LIPIDS

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Bsc; Msc

- Introduction
- Classification
- Functions
- Lipid storage disorders

- Heterogeneous group of compounds, water-insoluble organic biomolecules that can be extracted from cells and tissues by non-polar organic solvents (benzene, chloroform, ether, hot alcohol, acetone, etc).
- contain hydrocarbons
- make up building blocks of structure and function of living cells

Examples:

- –fats, oils, waxes, certain vitamins, hormones

Often combined with other biomolecules

- Glycolipids
- Lipoproteins

Specialised biological functions

1. Storage form of energy (triacylglycerol)
2. Structural components of biomembranes (phospholipids and cholesterol)
3. Metabolic regulators (steroid hormones and prostaglandins)
4. Act as surfactants, detergents and emulsifying agents (amphipathic lipids)
5. Act as electric insulators in neurons
6. Provide insulation against changes in external temperature (subcutaneous fat)
7. Give shape and contour to the body
8. Protect internal organs by providing a cushioning effect (pads of fat)
9. Help in absorption of fat soluble vitamins (A, D, E and K)
10. Improve taste and palatability of food.

Table: Functions of Lipids

Localised primarily in three compartments:

- Plasma
- Adipose tissue
- Biological membranes

CLASSIFICATION

Based on the chemical nature:

Simple lipids: Esters of fatty acids with glycerol or other higher alcohols.

Compound lipids: Fatty acids esterified with alcohol; but in addition contain other groups. Depending on these extra groups, they are subclassified:

a. Phospholipids, containing phosphoric acid.

b. Non-phosphorylated lipids

Derived lipids: Compounds derived from lipids or precursors of lipids, e.g. fatty acids, steroids.

Lipids complexed to other compounds

I Simple lipids
a. Triacylglycerol or Triglycerides or neutral fat
b. Waxes
II. Compound lipids
A. Phospholipids, containing phosphoric acid
1. Nitrogen containing glycerophosphatides:
i. Lecithin (phosphatidylcholine)
ii. Cephalin (phosphatidylethanolamine)
iii. Phosphatidylserine
2. Non-nitrogen glycerophosphatides
i. Phosphatidylinositol
ii. Phosphatidylglycerol
iii. Diphosphatidylglycerol (cardiolipin)
3. Plasmalogens, having long chain alcohol
i. Choline plasmalogen
ii. Ethanolamine plasmalogen
4. Phospho sphingosides, with sphingosine
Sphingomyelin
B. Non-phosphorylated lipids
1. Glycosphingolipids (carbohydrate)
i. Cerebrosides (ceramide monohexosides)
ii. Globosides (ceramide oligosaccharides)
iii. Gangliosides (ceramide + oligosaccharides + N-acetyl neuraminic acid)
2. Sulfolipids or sulfatides
i. Sulfated cerebrosides
ii. Sulfated globosides
iii. Sulfated gangliosides
III. Derived lipids
Fatty acids, steroids (see chapter 13), prostaglandins (see chapter 14), leukotrienes, terpenes, dolichols, etc.
IV. Lipids complexed to other compounds
Proteolipids and lipoproteins.

Table: Classification of Lipids

Name	*Saturated fatty acids (%)*	*Mono-unsaturated fatty acids(%)*	*PUFA (%)*
Coconut oil	(*) 86	12	2
Groundnut oil	18	46	36
Gingelly oil (Til oil)	13	50	37
Palm oil	42	52	6
Corn oil	13	25	62
Cotton seed oil	26	19	55
Seasame oil	12	48	40
Mustard oil (rapeseed)	34(**)	48	18
Safflower oil (Kardi)	9	12	79
Sunflower oil	12	24	64
Butter	75	20	5
Ox (Tallow)	53	42	5
Pig (Lard)	42	46	12
Fish oil	30	13	57

(*) these saturated fatty acids are medium chain fatty acids.
(**) contains erucic acid, 22 C, 1 double bond.

The composition of some of the common oils and fats

1. Depending on total number of carbon atoms:
a. Even chain:
They have carbon atoms 2,4,6 and similar series. Most of the naturally occurring lipids contain even chain fatty acids.
b. Odd chain:
They have carbon atoms 3, 5, 7, etc. Odd numbered fatty acids are seen in microbial cell walls. They are also present in milk.
2. Depending on length of hydrocarbon chain:
a. Short chain with 2 to 6 carbon atoms
b. Medium chain with 8 to 14 carbon atoms
c. Long chain with 16 and above, usually up to 24 carbon atoms
d. Very long chain fatty acids (more than 24 carbon).
3. Depending on nature of hydrocarbon chain:
a. Saturated fatty acids (Table 7.2)
b. Unsaturated fatty acids which may be subclassified into Monounsaturated (monoenoic) having single double bond or Polyunsaturated (polyenoic) with 2 or more double bonds. (Table 7.2)
c. Branched chain fatty acids
d. Hydroxy fatty acids

Table: Classification of fatty acids

A. Phospholipids-esters of the above type containing phosphoric acid residue

a) Glycerophospholipids-alcohol is glycerol

b) Sphingophospholipids-alcohol is sphingosine

B. Glycolipids (glycosphingolipids)- Lipids containing fatty acid, sphingosine and carbohydrate residues

C. Others-sulfolipids, amino lipids and lipoproteins (which are modified forms of lipids)

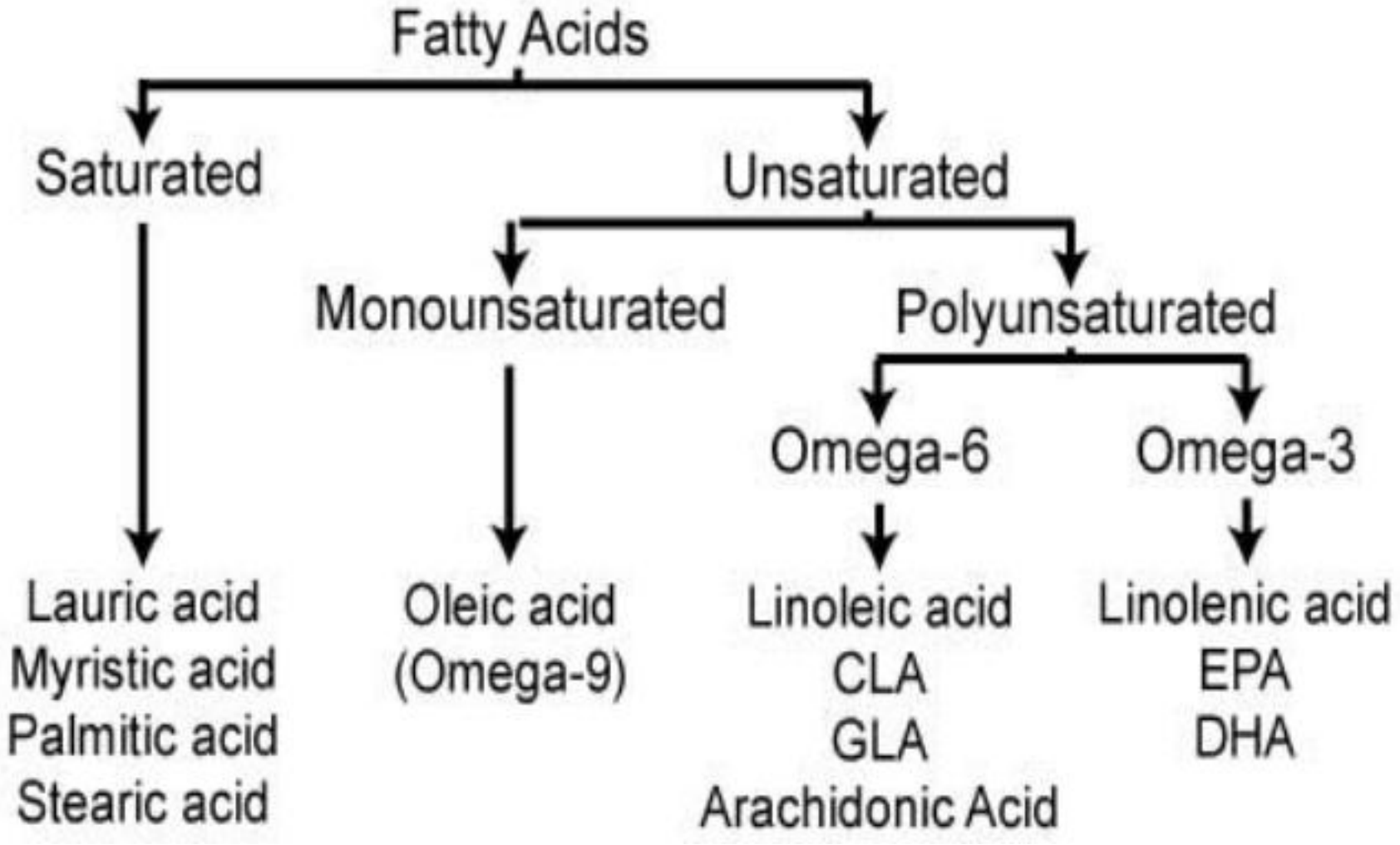
Derived lipids-hydrolytic products of the simple and complex lipids e.g Fatty acids, cholesterol etc

- Fatty acids are the simplest-plasma
- Triglycerides storage form-adipose tissue
- Phospholipids-major class of membrane lipids

FATTY ACIDS

- Fatty acids-free form and as components of more complex lipids
  - Long, straight chain of alkanoic acids-12 to 22 carbons-saturated or unsaturated
  - Unsaturated-1-5 double bonds in cis geometry
  - Double bonds not conjugated but separated by methylene groups

