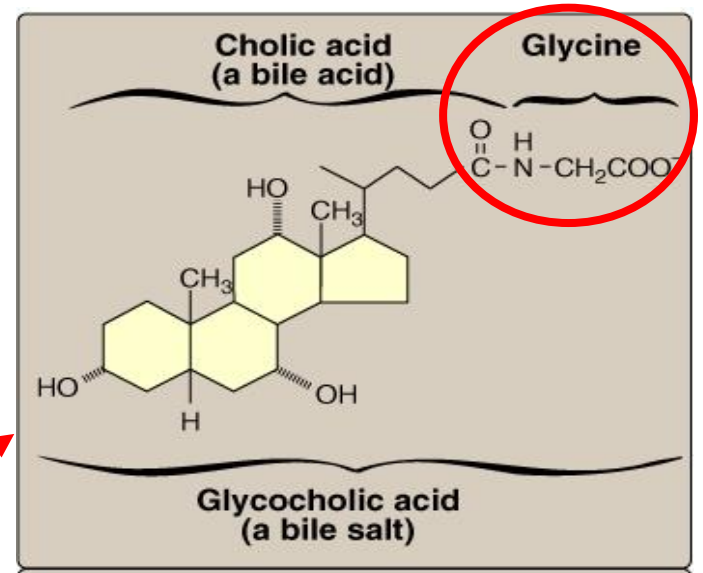
SER-associated cytochrome P450 monooxygenase found only in liver.

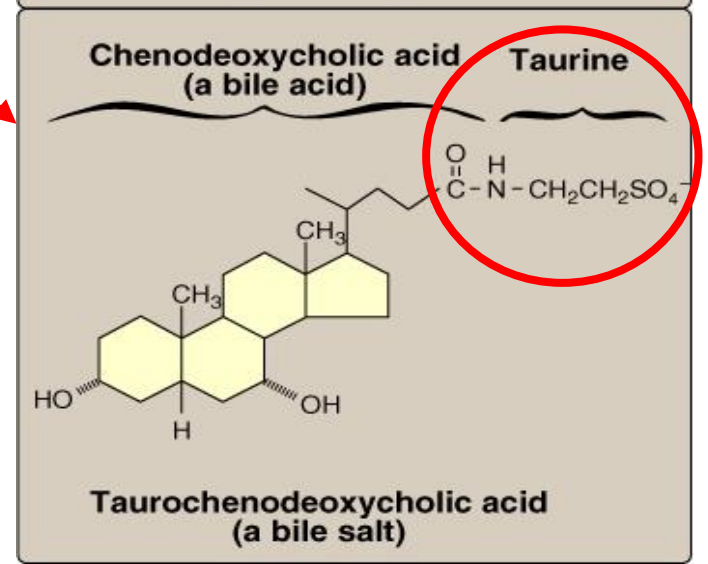
Inhibit the expression of cholesterol-7-hydroxylase

