Lipids

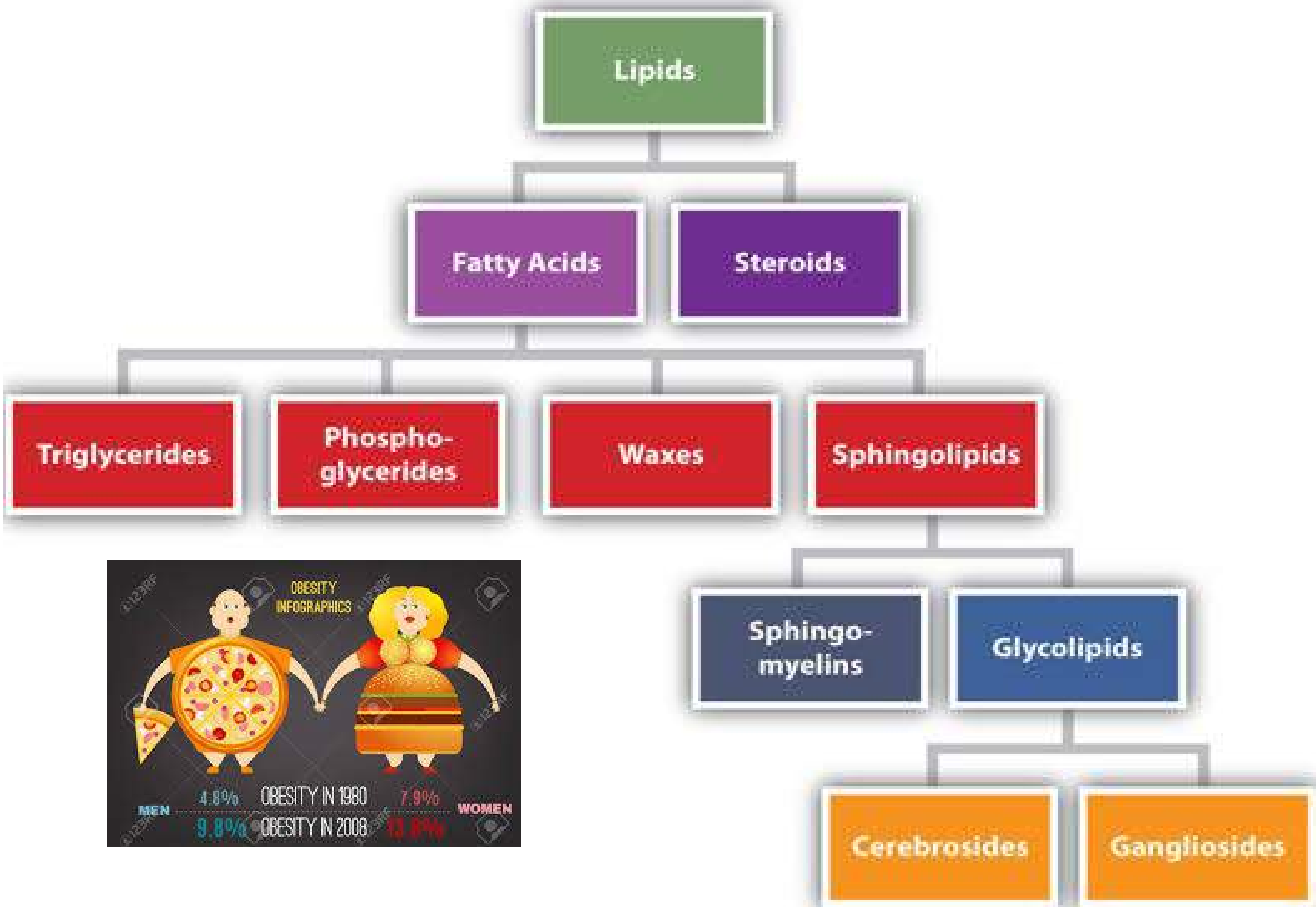
What are lipids?

Lipids are a heterogeneous class of naturally occurring organic compounds which includes: fats, waxes, sterols, fat-soluble vitamins , monoglycerides, diglyceride, phospholipids, and others.

Lipids contain fatty acids or a steroid nucleus.

They are soluble in organic solvents.

They are named for the Greek word “lipos”, which means “fat.”


Lipids
Fatty Acids
Steroids
Triglycerides
Phospho-
glycerides
Waxes
Sphingolipids
Sphingo-
myelins
Glycolipids
Cerebrosides
Gangliosides
OBESITY
INFOGRAPHICS
MEN
4.8%
OBESITY IN 1980
7.9%
WOMEN
9.8%
OBESITY IN 2008

Nature of lipids

- Lipids have a hydrophobic nature because of the predominance of hydrocarbon chains ($-CH_2-CH_2-CH_2-$) in their structure .

- They are insoluble or only poorly soluble in water , but readily soluble in nonpolar solvents such as ether and benzene .

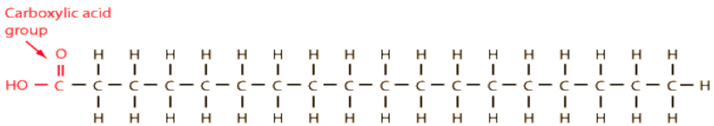
Classifications and Functions of Lipids :

Lipids	Primary Functions
Fatty acids	Energy sources , biosynthetic precursors
Triacyglycerols	Storage , transport
Phosphoglcerides	Membrane components
Ketone bodies	Energy sources
Sphingolipids	Membrane components
Eicosanoids	Modulators of physiologic activity
Cholesterol	Membrane components
Steroid hormones	Modulators of physiologic activity

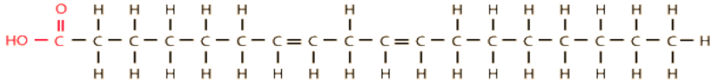
A. Fatty Acids

Fatty acids are carboxylic acids (long chain hydro-carbons with a carboxyl group at the end of the chain). They are:

- the structural components of many lipids
- have straight chain
- water insoluble
- saturated or unsaturated



Stearic acid, an example of a saturated fatty acid



Linoleic acid, an example of an unsaturated fatty acid

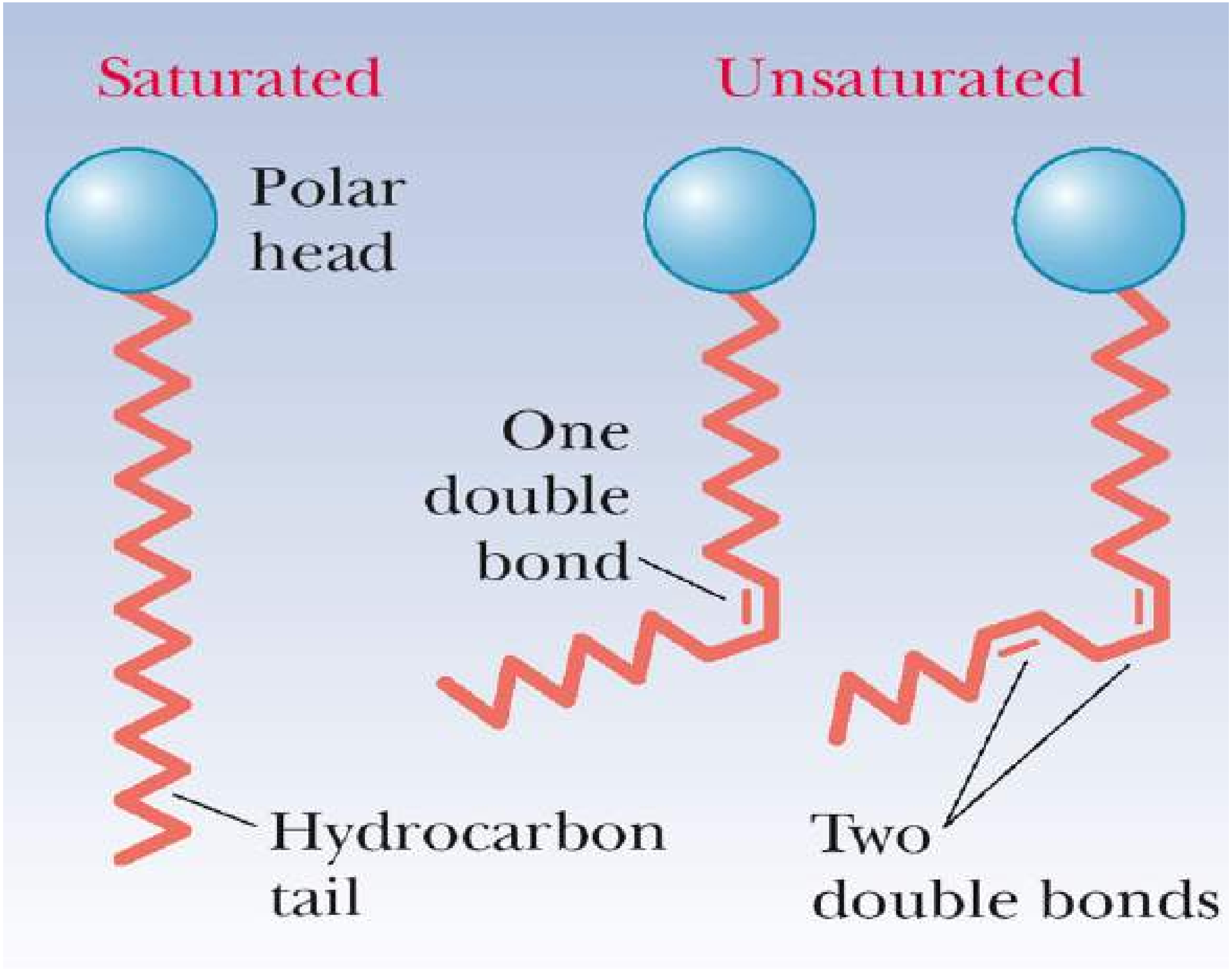

Saturated
Unsaturated
Polar head
One double bond
Hydrocarbon tail
Two double bonds

Fig. 8-12, p.193

Saturated fatty acids : do not have double bounds in the chain .

Nomenclature : The systematic name gives the number of carbons , with the suffix –anoic appended . **Palmitic acid** , for example , has 16 carbons and has the systematic name **hexadecanoic acid**.

Structure . The general formula of saturated fatty acids is CH3-(CH2)n-COOH where n is the number of methylene groups between the methyl and carboxyl carbons .

- **Unsaturated fatty acids** : have one or more double bonds . In naturally occurring fatty acids , these bonds are always in a cis as opposed to a trans configuration (i.e. , the hydrogens bonded to each carbon are oriented in the same direction) .
- The most commonly used system for designating the position of double bonds in an unsaturated fatty acid is the delta (Δ) numbering system .

Numbering system . The terminal carboxyl carbon is designated C-1 , and the double bond is given the number of the carbon on the carboxyl side of the double bond . For example , ***palmitoleic acid*** , which has 16 carbons and a double bond between C-9 and C-10 , is designated **16 :1Δ9 , or 16 : 1:9**

The systematic name gives the number of carbon atoms , number of double bonds (unless it has only one) , and bears the suffix – enoic . Thus ***linoleic acid*** , with 18 carbons and two cis double bonds , is **cis- Δ9, Δ12 , octadecadienoic acid .**

Common name	Systematic Name	No. Carbon Atoms	No. Double Bonds	Melting Point (°)
Lauric	Dodecanoic	12	0	43.5
Myristic	Tetradecanoic	14	0	54.4
Palmitic	Hexadecanoic	16	0	62.8
Stearic	Octabecanoic	18	0	69.6
Pamitoleic	Cis- Δ^{9} - Hexadecenoic	16	1	1.0
Oleic	Cis-Δ^{9} - Octadecenoic	18	1	13.0
Linoleic	All cis Δ^{9} , Δ^{12} - octadecadienoic	18	2	- 11.0
Linolenic	All cis-Δ^{9} , Δ^{12} , Δ^{15} – octadecatrienoic	18	3	- 11.2
Arachidonic	All cis-Δ^{5} , Δ^{8} , Δ^{11} , Δ^{14} – Eicosaletraenoic	20	4	- 49.5

1. Fatty acid have an **amphipathic nature** . They have non polar (CH_3) and polar (-COOH) ends
2. The melting point of fatty acids is related to chain length and degree of unsaturation .

