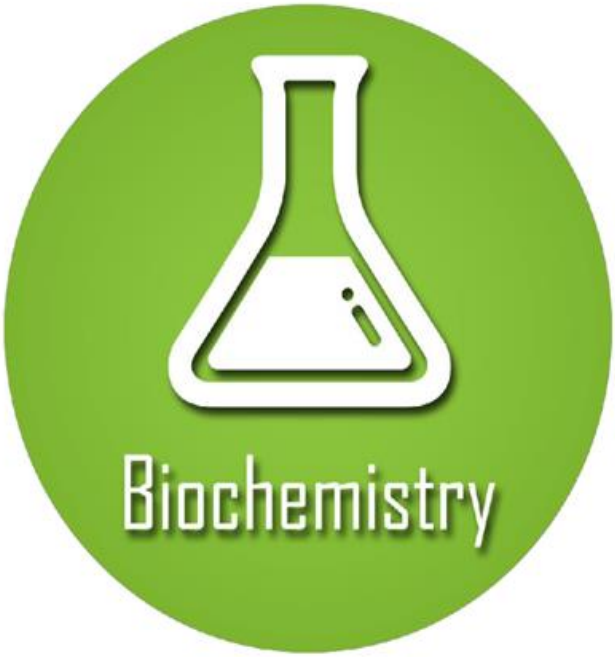


◉Sheet ○Slides

Number: **19**

Done by: **Abdullah Al-saa'd**

Corrected by: **Toqa Alhumaidi**

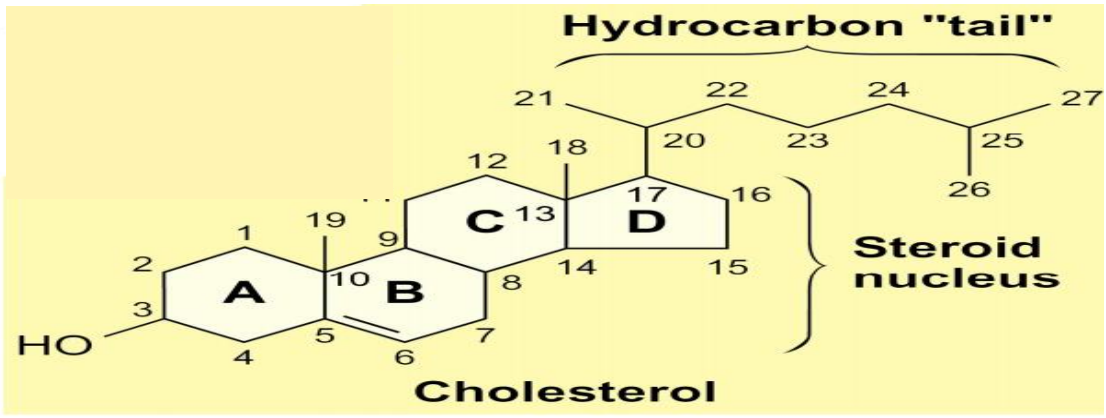
Subject: **Cholesterol metabolism 1**

Doctor: **Faisal Alkateeb**

This sheet covers slide number 8 and the pages (219 - 226) from chapter 18 except the regulation of cholesterol synthesis as we will take it next lecture.

Overview and the structure of Cholesterol:

Cholesterol reference: (chole) refers to gallbladder, (ster) from steroid, (ol) indicates that it is an alcohol → (so it is an alcoholic steroid that was isolated from the gallbladder).



Cholesterol consists of a Steroid Nucleus and a Hydrocarbon Tail.

The Steroid Nucleus is: 17 carbons bonded in four fused rings (three of them are six member rings (cyclohexane) and the fourth one is a five-member ring (cyclopentane).

The seventeen carbons are numbered depending on a special manner. Cholesterol rings have some substituents or modifications such as:

→Hydroxyl group on carbon #3 (from which the (OL) suffix was derived).

→A double bond between carbon #5 & #6.

→ Two methyl groups, one at carbon #13 (the C in this methyl group is carbon #18), the other one on carbon #10 (the C in this methyl group is carbon #19).

→ The Hydrocarbon tail (eight carbons long) that is attached to the carbon #17 of the steroid nucleus.

