Lipid metabolism – 2. Cholesterol metabolism. Regulation and pathology of lipid metabolism.

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Lecture plan

Cholesterol chemical composition, properties and biological role.

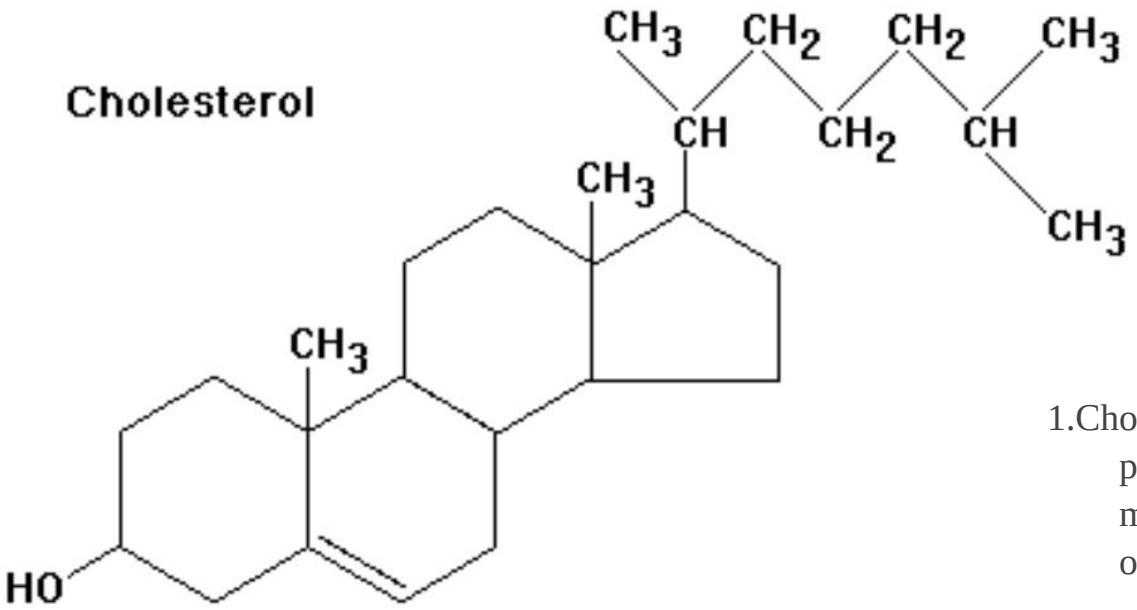
Cholesterol transport.

Biosynthesis of cholesterol.

Pathways of biotransformation of cholesterol.

Pathologies of lipid metabolism

Cholesterol



1.Cholesterol is a major constituent of the cell membranes. Cholesterol modulates physical properties of these membranes that in turn affect the function of membrane proteins such as receptors and transporters. Experimental depletion of membrane cholesterol cripples many cellular functions.

