◉ Sheet ○ Slides

Subject :	Metabolism of dietary fat
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Number :	27

RECAP

The chylomicrons originate from the small intestinal cells and are then released into the lymph, and they acquire Apo c2 and E which come from HDL.

- In Chylomicrons, the percentage of TAG is much higher than Cholesterol.

-The chylomicrons go to the venous; capillaries where there is an enzyme called Lipoprotein Lipase (LPL) which gets activated by (Apo C2) and then attaches to the Chylomicrons, thus hydrolyzing the TAG into (fatty acids + glycerol) (fatty acids will be taken mainly by the tissues)

-now, (Apo C2) will go back to HDL, and we have small chylomicrons known as chylomicron remnants which have much more cholesterol and cholesterol esters than TAG as well as Apo E which is important for the binding of chylomicron remnants to cell surface receptors on hepatocytes (liver cells) so they can be taken by endocytosis.

End of recap

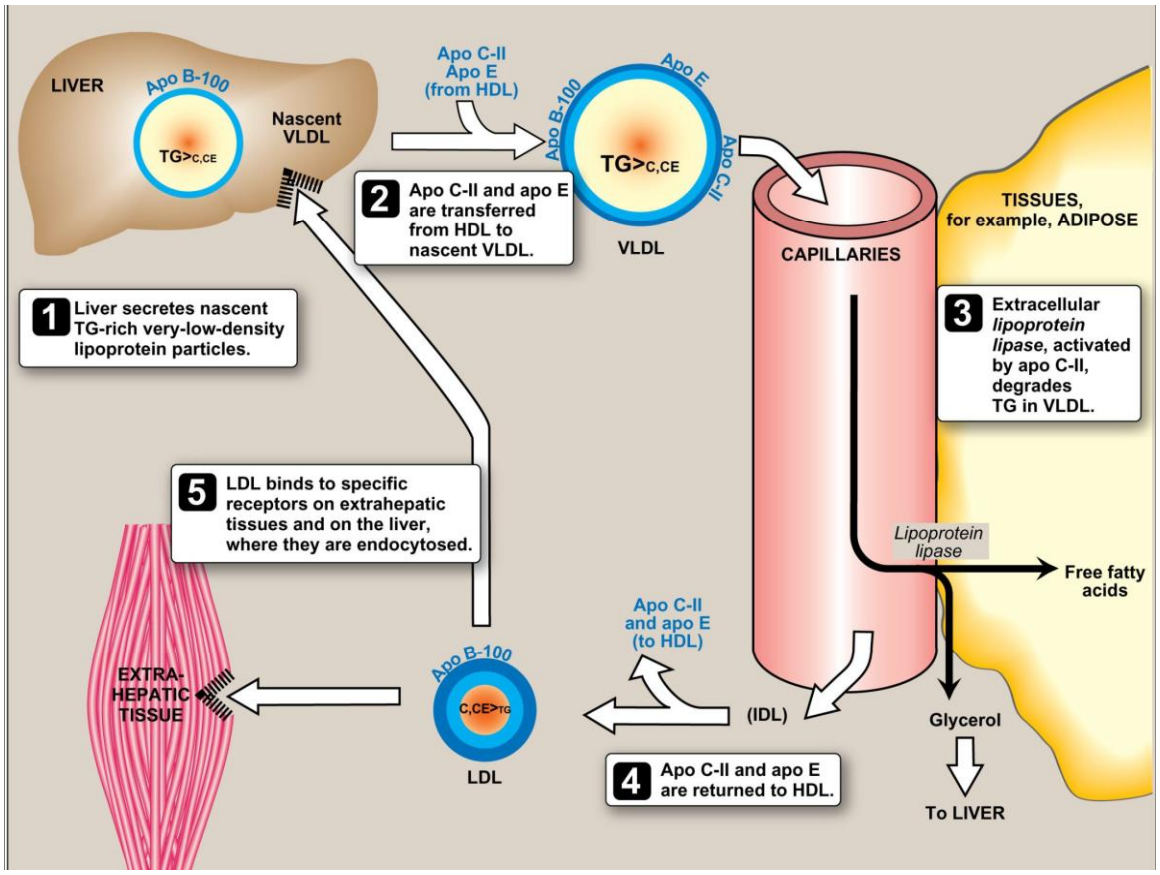
** Metabolism of Very-low-density lipoproteins (VLDLs):

It is similar to the one discussed previously but here the LIVER is producing **(VLDLs)** instead of the small intestines, and again the TAG is much higher than Cholesterol and Cholesterol Esters. The VLDLs are produced in the same manner as the Chylomicrons, so they acquire (**Apo E** and **Apo CII** from **HDL)** and they go through the capillaries where lipoprotein lipase **(LPL)** acts on (TAG) to hydrolyze it to (fatty acids +glycerol), the fatty acids are taken by tissues such as adipose tissue.

