CHOLESTEROL METABOLISM

By
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CHOLESTEROL

→ Cholesterol is a **light yellow crystalline solid**

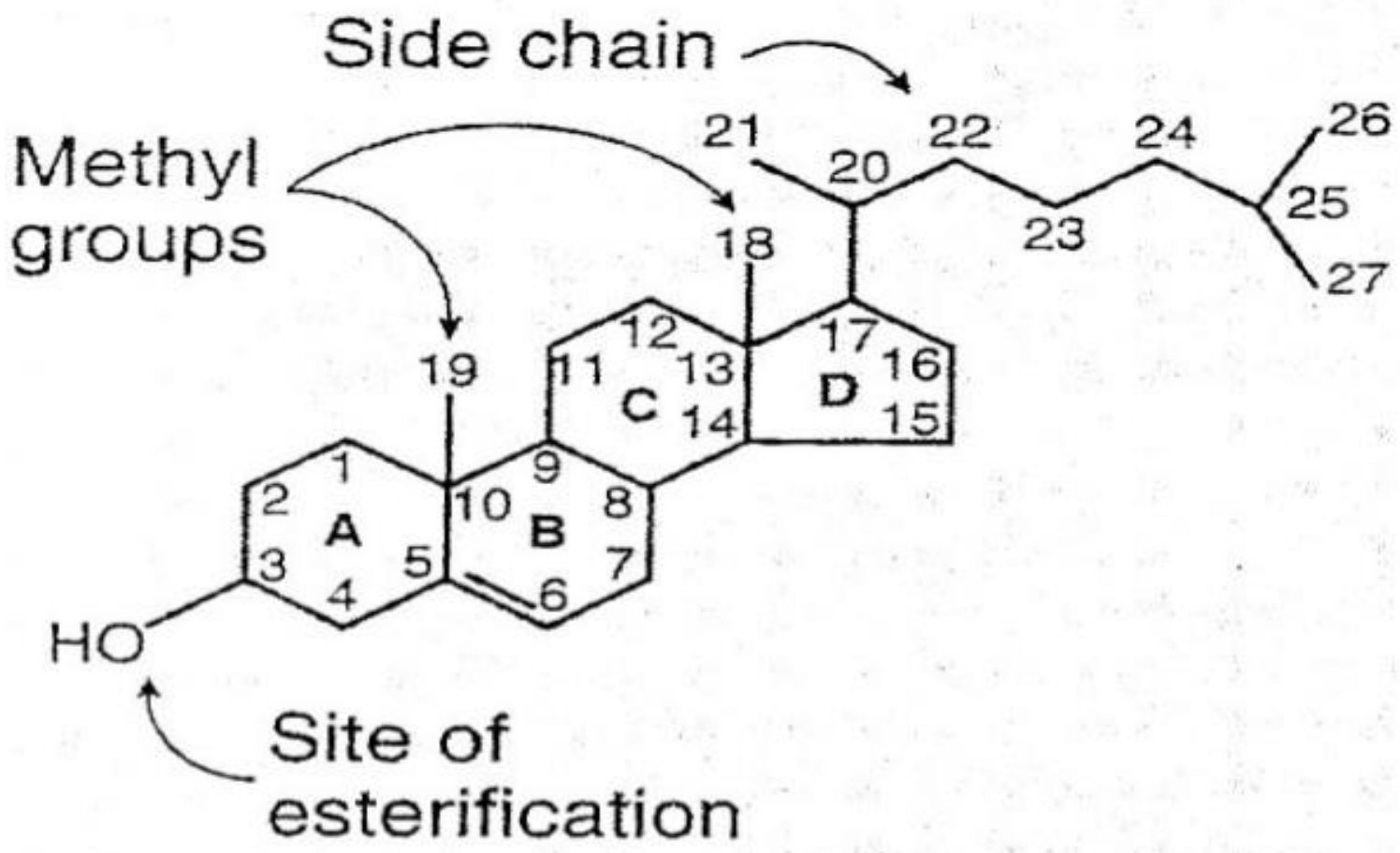
→ It is a **27 Carbon compound**

→ 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:

$$18\ \text{Acetyl CoA} + 18\ \text{ATP} + 16\ \text{NADPH} + 4\ O_2 \longrightarrow$$