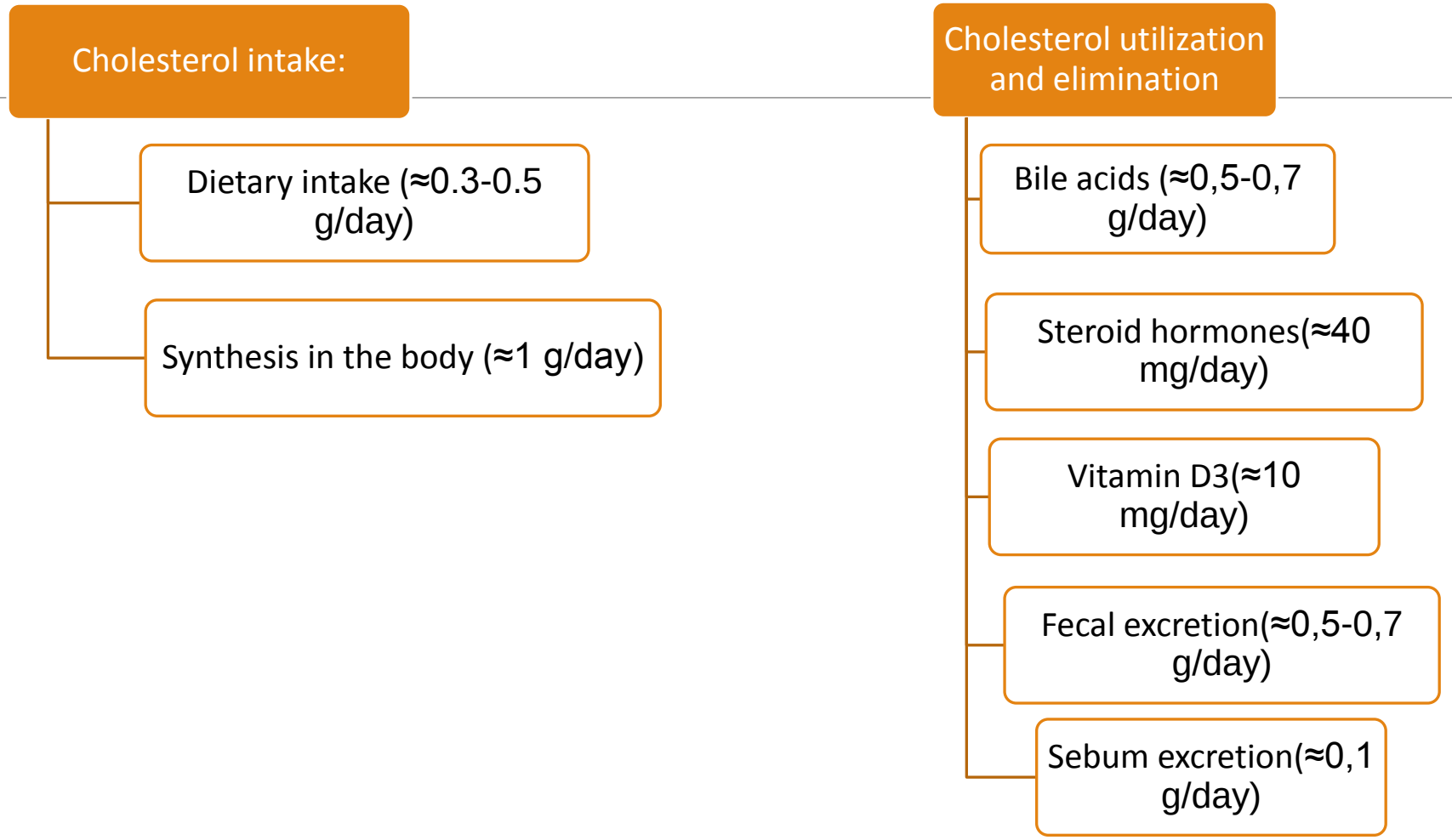
2.Cholesterol is the biosynthetic precursor of bile acids, which are essential for fat digestion.

3.Cholesterol is the precursor of all steroid hormones, namely, androgens, estrogens, progestins, glucocorticoids, and mineralocorticoids, as well as of calciferol (vitamin D).

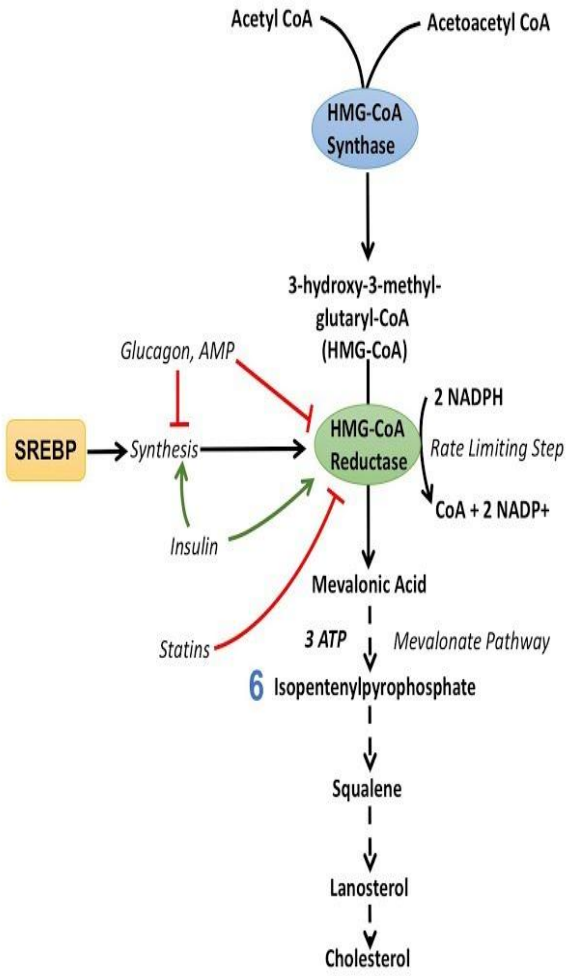
https://www.precisionnutrition.com/all-about-cholesterol

Cholesterol is a steroidal substance derived from cyclopentane perhydro phenanthrene.
It is hydrophobic.
It is not completely destroyed by enzymes in the body, only modified.
Has a flat structure.
This substance is only of animal nature.