- the size of VLDL is smaller now, and the density is higher, so it will become an intermediate-density lipoprotein (**IDL**) which has 2 pathways:

1)could be taken by endocytosis.

2) could continue as LDL after giving Apo CII and Apo E back to HDL so it will become smaller in size because it only has Apo B-100 (Cholesterol and Cholesterol Esters are higher than TAG) and the LDL will be taken again by endocytosis by Extra-hepatic tissue like muscles, fibroblasts or different cells AND the LIVER.

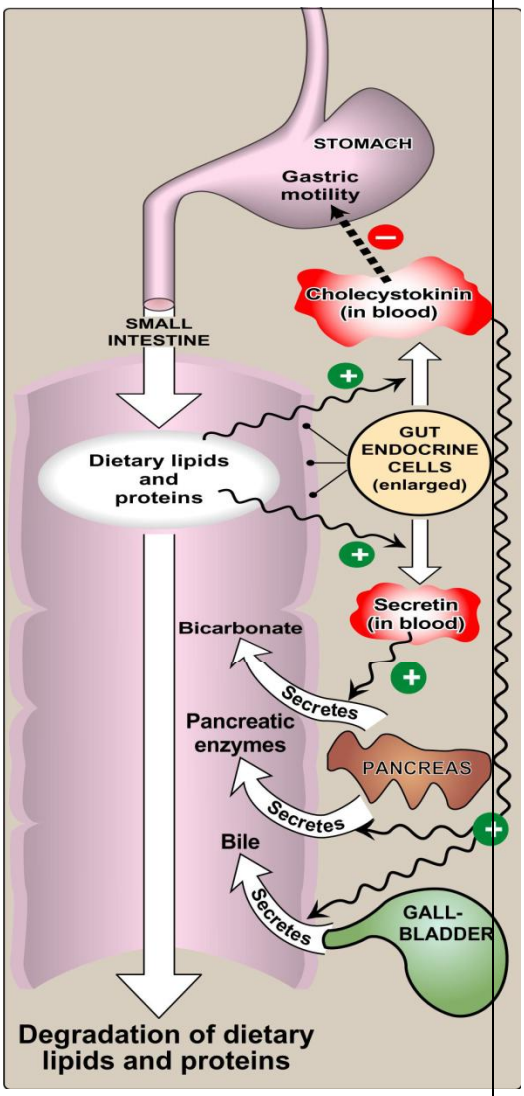


**HOW can we regulate the digestive process of lipids ?

we can do that by HORMONES

the main two hormones are :

cholecystokinin and secretin (both secreted by the endocrine cells of GI mucosa and released in the blood)



**CHOLECYSTOKININ : works on 3 places

1-gastric mucosa (smooth muscles there) *inhibition* of their contraction so it will decrease gastric motility.

2-pancreas (exocrine cells) stimulated to release their digestive enzymes

3-gallbladder : stimulation to release bile and bile salts

-the secretion of enzymes and bile is to *stimulate the digestion*

- the decrease in gastric motility results in *slower release of gastric contents* and lipids into the small intestine for digestion (gradual digestion)

**SECRETIN: is going to activate secretion of BICARBONATE in response to the low pH of the CHYME entering the intestine (chyme:acidic fluid that passes from the stomach to the small intestine, consisting of gastric juices and partly digested food) .Secretin causes the pancreas to release a solution rich in bicarbonate that helps neutralize the pH of the intestinal contents , bringing them to the appropriate pH for digestive activity by pancreatic enzymes.

