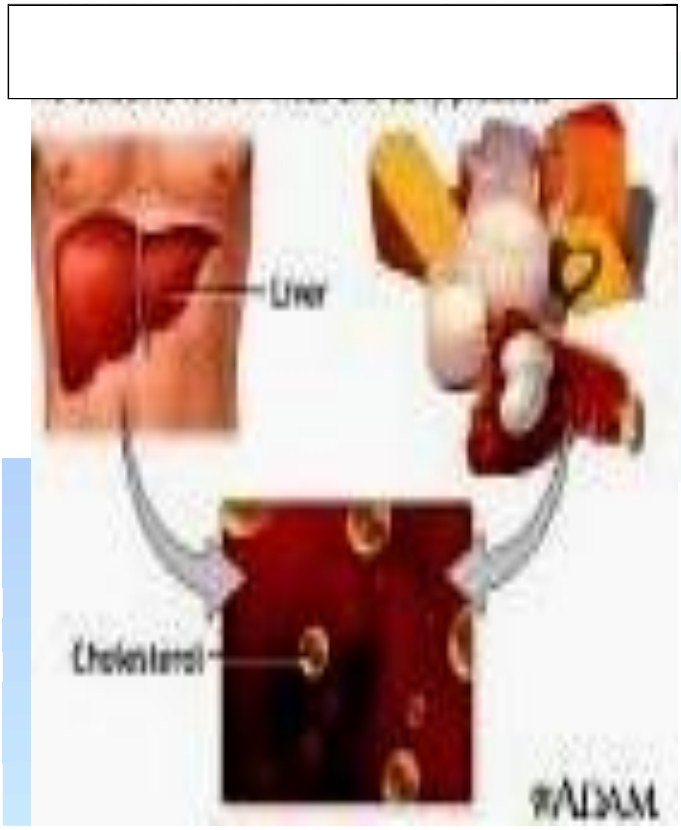
Cholesterol Metabolism



- Dr. Bariaa Ali maki

CHOLESTEROL

→Cholesterol is a light yellow crystalline solid

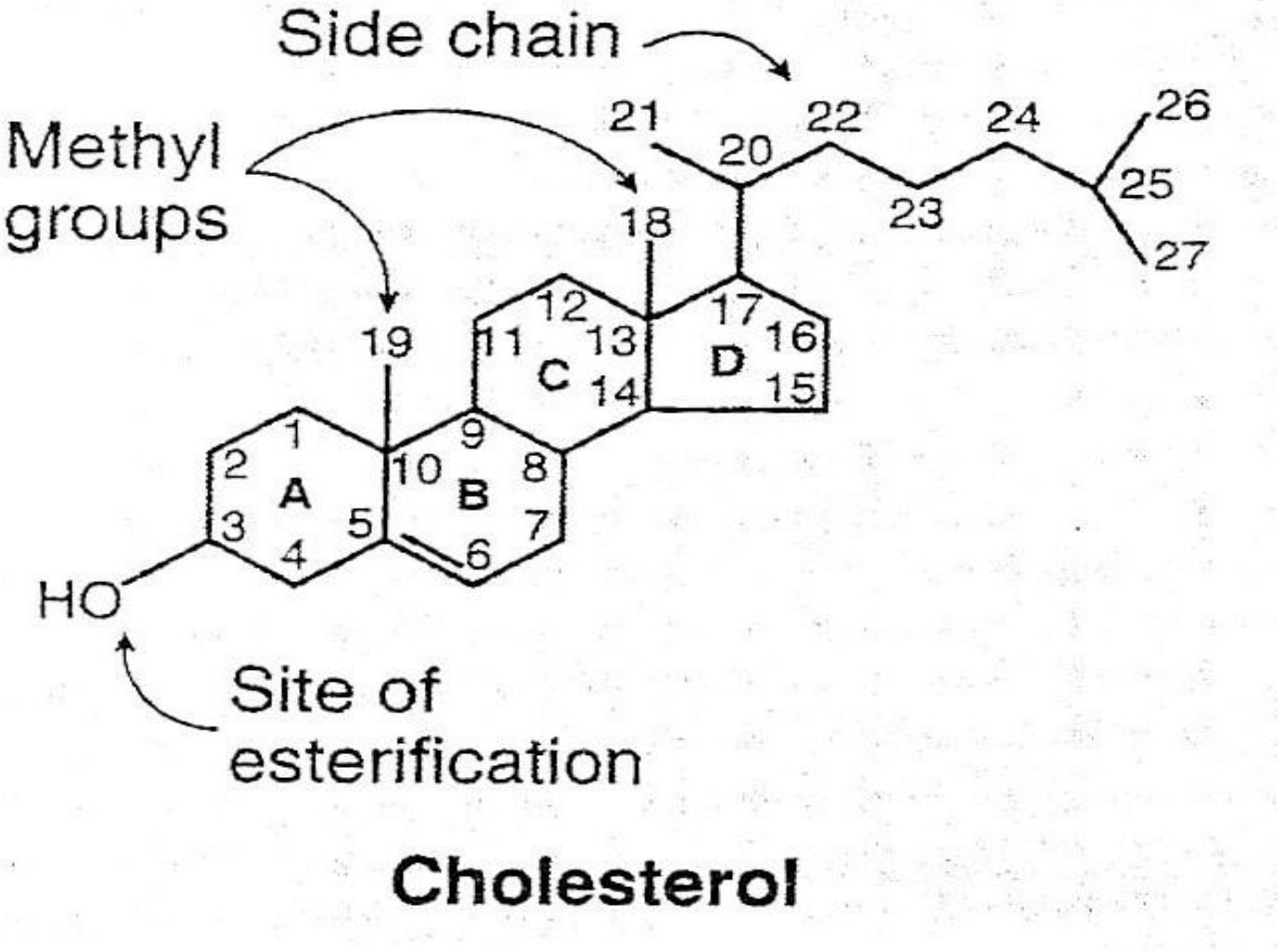
→It is a **27** Carbon compound

→contains ***cyclopentano perhydro phenanthrene*** ring

→**One hydroxyl group (OH) at 3rd position**

→**Double bond** between **5 & 6** Carbons

8 →**Carbon side chain at 17th Carbon**



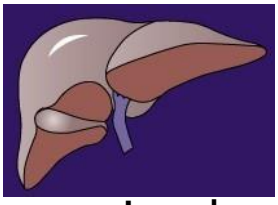
Cholesterol

Significance of Cholesterol

1) Normal level ***150 – 200 mg/dl*** . Increased levels increases the risk for ***Atherosclerosis***
2) Important ***component of cell membranes*** which affects fluid state of membrane
3) It is used to ***Insulate Nerve fibers***.
4) ***Bile acids*** (24 Carbon) are derived from Cholesterol
5) ***Steroid hormones*** (21 'C' glucocorticoids, 19 'C' androgens and 18 'C' estrogens) are produced from cholesterol
6) ***Vitamin D*** formed from Cholesterol