Balance of cholesterol in the body



Cholesterol biosynthesis



The process of cholesterol synthesis can be considered to be composed of five major steps where the reactions that culminate in the synthesis of isopentenyl pyrophosphate, and its isomeric form dimethylallyl pyrophosphate, are commonly referred to as the mevlonate pathway:

1.Acetyl-CoAs are converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)

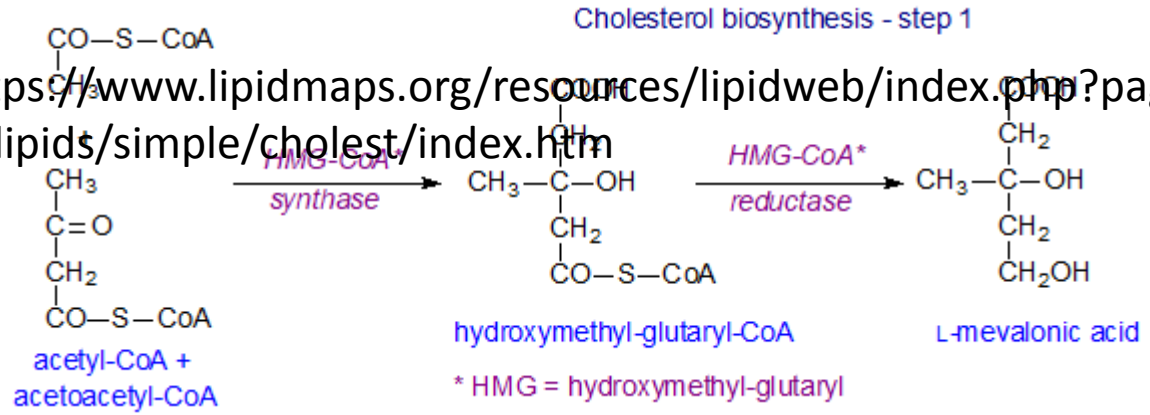
2.HMG-CoA is converted to mevalonate

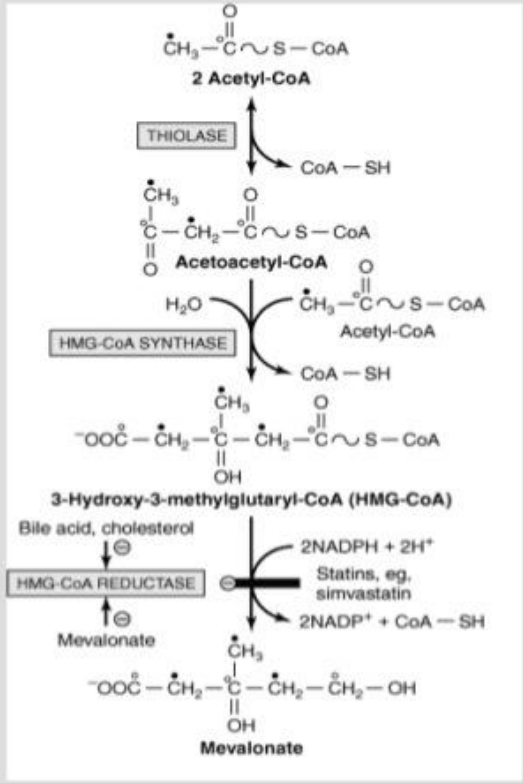
3.Mevalonate is converted to the isoprene based molecule, isopentenyl pyrophosphate (IPP)

4.IPP molecules are converted to squalene

5.Squalene is converted to cholesterol

https://www.lipidmaps.org/resources/lipidweb/index.php?page=lipids/simple/cholest/index.htm





- The synthesis of mevalonate is the committed step in cholesterol formation.
- The enzyme catalyzing this irreversible step,
- 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase), is an important control site in cholesterol biosynthesis,
- and is the site of action of the most effective class of cholesterol-lowering drugs, the HMG-CoA reductase inhibitors (statins).

https://www.slideshare.net/namarta28/cholesterol-synthesis-steps-and-regulation

reductase and results in an increase in the rate of cholesterol synthesis

- Cholesterol synthesis ceases when the ATP level is low

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REGULATION OF CHOLESTEROL BIOSYNTHESIS

Feed back inhibition

- HMG Co A reductase is inhibited by Mevalonate and Cholesterol.
- Mevalonate is the immediate product of HMG Co A reductase catalyzed reaction whereas Cholesterol is the ultimate product of the reaction pathway.