So cholesterol molecule consists of 27 carbons:

***19 carbons → the steroid nucleus carbons + carbons of the two methyl groups.**

***8 carbons → in the hydrocarbon chain.**

Cholesterol is a component of the cell bilayer membrane; this is due to its amphipathic structure. (Amphipathic structure is due to having the hydrophobic chain and a hydrophilic portion (because we have oxygen atom in "OH" on carbon #3). In general, cholesterol is hydrophobic as its hydrophobic portion is greater than its hydrophilic portion (the only hydrophilic group (OH)).

The gallbladder stones are actually cholesterol precipitants that accumulate due to the poor solubility of cholesterol. Remember that the gallbladder is the site of bile storage.

Cholesterol Ester is a Cholesterol with a Fatty Acid connected to it by an ester bond, making the structure more hydrophobic (less soluble than cholesterol / almost non-soluble!).

Ergosterol is a plant sterol which is poorly absorbed by human (as other plant sterols), but plant sterols can reduce the cholesterol level by decreasing its absorption because there is competition between sterols (to be absorbed).

Cholesterol synthesis:

Cholesterol is a vital molecule so it is synthesized the body (1000 mg of cholesterol is synthesized per day in our bodies). It is mainly synthesized in the liver, adrenal cortex, intestines, etc. and other cells gain their needs of it from the circulation (but they are capable to synthesize it). However it can be fatal (harmful).

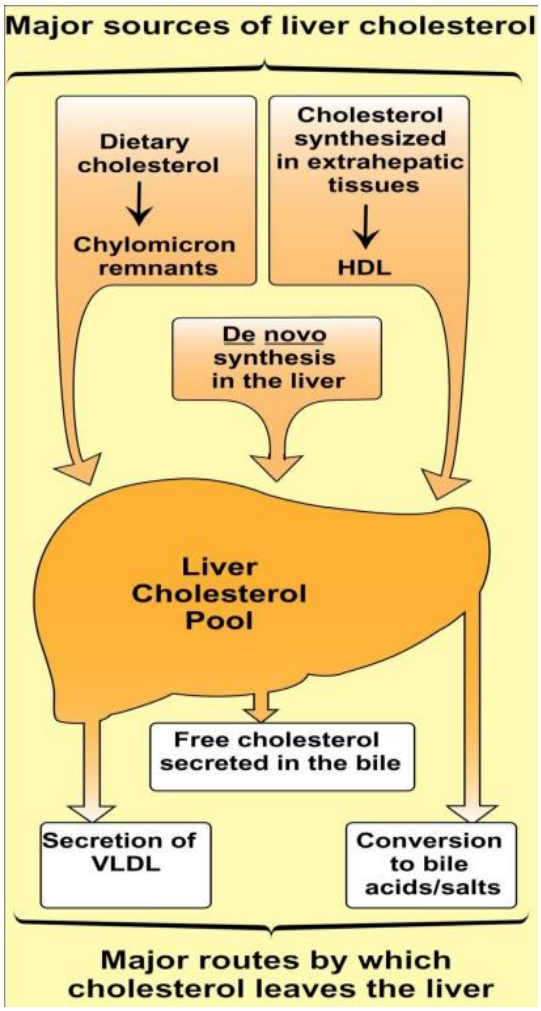
The daily diet intake of cholesterol should be ≤ 300 mg (low cholesterol diet).

Cholesterol isn't degraded to produce energy in contrast to fatty acids, it is eliminated and excreted in the bile and some of it is converted to bile acids and bile salts for excretion.

→ Cholesterol is not a source of energy, it is degraded only to produce bile acids & bile salts.

The role of the liver in cholesterol metabolism:

This figure shows the role of the liver in the cholesterol metabolism:



→The liver synthesizes cholesterol by a certain pathway as De novo synthesis or synthesis from scratch (synthesis from zero).

→ Dietary cholesterol that is obtained from the food is transported to the liver as chylomicrons that are converted to chylomicrons remnants (those are rich with cholesterol and will be taken up by the hepatocytes).

→The cholesterol that is in excess or synthesized in extrahepatic tissues is transferred in the form of HDL back to the liver.

→The liver distributes cholesterol to different tissues by secretion of the VLDL (excreted in the bile as such or converted to bile acids and then excreted in the bile).

So the homeostasis of the cholesterol occurs mainly in the liver.

