METABOLISM OF CHOLESTEROL

Cholesterol is derived **from diet**. It is **also synthesized in various tissues** in the body. About 50% of the normal intake of dietary cholesterol is absorbed by the small intestine while the rest of it is excreted in the feces.

Nearly 0.3 g of **cholesterol is absorbed** from the diet, daily. Ingested cholesterol is absorbed with other lipids and is incorporated into chylomicrons and VLDL. More than 80% of it is esterified in the intestinal mucosa and is transported with lipoproteins.

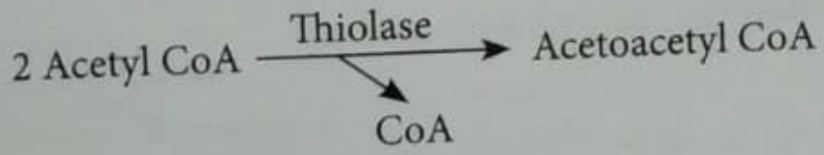
Biosynthesis of Cholesterol

A large quantity of cholesterol (about 1 g/day) is synthesized in the extramitochondrial compartment of the cell. Important sites for cholesterol biosynthesis include liver, skin, intestine, adrenal cortex and reproductive tissues, including ovaries, testes and placenta.

All the carbon atoms of **cholesterol** are derived **from acetate** (acetyl CoA), which is obtained from several sources such as oxidation of long chain fatty acids, ketogenic amino acids and glucose (via pyruvate).

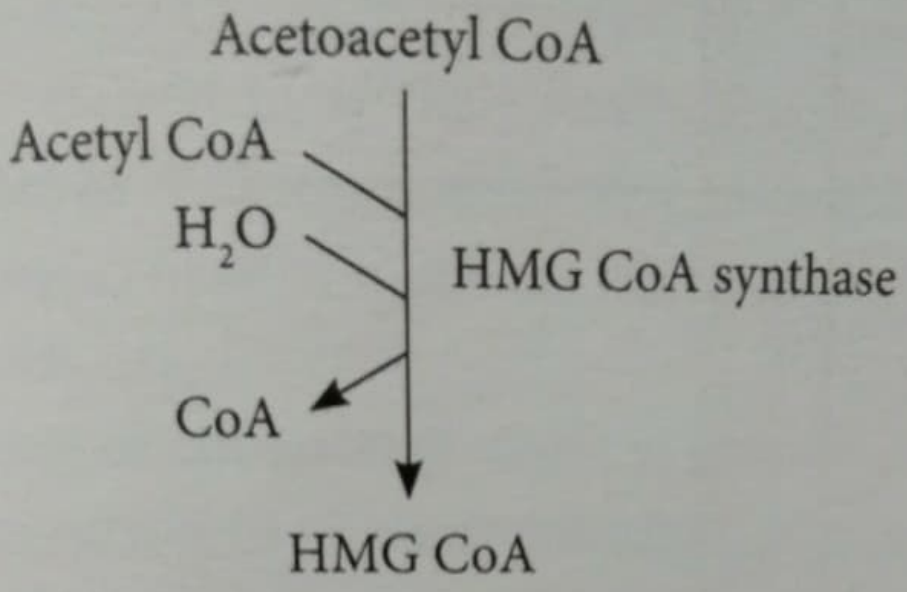
De novo synthesis of cholesterol takes place in the body, as shown in Fig. 9.27.

- First, **two molecules of acetyl CoA** condense to **form acetoacetyl CoA.**
  This reaction is catalyzed by the enzyme **acetoacetyl CoA thiolase.**



- In the presence of the enzyme β-hydroxy-β-methylglutaryl CoA synthase (**HMG CoA synthase**), **acetoacetyl CoA** further **condenses with** another molecule of **acetyl CoA** and **forms** β-hydroxy-β-methylglutaryl CoA (**HMG CoA**).

