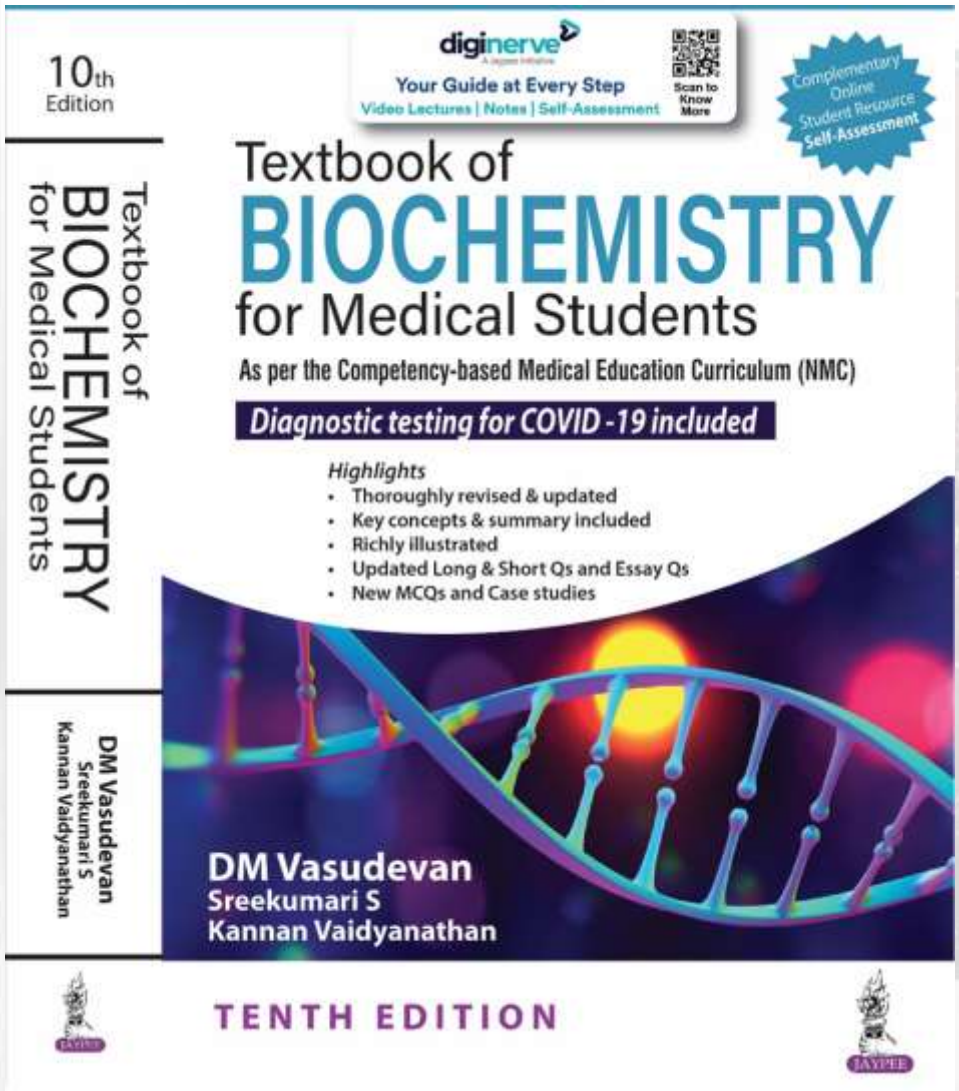
Chapter 12:

Cholesterol and lipoproteins



Textbook of
BIOCHEMISTRY
for Medical Students

By DM Vasudevan, *et al.*

TENTH EDITION

Cholesterol

Cholesterol is widely distributed in animal tissues. It is absent in prokaryotes. **In plants, cholesterol is absent**, but other plant sterols are present. In bacteria and plants, compounds similar to steroids exist, known as **hopanoids**.

Clinical significance of cholesterol

The level of cholesterol in blood is related to the development of **atherosclerosis** and **myocardial infarction**.

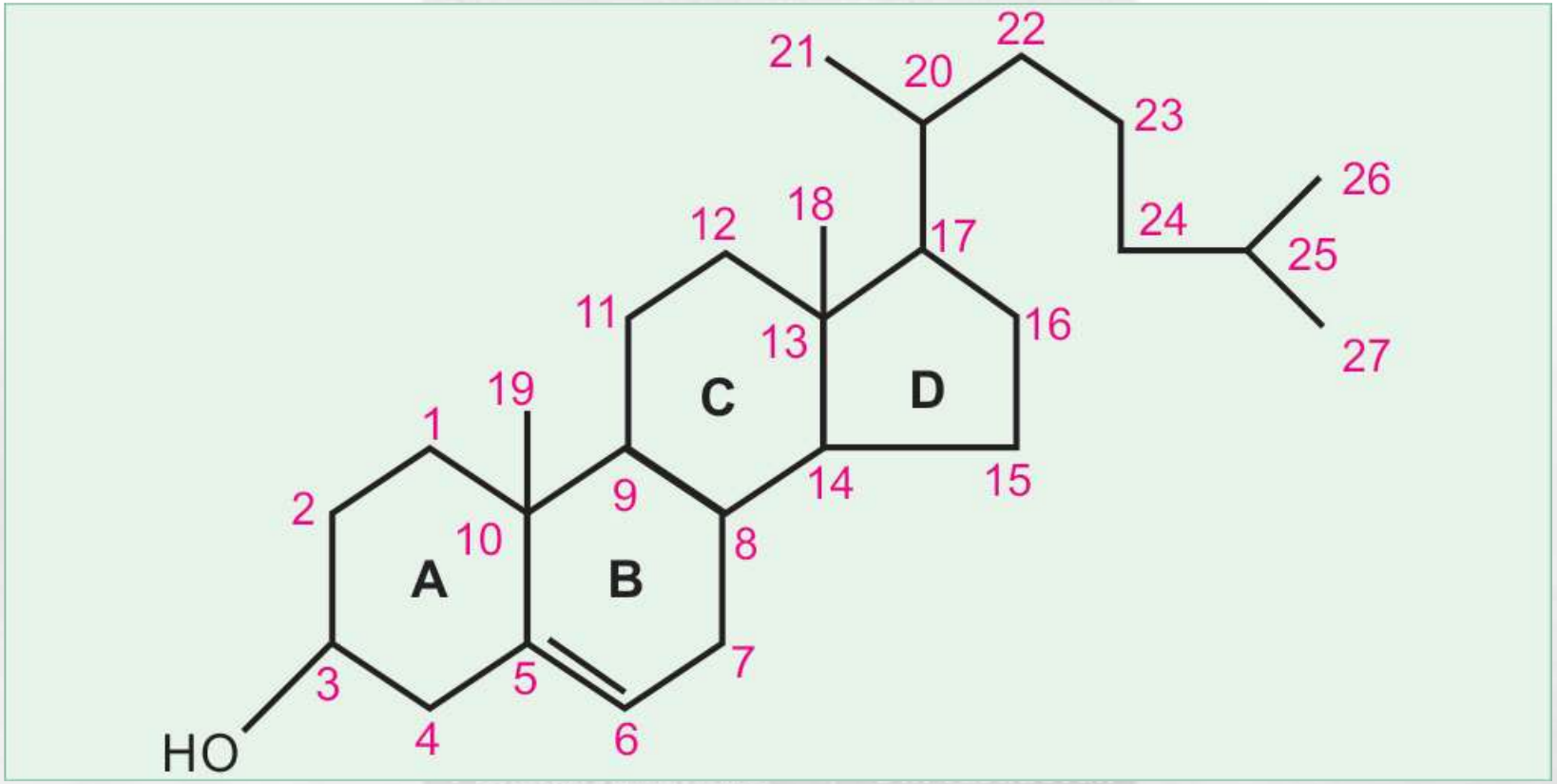
Abnormality of cholesterol metabolism may lead to cardiovascular accidents and heart attacks.

Functions of cholesterol

1. **Cell membranes:** Cholesterol is a component of membranes.
2. **Nerve conduction:** Cholesterol has an insulating effect onnerve fibers.
3. **Bile acids and bile salts** are derived from cholesterol. Bile salts are important for fat absorption.
4. **Steroid hormones:** Glucocorticoids, androgens and estrogens are from cholesterol.
5. **Vitamin D3** is from 7-dehydrocholesterol.
6. **Esterification:** The OH group of cholesterol is esterified to fatty acids to form cholesterol esters. This esterification occurs in the body by transfer of a PUFA moiety by **lecithin-cholesterol acyl-transferase.**

Salient features of steroids

Name of steroid	Total no of carbon atoms	No of carbon atoms in side chain	Importance
Cholesterol	27	8	Most important animal sterol
Bile acids	24	5	Emulsifying agents
Glucocorti- coids and Mineralo- corticoids	21	2	Influences Metabolism as well as fluid and electrolyte balance
Testosterone	19	-	Male sex hormones
Estrogens	18	-	Female sex hormones



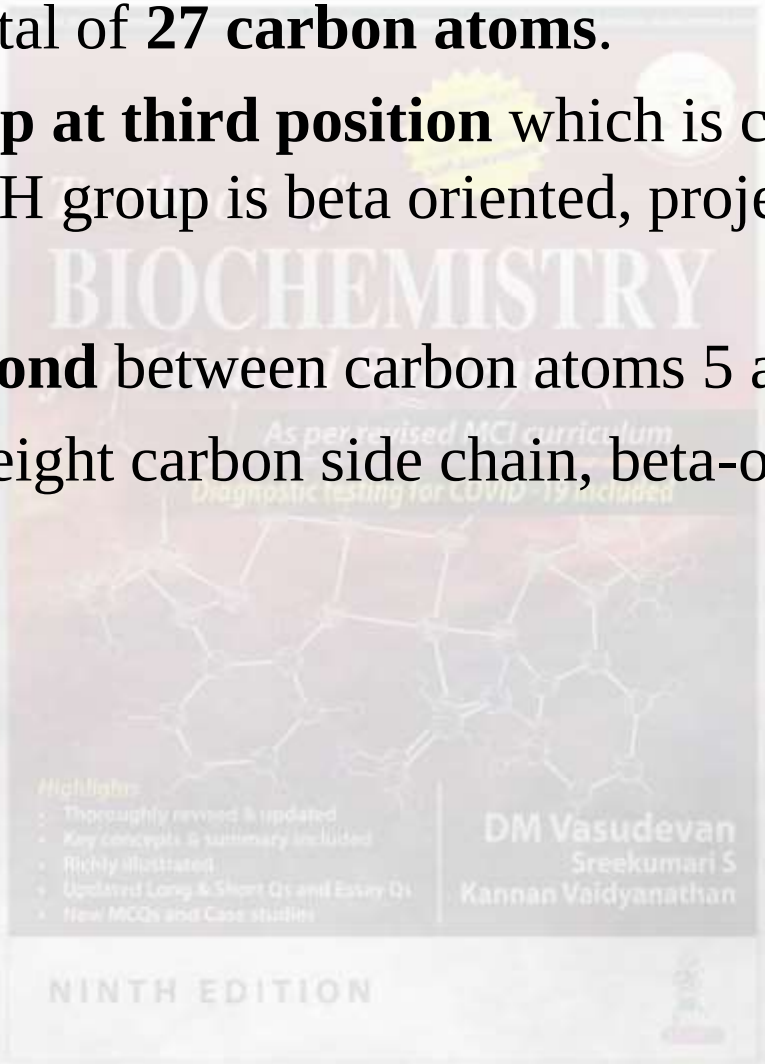
Structure of Cholesterol

Cholesterol has a total of **27 carbon atoms**.

One **hydroxyl group at third position** which is characteristic of all sterols. The OH group is beta oriented, projecting above the plane of ring.

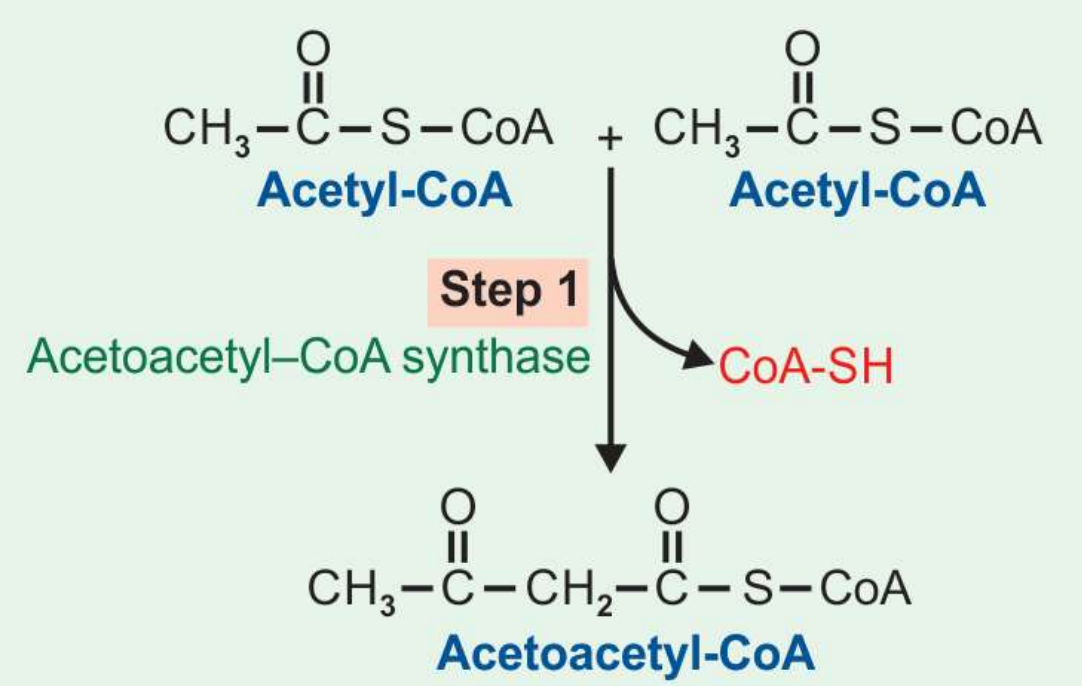
There is a **double bond** between carbon atoms 5 and 6.

Further, there is an eight carbon side chain, beta-oriented attached to 17th carbon



Biosynthesis of Cholesterol

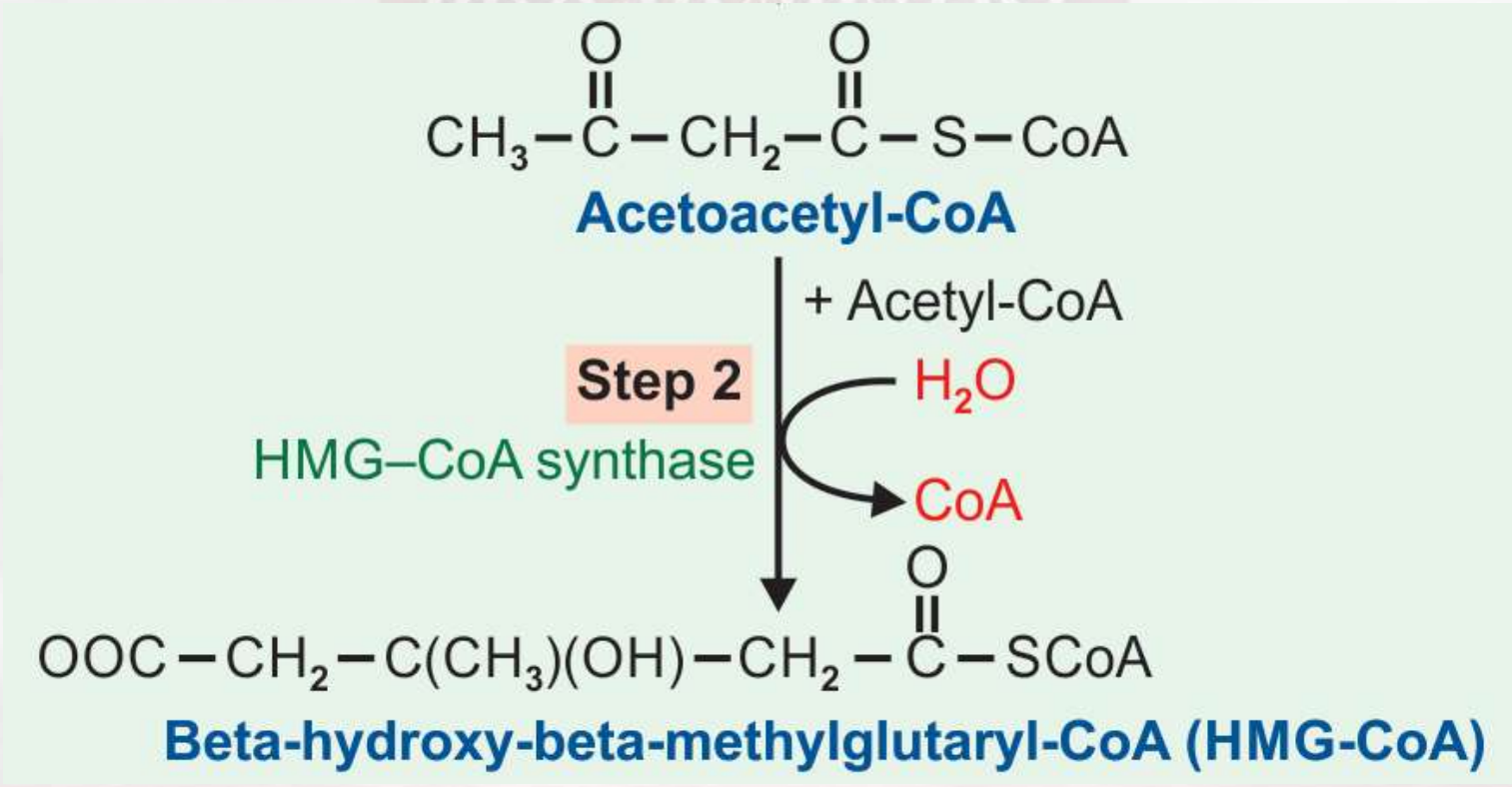
The acetyl-CoA is provided by the ATP-citrate lyase reaction as in the case of fatty acid synthesis. Two molecules of acetyl-CoA condense to form acetoacetyl-CoA catalyzed by **cytoplasmic acetoacetyl-CoA synthase**



Step 2: Production of HMG-CoA

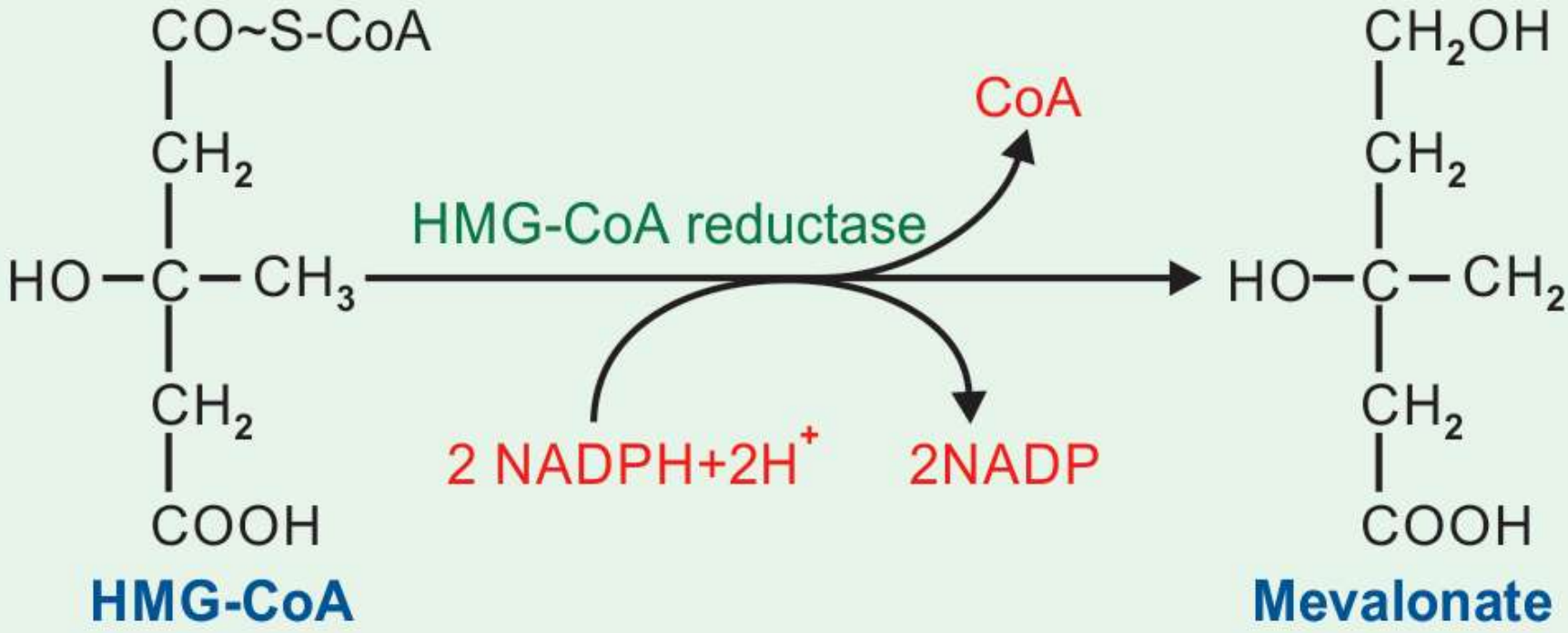
A third molecule of acetyl-CoA condenses with acetoacetyl-CoA to form beta-hydroxy-beta-methylglutaryl CoA (HMGCoA).