$$\text{cholesterol} + 9\ CO_2 + 16\ NADP^+ + 18\ \text{ADP} + 18\ P_i$$

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***

Cytosol → **Cholesterol Synthesis**

Mitochondria → **Ketone bodies synthesis**

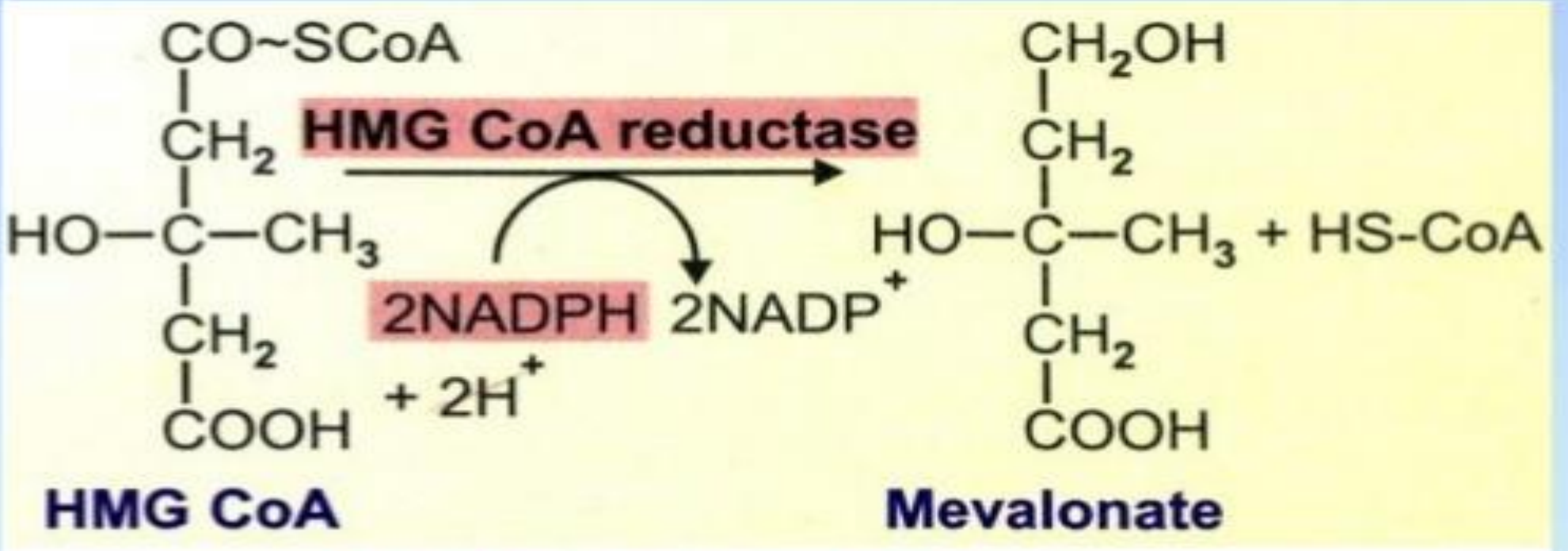
Step III – Regulating Step

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)**

