

CHOLESTEROL & LIPOPROTEIN

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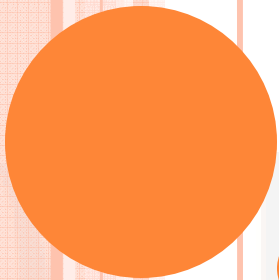
INTRODUCTION

- The word cholesterol is derived from Greek words, **chole =bile, steros =solid, ol=alcohol.**
- It is widely distributed in the body.
- It is soluble in chloroform and other fat solvents.
- It is the most important animal steroid from which other steroid compounds are formed.

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A. Sterols

- Major sterol in animal tissues.
- Plant sterols, such as β -sitosterol are poorly absorbed by humans.
- It block the absorption of dietary cholesterol.
- Useful dietary treatment of hypercholesteremia.
-



FUNCTIONS OF CHOLESTEROL

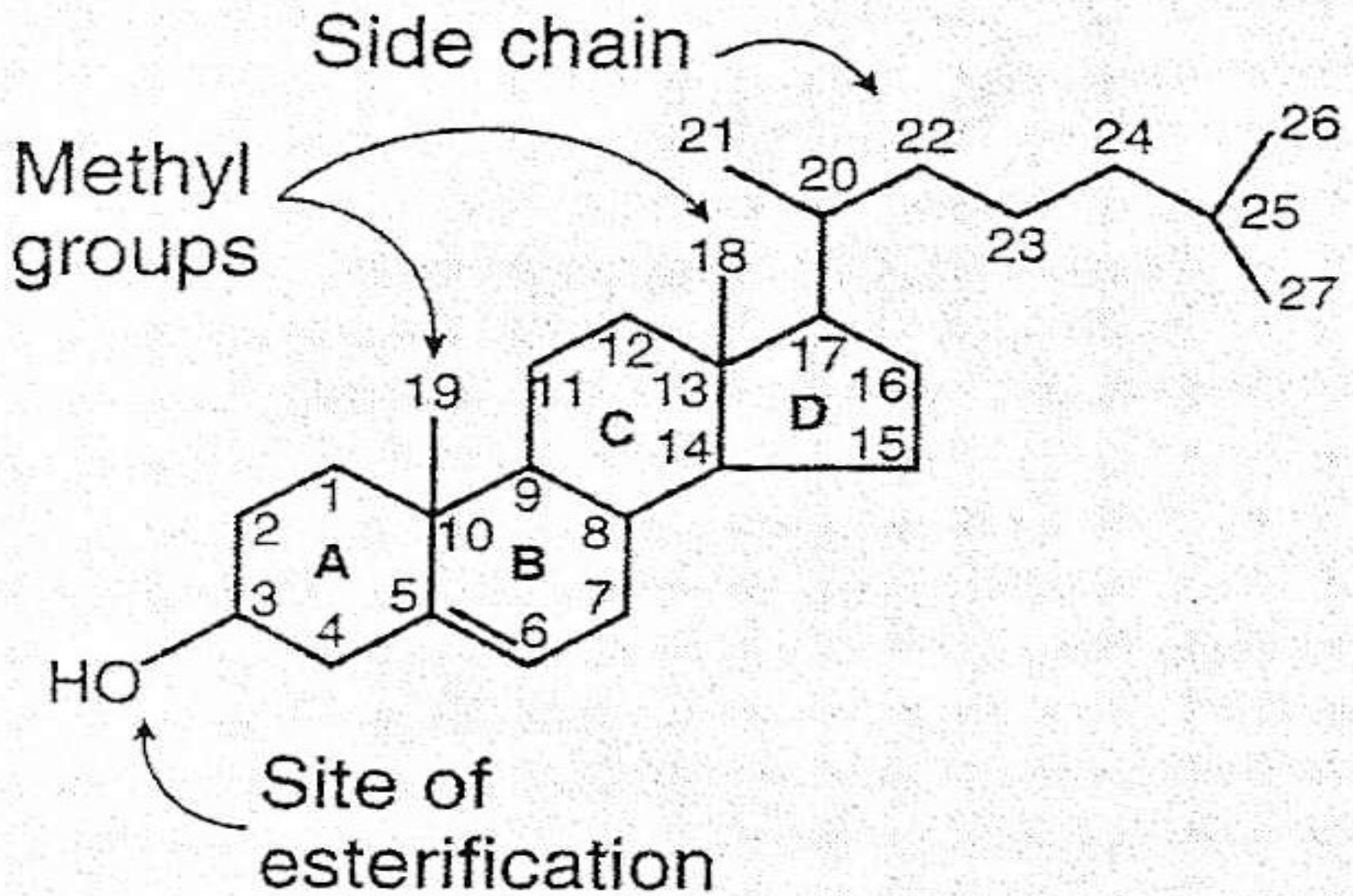
1. **Cell membranes**: it is a component of cell membranes and has a modulating effect on the fluid state of the membrane.
2. **Nerve conduction**: it is a poor conductor of electricity, and helps to insulate nerve fibers.
3. **Bile acids and bile salts**:
4. **Steroid hormones**: 21C glucocorticoids, 19C androgens and 18C estrogens are synthesized from cholesterol.
5. **Vitamin D3**: it is synthesized from 7-dehydrocholesterol.
6. **Esterification**: the OH group in the 3rd position can get esterified to fatty acids to form cholesterol esters.
 1. This esterification occurs in the body by transfer of a PUFA moiety by lecithin cholesterol acyl transferase.
 2. This has important role in regulation of cholesterol level in body fluids.

CLINICAL SIGNIFICANCE

HEART DISEASE

- The level of cholesterol in blood is related to the development of atherosclerosis.
- Abnormality of cholesterol metabolism may lead to cerebrovascular accidents and coronary artery disease.

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Cholesterol

STRUCTURE OF CHOLESTEROL

- Cyclopenteno perhydro phenanthrene ring system.
- 3 cyclohexane rings & one Cyclopentane ring.
- Total 27 carbon atoms.
- One OH group at third position which is characteristic of all sterols.
- The OH group is beta-oriented projecting above the plane of ring.
- Double bond between 5-6 C.
- 8 Carbon side chain, attached to 17th C.

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ABSORPTION OF CHOLESTEROL

- Absorption needs miceller formation.
- Inside the mucosal cell, cholesterol is re-esterified and incorporated into chylomicrons.
- The chylomicrons reach the blood stream through lymphatics.
- This dietary cholesterol reaches the liver through chylomicrons remnants.
- Plant sterols (sitosterol) decrease absorption of cholesterol.

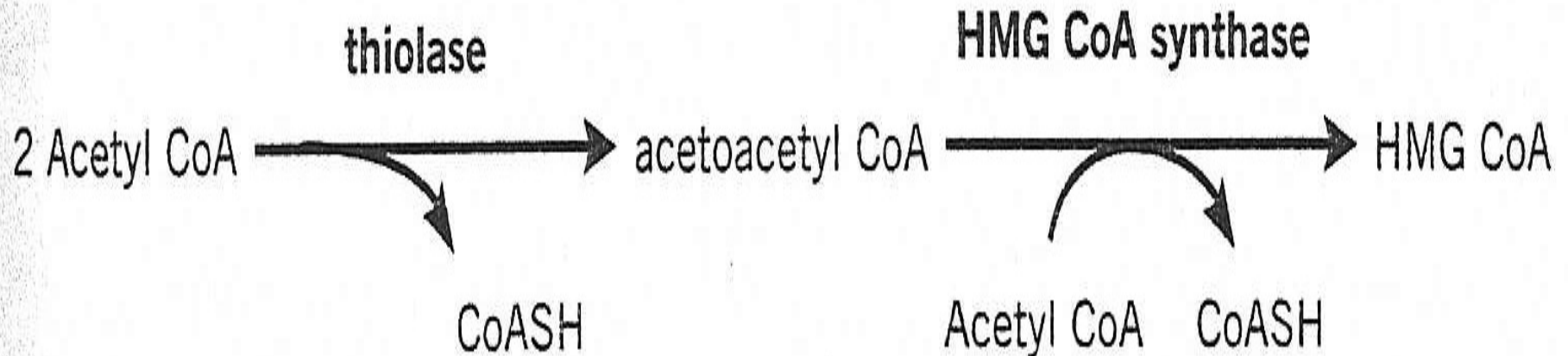
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BIOSYNTHESIS OF CHOLESTEROL

- Cholesterol is synthesised from Acetyl CoA.
- Partly cytoplasmic & Partly in endoplasmic reticulum.
- Primary site: liver (~1g/d)
- Secondary sites: adrenal cortex, ovaries, testes
- All nucleated cells can synthesize cholesterol, including arterial walls.

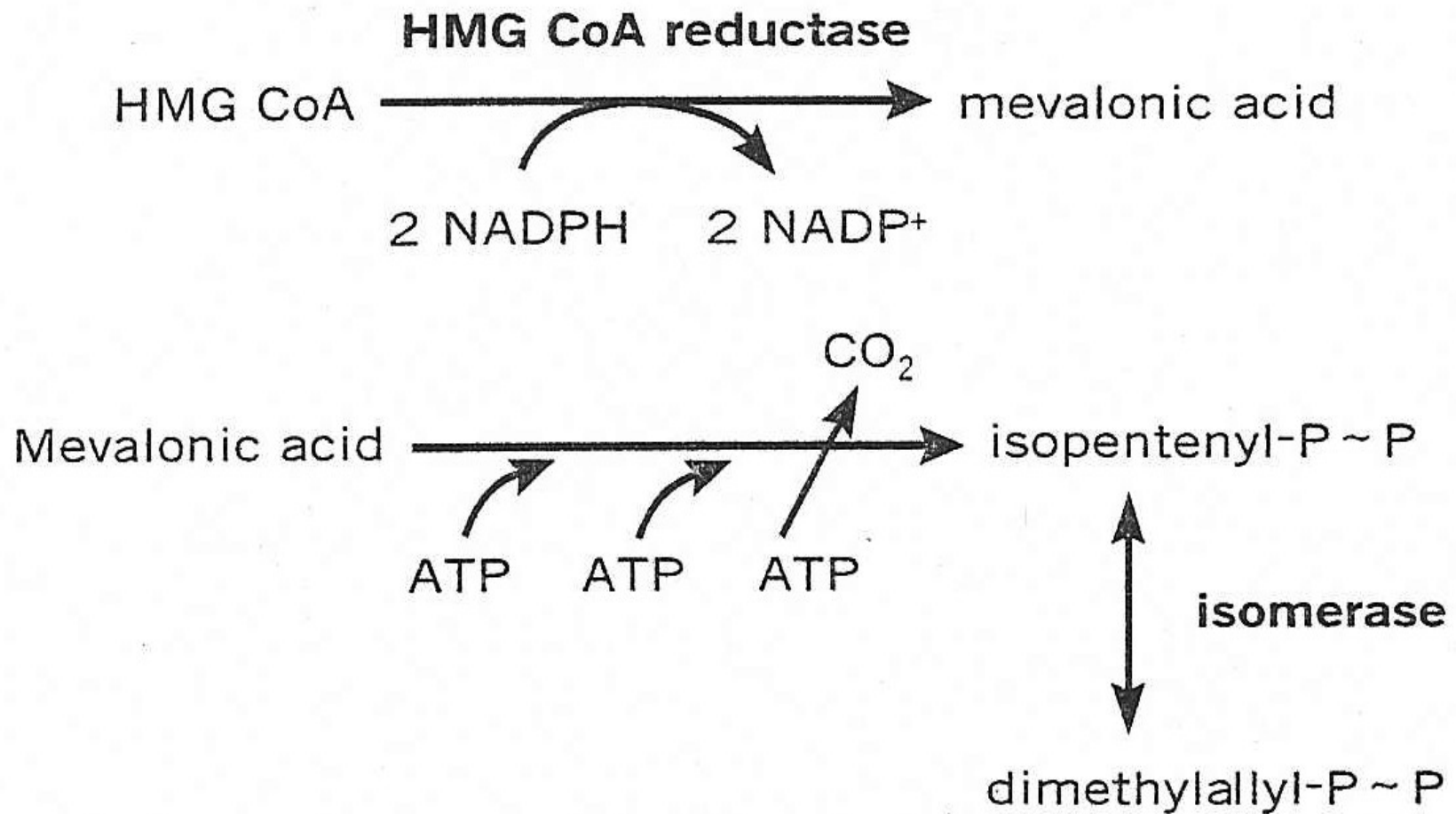
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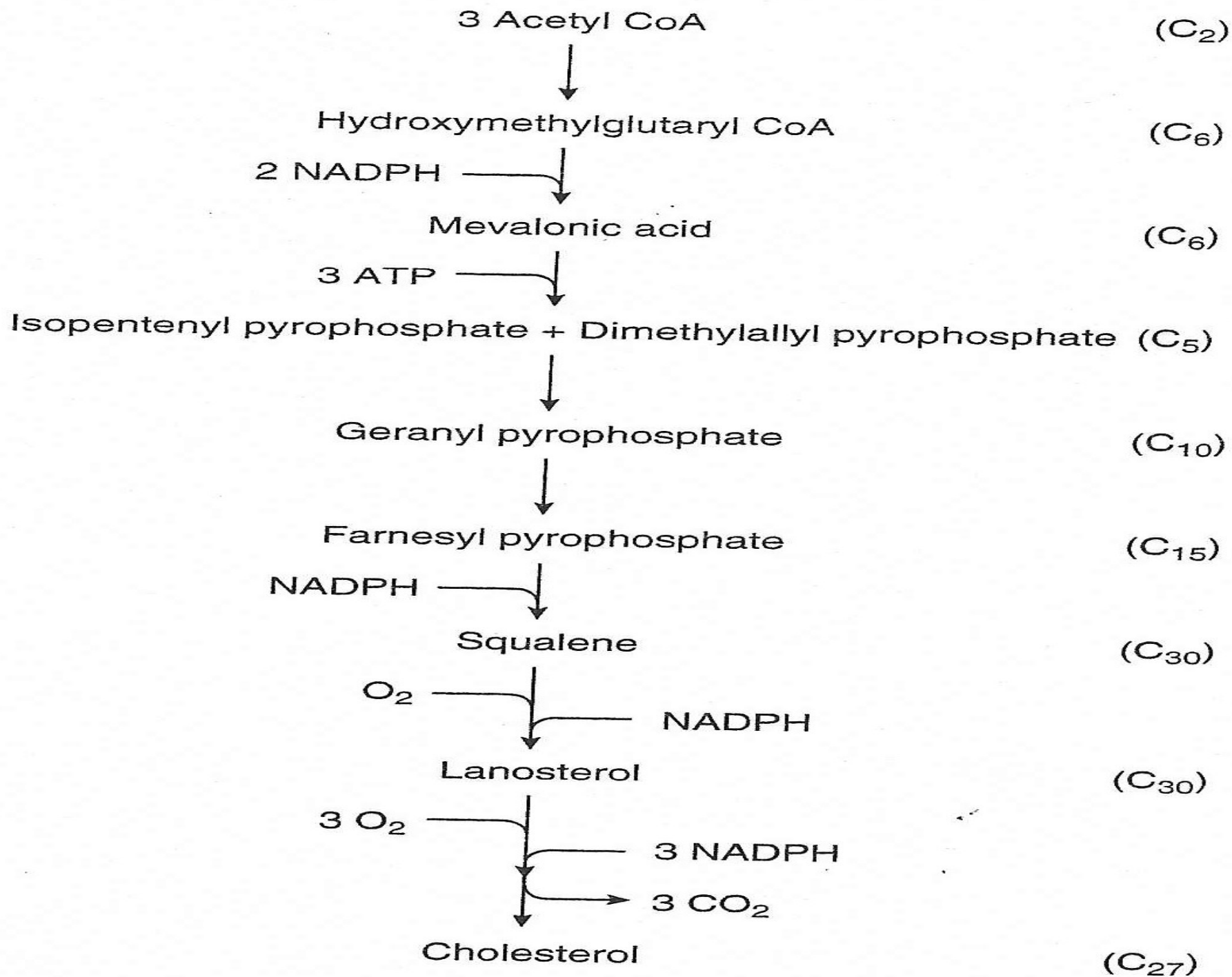
SYNTHESIS OF CHOLESTEROL



- **HMG CoA (3-hydroxy-3-methylglutaryl-CoA)** is present in both cytosol as well as mitochondria of liver.
- Mitochondrial pool = for ketone body synthesis
- Cytosolic pool = for cholesterol synthesis.

