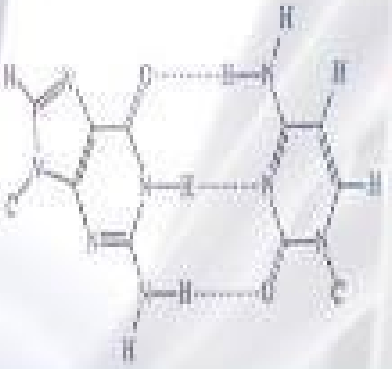
Medical Committee
The University of Jordan

SLIDE ○ SHEET

SLIDE : 22

DR.NAME: Dr Faisal

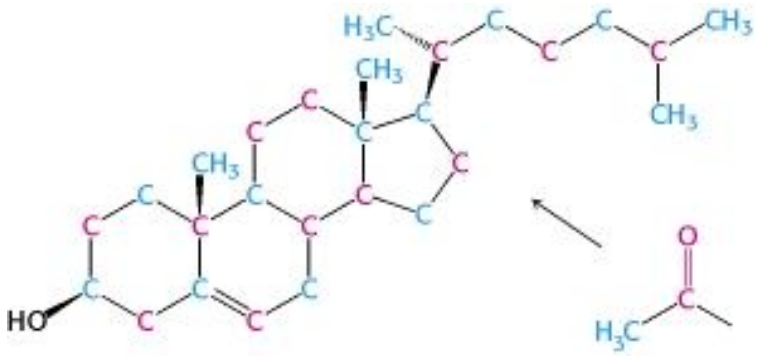
Biochemistry



Majida Al-Foqaraa'

Cholesterol Synthesis Requires

- Carbon Source: Acetyl CoA
- Energy: ATP
- Reducing Power: NADPH
- O_2



Stages in Cholesterol Synthesis

Acetyl CoA (C2)

↓

Mevalonate (C6)

↓

Isoprene Units (C5)

↓

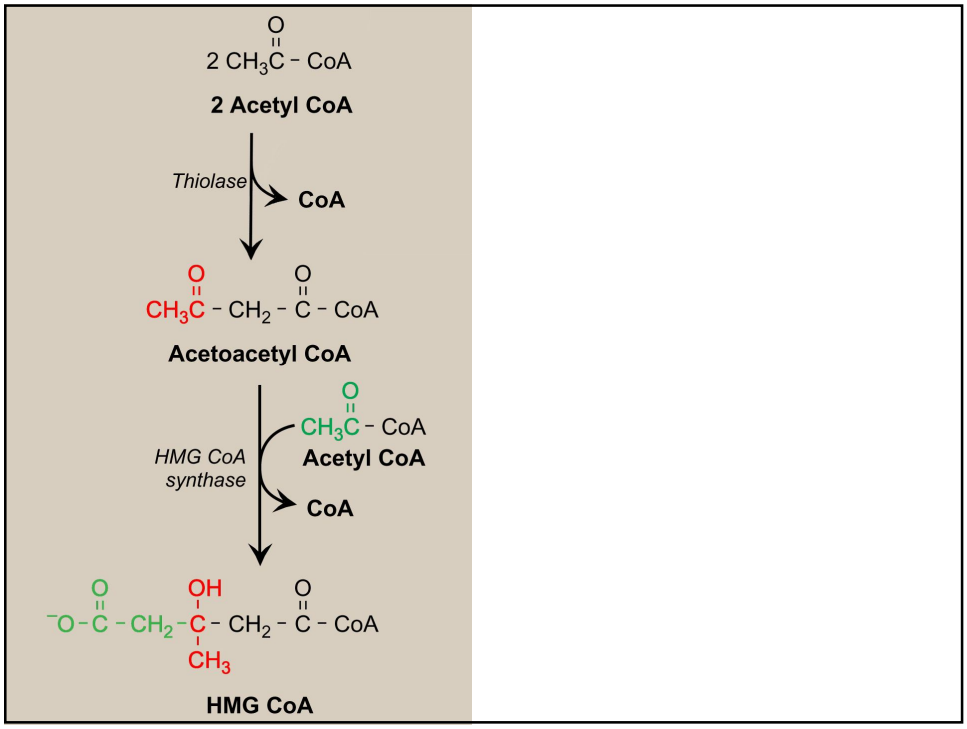
Squalene (C30)

