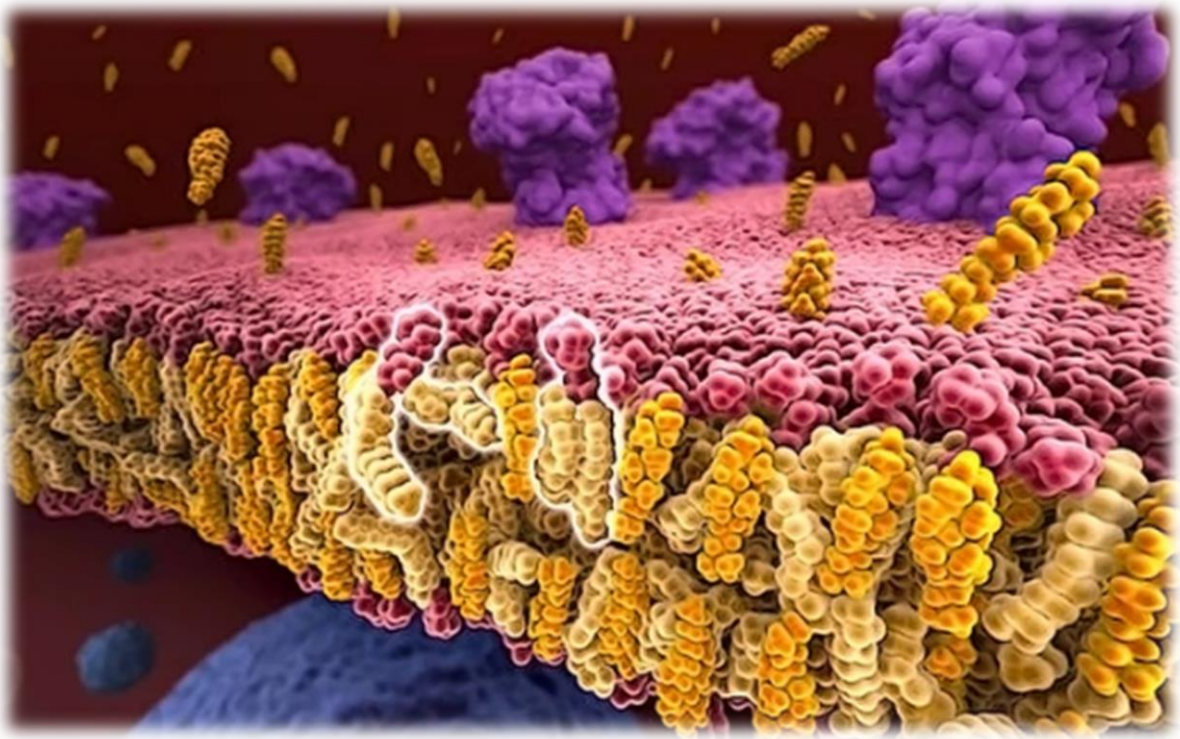
Lipids Metabolism



Lipids are a family of biomolecules that have the common property of being soluble in organic solvents, like ether or chloroform, but not in water. They serve multiple purposes in the body, such as storing energy, protecting and insulating internal organs, and acting as chemical messengers. Because they are not soluble in water, lipids are also important components of cellular membranes that function to separate the internal contents of cells from the external environment.

Unlike the polysaccharides, proteins and nucleic acids, lipids are not polymers. Further, lipids are mostly small molecules.

Classification of lipids

Lipids are broadly classified into simple, complex, derived and miscellaneous lipids.

1. Simple lipids : Esters of fatty acids with alcohols. These are mainly of two types

(a) Fats and oils (triacylglycerols) : These are esters of fatty acids with glycerol.

The difference between fat and oil is only physical. Thus, oil is a liquid while fat is a solid at room temperature.

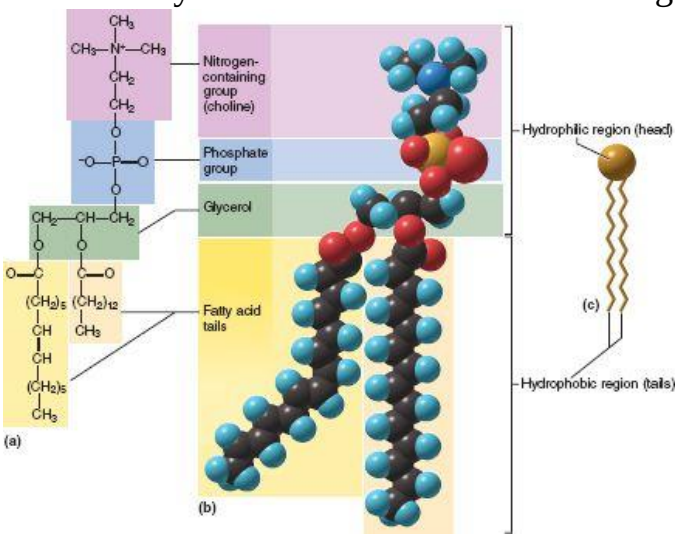
(b) Waxes : Esters of fatty acids (usually long chain) with alcohols other than glycerol. Waxes are used in the preparation of candles, lubricants, cosmotics, ointments, polishes etc.

2. Complex (or compound) lipids : These are esters of fatty acids with alcohols containing additional groups such as phosphate, nitrogenous base, carbohydrate, protein etc.

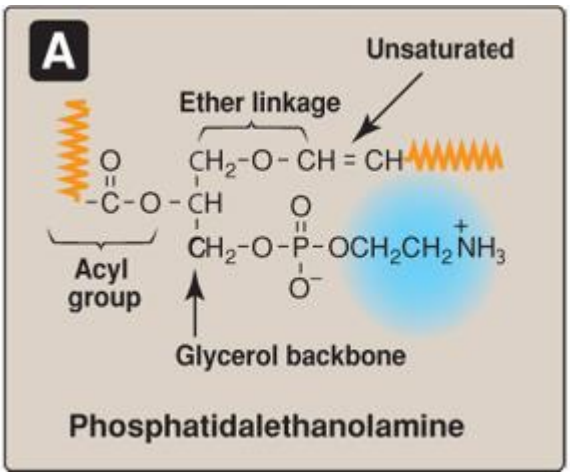
They are further divided as follows

(a) Phospholipids : They contain phosphoric acid and frequently a nitrogenous base. This is in addition to alcohol and fatty acids.

(i) Glycerophospholipids: These phospho- lipids contain glycerol as the alcohol e.g., lecithin, cephalin (figure A).



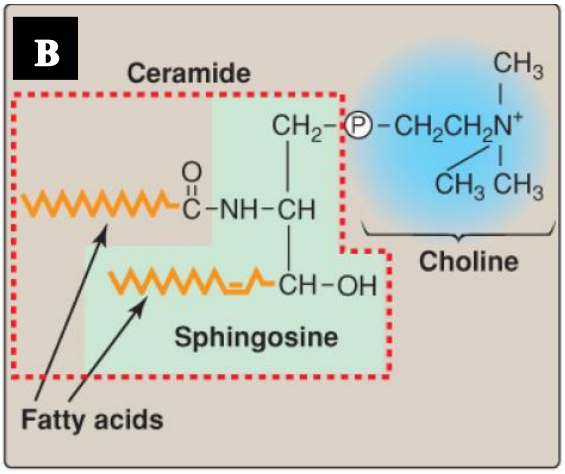
(ii) Sphingophospholipids : Sphingosine is the alcohol in this group of phospho- lipids e.g., sphingomyelin (figure B).



(b) Glycolipids : These lipids contain a fatty acid, carbohydrate and nitrogenous base.

The alcohol is sphingosine, hence they are also called as glycosphingolipids. e.g., cerebrosides, gangliosides.

