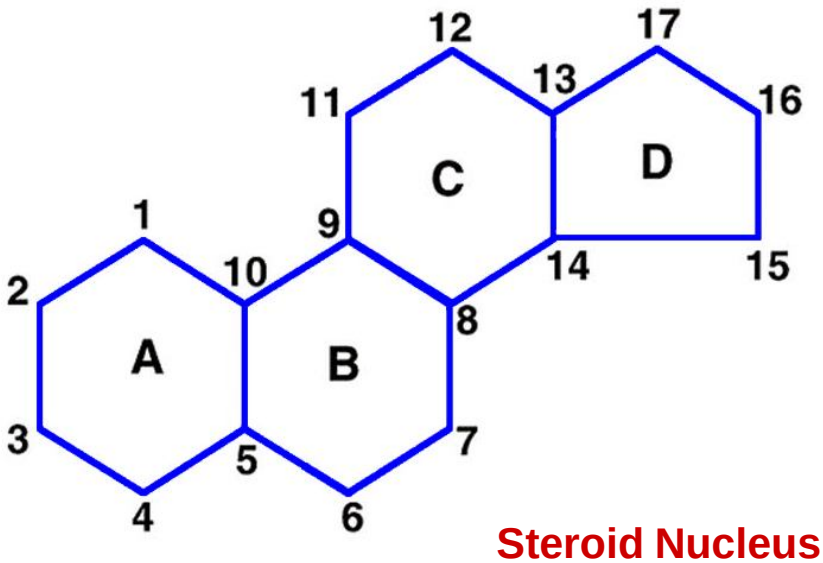
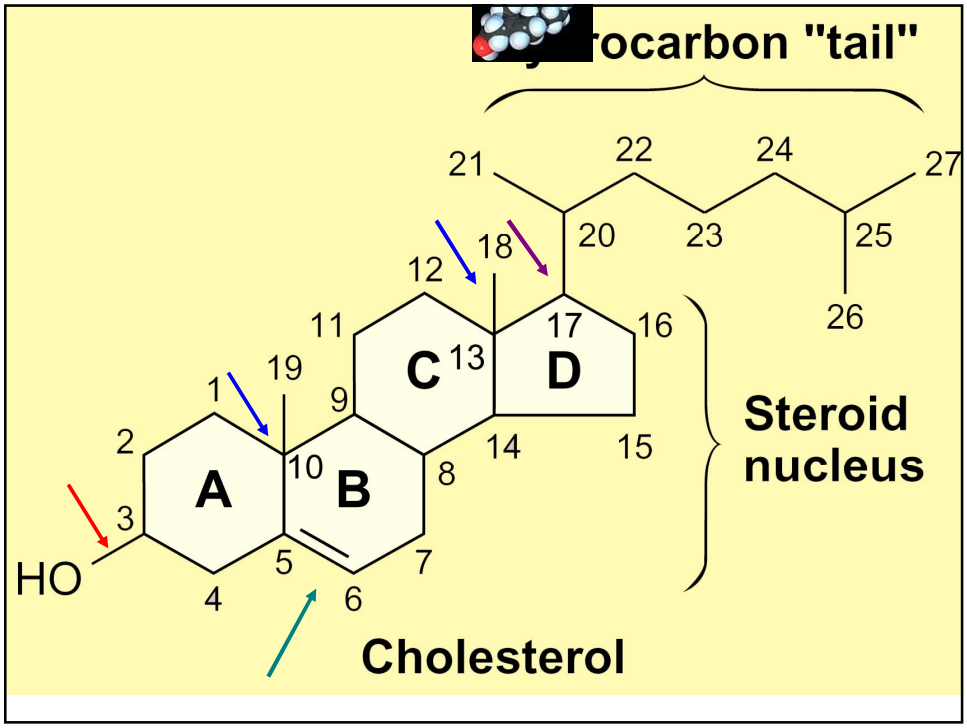
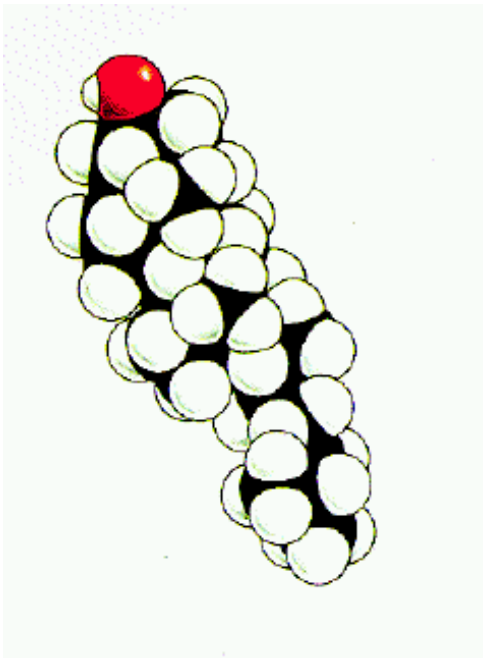
Cholesterol Metabolism

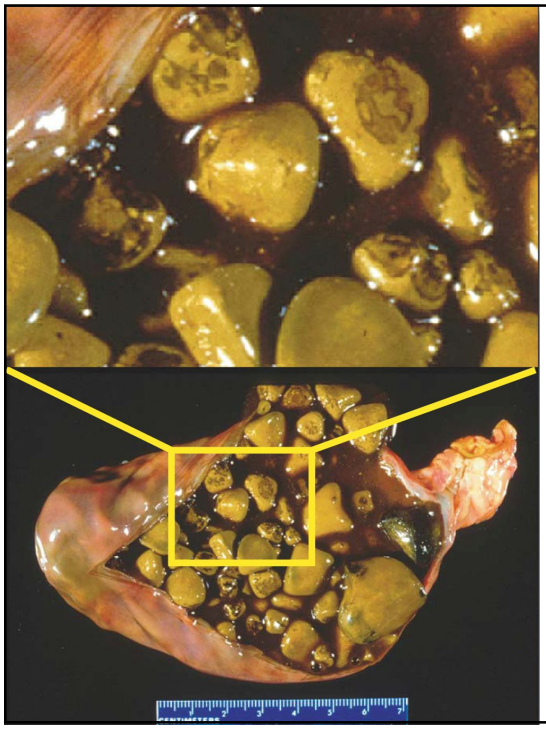
Lippincott's Illustrated Review
Chapter 18



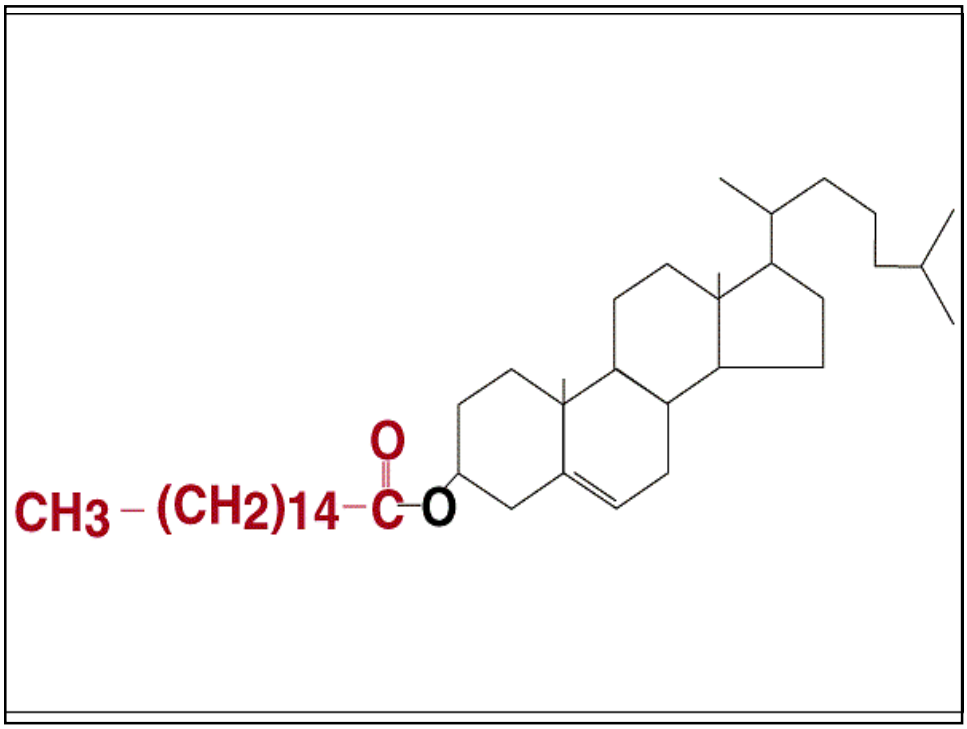
Steroid Nucleus


ocarbon "tail"
21
22
24
27
20
23
25
26
18
12
11
17
16
C
13
D
19
1
9
Steroid
nucleus
2
14
15
10
A
B
8
3
HO
5
7
4
6
Cholesterol