**** Lipoproteins have the ability to <u>exchange</u>**

different components

-this figure shows the exchange process

between VLDL and HDL

HDL gives cholesterol esters to VLDL

HDL takes TAG from VLDL

this process is mediated by

(CETP) *cholesteryl ester transfer protein*

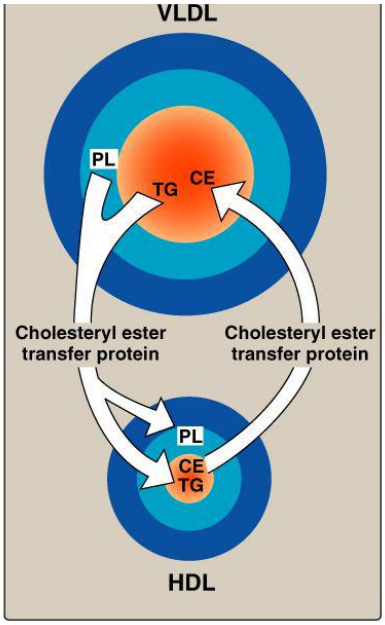


Figure 18.18
Transfer of cholesteryl esters (CE) from HDL to VLDL in exchange for triacylglycerol (TG) or phospholipids (PL).

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****CHOLESTEROL METABOLISM:**

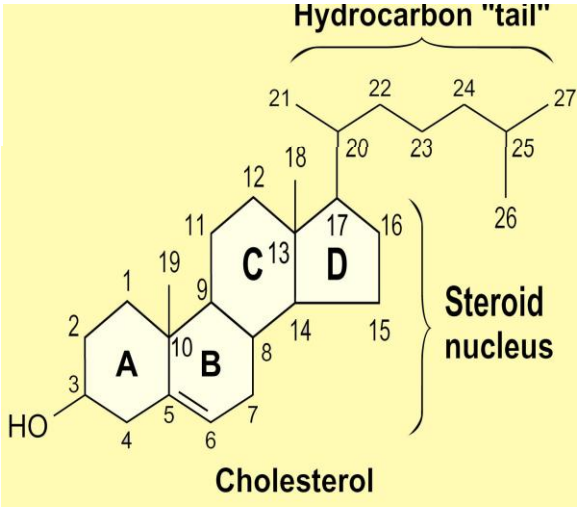
If we analyze the word cholesterol:

CHOLE: indicates the origin of the cholesterol which is the GALLBLADDER.

STER: indicates that it contains **Steroid Nucleus** ** (described below)

OL: indicates that it is an ALCOHOL.

** steroid nucleus (which is formed from 4 rings A, B, C, D total of 17 carbons with only carbon and hydrogen forming these rings. Three 6-membered rings and One five-membered ring.



the numbering of these carbons is standard and shown in the figure and we use them when talking about compounds derived from cholesterol (same numbers for all the structures)

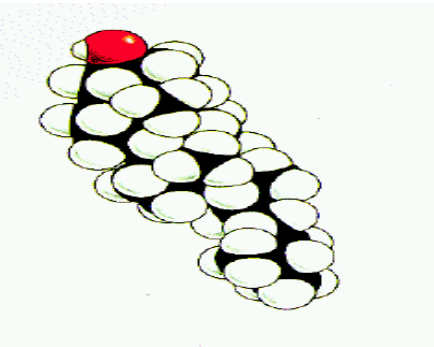
****CHOLESTEROL STRUCTURE (refer to the picture above)**

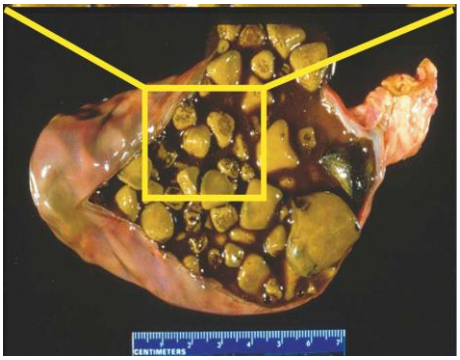
We have some modifications: we have hydroxyl group on carbon 3, between carbon 5 and 6 there is a double bond, on carbon 10, carbon 13 there is a methyl group on each (we consider the methyl groups carbon 18, carbon 19), on carbon 17 we have an 8-membered side chain which makes the total number of carbons 27.

