CHOLESTEROL METABOLISM

By

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(M.Sc 201-II)

CHOLESTROL BIOSYNTHESIS

- **CHOLESTROL**

1. Animal Sterol
2. 70kg/body weight------2gm /kg -----140 gm cholesterol/70kg body weight
3. Amphipathic in nature ie has hydrophilic& hydrophobic regions
4. Cholesterol biosynthesis in human body =1 gm/day
5. Organs involved in synthesis---- Cytosol /microsomes of adrenal cortex Liver/intestine/testes/ovaries/skin/adrenal cortex

UTILIZATION OF CHOLESTEROL

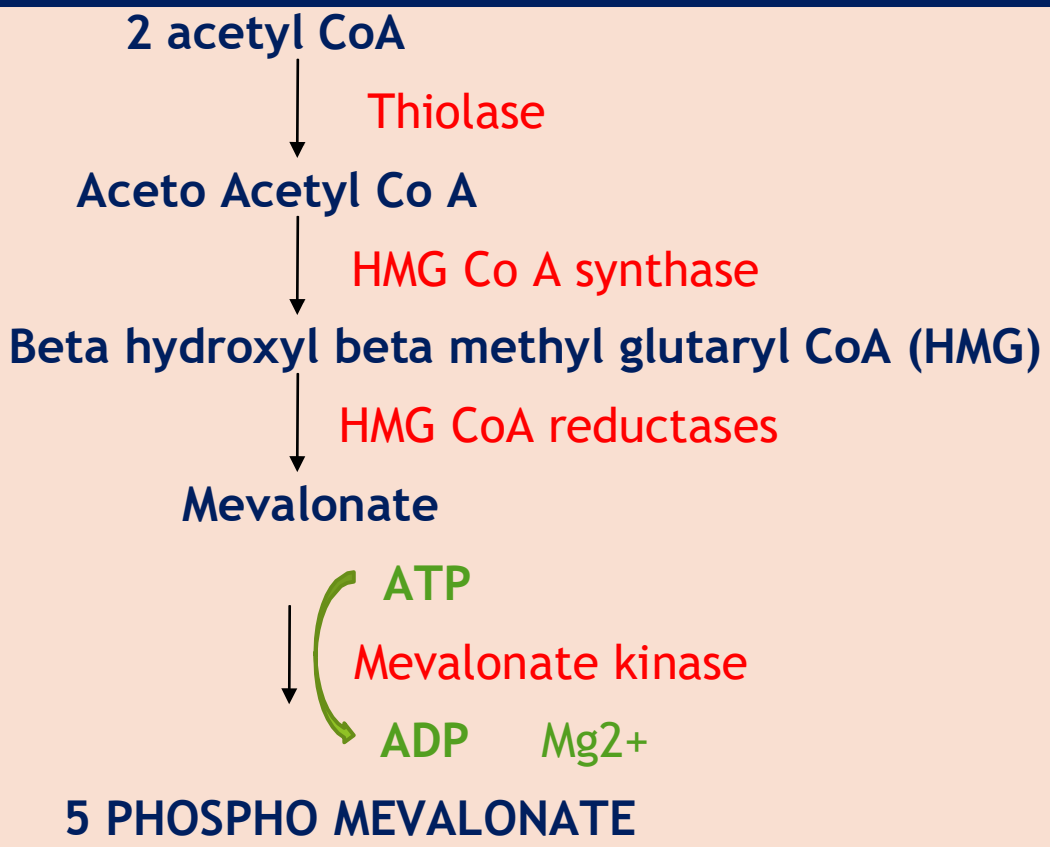
- CELL MEMBRANE FORMATION
- FATTY ACID TRANSPORT FOR BETA OXIDATION
- Utilization in Synthesis of

A. Lipoproteins
B. Steroid Hormones
C. Glucocorticoid (Cortisol)
D. Minero corticoid (Aldosterone)
E. Sex hormones ---Progesterone//estradiol/Testosterone
F. Bile salts