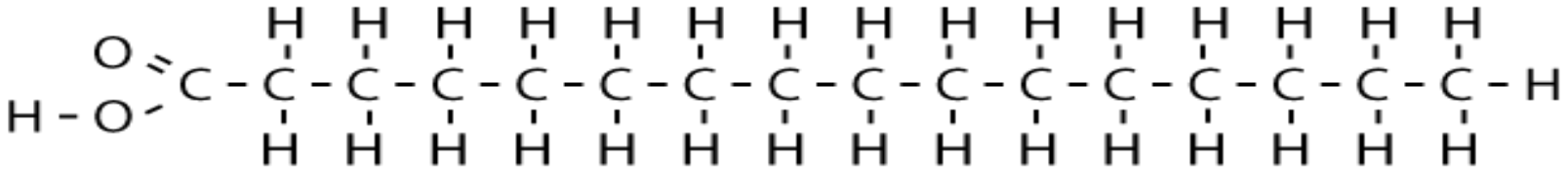
CLASSIFICATION



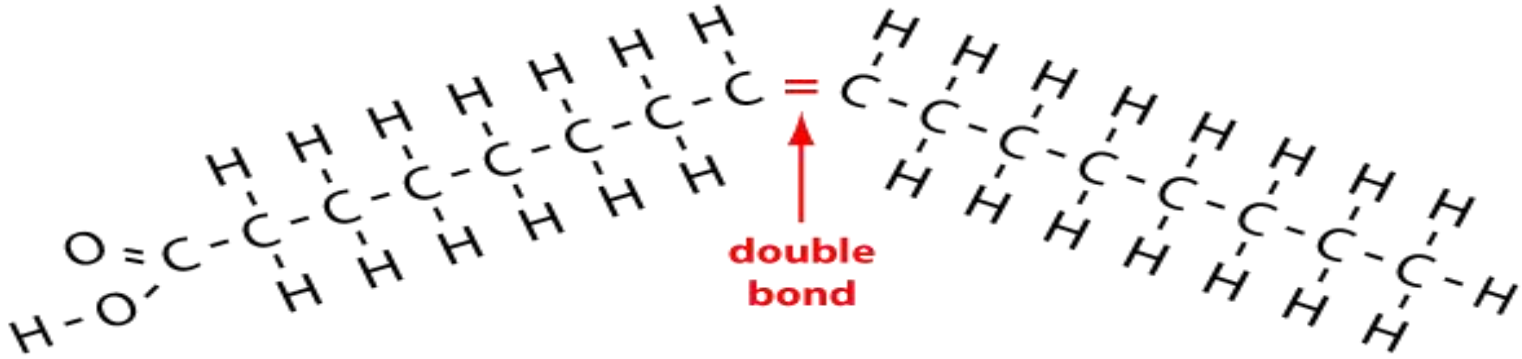
- Monounsaturated-single double bond
- Polyunsaturated-2 or more double bonds

- Melting point increases with the chain length
- Decreases with the number of double bonds

saturated fatty acid



unsaturated fatty acid



- Number of key roles in metabolism – major metabolic fuel (storage and transport of energy)
- Essential components of all membranes
- Gene regulators

Polyunsaturated fatty acids (PUFAs) that are precursors of powerful locally acting metabolites, the eicosanoids

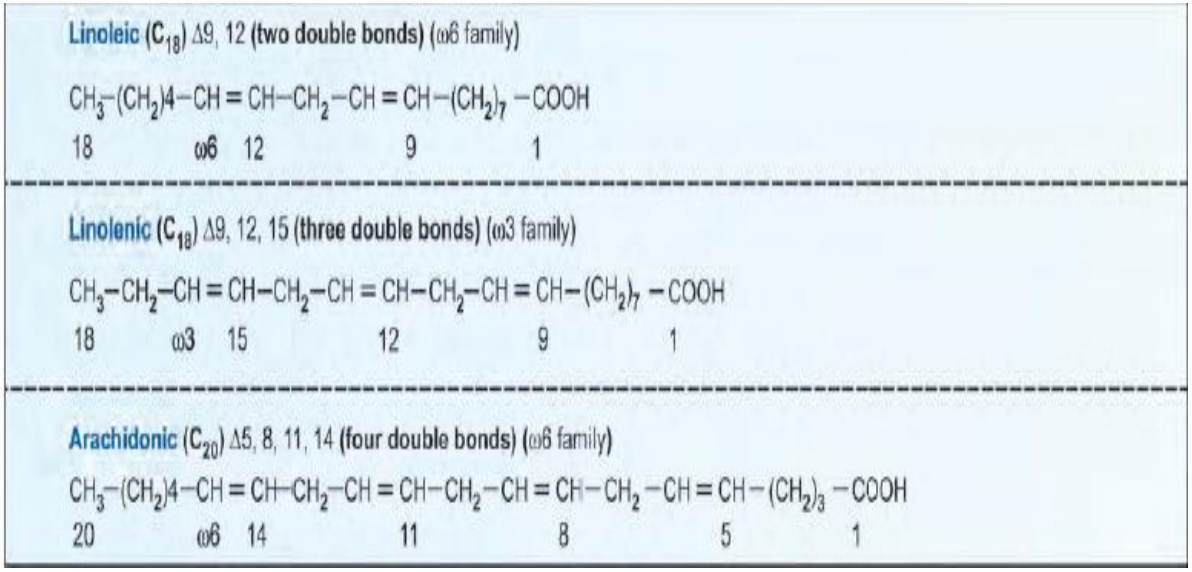


Fig: Polyunsaturated fatty acids (PUFA)

Thermal and electrical insulation and for mechanical protection

Salts may function as detergents and soaps owing to their amphipathic properties

Fatty Acid Structure

- Carbon chains with a methyl group at one end of the molecule (designated omega) and a carboxyl group at the other end

The carbon atom next to the carboxyl group is called the α carbon, and the subsequent one, β

$CH_3 - (CH2)_n - CH_2 - CH_2 - COOH$

Nomenclature

- Symbol
  - –Linoleic acid-18:2; ω-6 $\Delta^{9,12}$
  - –Arachidic acid-20:0

PUFA (Polyunsaturated fatty acids)- essential fatty acids-required in the body and cannot be synthesized- Inclusion in the diet

Linoleic acid 18: 2; 9 (12)

Linolenic acid 18: 3; 9 (12, 15)

Arachidonic acid 20: 4; (5, 8, 11, 14)

- Arachidonic acid is semi essential fatty acid

TRIGLYCERIDES

- Fat-solid
- Oil-liquid
- Main component of olive oil, corn oil, butter, whale oil, fish oil, belly fat
- (Butter vs margarine?)

- One molecule of glycerine and three molecules of unique fatty acid

Esters of fatty acids with the alcohol, glycerol

storage forms of lipids (depot lipids)

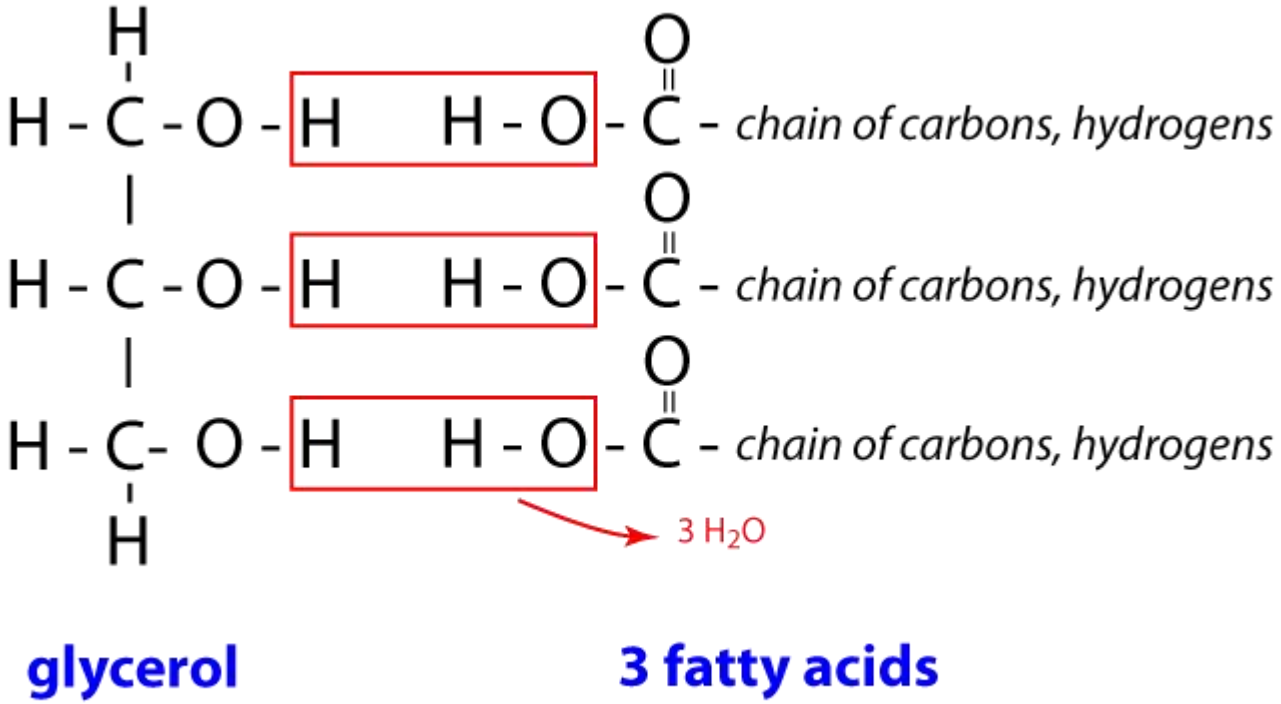
(Triacylglycerols)