- notice that cholesterol is only made of carbons and hydrogens with only one oxygen atom (so it is very nonpolar (hydrophobic) thus its solubility in water is very low)

- cholesterol is an (amphipathic molecule) found in the membrane and affects its rigidity, all of it is nonpolar except for the oxygen atom which faces the water. (figure to the left, red in color)

-this figure (on right) shows GALLBLADDER STONES which are made of CHOLESTEROL, and when they are produced, there is no way that we can solubilize them again

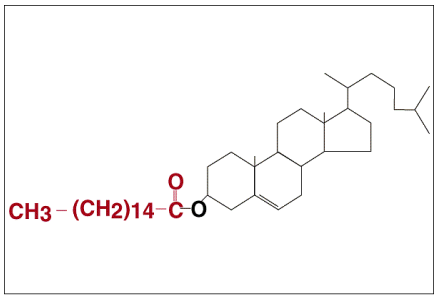




-precipitation of cholesterol in the bile is the reason of this phenomena we treat it by removing the gallbladder.

-Cholesterol is essential for life but it can also be a cause of death.

-this figure shows an esterified cholesterol which is the form of storage of cholesterol (fatty acid ester of cholesterol), most cholesterol in the body is found in the esterified form and this form can't be found in the membrane, **why?** because it is not amphipathic anymore.



SOURCES AND ELIMINATION OF CHOLESTEROL:

-most of the cholesterol is **synthesized** in the body (about 1000 mg)

*all cells have the ABILITY to synthesize cholesterol which reflects its importance for the cells, but not all of them actually do synthesize it (has the ability but doesn't use it).

-so, if the cell is provided with cholesterol there is no need to synthesize it such as the muscle cells (they only need little amounts of cholesterol)

- it is synthesized MAINLY in the liver (to make bile acids and lipoproteins), and to a lesser extent in the small intestine (to make chylomicrons), adrenal cortex (because it's the source of steroids) and reproductive tissues.

-**DIETARY** (about 300 mg/day if it was a low cholesterol diet): in food that is low in cholesterol.

- one egg can provide up to 250 mg of cholesterol.

- So, can u reduce the cholesterol intake from the food (dietary)?

no, it is very difficult. As we said that cholesterol is found in all animal cells, so whatever you eat from the animal whether it was egg, milk, yoghurt, ice cream you will find cholesterol there, but if you eat only foods with vegetable origin, the intake of cholesterol will be zero, which is very hard.

CHOLESTEROL DEGRADATION:

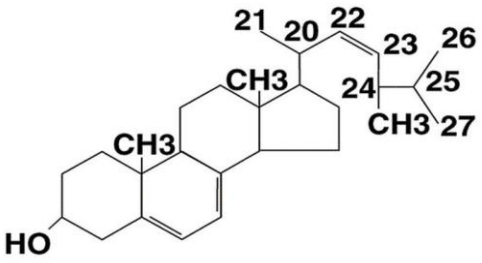
It's not degraded to CO2, H2O (so it doesn't undergo OXIDATION to produce energy).

- it is ELIMINATED via bile as:

1-free cholesterol.

2-after the conversion to bile salts

-You may mistake this structure for cholesterol but it is **not**, it is called (**ERGOSTEROL**) which is a (Plant Sterol)**.**



There is no cholesterol in plants, but they make STEROLS and Ergosterol is one of them

-Plant Sterols are **Poorly ABSORBED** by Humans.

Plants manufacture **phytosterols**(substances chemically similar to

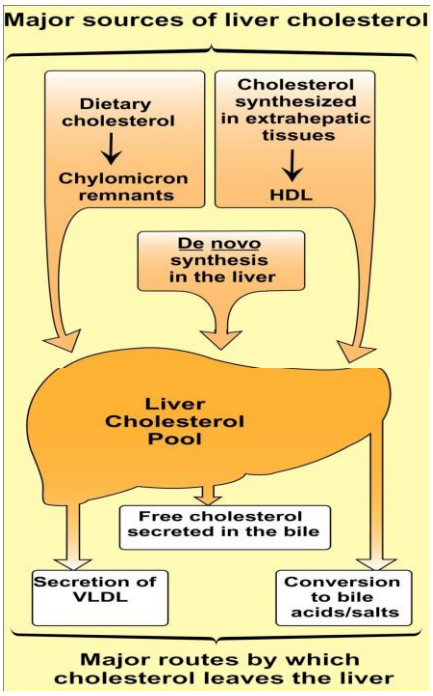
cholesterol produced within plants), which can compete with cholesterol for reabsorption in the intestinal tract, thus potentially reducing cholesterol reabsorption. When intestinal lining cells absorb phytosterols, in place of cholesterol, they usually excrete the phytosterol molecules back into the GI tract, an important protective mechanism

-they will be absorbed by the cells **BUT** they will be **re-excreted** again into the lumen of the small intestine and they will excrete some cholesterol with them while being re-excreted.