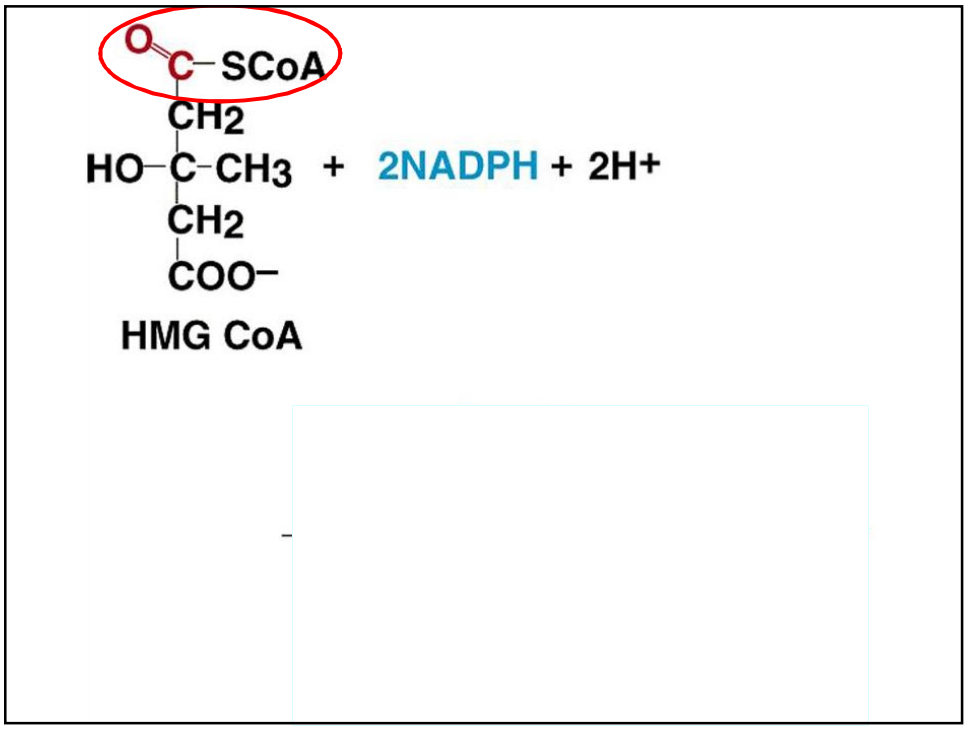
↓

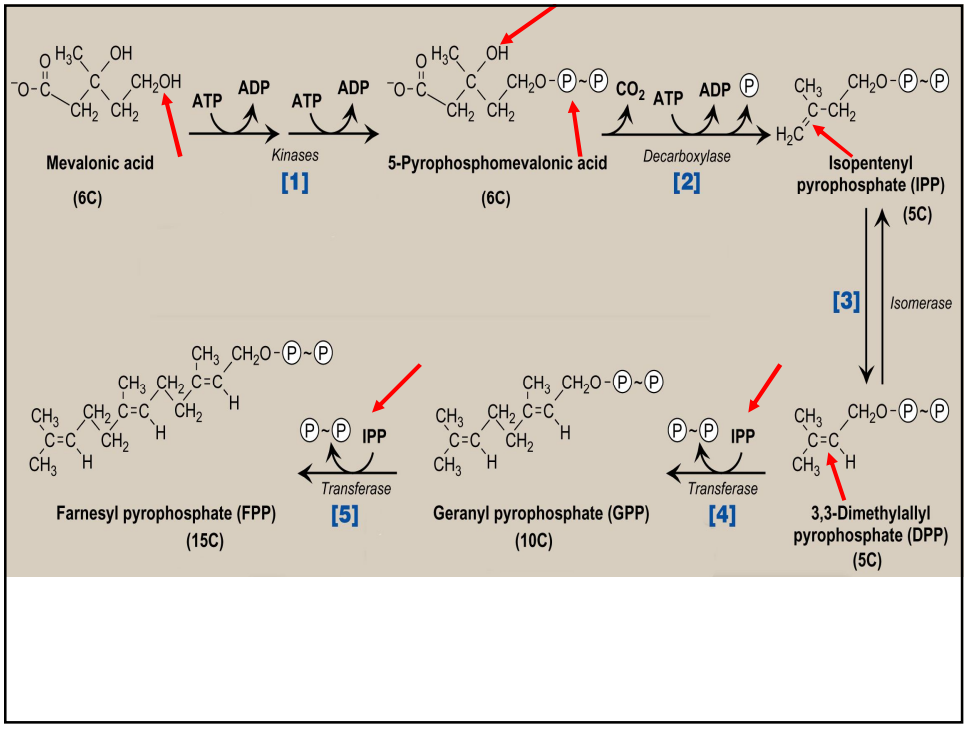
Lanosterol (C30)

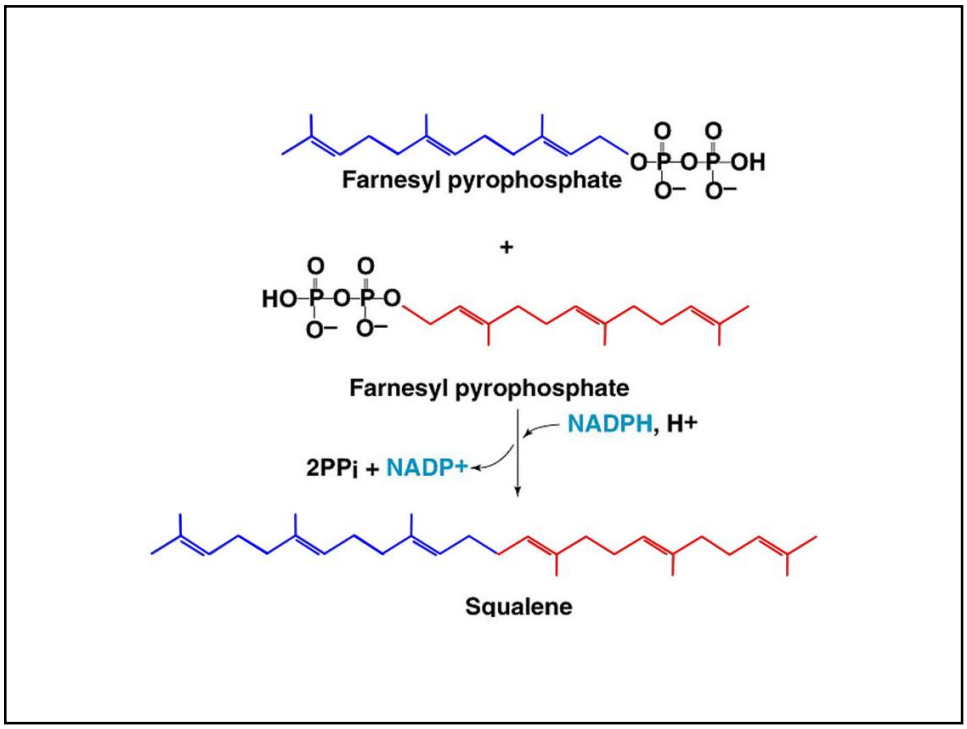
↓

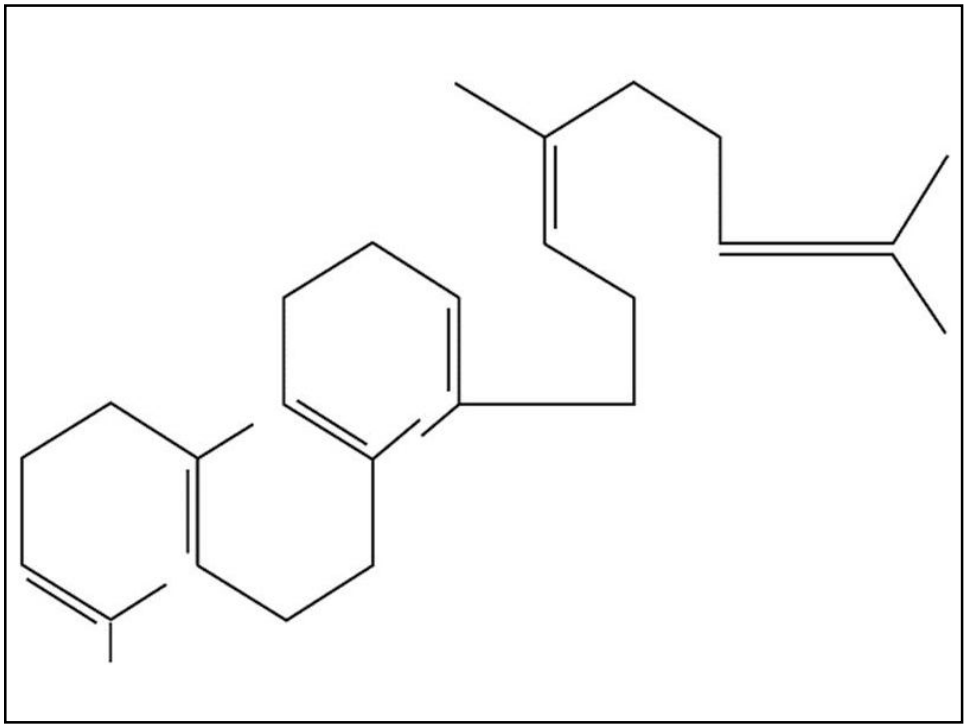
Cholesterol (C27)

