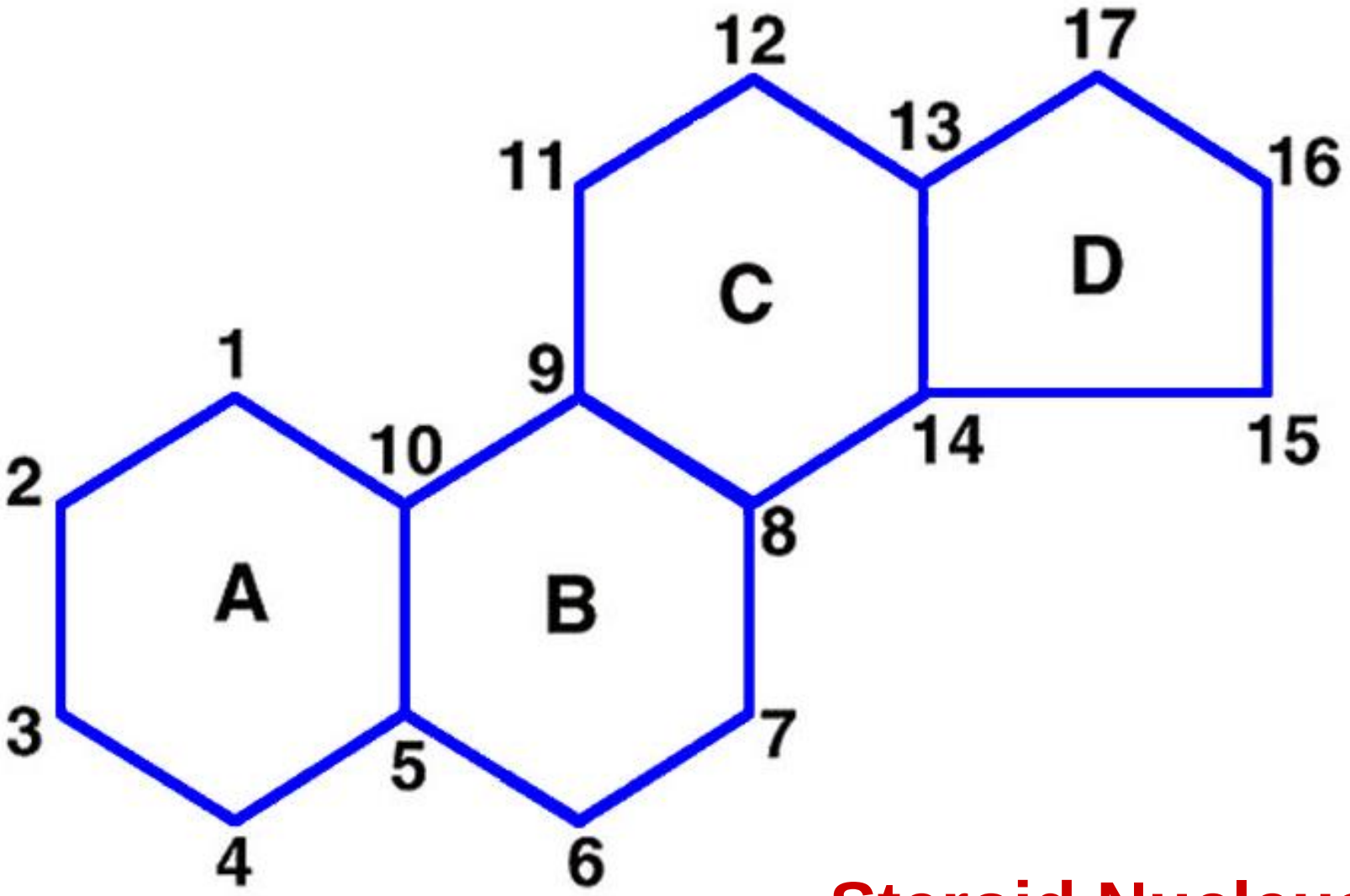
Cholesterol Metabolism

Lippincott's Illustrated Review
Chapter 18



Steroid Nucleus

Hydrocarbon "tail"

21 22 24 27

20 23 25

26

18 12

11 17 16

19 C 13 D

1 9

2 14 15

10 A B 8

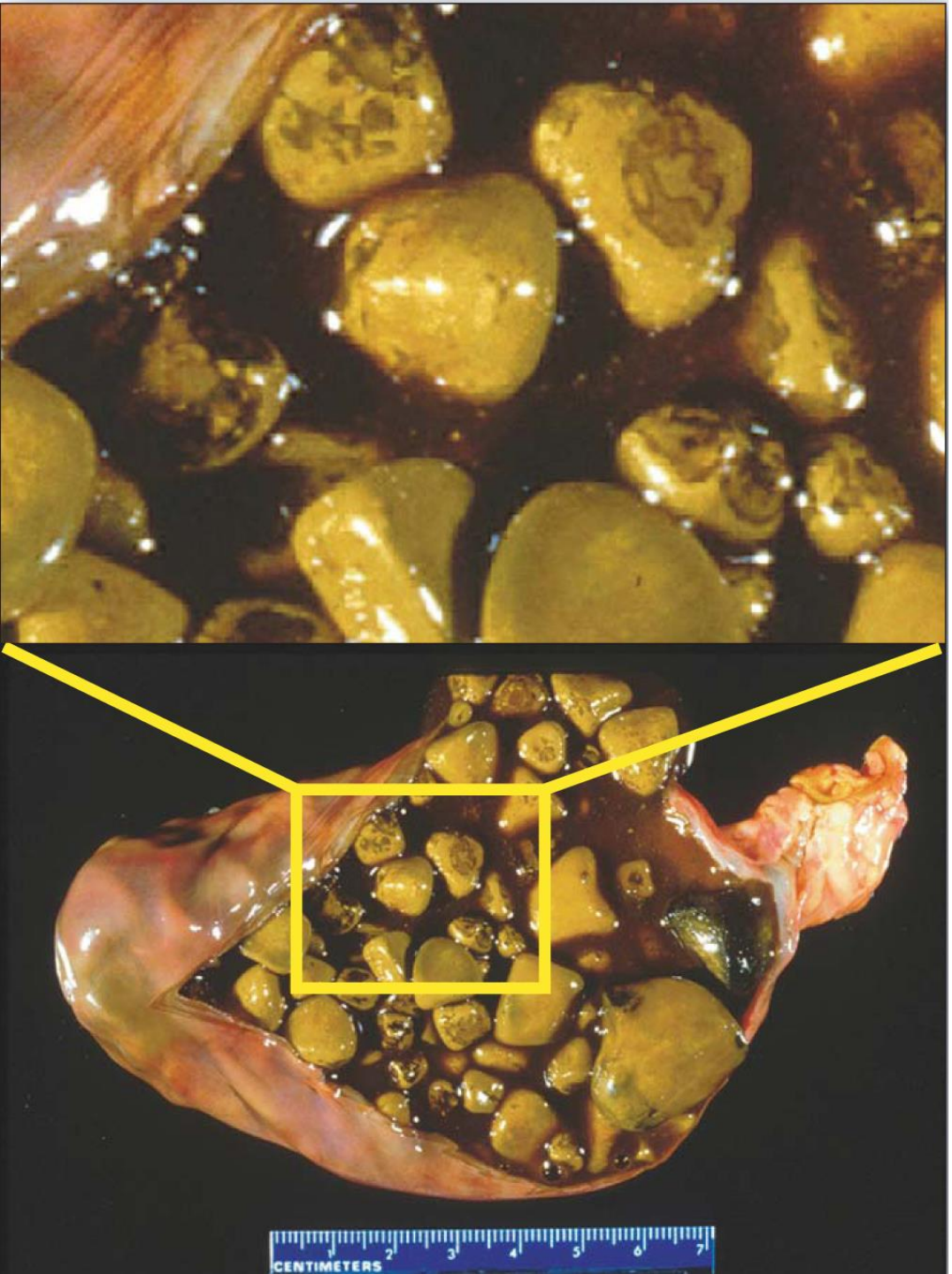
3

HO 5 7

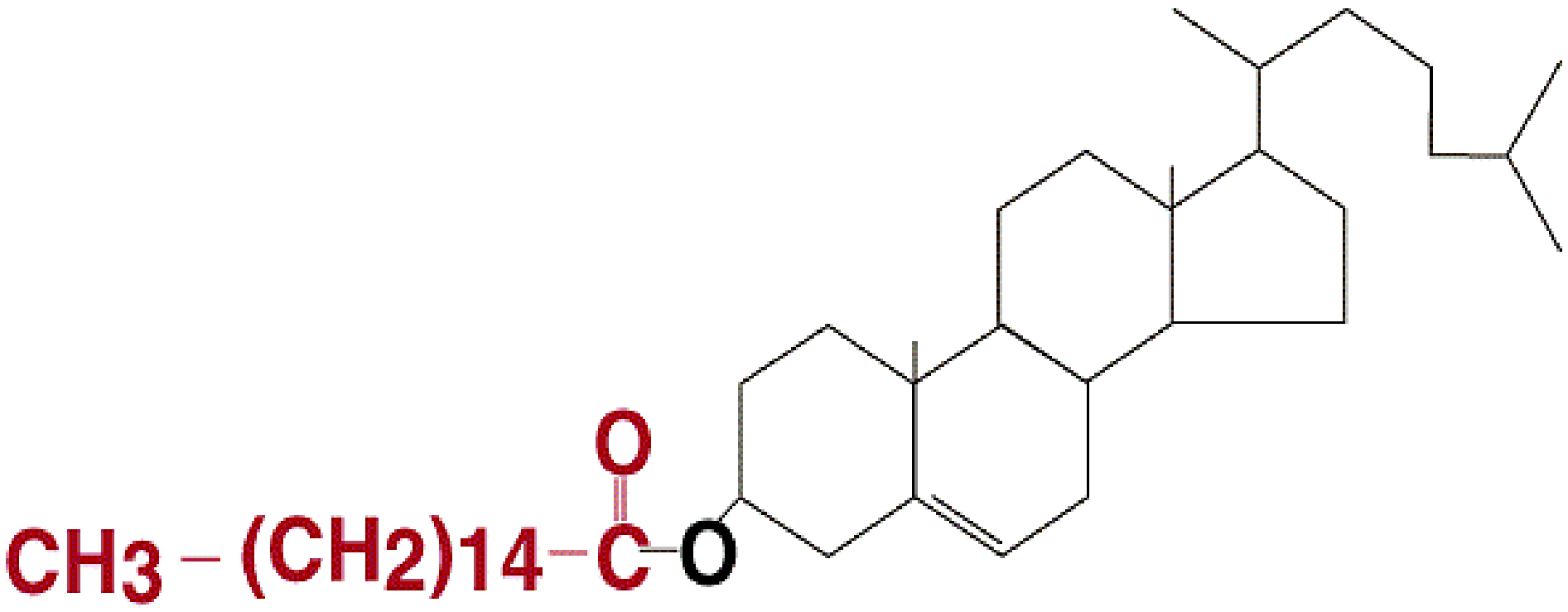
4 6

Steroid nucleus

Cholesterol



Cholesterol was isolated from gall bladder stones in 1774


O
CH3 – (CH2)14 – C – O

Sources and Elimination of Cholesterol

Synthesis: ≈ 1000 mg

Liver, Small Intestine, Adrenal Cortex …

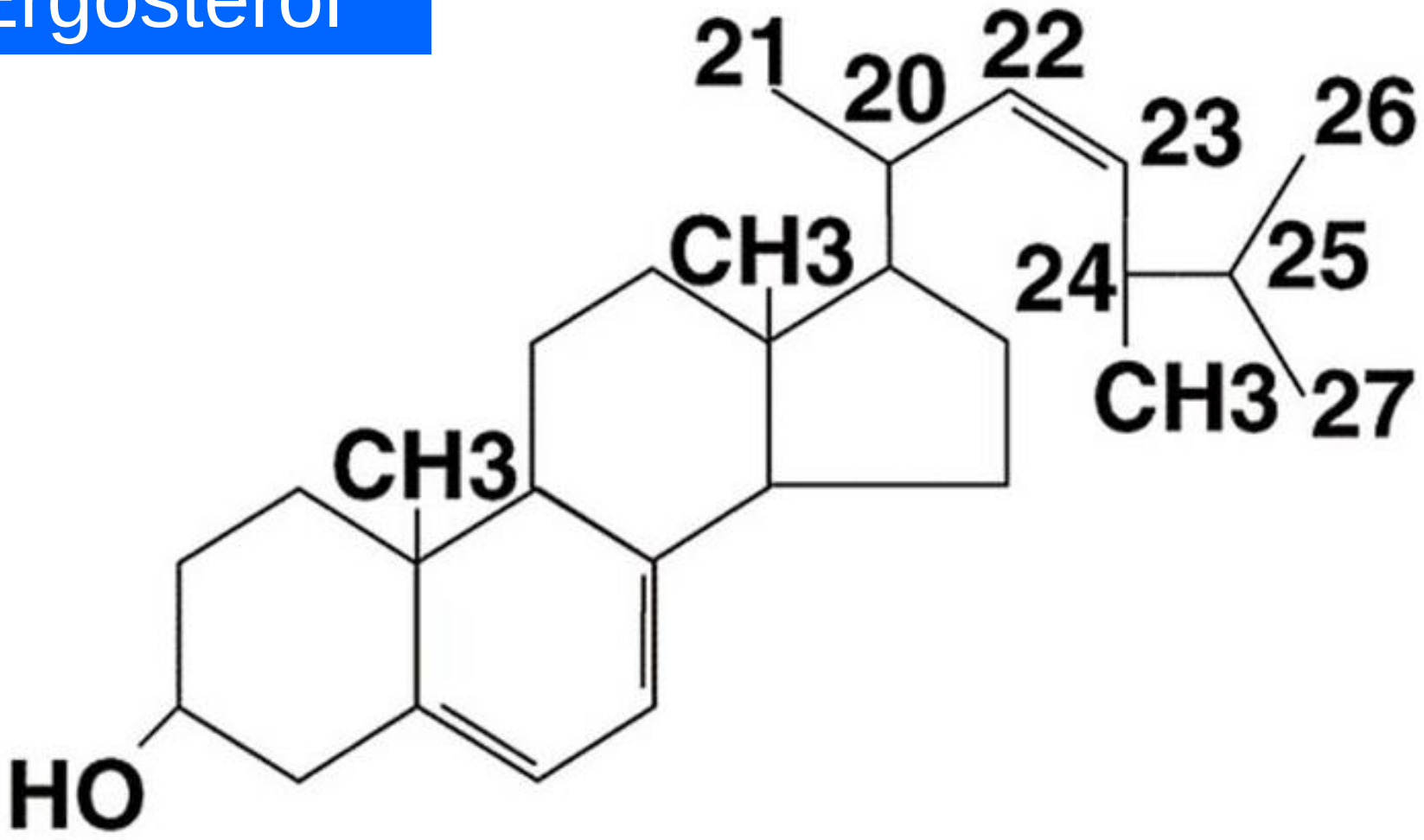
Dietary: ≈ 300 mg

(Low Cholesterol Diet)

