Cholesterol degradation & cell membrane structure

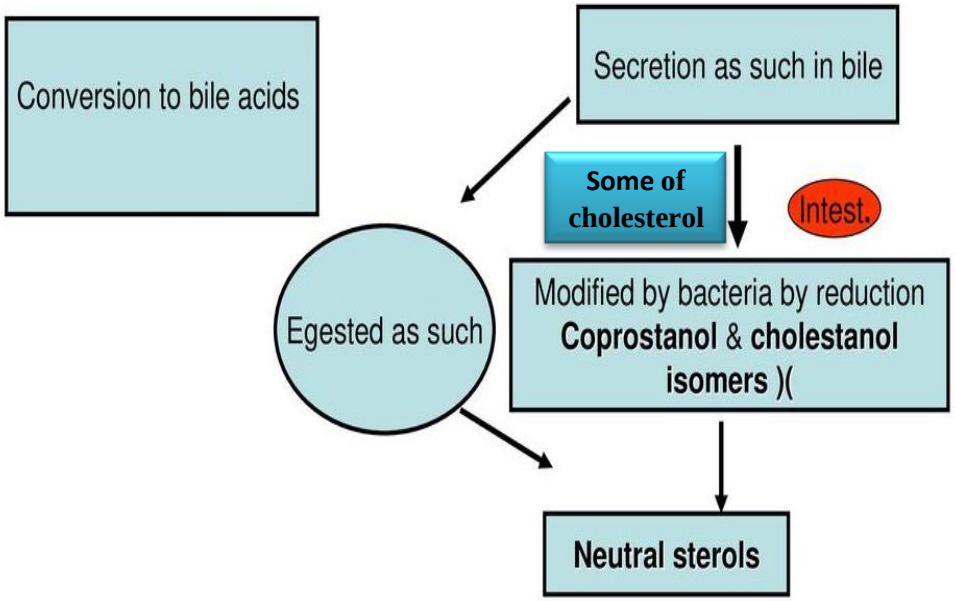
Basem Battah, Pharm, Msc, PhD

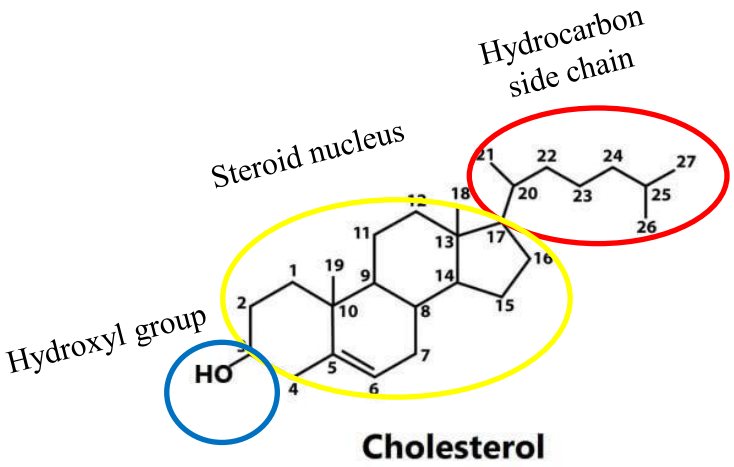
Degradation of cholesterol

•Ring of **cholesterol** cannot be metabolized to **CO2** and **H2O** in humans.

•The sterol nucleus is **eliminated** by conversion into **bile acids** and **bile** salts (secreted in the feces).

•**Coprostanol** and **cholestanol** together with cholestrol form the bulk of Neutral **fecal sterols**.





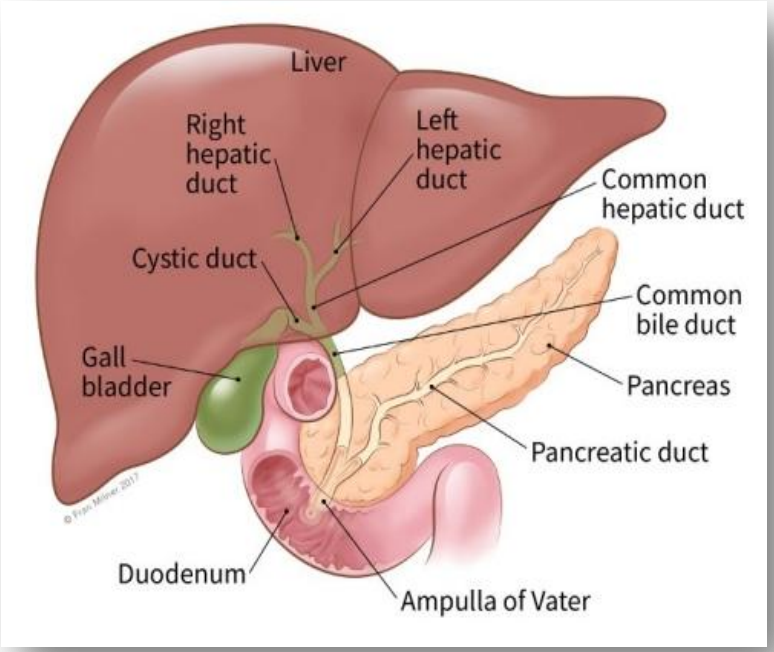
Cholesterol

C27H45OH

Bile acids and bile salts

•The **bile** consist of mixture of many compounds like **phosphatidycholine** and **bile salts** which is the most important compounds.

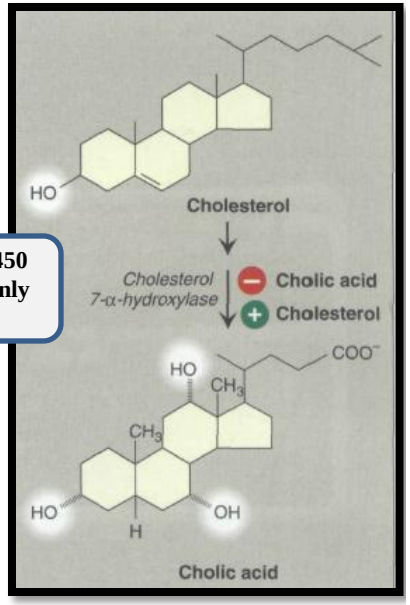
•**Bile** can directly **pass** from the liver to the **duodenum** by the bile duct or can be stored in the **gallbladder** and not immediately being digested .

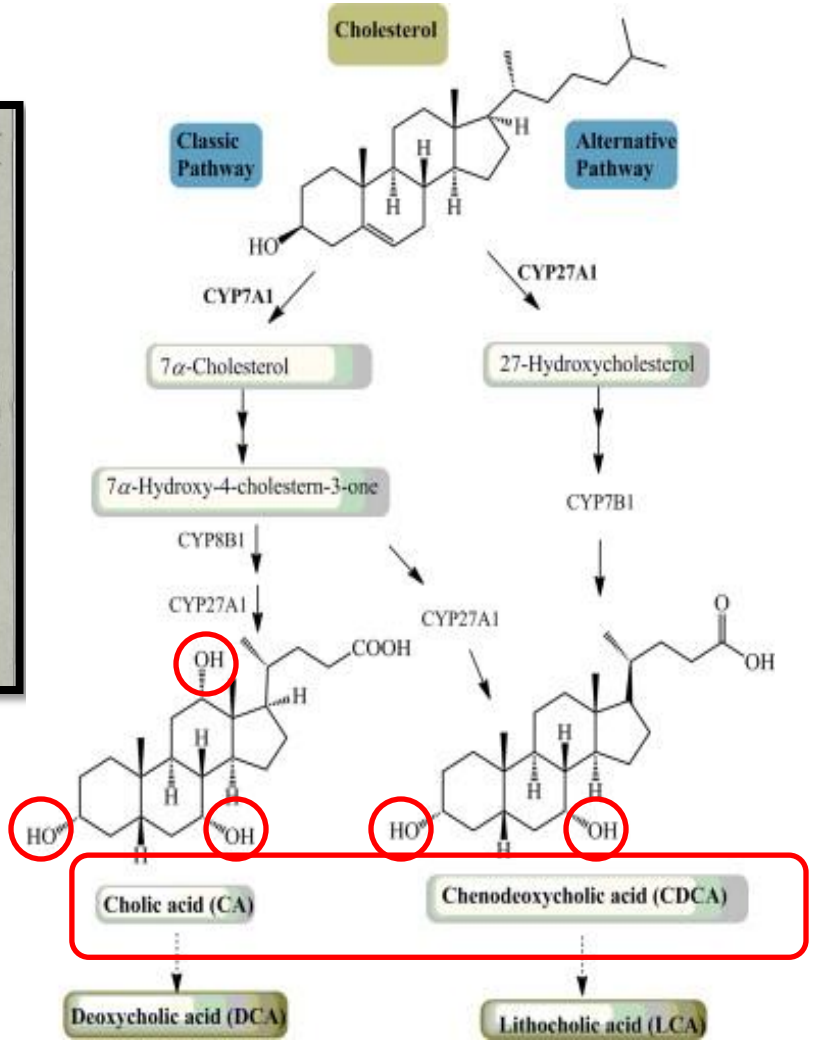


Bile acids

•The bile acids are synthesized in the liver form the **cholestrol** by many steps mediated by liver **cytochrome enzyme** leads to major compounds of the bile acids (**cholic acids- triol** and **chenodeoxycholic acids – diol**).