12/14/13 Biochemistry for medics

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REGULATION OF CHOLESTEROL BIOSYNTHESIS

Covalent modification (Role of hormones)

- Phosphorylation decreases the activity of the reductase.
- Glucagon favors formation of the inactive (phosphorylated form) form, hence decreases the rate of cholesterol synthesis
- In contrast , insulin favors formation of the active(dephosphorylated)form of HMG Co A reductase and results in an increase in the rate of cholesterol synthesis
- Cholesterol synthesis ceases when the ATP level is low

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Regulation of Cholesterol Synthesis

HMG-CoA Reductase, the rate-limiting step on the pathway for synthesis of cholesterol, is a major control point. Regulation relating to cellular uptake of cholesterol will be discussed in the next class.

Short-term regulation:

HMG-CoA Reductase is inhibited by **phosphorylation**, catalyzed by **AMP-Dependent Protein Kinase**.

This kinase is active when cellular AMP is high, corresponding to when ATP is low.

Thus, when cellular ATP is low, energy is not expended in synthesizing cholesterol.

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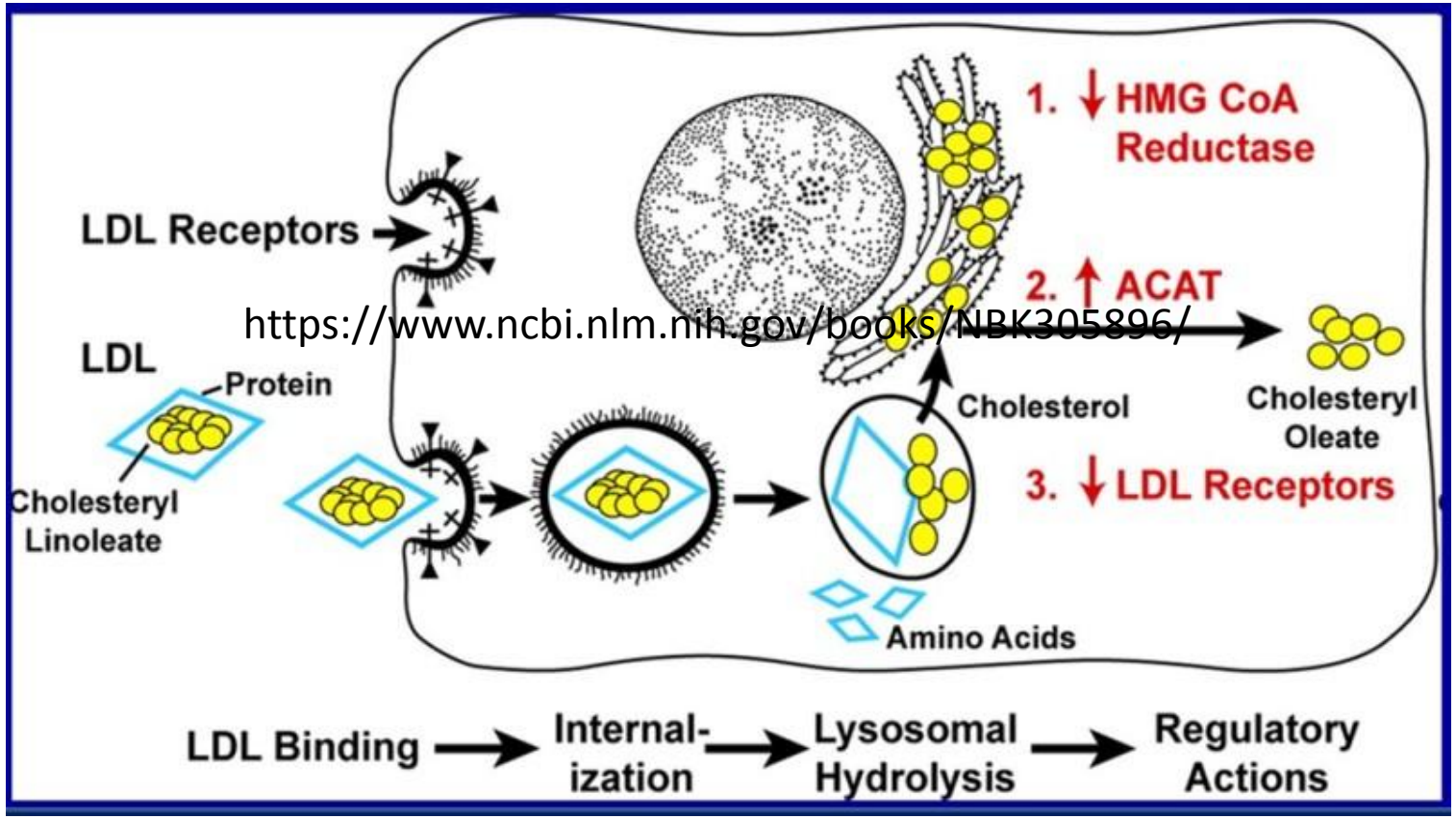
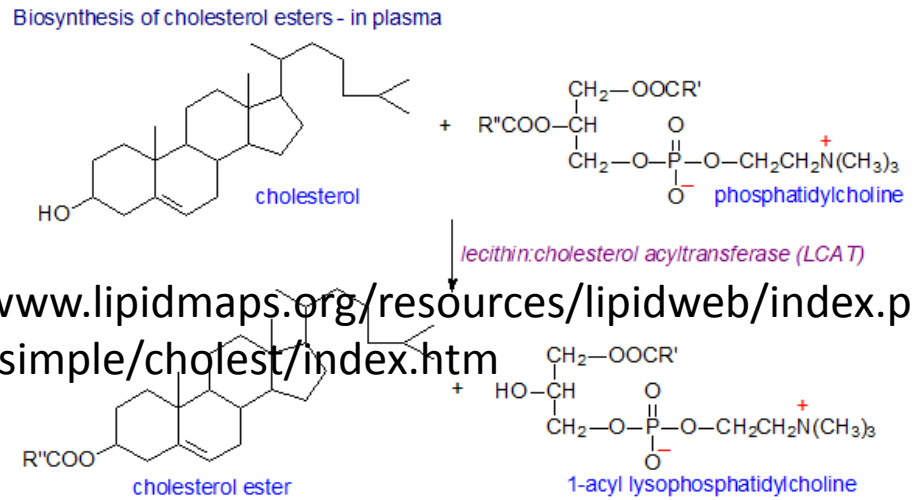

