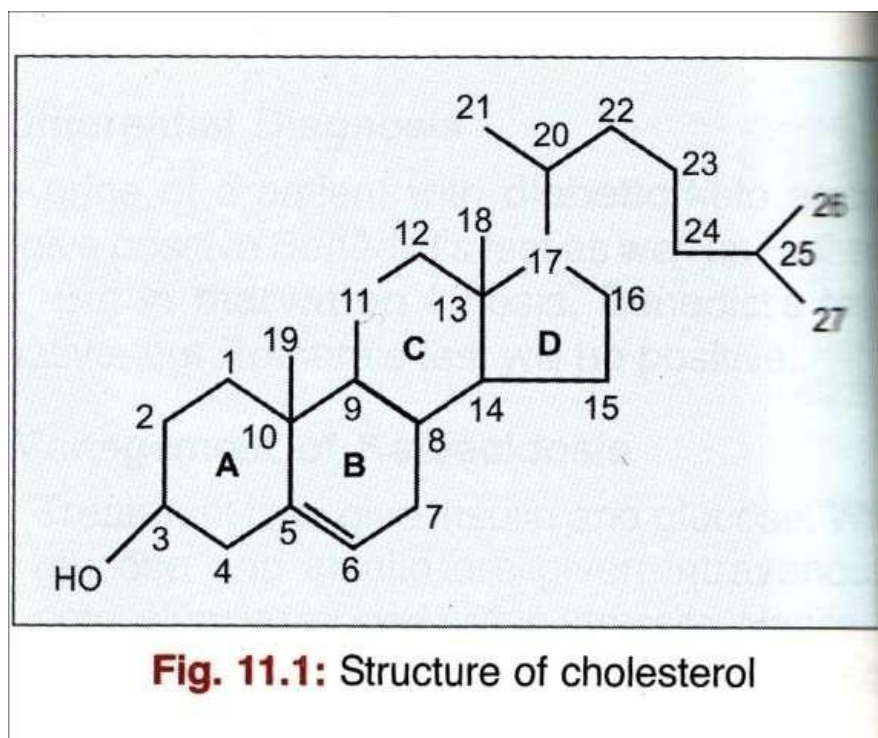




BIOLOGICAL SIGNIFICANCE OF CHOLESTEROL

INTRODCUTION:

Cholesterol is a light yellow crystalline solid. It's Soluble in chloroform, & fat solvents. It's distributed in brain, nerves, muscle, adipose tissue, skin, blood, liver, & spleen.



Function:

- Cholesterol is precursor for synthesis of vitamin D & bile acids.
- Cell membrane- it has modulating effect on fluid state of membrane.
- Nerve conduction –it is used to insulate nerve fibers.
- Fatty acids transported to liver as cholesterol esters for oxidation.
- Steroid hormones -glucocorticoids ,androgens, estrogen are synthesized from cholesterol.
- Essential ingredient in structure of lipoprotein.



Synthesis of Cholesterol:

Biosynthesis of cholesterol generally takes place in the endoplasmic reticulum of hepatic cells and begins with acetyl- CoA, which is mainly derived from an oxidation reaction in the mitochondria.