Cytochrome P450 enzyme found only in the liver





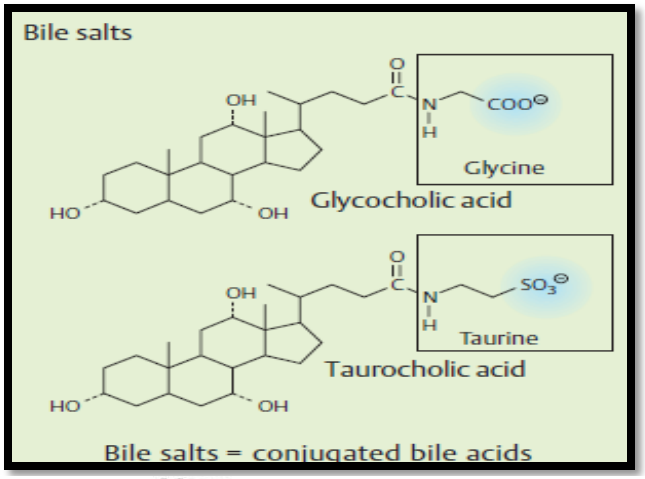
Bile salts

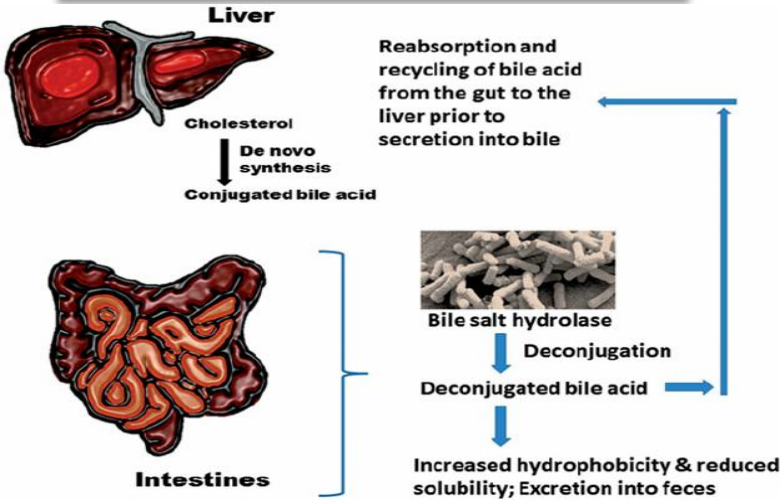
•The **bile acid** leaving the liver as a bile salts by binding to **Glycine** and **Taurin** by forming **an amide bond**.

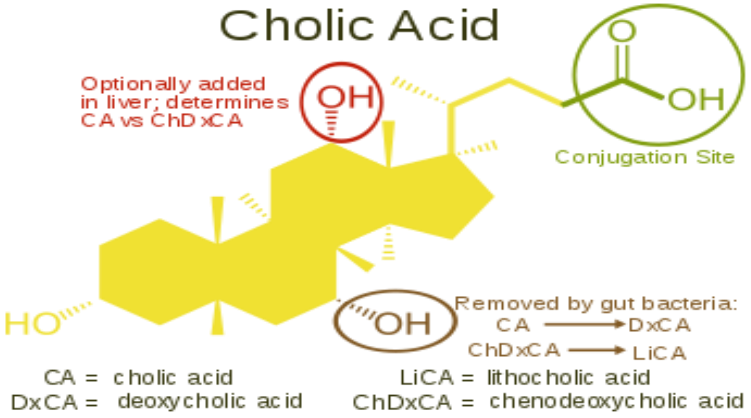
•**Bile salts:** include **glycocholic** and **chenodeoxycholic acids**, and **taurocholic** and **taurochenodeoxycholic acids**.

•Bile salts provide the only significant mechanism for **cholesterol excretion**, both as a **metabolic product** of cholesterol and as an essential **solubilizer** for cholesterol excretion in bile.

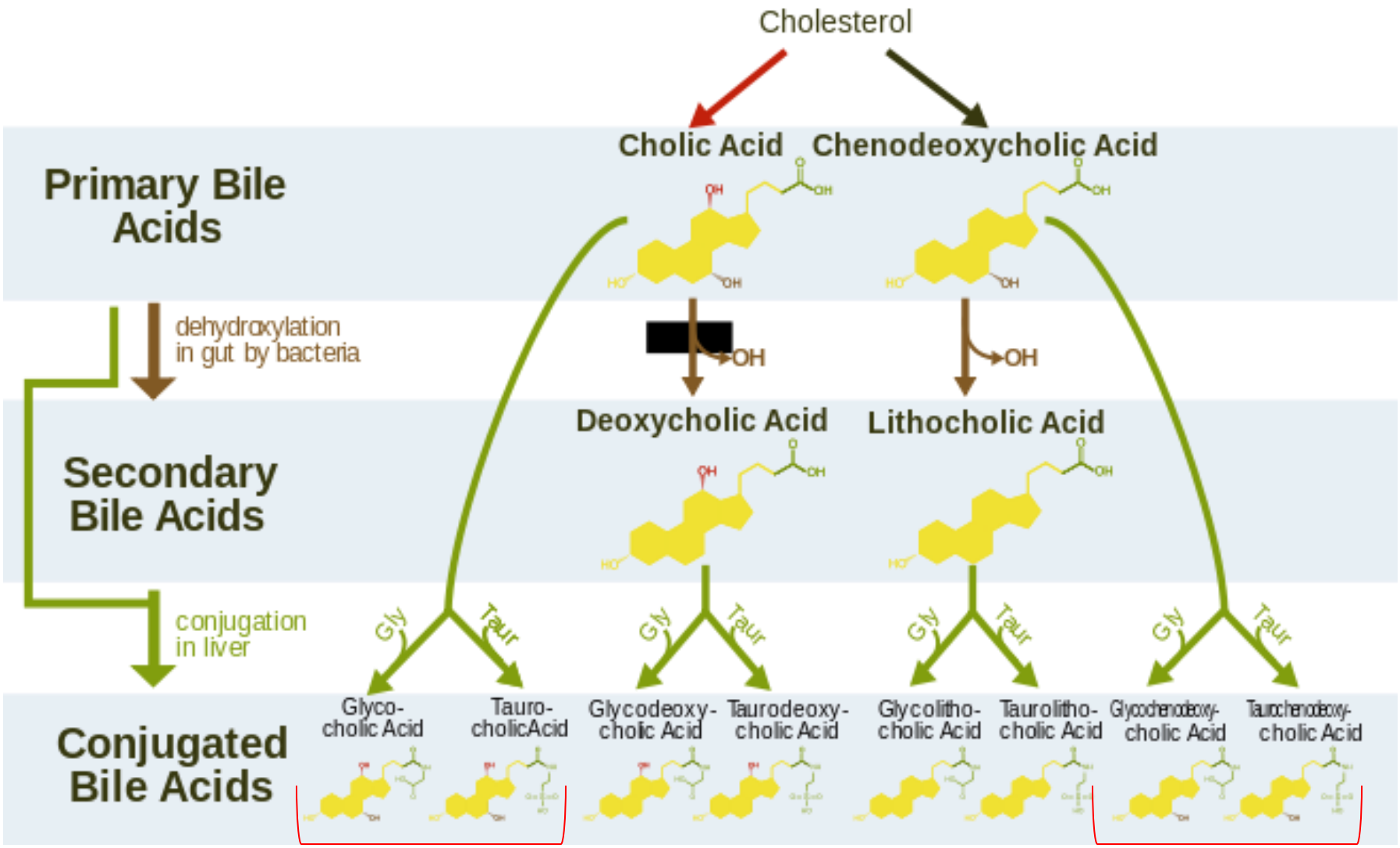
•In the intestine the bacterial flora can convert the **bile salts** to acids by removing the **glycine and taurine**. Furthermore, converting the bile acids to **secondary forms deoxy cholic** acids and **lithocholic** acid by removing the hydroxyl groups.