The enzyme is **HMG-CoA synthase**



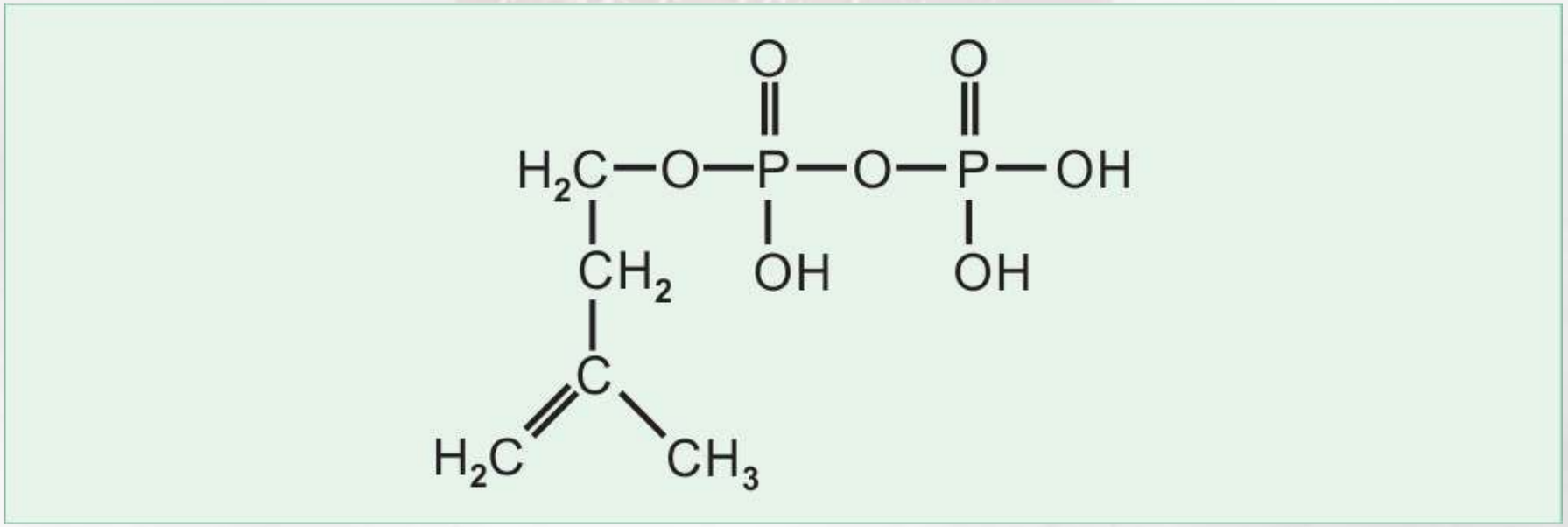
Step 3: The Committed Step

The reduction of HMG-CoA to mevalonate is catalyzed by **HMG-CoA reductase**. It is a **microsomal** enzyme. It uses 2 molecules of NADPH.



Step 4: Production of 5 Carbon Unit

Mevalonate is phosphorylated to 3-phospho-5-pyrophospho mevalonate. This then undergoes **decarboxylation** to give rise to **isopentenyl pyrophosphate**, a 5 carbon unit. This requires 3 molecules of ATP



Isopentenyl pyrophosphte

Step 5: Condensation of 5-Carbon Units

Six 5-carbon units are condensed to form a 30 carbon compound, **Squalene**. In summary:

IPP(5C) + DMAPP(5C) → GPP(10C) + IPP(5) →

FPP(15C) + FPP(15C) → Squalene (30C)

Step 6: Cyclization

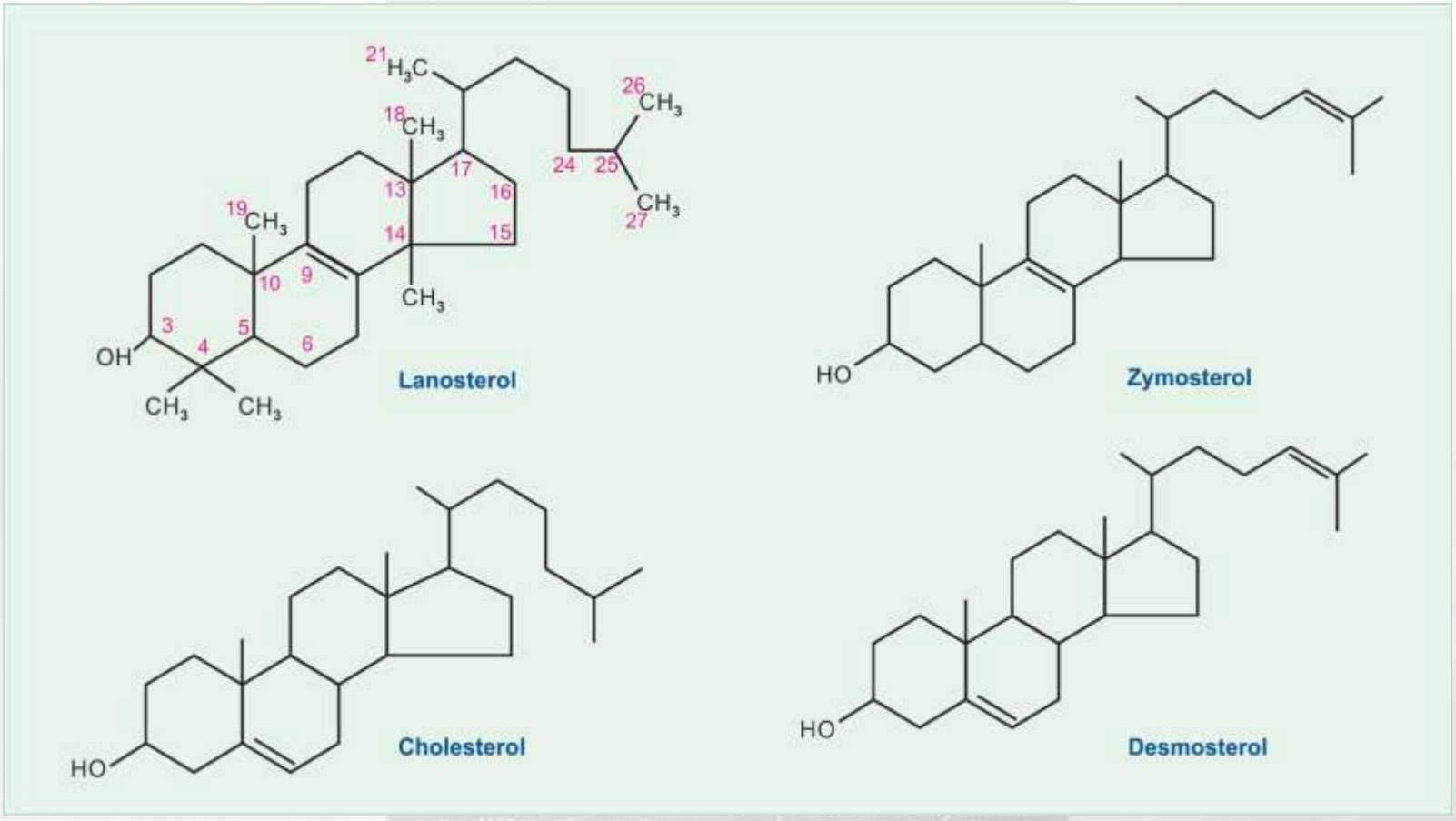
Squalene is a straight line structure. Then squalene undergoes oxidation by epoxidase, using molecular oxygen and **NADPH** to form squalene epoxide. A cyclase converts it to 30C **lanosterol**. It is the first steroid compound synthesized.

Step 7: Cutting to size

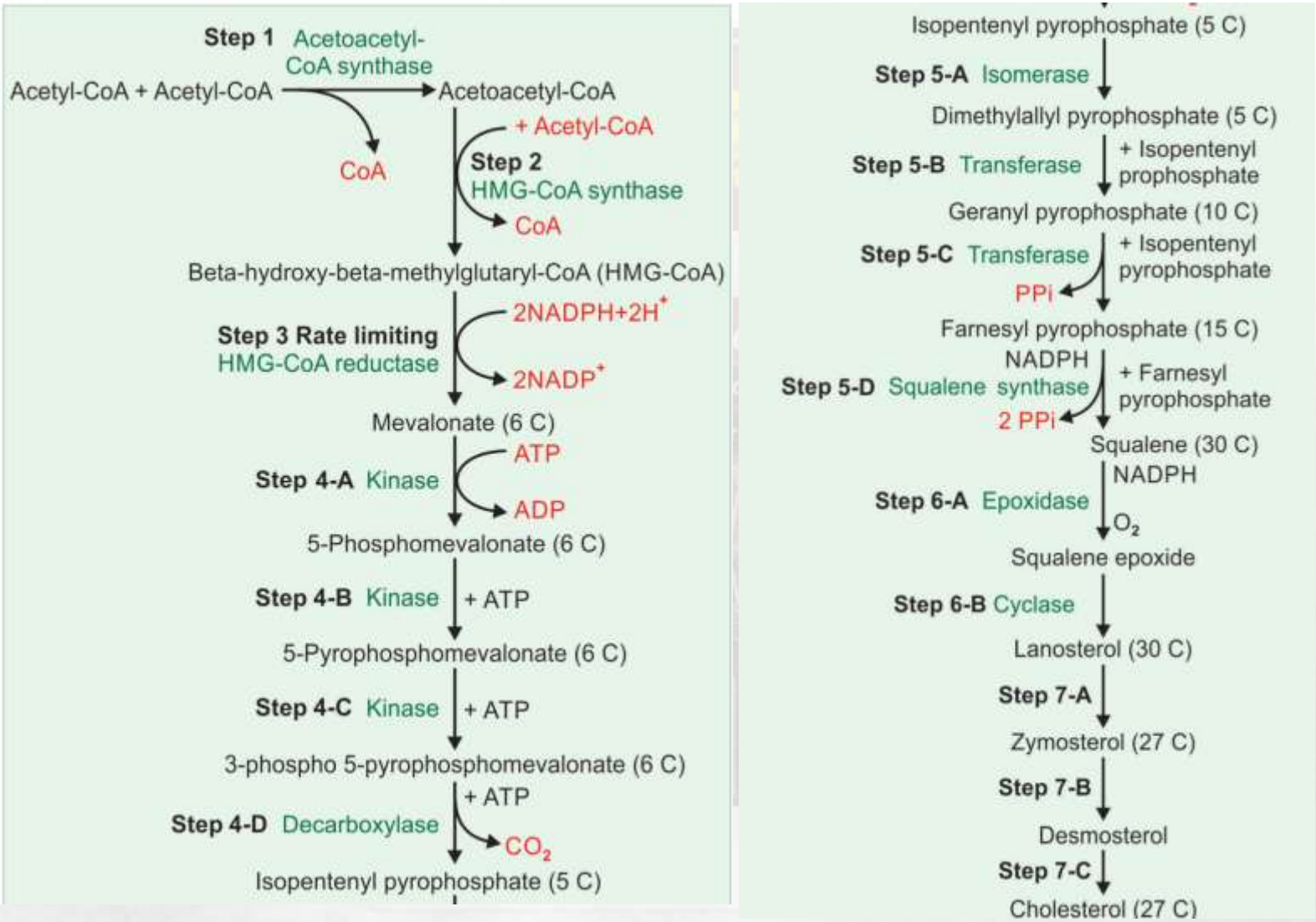
From Lanosterol, the 3 additional methyl groups on carbon atoms 4 and 14 are removed to produce **zymosterol.**

Then the double bond migrates from 8-9 position to 5-6 position, when **desmosterol** is formed.

Finally, the double bond in theside chain (between carbon 24-25) is reduced by NADPH when **cholesterol** is formed.



Lanosterol, zymosterol, desmosterol and cholesterol; the last 4 compounds in the cholesterol synthesis pathway


Step 1 Acetoacetyl-CoA synthase
Acetyl-CoA + Acetyl-CoA
Acetoacetyl-CoA
CoA
+ Acetyl-CoA
Step 2 HMG-CoA synthase
CoA
Beta-hydroxy-beta-methylglutaryl-CoA (HMG-CoA)
Step 3 Rate limiting HMG-CoA reductase
2NADPH+2H+
2NADP+
Mevalonate (6 C)
Step 4-A Kinase
ATP
ADP
5-Phosphomevalonate (6 C)
Step 4-B Kinase
+ ATP
5-Pyrophosphomevalonate (6 C)
Step 4-C Kinase
+ ATP
3-phospho 5-pyrophosphomevalonate (6 C)
Step 4-D Decarboxylase
+ ATP
CO2
Isopentenyl pyrophosphate (5 C)
Step 5-A Isomerase
Dimethylallyl pyrophosphate (5 C)
Step 5-B Transferase
+ Isopentenyl prophosphate
Geranyl pyrophosphate (10 C)
Step 5-C Transferase
+ Isopentenyl pyrophosphate
PPi
Farnesyl pyrophosphate (15 C)
Step 5-D Squalene synthase
NADPH
+ Farnesyl pyrophosphate
2 PPi
Squalene (30 C)
Step 6-A Epoxidase
NADPH
O2
Squalene epoxide
Step 6-B Cyclase
Lanosterol (30 C)
Step 7-A
Zymosterol (27 C)
Step 7-B
Desmosterol
Step 7-C
Cholesterol (27 C)

Regulation of Cholesterol Synthesis

Regulation at transcription: Long-term regulation involves regulation of transcription of the gene for HMG-CoA reductase by suppression.

Cholesterol regulates the expression of HMG-CoA reductase gene.

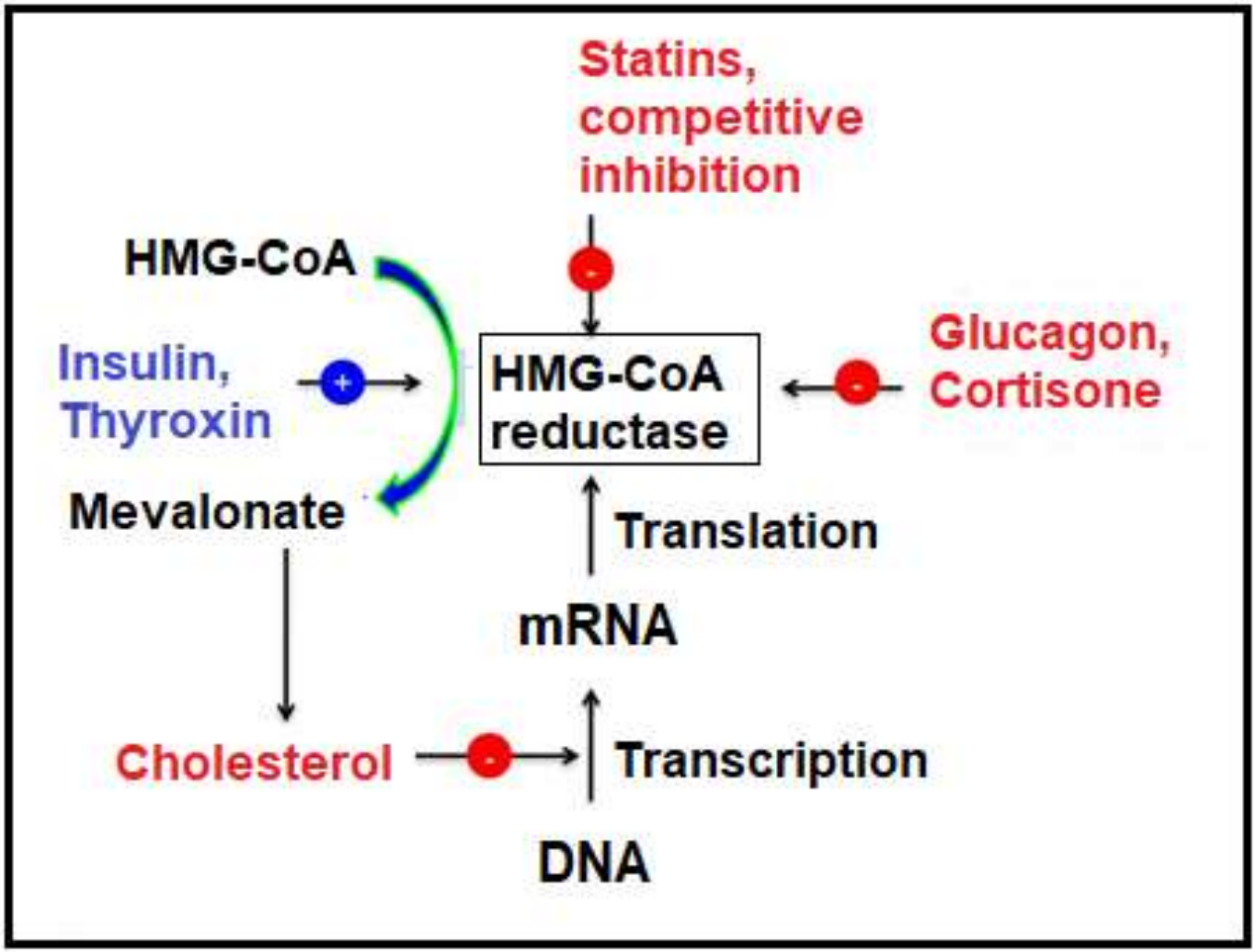
Covalent modification: Short-term regulation is by covalent modification of the enzyme. Cyclic AMP mediated cascade phosphorylates the enzyme which is inactive. Dephosphorylated form is active.