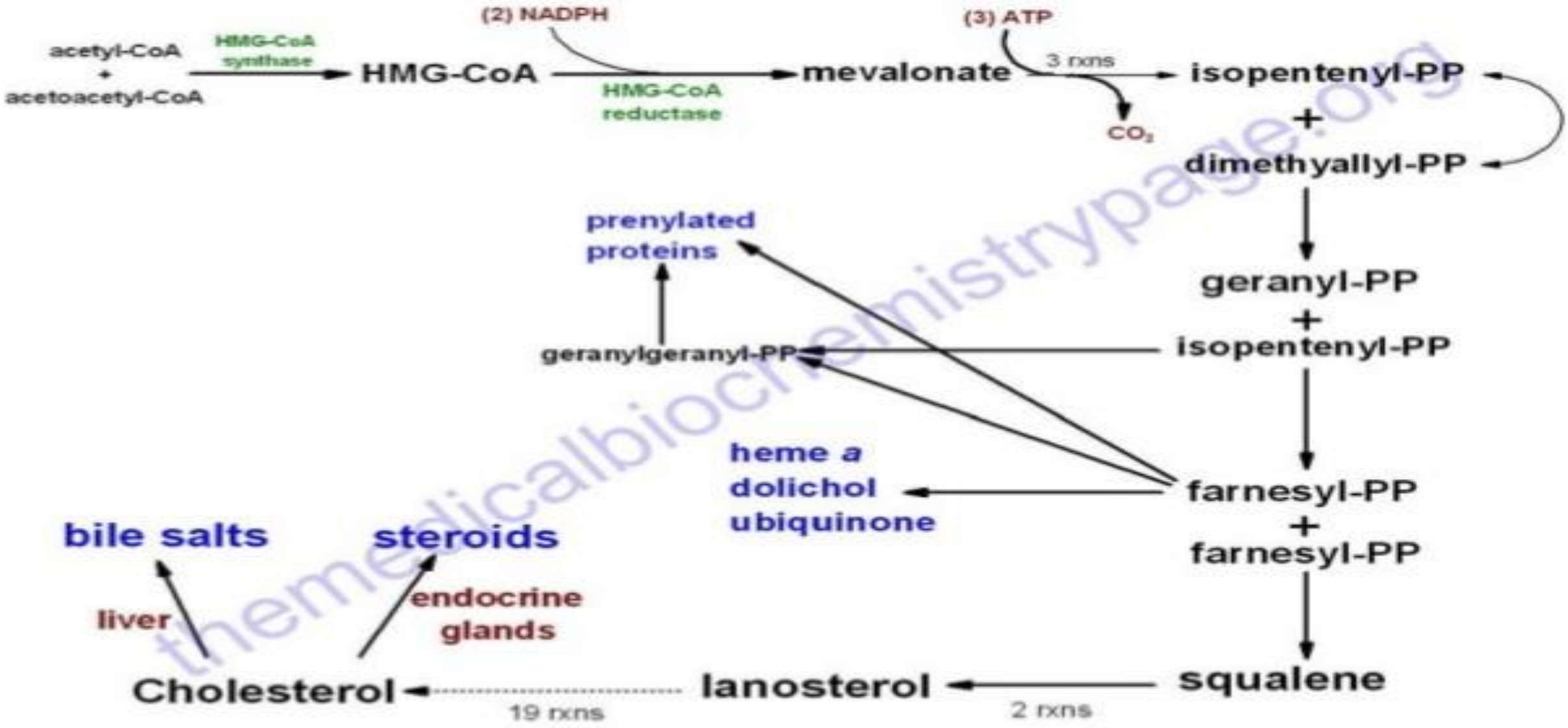
Step 6 : ***Cyclization***

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

Lanosterol first formed steroid compound.

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

Biosynthesis of Cholesterol



Regulation of Cholesterol Synthesis

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.