Elimination: Via the Bile

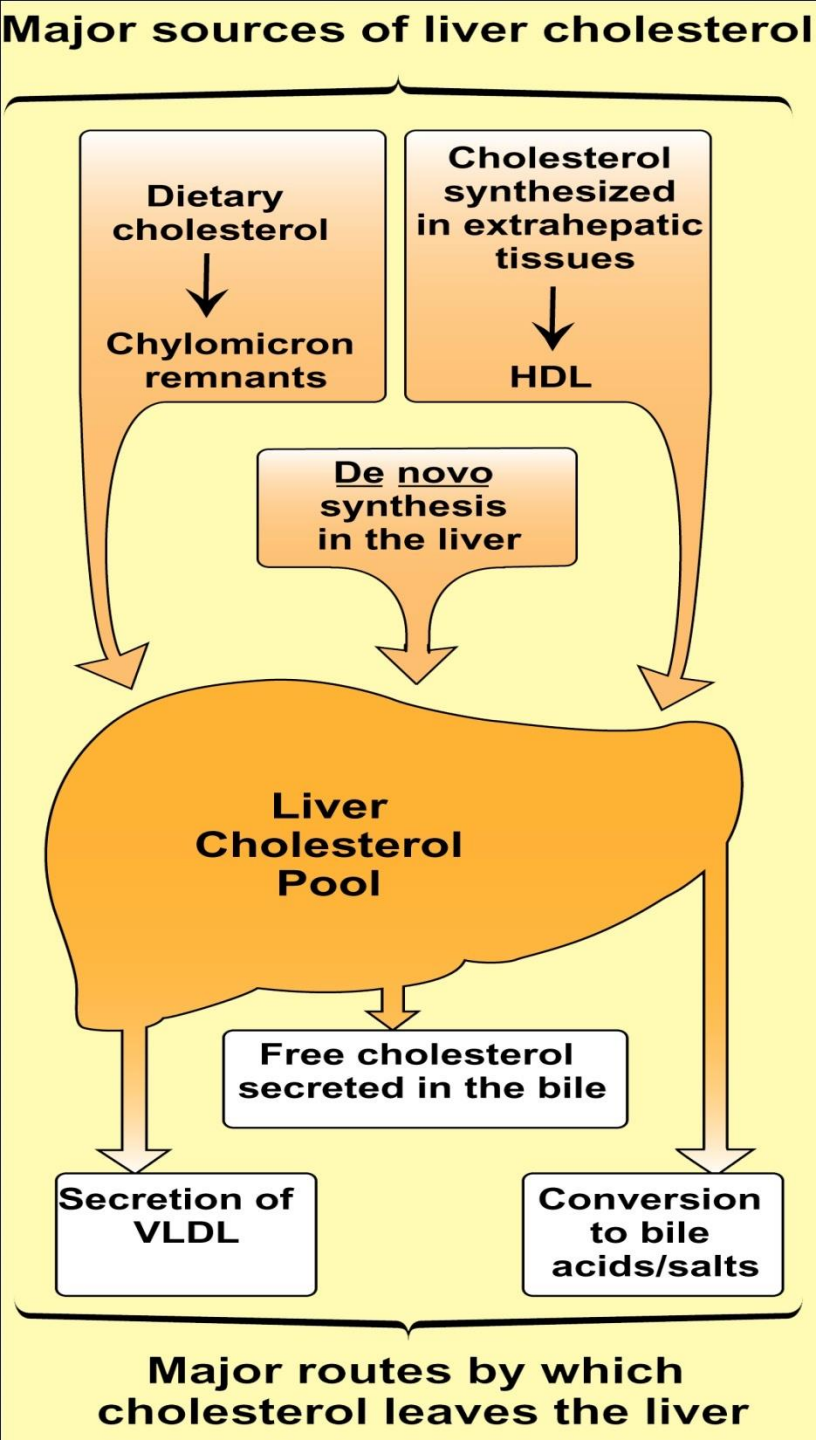
Cholesterol, Bile Salts

Ergosterol



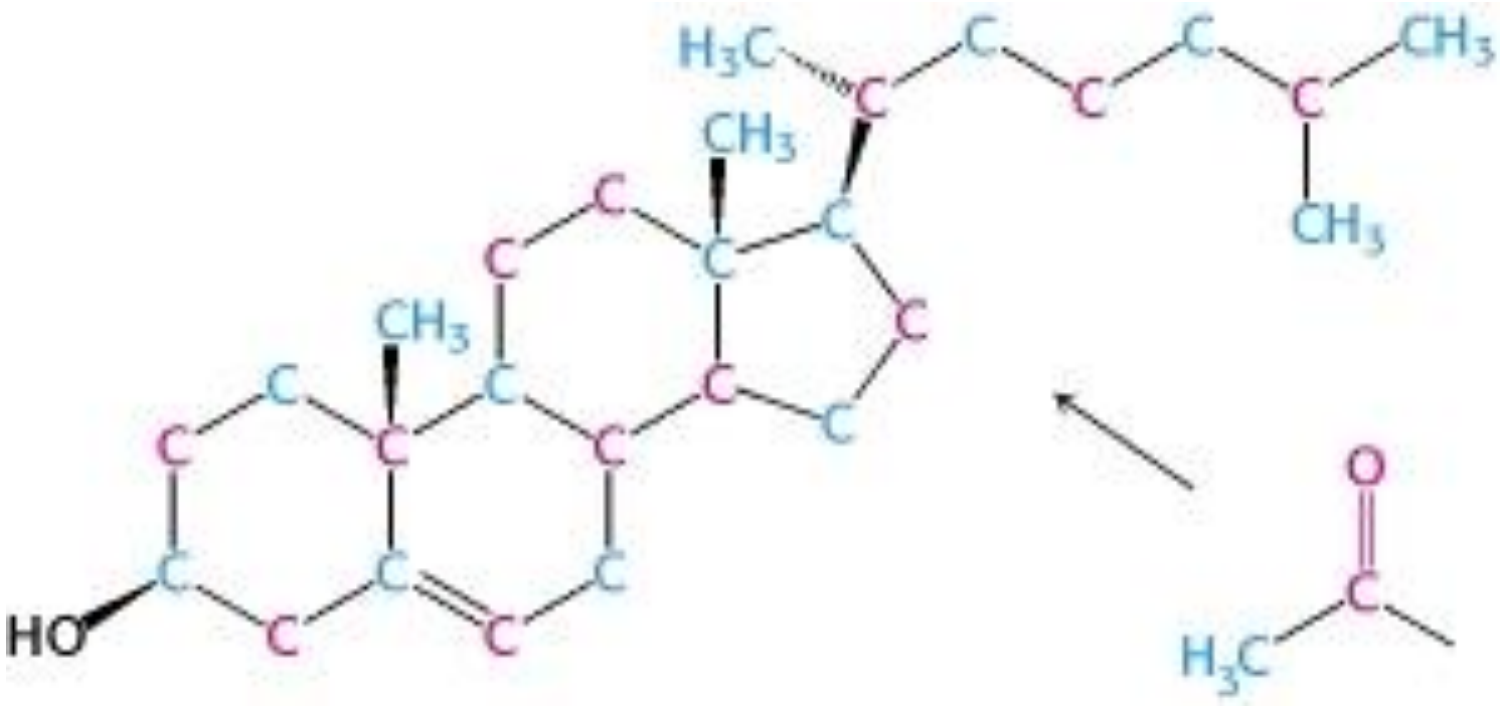
Plant Sterols are Poorly Absorbed by Human

- 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.


Major sources of liver cholesterol
Dietary cholesterol
Chylomicron remnants
Cholesterol synthesized in extrahepatic tissues
HDL
De novo synthesis in the liver
Liver Cholesterol Pool
Free cholesterol secreted in the bile
Secretion of VLDL
Conversion to bile acids/salts
Major routes by which cholesterol leaves the liver

Cholesterol Synthesis Requires

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



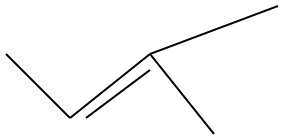
Stages in Cholesterol Synthesis

Acetyl CoA (C2)

↓

Mevalonate (C6)

↓



Isoprene Units (C5)

↓

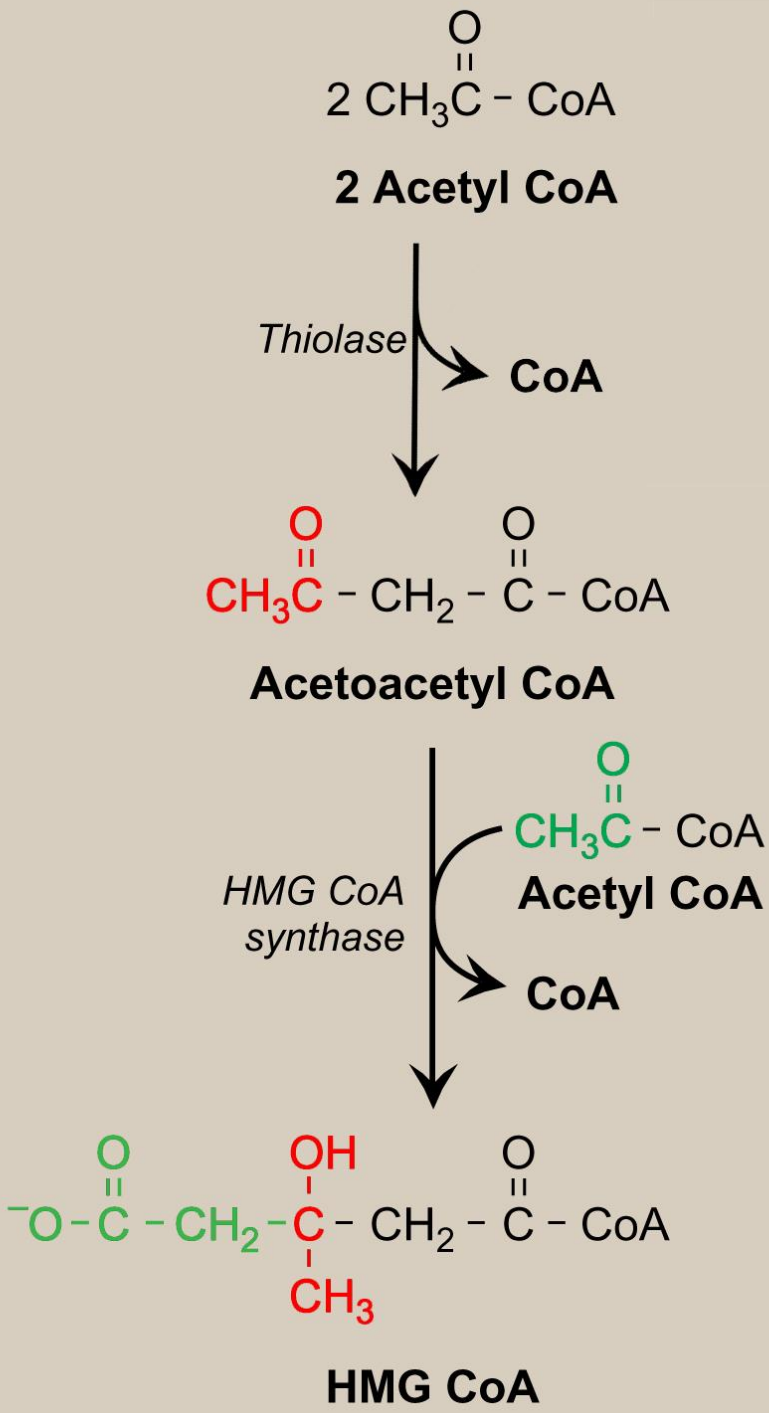
Squalene (C30)

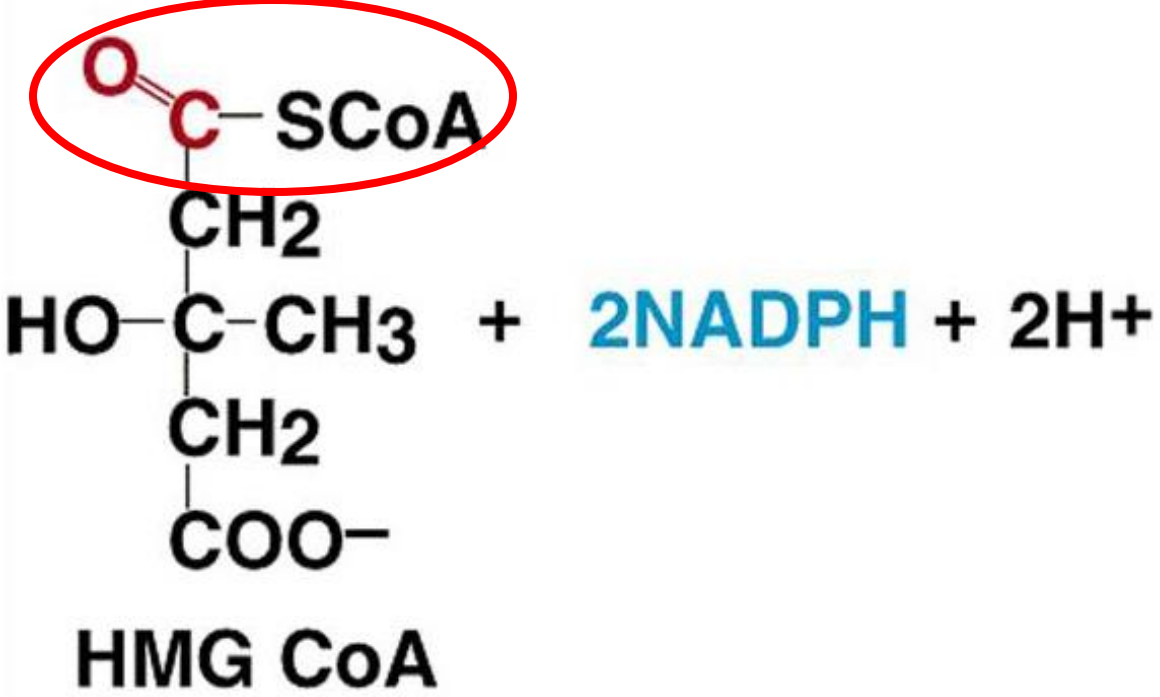
↓

Lanosterol (C30)