1. ↓ HMG CoA Reductase
LDL Receptors
2. ↑ ACAT
https://www.ncbi.nlm.nih.gov/books/NBK305896/
LDL
Protein
Cholesteryl Linoleate
Cholesterol
Cholesteryl Oleate
3. ↓ LDL Receptors
Amino Acids
LDL Binding
Internal-ization
Lysosomal Hydrolysis
Regulatory Actions



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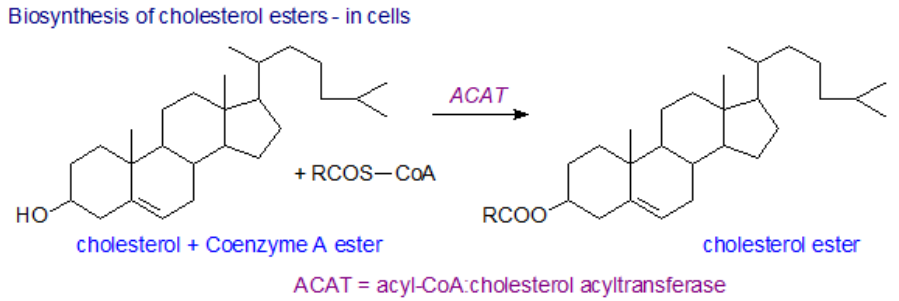
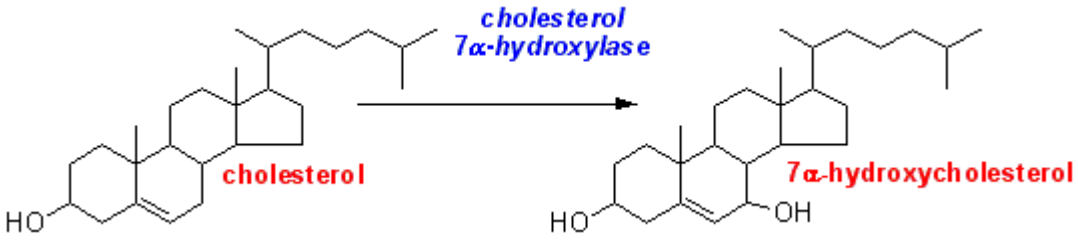