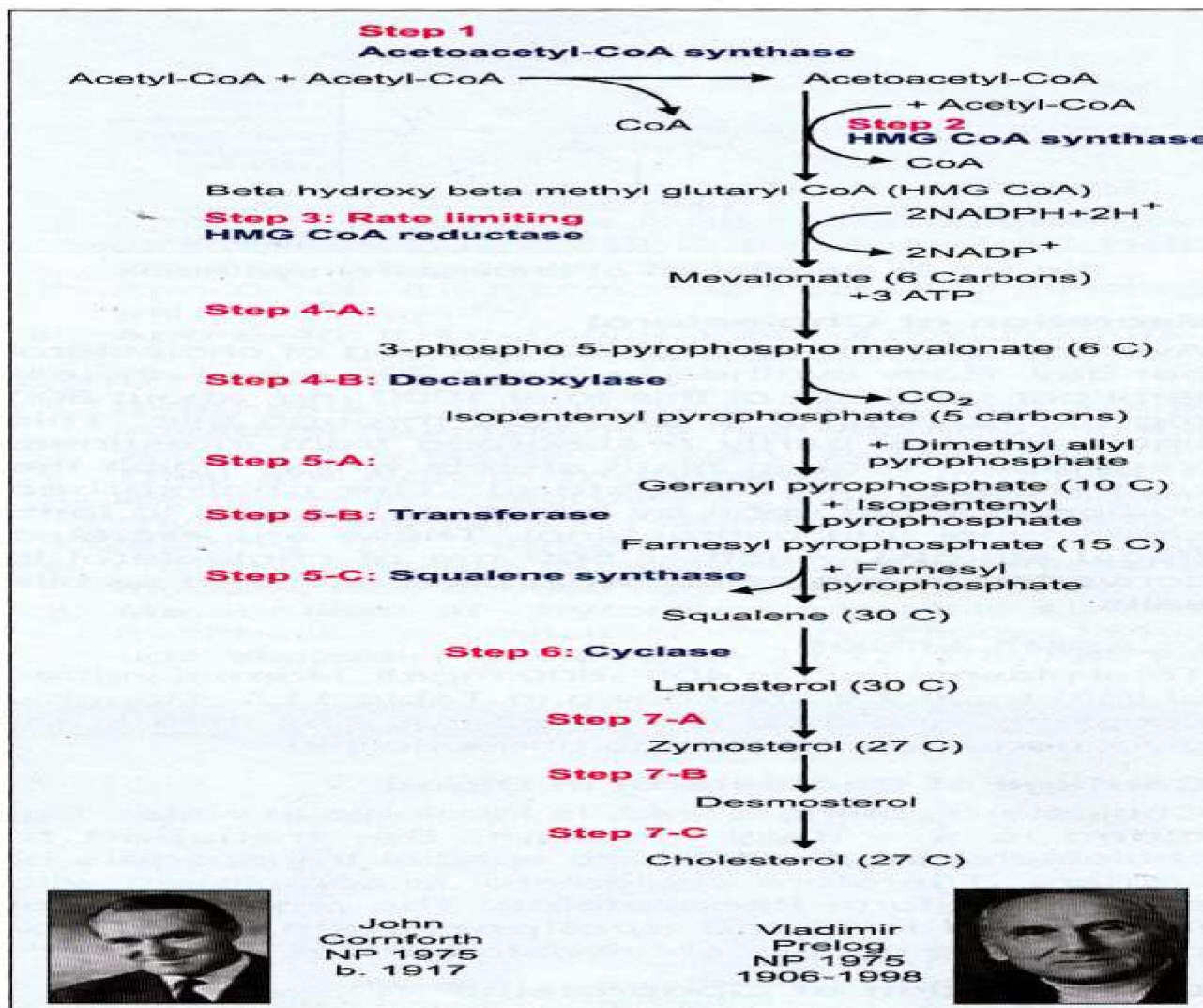


Fig.11.2: Cholesterol biosynthesis

Cholesterol level:

Total **cholesterol** levels less than 200 milligrams per deciliter (mg/dL) are considered desirable for adults. A reading between 200 and 239 mg/dL is considered borderline high and a reading of 240 mg/dL and above is considered high. LDL **cholesterol** levels should be less than 100 mg/dL.



Excretion:

Cholesterol is excreted through bile prior esterification with PUFA

Partly reabsorbed from intestine

Unabsorbed portion is acted by intestinal bacteria to form cholestanol & coprostanol which is excreted as fecal sterols

Another part is converted into bile acids, excreted as bilesalts.

Transport of Cholesterol in blood:

Being lipid it is insoluble in water. Cholesterol is complexed with protein to form lipoprotein.

LACT (lecithin cholesterol acyltransferase) is responsible for transport & elimination of cholesterol from body

Classification of lipoprotein:

1. Chylomicrons
2. Very low density lipoprotein (VLDL)
3. Intermediate density lipoprotein (IDL)
4. Low density lipoprotein (LDL)
5. High density lipoprotein (HDL)
6. Free fatty acids

Function of lipoprotein:

Chylomicrons - transport of dietary triglycerides from intestine to adipose tissue for storage.