↓

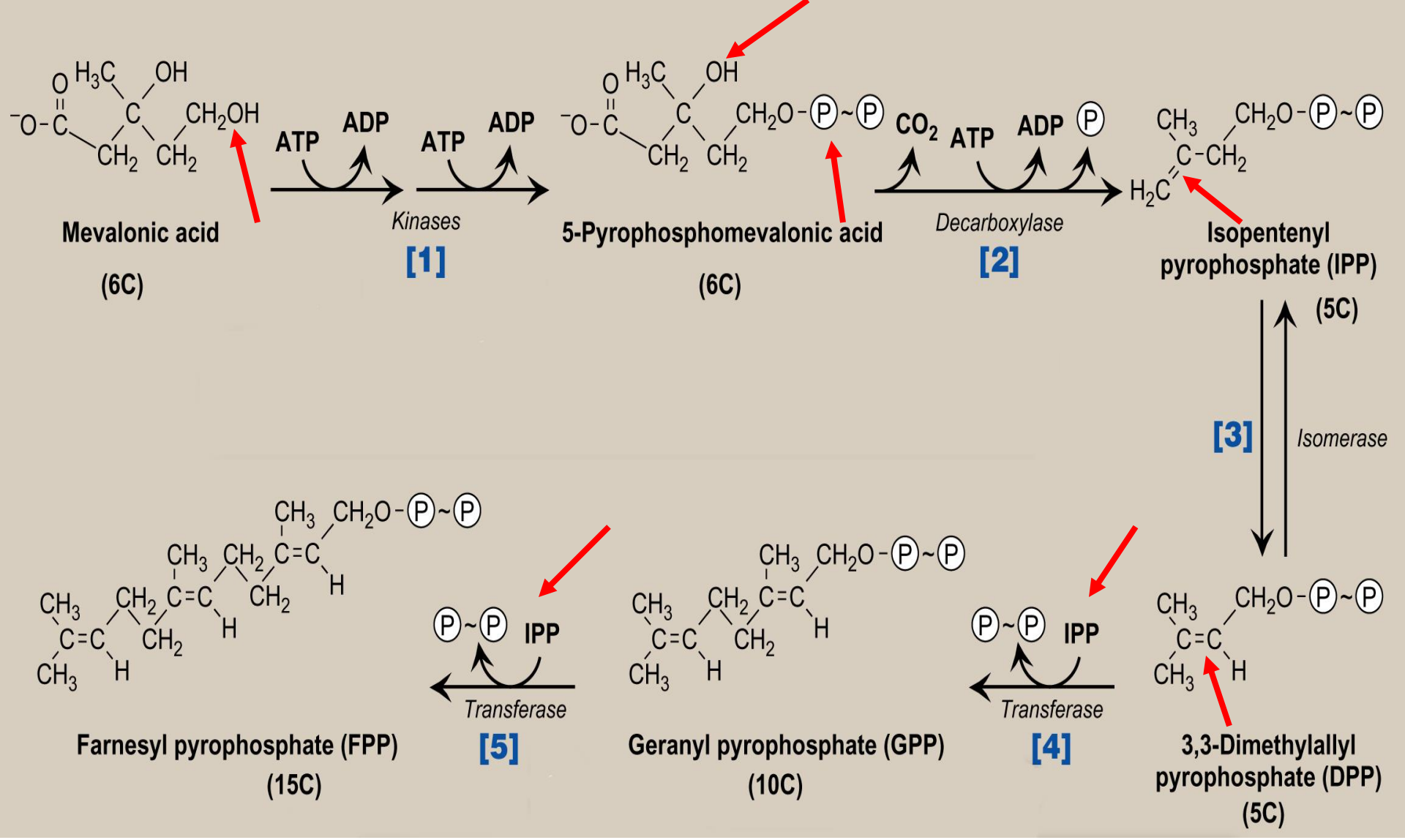
Cholesterol (C27)

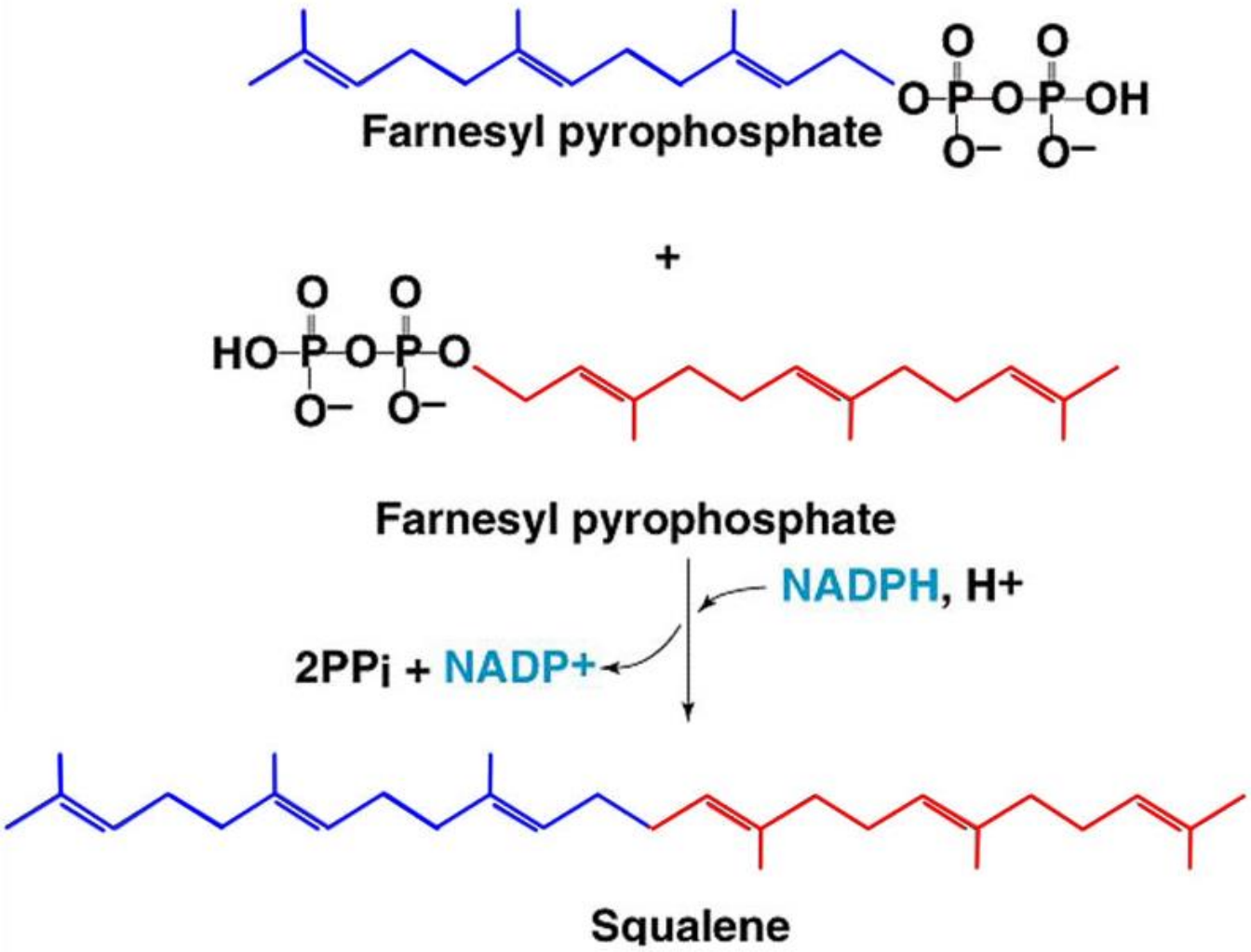

2 CH3C – CoA
2 Acetyl CoA
Thiolase
CoA
CH3C – CH2 – C – CoA
Acetoacetyl CoA
HMG CoA synthase
CH3C – CoA
Acetyl CoA
CoA
⁻O – C – CH2 – C – CH2 – C – CoA
CH3
HMG CoA

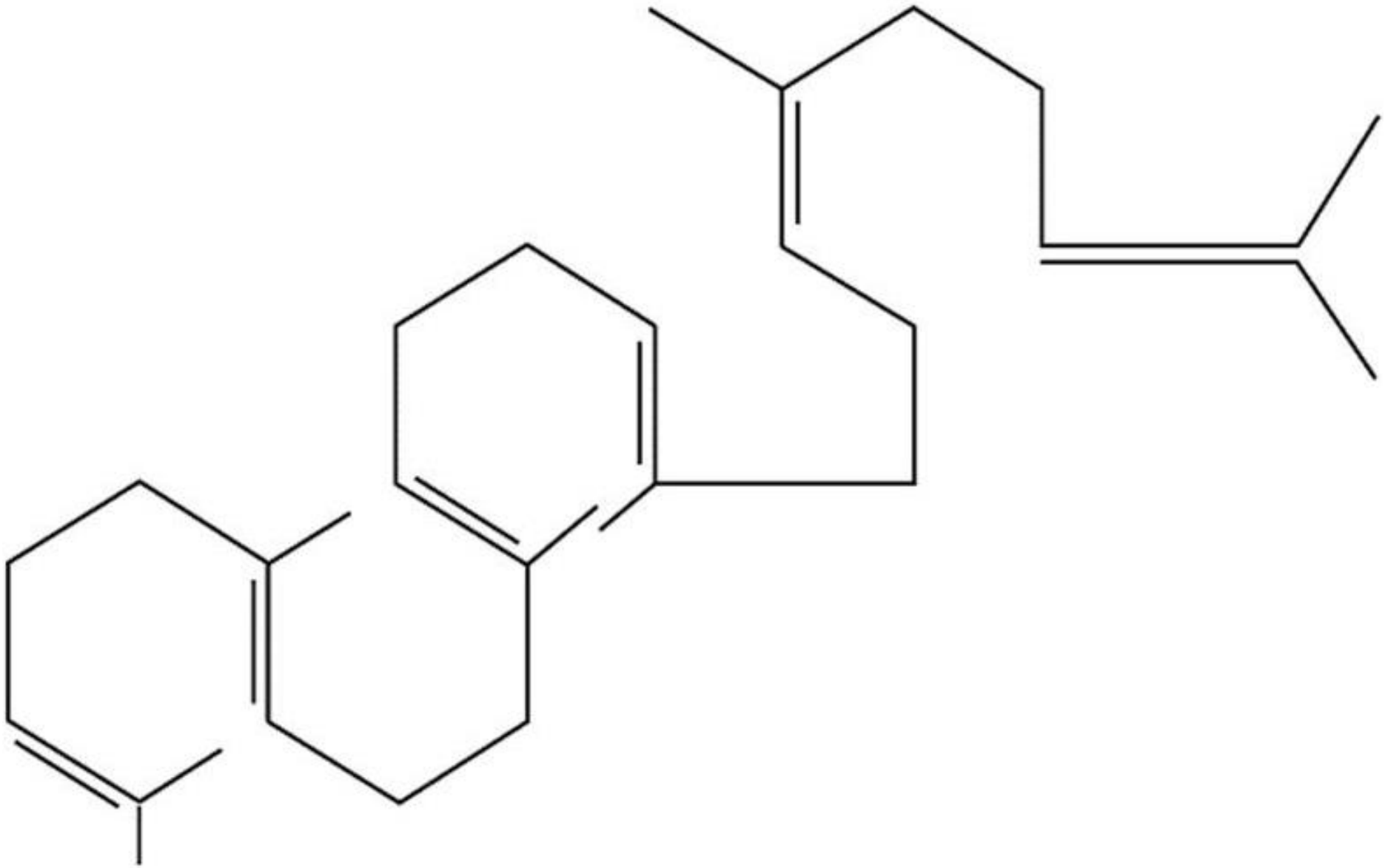


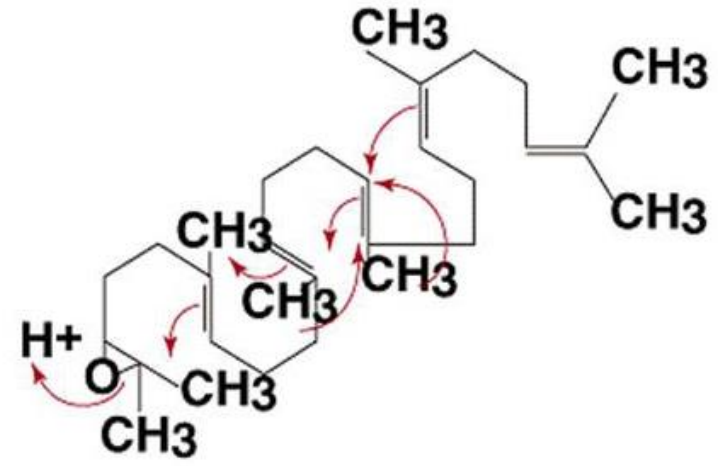
HMG CoA

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)