Animal livers' are the richest source of cholesterol. Eggs and animal fat are sources of cholesterol too.

Cholesterol synthesis pathway:

Cholesterol synthesis requires:

1) Acetyl CoA; as it is the carbon source. All carbon atoms of cholesterol (27 carbons) come from Acetyl-CoA molecules. (Including the methyl groups too).

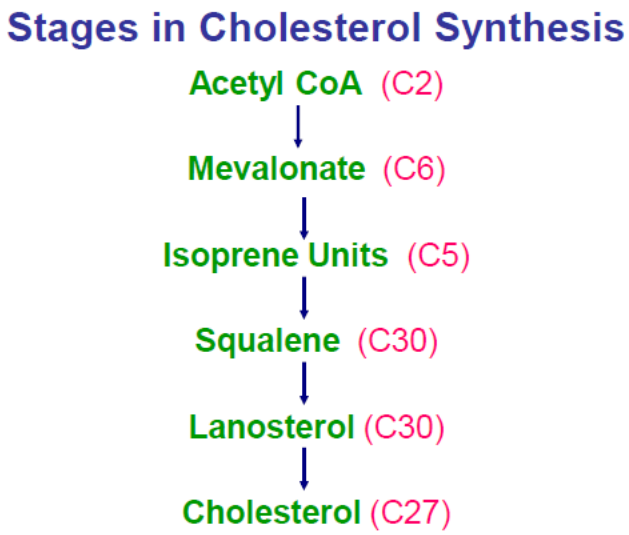
2) Energy: Energy is needed to join molecules together.

→ Whenever we are synthesizing large molecules from small precursors energy is required in the form of ATP.

3) Reducing power (NADPH): we need this because the end product (the cholesterol) is highly reduced as it mainly consists of carbon and hydrogen.

4) Oxygen: The only oxygen atom of cholesterol is derived from O_2.

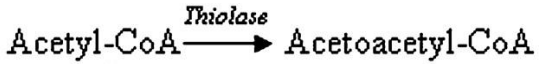
Now we will explain the reactions in the pathway:



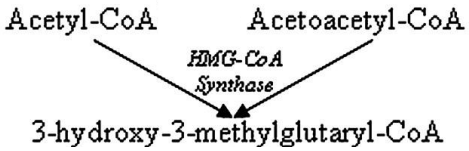
***P.S. we should memorize the intermediates above ↑ and the number of carbons they contain.**

The first two reactions (similar to those in ketone bodies synthesis):

1. **The condensation of two Acetyl groups from Acetyl CoA to form Acetoacetyl CoA by an enzyme called Thiolase.**



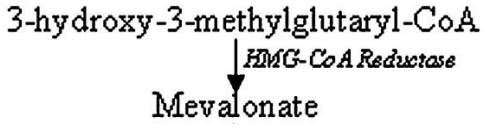
2. **Then one more Acetyl CoA will be condensed with Acetoacetyl CoA to form a six carbons compound called HMG-CoA (3-hydroxy-3-methylglutaryl CoA→that is a glutamic acid with methyl and hydroxyl groups on its carbon number 3), this is catalyzed by HMG CoA synthase.**



→These two reactions differ from ketone bodies synthesis that they occur in the cytoplasm whereas in ketone bodies synthesis they occur in the mitochondria.

The third reaction:

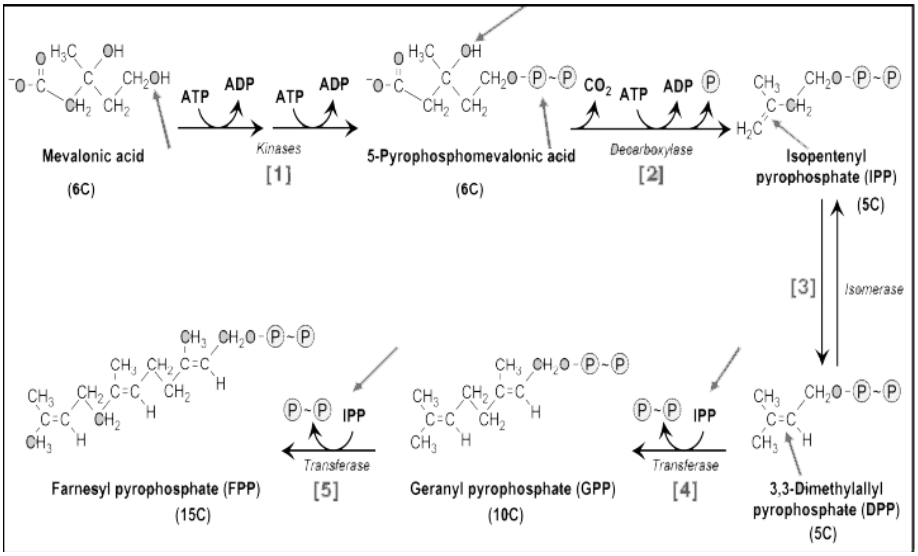
It is a reduction of HMG-CoA to Mevalonate (which is a six carbons molecule too), by an enzyme called HMG-CoA reductase.