Cholesterol was isolated from gall bladder stones in 1774



Sources and Elimination of Cholesterol

Synthesis: ≈ 1000 mg

Liver, Small Intestine, Adrenal Cortex …

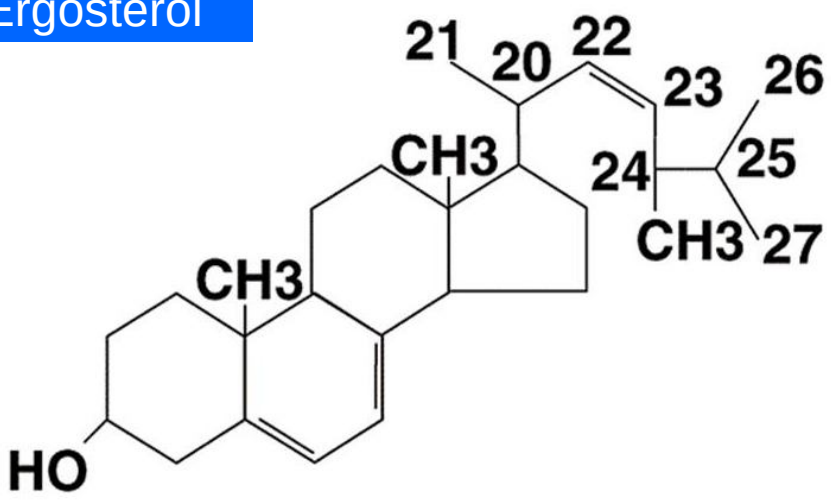
Dietary: ≈ 300 mg

(Low Cholesterol Diet)

Elimination: Via the Bile

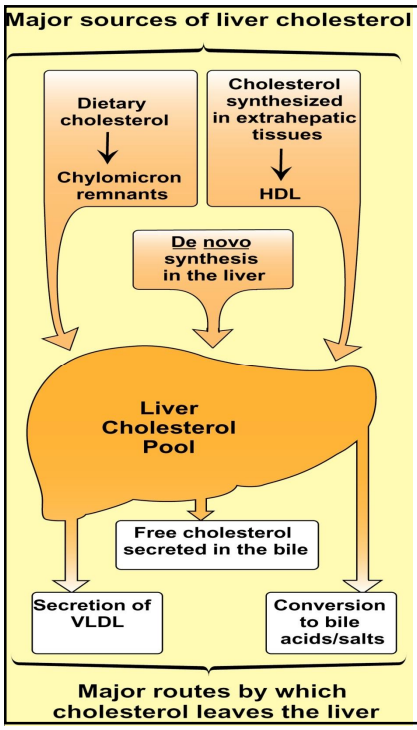
Cholesterol, Bile Salts

Ergosterol



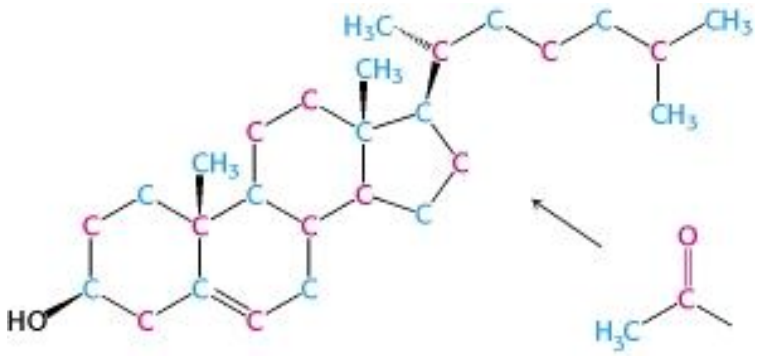
Plant Sterols are Poorly Absorbed by Human

- Plants manufacture phytosterols (substances chemically similar to cholesterol produced within plants), which can compete with cholesterol for reabsorption in the intestinal tract, thus potentially reducing cholesterol reabsorption.[12] When intestinal lining cells absorb phytosterols, in place of cholesterol, they usually excrete the phytosterol molecules back into the GI tract, an important protective mechanism.



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)

↓

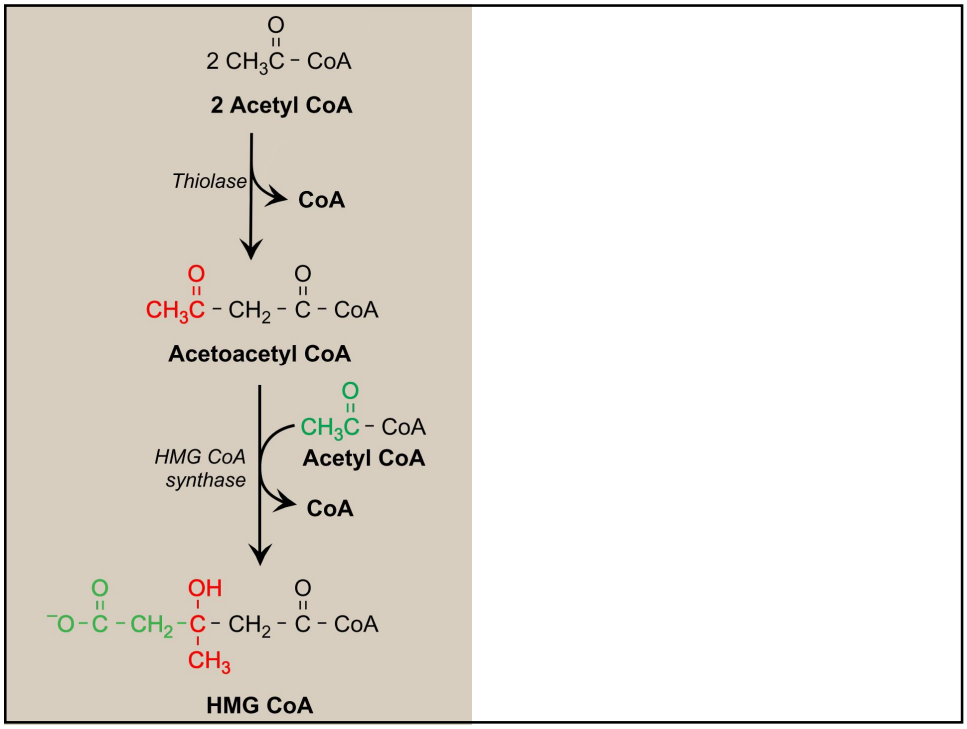
Squalene (C30)

