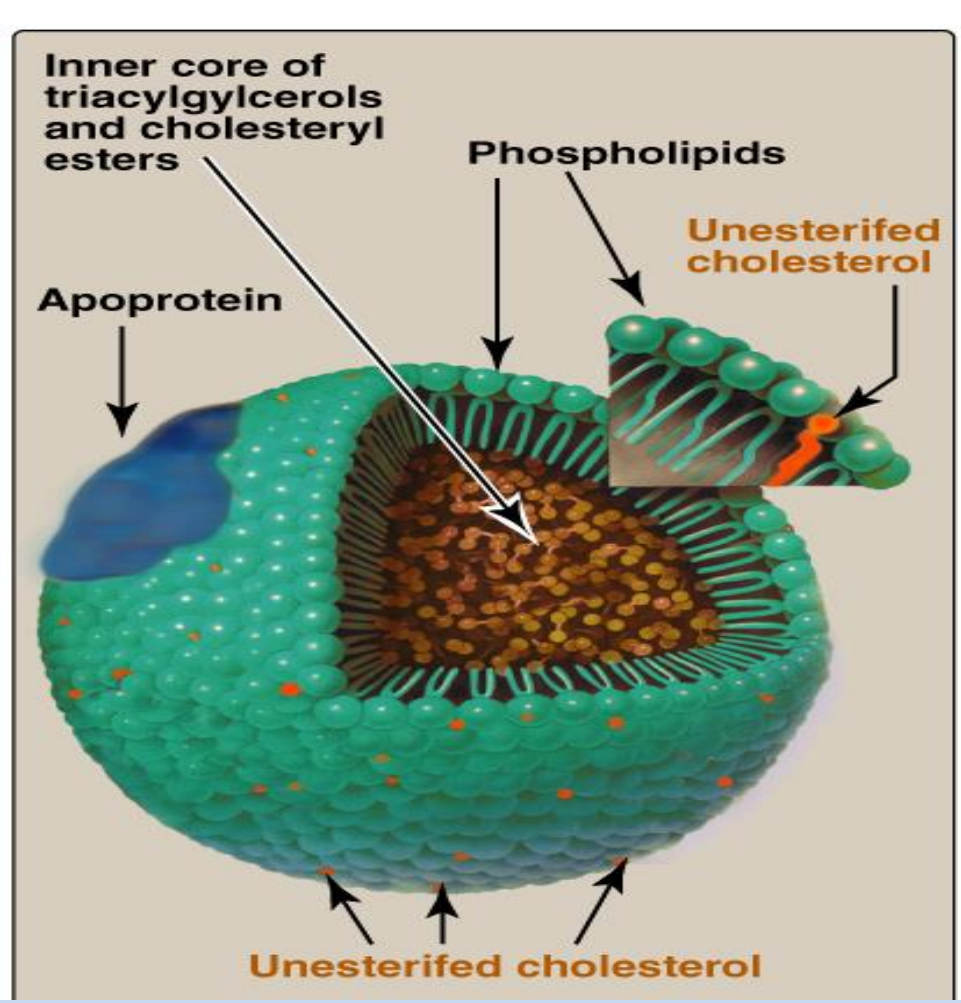
Lipoproteins



- **Plasma lipoproteins**

- **Lipoproteins function in the body is to transport lipids (triacylglycerols and cholesterol) from the small intestine or the liver out to peripheral tissues and then back again to the liver.**

- **Lipoproteins differ in the ratio of protein to lipids, and in the particular apoproteins and lipids that they contain.**

- **The lipoprotein particles include:**
- **Chylomicrons, very-low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL).**

- **Lipoprotein Structure**
- **The lipoproteins are spherical complexes of lipids and specific proteins (apoproteins).**

1- A polar monolayer of phospholipid and free cholesterol located on the outer part of the lipoprotein with their charged groups pointing out towards the water molecules.