Regulation of Cholesterol Synthesis

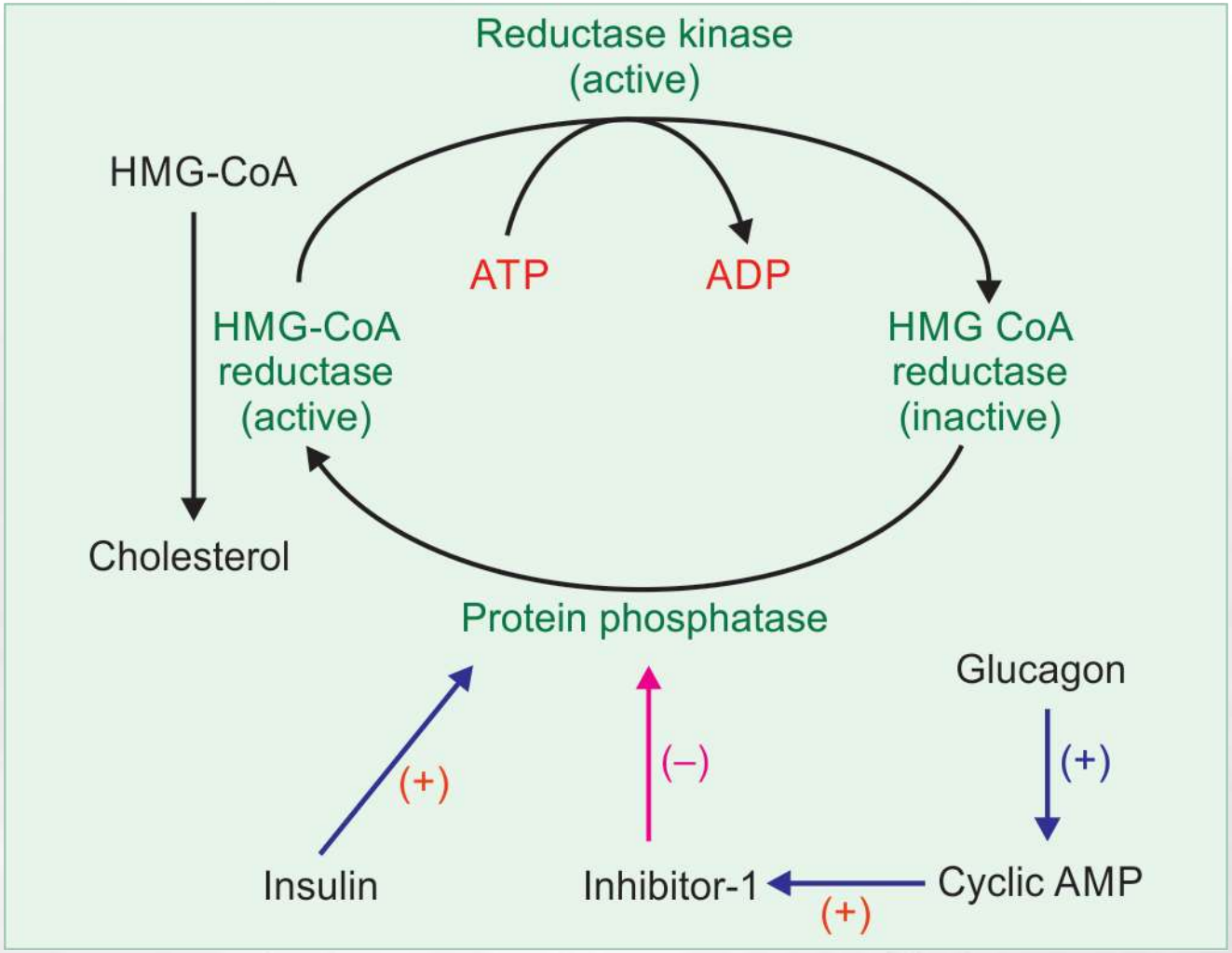
Further, **Insulin** and thyroxine increase the activity of HMG-CoA reductase.

Cortisol and glucagon decreases its activity.

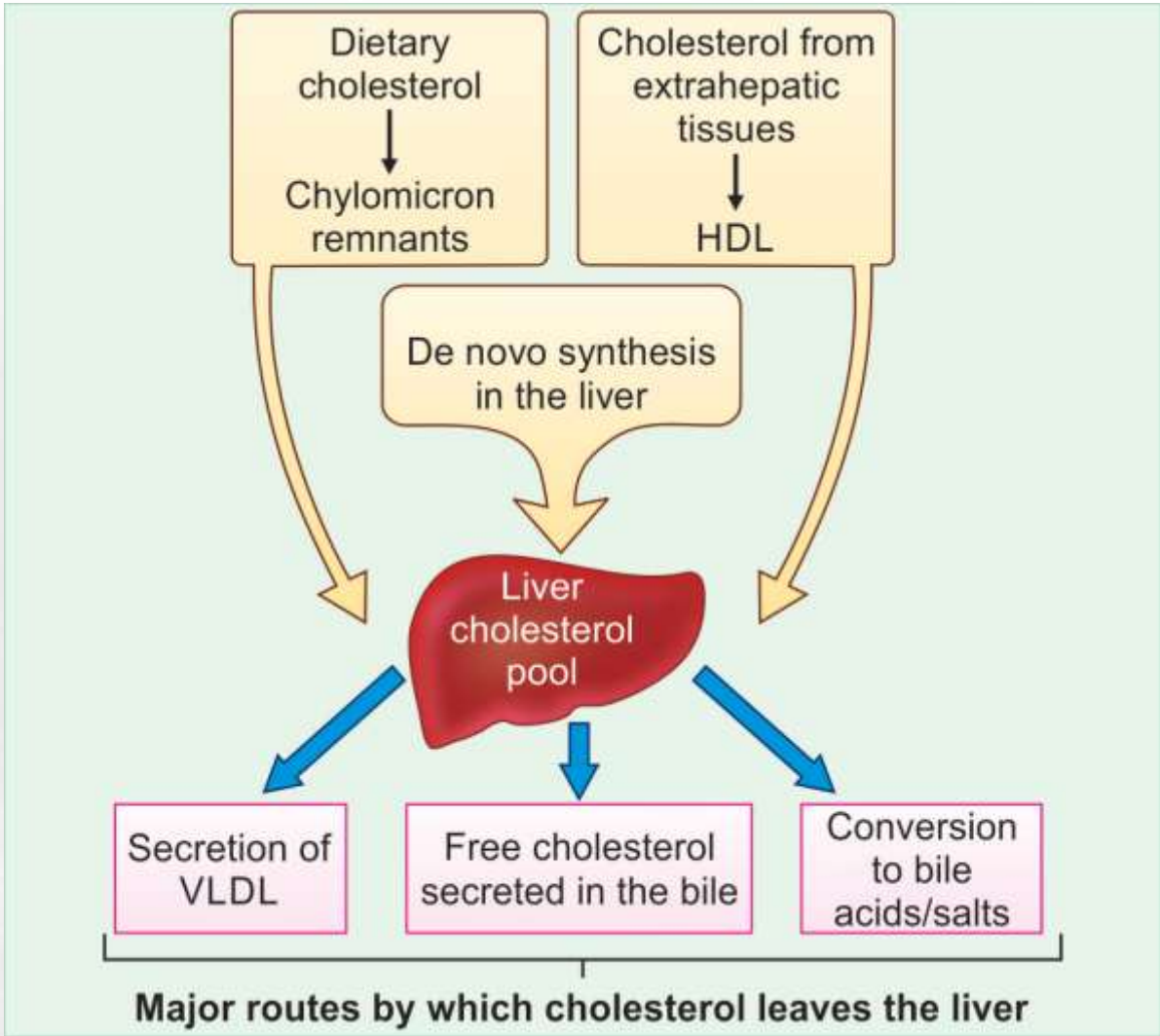
Drugs: Lovastatin and other "statin" group of drugs are competitive inhibitors of HMG-CoA reductase. So, they are used in clinical practice to reduce the cholesterol level in blood.



Regulation of cholesterol synthesis



Regulation of HMG CoA reductase

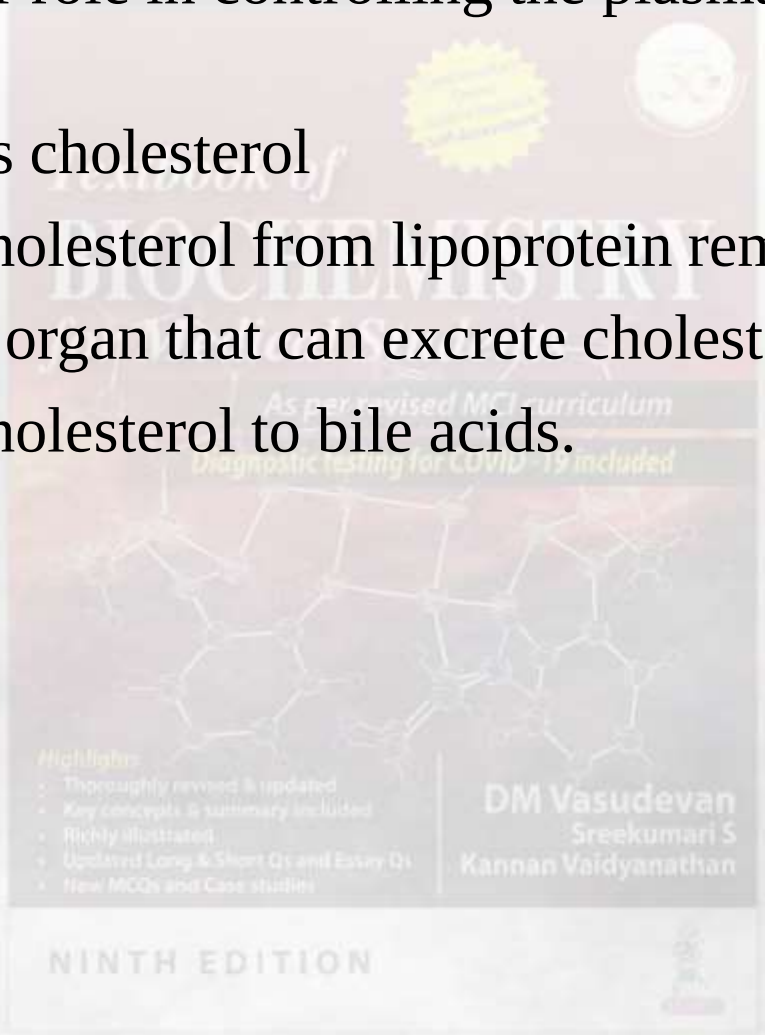


Major routes by which cholesterol leaves the liver

Liver and Cholesterol

The liver has a major role in controlling the plasma levels of LDL cholesterol.

1. Liver synthesizes cholesterol
2. Liver removes cholesterol from lipoprotein remnants.
3. Liver is the only organ that can excrete cholesterol through bile.
4. Liver converts cholesterol to bile acids.



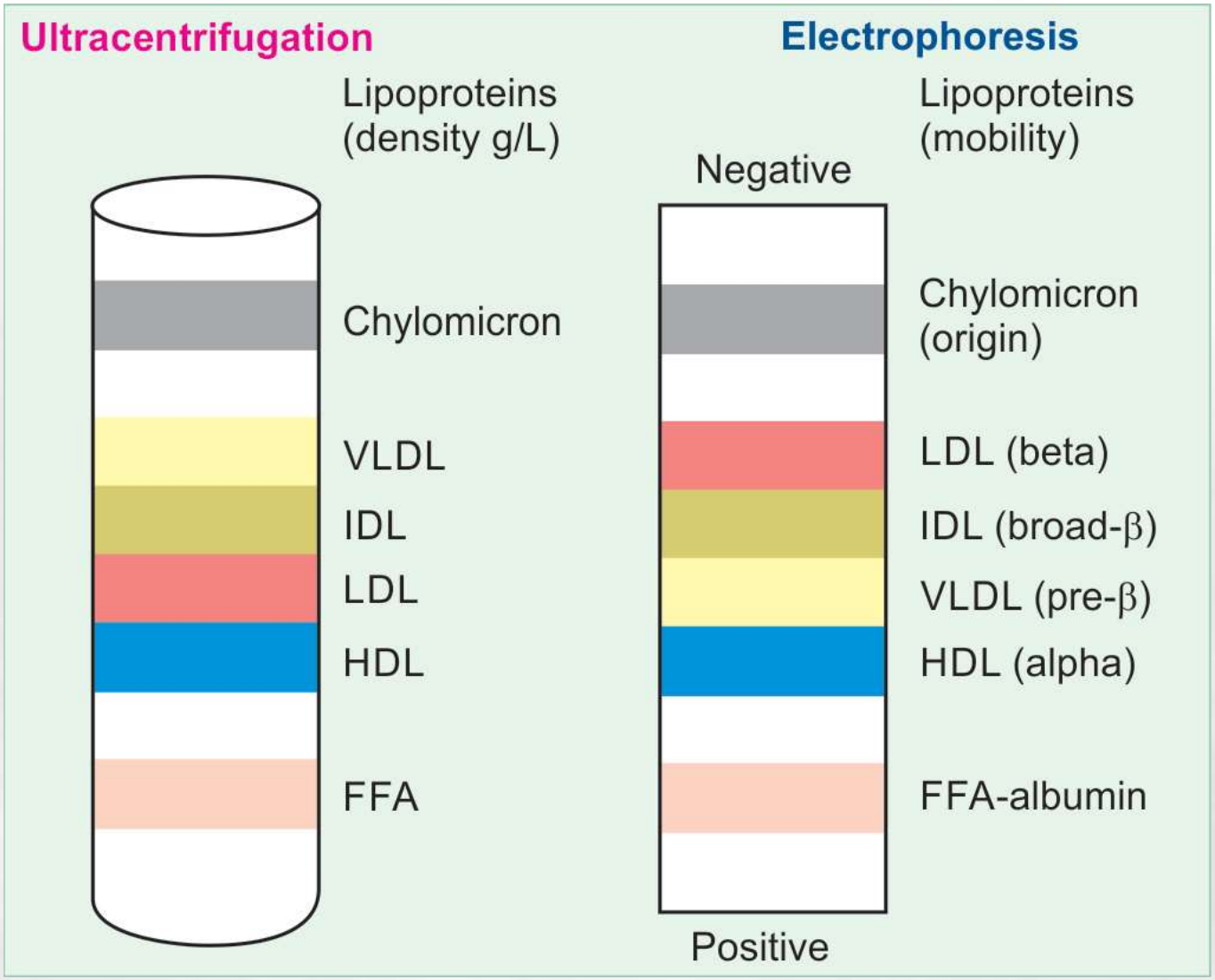
Plasma lipid profile (normal values)

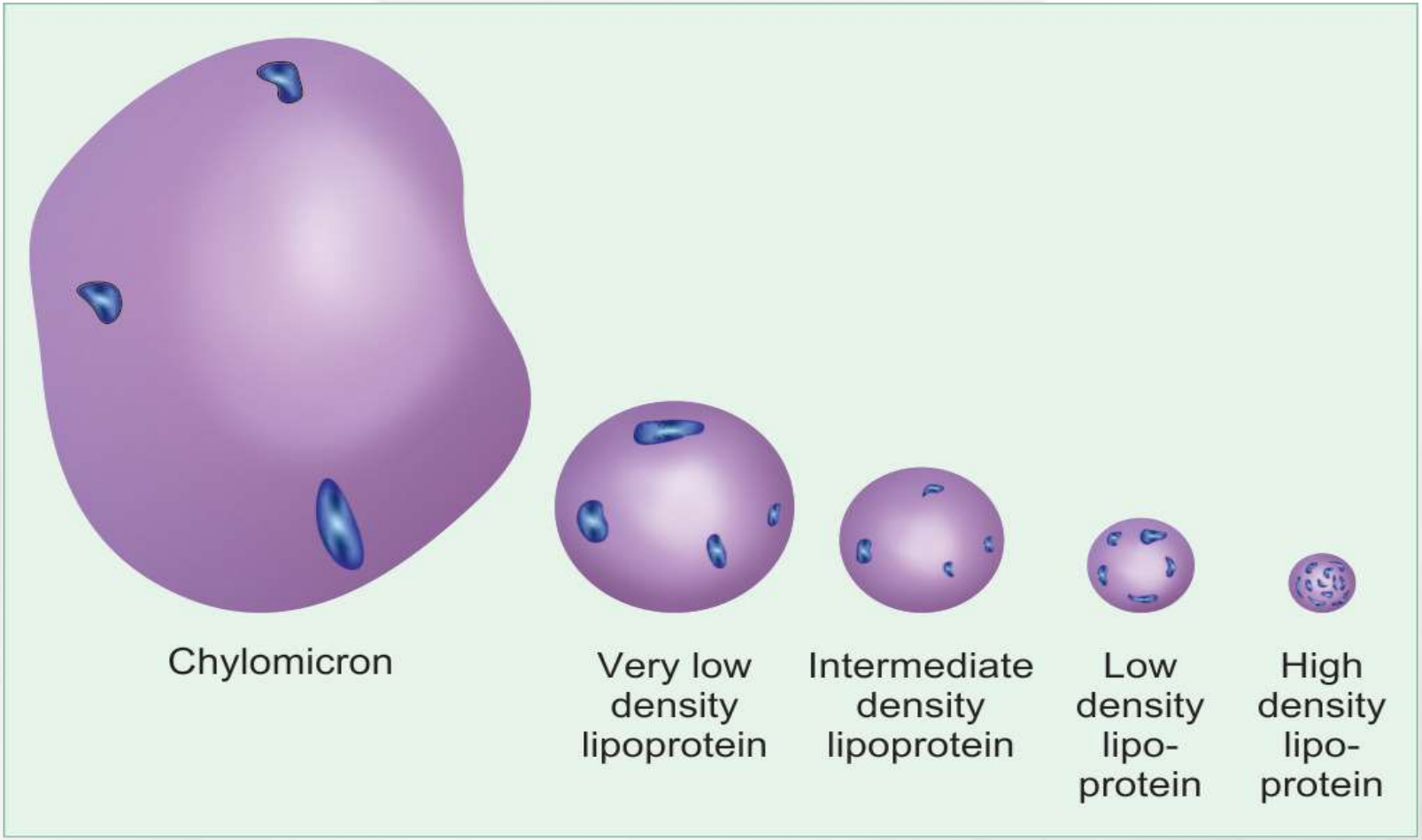
Analyte	Normal value
Total plasma lipids	400-600 mg/dl
Total cholesterol	140-200 mg/dl
HDL cholesterol, male	30-60 mg/dl
HDL cholesterol, female	35-75 mg/dl
LDL cholesterol, 30-39 yrs	80-130 mg/dl
Triglycerides, male	50-150 mg/dl
Triglycerides, female	40-150 mg/dl
Phospholipids	150-200 mg/dl
Free fatty acids (FFA) (NEFA)	10-20 mg/dl

Classification of Lipoproteins

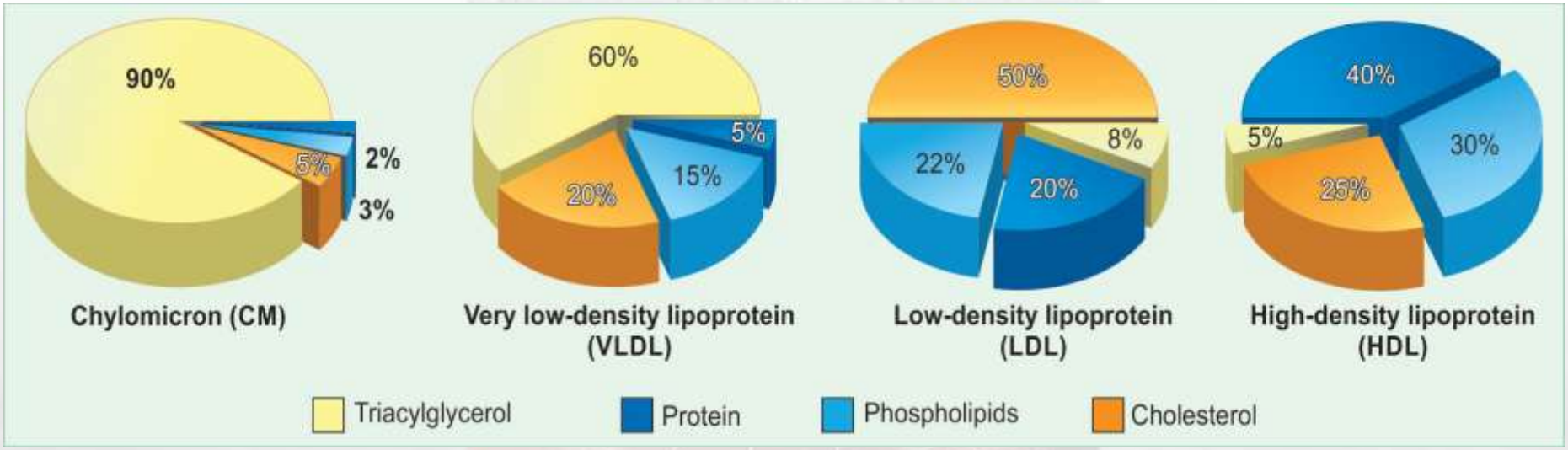
1. **Chylomicrons:** Contains apoprotein B-48.
2. **Very low-density lipoproteins** (VLDL). Main apoprotein is B-100.
3. **Intermediate density lipoproteins** (IDL)
4. **Low-density lipoproteins** (LDL). Major apoprotein in LDL is B-100.
5. **High-density lipoproteins** (HDL). Major apoprotein in HDL is apo A.