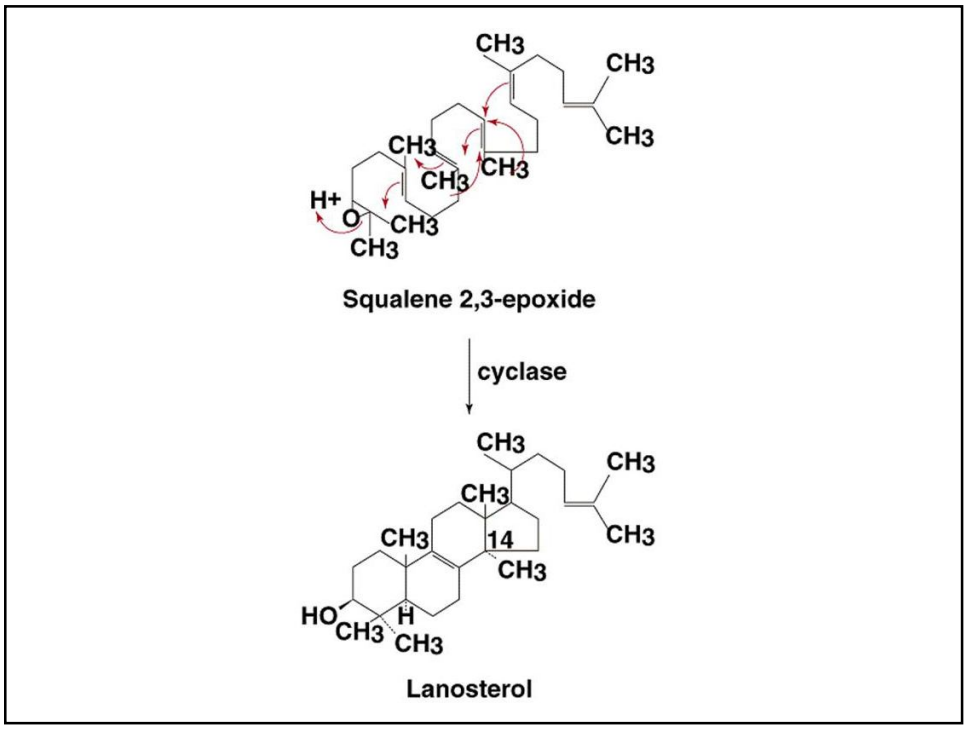

2 CH3C - CoA
2 Acetyl CoA
Thiolase
CoA
CH3C - CH2 - C - CoA
Acetoacetyl CoA
HMG CoA synthase
CH3C - CoA
Acetyl CoA
CoA
⁻O-C - CH2-C - CH2 - C - CoA
CH3
HMG CoA

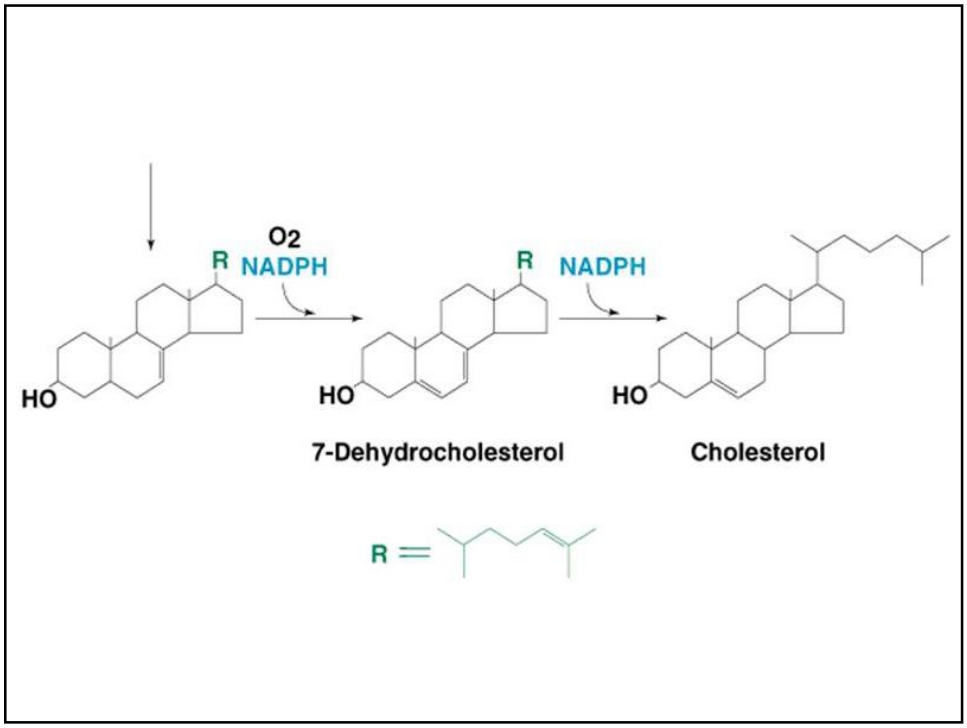

C–SCoA
CH2
HO–C–CH3
CH2
COO–
HMG CoA
+ 2NADPH + 2H+


Mevalonic acid
(6C)
ATP
ADP
ATP
ADP
Kinases
[1]
5-Pyrophosphomevalonic acid
(6C)
CO2
ATP
ADP
Decarboxylase
[2]
Isopentenyl
pyrophosphate (IPP)
(5C)
[3]
Isomerase
3,3-Dimethylallyl
pyrophosphate (DPP)
(5C)
IPP
Transferase
[4]
Geranyl pyrophosphate (GPP)
(10C)
IPP
Transferase
[5]
Farnesyl pyrophosphate (FPP)
(15C)