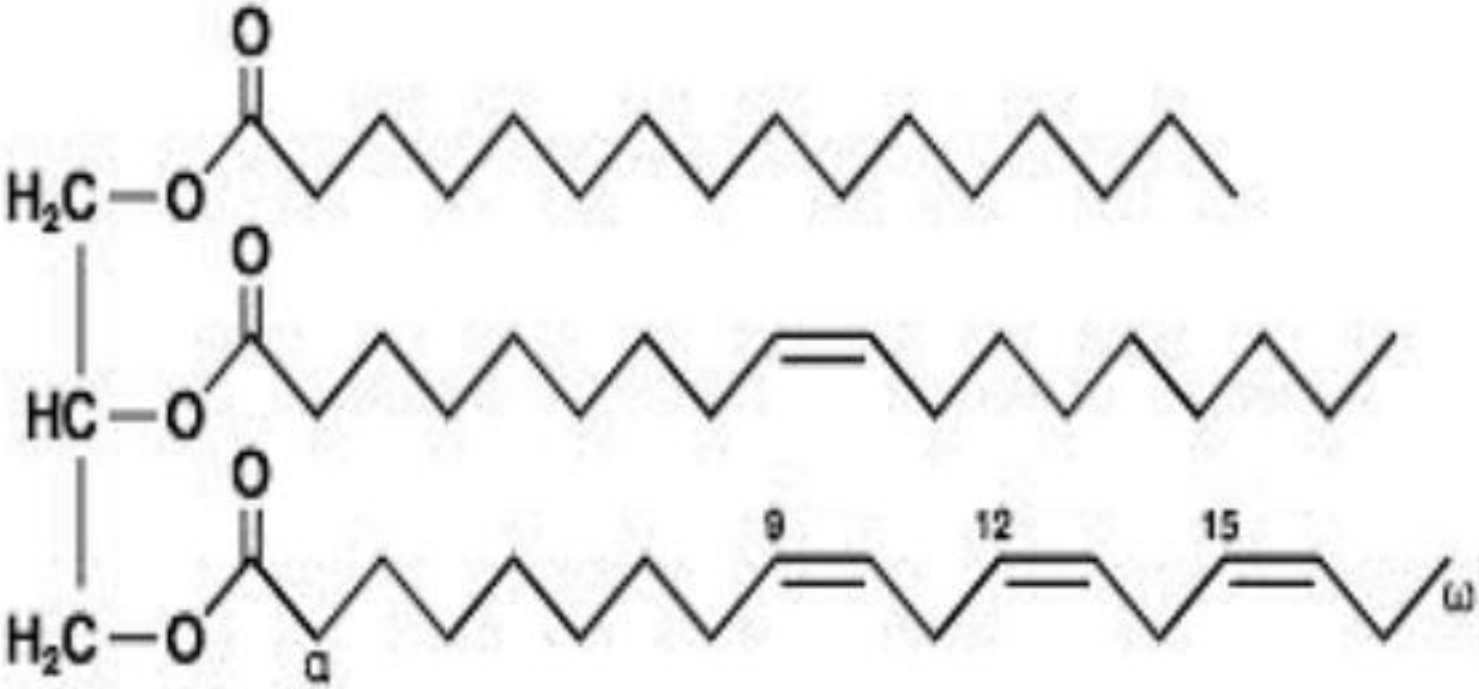
exist as simple or mixed types depending on the type of fatty acids that form esters with the glycerol

- Both saturated and/or unsaturated fatty acids can form the ester linkage with the backbone alcohol

Found in special cells called adipocytes (fat cells), of the mammary gland, abdomen and under skin of animals

Produce twice as much energy as that of carbohydrates per gram


chain of carbons, hydrogens
chain of carbons, hydrogens
chain of carbons, hydrogens
3 H2O
glycerol
3 fatty acids


O
H2C—O
O
HC—O
O
H2C—O
9
12
15
ω
α

- In humans
  - Stored in solid form (fat) in adipose tissue

- Degraded to glycerol and fatty acids in response to hormonal signals-released into plasma for metabolism in other tissues- muscles and liver

- Hydrolysis of ester bond by strong base such as sodium hydroxide to give glycerol and free fatty acids

- Sodium salt of fatty acid is soap

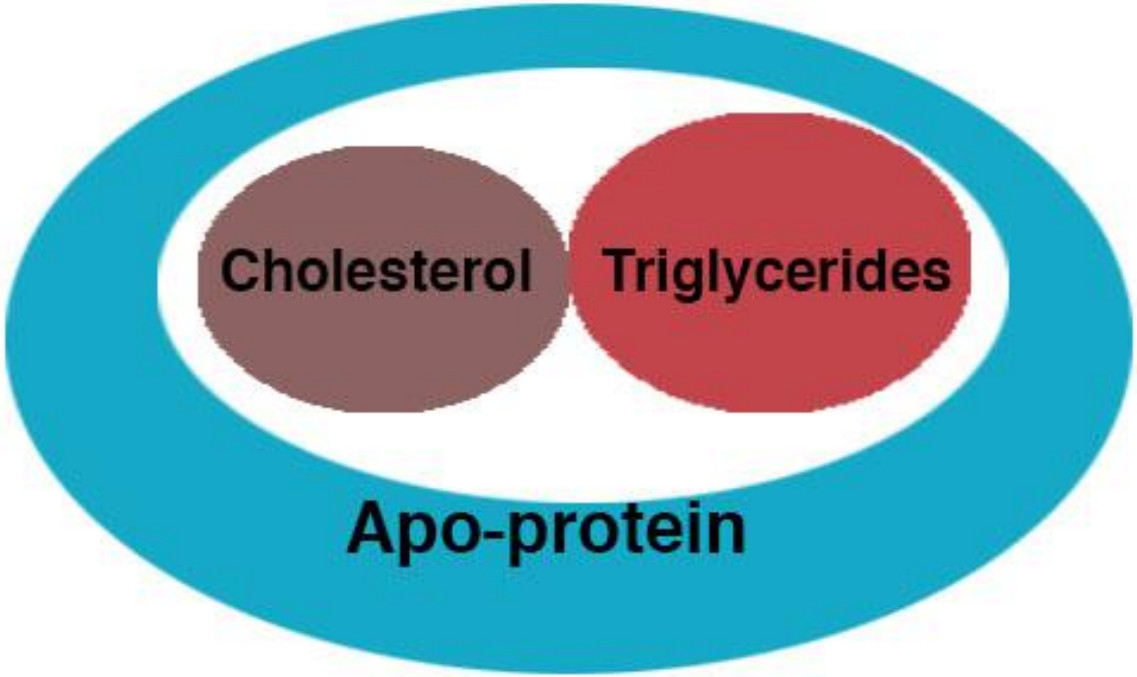
(Saponification)

Fat Digestion and Absorption

- Triglycerides unable to enter blood stream directly
- Digestive enzymes break the triglycerides down into smaller molecules that can enter blood stream

- Large fatty acids packaged into triglyceride plus cholesterol and a special protein, Apo-protein

Apo-protein packages cholesterol and triglycerides



Lipo-protein Package

- Destination
  - –Fat cells-utilise the fatty acids
  - –Muscles-burn the fat
  - –Liver-breaks into fatty acids

Note that carbohydrates can also be converted to fatty acids in the liver

Liver capable to turn carbohydrate into fatty acid
Liver capable to break down fatty acid into carbohydrate

(works based on supply and demand)

- If body is active and asking for more fuel, liver breaks down fatty acids-releases them as glucose in the blood-muscles then use this glucose as fuel

- If body gets more carbohydrate than it needs, liver takes up the glucose from blood and uses it to make fatty acids

Function: Fuel molecules-
stored as triacylglycerols-
Oxidation leads to production of energy

Highly concentrated stores of energy because they exist in:

- Reduced form
- Anhydrous form

Complete oxidation of fatty acid yields about 9 kcal/g (38 KJ/g) of energy

A gram of nearly anhydrous fat, stores more than six times as much energy as a gram of hydrated glycogen

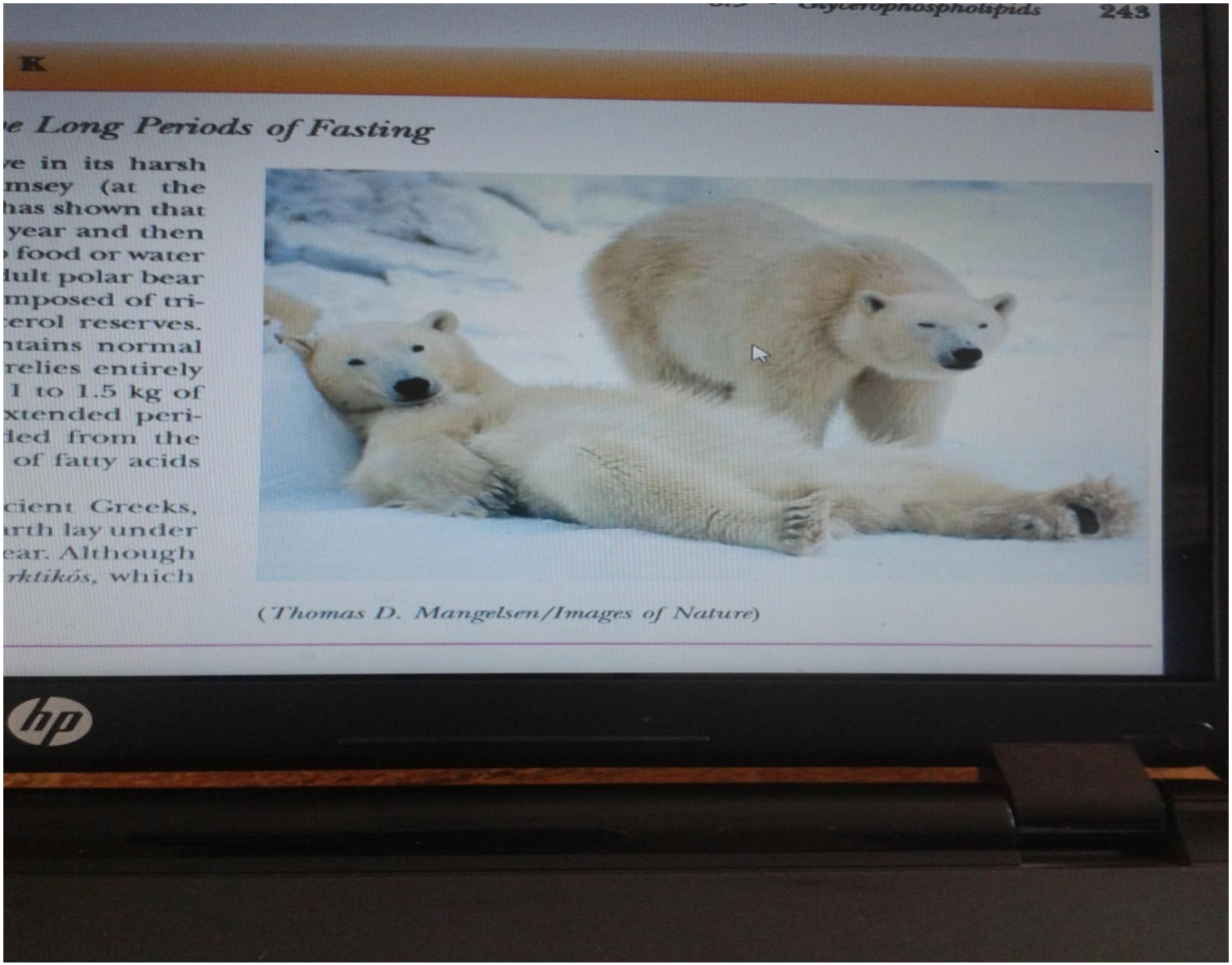
- Glycogen and glucose store provide enough energy to sustain biological functions for about 24hrs
- Triacylglycerols store allows survival for several weeks

