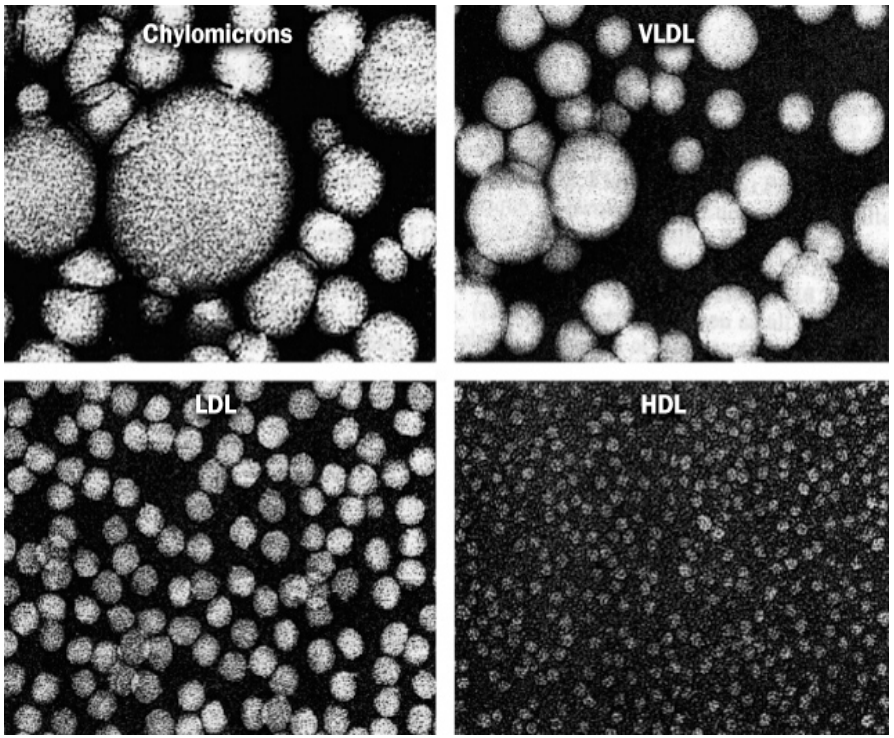
SB29 Hypercholesterolemia and Synthesis of Bile Salts and Vitamin D

Objective 1

- **Id**entify the four major groups of plasma lipoproteins and the four major lipid classes they carry

- **Chilomicrons**
- **VLDL (Very Low Density Lipoprotein)**



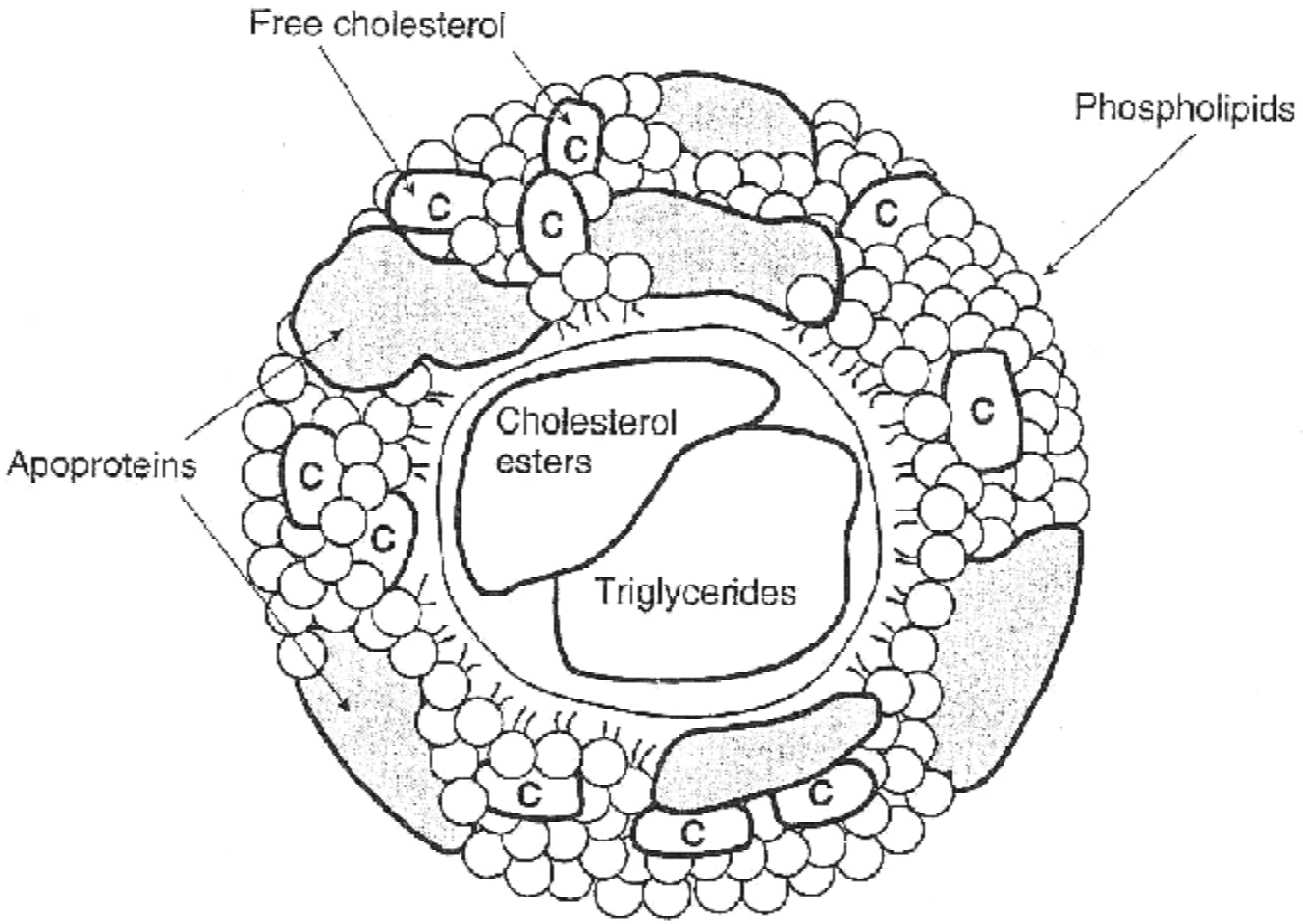
- **LDL (Low Density Lipoprotein)**
- **HDL (High Density Lipoprotein)**

Four major lipid classes in lipoproteins

- triacylglycerols
- phospholipids
- cholesterol
- cholesteryl esters

Objective 2

- Ilustrate the structure of lipoprotein particle



- LP core
  - Triglycerides
  - Cholesterol esters
- LP surface
  - Phospholipids
  - Proteins
  - Cholesterol

Objective 3

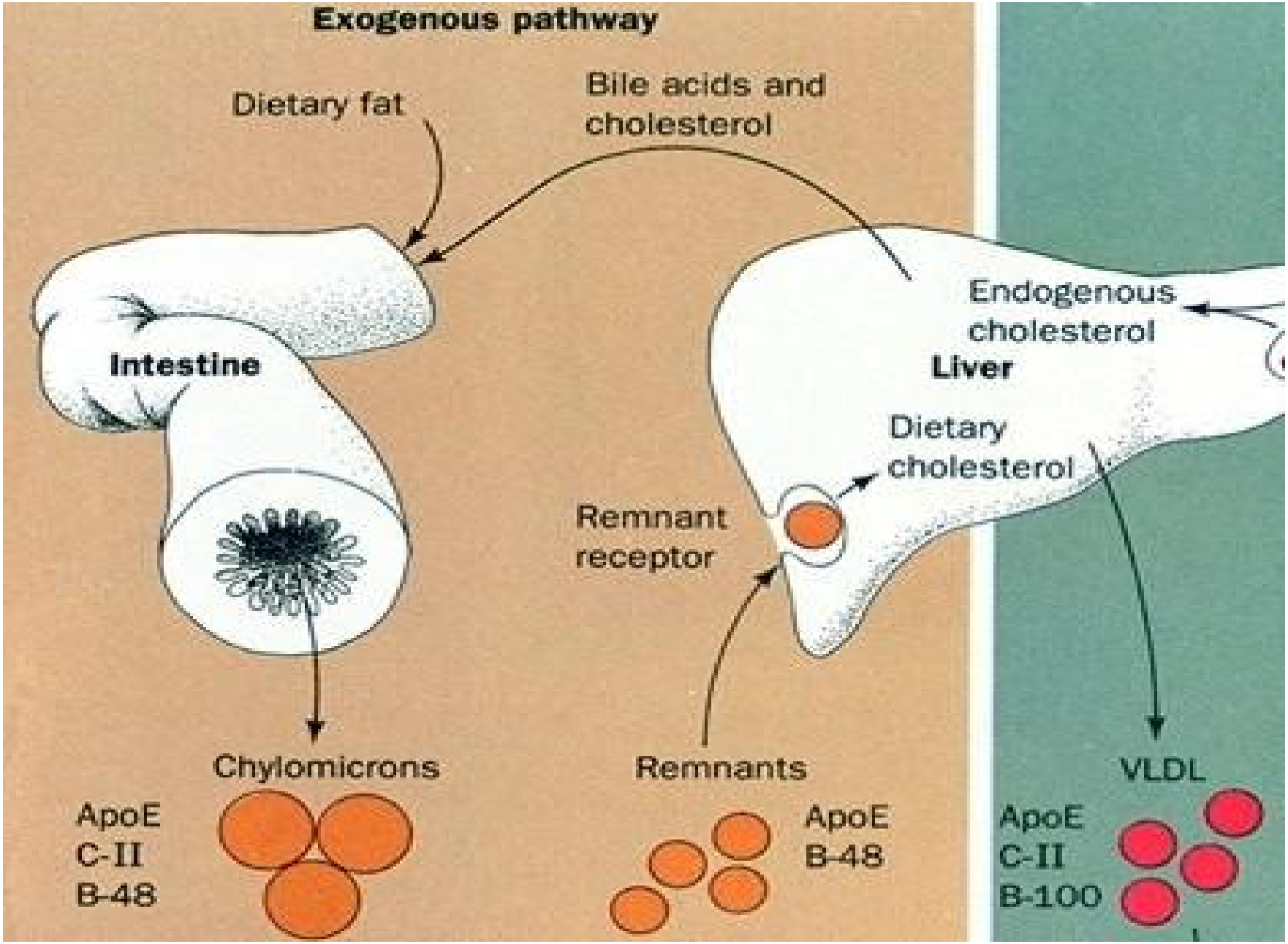
- Indicate the major types of apolipoprotein found in different lipoprotein classes

Apolipoproteins carry out several roles

- **(1) form part of the structure of the lipoprotein, eg, apo B**
- **(2) enzyme cofactors, eg, C-II for lipoprotein lipase**
- **(3) act as ligands for interaction with lipoprotein receptors in tissues, eg, apo B-100 for the LDL receptor**

Objective 4

- **Explain that triacylglycerol is carried from the intestine (after intake from the diet) to the liver in the chilomicrons**
- **and from the liver to extrahepatic tissues in VLDL**
- **and these particles are sythesized in intestinal and liver cells, respectively, by similar processes**


Exogenous pathway
Dietary fat
Bile acids and cholesterol
Intestine
Endogenous cholesterol
Liver
Dietary cholesterol
Remnant receptor
Chylomicrons
ApoE
C-II
B-48
Remnants
ApoE
B-48
VLDL
ApoE
C-II
B-100

Objective 5

- Ilustrate the processes by which chilomicrons are metabolized by lipases
- to form chilomicron remnants,
- which are then removed from the circulation by the liver