Biosynthesis of cholesterol

- **SITES of biosynthesis of cholesterol :CYTOSOL OF ALL TISSUES AND MICROSOMES**
- **NADPH used as reducing equivalent**
- **ENERGY supplemented in the form of ATP**
- **CARBON SKELETON------Carbon 1,3,5,7,9,11,13,15,17,18,19,22,24,26**

Synthesis of cholesterol



Synthesis of cholesterol

5 PHOSPHO MEVALONATE (6C)

ATP

PHOSPHO MEVALONATE KINASE

ADP

5 PYRO PHOSPHATE MEVALONATE (6C)

ATP

KINASE

ADP

3 PHOSPHO 5 PYROPHOSPHO MEVAVOLANATE(6C)

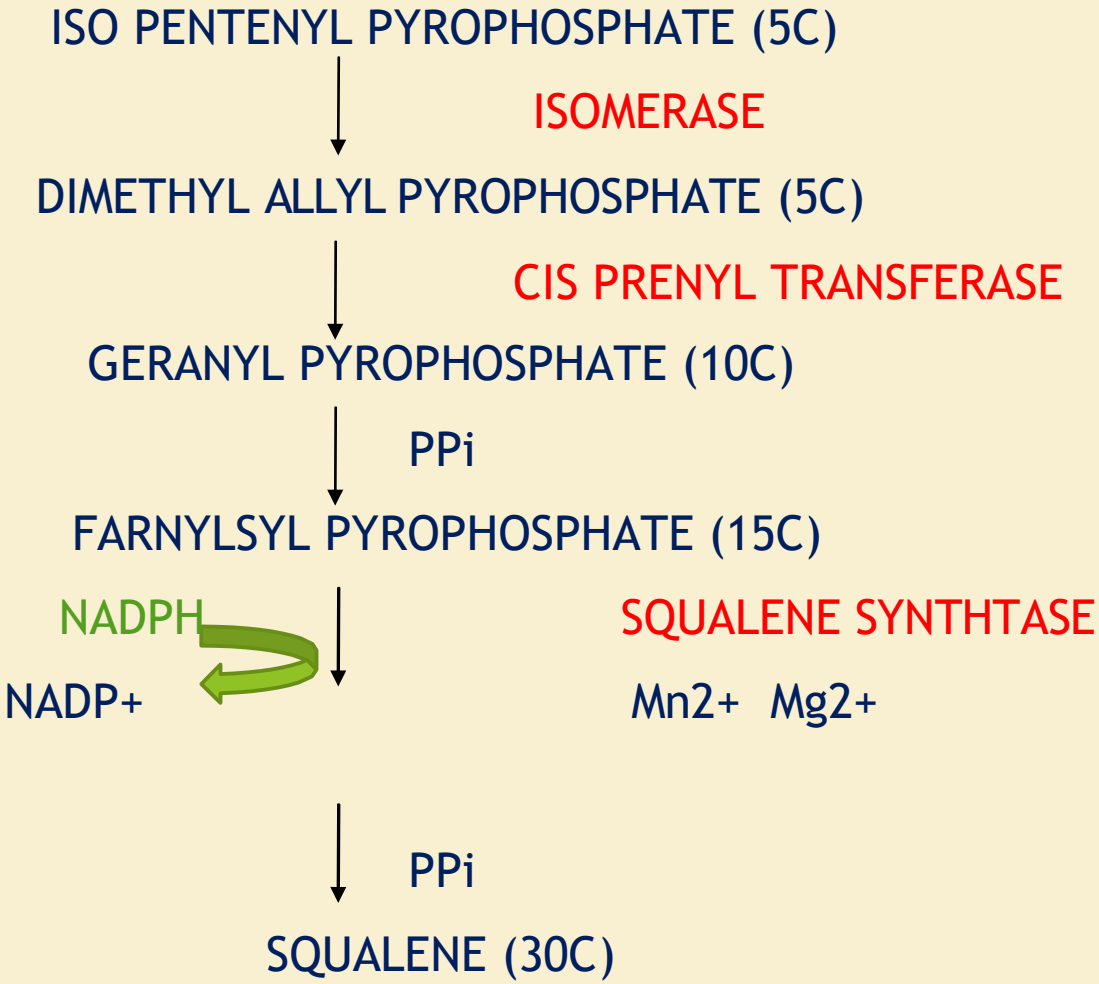
PYRO PHOSPHO MEVAVONATE DECARBOXYLASE

ISO PENTENYL PYROPHOSPHATE (5C)