- The longer the chain length , the higher the melting point ; the greater the number of double bonds, the lower the melting point .

Source :

1. **Nonessential fatty acids** : Nonessential fatty acids can be synthesized from products of glucose oxidation and don't, therefore, have to be included in the diet.

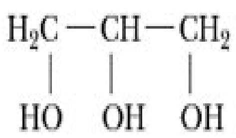
2. **Essential fatty acids** : Fatty acids of the linoleic ($18{:}2\Delta^{9,12}$) and linolenic ($18{:}3\Delta^{9,12,15}$) families must be obtained from the diet.

B.Triacylglerols (triglycerides):

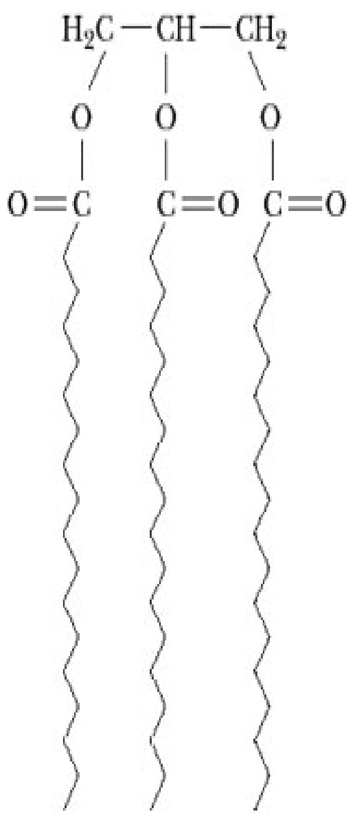
1. **Structure :** Tricyglycerols are triesters of glycerol and three fatty acids .
2. **Function :** Fatty acids are converted to triacylglycerols for transport between tissues and for storage of metabolic fuel.

A. The main stores of metabolic fuel in humans are the fat deposits in fat cells **(adipocytes)** .

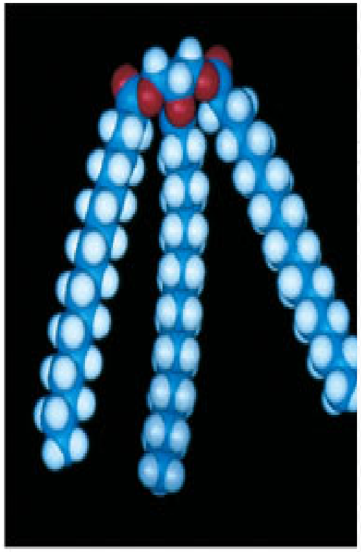
These serve long-term needs for metabolic fuel .



Glycerol



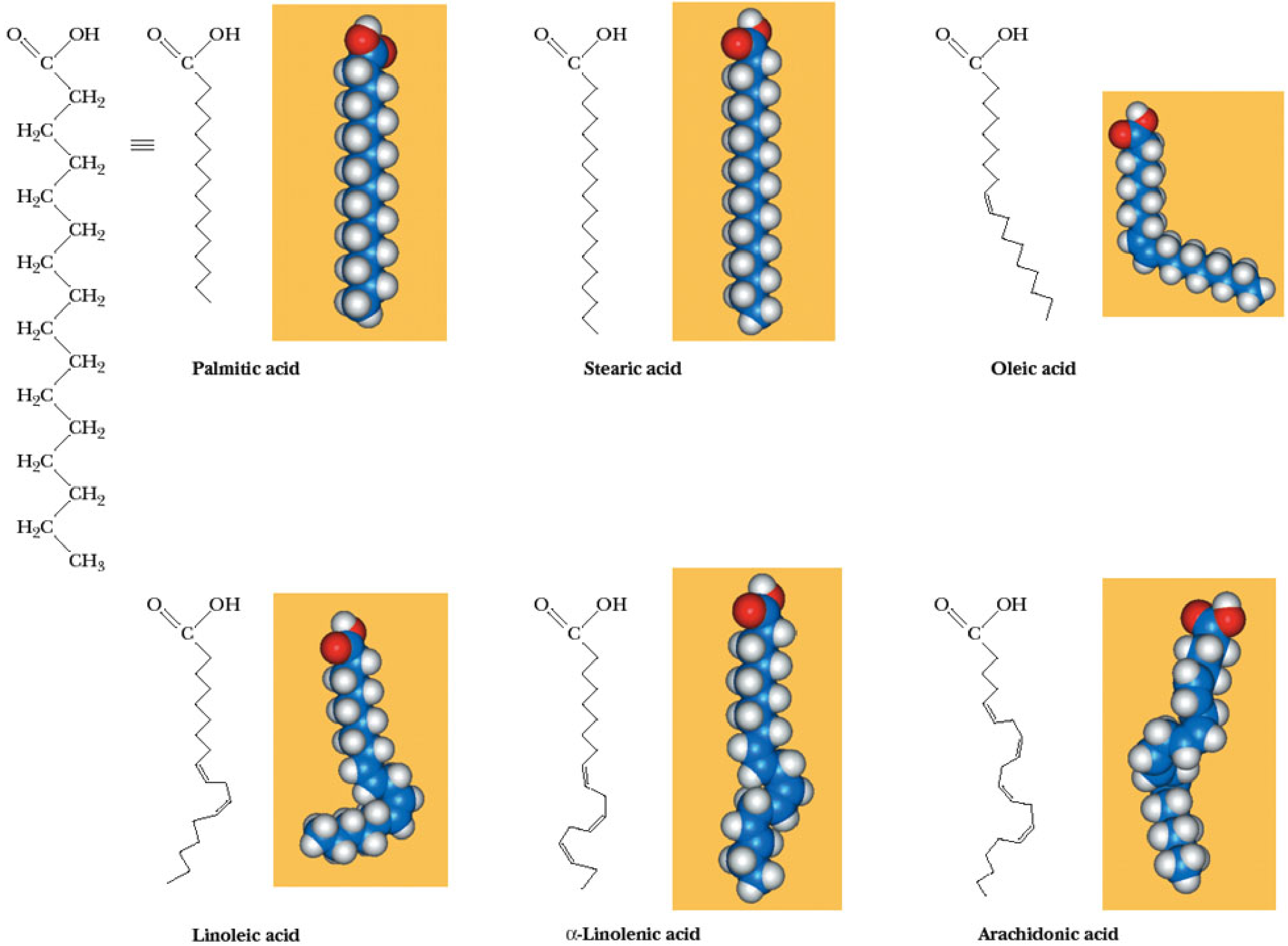
Tristearin
(a simple triacylglycerol)



Triglycerides consist of a **single glycerol** molecule and **three fatty acids.**

Triglycerides form by **condensation** (dehydration) reactions between the **hydroxyl** (OH) groups of the **glycerol** and the **carboxyl** (COOH) group of **three fatty acids.**

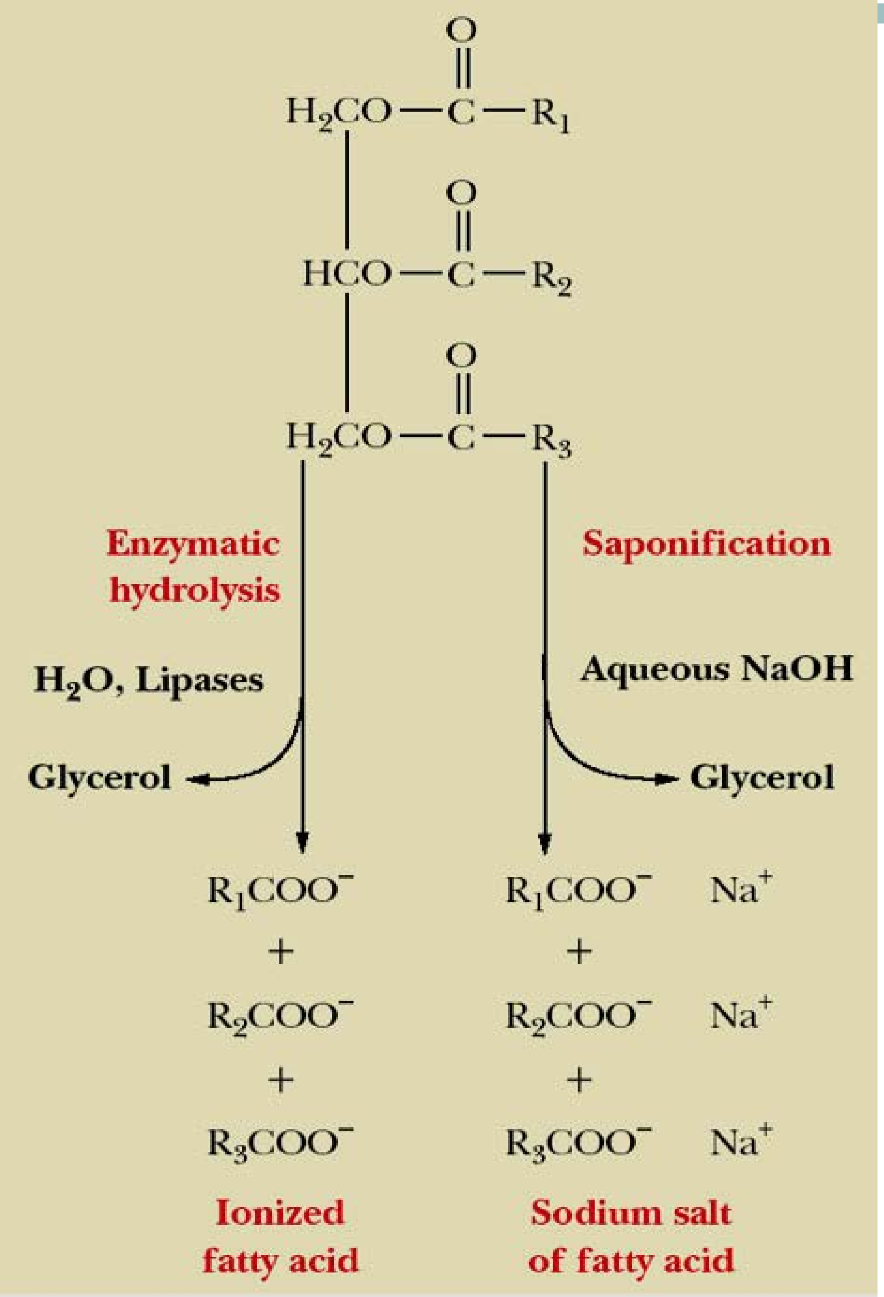
Triglycerides are **esters** being derived from an **alcohol** and a **fat**


O
OH
C
CH2
H2C
CH3
Palmitic acid
Stearic acid
Oleic acid
Linoleic acid
α-Linolenic acid
Arachidonic acid

Triacylglycerols have two major advantages over other forms of metabolic fuel .

1. Triacylglycerols provide a concentrated form of fuel because their complete combustion to carbon dioxide (CO2) and water releases 9kcl/g as opposed to 4kcl/g for carbohydrate .
2. Because they are water insoluble , triacylglcerols present no osmotic problems to the cell when stored in large amounts .