- so, if u have noticed, by this way we can decrease the cholesterol absorption (by the taking of plant sterols, which will be re-excreted from the cells, taking cholesterol with them)

- this figure shows the main sources

of cholesterol and how it is eliminated



SOURCES:

- **dietary cholesterol** in **chylomicrons**
- cholesterol is synthesized in extrahepatic

tissue (like the cholesterol which is released

by the death of cells) in **HDL**

- **De novo synthesis** in the liver

*De novo: means that it is synthesized from scratch (from nothing), not mixing other compounds.

ELIMINATION:

- **free cholesterol** secreted in the bile
- **conversion to bile acids\salts**
- secretion of **VLDL**

****CHOLESTEROL SYNTHESIS:**

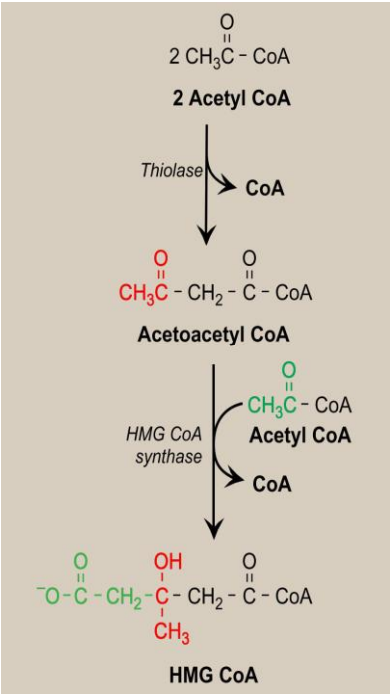
Animal livers that we eat are rich in cholesterol, even more than egg. But because we eat eggs much more than livers, we give eggs more attention.

***cholesterol synthesis requires:**

- ✓ carbon source: **acetyl CoA**
- ✓ Energy: **ATP**
- ✓ reducing power: **NADPH**
- ✓ **O2**

-ALL 27 carbons of cholesterol come from **acetyl CoA**

NOTE: the cholesterol is **very much reduced** because it has 27 carbons with ONLY one oxygen atom, that's why we need a high reduction power (NADPH)



<u>first step:</u>

condensation of two Acetyl groups from <u>2 Acetyl CoA</u>

which gives <u>Acetoacetyl CoA</u>, the enzyme is **Thiolase**,

the reaction occurs in the cytoplasm.

<u>second step:</u>

transfer of acetyl group from <u>acetyl CoA</u> to

acetoacetyl CoA to give <u>HMG CoA</u> by the enzyme

HMG CoA synthase.

NOTE: these two reactions are similar to the (KETONE BODIES SYNTHESIS) with only one difference:

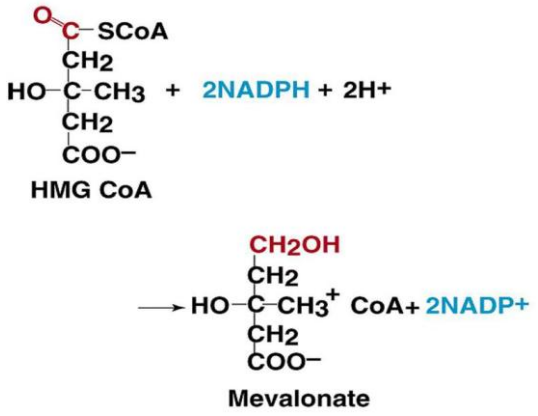
- <u>ketone bodies</u> synthesis occurs in MITOCHONDIA, while <u>cholesterol</u> synthesis occurs in CYTOPLASM.