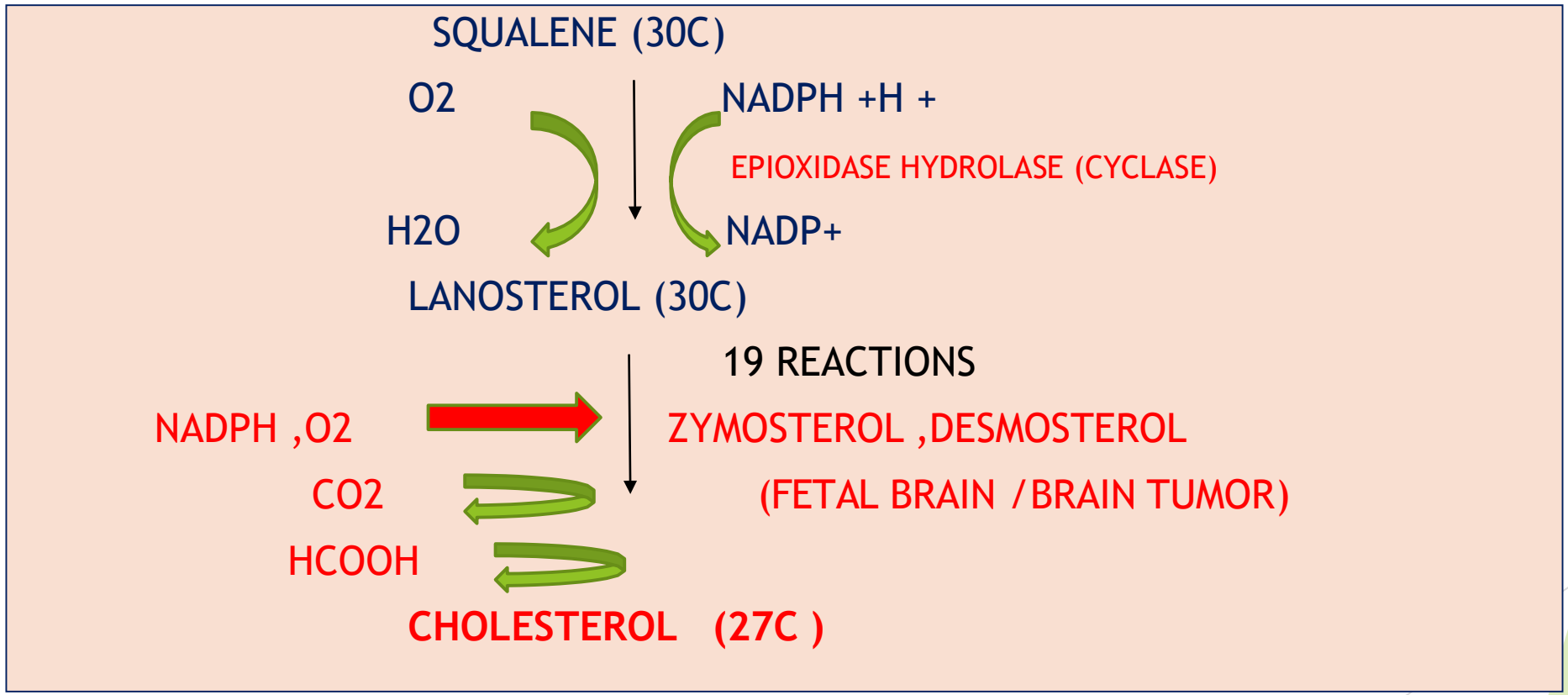
ISOMERASE

DIMETHYL ALLYL PYROPHOSPHATE (5C)