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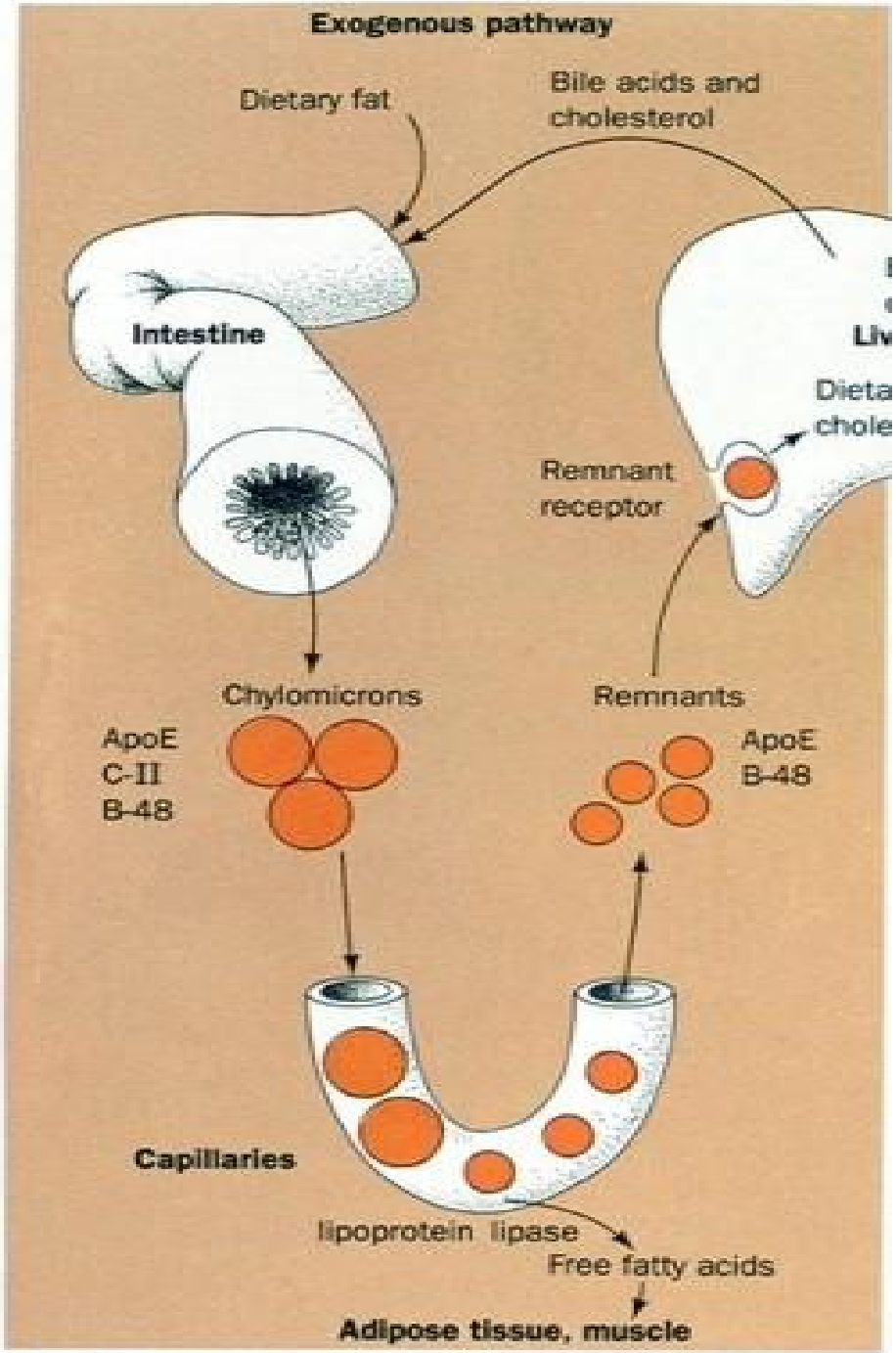
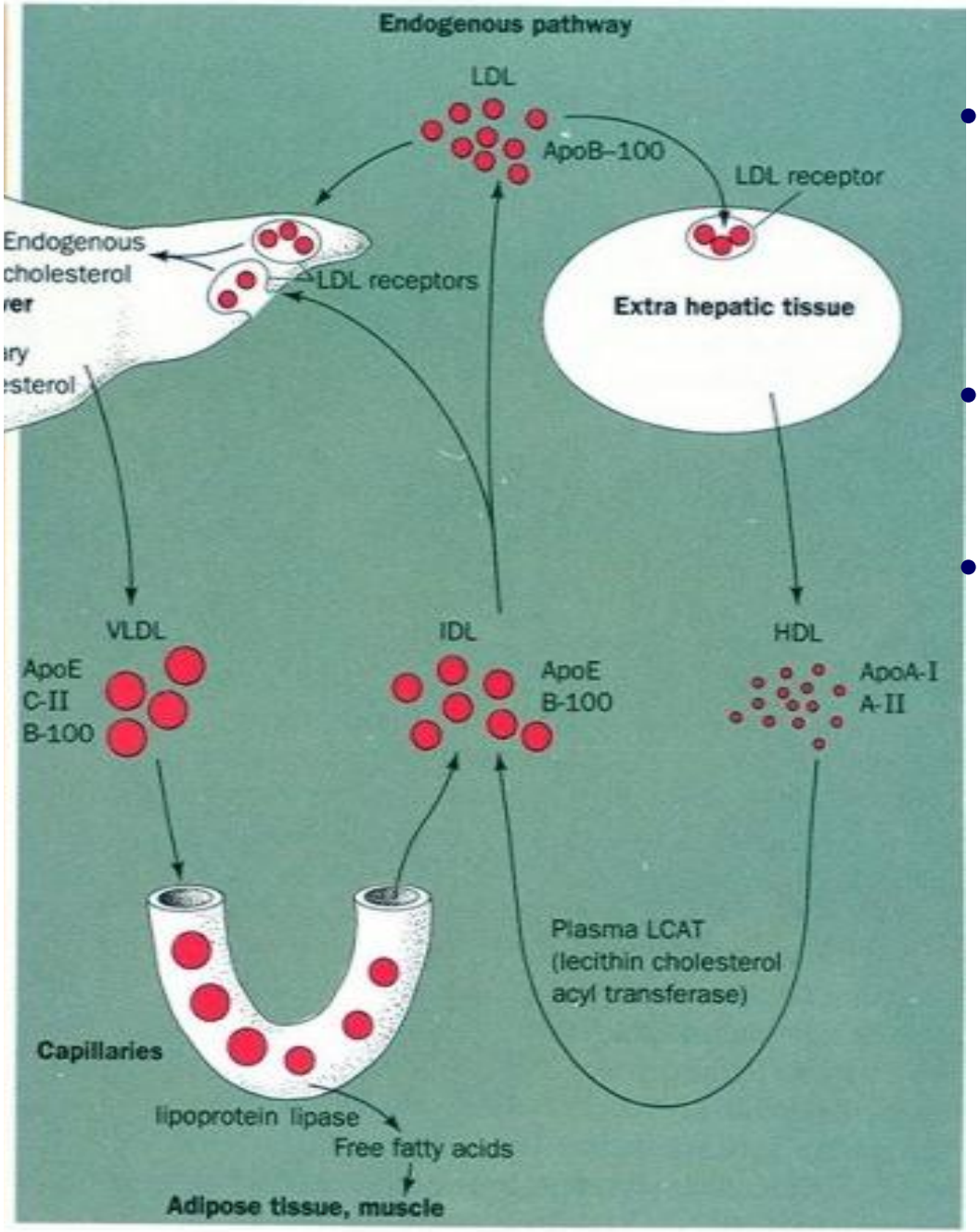




Objective 6

- **Explain how VLDL is metabolized by lipases to VLDL remnants (also called intermediate-density lipoprotein, IDL)**
- **which may be cleared by the liver or converted to LDL,**
- **which functions to deliver cholesterol from the liver to extrahepatic tissues and is taken up via the LDL (apoB100) receptor**

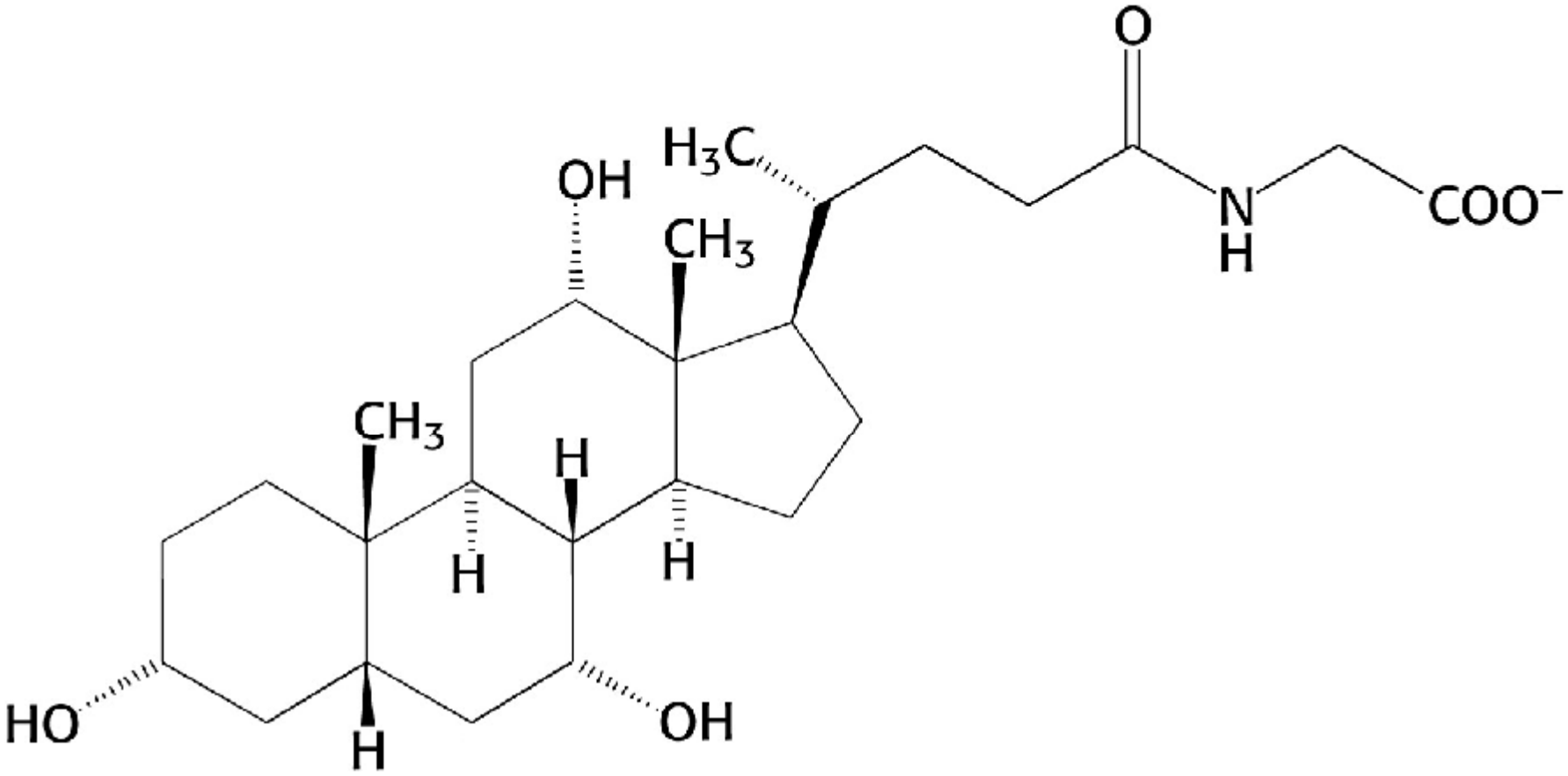
- **HDL removes cholesterol from the tissues and return it**
- **to the liver for excretion in the process known as reverse cholesterol transport**

Objective 7

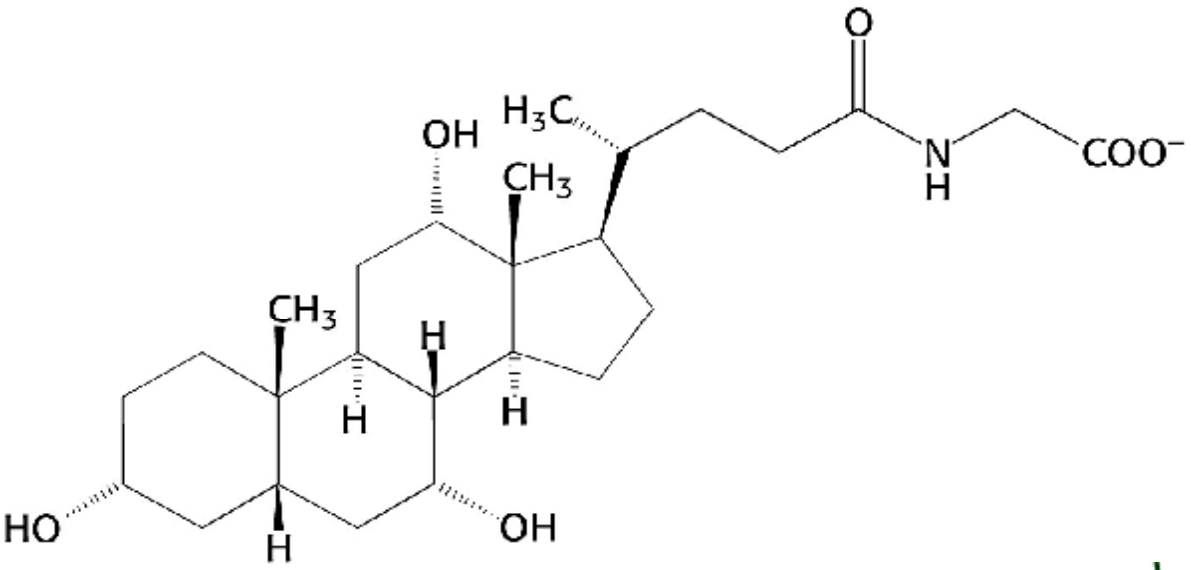
- **Understand how the liver plays a central role in lipid transport and metabolism**
- **and how hepatic VLDL secretion is regulated by the diet and hormones**

THE LIVER PLAYS A CENTRAL ROLE IN LIPID TRANSPORT & METABOLISM

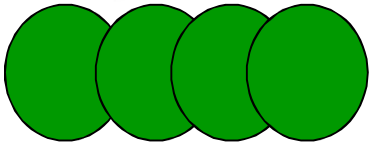
- **1. It facilitates the digestion and absorption of lipids by the production of bile,**
- **which contains cholesterol and bile salts**
- **synthesized within the liver de novo or after uptake of lipoprotein cholesterol**



