Cholesterol and its transport

PROF. DR. SHAKIR F. T. ALAARAJI

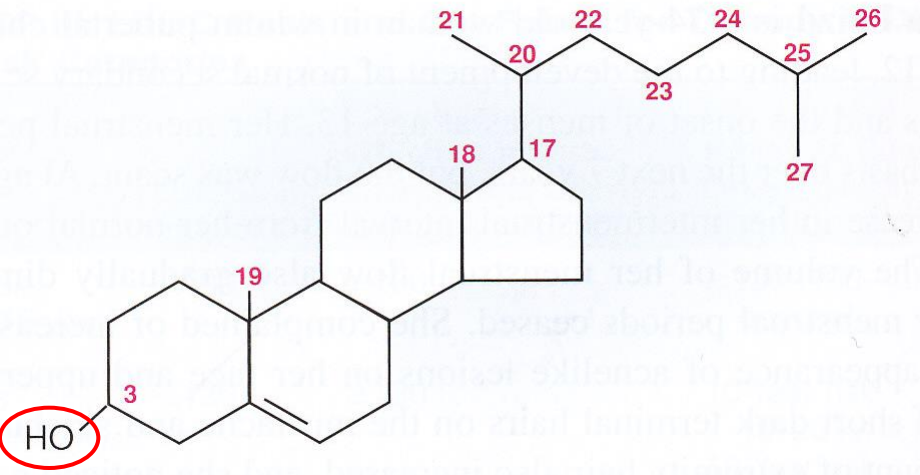
PH. D. BIOCHEMISTRY

UNIVERSITY OF ANBAR

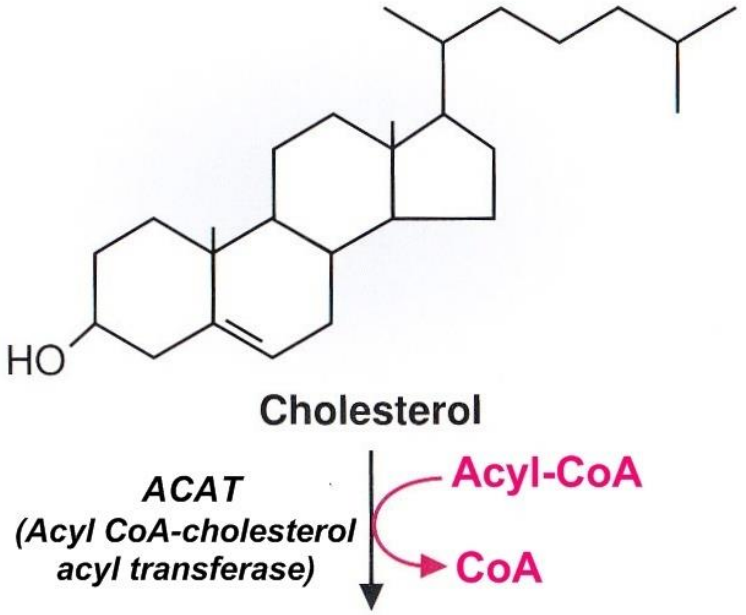
COLLEGE OF EDUCATION FOR PURE SCIENCES

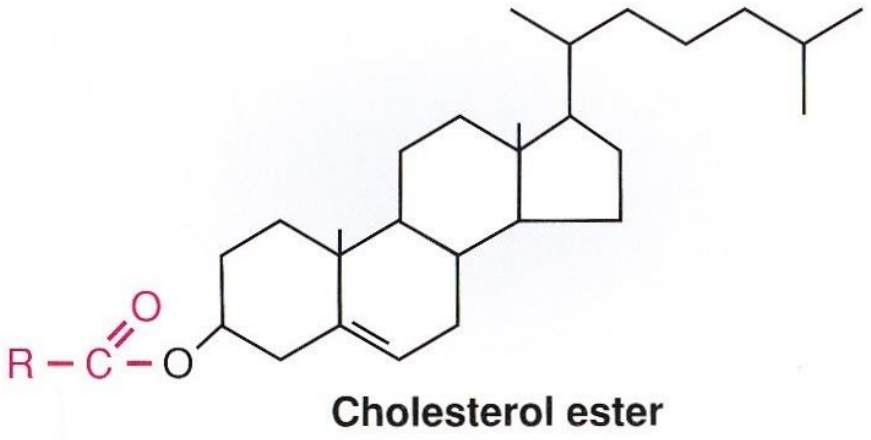
CHEMISTRY DEPARTMENT

Cholesterol - structure



27 carbons





Cholesterol importance

- A stabilizing component of cell membranes
- A precursor of bile salts
- A precursor of steroid hormones
- A cholesterol precursor is converted to cholecalciferol (vit. D)

Cholesterol sources

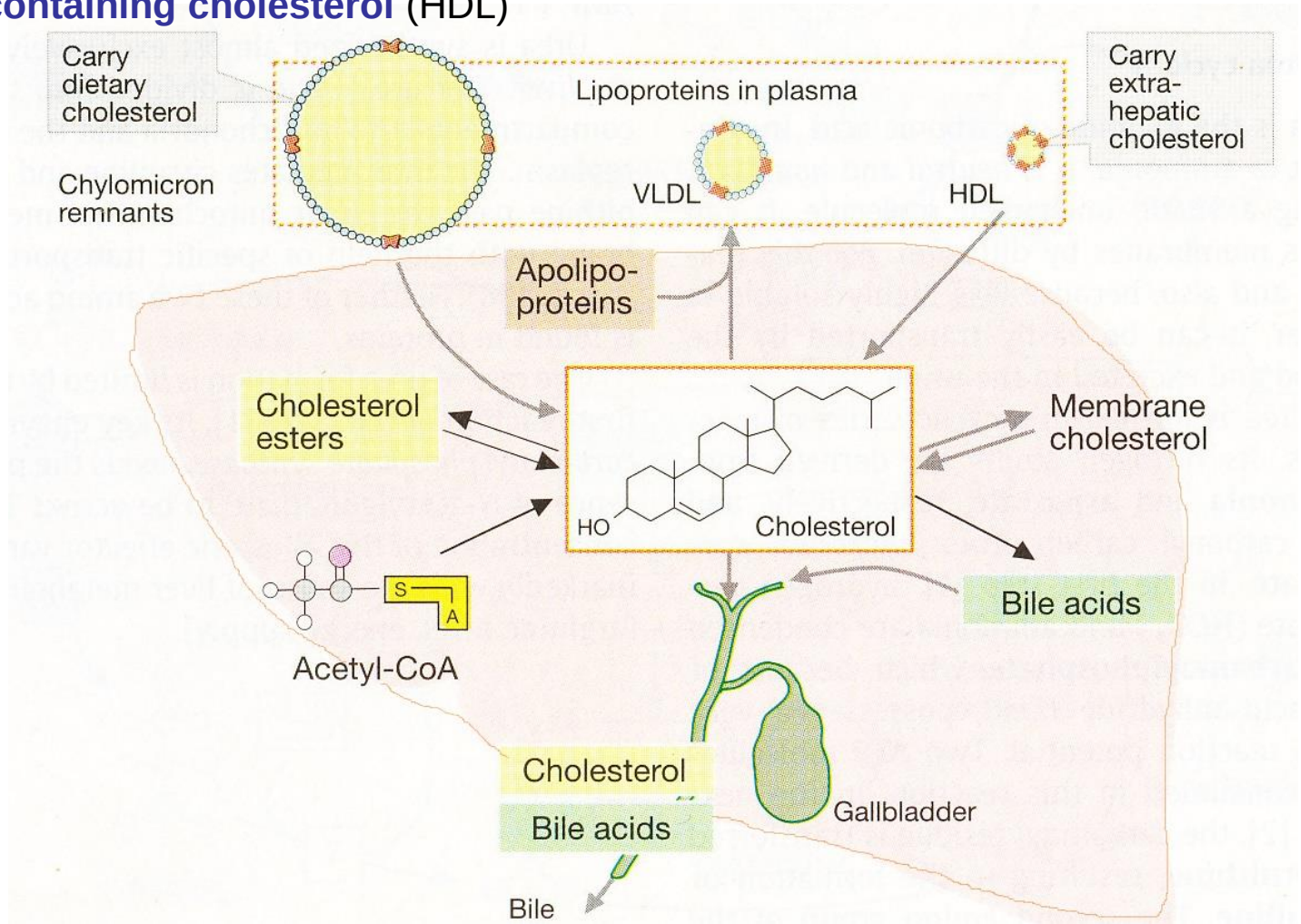
1) Endogenous biosynthesis (liver - 50%, skin, intestine)
2) Exogenous intake (from the diet)

Cholesterol in the blood:

1) The free form (1/3)
2) Cholesterol esters (2/3)

Cholesterol metabolism

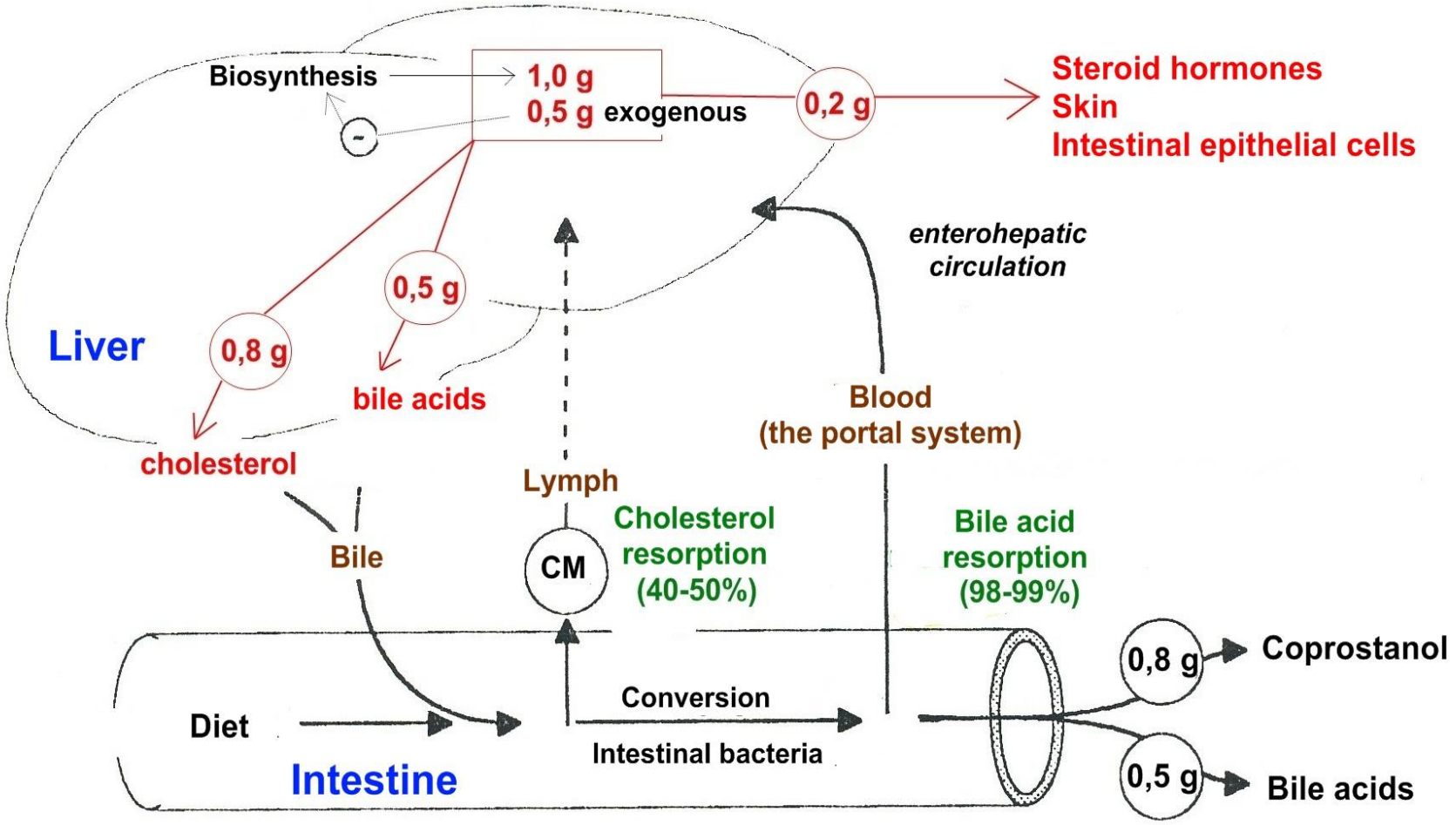
- **Sources of cholesterol:** 1. the diet, 2. de novo synthesis from acetyl-CoA (liver)
- **Utilization of cholesterol**: 1. the synthesis of bile acids, 2. building block for cell membranes, 3. stored in the form of lipid droplets, following esterification with fatty acids, 4. formation of VLDL (supply other tissues)
- **The liver takes up from the blood and degrades lipoprotein complexes containing cholesterol** (HDL)