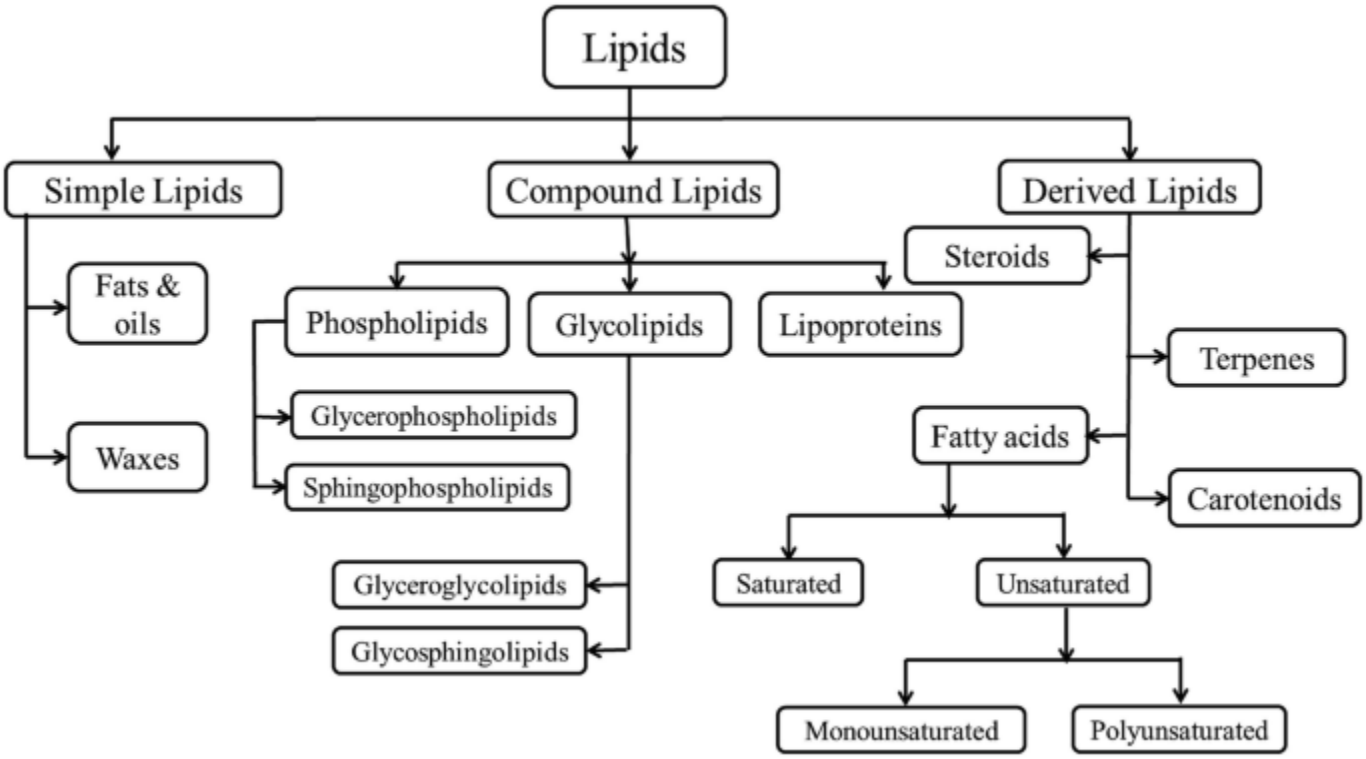
(c) Lipoproteins : Macromolecular complexes of lipids with proteins.



(d) Other complex lipids : Sulfolipids, amino- lipids and lipopolysaccharides are among the other complex lipids.

3. Derived lipids : These are the derivatives obtained on the hydrolysis of group 1 and group 2 lipids which possess the characteristics of lipids. These include glycerol and other alcohols, fatty acids, mono- and diacylglycerols, lipid (fat) soluble vitamins, steroid hormones, hydro- carbons and ketone bodies.

4. Miscellaneous lipids : These include a large number of compounds possessing the characteristics of lipids e.g., carotenoids, squalene, hydrocarbons such as pentacosane (in bees wax), terpenes etc.



Metabolism of lipids

In both animals and plants, the excessive fat is stored in various parts of the body in large quantities in the form of neutralized and insoluble triglycerides (fat). It decomposes and quickly destroys to provide energy necessary for the cell.

Fat has an important role in nutrition, because it has a high energy value (9.3 kilocalories per gram)

Oxidation (catabolism) of fatty acid

The main path to catabolize fatty acid is β-oxidation. β-Oxidation may be defined as the **oxidation of fatty acids on the β-carbon atom**. This results in the sequential removal of a two carbon fragment from the carboxyl end of the fatty acyl CoA, producing acetyl CoA, NADH, and $FADH_2$. β-oxidation of fatty acid are performed within mitochondrial matrix which contains all the enzymes and coenzymes necessary for catabolism.

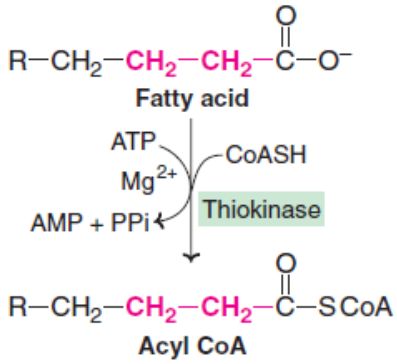
The β-oxidation of fatty acids involves three stages

I. Activation of fatty acids occurring in the cytosol

Fatty acids are found in the cytoplasm in their inactive raw form, so they must be activated in the cytoplasm before they enter the mitochondrial matrix. This is the only step in the complete degradation of a fatty acid that requires energy

from ATP. In the presence of ATP and coenzyme A, the enzyme acyl-CoA synthetase (thiokinase) catalyzes the conversion of a fatty acid (or FFA) to an "active fatty acid" or acyl-CoA, using ATP and forming AMP and PPi.

$$\text{Fatty acid} + \text{CoA} + \text{ATP} \rightleftharpoons \text{fatty acyl–CoA} + \text{AMP} + \text{PP}_i$$



II. Transport of long-chain fatty acids into mitochondria

The inner mitochondrial membrane is impermeable to fatty acids. A specialized

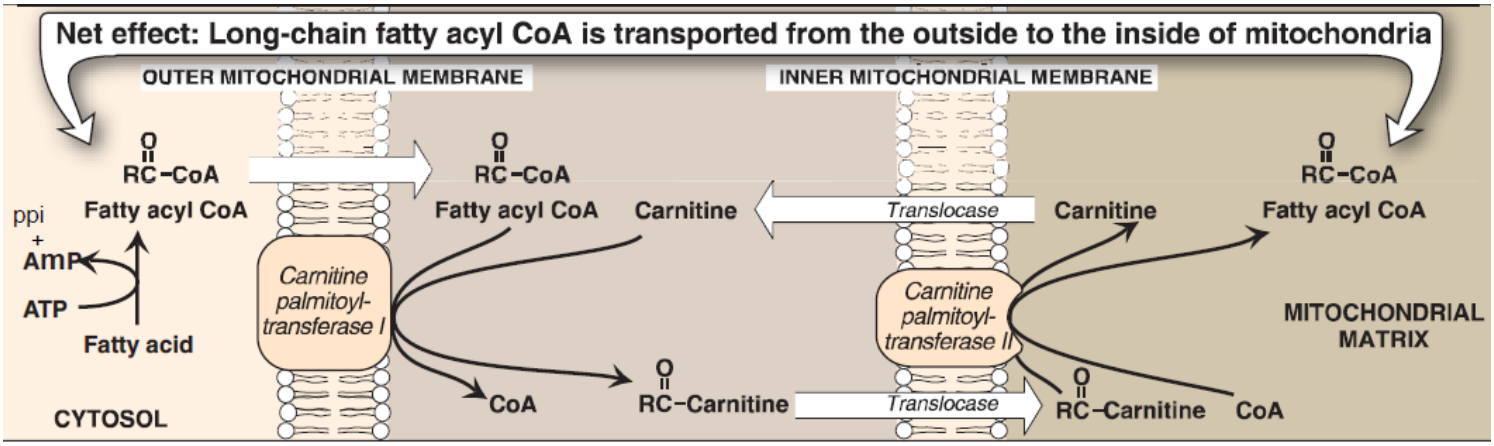
carnitine carrier system (**carnitine shuttle**) operates to transport activated fatty acids from cytosol to the mitochondria. This occurs in **four** steps (figure 1)

1. Acyl group of acyl CoA is transferred to **carnitine** (β-hydroxy γ-trimethyl aminobutyrate), catalyzed by carnitine acyltransferase I (present on the outer surface of inner mitochondrial membrane).

