27

◉Sheet ○Slides

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*In the 1st part of this lecture, we're going to discuss **Sphingolipids Metabolism***

Please refer back to the slides for the given pictures/figures

In the beginning, let's revise some important structural information:

* Sphingosine that is bound to a fatty acid by an amide bond = **Ceramide**

* Ceramide joined to phosphocholine= **Sphingomyelin**

- **Remember: Glycolipids are formed by linking one or more sugars to ceramide.**

If there's no phosphate, i.e. only sugars, we have several classes:

* **Cerebrosides**: one sugar (monosaccharide) – can be glucose or galactose.

* **Globosides**: oligosaccharides bound to ceramide

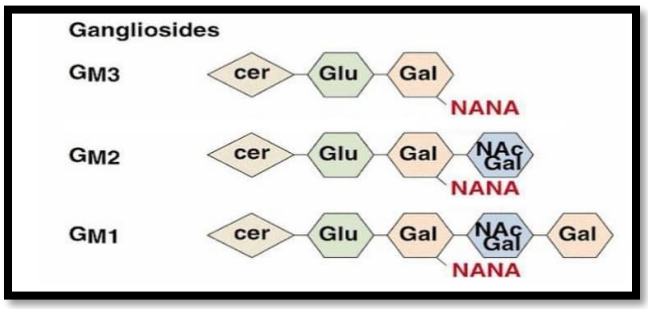
Note that glycolipids do not contain phosphate

* **Sulfoglycosphingolipids:** Sulfated Galactose bound to ceramide

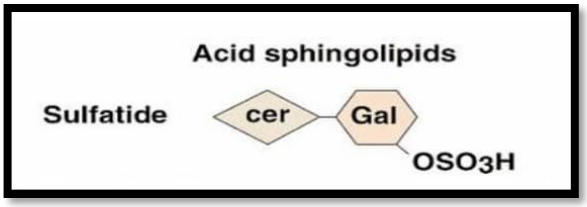
* **Gangliosides**: Contain N-Acetylneuraminic acid (NANA) in addition to the ceramide.

> Neuraminic acid: An acidic amino sugar with a backbone formed by nine carbon atoms, by which the $–CH_2OH$ at position 1 is oxidized into a carboxyl group (–C(=O)OH).

- Gangliosides are commonly known by the abbreviations (GM1, GM2,GM3): G: Stands for ganglioside. Thus, gangliosides by definition should contain N-Acetylneuraminic acid. Otherwise, they will be considered as globosides.



- ✓ If they have only one N-Acetylneuraminic, we add the letter M, i.e. mono.
- ✓ The numbers 3-1 refer to the sequence.
- ✓ Note that the numbers are given according to the degradation pathway, by which 2 is produced from 1 during degradation and 3 is produced from 2, that's why 3 has the shortest oligosaccharide chain.



* **Sulfate groups may be added, and their presence indicates a strong acid (negative charge) = Acidic or Anionic Glycolipids.**