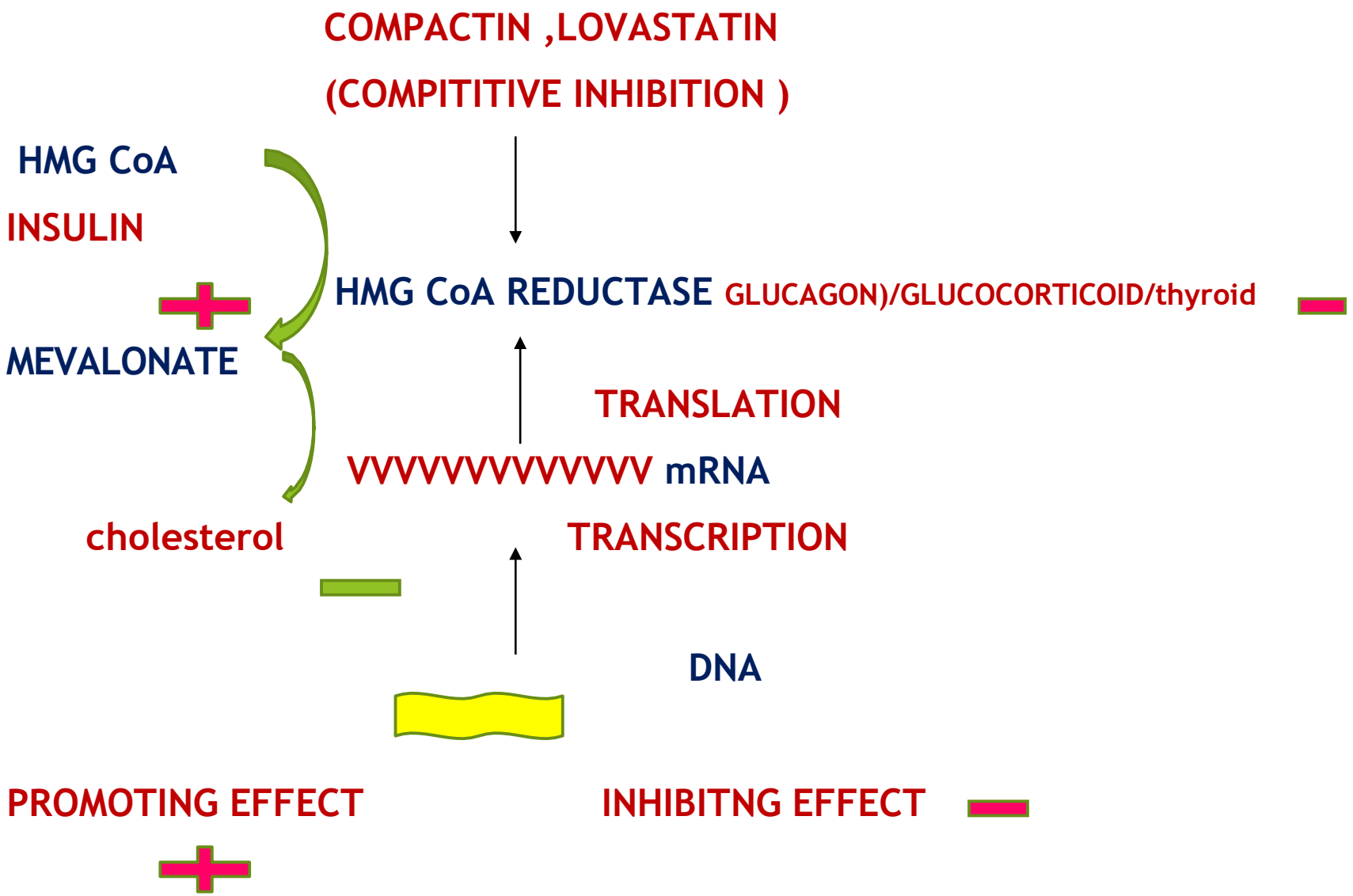
Synthesis of cholesterol



Synthesis of cholesterol



REGULATION OF CHOLESTEROL BIOSYNTHESIS



REGULATION OF CHOLESTEROL BIOSYNTHESIS

- **Limiting Enzymes : HMG CoA reductase**
- 1) Feedback Control : Increase cholesterol leads to decrease transcription of HMG CoA reductases
- **2) Hormonal regulation**