Biosynthesis of Cholesterol

Major sites – ***Liver, Adrenal Cortex, testis, ovaries*** and ***Intestine***



80% by Liver

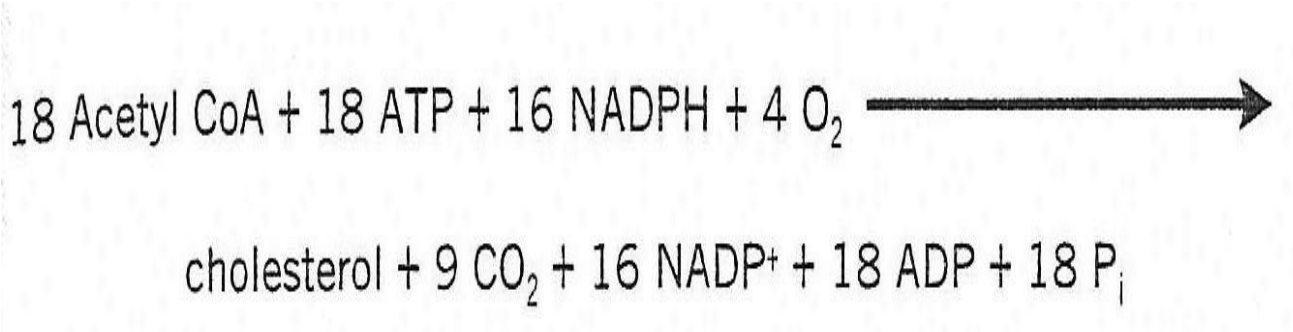
The enzymes involved in synthesis are located partly in ***cytoplasm*** and ***endoplasmic reticulum.***

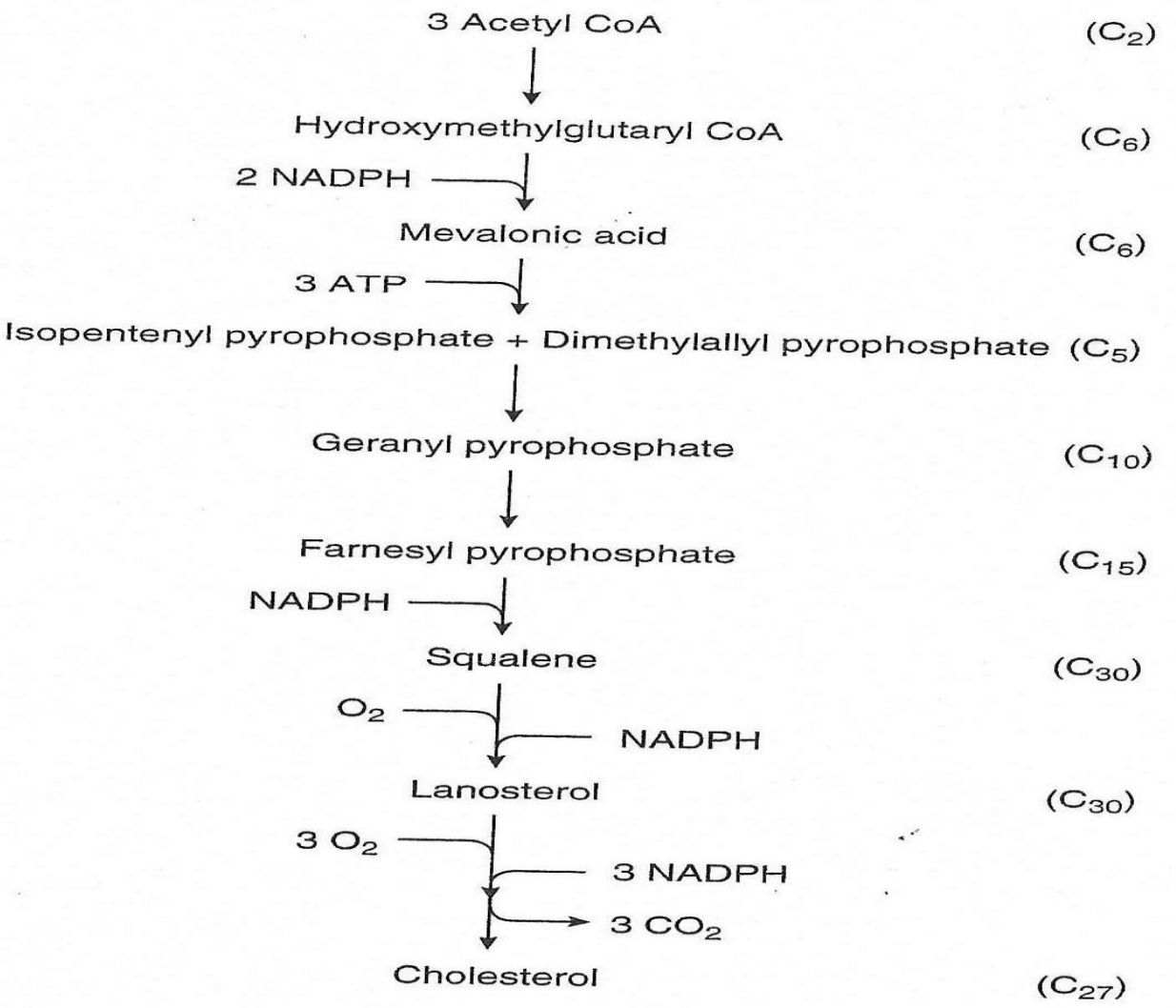
Requirements:

1) Acetate of **acetyl CoA** provides all the carbon atoms of cholesterol
2) Reducing equivalents by **NADPH**
3) Energy from **ATP.**

De novo Synthesis of Cholesterol

- Primary site: liver (~1g/d(
  - Secondary sites: adrenal cortex, ovaries, testes
- Overall equation:





Cholesterol Synthesis in 5 stages

1) Synthesis of **HMG CoA (6 C(**
2) Formation of **mevalonate** (6 C(
3) Production of **Isoprenoid Units** (5 C(
4) Synthesis of **squalene** (30 C(
5) Conversion of **Squalene to cholesterol** (27 C(

2C ▶ 6C ▶ 6C ▶ 5C ▶ 10C ▶ 15C ▶ 30C ▶ 27C

Step I : Condensation

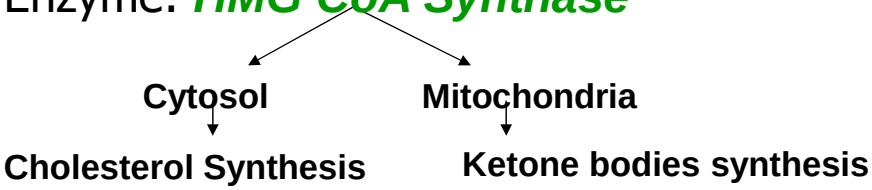
Two molecules of Acetyl CoA condense to form **Acetoacetyl CoA**

Enzyme: ***Acetoacetyl CoA Synthase***

Step II : *Production of HMG CoA*

One acetyl CoA condenses with Acetoacetyl CoA to form ***β-hydroxy β-methyl glutaryl CoA*** (HMG CoA(

Enzyme: ***HMG CoA Synthase***



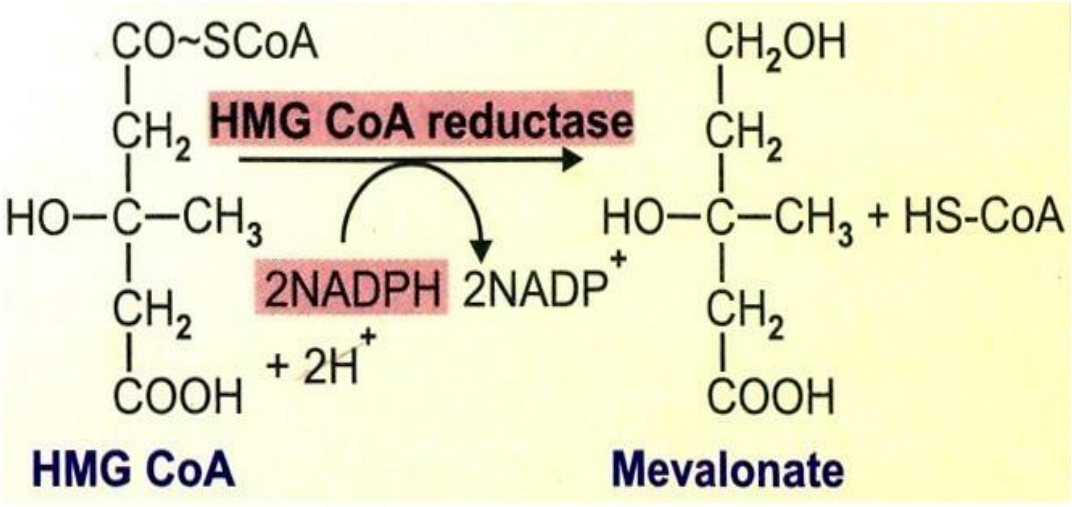
Step III – Regulating Step

Formation of Mevalonate

Reduction of HMG CoA to Mevalonate

Enzyme: ***HMG CoA reductase***

requires 2 NADPH



Step 3 of cholesterol synthesis

Step 4 : Formation of Isoprenoid Unit (5 C)

Mevalonate is ***phorphorylated*** three times to form ***3" phospho 5" pyrophospho mevalonate***, requires 3 ATP.