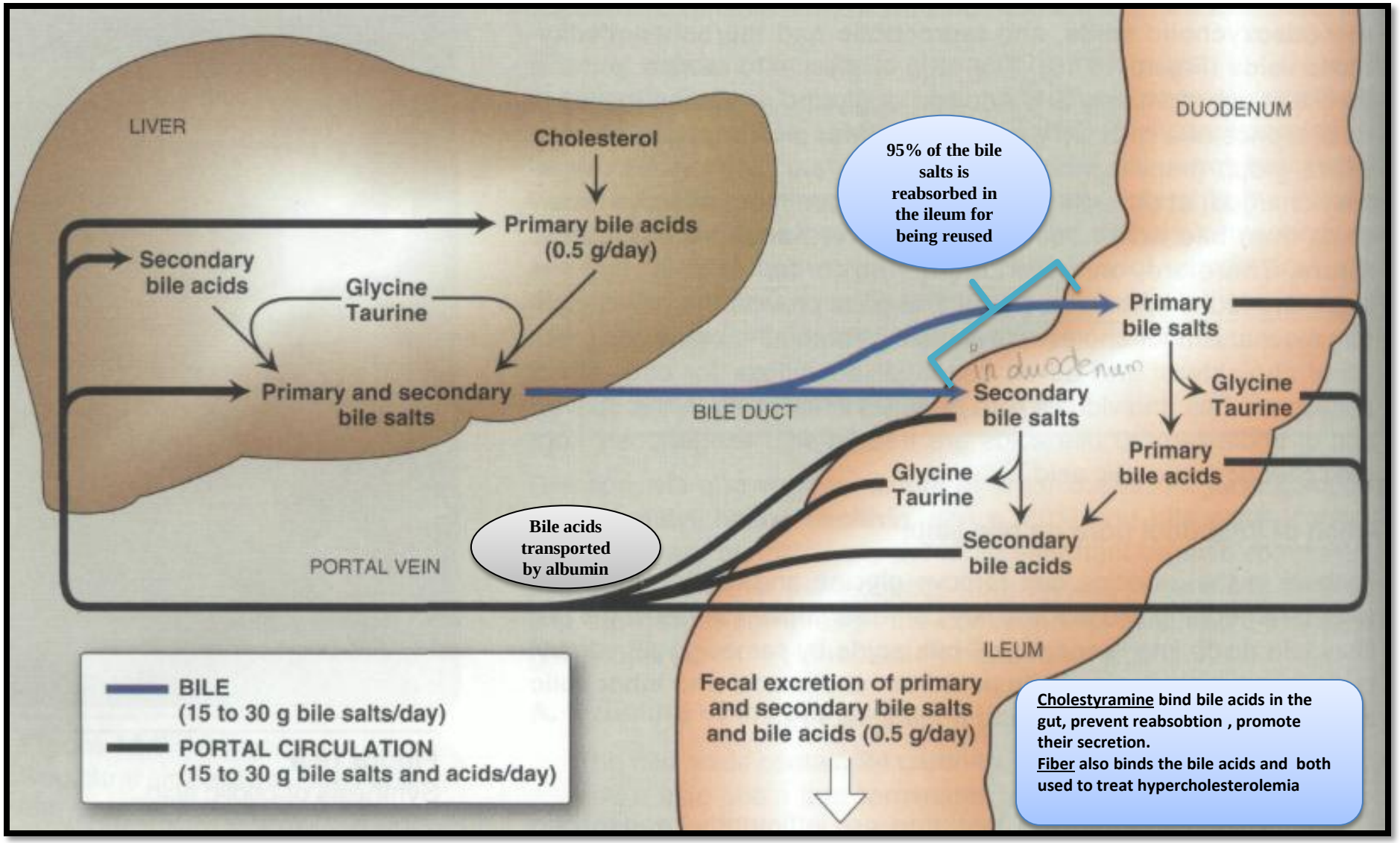




Primary and secondary bile acids

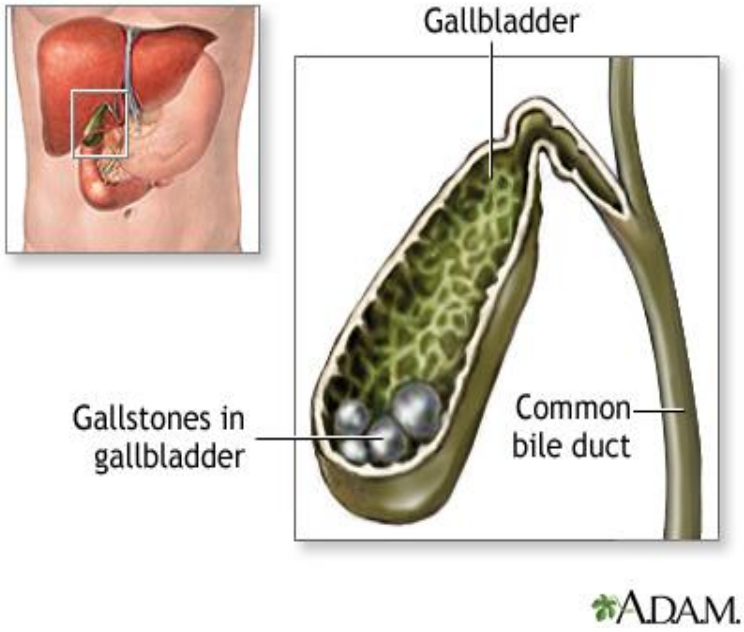


Enterohepatic circulation of the bile acids and bile salts



Cholelithiasis

- The **bile acids** and **phospholipids** like lecithin combine the secretion of the cholesterol to the bile.
- in this disorder more **cholesterol** is present in the **gallbladder** more than the other components of the bile (solubilizer) leads to precipitation of the cholesterol as a **gallstone in the gallbladder**.



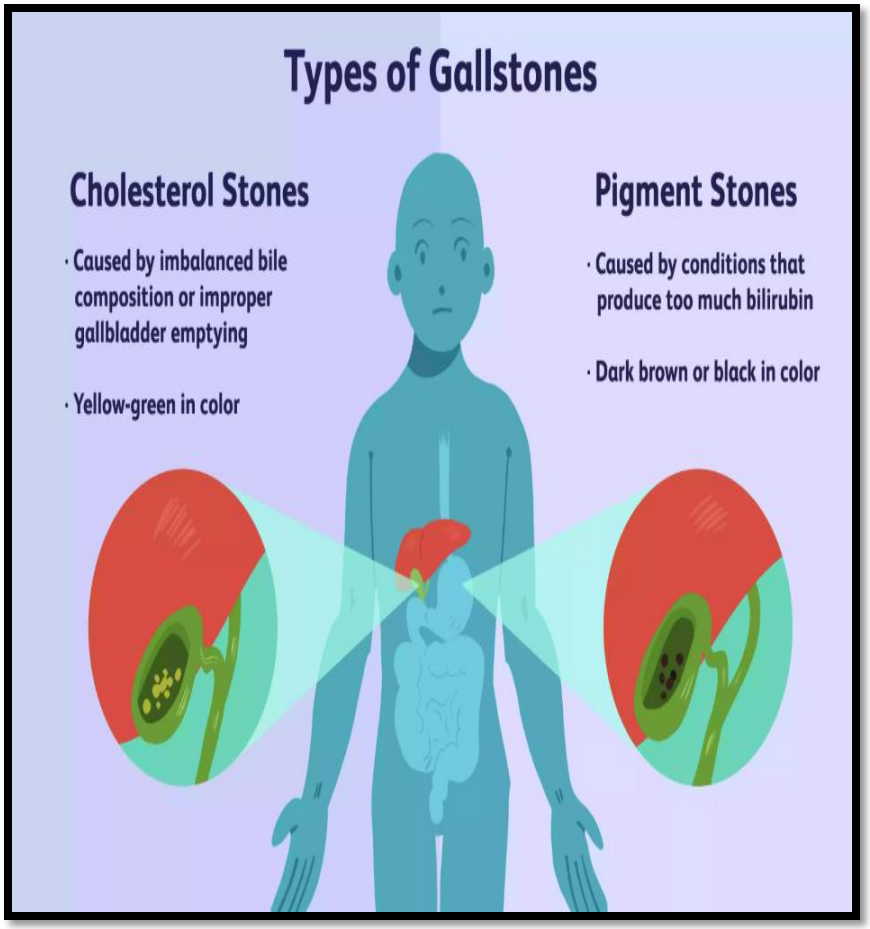
- **Causes:**
  - Obstruction of the biliary tract.
  - Gross metabolism of the bile acids in the intestine in some diseases.
  - Liver dysfunction in decreasing synthesis of the bile salts.
  - Feed back suppression of the bile acid synthesis in case of accelerating rate of bile acid recycling.

Types of gallstones

- **Cholesterol stones:** are the result of bile that is made of **too much cholesterol** and not **enough bile salts**. Cholesterol stones may also form when the gallbladder fails to empty during the digestive process. (**yellow –green**).

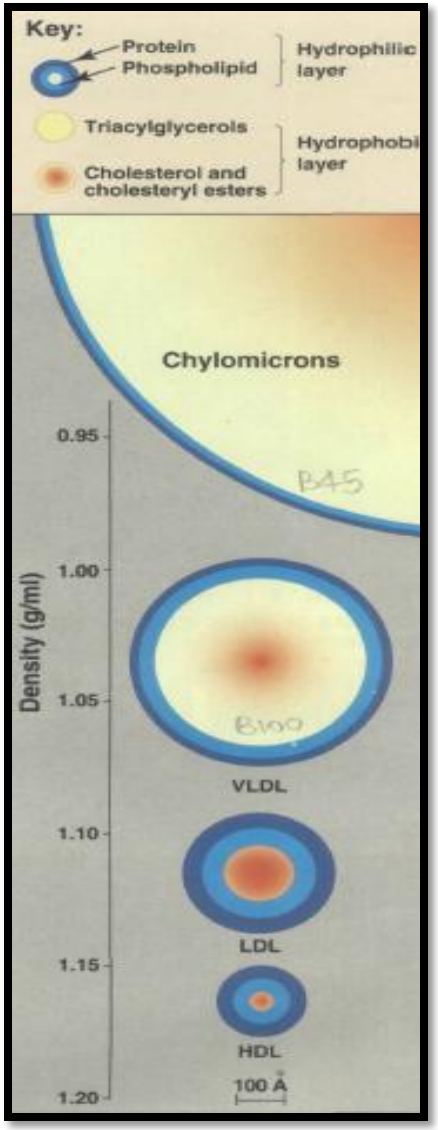
- **Pigment stones**: People who develop pigment stones are typically people who have **cirrhosis** of the liver, **biliary tract infections**, and **hereditary blood disorders**, including sickle cell **anemia.** These are all conditions that cause too **much bilirubin**, which is what the stones are made of. (**dark brown or black**).

- **Treatment:**
  - Laparoscopic cholecystectomy.
  - Chenodeoxycholic acid when the surgery is not possible choice.