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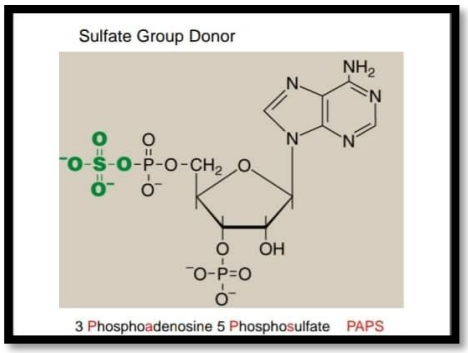
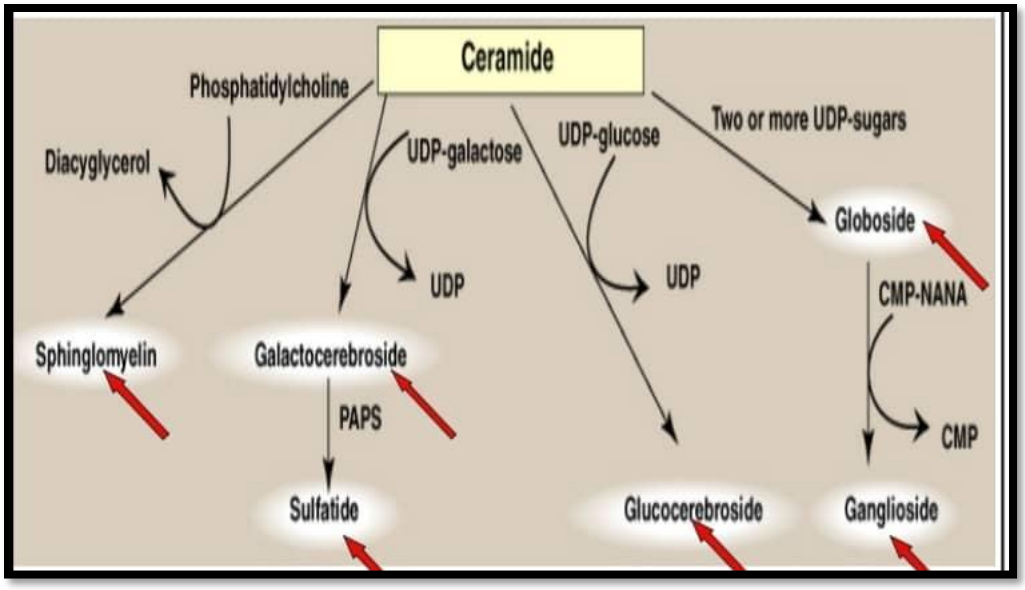
*The sulfate donor in the biosynthesis of sulfolipids or **Glycosaminoglycans** that contain sulfated sugars is "PAPS" = **3PHOSPHOADENOSINE 5 PHOSPHOSULFATE**



It reminds us with ADP, but instead of the phosphate there's a sulfate group.

***Activated Donors in Glycolipids Synthesis:**

- UDP-Glucose
- UDP-Galactose
- UDP-N-Acetylgalctoseamine
- CMP- N-Acetylneuraminic Acid



***Degradation of sphingolipids**

- Degradation of sphingolipids is more important than their synthesis, because their synthesis proceeds in every cell. Moreover, no defect has been identified in the synthesis of glycolipid, but there's a defect in the degradation of sphingolipids.

- Degradation of sphingolipids occurs in the lysosomes due to the presence of hydrolytic enzymes; each is specific for the sugar it removes and to the glycosidic bond it cleaves. It's not only one hydrolytic enzyme that removes all sugars, instead, each sugar is removed (degraded) by an enzyme.

- **Glycolipids in general are found in the outer leaflet of the plasma membrane and they undergo continuous balanced takeover (synthesis & degradation), but their degradation is very slow and occurs for the regeneration of the membranes after endocytosis (where parts of the membranes are taken).**

***Examples of the hydrolytic enzymes include:**

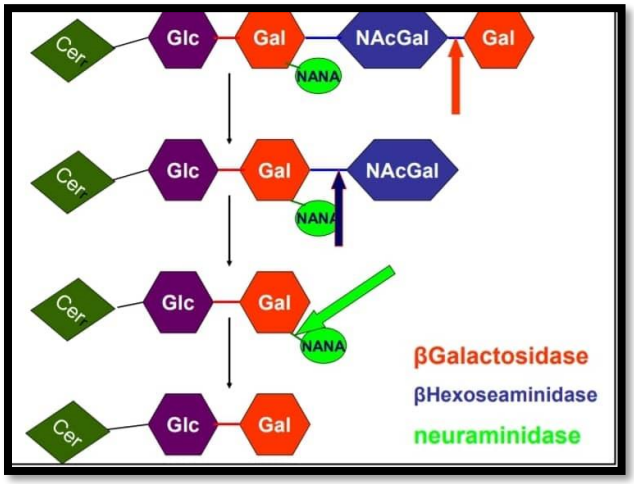
- α Galactosidase
- β Galactosidase
- Neuraminidase: For **Neuraminic Acid.**
- Hexoaminidase: For **N-Acetylglucosamine** or **N-Acetylgalactosamine**

❖ These enzymes cannot escape the lysosome because they're firmly (tightly) bound to the lysosomal membrane. Otherwise, they'll degrade other constituents in the cell.

❖ The pH Optimum is 3.5-5.5, which is the same pH found in the lysosome. Thus, they are not active in the cytoplasm due to its basic /alkaline pH.

❖ The degradation occurs by stepwise sequential process, i.e. one by one., and the last sugar that was added during synthesis is the first sugar that is going to be degraded- "Last on, First off".