Glucagon /glucocorticoids/thyroxin

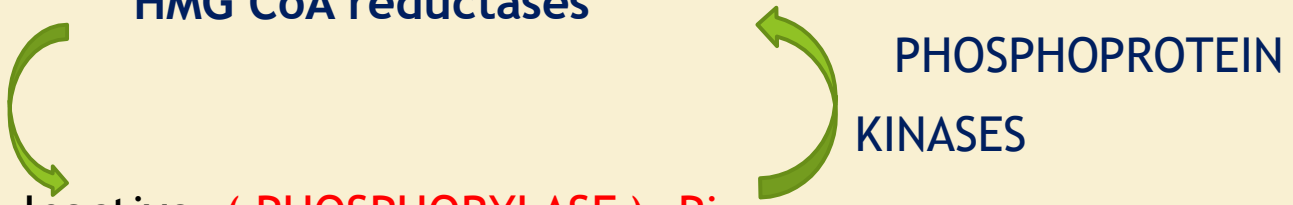
Active ----------→ Inactive HMG Co A reductases

(phosphorylated forms)

Increase Glucagon-----→ Decrease cholesterol

Active (PHOSPHORYLASE)

KINASES **HMG CoA reductases**



REGULATION OF CHOLESTEROL BIOSYNTHESIS

(1) **insulin (lipogenic)**

Inactive ----------→**ACTIVE HMG CoA reductases (**Dephosphorylated form)

Increase Insulin → increase cholesterol

(2) Diabetes Mellitus → Decrease Insulin →Increase Lipolysis →Increase Acetyl CoA → → Increase Cholesterol

(3) Inhibition by Drugs

Lovastatin /compactin (fungal product)

Competitive inhibitors of HMG CoA reductases -----→**Hypochosterolemia**

(4) Inhibition by bile acids

Decrease HMG CoA Reductase → decrease cholesterol

CLINICAL SIGNIFICANCE OF CHOLESTEROL ESTIMATION

- Normal Serum Cholesterol levels =150-200 mg/dl (adult)
- Normal Serum Cholesterol levels in New born =100 mg /dl
- Women < men (low level of serum estrogen→ low cholesterol)
- Estimation of Serum Cholesterol levels by Liebermann Bur chard reactions

  CHOLESTEROL + ACETIC UNHYDRIDE -------→H_2SO_4 →GREEN COMPLEX
- TOTAL CHOLESTROL = HDL+ LDL+VLDL
- **TG /5= VLDL**
- AFTER THE Precipitation of LDL & VLDL BY Polyethylene glycol (PEG)
- LDL CHOLESTEROL = Total cholesterol – (HDL + VLDL)

  = Total cholesterol – (HDL + TG/5)
- LDL CHOLESTEROL=70-200 mg/dl
- Serum HDL CHOLESTEROL = 30-60 mg/dl (increase in HDL cholesterol is beneficial → /decrease in HDL harmful &leads to Coronary Heart Disease (CHD) ATHEROSCLROSIS
- Increase in Serum Cholesterol levels Coronary Heart Disease (CHD) ATHEROSCLROSIS

CLINICAL SIGNIFICANCE OF CHOLESTEROL ESTIMATION

- **HYPERCHOLESTEROLEMIA** = Serum Cholesterol levels > 200 mg/dl
- **HYPERCHOLESTEROLEMIA associated with**

a) Diabetes Mellitus (increase availability of acetyl CoA due to unavailability of oxaloacetate)

b) Hypothyroid / myxedema (associated decrease HDL receptors on Hepatocytes)

c) Obstructive Jaundice (obstruction in excretion of cholesterol through bile)

d) Nephrotic syndrome (increase globulins & increase in plasma lipoproteins)