Free fatty acids (FFA) are complexed with albumin. (FFAs are not generally included in the classification of lipoproteins, because they are loosely bound).


Ultracentrifugation
Lipoproteins (density g/L)
Chylomicron
VLDL
IDL
LDL
HDL
FFA
Electrophoresis
Lipoproteins (mobility)
Negative
Chylomicron (origin)
LDL (beta)
IDL (broad-β)
VLDL (pre-β)
HDL (alpha)
FFA-albumin
Positive



Comparison of sizes of lipoproteins



Composition of different lipoproteins

Characteristics of different classes of lipoproteins

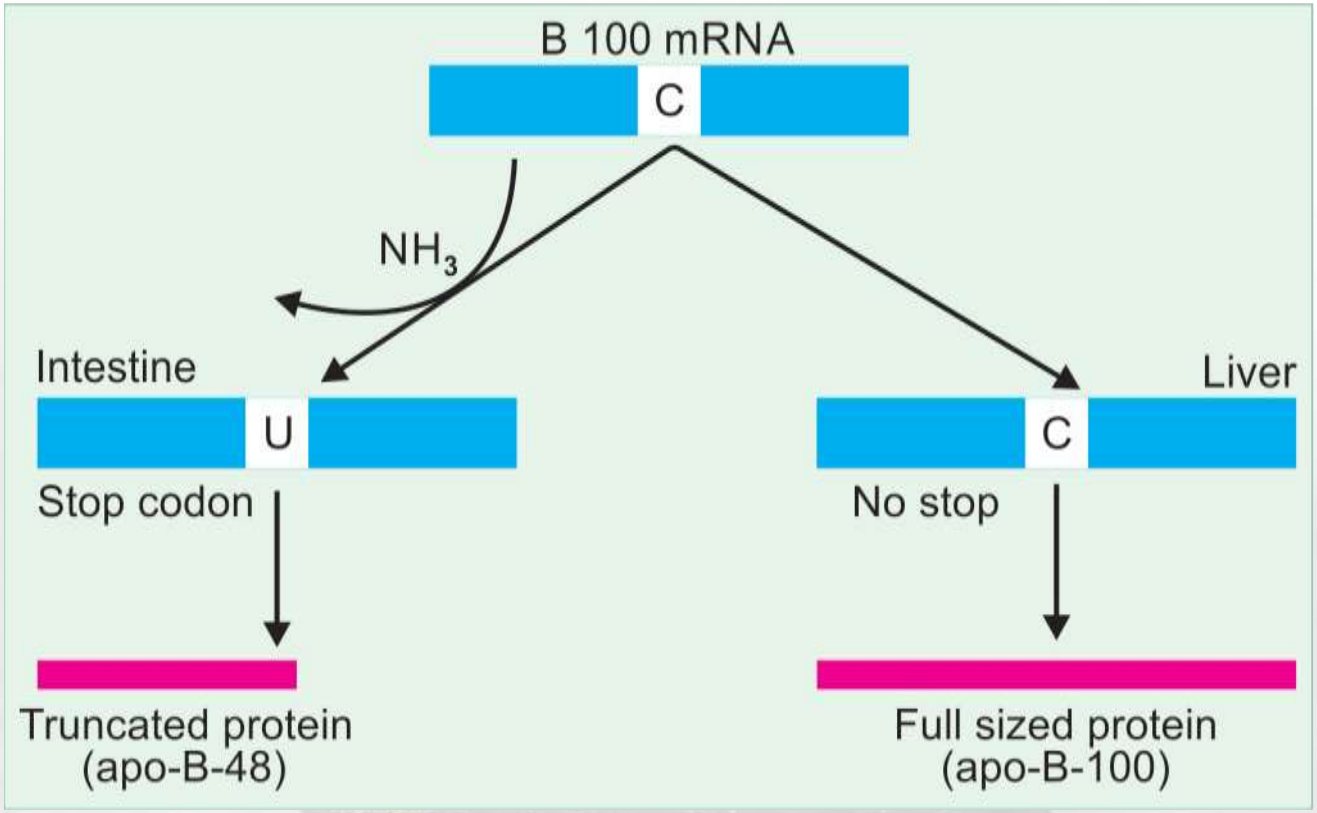
	Chylomicron	VLDL	IDL	LDL	HDL	FFA (*)
Density g/ml	<0.95	0.95-1.006	1.006-1.019	1.019-1.063	1.063-1.121	**1.28-1.3**
Diameter (nm)	500	70	30	25	15	**-**
Compo-sition						
Protein	2	10	20	20	30-60	**99**
TAG	80	50	30	10	10	**0**
Phospho-lipid	10	20	20	20	20-30	**0**
Chole-sterol	8	20	30	50	10-30	**0**
FFA	0	0	0	0	0	**1**
Apoproteins	A, B-48, C-II, E	B-100, C-II, E	B-100, E	B-100	A-I, C, E	**Albumin**
Transport function	TAG from gut to muscle	TAG from liver to muscle		Cholesterol from liver to peripheral tissues	Cholesterol from peripheral tissues to liver	FFA from fat depot to muscle and liver

Characteristics of apoproteins and their functions

Apoprotein	Component of	Functions	Mol. wt.	Site of production
apo A-I	HDL-2	Activation of LCAT; ligand for HDL receptor; Anti-atherogenic	28,000	Intestine; liver
apo A-II	HDL-3	Inhibits LCAT; stimulates lipase	17,000	Intestine; liver
apo B-100	LDL; VLDL	Binds LDL receptor	550,000	Liver
apo B-48	Chylomicrons	48% size of B-100	250,000	Intestine
apo C-I	Chylo-microns; VLDL	Activation of LCAT	7,000	Liver

Characteristics of apoproteins and their functions, continued

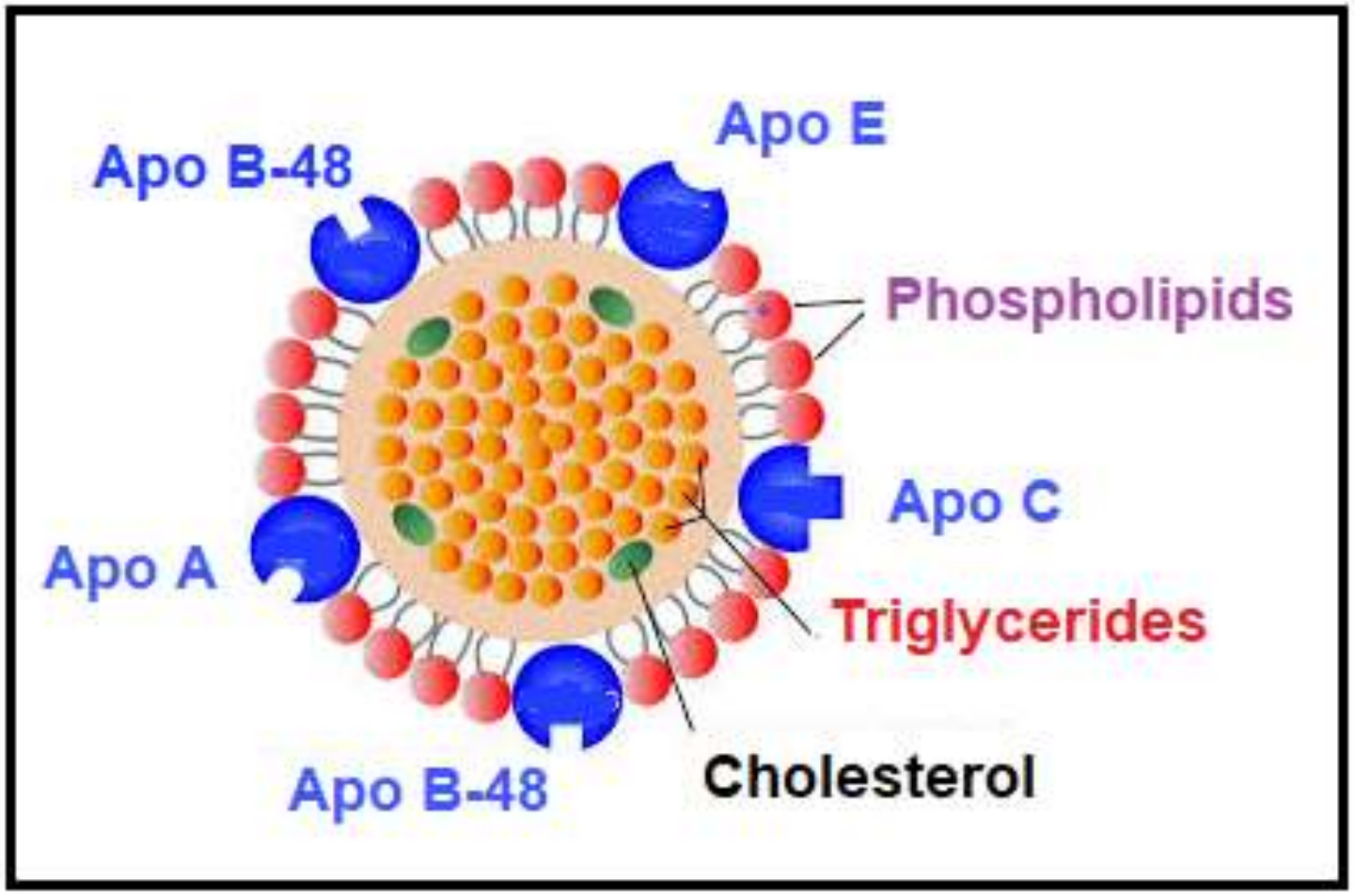
Apo-protein	Compo-nent of	Functions	Mol. wt.	Site of production
apo C-II	do	Activates extrahepatic lipoprotein lipase in vessel walls; clearance chylomicrons and VLDL	9,000	Liver
apo C-III	do	Inhibits lipoprotein lipase; antiatherogenic	8,500	Liver
apo E	LDL; VLDL; chylo	Arginine rich; ligand for hepatic uptake	30,000	Liver
apo Lp (a)	Lp (a)	Attached to B-100; impairs fibrinolysis; highly atherogenic		Liver



Apo B-48 and apo B-100 are produced from the same gene. In liver, the mRNA is translated as B-100. But in intestine, a stop codon is generated in the middle, and a short protein is produced in intestine (B48). Apo B-48 is only 48% of the size of B-100.

Chylomicrons

- **Synthesis of Chylomicrons**
- Chylomicrons are formed in the **intestinal mucosal** cells, and secreted into the lacteals of lymphatic system.
- They are **rich in triglyceride**.
- If lipemic serum is kept overnight in the refrigerator, chylomicrons rise as a creamy layer to the top, leaving the subnatant clear.
- When the chylomicrons are synthesized by the intestinal mucosa, they contain only **apo-B-48** and apo-A.
- Apo-C and apo-E are added from HDL in blood during transport,



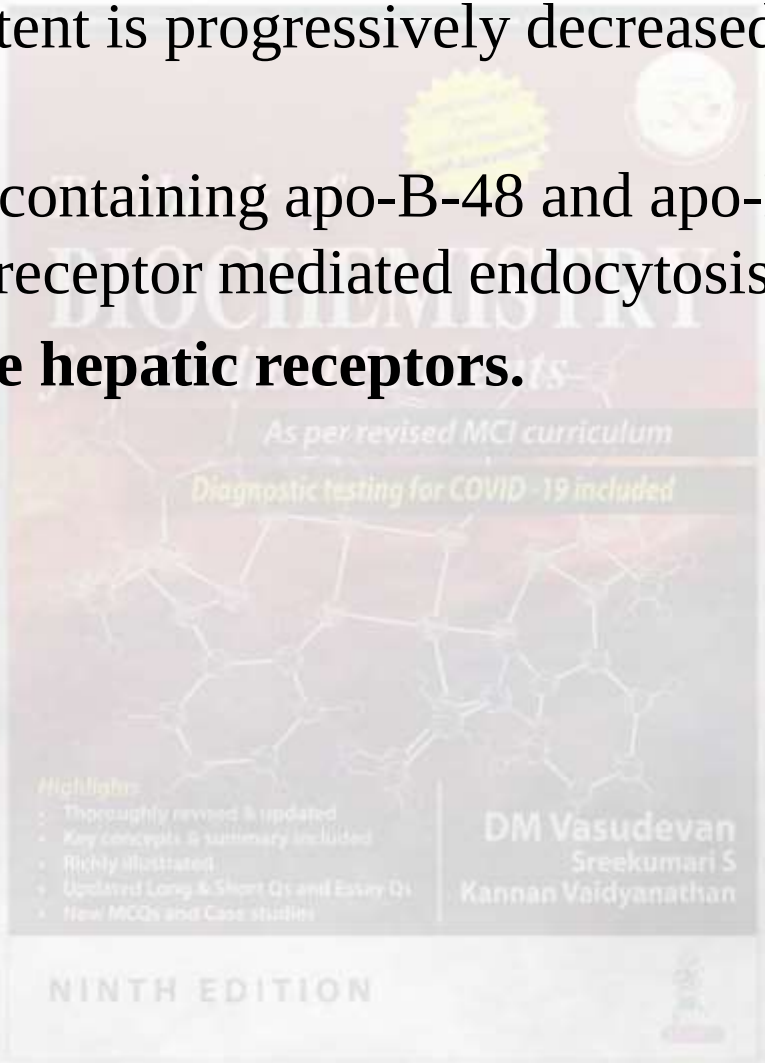
Chylomicron

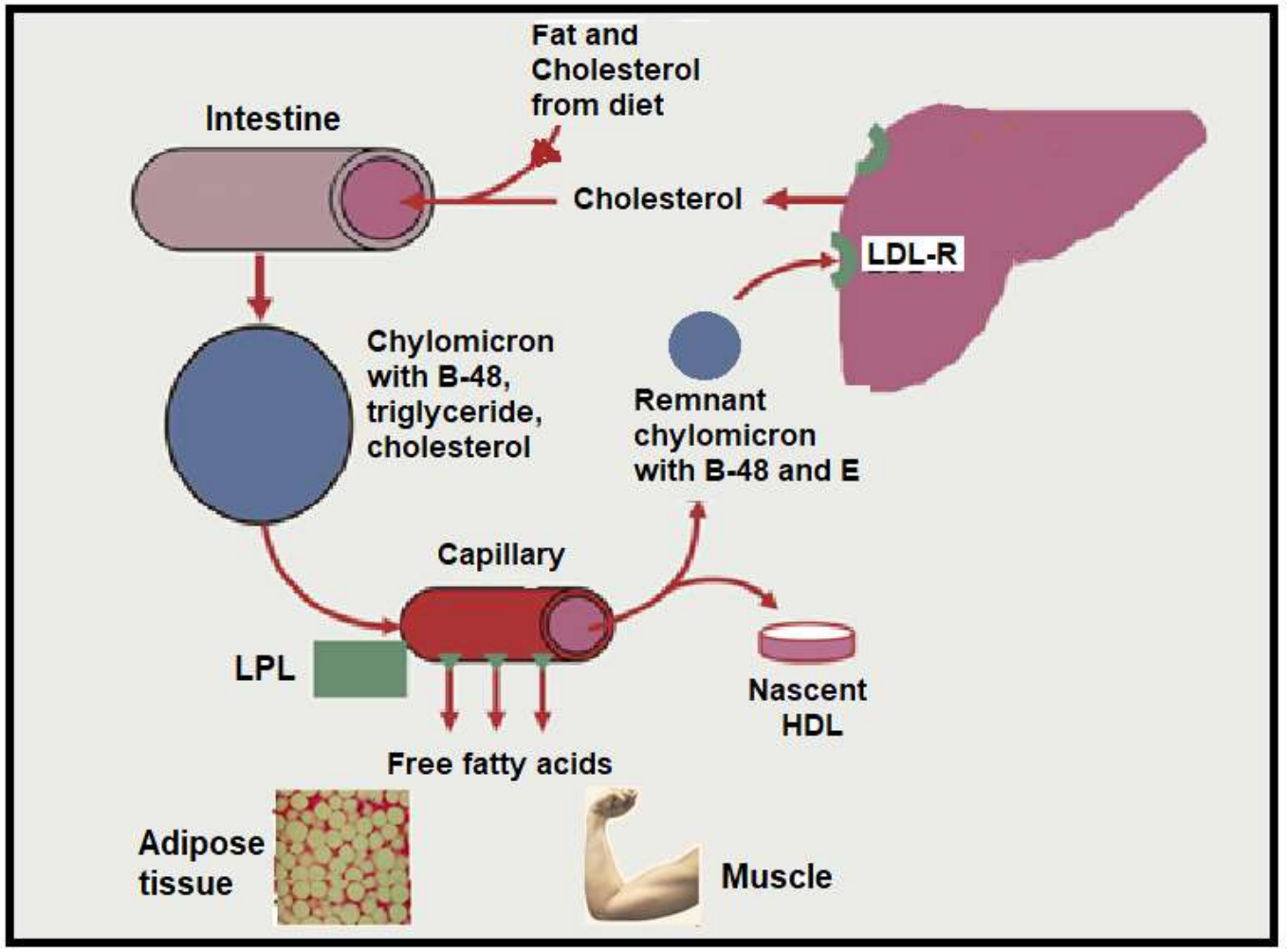
Metabolism of Chylomicrons

- Main sites of metabolism of chylomicrons are **adipose tissue** and **skeletal muscle**.
- 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 chylomicrons activates LpL.
- LpL hydrolyzes triglycerides present in chylomicrons into fatty acids and glycerol.
- Muscle and adipose tissue cells take up liberated fatty acids.

Liver Takes up Chylomicron 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.**

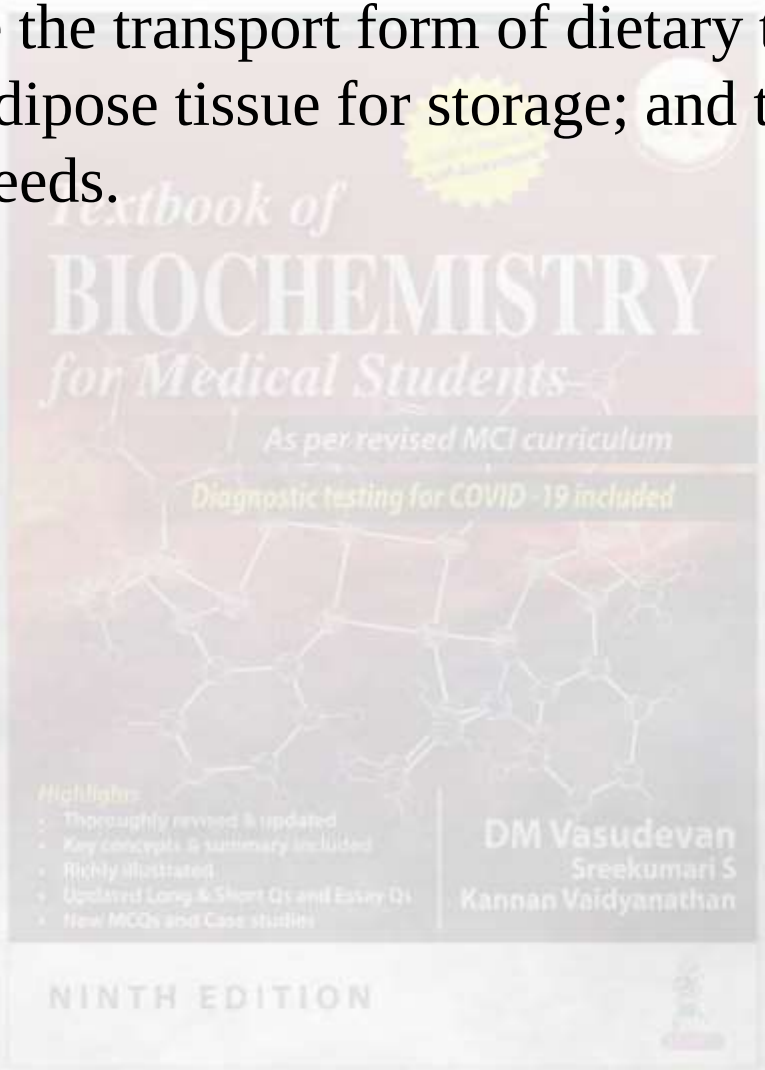




Metabolism of chylomicrons. LDL-R = LDL-receptor. LPL = lipoprotein lipase.