In the figure:



The first glycolipid is **GM1 (the one with the longest oligosaccharide chain).**

✓ Galactose is removed by **β Galactosidase**, producing GM2.
✓ N-Acetylgalactosamine is removed by **β Hexoseaminidase**, producing GM3.
✓ **Neuraminidase** catalyzes the removal of N-Acetylneuraminic acid.

*Sphingolipidoses:

- Sphingolipidoses are group of diseases. The termination (ses) refers to a disease state. When they were first identified, they were called “lipid storage diseases” because they thought that the presence of lipids is the storage form, but in fact they’re present in the lysosomes for degradation not as a storage form. Thus, the nomenclature has changed.

- Sphingolipidoses result from a defect in one of the hydrolytic enzymes, which leads to the accumulation of a lipid that is the substrate of the defected enzyme.

- They’re inherited as autosomal recessive diseases, i.e. they don’t appear if an individual has only one defected allele from one parent , because having one normal gene is sufficient for preventing the occurrence of the disease, and this can be understood by the fact that the process of degradation is a very slow process, and even having 10% of the enzyme activity could be sufficient for preventing the appearance of the disease.

- The disease occurs when the enzymatic activity is almost zero.

- The brain is mostly affected because the accumulation of lipids in the cell leads to its destruction. Moreover, once the neuronal cell is damaged, it cannot be replaced. So, the individual might be born normal, but with time the accumulation occurs, and the disease starts to appear.

- The manifestations of the CNS include mental retardation and movement problems.

- The Extent of Enzyme deficiency is the same in different tissues, but the generation of neuronal tissues isn’t the same as other tissues. Once they’re destructed, they cannot be replaced.
  This is important for the diagnosis: we can take a cell sample from different tissues and measure the enzyme activity to diagnose the condition.

***Degradation of Sphingomyelin:**

- ✓ Sphingomyelin is degraded by sphingomyelinase, that converts sphingomyelin into ceramide and phosphocholine.

- ✓ Ceramide is degraded by ceramidase that hydrolyzes the fatty acid to produce sphingosine.

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*The diseases that we have to know are the ones inside the red boxes in the slides. I will write their details in the next page:

***TAY-SACHS DISEASE:**

- It is a classic example of lipidoses that affects Jewish population (Because of marriage among relatives and the same ethnic groups).
- Accumulation of gangliosides (GM2)
- Rapid, progressive, and fatal neurodegeneration.
- Blindness, cherry-red macula, muscular weakness and seizures.
- Deficiency of activator protein (GM2 ACTIVATOR) in some cases

***GAUCHER DISEASE:**

- **The most common lysosomal storage disease**
- Accumulation of glucocerebrosides. Causes hepatosplenomegaly, osteoporosis of long bones.
- CNS involvement in rare infantile and juvenile forms, enzyme replacement therapy can be used.

***FARBER DISEASE:**

- Accumulation of ceramide
- Painful and progressive joint deformity
- Subcutaneous nodules of lipid-laden cells, hoarse cry, tissues show granulomas

***NIEMANN-PICK Disease (A+B)**

- Accumulation of sphingomyelin. Causes hepatosplenomegaly, cherry-red macula
- Neurodegenerative course (type A)

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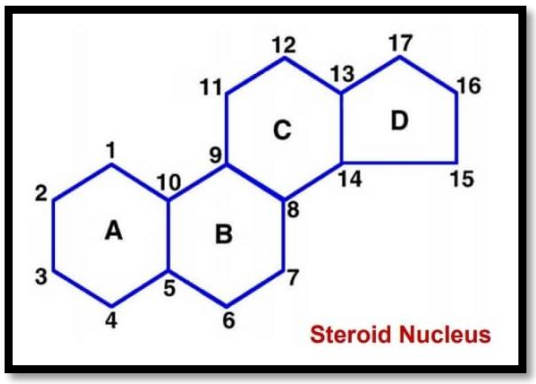
*In the 2nd (last) part of this lecture, we're going to discuss **cholesterol metabolism***

CHOLESTREOL

- CHOLE:RELATED TO THE GALLBLADDER
  - CHOLECYSTITIS: التهاب المرارة
  - Cholesterol was isolated first in the gallbladder
- STER: STEROID
- OL: ALCOHOL