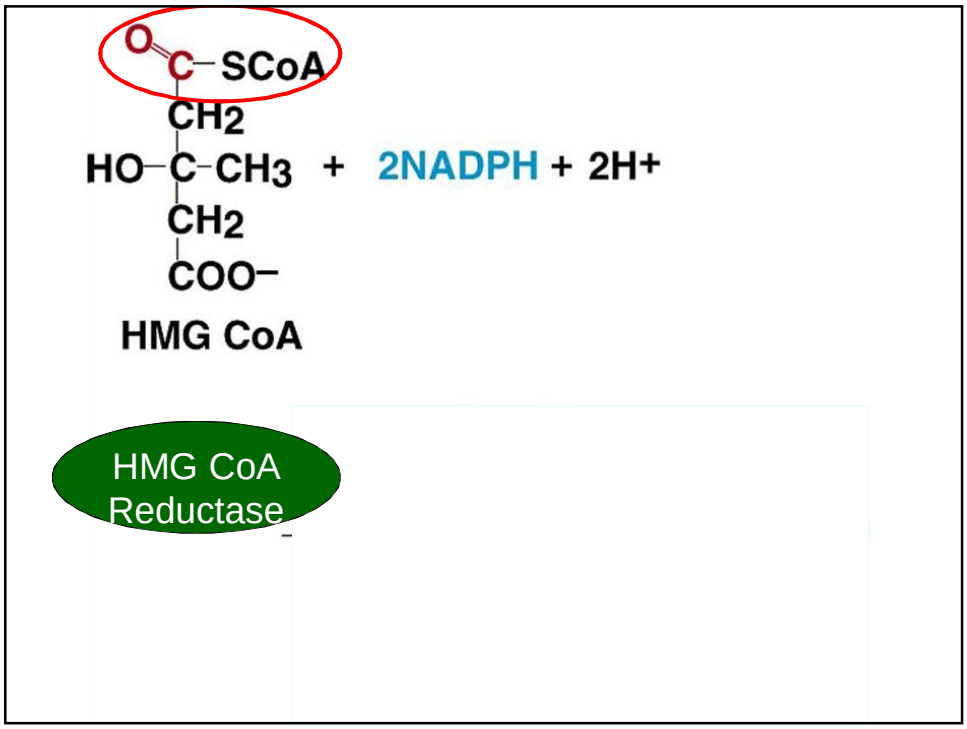
↓

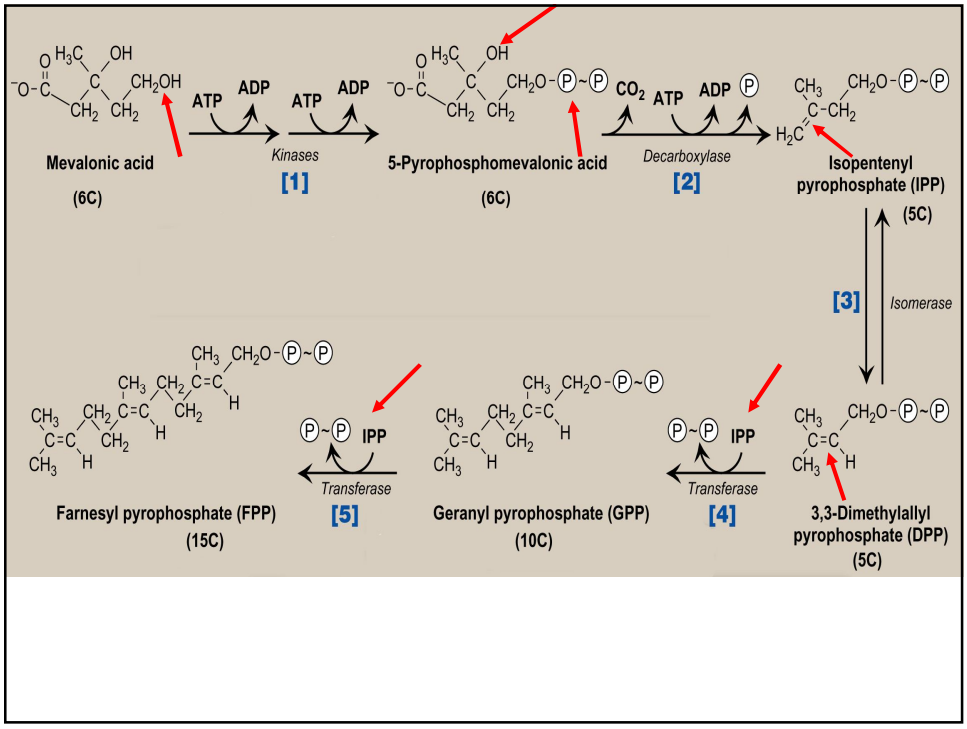
Lanosterol (C30)

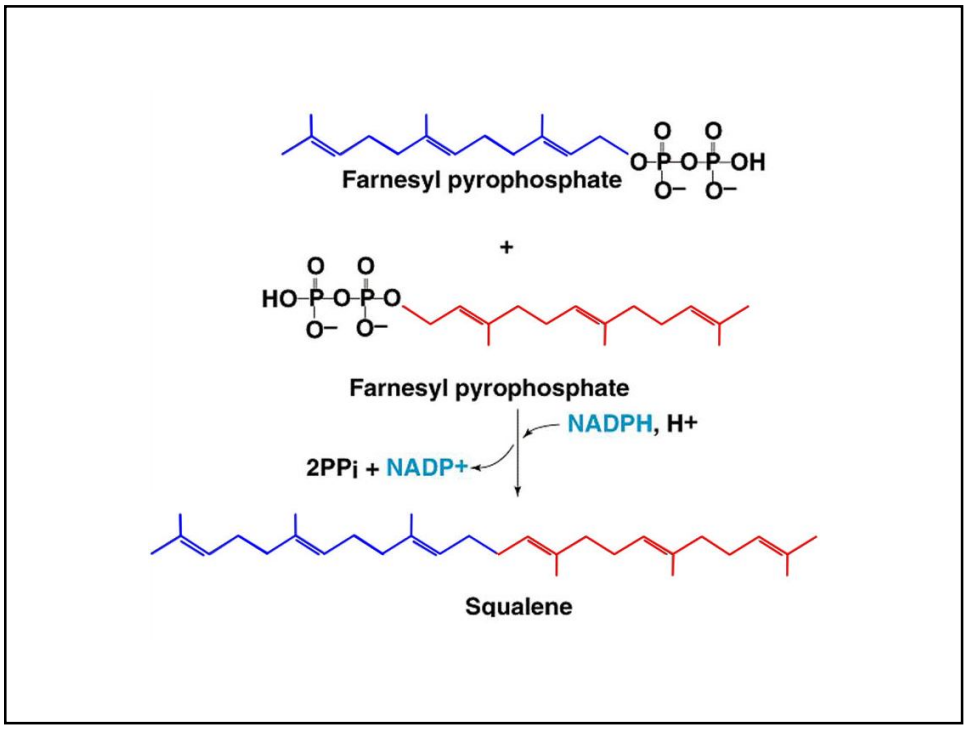
↓

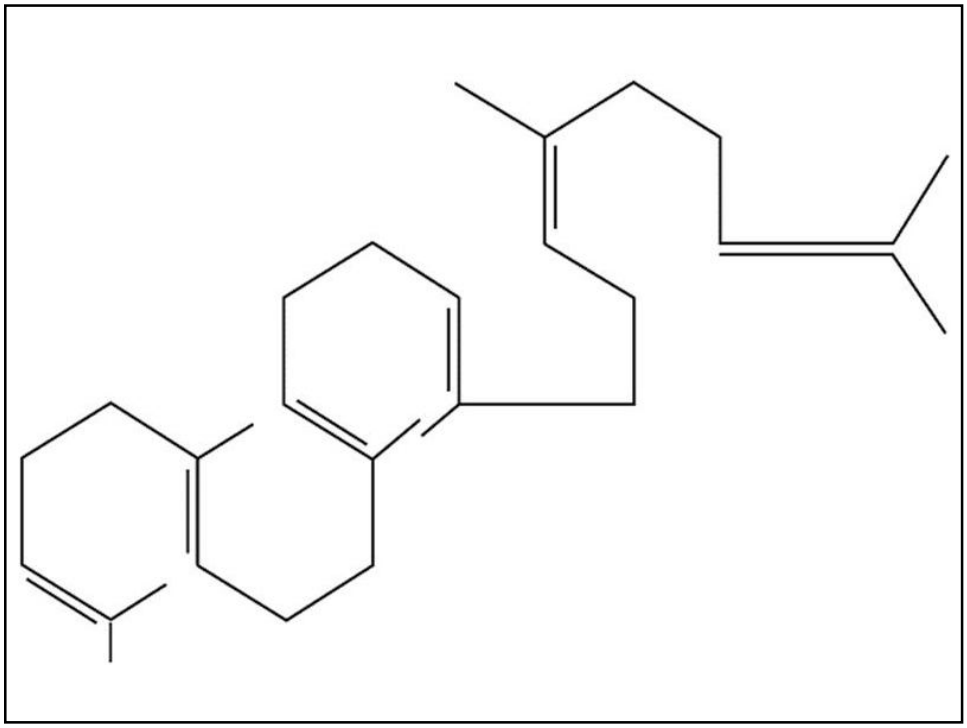
Cholesterol (C27)