CONVERSION OF HMG COA TO ACTIVATED ISOPRENOIDS





Step -1 Condensation

- The acetyl CoA is provided by the ATP-citrate lyase reaction as in the case of fatty acid synthesis.
- Two molecules of acetyl CoA condense to form acetoacetyl CoA catalyzed by cytoplasmic acetoacetyl CoA synthase.

Step-2 Production of HMG CoA

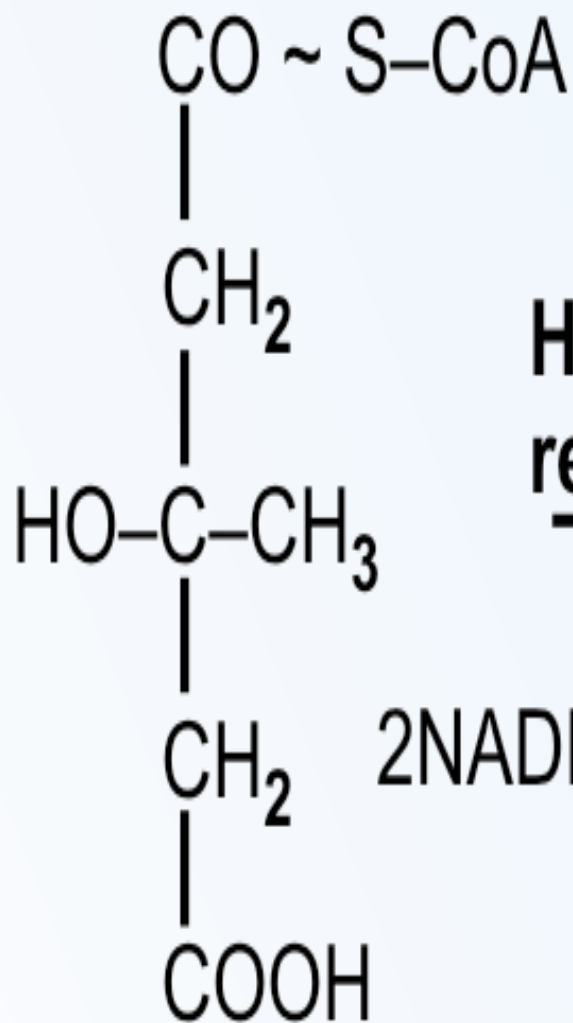
- A third molecule of acetyl CoA condenses with acetoacetyl CoA to form beta hydroxy beta methyl gluteryl CoA (HMG CoA).
- The enzyme is HMG CoA synthase.
- HMG CoA is present in both cytosol as well as mitochondria of liver.
- The mitochondrial pool is used for ketogenesis whereas the cytosolic fraction is utilized for cholesterol synthesis.

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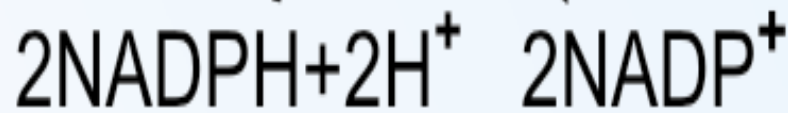
Step -3 The committed step

- The reduction of HMG CoA to **mevalonate** is catalyzed by HMG CoA reductase .
- It is a microsomal (endoplasmic reticulum) enzyme.
- It uses 2 molecules of NADPH.
- First 2 steps are same as ketogenesis but step 3 is the first reaction that is unique to the cholesterol biosynthetic pathway.
- It is the rate limiting step.

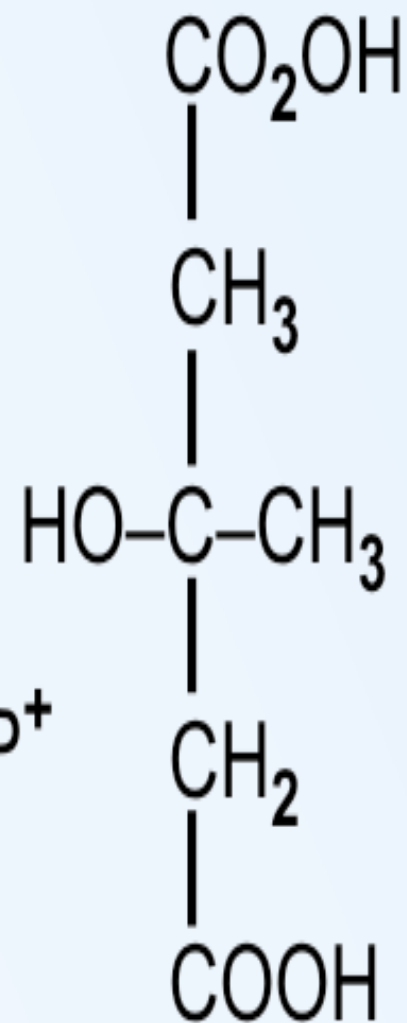
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**HMG CoA
reductase**



CoA



HMG CoA

Mevalonate

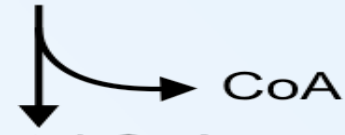
Step -4 Production of 5C unit

- Mevalonate is successively phosphorylated to phospho-mevalonate, to pyrophospho -mevalonate, then to 3-phospho 5-pyrophosphomevalonate.
- This then undergoes decarboxylation to give **isopentenyl pyrophosphate**, a **5 C** unit.
- Step -4 requires 3 molecules of ATP (step 4A, 4B , 4C and 4D).
- One molecule of CO₂ is eliminated .
- Steps 1, 2, 3, 4 together may be considered as the first phase of the cholesterol synthesis.

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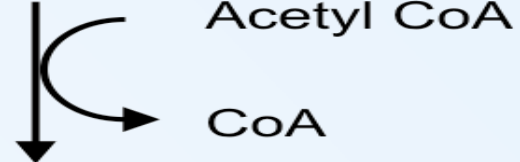
Acetyl CoA + Acetyl CoA

Step 1
Acetoacetyl CoA synthase



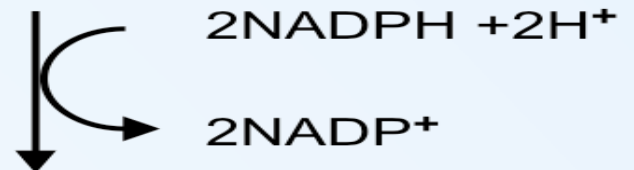
Acetoacetyl CoA

Step 2
HMG CoA synthase



Beta hydroxy beta methyl glutaryl CoA (HMG CoA)

Step 3; rate limiting
HMG CoA reductase



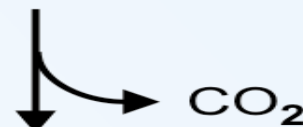
Mevalonate (6 Carbons)

Step 4-A

+ 3 ATP

3-phospho 5-pyrophospho mevalonate (6C)

Step 4-B; Decarboxylase



Isopentenyl pyrophosphate (10 C)

Step 5-A

+ Dimethyl allyl pyrophosphate

Geranyl pyrophosphate (10 C)

Step 5-B Transferase

+ Isopentenyl pyrophosphate

Farnesyl pyrophosphate (15 C)

Farnesyl pyrophosphate (15 C)

Step 5-C;
Squalene synthase

+ Farnesyl pyrophosphate

Squalene (30 C)

Step 6; Cyclase

Lanosterol (30 C)

Step 7-A

Zymosterol (27C)

Step 7-B

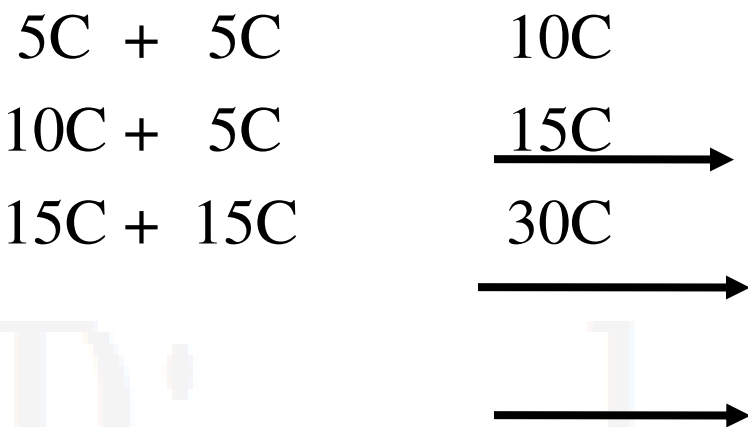
Desmosterol

Step 7-C

Cholesterol (27 C)

Step-5 Condensation of 5C units

- 6 numbers of 5C units are condensed to form a 30C compound, **Squalene**.
- In summary,



Step-6 Cyclisation

- Squalene now undergoes oxidation by epoxidase, using molecular oxygen and NADPH to form squalene epoxide.
- A Cyclase converts it to lanosterol.
- **Lanosterol** is the first steroid compound synthesized and is a 30C sterol.

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Step-7 Cutting to size

7-A: next, the 3 additional methyl groups on carbon atoms 4 and 14 are removed to produce **Zymosterol**.

7-B: then the double bond migrates from 8-9 position to 5-6 position, when **Desmosterol** is formed.

- Desmosterol is present in fetal brain, absent in adult brain and re-appeared in gliomas (brain tumor).

7-C: finally, the double bond in the side chain (between carbon 24-25) is reduced by NADPH when **Cholesterol** is formed.

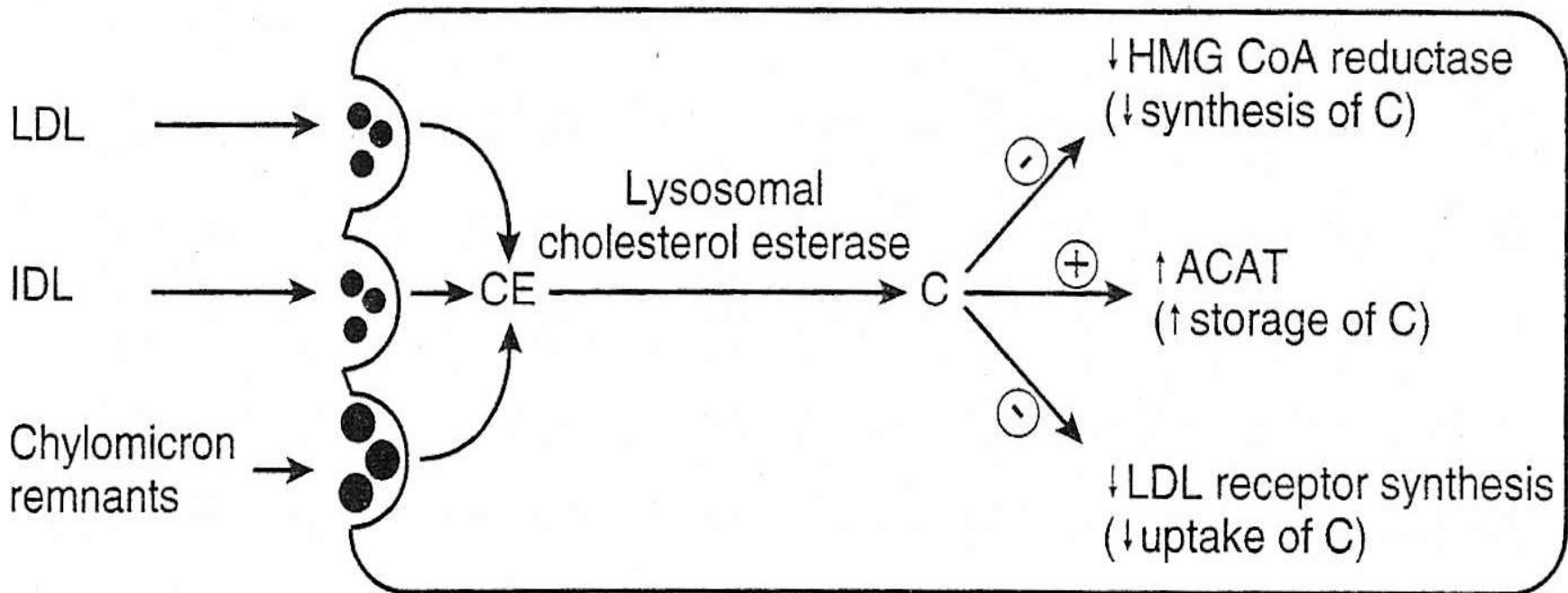
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REGULATION OF CHOLESTEROL SYNTHESIS

- Rate limiting enzyme is *HMG CoA reductase*.

1. Regulation at transcription

- Long term regulation involves regulation of transcription of the gene for HMG CoA reductase.
- When sufficient cholesterol is present in the cell , transcription of the gene for HMG CoA reductase is suppressed and cellular synthesis of cholesterol is decreased.
- When cholesterol in diet is low, synthesis is increased.



2. Covalent modification of enzyme:

- cAMP mediated phosphorylates enzyme (inactive).
- Dephosphorylated form is active.