Farnesyl pyrophosphate
+
Farnesyl pyrophosphate
NADPH, H+
2PPi + NADP+
Squalene




CH3
CH3
CH3
CH3
CH3
CH3
H+
O
CH3
CH3
Squalene 2,3-epoxide
cyclase
CH3
CH3
CH3
CH3
14
CH3
CH3
HO
CH3
H
CH3
Lanosterol



Acetyl CoA → **HMG CoA** → Mevalonate (C6)

↓

Dimethylallyl Pyrophosphate ⇌ İsopentenyl Pyrophosphate (C5)

↓

Geranyl Pyrophosphate (C10)

↓

FarnesylPyrophosphate (C15)

↓

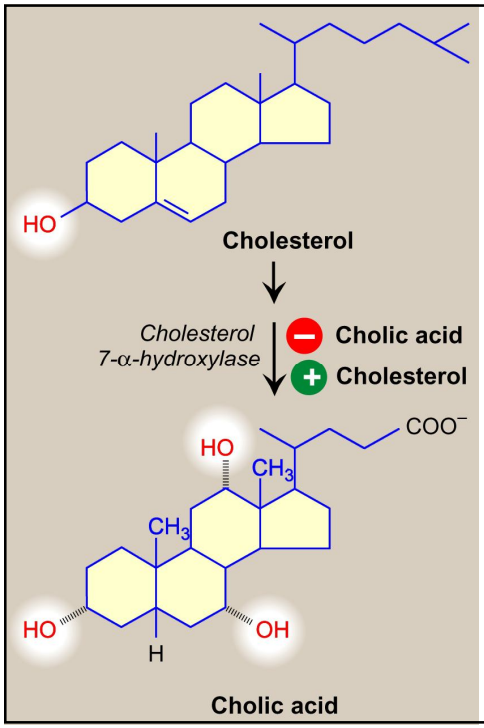
Squalene (C30)

↓

Lanosterol

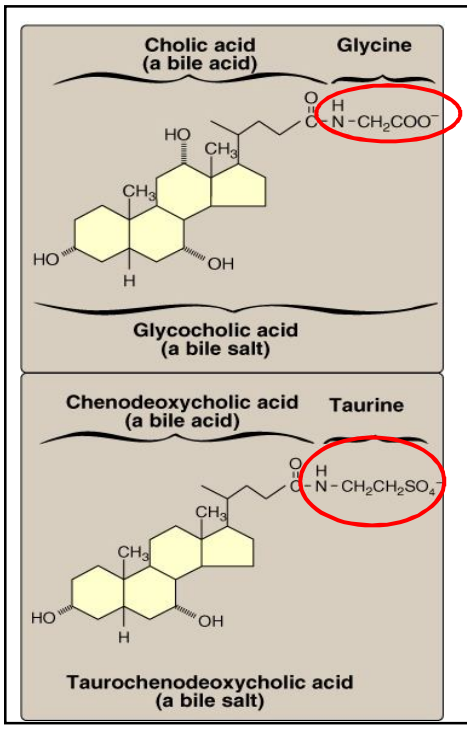
↓

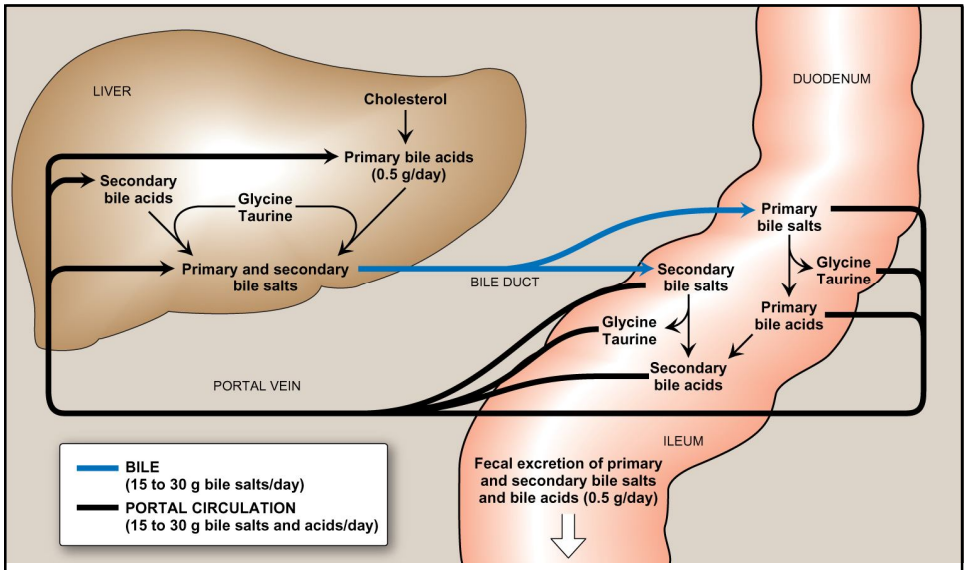
Cholesterol



Synthesis of Bile Acids

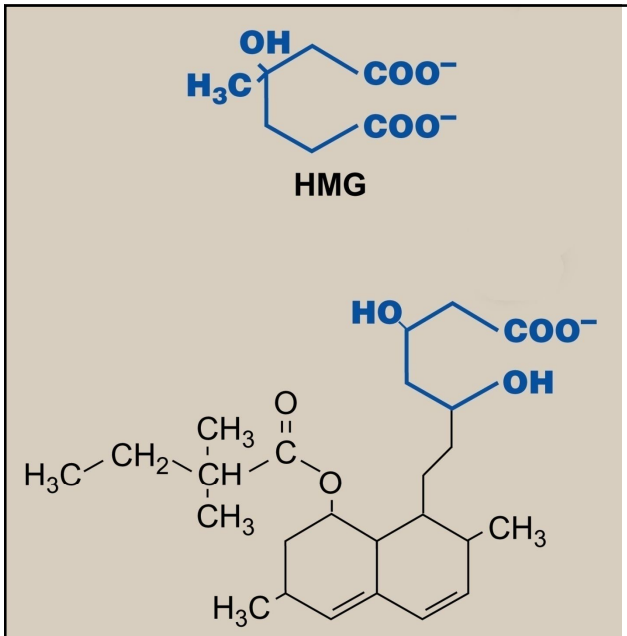
Hydroxylation at Carbon 7 is the Rate-limiting Step