This undergoes **decarboxylation** to form ***Isopentanyl Pyrophosphate*** (5 C)

Step 5: Synthesis of Squalence (30 C)

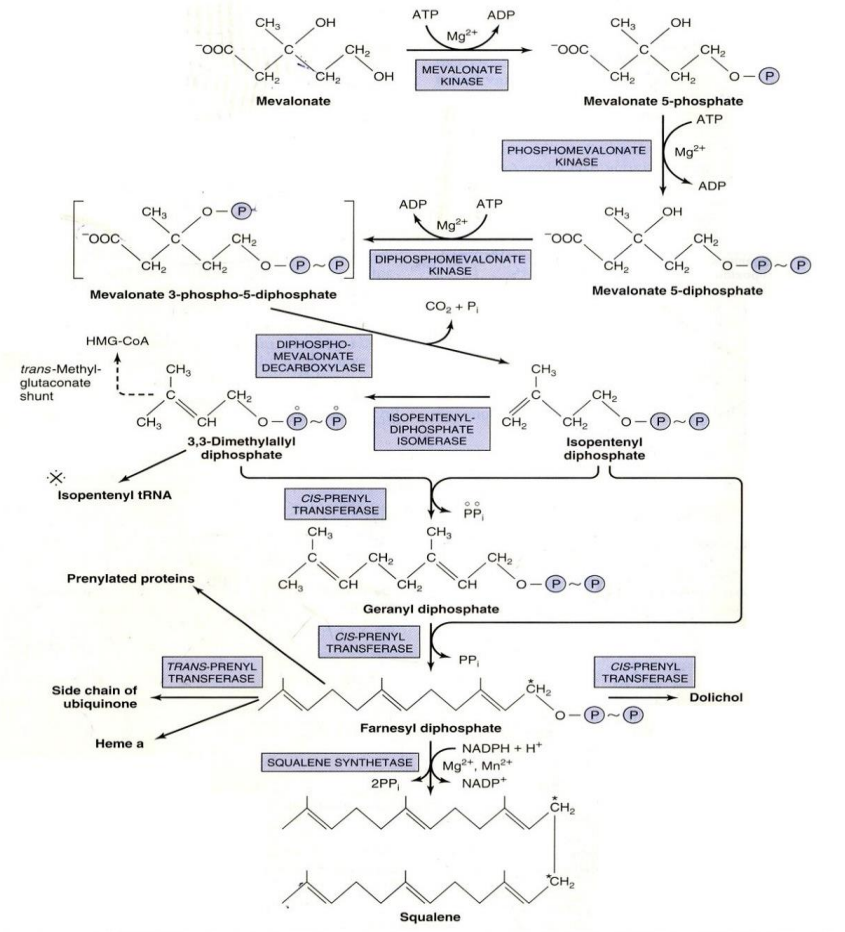
Isopentanyl pyrophosphate Isomerizes to form

Di methyl allyl pyrophosphate

One molecule of IPP (5 C) condenses with DMP (5 C) to form **Geranyl pyrophosphate** (10 C)

One molecule of IPP (5 C) condenses with GP (10 C) to form **Farnesyl pyrophosphate** (15 C)

Two molecules of Farnesyl pyrophosphate (15 C) condenses to form **Squalene (30 C**)



Biosynthesis of squalene, ubiquinone, dolichol, and other polyisoprene derivatives. (HMG, 3-hydroxy-3-methylglutaryl; ⁂, cytokinin.) A farnesyl residue is present in heme a of cytochrome oxidase. The carbon marked with asterisk becomes C_{11} or C_{12} in squalene. Squalene synthetase is a microsomal enzyme; all other enzymes indicated are soluble cytosolic proteins, and some are found in peroxisomes.

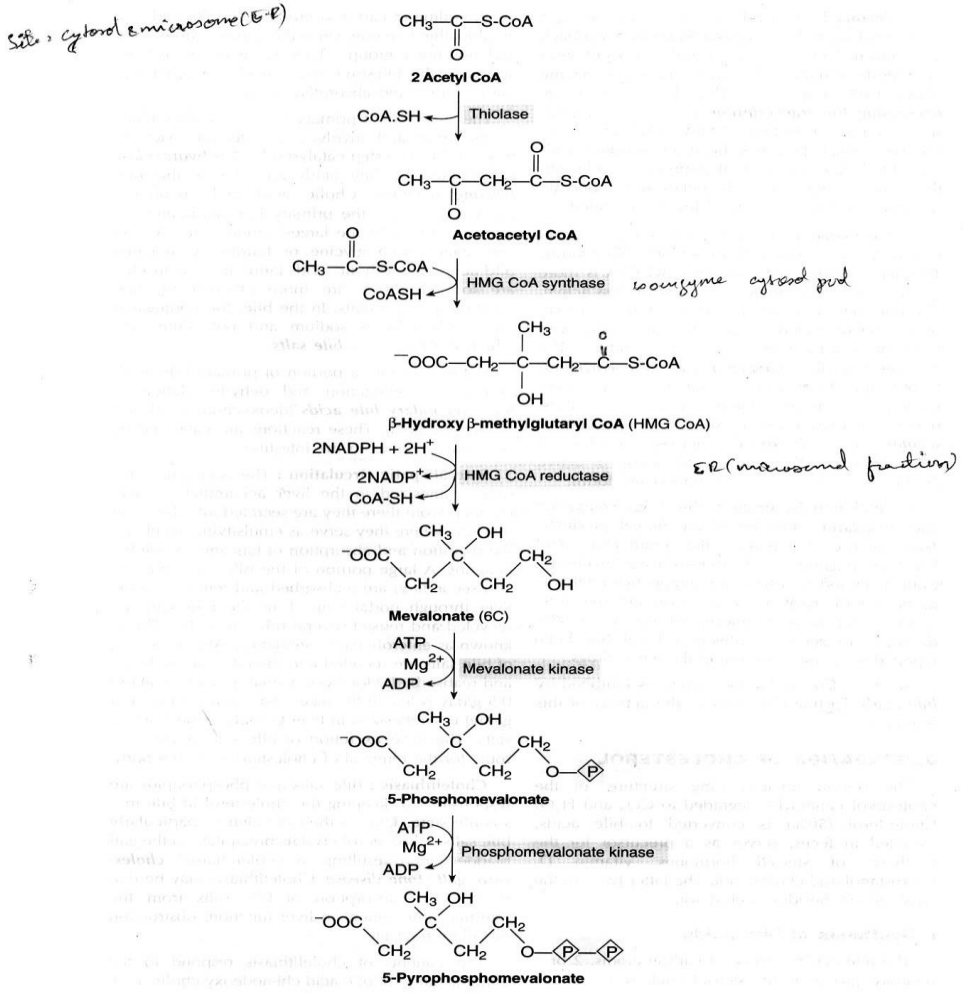
Step 6 : ***Cyclization***

Squalene undergoes oxidation and cyclization to form **Lanosterol**

Lanosterol first formed steroid compound.