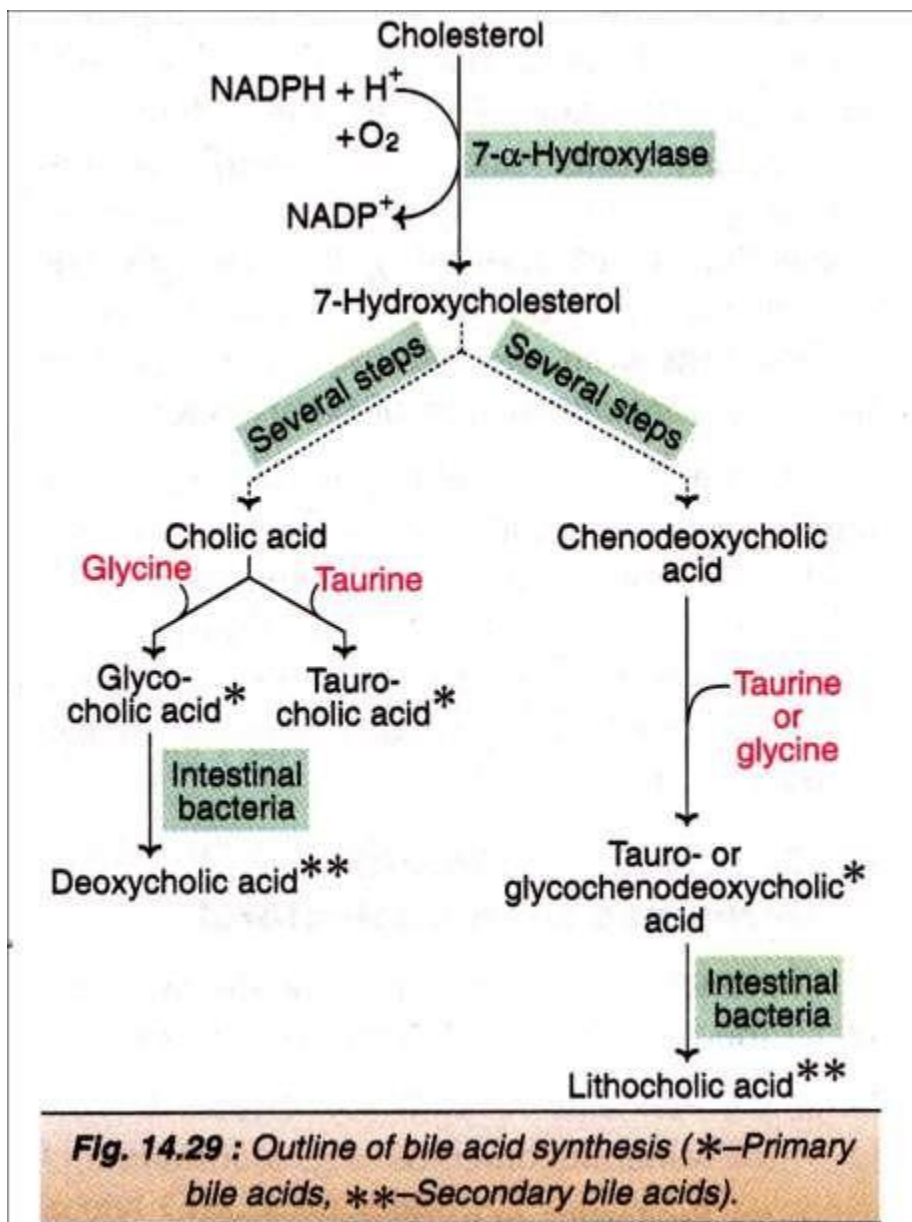
VLDL - transport of endogenous triglycerides from liver to peripheral tissues for energy

LDL - transport cholesterol from liver to peripheral tissues

HDL - transport of cholesterol from peripheral tissue to liver (**reverse cholesterol transport**).

Degradation of Cholesterol into Bile salts:

Synthesis of bile acids:





Cholesterol (50%) is converted to bile acids:

The **bile acids** are synthesized in the liver from cholesterol. It contains 24 carbon atoms, 2 or 3 OH groups in steroid nucleus & side chain ending in carboxyl group.