This reaction is <u>two steps reduction reaction</u> to convert the carboxyl group to a hydroxyl group by consuming two NADPH and 2H+ and converting them to 2NADP+.

The first reduction reaction converts the carboxyl group to an aldehyde group and the second converts it to a hydroxyl group.

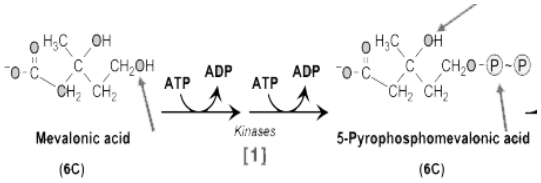
This reaction is very important in the synthesis of cholesterol as it is <u>the regulatory step</u>.



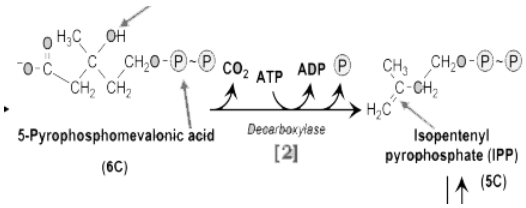
***Now we want to prepare Mevalonate (Mevalonic acid) for condensation (the steps below for the figure above).**

[1] A phosphate group is added Mevalonic acid converting it to a phosphomevalonic acid, then another phosphate is added producing Pyrophosphomevalonic acid (mevalonic pyrophosphate) which is the activated form (the prepared monomer for condensation).

→Two ATP molecules are consumed in this step.

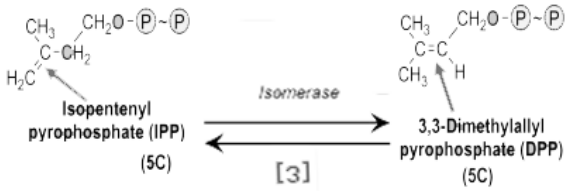


[2] A Removal of carboxyl group (Decarboxylation) by a decarboxylase with introduction of a double bond producing a five-carbon compound called Isopentenyl Pyrophosphate (IPP), [(pent) → five carbon compound, (enyl) refers to a double bond].



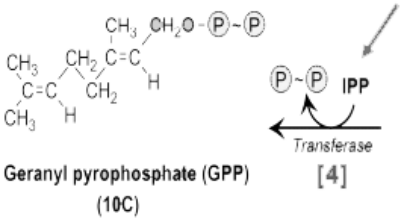
→IPP is the monomer for condensation as it is activated by having the Pyrophosphate. This step consume one ATP (the doctor said that he doesn't know why, maybe because of the introduction of the double bond).

[3] Now the double bond is isomerized by an <u>isomerase</u> producing <u>(DPP)</u> " the doctor said that we don't have to memorize the name of this intermediate", this step helps in the condensation.



→Until now we need 3 ATP molecules for the formation of each (IPP) or (DPP); so if we want to produce 2 compounds we need 6 ATP molecules and so on.

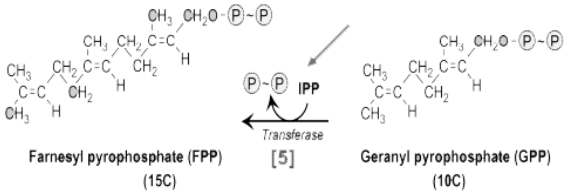
[4] Now (IPP) together with its isomer (DPP) condense and produce a 10 carbons compound called Geranyl Pyrophosphate (GPP) and a pyrophosphate by the action of the transferase enzyme.