Cholesterol balance:

The body contains: 150 g of cholesterolu

3-5 g of bile acids



Biosynthesis of cholesterol

In the cytosol + ER

Precursor - acetyl CoA from:

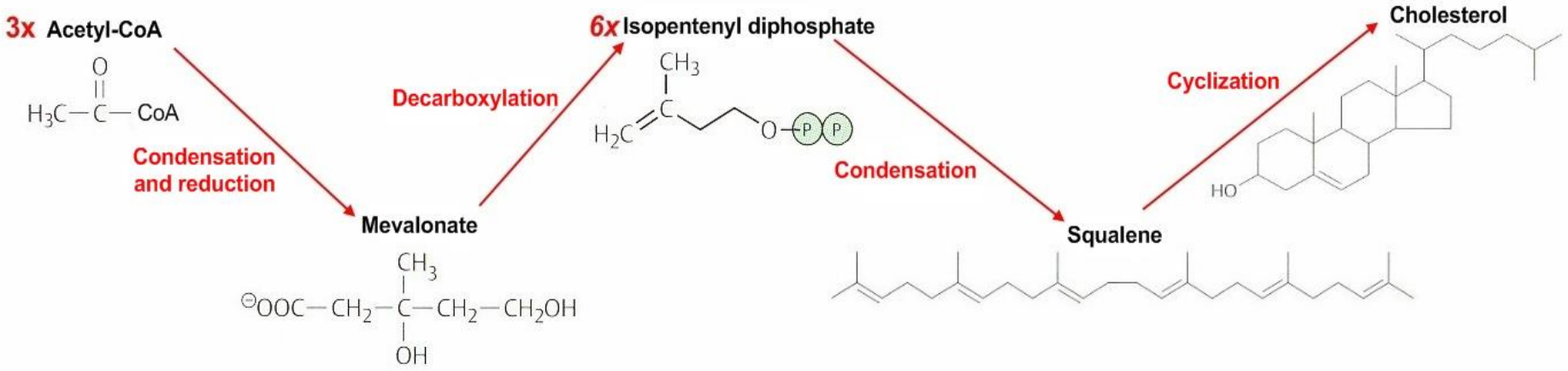
1. The β-oxidation of fatty acids
2. The oxidation of ketogenic amino acids
3. The pyruvate dehydrogenase reaction

The reducing agent - NADPH

- from PPP

Energy for synthesis

- hydrolysis of CoA and ATP



1) Formation of 3-HMG CoA:

- In the biosynthesis of ketone bodies (in the mitochondria)
- In the cytosol!

2) Reduction to mevalonate:

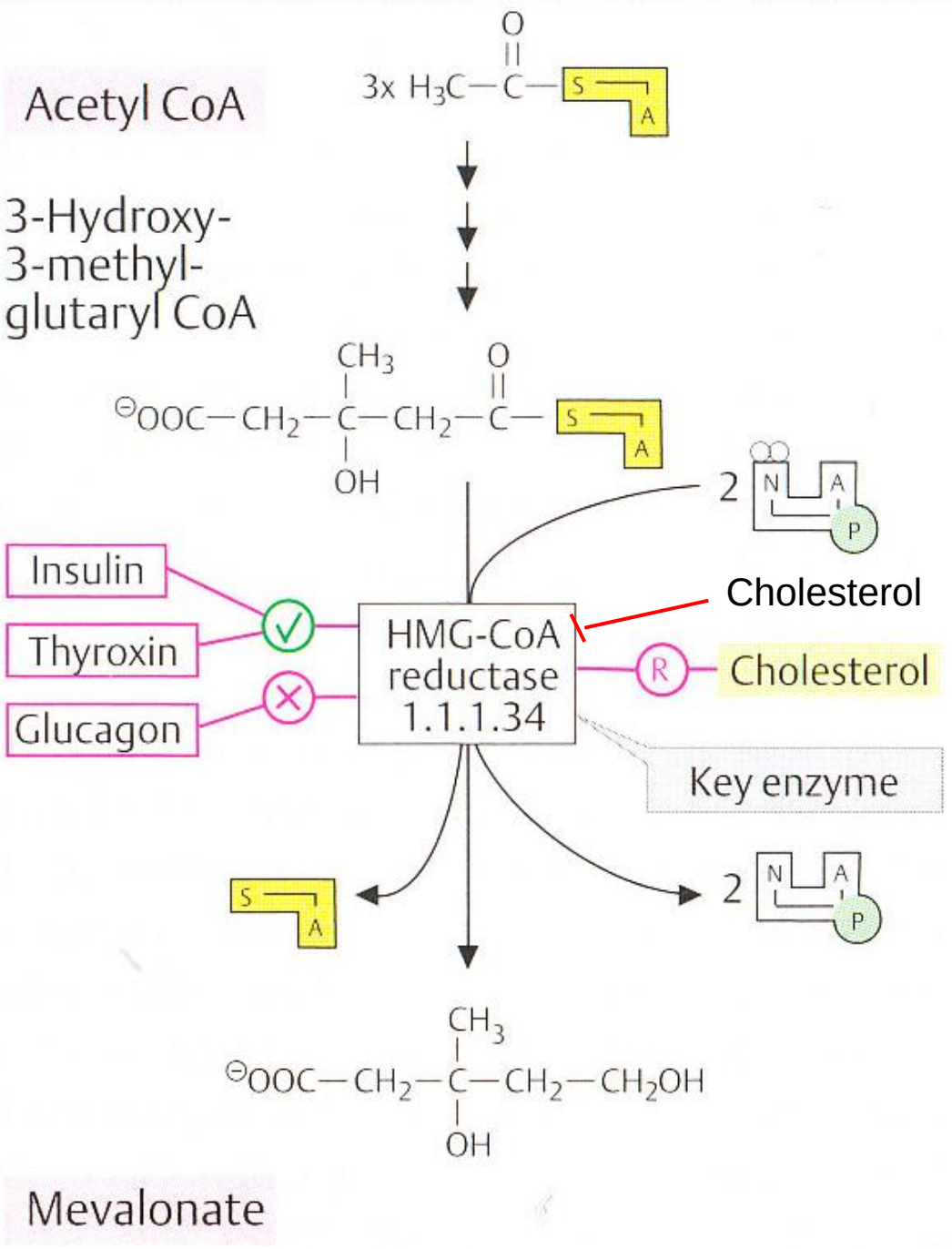
- NADPH
- HMG CoA reductase (in the ER)

Regulation of HMG CoA reductase:

A. Control of transcription (cholesterol)

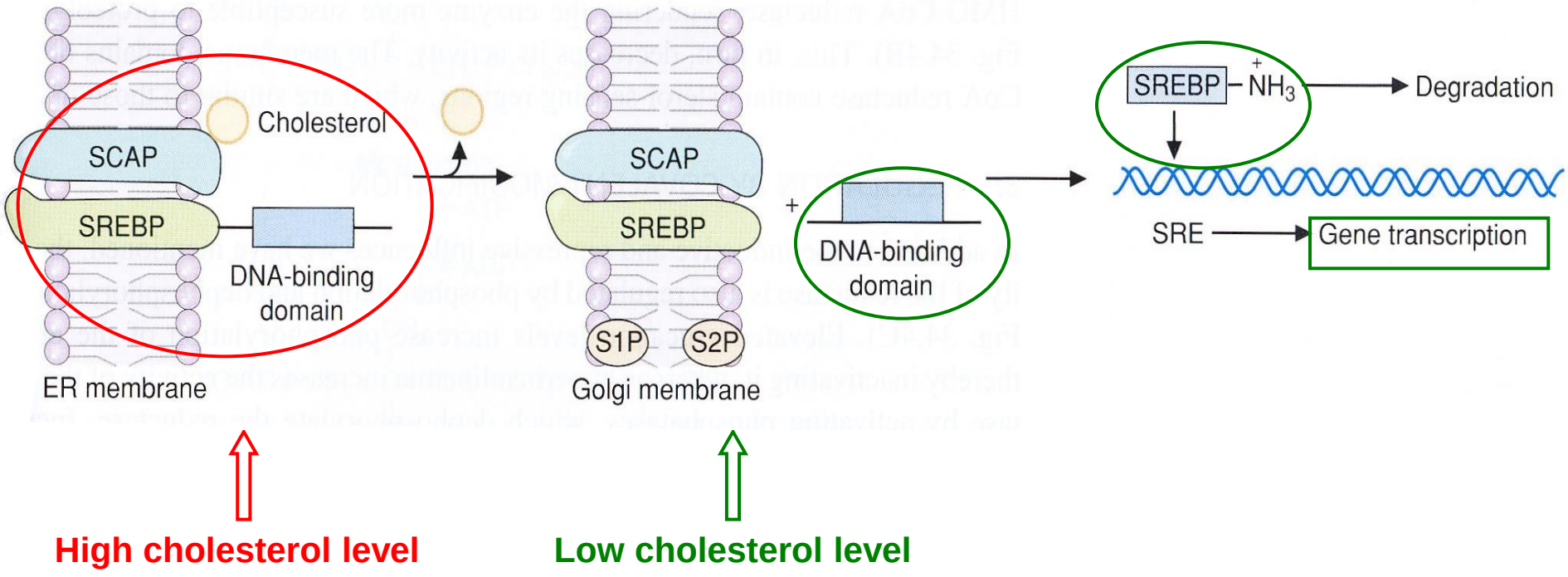
B. Proteolysis (cholesterol)

C. Phosphorylation (hormones)



Regulation of HMG CoA reductase

1. Transcriptional control:



High cholesterol level **Low cholesterol level**

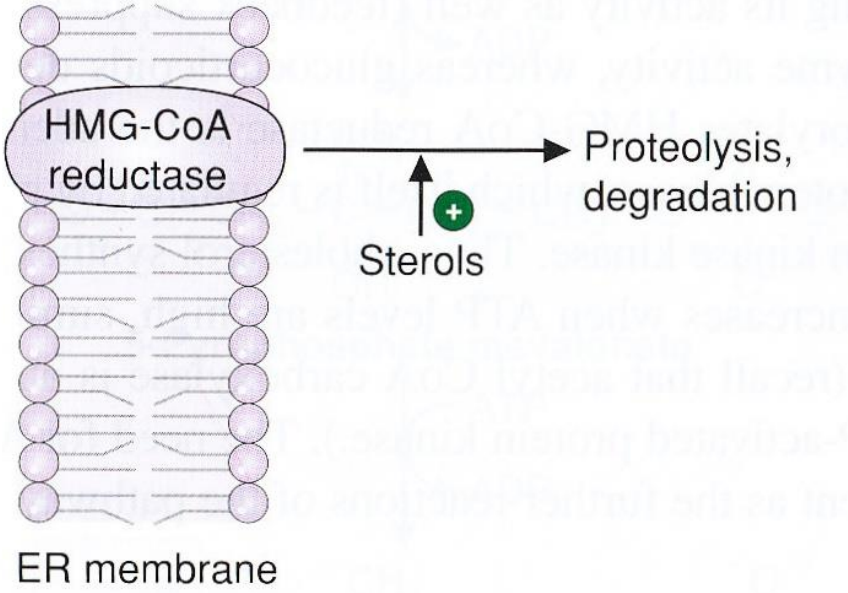
Transcription factor - SREBP (sterol-regulatory element-binding proteins)