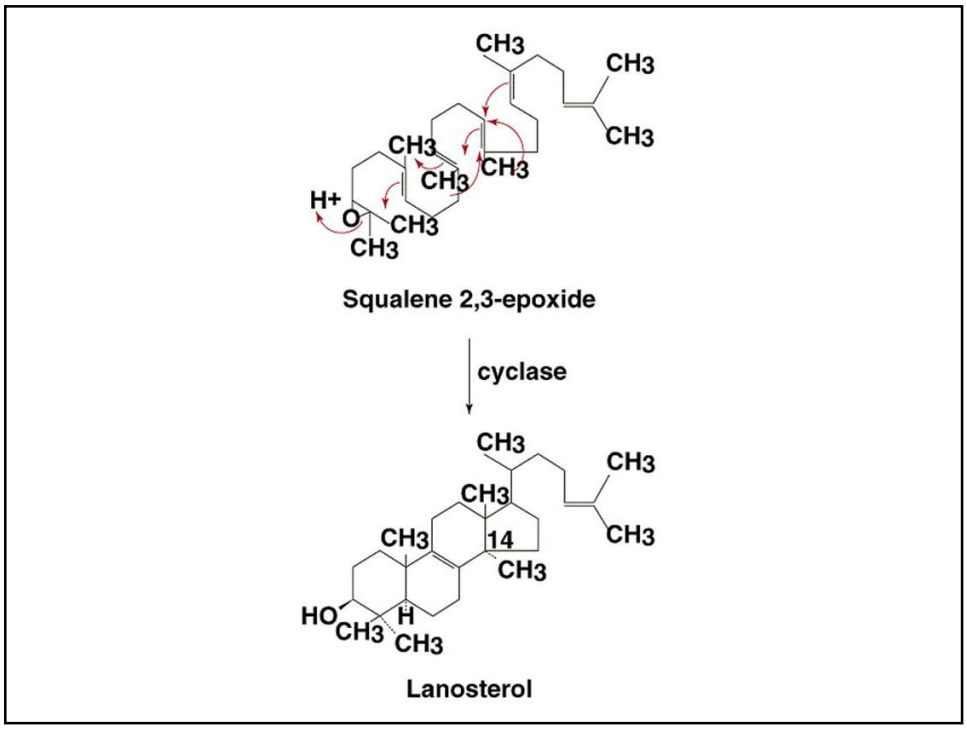

2 CH3C – CoA
2 Acetyl CoA
Thiolase
CoA
CH3C – CH2 – C – CoA
Acetoacetyl CoA
HMG CoA synthase
CH3C – CoA
Acetyl CoA
CoA
⁻O – C – CH2 – C – CH2 – C – CoA
CH3
HMG CoA

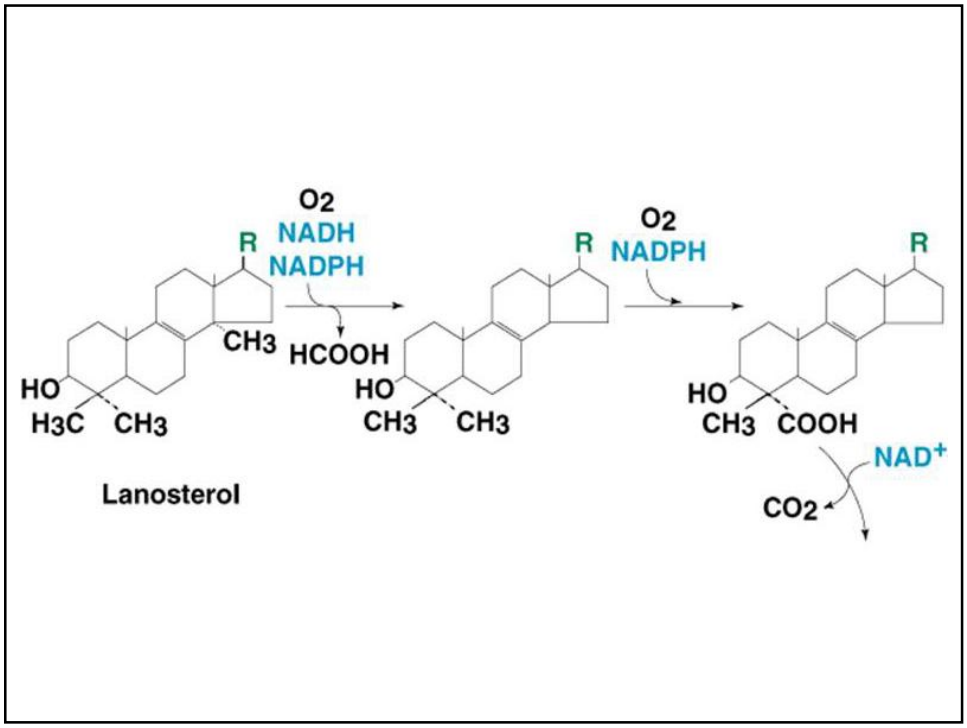

C – SCoA
CH2
HO – C – CH3
CH2
COO–
HMG CoA
+ 2NADPH + 2H+
HMG CoA Reductase

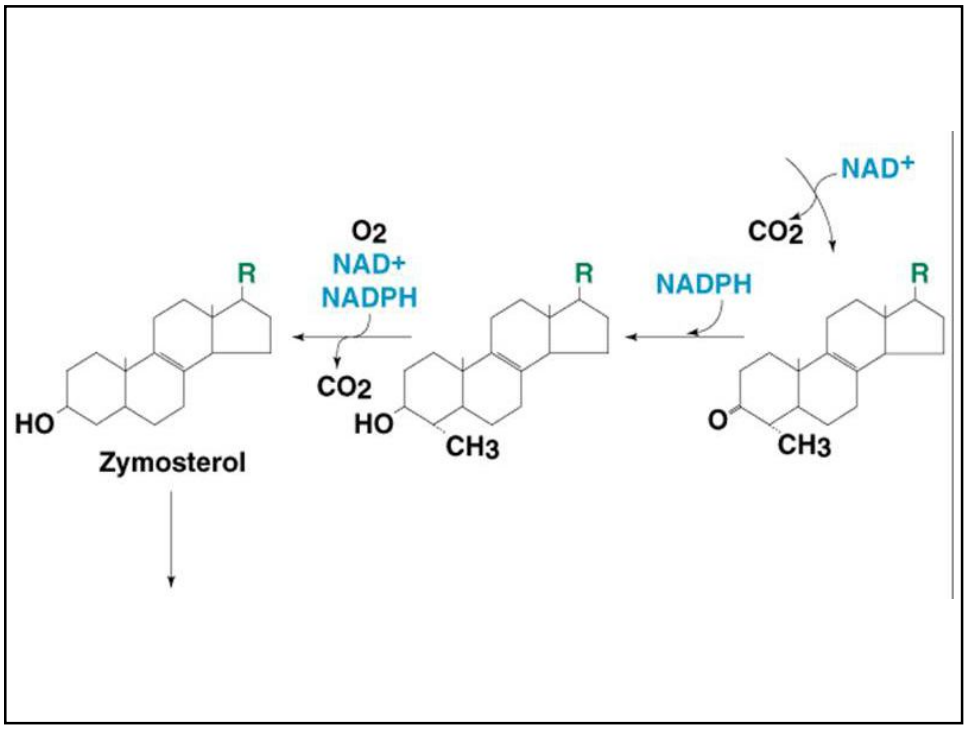

Mevalonic acid
(6C)
ATP
ADP
ATP
ADP
Kinases
[1]
5-Pyrophosphomevalonic acid
(6C)
CO2
ATP
ADP
Decarboxylase
[2]
Isopentenyl pyrophosphate (IPP)
(5C)
[3]
Isomerase
3,3-Dimethylallyl pyrophosphate (DPP)
(5C)
IPP
Transferase
[4]
Geranyl pyrophosphate (GPP)
(10C)
IPP
Transferase
[5]
Farnesyl pyrophosphate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