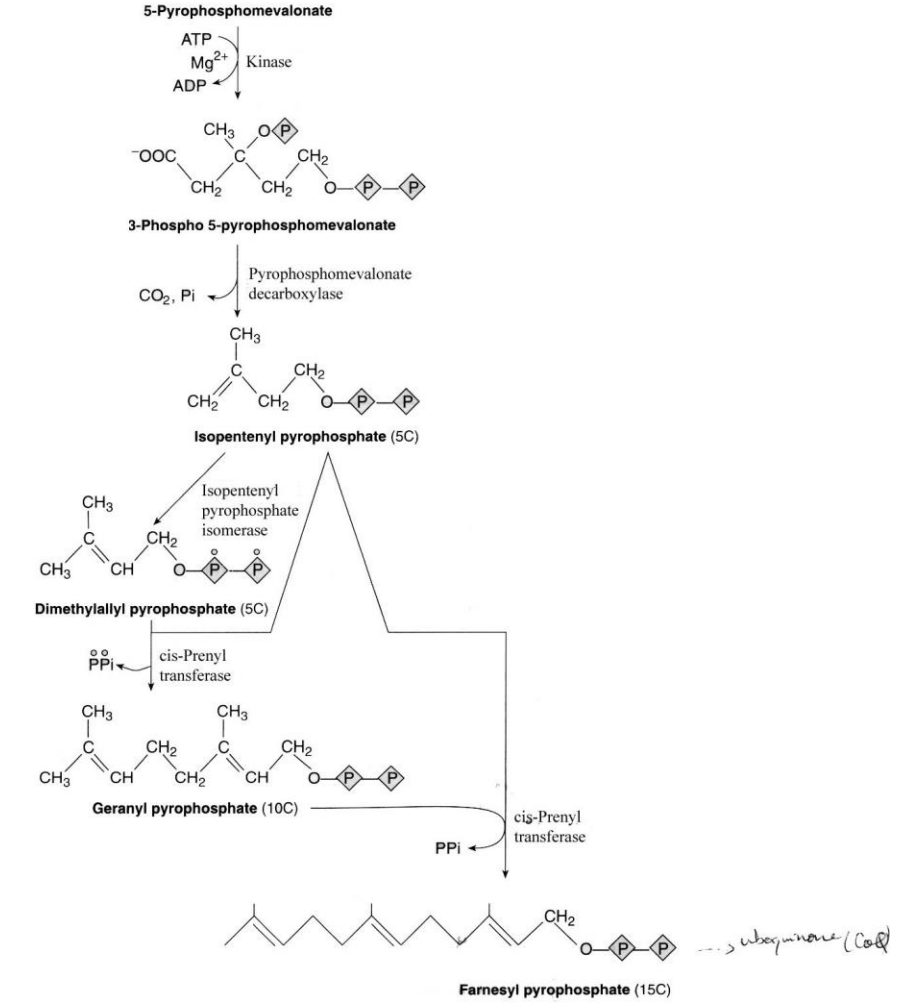
2C ► 6C ► 6C ► 5C ► 10C ► 15C ► 30C ► 27C

Site : cytosol & microsome (ER)

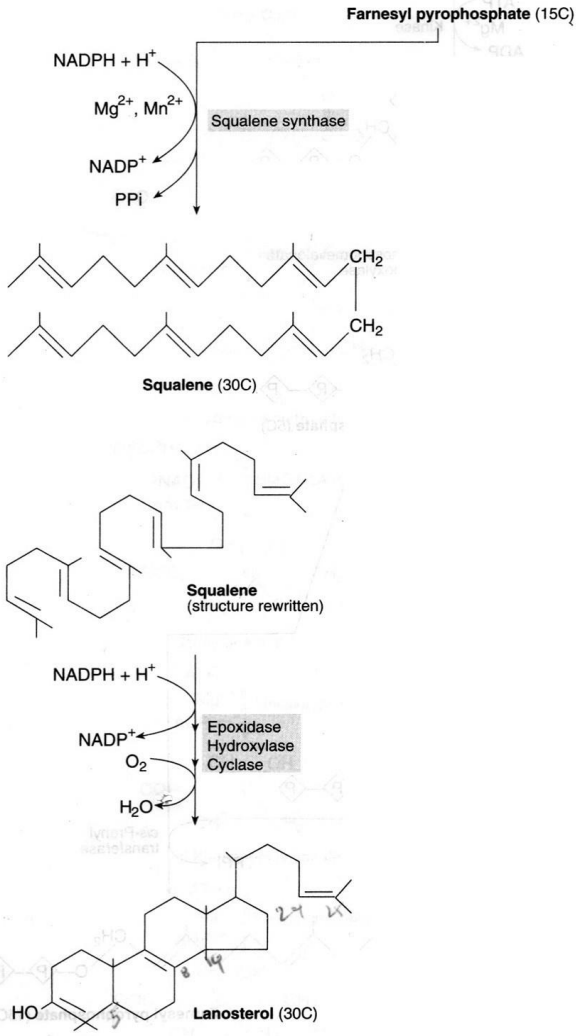


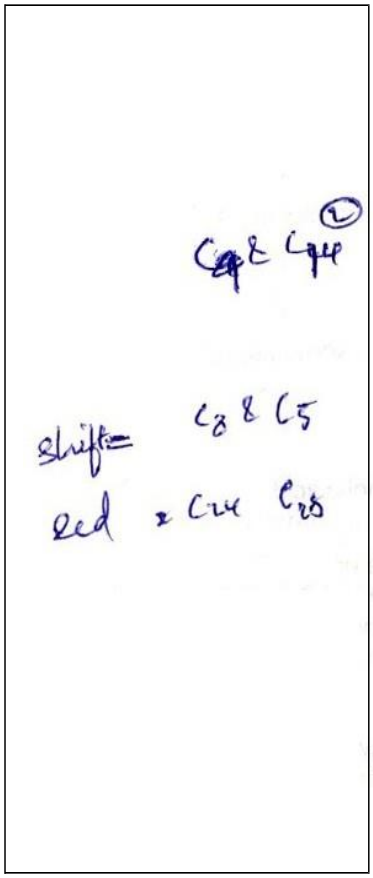
enzyme cytosol prd

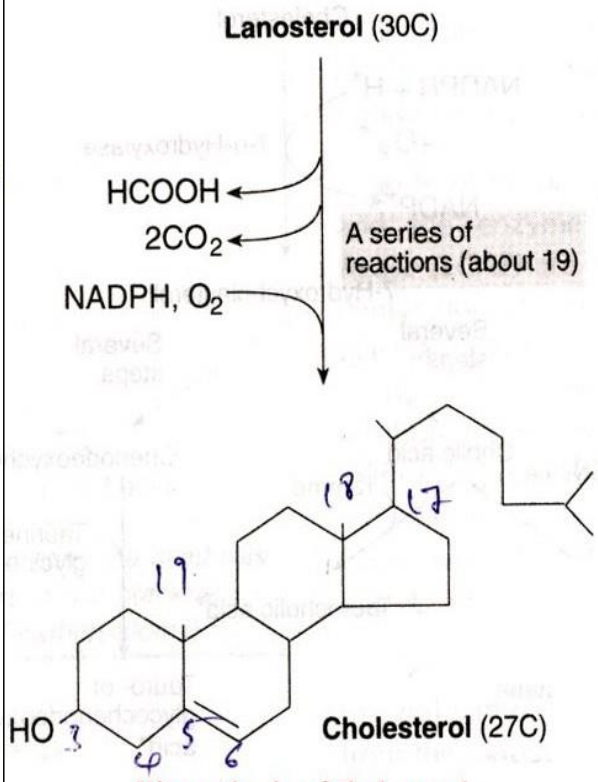
ER (microsomal fraction)



→ ubiquinone (CoQ)







Biosynthesis of cholesterol

Regulation of CholesterolSynthesis

HMG CoA reductase is the regulating Enzyme

1. Feed back Inhibition:

   The end product cholesterol in excess inhibits the gene which is responsible for production of HMG CoA reductase

2. Hormonal regulation:

   Glucogon & Glucocorticoids favor the formation of Inactive HMG CoA reductase, thus decreases the cholesterol synthesis

   Insulin increases cholesterol synthesis by enhancing the formation of active HMG CoA reductase.