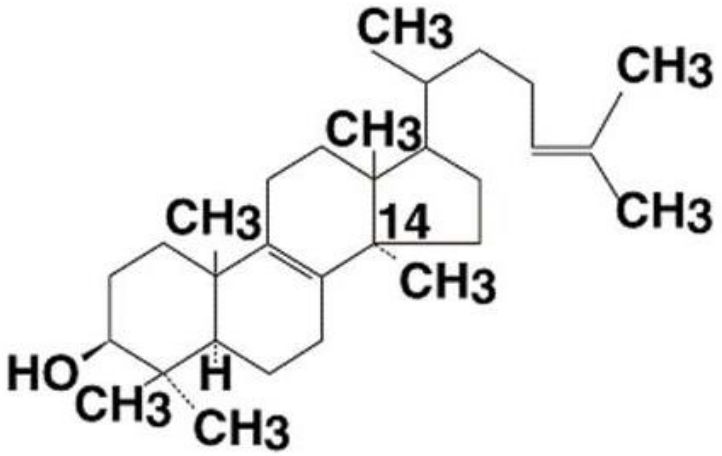

Farnesyl pyrophosphate
+
Farnesyl pyrophosphate
NADPH, H+
2PPi + NADP+
Squalene



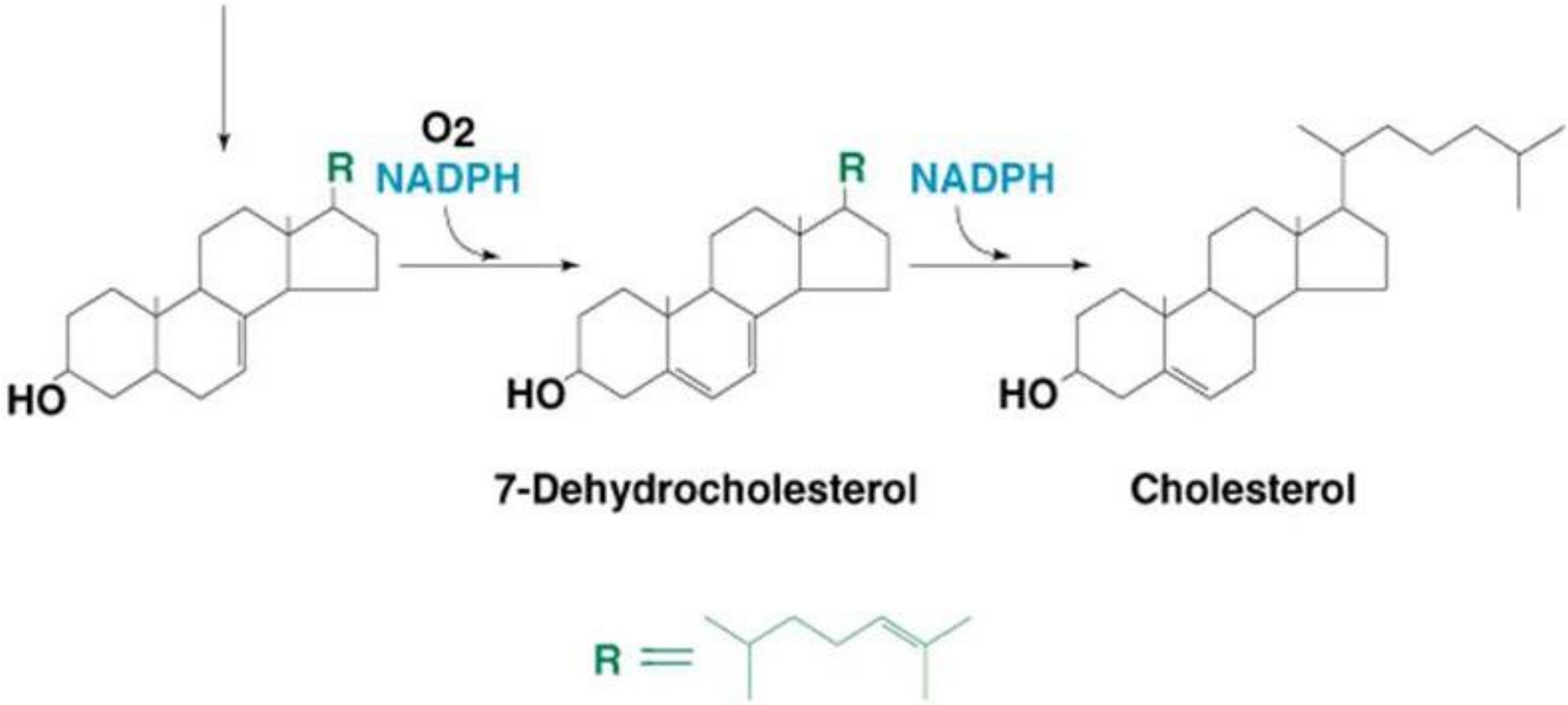


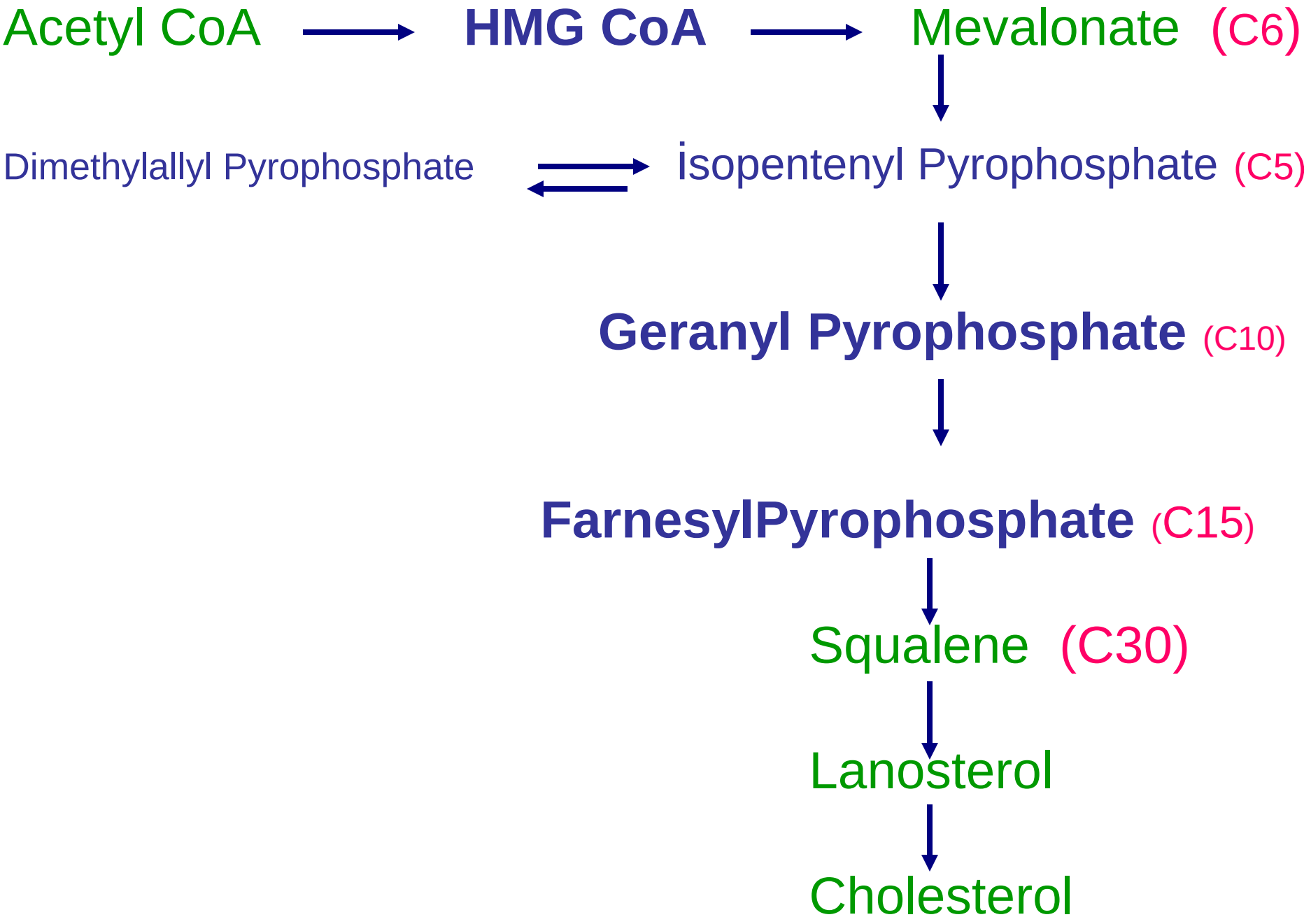
Squalene 2,3-epoxide

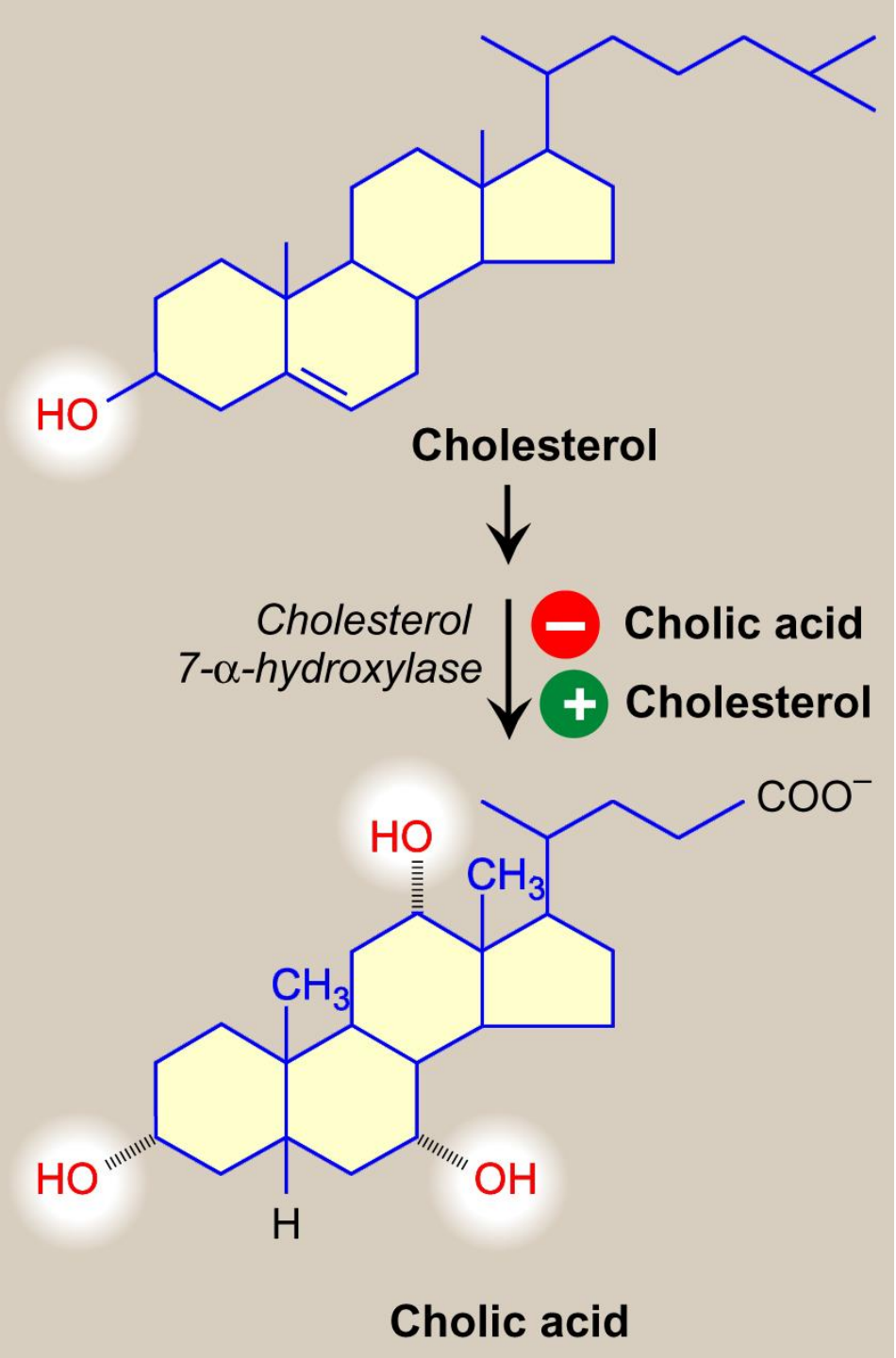
cyclase



Lanosterol

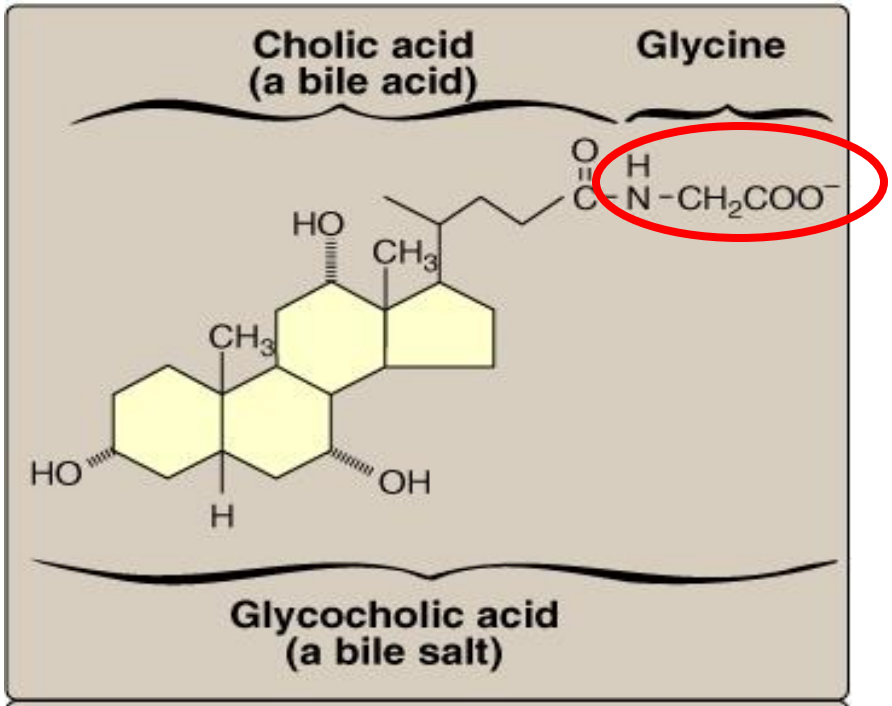

O2
NADPH
R
HO
NADPH
R
HO
HO
7-Dehydrocholesterol
Cholesterol
R =

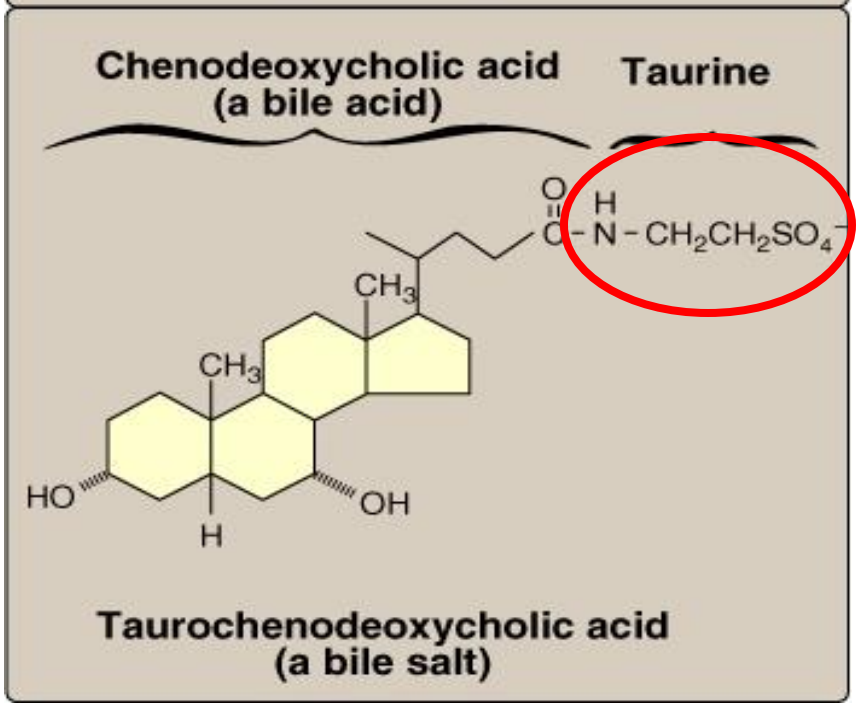

Acetyl CoA
HMG CoA
Mevalonate (C6)
Dimethylallyl Pyrophosphate
İsopentenyl Pyrophosphate (C5)
Geranyl Pyrophosphate (C10)
FarnesylPyrophosphate (C15)
Squalene (C30)
Lanosterol
Cholesterol