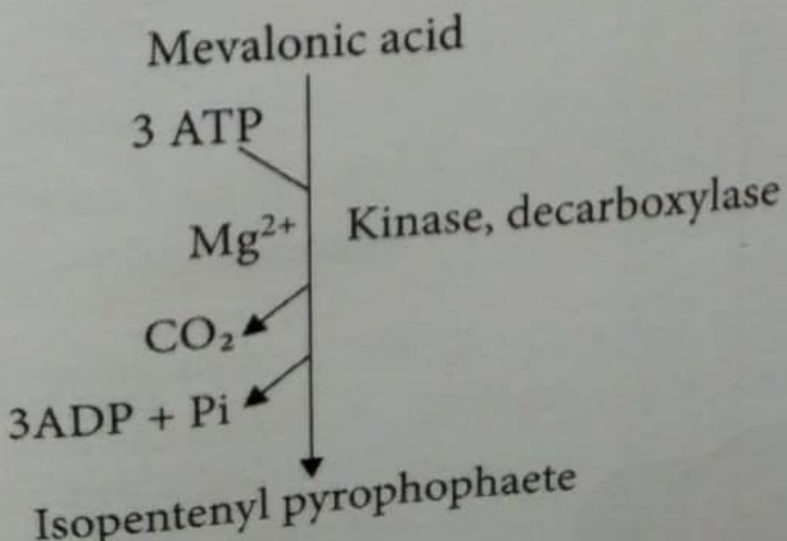
- An NADPH dependent enzyme, **HMG CoA reductase**, converts HMG CoA to **mevalonic acid.**



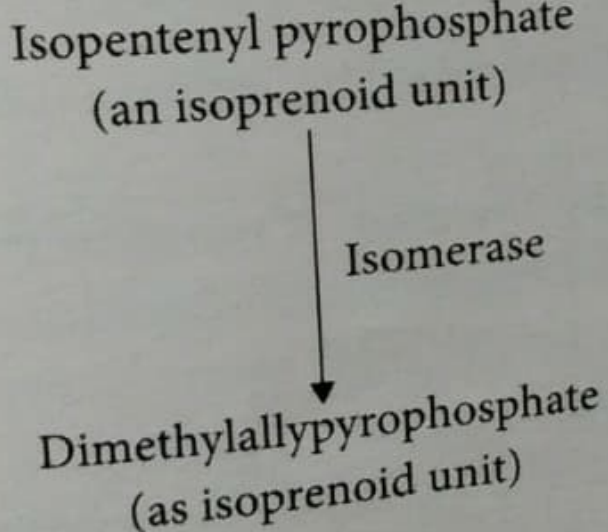
This is the **regulatory step** in cholesterol biosynthesis.

- Thereafter, there is stepwise transfer of two g-phosphate groups, from two molecules of ATP. These reactions are catalyzed by two kinases, called **mevalonate kinase** (enzyme I) and **phosphomevalonate kinase** (enzyme II).

Subsequently, decarboxylation takes place by the enzyme decarboxylase (pyrophosphomevalonate decarboxylase). Thus, phosphorylation and decarboxylation of **mevalonic acid forms isopentenyl pyrophosphate (5C),** which is also called **active isoprenoid unit.**



- In the next step, the isoprenoid unit (isopentenyl pyrophosphate) is isomerised to another isoprenoid unit designated as 3,3,-dimethylallylpyrophosphate, by the enzyme isopentenyl pyrophosphate isomerase.



- **Stepwise condensation of the three isoprenoid units (5C units)** leads to the formation of a 15-carbon unit, called **farnesyl pyrophosphate** (15C).