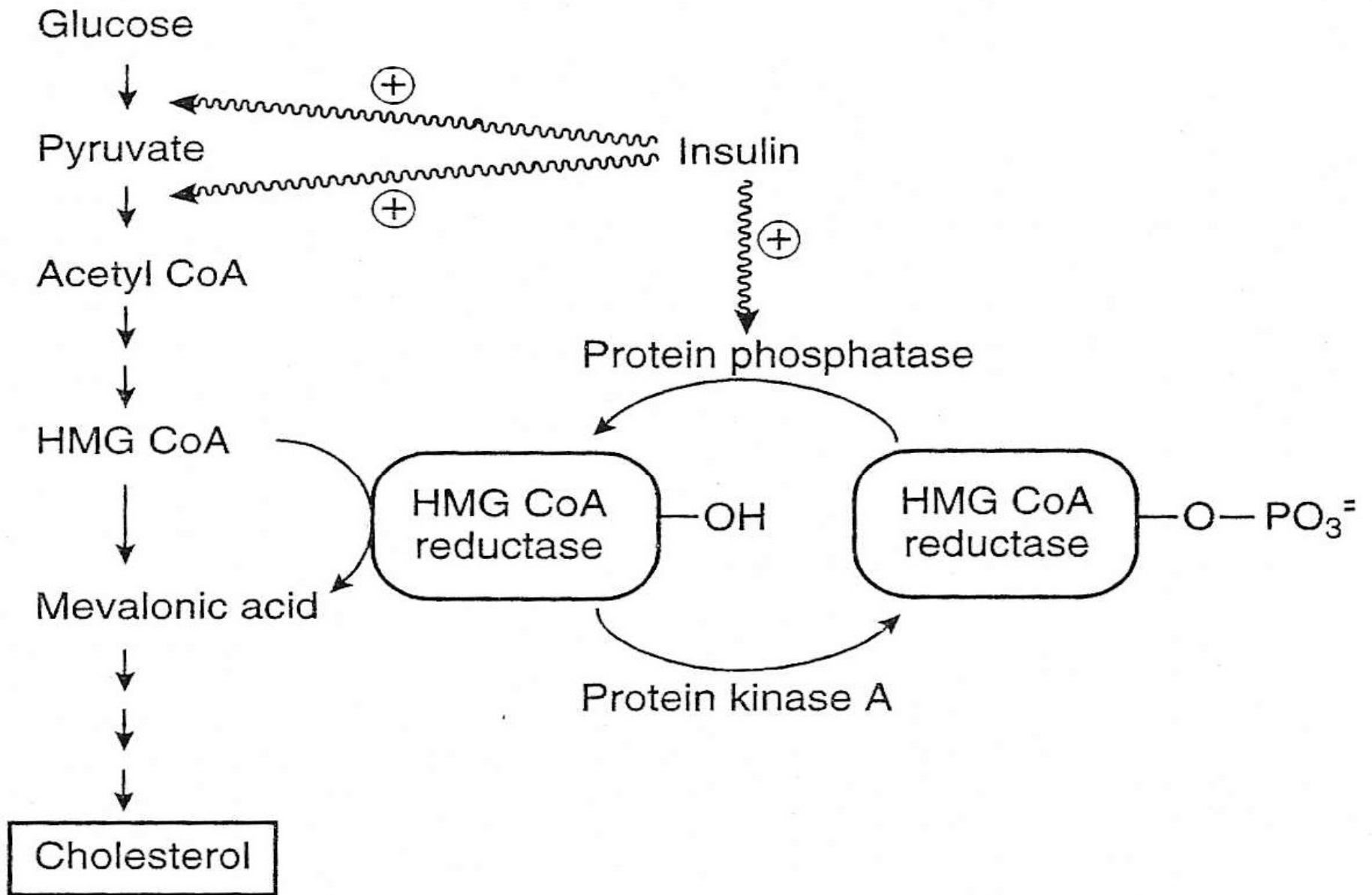
3. Insulin and thyroxine increase the activity of HMG CoA reductase.

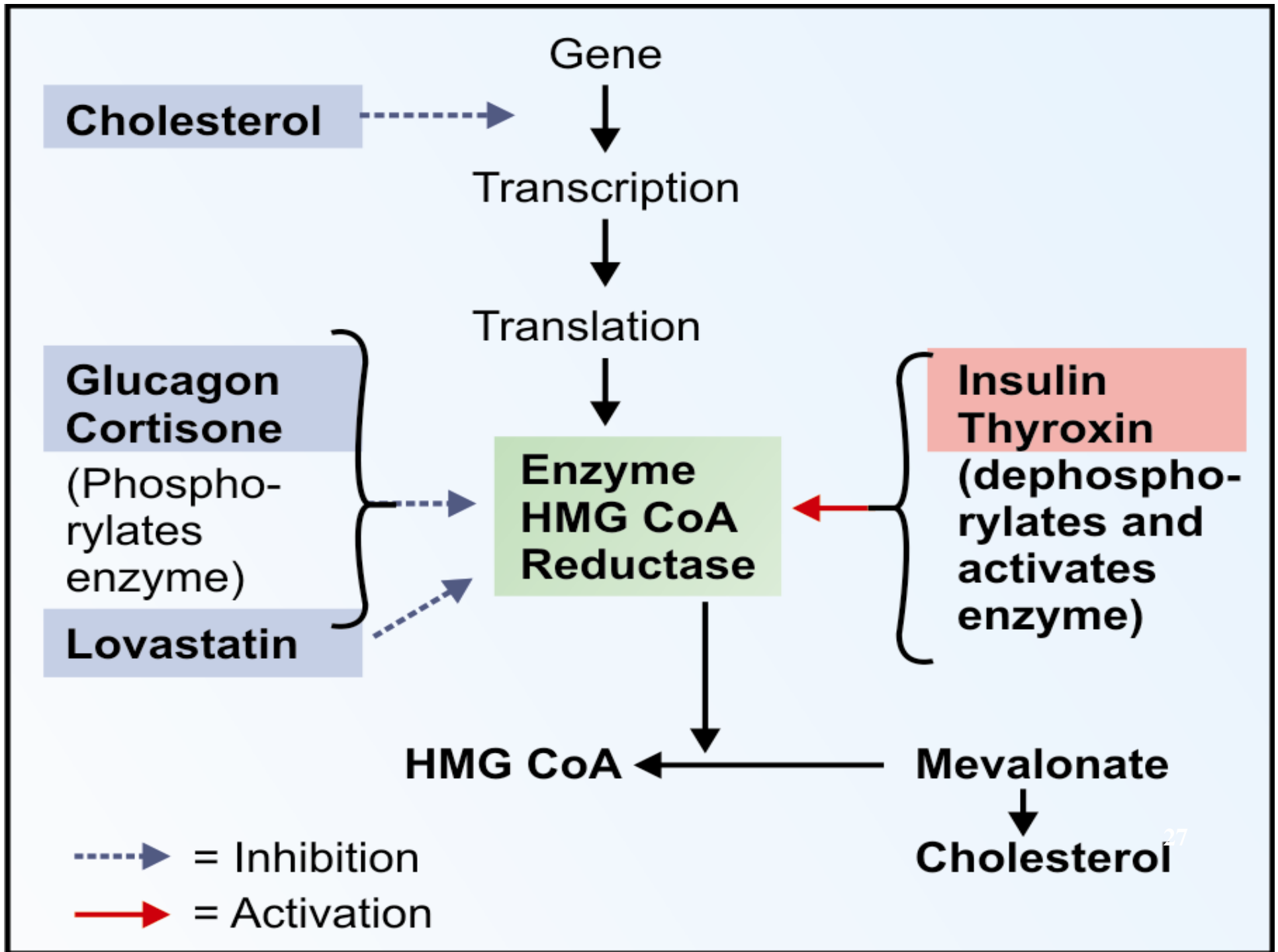
4. Cortisol and glucagon decrease its activity.

5. Drugs : ‘Statin’ group of drugs are competitive inhibitors of HMG CoA reductase.

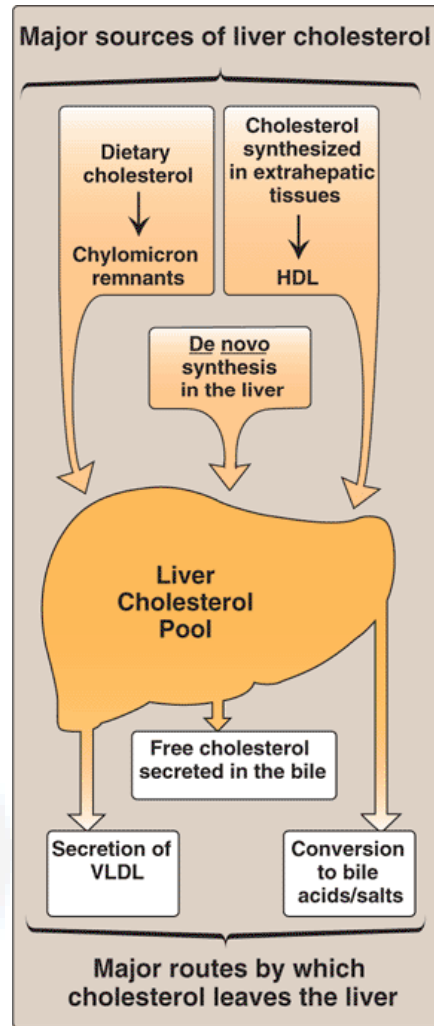
e.g. Atorvastatin. Simvastatin

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CHOLESTEROL POOL



EXCRETION OF CHOLESTEROL

- Average diet = 300 mg of cholesterol/day.
- Body synthesise = 700 mg of cholesterol/day.
- Total 1000mg
- About 500 mg of cholesterol = excreted through bile.
- This cholesterol is partly reabsorbed from intestines.
- Plant sterols = inhibit the reabsorption of cholesterol.

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FAMILIAL HYPERCHOLESTEROLEMIA

- 8 yo girl
 - Admitted for heart/liver transplant
- History
 - CHD in family
 - 2 yo xanthomas appear on legs
 - 4 yo xanthomas appear on elbows
 - 7 yo admitted w/ MI symptoms
 - [TC] = 1240 mg/dl
 - [TG] = 350 mg/dl
 - [TC]father = 355 mg/dl
 - [TC]mother = 310 mg/dl
 - 2 wks after MI had coronary bypass surgery
 - Past year severe angina & second bypass
 - Despite low-fat diet, cholestyramine, & lovastatin, [TC] = 1000 mg/dl

XANTHOMAS

- Raised, waxy appearing, often yellow skin lesions (shown here on knee)
 - Associated with hyperlipidemia
- Tendon xanthomas common on Achilles and hand extensor tendons



XANTHOMAS

RAISED LESIONS RELATED TO HYPERLIPIDEMIA

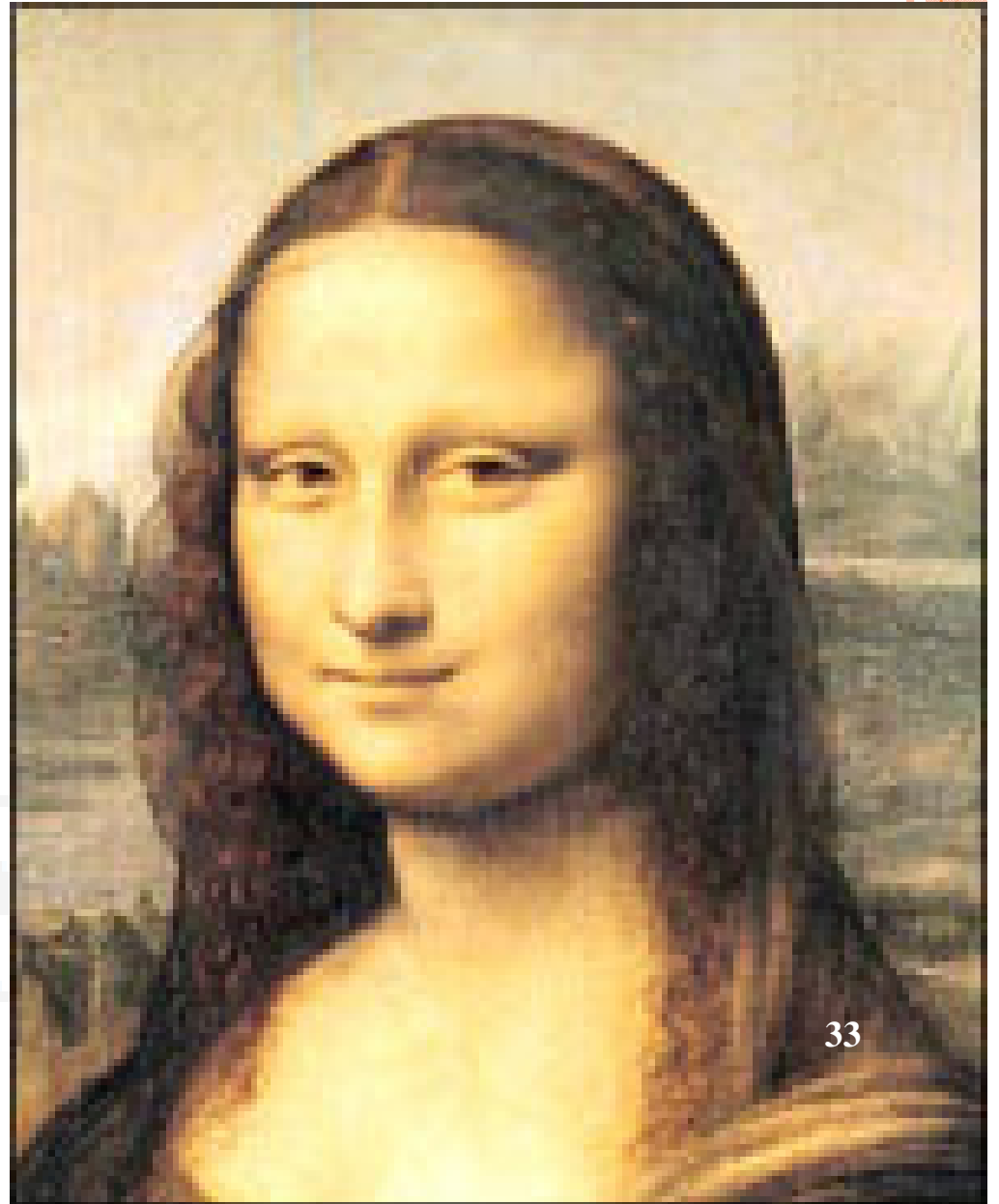


Eruptive Xanthomas
-generally associated with
hypertriglyceridemia



Xanthomas of the eyelid
-generally associated with
hypercholesterolemia

DID DA VINCI'S
MONA LISA
HAVE HYPER-
CHOLESTEROL
EMIA?