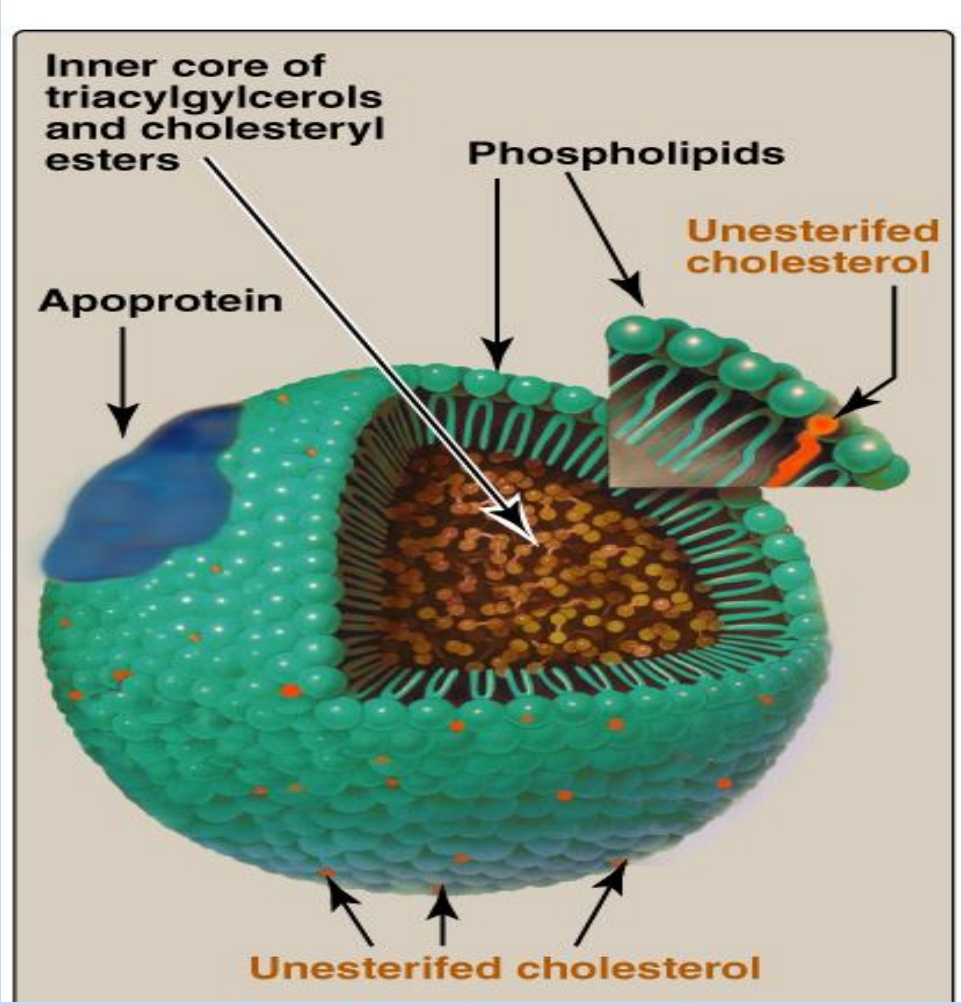
2-Hydrophobic lipids (esterified cholesterol and triacylglycerol), which are located in the core of the lipoprotein particle. These form the central droplet

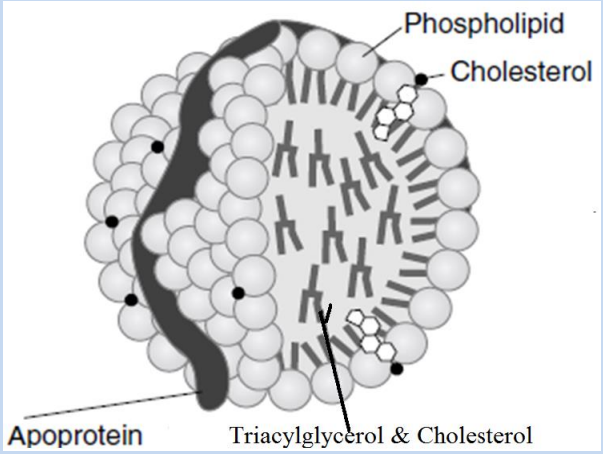
3- Apoproteins, these can span the region between the central core and the outer envelope, and have part of their structure exposed at the surface.

4- Enzymes

Lipoprotein Structure

Spherical molecules of lipids and proteins





Outer coat:

- Apoproteins.
- Phospholipids.
- Cholesterol(Unesterified)

Inner core:

- Triacylglycerol (TAG).
- Cholesteryl ester (CE)

Size and density of lipoprotein

Depending on the size of the lipoprotein, and the ratio of protein to lipid, lipoproteins have different densities as determined by density gradient centrifugation:

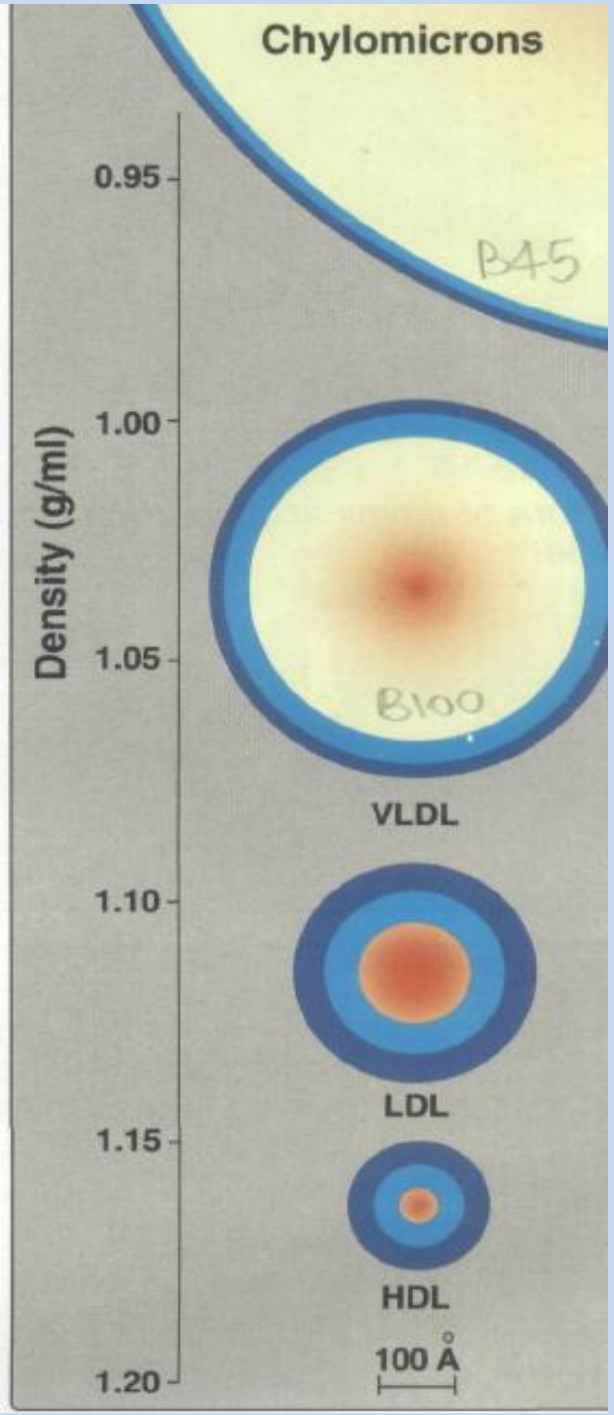
Chylomicrons are the lipoprotein particles lowest in density and largest in size, and contain the highest percentage of lipid and the smallest percentage of protein.

VLDLs and LDLs are successively denser, having higher ratios of protein to lipid.

HDL particles are the densest.

Triacylglycerol (TAG) is the predominant lipid in chylomicrons and VLDL,

whereas cholesterol and phospholipid (PL) are the predominant lipids in LDL and HDL.



Composition of lipoproteins

Lipoprotein classes	Total protein (%)	Total lipids (%)	Percent composition of lipid fractions			
			PL	ChE	Ch	TAG
CM						
VLDL	5-10	90-95	15-20	10-15	5-10	50-65
LDL	20-25	75-80	15-20	35-40	7-10	7-10
HDL	40-45	55	35	12	4	5

Separation of Plasma lipoproteins

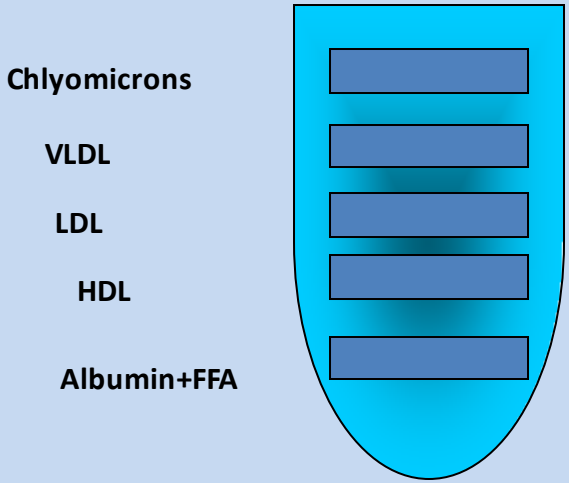
Ultracentrifugation:

- Lipoproteins are separated according to their density.
- The higher the protein content the higher the density of the particles.