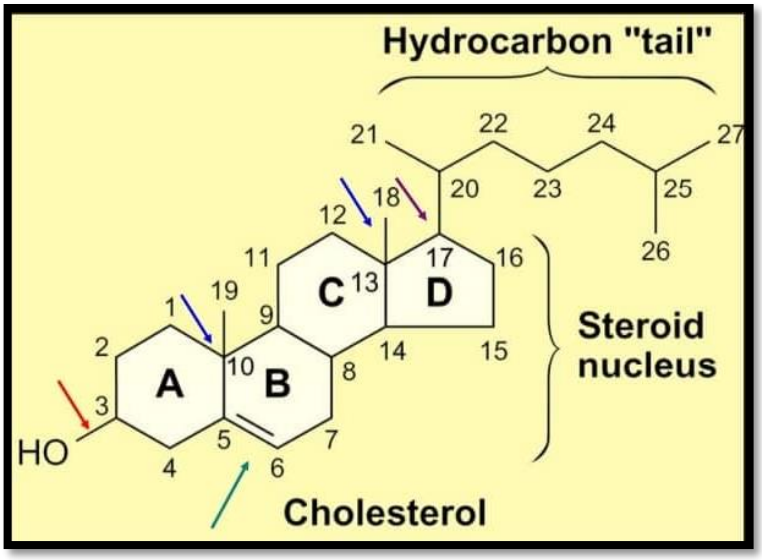


- ✓ The steroid nucleus is made of four rings: 3 of them are six-membered rings
  - The 4th is a 5-membered ring.
- ✓ The total number of carbon atoms in the steroid nucleus is 17.
  The steroid nucleus is found in all steroids.
- ✓ **Note: Numbering is very important.**
  We are required to know the structure of cholesterol by numbers.

***Cholesterol structure:**

- A steroid nucleus containing 17 carbons. In addition, there are 2 methyl groups attached to carbons 10 and 13 and given the numbers 19 and 18 respectively.
- 8-hydrocarbon chain
- The total number of carbon atoms in Cholesterol is (17+2+8)= 27
- Cholesterol has a hydroxyl group attached to carbon #3.

- A double bond between carbon #5 & #6.
- The total number of carbon atoms is 27.



- **The methyl group can be represented by a solid line (found in one region/part/side of the steroid nucleus/either cis or trans/in the front) or dashed line.**

- Cholesterol is formed only from carbon and hydrogen, except for the only oxygen atom that is attached to carbon #3. Thus, it's a non-polar/hydrophobic molecule and is also insoluble in water. The only hydrophilic group is the hydroxyl group and it isn't sufficient for making it soluble.

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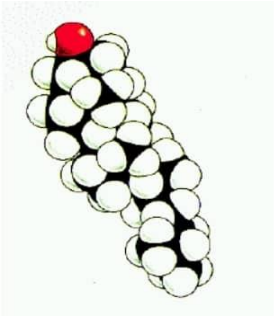
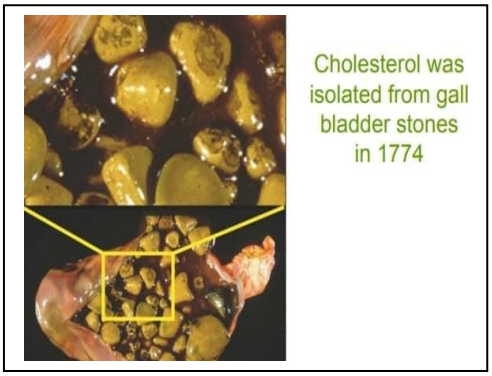
- This is a space filling model that represents the atoms of cholesterol. It looks like a small rod that has the hydroxyl group at the tip.
- Cholesterol is found as a membrane component in all animal cells. **Plant cells do not contain cholesterol.**



❖ This photo represents gallbladder stones that are made of cholesterol.

Cholesterol tends to precipitate (because it's insoluble in water), and the presence of phospholipids and bile salts prevents it from precipitation. If an imbalance occurs, cholesterol will precipitate forming the gallbladder stones then the gallbladder must be removed surgically (cholecystectomy). And the flow of bile becomes continuous.



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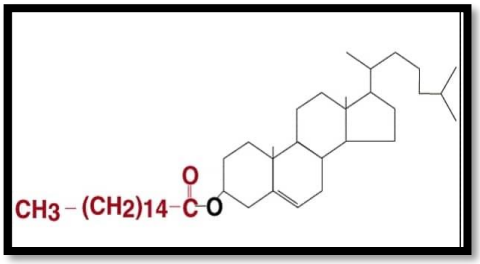
- Cholesterol joined to a fatty acid = **cholesterol ester** (even more hydrophobic and less soluble in water). It's completely non-polar.