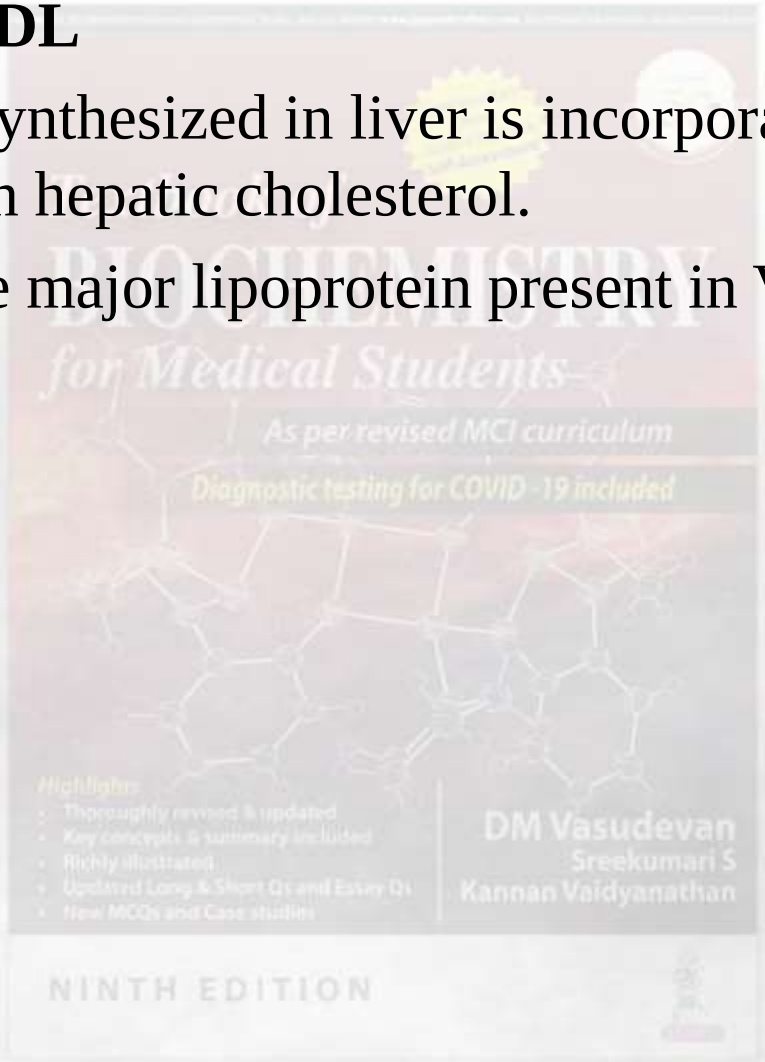
Function of Chylomicrons

- Chylomicrons are the transport form of dietary triglycerides from intestines to the adipose tissue for storage; and to muscle or heart for their energy needs.



Very Low Density Lipoproteins

- **Synthesis of VLDL**
- Triacylglycerol synthesized in liver is incorporated into VLDL along with hepatic cholesterol.
- **Apo-B-100** is the major lipoprotein present in VLDL when it is secreted.

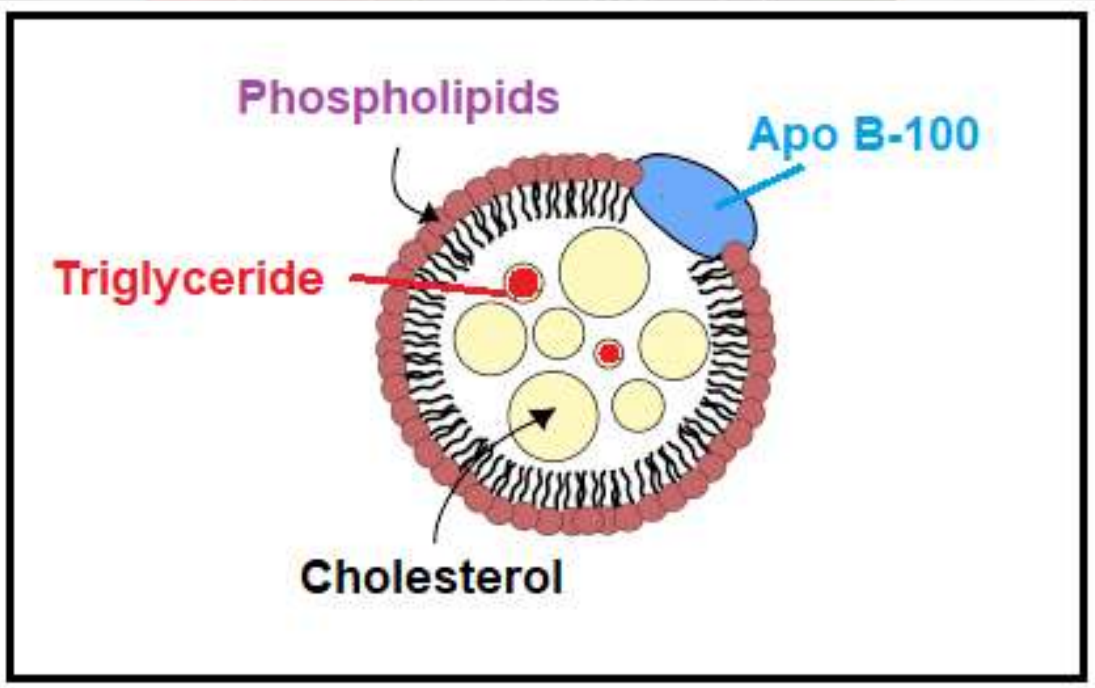


Metabolism of VLDL

- When they reach the peripheral tissues, **apo-C-II activates LpL** which liberates fatty acids that are taken up by adipose tissue and muscle.
- The remnant is now designated as **IDL (intermediate density lipoprotein)** and contains less of TAG and more of cholesterol.
- The major fraction of IDL further loses triglyceride, so as to be converted to LDL (low density lipoprotein).
- 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.
- VLDL carries **endogenous TAG** from liver to peripheral tissues for energy needs.

Low Density Lipoproteins

- Low density lipoproteins (LDL) transports cholesterol from liver to peripheral tissues.
- The only apoprotein present in LDL is **apo-B-100**.
- Most of the LDL particles are derived from VLDL.
- The half-life of LDL in blood is about 2 days.



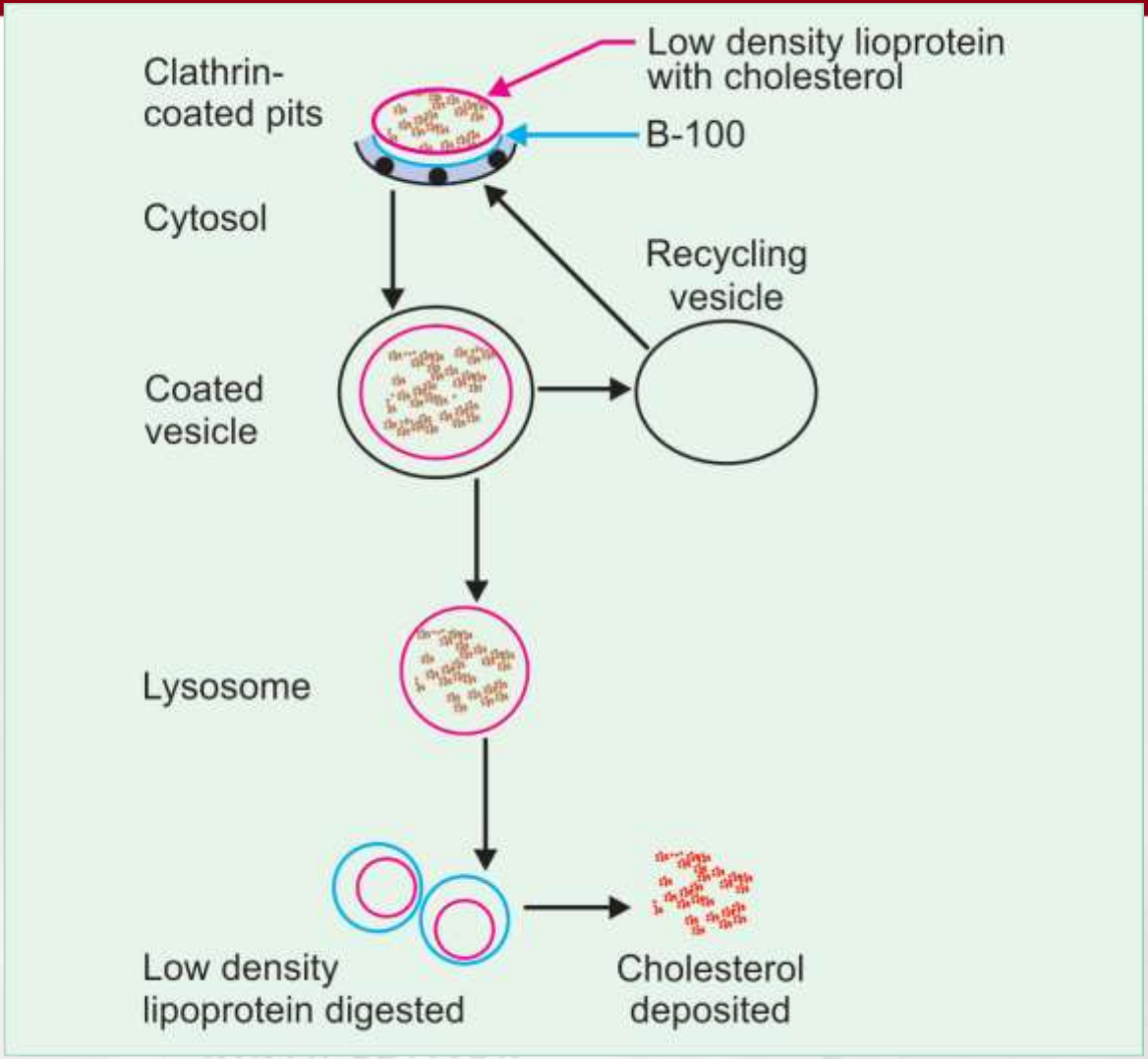
Metabolism of LDL and LDL Receptors

- The LDL is taken up by peripheral tissues by receptor mediated endocytosis.
- LDL receptors are present on all cells but most abundant in hepatic cells.
- LDL receptors are located in specialized regions called **clathrin-coated pits**.
- Binding of LDL to the receptor is by apo-B-100.
- When the apo-B-100 binds to the apo-B-100 receptor, the receptor-LDL complex is internalized by endocytosis.

- The endosome vesicle thus formed fuses with lysosomes.
- The LDL particle, along with apoproteins and cholesterol ester are hydrolyzed to form free cholesterol.
- The free receptors can now return to the membrane surface to bind further LDL molecules.
- The free cholesterol is either incorporated into plasma membranes or esterified (by ACAT) and stored within the cell.
- The excess cholesterol tends to be deposited within the arteries, leading to atherosclerosis.

Function of LDL

- About 75% of the plasma cholesterol is incorporated into the LDL particles.
- LDL transports cholesterol **from liver to the peripheral tissues**.
- The cholesterol thus liberated in the cell has three major fates:
  i. It is used for the synthesis of other steroids like steroid hormones.
  ii. Cholesterol may be incorporated into the membranes.
  iii. Cholesterol may be esterified to a MUFA by acyl cholesterol acyl transferase (ACAT) for storage.
- The cellular content of cholesterol regulates further endogenous synthesis of cholesterol by regulating HMG-CoA reductase.

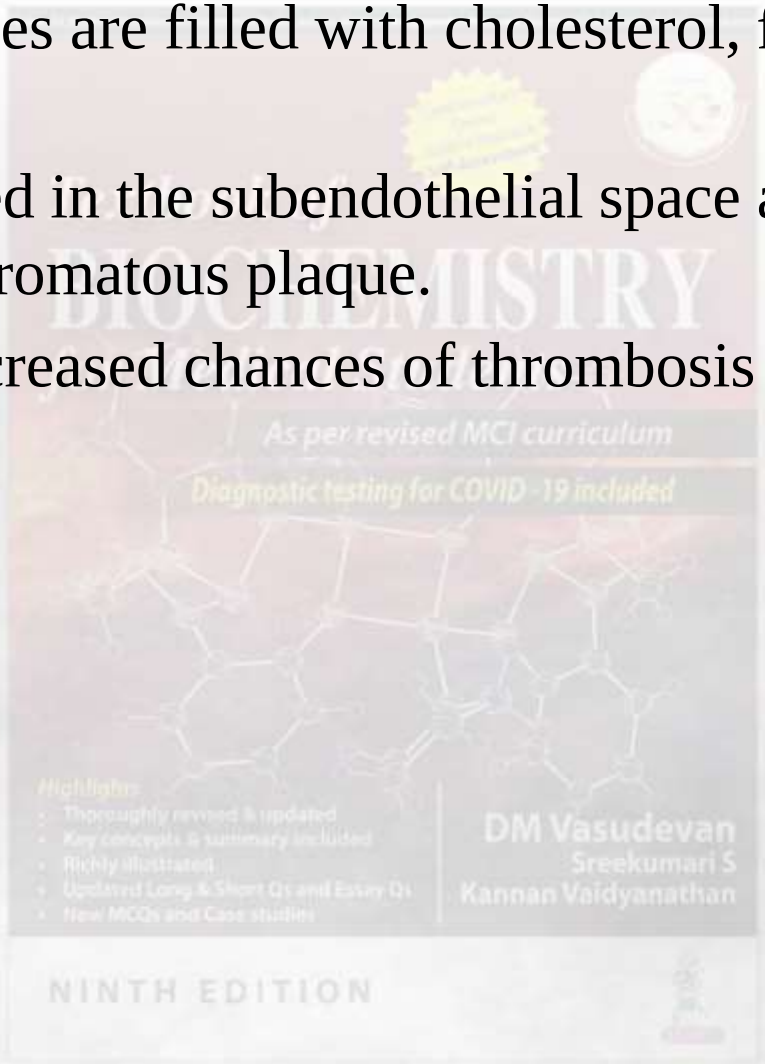


Uptake and fate of LDL.

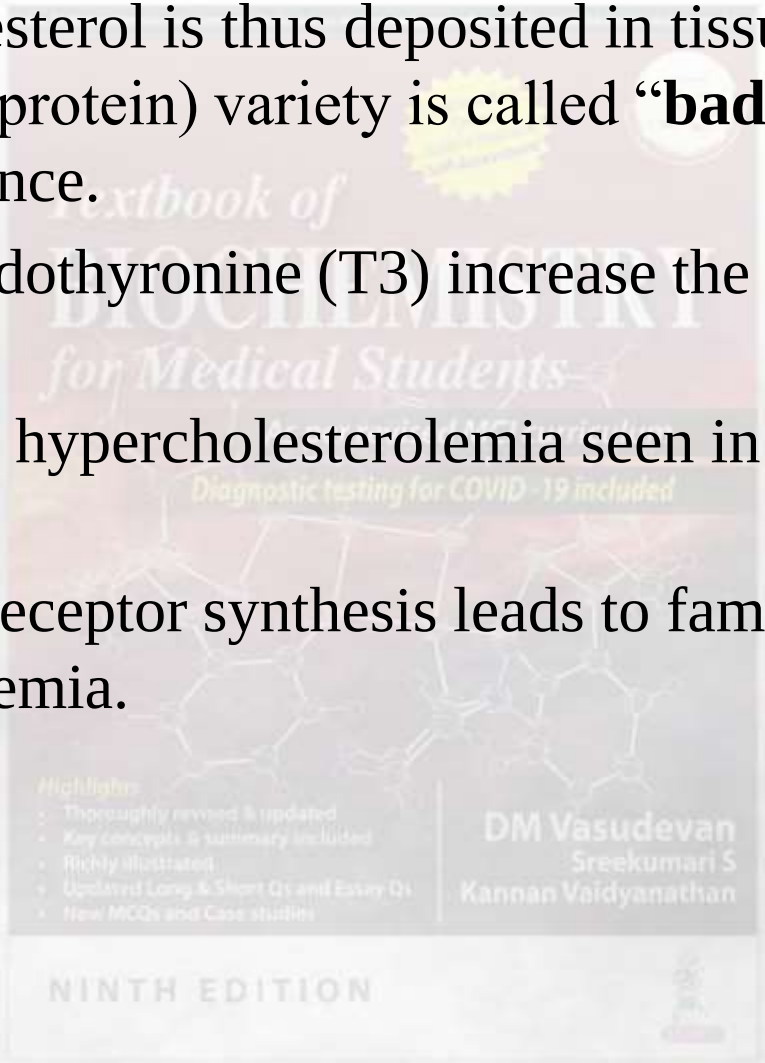
LDL and Clinical Applications

- The LDL concentration in blood has positive correlation with incidence of **cardiovascular diseases**.
- A fraction of cholesterol is taken up by macrophages.
- Increased levels of LDL or oxidation of LDL increases uptake of cholesterol by macrophages.
- LDL infiltrates through arterial walls, and are taken up by macrophages.
- This is the starting event of **atherosclerosis** leading to myocardial infarction.

- When macrophages are filled with cholesterol, foam cells are formed.
- They get deposited in the subendothelial space and leads to the formation of atheromatous plaque.
- This results in increased chances of thrombosis and coronary artery disease.



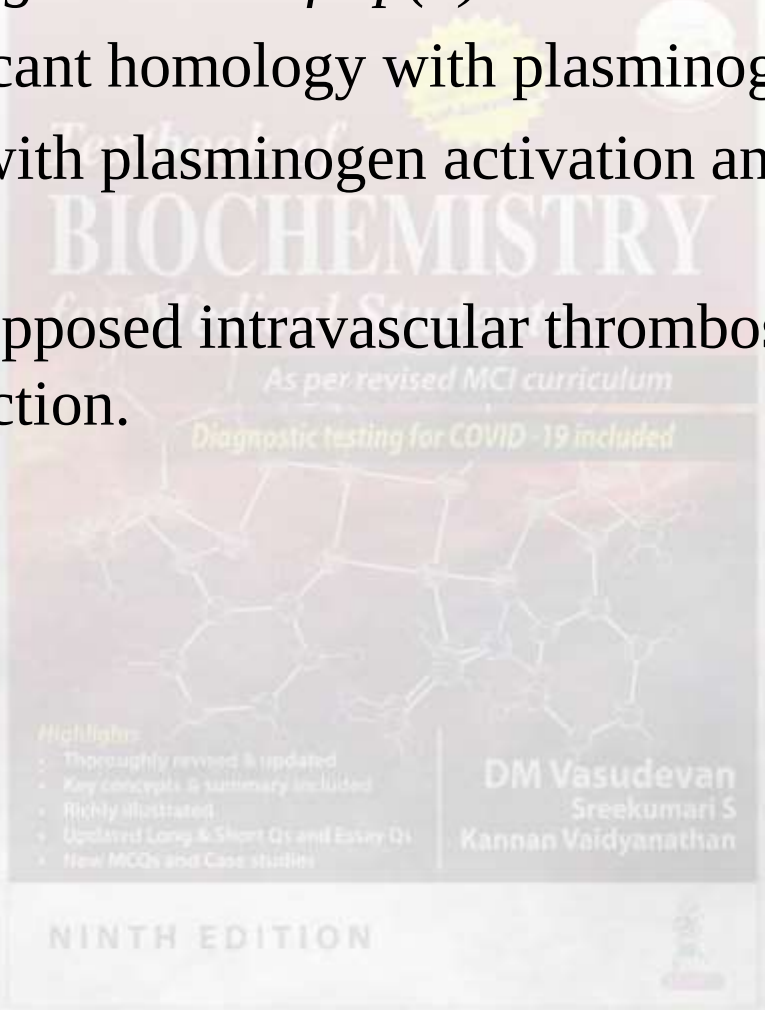
- Since LDL-cholesterol is thus deposited in tissues, the LDL (low density lipoprotein) variety is called "**bad cholesterol**" in common parlance.
- Insulin and tri-iodothyronine (T3) increase the binding of LDL to liver cells.
- This explains the hypercholesterolemia seen in diabetes and hypothyroidism.
- Defects in LDL receptor synthesis leads to familial hypercholesterolemia.