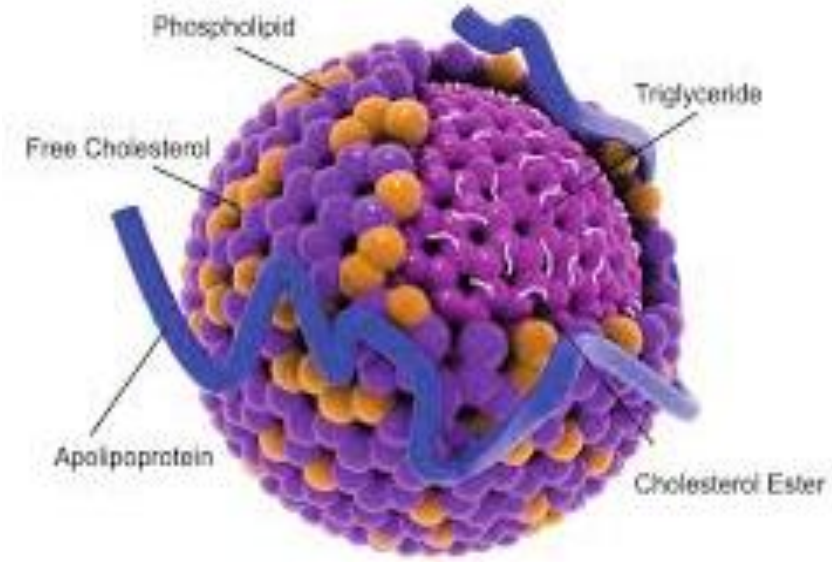
Lipoproteins

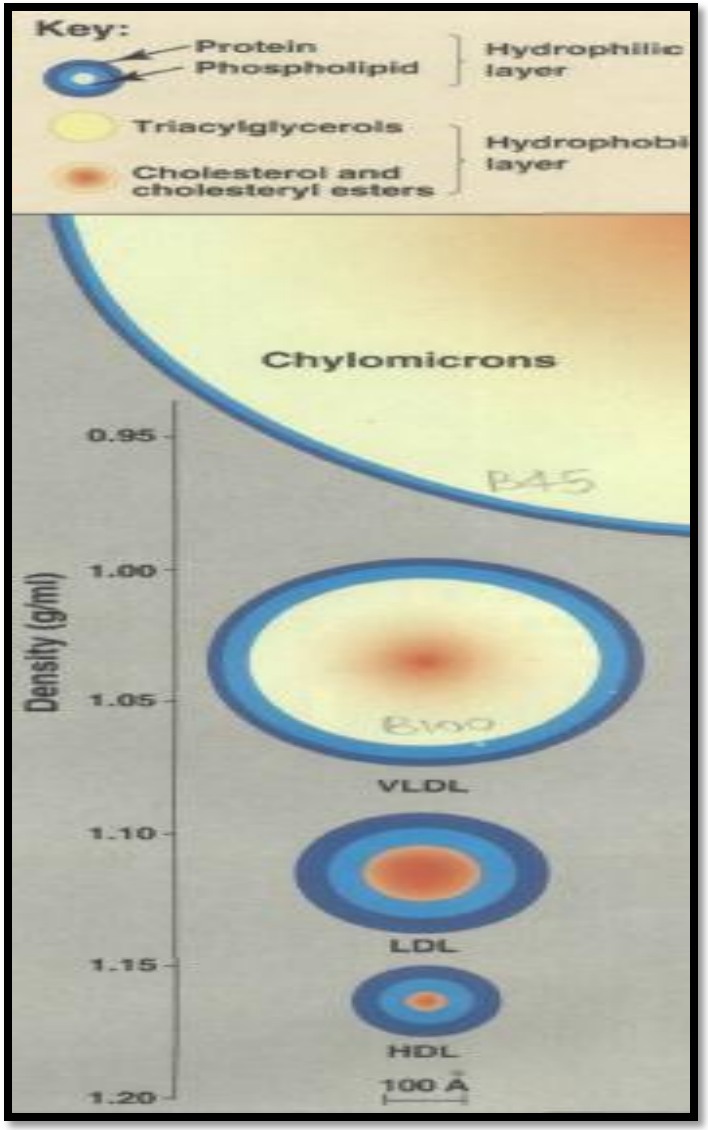
- Are **spherical macromolecular** complexes of **lipids** and specific **proteins** (apolipoproteins or apoproteins).
- The lipoprotein particles include **chylomicrons**, very-low-density lipoproteins (**VLDL**), low-density lipoproteins (**LDL**), and high-density lipoproteins (**HDL**). They differ in lipid and protein composition, size, and density.
- Its main function **transporting** lipids in the plasma and within tissue.
- The **proportions** of apoproteins range from **1%** in chylomicrons to over **50%** in HDLs. These proteins serve less for solubility purposes, but rather function as recognition molecules for the membrane receptors and enzymes that are involved in lipid exchange, **apolipoproteinsare** divided by structure and function into five major classes, from **A to E**.



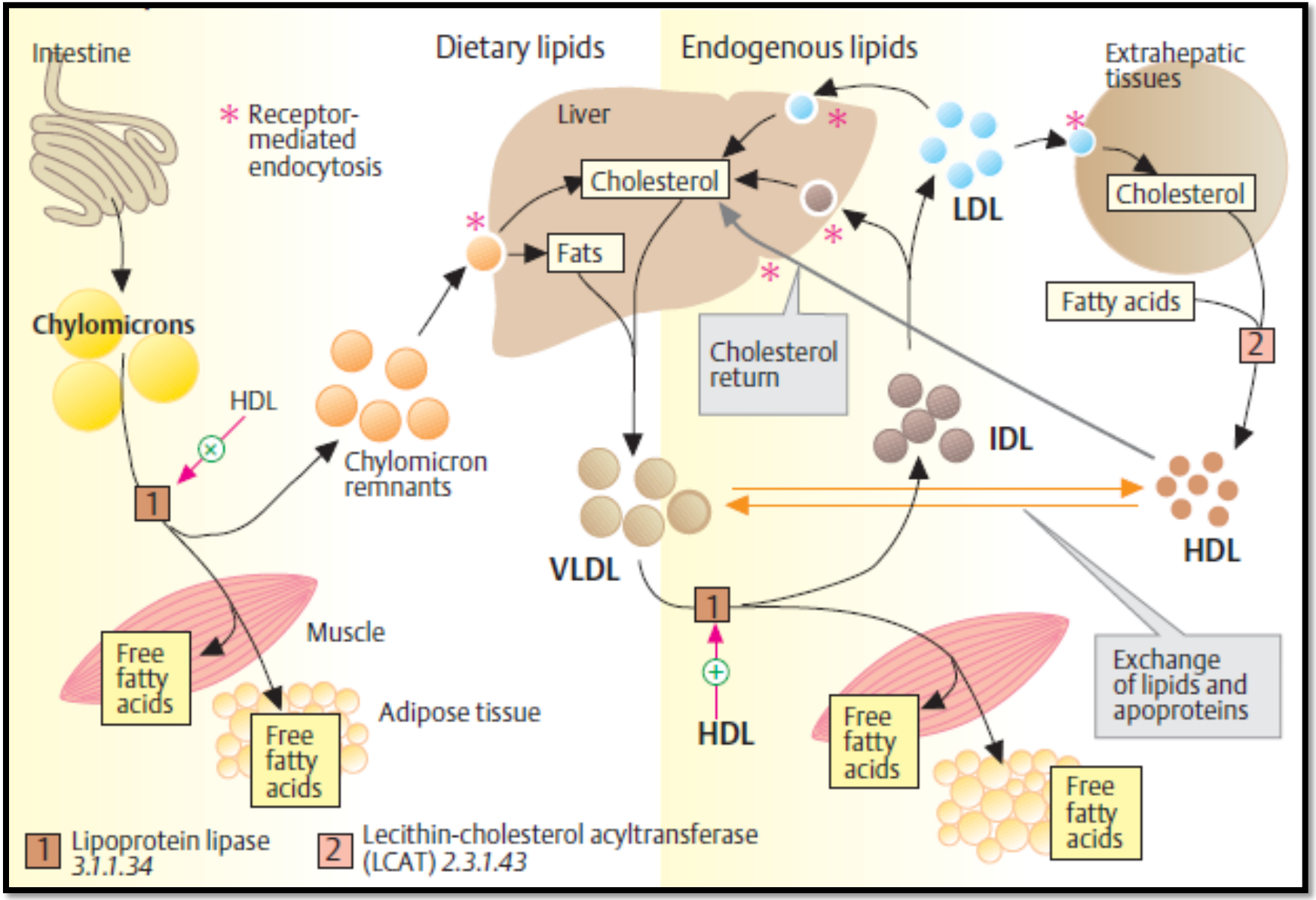
Lipoproteins

- **Chylomicrons** are the lipoprotein particles lowest in density and largest in size, and contain the **highest percentage of lipid** and the **smallest** percentage of **protein**.
- **VLDLs** and **LDLs** are successively **denser**, having high percentage of protein to lipid.
- **HDL** particles are the **densest.**





Lipoproteins transport function



Lipoproteins transport function

- The **chylomicrons** take care of the transport of **triacylglycerols** from the **intestine** to the **tissues**. They are formed in the intestinal mucosa.

- **Chylomicrons** reach the blood via the **lymphatic system**. In the peripheral vessels particularly in muscle and adipose tissue. **lipoprotein lipase** on the surface of the vascular endothelia hydrolyzes most of the t**riacylglycerols**.

- **Chylomicron** breakdown is activated by the transfer of **apoproteins E** and **C from HDL**.While the **fatty acids** released and the **glycerol** are taken up by the cells, the chylomicrons gradually become converted into **chylomicron remnants**, which are ultimately removed from the **blood by the liver**.

- **VLDLs**, **IDLs**, and **LDLs** are closely related to one another. **VLDLs** formed in the liver transport **triacylglycerols**, **cholesterol**, and **phospholipids** to other tissues. Like chylomicrons, they are gradually converted into IDL and LDL under the influence of **lipoprotein lipase.**

Lipoproteins transport function

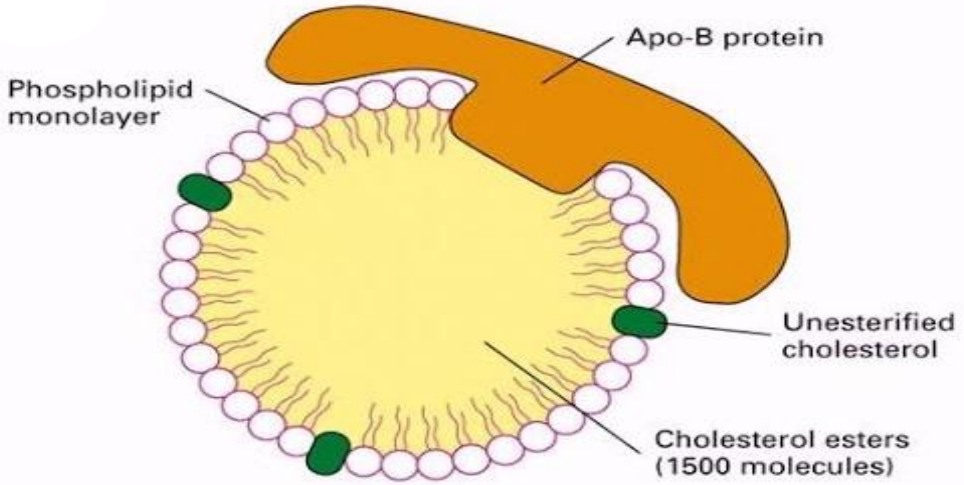
- After **LDL** binding to receptor mediated **endocytosis**, **clathrin** promotes **invagination** of the pits and pinching off of vesicles. The clathrin then dissociates off and is reused. After fusion of the vesicle with lysosomes, the LDL particles are broken down, and **cholesterol** and other **lipids** are used by the cells.