- The main fractions separated are:

1. CM. 2. VLDL. 3. LDL. 4. HDL.

5. Free fatty acids- albumin complex (not true lipoprotein)



Ultracentrifugation fractions

Apoproteins functions

(1) They form part of the structure of the lipoprotein
eg, apo B

(2) They are enzyme cofactors, eg, apo C-II for lipoprotein lipase
or enzyme inhibitors, eg, apo A-II and apo C-III for lipoprotein lipase

(3) They act as ligands for interaction with lipoprotein receptors in tissues (bind to cell surface receptors)
eg, apo B-100 and apo E for the LDL receptor

- **Chylomicrons**

Function: carry dietary lipids from intestine to the peripheral tissues.

- **Fate of chylomicrons**
- **Chylomicrons are synthesized in intestinal mucosal cells, secreted by the process of exocytosis into the lymph, pass into the blood, and become mature chylomicrons.**

- **On capillary walls in adipose tissue and muscle particularly cardiac muscle, lipoprotein lipase (LPL) an extracellular enzyme digests the triacylglycerols of chylomicrons to fatty acids and glycerol. Fatty acids are delivered mainly to adipose tissue, heart, and muscle (80%), while about 20% goes to the liver.**
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- **In this way, the circulating chylomicron becomes progressively smaller, its triacylglycerols content decreases and it becomes relatively richer in cholesterol and proteins.**

VLDL:

- Are produced in the liver.
- Function: is to carry lipid from the liver to the peripheral tissues.
- Fatty acids for VLDL synthesis in the liver may be obtained from the blood or they may be synthesized from glucose.
- In a healthy individual, the major source of the fatty acids of VLDL triacylglycerol is excess dietary glucose.

- **Formation of LDL**

- **As VLDL pass through the circulation, the triacylglycerol they contain is degraded by lipoprotein lipase, causing the release of fatty acids and glycerol from a portion of core triacylglycerols.**

- **When additional core triacylglycerols are removed then VLDL is transformed to Intermediate-Density Lipoprotein (IDL) .**

- **With the removal of additional triacylglycerols from IDL, LDL is generated.**

- **LDL (the bad cholesterol)**

- **The primary function of LDL particles is to provide cholesterol to the peripheral tissues.**

- **LDL particles are rich in cholesterol and cholesterol esters.**
- **Approximately 60% of the LDL is transported back to the liver.**

- **The remaining 40% of LDL particles are carried to extrahepatic tissues (outside liver) such as adrenocortical and gonadal cells for the synthesis of steroid hormones.**

- **The elevated levels of LDL, leads to the formation of atherosclerotic plaques**

(HDL) (the good cholesterol)

1. Synthesis of HDL

- **HDL particles can be created by a number of mechanisms.**

One mechanism is the synthesis of nascent HDL by the liver and intestine as a relatively small molecule whose shell, like that of other lipoproteins, contains phospholipids, free cholesterol, and a variety of apoproteins.

2. Maturation of nascent HDL

In the process of maturation, the nascent HDL particles accumulate phospholipids and cholesterol from cells lining the blood vessels. As the central hollow core of nascent HDL progressively fills with cholesterol esters, HDL takes on a more globular shape to eventually form the mature HDL particle.

- **HDL accepts free cholesterol from peripheral tissues, such as cells in the walls of blood vessels.**
-
- **This cholesterol is converted to cholesterol ester, part of which is transferred to VLDL, and returned to the liver by IDL and LDL.**

- **The remainder of the cholesterol is transferred directly as part of the HDL molecule to the liver.**

- **The liver reutilizes the cholesterol in the synthesis of VLDL, converts it to bile salts, or excretes it directly into the bile. HDL therefore tends to lower blood cholesterol levels.**

- **3. Reverse cholesterol transport**

- **A major benefit of HDL particles derives from their ability to remove cholesterol from cholesterol loaded cells and to return the cholesterol to the liver, a process known as reverse cholesterol transport.**

- **This is particularly beneficial in vascular tissue; by reducing cellular cholesterol levels**

- **The esterification of cholesterol in the HDL particle prevent cholesterol from leaving the HDL**

- **High levels of HDL in the blood, therefore, are believed to be vasculoprotective, because these high levels increase the rate of reverse cholesterol transport "away" from the blood vessels and "toward" the liver.**

The desired values in most adults are (from NIH U.S.A):

- **LDL cholesterol: Optimal Less than 100 mg/dL and borderline high 130-159 mg/dL**
- **HDL cholesterol: Greater than 40-60 mg/dL (higher numbers are desired)**
- **Total cholesterol: Desirable Less than 200 mg/dL and borderline high is 200-239 mg/dL**
- **Triglycerides: 10-150 (lower numbers are desired)**
- **VLDL: 2-38**

High blood cholesterol (hypercholesterolemia) caused by:

1. Heredity—genetic disease- known as Familial hypercholesterolemia that run in families.
- The defect makes the body unable to remove LDL from the blood. This results in high levels of LDL in the blood.