→This reaction is derived to the forward direction by the rapid hydrolysis of Pyrophosphate.

[5] Now another condensation happens by the adding of another (IPP) molecule to (GPP) producing a 15 carbons compound called Farnesyl pyrophosphate (FPP) and a Pyrophosphate by the action of transferase enzyme.

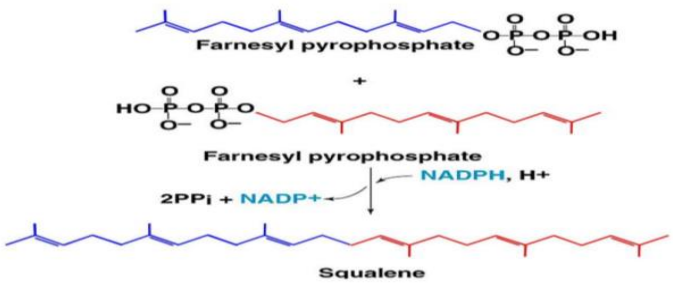
→This reaction is also derived to the forward direction by the rapid hydrolysis of pyrophosphate.



The coming steps aren't illustrated in the previous figure.

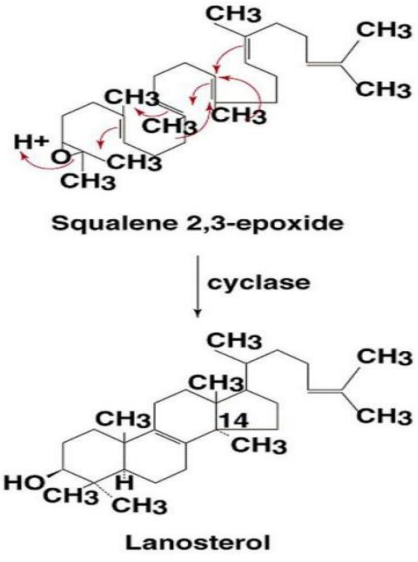
[6] Tow molecules of (FPP) are condensed by the releasing of <u>two</u> molecules of pyrophosphate to produce a 30 carbons compound called Squalene by an enzyme called Squalene synthase.

→Squalene consists only of carbons and hydrogens (it is a hydrocarbon compound), so it is similar to Petroleum. This step convert NADPH and H+ to NADP+.



NOTE: In the body there are many compounds like Squalene which are called polyisoprene units (have a methyl branch every 4 carbon units). They are found in many compounds such as Vitamin A, Vitamin E, Vitamin K and fat soluble vitamins. Coenzyme Q also is a polyisoprene which has a very long hydrocarbon chain (i.e. Coenzyme Q 10, it is made in the same manner). The natural rubber from the rubber tree is a polyisoprene which is made by the same manner too.

[7] Introduction of oxygen , the oxygen atom is added to carbon #2 & #3 at the same time, producing Squalene 2,3-epoxide which is an active and unstable molecule because the oxygen is bound making a 60° angle, so it is ready to form a cyclic compound by a cyclase enzyme called Lanosterol (steroid). Here we convert NADPH and H+ to NADP+.

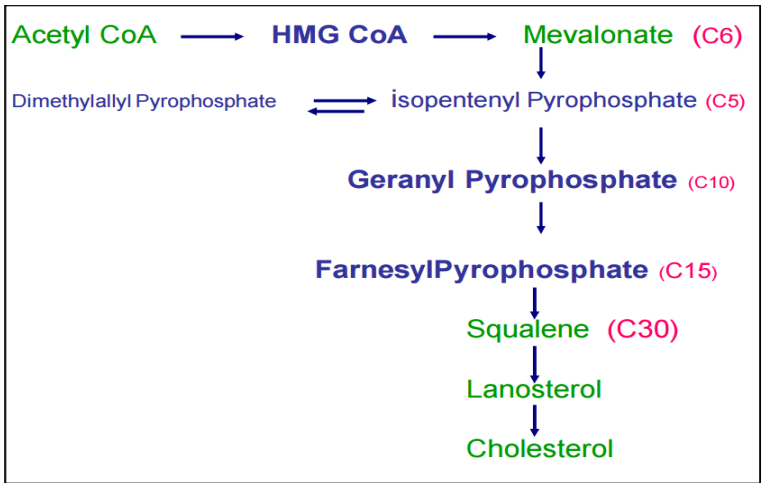


Lanosterol indicates that we have a steroid now (alcohol steroid), but it includes 30 carbons not 27. Now we are so close to the Cholesterol as it is synthesized after several steps that we aren't required to know including shortening of the side-chain, reduction and migration of double bonds and the oxidative removal of methyl groups.