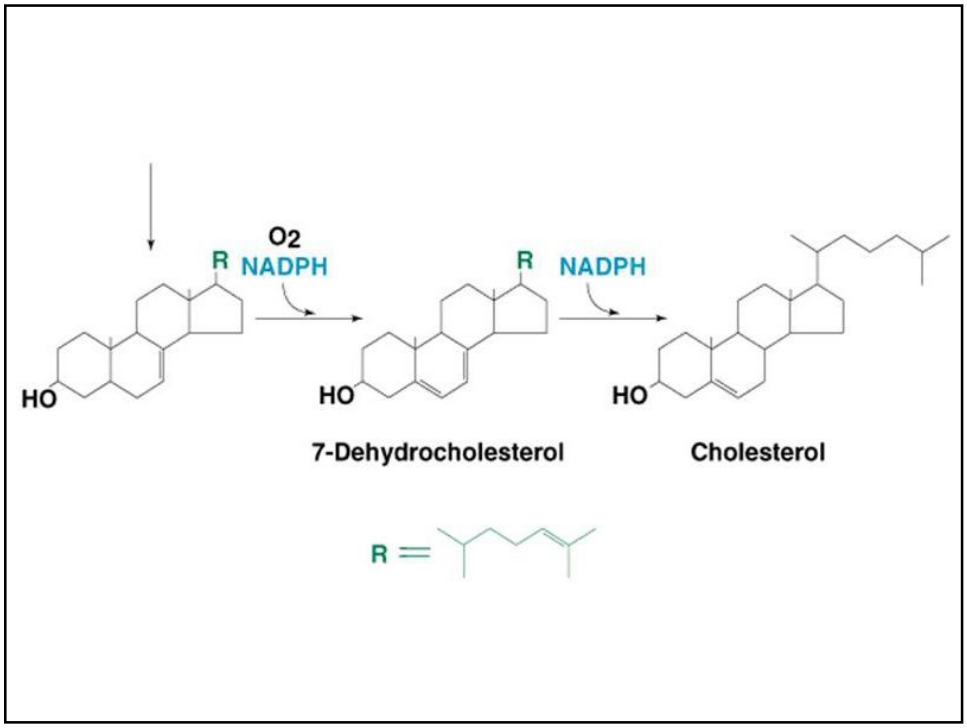

Farnesyl pyrophosphate
+
Farnesyl pyrophosphate
NADPH, H+
2PPi + NADP+
Squalene




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


O2
NADH
NADPH
R
CH3
HCOOH
HO
H3C
CH3
Lanosterol
O2
NADPH
COOH
NAD+
CO2


NAD+
CO2
O2
NAD+
NADPH
NADPH
R
HO
O
CH3
Zymosterol



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

↓

Dimethylallyl Pyrophosphate ⇌ İsopentenyl Pyrophosphate (C5)

↓

Geranyl Pyrophosphate (C10)

↓

FarnesylPyrophosphate (C15)

↓

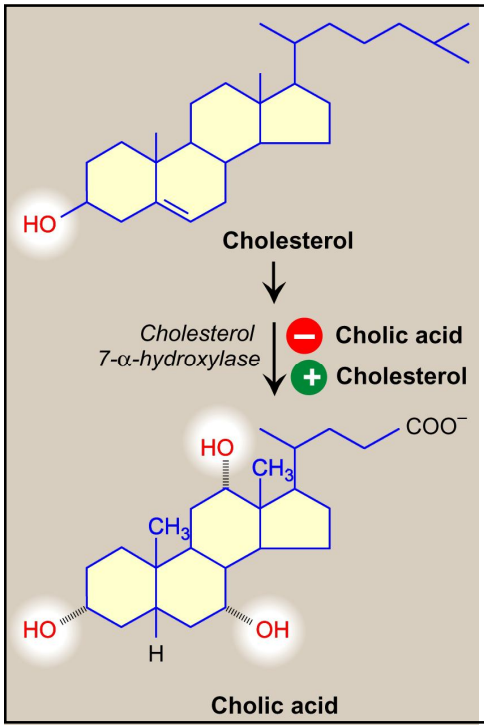
Squalene (C30)