<u>third step: (rate-limiting step)</u>

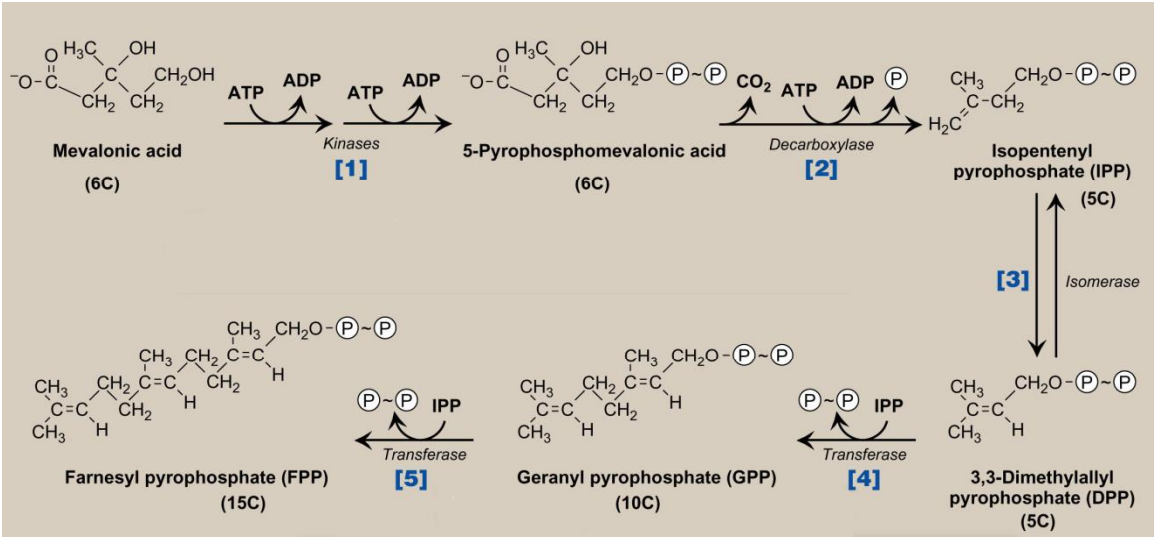
The reduction of carboxyl group of <u>HMG CoA</u> into aldehyde then into alcohol by 2 NAPDH to produce <u>MEVALONATE</u>. the enzyme is **HMG CoA Reductase**

NOTE: when we use NAPDH we can't call the enzyme hydrogenase

- this is the rate-limiting step in cholesterol synthesis, which means it is the step that is regulated.



Refer to this figure while going through the steps mentioned below:



<u>fourth step:</u>

then we activate MEVALONATE by adding 2 phosphate groups from 2 ATP (these 2 phosphate groups will appear as pyrophosphate)

<u>fifth step:</u>

decarboxylation reaction where we remove CO2 by **decarboxylase <u>(this step requires ATP!!)</u>** to produce <u>Isopentenyl pyrophosphate (IPP)</u>

*isopentenyl = hydrocarbon chain

*pent= 5 carbons

*en=double bond

sixth step:

isomerization of IPP into Dimethylallyl pyrophosphate (DPP) by **Isomerase**

seventh step:

another IPP is added to DPP by **Transferase** (condense together) to give Geranyl pyrophosphate (GPP) which is a 10-carbon compound.

**the release of pyrophosphate is what helps this reaction to occur and makes it IRREVERSIBLE.

eighth step:

addition of one more IPP to GPP by **Transferase** also to produce Farnesyl pyrophosphate (FPP) which is a 15-carbon compound.

**the release of pyrophosphate is what helps this reaction to occur and makes it IRREVERSIBLE.

Refer to the slides for the rest of the figures:

ninth step:

Joining of 2 (FPP) together and releasing 2 pyrophosphates, and the double bond that is produced will be reduced by NADPH to produce SQUALENE (30 carbons compound), the enzyme here is **Squalene Synthase.**

-So, the SQUALENE is 30-carbon compound, thus it came from 6 isopentane, and each isopentane came from 3 Acetyl CoA.

- if we calculated the Acetyl CoA needed to produce one SQUALENE it will be (18 Acetyl CoA) 3 * 6 = 18

- you can consider SQUALENE as a poly-isoprene compound, the isoprene unit is a 5-carbon unit with branch and a double bond it is also composed of only CARBON and HYDROGEN (hydrocarbon compound).