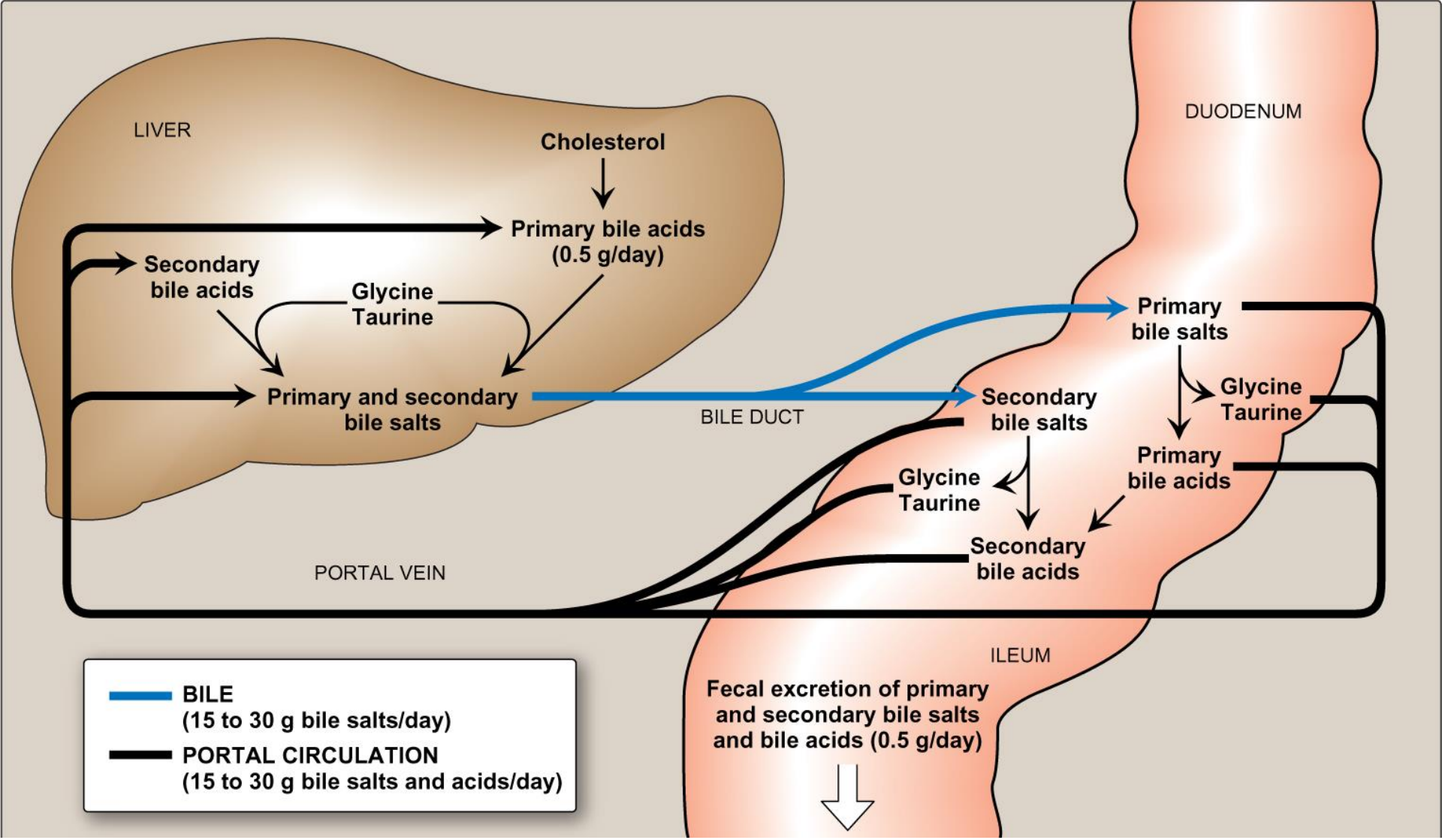


Synthesis of Bile Acids

Hydroxylation at Carbon 7 is the Rate-limiting Step

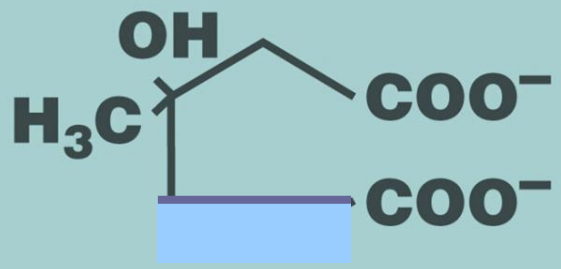

Cholic acid
(a bile acid)
Glycine
O
H
C – N – CH2COO–
HO
CH3
CH3
HO
OH
H
Glycocholic acid
(a bile salt)


Chenodeoxycholic acid
(a bile acid)
Taurine
O
H
C – N – CH2CH2SO4–
CH3
CH3
HO
OH
H
Taurochenodeoxycholic acid
(a bile salt)

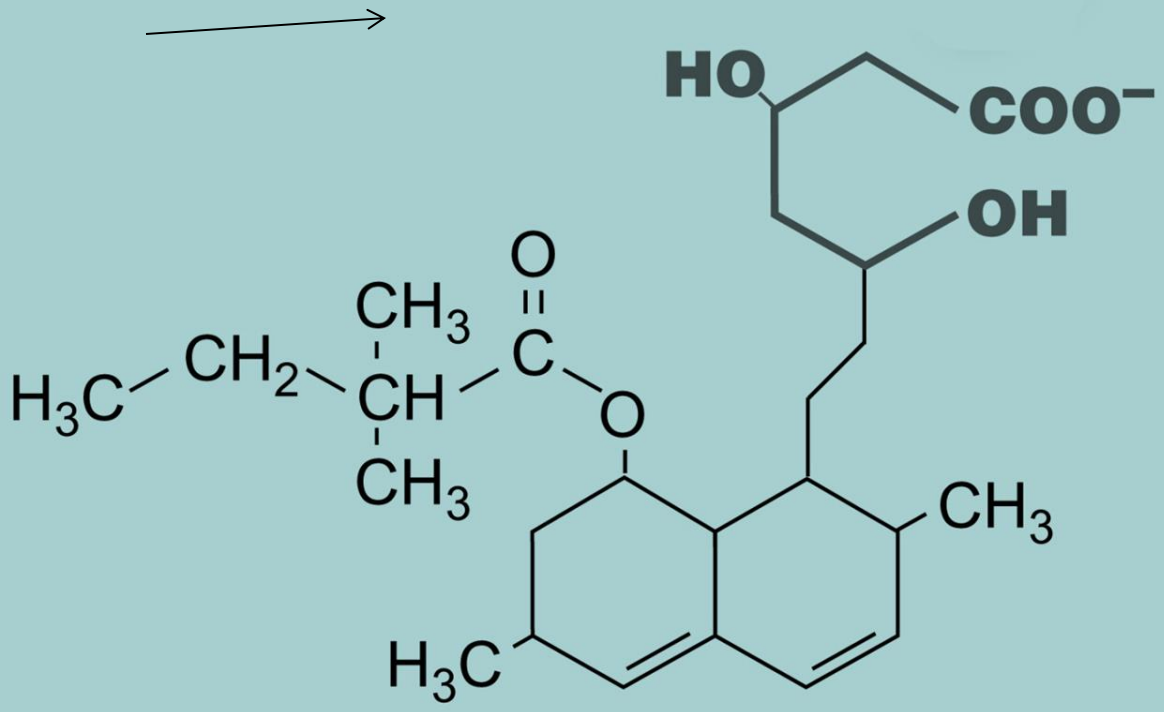

LIVER
Cholesterol
Primary bile acids
(0.5 g/day)
Secondary
bile acids
Glycine
Taurine
Primary and secondary
bile salts
BILE DUCT
DUODENUM
Primary
bile salts
Glycine
Taurine
Secondary
bile salts
Primary
bile acids
Glycine
Taurine
Secondary
bile acids
PORTAL VEIN
ILEUM
Fecal excretion of primary
and secondary bile salts
and bile acids (0.5 g/day)
BILE
(15 to 30 g bile salts/day)
PORTAL CIRCULATION
(15 to 30 g bile salts and acids/day)