Lowering Cholesterol Level

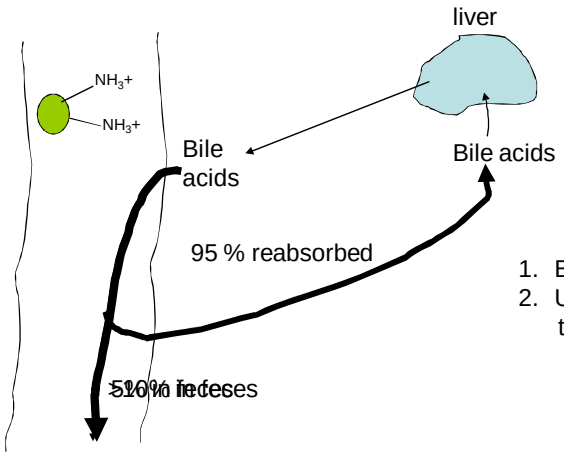
- Dietary
  - ↓Cholesterol intake
  - ↑ PUSFA / SFA
  - ↑ Fiber
  - Daily Ingestion of Plant Steroid Esters
- Inhibition of Synthesis
- ↓ Enterohepatic Circulation of Bile Acids



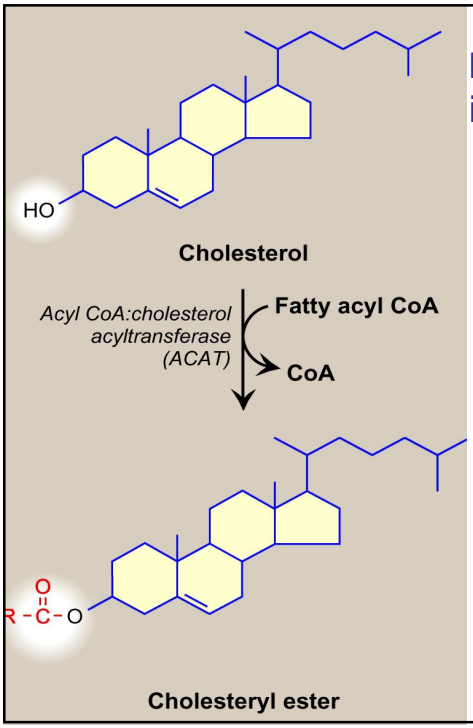
Inhibitors of HMG CoA reductase

Lowering Cholesterol

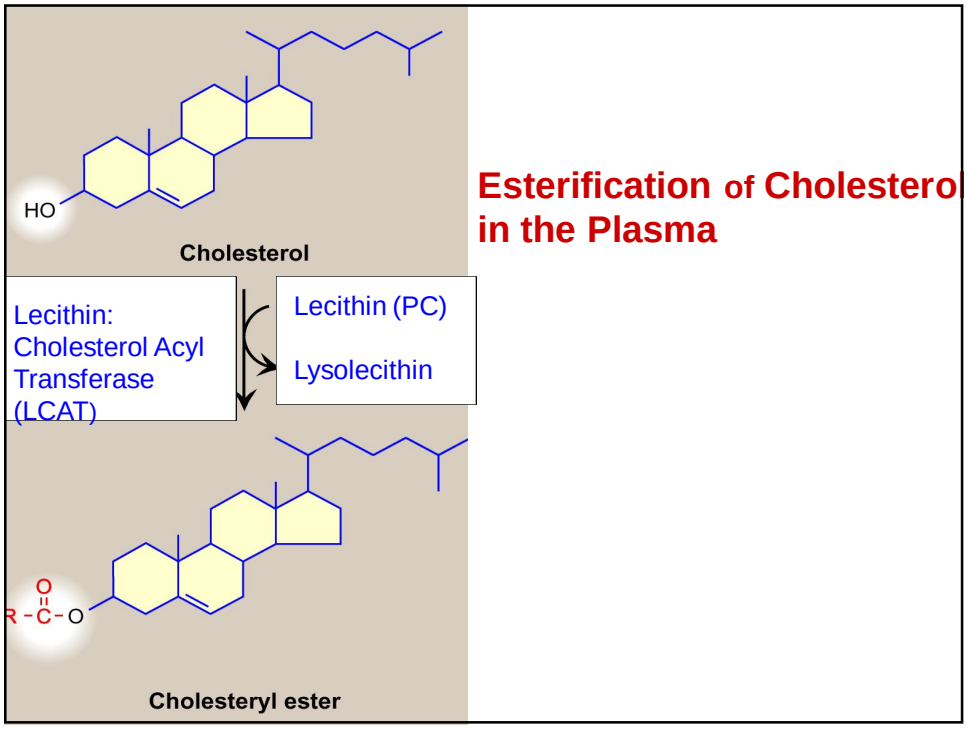
- Bile sequestering agents



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



Esterification of Cholesterol in the Cells

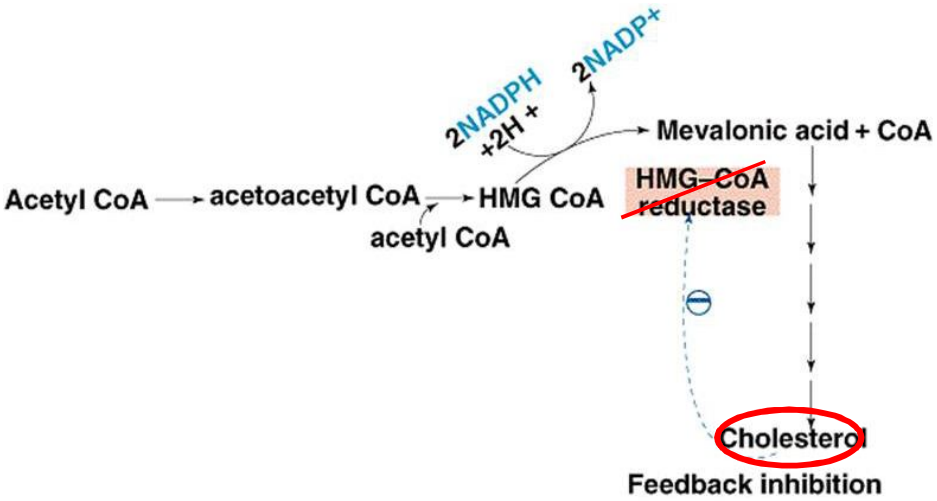


Esterification of Cholesterol in the Plasma

Regulation of Cholesterol Synthesis

- Regulation of Gene Expression
- Covalent Modification
- Hormonal Regulation
- Proteolytic Regulation