2. The acyl-carnitine is transported across the membrane to mitochondrial matrix by a specific carrier protein.

3. Carnitine acyl transferase II (found on the inner surface of inner mitochondrial membrane) converts acyl-carnitine to acyl CoA.

4. The carnitine released returns to cytosol for reuse.



[(figure 1) carnitine shuttle for transport of activated fatty acid (acyl CoA) into mitochondria]

III. β-Oxidation proper in the mitochondrial matrix.

Each cycle of β-oxidation, liberating a two carbon unit-acetyl CoA, occurs in a sequence of four reactions (**Fig.2**).

1. **Oxidation :** Acyl CoA undergoes dehydrogenation by an FAD-dependent flavoenzyme, acyl CoA dehydrogenase. A double bond is formed between β and α carbons (i.e., 2 and 3 carbons).

2. **Hydration :** Enoyl CoA hydratase brings about the hydration of the double bond to form β-hydroxyacyl CoA.

3. **Oxidation :** β-Hydroxyacyl CoA dehydrogenase catalyses the second oxidation and generates NADH. The product formed is β-ketoacyl CoA.

4. **Cleavage :** The final reaction in β-oxidation is the liberation of a 2 carbon fragment, acetyl CoA from acyl CoA. This occurs by a thiolytic cleavage catalysed by β-**ketoacyl CoA thiolase** (or simply thiolase).

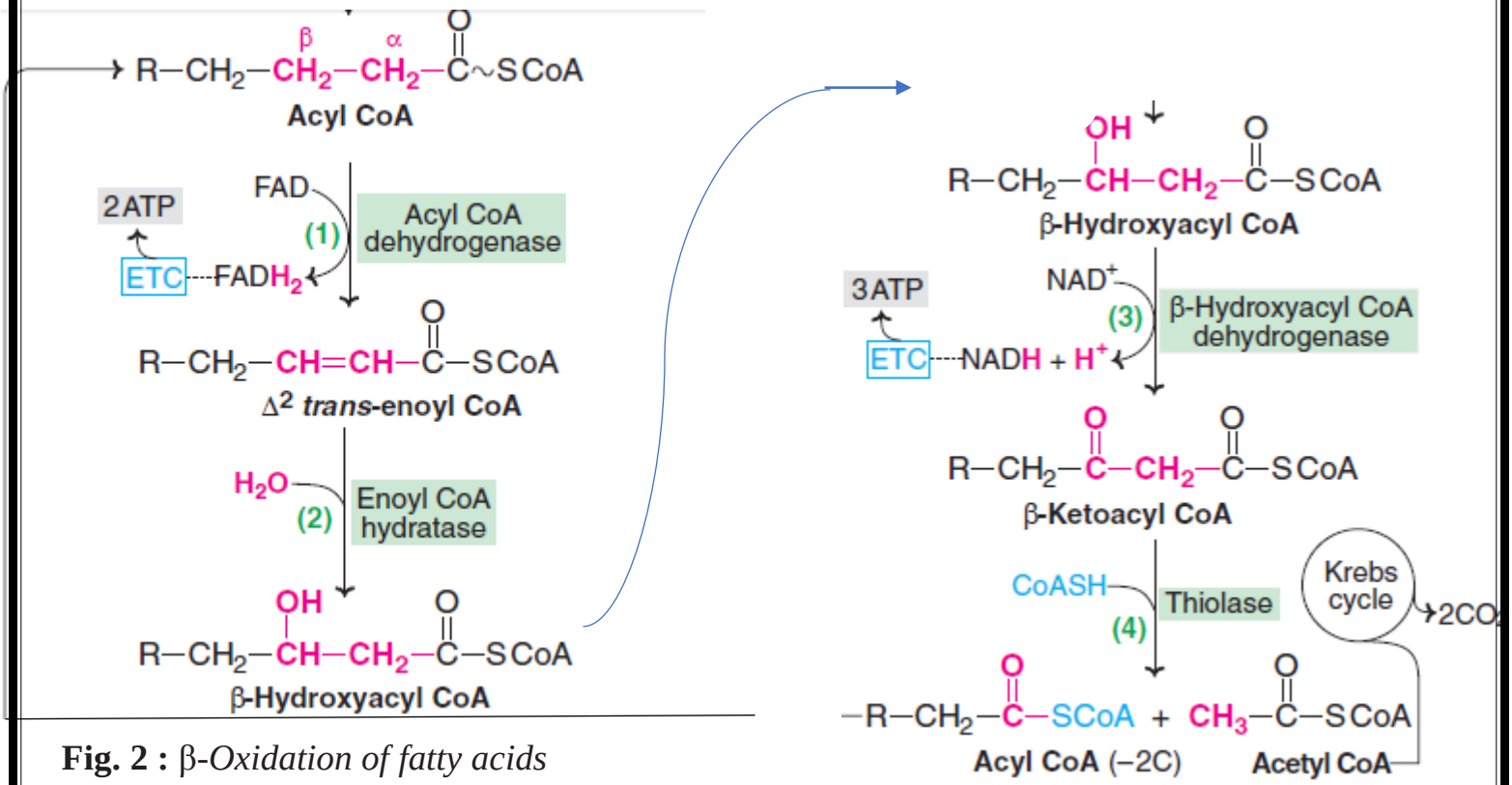
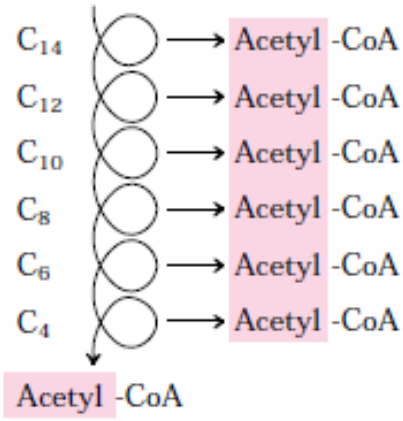


Fig. 2 : β-*Oxidation of fatty acids*

The new acyl CoA, containing two carbons less than the original, reenters the β-oxidation cycle. The process continues till the fatty acid is completely oxidized.



The overall reaction for each cycle of β-oxidation

C_n Acyl CoA + FAD + NAD^+ + H_2O + CoASH ⟶ $C_{(n-2)}$ Acyl CoA + Acetyl CoA + $FADH_2$ + NADH + H^+.

Energy yield from fatty acid oxidation

The energy yield from the β-oxidation pathway is high. For example, the oxidation of a molecule of palmitoyl CoA to CO2 and H2O produces 8 acetyl CoA, 7 NADH, and 7 FADH2, from which 131 ATP can be generated; however, activation of the fatty acid requires 2 ATP. Thus, the net yield from palmitate is 129 ATP (Figure 3)