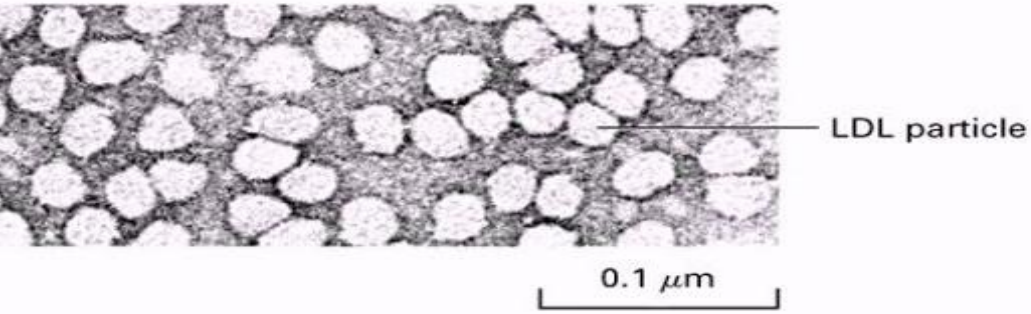
- The **HDLs** also originate in **the liver**. They return the **excess cholesterol** formed in the tissues to the liver, While it is being transported, cholesterol is **acylated** by **lecithin cholesterolacyltransferase** (LCAT), no longer **amphipathic** and can be transported in the core of the **lipoproteins**.

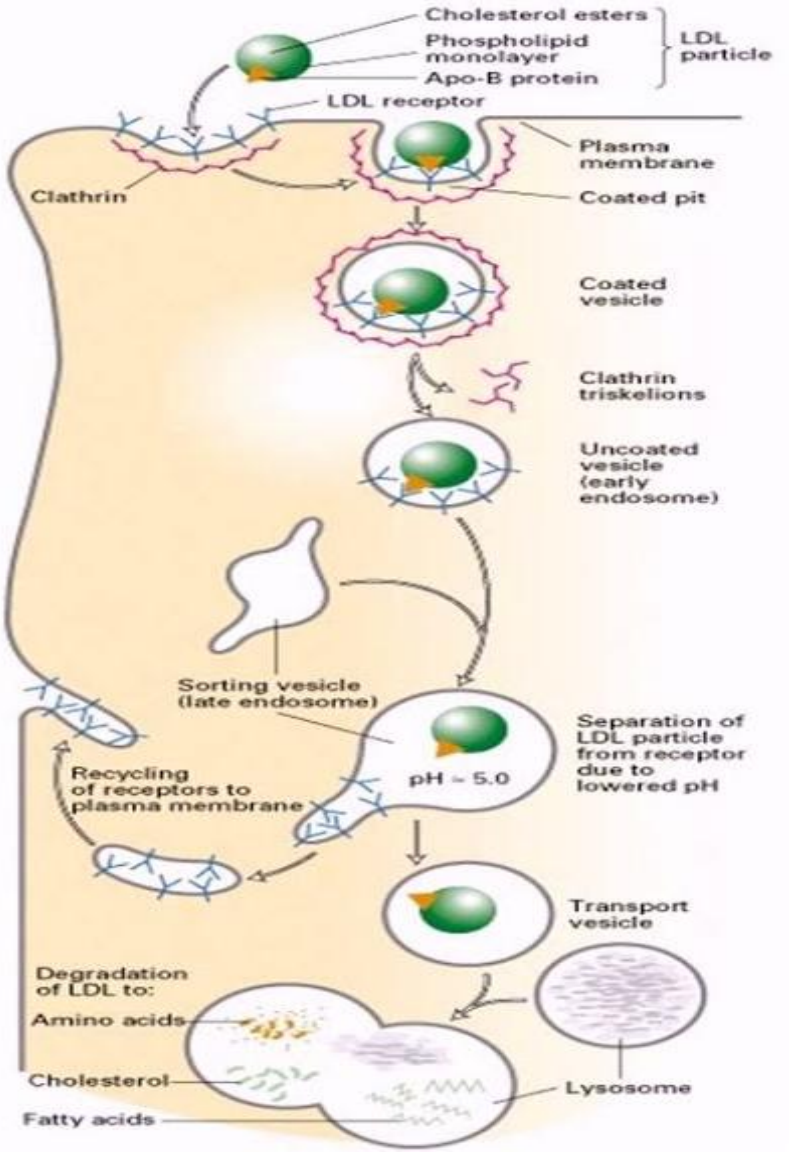
- In addition, **HDLs** promote **chylomicron** and **VLDL** turnover by exchanging lipids and apoproteins with them.

LDL endocytosis

The LDL receptor binds and internalizes cholesterol-containing particles







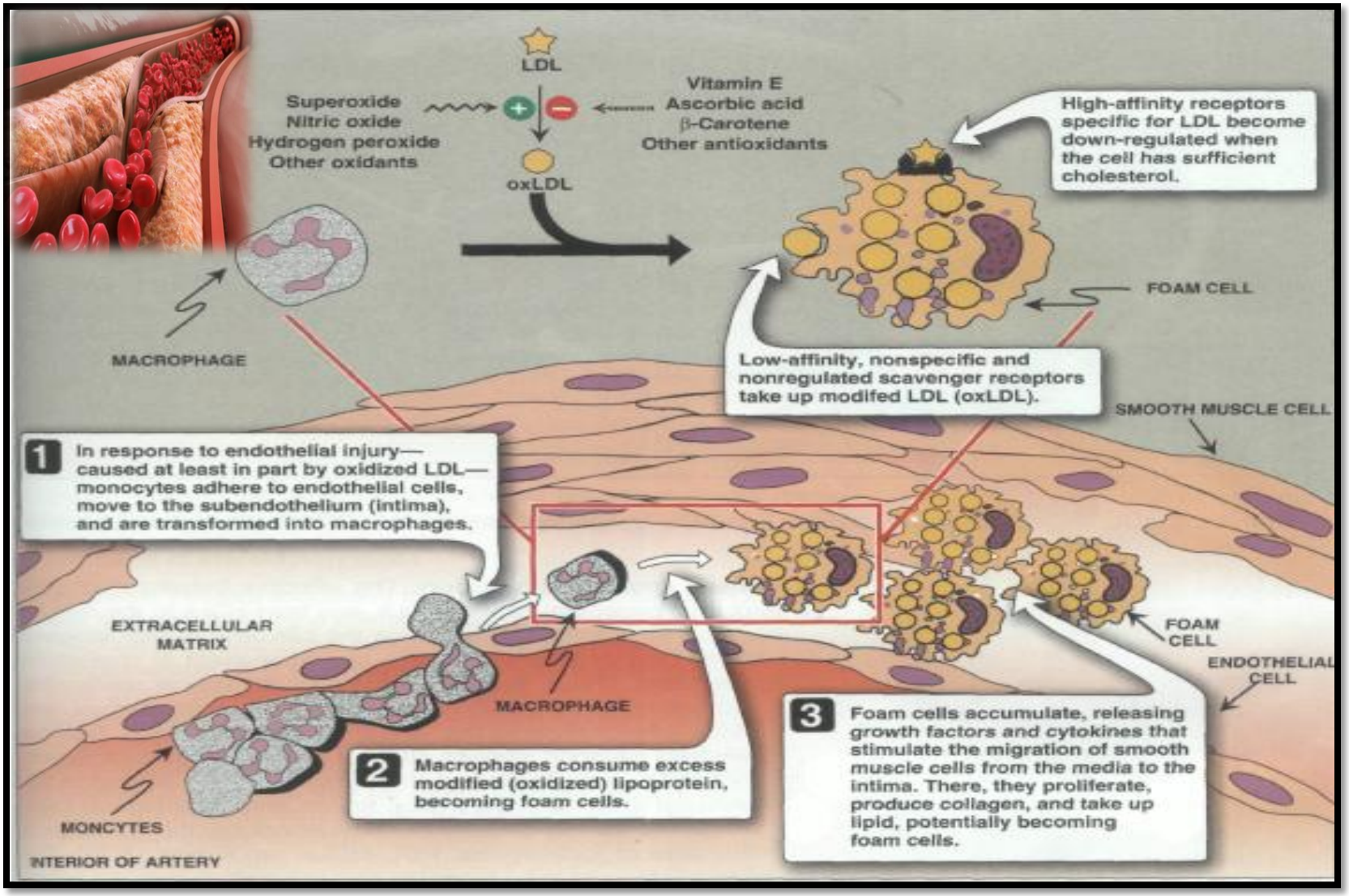
LDL and plaque formation

- The **Chemical modifications** of the **LDL** include its **oxidation** (for example by ROS) that convert circulating **LDL** into **Oxy-LDL** (ligands) that can be recognized by **SR-A** receptors include oxidation of the lipid components and apolipoprotein B.

- **Macrophages** possess high levels of scavenger receptor activity. These receptors, known as scavenger receptor class A (SR-A), can bind a broad range of ligands, and mediate the endocytosis of chemically modified LDL .

- Unlike the **LDL receptor**, the scavenger receptor is not down-regulated in response to increased intracellular cholesterol. Cholesteryl esters **accumulate** in macrophages and cause their transformation into **"foam" cells, which participate in the formation of atherosclerotic plaque.**

LDL and plaque formation



Cellular cholesterol homeostasis

- The **chylomicron remnant-**, **IDL-**, and **LDL**-derived cholesterol affects cellular cholesterol content in several ways:

  - **HMG CoA** reductase is inhibited by high cholesterol, as a result of which, de novo cholesterol synthesis decreases.

  - **Synthesis of new LDL receptor** protein **is reduced** by decreasing the expression of the LDL receptor gene, thus limiting further entry of LDL cholesterol into cells.