2. Diet

overconsumption of high cholesterol also play a part

3. Weight:

being overweight increases your cholesterol and is a risk factor for heart disease.

4. Physical Activity:

physical activity can help lower LDL and raise HDL levels

5. Age and Gender

As women and men get older, their cholesterol levels rise.

- Before the age of menopause, women have lower total cholesterol levels than men of the same age. After the age of menopause, women's LDL levels tend to rise.

Cholesterol synthesized in the liver has essentially three fates

1) It can be esterified with a fatty acid by the enzyme acyl-CoA-cholesterol acyl transferase (ACAT) to make cholesterol esters that are stored in lipid droplets

2) It can be exported to the peripheral tissues through packaging into lipoprotein particles

3) It can be converted into bile acids which are transported to the bile duct and secreted into the small intestine to aid in fat absorption.

- As much as 50% of the cholesterol synthesized in liver cells on a daily basis is converted to bile acids.
- Bile acids, are amphipathic molecules that are stored in the gall bladder and secreted into the intestine through the bile duct.
- Most of the bile acid is reabsorbed and returned to the liver (greater than 95 percent) and the rest is excreted as waste

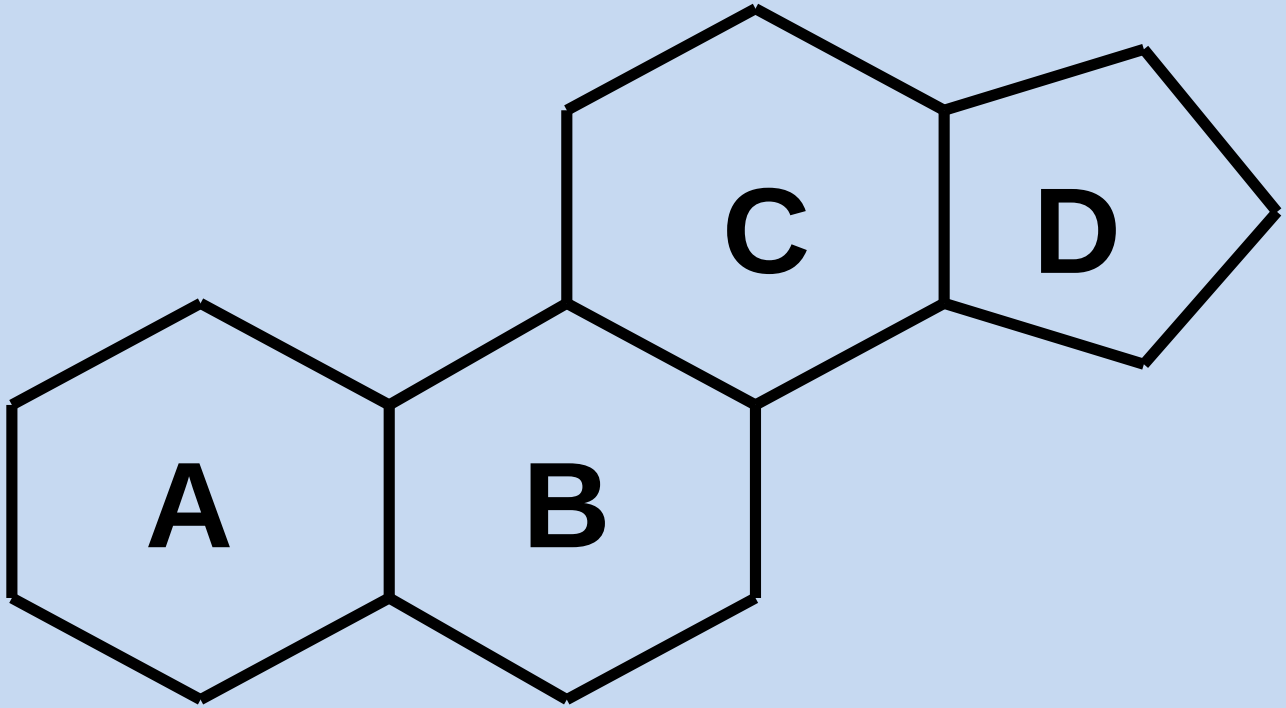
Atherosclerosis

- **Is the Hardening of the arteries due to cholesterol build up in the walls of arteries**

- **Over time, these plaques can block the arteries and cause problems throughout the body for example heart attacks, strokes, and peripheral vascular disease -which together are called "cardiovascular diseases."**