↓

Lanosterol

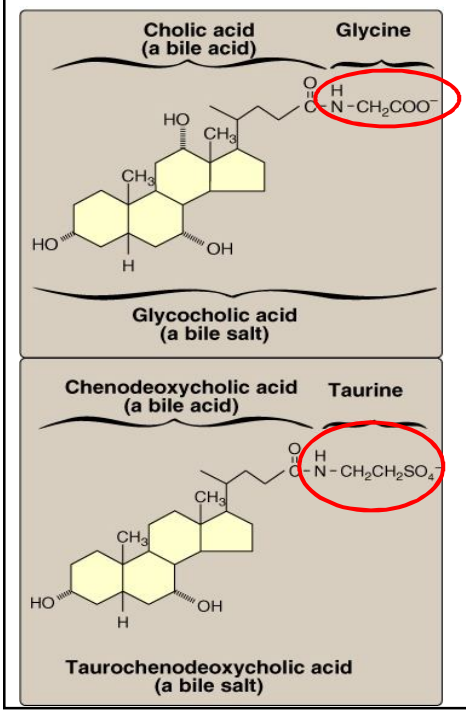
↓

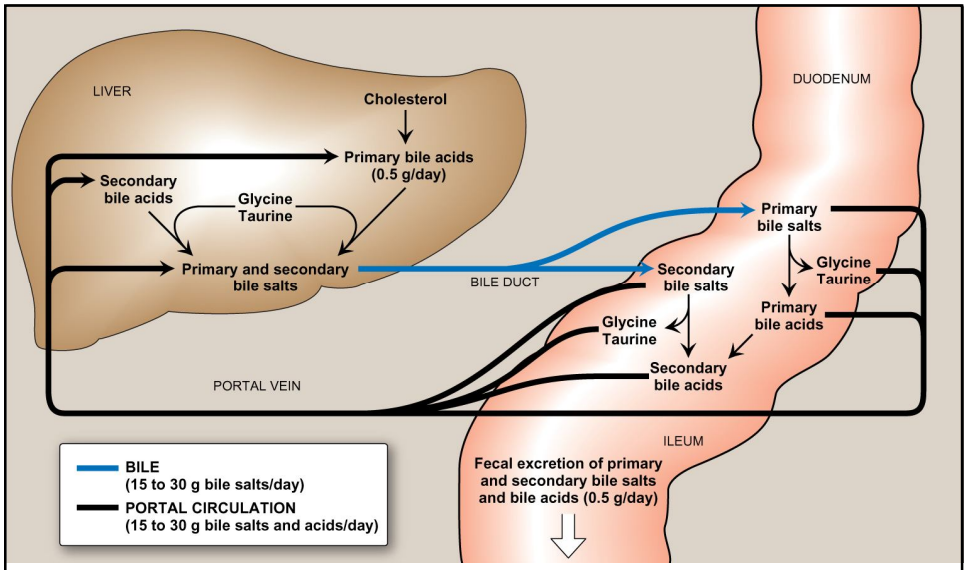
Cholesterol



Synthesis of Bile Acids

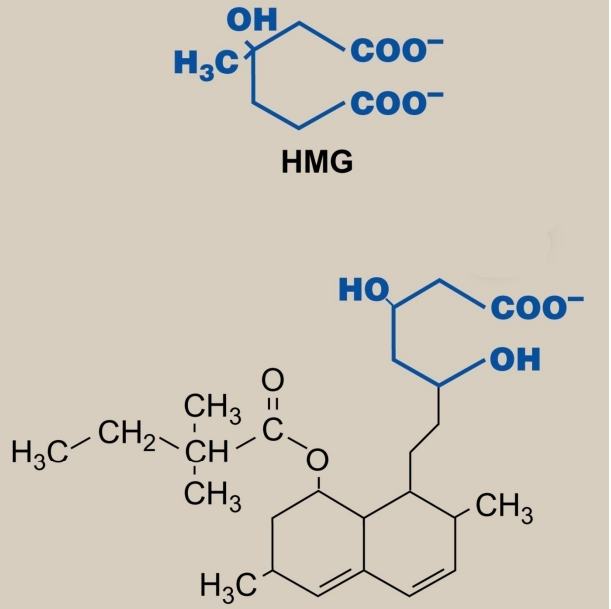
Hydroxylation at Carbon 7 is the Rate-limiting Step