  - If the cholesterol is not required immediately for some structural or synthetic purpose, it is esterified by acyl CoA cholesterol acyltransferase .

- **ACAT** transfers a fatty acid from a fatty acyl CoA derivative to cholesterol, producing a cholesteryl ester that can be stored in the cell.

- The HDL (the good cholesterol carrier) play a key role in the cholesterol homeostasis by transforming the cholesterol from the **peripheral cells** to the liver for **bile acid synthesis** and **cholesterol excretion** by bile and to **steroidogenic cells for hormone synthesis.**

Lipid metabolism in the liver

- **The liver** is the most important site for the formation of fatty acids, fats (triacylglycerols), ketone bodies, and cholesterol. Most of these products are released into the blood. In contrast, the triacylglycerols synthesized in adipose tissue are also stored there.
- The liver converts **glucose** via **acetyl CoA** into **fatty acids. The liver can also take up fatty** acids from chylomicrons, which are supplied by the intestine.
- **Fatty acids** from both sources are converted into **fats and phospholipids.** Together with apoproteins, they are packed into very-low-density lipoproteins **and then released into** the blood by exocytosis. The VLDLs supply extrahepatic tissue, particularly adipose tissue and muscle.

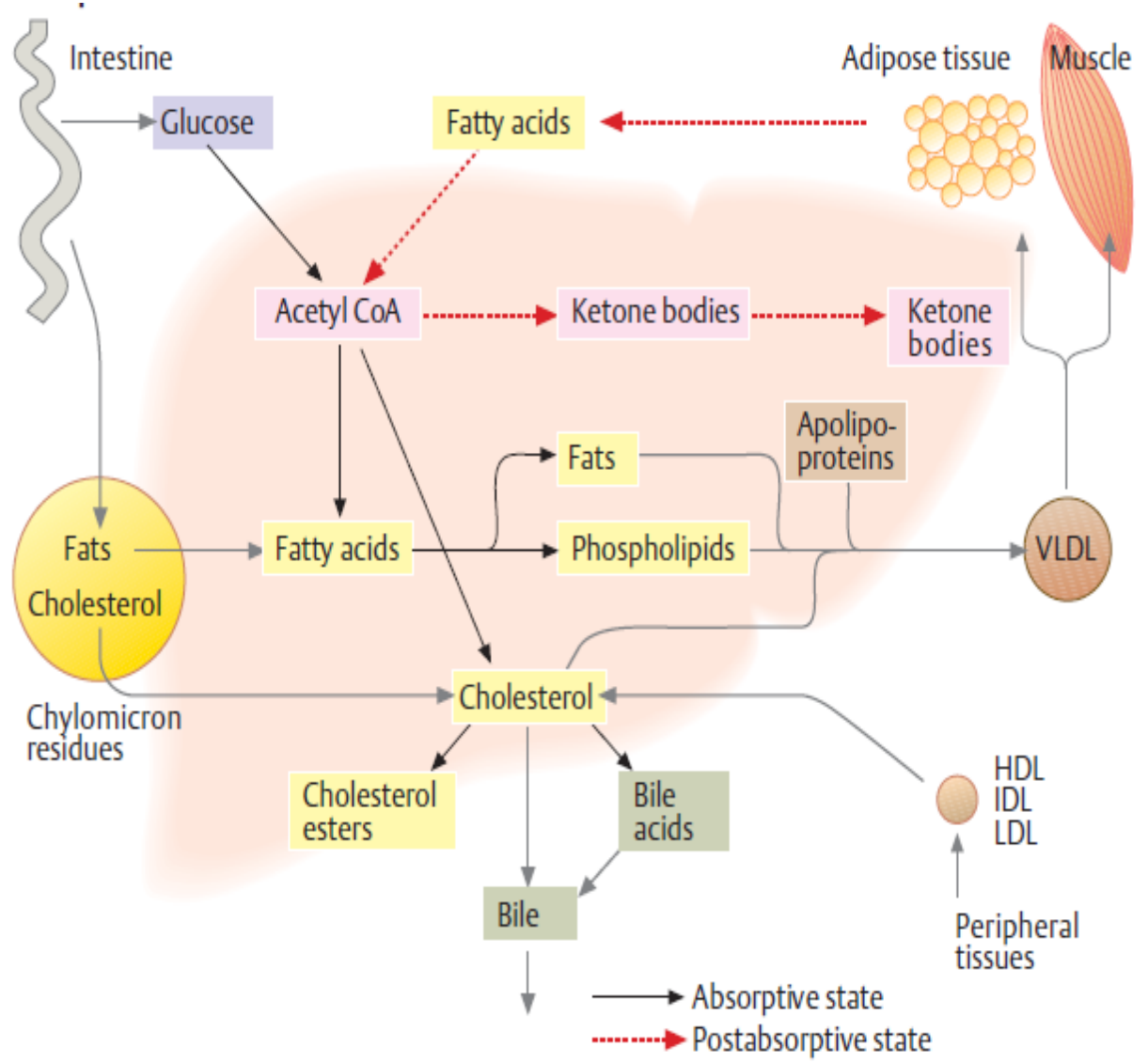
- **Cholesterol can be derived from two sources—** food or endogenous synthesis from acetyl-CoA.
- Some cholesterol is required for the synthesis of **bile acids. In addition,** it serves as a building block for **cell membranes** The rest is released together into the blood in the form of lipoprotein complexes (VLDLs) and supplies other tissues. The liver also contributes to the cholesterol metabolism by taking up from the blood and breaking down lipoproteins that contain cholesterol and cholesterol esters (LDL, HDL, IDL).

Formation of ketone body

- At high concentrations of acetyl-CoA in the liver mitochondria, two molecules condense to form **acetoacetyl CoA.**
- The transfer of another acetyl group, gives rise to 3-hydroxy-3-methylglutaryl-CoA (**HMG CoA),** which after **release of acetyl CoA** , yields free **acetoacetate.**
- **Acetoacetate** can be converted to **3-hydroxybutyrate by** reduction, or can pass into acetone by nonenzymatic decarboxylation.
- These all three compounds are called **ketone bodies**.

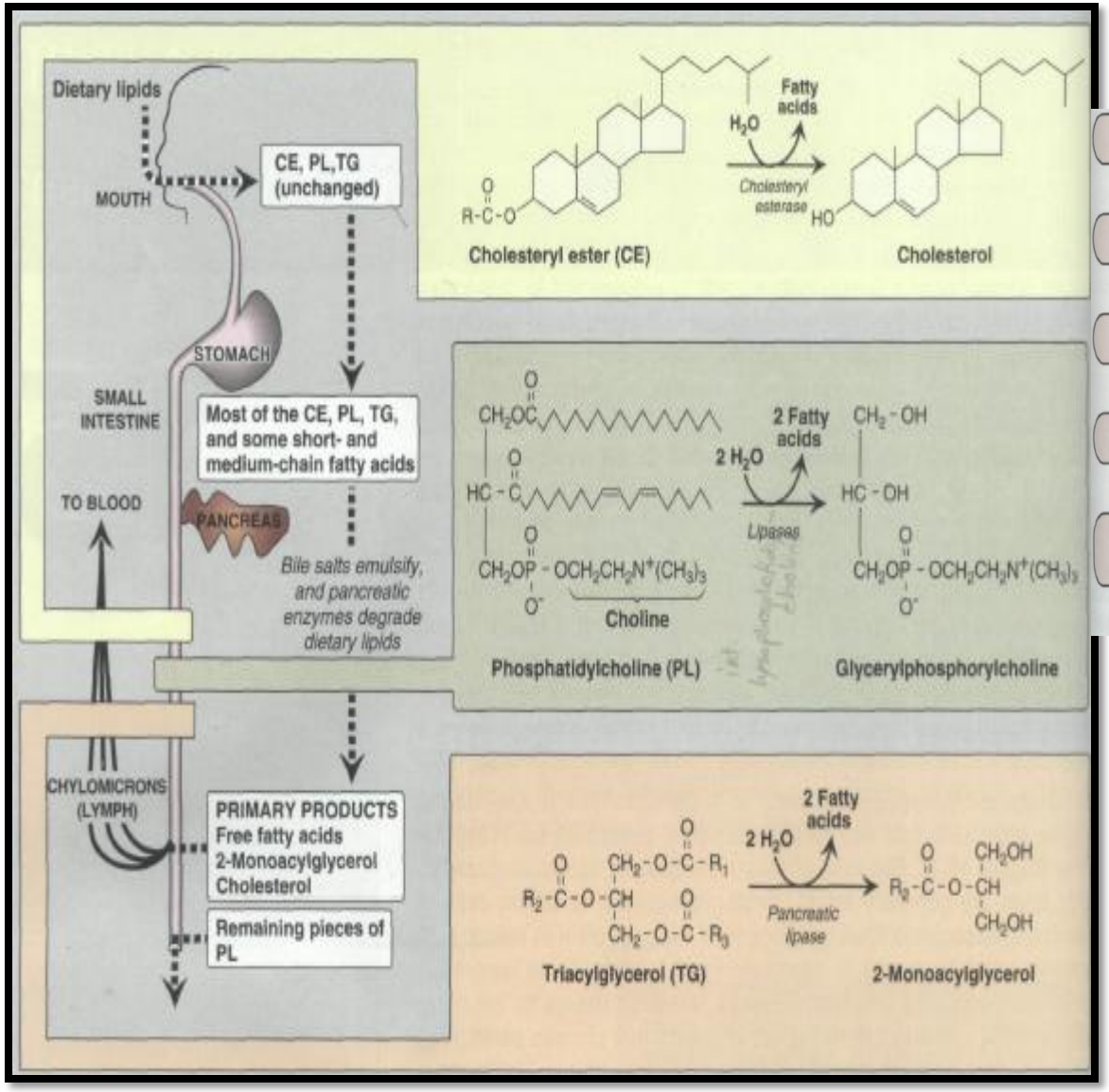
- If the production of ketone bodies exceeds the demand for them outside the liver, there is an increase in the concentration of ketone bodies in the plasma **(ketonemia)** and they are also eventually excreted in the urine **(ketonuria).**
- Both observed in Prolonged **starvation** and in inadequately treated **diabetes mellitus.**
- In severe cases could cause electrolyte shifts and loss of consciousness, and is therefore lifethreatening **(ketoacidotic coma).**