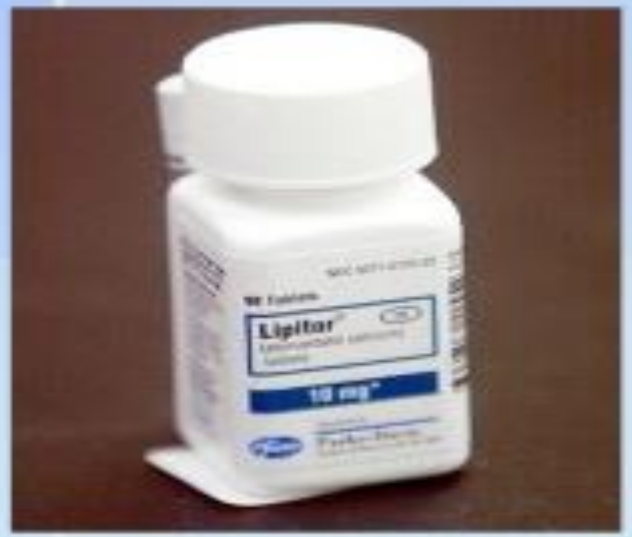
3. **Inhibition by drugs:**

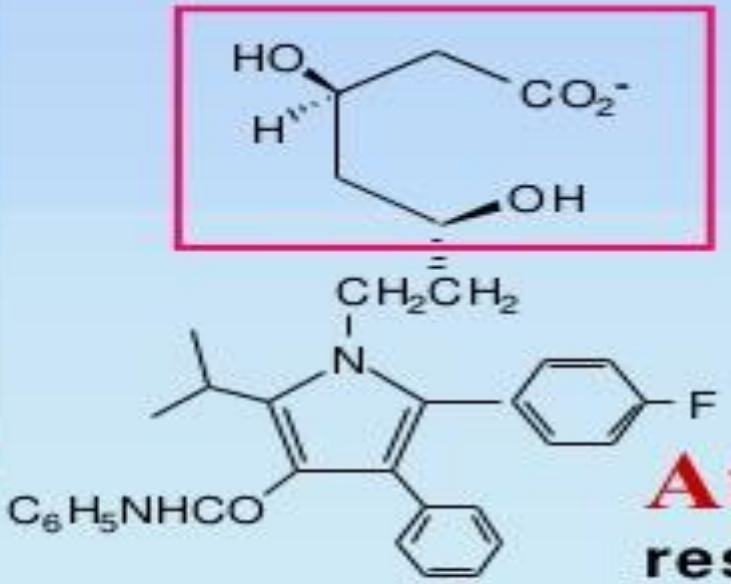
Compactive

Lovastatin

Competitive Inhibitors for HMG CoA reductase.