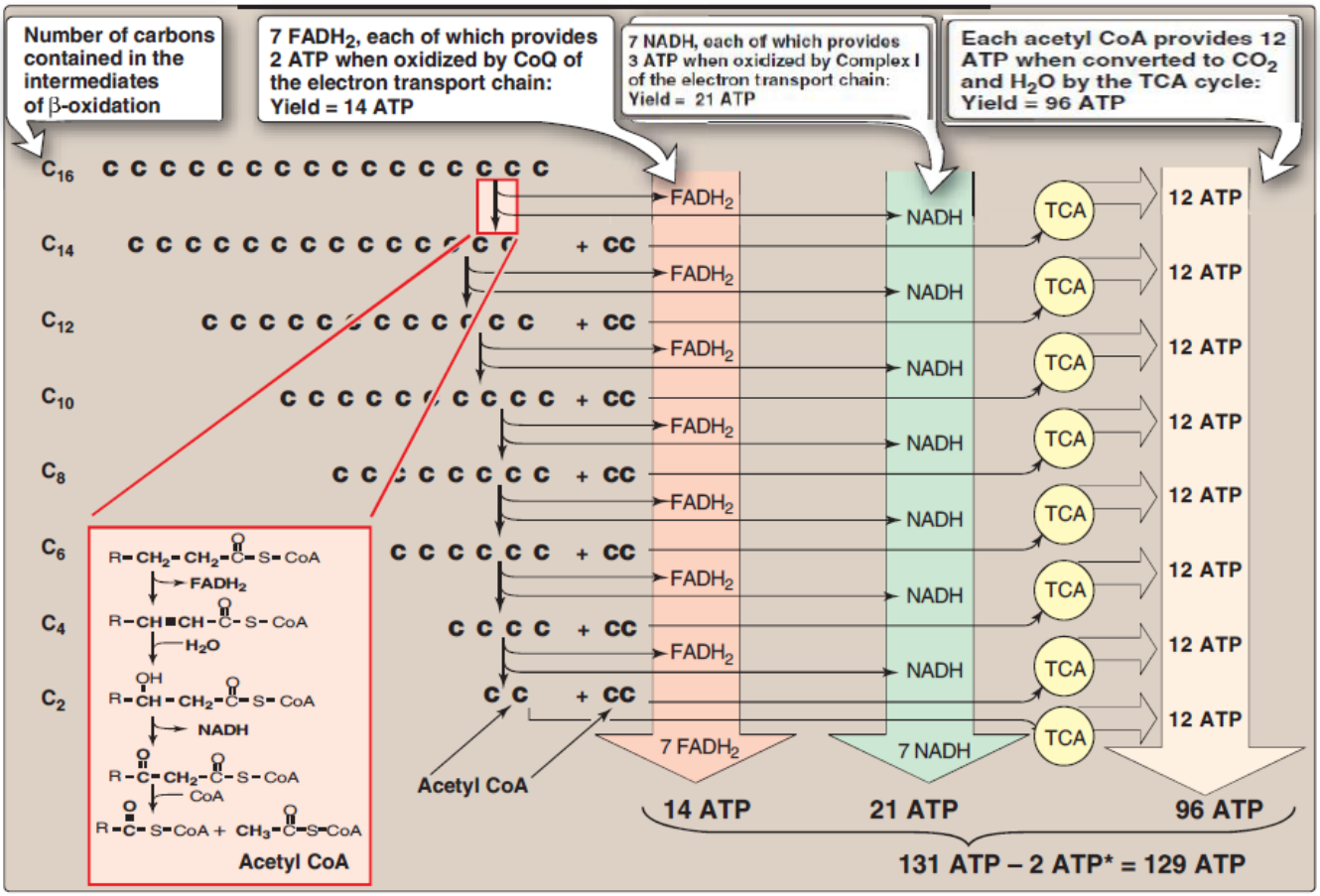


Figure (3) Summary of the energy yield from the oxidation of palmitoyl CoA (16 carbons). CC = acetyl CoA. *Activation of palmitate to palmitoyl CoA requires the equivalent of 2 ATP.

Energy calculation:

Number of round = number of carbon atom of fatty acid / 2 = 16/2= 8 round

8 rounds give 7 $FADH_2$ = 7 *2 = 14 ATP

8 rounds give 7 NADH = 7 *3 = 21 ATP

8 rounds give 8 acetyl CoA (8 TCA cycle)= 8 * 12= 96 ATP

Activation step of fatty acid consumed two ATP = - 2 ATP

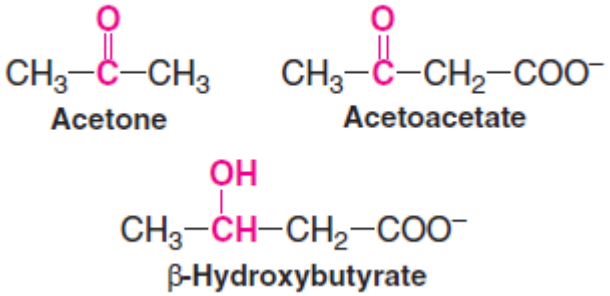
Overall net energy = 14 + 21+ 96 – 2 = 129 ATP

Ketone bodies (an alternate fuel for cells)

In humans and most other mammals, acetyl-CoA formed in the liver during **oxidation of fatty acids** can either enter the citric acid cycle or undergo conversion to the "ketone bodies,".

The compounds namely **acetone, acetoacetate** and β-**hydroxybutyrate** (or 3-hydroxybutyrate) are known as **ketone bodies** Only the first two are true ketones while β-hydroxybutyrate does not possess a keto (C=O) group.

Ketone bodies are water-soluble and **energy yielding**. Acetone, however, is an exception, since it cannot be metabolized.



Ketone bodies are formed in the mitochondrial matrix in the liver and are released from the liver to the blood, generating what is called **ketosis**, then they are transported through the blood to the surrounding tissues such as the brain, heart, kidney and muscles, where they are oxidized by TCA. ketone bodies reach the highest levels in the event of extreme hunger or eating large quantities of fat or diabetes.

Ketone bodies are important sources of energy for the peripheral tissues because:

1) they are soluble in aqueous solution and, therefore, do not need to be incorporated into lipoproteins or carried by albumin as do the other lipids.
2) serve as important sources of energy for the **peripheral tissues** such as skeletal muscle, cardiac muscle, renal cortex etc. Also during prolonged **starvation**, ketone bodies are the major **fuel source for the brain** and other parts of central nervous system.
3) The production of ketone bodies and their utilization become more benefit when glucose is in short supply to the tissues, as observed in **starvation**, and **diabetes mellitus**.

Synthesis of ketone bodies by the liver (Ketogenesis)

The synthesis of ketone bodies occurs in the **liver**. The enzymes for ketone body synthesis are located in the **mitochondrial matrix**. Acetyl CoA, formed by oxidation of fatty acids, pyruvate or some amino acids, is the precursor for ketone bodies. **Ketogenesis occurs through the following reactions** (**Fig.4**).

1. Two moles of acetyl CoA condense to form acetoacetyl CoA. This reaction is catalysed by thiolase, an enzyme involved in the final step of β-oxidation. Hence, acetoacetate synthesis is appropriately regarded as the reversal of thiolase reaction of fatty acid oxidation.
2. Acetoacetyl CoA combines with another molecule of acetyl CoA to produce β-hydroxy β-methyl glutaryl CoA (HMG CoA). **HMG CoA synthase**, catalysing this reaction, **regulates the synthesis of ketone bodies**.
3. HMG CoA lyase cleaves HMG CoA to produce acetoacetate and acetyl CoA.
4. Acetoacetate can undergo spontaneous decarboxylation to form acetone.
5. Acetoacetate can be reduced by a dehydrogenease to β-hydroxybutyrate.