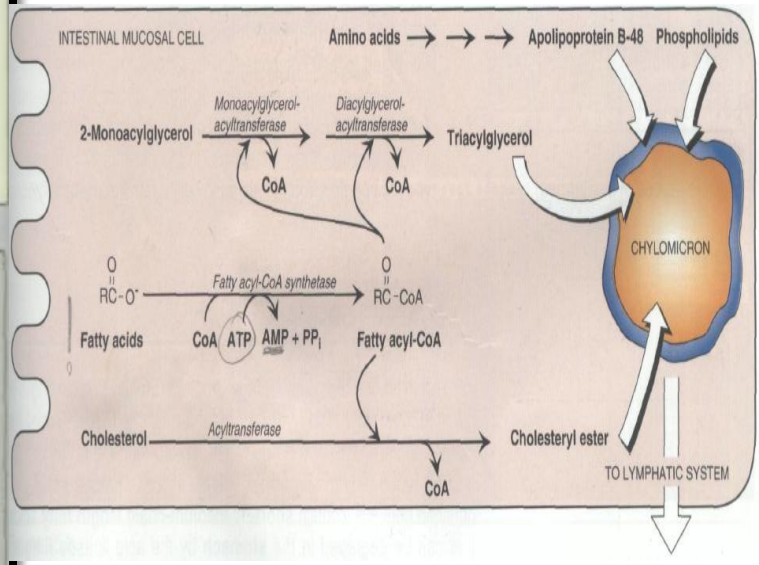
Lipid metabolism in the liver



In the postresorptive state particularly during fasting and starvation. In these conditions, adipose tissue releases fatty acids.
They are taken up by the liver and are mainly converted into ketone bodies.

Lipid metabolism in the liver



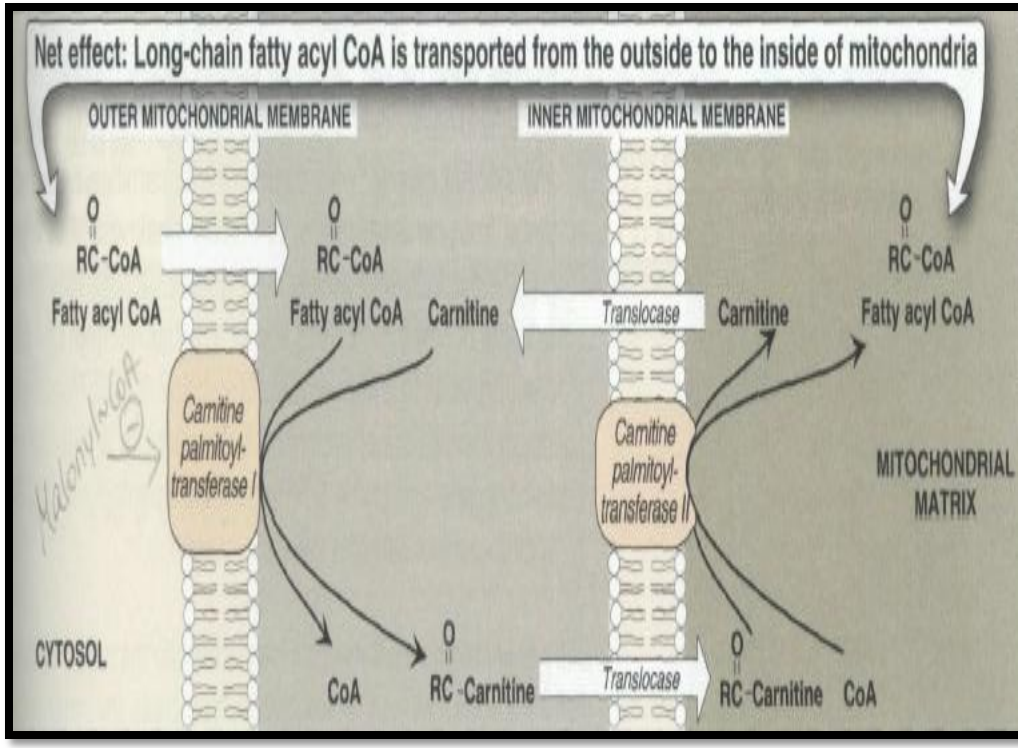


The **chylomicrons take care of the transport** of triacylglycerols and cholesteryl ester from the intestine to the tissues.

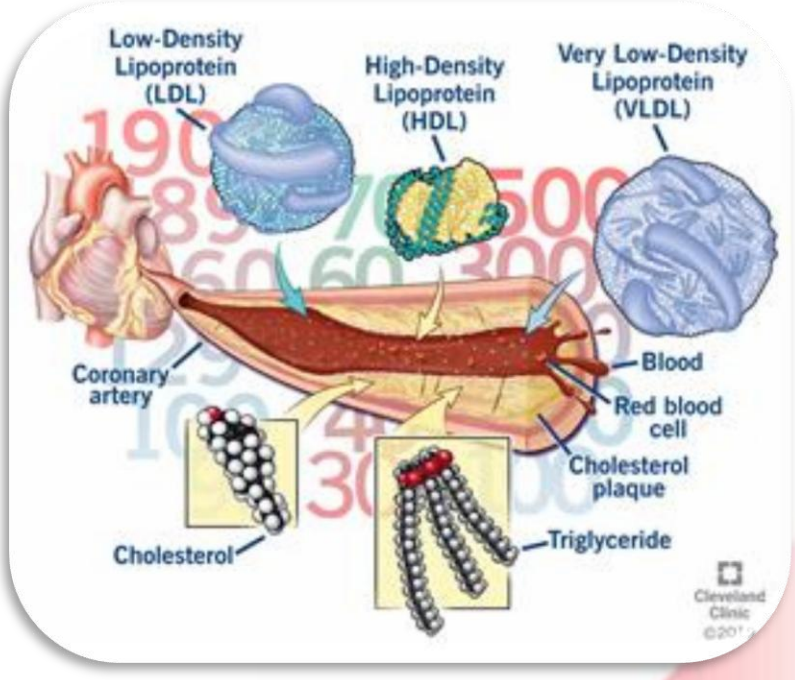
Carnitine shuttel in fatty acid oxidation

- **Fatty acid oxidation includes:**

  - Release **fatty acid** from **TAG**
  - **B oxidation** of fatty acid in which two two-carbon fragments are successively removed from the carboxyl end of the fatty CoA, producing **acetyl CoA, NADH, and FADH2.**
- After a long chain fatty acid enters a cell, it is converted to the CoA derivative by long-chain fatty acyl CoA synthetase (thiokinase) in the cytosol .
- **specialized carrier** transports the **long-chain acyl group** from the **cytosol** into the **mitochondrial matrix**. This carrier is **carnitine.**



Lipids profile

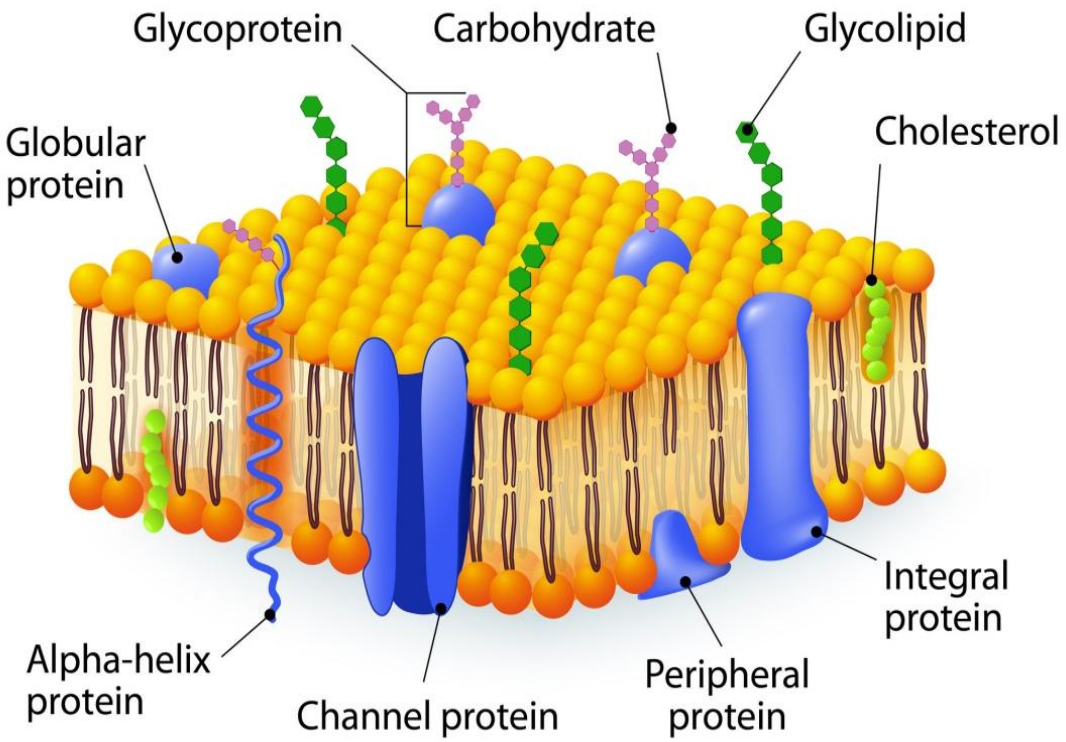


Lipid Profile

	Desirable	*Borderline*	*High Risk*
HDL Cholesterol	*60 mg/dl*	*35-45 mg/dl*	*<35 mg/dl*
LDL Cholesterol	*60-130 mg/dl*	*130-159 mg/dl*	*160-189 mg/dl*
Triglycerides	*<150 mg/dl*	*150-199 mg/dl*	*200-499 mg/dl*
Total Cholesterol	*<200 mg/dl*	*200-239 mg/dl*	*240 mg/dl*

Cell membrane structure

- The cell membrane is primarily composed of a mix of proteins and lipids.
- Lipids make up from 20-80% from the membrane depending on the membrane location and its role in the body.
- lipids help to give membranes their flexibility.
- proteins monitor and maintain the cell's chemical climate and assist in the transfer of molecules across the membrane.