Lipolysis involves the hydrolysis of **triaclglycerols to free glycerol and free fatty acids** (also known as nonesterified fatty acids (NEFA) with both products leaving the adipocyte . The appearance of fatty acids in the blood during fasting is due to the mobilization of fat stores by this process .


O
H2CO—C—R1
O
HCO—C—R2
O
H2CO—C—R3
Enzymatic hydrolysis
H2O, Lipases
Glycerol
Saponification
Aqueous NaOH
Glycerol
R1COO⁻ + R2COO⁻ + R3COO⁻
R1COO⁻ Na⁺ + R2COO⁻ Na⁺ + R3COO⁻ Na⁺
Ionized fatty acid
Sodium salt of fatty acid

1. Utilization of fatty acids

Fatty acids are used by most tissues , except the brain , as a metabolic fuel .

2.Utilization of glycerol .

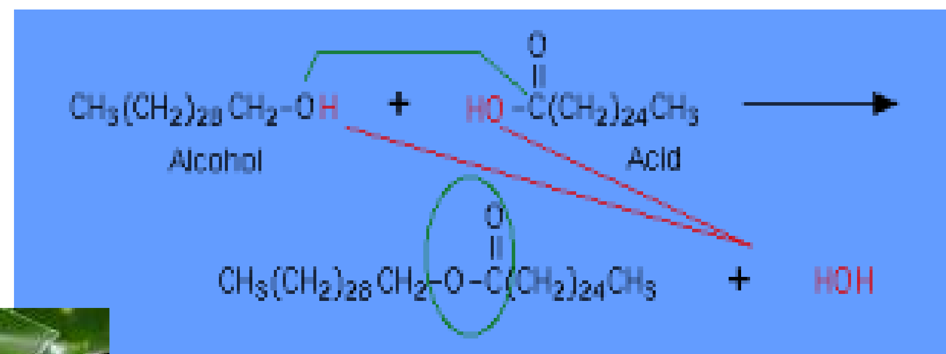
Glycerol is used by the liver as a substrate for gluco-neogenesis

Differences between oils and fats

Differences	Fats	Oils
Sources	Mainly animals	Mainly plants
Fatty acid	Saturated	Unsaturated
Bonding	No double bond	Have double bond
State at room conditions	Solid	Liquid
Melting point	High	Low

Waxes

A **wax** is complex mixtures of esters of long-chain fatty acids and long chain alcohols. The alcohol may contain from 12-32 carbon atoms. **Waxes** are found in nature as coatings on leaves and stems.

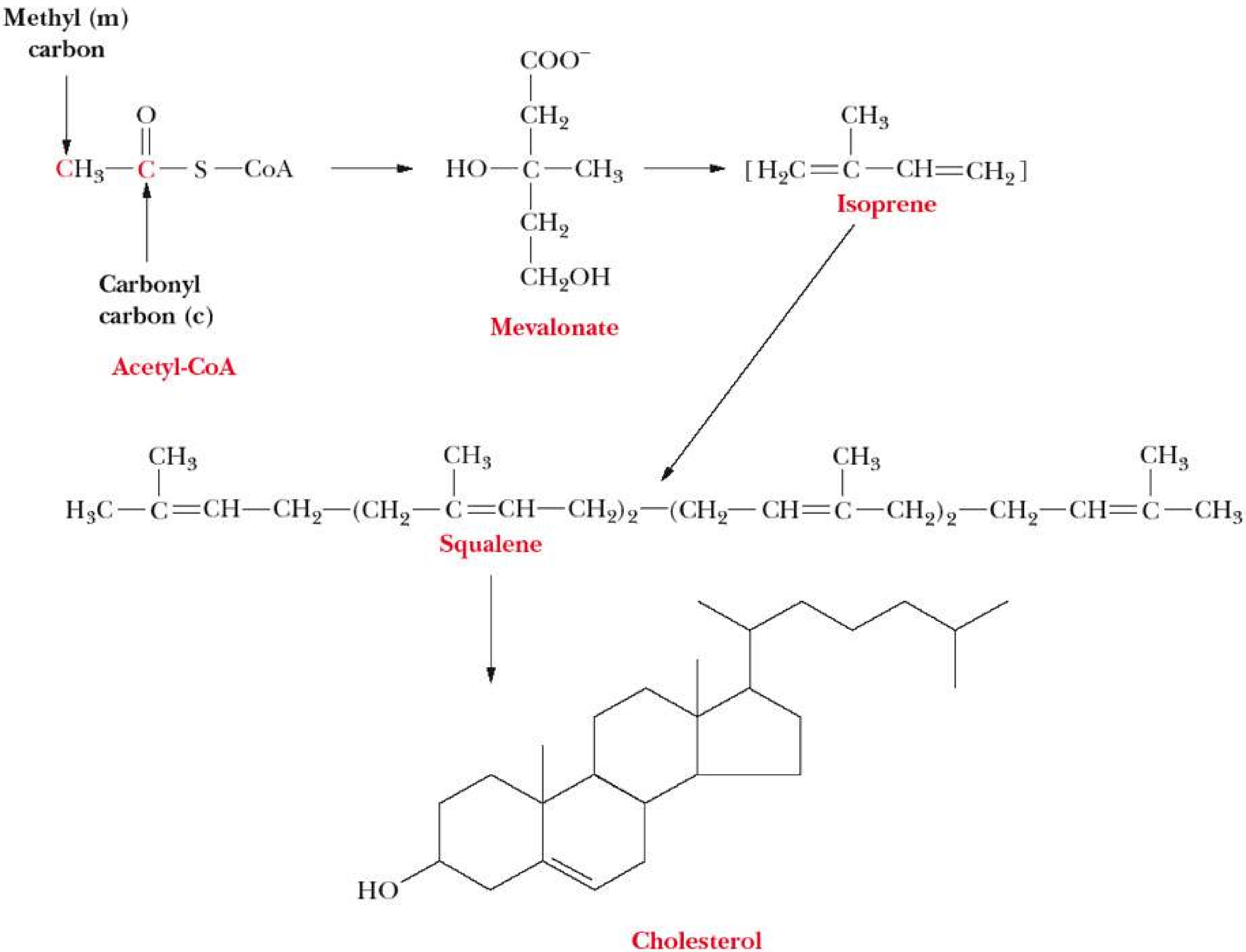


Steroids

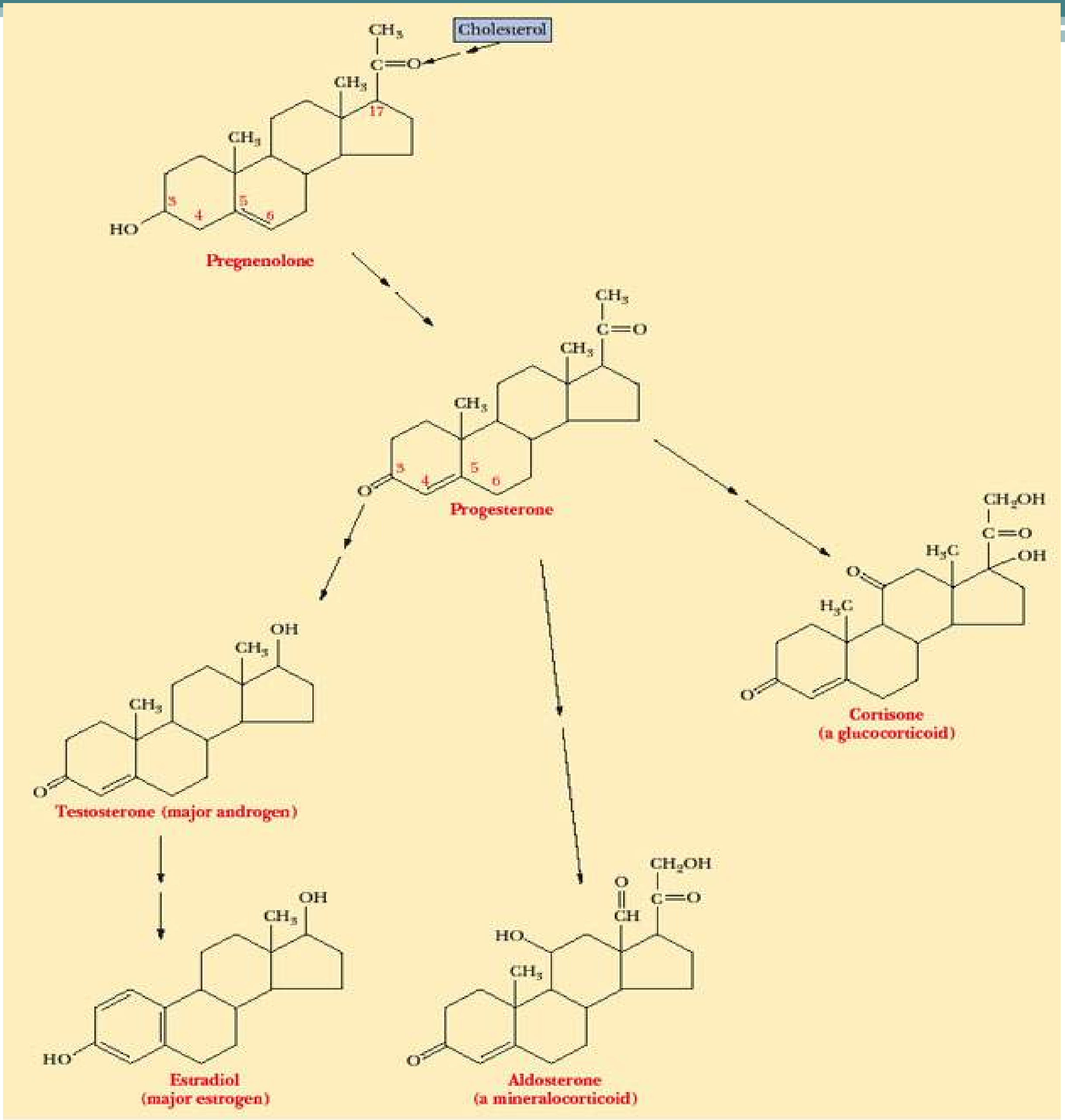
Steroids are lipids that contain four fused carbon rings that form the **cyclopentano-perhydrophenanthrene** steroid nucleus .

Cholesterol : is the major **sterol** in the human body . Sterols are a class of steroids characterized by a hydroxyl group at carbon 3 , and an aliphatic chain of at least eight carbons at C-17 .

1. Cholesterol is a **structural component** of cell membranes and plasma lipoproteins .
2. It is the **precursor** from which steroid hormones and bile acids are synthesized .



Methyl (m) carbon
Carbonyl carbon (c)
Acetyl-CoA
Mevalonate
Isoprene
Squalene
Cholesterol


Cholesterol
Pregnenolone
Progesterone
Cortisone
(a glucocorticoid)
Testosterone (major androgen)
Estradiol
(major estrogen)
Aldosterone
(a mineralocorticoid)

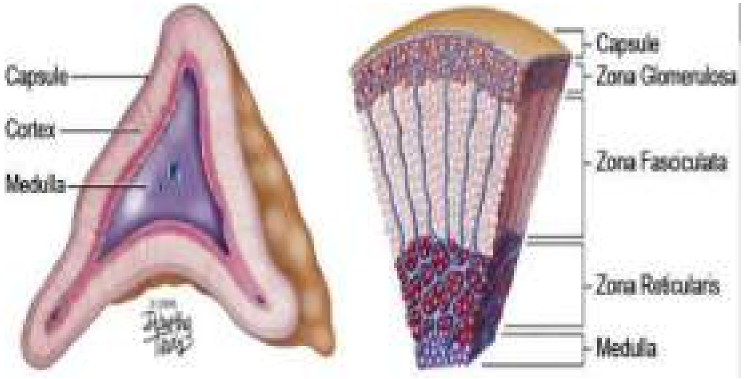
Steroid hormones

Steroid hormones produced in humans are formed and secreted by the **adrenal cortex** , the **testis** , the **ovary** , and the **placenta** .