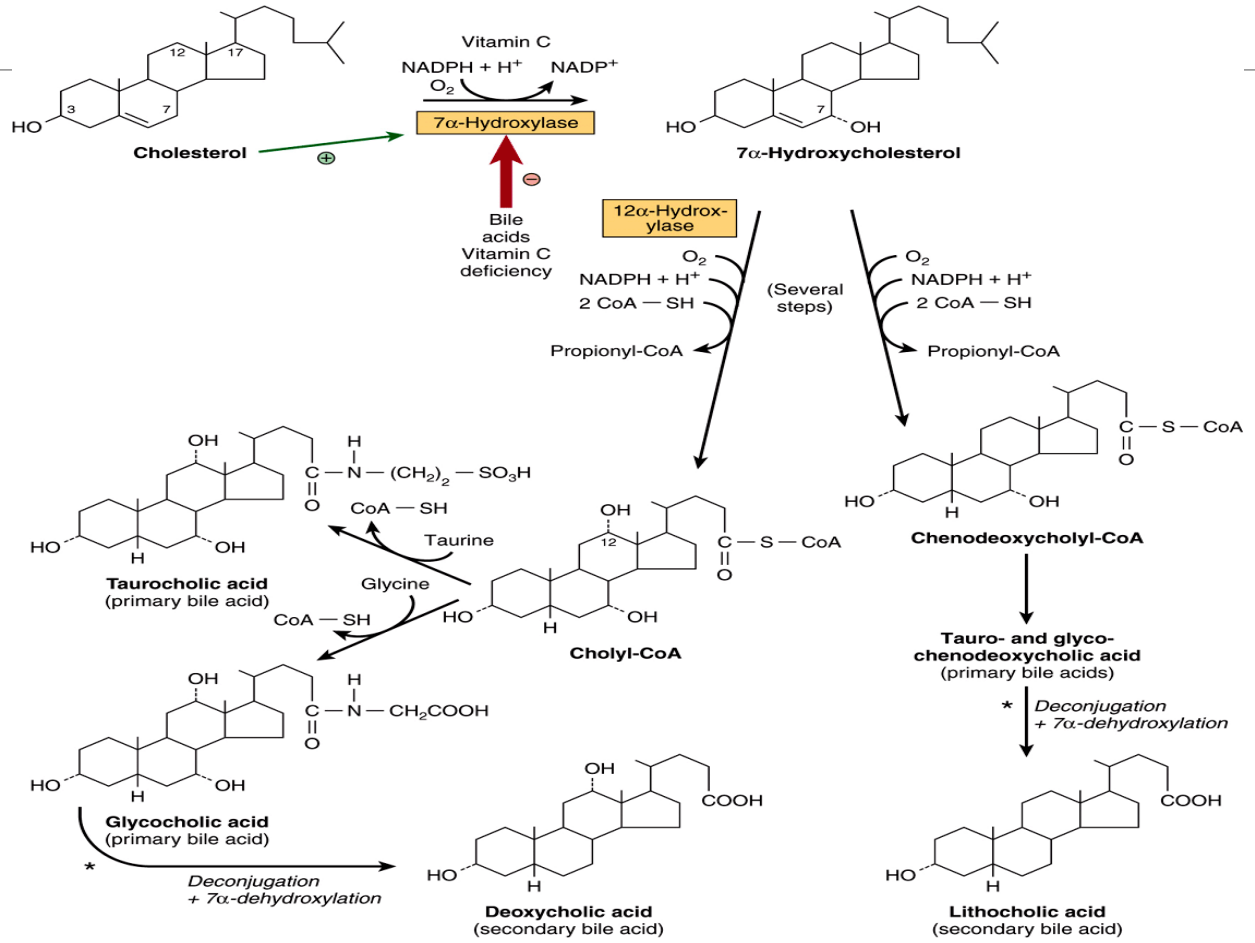
Cholesterol hydroxylation



https://www.david-bender.co.uk/metabonline/lipids/bile/bile16.html

Cholesterol 7 alpha-hydroxylase also known as **cholesterol 7-alpha-monooxygenase**. Cholesterol 7 alpha-hydroxylase is a cytochromeP450 heme enzyme that oxidizes cholesterol in the position 7. Regulation of enzyme occurs at several levels including synthesis. Bile acids, steroid hormones, inflammatory cytokines, insulin, and growth factors inhibit enzyme transcription. Activity can be regulated by phosphorylation-dephosphorylation.