Lowering Cholesterol Level in the Plasma

- 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

Pfizer

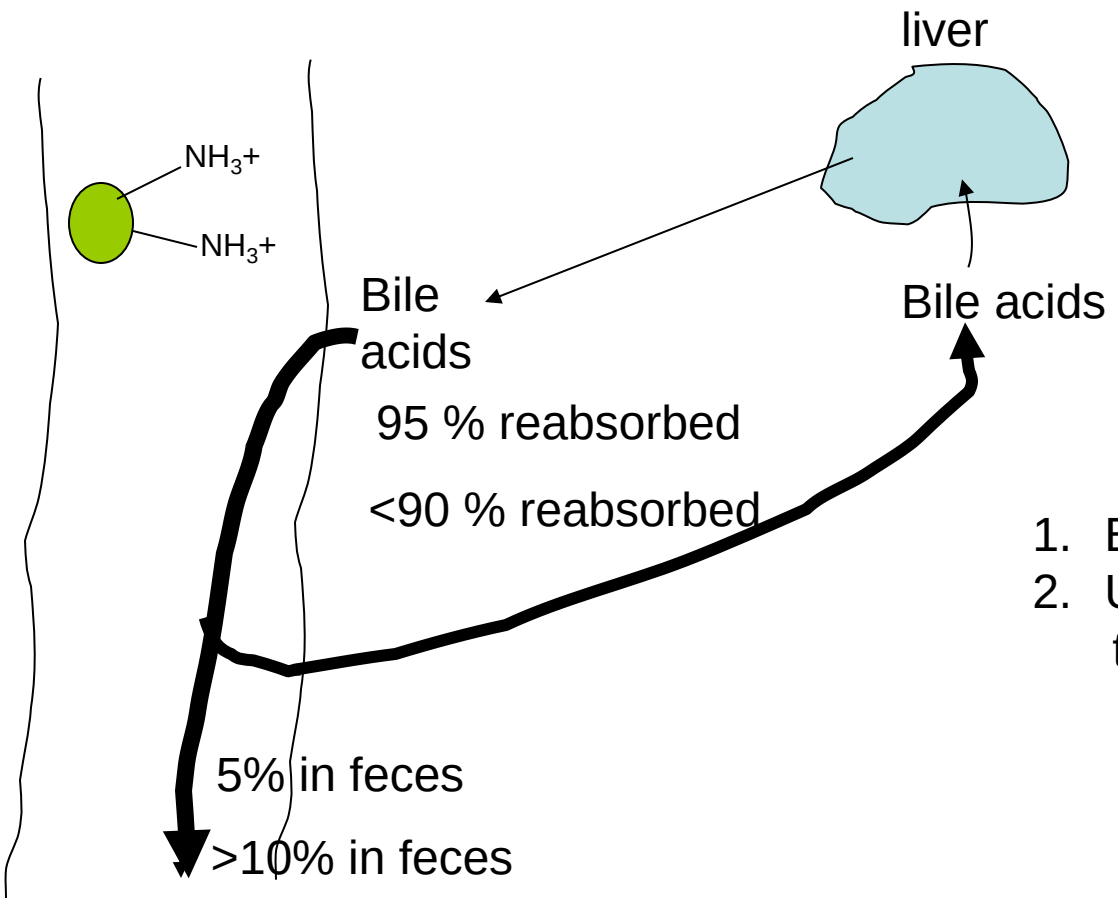
Lipitor™

10 mg ATORVASTATIN

30 filmcoated tablets each
containing atorvastatin 10 mg

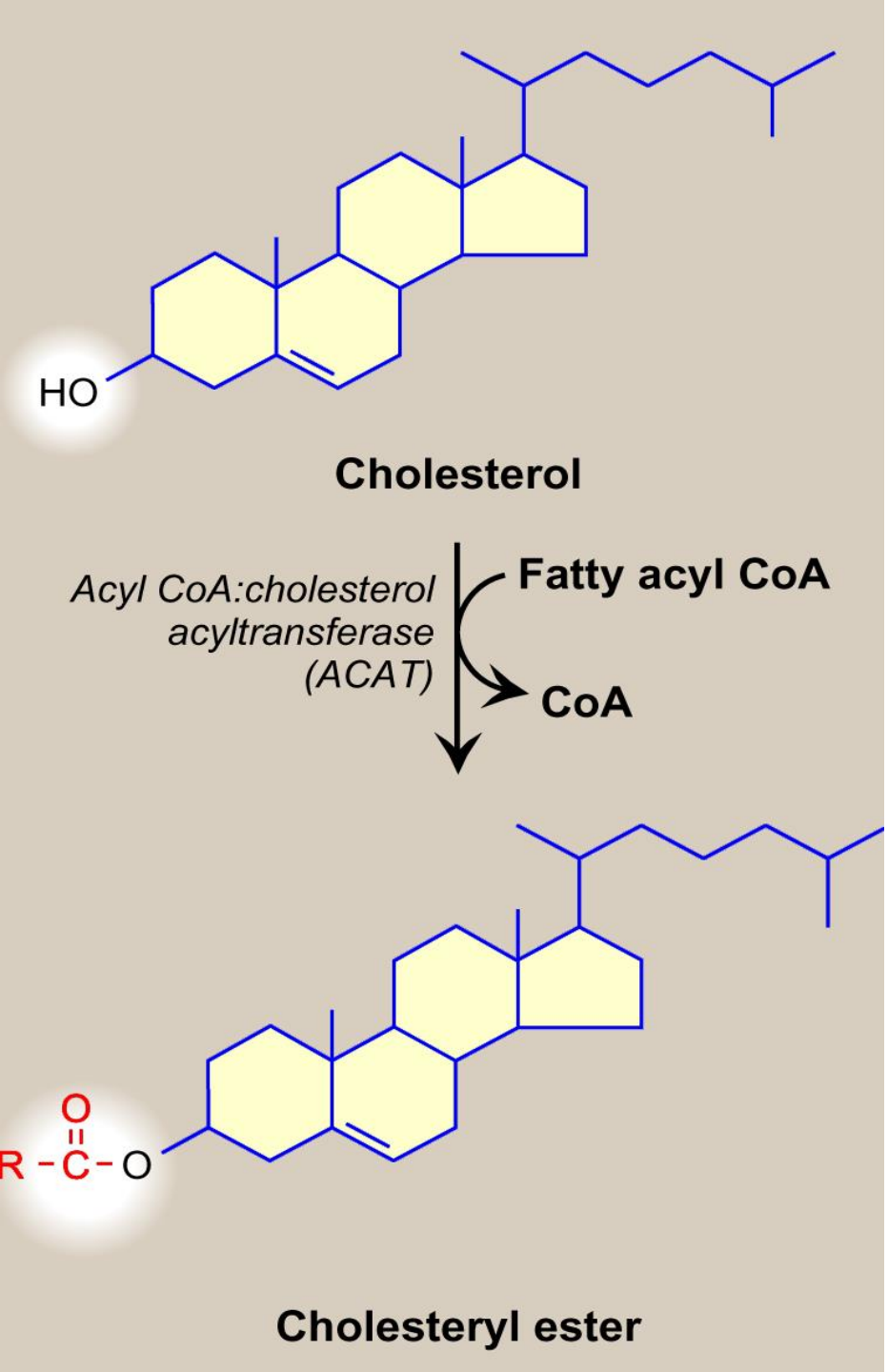
Sealed For
Your Protection

Lowering Cholesterol

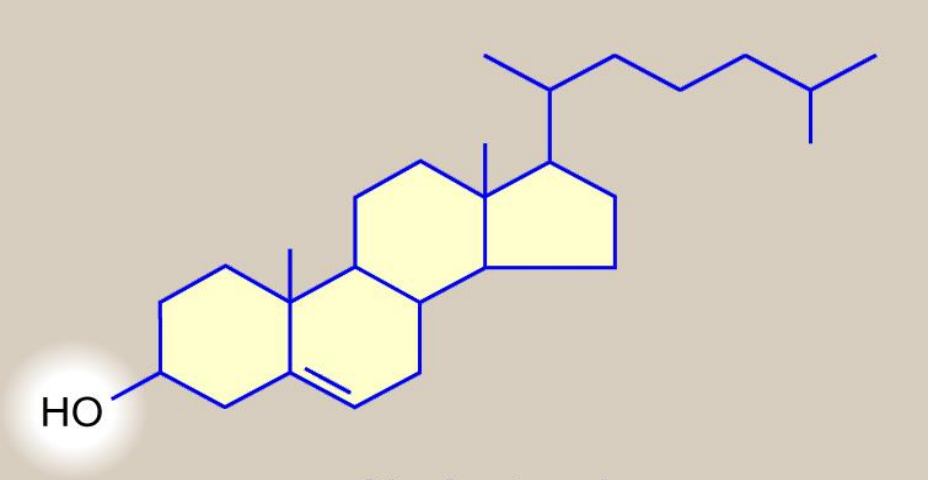


1. Bind bile acid
2. Utilize more cholesterol to make bile acids

Esterification of Cholesterol in the Cells



Esterification of Cholesterol in the Plasma

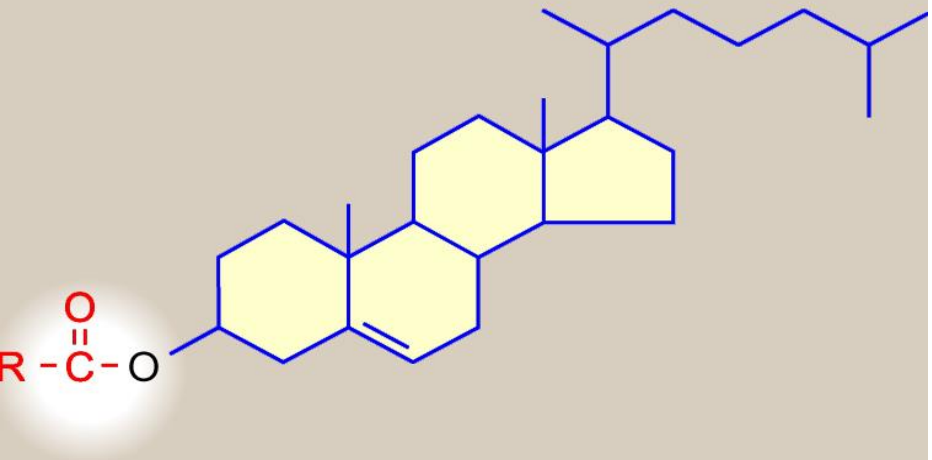


Cholesterol

Lecithin: Cholesterol Acyl Transferase (LCAT)

Lecithin (PC)

Lysolecithin

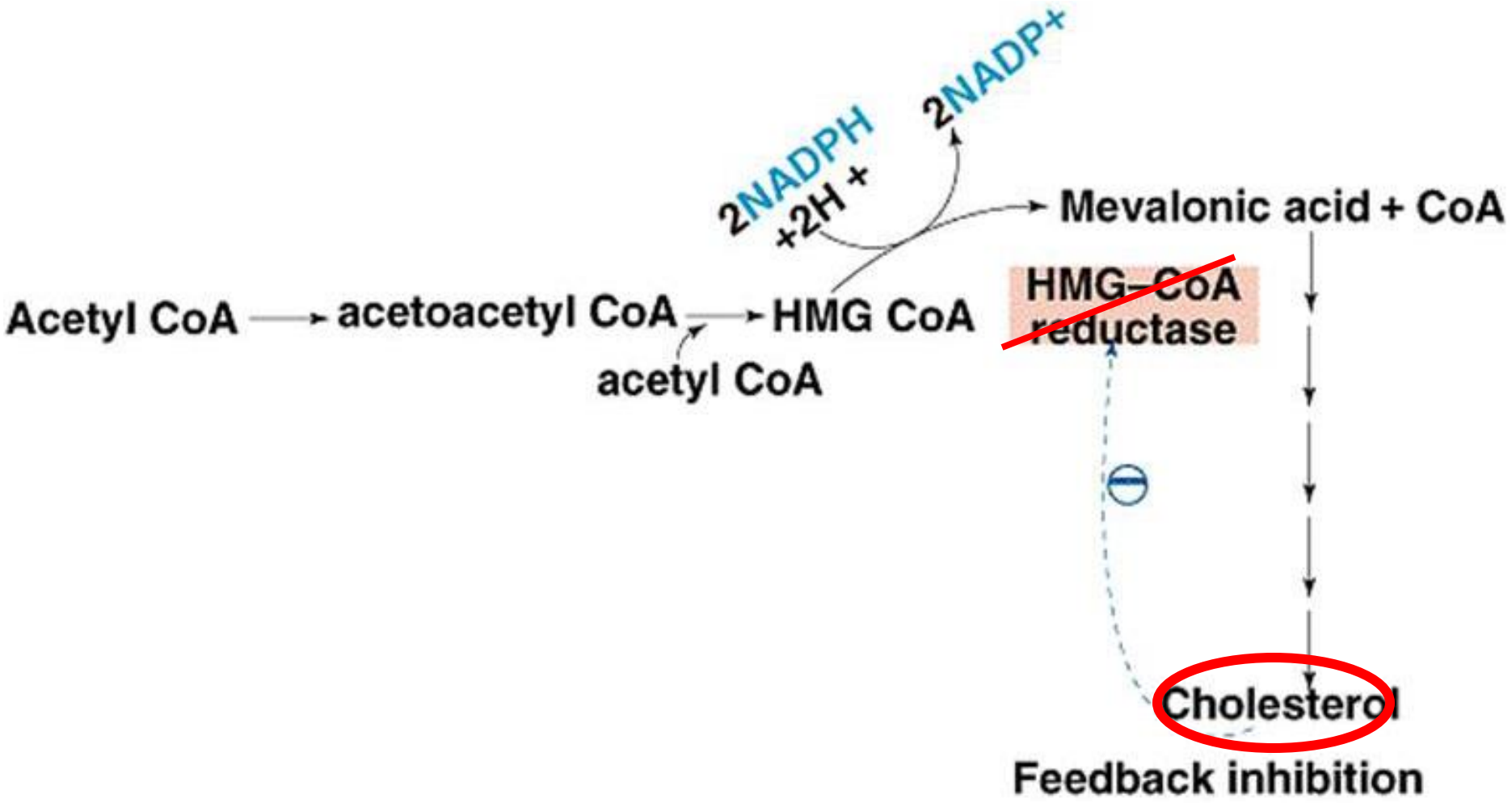


Cholesteryl ester

Regulation of Cholesterol Synthesis

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

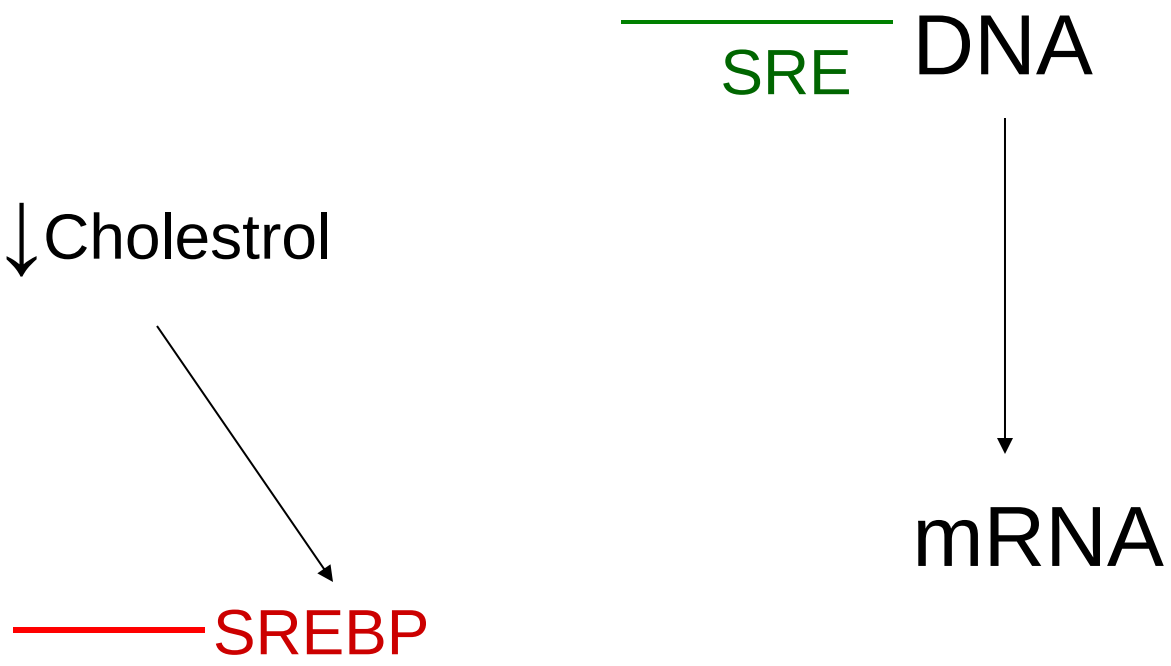
Regulation of Cholesterol Synthesis



Regulation of Cholesterol Synthesis

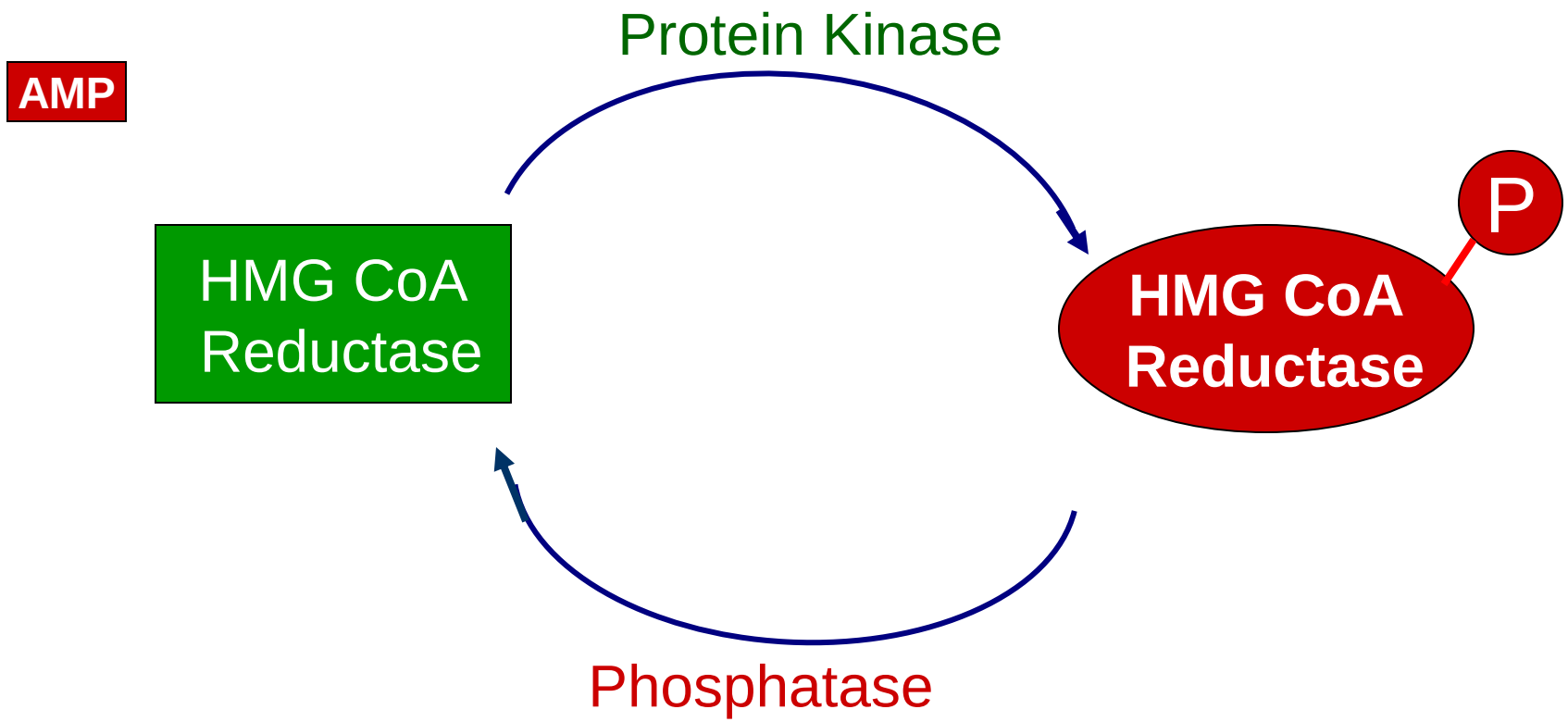
- Regulation of Gene Expression

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)