Inhibition of Cholesterol Biosynthesis





Atorvastatin (Lipitor):
resembles intermediate

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

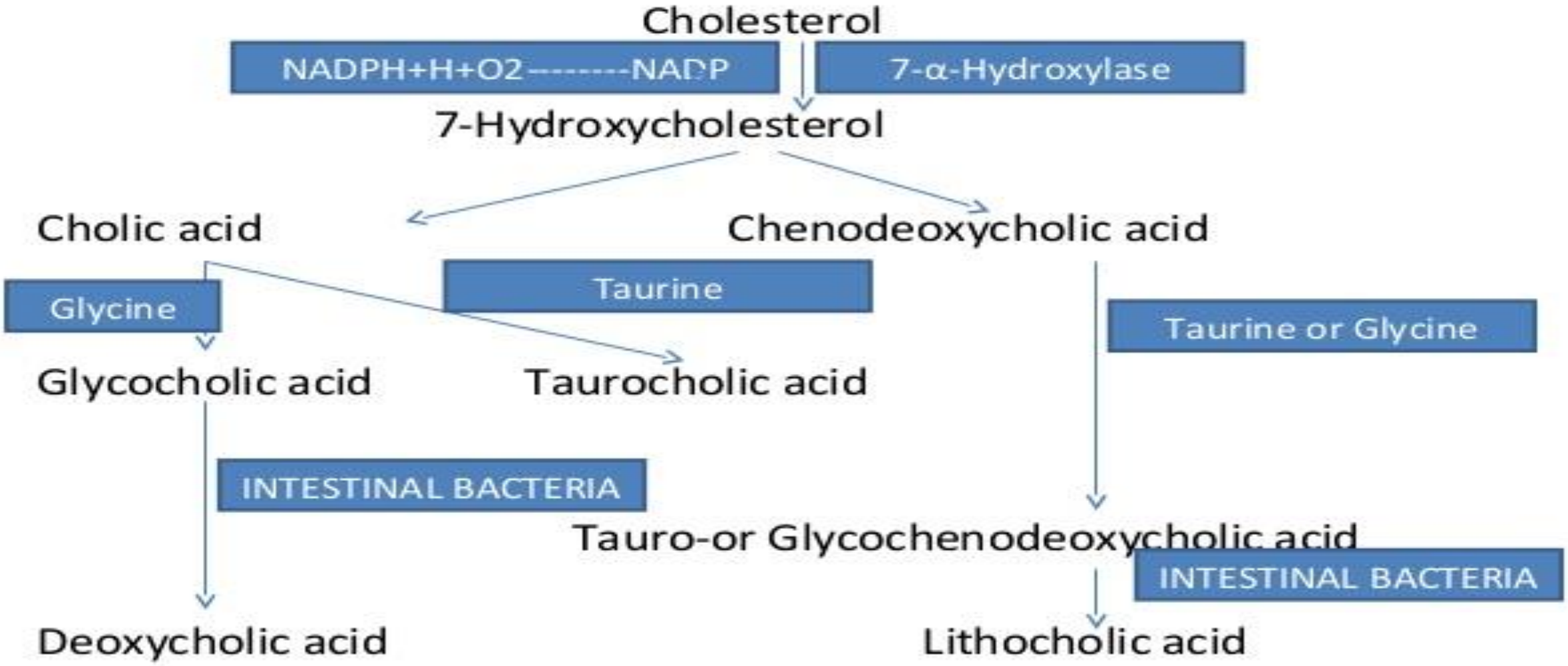
Primary Bile acids –

cholic acid, chenodeoxy cholic acid

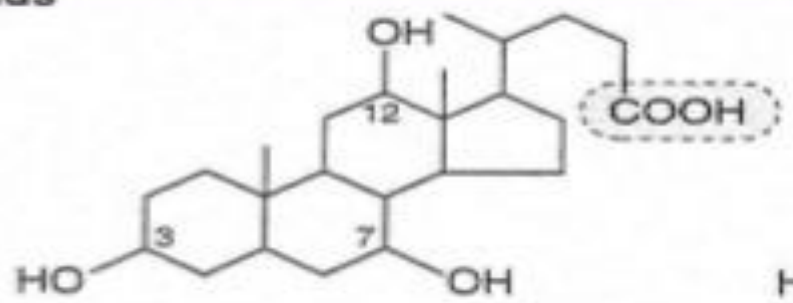
Secondary Bile acids –

deoxycholic acid, Lithocholic acid

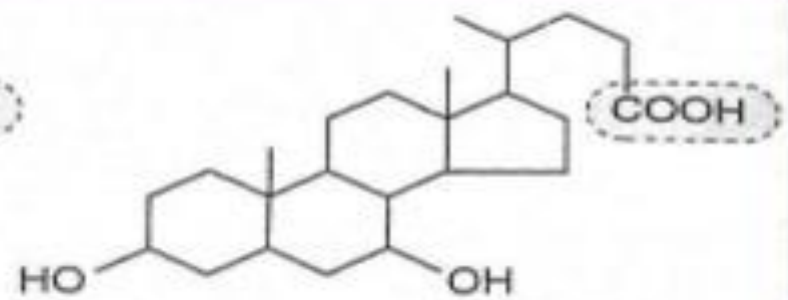
SYNTHESIS OF BILE ACIDS



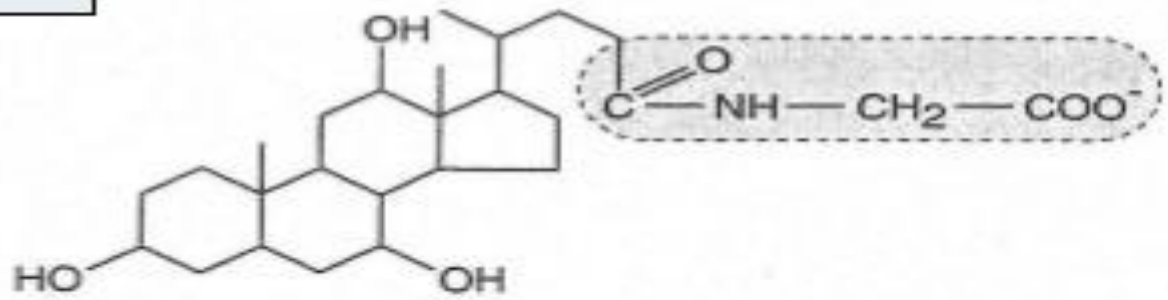
Bile acids



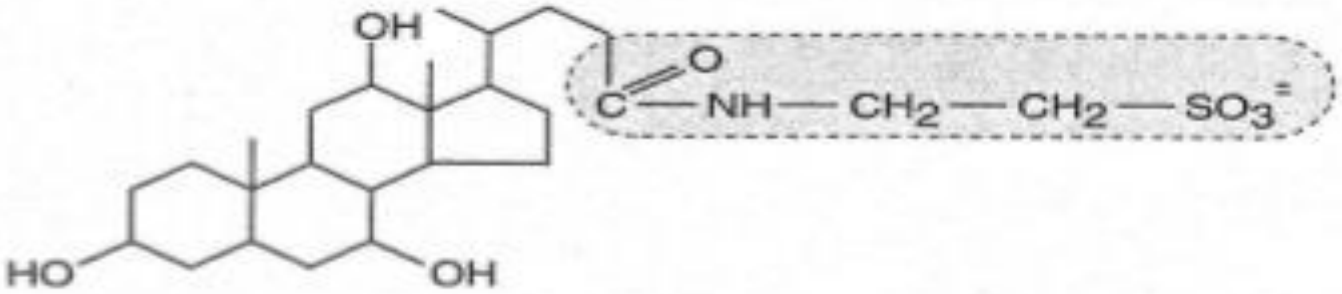