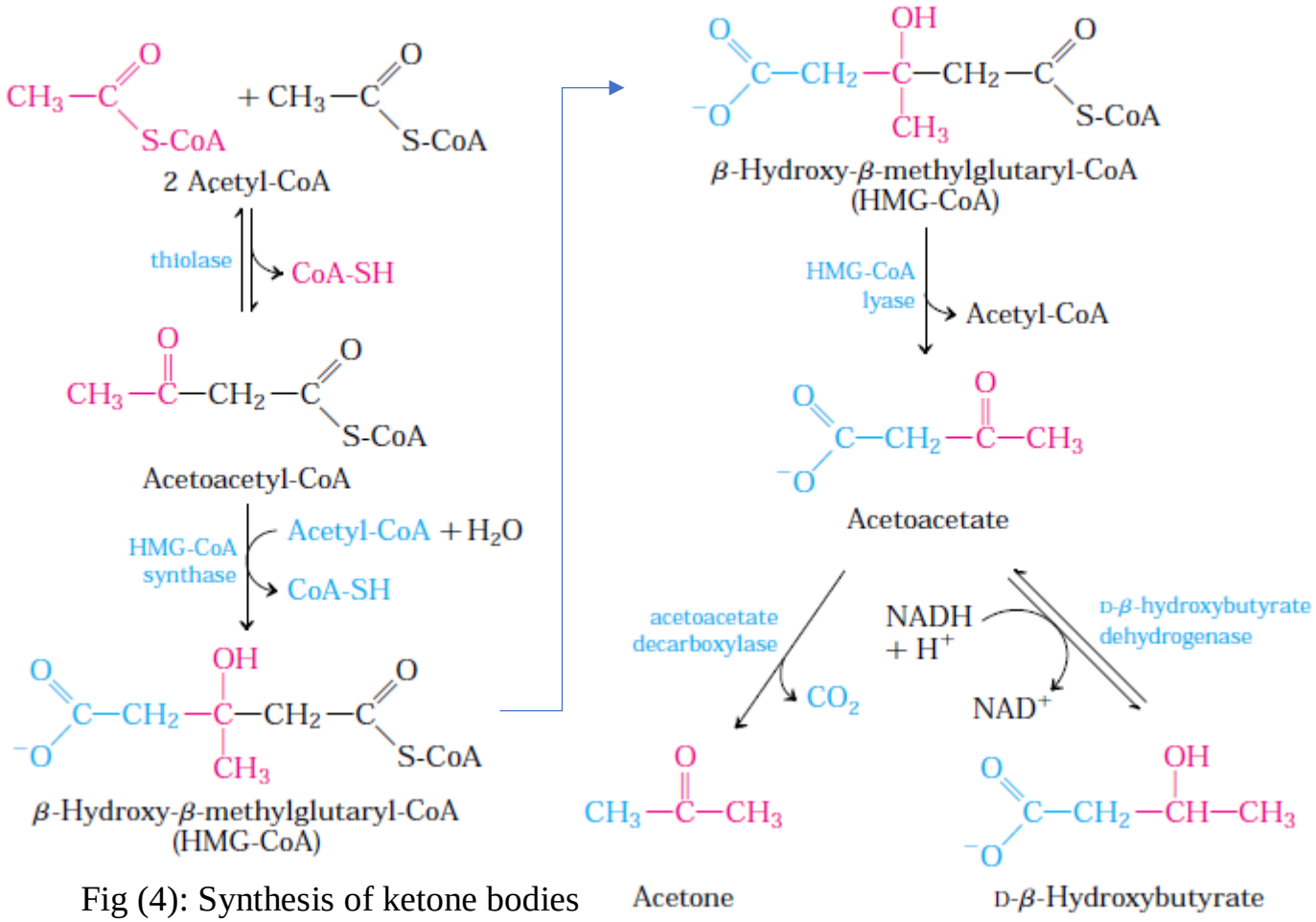
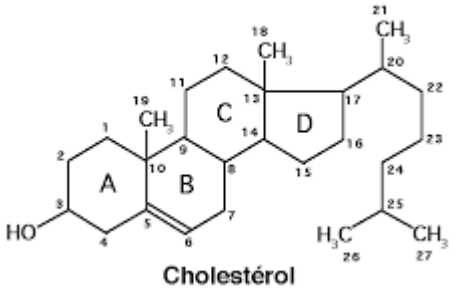


Fig (4): Synthesis of ketone bodies

Metabolism of cholesterol

Cholesterol is found exclusively in animals; hence it is often called as **animal sterol**. The total body content of cholesterol in an adult man weighing 70 kg is about 140 g i.e., around 2 g/kg body weight. Cholesterol is **amphipathic** in nature, since it possesses both hydrophilic and hydrophobic regions in the structure.



Cholestérol

Functions of cholesterol

Cholesterol is essential to life, as it performs a number of important functions

1. It is a **structural component** of cell membrane.
2. Cholesterol is the precursor for the **synthesis of all other steroids** in the body. These include steroid hormones, vitamin D and bile acids.
3. It is an essential ingredient in the structure of **lipoproteins** in which form the lipids in the body are transported.
4. Fatty acids are transported to liver as cholesteryl esters for oxidation.

Cholesterol biosynthesis

About 1 g of cholesterol is synthesized per day in adults. Almost all the tissues of the body participate in cholesterol biosynthesis. The largest contribution is made by **liver** (50%), **intestine** (15%), skin, adrenal cortex, reproductive tissue etc.

The enzymes involved in cholesterol synthesis are found in the **cytosol** and **microsomal fractions** of the cell. Acetate of **acetyl CoA** provides all the carbon atoms in cholesterol.

The reducing equivalents are supplied by **NADPH** while energy are provided by **ATP**. For the production of one mole of cholesterol, 18 moles of acetyl CoA, 36 moles of ATP and 16 moles of NADPH are required.

The synthesis of cholesterol may be learnt in 5 stages

1. Synthesis of HMG CoA
2. Formation of mevalonate (6C)
3. Production of isoprenoid units (5C)
4. Synthesis of squalene (30C)
5. Conversion of squalene to cholesterol (27C).

The detailed reactions of cholesterol biosynthesis are given in figure (5) as follow:

1. **Synthesis of β-hydroxy β-methylglutaryl CoA (HMG CoA) :**

   Two moles of acetyl CoA condense to form acetoacetyl CoA. Another molecule of acetyl CoA is then added to produce HMG CoA.

2. **Formation of mevalonate :**

   HMG CoA reductase is the **rate limiting enzyme** incholesterol biosynthesis. This enzyme is present in endoplasmic reticulum and catalyses the reduction of HMG CoA to mevalonate. The reducing equivalents are supplied by NADPH.

3. **Production of isoprenoid units :**

   In a threestep reaction catalysed by kinases, mevalonate is converted to 3-phospho 5-pyrophosphomevalonate which on decarboxylation forms isopentenyl pyrophosphate (IPP). The latter isomerizes to dimethylallyl pyrophosphate (DPP). Both IPP and DPP are 5-carbon isoprenoid units.

4. **Synthesis of squalene:**

   IPP and DPP condense to produce a 10-carbon geranyl pyrophosphate (GPP). Another molecule of IPP condenses with GPP to form a 15-carbon farnesyl pyrophosphate (FPP). Two units of farnesyl pyrophosphate unite and get reduced to produce a 30-carbon squalene.

5. Conversion of squalene to cholesterol :

Squalene undergoes hydroxylation and cyclization utilizing O_2 and NADPH and gets converted to lanosterol. The formation of cholesterol from lanosterol is a multistep process with a series of about 19 enzymatic reactions. The following are the most important reactions

- Reducing the carbon atoms from 30 to 27.
- Removal of two methyl groups from C4 and one methyl group from C14.
- Shift of double bond from C_8 to C_5.
- Reduction in the double bond present between C_{24} and C_{25}.