PLASMA LIPIDS

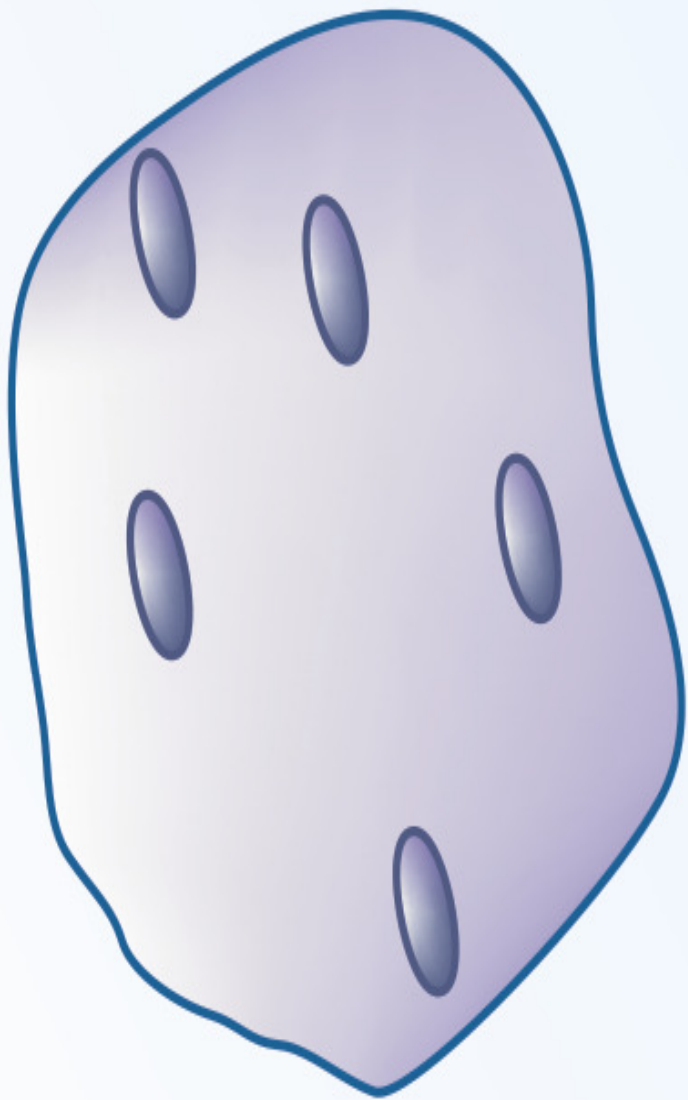
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PLASMA LIPIDS

- Total plasma lipid is 400-600 mg/dl.
- One-third is cholesterol; one-third is TGs and one-third is phospholipid.
- Since lipids are insoluble in water, they need the help of carriers in plasma.
- Therefore they are complexed with proteins to form **lipoproteins (Lp)**.
- The protein part of lipoprotein is called **apolipoprotein**.

CLASSIFICATION OF LIPOPROTEINS

- Depending on the density (by ultracentrifugation) or on the electrophoretic mobility, the lipoproteins in plasma are classified into five major types:
 1. Chylomicrons
 2. VLDL or pre beta lipoproteins
 3. IDL or broad beta lipoproteins
 4. LDL or beta lipoproteins
 5. HDL or alpha lipoproteins
- 6. Free fatty acids (FFA) or non-esterified fatty acids (NEFA) are complexed with albumin, not generally considered as lipoproteins.



Chylomicron



VLDL



IDL



LDL



HDL

- Outer Part made up of
 - Polar part of proteins
 - Polar heads of phospholipids
 - Cholesterol.
- This inner core consists
 - Hydrophobic TAGs
 - Tails of phospholipids.
- The apoproteins increase the solubility of lipids.

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Separation by ultracentrifugation

- The lipoproteins are characterized on the basis of their density.
- Fat is less dense than water; so fat floats on water.
- Lipoproteins with high lipid content will have a low density and so floats on centrifugation.
- Lipoproteins with high protein content will sediment easily and have a high density.

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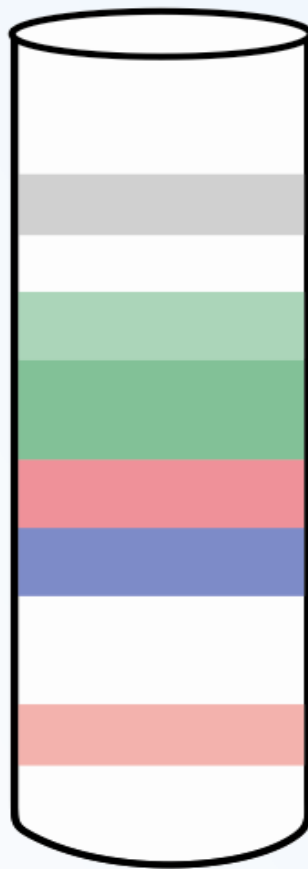
Separation by Electrophoresis:

- The serum is applied on cellulose acetate, electric current is applied for 2 hours, the strip is dried and stained with lipid dyes such as **Oil red O**.
- As a general rule,
 - Higher protein content will move faster towards the anode
 - Less proteins have minimum mobility.

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ULTRACENTRIFUGATION

LIPOPROTEINS
(density g/L)



Chylomicron

VLDL

IDL

LDL

HDL

FFA

ELECTROPHORESIS

LIPOPROTEINS
(mobility)



Chylomicron
(origin)

VLDL(beta)

IDL(broad β)

LDL(broad β)

HDL(alpha)

FFA=albumin

Positive

VLDL = very low density lipoproteins; IDL= intermediate density lipoproteins; LDL = low density lipoproteins; HDL= high density lipoproteins; FFA = free fatty acid

APO-LIPOPROTEINS

1. **Apo-A:**

- HDL
- Activates Lecithin Cholesterol Acyl Transferase (LCAT);
- ligand for HDL receptors; anti- atherogenic.

2. **Apo-B-100:**

- only apoprotein in LDL
- binds to LDL receptor on tissues.

3. **Apo-B-48:**

- Chylomicrons
- Apo-B-100 and Apo-B-48 are the products of the same gene

4. **Apo-C-II:**

- activates lipoprotein lipase. chylomicrons, LDL and VLDL;

5. **Apo-E:**

- Arginine rich protein, present in chylomicrons, LDL and VLDL.

TABLE 21-3 Apolipoproteins of the Human Plasma Lipoproteins

<i>Apolipoprotein</i>	<i>Molecular weight</i>	<i>Lipoprotein association</i>	<i>Function (if known)</i>
ApoA-I	28,331	HDL	Activates LCAT; interacts with ABC transporter
ApoA-II	17,380	HDL	
ApoA-IV	44,000	Chylomicrons, HDL	
ApoB-48	240,000	Chylomicrons	
ApoB-100	513,000	VLDL, LDL	Binds to LDL receptor
ApoC-I	7,000	VLDL, HDL	
ApoC-II	8,837	Chylomicrons, VLDL, HDL	Activates lipoprotein lipase
ApoC-III	8,751	Chylomicrons, VLDL, HDL	Inhibits lipoprotein lipase
ApoD	32,500	HDL	
ApoE	34,145	Chylomicrons, VLDL, HDL	Triggers clearance of VLDL and chylomicron remnants

1. CHYLOMICRONS

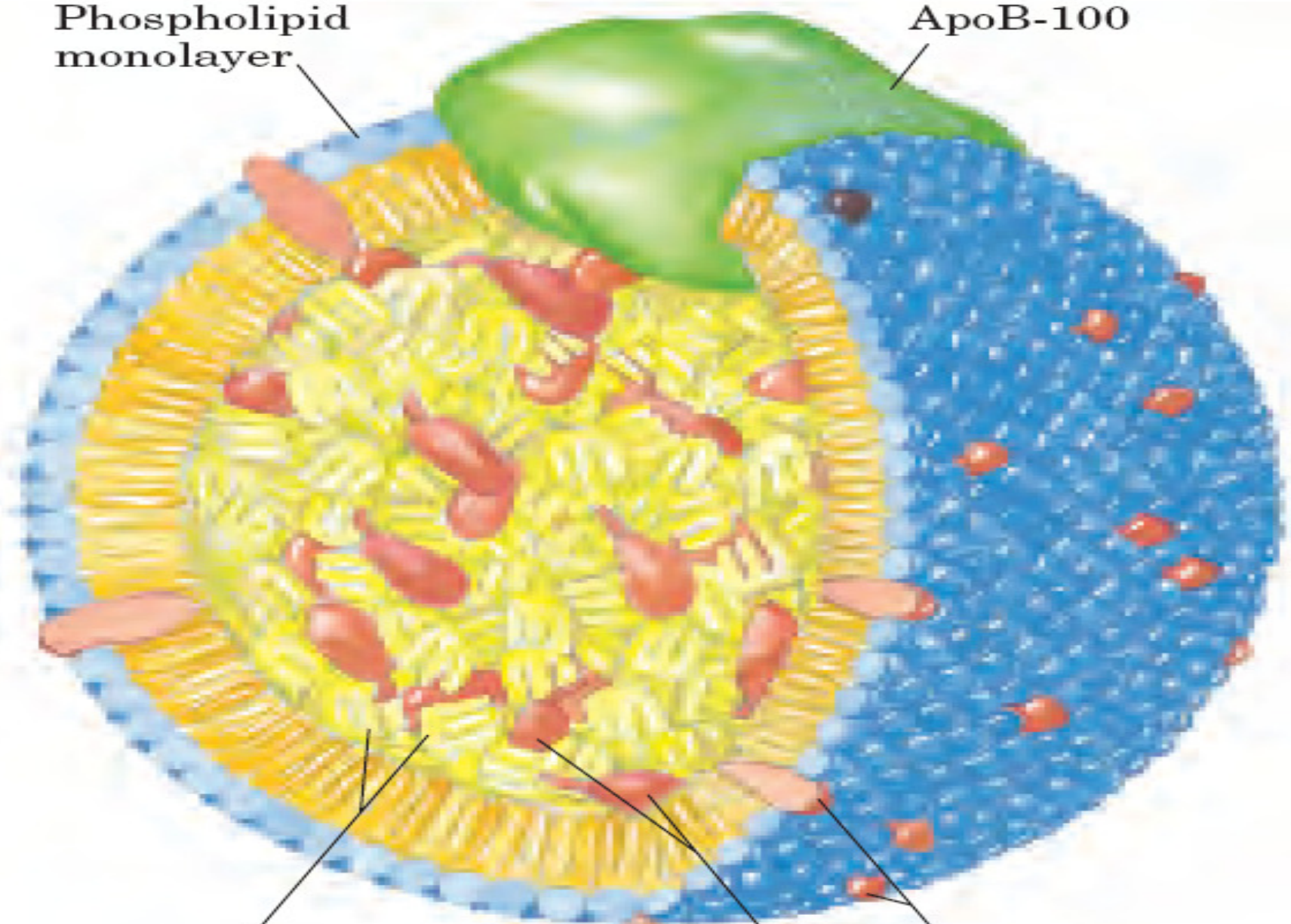
Synthesis :

- Formed in the intestinal mucosal cells
- Secreted into the lymphatic system.
- They are **rich in TGs**.
- If the lipemic serum is kept overnight in the refrigerator, chylomicrons rise as a creamy layer to the top.
- They contain only Apo-B-48 and Apo-A
- But Apo-C and Apo-E are added from HDL in blood during transport.