Lowering Cholesterol Level

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



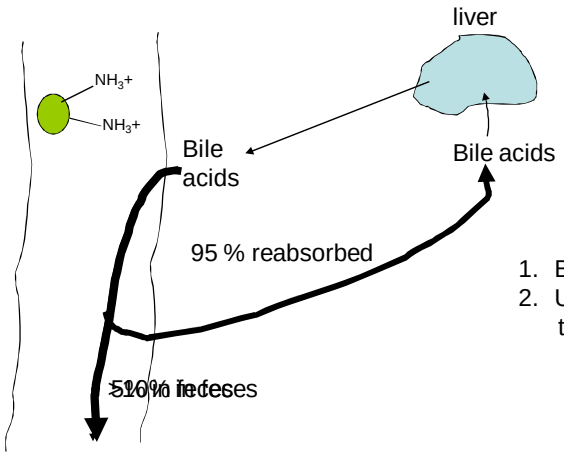
HMG

Simvastatin

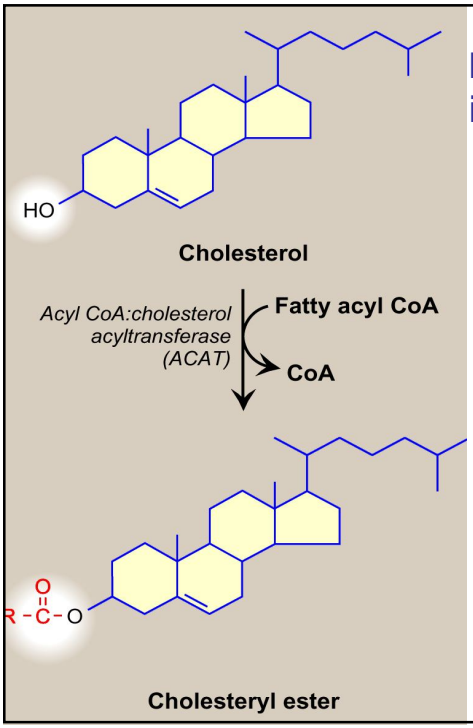
Inhibitors of HMG CoA reductase

Lowering Cholesterol

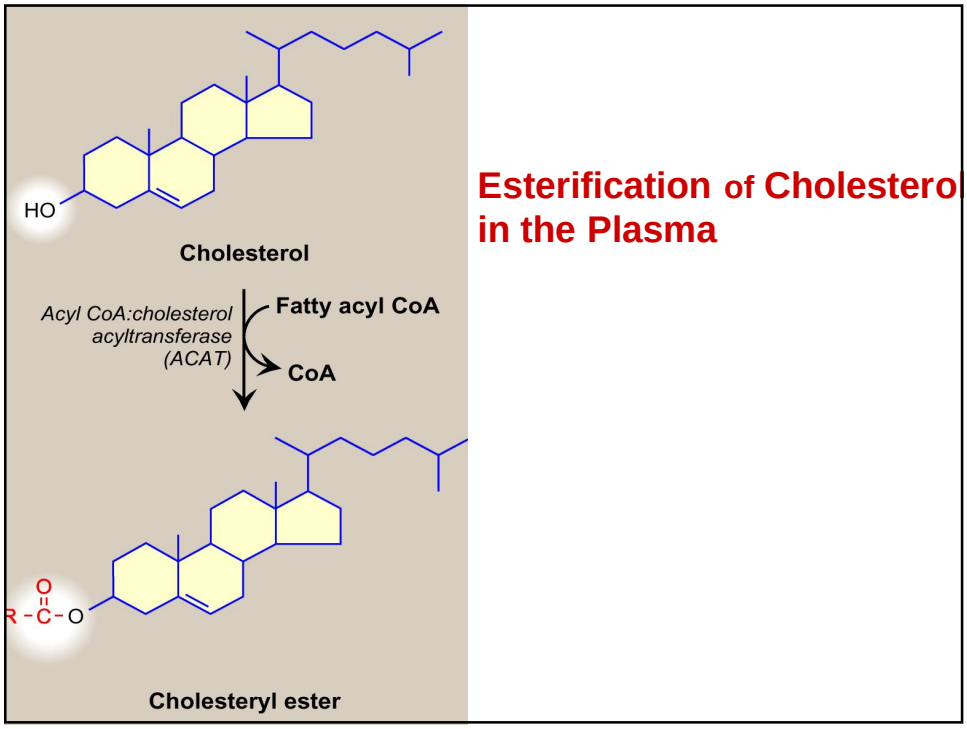
- Bile sequestering agents



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

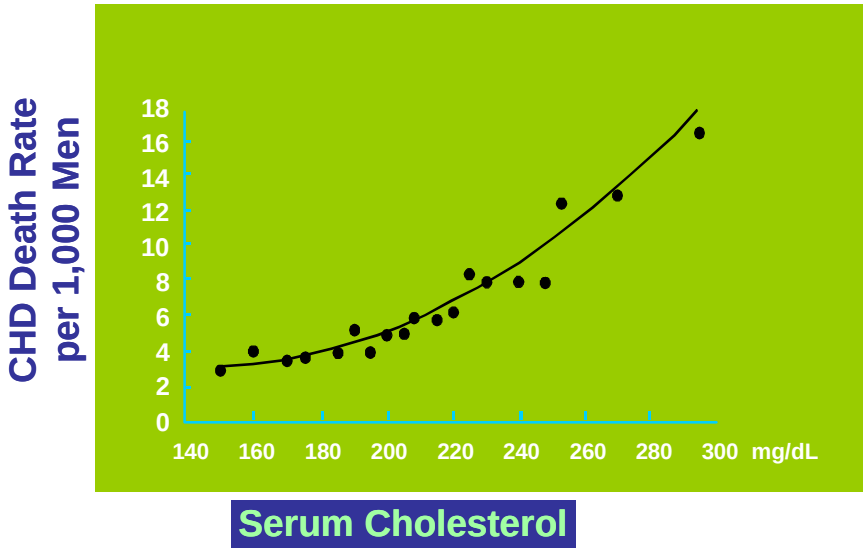


Esterification of Cholesterol in the Cells



Esterification of Cholesterol in the Plasma

Serum Cholesterol and CHD

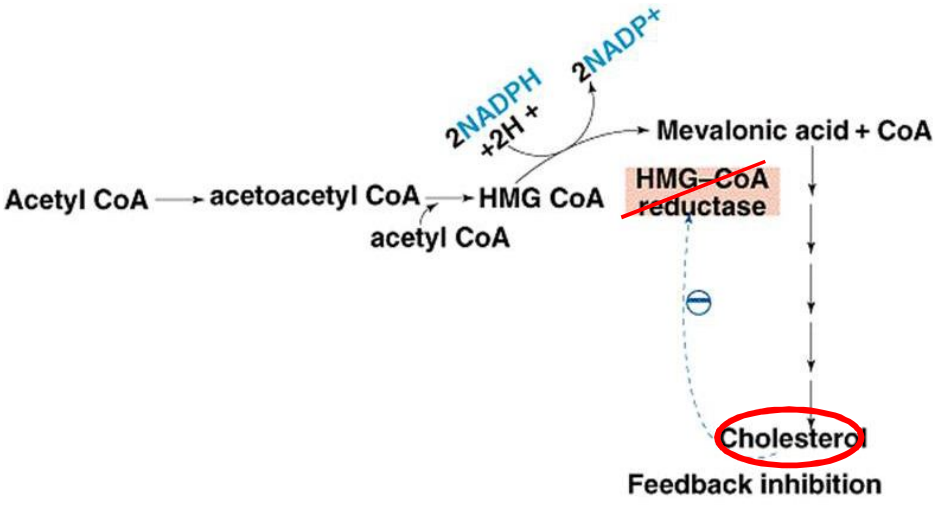


Martin M. Lancet 1986;11:933-936

Regulation of Cholesterol Synthesis

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

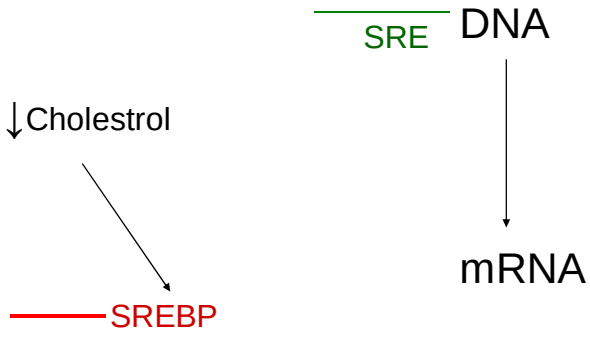
Regulation of Cholesterol Synthesis



Regulation of Cholesterol Synthesis

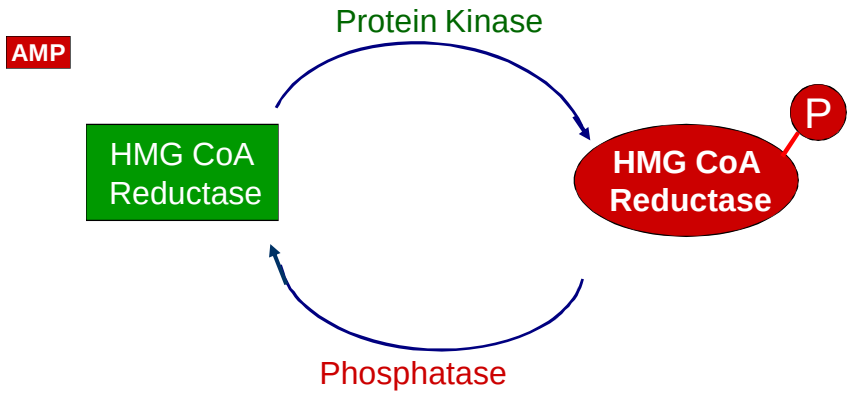
- Regulation of Gene Expression

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



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)