The last intermediate before cholesterol is called 7-dehydrocholesterol "we have to memorize it".

→This intermediate is a precursor for the synthesis of Vitamin D in our body. The active form of Vitamin D is 1, 25-dihydroxycholecalciferol.

The figure below summarizes cholesterol synthesis:



Synthesis of bile acid

Bile acids are synthesized from cholesterol and the synthesis involves some modifications:

1) Bile acids contain hydroxyl group at carbon #7 and carbon #12.

2) The side chain consists of 5 carbons, which is lesser by 3 carbons than cholesterol side chain. This side chain is connected to a carboxyl group.

These simple modifications make the bile acids amphipathic molecules and having emulsifying properties; so it is required for

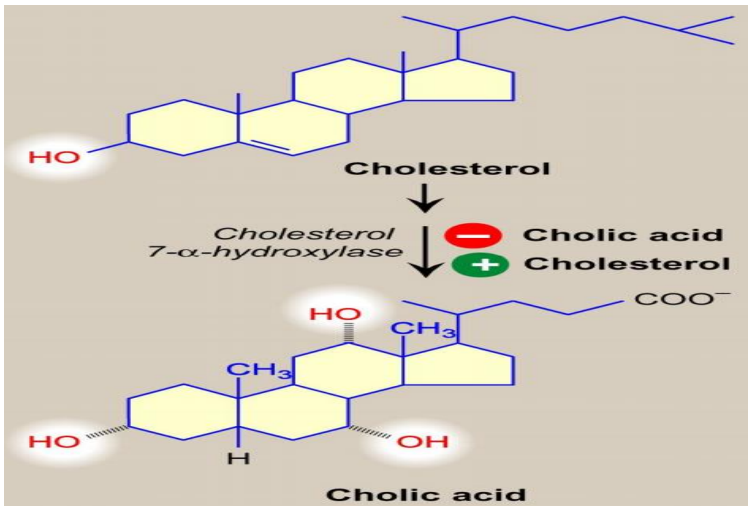
the digestion of the fat. Fat digestion (TAG digestion) involves hydrolysis, so there should be mixing of fat and water for the fat to be digested.

How can we mix them when they are insoluble in each other?

This happens by bile salts.

***(NO bile salts→NO digestion and therefore NO absorption).**

The rate limiting step in the synthesis of bile acid is <u>the first hydroxylation</u> at carbon #7 (and it is regulated), this reaction produces Cholic acid. Cholesterol is an activator for this reaction and Bile acids (the end products) are inhibitors by feedback inhibition.



Cholic acid has a carboxyl group, this carboxyl group usually is considered as a week acid group (its pKa is close to 5). The acidity can be greatly strengthen by joining of Cholic acid with amino acid Glycine by an amide bond, this makes the carboxyl group a stronger acidic group (its pKa is reduced to 2). This is a conjugated bile acid called <u>bile salt</u> (it is a stronger acid) and it will be found mainly in its ionized form.

***"Most of the books don't differentiate between bile acid and bile salt and they use one instead of another ".**

The conjugated acid can be <u>Glycine</u> or sulfur containing amino acid called <u>Taurine</u> (contains a sulfate, which is a strong acid, instead of carboxyl group).