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Phospholipid monolayer

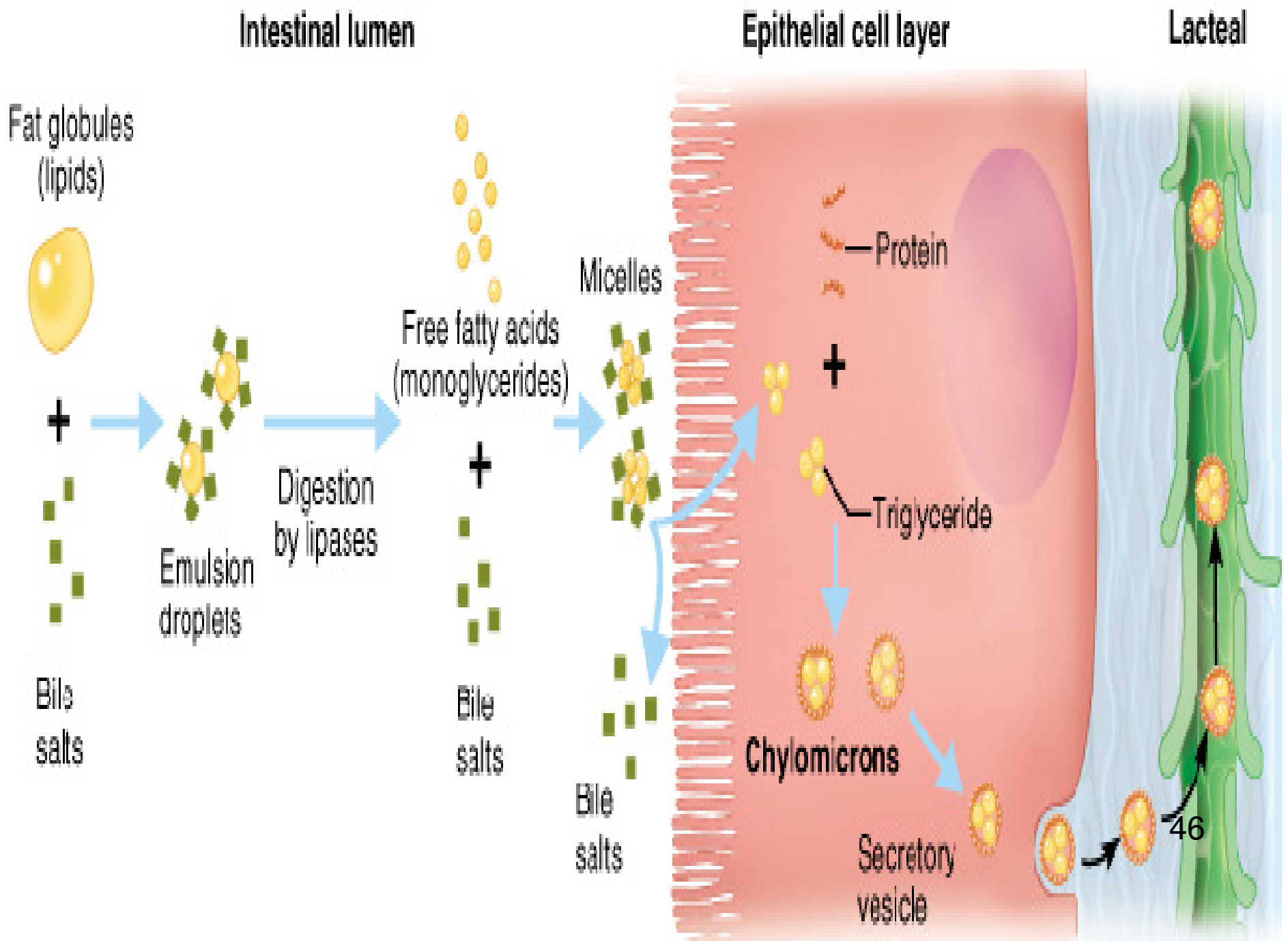
ApoB-100



Triacylglycerols

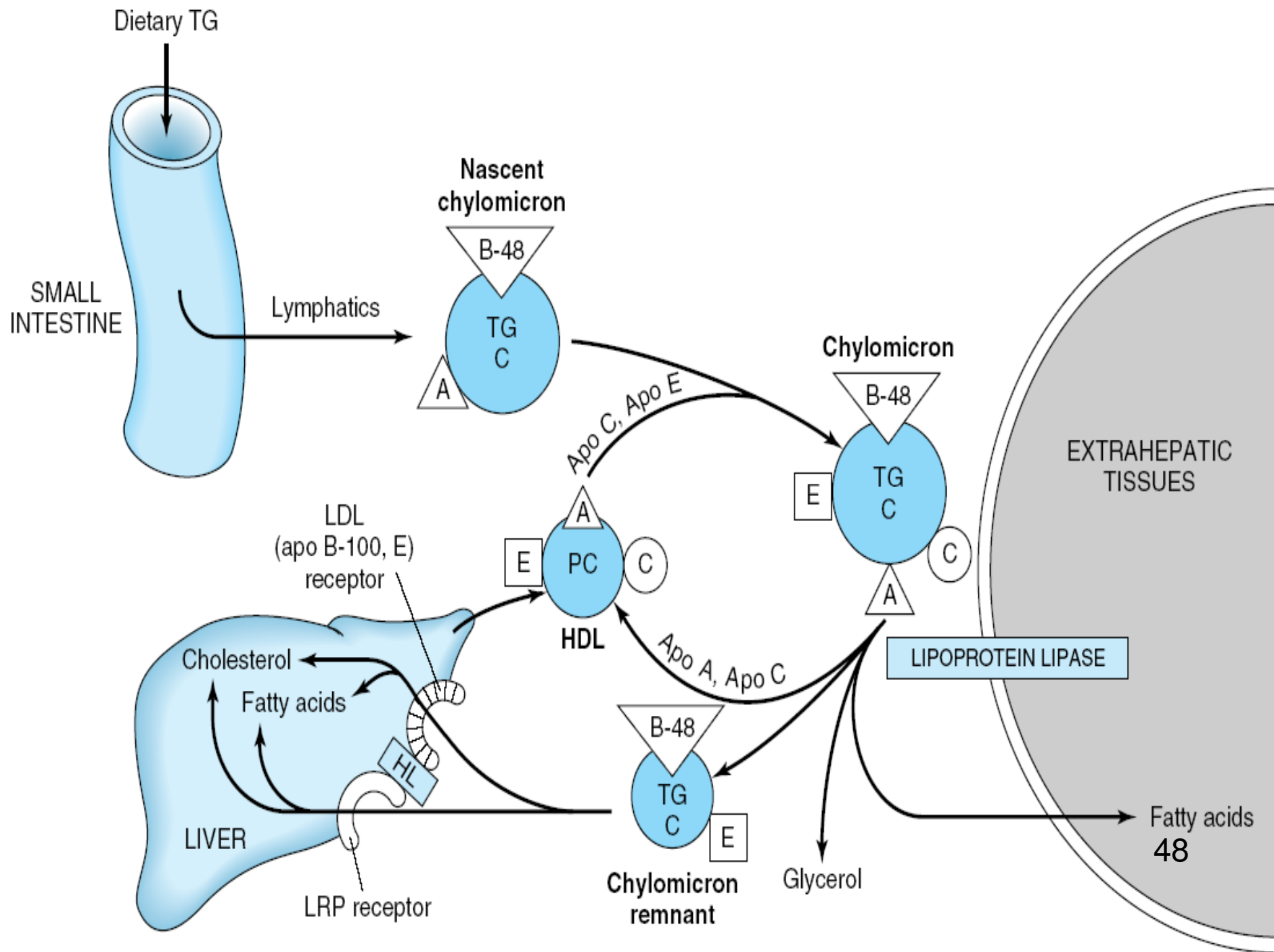
Free (unesterified) cholesterol

Cholesteryl esters



Metabolism:

- Sites: adipose tissue and skeletal muscle
- Half life of CMs in blood is about 1 hour.
- The enzyme lipoprotein lipase (**LpL**) is located at the endothelial layer of capillaries of adipose tissue, muscles and heart; but **not in liver**.
- Apo-C-II present in the CMs activates the LpL. The LpL hydrolyzes TGs and glycerol.
- Muscle or adipose tissue cells take up the liberated fatty acids.
- Following injection of heparin, the LpL is released from the tissues and lipemia is cleared. This is called post-heparin lipolytic activity.
- Lack of C-II leads to decreased LpL activity and consequent accumulation of chylomicrons and VLDL in blood.
- Insulin increases LpL activity.



Liver takes up chylomicrons remnants:

- As the TAG content is progressively decreased, the chylomicrons shrink in size. These remnants containing apo-B-48 and apo-E are taken up by hepatic cells by receptor mediated endocytosis.
- Apo-E binds the hepatic receptors.

Function:

- Transport form of dietary TGs from intestines to the adipose tissue for storage ; and to muscle or heart for their energy needs.

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2. VERY LOW DENSITY LIPOPROTEINS

Synthesis:

- They are synthesized **in liver** from glycerol and FAs and incorporated into VLDL along with hepatic cholesterol, apo-B-100, C-II and E.
- Apo-B-100 is the major lipoprotein present in VLDL when it is secreted.

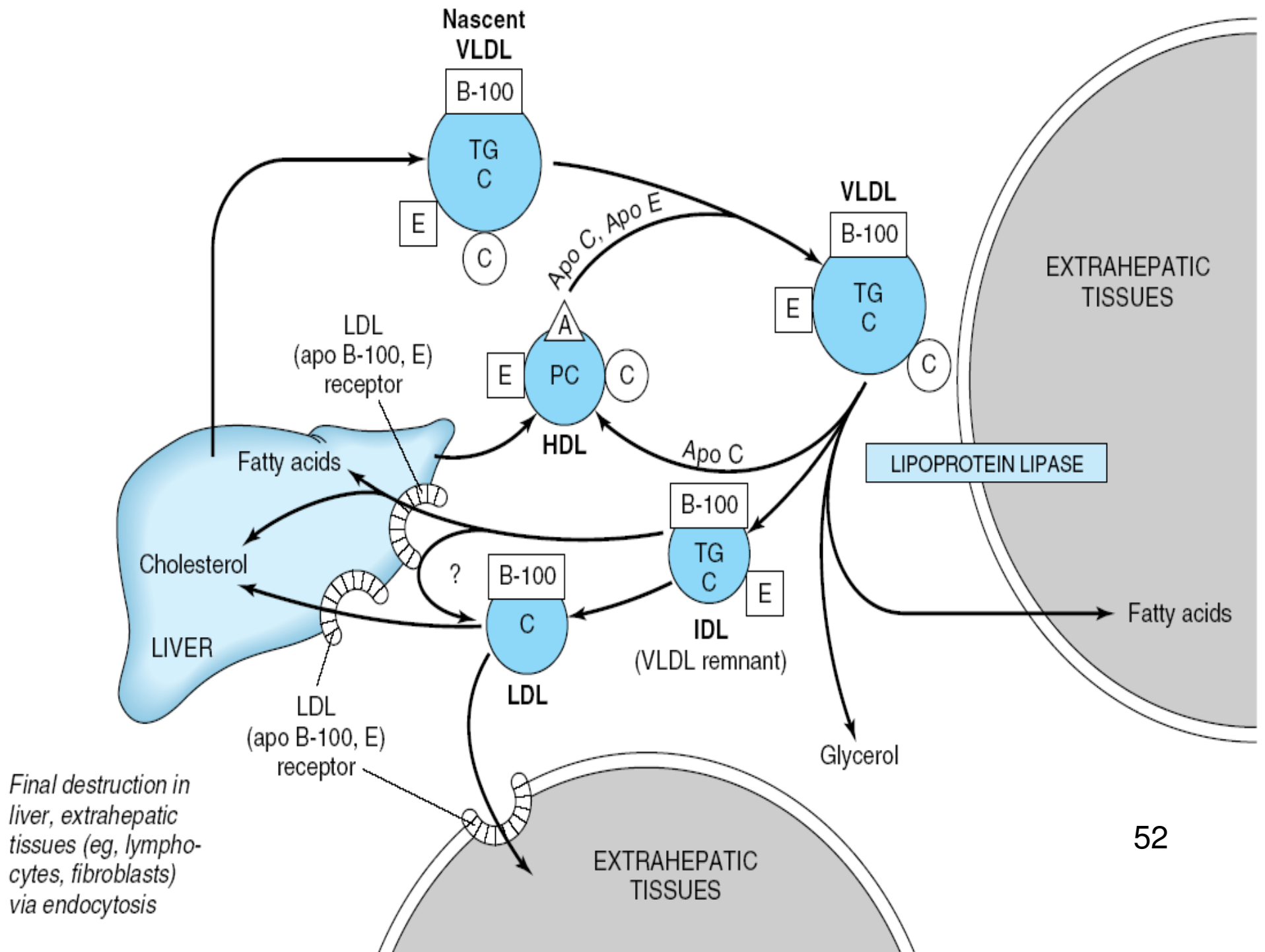
Metabolism:

- The half-life of VLDL in serum is only 1-3 hrs. when they reach the peripheral tissues, apo C-II activates LpL which liberates FAs taken by adipose tissue and muscle.

- The remnant is now designated as **IDL** and contains **less of TAG and more of cholesterol**.
- The major fraction of IDL further loses triglyceride, so as to be converted to LDL.
- This conversion of VLDL to IDL and then to LDL is referred to as lipoprotein cascade pathway.
- a fraction of IDL is taken up by the hepatic receptors.

Function:

- VLDL carries **Triglycerides** (endogenous triglycerides) **from liver to peripheral tissues** for energy needs.



3. LOW DENSITY LIPOPROTEINS

- Cholesterol rich lipoprotein molecules containing **only apo-B-100**.
- Most of the LDL particles are derived from VLDL.

Metabolism:

- LDL receptors are present on all cells but most abundant in hepatic cells.
- LDL receptors are located in specialized regions called **clathrin - coated pits**.
- When the apo-B-100 binds to the receptor, the receptor-LDL complex is internalized by endocytosis.
- These vesicles would fuse with lysosomes. The lysosomal enzymes now degrade the apoproteins of the LDL and also hydrolyze the cholesterol esters to free cholesterol.
- The free receptors can now return to the membrane surface to bind further LDL molecules.

Function:

- LDL transports **cholesterol from liver to the peripheral tissues.**
- LDL concentration in blood has positive correlation with incidence of cardiovascular diseases. About 75% of the plasma cholesterol is incorporated into the LDL particles.

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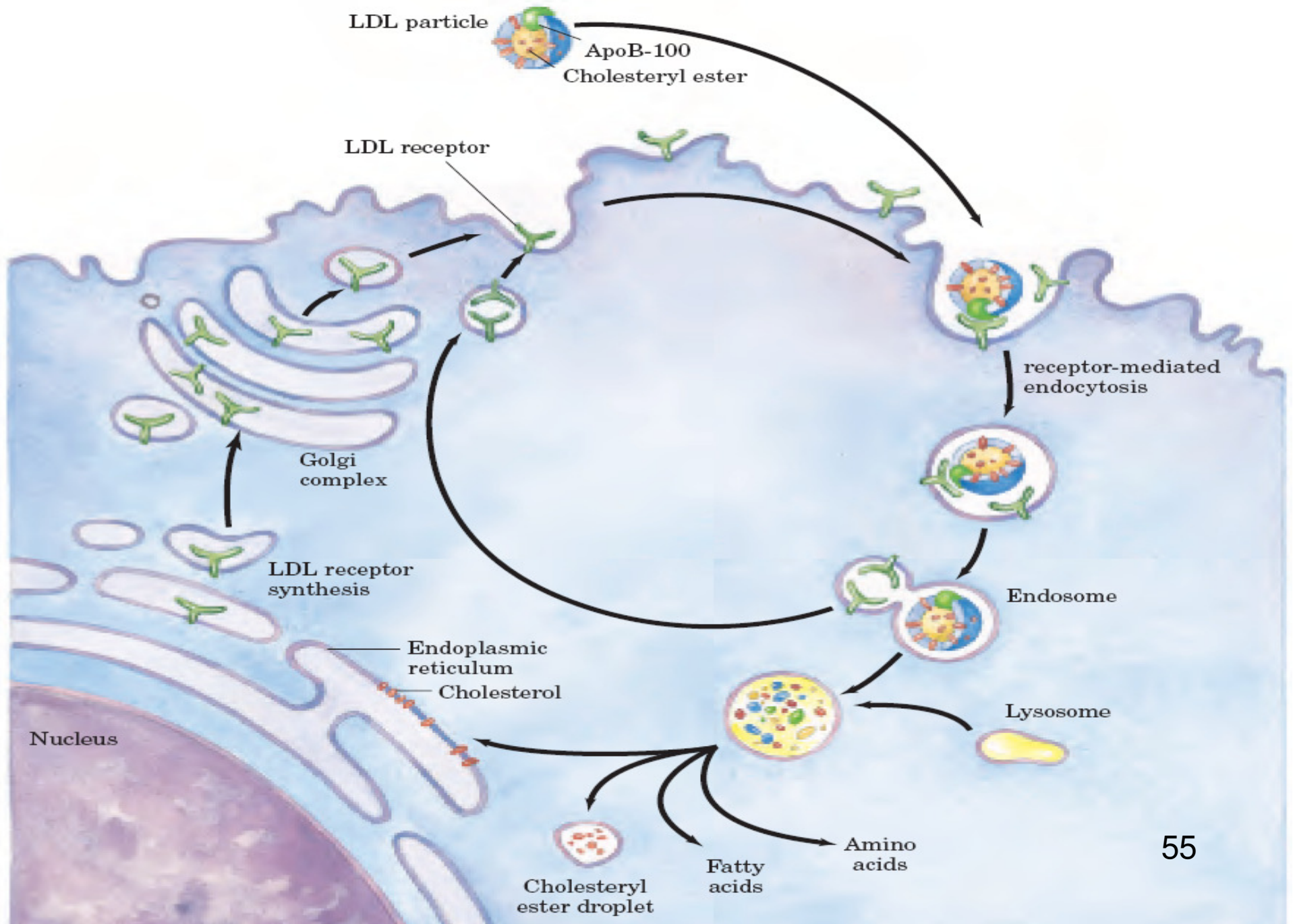
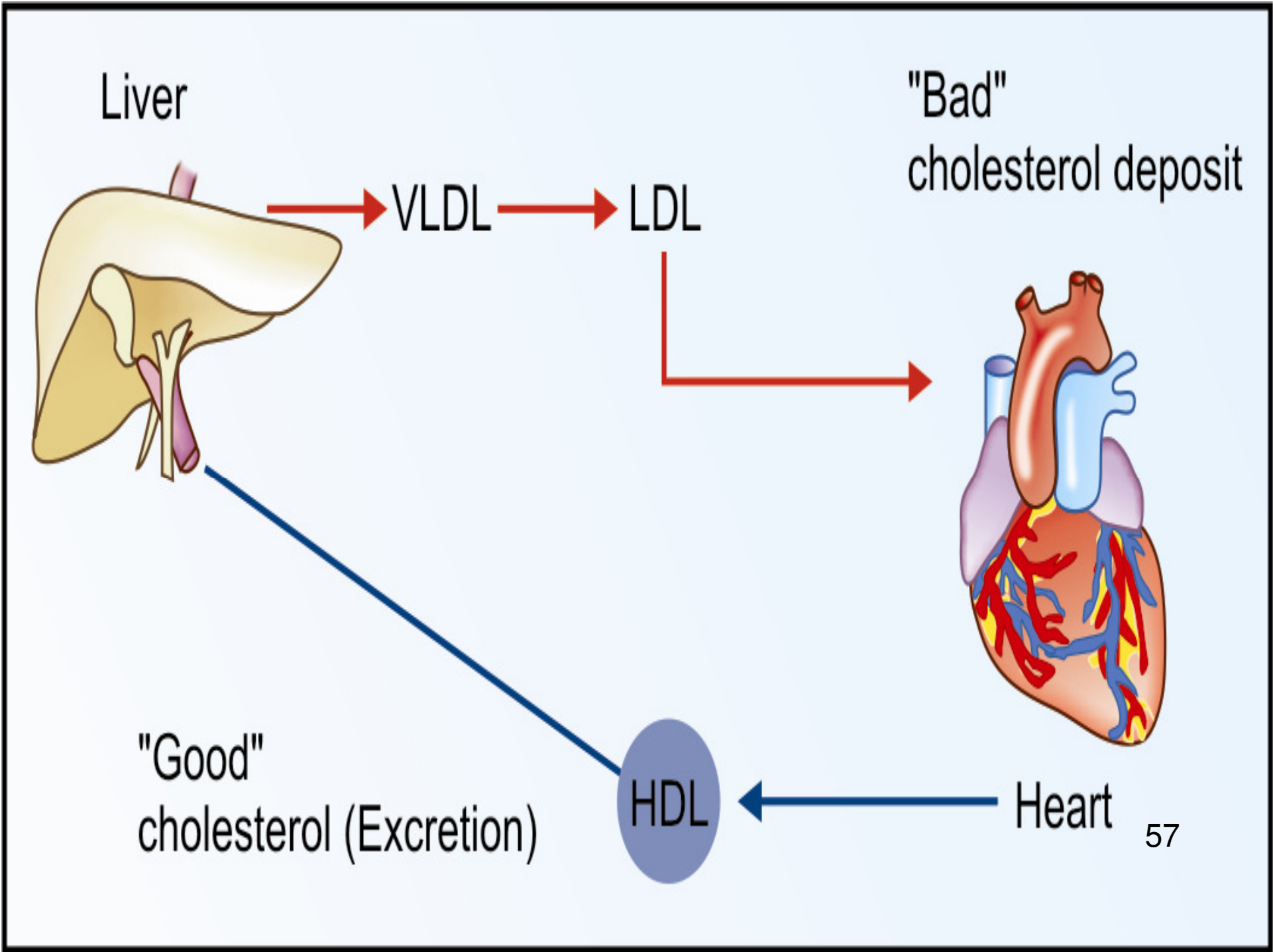