*Cholesterol ester is the storage form of cholesterol. It's found in the interior (core) of lipoproteins, whereas the free cholesterol is found on the surface of the lipoproteins due to the presence of a hydroxyl group that can interact with water.



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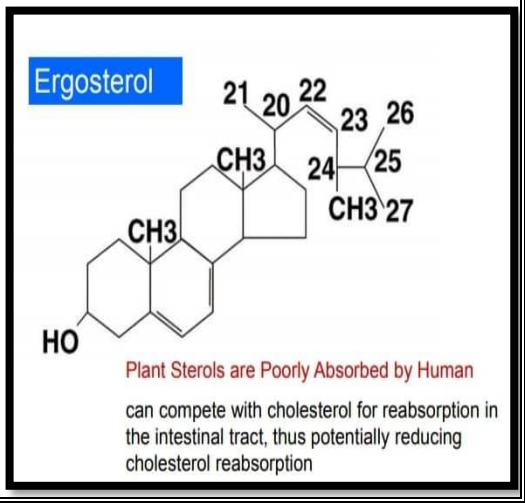
*Sources and Elimination of Cholesterol:

- The fact that cholesterol is found in all animal cells reflects its importance to the cells.
- The body can synthesize daily 1000 mg of cholesterol, mainly in the Liver, Small Intestine, Adrenal Cortex.
- All cells are capable of synthesizing cholesterol, but by regulation most cells do not produce it because they get it already made.
- Cholesterol is the starting material for synthesis of steroid hormones.
- The dietary source is roughly 300 mg in low cholesterol diet. (one egg contains approximately 250 mg!).
- The elimination of cholesterol occurs via the bile, cholesterol isn't oxidized to produce energy. It's not a source of energy, it's degraded as such to bile acids/salts, and can be excreted as cholesterol in bile.

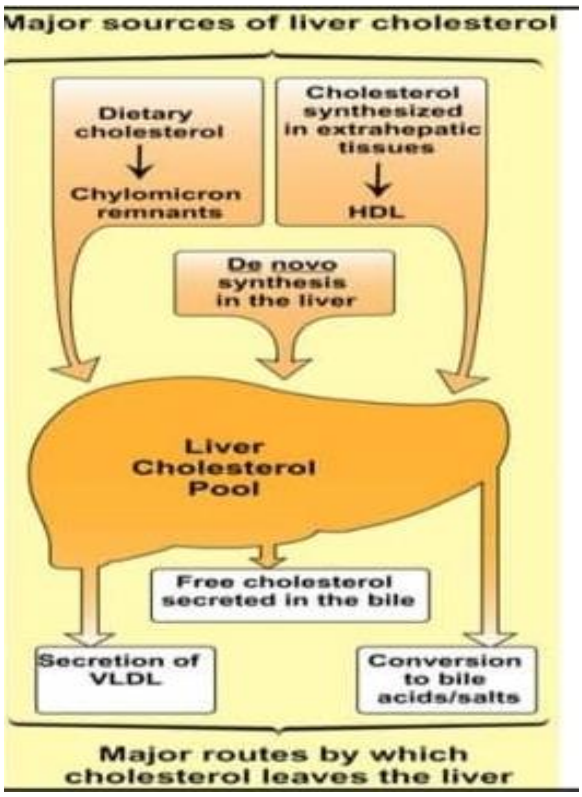
- ***This is not cholesterol. Ergosterols are plant sterols.**

- Plants do not synthesize cholesterol, meaning that any food derived from plant origin doesn't contain cholesterol.
- Plant sterols are poorly absorbed by humans and help in reducing the cholesterol level. They can be eliminated from the intestines along with the cholesterol.



The liver is the central organ for the metabolism of cholesterol

Chylomicrons carry triacylglycerol and cholesterol to different tissues, and what remains >>> 'Chylomicron Remnants' are taken by endocytosis by liver. Cholesterol is also transported from other tissue when they have excess cholesterol (e.g. Dead cells), HDL carry the cholesterol back to the liver. In the liver, DE NOVO Synthesis (synthesis from scratch/from the beginning) occurs. The liver exports cholesterol by VLDL, free cholesterol is secreted in the bile and cholesterol is converted into bile acids/bile salts and also excreted in the bile.