Lipoprotein (a)

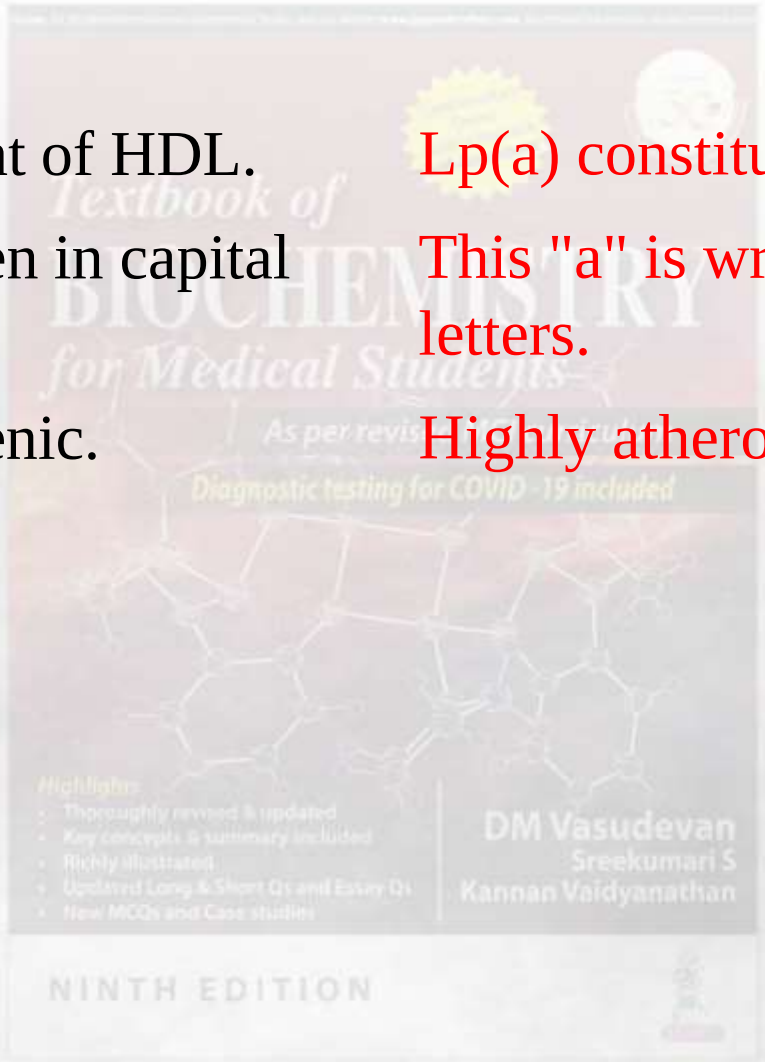
- Lp(a) is very strongly associated with myocardial infarction and is sometimes called the “little rascal”.
- Lp(a), when present, is attached to apo-B-100 by a disulfide bond. In 40% population, there is no detectable level of Lp(a) in serum.
- In 20% of population, the Lp(a) concentration in blood is more than 30 mg/dL; and these persons are susceptible for heart attack at a younger age.
- Lp(a) is associated with heart attacks at the age of 30 or 40 years.

- *Indians have a higher level of Lp(a) than Western populations.*
- Lp(a) has significant homology with plasminogen.
- So, it interferes with plasminogen activation and impairs fibrinolysis.
- This leads to unopposed intravascular thrombosis and possible myocardial infarction.

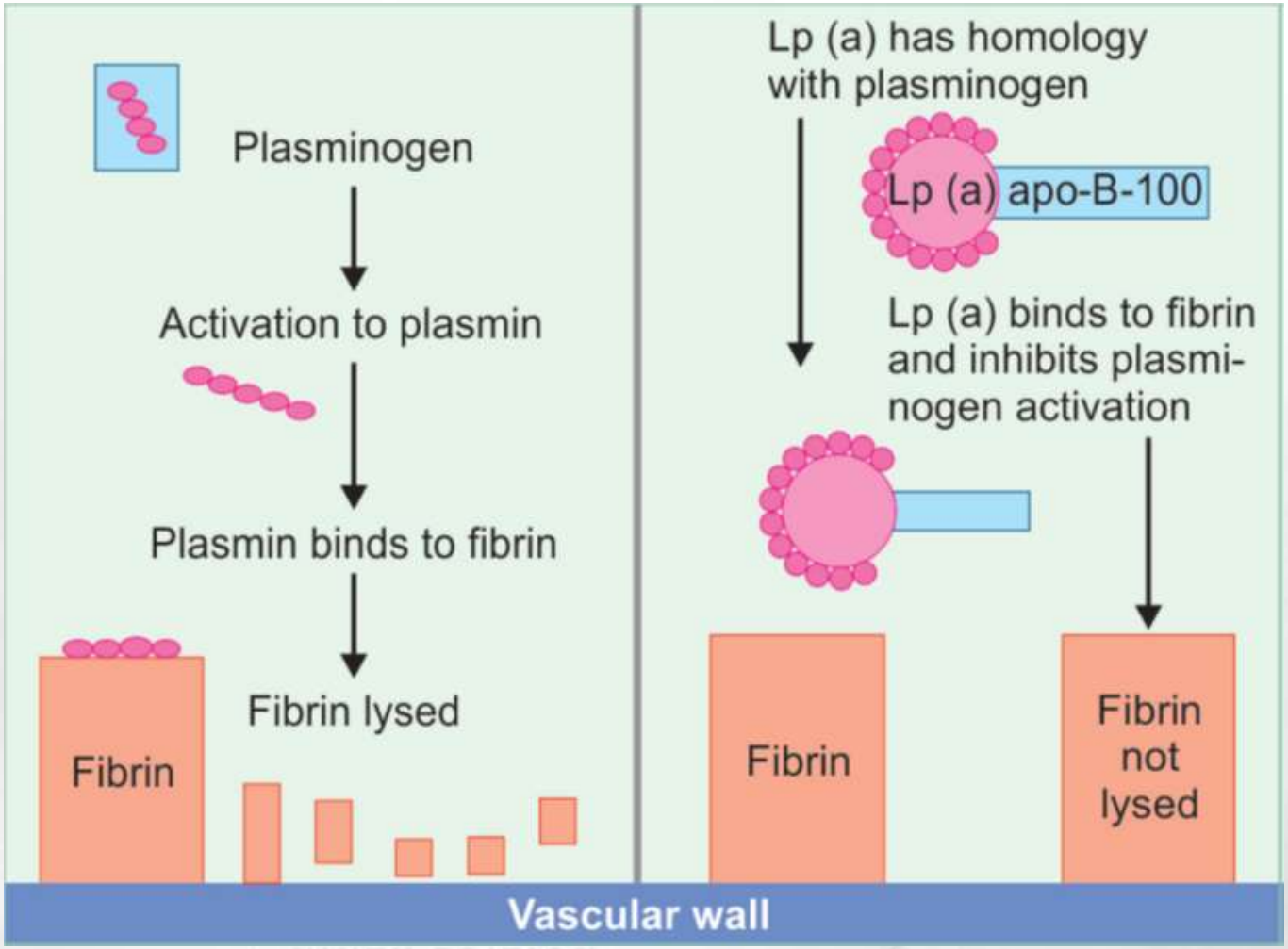


Apo-A and Lp(a) are different

Apo-A constituent of HDL.	Lp(a) constituent of LDL.
This "A" is written in capital letters.	This "a" is written in small letters.
It is anti-atherogenic.	Highly atherogenic

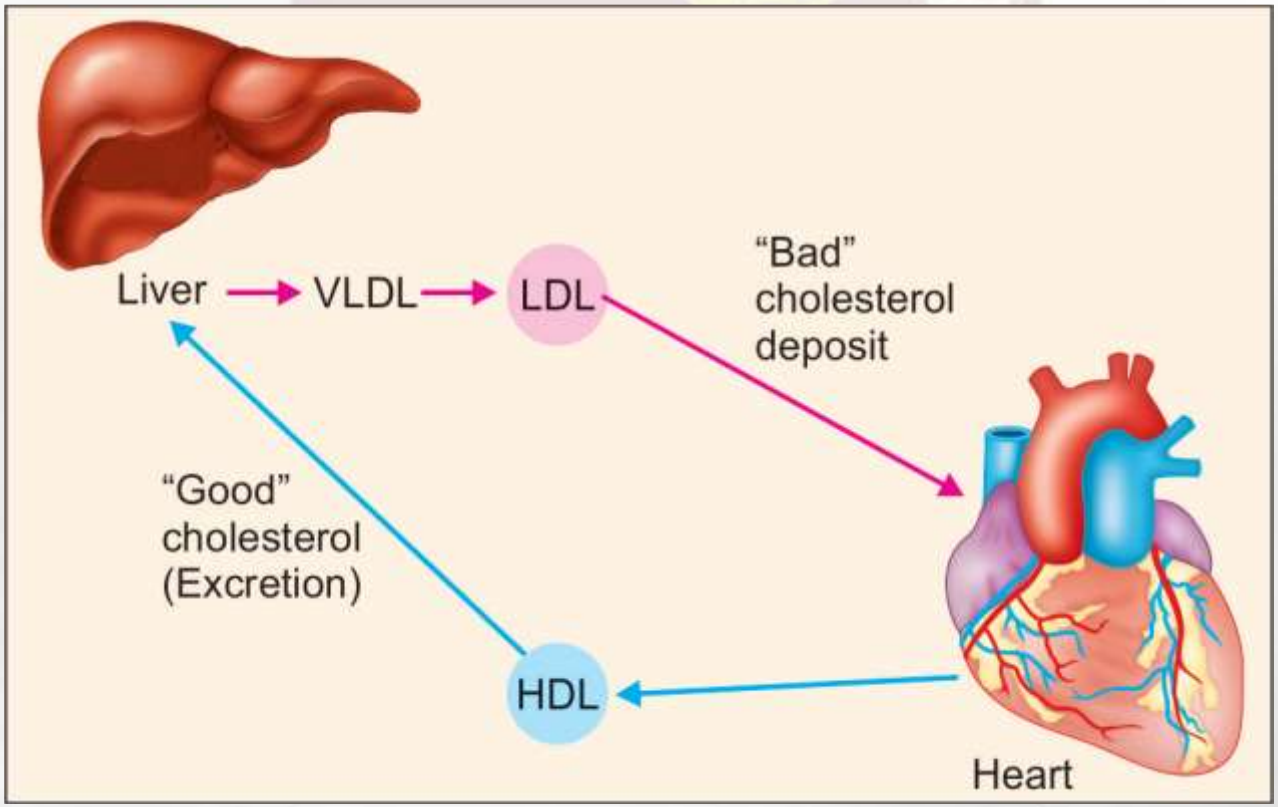


Mechanism of action of Lp(a)



Lp(a) competitively inhibits plasminogen activation; and so inhibits fibrinolysis.

Forward and reverse transport of cholesterol



High Density Lipoprotein

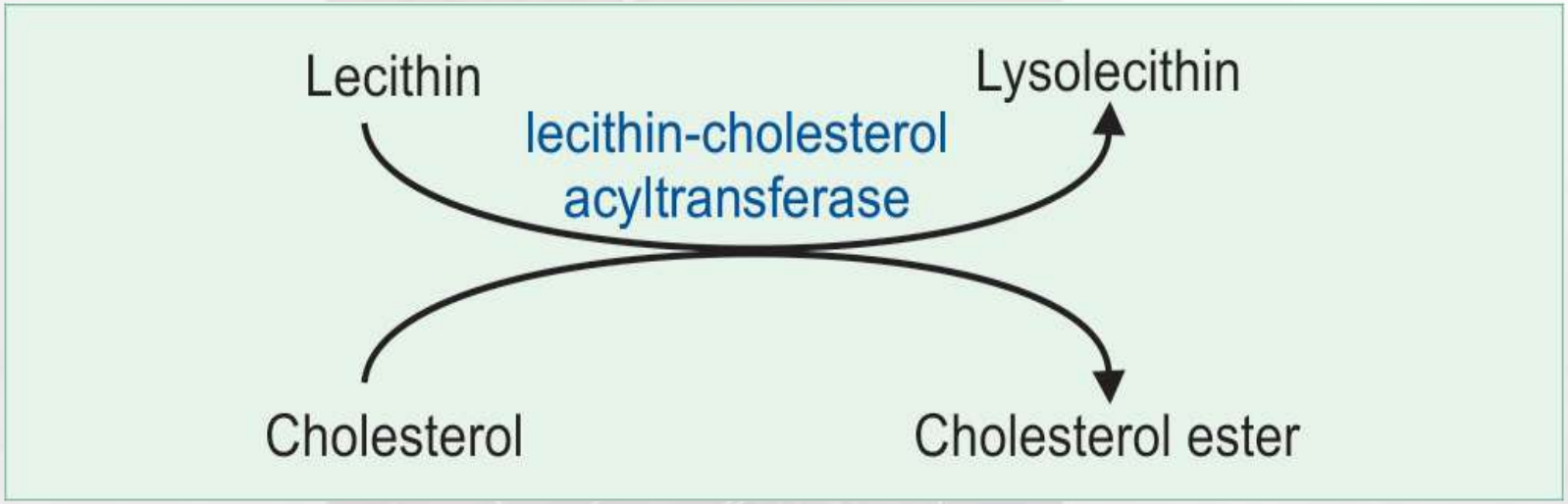
- High density lipoproteins (HDL) transport cholesterol from peripheral tissues to the liver.
- The major apoprotein in HDL is Apo-A-I.
- The intestinal cells synthesize components of HDL and release into blood.
- The nascent HDL in plasma are discoid in shape.
- The free cholesterol derived from peripheral tissue cells are taken up by the HDL.
- The **apo-A-l** of HDL activates **LCAT** (lecithin cholesterol acyl transferase) present in the plasma.
- The LCAT then binds to the HDL disk.

- **Lecithin** is a component of phospholipid bilayer of the HDL disk.
- The second carbon of lecithin contains one molecule of polyunsaturated fatty acid **(PUFA)**.
- It is transferred to the third hydroxyl group of cholesterol to form cholesterol ester.
- The esterified cholesterol which is more hydrophobic, moves into the interior of the HDL disk.
- This reaction continues; till HDL becomes spherical and a lot of cholesterol esters are formed.

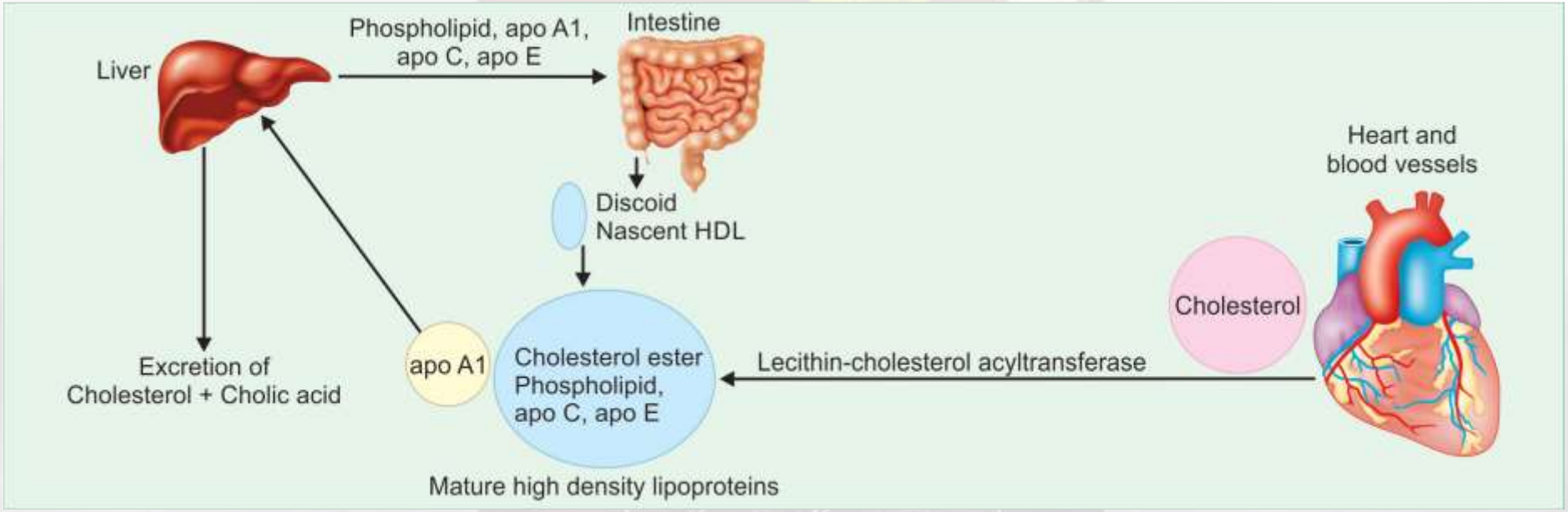
High Density Lipoprotein (HDL)

- Transport of cholesterol from **peripheral tissue to liver**, then excreted through bile
- HDL in serum is inversely related to myocardial infarction.
- "Anti-atherogenic" or "protective" "good cholesterol"
- HDL level below 35 mg/dl increases the risk
- HDL level above 60 mg/dl gives protection from coronary artery diseases

HDL activates **LCAT** (lecithin cholesterol acyl transferase)


Lecithin
Lysolecithin
lecithin-cholesterol
acyltransferase
Cholesterol
Cholesterol ester

HDL metabolism



- Mature HDL spheres are taken up by liver cells by **apo-A-l** mediated receptor mechanism.
- Hepatic lipase hydrolyzes HDL phospholipid and TAG.
- Cholesterol esters are released into liver cells.
- The cholesterol that reaches the liver is used for synthesis of bile acids or excreted as such in bile.
- The cholesterol ester from HDL is transferred to VLDL, IDL and LDL by a **Cholesterol Ester Transfer Protein (CETP).**

Functions of HDL

i. HDL is the main transport form of cholesterol from **peripheral tissue to liver**, which is later excreted through bile.

- This is called **reverse cholesterol transport** by HDL.