FIGURE 21-42 Uptake of cholesterol by receptor-mediated endocytosis.

Clinical Applications:

- LDL infiltrates through arterial walls
- Taken up by macrophages = scavenger cells.
- “FOAM CELL”
- Starting event of atherosclerosis
- Leading to myocardial infarction .
- LDL-cholesterol is thus deposited in tissues, the LDL variety is called “**Bad Cholesterol**” and “**Lethally Dangerous Lipoprotein**” in common terms.
- “Small dense LDL” (sdLDL) = Worst fraction of LDL, associated with coronary artery diseases.



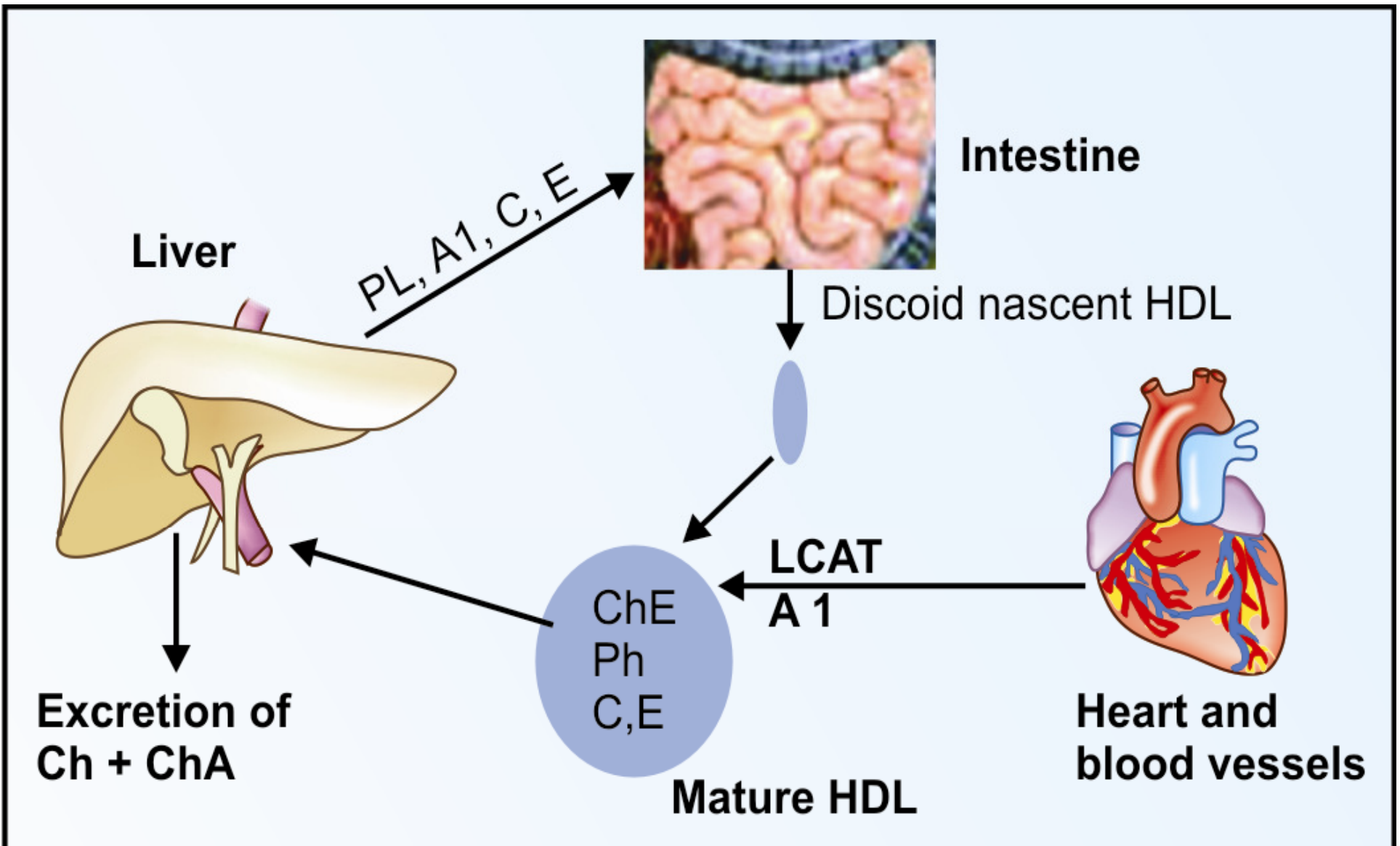
LIPOPROTEIN (a)

- Lipoprotein (a) or Lp(a) should not be confused with apo-A.
- **Apo-A:** constituent of HDL. This 'A' is always written in capital letters. It is seen in all persons. It is **anti- atherogenic**.
- **Lp(a) :** it is associated with LDL. This 'a' is always written in small letters. It is **highly atherogenic** and connected with heart attacks in younger age group. Very strongly associated with myocardial infarction.
- **attached to apo-B-100** by a disulfide bond.
- Associated with heart attacks.
- Lp(a) has significant homology with plasminogen.
- So it interferes with plasminogen activation
- **impairs fibrinolysis.**
- This leads to unopposed intravascular thrombosis and possible myocardial infarction.

4. HIGH DENSITY LIPOPROTEIN

Metabolism:

- Free cholesterol from peripheral tissue are taken by the HDL.
- The apo-A-I of HDL activates **LCAT** present in the plasma.
- Lecithin is a component of phospholipid bilayer of the HDL disc.
- The second carbon of lecithin contains one molecule of PUFA. It is transferred to cholesterol to form cholesterol ester.
- The esterified cholesterol moves into the interior of the HDL disc. This reaction continuous till HDL spheres, with lot of cholesterol esters are formed.
- Mature HDL spheres are taken up by liver cells by apo-A-I mediated receptor mechanism.
- Hepatic lipase hydrolyzes HDL phospholipid and TAG, and cholesterol esters are released into liver cells.



PL= phospholipid, HDL= high density lipoproteins, Ch = cholesterol, ChE = cholesterol ester; ChA= cholic acid, LCAT= lecithin cholesterol acyl transferase

- **CETP** (cholesterol ester transfer protein) transfers cholesterol from HDL to VLDL and LDL in exchange for TAG.
- The cholesterol content of LDL is increased, making it more atherogenic.
- The efflux of cholesterol from peripheral cells to HDL is mediated by the ABC transporter protein. The reverse cholesterol transport to liver through HDL needs the activity of LCAT, CEPT and apo-D.

Function :

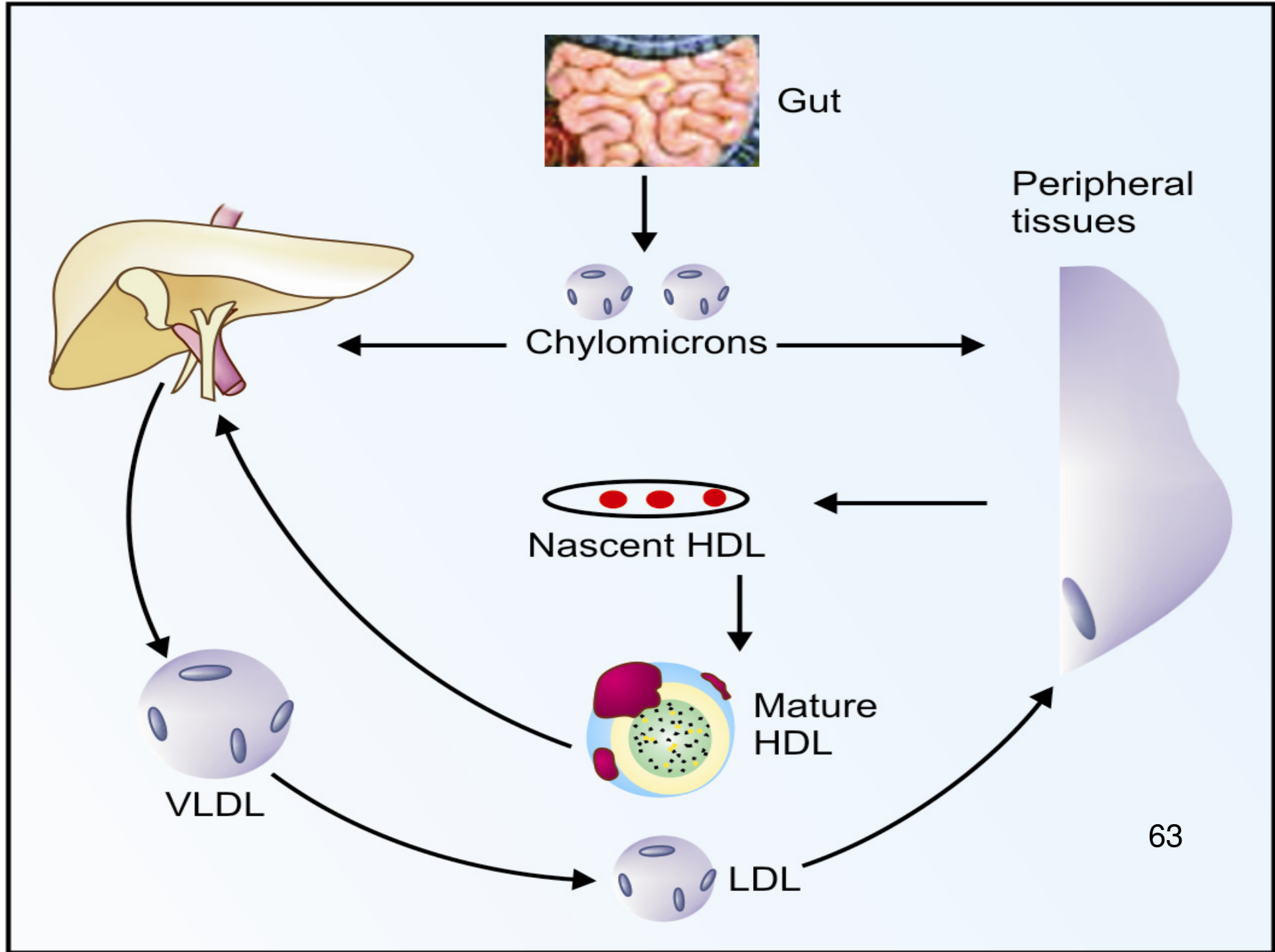
- Transport form of **cholesterol from peripheral tissue to liver**, which is later excreted through bile. This is called reverse cholesterol transport by HDL.
- The only excretory route of cholesterol from the body is the bile.
- Excretion of cholesterol needs prior esterification with PUFA. Thus, PUFA will help in lowering of cholesterol in the body, and so **PUFA is anti-atherogenic.**

Clinical Significance :

- As it is ‘anti-atherogenic’ or ‘protective’ in nature, HDL is known as “**Good Cholesterol**” or “**Highly Desirable Lipoprotein**” in common terms.
- HDL level **below 35 mg/dl increases the risk**, while level **above 60 mg/dl protects** the person from coronary artery diseases.

HDL subfractions :

- HDL-1, HDL-2 and HDL-3 .
- HDL-2 is again sub fractionated into 2a and 2b. HDL-2 is ‘Good’.
- HDL-3 further fractionated into 3a,3b and 3c.