1. The ***adrenal cortex*** produces hormones with two kinds of physiologic activities .

a. The zona fasciculta of the adrenal cortex primarily produces cortisol in humans . **Cortisol** regulates a number of key metabolic steps and also inhibits the inflammatory response . It is called a **glucocorticoid** ,

b. The adrenal zona glomerulosa produces **aldosterone** which controls the reabsorption of Na in the kidney . Aldosterone is called a **mineralocorticoid.**



2 . ***Gonadal steroids*** :

a. The leydig cells of the **testis** produce **testosterone** , the hormone responsible for the development of the male secondary sexual characteristics .

b. The **ovary** produces **estradiol** in the graafian follicle and **progesterone** in the corpus luteum , progesterone is also formed by the **placenta** in pregnancy as well

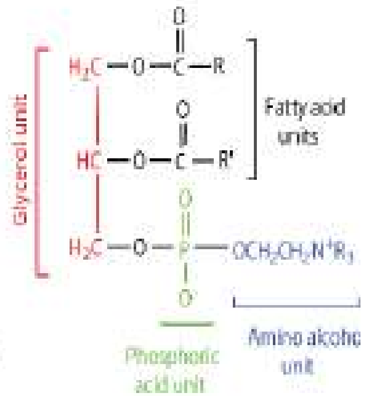
Phosphoacylglycerols

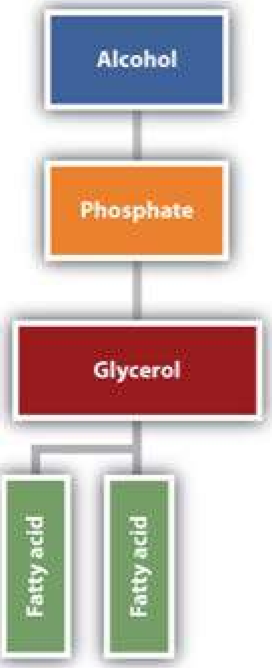
Phospholipids: are the major lipid constituents of cellular membranes .

They comprise approximately 40 % of the lipids in the erythrocyte membrane and more that 95 % of the lipids in the inner mitochondrial membrane .

Phosphoglycerides: are triesters of glycerol in which two esters have been formed between the two hydroxyl groups of glycerol and fatty acids side chain (R1, and R2) and the third hydroxyl group are esterfied by phosphoric acid molecule.

The resulting compound is called **phosphatidic acid**. Phosphate can form other ester bonds with other alcohol, creating a phosphatidyl ester.





Phosphoglyceride (a phospholipid)

Classification of phosphglycerides :

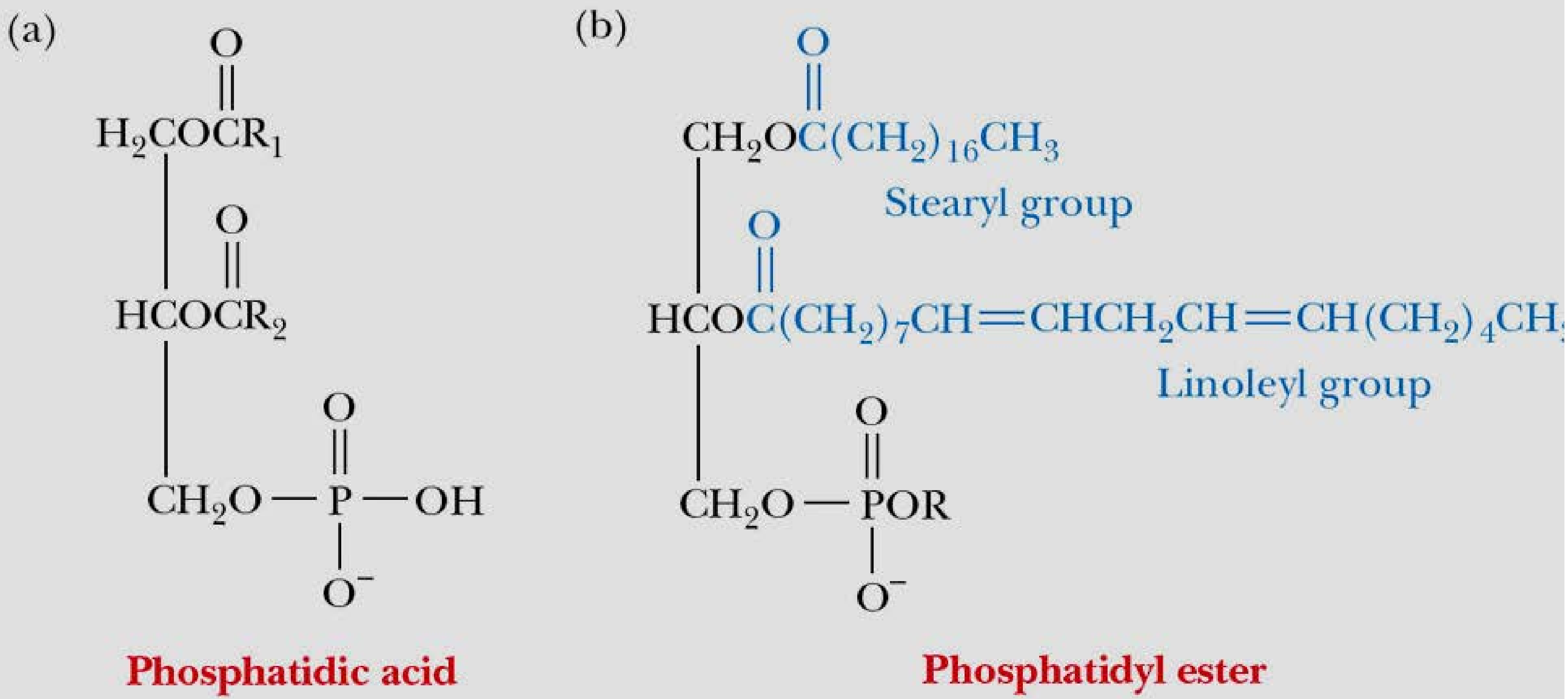
Phosphoglycerides include the following compounds :

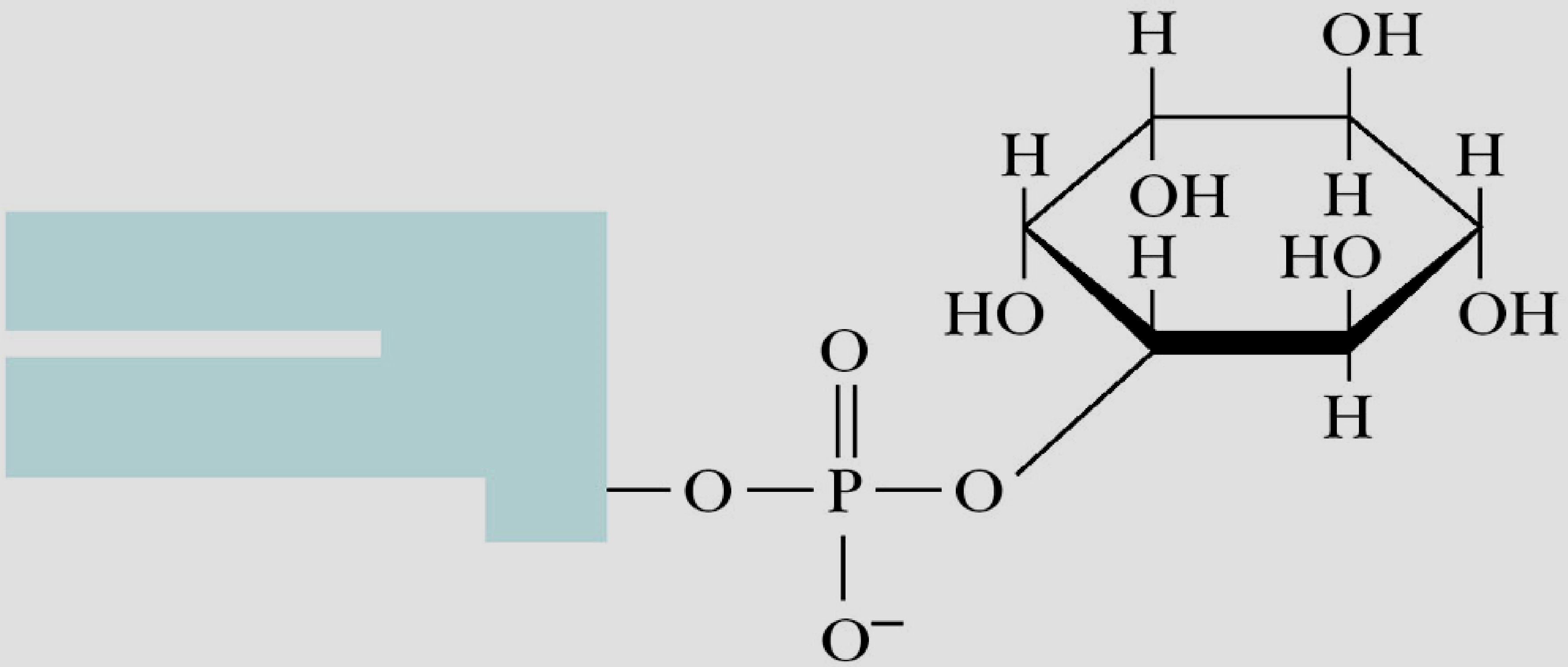
1.Phosphatidylcholine (lecithin)

2.Phosphatidylethanolamine (a cephalin) .

3.Phosphatidylinositol

4.Diphosphatidyl Glycerol (Cardiolipin), which comprises approximately 20 % of the lipids of the inner mitochondrial membrane .


(a)
H2COCR1
HCOCR2
CH2O — P — OH
O⁻
Phosphatidic acid
(b)
CH2OC(CH2)16CH3
Stearyl group
HCOC(CH2)7CH=CHCH2CH=CH(CH2)4CH
Linoleyl group
CH2O — POR
O⁻
Phosphatidyl ester

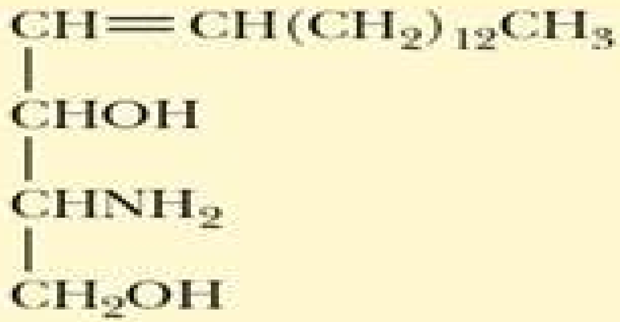


Phosphatidylinositol

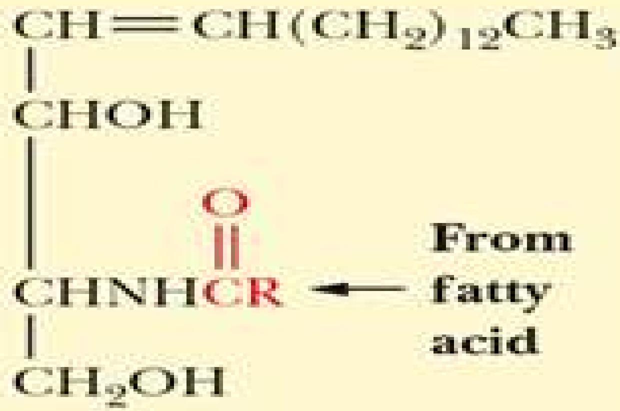
Sphingolipids

- Sphingolipids do not contain glycerol, but they contain the long-chain amino alcohol : Sphingosine, from which this class of compounds takes it's name. They are present in nearly all human tissues .