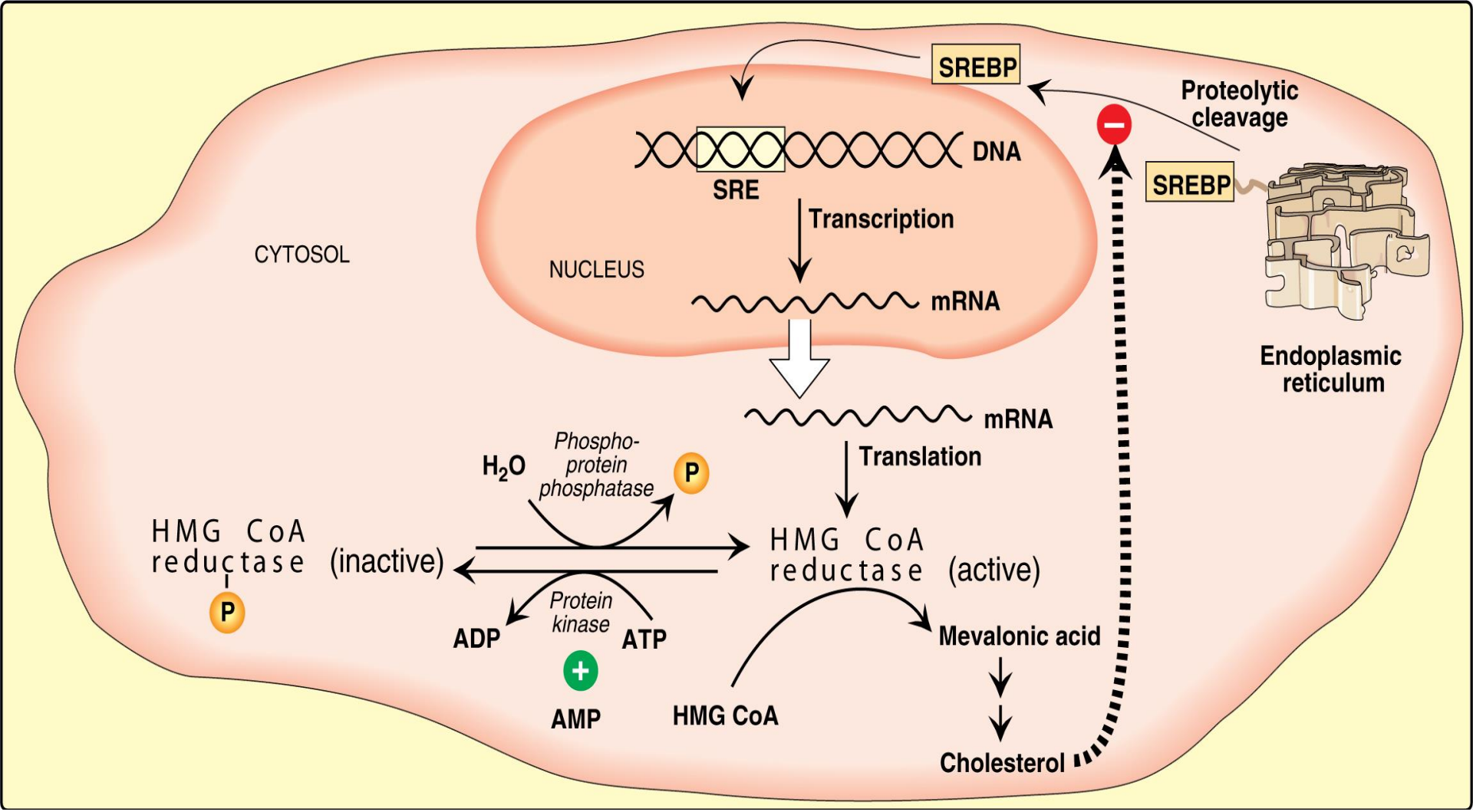
Regulation of Cholesterol Synthesis

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

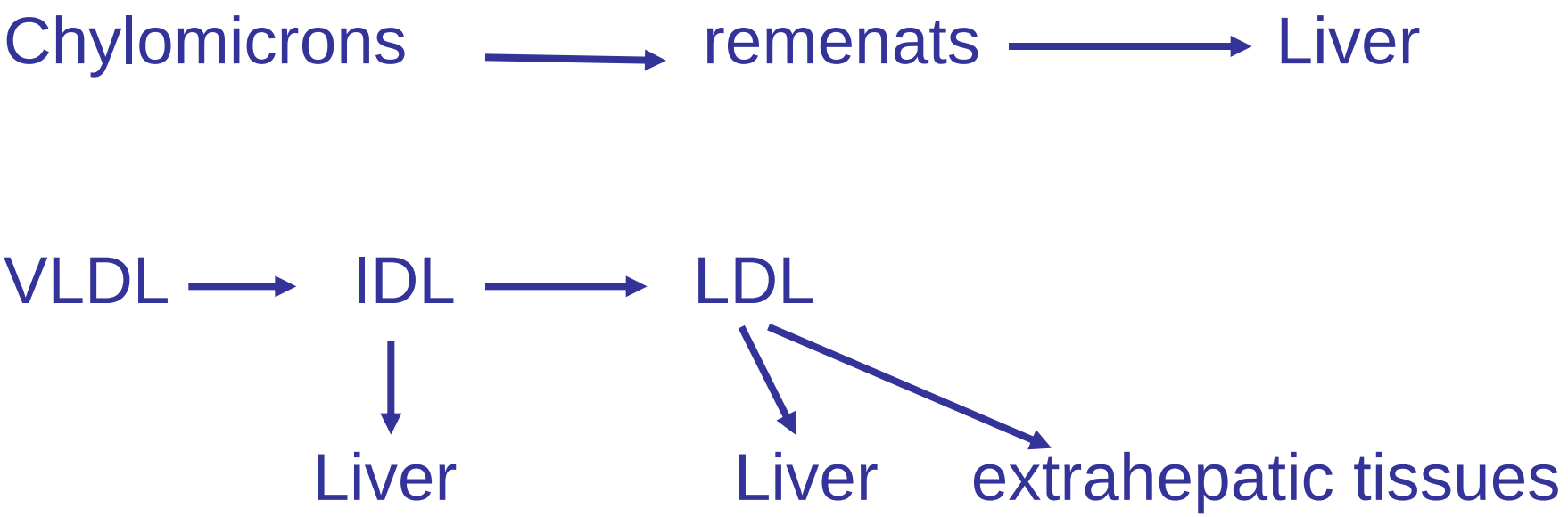
↑ **Cholesterol**

↑↑**HMG CoA Reductase** Proteolysis

↓ HMG CoA Reductase


SREBP
Proteolytic cleavage
DNA
SRE
Transcription
SREBP
CYTOSOL
NUCLEUS
mRNA
Endoplasmic reticulum
mRNA
Translation
H_2O
Phospho-protein phosphatase
P
HMG CoA reductase (inactive)
HMG CoA reductase (active)
P
Protein kinase
ADP
ATP
Mevalonic acid
AMP
HMG CoA
Cholesterol