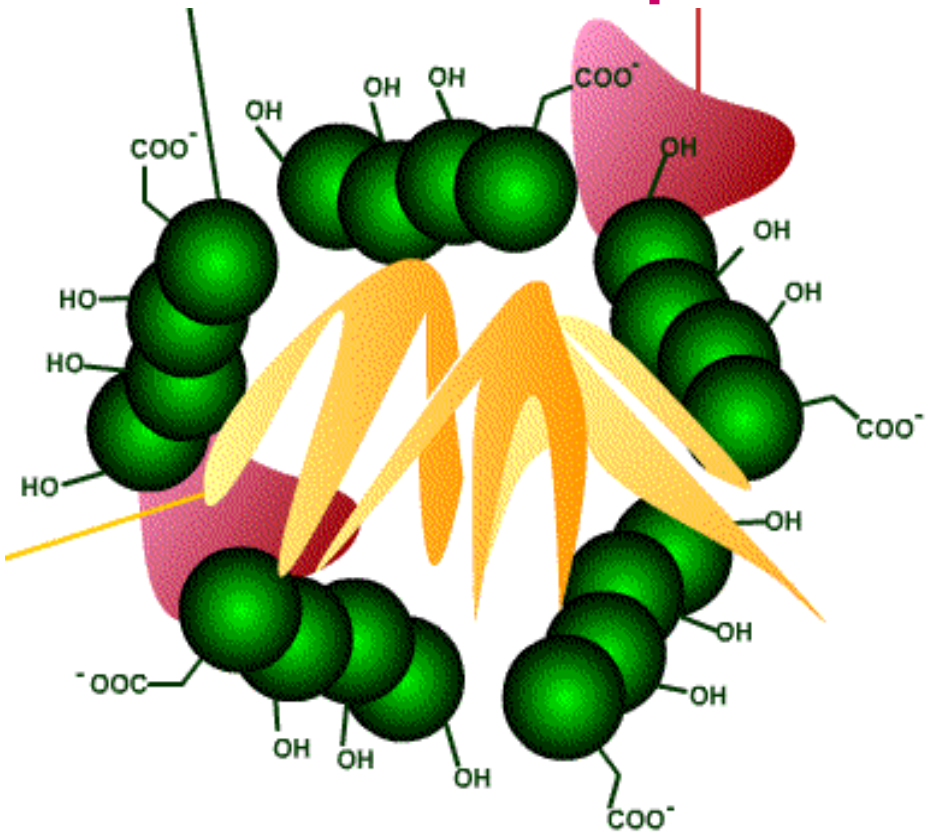
Glycocholate



Glycocholate



lipase

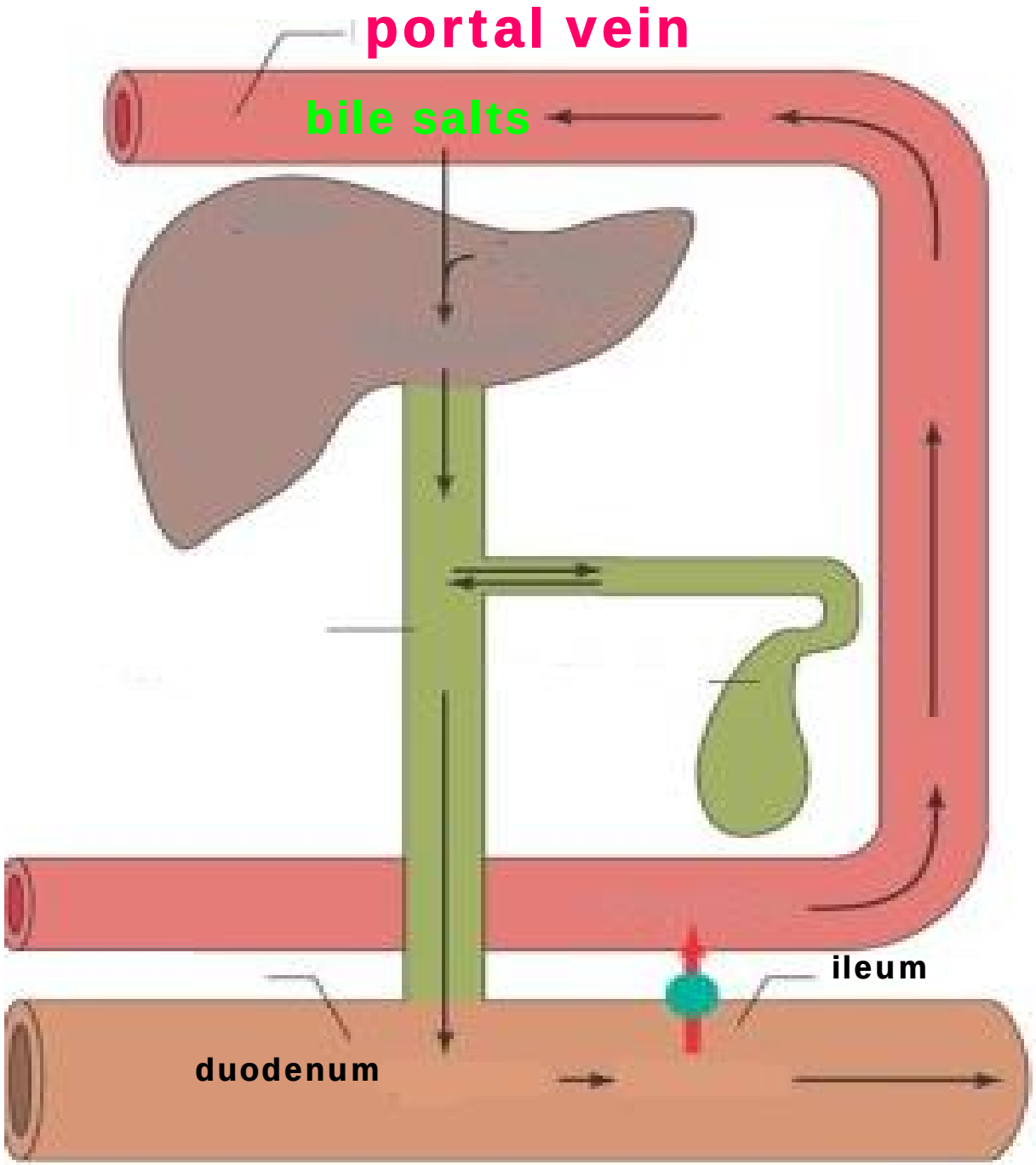


Triacyl-glicerol

- **Bile acids in the digestion and absorption of fats**

Excess cholesterol is excreted from the liver in the bile as cholesterol or **bile salts**

A large proportion of bile salts is absorbed into the portal circulation and **returned to the liver** as part of the enterohepatic circulation



THE LIVER PLAYS A CENTRAL ROLE IN LIPID TRANSPORT & METABOLISM

- 1. It facilitates the digestion and absorption of lipids by the production of bile,
- which contains cholesterol and bile salts
- synthesized within the liver de novo or after uptake of lipoprotein cholesterol

- **2. It actively synthesizes and oxidizes fatty acids**
- **and also synthesizes triacylglycerols and phospholipids**

- **3. It converts fatty acids to ketone bodies (ketogenesis)**

- **4. It plays an integral part in the synthesis and metabolism of plasma lipoproteins**

Factors that enhance both the synthesis of triacylglycerol and the secretion of VLDL by the liver

- **(1) the fed state rather than the starved state**
- **(2) the feeding of diets high in carbohydrate (particularly if they contain sucrose or fructose) leading to high rates of lipogenesis and esterification of fatty acids**
- **(3) high levels of circulating free fatty acids**
- **and…**

Factors that enhance
both the synthesis of triacylglycerol
and the secretion of VLDL by the liver

- **(4) ingestion of ethanol**

- **(5) the presence of high concentrations of insulin**
- **and low concentrations of glucagon,**
- **which enhance fatty acid synthesis and esterification**
- **and inhibit their oxidation**

Objective 8

- Indicate the causes of alcoholic fatty liver disease

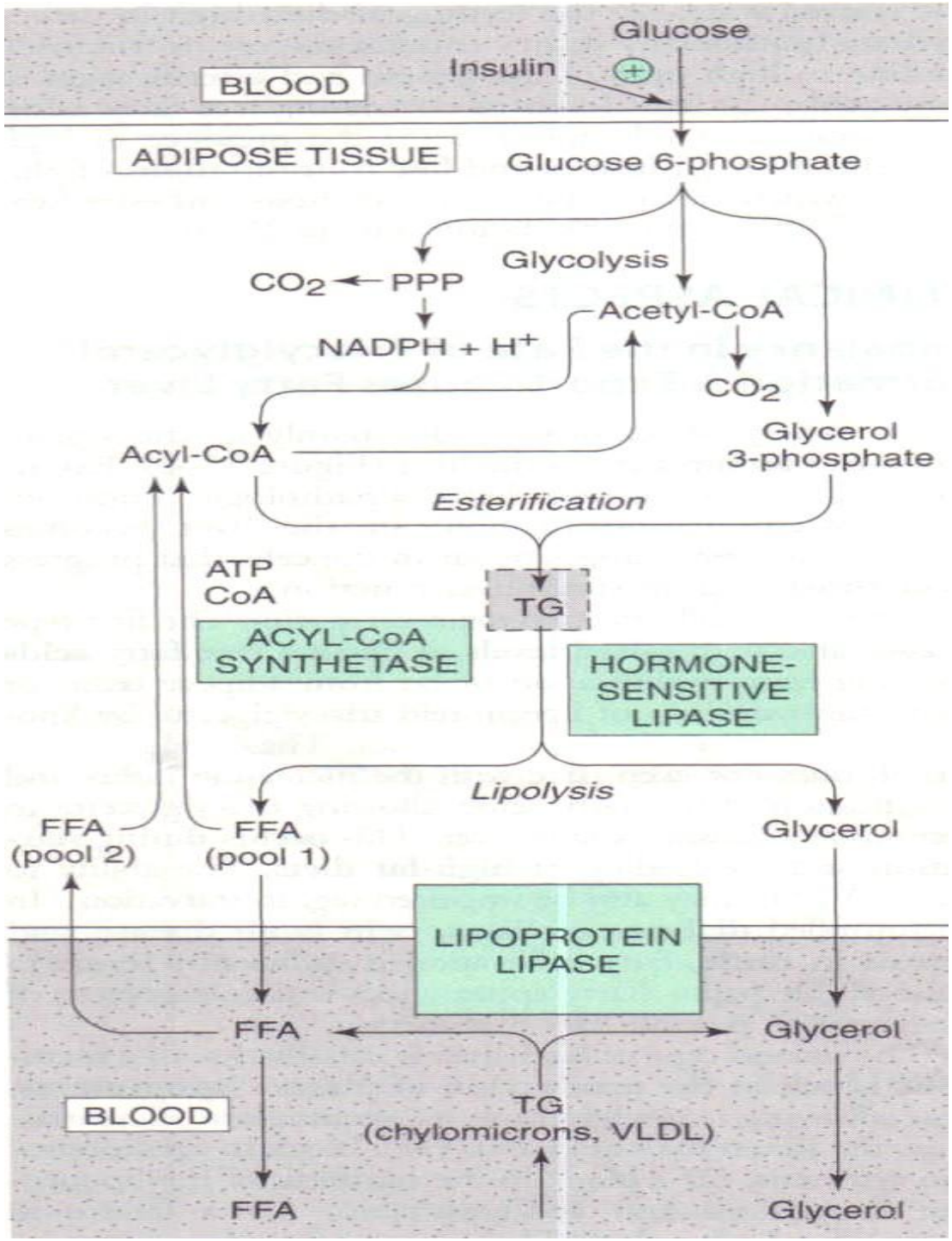
Alcoholic fatty liver
is the first stage
in **alcoholic liver disease**

- $CH_3\text{-}CH_2\text{-}OH + NAD^+ \rightarrow CH_3\text{-}CHO + NADH + H^+$

- 1. Which coenzyme is needed for fatty acid β-oxidation?
- 2. Will fatty acid β-oxidation be increased or decreased in the presence of ethanol?
- 3. Which reaction undergo fatty acid if there is not coenzime NAD^+ available?