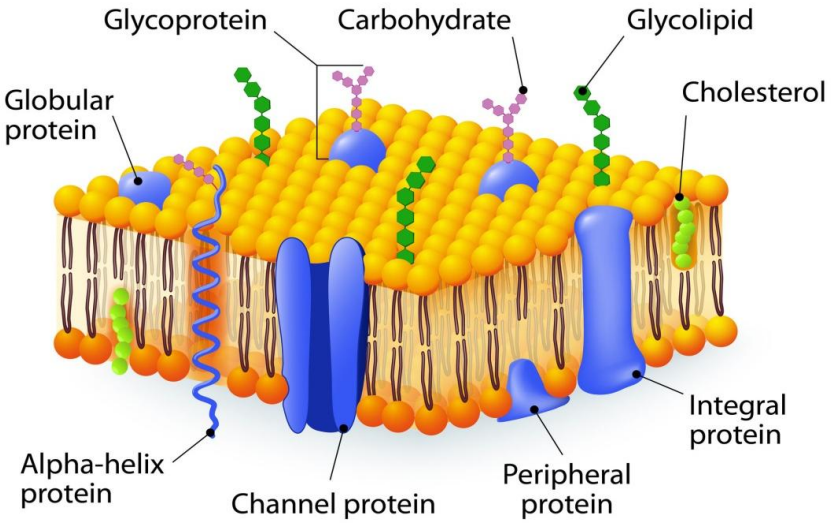


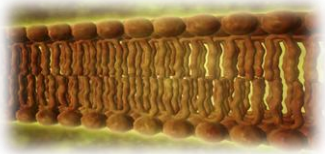
Cell membrane lipids

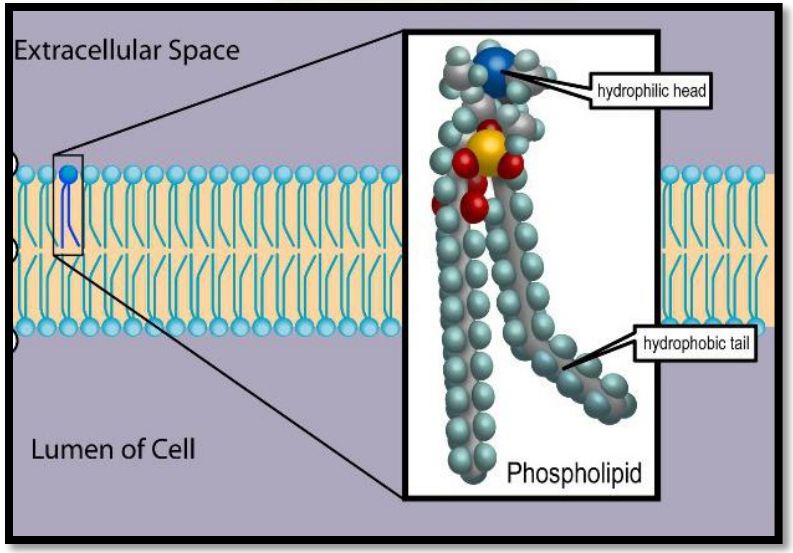
- **Phospholipids:** are a major component of cell membranes and form lipid bilayer in which their hydrophilic head areas spontaneously arrange to face the aqueous cytosol and the extracellular fluid, while their hydrophobic tail areas face away from the cytosol and extracellular fluid. The lipid bilayer is semi-permeable, allowing only certain molecules to diffuse across the membrane.

- **Cholesterol:** Cholesterol molecules are selectively dispersed between membrane phospholipids. This helps to keep cell membranes from becoming stiff by preventing phospholipids from being too closely packed together.

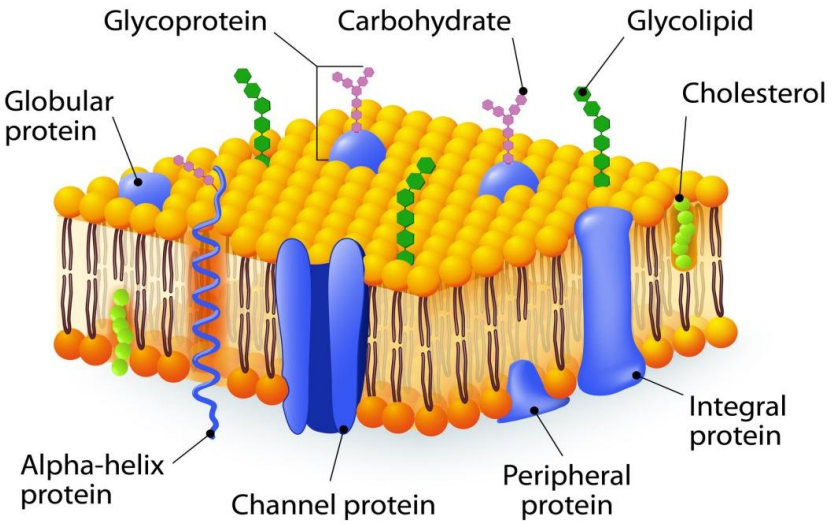
- **Glycolipids:** are located on cell membrane surfaces and have a carbohydrate sugar chain attached to them. They help the cell to recognize other cells of the body.



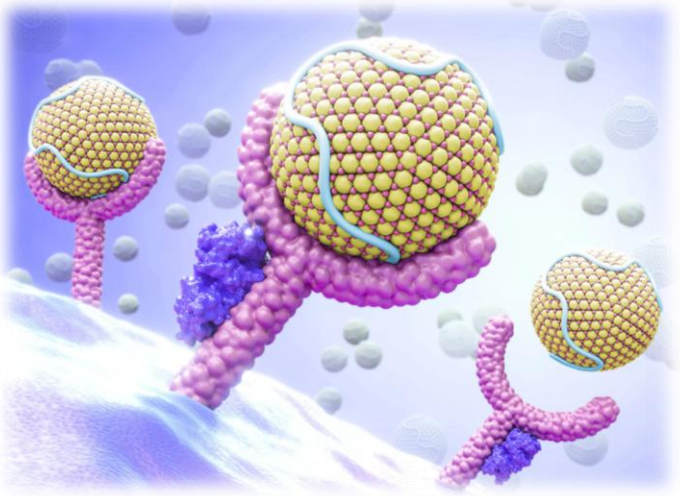




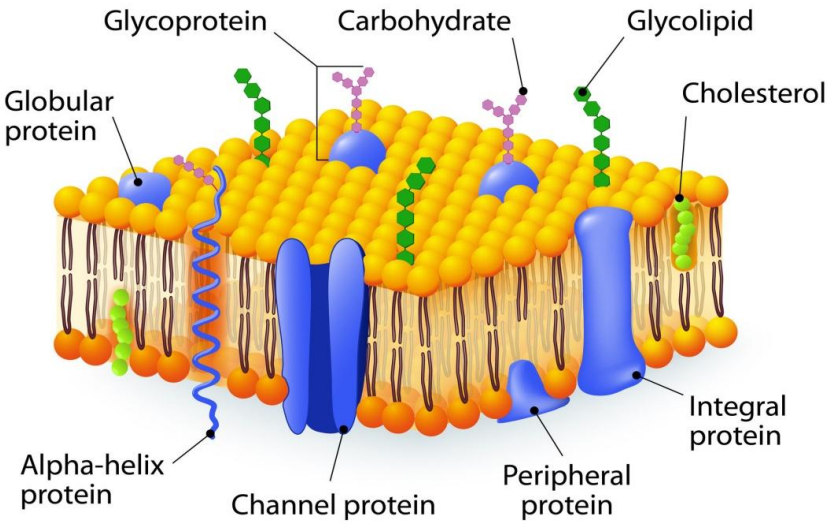
Cell membrane proteins



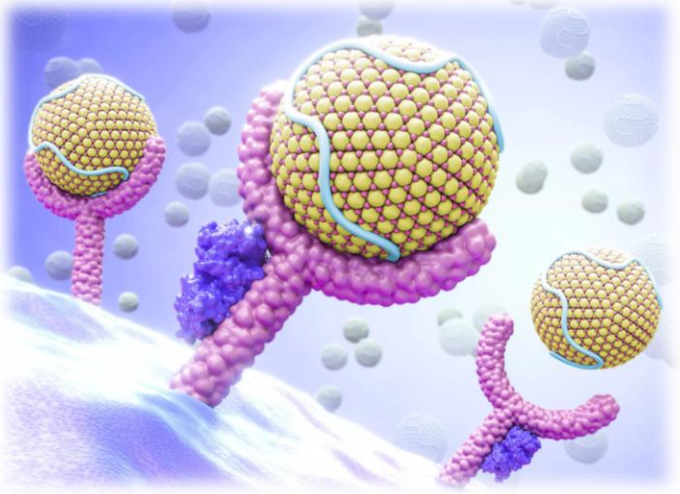
- There is two types of the membrane associated proteins:
  - **Peripheral membrane proteins:** are exterior to and connected to the membrane by interactions with other proteins.
  - **Integral membrane proteins:** are inserted into the membrane and most pass through the membrane.
- Portions of these transmembrane proteins are exposed on both sides of the membrane.



Cell membrane proteins functions



- **Structural proteins** help to give the cell support and shape.
- **Cell membrane receptor proteins** help cells communicate with their external environment through the use of hormones, neurotransmitters, and other signalling molecules.
- **Transport proteins** such as globular proteins, transport molecules across cell membranes through facilitated diffusion.
- **Glycoproteins** have a carbohydrate chain attached to them. They are embedded in the cell membrane and help in cell to cell communications and molecule transport across the membrane.



Thank you