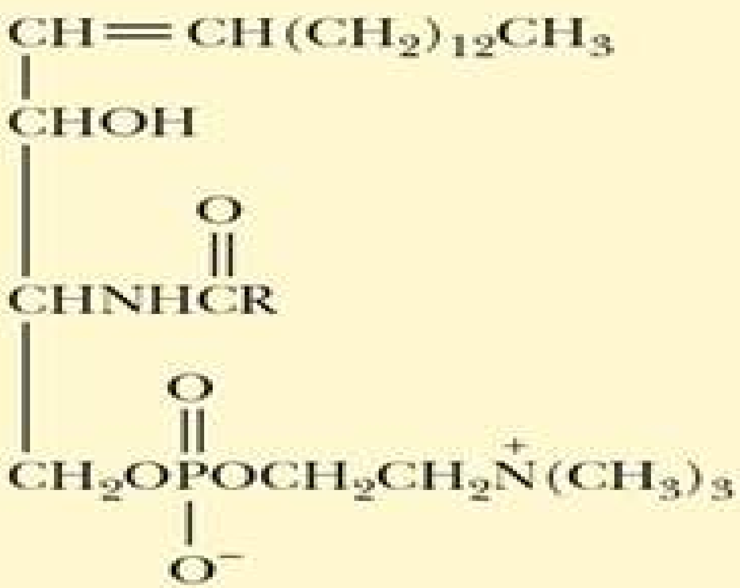
- The greatest concentration of sphingolipids is found in the central nervous system (CNS) , particularly in white matter المادة البيضاء.



Sphingosine



A ceramide (*N*-acylsphingosine)

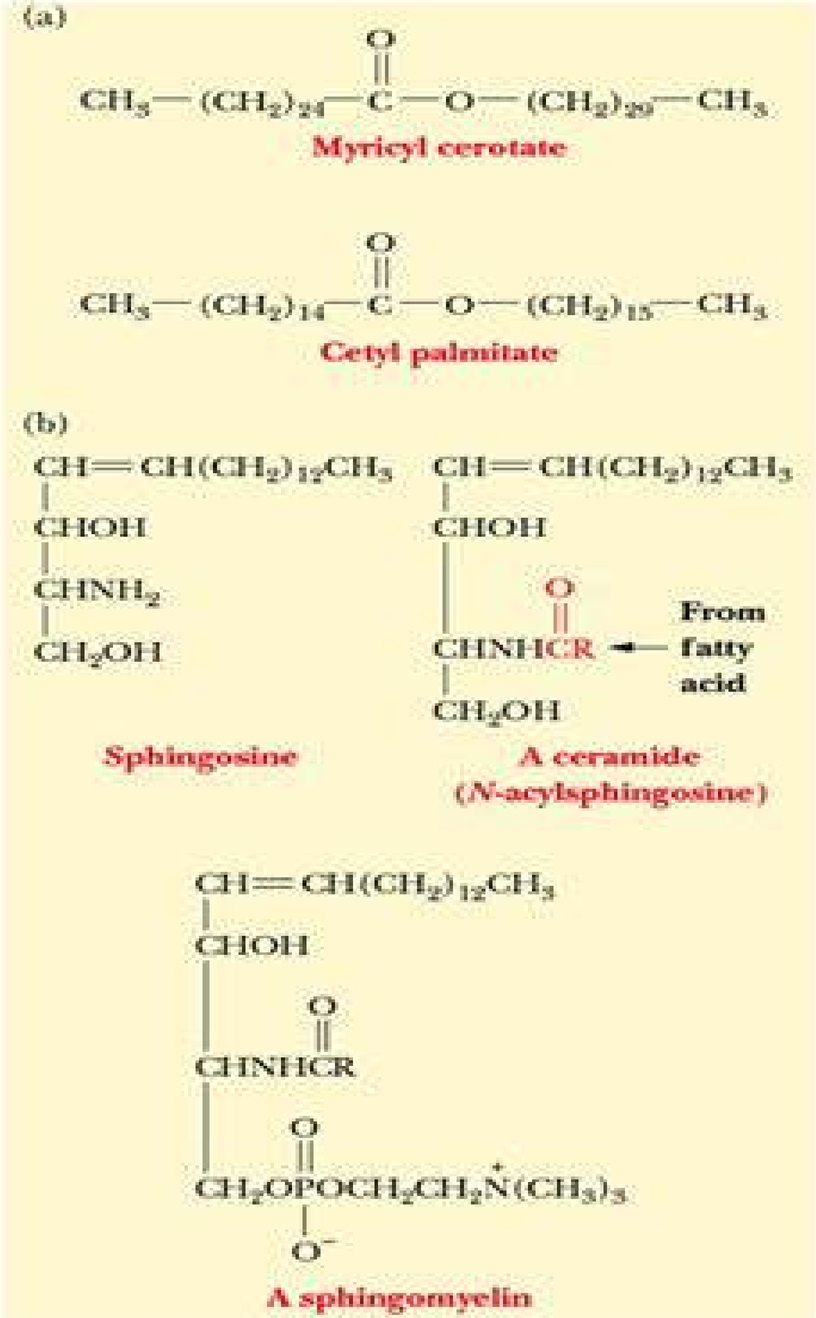


A sphingomyelin

Sphingomyelins:

In sphingomylins, the primary alcohol group of sphingosine is esterfied to phosphoric acid, which, in turn, is esterfied to another amino alcohol, cholin.

Sphingomyelin is the major phosolipids components of membranes in neural tissues.



(a)
Myricyl cerotate
Cetyl palmitate
(b)
Sphingosine
From fatty acid
A ceramide (N-acylsphingosine)
A sphingomyelin

Glycolipids

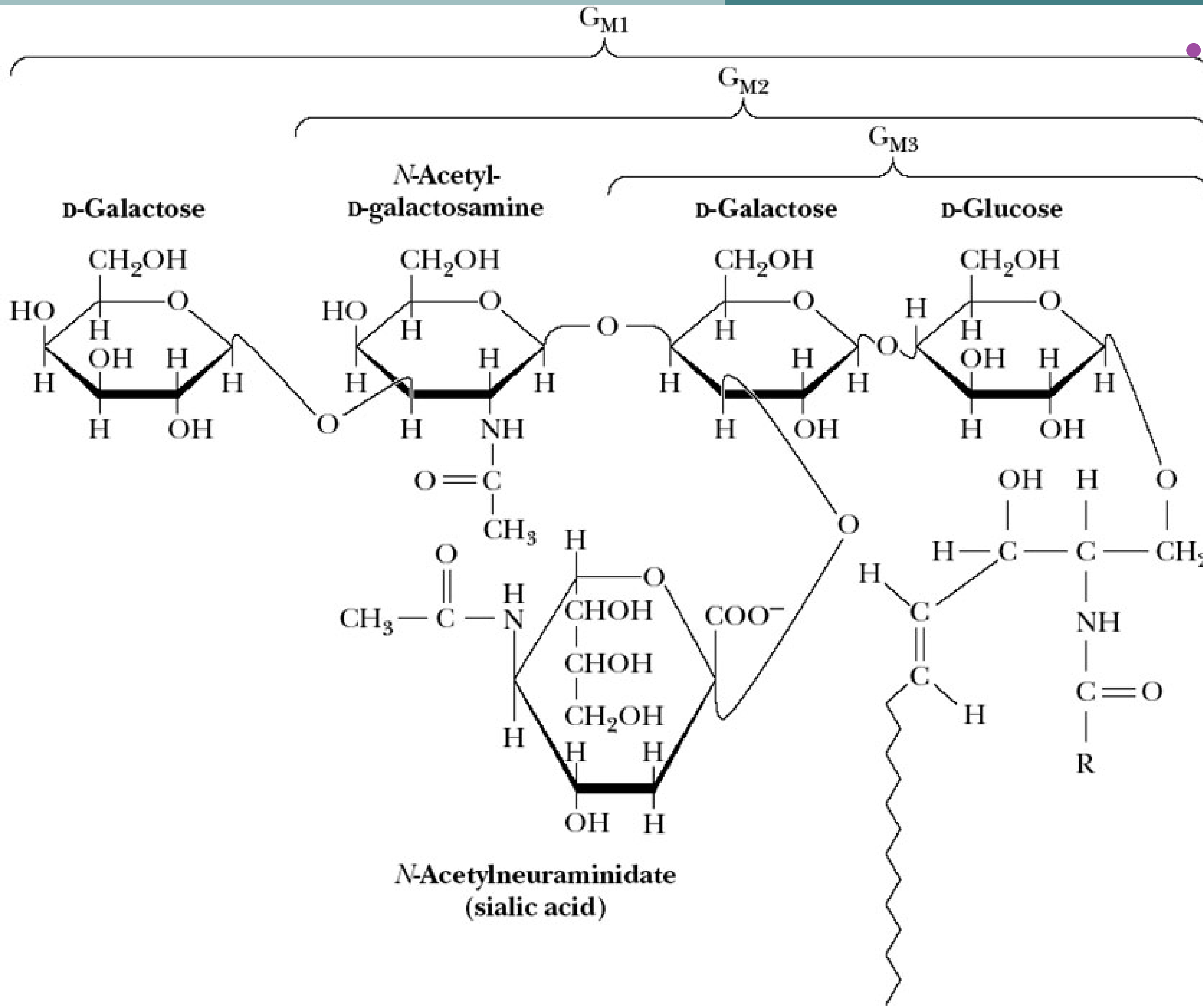
When a glycosidic bond is formed between the primary alcohol group of the ceramide and a sugar residue. The resulting compound is called a cerebroside.

the most important being **galactocerebroside** and **glucotocerebroside** . Cerebrosides are found in neural tissue membranes particularly the myelin sheath .

Gangliosides

- Gangliosides are glycolipids with a complex carbohydrate moiety (one of them is: N-acetylneuraminic NANA, which is sialic acid).

- They are found in high concentration in ganglion cells of the CNS and in lower concentration in the membranes of most cells.



Gangliosides G_{M1}, G_{M2}, and G_{M3}

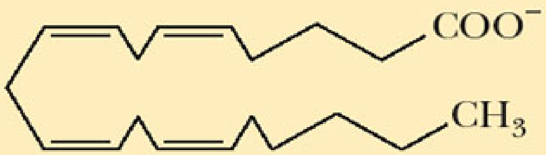
Prostaglandins

•Prostaglandins are group of compounds derived form arachidonic acid and have a wide range of physiologic activities.