Synthesis of bile acids

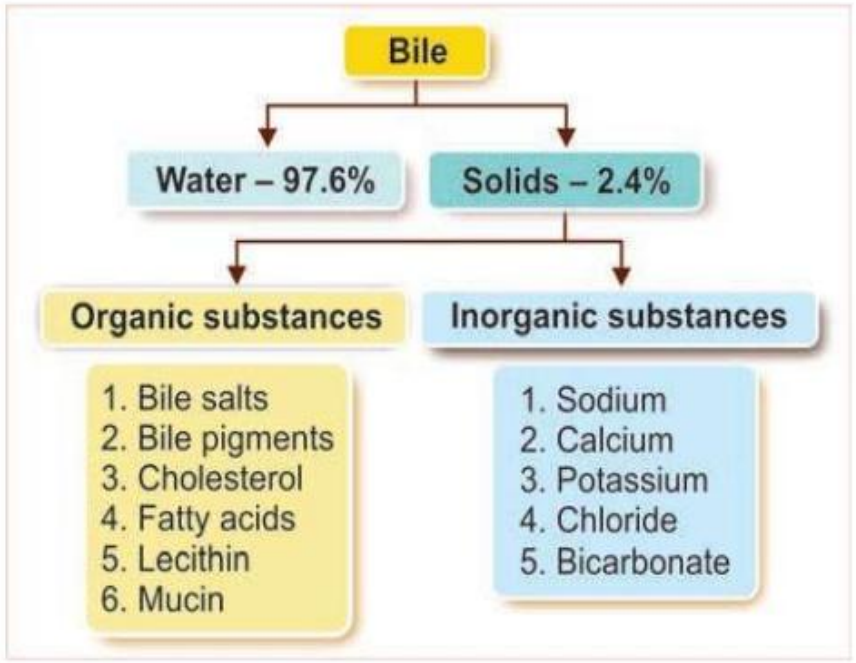


https://basicmedicalkey.com/cholesterol-synthesis-transport-excretion/

Bile

COMPOSITION OF BILE

- Bile contains 97.6% of water and 2.4% of solids. Solids include organic and inorganic substances.



FUNCTIONS OF BILE

- Most of the functions of bile are due to the bile salts.

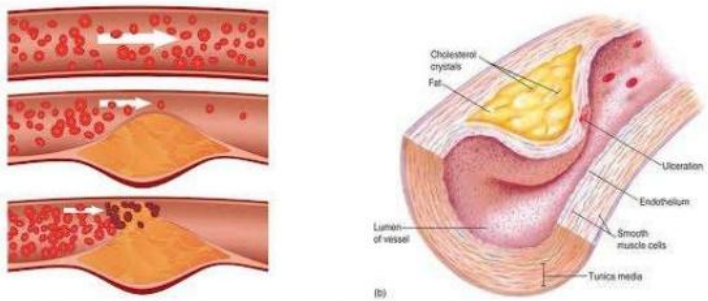
1. DIGESTIVE FUNCTION
2. ABSORPTIVE FUNCTIONS
3. EXCRETORY FUNCTIONS
4. LAXATIVE ACTION
5. ANTISEPTIC ACTION
6. CHOLERETIC ACTION
7. MAINTENANCE OF pH IN GASTROINTESTINAL TRACT
8. PREVENTION OF GALLSTONE FORMATION
9. LUBRICATION FUNCTION
10. CHOLAGOGUE ACTION

https://www.slideshare.net/VamsiIntellectual/physiology-properties-of-bile-composition-of-bile-functions-of-bile-functional-anatomy-of-small-intestine-functional-anatomy-of-si-functional-anatomy-of-li-functions-of-li

Atherosclerosis

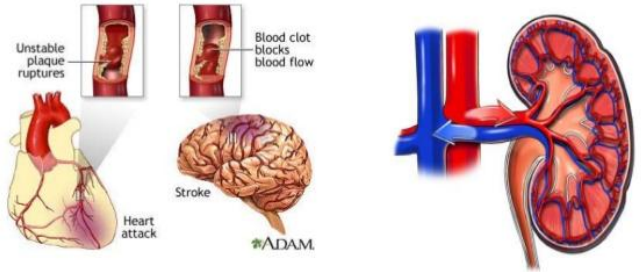
- Atherosclerosis is a disease of large and medium-sized muscular arteries and is characterized by –
- endothelial dysfunction,
- vascular inflammation, and
- the buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall.

Atheromatous plaque



Atherosclerosis or Arteriosclerosis is a slow and progressive building up of plaque, fatty substances, cholesterol, cellular waste products, calcium and fibrin in the inner lining of

Atherosclerosis



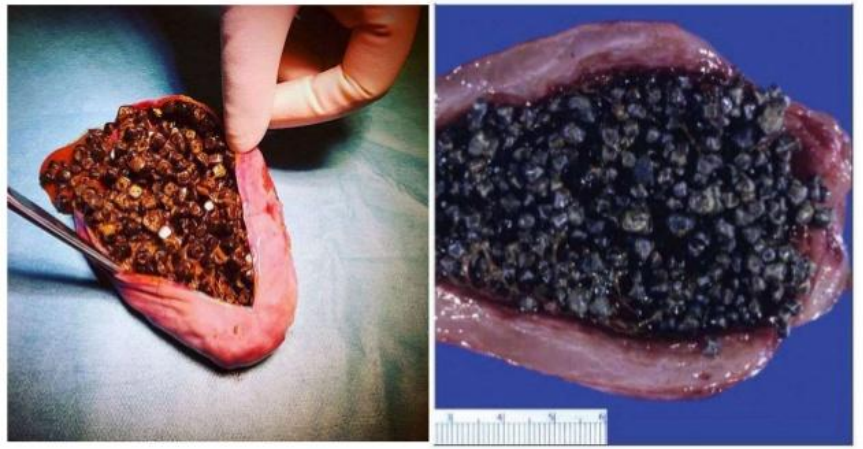
- Atherosclerosis also takes a toll through other consequences of acutely or chronically diminished arterial perfusion, *such as mesenteric occlusion, sudden cardiac death, chronic IHD, and ischemic encephalopathy.*