Objective 9

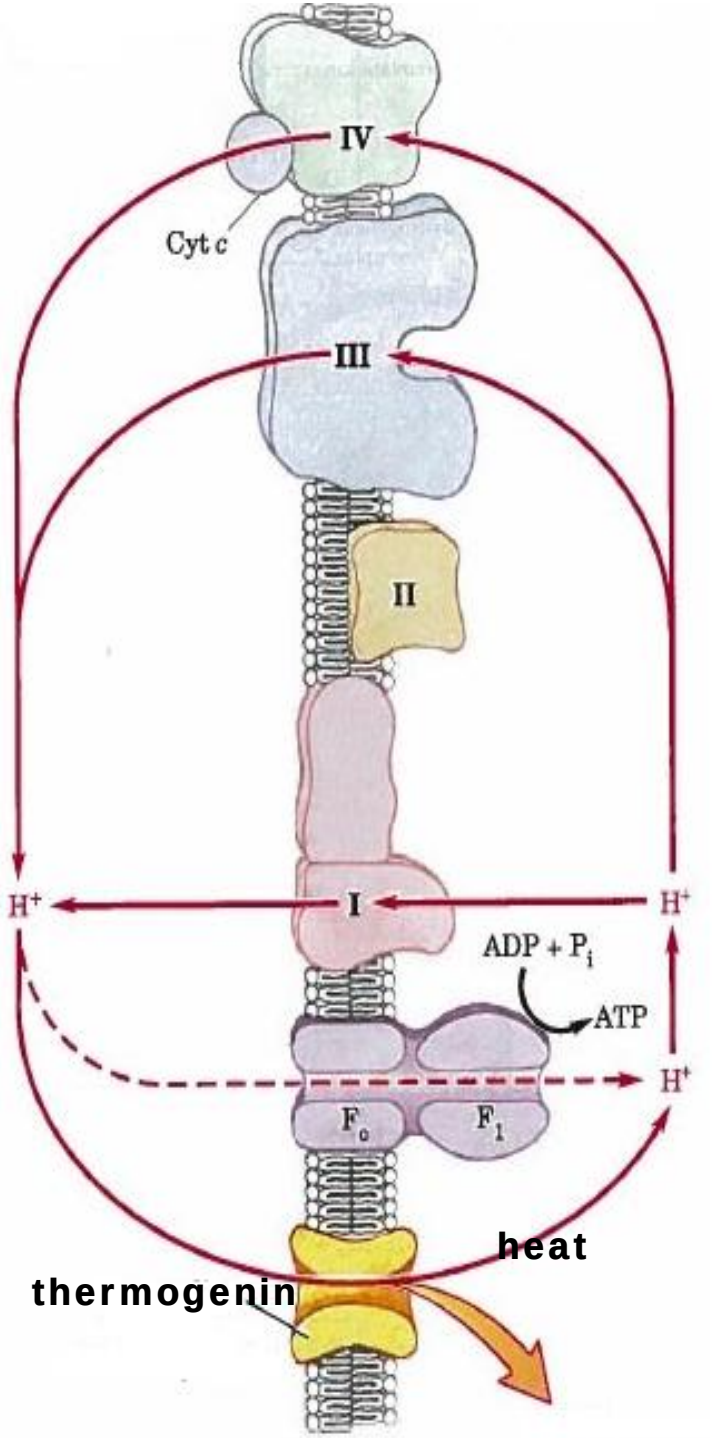
- Appriciate that adipose tissue is the main store of triacylglycerol in the body and explain the processes by which fatty acids are released and how they are regulated



- **FIGURE 25–7 Triacylglycerol metabolism in adipose tissue.**
- **Hormone-sensitive lipase is activated by**
- **ACTH, TSH, glucagon, epinephrine, norepinephrine, and vasopressin**
- **and inhibited by insulin, prostaglandin E1, and nicotinic acid.**

Objective 10

- Understand the role of brown adipose tissue in the generation of body heat

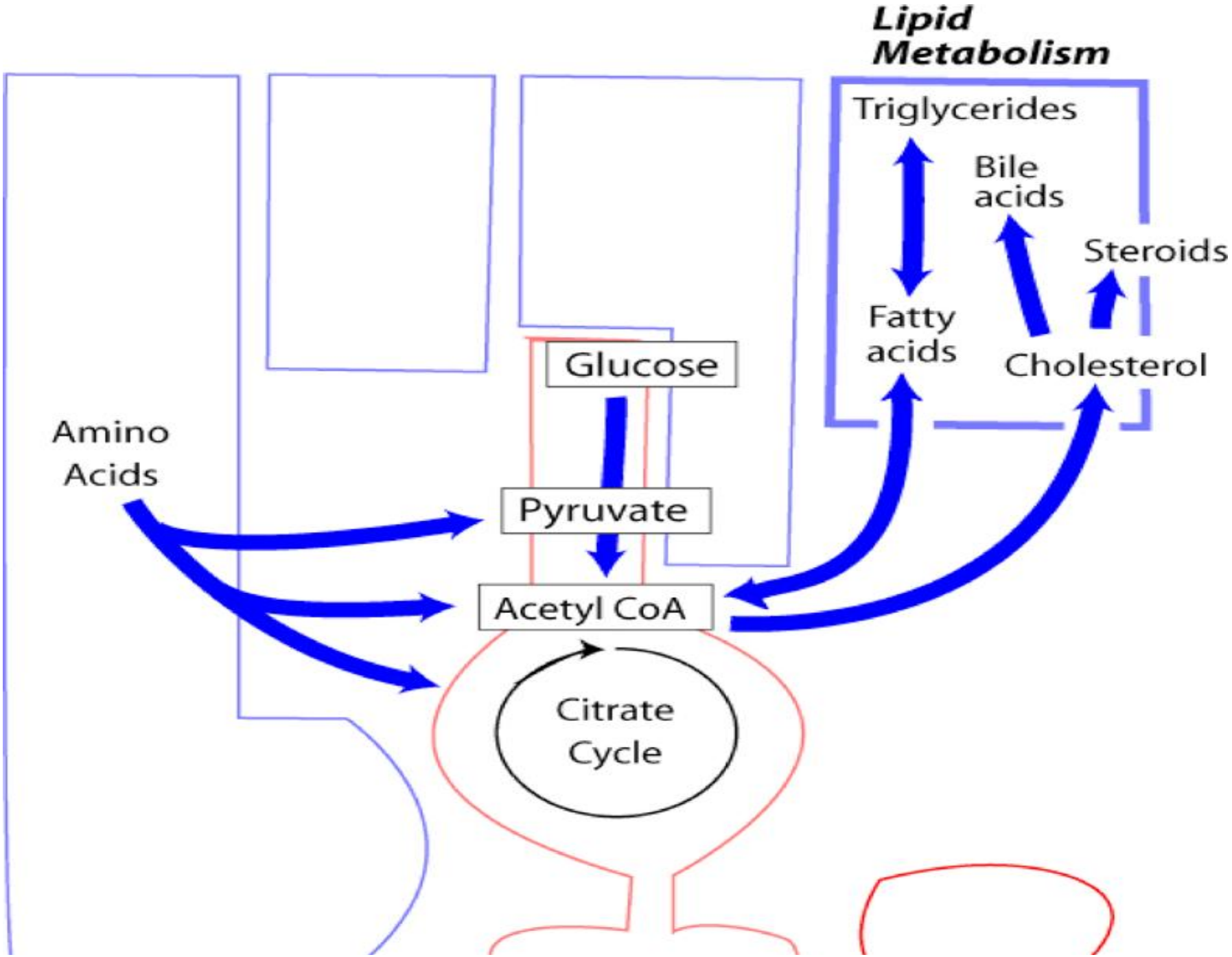


- **Brown adipose tissue is the site of "nonshivering thermogenesis"**
- **It is found in hibernating and newborn animals and is present in small quantity in humans**
- **Thermogenesis results from the presence of an uncoupling protein, thermogenin, in the inner mitochondrial membrane**

Cholesterol

- **Presursor of all other steroids**
  - **Corticosteroids**
  - **Sex hormones**
  - **Bile acids**
  - **Vitamin D**

- **Important structural role in**
  - **Membrane**
  - **Outher layer of lipoproteins**


Lipid Metabolism
Triglycerides
Bile acids
Steroids
Fatty acids
Cholesterol
Glucose
Amino Acids
Pyruvate
Acetyl CoA
Citrate Cycle

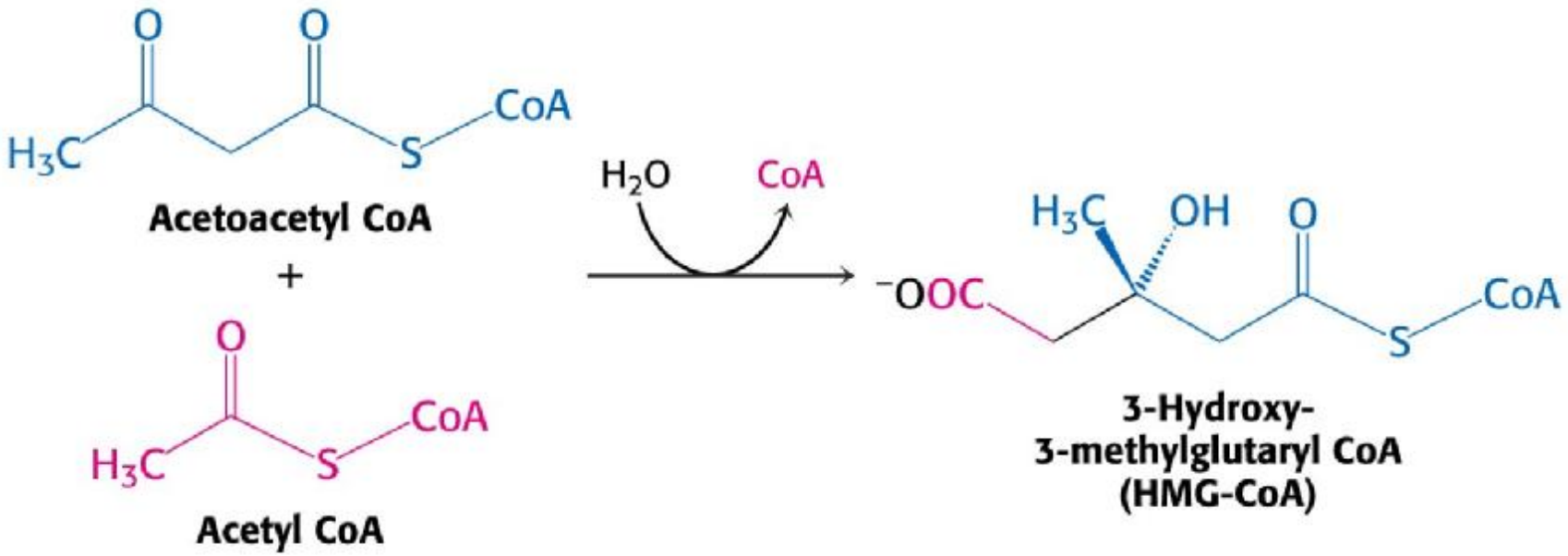
Objective 11

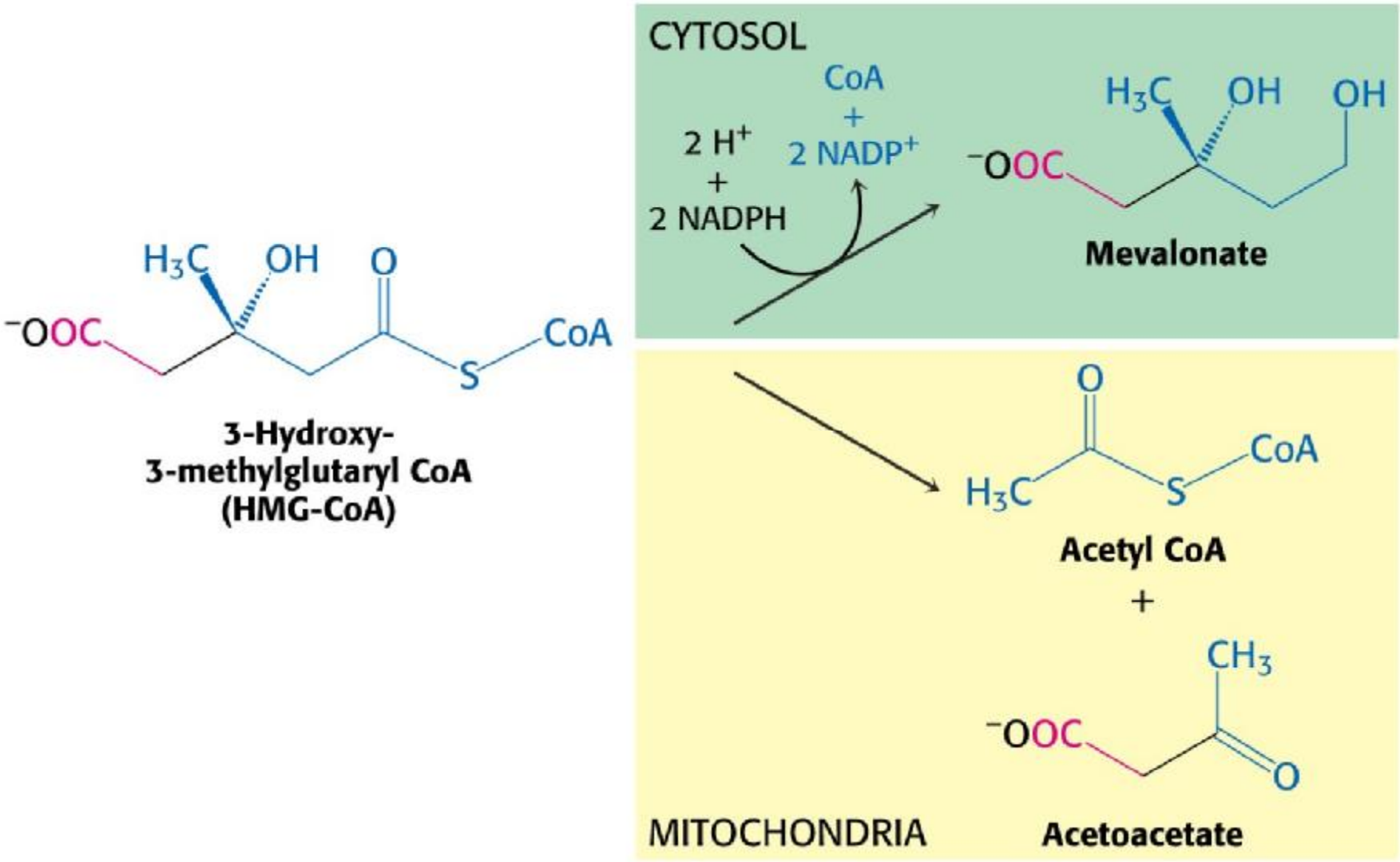
- **Identify the five stages in the biosynthesis of cholesterol from acetyl-CoA.**