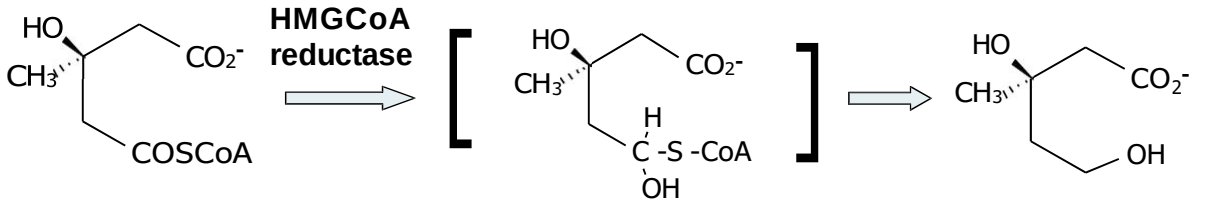
3. Inhibition by drugs:

   Compactive

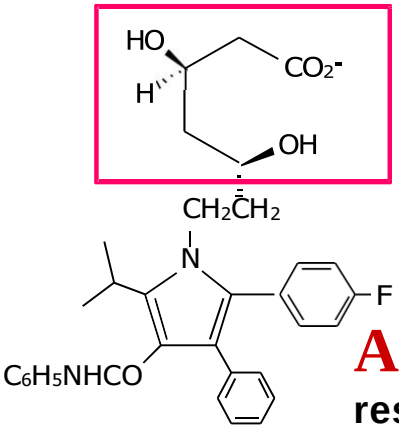
   Lovastatin

Competitive Inhibitors for HMG CoA reductase.

Inhibition of Cholesterol Biosynthesis



HMG CoA **Intermediate** **Mevalonate**



Atorvastatin (Lipitor):
resembles intermediat$_2$e$_1$

Degradation of cholesterol

Cholesterol is not completely degraded to Co_2 & H_2o.

It is converted to Bile acids
Steroid hormones
Vitamin D

Bile acids:

24 Carbon compounds with steroid ring.

Helps in digestion & absorption of lipids.