https://www.slideshare.net/mpattani/atherosclerosis-59199971

Gallstones

Composition of Gall stones

- Gallstones -composed mainly of cholesterol, bilirubin, and calcium salts, with smaller amounts of protein and other materials
- Three types of gallstones
  - (i) Pure cholesterol stones-contain at least 90% cholesterol,
  - (ii) pigment stones (brown or black)-contain at least 90% bilirubin
- Brown pigment stones are mainly composed of **calcium bilirubinate** and **Black pigment** stones contain **bilirubin**, calcium and/or tribasic phosphate
- **Brown pigment stones** are soft and greasy, consisting of bilirubinate and fatty acids (Ca palmitate or stearate). They form during infection, inflammation, and parasitic infestation
  - (iii) mixed composition stones, which contain varying proportions of cholesterol, bilirubin and other substances such as $CaCO_3$, $Ca_3(PO_4)_2$ and calcium palmitate



- Cholesterol gallstone formation begins with the secretion of bile supersaturated with cholesterol from the liver. Initiated by nucleating factors such as mucin, microscopic crystals then precipitate in the gallbladder
- Excessive cholesterol biosynthesis, -main lithogenic mechanism in obese persons.
- In the non-obese, defective conversion of cholesterol to bile acids, due to a relatively low activity of cholesterol 7α hydroxylase, the rate limiting enzyme for bile acid biosynthesis and cholesterol elimination could result in excessive cholesterol secretion.
- Interruption of the enterohepatic circulation of bile acids could increase bile saturation.
- Pigment stones occur when RBCs are destroyed, leading to excessive bilirubin in the bile.
- Gallbladder sludge, i.e., **Thickened gallbladder mucoprotein with tiny entrapped cholesterol crystals is thought to be the usual precursor of gallstones**

https://www.slideshare.net/akashmahadev/steatorrhea-chyluria-gallstone-cholelithiasis-pancreatitis-chronic-and-

Major Risk Factors

Unhealthy blood cholesterol levels. This includes high LDL cholesterol (sometimes called "bad" cholesterol) and low HDL cholesterol (sometimes called "good" cholesterol).

High blood pressure. Blood pressure is considered high if it stays at or above 140/90 mmHg over time. If you have diabetes or chronic kidney disease, high blood pressure is defined as 130/80 mmHg or higher. (The mmHg is millimeters of mercury—the units used to measure blood pressure.)

Smoking. Smoking can damage and tighten blood vessels, raise cholesterol levels, and raise blood pressure. Smoking also doesn't allow enough oxygen to reach the body's tissues.

Insulin resistance. This condition occurs if the body can't use its insulin properly. Insulin is a hormone that helps move blood sugar into cells where it's used as an energy source. Insulin resistance may lead to diabetes.

Diabetes. With this disease, the body's blood sugar level is too high because the body doesn't make enough insulin or doesn't use its insulin properly.

Overweight or obesity. The terms "overweight" and "obesity" refer to body weight that's greater than what is considered healthy for a certain height.

Lack of physical activity. A lack of physical activity can worsen other risk factors for atherosclerosis, such as unhealthy blood cholesterol levels, high blood pressure, diabetes, and overweight and obesity.

Unhealthy diet. An unhealthy diet can raise your risk for atherosclerosis. Foods that are high in saturated and trans fats, cholesterol, sodium (salt), and sugar can worsen other atherosclerosis risk factors.

Older age. As you get older, your risk for atherosclerosis increases. Genetic or lifestyle factors cause plaque to build up in your arteries as you age. By the time you're middle-aged or older, enough plaque has built up to cause signs or symptoms. In men, the risk increases after age 45. In women, the risk increases after age 55.

Family history of early heart disease. Your risk for atherosclerosis increases if your father or a brother was diagnosed with heart disease before 55 years of age, or if your mother or a sister was diagnosed with heart disease before 65 years of age.

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Chylomicrons%20are%20the%20least%20dense,HDL%20(high-density)

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