- transcription of the HMG CoA reductase gene (binds to SRE - sterol-regulatory element)

a) High cholesterol level - SREBP is bound in ER to SCAP (SREBP cleavage-activation enzyme)

b) Low cholesterol level - transfer to GA - cleavage - binding to DNA

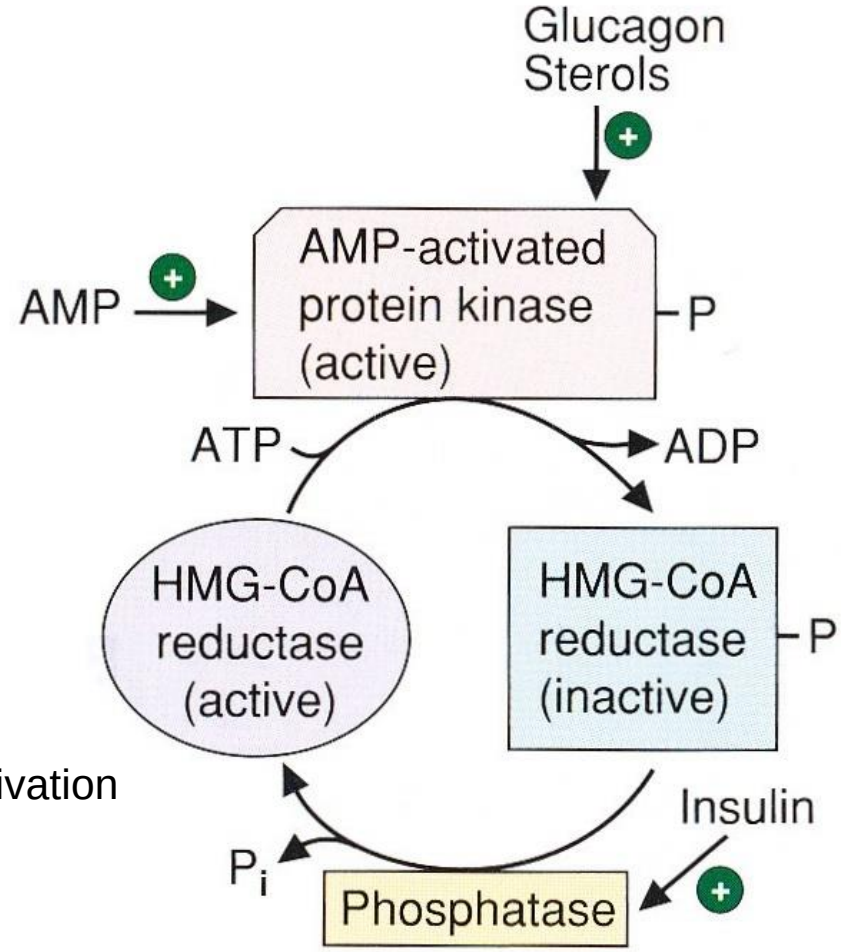
2. Proteolytic degradation of HMG CoA reductase:



High levels of cholesterol and bile acids

- binding to HMG CoA reductase - structural changes - more susceptible to proteolysis

3. Regulation by phosphorylation:



Glucagon, sterols (= feedback suprese)

- increase phosphorylation of the enzyme - inactivation

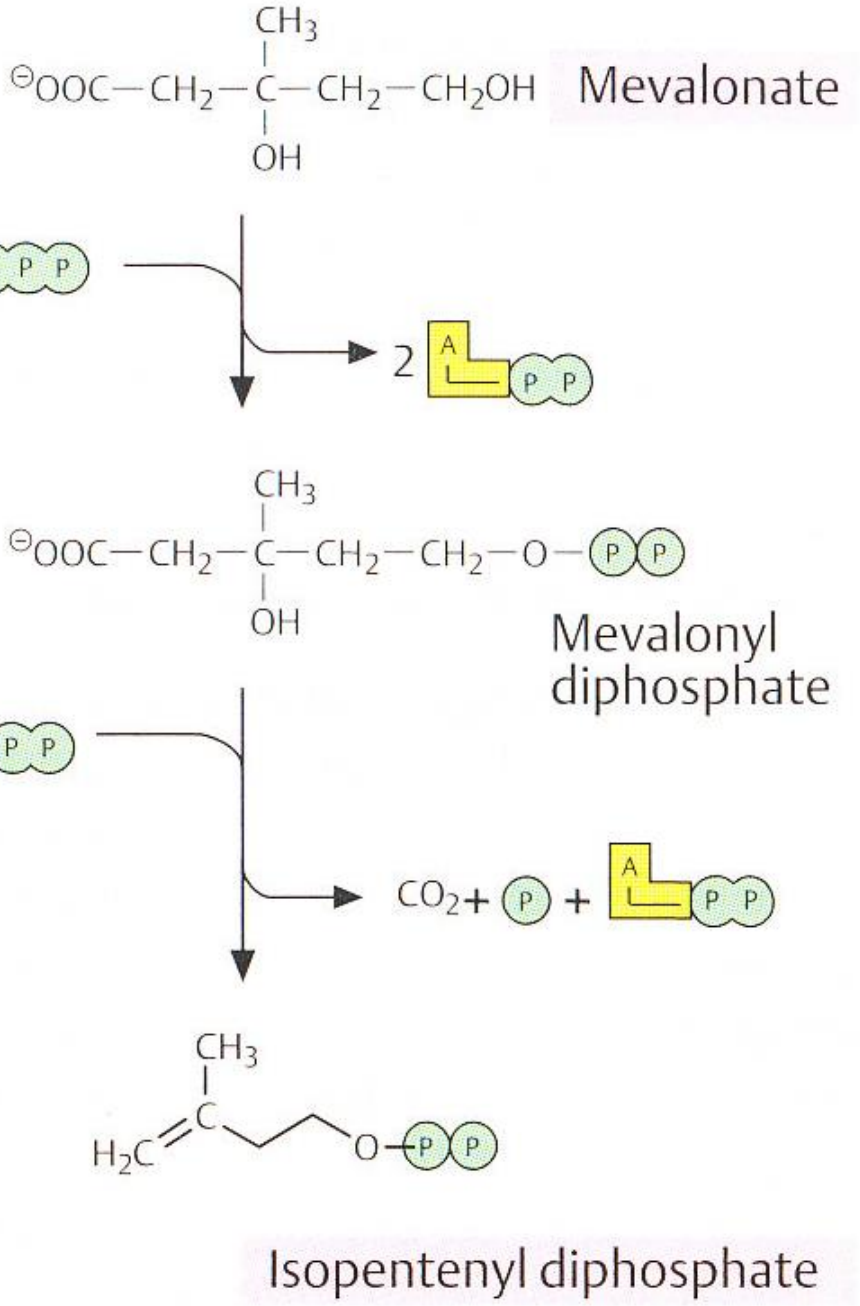
Insulin

- increase dephosphorylation - activation

AMP-activated proteinkinase

- the need of ATP

3) Phosphorylation



4) Decarboxylation to isopentenyl diphosphate („activated isoprene“)

- ATP
- intermediate for the formation of other isoprenoids

(tocopherol, ubiquinone, carotenoids)

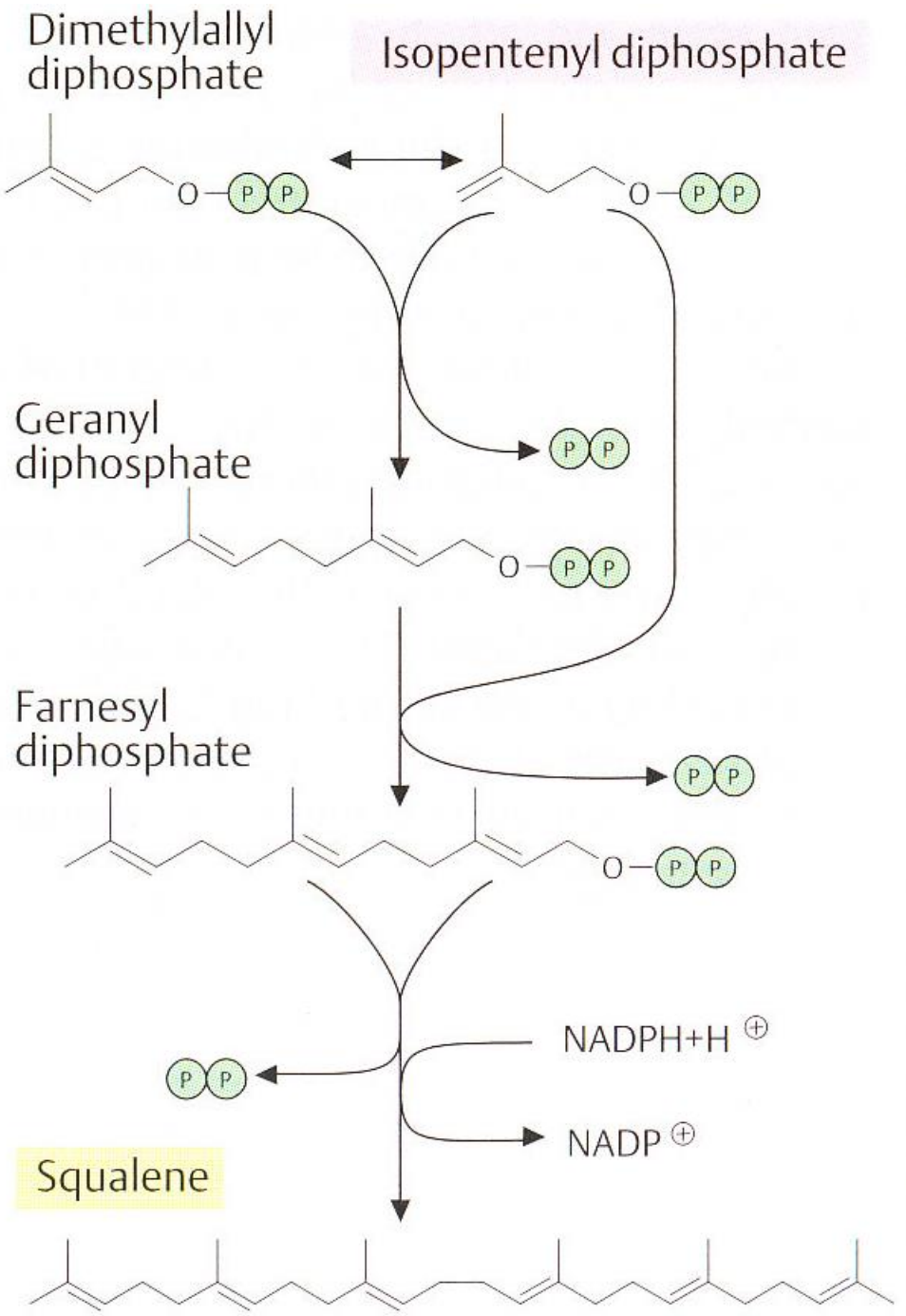
5) Isomerization

6) Condensation to geranyl diphosphate

7) Formation of farnesyl diphosphate

- the addition of another isopentenyl diphosphate
- intermediate of other polyisoprenoids (dolichol, ubiquinone)