Cholic acid



Chenodeoxycholic acid



Glycholate



Taurocholate

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

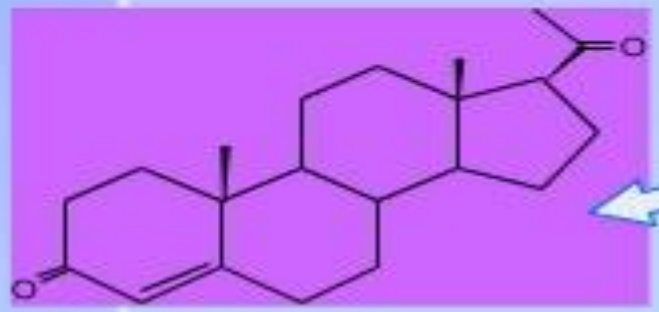
Deficiency of Bile salts, leads to precipitation of cholesterol into crystals in gall bladder resulting in Gall stones or cholelithiasis

Causes:

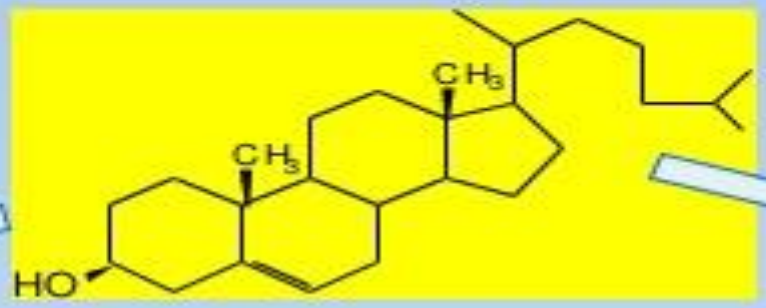
- Impairment in Liver
- Obstruction of biliary tract
- Defect in Enterohepatic circulation of bile salts

Transformations of Cholesterol:

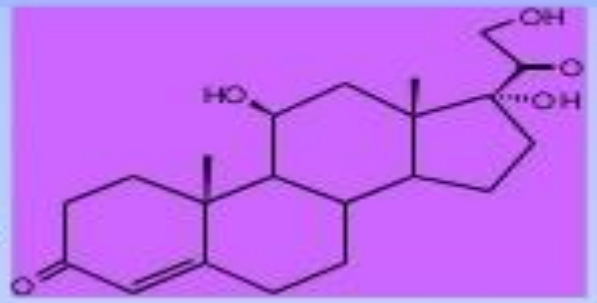
Steroid Hormones



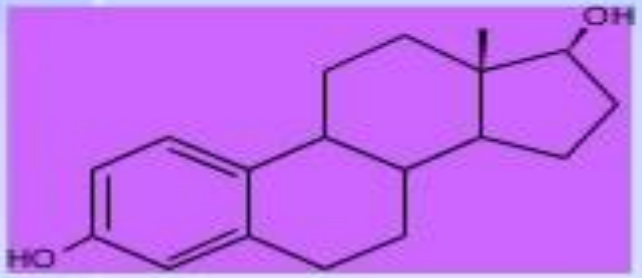
Progesterone



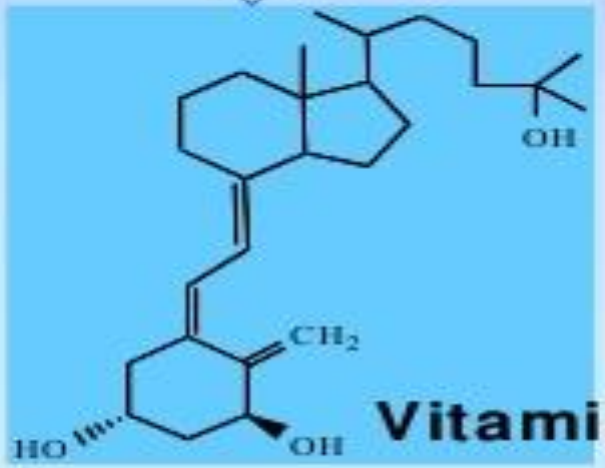
Cholesterol



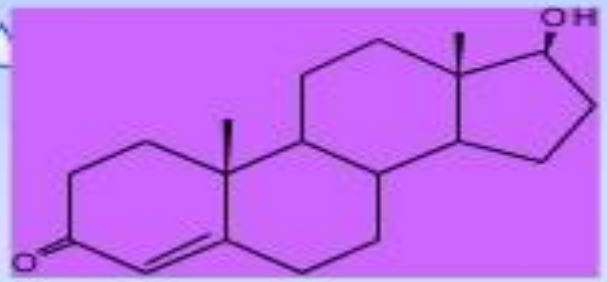
Cortisol



Estradiol



Vitamin D



Testosterone

HYPER CHOLESTEROLEMIA

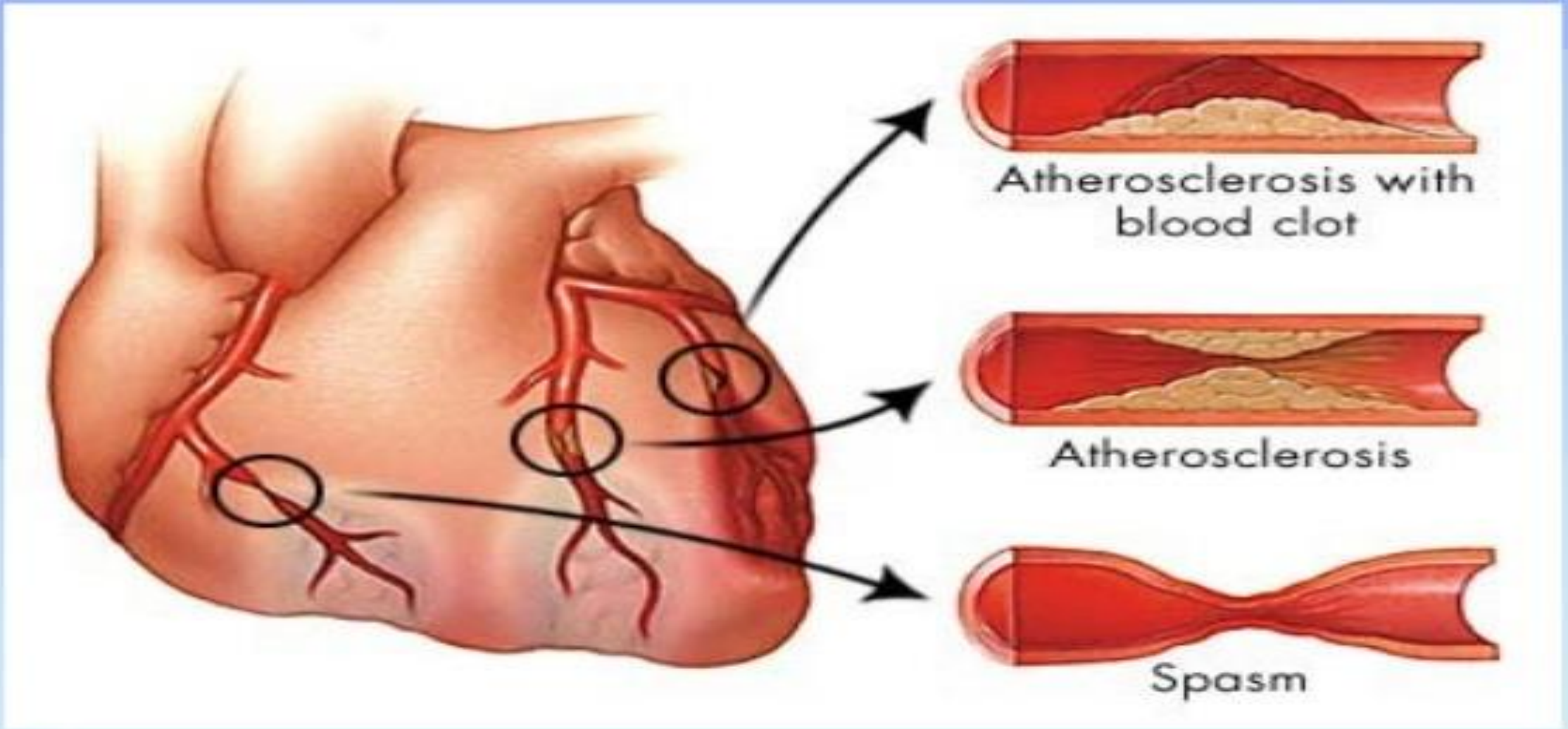
Serum cholesterol level is more than **200mg/dl** it is considered as Hypercholesterolemia