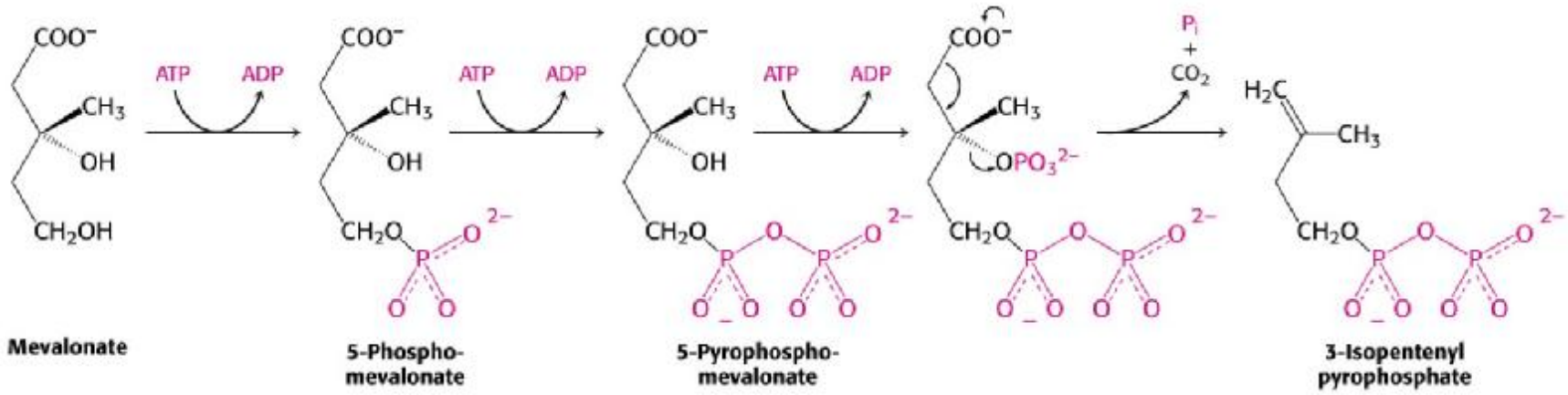
Cholesterol is synthesized in the body entirely from acetyl-CoA

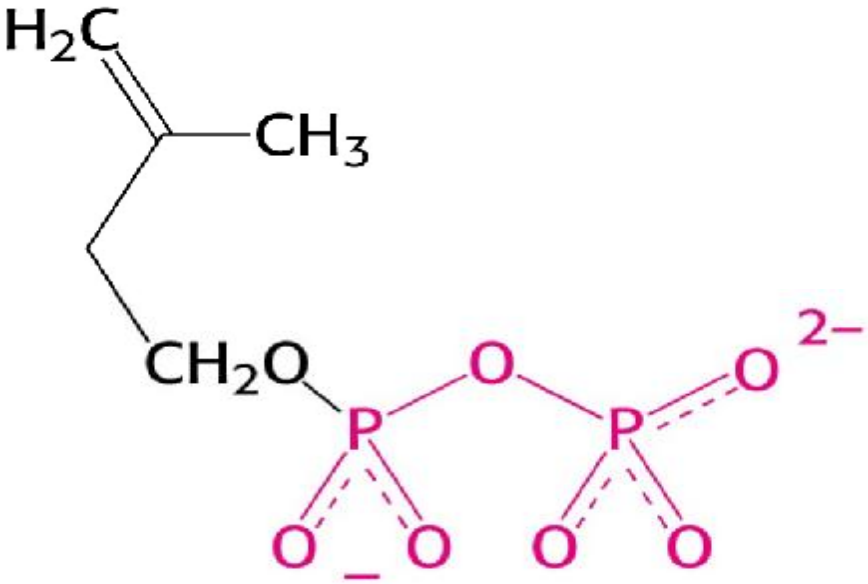
- 1. Three molecules of acetyl-CoA form mevalonate via the important regulatory reaction for the pathway, catalyzed by HMG-CoA reductase.
- 2. Next, a five-carbon isoprenoid unit is formed,
- 3. and six of these condense to form squalene.
- 4. Squalene undergoes cyclization to form the parent steroid lanosterol,
- 5. which, after the loss of three methyl groups and other changes, forms cholesterol.

1. Three molecules of acetyl-CoA form mevalonate via the important regulatory reaction for the pathway, catalyzed by HMG-CoA reductase



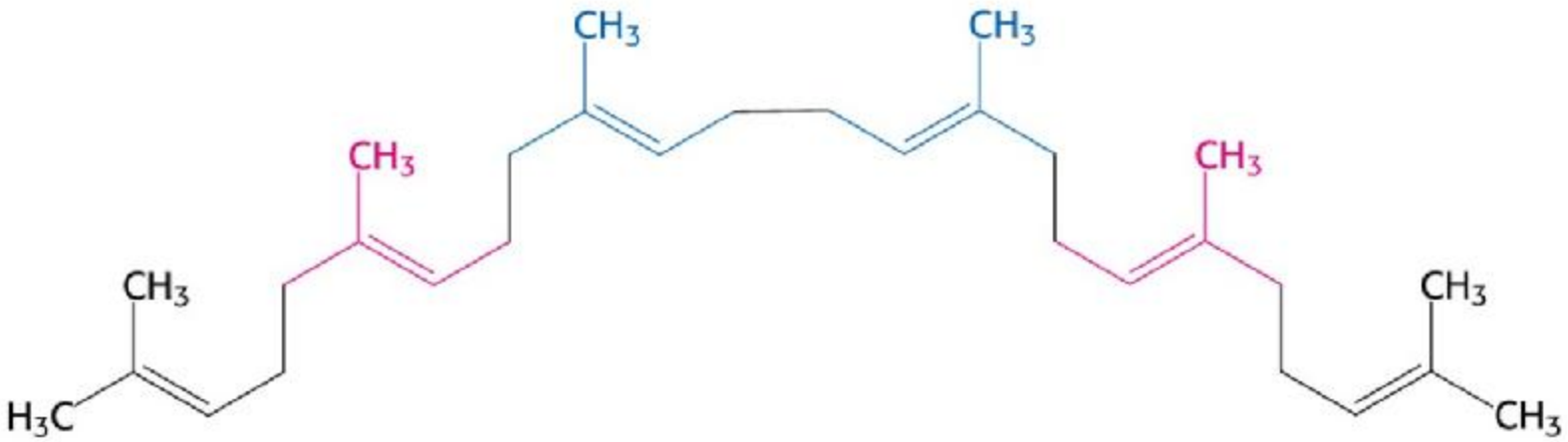

CYTOSOL
CoA
+
2 NADP+
2 H+
+
2 NADPH
H3C
OH
OH
−OOC
Mevalonate
H3C
OH
O
−OOC
CoA
S
3-Hydroxy-
3-methylglutaryl CoA
(HMG-CoA)
O
H3C
S
CoA
Acetyl CoA
+
CH3
−OOC
O
MITOCHONDRIA
Acetoacetate





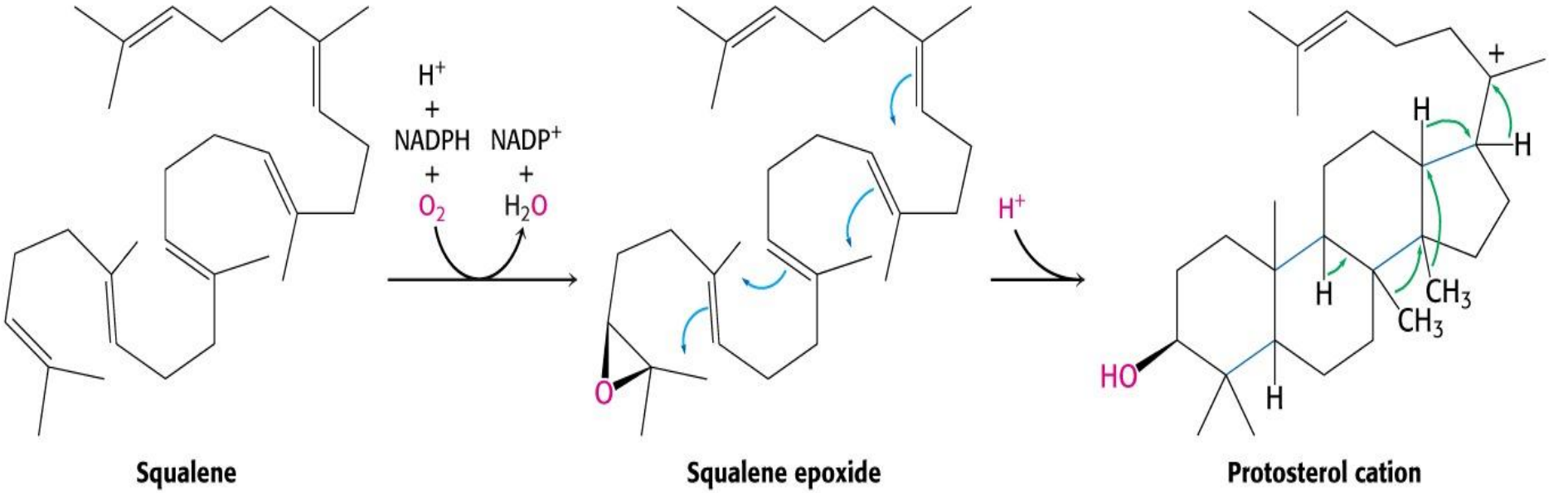
3-Isopentenyl pyrophosphate

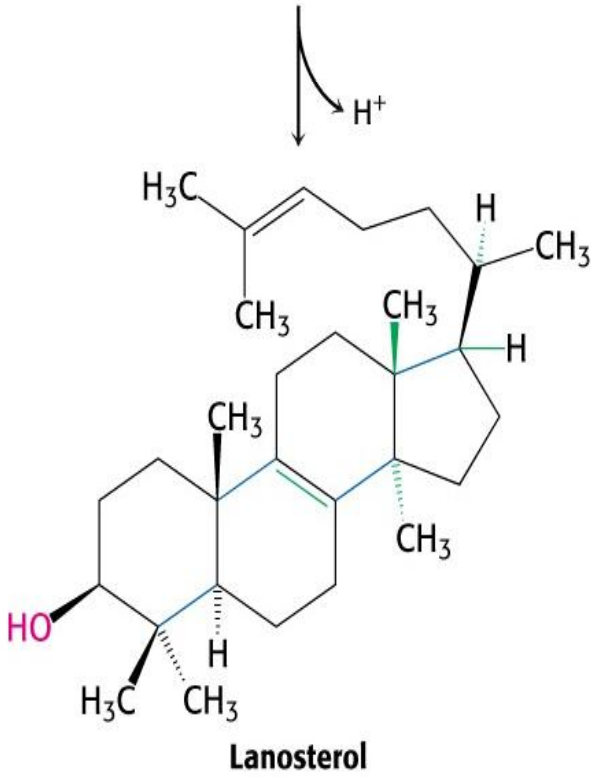
2. Five-carbon isoprenoid unit is formed