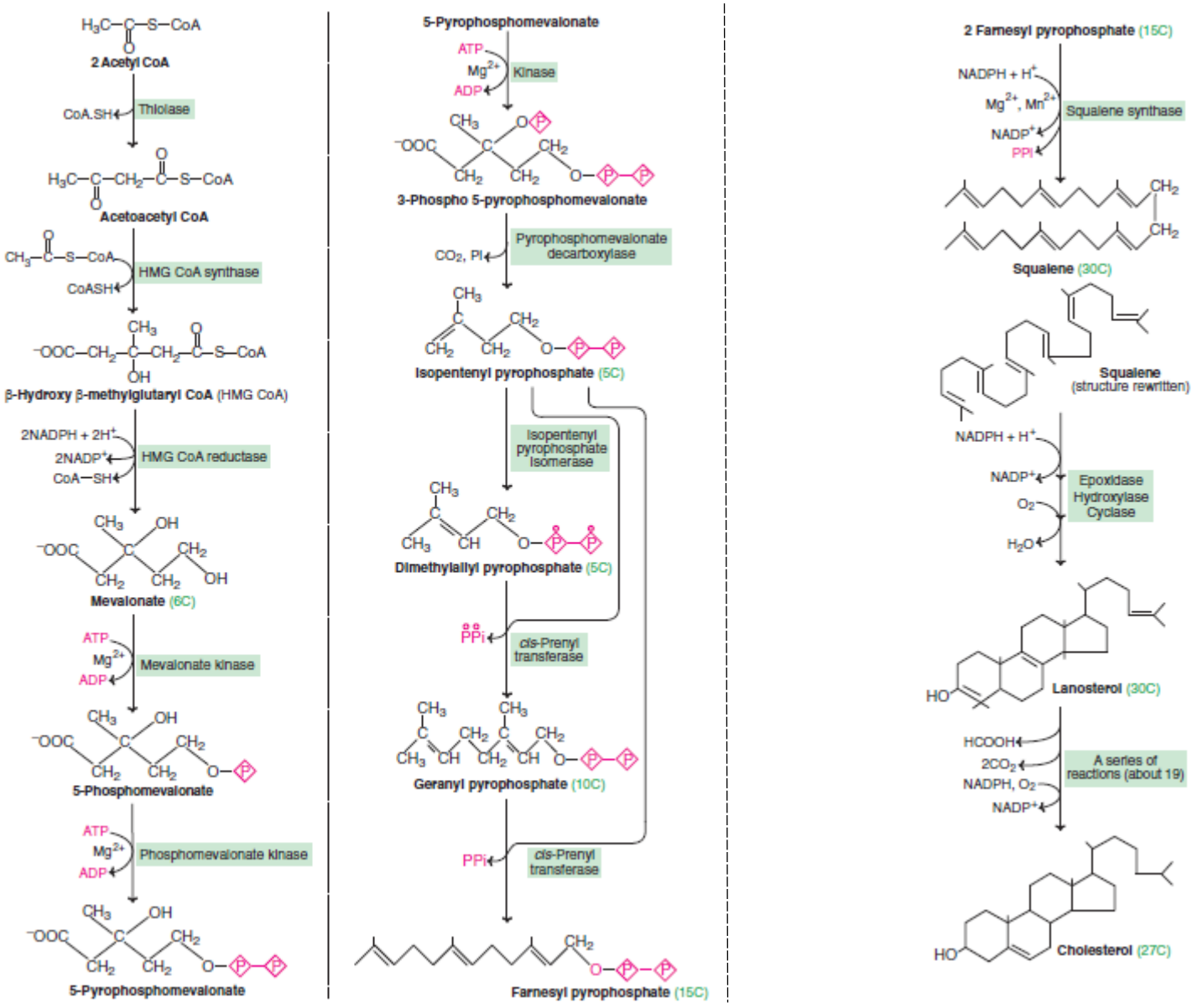


Figure (5): Biosynthesis of cholesterol

Degradation of cholesterol

The steroid nucleus (ring structure) of the cholesterol cannot be metabolized in humans.

Cholesterol (50%) is converted to bile acids, excreted in feces, serves as a precursor for the synthesis of steroid hormones, vitamin D, coprostanol and cholestanol. The latter two are the fecal sterols, besides cholesterol.

I. Synthesis of bile acids

The bile acids serve as emulsifying agents in the intestine and actively participate in the digestion and absorption of lipids. The synthesis of primary bile acids takes place in the liver and involves a series of reactions (**Fig.6**). Cholic acid and chenodeoxycholic acid are the primary bile acids and the former is found in the largest amount in bile. In the bile, the conjugated bile acids exist as sodium and potassium salts which are known as **bile salts**.

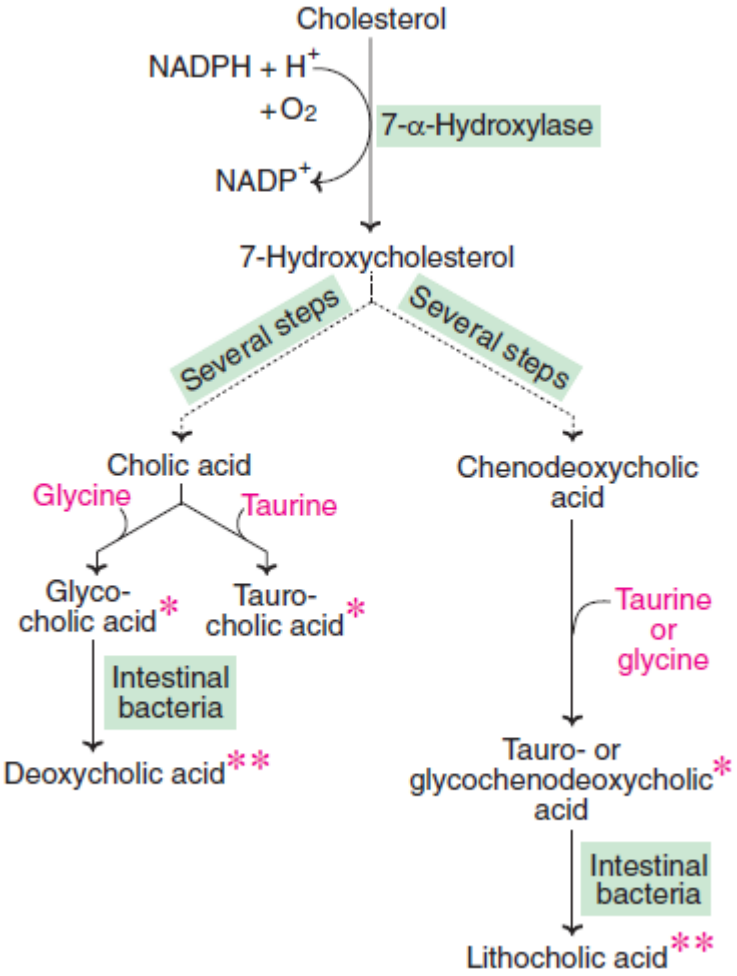
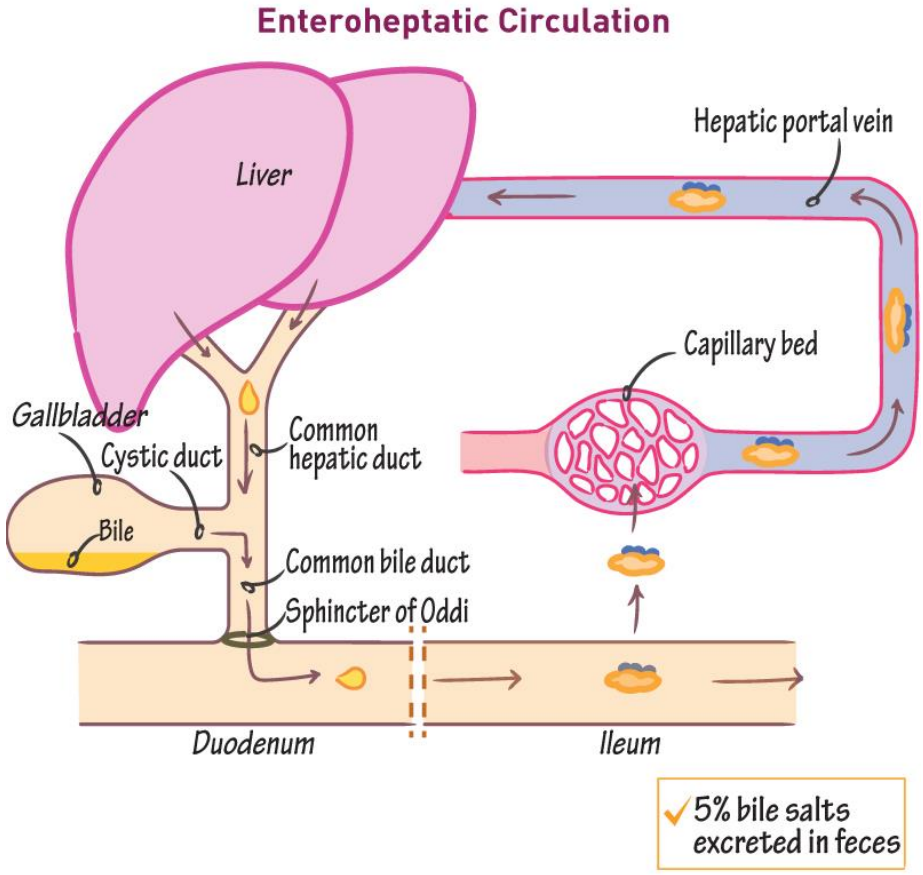


Figure (6) Outline of bile acid synthesis (*–Primary bile acids, **–Secondary bile acids).