- Polar Bears use triacylglycerols to survive long periods of fasting. Magnificently adapted to thrive in its harsh arctic environment

- Research by Malcolm Ramsey (at the University of Saskatchewan in Canada) and others has shown that polar bears eat only during a few weeks out of the year and then fast for periods of 8 months or more, consuming no food or water during that time

- Eating mainly in the winter, the adult polar bear feeds almost exclusively on seal blubber (largely composed of triacylglycerols), thus building up its own triacylglycerol reserves

POLAR BEAR


243
K
e Long Periods of Fasting
ve in its harsh
msey (at the
has shown that
year and then
food or water
dult polar bear
mposed of tri-
cerol reserves.
ntains normal
relies entirely
1 to 1.5 kg of
xtended peri-
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of fatty acids
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(Thomas D. Mangelsen/Images of Nature)
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Body fat (mainly triacylglycerols) also provides good insulation. *Whales and Arctic mammals rely on body fat for both insulation and energy reserves*

FATTY ACID OXIDATION

Beta oxidation-major mechanism-occurs in the mitochondria matrix. (2-C units released as acetyl CoA per cycle)

Alpha oxidation-brain and liver mainly-(one carbon atom lost in the form of CO_2 per cycle)

Omega oxidation-minor mechanism but becomes important in conditions of impaired Beta oxidation

Peroxisomal oxidation-trimming of very long chain fatty acids

Energy yield from Beta oxidation of fatty acids = 106 ATP

DISORDERS ASSOCIATED WITH IMPAIRED BETA OXIDATION

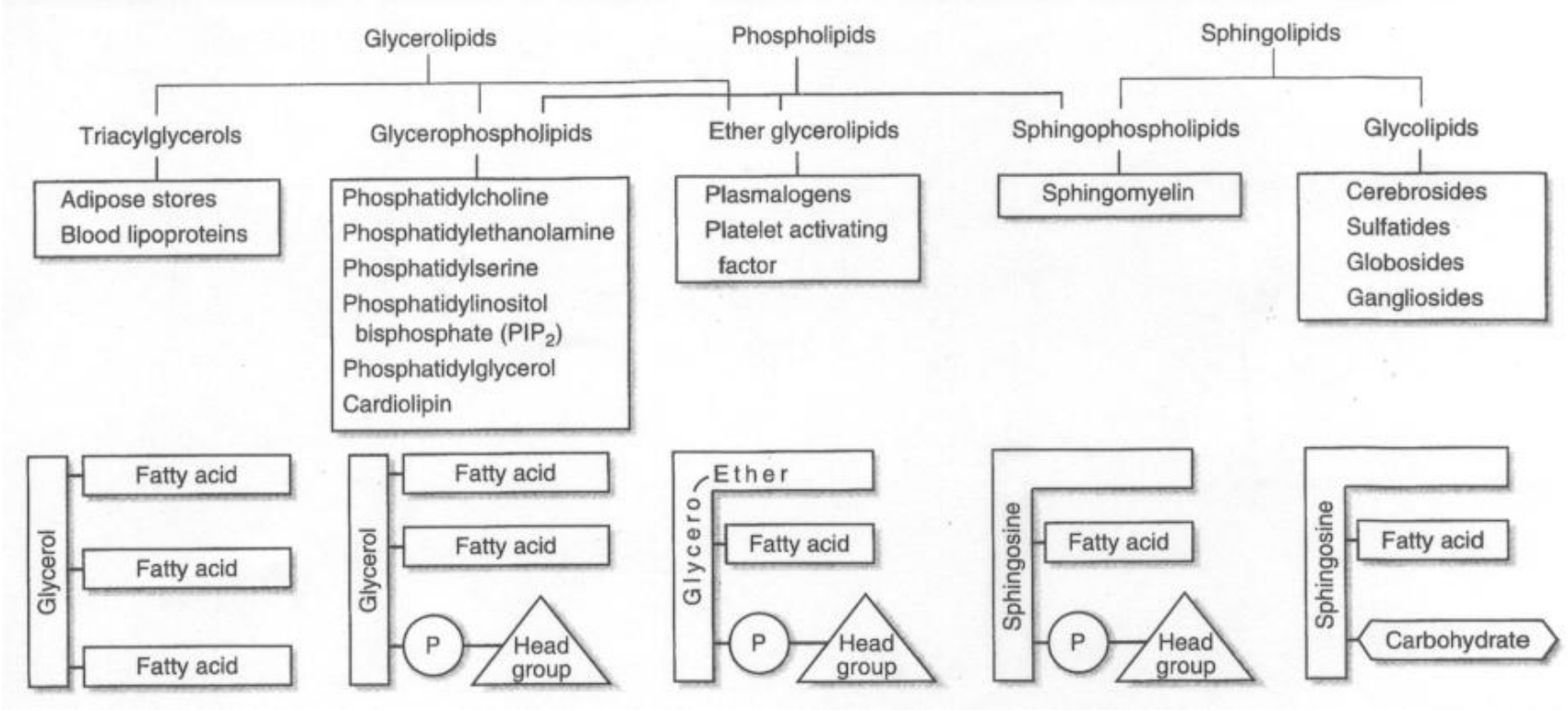
- Muscle weakness
- Hypoglycemia
- Hypoketosis

PHOSPHOLIPIDS

-Glycerophospholipids

-Ether glycerolipids

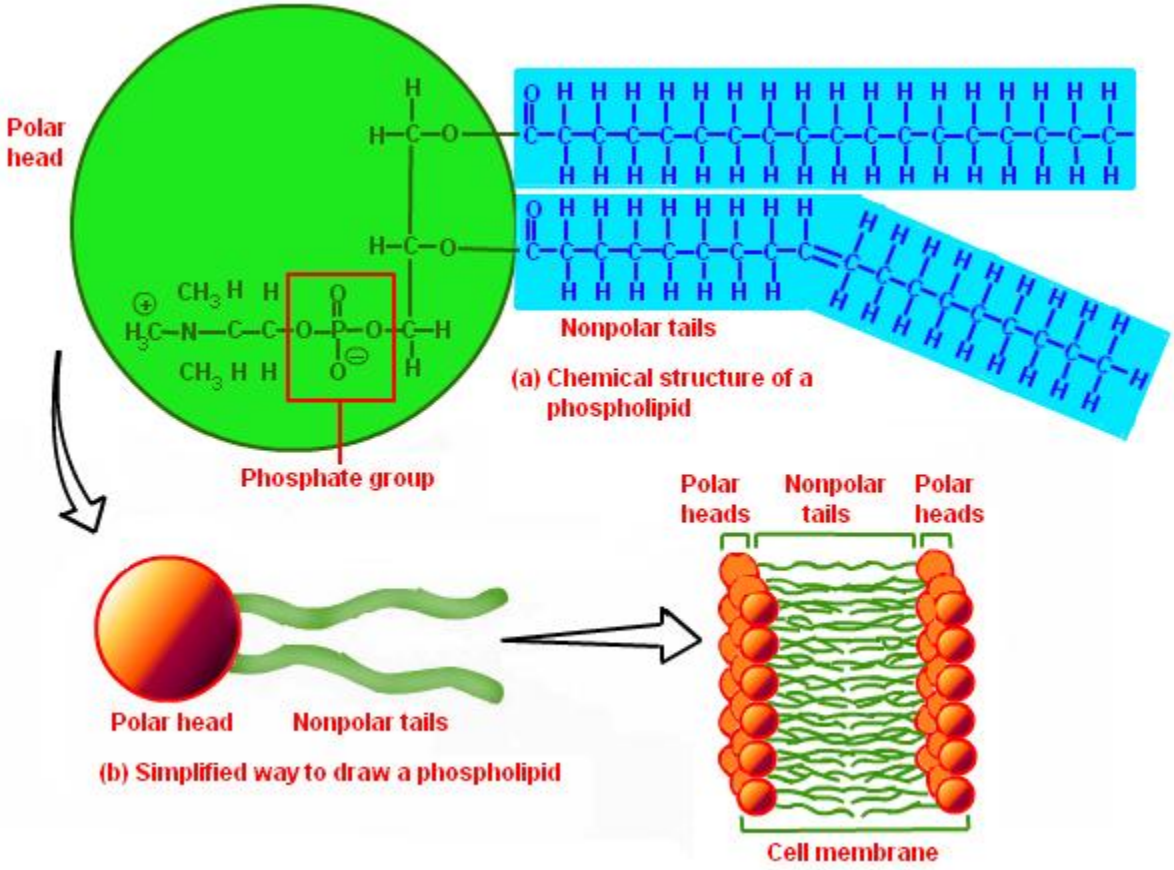
-Sphingophospholipids


Glycerolipids
Phospholipids
Sphingolipids
Triacylglycerols
Glycerophospholipids
Ether glycerolipids
Sphingophospholipids
Glycolipids
Adipose stores
Blood lipoproteins
Phosphatidylcholine
Phosphatidylethanolamine
Phosphatidylserine
Phosphatidylinositol bisphosphate (PIP_2)
Phosphatidylglycerol
Cardiolipin
Plasmalogens
Platelet activating factor
Sphingomyelin
Cerebrosides
Sulfatides
Globosides
Gangliosides
Glycerol
Fatty acid
Fatty acid
Fatty acid
Glycerol
Fatty acid
Fatty acid
P
Head group
Glycero
Ether
Fatty acid
P
Head group
Sphingosine
Fatty acid
P
Head group
Sphingosine
Fatty acid
Carbohydrate