8) Dimerization to squalene

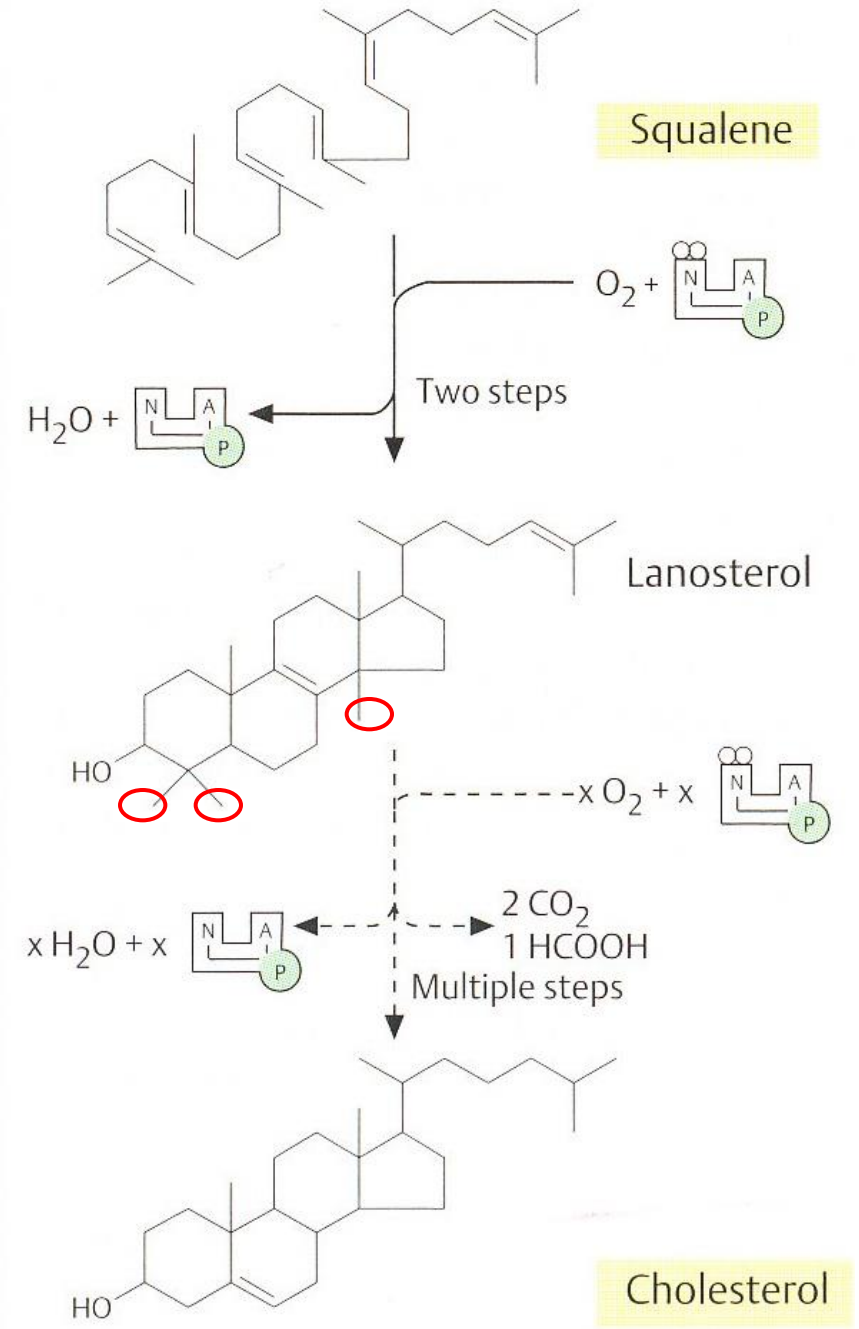


9) Cyclization of squalene

- oxygen
- monooxygenase (cytochrome P450 system)

10) Formation of cholesterol

- cleavage of 3 methyl groups
- double bond changes



Bile acid metabolism

- **Bile acids:**

  -synthesized in the liver from cholesterol

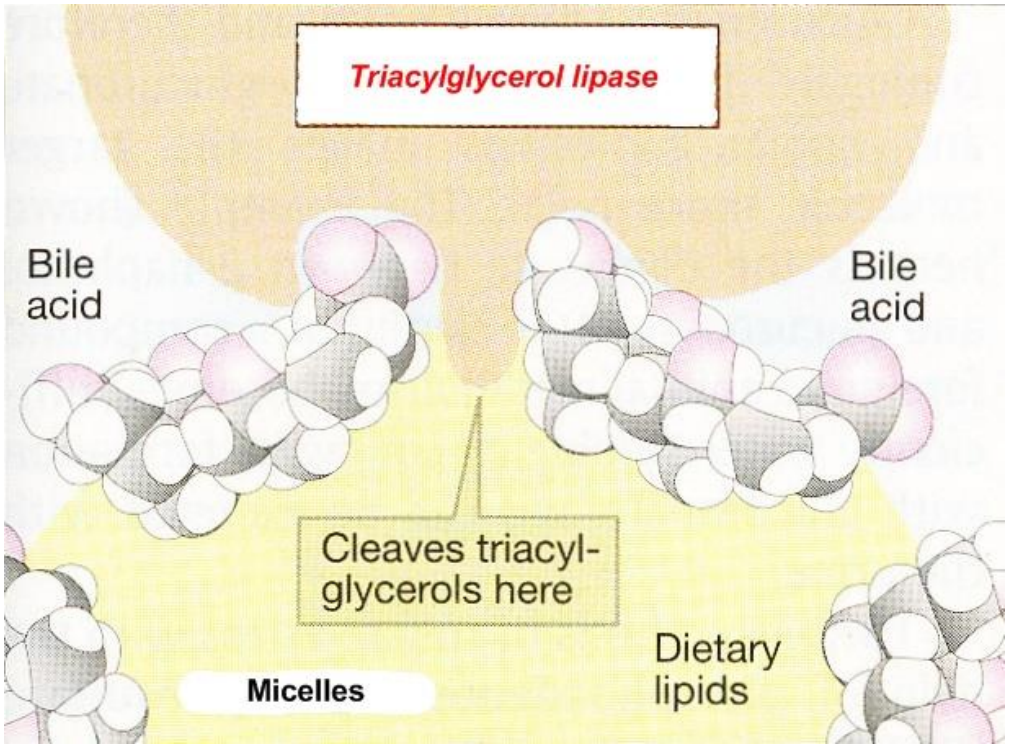
  -amphipathic, act as detergents

  -linked with an amino acid (glycine or taurine) - bile salts

  -primary bile acids are formed in the liver, secondary bile acids in the intestine (by dehydroxylation of the primary bile acids)

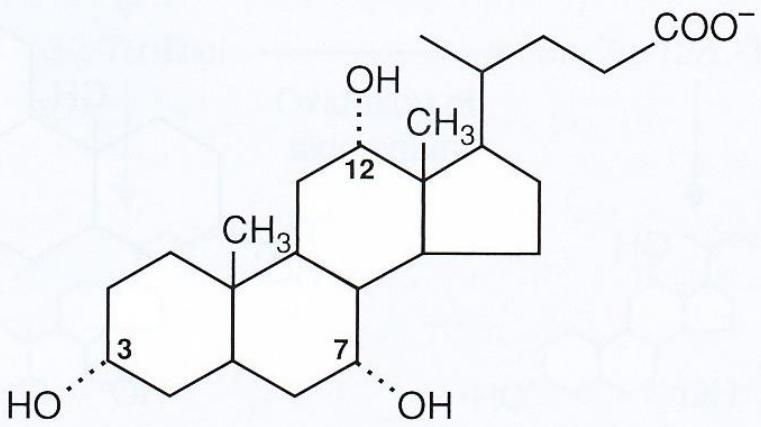
- **Lipid digestion:**

  -facilitate the solubilization of dietary lipids during the process of digestion by promoting micelle formation