Enterohepatic circulation : The conjugated bile salts synthesized in the liver accumulate in gall bladder. From there they are secreted into the small intestine where they serve as emulsifying agents for the digestion and absorption of fats and fat soluble vitamins. A large portion of the bile salts (primary and secondary) are reabsorbed and returned to the liver through

portal vein. Thus the bile salts are recycled and reused several times in a day. This is known as enterohepatic circulation. About 15-30 g of bile salts are secreted into the intestine each day and reabsorbed. However, a small portion of about 0.5 g/day is lost in the feces. An equal amount (0.5 g/day) is synthesized in liver to replace the lost bile salts. The fecal excretion of bile salts is the only route for the removal of cholesterol from the body.



Cholelithiasis: Bile salts and phospholipids are responsible for keeping the cholesterol in bile in a soluble state. Due to their deficiency (particularly bile salts), cholesterol crystals precipitate in the gall bladder often resulting in cholelithiasis—cholesterol gall stone disease **figure (7)**. Cholelithiasis may be due to defective absorption of bile salts from the intestine, impairment in liver function, obstruction of biliary tract etc.

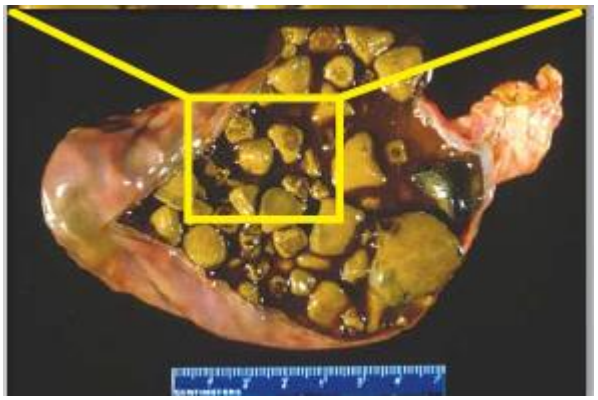


figure (7) cholesterol gall stone disease

II. Synthesis of steroid hormones from cholesterol

Cholesterol is the precursor for the synthesis of all the five classes of steroid hormones

(a) Glucocorticoids (e.g. cortisol)

(b) Mineralocorticoids (e.g. aldosterone)

(c) Progestins (e.g. progesterone)

A brief outline of steroid hormonal synthesis is given in figure (8).

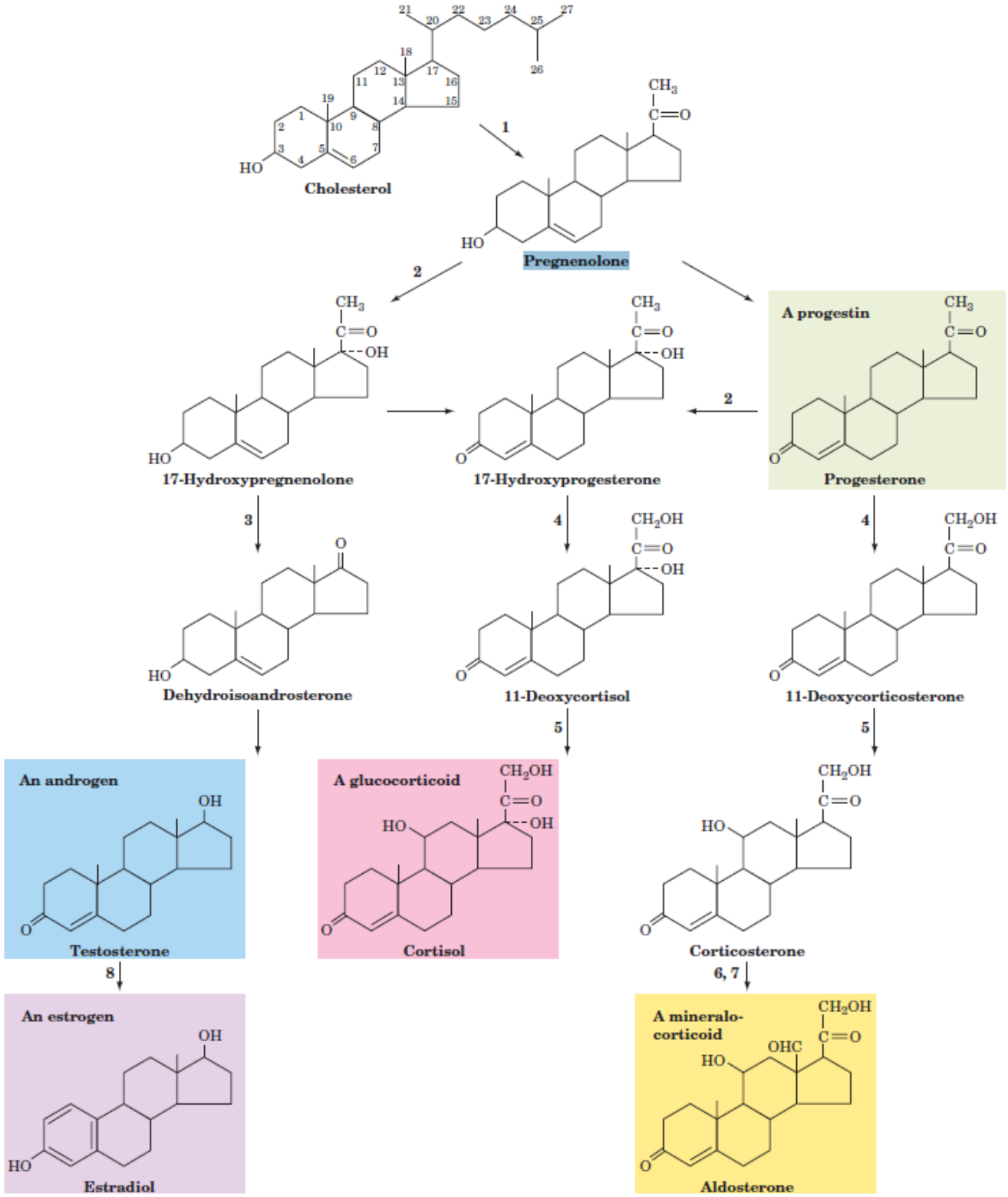
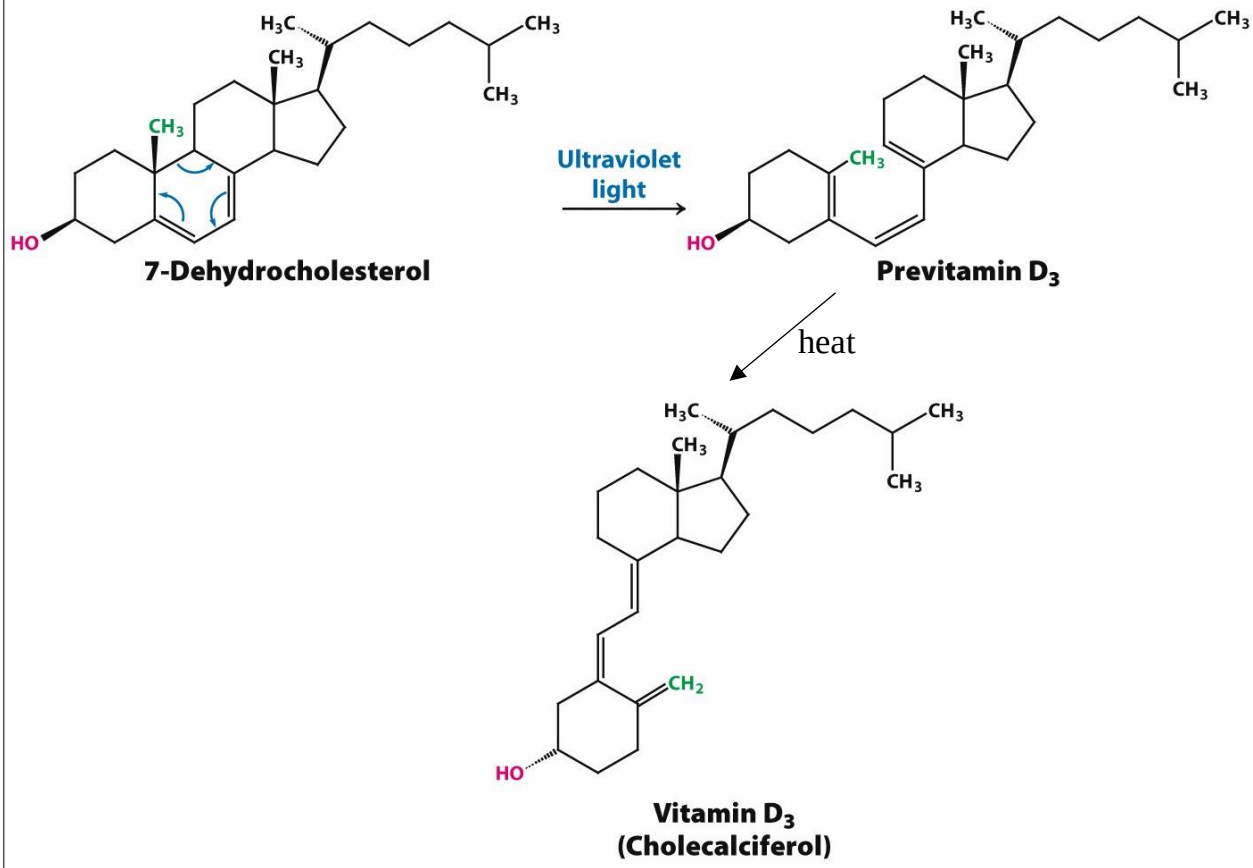