Squalene

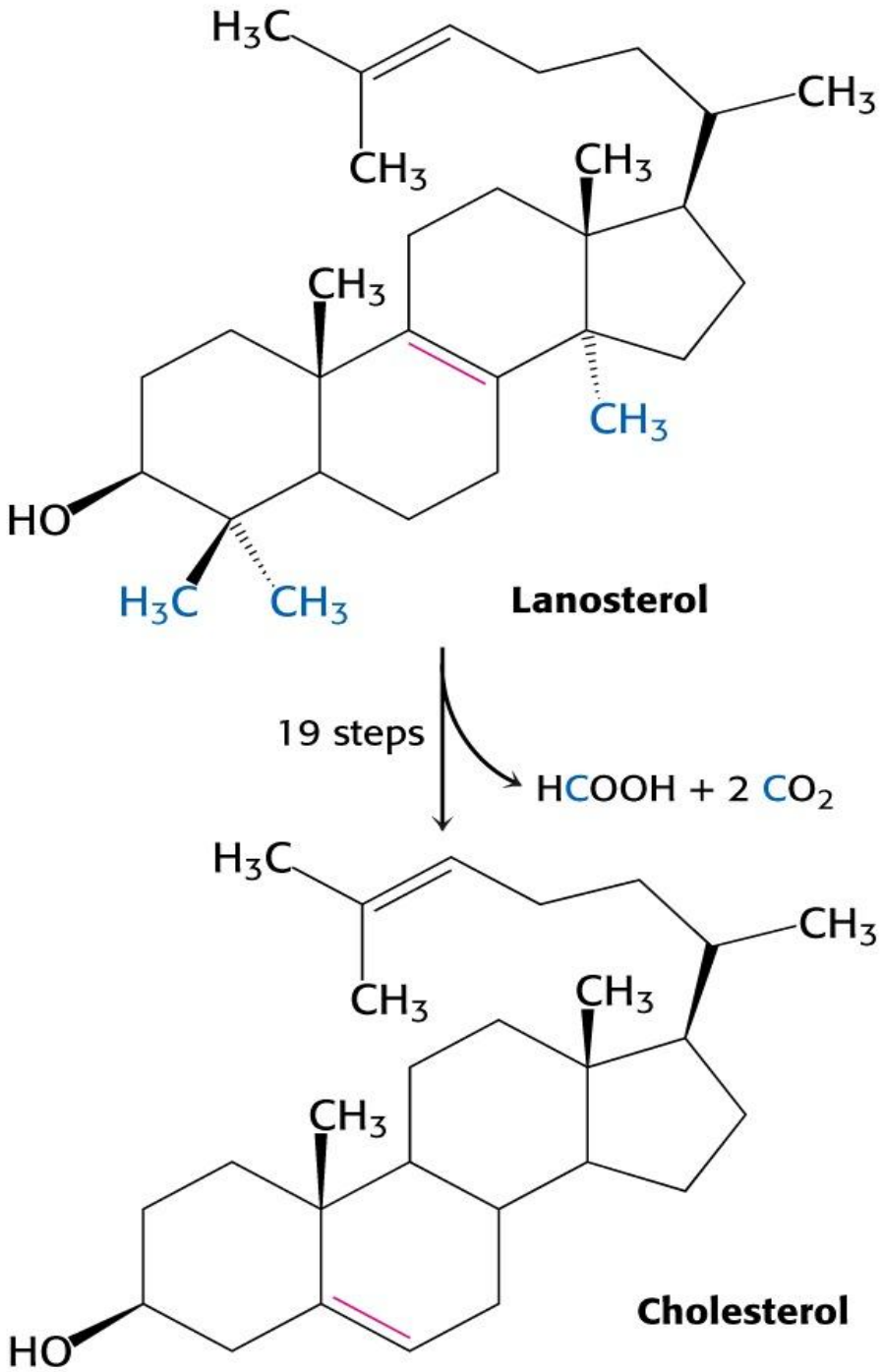
3. Six isoprenoids condense to form squalene





4. Squalene undergoes cyclization to form the parent steroid lanosterol

5. Lanosterol, after the loss of three methyl groups and other changes, forms cholesterol



Objective 12

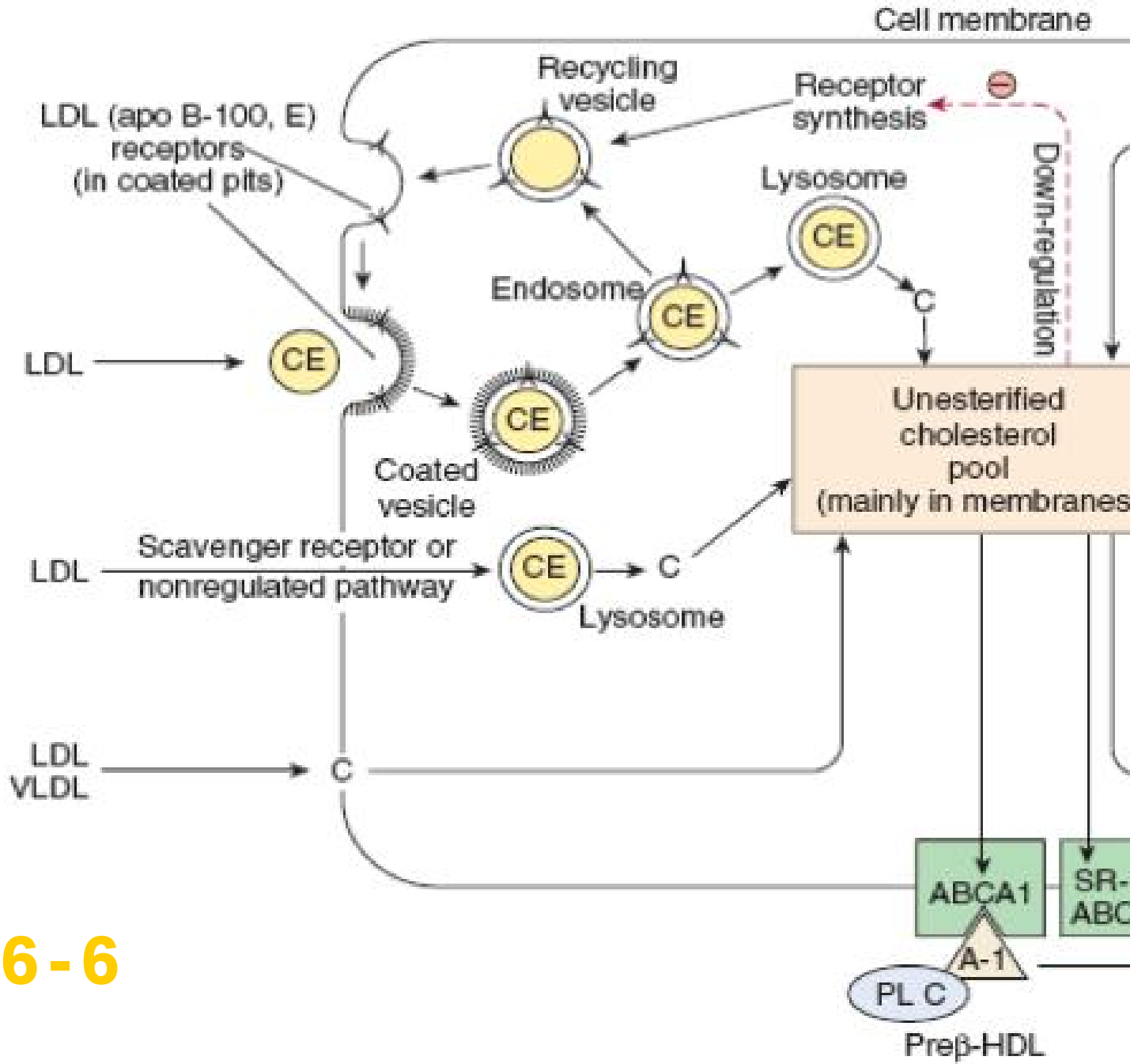
- Understand the role of 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase)
- in controlling the rate of cholesterol synthesis
- and explain the mechanisms by which its activity is regulated

- **Cholesterol represses transcription of the HMG-CoA reductase**

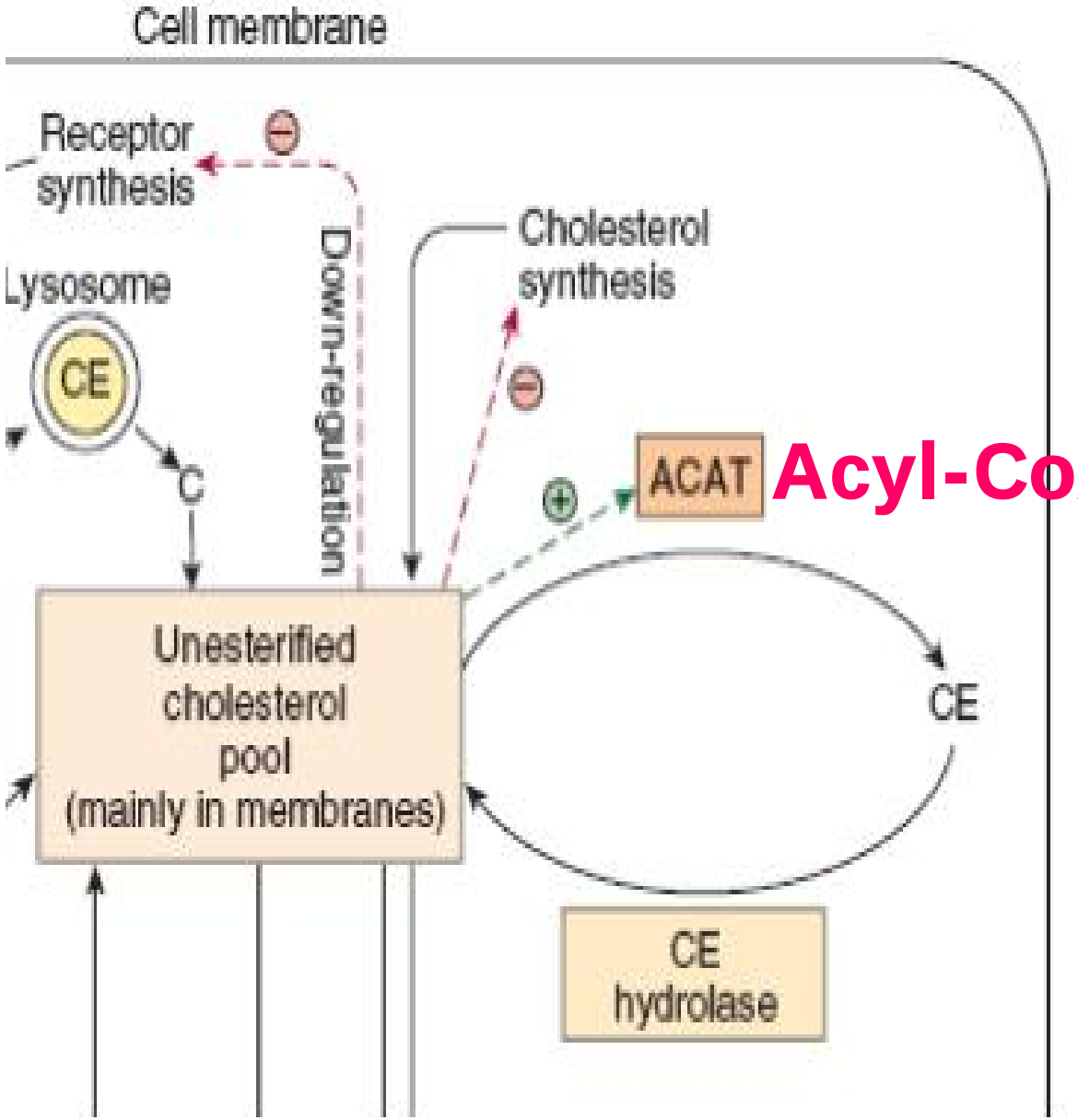
- **via activation of a sterol regulatory element-binding protein (SREBP)**

Objective 13

- **Appreciate that cholesterol balance in cells is tightly regulated and indicate the factors involved in maintaining the correct balance.**


Cell membrane
Recycling vesicle
Receptor synthesis
LDL (apo B-100, E) receptors (in coated pits)
Lysosome
CE
Endosome
CE
C
Down-regulation
LDL
CE
CE
Coated vesicle
Unesterified cholesterol pool (mainly in membranes
LDL
Scavenger receptor or nonregulated pathway
CE
C
Lysosome
LDL
VLDL
C
ABCA1
SR-
ABC
A-1
PL C
Preβ-HDL