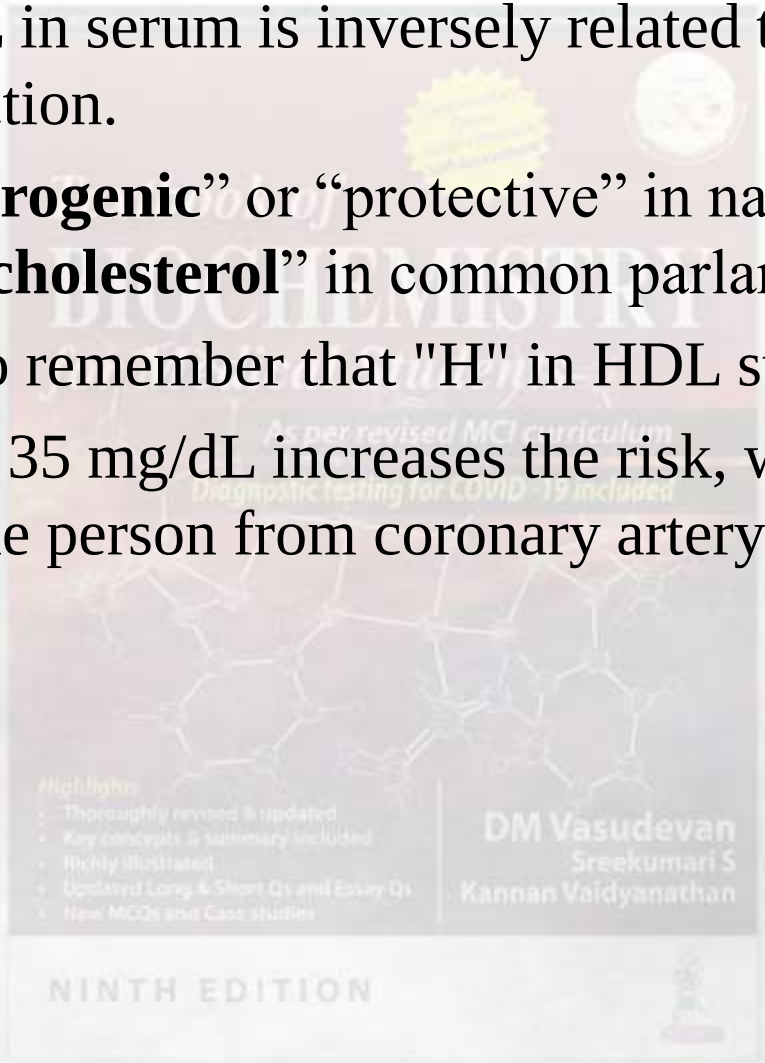
ii. The only excretory route of cholesterol from the body is the bile.

iii. Excretion of cholesterol needs prior esterification with PUFA.

- Thus *PUFA will help in lowering of cholesterol in the body,* and so **PUFA is antiatherogenic**.

Clinical Significance of HDL

- The level of HDL in serum is inversely related to the incidence of myocardial infarction.
- As it is "**antiatherogenic**" or "protective" in nature, HDL is known as "**good cholesterol**" in common parlance.
- It is convenient to remember that "H" in HDL stands for "Healthy".
- HDL level below 35 mg/dL increases the risk, while level above 60 mg/dL protects the person from coronary artery diseases.

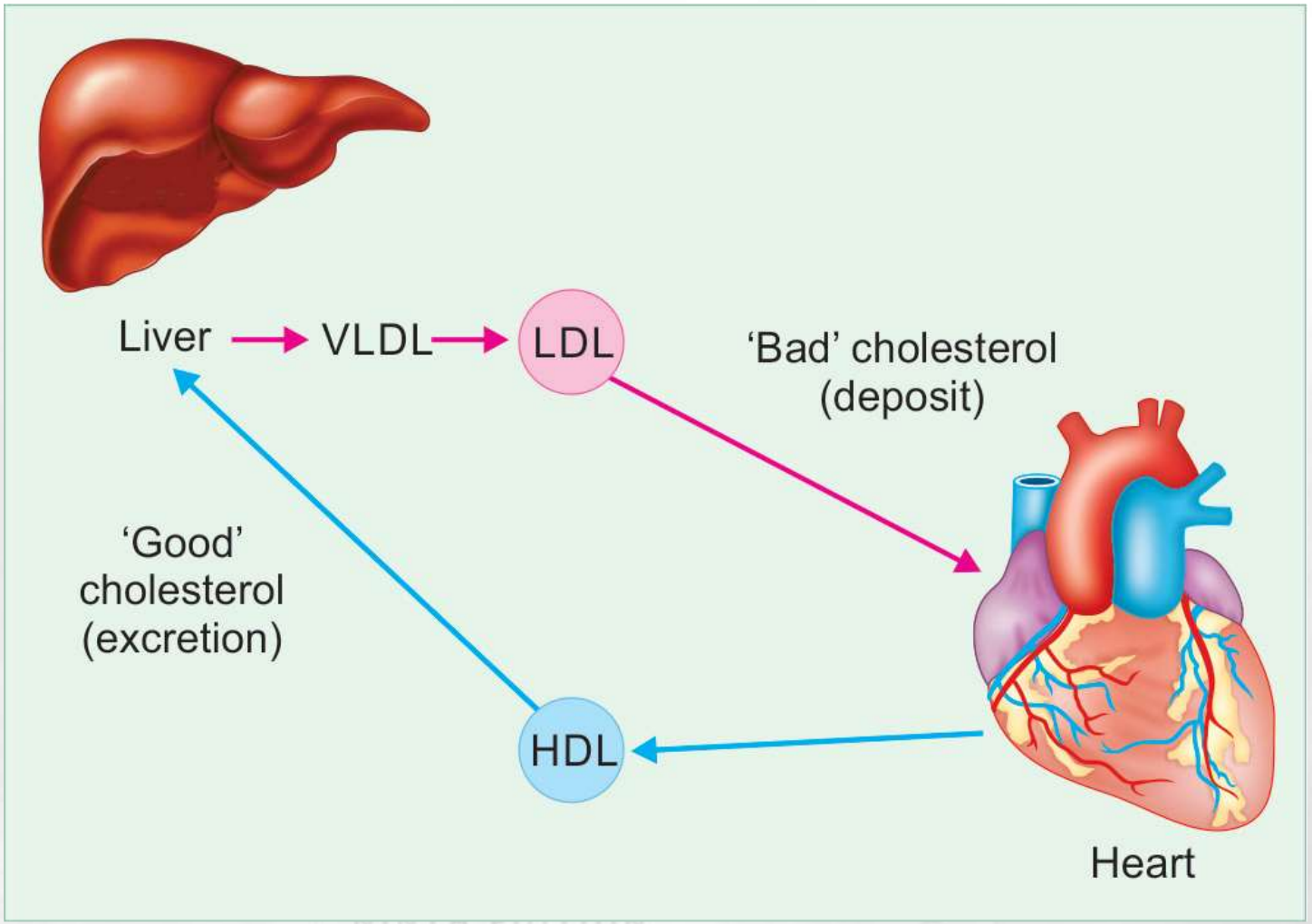


Clinical Significance of HDL

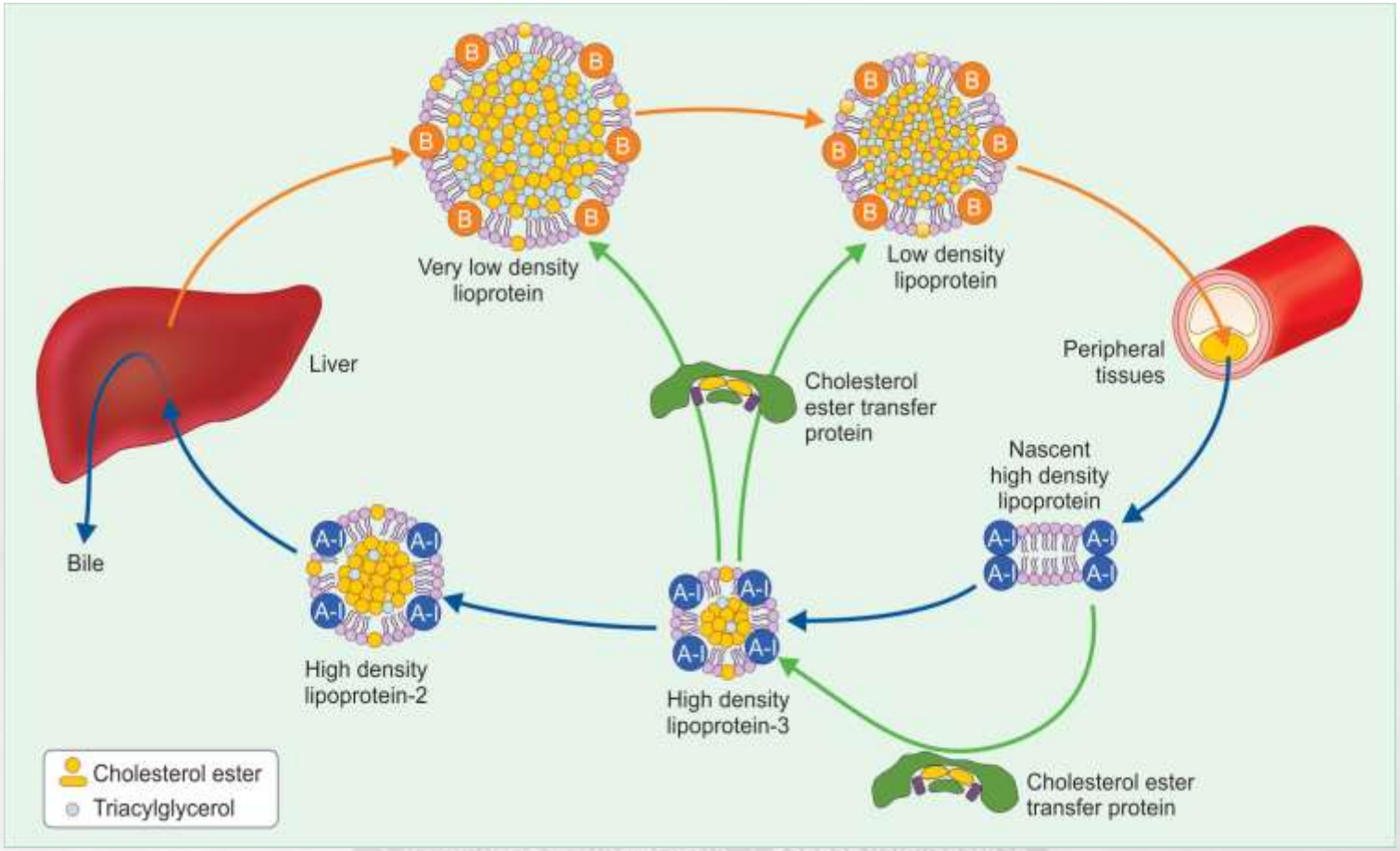
HDL can bind to the antioxidant enzyme **paraoxonase** (PON1). Since PON1 can inhibit lipid oxidation and macrophage foam cell formation, the measurement of PON1 activity of HDL particles is a better biomarker of its atheroprotective effect.

Myeloperoxidase (MPO) is another enzyme which can bind HDL at the same site as PON1. In dyslipidemic patients, MPO levels are higher than normals. Hence the reciprocal modulation of the activity of these two enzymes associated with HDL particles will decide the antioxidant and anti-inflammatory properties of these particles.

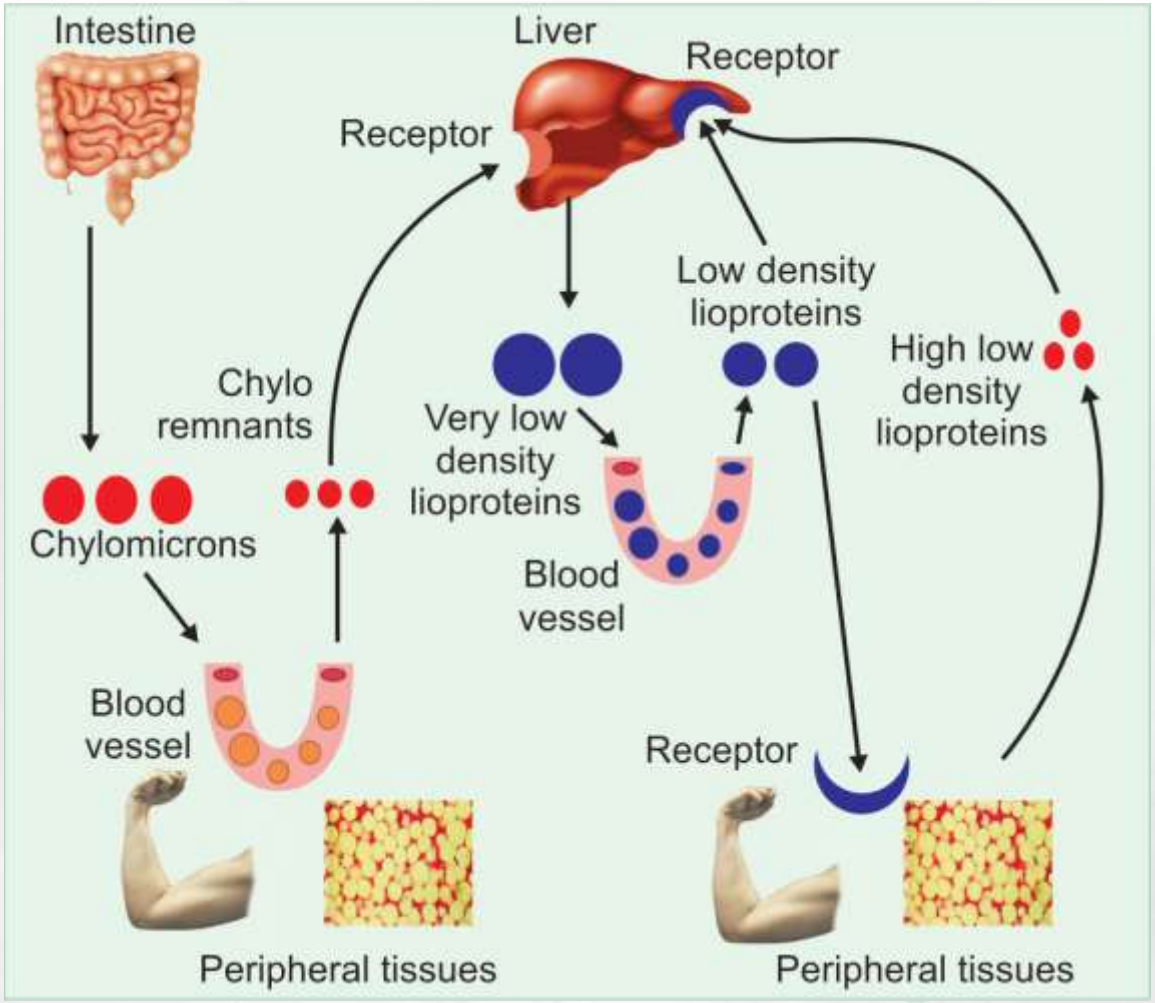
The accumulation of cholesterol in beta cells of Langerhans causes perturbations in glucose metabolism, and reduction in insulin secretion. If cholesterol accumulation is too much, It can cause beta-cell destruction.



Forward and reverse transport of cholesterol



Interrelation of HDL and LDL. LDL cholesterol is deposited in tissues, while HDL cholesterol is the excretory form of cholesterol



Summary of lipoprotein metabolism

Lipoproteins and Their Fate

Lipo-protein	Site of production	Major lipid trans-ported	Major apoproteins	Function
Chylo-microns	Intestine	Triacylglycerol	B-48, Apo A-1, CII and E from HDL	Dietary lipids to peripheral tissues and liver (TAG, cholesterol)
VLDL	Liver	Triacyl-glycerol	B-100, CII and E from HDL	Endogenous TAG from liver to peripheral tissues
LDL	From VLDL	Chole-sterol	B-100	Cholesterol from liver to peripheral tissues
HDL	Inte-stine, liver	Chole-sterol; Phos-pholipids	A1, CII, E	Cholesterol from peripheral tissues to liver (RCT)

Free Fatty Acid (FFA)

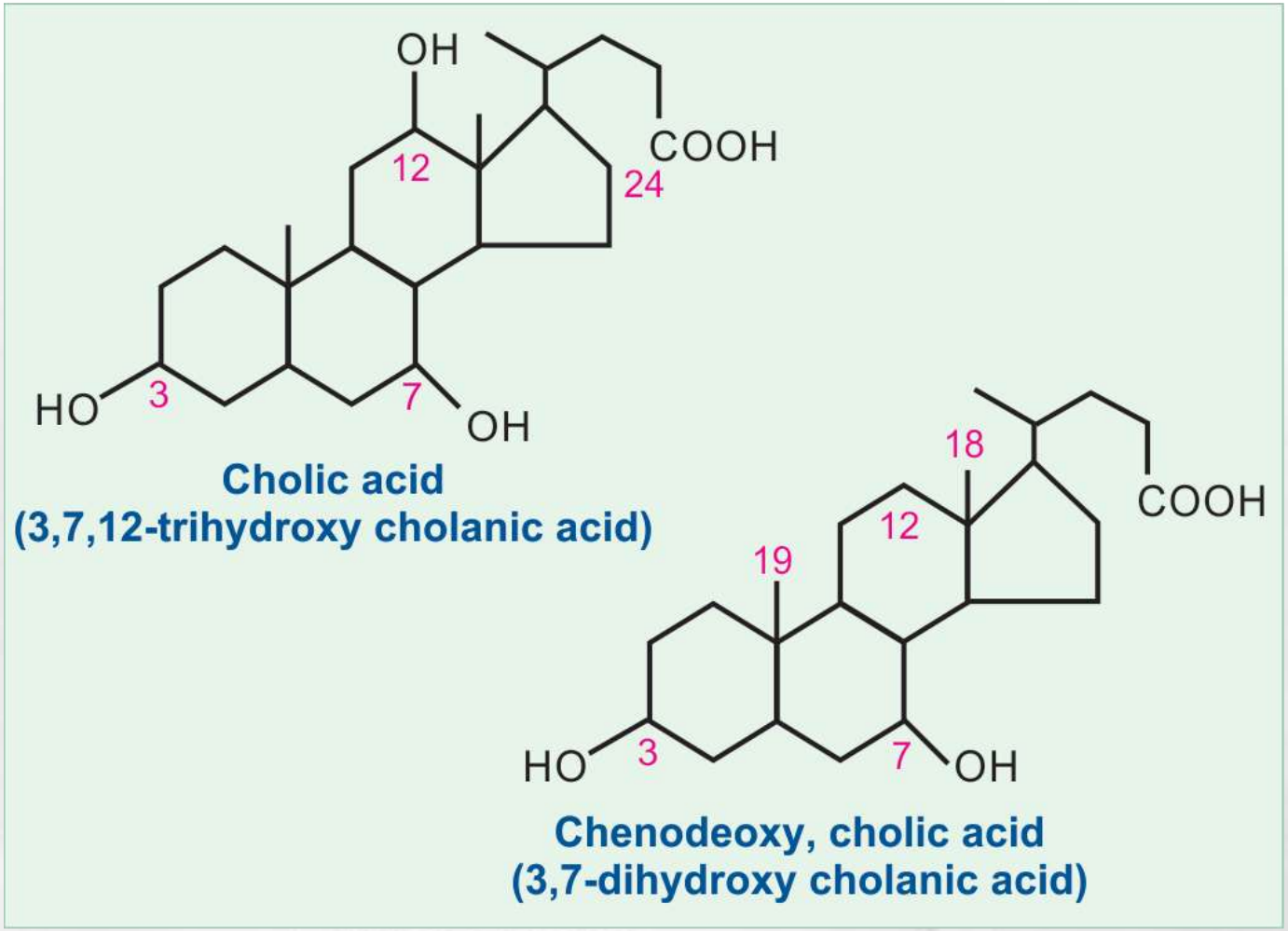
- It is also known as nonesterified fatty acids **(NEFA).**
- It is complexed with **albumin** in plasma.
- The FFA is derived from lipolysis of triglyceride stored in adipose tissue by **hormone-sensitive lipase**.
- Free fatty acids may be either long chain saturated or unsaturated fatty acids.
- The FFA molecules are transported to peripheral tissues in combination with albumin.

- In the tissue cells, FFA-albumin complex is dissociated.
- Then FFA is taken into the cell.
- During starvation, about 40–50% energy requirement of the body is met by oxidation of FFA.
- Blood level of FFA is very low in the fully fed condition, high in the starved state, and very high in uncontrolled diabetes mellitus.

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.