What is the food that is very rich in cholesterol?

-Liver of animals: الكبدة

-Eggs

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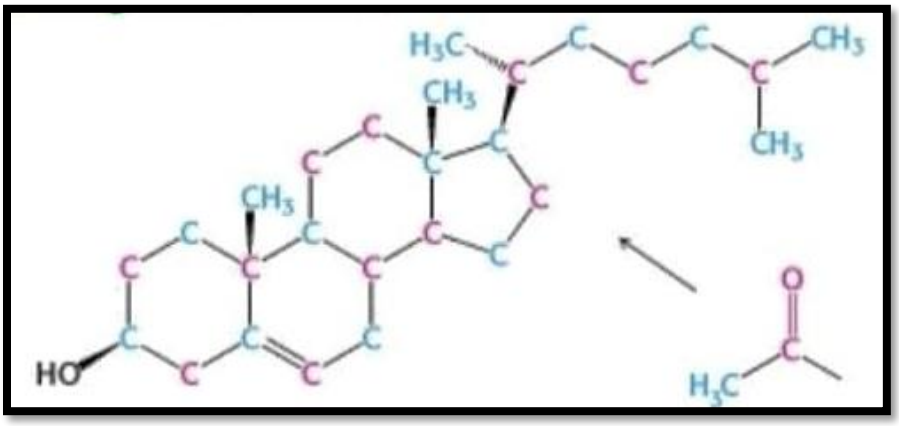
*Cholesterol Synthesis Requirements:

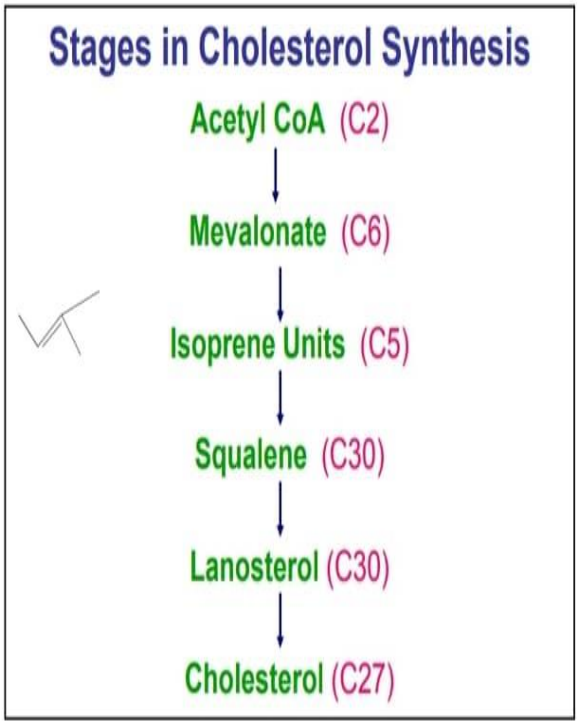
- The source of all carbon atoms in cholesterol is Acetyl Co-A
- The scientists were able to determine whether each carbon comes from the carboxyl carbon or from the methyl.
- Energy is required in the form of ATP. (WE ARE JOINING MOLECULES TOGETHER.THUS, WE NEED ENERGY).
- Reducing Power: NADPH, because the end product is very highly reduced compared with the acetyl CoA.
- The same requirements of fatty acid synthesis, but the two pathways are certainly different.

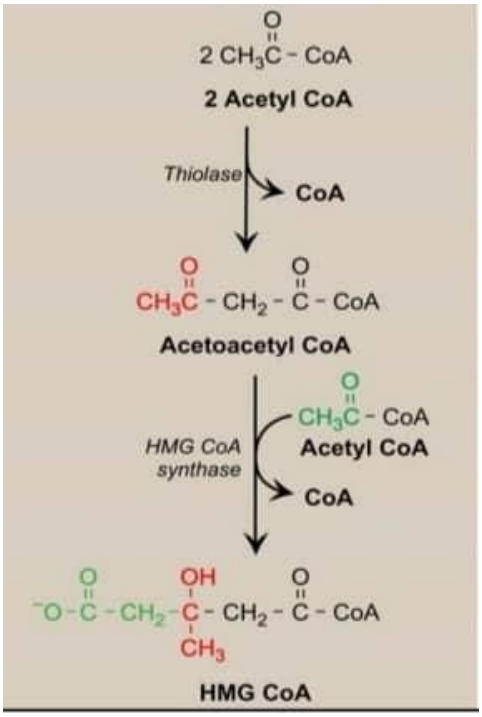
- Molecular oxygen is required only one oxygen molecule is required to add the oxygen atom in the hydroxyl group.