The fate of the bile acid synthesized from cholesterol:

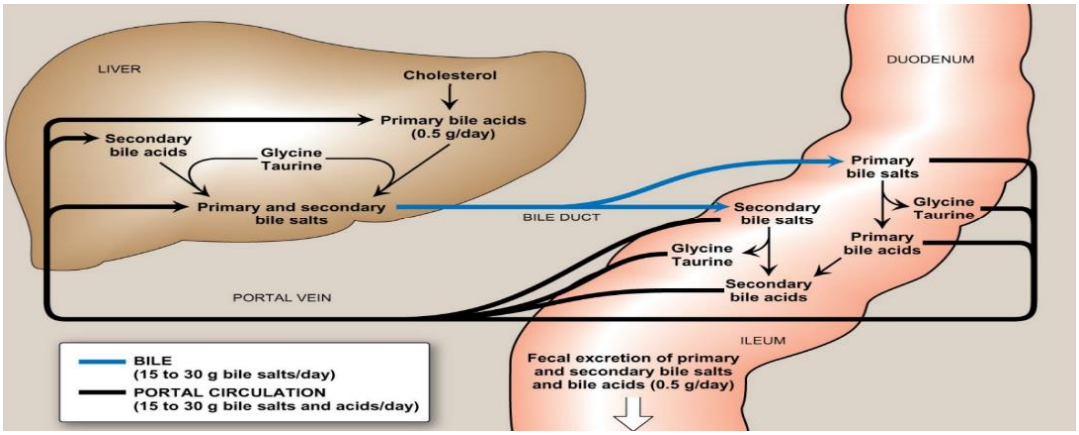
Cholesterol is converted to primary bile acids at a rate of about 0.5 g/day. They are called primary bile acids because they are the first synthesized bile acids.

Now these Primary bile acids are conjugated with Glycine or Taurine then excreted in the bile, then in the small intestines they do their job which is aiding in digestion of fat.

After doing their job, they are converted into secondary bile acids by removal one of the hydroxyl groups by bacterial enzymes (Dehydroxylation).

Now both primary and secondary bile acids are reabsorbed through the portal vein back to the liver where they are reconjugated again and secreted.
So the circulation is from liver to intestines and back to the liver and so on. This circulation is called Enterohepatic circulation.

It doesn't have a 100% recycling (reabsorption) efficiency. It has a 95% efficiency→ 95% of the bile acids that are secreted each time are reabsorbed. The rest 5% is equivalent to 0.5 gram which won't be reabsorbed and are excreted as such in the feces .We compensate this 0.5 gram by synthesis of 0.5 gram from cholesterol per day. So this is how cholesterol is eliminated from the body (by converting it to bile salts and 5% of it is eliminated with feces).



Test yourself:
According to Cholesterol metabolism choose the best answer in the following questions [1) simple Q, 2) moderate Q, 3) hard Q]

1) The rate limiting steps of Cholesterol synthesis and bile salt synthesis respectively are:

A) Synthesis of HMG CoA, Hydroxylation at carbon number 7.
B) Synthesis of HMG CoA, Hydroxylation at carbon number 12.
C) Reduction of HMG CoA, Hydroxylation at carbon number 7.
D) Reduction of HMG CoA, Hydroxylation at carbon number 12.

2) Which one of the following statements is incorrect?

A) Cholesterol consists of 3 hexose rings and 1 pentose ring.
B) The cholesterol which is synthesized from extrahepatic tissues is transformed to the liver in the form of HDL whereas the dietary cholesterol is transported as chylomicrons remnants.
C) We can't use cholesterol as a source of energy by degrading it.
D) The rapid cleavage of CoA triggers the condensation of FPP in the forward reaction.

3) How many ATP and NADPH are consumed for the synthesis of 3 molecules of Squalene from Acetyl CoA?

A) 54 ATP and 36 NADPH
B) 54 ATP and 39 NADPH
C) 18 ATP and 36 NADPH
D) 18 ATP and 39 NADPH

Answers:

1) C.
2) D; because the rapid hydrolysis of pyrophosphate triggers the condensation in the forward reaction.
3) B ; Squalene consists of 30 carbons that are derived from 2 FPP , each FPP requires 2 IPP and 1 DMP (5 carbon molecules) , each 5 carbon molecule of them is derived from Mevalonate by consuming 3 ATP, so 1 FPP needs 9 ATP , and 1 Squalene need 18 ATP , so for 3 Squalene molecules we consume 18*3= 54.
   2NADPH are consumed during the reduction of HMG CoA to a Mevalonate , and as we need 6 Mevalonate molecules for each Squalene so we consume 12 NADPH , for 3 Squalene molecules it requires 36 NADPH, but each 2 FPP converted to 1 Squalene consume 1 NADPH , for three molecules we consume 3 NADPH so the result is 39 NADPH.

Send me your feedback as this is the first sheet for me, good luck and much love <3

THE END