Conjugation

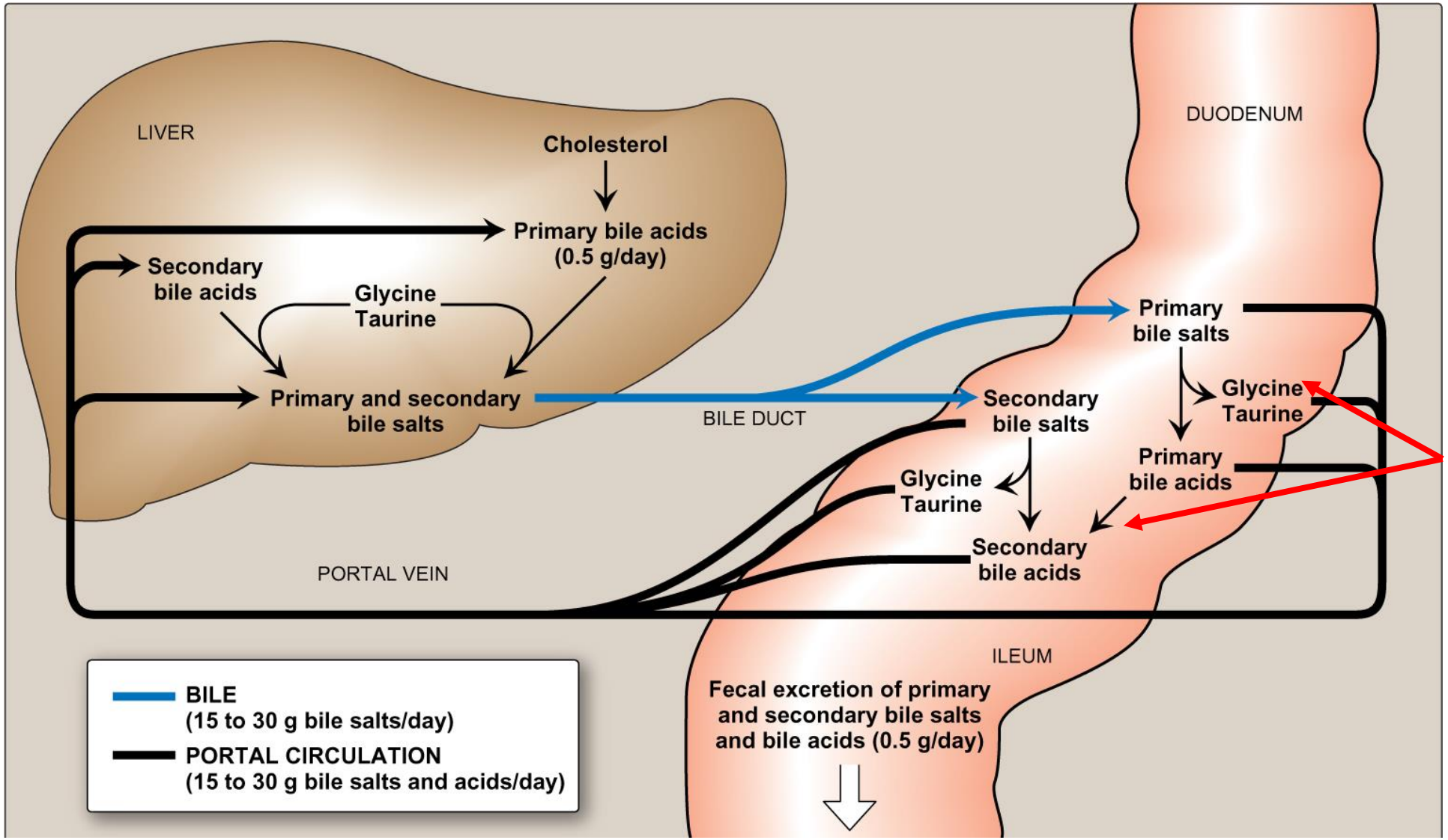






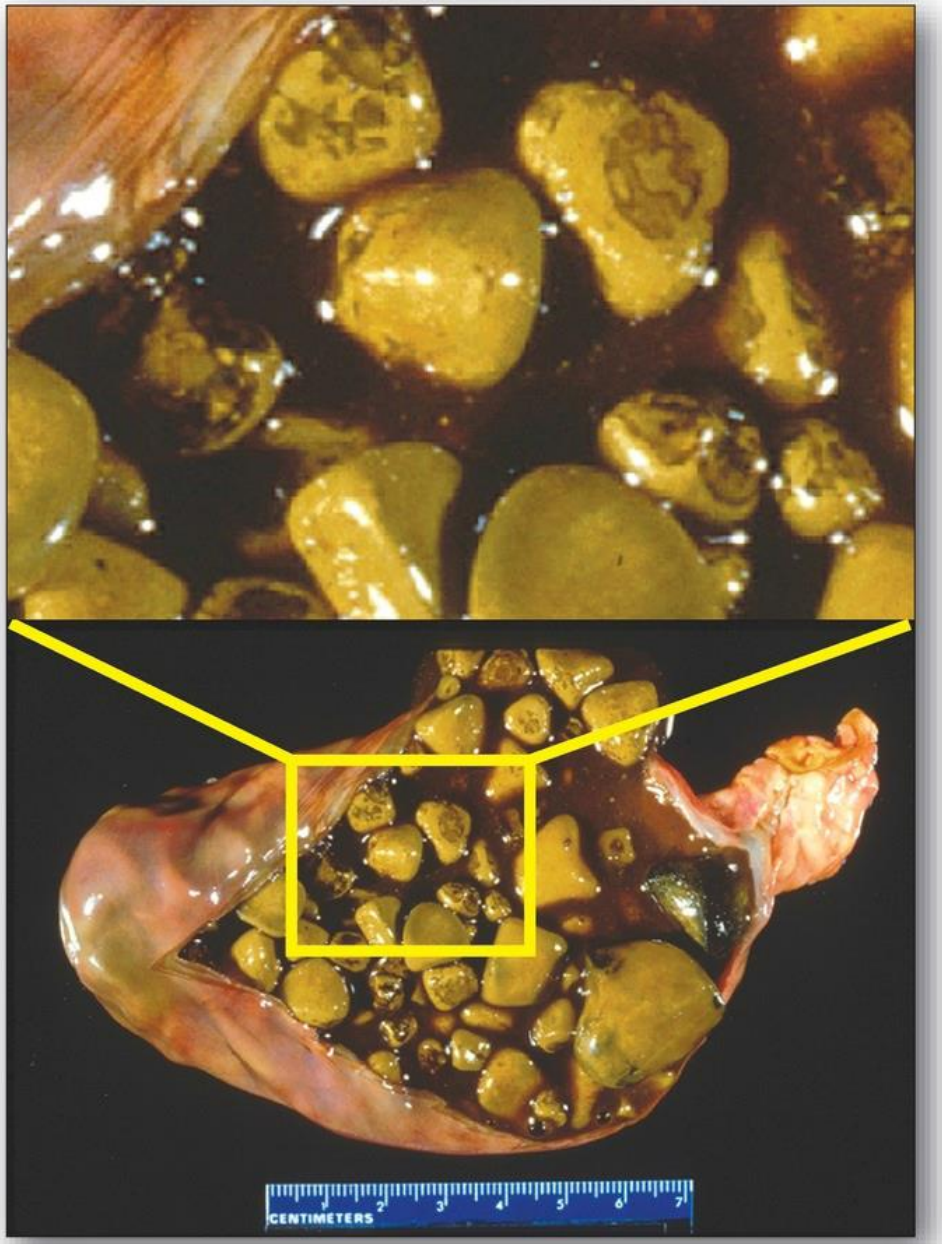


Enterohepatic circulation



Application: Cholelithiasis

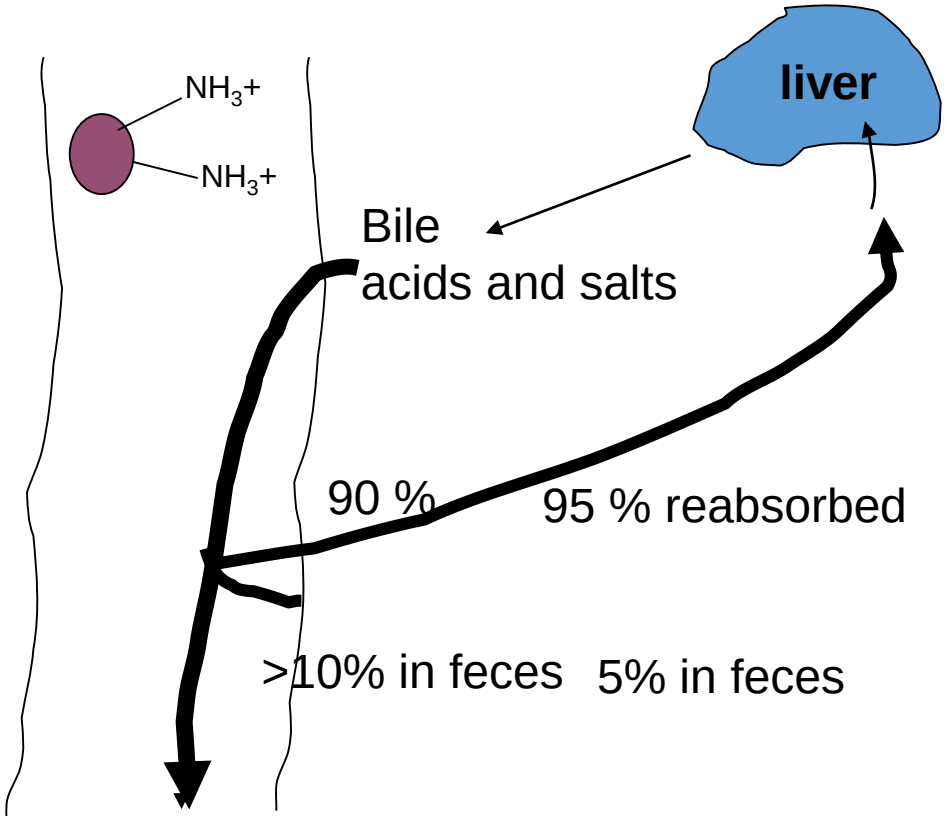
- ↑Cholesterol or ↓bile acids → insolubility → gallbladder stones (cholelithiasis)
- Treatment: cholecystectomy
  - Alternatively: oral administration of chenodeoxycholic acid results in a gradual (months to years) dissolution of the gallstones.