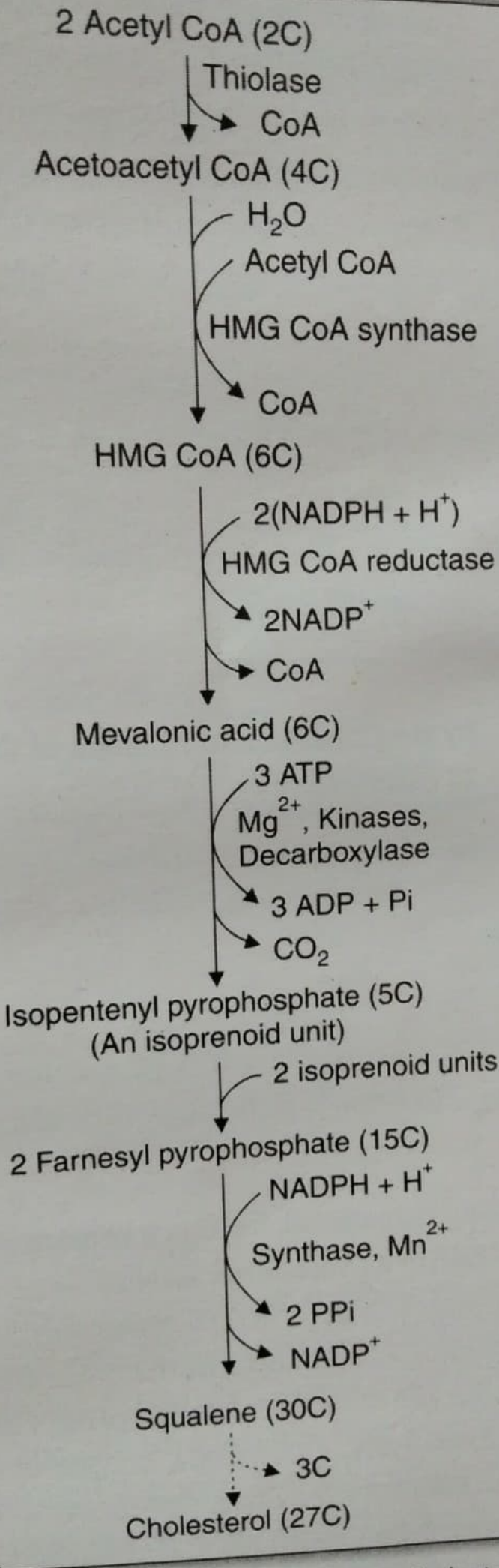
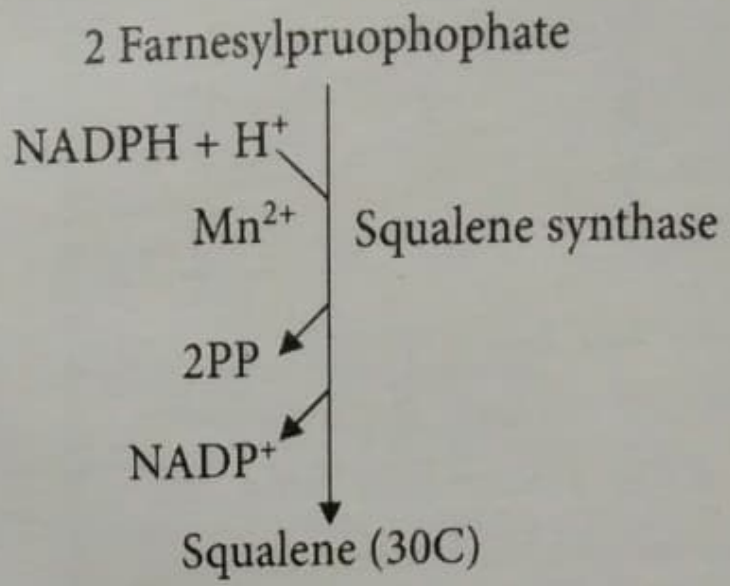


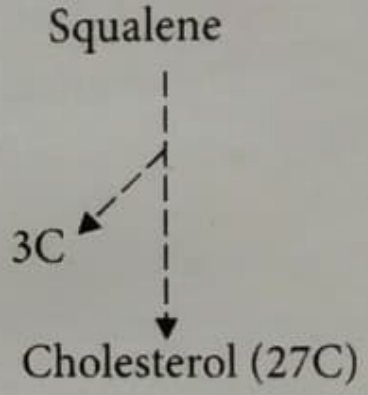
Fig. 9.27. *De novo* synthesis of cholesterol.

catalyzed by the

- Fusion of the **two molecules of farnesylpyrophosphate forms a 30-carbon compound called squalene** (30C).



- By ring closure and removal of the three methyl groups, **squalene is converted to cholesterol**, which has 27 carbons.



Regulation of Cholesterol Biosynthesis

Dietary cholesterol, feedback inhibition and its disposal from the liver, regulate cholesterol synthesis.

Dietary cholesterol: Rate of de novo synthesis of cholesterol is inversely related to the amount of dietary cholesterol. When dietary cholesterol intake is reduced, cholesterol synthesis is increased in the liver and the intestine, to meet needs of the other tissues.

On the other hand, when dietary cholesterol intake is increased, its synthesis is reduced.

Feed back inhibition: Cholesterol inhibits its own synthesis by feed back inhibition. The enzyme HMG CoA reductase regulates cholesterol synthesis. Cholesterol inhibits the activity of HMG CoA reductase, by suppressing its synthesis and promoting inactivation.

Disposal by the liver: Liver removes cholesterol by different processes:

- **Esterification of cholesterol:** Both, HDL and lecithin:cholesterol acyltransferase (LCAT) are important for the removal of cholesterol from the body.

  LCAT is a plasma enzyme which is produced mainly by the liver. It transfers one fatty acid from carbon 2 of lecithin to the 3-hydroxy group of cholesterol. This reaction is freely reversible and utilizes cholesterol, which is present in **HDL**.