Synthesis takes place in Liver

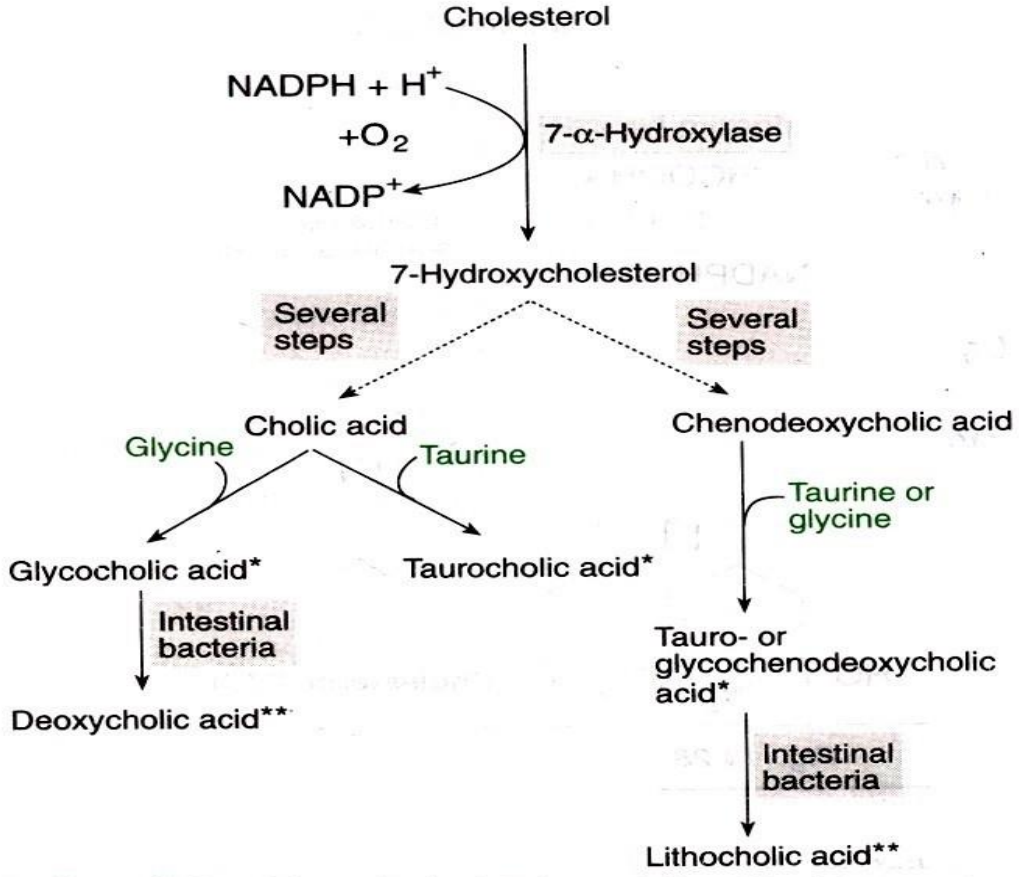
7-hydroxylase is the regulating Enzyme

Primary Bile acids –

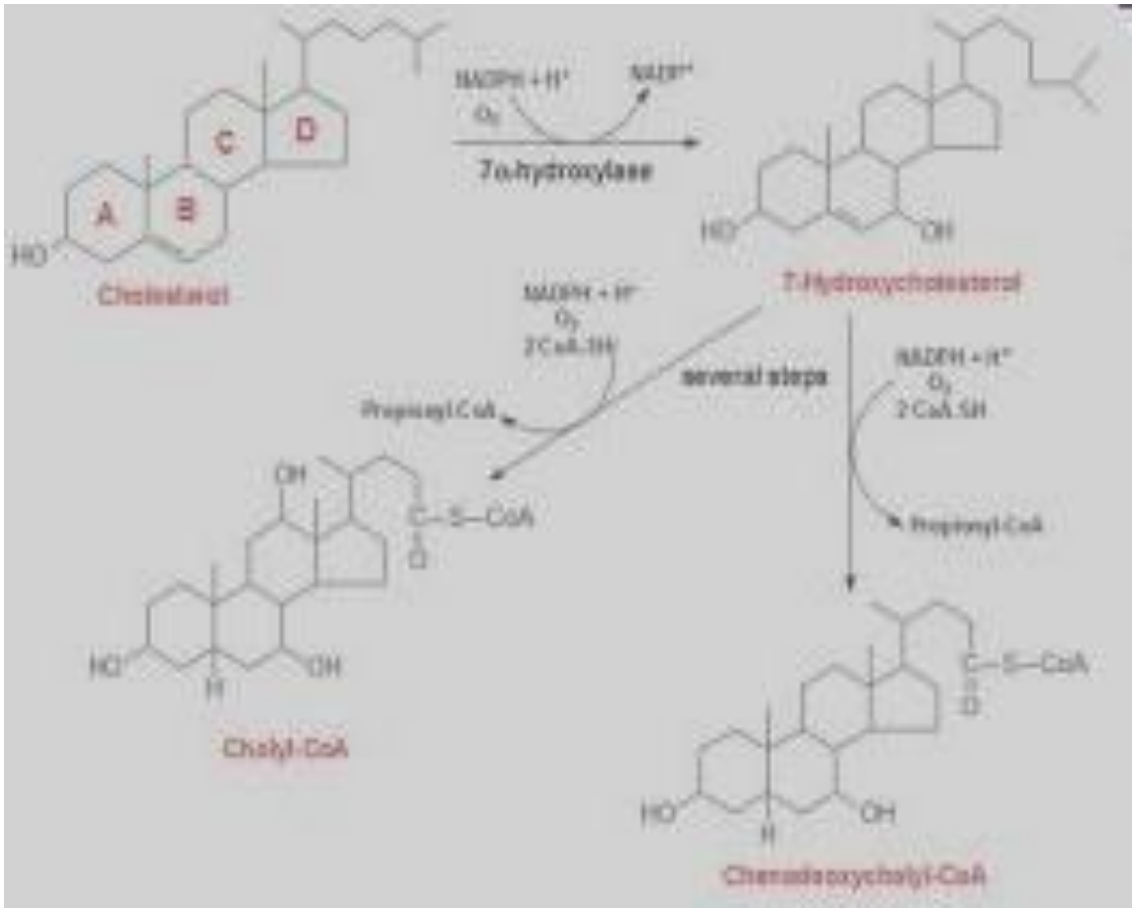
cholic acid, chenodeoxy cholic acid

Secondary Bile acids –

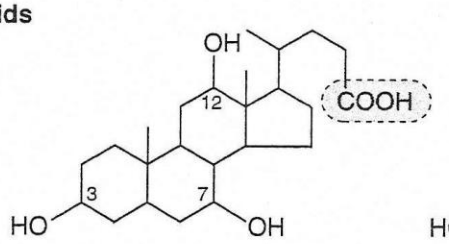
deoxycholic acid, Lithocholic acid



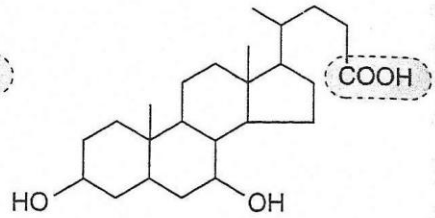
Outline of bile acid synthesis (*-Primary bile acids, **-Secondary bile acids)