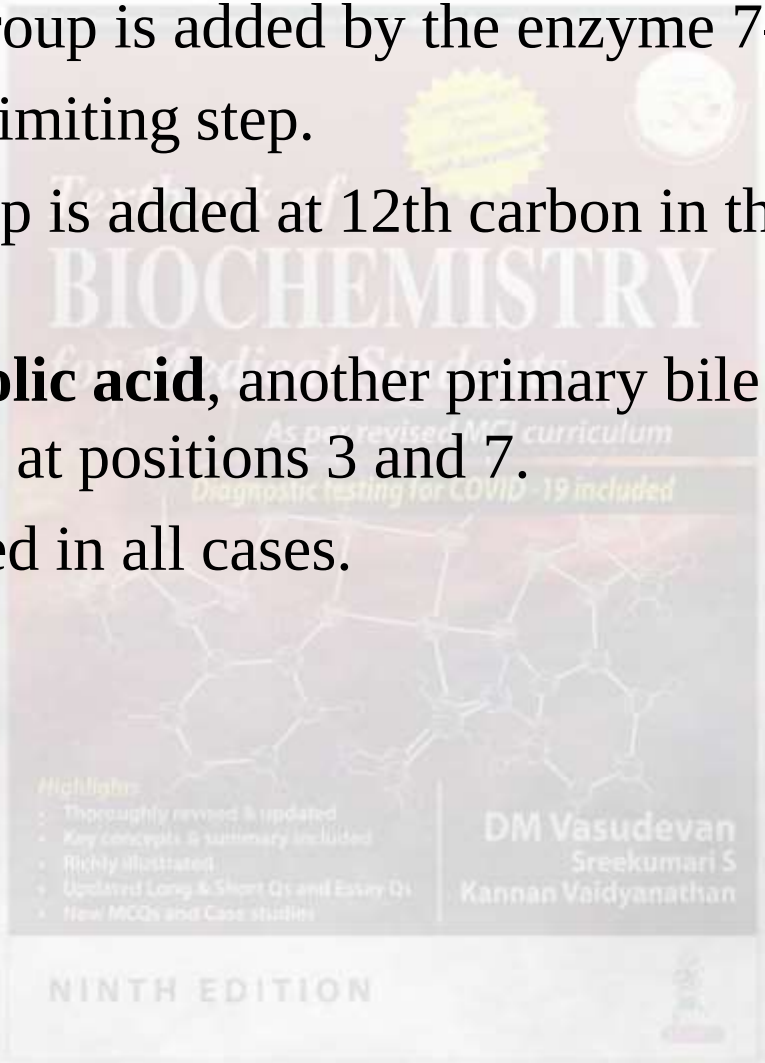
1. Cholesterol hydroxylated at 3/7/12 positions
2. Removal of 3-carbon unit, to make it 24 C
3. Conjugation with glycine
4. Secretion into intestinal canal
5. In the intestine, deconjugation and removal of hydroxyl groups.



Structure of Primary bile acids

Hydroxylation Reactions

- One hydroxyl group is added by the enzyme 7-alphahydroxylase.
- This is the rate-limiting step.
- A third OH group is added at 12th carbon in the case of Cholic acid.
- **Chenodeoxycholic acid**, another primary bile acid has only two hydroxyl groups at positions 3 and 7.
- Ring B is reduced in all cases.

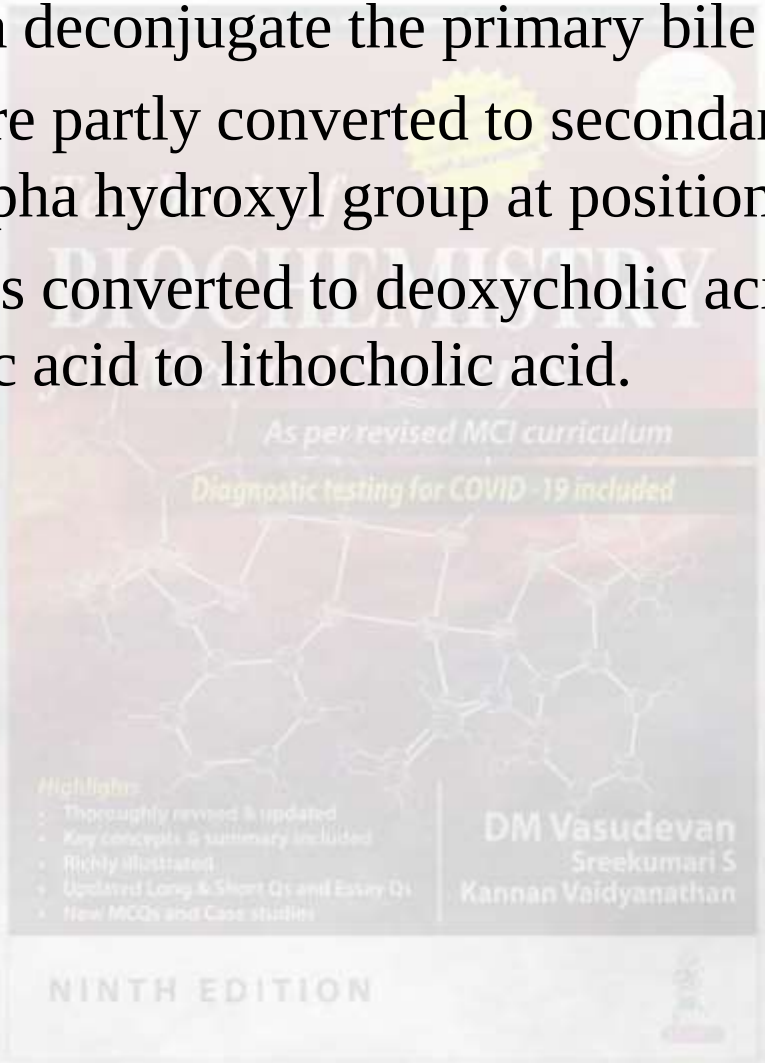


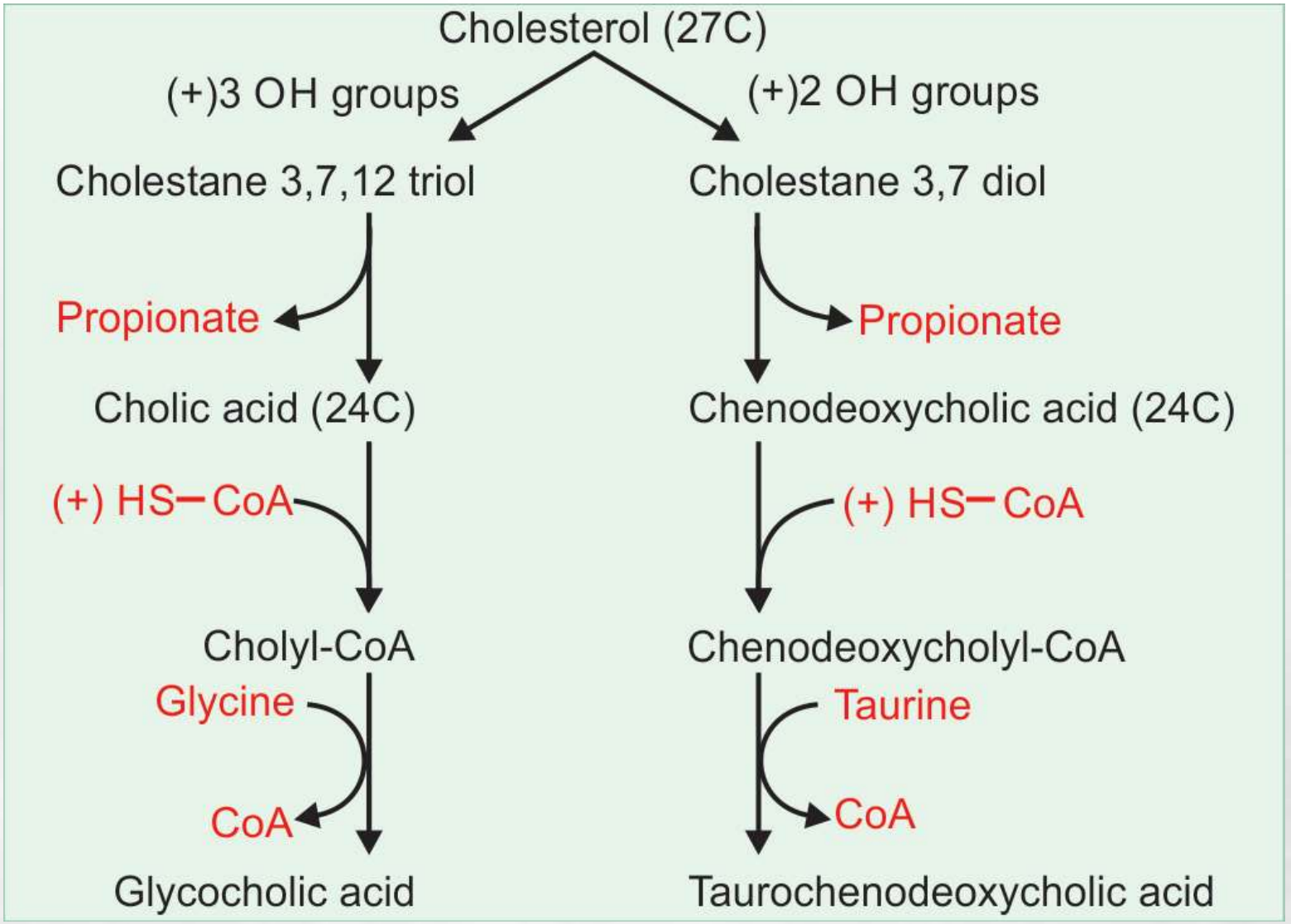
Formation of Bile Salts

- Cleavage takes place at 24 C, with removal of propionic acid (3 carbon) unit.
- The primary bile acids are now conjugated with either **glycine or taurine** to form bile acids.
- The major conjugated bile acid is glycocholic acid.
- Conjugation adds more polar groups and increases the efficiency of bile acids as surfactants.
- The conjugated bile acids are excreted through the bile.
- In the bile they exist as bile salts (sodium or potassium salts of conjugated bile acids).

Secondary Bile Acids/Bile Salts

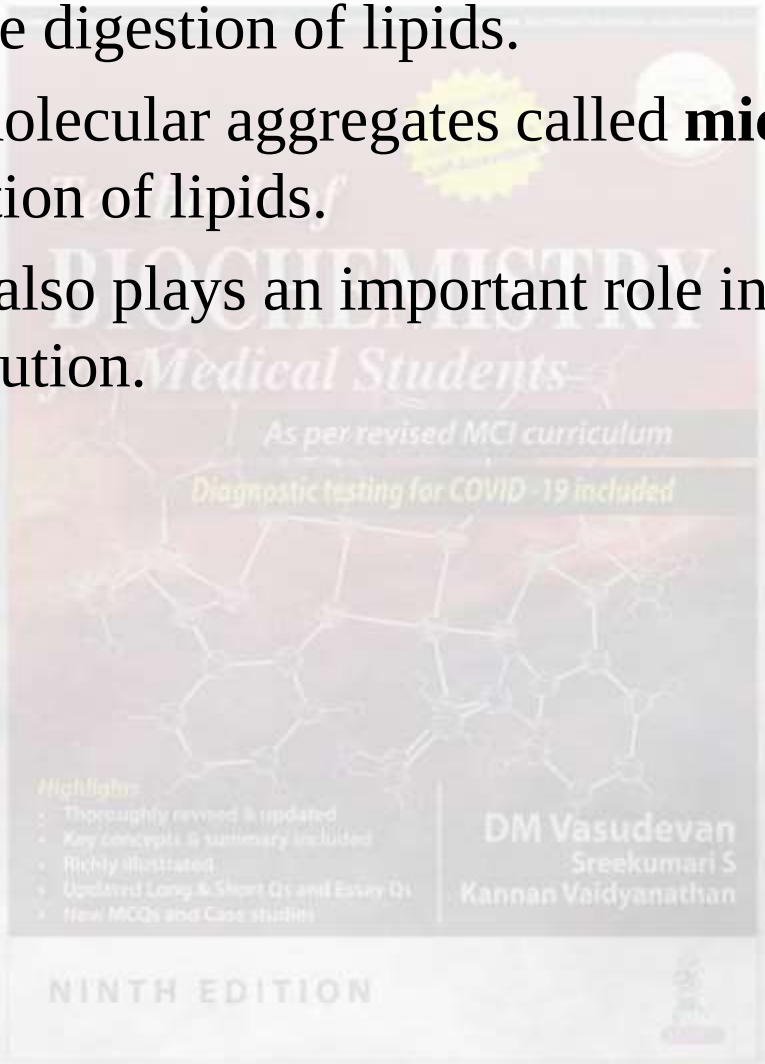
- Intestinal bacteria deconjugate the primary bile acids.
- Then bile acids are partly converted to secondary bile acids by removal of the alpha hydroxyl group at position 7.
- Cholic acid is thus converted to deoxycholic acid and chenodeoxycholic acid to lithocholic acid.




Cholesterol (27C)
(+)3 OH groups
(+)2 OH groups
Cholestane 3,7,12 triol
Cholestane 3,7 diol
Propionate
Propionate
Cholic acid (24C)
Chenodeoxycholic acid (24C)
(+) HS–CoA
(+) HS–CoA
Cholyl-CoA
Chenodeoxycholyl-CoA
Glycine
Taurine
CoA
CoA
Glycocholic acid
Taurochenodeoxycholic acid

Functions of Bile Salts

- They facilitate the digestion of lipids.
- They can form molecular aggregates called **micelle** which bring about the absorption of lipids.
- Bile salt micelle also plays an important role in keeping the cholesterol in solution.

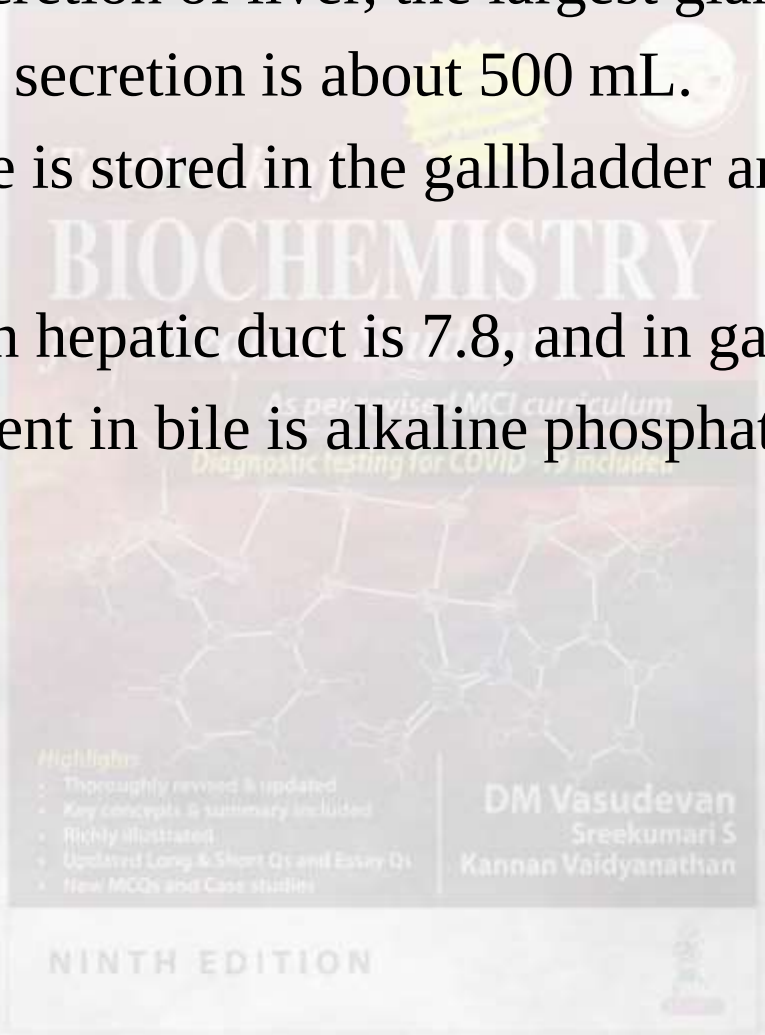


Enterohepatic Circulation of Bile Salts

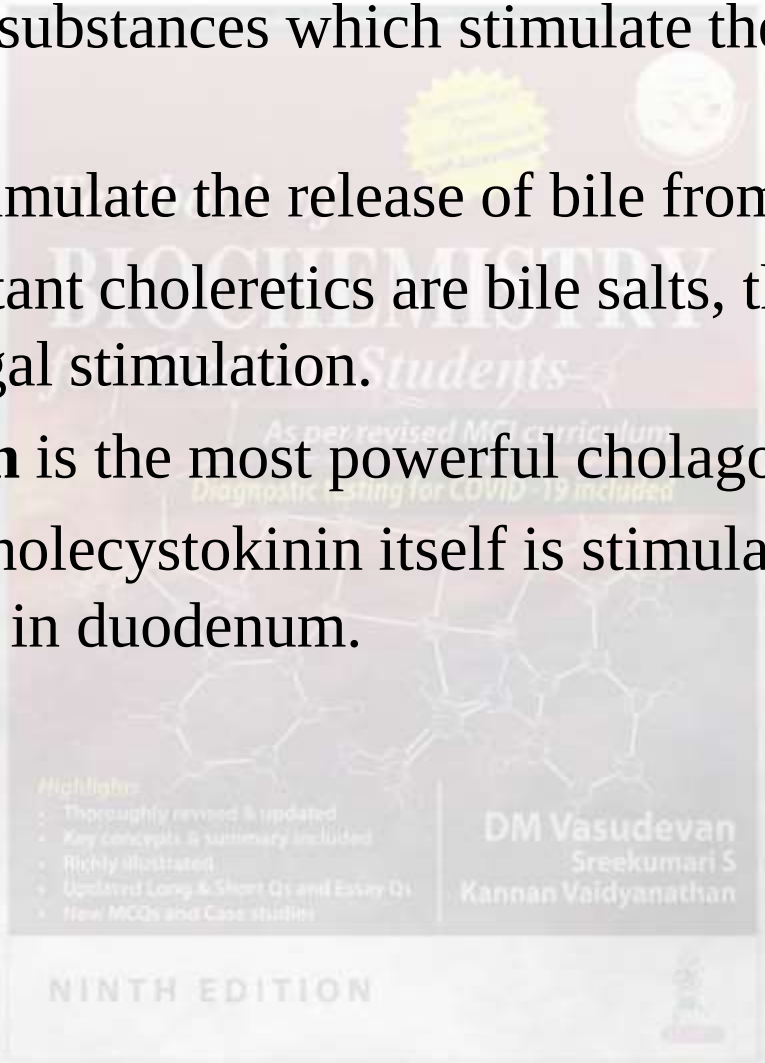
- Of the total bile salts reaching the intestine (15–30 g/day) only a very small fraction, about 300–500 mg/day is excreted through feces.
- The rest is reabsorbed from ileum, reaches liver and re-excreted through bile.
- This is referred to as the enterohepatic circulation.
- When bile acid binding resin (cholestyramine) is given, the reabsorption of bile acids is inhibited.
- Hence more cholesterol gets converted to bile acids and cholesterol is decreased.

Bile

- It is the chief secretion of liver, the largest gland in the body.
- Daily volume of secretion is about 500 mL.
- The secreted bile is stored in the gallbladder and released on demand.
- The pH of bile in hepatic duct is 7.8, and in gallbladder is 7.4.
- An enzyme present in bile is alkaline phosphatase.



- **Choleretics** are substances which stimulate the secretion of bile by the liver.
- **Cholagogues** stimulate the release of bile from the gallbladder.
- The most important choleretics are bile salts, the hormone **secretin** and vagal stimulation.
- **Cholecystokinin** is the most powerful cholagogue.
- The release of cholecystokinin itself is stimulated by fatty acids and amino acids in duodenum.



Functions of Bile

i. The alkaline pH of the bile serves to neutralize the acidity of the gastric juice.

ii. The bile salts are efficient surfactants and detergents.

iii. Bile is the only route of excretion for bilirubin, the end product of heme catabolism.

iv. It serves to excrete cholesterol, thus regulating the body cholesterol pool.

v. Bile serves as the medium of excretion for several drugs, which are detoxified by the liver.