Glycerophospholipids

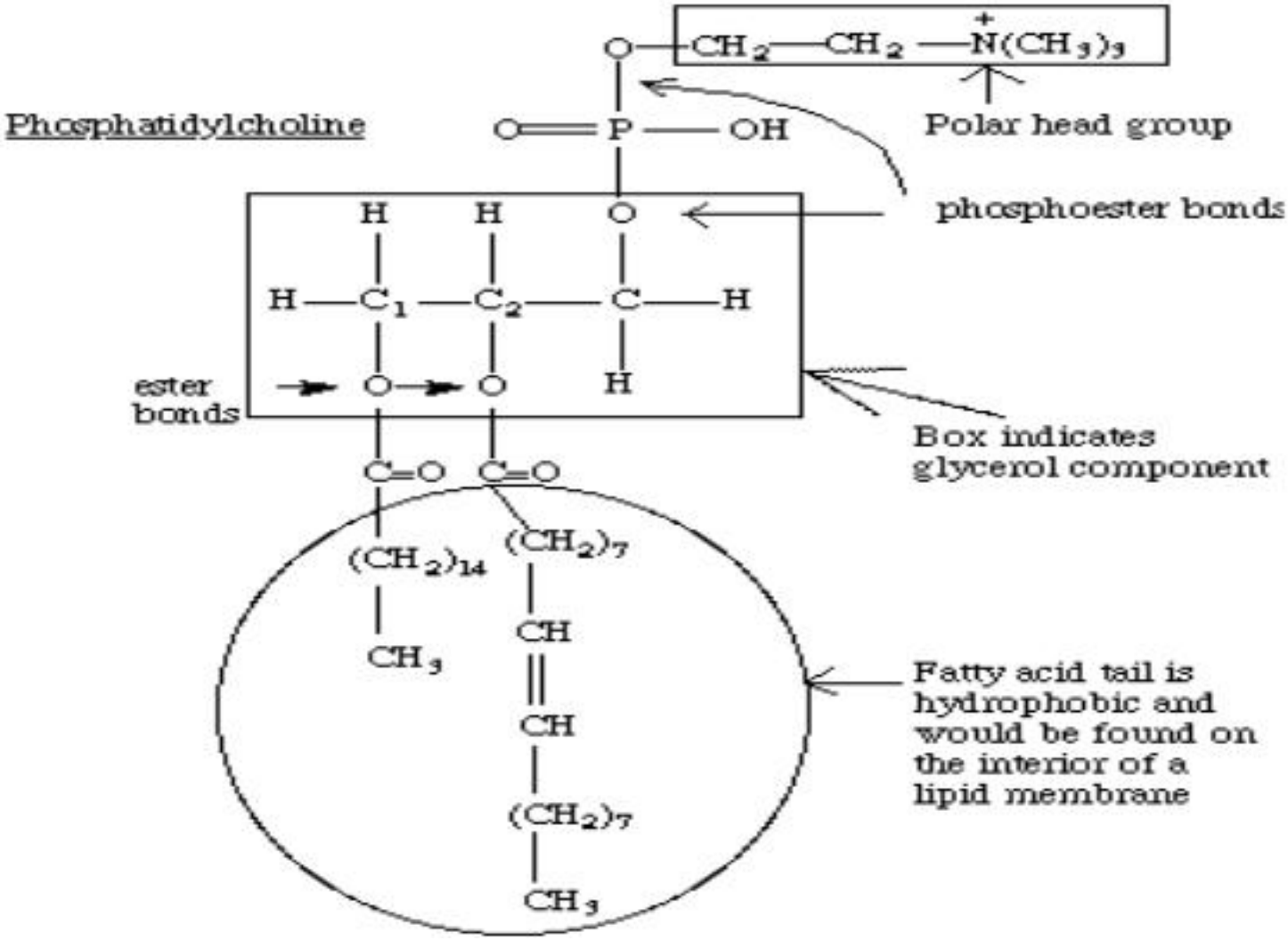
- Fatty acids, alcohol and a phosphoric acid residue
- Main lipid constituents of membranes

Largest classes of natural lipids and one of the most important. Essential components of cell membranes-small concentrations in other parts of the cell

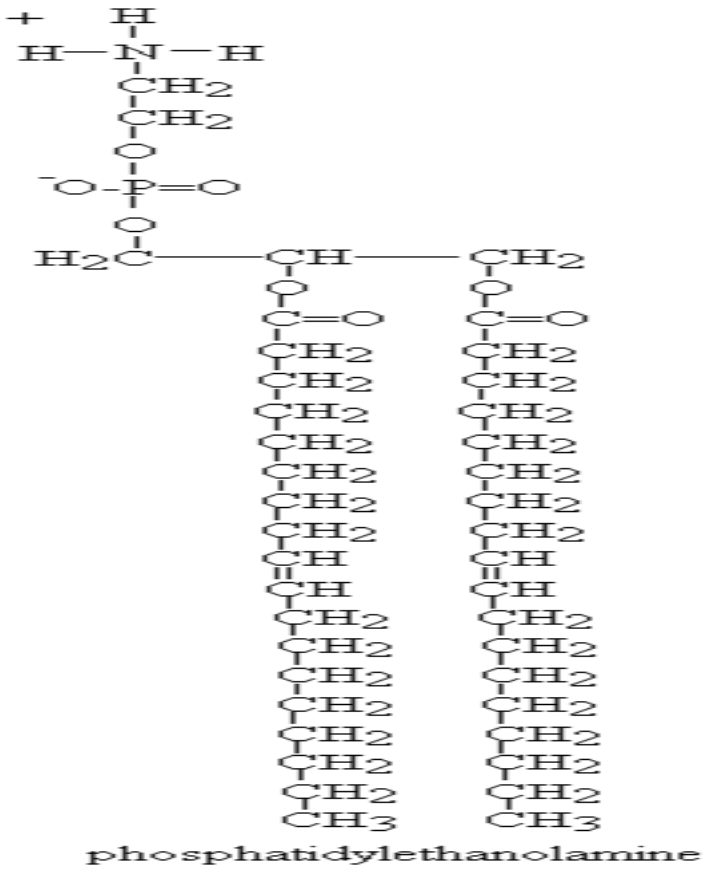

Polar head
Phosphate group
Nonpolar tails
(a) Chemical structure of a phospholipid
Polar head
Nonpolar tails
(b) Simplified way to draw a phospholipid
Polar heads
Nonpolar tails
Polar heads
Cell membrane

- choline
- serine
- ethanolamine

Phosphatidylcholine



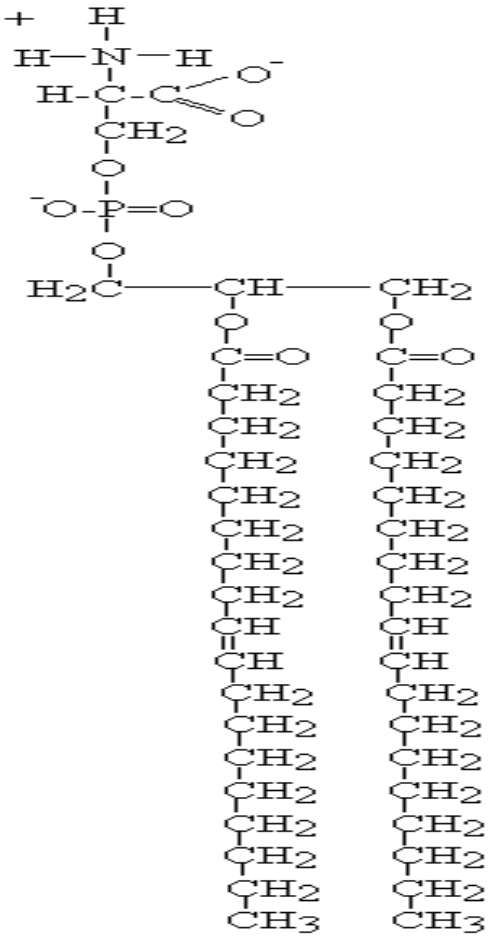
Phosphatidylethanolamine



phosphatidylethanolamine

Phosphatidylethanolamine
Note that if the 3 hydrogen atoms bonded to the N atom were replaced with methyl groups, you have phosphatidylcholine.

Phosphatidylserine



Phosphatidylserine

Note that the only difference betwen this molecule and phosphatidylethanolamine is the carboxyl group that makes the ethanolamine moiety into a serine molecule.