-**Coenzyme Q 10** is called 10 because it contains 10 isoprene units (how many carbons? 50) in its side chains so it is very hydrophobic. It is located in the inner mitochondrial membrane.

vitamin A, E, K contain poly-isoprene side chains that make them very hydrophobic, soluble in fat.

tenth step:

Oxygen atom is added to squalene to produce Squalene 2,3 epoxide (oxygen is connected to carbon 2 and 3, which makes it unstable as the angle is 60 degree)

eleventh step:

By the presence of enzyme Cyclase, closure of the four rings happen to give us Lanosterol (the first sterol intermediate (contains steroid nucleus))

**now several steps convert lanosterol into cholesterol with several intermediates (not to be memorized) but only memorize (7-Dehydrocholesterol) because it is the precursor of (Vitamin D).

-vitamin D can be synthesized in the body after exposure to sunlight. but why do we consider it as Vitamin? (vitamin by definition: cannot be synthesized in body in adequate amounts)

-the active form of Vitamin D is (**1**,**25**-dihydroxycholecalciferol)

the numbers here are the same we used in numbering carbons of cholesterol, so they are standard.

We need 3 ATP molecules for the synthesis of a 5 carbons fragment so we need a total of 18 ATP molecules to synthesize one cholesterol molecule.

*SYNTHESIS OF BILE ACIDS:

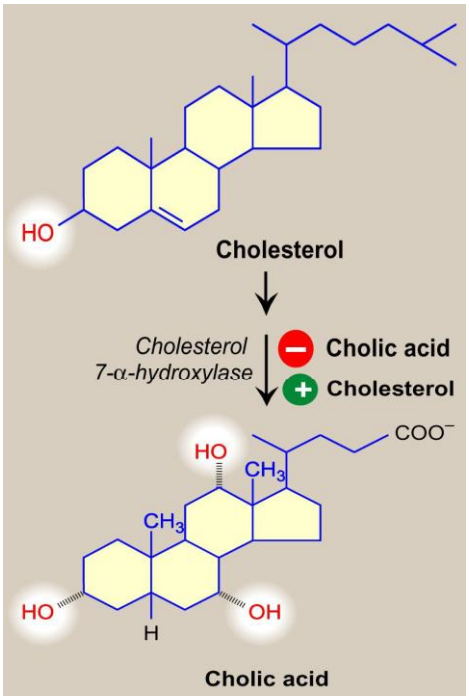
synthesized in the LIVER.

The first step is Hydroxylation at Carbon 7 which is the Rate-limiting Step by **Cholesterol 7- α-hydroxylase**

- it is inhibited by **Cholic Acid** which is the final product.

- it is activated by **Cholesterol** which is the reactant

-this reaction also involves the reduction of double bond between carbon 5 and 6 and reducing the side chain from 8 carbons to 5.



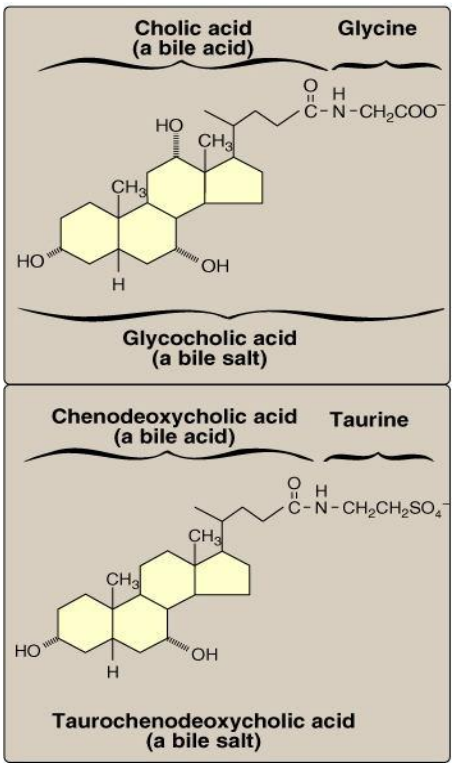
NOTE: it is produced in the LIVER , but stored in GALLBLADDER

NOTE: the hydroxyl group on carbon 7 is always there , but the one on carbon 12 may or may not be there .

-Bile acid is then joined to GLYCINE or TAURINE (both are amino acids) but glycine is a carboxylic acid while taurine is a sulfur-containing acid.

-these are stronger acids than the non-conjugated ones.