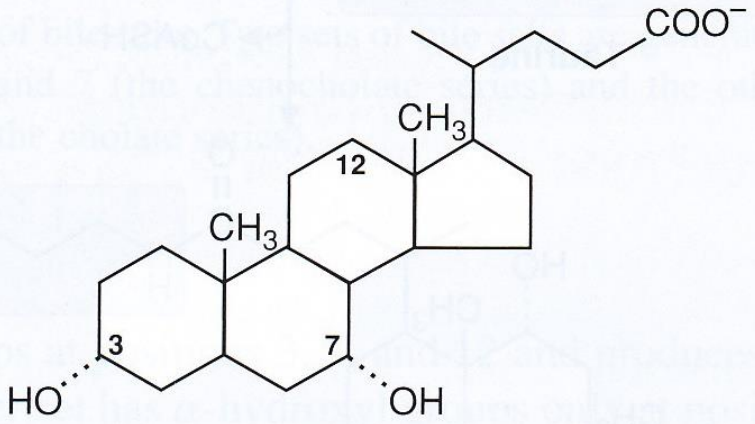


Bile acids - the structure

Primary bile salts

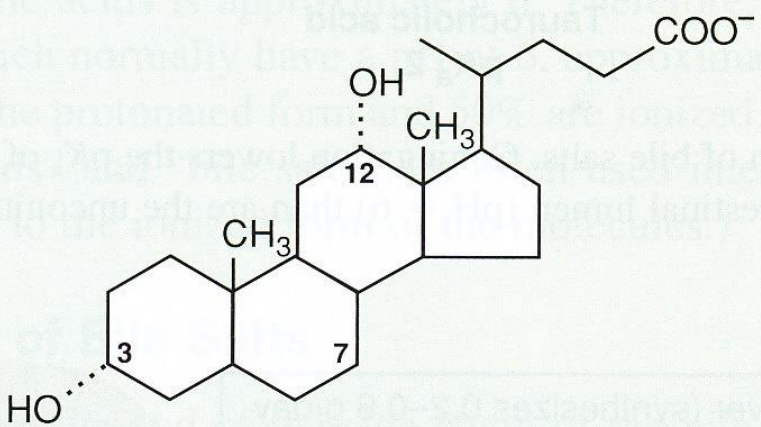


Cholic acid

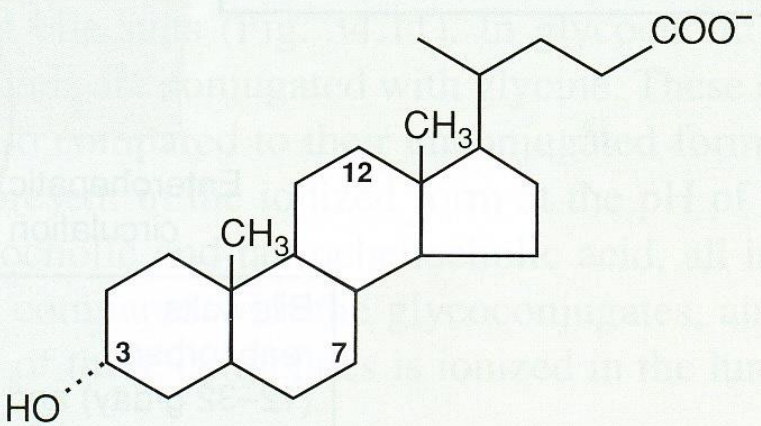


Chenodeoxycholic acid

Secondary bile salts



Deoxycholic acid

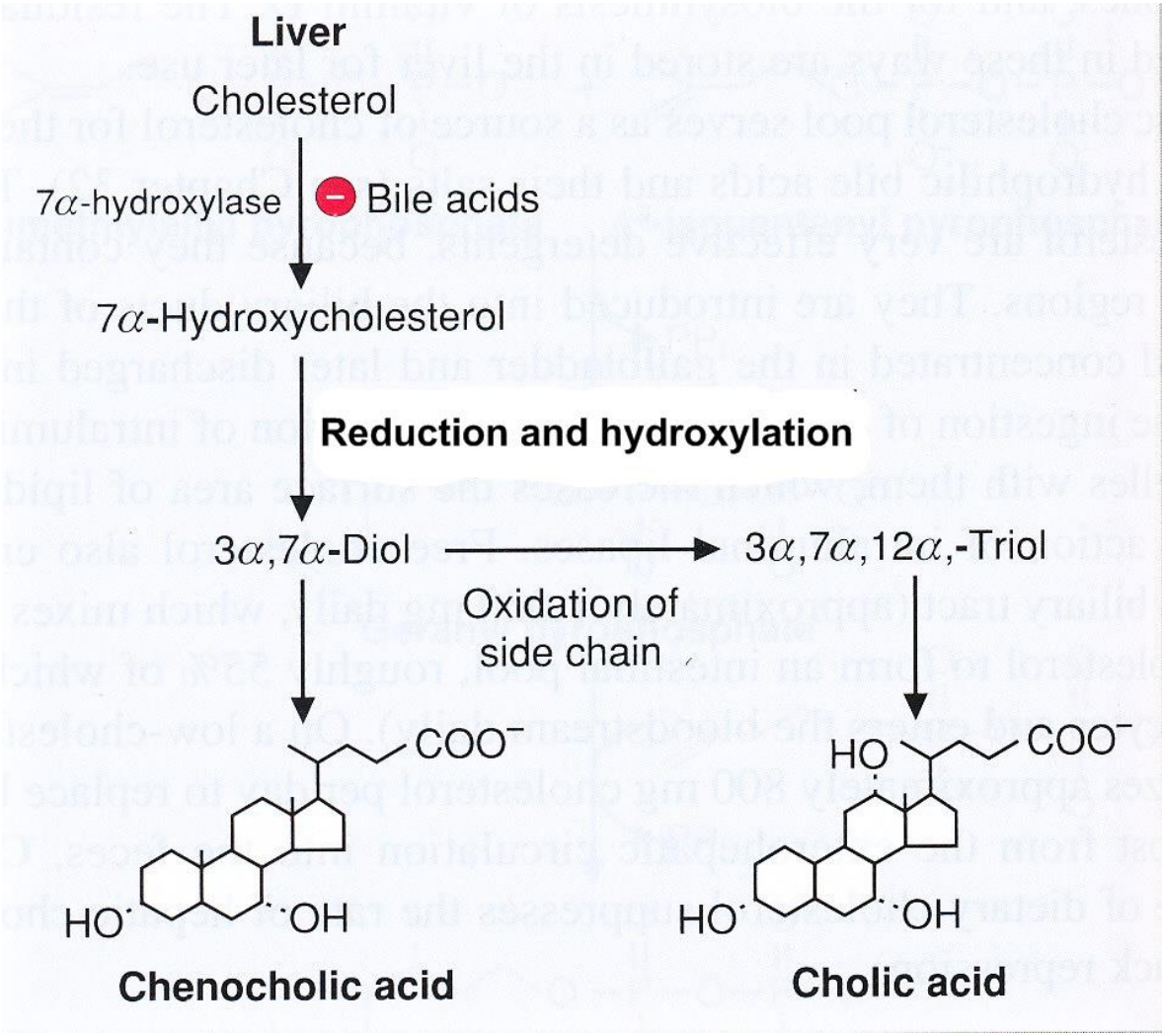


Lithocholic acid

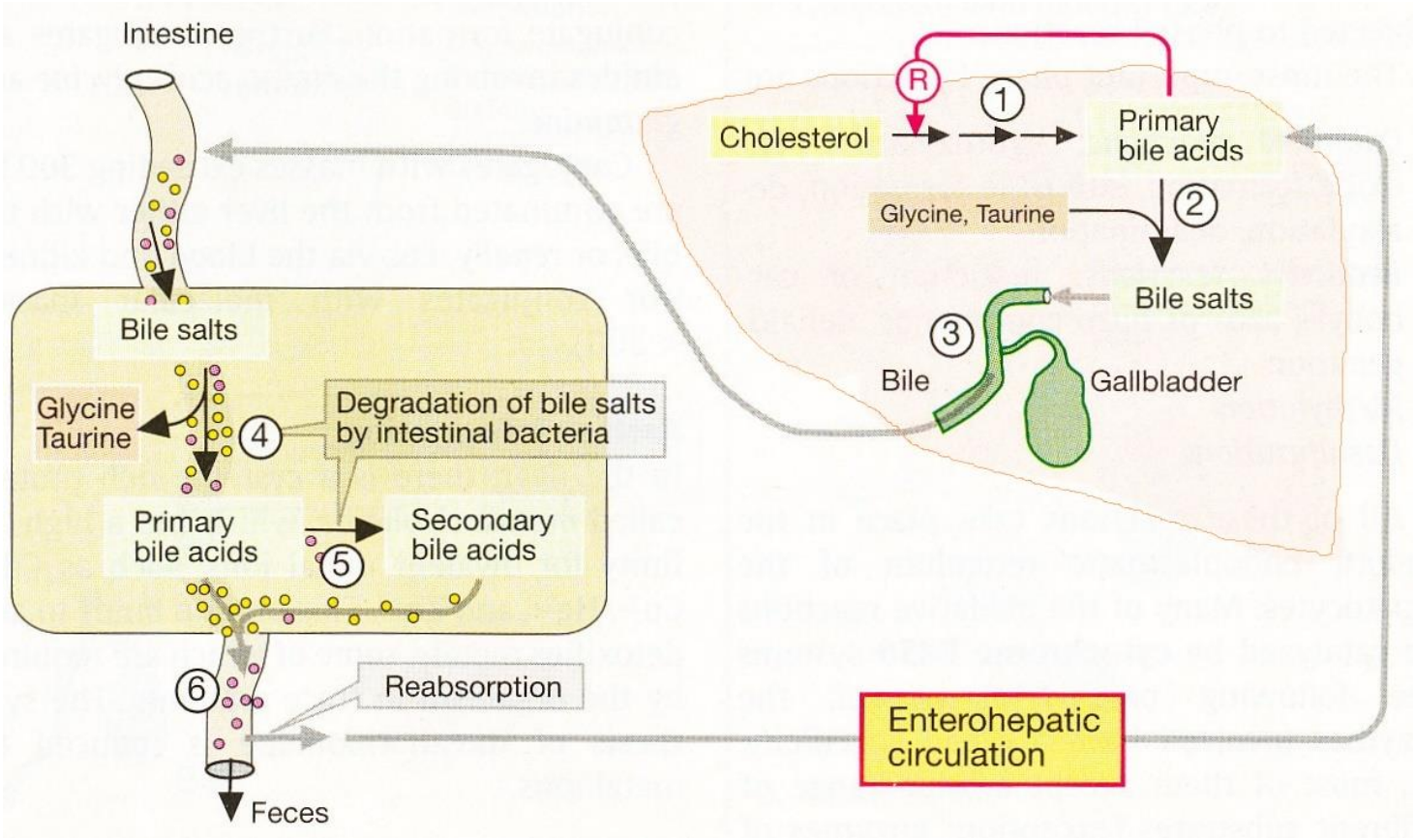
Synthesis of bile acids

- Hydroxylation

  (rate-limiting reaction)
- Reduction of the double bond
- Further oxidation
- Cleavage of 3 C
- A carboxyl group



Metabolism of bile salts (exlusively in the liver)



1. The biosynthesis of bile acids from cholesterol

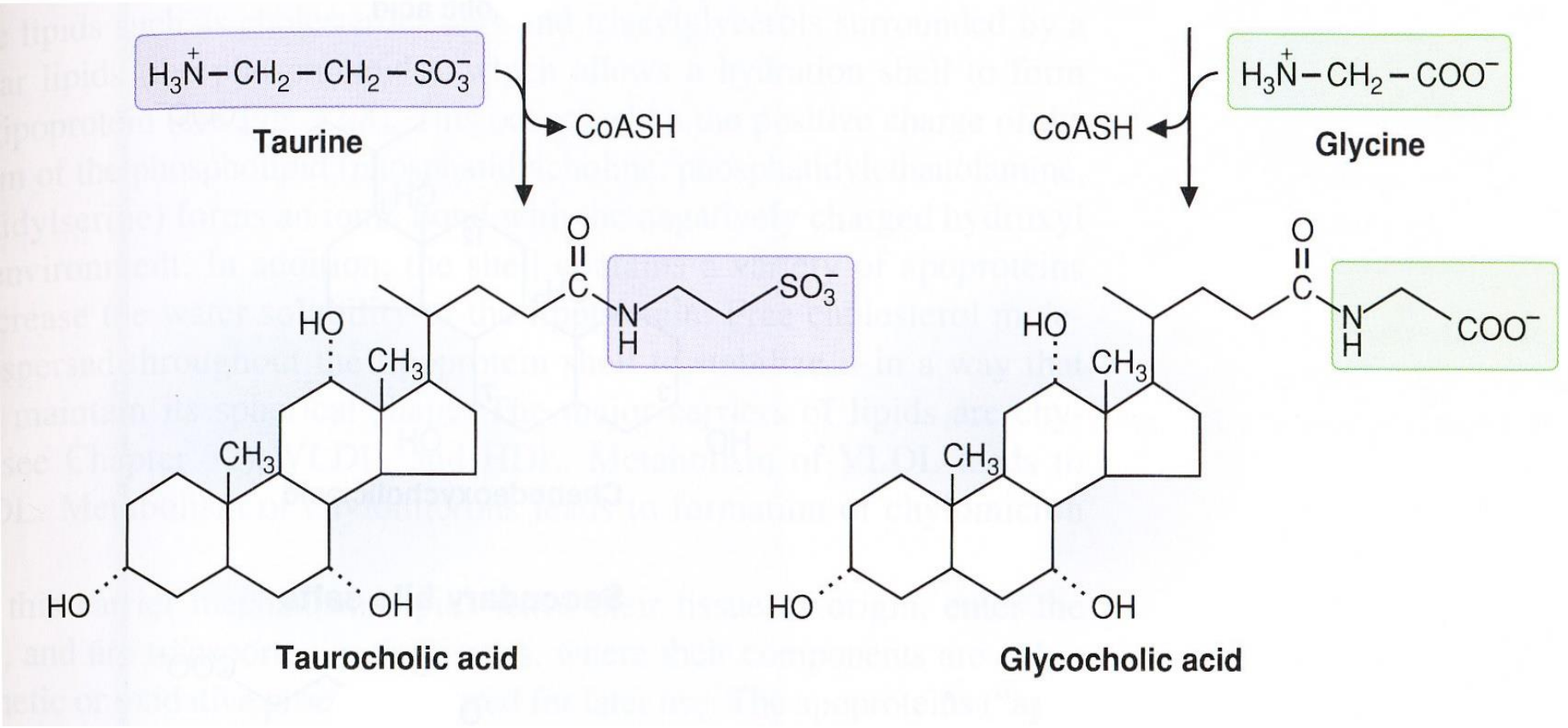
2. The conjugation with the amino acids

3. The concentration in the gallbladder by removal of water

4. a 5. Intestinal bacteria in the colon produce enzymes that can attack and alter the bile salts

6. Most of the bile acids are reabsorbed from the intestine and, following transport to the liver, returned once again into the bile (enterohepatic circulation)