- PhosphatidylSerine (PS) is present in all biological membranes of animals, higher plants and microorganisms

- In humans, PS is most concentrated in the brain where it comprises 15% of the total phospholipid pool

- In other human tissue the ratio of PS in the phospholipid pool varies: lungs (7.4%), testes (6.4%), kidneys (5.7%), liver (3.8%), skeletal muscle (3.3%), heart (3.2%) and blood plasma (0.2%)

- Impart fluidity and flexibility to the membrane
- Act as surfactant and lowers the surface tension in alveoli of lungs
- Maintains the shape of alveoli and prevents their collapse due to high surface tension of the surrounding medium

Some premature infants can't secrete phosphatidylcholine (lecithin); therefore suffer from respiratory distress syndrome

- Intra cellular signals (for second messengers) like inositol triphosphate and diacylglycerol during the action of hormones

- Anchors certain proteins to cell membranes. Amphipathic - interact with non-polar and polar substances-link proteins to non-polar membranes

- Solubilization of cholesterol
- Lipids are transported as lipoproteins

Venoms of poisonous snakes:

class of enzymes known as phospholipases-breakdown of phospholipids

Phospholipase A2, catalyzes the hydrolysis of fatty acids at the C-2 position of glycerophospholipids

Product of this reaction, lysolecithin, acts as a detergent and dissolves the membranes of red blood cells, causing them to rupture

Phospholipids also make up the membranes of a human cell (nuclear membrane, lysosomal membrane, mitochondrial membranes, endoplasmic reticulum, Golgi apparatus)

-a polar, hydrophilic head and two non-polar, hydrophobic tails

-a saturated fatty acid (no double bonds between carbons) on C-1 and an unsaturated fatty acid (double bonds between carbons) on C-2 of the glycerol backbone

Ether Glycerolipid

Two very important molecules in the body

- **Platelet Activating Factor (PAF)**- turns on platelets to form plugs
- Platelet activating factor (PAF) was first identified by its ability (at low levels) to cause platelet aggregation and dilation of blood vessels, but it is now known to be a potent mediator in inflammation, allergic responses, and shock. PAF effects are observed at tissue concentrations as low as 10^{-12} M.

– Beneficial effects:

- In reproduction, PAF secreted by the fertilized egg is instrumental in the implantation of the egg in the uterine wall

- *PAF is produced in significant quantities in the lungs of the fetus late in pregnancy- stimulates the production of fetal lung surfactant, a protein–lipid complex that prevents collapse of the lungs in a newborn infant*

Plasmalogens-predominant membrane lipid in neurons

-protect mammalian cells against the damaging effects of reactive oxygen species

In addition, they have been implicated as being signaling molecules and modulators of membrane dynamics

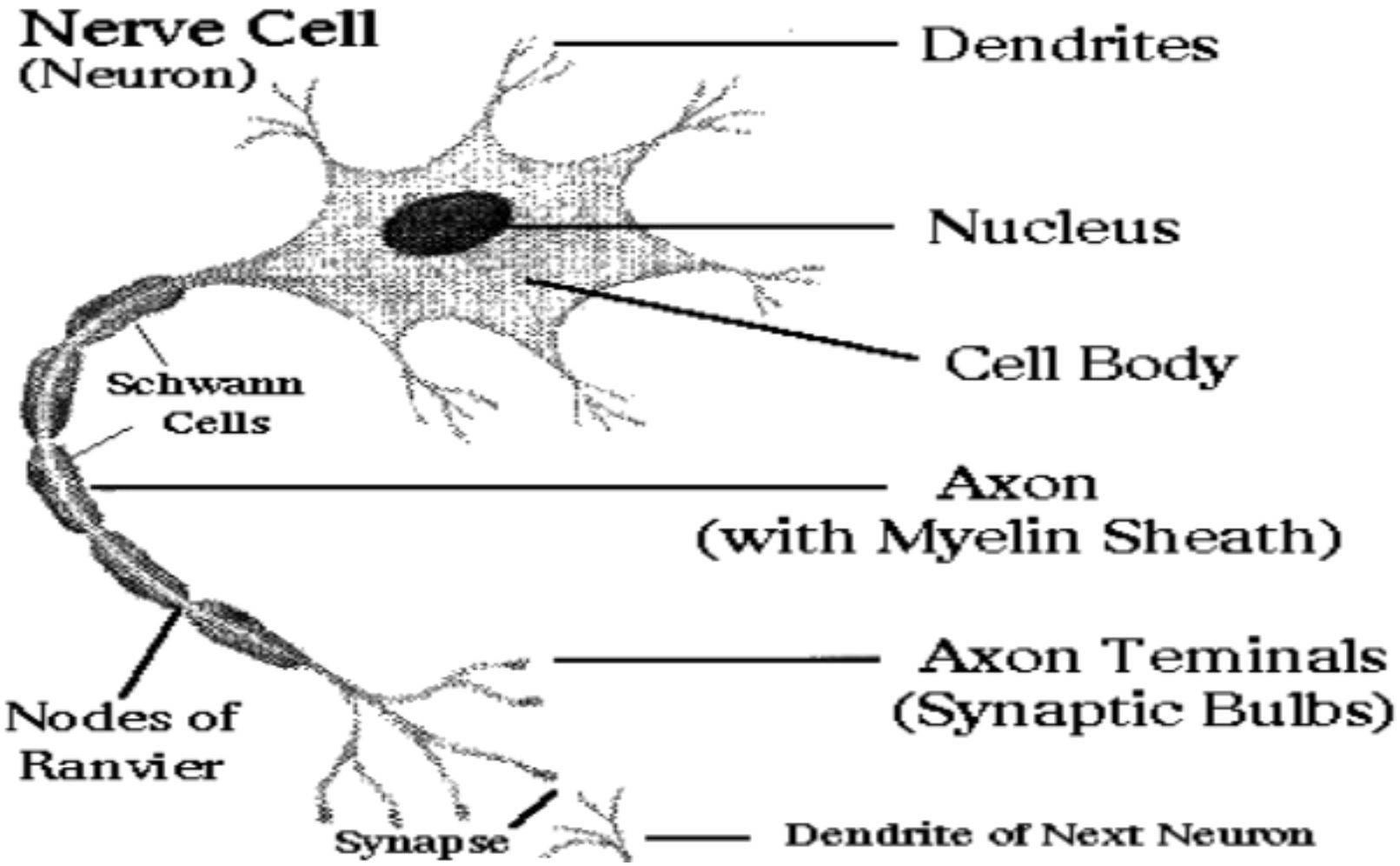
Sphingophospholipids

Sphingomyelin

-surrounds and electrically insulates many nerve cell axons

-cell signaling pathways

- Sphingomyelin-in the membranous myelin sheath that surrounds some nerve cell axons


Nerve Cell
(Neuron)
Dendrites
Nucleus
Cell Body
Schwann
Cells
Axon
(with Myelin Sheath)
Axon Teminals
(Synaptic Bulbs)
Nodes of
Ranvier
Synapse
Dendrite of Next Neuron

SPHINGOLIPIDS

In mammals they are abundant in the tissues of the central nervous system

Three major families:

Sphingomyelins (contain phosphate)- Phospholipids

Cerebrosides (contain carbohydrate residues)- Glycosphingolipids

Gangliosides contain carbohydrate residues)- Glycosphingolipids

- Phosphate group replaced with a sugar (carbohydrate group) These are the **Glycolipids**. Two most common and most related to diseases: **Cerebrosides** and **Gangliosides**

- Glycosphingolipids:

  -important cellular functions, despite the fact that they are present only in small amounts in most membranes

Glycosphingolipids at cell surfaces appear to determine, at least in part, certain elements of tissue and organ specificity

- Cell–cell recognition and tissue immunity appear to depend upon specific glycosphingolipids

Gangliosides are present in nerve endings and appear to be important in nerve impulse transmission

A number of genetically inherited diseases involve the accumulation of specific glycosphingolipids-absence of the enzymes needed for their degradation

- Genetically inherited defects in ganglioside metabolism- responsible for a number of debilitating and often lethal diseases such as Tay-Sachs disease and generalised gangliosidosis

Certain rare defects lead to deficiency in enzymes responsible for the degradation of sphingolipids in the lysosomes of cells

In Tay-Sachs-deficiency of a hydrolase-leading to accumulation of gangliosides in lysosomes

Lysosomes swell, leading to tissue enlargement. In CNS, there is little room for expansion and so nerve cells die leading to blindness, mental retardation and death

Nieman-Pick disease - Sphingomyelin accumulates in brain, liver and spleen.

-due to deficiency of sphingomyelinase-mental retardation and early death

Gaucher’s disease- Glucocerebroside accumulates in liver, spleen, brain and bone marrow, due to the deficiency of glucocerebrosidase. Patient suffers from mental retardation