Causes-

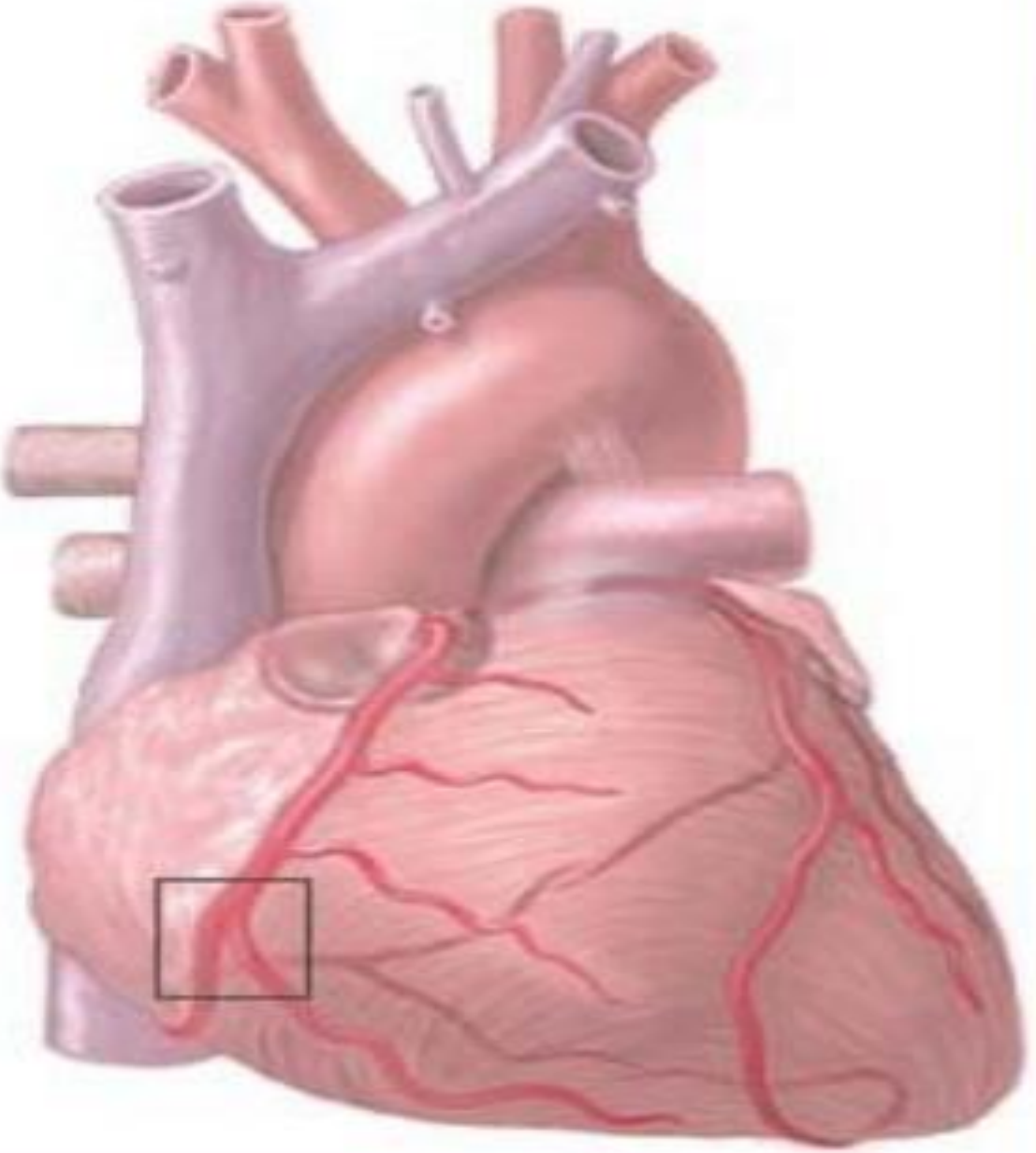
1) **Diabetes mellitus**
2) **Hypothyroidism**
3) **Obstructive jaundice**
4) **Nephrotic syndrome**

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