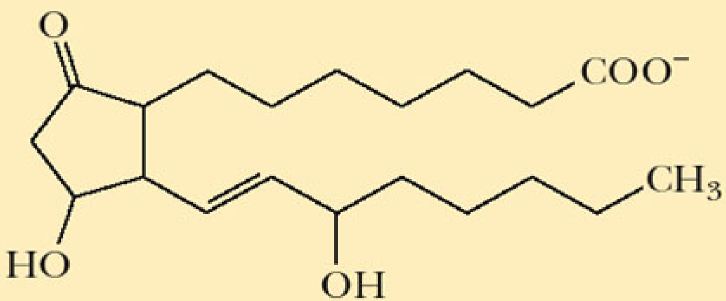
•They are called prostaglandins because they were first detected in seminal fluid, which is produced by prostate gland. The 20-carbon ***prostaglandins and leukotrienes are also called eicosinoids.***

1. **Function** : Postaglandins are widely distributed in tissues , but their role is not fully understood . At low concentrations , postaglandins have been shown to modulate wide range of biologic activities , including:

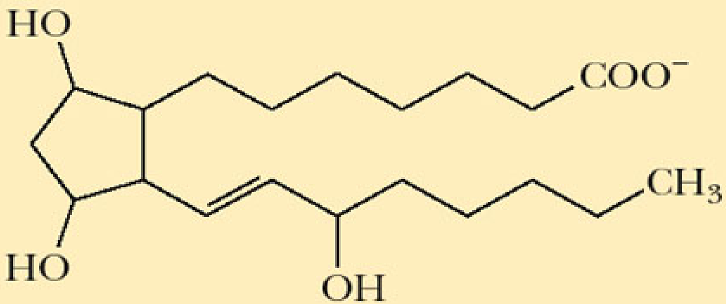
    a. **Smooth muscle contraction and relaxation.**
    b. **Gastic secretion .**
    c. **Platelet aggregation .**
    d. **Inflammatory response .**
    e. **Response to trophic hormones .**
    f. **Retention by kidney tubules .**



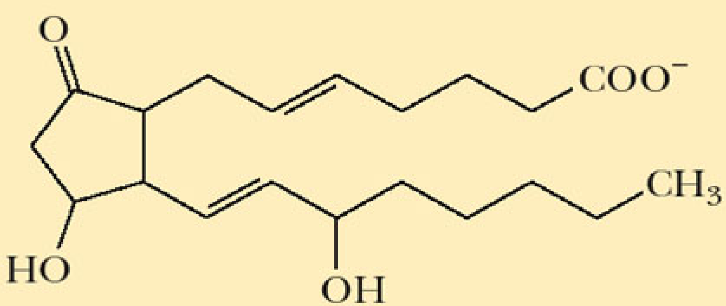
Arachidonic acid (Arachidonate form)



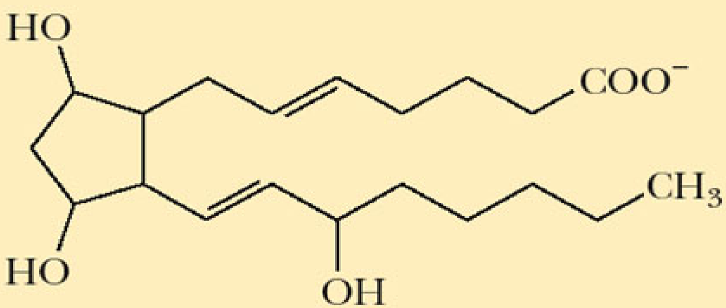
PGE_1



PGE_{3a}



PGE_2



PGE_{2a}

Prostaglandins: Thromboxanes

Function :

A. Thromboxane A2 (TXA2) is produced by platelets.

B. It causes contraction of arteries and triggers platelet aggregation. These effects are exactly the opposite of those caused by prostacyclin (PGI2) which is produced by the endothelial cells of the vascular system .

C. Thromboxane and Prostacyclin are antagonistic and have a balance working relationship

Aspirin inhibits the synthesis of prostaglandins, particularly in blood platelets, a property that accounts also for its anti-inflammatory and fever reducing properties. Cortisone and other steroids also have anti-inflammatory effects because of their inhibition of prostaglandin synthesis.

Some Prostaglandins are known to inhibit the aggregation of platelets. They may thus be of therapeutic value by preventing the formation of blood clots.

Leukotrienes

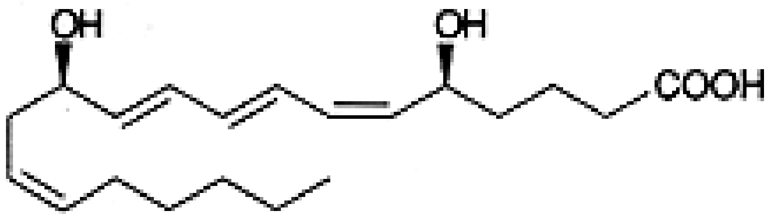
Leukotrienes are compounds that like prostaglandins, are derived from arachidonic acid. They are found in leukocytes and have 3 conjugated double bonds.

2 - Functions :

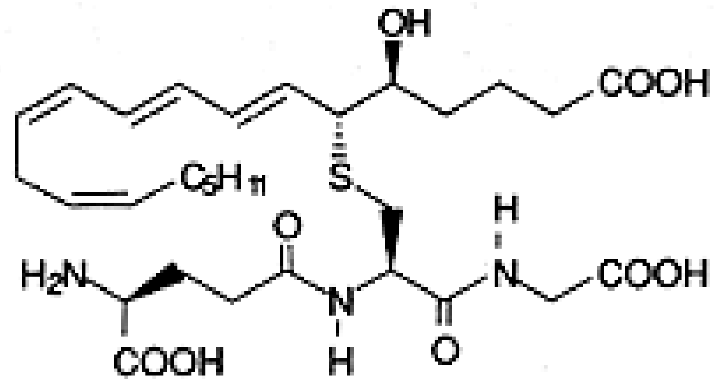
Leukotrienes are involved in chemotaxis , inflammation , and allergic reactions .

Leukotriene D4 (LTD4) has been identified as the slow reacting substance of anphylaxis (SRS-A) , which causes smooth muscle contraction and is approximately 1000 times more potent than histamine in constricting the pulmonary air-ways .

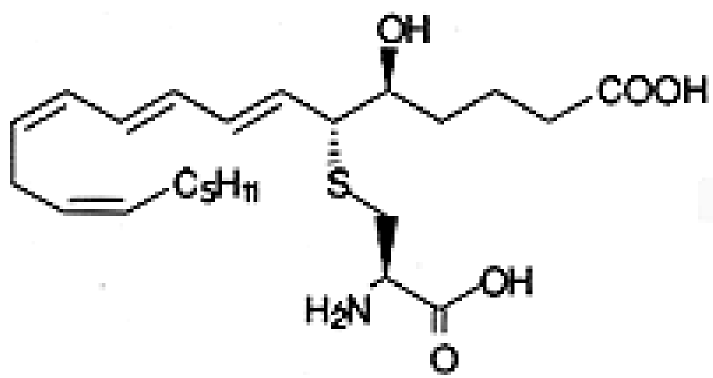
Drugs that inhibit the synthesis of certain leukotriens are now being used in the treatment of asthma



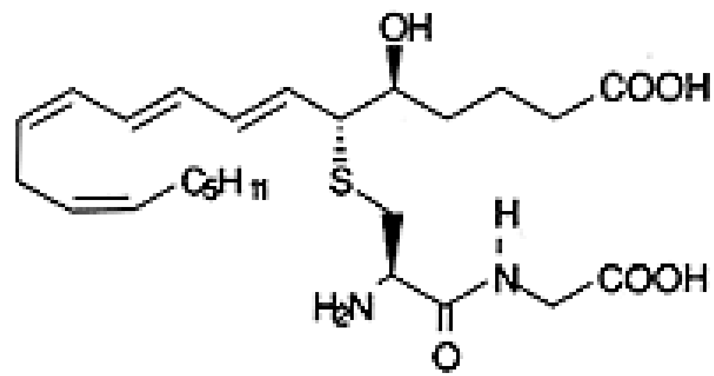
LEUKOTRIENE B_4



LEUKOTRIENE C_4



LEUKOTRIENE E_4



LEUKOTRIENE D_4

Biochemical Connections:

Omega-3 fatty acids

and platelets in heart disease

Platelets are elements in the blood that initiate blood clotting and tissue repair by releasing clotting factors and platelet derived growth factor (PDGF).

Turbulence in the bloodstream may cause platelets to rupture. Fat deposits and bifurcations of arteries lead to such turbulence, so platelets and PDGF are implicated in blood clotting and growth of atherosclerotic plaque.

In cultures that depend on fish as a major food source including some Eskimo tribes, very little heart disease is diagnosed, even though people in these groups eat high-fat diets and have high levels of blood cholesterol.

Analysis of their diet led to the discovery that certain highly unsaturated fatty acids are found in the oils of fish and diving mammals. One class of these fatty acids is called omega-3 (ω_3), and example of which is eicosapentenoic acid (EPA).

$$CH_3CH_2(CH{=}CHCH_2)_5(CH_2)_2COOH$$

Eicosapentenoic acid (EPA)

The omega-3 fatty acids inhibit the formation of certain prostaglandins and thromboxane A, which is similar in structure to prostaglandins.

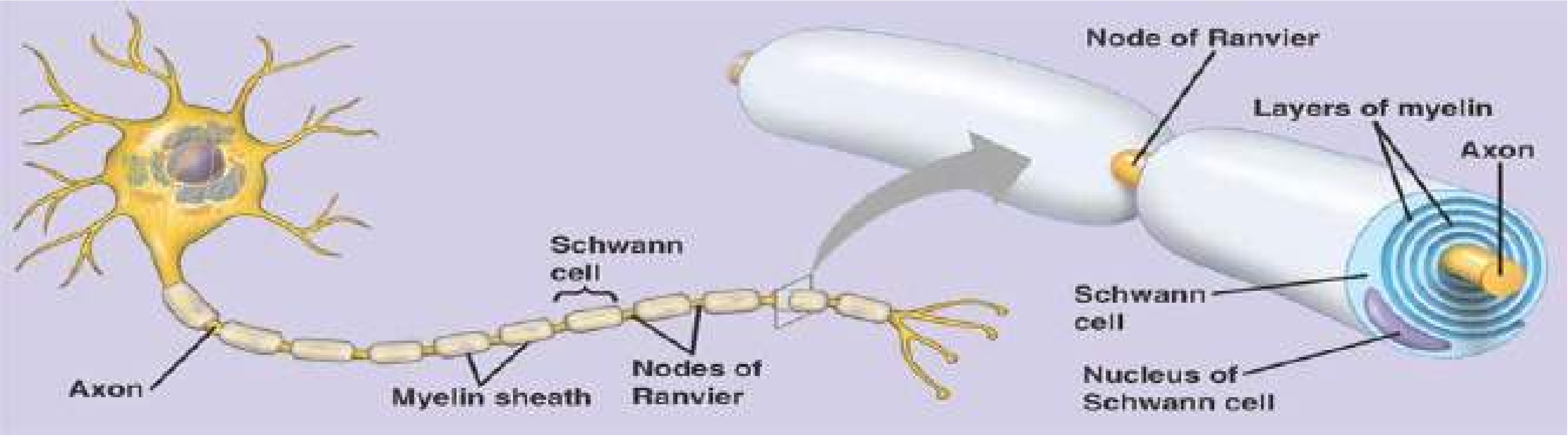
Thromboxane released by ruptured arteries causes other platelets to clump in the immediate area and to increase the size of blood clot.

Any disruption in thromboxane synthesis will result in lower potential for artery damage.

Biochemical Connections

Myelin and Multiple sclerosis

Myelin is the lipid–rich membrane sheath that surrounds the axons of nerve cells; it has a particularly high content of sphingomeylins.



In multiple sclerosis, a crippling and eventually fatal disease, the myelin sheath is progressively destroyed by sclerotic plaques, which affect the brain and spinal cord.

These plaques appear to be of autoimmune origin, but epidemiologists have raised questions about involvement of viral infections in the onset of disease.

Persons affected by multiple sclerosis suffer from weakness, lack of coordination, and speech and vision problems.