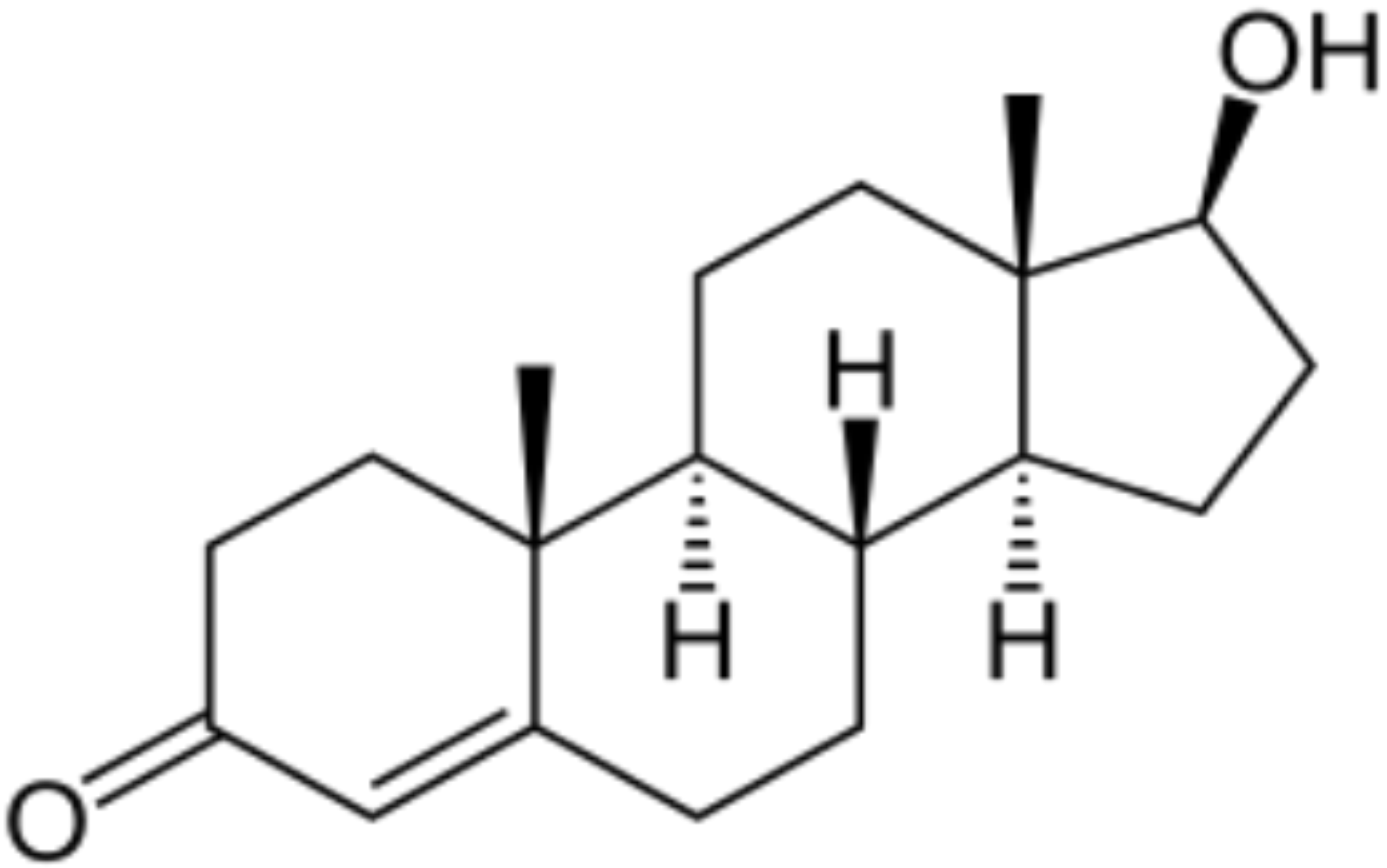
STEROIDS

Organic compounds with four rings arranged in a specific configuration

A common structural motif of three six-membered rings and one five-membered ring all fused together

Dietary lipid cholesterol, sex hormones, etc

GENERAL STRUCTURE



A large and important class of lipids whose members effect an amazing array of cellular functions

Cholesterol- is the most common steroid in animals and the precursor for all other animal steroids

Extremely important biological molecule

-roles in membrane structure

-precursor for synthesis of steroid hormones

-Bile acids and Vitamin D

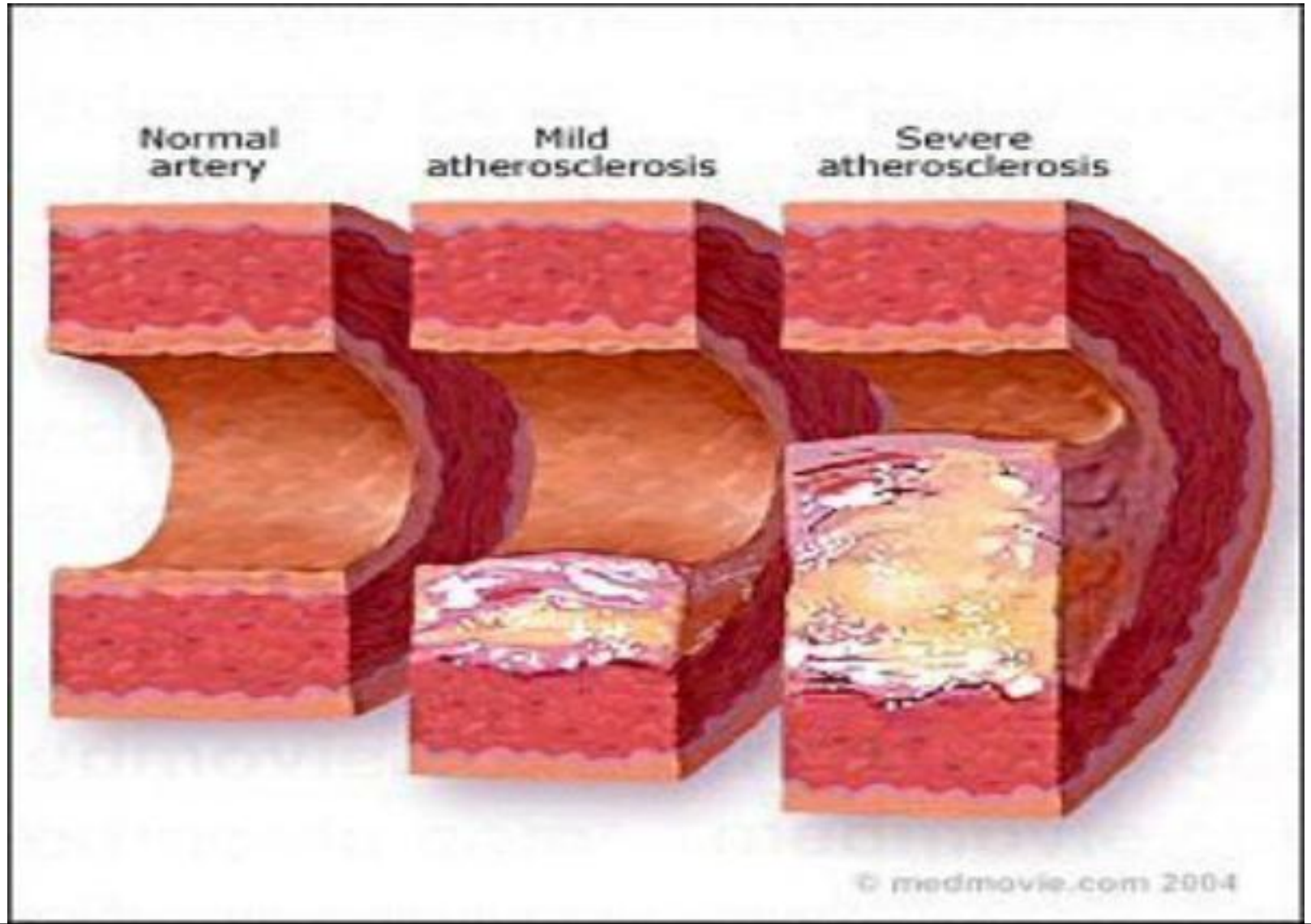
- Both dietary cholesterol and that synthesized de novo transported through circulation in lipoprotein particles
- Cholesterol esters-storage form of cholesterol
- All cells express enzymes of cholesterol biosynthesis-underscores the important role in membrane function

- Tight regulation of synthesis and utilisation to prevent over accumulation and abnormal deposition

Clinical importance-abnormal deposition of cholesterol and cholesterol rich lipoproteins in coronary arteries-atherosclerosis

- Cholesterol often accumulates in lipid deposits on the walls of blood vessels-implicated in cardiovascular disease-heart attacks or strokes

Limit intake of animal fat and instead increase intake of plant oils as a strategy


Normal artery
Mild atherosclerosis
Severe atherosclerosis
© medmovie.com 2004

- Biosynthesis of cholesterol
  - –Less than half from de novo
    - Liver-10% and intestines - 15% of amount produced each day

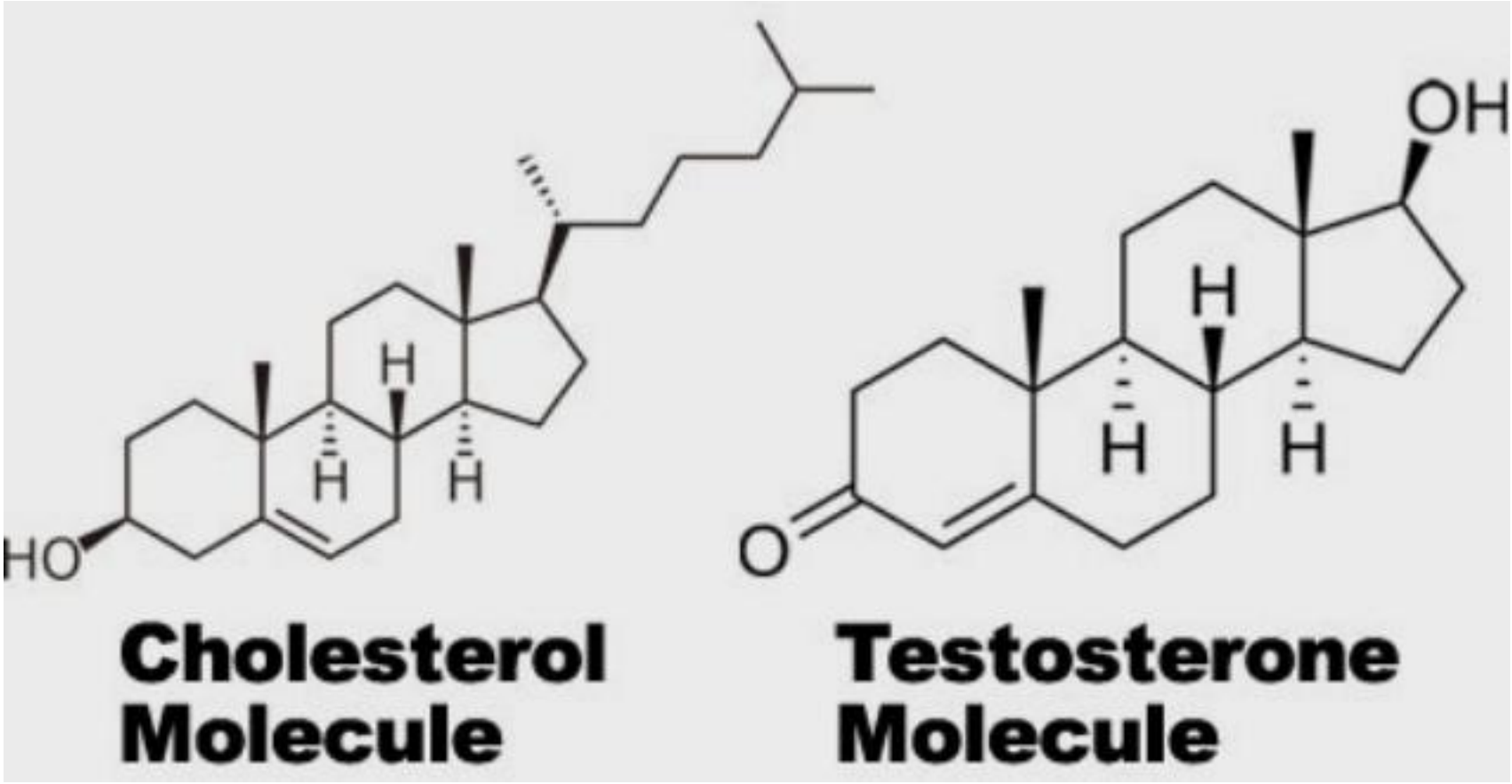
Regulation of cholesterol synthesis

- Normal healthy adult synthesizes @ a rate 1g/day and consumes 0.3g/day
- Constant level maintained by controlling the level of de novo synthesis