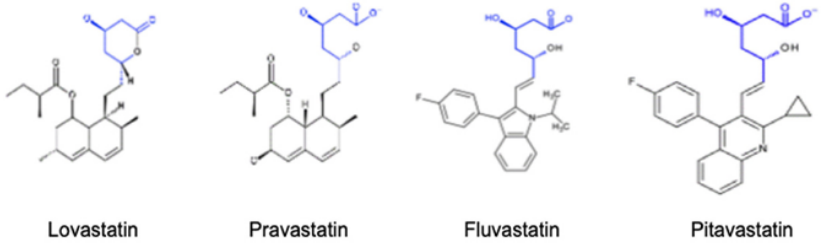


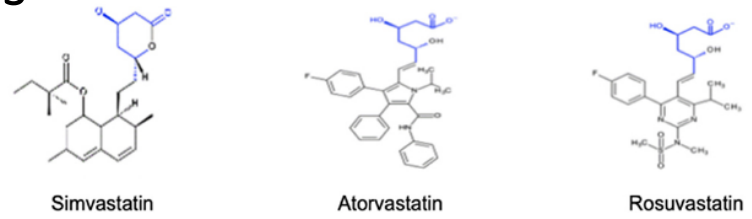
Lowering Cholesterol Level

1. Dietary

- ↓Cholesterol intake
- ↑ PUSFA / SFA
- ↑ Fiber
- Daily Ingestion of plant steroid esters







Inhibitors of HMG CoA reductase (statins)

2. Inhibition of Synthesis

3. Bile sequesterants such as cholestyramine

↓ Enterohepatic circulation of bile acids