- Three Acetyl CoA are condensed to produce Mevalonate.
- 6-Carbon Compound Mevalonate will be activated, decarboxylated producing isoprene units.
- 6 isoprene units are condensed to produce Squalene which is converted to lanosterol then to cholesterol.

- The first two reactions are similar to those in ketone bodies synthesis, except that these reactions occur in the cytoplasm whereas they occur in the mitochondria in the case of ketone bodies synthesis.

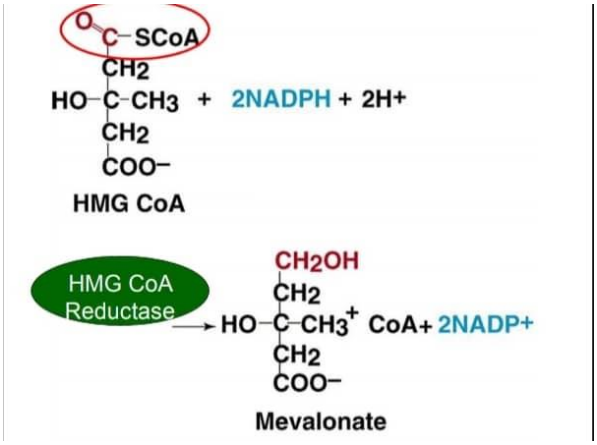




- The next step involves the reduction of carboxyl group to hydroxyl. (REMEMBER THAT THE REDUCTION OF CARBOXYL RESULTS IN ALDEHYDE THEN ALCOHOL=TWO REDUCTION STEPS).

- **HMG – Hydroxymethylglutarate- IS A DICARBOXYLIC ACID. One of the carboxyl groups is joined to CoA.**

- **Mevalonate results from the reduction of** HMG. The name of the enzyme is **HMG-CoA Reductase**- (one-way reaction)/ not reversible/ it's not a way of getting NADPH FROM NADP+.
- Being irreversible, it's a committed step in cholesterol synthesis: once we reach Mevalonate, we cannot go back.
- The committed step is usually a rate limiting step and is highly regulated.
- **This is the most important enzyme in cholesterol synthesis.**



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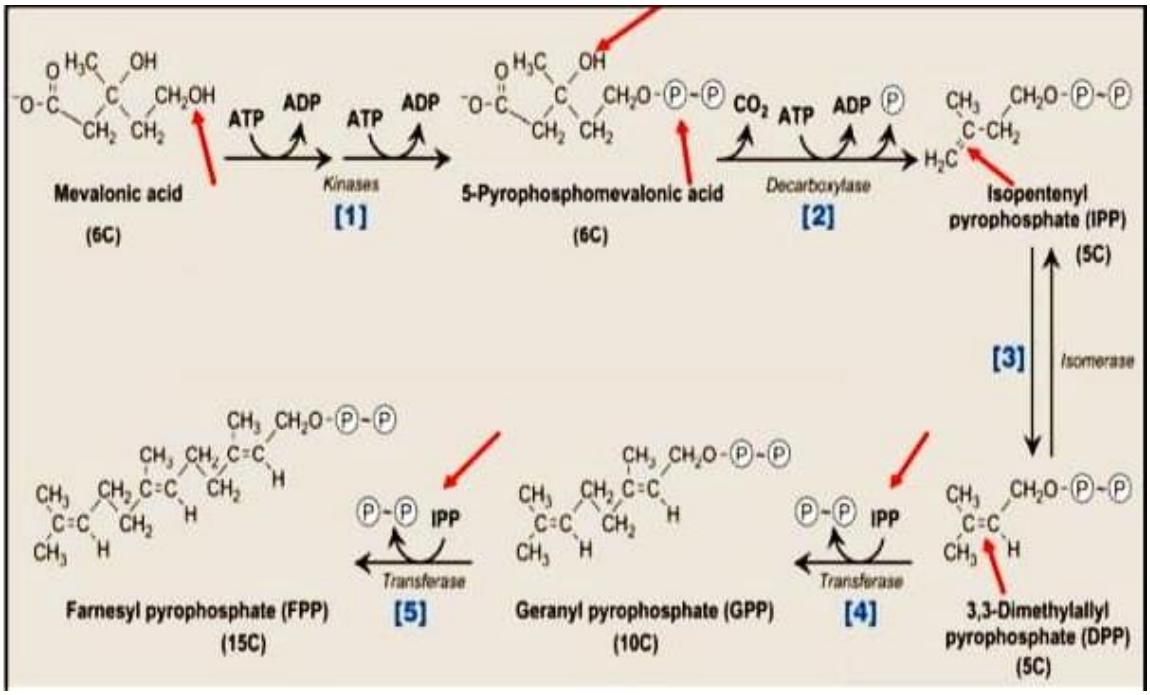
- Mevalonic Acid or Mevalonate can be activated by adding two phosphates to the hydroxyl group. One phosphate is added from ATP, the other phosphate is added from another ATP, producing pyrophosphomevalonic acid. Then, Pyrophosphomevalonic acid undergoes decarboxylation in an ATP-Requiring Reaction producing Isopentenyl Pyrophosphate (IPP).
- Isopentenyl Pyrophosphate (IPP): 5-CARBON COMPOUND, related to Isopentane, ene<< because of the double bond, with a hydroxyl group attached to the pyrophosphate.