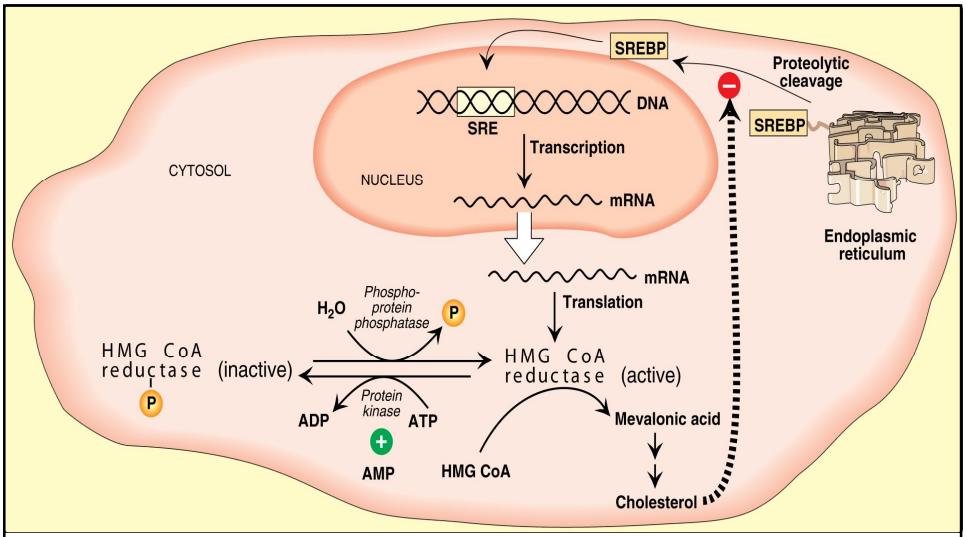
Regulation of Cholesterol Synthesis

- 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

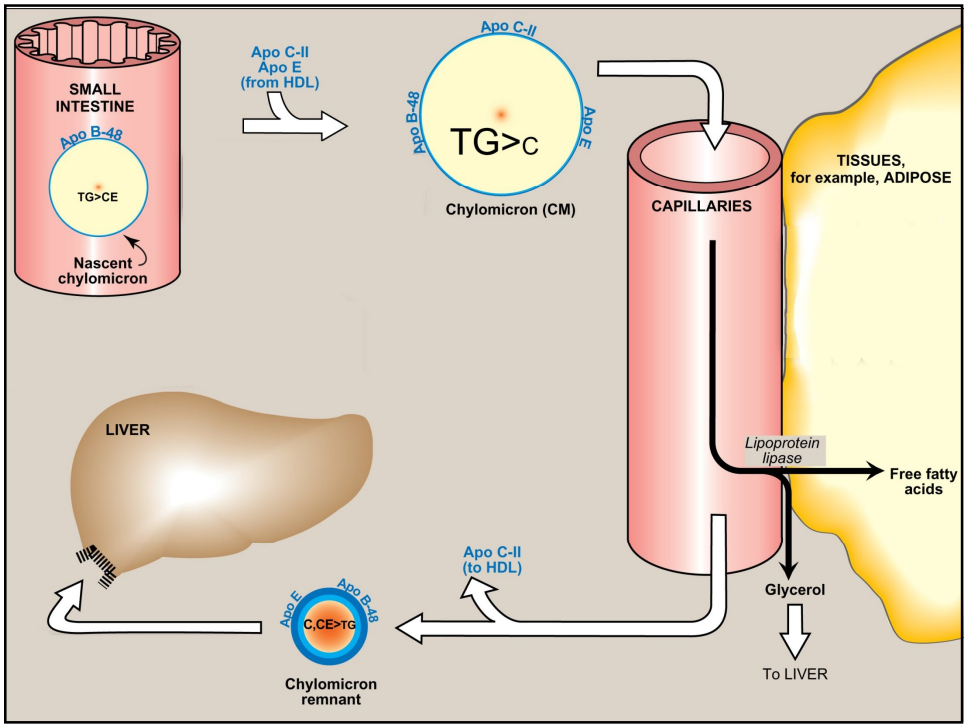
IDL → Liver

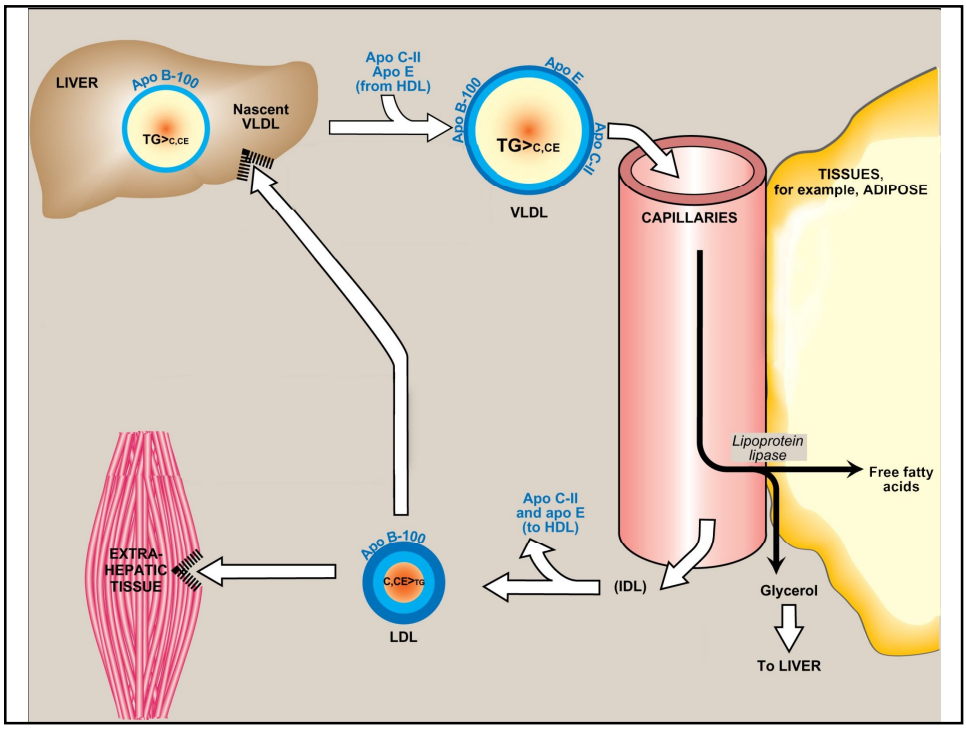
LDL → Liver, extrahepatic tissues

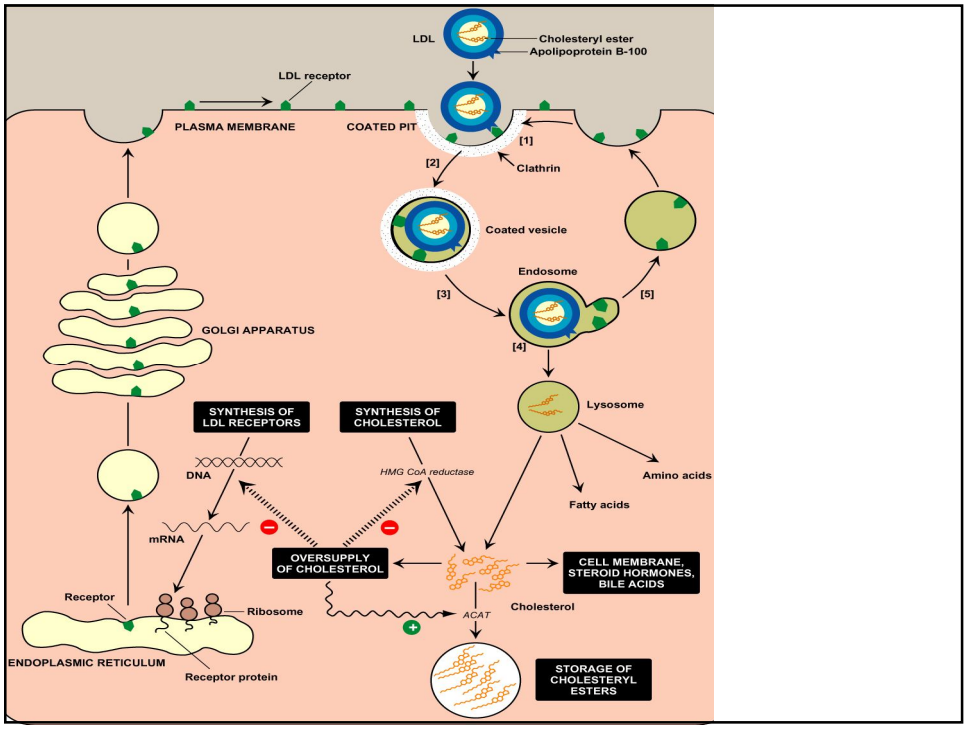
HDL

Importance Vital or lethal ?

Risk factor for coronary heart disease.


SMALL INTESTINE
Apo B-48
TG>CE
Nascent chylomicron
Apo C-II
Apo E
(from HDL)
Apo C-II
Apo B-48
TG>C
Apo E
Chylomicron (CM)
CAPILLARIES
TISSUES, for example, ADIPOSE
LIVER
Lipoprotein lipase
Free fatty acids
Glycerol
To LIVER
Apo C-II
(to HDL)
Apo E
Apo B-48
C,CE>TG
Chylomicron remnant


LIVER
Apo B-100
TG>C,CE
Nascent VLDL
Apo C-II
Apo E
(from HDL)
Apo B-100
Apo E
TG>C,CE
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



Macrophage Scavenger Receptor

Non specific

modified (damaged) LDL

No down regulation

Macrophage ← LDL → foam cells

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

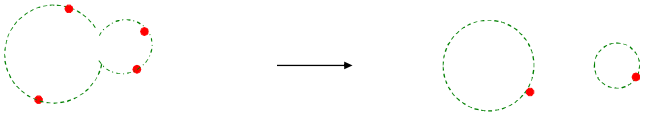
Atherosclerosis Death in childhood

HDL

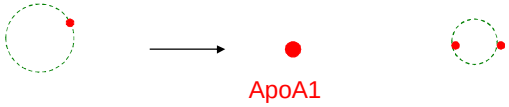
Origin

- Liver and Intestine: Nascent Discoid Shape

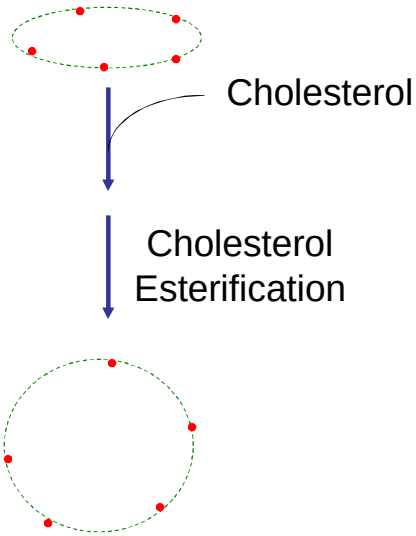
- Budding from other Lipoproteins Particles



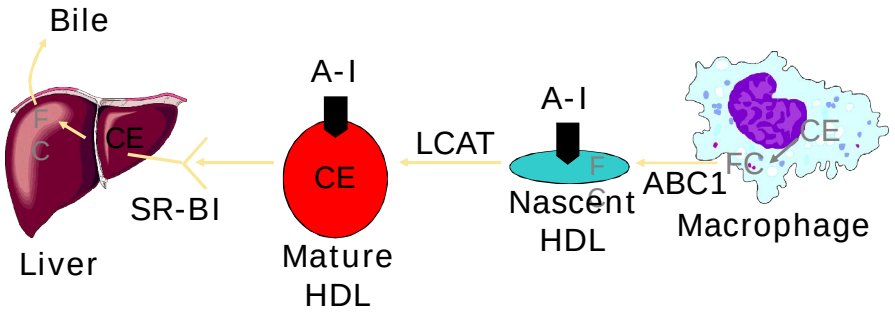
- From Free Apo A



Maturation of HDL



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.