- ✓ Bile acids are amphipathic in nature.
- ✓ Possess both polar & non-polar groups.
- ✓ Serve as emulsifying agents in the intestine.
- ✓ Participate in digestion & absorption of lipids.
- ✓

Hydroxylation reaction:

Cholesterol is converted to 7-hydroxy cholesterol by the action of the enzyme **7 α -hydroxylase** (a **microsomal enzyme**). It is a rate limiting reaction. Incorporation of **OH group at 7th** carbon atom.

A third OH group is added at 12th carbon atom in cholic acid. **Chenodeoxycholic acid & cholic acid** are **primary bile acids**. On conjugation with glycine or taurine, conjugated bile acids formed, namely **Glycocholic acid & taurocholic acid**. These are **more efficient** in their function as surfactant. The **conjugated bile acids** are excreted through the bile.

Bile salts:

In the bile conjugated bile acids exist as **sodium & potassium salts** which are known as **bile salts**.

Secondary bile acids:

The primary bile acids are acted upon by the intestinal bacteria, which results in **deconjugation & decarboxylation** to form **secondary bile acids**.

The deconjugated bile acids are partly converted to secondary bile acids by **removal of OH group at 7th** carbon.

Cholic acid is converted to deoxycholic acid & chenodeoxycholic acid is converted to lithocholic acid. **Deoxycholic acid & lithocholic acid** are **secondary bile acids**.



Enterohepatic Circulation:

The conjugated bile salts synthesized in the liver and accumulate in gall bladder. It's secreted into the small intestine & they serve as emulsifying agents.

A large portion of the bile salts (primary & secondary) are reabsorbed & returned to the liver through portal vein.

The bile salts are recycled & reused several times in a day. This is known as enterohepatic circulation. About 15-30g of bile salts are secreted into the intestine each day & reabsorbed.

Fecal excretion of bile salts is only route for removal of cholesterol from body.

Cholelithiasis:

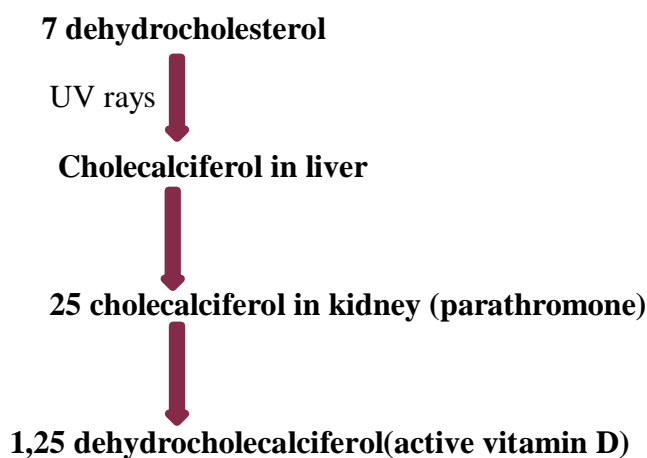
Bile salts & phospholipids are responsible for keeping the cholesterol in bile in a soluble state.

Due to **bile salts & phospholipids deficiency** (particularly bile salts), crystals precipitate in the gall bladder often resulting in **cholelithiasis- cholesterol gall stone disease**.

Cholelithiasis may be due to defective absorption of bile salts from the intestine, impairment in liver function, obstruction of biliary tract etc.