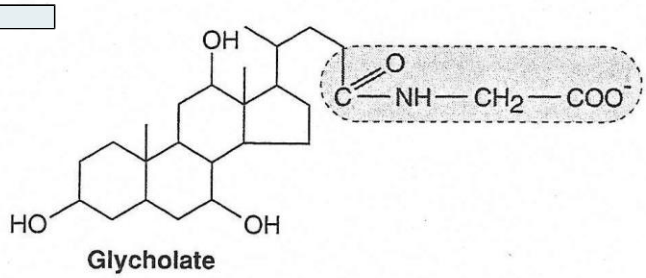
Bile acids



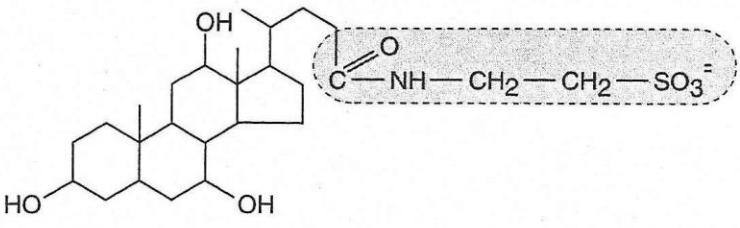
Cholic acid



Chenodeoxycholic acid



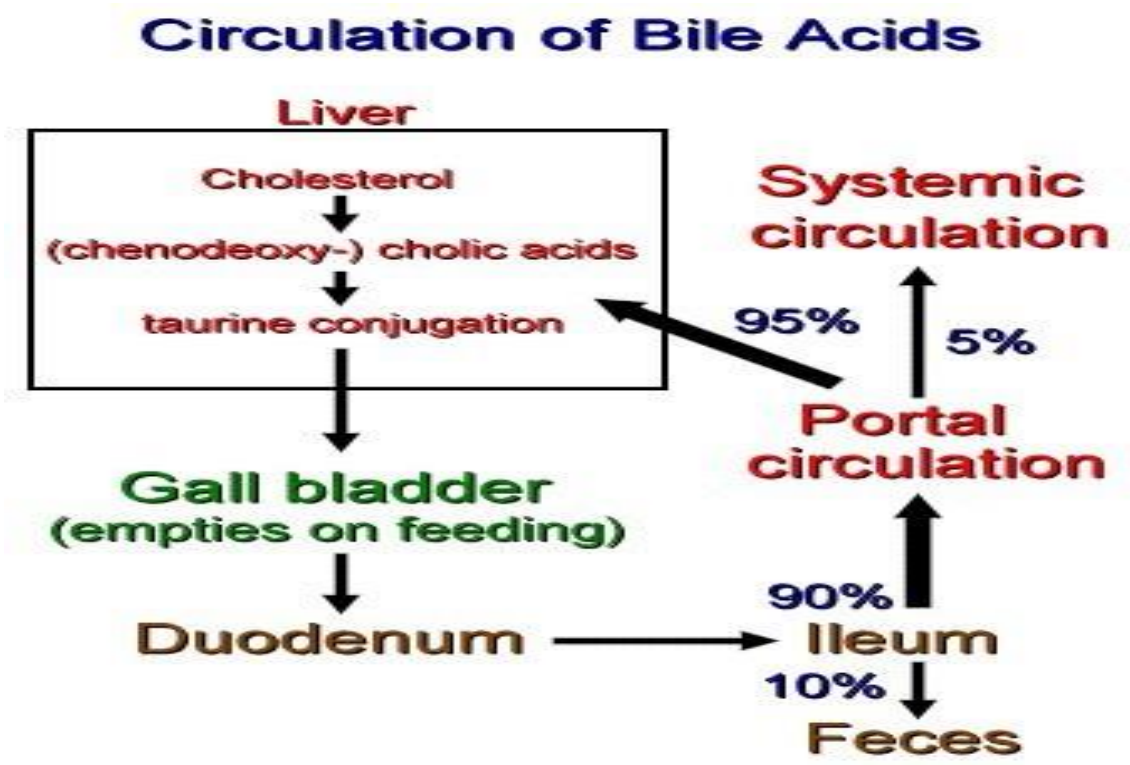
Glycholate



Taurocholate

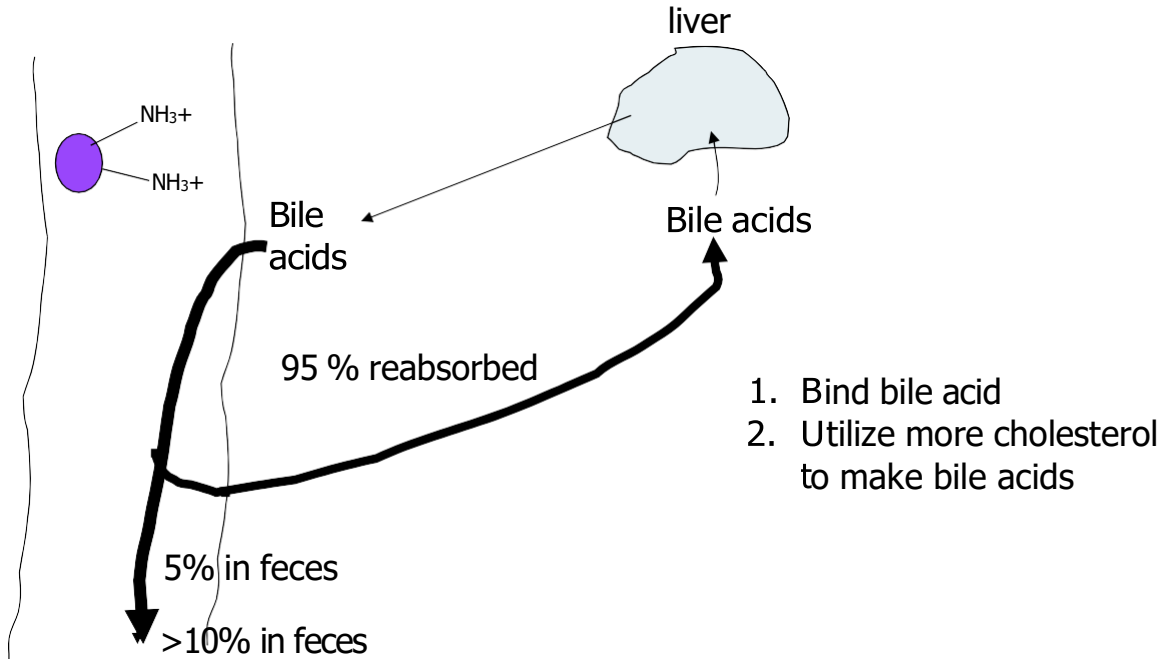
Enterohepatic circulation

The bile salts which are secreted into the intestine are reabsorbed and returned to the liver. This is known as entero hepatic circulation.

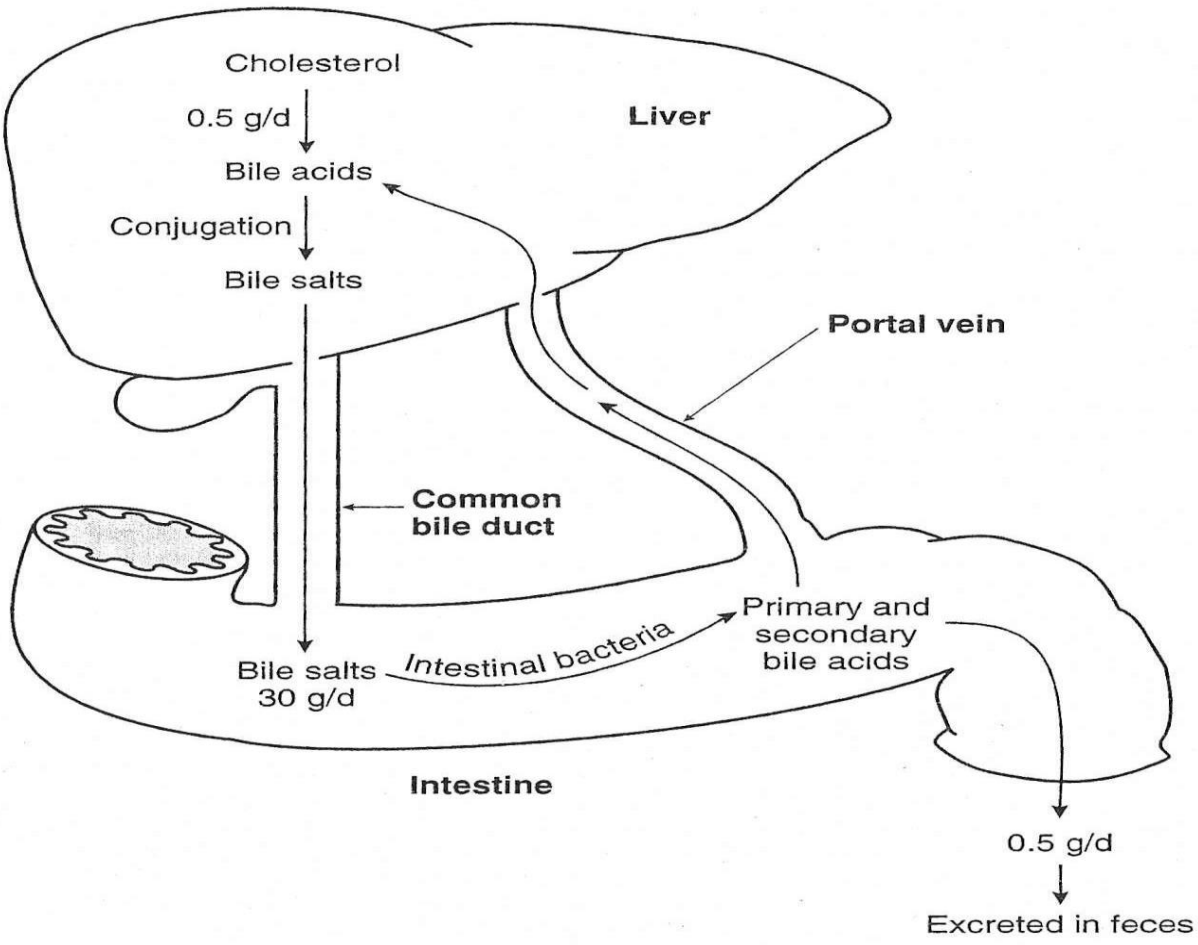


Lowering Cholesterol

- Bile sequestering agents



1. Bind bile acid
2. Utilize more cholesterol to make bile acids



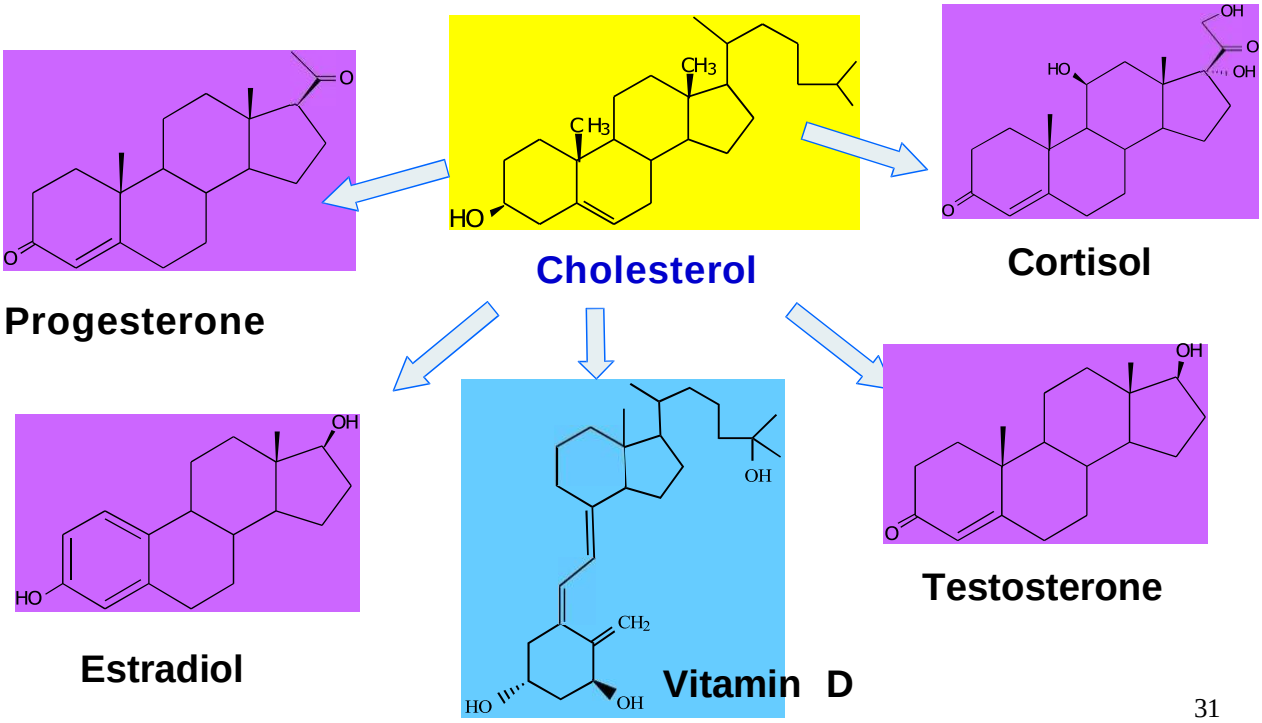
Cholelithiasis: Bile salts and phospholipids are responsible to keep cholesterol in bile in a soluble state.