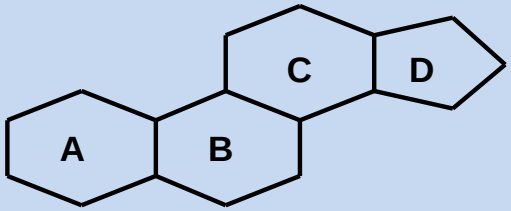
- **Complications of atherosclerosis are the most common causes of death in Western societies.**

Steroids



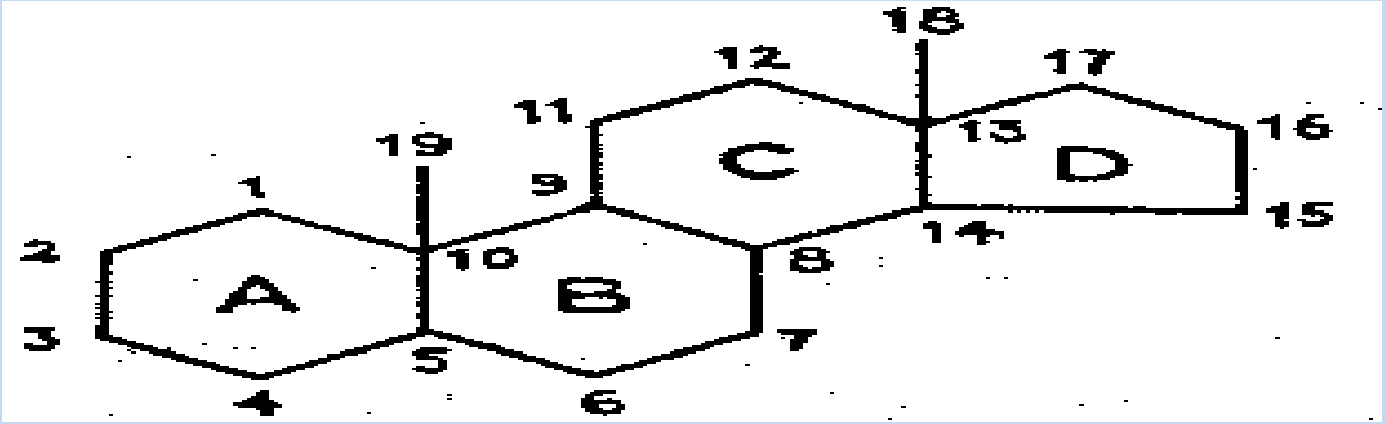
Steroids

- **Steroids are group of plant and animal lipids that have a similar tetracyclic nucleus.**



Steroid nucleus:

- **So this tetracyclic nucleus is composed of 17 carbon atoms besides two methyl groups (C_{18}, C_{19}).**
- **There is a methyl group at C_{10} (it makes C 19).**
- **And there is another methyl group at C_{13} (it makes C18).**



Steroids include:

1. **Sterols.**
2. **Bile acids and salts.**
3. **Steroid hormones.**
4. **Vitamin D.**

STEROLS:

- **This group of steroids has a hydroxyl group (OH) at C_3 i.e. it is an alcohol, and an aliphatic side chain at C_{17}.**

Types of sterols:

A. Animal sterols:

- **Cholesterol and its derivative 7-dehydrocholesterol.**

B. Plant sterols:

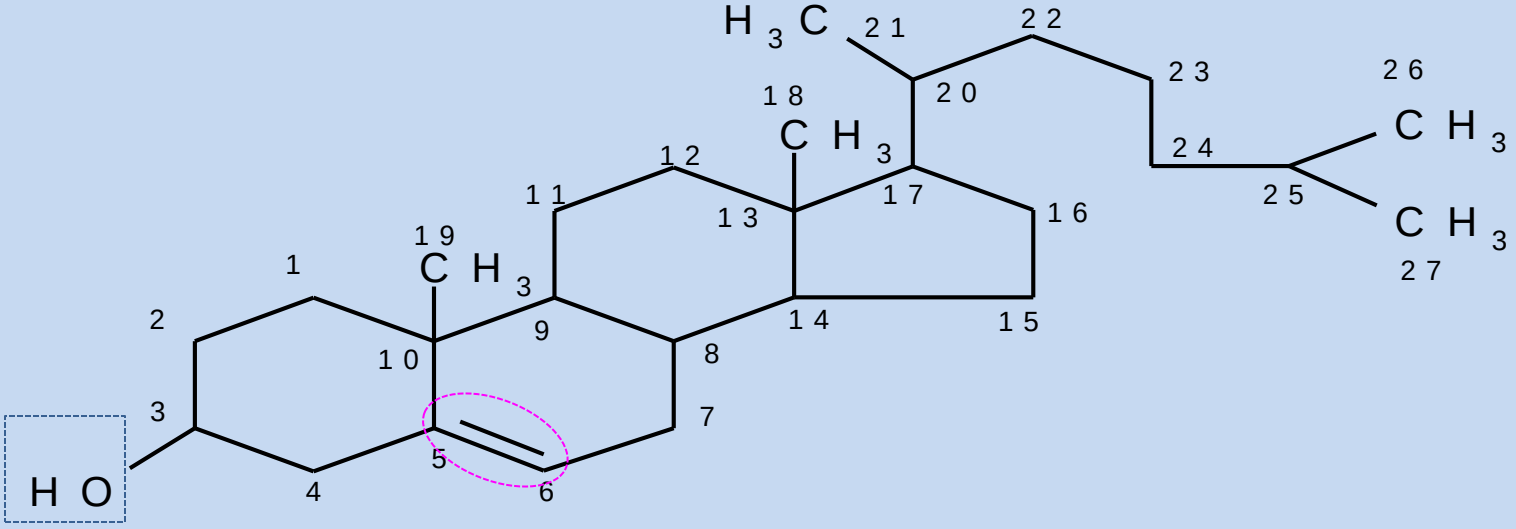
- **Ergosterol.**

Cholesterol

- **Naming: The word cholesterol is derived from Greek words; chole= bile, steros= solid, ol= alcohol.**

Chemistry of cholesterol:

- **It is a solid alcohol of 27 carbon atom and contains steroid ring.**
- **it has a double bond between C_5 and C_6.**
- **One hydroxyl group at C3 which is characteristic to all sterols.**
- **The OH group is beta oriented, projecting above the plane of ring.**



Properties of cholesterol:

- **It has amphipathic properties which allow it to play structural role in *membrane* and in the outer layer of *lipoprotein.***

Cholesterol Sources

1. **It is formed in the body from acetyl CoA. Most of the cholesterol is synthesized by the liver.**
2. **It is present in diet: egg yolk, meat, liver and brain. (It occurs in animal fats but not in plant fats).**

Biomedical importance:

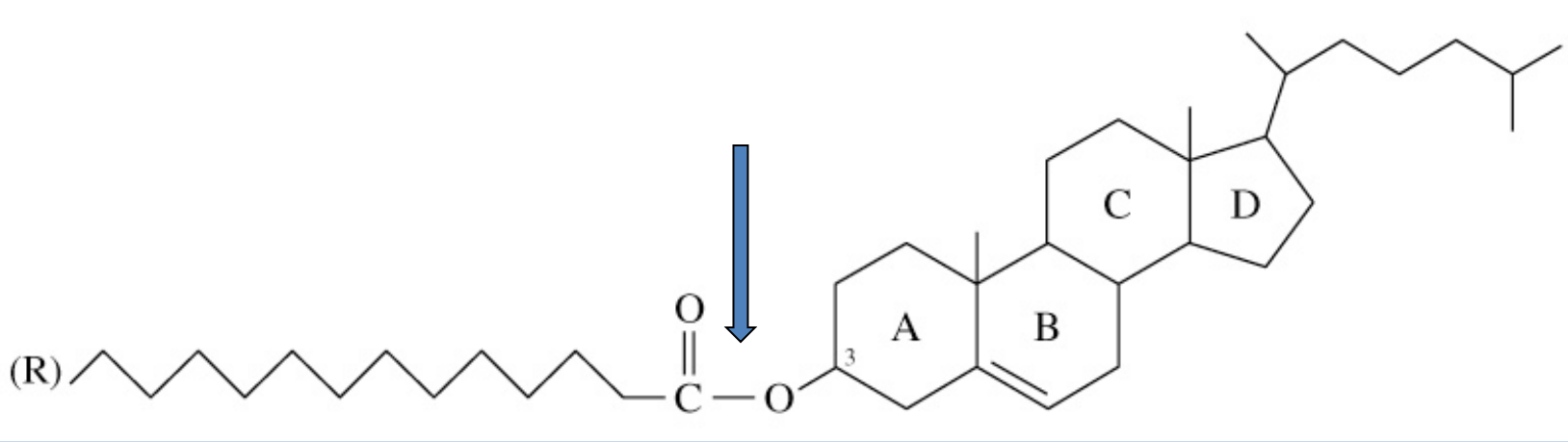
1- **It is the main sterol in human body (Nervous tissue, brain, suprarenal gland, and in bile, ,,).**