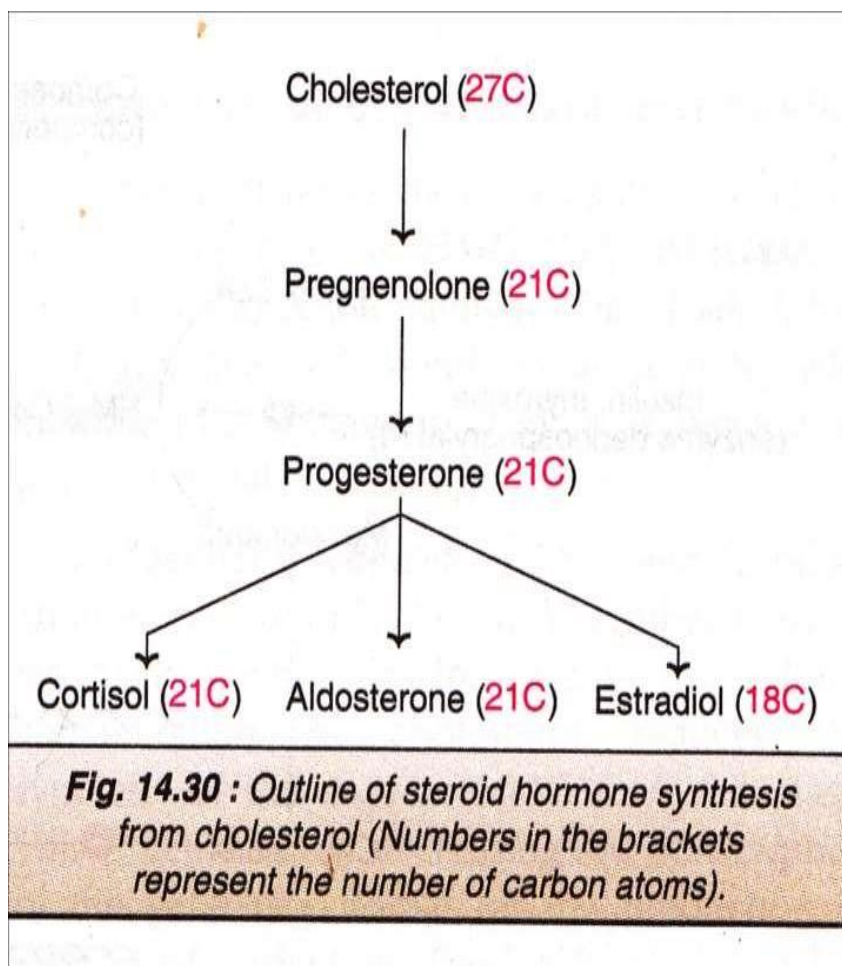
SYNTHESIS OF VITAMIN D FROM CHOLESTEROL

7-Dehydrocholesterol, an intermediate in the synthesis of cholesterol, is converted to **cholecalciferol (vitamin D₃)** by UV rays in the skin.





SYNTHESIS OF STEROID HORMONE FROM CHOLESTEROL:



Progesterone is an endogenous steroid and progestogen sex hormone involved in the menstrual cycle, pregnancy, and embryogenesis of humans and other species. It belongs to a group of steroid hormones called the progestogens and is the major progestogen in the body. Progesterone has a variety of important functions in the body. It is also a crucial metabolic intermediate in the production of other endogenous steroids, including the sex hormones and the corticosteroids, and plays an important role in brain function as a neurosteroid



Cortisol is a steroid hormone, in the glucocorticoid class of hormones. When used as a medication, it is known as hydrocortisone. It is produced in many animals, mainly by the zona fasciculata of the adrenal cortex in the adrenal gland.

Aldosterone, the main mineralocorticoid hormone, is a steroid hormone produced by the zona glomerulosa of the adrenal cortex in the adrenal gland. It is essential for sodium conservation in the kidney, salivary glands, sweat glands and colon. It plays a central role in the homeostatic regulation of blood pressure, plasma sodium (Na^+), and potassium (K^+) levels.

Estradiol also spelled **oestradiol**, is an estrogen steroid hormone and the major female sex hormone. It is involved in the regulation of the estrous and menstrual female reproductive cycles. Estradiol is responsible for the development of female secondary sexual characteristics such as the breasts, widening of the hips, and a female-associated pattern of fat distribution and is important in the development and maintenance of female reproductive tissues such as the mammary glands, uterus, and vagina during puberty, adulthood, and pregnancy.

Transport of Cholesterol:

Cholesterol is present in the plasma lipoproteins in **two forms**

About 70-75% of it is in an **esterified form with long chain fatty acids**.

About 25-30% as **free cholesterol**. Free cholesterol readily exchanges between different lipoproteins & also with the cell membranes.

Role of LCAT:

High density lipoproteins (**HDL**) & the **enzyme lecithin-cholesterol acyltransferase (LCAT)** are responsible for the **transport & elimination of cholesterol from the body**. LCAT is a **plasma enzyme, synthesized by the liver**. It catalyses the transfer of **fatty acid from the second position of phosphatidyl choline (lecithin) to the hydroxyl group of cholesterol**.

HDL-cholesterol is the real substrate for LCAT & this reaction is freely reversible. **LCAT activity is associated with apo-A1 of HDL**.