- Hypercholesterolemia----atherosclerosis ----CHD ----- POSITIVE correlation of LDL-------- NEGATIVE correlation HDL

- **CONTROL OF HYPERCHOLESTEROLEMIA**

(A) Intake of PUFA →increase synthesis of of LCAT→ Cholesterol Transport→Excretion of Cholesterol → decrease in serum CHOLESTEROL levels

(Sources of PUFA : COTTON SEED OIL,SOYABEAN OIL,CORN OIL,FISH OIL,SUN FLOWER OIL)

(B) Dietary fibers -decrease in cholesterol absorption

(C) Avoid carbohydrate diet

(D) Drugs

CHOLESTEROL LOWERING DRUGS

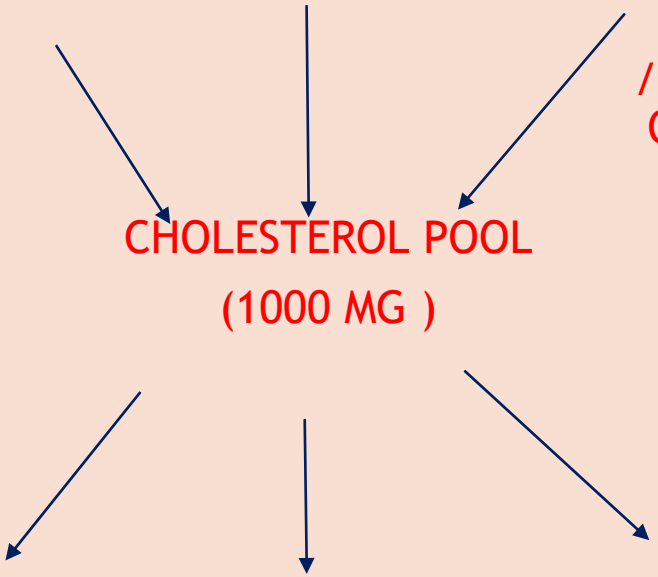
DRUG	ACTION
LOVASTATIN	INHIBITORS OF HMG Co A reductase
SITOSTEROL	ESTERIFICATION OF CHOLESTROL
CHOLETYRAMIN	ABSORBTION OF DECREASED ,EXCRETION INCREASED ALONG WITH BILE SALTS
ESTROGEN /NEOMYCIN	FEED BACK INHIBITION
CLOFIBRATE	DECREASE VLDL METABOLISM INLIVER INCREASES INCREASE LIPOPROTEIN LIPASE DECREASE CHOLESTEROL/DECREASE TG

Sources and utilization of Cholesterol

DIETARY CHOLESTEROL

CHOL ESTEROL SYNTHESIS

CHOLESTEROL FROM EXTRA HEPATIC TISSUE VAIABLE(SKIN /INTESTINE/REPRODUCIVE ORGANS



CHOLESTEROL POOL (1000 MG)

LIPOPROTEIN VARIABLE BILE

BILE SALTS /BILE ACIDS (250MG)

CHOLESTEROL LOST IN (500 MG /DAY)

TRANSPORT OF CHOLESTEROL

- Existence of cholesterol in circulation

a) 70—75% Esters with long chain fatty acids

b) 20-25% free cholesterol

LIPOPROTEIN CELL MEMBRANE

- **Transport & Elimination in the form of**

a) HDL

b) LCAT (LECITHIN –CHOLESTEROL ACYL TRANFERASE)

I

2ND POSITION LECITHIN ----- OH CHOLESTEROL OF HDL

LCAT (LECITHIN –CHOLESTEROL ACYL TRANFERASE)

LCAT (LECITHIN –CHOLESTEROL ACYL TRANFERASE)