Conjugation of bile salts

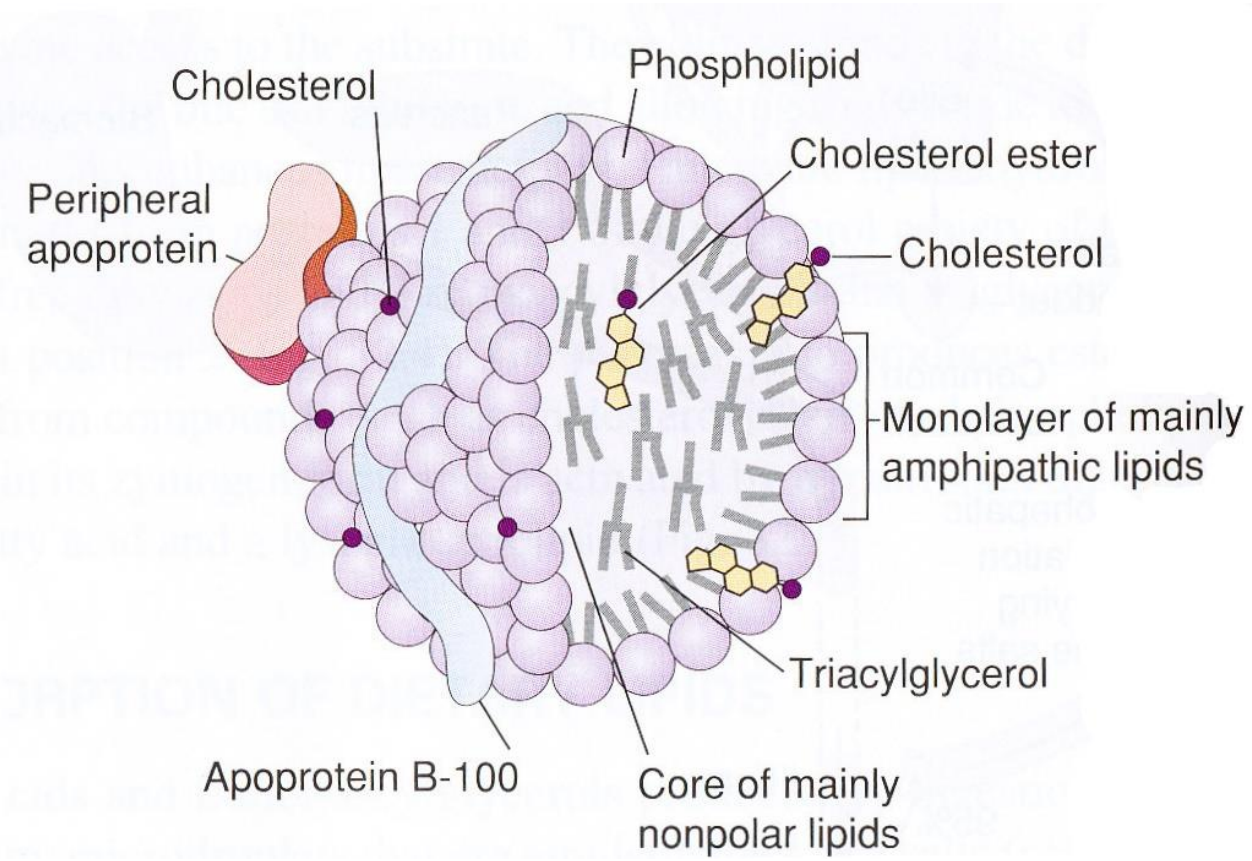


Lipoproteins

Function:

- Lipid transport (cholesterol, cholesterol esters, triacylglycerols, phospholipids)

Structure:

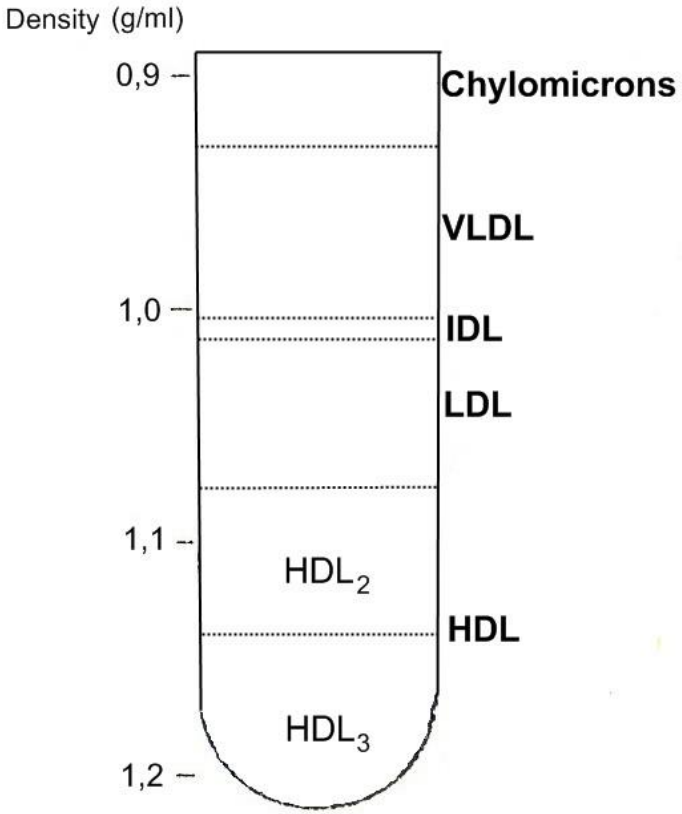


A nucleus: triacylglycerols, cholesterol esters

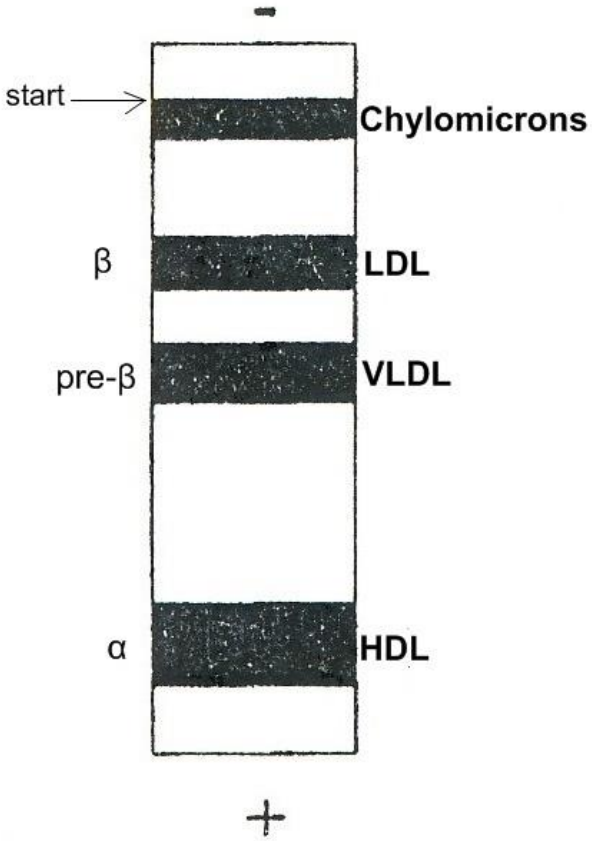
A shell: phospholipids, apoproteins, cholesterol

Separation of lipoproteins

a) Ultracentrifugation (density)



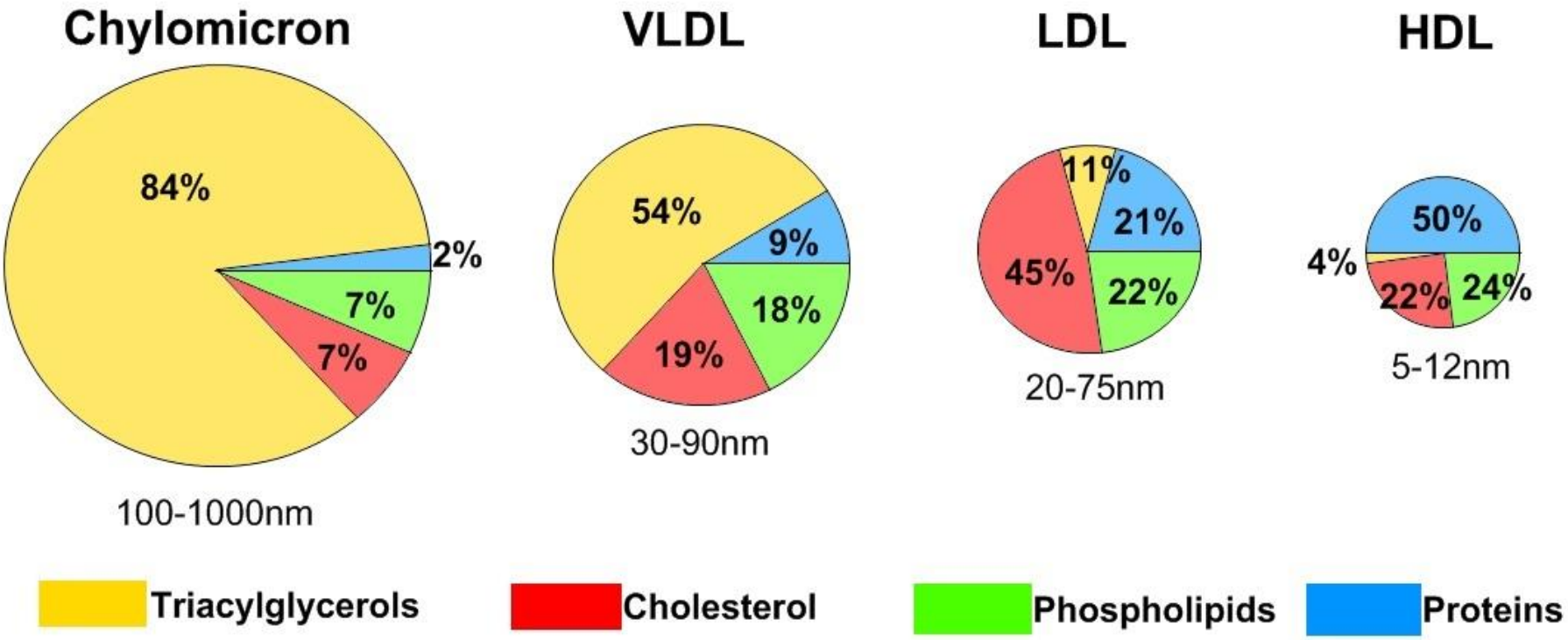
b) elecroforesis (size)



Characteristics of the major lipoproteins

Lipoprotein	Origin	Halftime in blood	Major apoproteins	Major lipids	Function
Chylomicrons	intestine	5-15 min	B-48, C-II, E	TG	Deliver dietary lipids
VLDL	liver	2h	B-100, E, C-II	TG	Deliver endogenous lipids
IDL	plasm	2h	B-100, E, C-II	TG/CHE	Precursor of LDL
LDL	plasm	2-4 dny	B-100	CHE	Deliver cholesterol to cells
HDL (nascent)	liver, intestine, plasm	10h ?	A-I, C-II, E	PL/CHE	Reverse cholesterol transport