-we call them primary bile acids initially ,which means they didn't reach the small intestine yet such as : cholic acid and chenodeoxycholic acid.



-ENTEROHEPATIC CIRCULATION:

primary bile acids are conjugated in the liver as discussed before , then released via the BILE DUCT into the duodenum .

-those primary bile salts act to solubilize fat.

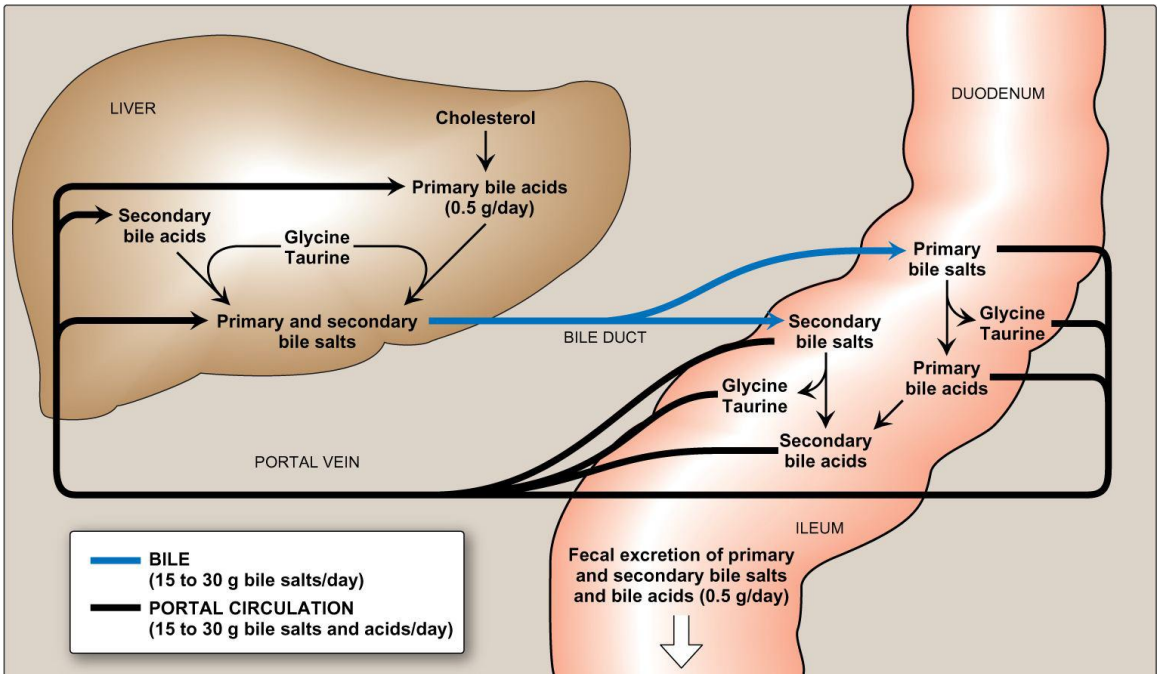
-then Bacteria (intestinal flora) acts on these primary bile acids and deconjugates them and dehydroxylates them.

-after that we can call them SECONDARY bile acids.

-now primary and secondary bile acids are reabsorbed through a co-transporter with Na^+ via PORTAL VEIN into the liver again , and this process is done again and again , that's why we call it **ENTEROHEPATIC CIRCULATION**.

-this circulation is not 100% efficient , as 5% of the bile acids are not reabsorbed (0.5 g/day) which is excreted in the feces .

- we can compensate for those 5% by converting 0.5 g of cholesterol into bile acids in the liver.



**LOWERING CHOLESTEROL LEVEL:

Dietary

- ↓Cholesterol intake
- ↑ PUSFA / SFA
- ↑ Fiber
- Daily Ingestion of Plant Steroid Esters
- Inhibition of Synthesis
- ↓ Enterohepatic Circulation of Bile Acids

cholesterol level normally is around 200 mg .

high levels of cholesterol may result in Atherosclerosis (vascular disease).But to protect against this disease we have to lower the cholesterol level in the plasma, but how? it is not efficient to only reduce the intake of dietary cholesterol , because we can produce cholesterol within the body (this way can reduce the level by 5-10% only)

we will discuss the rest of the ways in next lecture ***GOOD LUCK***