- **Figure 26-6**

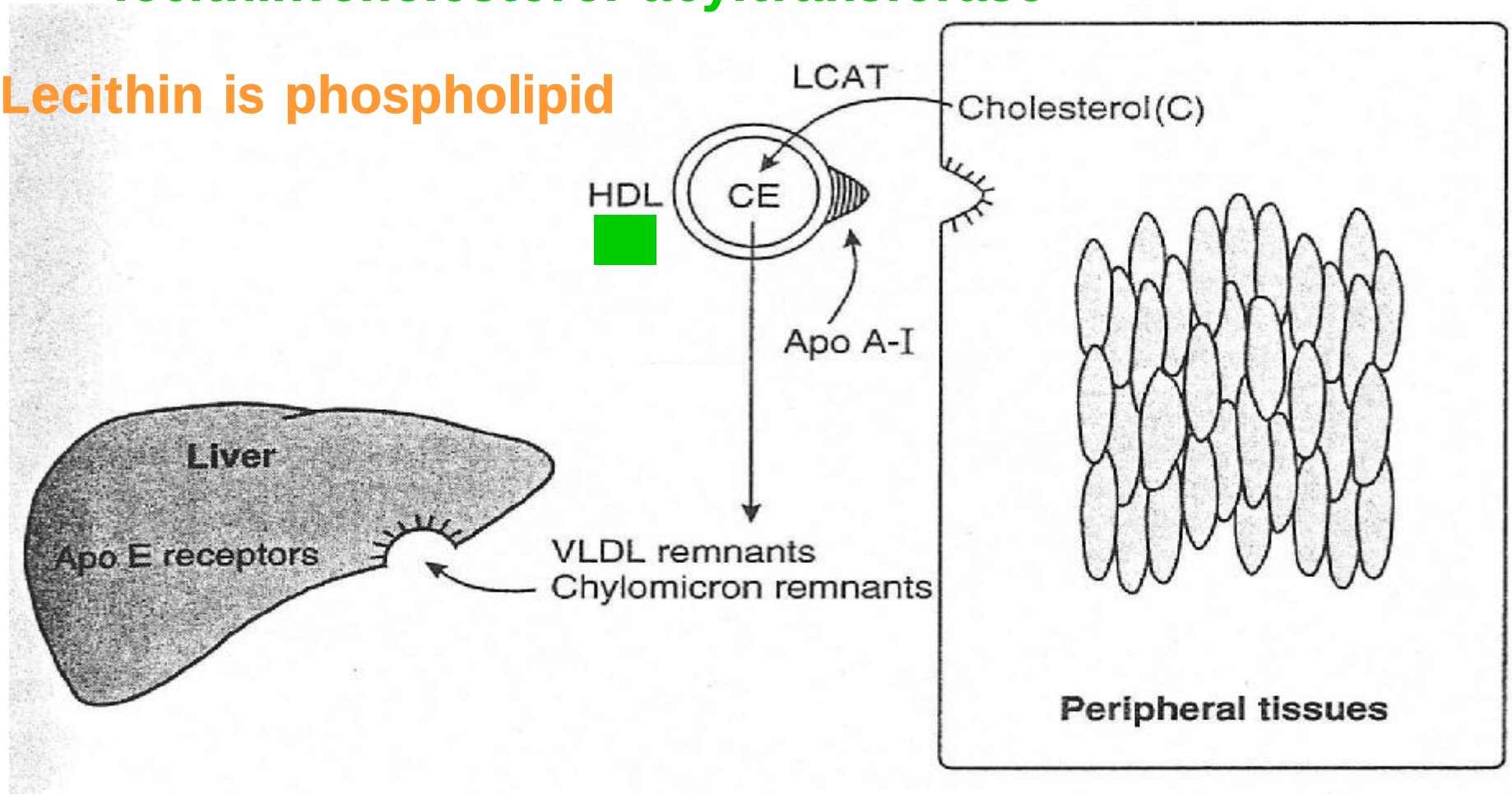


Acyl-CoA:cholesterol acyltransferase

Reverse cholesterol transport

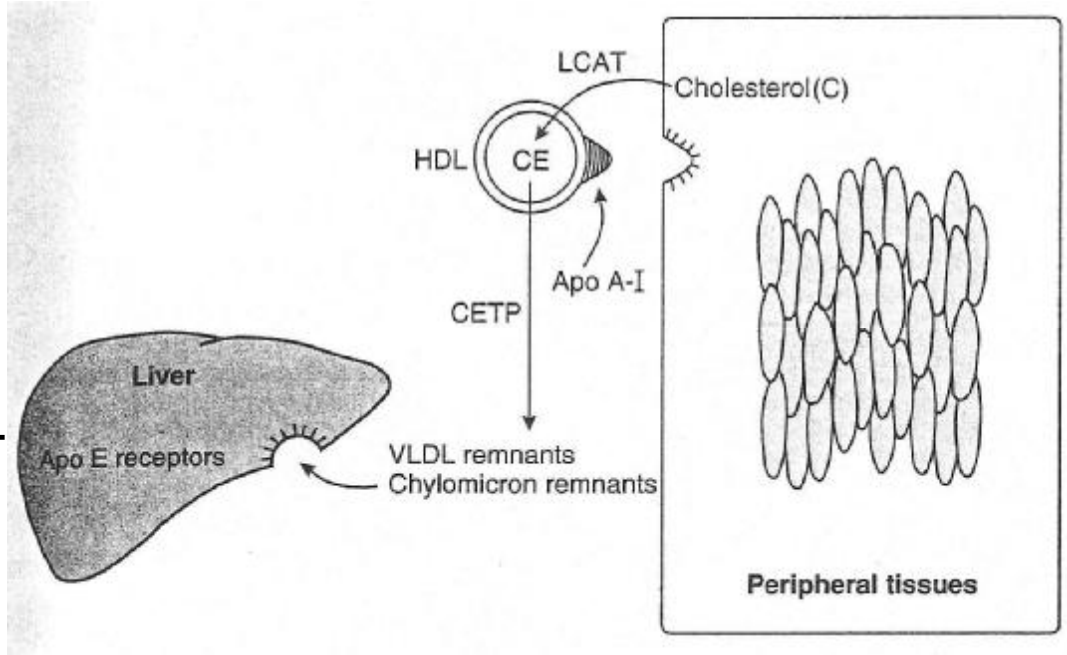
lecithin:cholesterol acyltransferase

Lecithin is phospholipid



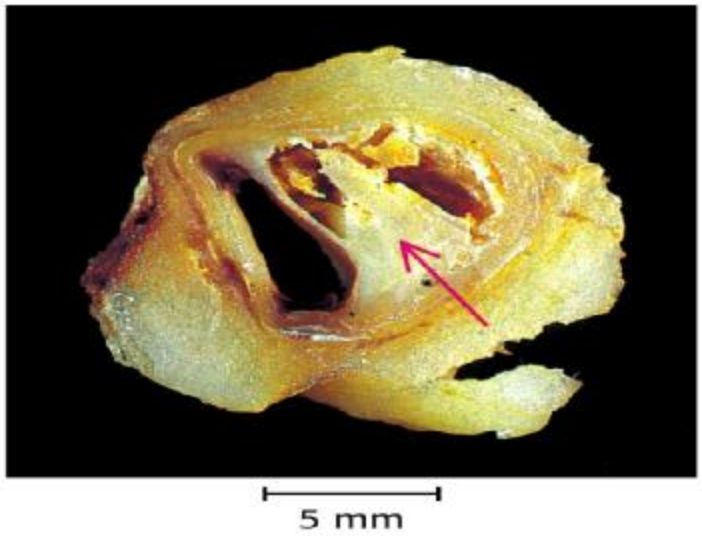
Reverse cholesterol transport

- Uptake of cholesterol from peripheral tissues (binding by apo-A-I)
- Esterification of HDL-C by LCAT
  - LCAT activated by apoA1
- Transfer of CE to lipoprotein remnants (IDL and CR)
- removal of CE-rich remnants by liver, converted to bile acids and excreted

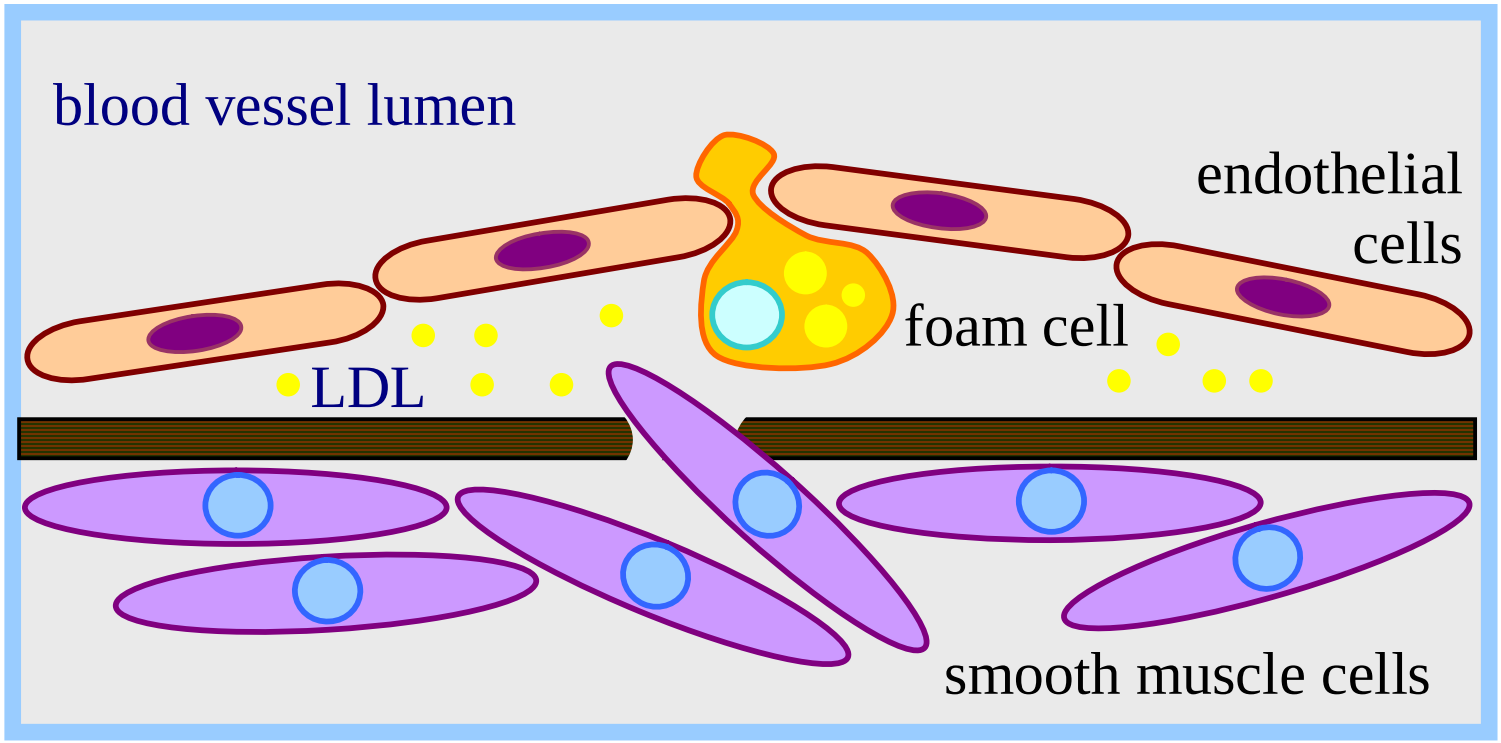


Objective 14

- **Indicate pathological role of cholesterol in atherosclerosis development**
- **Be aware of the roles of LDL and HDL in promoting and retarding, respectively, the development of atherosclerosis**

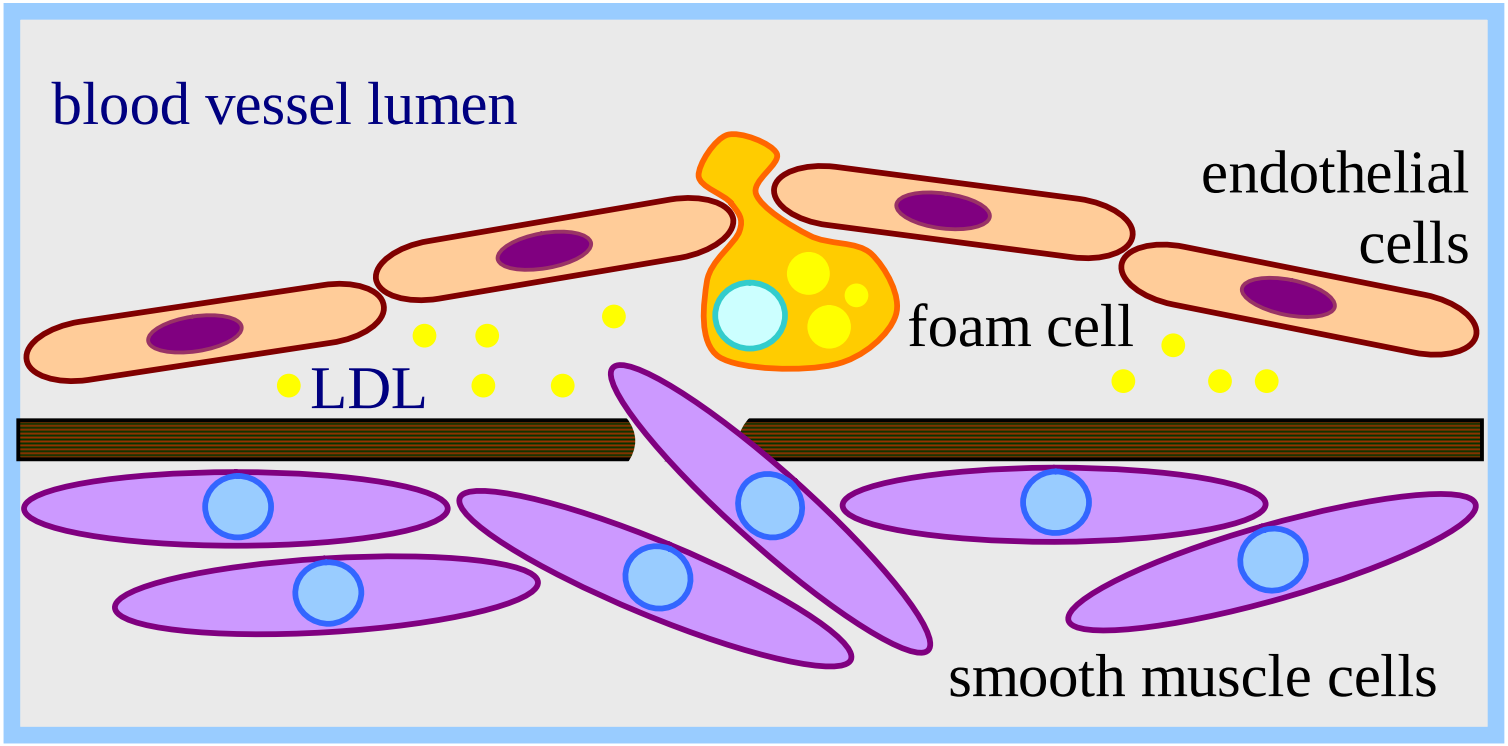


Lipid deposits



Macrophages have on their surface **scavenger receptors** that cause them to **take up oxidized lipoproteins** becoming "**foam cells**" that have many cytoplasmic lipid droplets.