Composition of lipoproteins



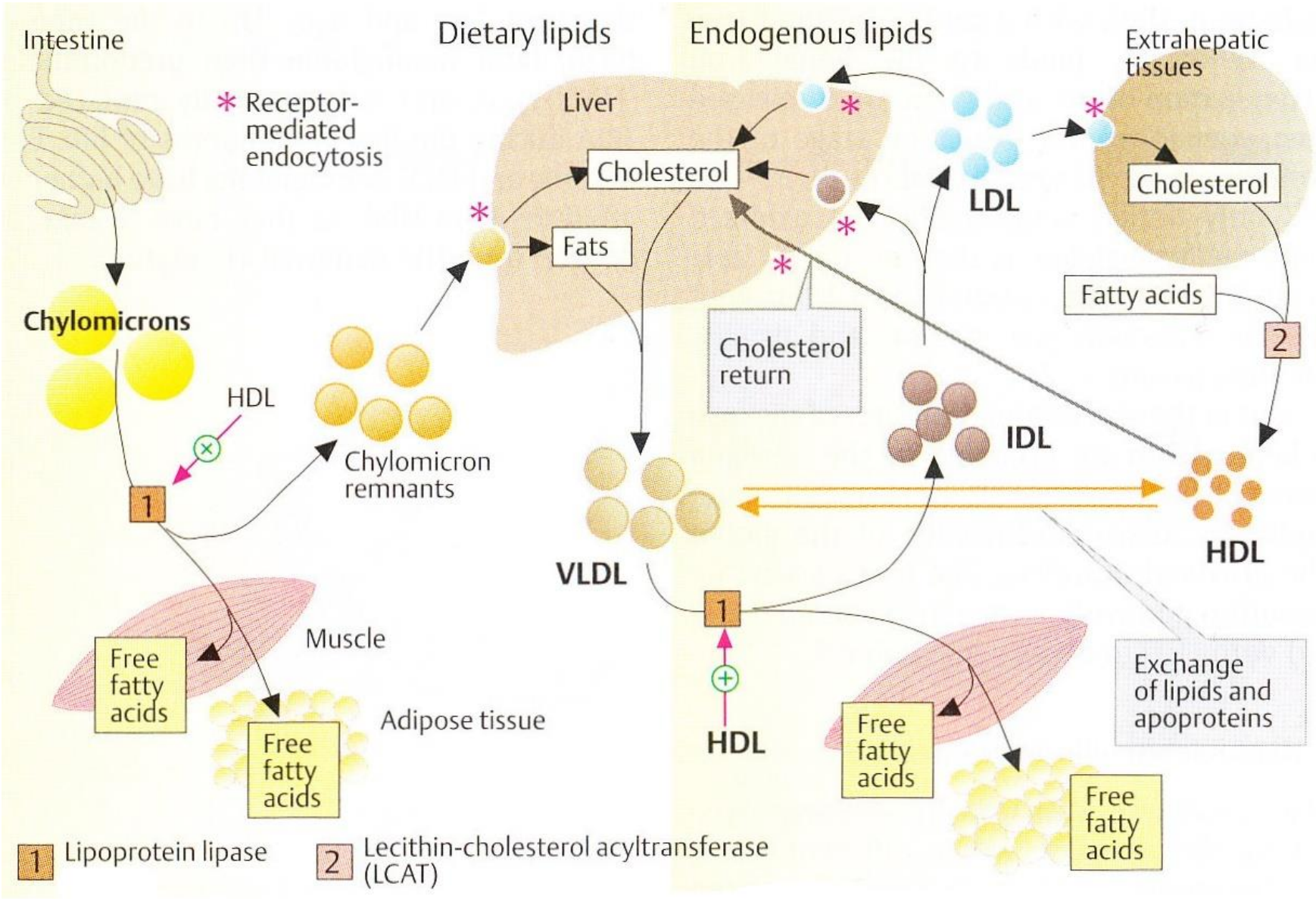
Apoproteins

Major function:

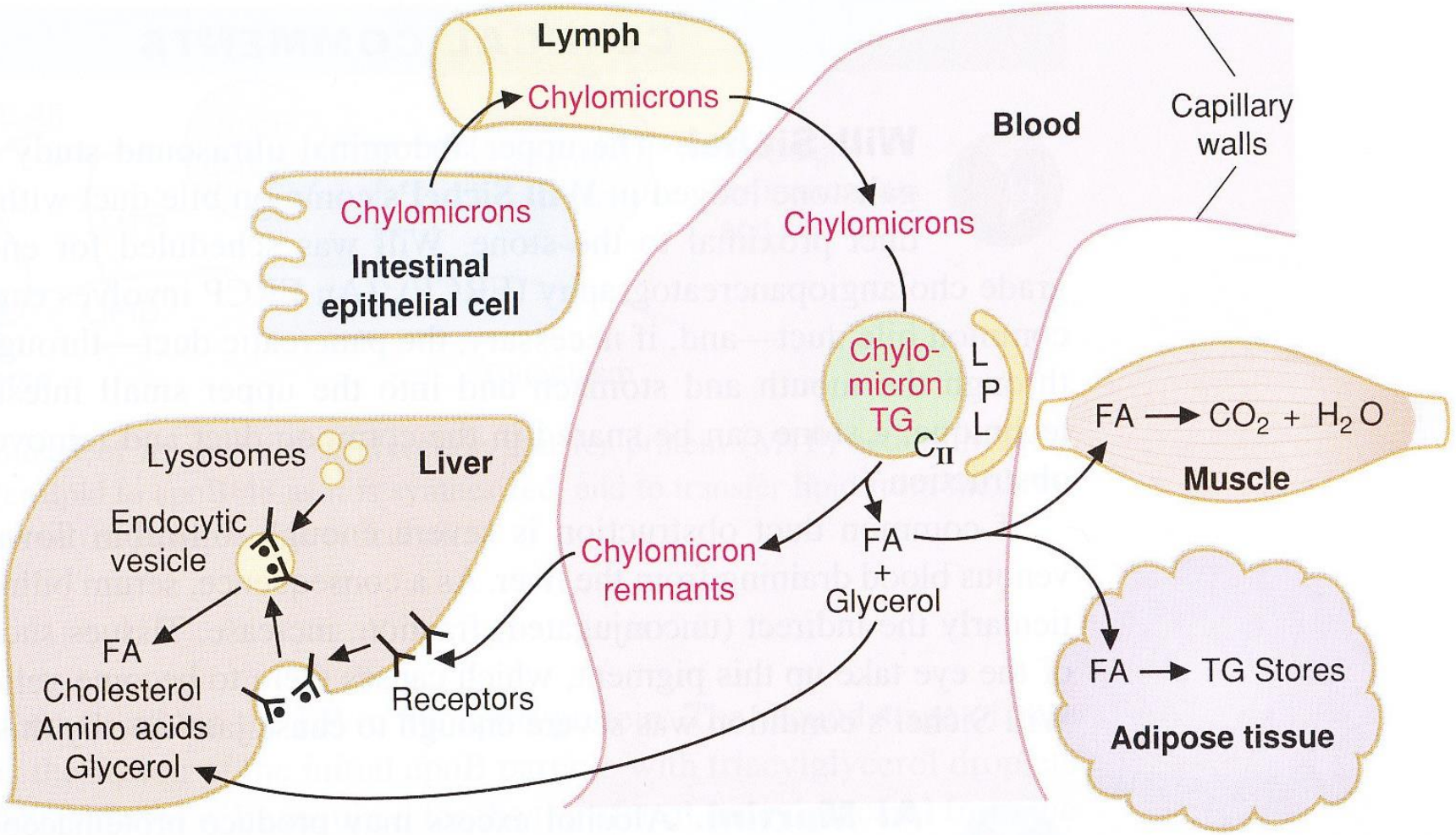
- structure, solubility, activation of enzyme, ligands for receptors

Apoprotein	**Function**
Apo A-I	activates LCAT, structural component of HDL
Apo B-48	Assembly and secretion of chylomicrons
Apo B-100	VLDL assembly and secretion; structural protein of VLDL, IDL and LDL; ligand for LDL receptor
Apo C-II	Activator of lipoprotein lipase (LPL)
Apo E	ligand to LDL receptor; ligand to Apo E receptor

Lipoproteins - metabolism



Metabolism of chylomicrons



Lipoprotein lipase (LPL)

- On capillary walls in adipose tissue and muscle
- Cleaves TG

Chylomicrons remnants

- receptors in the liver, lysosoms

Chylomicrons

Formation:

- intestinal epithelial cells
- secretion into the lymph

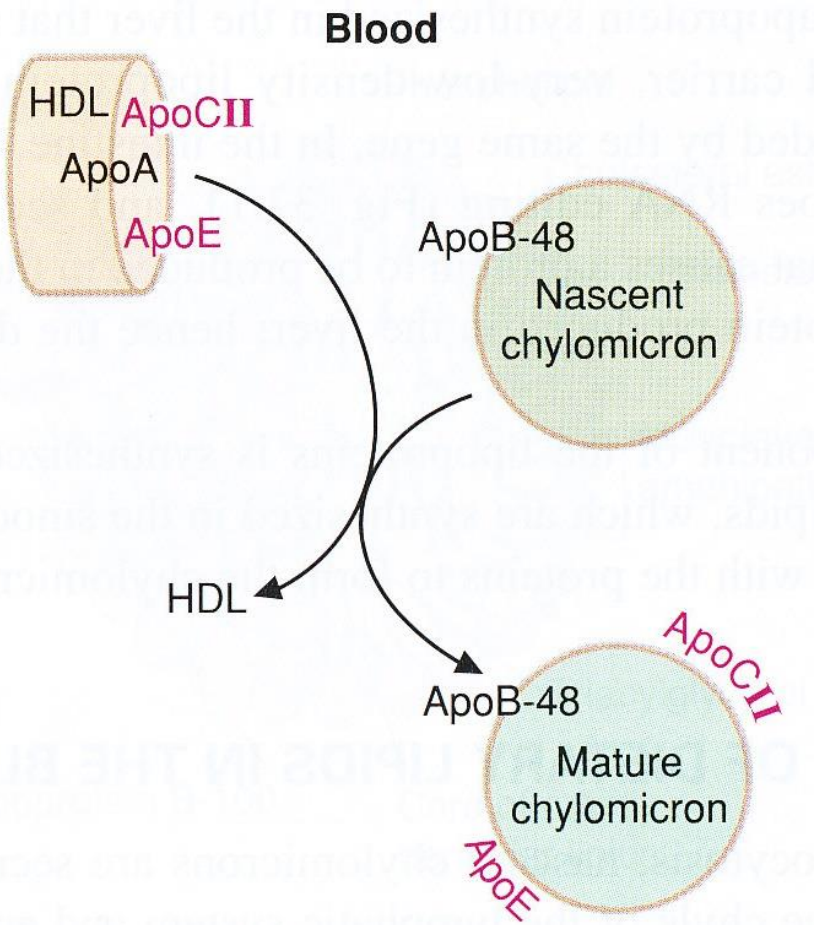
Major apoproteins:

Apo B-48 (nascent)

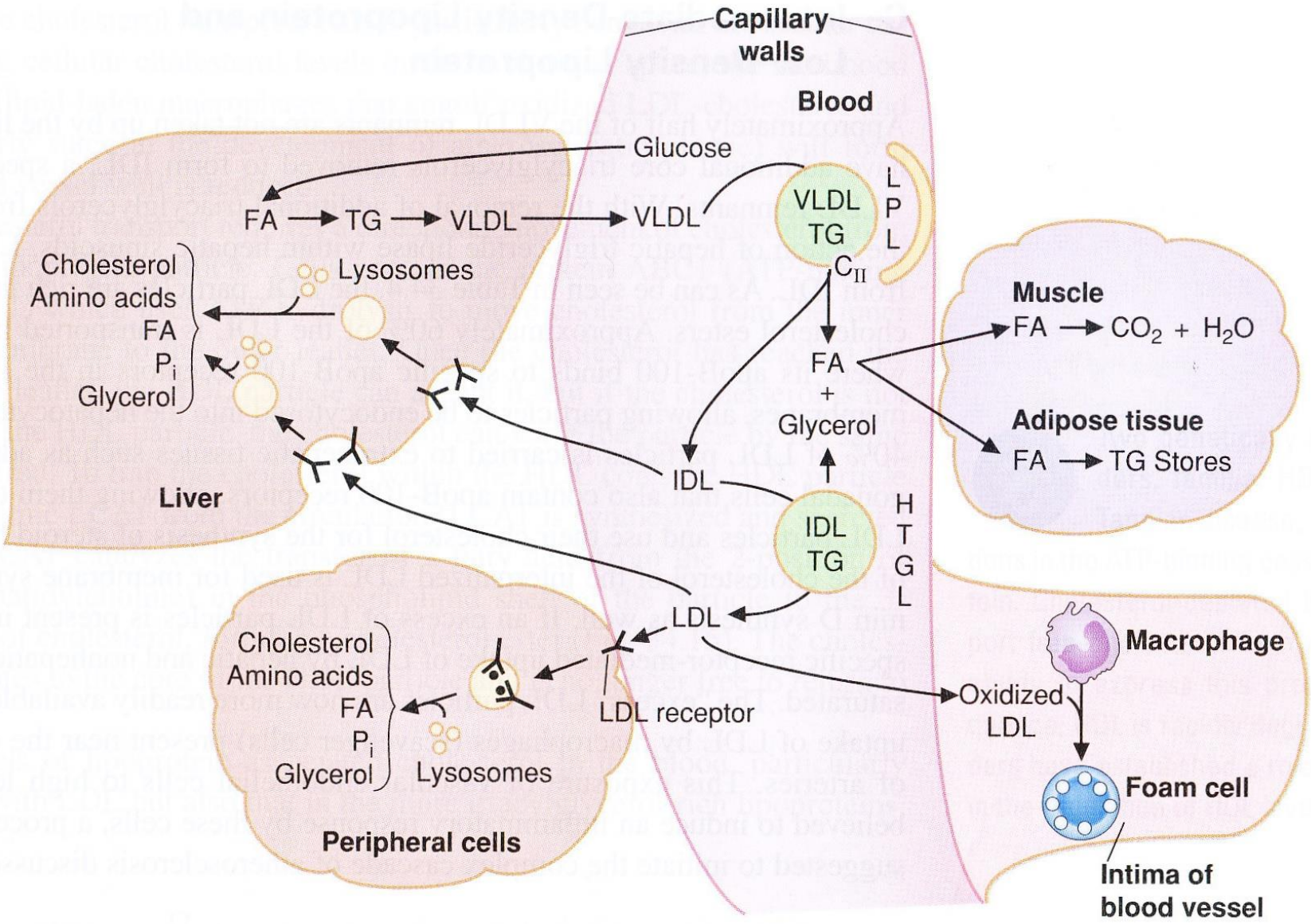
Apo C-II, Apo E (from HDL)