2- **It is present in blood (normal level 150-200 mg / dl).**

3- **It is often found as cholesterol ester (in combination with fatty acids). The fatty acid is attached to the hydroxyl group e.g. Cholesteryl oleate or linoleate.**

Cholesterol esters (CE)

- **Cholesterol is converted to cholesteryl esters for cell <u>storage</u> or <u>transport</u> in blood**
- **Fatty acid is esterified to C-3 OH of cholesterol**
- **Cholesterol esters are very water insoluble (hydrophobic) and must be complexed with phospholipids or amphipathic proteins for transport**



Biomedical importance:

4- It is a major constituent of the plasma membrane.The fused ring system makes cholesterol less flexible than most other lipids.

5- It is the precursor of:

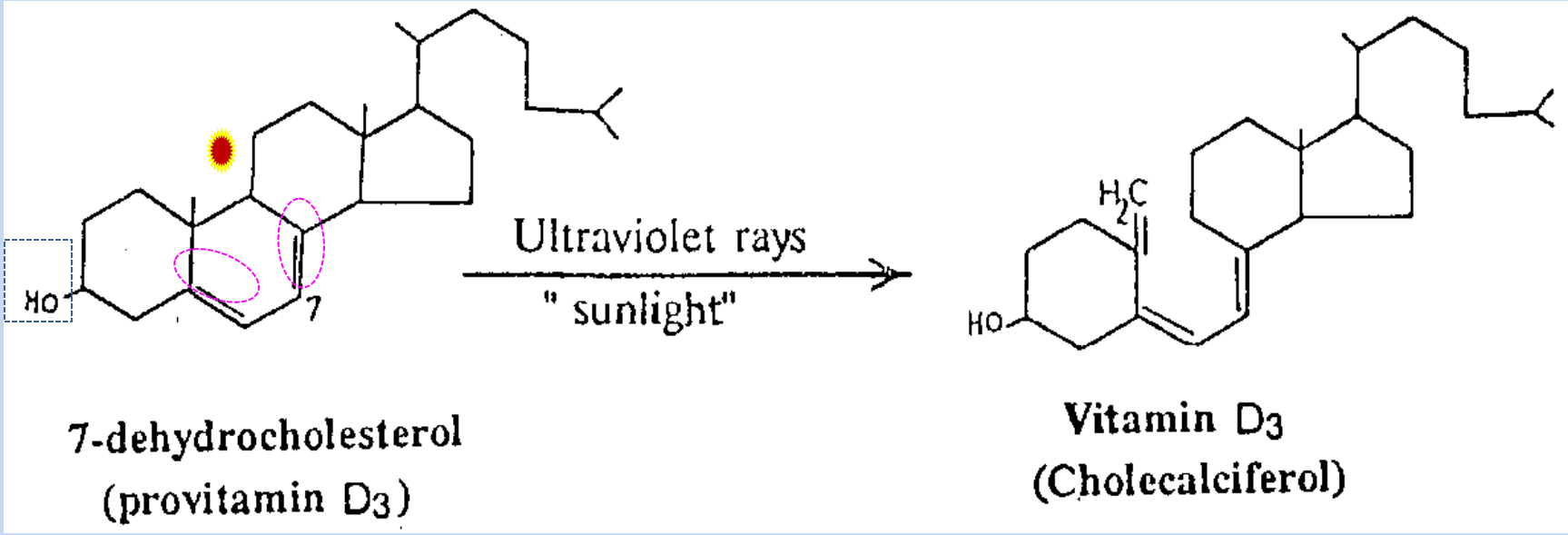
- **Sex hormones**
- **Cortical hormones**
- **Vitamin D**
- **Bile acids.**

6- High level of cholesterol in blood will lead to its precipitation in the wall of blood vessels "atherosclerosis". Also high levels of blood cholesterol may lead to stones in gall bladder (gall stone).

7-dehydrocholesterol (pro-vitamin D3)

- **7-dehydrocholesterol is stored under the skin, and by the effect of ultraviolet rays(in sunlight) it is transformed to cholecalciferol (vit. D_3 .)**

Insufficient sunlight can lead to a deficiency of vitamin D_3, interfering with Ca^{2+} transport and bone development. Rickets can result.



Clinical correlation

- Low density lipoproteins (LDL) transports cholesterol from liver through blood to the tissues (Bad cholesterol)

- High density lipoprotein (HDL) transports cholesterol from blood to the liver where it is metabolised (Good cholesterol)

- ↑LDL, ↑ Cholesterol High risk of heart attack

- ↑HDL, ↓ Cholesterol Low risk of heart attack