5. FREE FATTY ACID (FFA)

- It is also known as **non-esterified fatty acids (NEFA)**. It is complexed with **albumin** in plasma.
- Derived from lipolysis of TGs
- The FFA molecules are transported to heart, skeletal muscle, liver and other soft tissues.
- Oxidized to supply energy or incorporated into tissue lipids by esterification.
- The half life of FFAs in plasma is very short; only 1-2 minutes.

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HYPOLIPOPROTEINEMIAS

1. Abeta Lipoproteinemia :

- All apo-B containing lipoproteins are reduced since microsomal triglyceride transfer protein is defective.
- Hence TAG is not incorporated into VLDL and chylomicrons. Beta lipoprotein (LDL) is absent.
- Fat soluble vitamins are not absorbed , causing mental and physical retardation.
- Serum levels of TGs, cholesterol and phospholipids are extremely low. Blindness may occur as a result of degenerative changes in retina. Erythrocytes have spiny projections (**acanthocytes**).

2. Hypoalphalipoproteinemia :

- Autosomal dominant condition in which serum HDL is decreased and increased risk of coronary artery diseases.

3. Tangier Disease:

- It was first described in patients from Tangier island in North-West Africa and is benign autosomal dominant condition.
- It is characterized by a defect in the efflux of cholesterol from cells and reduction of HDL levels in the blood.
- The biochemical abnormality is the defective “**ATP Binding Cassette Transporter-1**” (**ABC-1**), which is involved in transferring cellular cholesterol to HDL, so plasma HDL is low and alpha band is absent in electrophoresis.
- Cholesterol esters are accumulated in tissues.
- Manifestations are large orange yellow tonsils, muscle atrophy, recurrent peripheral neuropathies and atherosclerosis.

HYPERLIPIDEMIAS

- It is classified by **Frederickson**.
- Deposition of cholesterol on the arterial walls, leading to atherosclerosis.
- The coronary and cerebral vessels are more commonly affected, lead to ischemic heart disease and cerebrovascular accidents.
- The deposition of lipids in subcutaneous tissue leads to **Xanthomas** (yellow plaques containing TGs and cholesterol).

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Type IIA- Primary Familial Hypercholesterolemia:

- LDL receptor defect & elevation of LDL.
- Patients seldom survive the second decade of life due to ischemic heart disease.
- The LDL receptor defect is due to :
 - LDL receptor deficiency
 - Defective binding of B-100 to the receptor.
- A substitution of glutamine for arginine at 3500th amino acid results in poor binding to LDL receptors.
- This defect is known as B-3500 or Familial defective apo-B.
- Receptor-LDL complex is not internalized.

Type IIB- Hyperlipoproteinemia:

- There is elevation of both cholesterol and TGs with excessive production of apo-B, therefore LDL and VLDL are elevated.
- The abnormalities are manifested only by the third decade of life.
- **Secondary type II Hyperlipoproteinemia** is seen in
 - Hyperthyroidism,
 - Diabetes Mellitus
 - Nephrotic syndrome
 - Cholestasis.

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Type IV- Familial endogenous Type :

- This is due to over production of TGs by liver. The VLDL level in plasma is elevated.
- Other causes of Hyperlipoproteinemia include hepatic lipase defect, LCAT defect and Lp(a) excess etc.

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ATHEROSCLEROSIS

- Greek word, **sclerosis** means **hardening**.
- Coronary artery obstruction and myocardial infarction are important consequences of atherosclerosis.
- In India 20% deaths are due to coronary artery disease (CAD).
- It is estimated that by the year 2020. it will account for 33% of all deaths.

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ATHEROSCLEROSIS AND LDL

- Especially oxidized LDL particles are deposited in the subintimal regions of arteries.
- Free radical induced oxidative damage of LDL will accelerate this process.
- Later, the macrophages become overloaded with cholesterol called “**Foam cells**” & form atherosclerotic plaques.
- During early stages the condition is reversible if plasma lipid level especially LDL-cholesterol are lowered but when lipid is accumulated the lesion progresses unchecked and the arterial changes become irreversible.
- The formation of atherosclerotic plaque leads to narrowing of vessel wall and proliferative changes occur.
- This fibrous proliferation is due to liberation of various growth factors by macrophages and platelets.

Coronary artery disease (CAD)

- The blood flow through the narrow lumen is more turbulent and there is tendency for clot formation.
- Finally a clot is formed which occludes one of the major vessels.
- Thrombosis (coronary, cerebral or peripheral vascular) leads to ischemia of the tissue supplied, due to hindrance to oxygen supply.
- Finally, Infarction (death of tissue) occurs.

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PLASMA LIPID PROFILE

- The sample of serum should be taken after 12-14 hours of fasting.
- Following parameters should be looked for:
 1. Total cholesterol
 2. HDL- cholesterol
 3. LDL-cholesterol
 4. Triglycerides
 5. Apo-B level
 6. Apo-A-I level
 7. Lp(a) level
 8. Small dense LDL

RISK FACTORS FOR ATHEROSCLEROSIS

1. Serum cholesterol level:

- In normal persons, cholesterol level varies from 150-200 mg/dl. It should be preferably below 180 mg/dl.
- Values around 220 mg/dl will have moderate risk and values more than 240 mg/dl will need active treatment.
- Females have lower cholesterol level which affords protection against atherosclerosis.
- In the newborn, normal level is 100 mg/dl which slowly rises to about 160 mg/dl during the 1st year itself.
- Plasma cholesterol levels would tend to slowly rise after 4th decade of life in men and post-menopausal women.

2. LDL-cholesterol:

- Blood levels under 130 mg/dl are desirable .
- Levels between 130-159 are borderline; while above 160 mg/dl carry risk so LDL is “Bad cholesterol”.

3. HDL- cholesterol:

- HDL level above 60 mg/dl protects against heart disease. Hence it is “Good cholesterol”.
- A level below 40 mg/dl increases the risk of CAD.
- For every 1 mg/dl drop in HDL, the risk of heart disease rises 3%.
- Total cholesterol/HDL ratio > 3.5 , dangerous.
- LDL:HDL ratio > 2.5 , dangerous.

4. Apoprotein levels and ratios:

- Apo-A-I is a measure of HDL-cholesterol(good) and apo-B measures LDL-cholesterol(bad).
- Ratio of Apo B:A-I is the most reliable index.
- The ratio of 0.4 is very good;
- the ratio 1.4 has the highest risk of cardiovascular accidents.

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5. Lp(a) :

- Lp(a) inhibits fibrinolysis.
- > 30 mg/dl increase the risk 3 times;
- when increased Lp(a) is associated with increased LDL, the risk is increased 6 times.

6. Cigarette Smoke:

- Nicotine of cigarette will cause lipolysis and thereby increase the acetyl CoA and cholesterol synthesis.
- Nicotine also causes transient constriction of coronary and carotid arteries.

7. Hypertension :

- Systolic blood pressure > 160 further increases the risk of CAD.
- An increase in 10 mm of BP will reduce life expectancy by 10 years.

8. Diabetes Mellitus:

- In the absence of insulin, hormone sensitive lipase is activated, more free fatty acids are formed, these are catabolised to produce acetyl CoA.
- These cannot be readily utilised, as the availability of oxaloacetate is reduced and citric acid cycle is slowed. So acetyl CoA pool is increased, and it is channelled to cholesterol synthesis.

9. Serum Triglyceride:

- Normal level is 50-150 mg/dl, blood level more than 150 mg/dl is injurious to health.

10. Homocysteine level:

- Plasma level above 15 micromol/L will increase the risk of coronary artery disease and stroke at a younger age.
- An increase of every 5 micromol/L of Homocysteine in serum elevates the risk of coronary artery disease by as much as cholesterol increase of 20 mg/dl.
- Administration of pyridoxine, vitamin B12 and folic acid may lower the Homocysteine level.

11. Obesity and sedentary lifestyle:

- People with “apple type” of obesity (truncal obesity) are more prone to get myocardial infarction.

12. High sensitive C reactive protein:

- Increased hs-CRP in blood is a predictor of future coronary events.

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PREVENTION OF ATHEROSCLEROSIS

- Aim of prevention: reduce total cholesterol below 180 mg/dl; decrease LDL-cholesterol below 130 mg/dl and keep HDL-cholesterol above 40 mg/dl.

1. Reduce Dietary cholesterol:

- Eggs and meat contain high cholesterol so it should be avoided.

2. Vegetables oils and PUFA:

- Vegetable oils (sunflower oil) and fish oils contain PUFA.
- Omega-3 fatty acids from fish oils reduce LDL and decrease the risk of CAD.

3. Moderation in Fat intake:

- The recommended daily allowance will be about 20-25 g of oils and about 2-3 g of PUFA per day for normal adult.

4. Green leafy vegetables:

- Due to their high fibre content, leafy vegetables will increase the motility of bowels and reduce reabsorption of bile salts.
- Vegetables also contain plant sterols (sitosterol) which decrease the absorption of cholesterol.
- About 400 mg/dl of fruit and vegetables are desired

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5. Avoid sucrose and cigarette:

- Sucrose will raise plasma triglycerides. High carbohydrate diet, especially sucrose, should be avoided.

6. Exercise :

- Regular moderate exercise will lower LDL and raise HDL levels in blood. It will also reduce obesity.

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7. Hypolipidemic drugs:

- a. **Bile acid binding resins** (cholestyramine) decrease the reabsorption of bile acids.
- b. **HMG CoA reductase inhibitors** (“statins”)
- c. **Nicotinic acid** inhibits lipolysis and so VLDL level is decreased.
- d. **Ezetimibe** is a drug which selectively inhibits absorption of cholesterol from mixed micelle.
- e. **Aspirin** is widely used to prevent thrombus formation, because of its anti-platelet activity.
- f. **Anti-oxidants** will minimize oxidation of LDL and **Fibrates** lower TAG levels by activating LPL.

8. Avoid trans fatty acids :

- Trans fatty acids (with double bonds having trans configuration) are formed during the partial hydrogenation of vegetable oils.
- TFA are found to be more atherogenic than saturated FAs. TFA will alter the membrane fluidity.
- TFA is also implicated in modulating metabolism. It alters secretion and composition of apo-B100 containing lipoproteins (LDL and VLDL).
- It increase catabolism of apo-A-I, decreases HDL and increase LDL levels.
- Reducing the intake of TFA to 2-7g/day is now strongly advised.

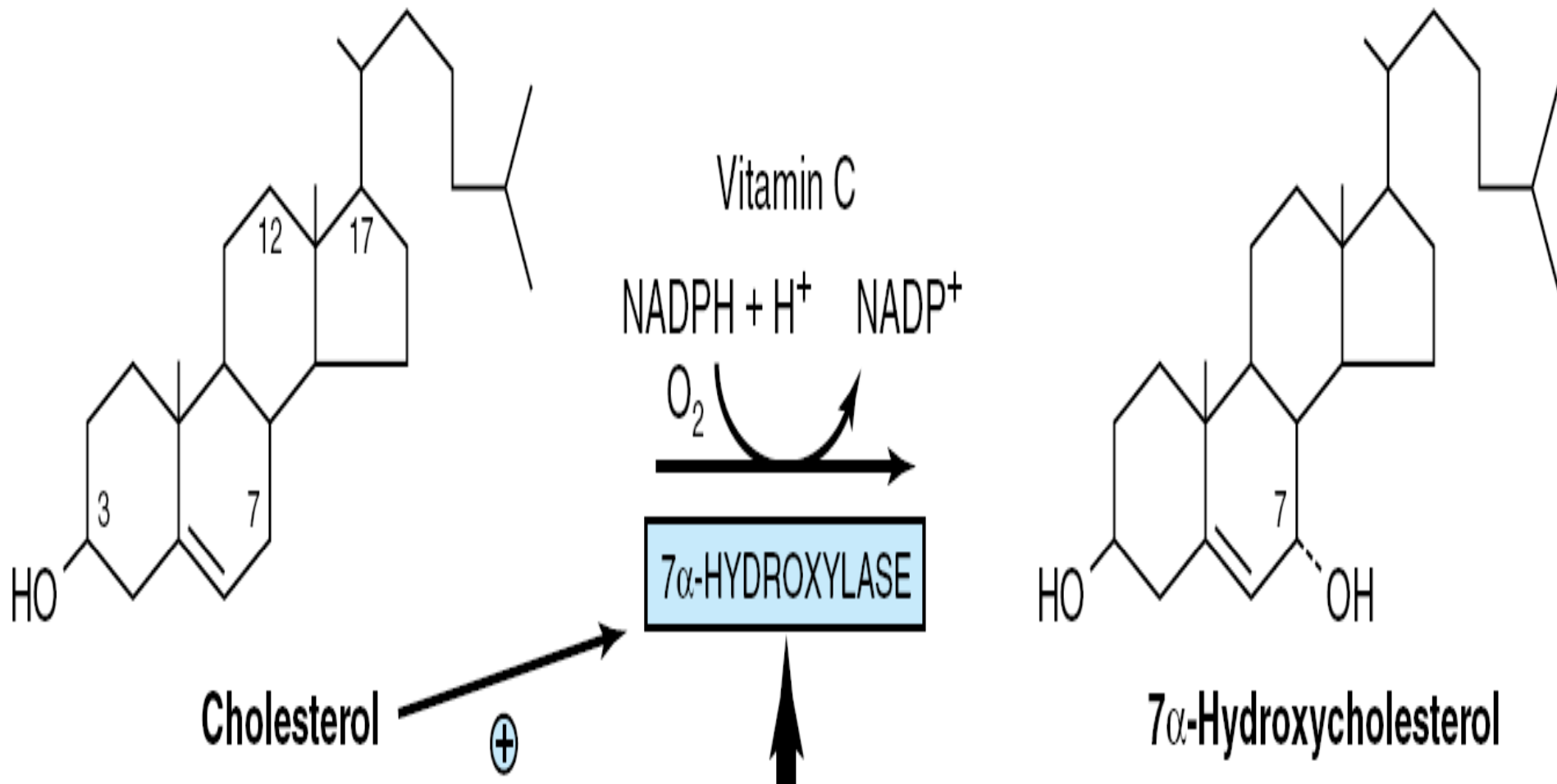
FORMATION OF BILE ACIDS

- Bile acids are synthesized in the liver from cholesterol.
- They contain 24 carbon atoms. All of them have an alpha-oriented (projecting below the plane of ring) hydroxyl group at position 7.