Deficiency of Bile salts, leads to precipitation of cholesterol into crystals in gall bladder resulting in Gall stones or cholelithiasis

Causes:

- Impairment in Liver
- Obstruction of biliary tract
- Defect in Enterohepatic circulation of bile salts

Transformations of Cholesterol: Steroid Hormones



HYPER CHOLESTEROLEMIA

Serum cholesterol level is more than 200mg/dl it is considered as Hypercholesterolemia

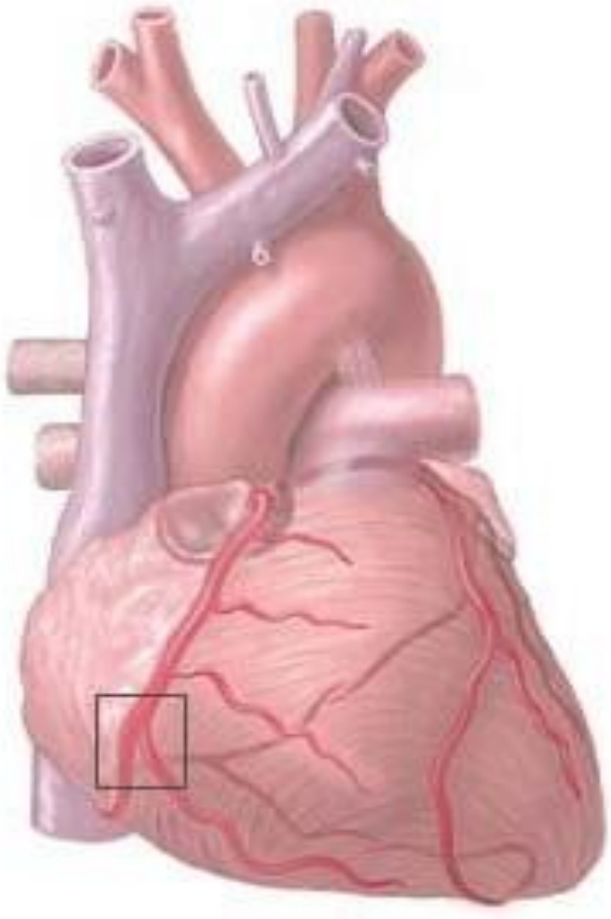
Causes-

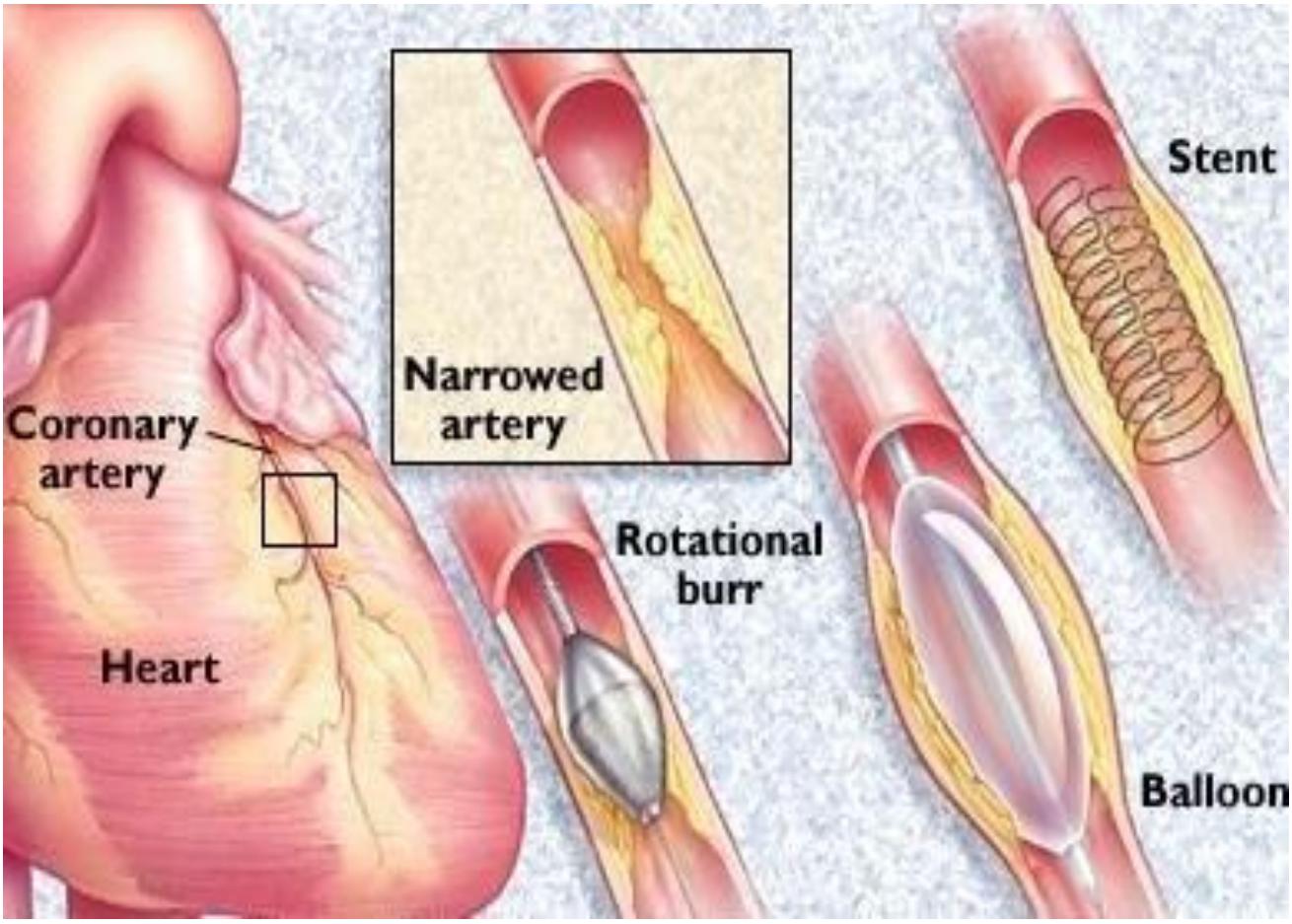
1) Diabetes mellitus
2) Hypothyroidism
3) Obstructive jaundice
4) Nephrotic syndrome

Atherosclerosis : Deposition of cholesterol esters and other lipids in the internal layers of arterial walls, leading to hardening and closure of coronary & cerebral arteries

ATHEROSCLEROSIS

Blockage in right coronary artery





Treatment for Hypercholesterolemia

1) Consumption of PUFA
2) Dietary fiber
3) Avoiding high carbohydrate diet
4) Drugs like Lovastatin

Atorvastatin } Inhibit HMG CoA reductase

Cholestyramine
Cholestipol } bind with bile acid decreases Entero hepatic circulation

- ***Thank you***