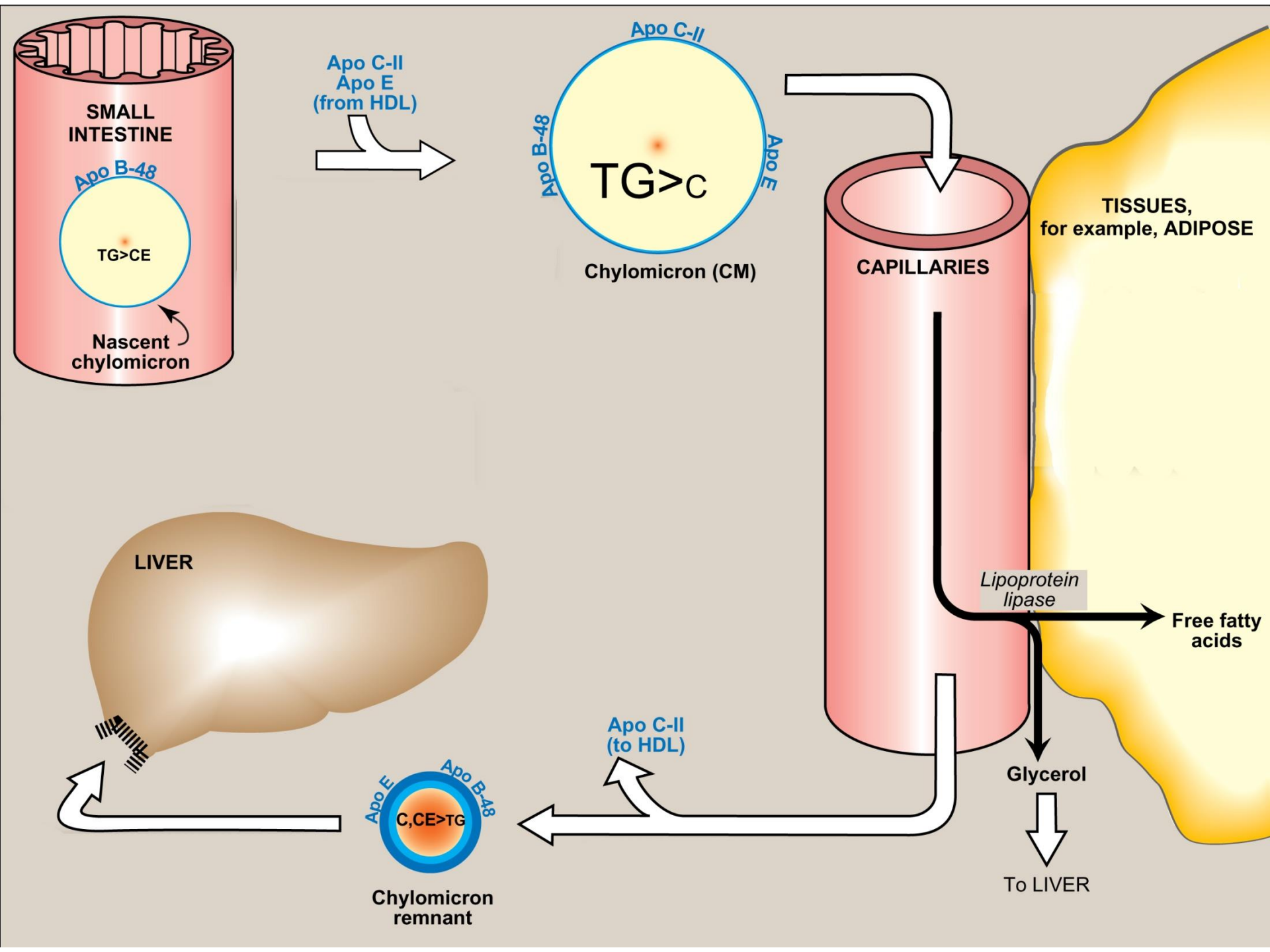
Transport of Cholesterol in the Blood

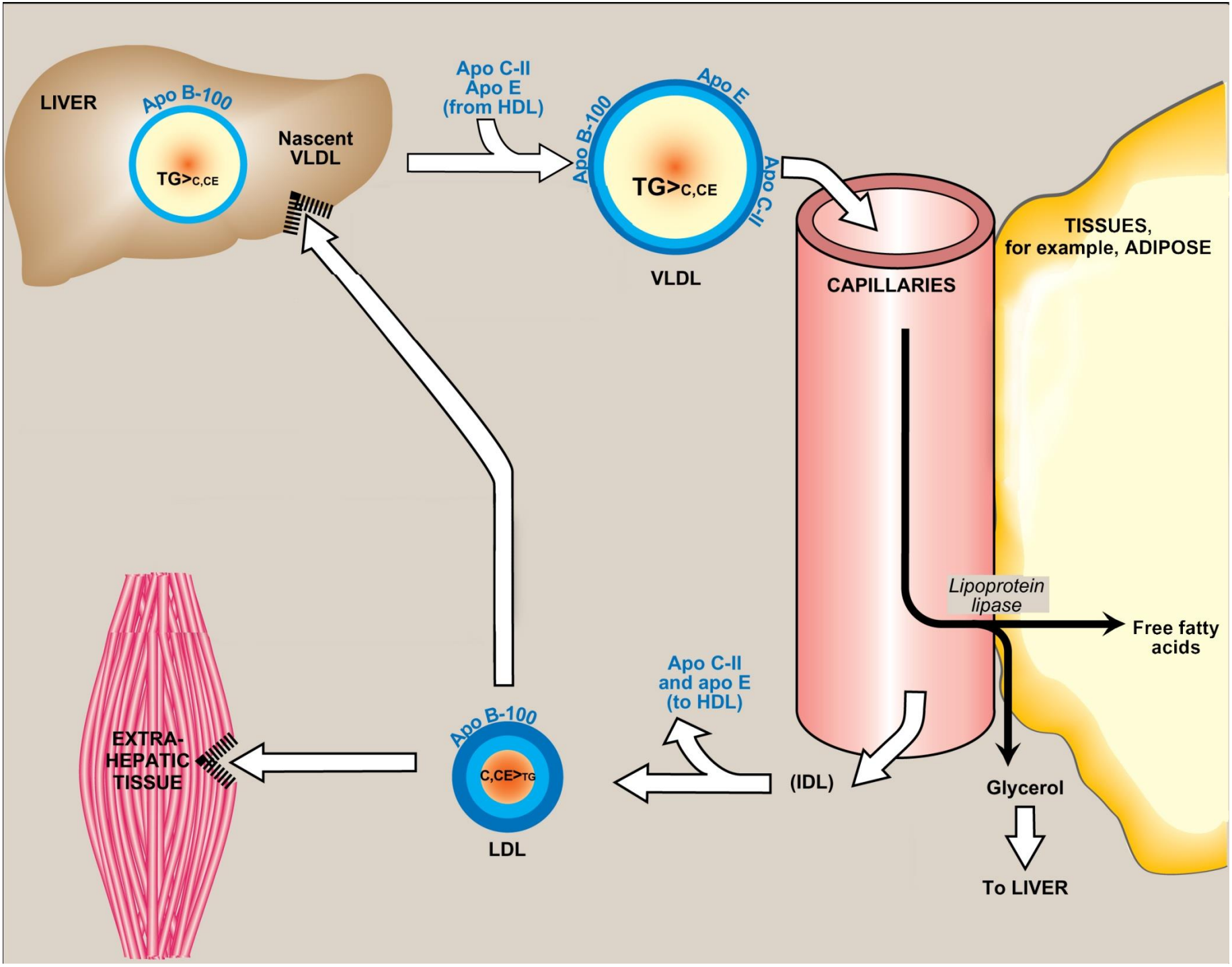


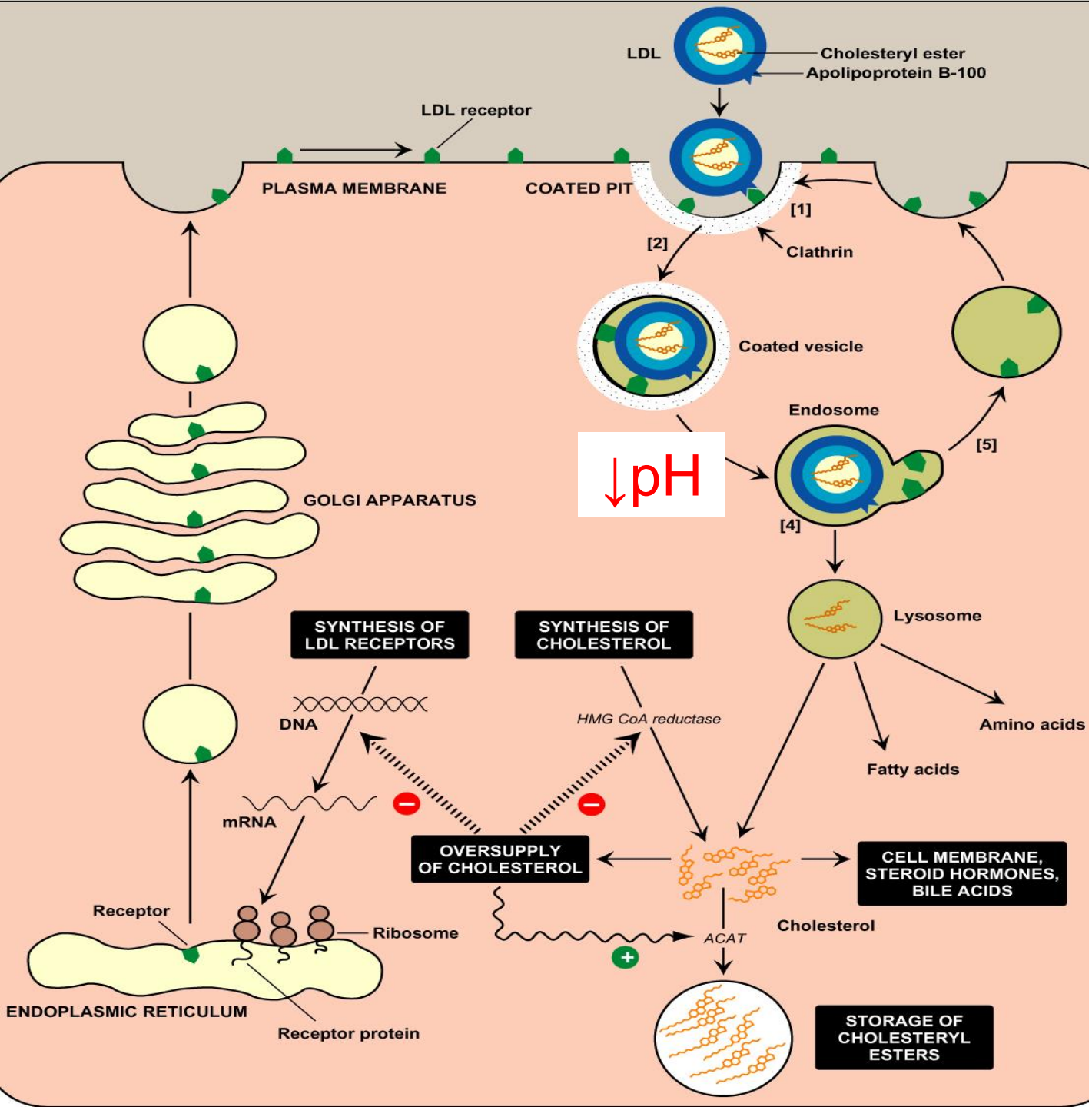
HDL

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



LDL Receptors
-ve charge
Bind Apo B-100, Apo E

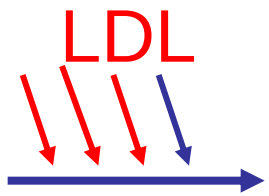
Macrophage Scavenger Receptor

Scavenger **R**eceptor Class **A** (**SR-A**)

Non specific

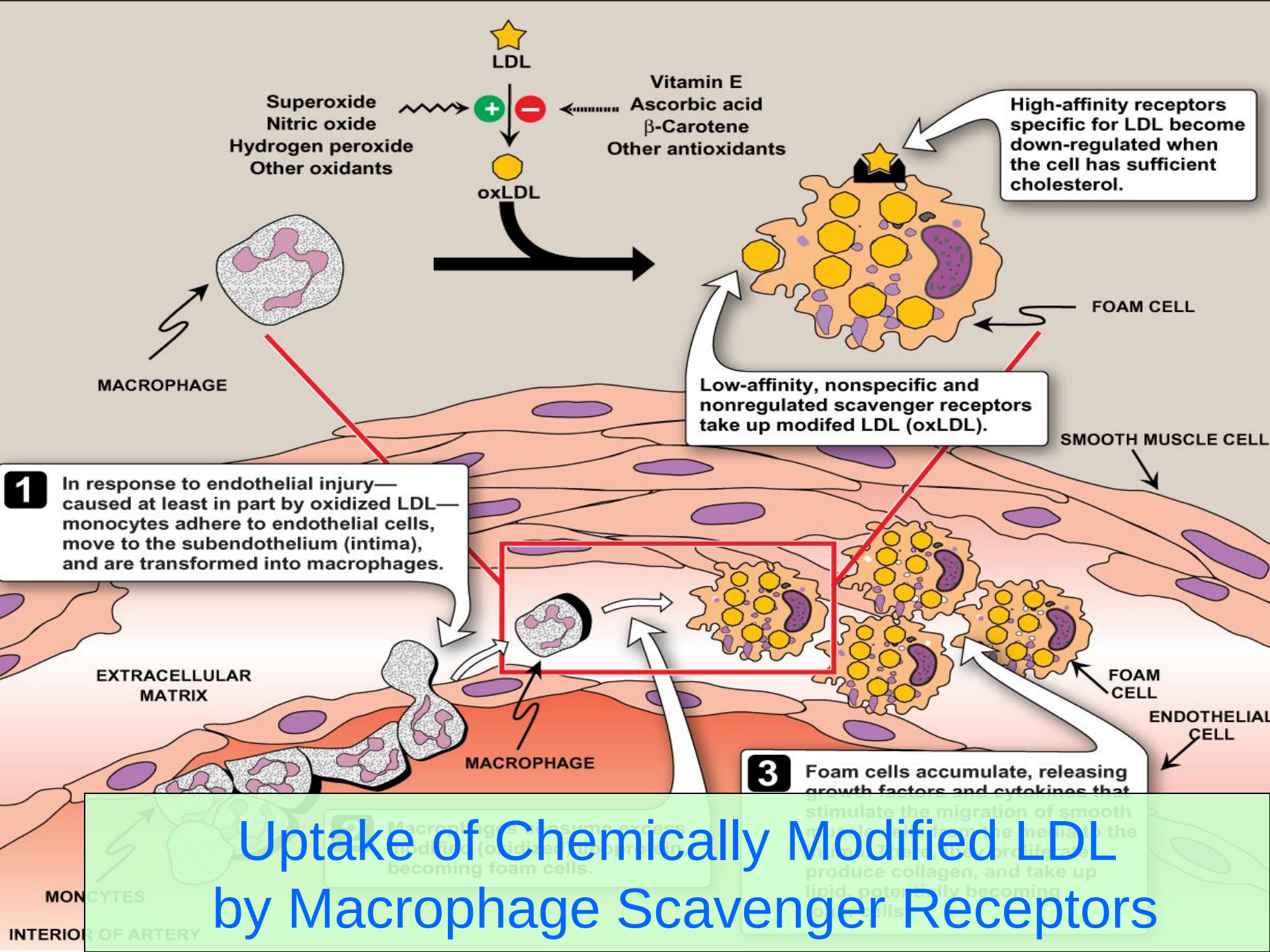
modified (damaged) LDL

No down regulation



Macrophage → foam cells

Accumulation of foam cells in the subendothelial space → Early evidence of atherosclerotic plaque



Uptake of Chemically Modified LDL by Macrophage Scavenger Receptors

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

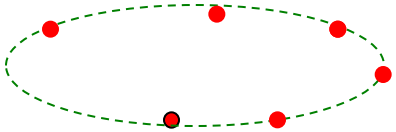
Cholesterol deposition in tissues

Atherosclerosis Death in childhood

HDL

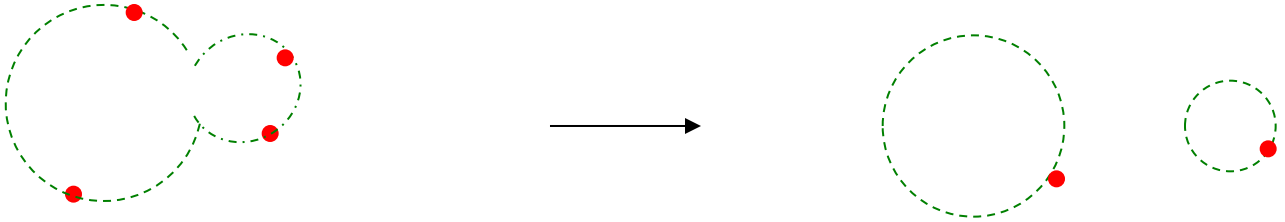
Origin

- Liver and Intestine: Nascent Discoid Shape

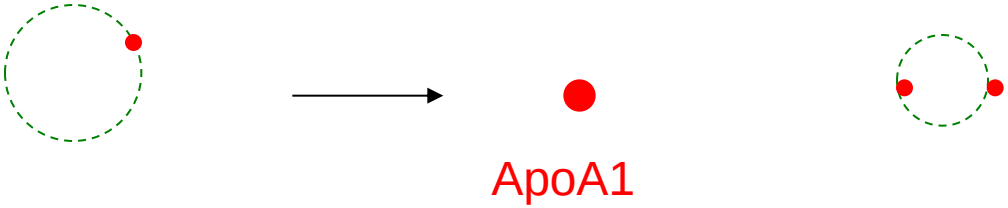


ApoA1

- Budding from other Lipoproteins Particles

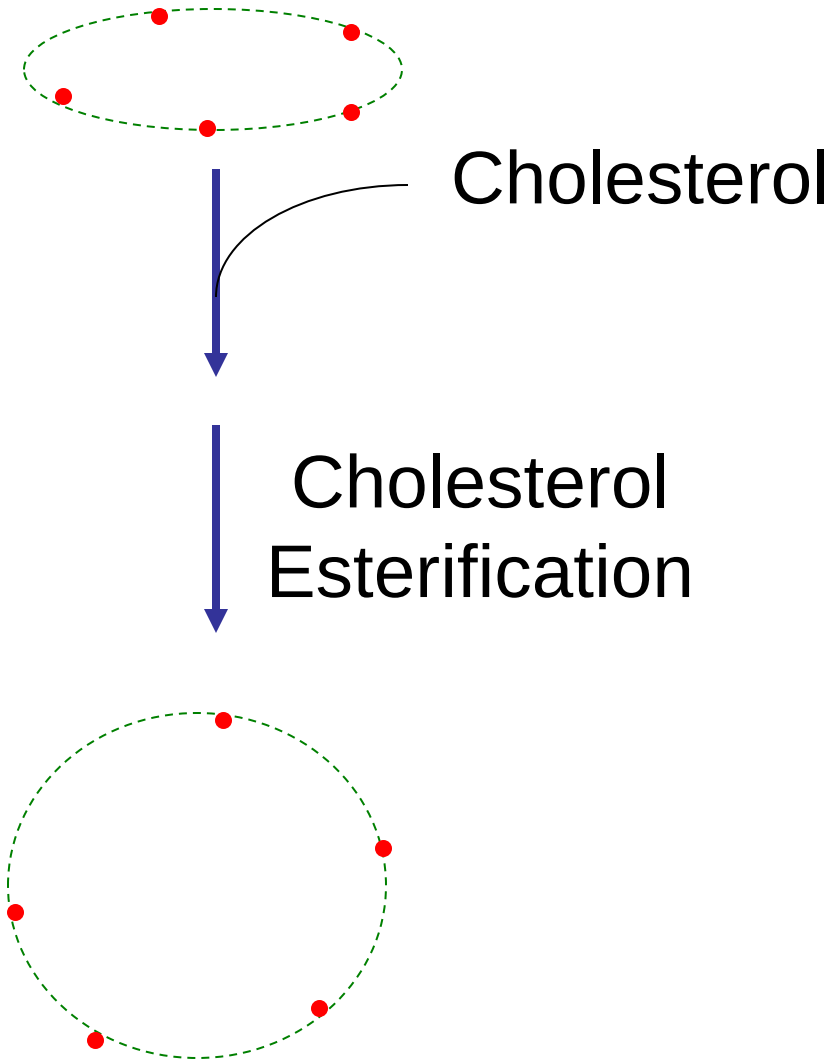


- From Free Apo A



ApoA1

Maturation of HDL

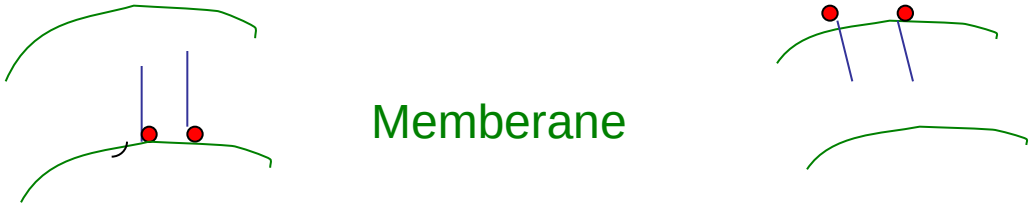


Reverse Transport of Cholesterol

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

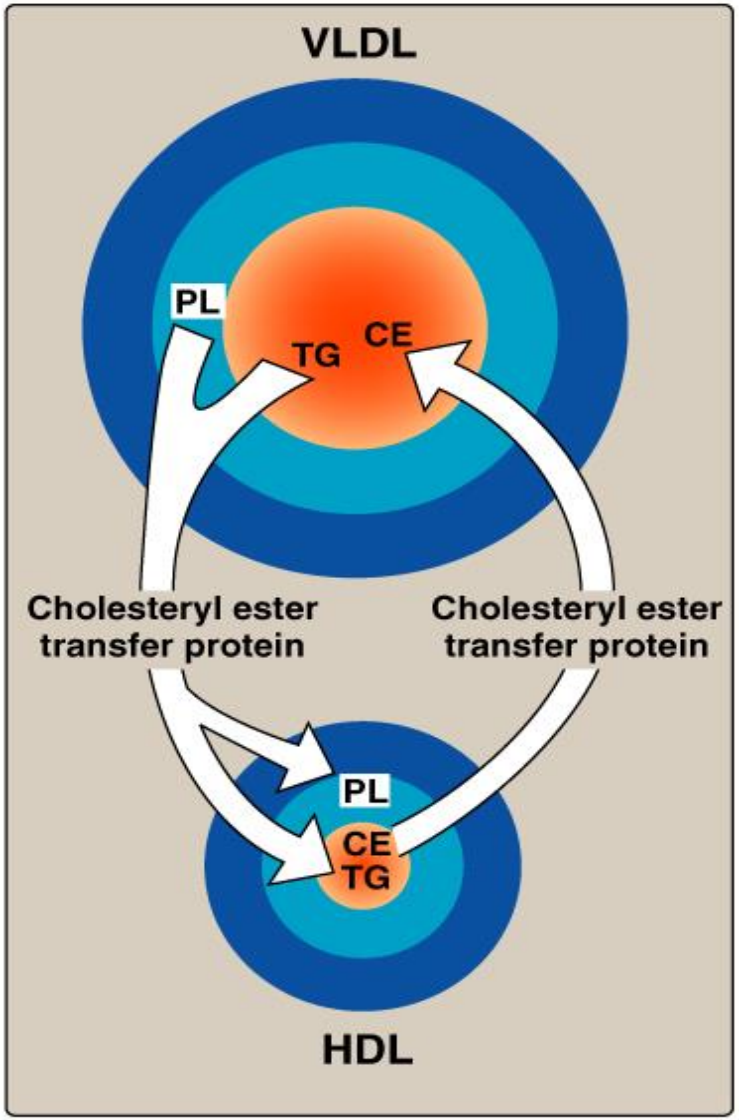


Figure 18.18

Transfer of cholesteryl esters (CE) from HDL to VLDL in exchange for triacylglycerol (TG) or phospholipids (PL).