- **SITE OF SYNTHESIS : LIVER**
- **FUNCTION OF LCAT :TRANSFFER OF FATTY ACIDS FROM SECOND POSITION OF LECITHIN TO HYDROXYL GROUP OF CHOLESTEROL**
- **REAL SUBSTRATE is HDL CHOLESTEROL**
- **ACTIVITY α concentration of APO A1 OF HDL**
- **ESTER OF CHOLESTEROL**

LCAT

HDL CHOLESTEROL

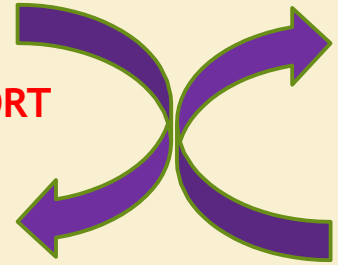
(TRANSPORTED TO LIVER)

DEGRADED AND EXCRETION

PERIPHERAL TISSUE **PERIPHERAL TISSUE**

REVERSED CHOLESTEROL TRANSPORT **TRANSPORT**

LIVER **LIVER**



EXCRETION OF CHOLESTEROL (ONLY ONE WAY)

CHOLESTEROL (50% COVERTED TO BILE ACIDS)

NADPH+ + H+

7 HYDROXYLASE (**RATE LIMITING** STEP **INHIBITED BY BILE ACIDS**)

O2 **(LIVER)**

NADP

SEVERAL STEPS

CHOLIC ACID

CHENO CHOLIC ACID

GLYCOCHOLIC ACD

TUARO CHOLIC ACID

TAURINE OR GLYCINE

DEOXY CHOLIC ACID

EXTRA HEPATIC CIRCULATION (30GMS)

TAURO OR GLYCOCHENO CHOLIC ACID

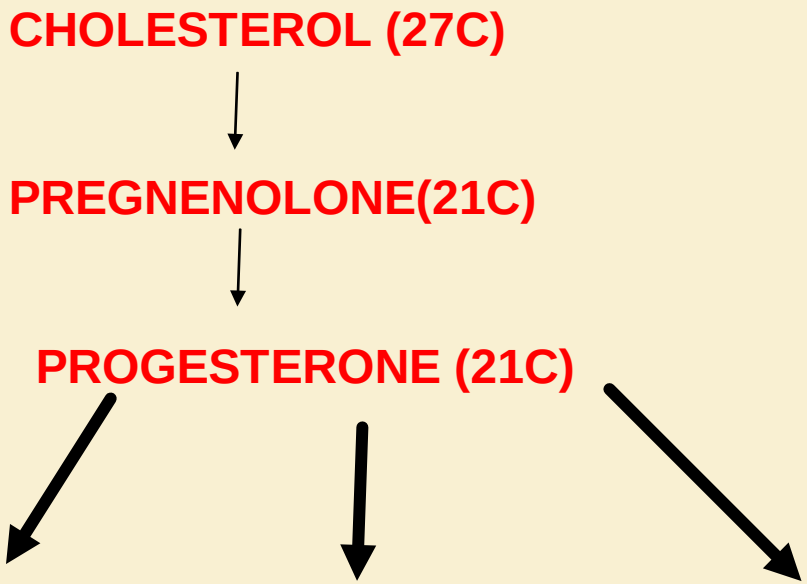
LITHOCHOLIC ACID

EXCRETION IN STOOL (0.5GM)

PRIMARY BILE ACIDS

SECONDARY BILE ACIDS

Utilization of cholesterol -synthesis of steroid Hormones



CHOLELITHIOSIS OBSERVED IN IMPAIRED LFT(DEFICIENCY OF BILE SALTS → DEFECTIVE ABSORBTION OF LIPIDS)

Utilization of cholesterol for Synthesis of VITAMIN D

Cholesterol

SKIN ↓

7 DEHYDRO CHOLESTEROL

↓ HYDROXYLATION AT 1,25 POSITION IN LIVER /KIDNEY

1,25 DIHYDROXY CHOLE CALCIFEROL (CALCITRIOL)

Thank you