Regulation of Cholesterol Synthesis



Regulation of Cholesterol Synthesis

- Regulation of Gene Expression

Expression of the HMG CoA Reductase Gene Requires a Transcriptional Factor (Protein):

SRE DNA

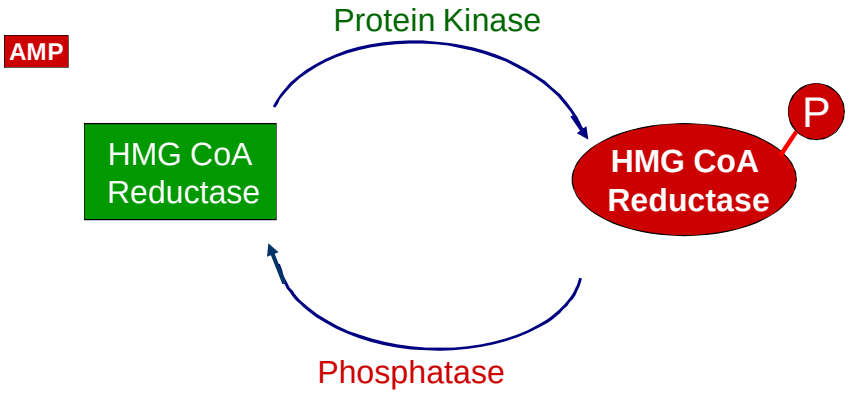
↓Cholestrol

SREBP

mRNA

Regulation of Cholesterol Synthesis

- Regulation of Gene Expression
- **Covalent Modification**



Regulation of Cholesterol Synthesis

- Regulation of Gene Expression
- Covalent Modification
- **Hormonal Regulation**

Glucagon: ↑Phosphorylated Form

Insulin:↑ **Dephosphorylated** Form (↑Phosphatase)

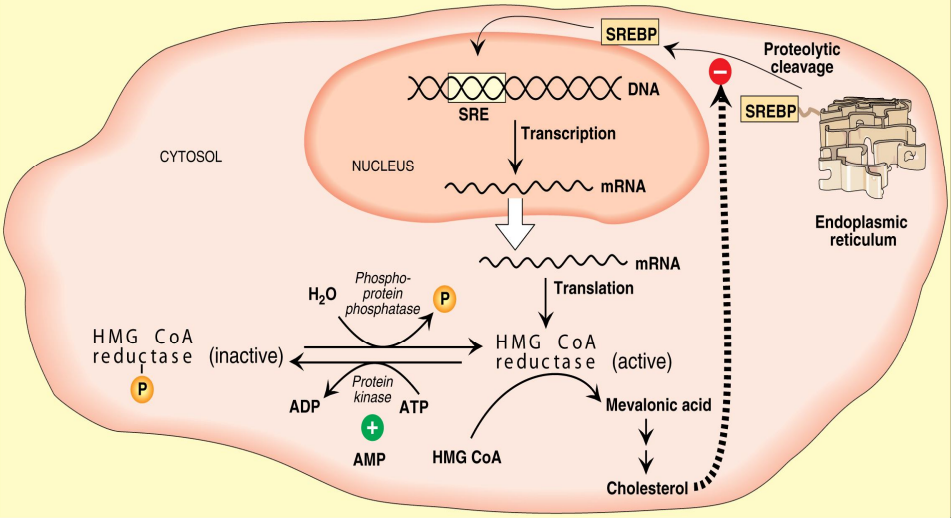
Regulation of Cholesterol Synthesis

- Regulation of Gene Expression
- Covalent Modification
- Hormonal Regulation
- **Proteolytic Regulation**