Function:

- Deliver dietary lipids



Metabolism of VLDL, IDL and LDL



VLDL

Formation:

- liver
- secretion into the blood
- lipoprotein lipase

Major apoproteins:

Apo B-100 (nascet)

Apo C-II, Apo E (from HDL)

Function:

- Deliver endogenous lipids

IDL

- hepatic triacylglycerol lipase (HTGL)

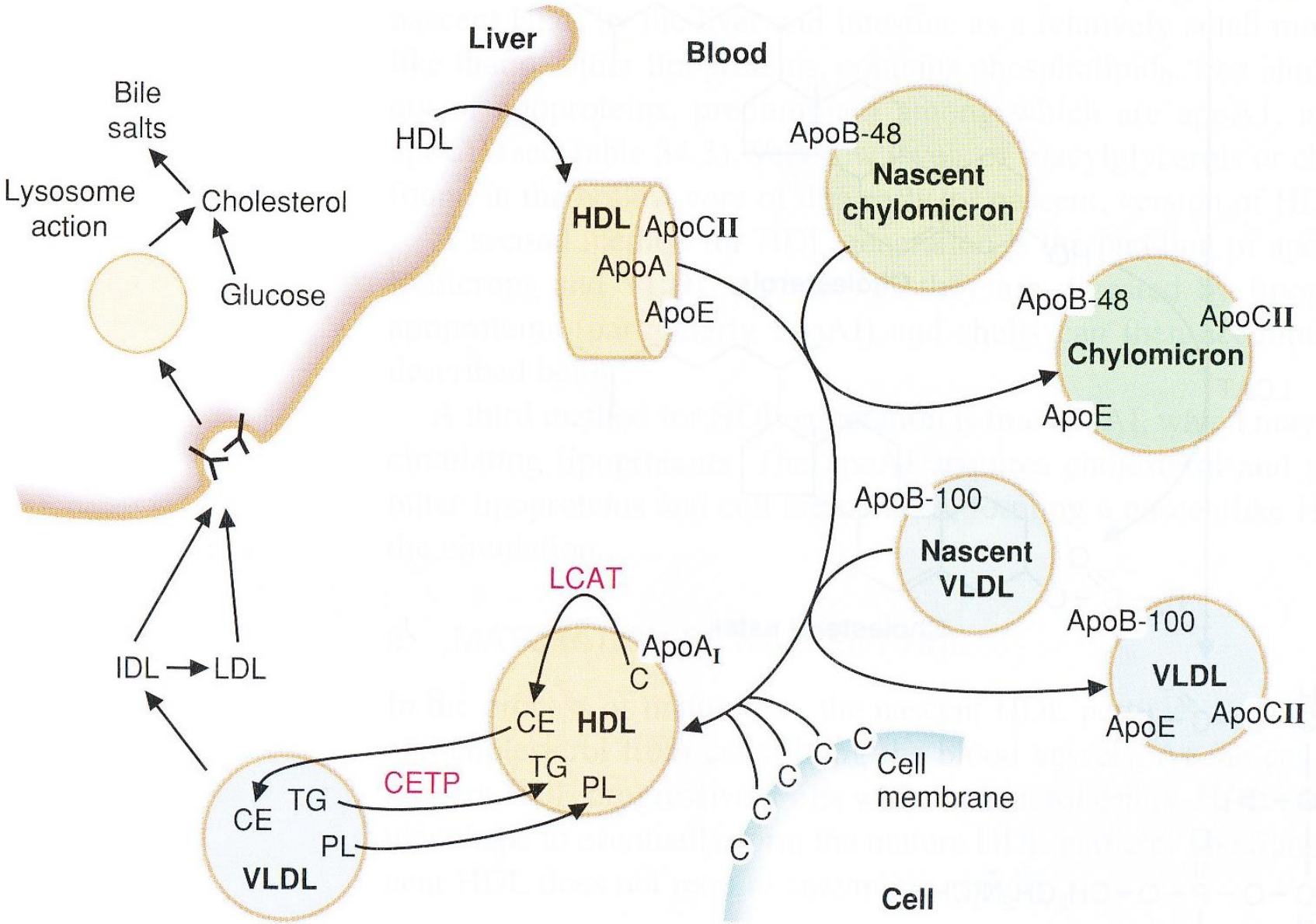
LDL

a) 60% - back to the liver (apo B-100 receptor)

b) 40% - to extrahepatic tissues (adrenocortical and gonadal cells)

c) The excess - nonspecific uptake by macrophages (scavenger cells) in the cell wall (atherosclerosis)

Metabolism of HDL



HDL

Formation:

1. Liver, intestine (nascent HDL)
2. Plasm (binding of cholesterol and phospholipids from other lipoproteins to Apo A-I)

Mature HDL

Accumulation of cholesterol esters in the core

Apoproteins:

Apo A-I, Apo C-II, Apo E

Function:

1. Reverse cholesterol transport = return the cholesterol to the liver

- Vascular tissue (protection agains atherosclerosis)
- LCAT (lecitin cholesterol acyltransferase) - formation of cholesterol esters!

2. Interaction with other lipoproteins

- Transfer of apoproteins (Apo C-II, Apo E) and lipids (CETP - cholesterol ester transfer protein)

Fate of HDL cholesterol:

- receptors in the liver, scavenger receptors, transfer to VLDL (to the liver)

Cholesterol uptake by receptor-mediated endocytosis:

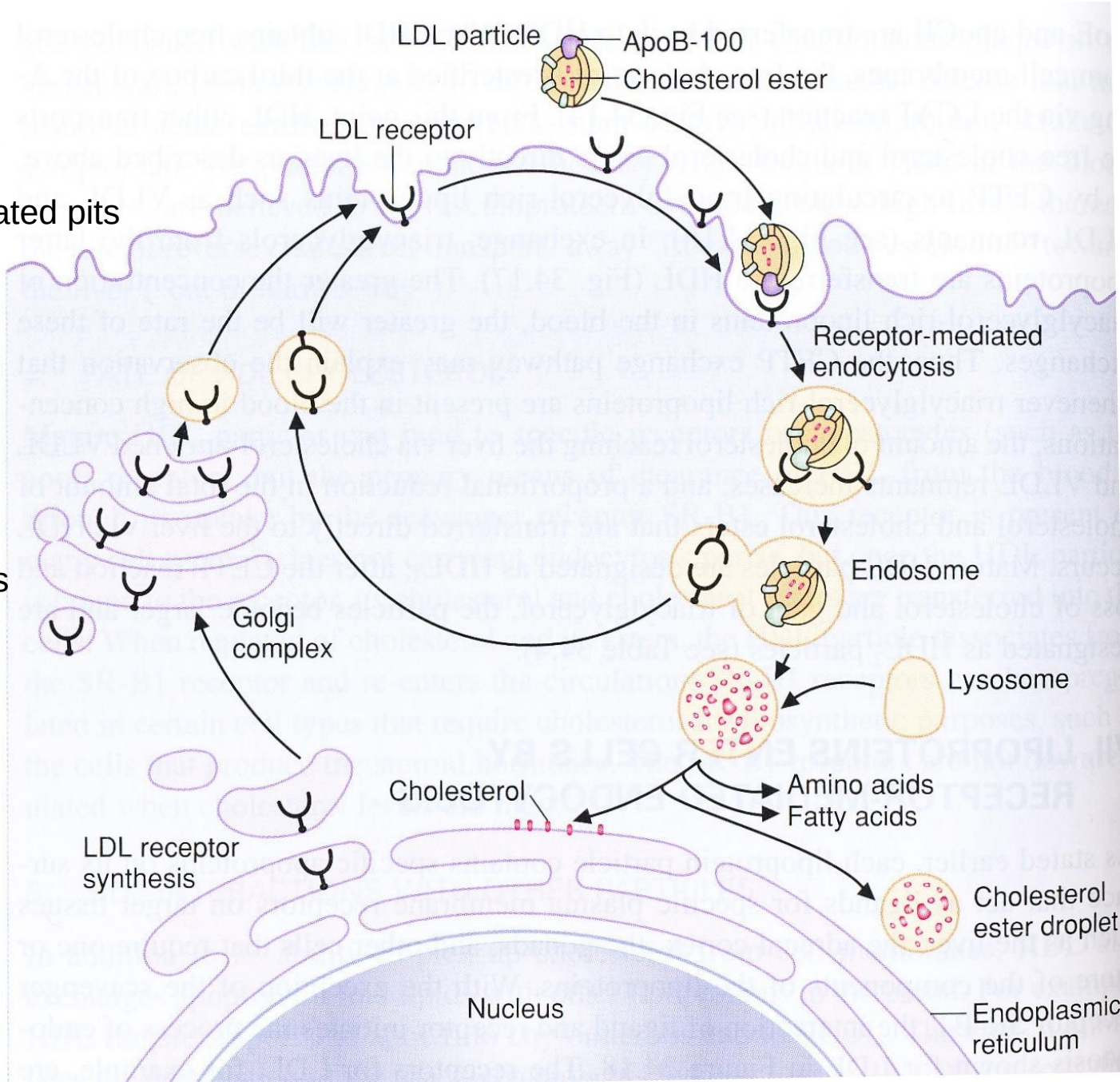
Apoproteins

- ligands for receptors

The clathrin-containing coated pits

Synthesis of LDL receptors

- inhibition by cholesterol



Lipoprotein receptors

LDL receptor

- Ligands - Apo B-100, Apo E (VLDL, IDL, LDL, chylomicron remnants)

Familial hypercholesterolemia

- Changes in the number of LDL receptors, in binding of LDL and in the postreceptor binding process - accumulation of LDL in the blood - atherosclerosis

Macrophage scavenger receptor

- nonspecific (oxidatively modified LDL)
- not down-regulated!

Foam cells - macrophages engorged with lipid

- accumulation - atherosclerosis

Pictures used in the presentation:

Marks´ Basic Medical Biochemistry, A Clinical Approach, third edition, 2009 (M. Lieberman, A.D. Marks)

Textbook of Biochemistry with Clinical Correlations, sixth edition, 2006 (T.M. Devlin)