Figure (8) Simplified scheme of steroid biosynthesis. The enzymes involved are (**1**) the cholesterol side chain cleavage enzyme, (**2**) steroid C17 hydroxylase, (**3**) steroid C17, C20 lyase, (**4**) steroid C21 hydroxylase, (**5**) steroid 11β-hydroxylase, (**6**) steroid C18 hydroxylase, (**7**) 18-hydroxysteroid oxidase, and (**8**) aromatase

III. Synthesis of vitamin D

7-Dehydrocholesterol, an intermediate in the synthesis of cholesterol, is converted to cholecalciferol (vitamin D_3) by ultraviolet rays in the skin.



Lipoproteins

Lipoproteins are **molecular complexes** that consist **of lipids and proteins** (conjugated proteins). They function as transport vehicles for lipids in blood plasma. Lipoproteins deliver the lipid components (cholesterol, triacylglycerol etc.) to various tissues for utilization.

Classification of lipoproteins

Five major classes of lipoproteins are identified in human plasma.

1. **Chylomicrons :** They are synthesized in the intestine and transport exogenous (dietary) triacylglycerol to various tissues. They consist of highest (99%) quantity of lipid and lowest

(1%) concentration of protein. The chylomicrons are the least in density and the largest in size, among the lipoproteins.

2. **Very low density lipoproteins (VLDL) :**

They are produced in liver and intestine and are responsible for the transport of endogenously synthesized triacylglycerols.

3. **Low density lipoproteins (LDL) :** They are formed from VLDL in the blood circulation. They transport cholesterol from liver to other tissues.

4. **High density lipoproteins (HDL) :** They are mostly synthesized in liver. HDL particles transport cholesterol from peripheral tissues to liver (reverse cholesterol transport).

5. **Free fatty acids—albumin :** Free fatty acids in the circulation are in a bound form to albumin. Each molecule of albumin can hold about 20-30 molecules of free fatty acids.

Metabolism of lipoproteins

Lipoprotein metabolism divided into two class

1.Transport of exogenous (dietary)lipids

(chylomicron processing)

2.Transport of endogenous lipids

Apo B-100 lipoprotein guided system

Apo A1 governed lipoprotein system

A general picture of lipoprotein metabolism is depicted in **Fig.9**. Chylomicrons (nascent) are synthesized in the small intestine during the course of fat absorption. They contain apoprotein B48 and mostly triacylglycerols. Apo B48 name is given since this apoprotein contains 48% of protein coded by apo B gene (apo B100 is found in LDL and VLDL). Chylomicrons are produced when nascent particles combine with apo C II and apo E, derived from HDL. The liver synthesizes nascent VLDL containing apo B100 which are rich in triacylglycerols and cholesterol. Circulating HDL donates apo C II and apo E to convert nascent VLDL to VLDL.

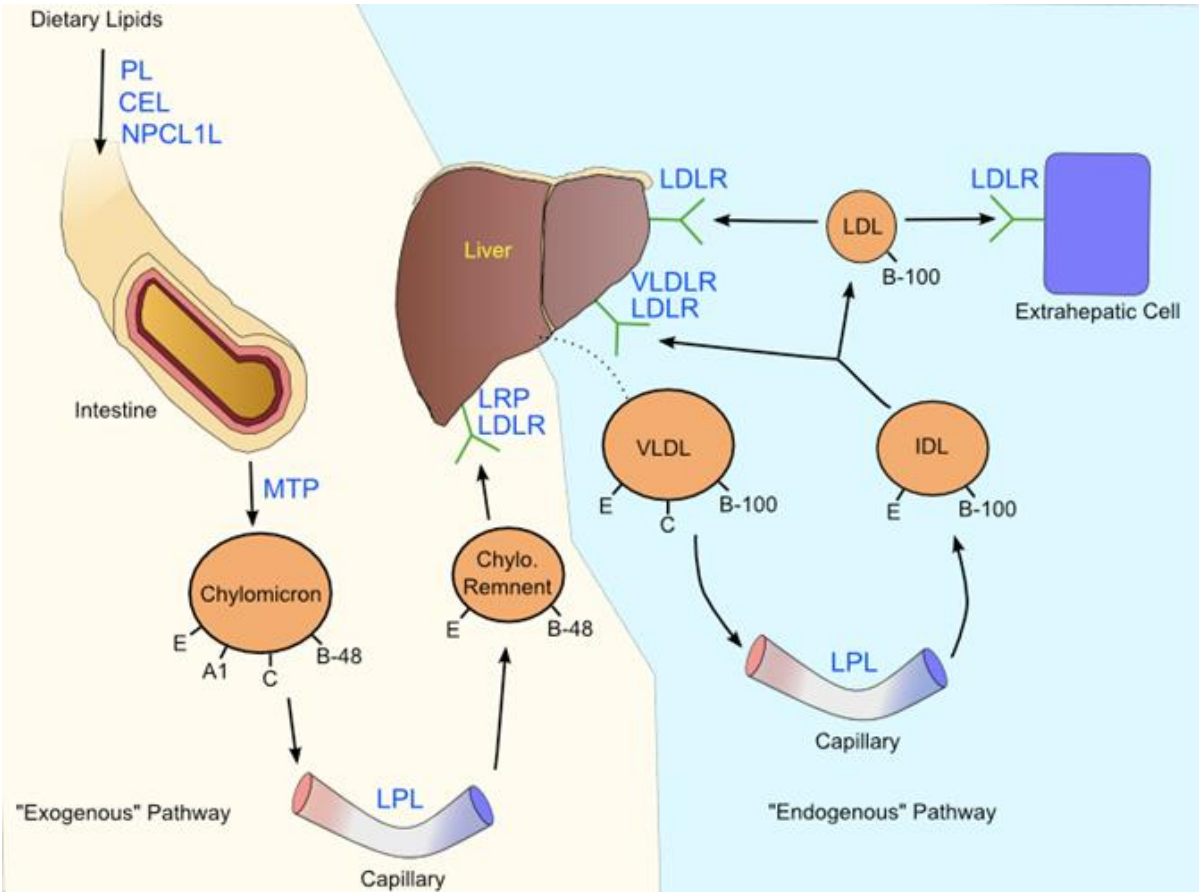


Figure (9) steps of lipoprotein metabolism