Step 1- Hydroxylation reactions:

- The first and rate-limiting step is the introduction of this hydroxyl group by the enzyme 7-alpha-hydroxylase.
- It is a microsomal enzyme

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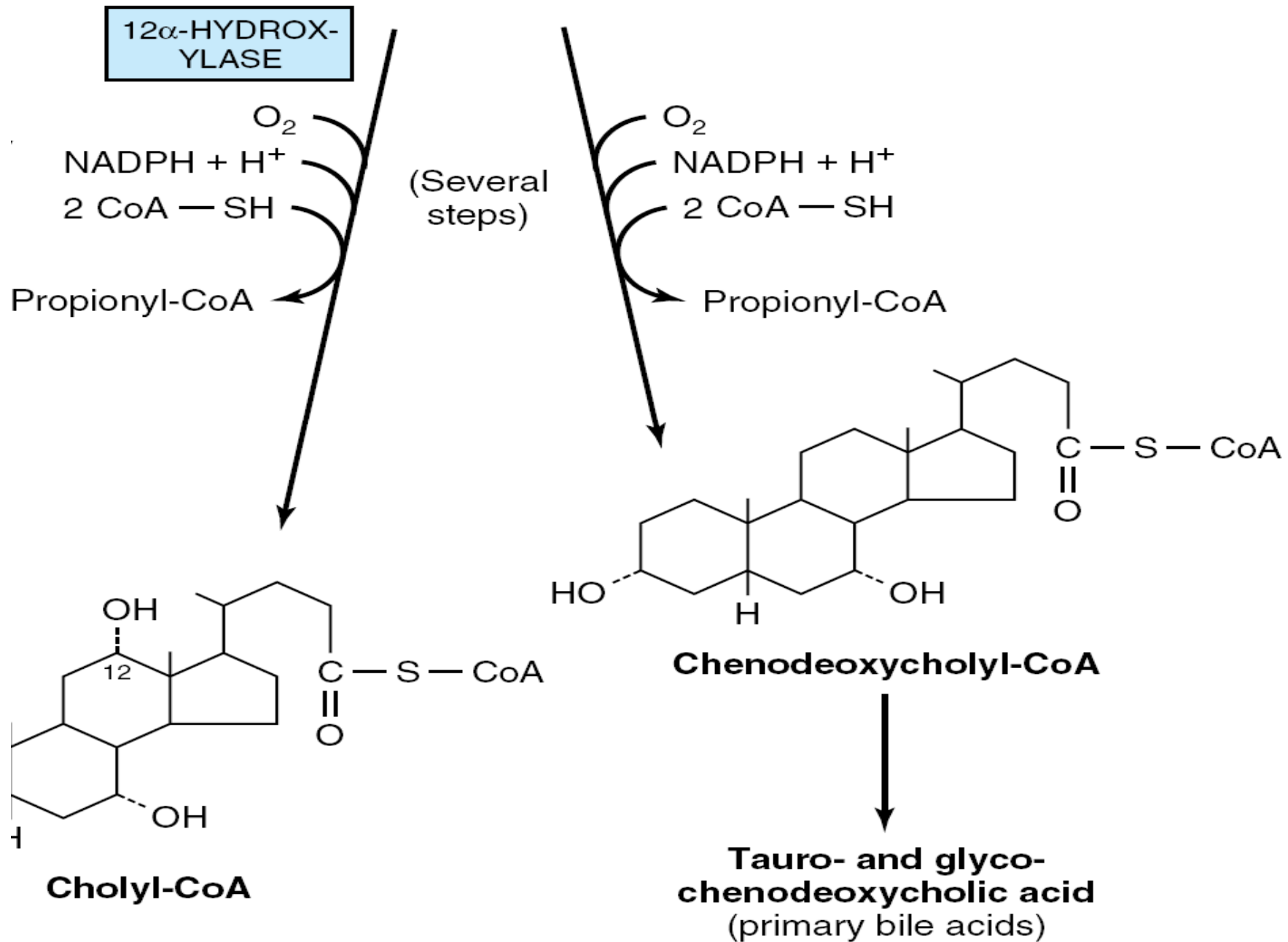
- Then the beta oriented OH group of C3 is converted to alpha type by an isomerase.
- A third OH group is added at 12th carbon in the case of colic acid.
- Chenodeoxycholic acid, another primary bile acid has only two hydroxyl group at positions 3 and 7. ring B is reduced in all cases.

Step 2- Removal of 3C unit:

- The side chain is first hydroxylated at 26C and then oxidized to COOH group. This is followed by cleavage of Propionic acid (3C) unit.

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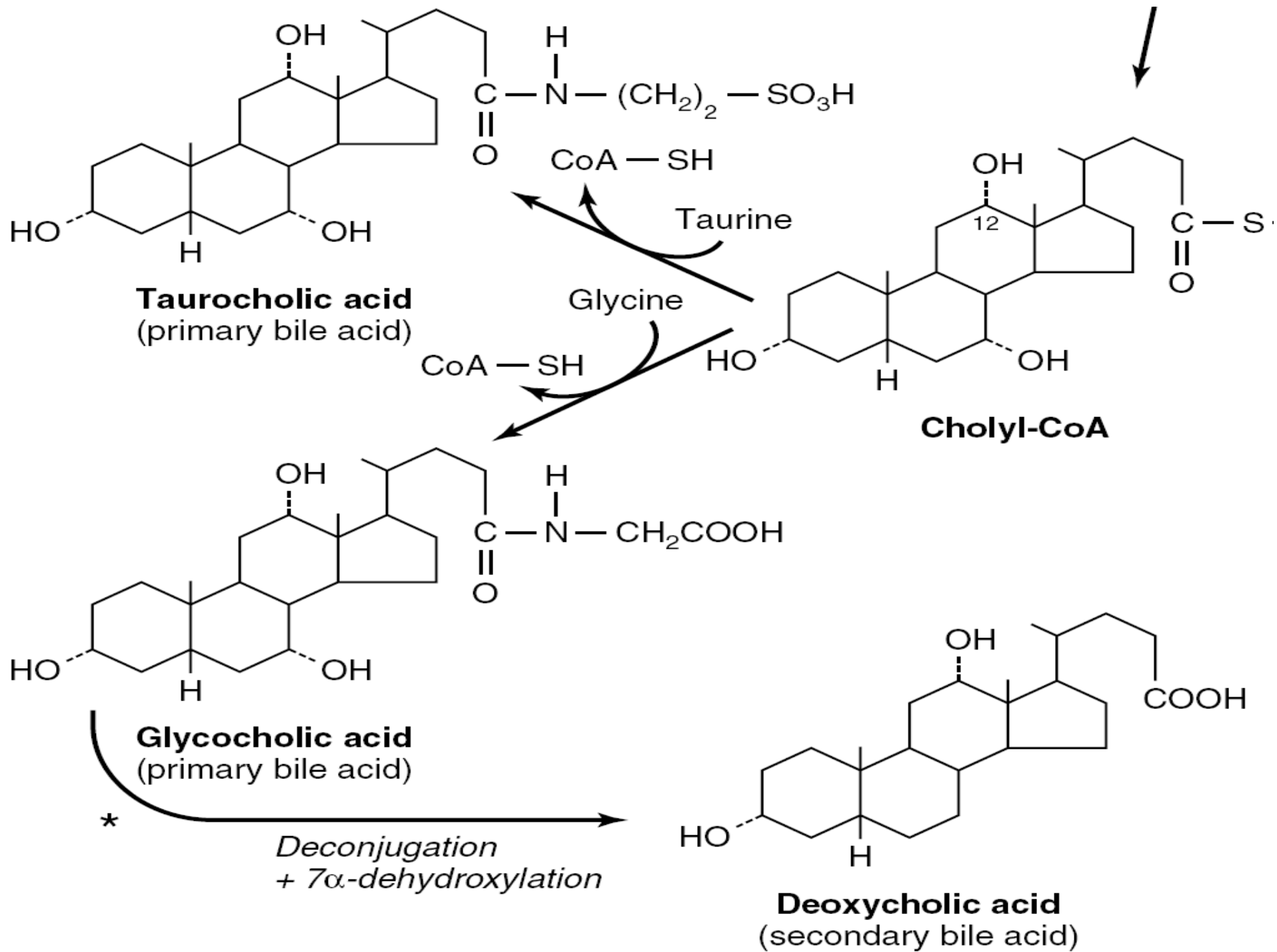
7 α -Hydroxycholesterol



Step 3- Formation of Bile Salts:

- The primary bile acids are now conjugated with either glycine or taurine to form bile salts
- They are glycocholic acid, taurocholic acid, glycochenodeoxycholic acid and taurochenodeoxycholic acid.

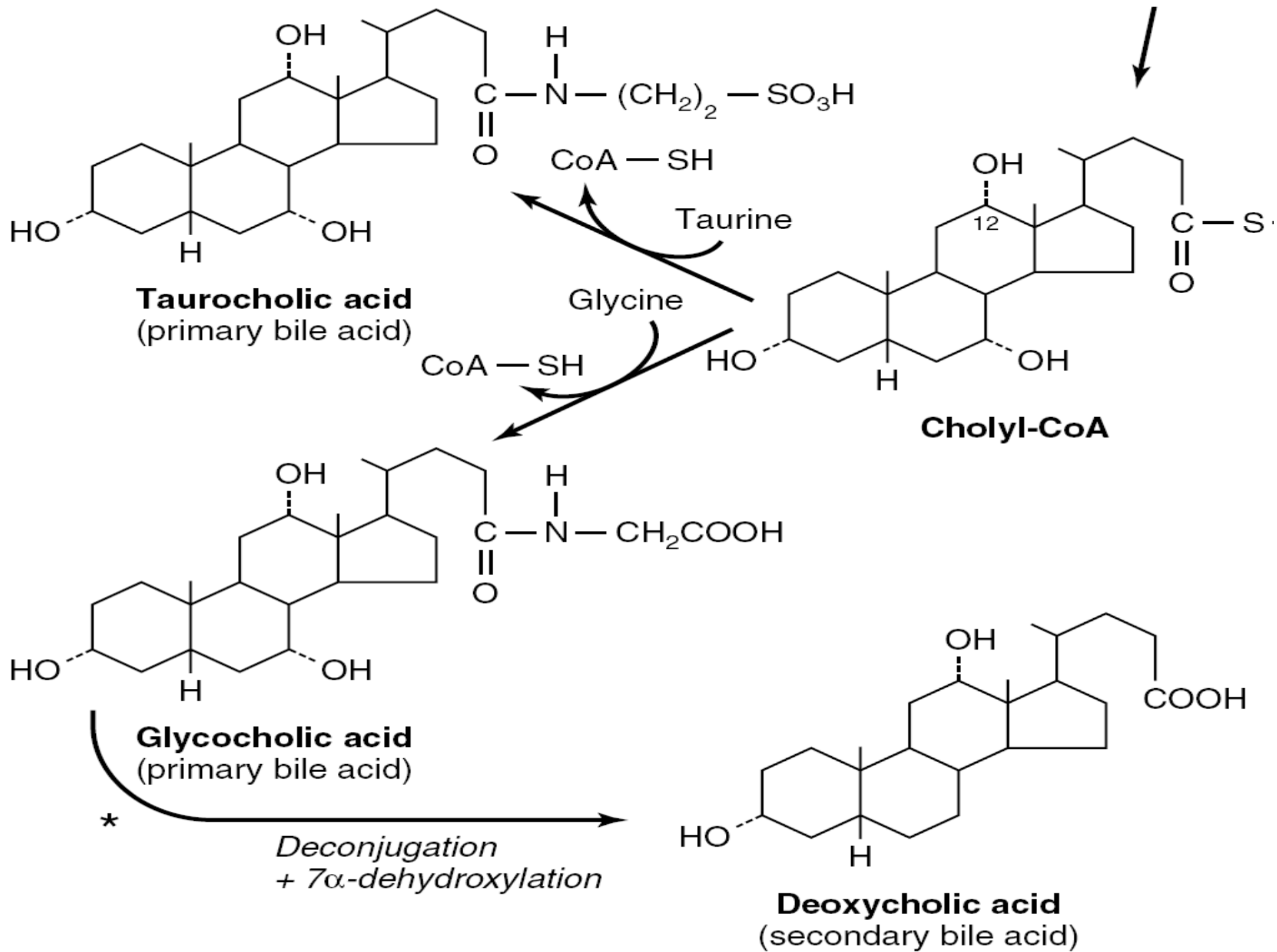
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Step 4- Secondary Bile acids/ Bile salts:

- Primary bile acids are acted upon by intestinal bacteria which result in deconjugation.
- The deconjugated bile acids are then partly converted to secondary bile acids by removal of the alpha hydroxyl group at position 7.
- Cholic acid is thus converted to deoxycholic acid and chenodeoxycholic acid to lithocholic acid.

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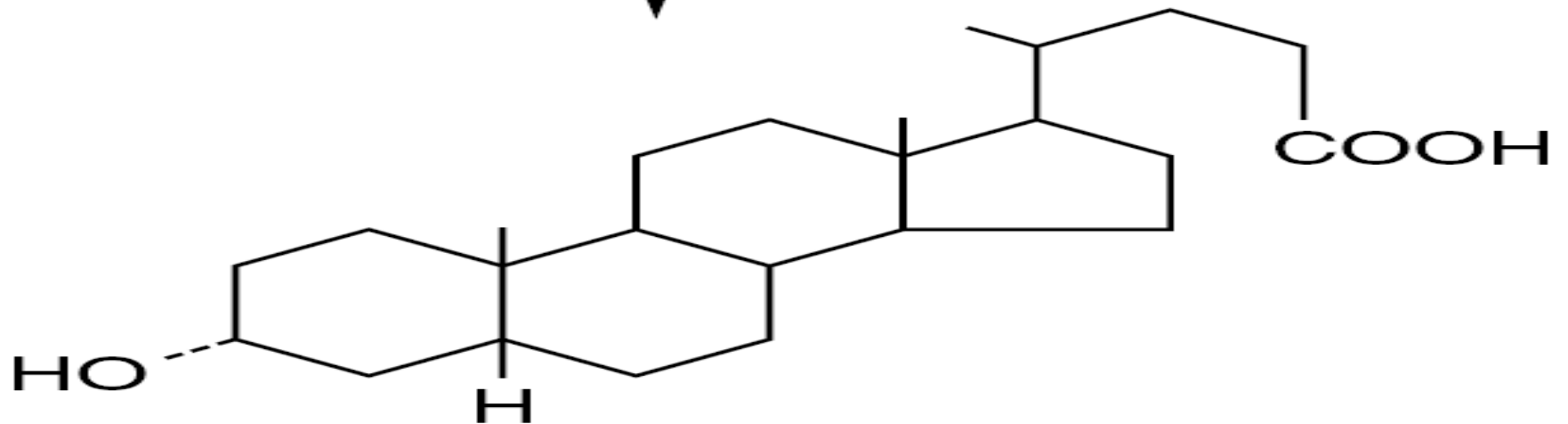


Chenodeoxycholyl-CoA



**Tauro- and glyco-
chenodeoxycholic acid**
(primary bile acids)

* *Deconjugation
+ 7 α -dehydroxylation*



Lithocholic acid
(secondary bile acid)