STEROID HORMONES

Contain same ring and atomic numbering as cholesterol

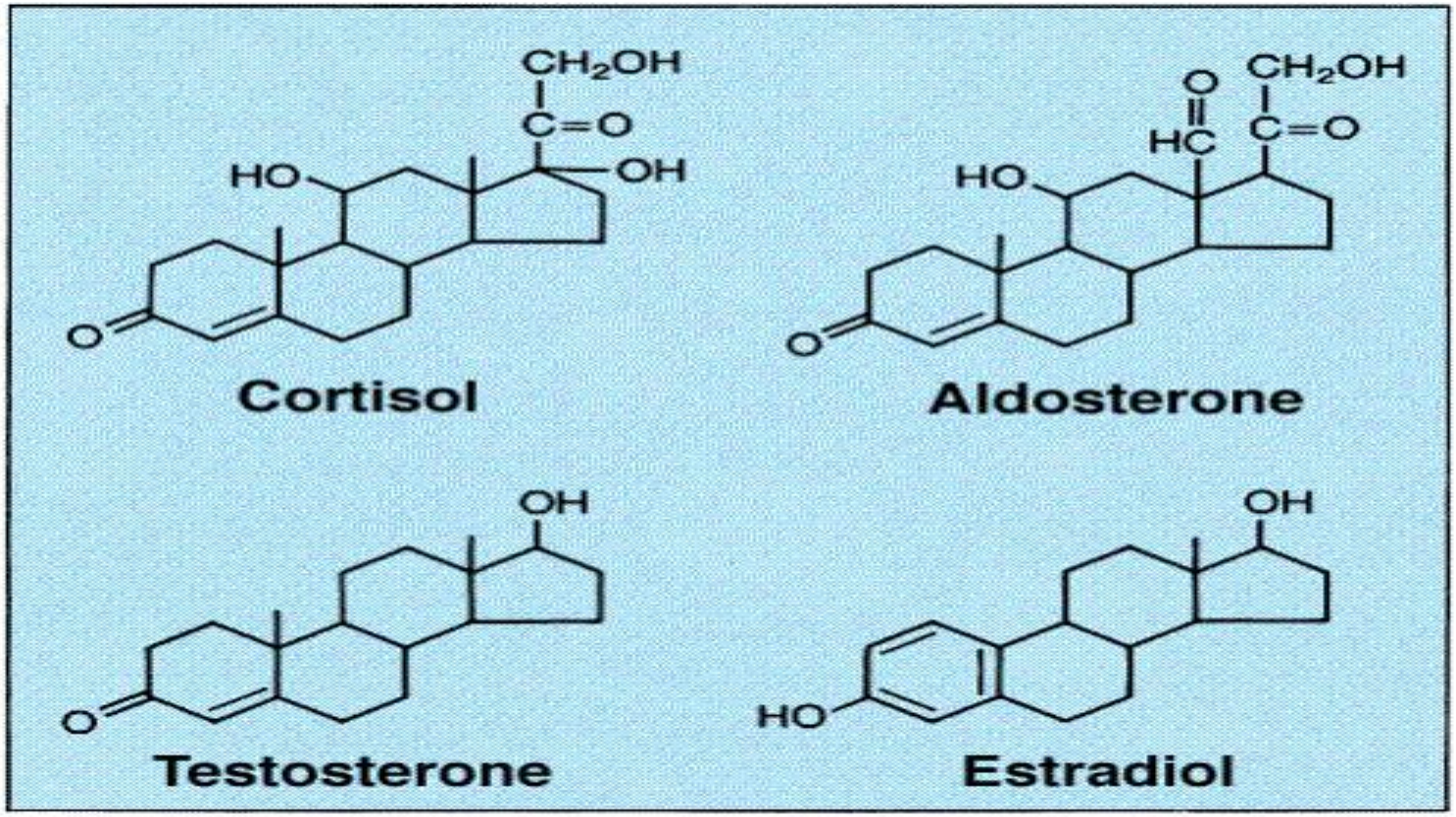
- Testosterone-an androgen-male sex hormone-sex characteristics
- Estradiol-an estrogen- principal female sex hormone-sex characteristics



Cholesterol Molecule

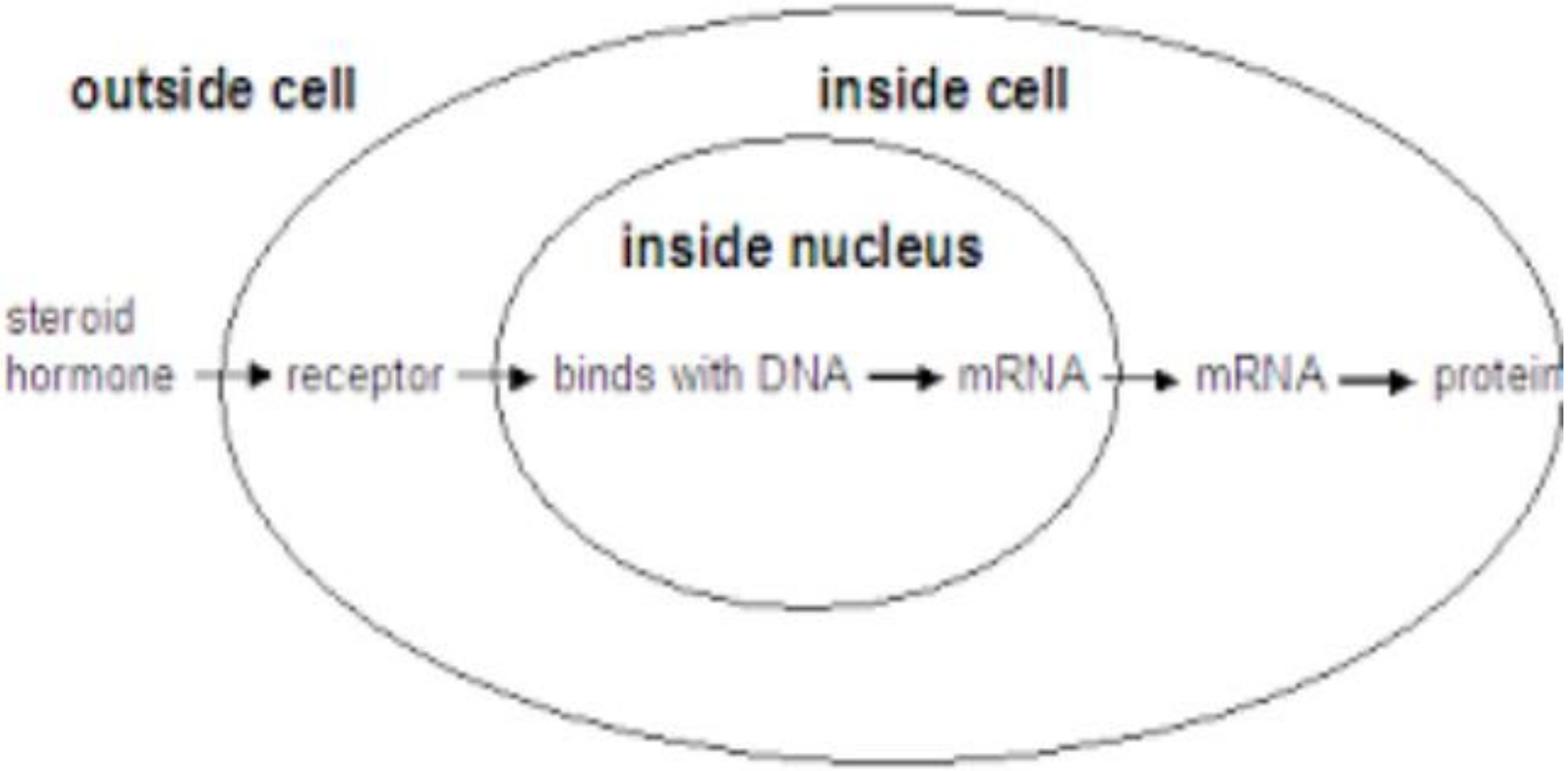
Testosterone Molecule

Steroid Hormones



All steroid hormones exert their action by:

- Passing through the plasma membrane
- Binding to the intracellular receptors
- Steroid-hormone receptor complexes exert their action by binding to specific nucleotide sequence in the DNA of responsive genes
- Interaction leads to altered rates of transcription of associated genes


outside cell
inside cell
inside nucleus
steroid hormone
receptor
binds with DNA
mRNA
mRNA
protein

EICOSANOIDS

Breakdown products of selected phospholipids

-Produce a wide range of biological effects on inflammatory responses

- Local hormones exert their effects at very low concentrations and usually act near their sites of synthesis-prostaglandins (PG), thromboxanes (Tx), leukotrienes

A variety of stimuli can trigger eicosanoid synthesis:

- Tissue injury
- Inflammation

- Lower gastric secretions, stimulate uterine contractions, lower blood pressure, influence blood clotting and induce asthma-like allergic responses
- Many properties of the common drug, aspirin, result from its effect on the cascade of reactions associated with these hormones

Laboratory tests

-Cholesterol

-Triglycerides