↑ **Cholesterol**

↑↑**HMG CoA Reductase** Proteolysis

↓ HMG CoA Reductase



Transport of Cholesterol in the Blood

Chylomicrons → remenats → Liver

VLDL → IDL → LDL

IDL → Liver

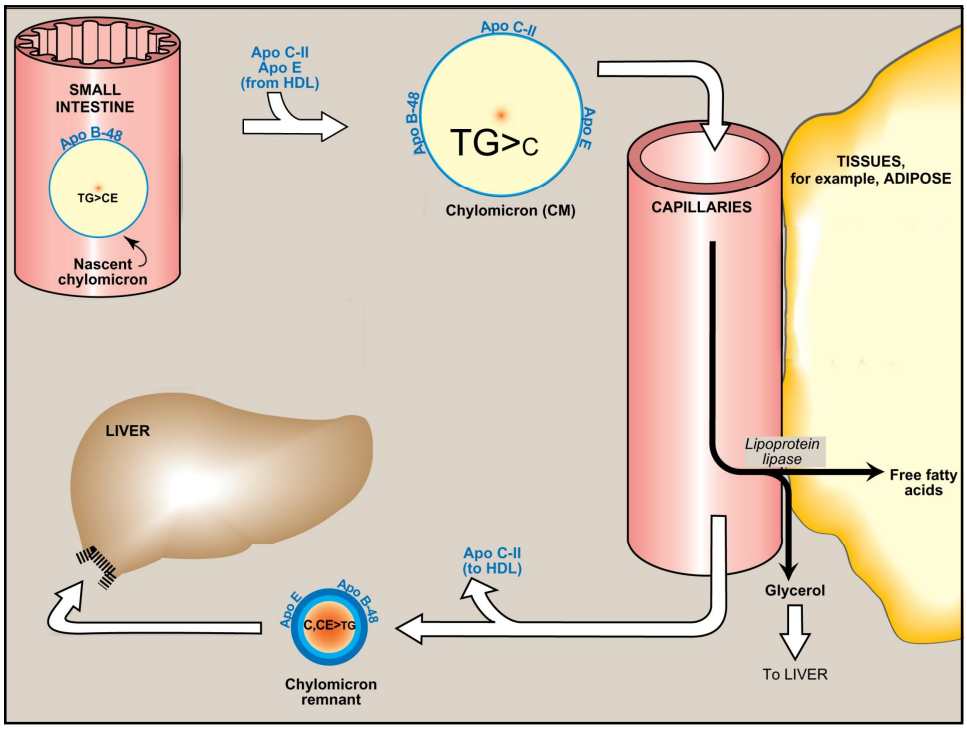
LDL → Liver

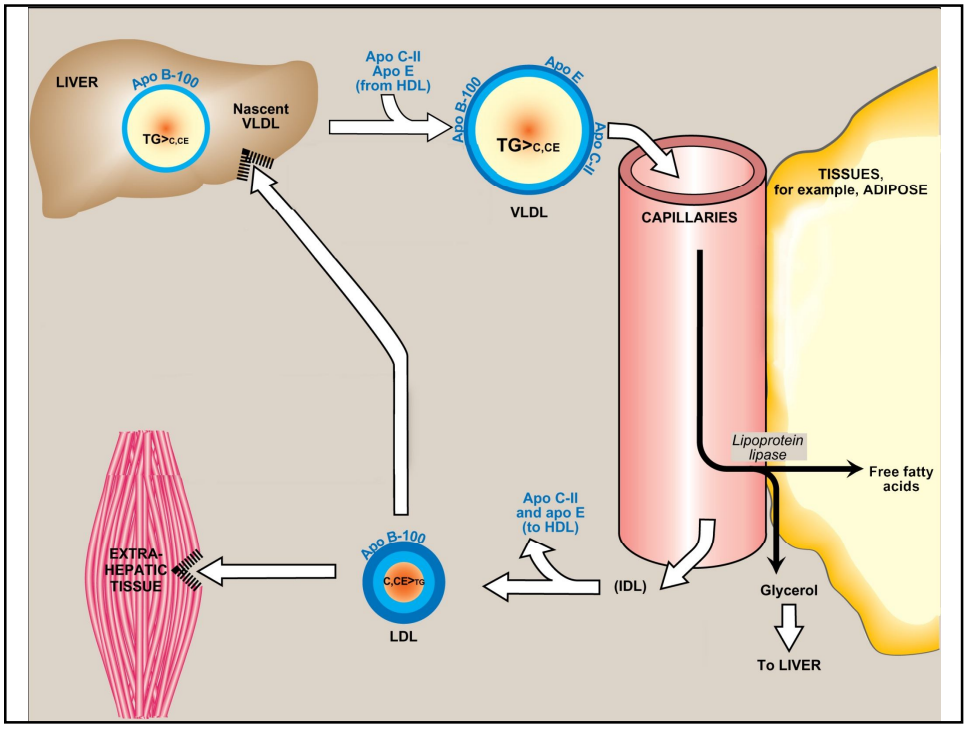
LDL → extrahepatic tissues

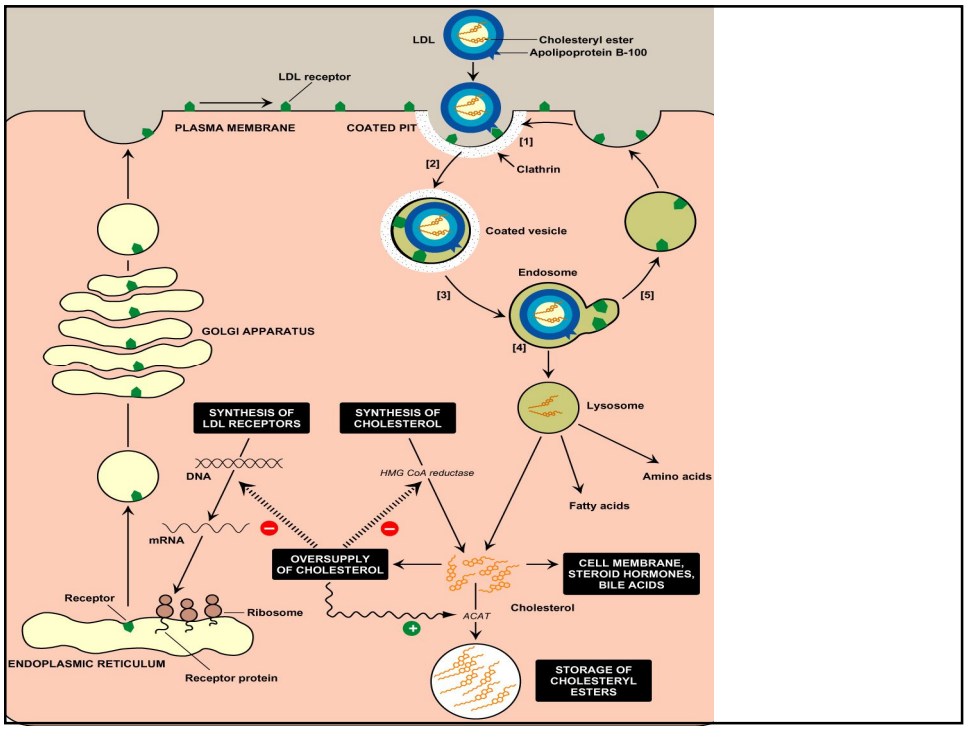
HDL

Importance Vital or lethal ?

Risk factor for coronary heart disease.




LIVER
Apo B-100
TG>C,CE
Nascent VLDL
Apo C-II
Apo E
(from HDL)
Apo B-100
TG>C,CE
Apo E
Apo C-II
VLDL
CAPILLARIES
TISSUES,
for example, ADIPOSE
Lipoprotein lipase
Free fatty acids
Glycerol
To LIVER
Apo C-II
and apo E
(to HDL)
(IDL)
Apo B-100
C,CE>TG
LDL
EXTRA-HEPATIC TISSUE


LDL
Cholesteryl ester
Apolipoprotein B-100
LDL receptor
PLASMA MEMBRANE
COATED PIT
[1]
[2]
Clathrin
Coated vesicle
Endosome
[3]
[4]
[5]
GOLGI APPARATUS
Lysosome
SYNTHESIS OF LDL RECEPTORS
SYNTHESIS OF CHOLESTEROL
DNA
HMG CoA reductase
Amino acids
Fatty acids
mRNA
OVERSUPPLY OF CHOLESTEROL
CELL MEMBRANE, STEROID HORMONES, BILE ACIDS
Receptor
Ribosome
Cholesterol
ACAT
ENDOPLASMIC RETICULUM
Receptor protein
STORAGE OF CHOLESTERYL ESTERS