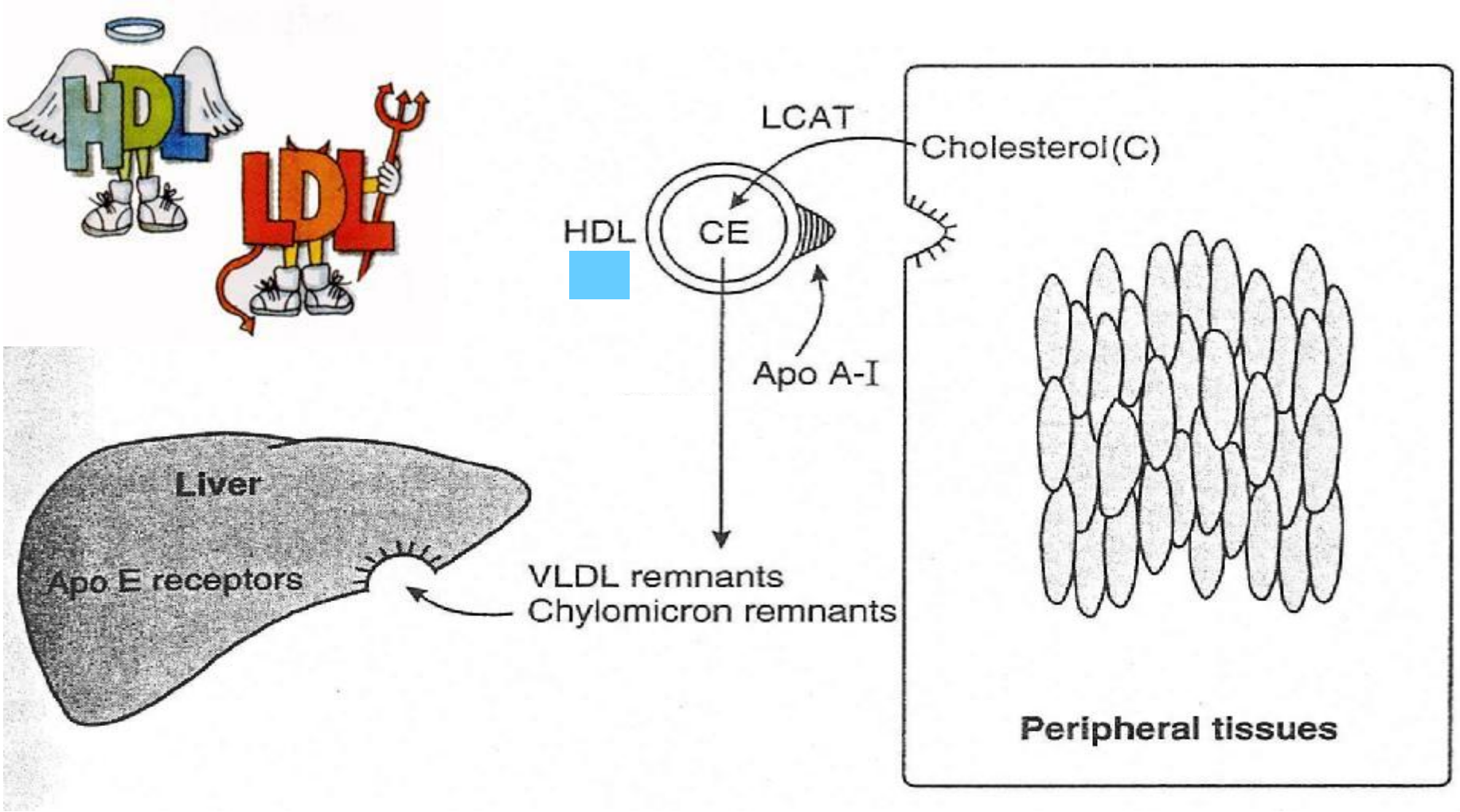
Although in humans **foam cells** mainly develop from macrophages, **smooth muscle cells** may also migrate into the subendothelial space & become foam



Foam cells aggregate within the developing arterial plaque.

Within the **plaque core** foam cells eventually undergo **necrotic death**, releasing harmful cellular contents that can promote plaque **rupture** & development of **blood clots**.

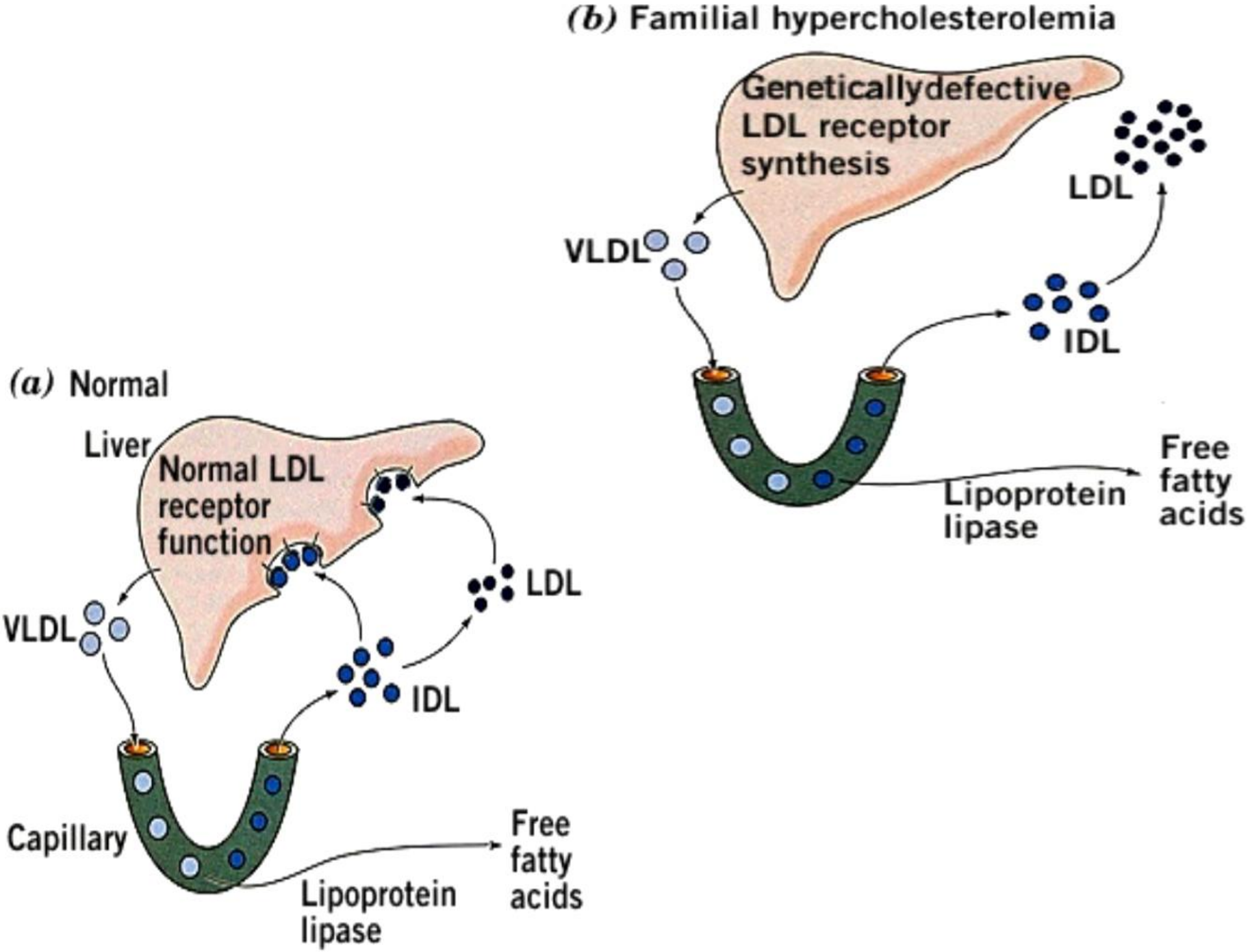
Reverse cholesterol transport

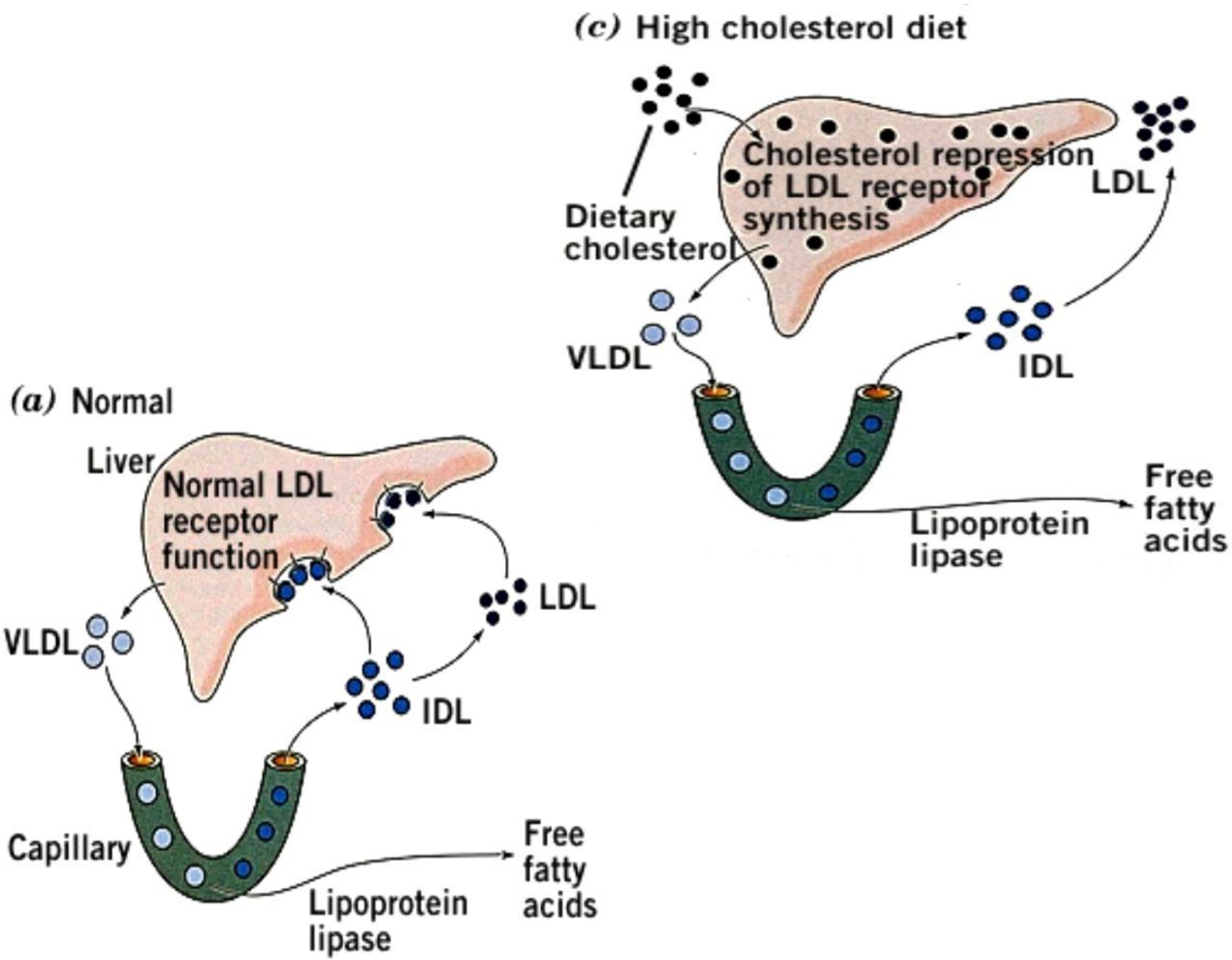


Objective 15

- **Identify the lifestyle factors that influence plasma cholesterol concentrations and thus affect the risk of coronary heart disease:**

- **Give examples of inherited and noninherited conditions affecting lipoprotein metabolism that cause hypo- or hyperlipoproteinemia.**


(b) Familial hypercholesterolemia
Genetically defective LDL receptor synthesis
LDL
VLDL
IDL
Lipoprotein lipase
Free fatty acids
(a) Normal
Liver
Normal LDL receptor function
LDL
VLDL
IDL
Capillary
Free fatty acids
Lipoprotein lipase


(c) High cholesterol diet
Cholesterol repression of LDL receptor synthesis
Dietary cholesterol
LDL
VLDL
IDL
Lipoprotein lipase
Free fatty acids
(a) Normal
Liver
Normal LDL receptor function
LDL
VLDL
IDL
Capillary
Lipoprotein lipase
Free fatty acids