- Condensation of Isopentenyl Pyrophosphate (IPP) and ***Dimethylallyl* pyrophosphate** (DPP) produces **Geranyl pyrophosphate** (GPP), a 10-Carbon compound.
- The release of pyrophosphate drives the reaction in the forward direction.
- One more Isopentenyl Pyrophosphate (IPP) is added, resulting in Farnesyl Pyrophosphate (FPP)
- The condensation of two FPPs now occurs head to head with reduction, resulting in Squalene.
- Squalene is a hydrocarbon that is made only from carbon and hydrogen, it is similar to the hydrocarbons that are present in oils. Synthesis of Squalene occurs in the body during the synthesis of something like CoQ10.
- CoQ10== Contains 10 units= 50 carbons
- Squalene=== six units = 30 carbons
- Rubber Tree synthesize rubber in a a similar pathway.



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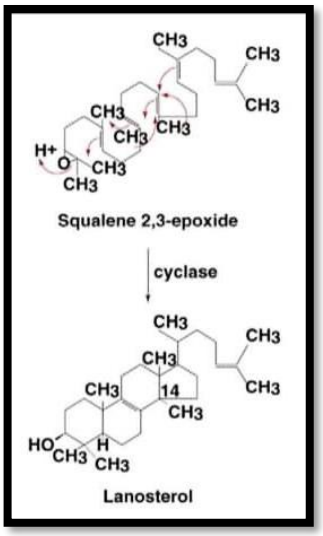
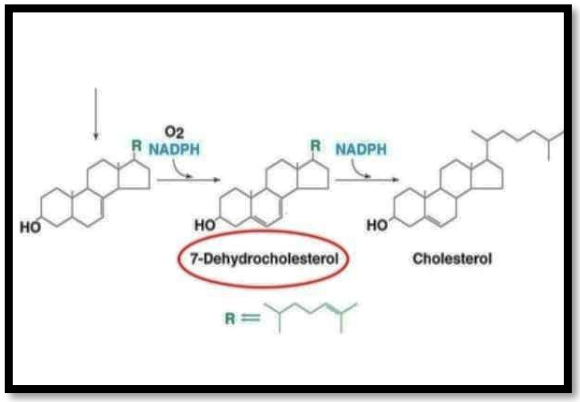
- **The next step involves adding oxygen to carbon #2 and #3 resulting in Squalene 2,3- epoxide that is unstable because the oxygen is connected to two adjacent carbons making the angle 60°.
- Squalene is converted into lanosterol.
- Several steps will convert lanosterol into different intermediates until we reach cholesterol.



- **The very last step involves 7-Dehydrocholesterol, the precursor of vitamin D.**
- **<u>7-Dehydrocholesterol</u> is converted into <u>vitamin D</u> by a photoactivated reaction, when we're exposed to ultraviolet sunlight. This is possible in humans.**



THE END

MAY GOD BLESS YOU ALL