Table 8.3

Lipid-Soluble Vitamins and Their Functions

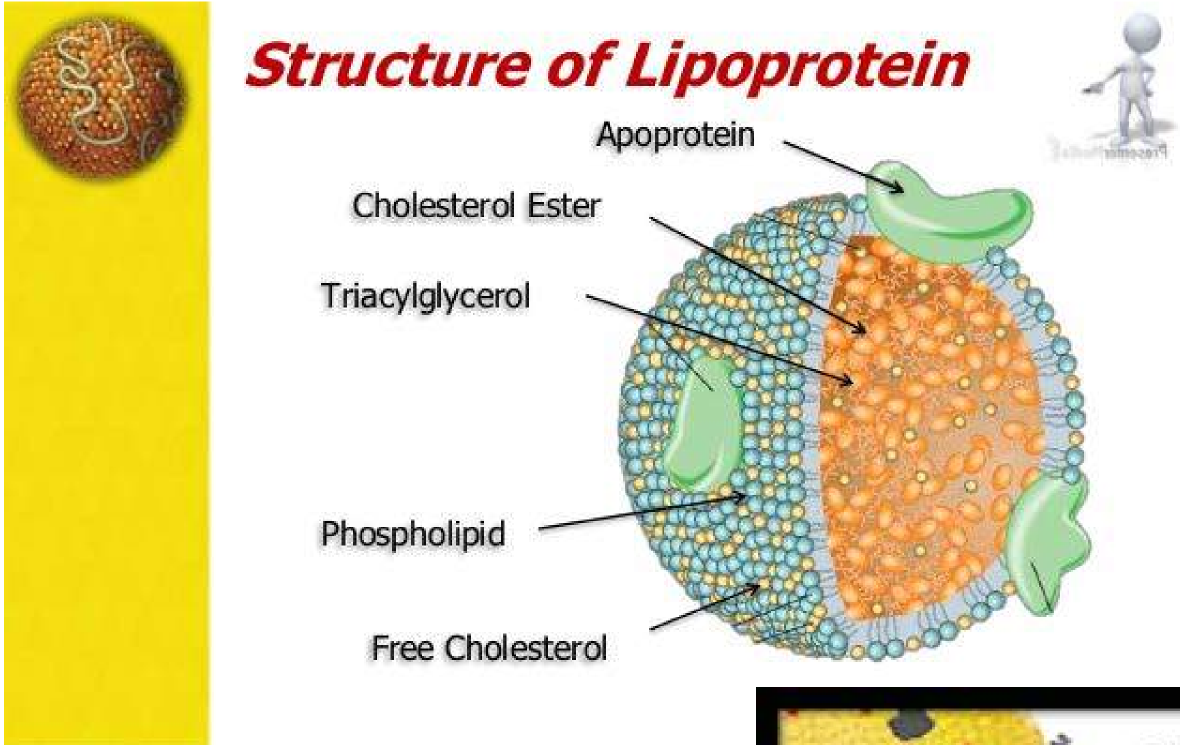
Vitamin	Function
Vitamin A	Serves as the site of the primary photochemical reaction in vision
Vitamin D	Regulates calcium (and phosphorus) metabolism
Vitamin E	Serves as an antioxidant; necessary for reproduction in rats and may be necessary for reproduction in humans
Vitamin K	Has a regulatory function in blood clotting

Table 8-3, p.203

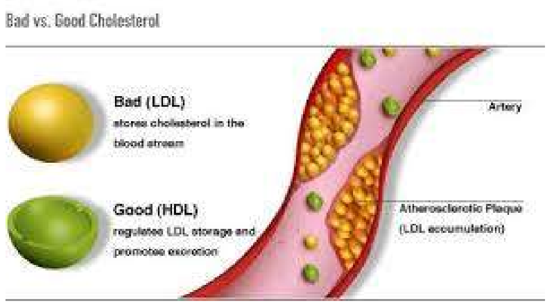
Lipoprotein

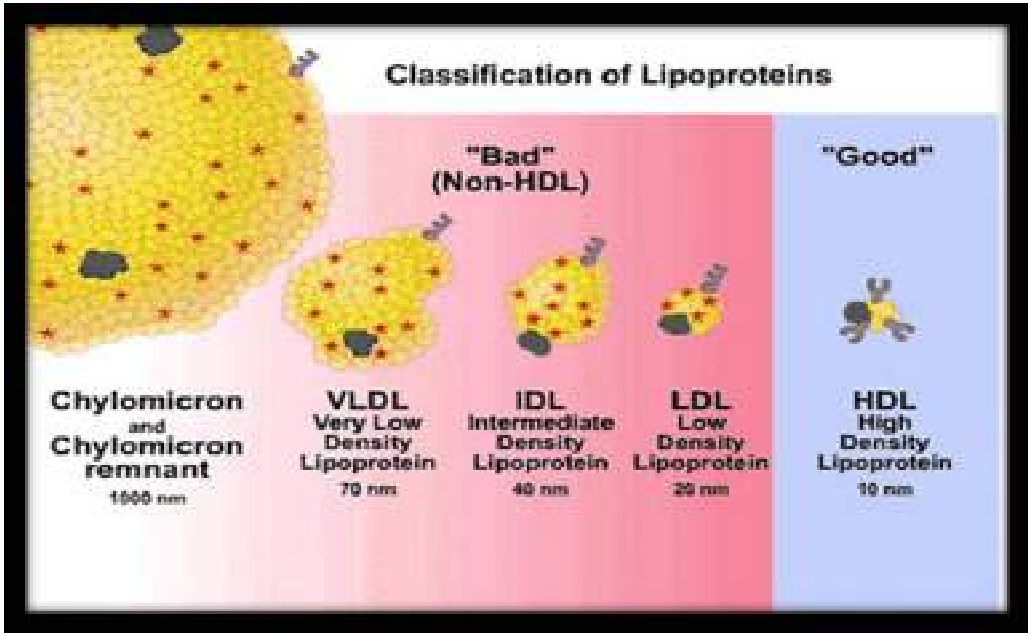
Plasma Lipoproteins are complexes of protein and lipids held together by noncovalent bonds . They function as clinically important transporters of lipids .

Classification : Two systems for classifying plasma lipoproteins are in use .


Structure of Lipoprotein
Apoprotein
Cholesterol Ester
Triacylglycerol
Phospholipid
Free Cholesterol


HDL
LDL


Bad vs. Good Cholesterol
Bad (LDL)
stores cholesterol in the blood stream
Good (HDL)
regulates LDL storage and promotes excretion
Artery
Atherosclerotic Plaque
(LDL accumulation)


Classification of Lipoproteins
"Bad"
(Non-HDL)
"Good"
Chylomicron
and
Chylomicron
remnant
1000 nm
VLDL
Very Low
Density
Lipoprotein
70 nm
IDL
Intermediate
Density
Lipoprotein
40 nm
LDL
Low
Density
Lipoprotein
20 nm
HDL
High
Density
Lipoprotein
10 nm

Structure

1. Lipoprotein components do not have an exact stoichiometric relationship (نسب متكافئة) but the different classes have characteristic **lipid protein ratios** , and characteristic lipid classes are associated with different apoproteins.

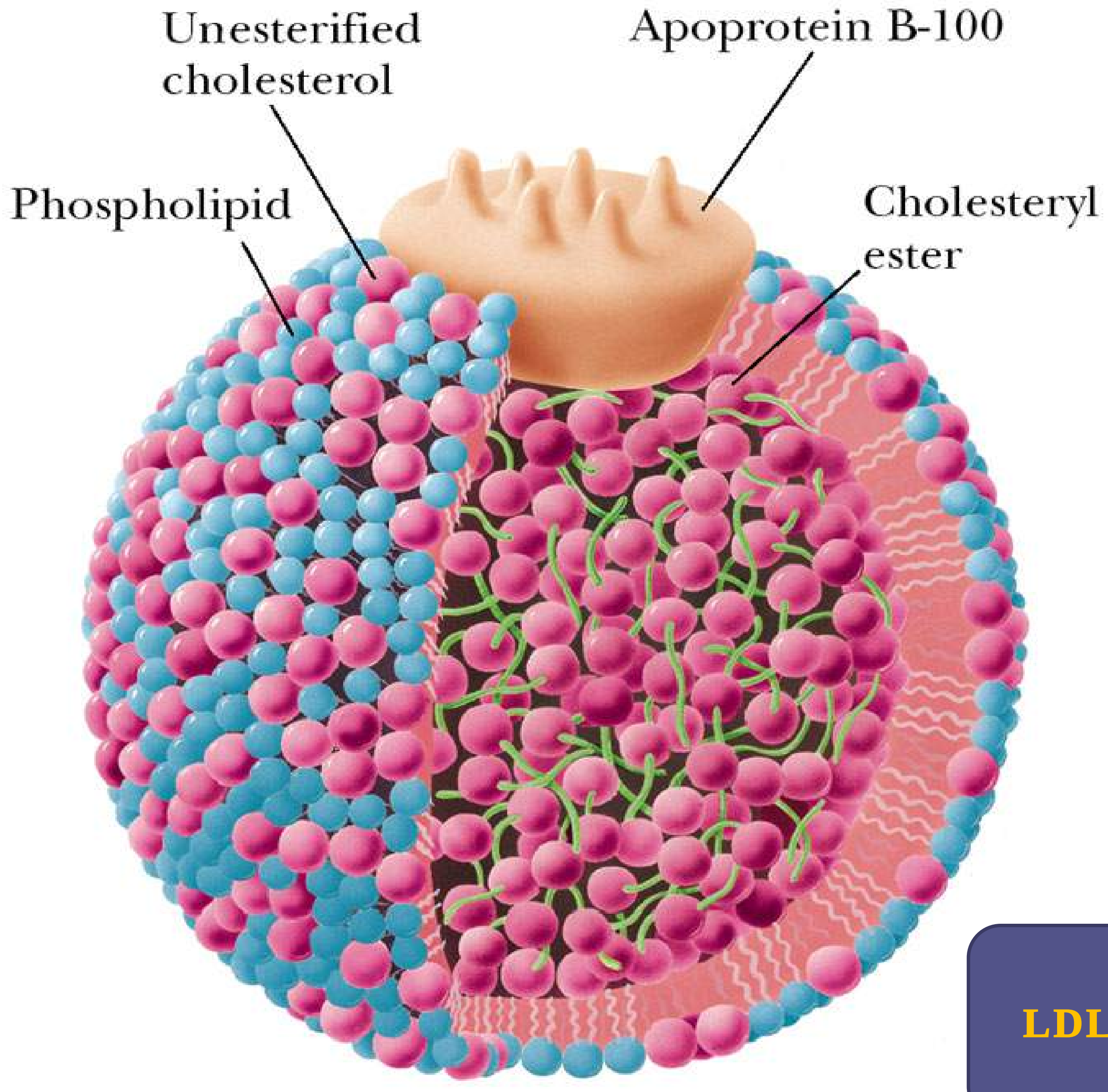
1.**Density** : This system is the most commonly used . Five fractions are distinguished .

2.**Electrophoretic mobility** : the other classification is based on electrophonetic mobility . In this system α , pre-β and β correspond to high-density lipoprotein (HDL) , very low-density lipoprotein (VLDL) , and low density lipoprotein (LDL), respectively , in the commonly used system .

Table 21.3

Major Classes of Lipoproteins in Human Plasma

Lipoprotein class	Density (g mL^{-1})
Chylomicrons	<0.95
VLDL	0.95–1.006
IDL	1.006–1.019
LDL	1.019–1.063
HDL	1.063–1.210



LDL particle

Lipoprotien complex	Lipid %	Protein %	Chol %	TG %	P- lipid %
CM	98	2	8	83	7
VLDL	90	10	22	50	18
LDL	75	25	50	4	21
HDL	60	40	30	8	22

LDL- Receptor

An important type of receptor is that for low-density lipoprotein (LDL), the principal carrier of cholesterol in the bloodstream.

LDL is a particle that consists of various lipids - in particular, cholesterol and phosphoglycerides – as well as a protein (ApoB100). ApoB100 binds to the LDL receptor of a cell.

A portion of the membrane with LDL receptor and bound LDL is taken into the cell as a vesicle in a process called endocytosis.

The receptor protein release LDL and is returned to the cell surface (recycles) when the vesicle fuses to the membrane.

LDL releases cholesterol in the cell. An oversupply of cholesterol inhibits synthesis of the LDL receptor protein.