Macrophage Scavenger Receptor

Non specific

modified (damaged) LDL

No down regulation

Accumulation of foam cells in the subendothelial space

Early evidence of atherosclerotic plaque

Modifiable and non-modifiable CAD risk factors

Cigarette smoking	Males > 45 years Females > 55 years
Obesity	Males
Hypertension (blood pressure >= 140 / 90 mmHg)	Family history of coronary artery disease
Physical inactivity	
Kidney disease	
Diabetes mellitus	
Alcohol consumption	
Stress	
Elevated LDL	
Reduced HDL	

Familial Hypercholesterolemia

Homozygotes 680 mg/dl

Heterozygotes 300 mg/dl

Absence of LDL receptor / Abnormal Receptor

Homozygotes No Receptors

Hetero ½ Normal Number

Accumulation of lDL more IDL ⟶ LDL

Cholesterol deposition in tissues

Atherosclerosis Death in childhood

HDL

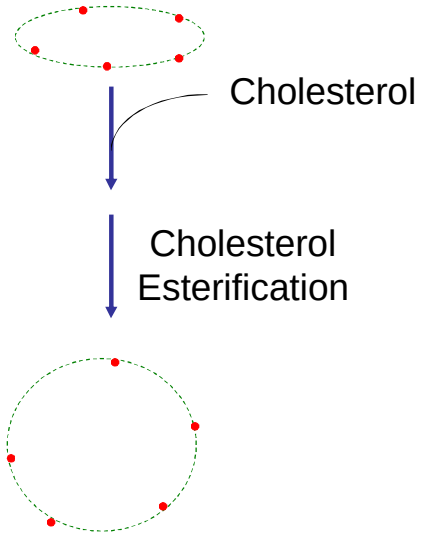
Origin

- Liver and Intestine: Nascent Discoid Shape

- Budding from other Lipoproteins Particles

- From Free Apo A

Maturation of HDL

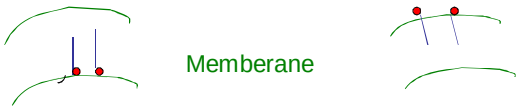


Reverse Transport of Cholesterol

From Cells to Liver

Foam Cells in Vascular Tissues

1) Directional Movment; Role of ABC1

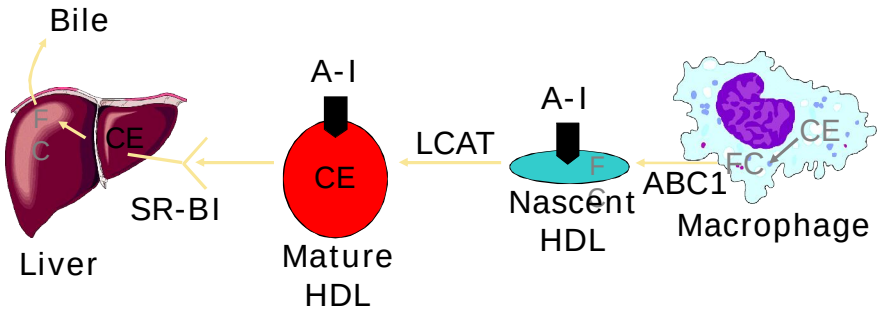


2) Esterification of Cholesterol

Ch $\xrightarrow{\text{LCAT}}$ Ch-FA

cholesterol is trapped within the core of HDL

HDL Metabolism and Reverse Cholesterol Transport



ABC1 = ATP-binding cassette protein 1; A-I = apolipoprotein A-I; CE = cholesteryl ester; FC = free cholesterol; LCAT = lecithin:cholesterol acyltransferase; SR-BI = scavenger receptor class BI

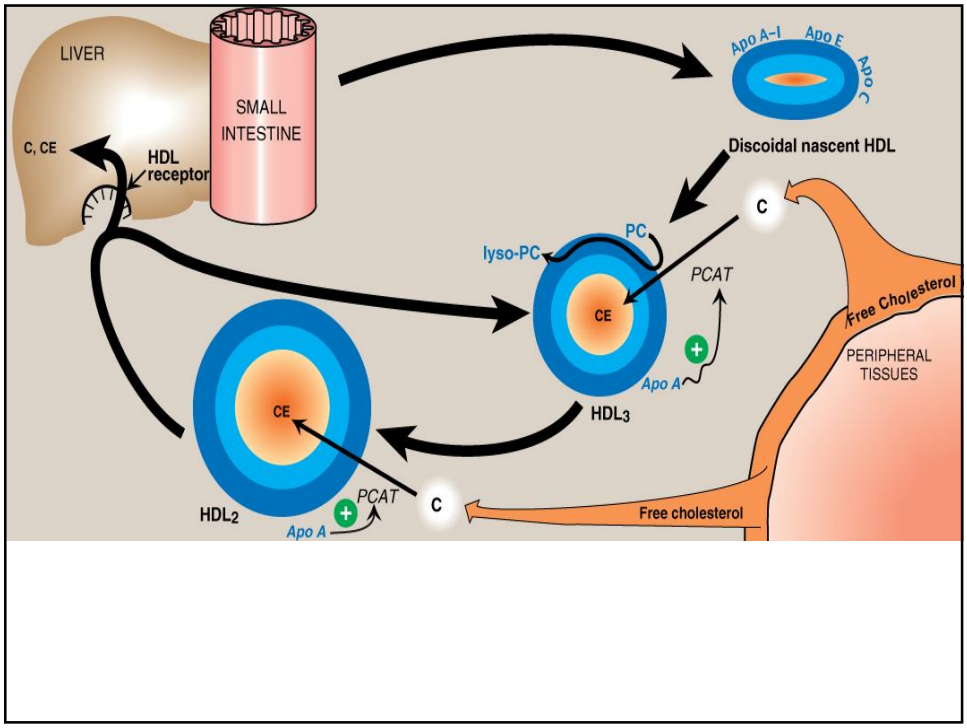
Fate of HDL cholesterol

* Uptake by liver

  Binding to Specific Receptor on Hepatocytes

* Transfer of cholestrol into cells scavenger receptor SR_B1
  - On many cell types
  - Can be upergulated if ch. Is needed
  - Not down regulated

* HDL interaction with other particles exchange of compnents.


LIVER
SMALL INTESTINE
C, CE
HDL receptor
Apo A–I
Apo E
Apo C
Discoidal nascent HDL
C
PC
lyso-PC
CE
PCAT
Apo A
HDL3
Free Cholesterol
PERIPHERAL TISSUES
CE
HDL2
PCAT
Apo A
C
Free cholesterol