An insufficient number of receptors leads to elevated levels of LDL and cholesterol in the bloodstream. Eventually, the excess cholesterol is deposited in the arteries, blocking them severely.

This blocking of arteries , called **atherosclerosis**, can eventually lead to heart attacks and strokes.

In many industrialized countries, typical blood cholesterol levels are high , and the incidence of heart attacks and strokes is correspondingly high.

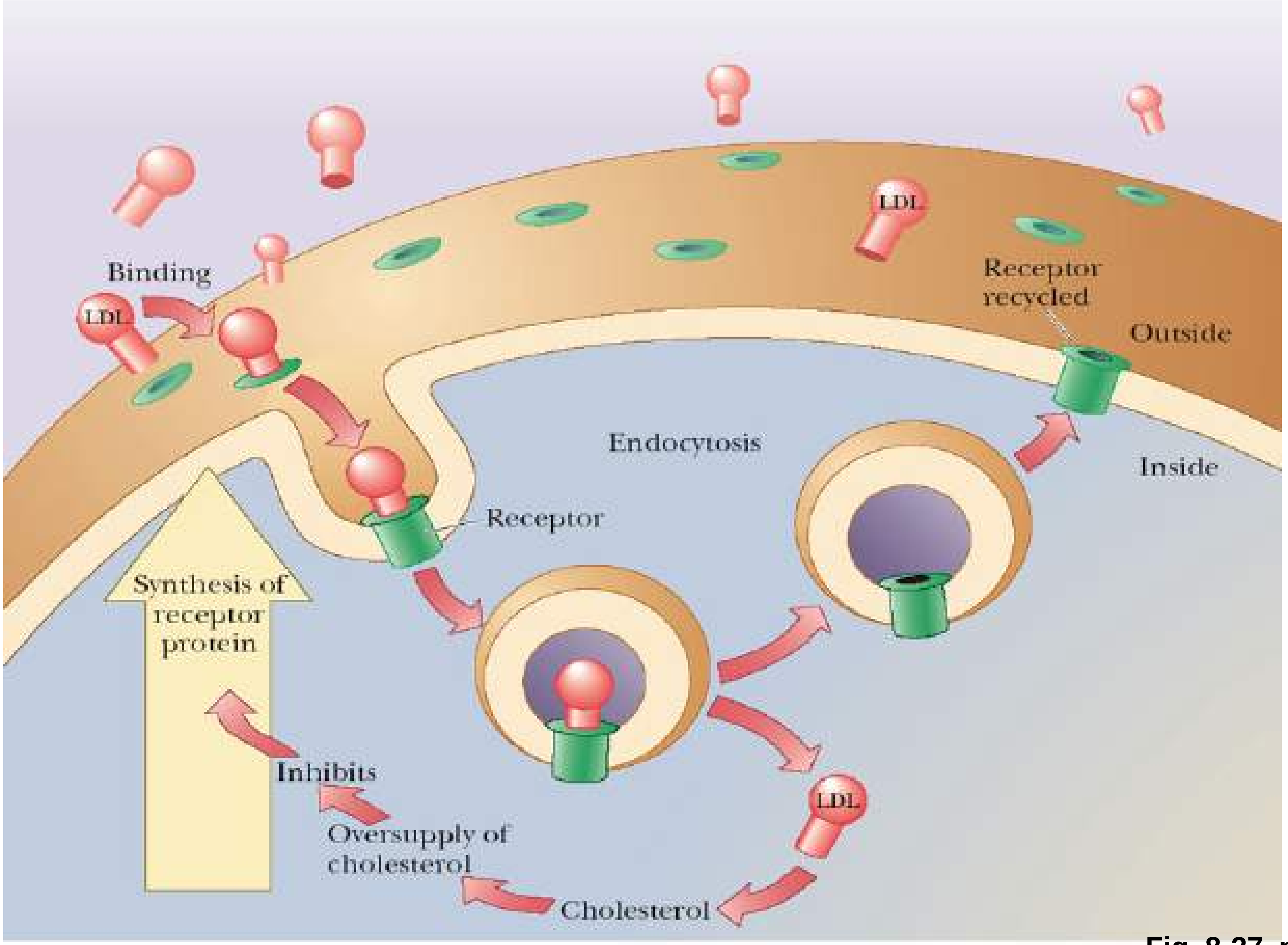
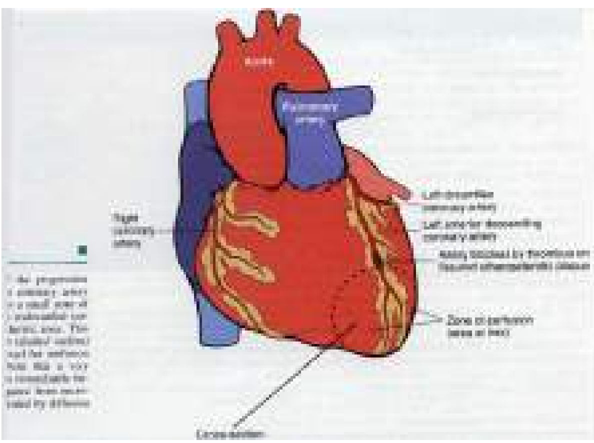
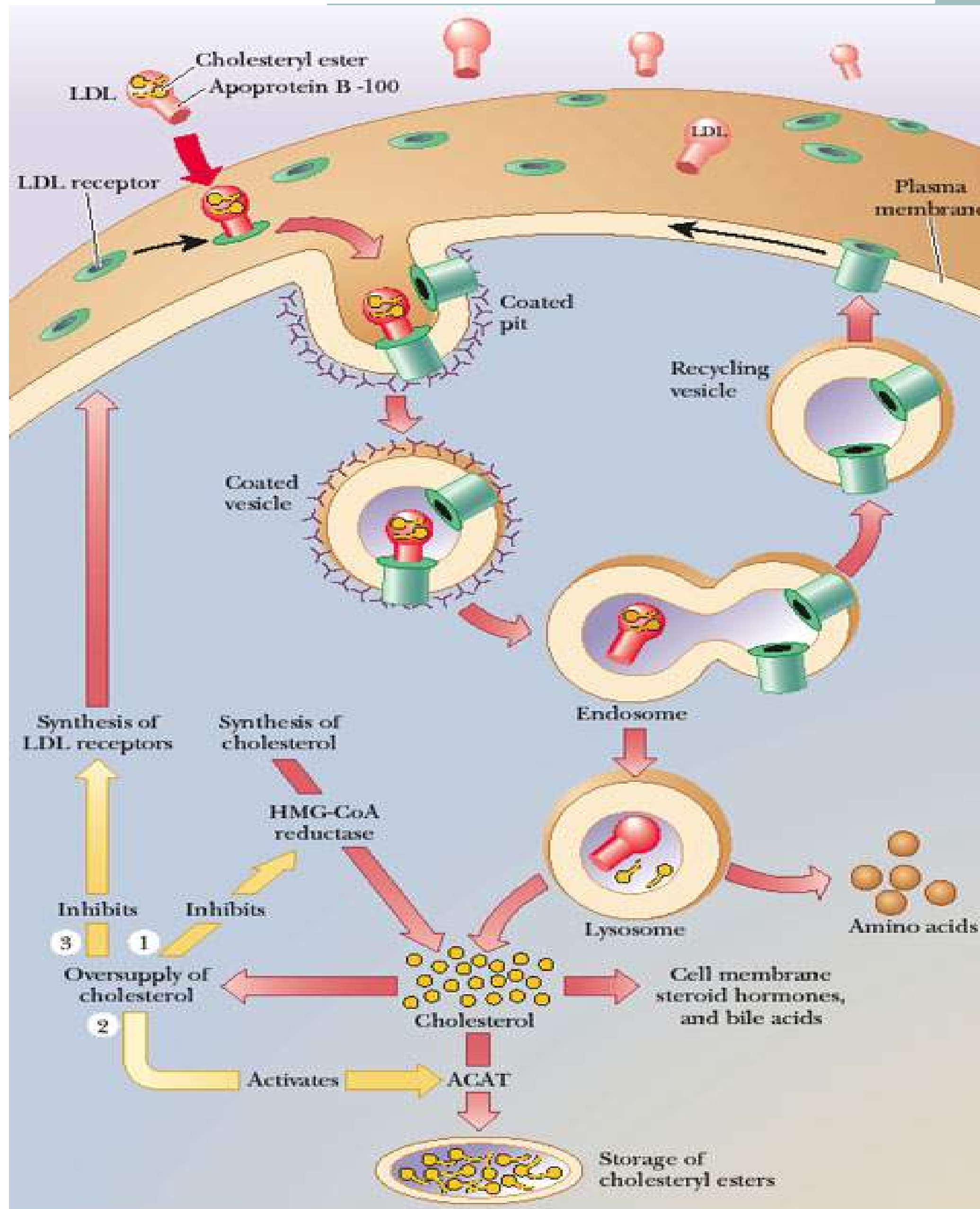

Binding
LDL
LDL
Receptor
recycled
Outside
Endocytosis
Inside
Receptor
Synthesis of
receptor
protein
Inhibits
Oversupply of
cholesterol
LDL
Cholesterol

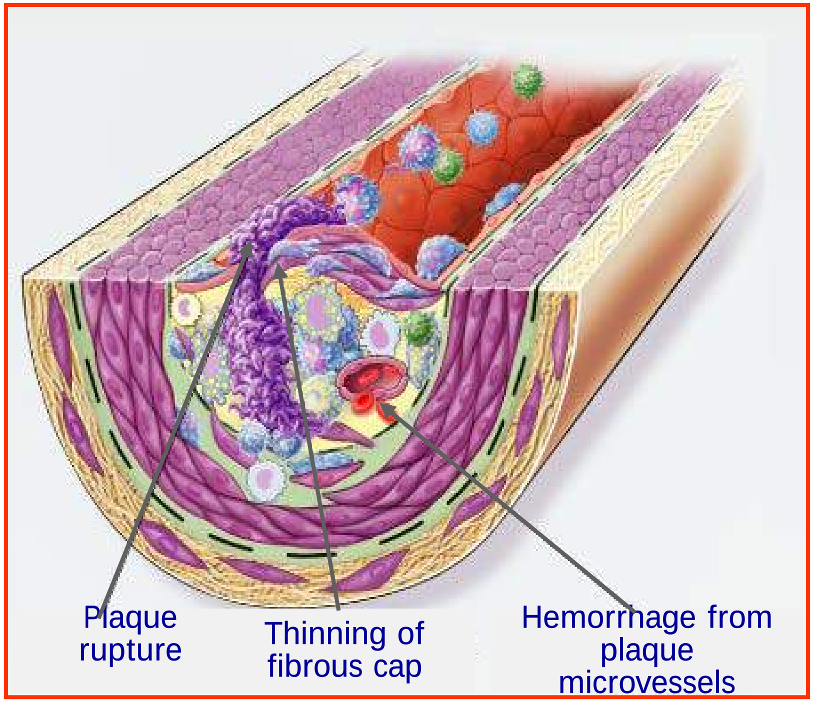
Fig. 8-27, p.203




Cholesteryl ester
LDL
Apoprotein B -100
LDL
LDL receptor
Plasma membrane
Coated pit
Recycling vesicle
Coated vesicle
Endosome
Synthesis of LDL receptors
Synthesis of cholesterol
HMG-CoA reductase
Inhibits
Inhibits
3
1
Oversupply of cholesterol
2
Lysosome
Amino acids
Cholesterol
Cell membrane steroid hormones, and bile acids
Activates
ACAT
Storage of cholesteryl esters

Pathophysiology of Atherosclerosis (IV)

- Plaque rupture and thrombosis:



Vessel wall

Ruptured plaque (coronary artery)

Ross R, N Engl J Med 340 (1999) & Davies, Circulation 94 (1996)