Amino Acids Metabolism

Lac.1

By

Dr. Muna M. Yaseen

- Proteins are the most abundant organic molecules of the living system.
- They occur in the every part of the cell and constitute about 50% of the cellular dry weight.
- Proteins form the fundamental basis of structure and function of life.
- In 1839 Dutch chemist G.J.Mulder while investing the substances such as those found in milk, egg, found that they could be coagulated on heating and were nitrogenous compounds.

- **The term protein is derived from a Greek word *proteios,* meaning first place.**
- ***Berzelius (Swedish chemist)* suggested the name proteins to the group of organic compounds that are utmost important to life.**
- **The proteins are nitrogenous macromolecules composed of many amino acids.**

Biomedical importance of proteins:

- Proteins are the main structural components of the cytoskeleton. They are the sole source to replace nitrogen of the body.
- Bio chemical catalysts known as enzymes are proteins.
- Proteins known as immunoglobulins serve as the first line of defense against bacterial and viral infections.

- Several hormones are protein in nature.
- Structural proteins like actin and myosin are contractile proteins and help in the movement of muscle fibre.

  Some proteins present in cell membrane, cytoplasm and nucleus of the cell act as receptors.
- The transport proteins carry out the function of transporting specific substances either across the membrane or in the body fluids.

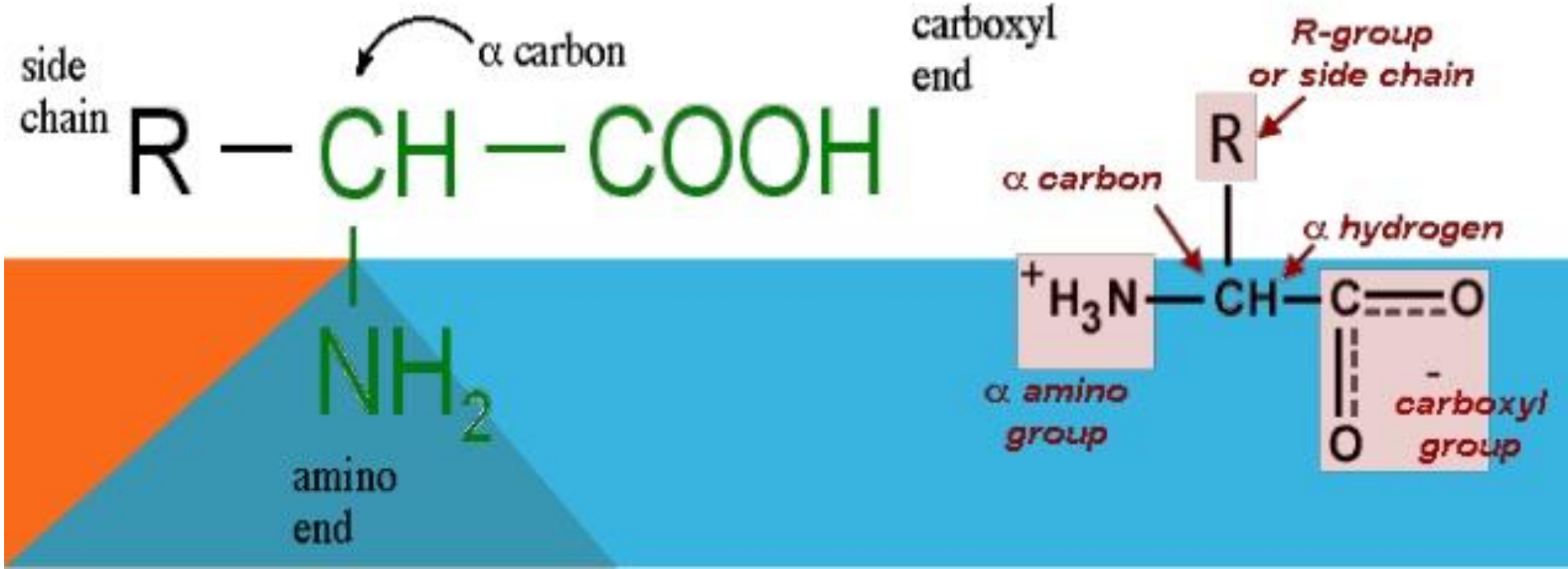
- **Storage proteins bind with specific substances and store them, e.g. iron is stored as ferritin.**
- **Few proteins are constituents of respiratory pigments and occur in electron transport chain, e.g. Cytochromes, hemoglobin, myoglobin**
- **Under certain conditions proteins can be catabolized to supply energy.**
- **Proteins by means of exerting osmotic pressure help in maintenance of electrolyte and water balance in the body.**

OBJECTIVES

- Digestion and absorption of proteins and amino acids
- Introduction to amino acids, structure and types
- Amino acid and nutrition
- General and individual Amino acid metabolism; and inborn errors of metabolism
- Metabolism of ammonia
- Clinical significance of amino acid and ammonia metabolism

WHAT IS AMINO ACID?

Amino acids are derivatives of carboxylic acids formed by substitution of α-hydrogen for amino functional group



WHAT DO AMINO ACIDS DO?

- Amino acids are essential to life, have a role in metabolism, and are important in nutrition.
- They form short polymer chains called peptides, as well as longer chains that are called polypeptides or proteins.
- About 75 percent of the human body is made up of chains of amino acids, which is why they are so vital to how your system functions.
- All the chemical reactions that occur in the body depend on amino acids and the proteins they build.

TYPES OF AMINO ACIDS

Amino acids are classified as

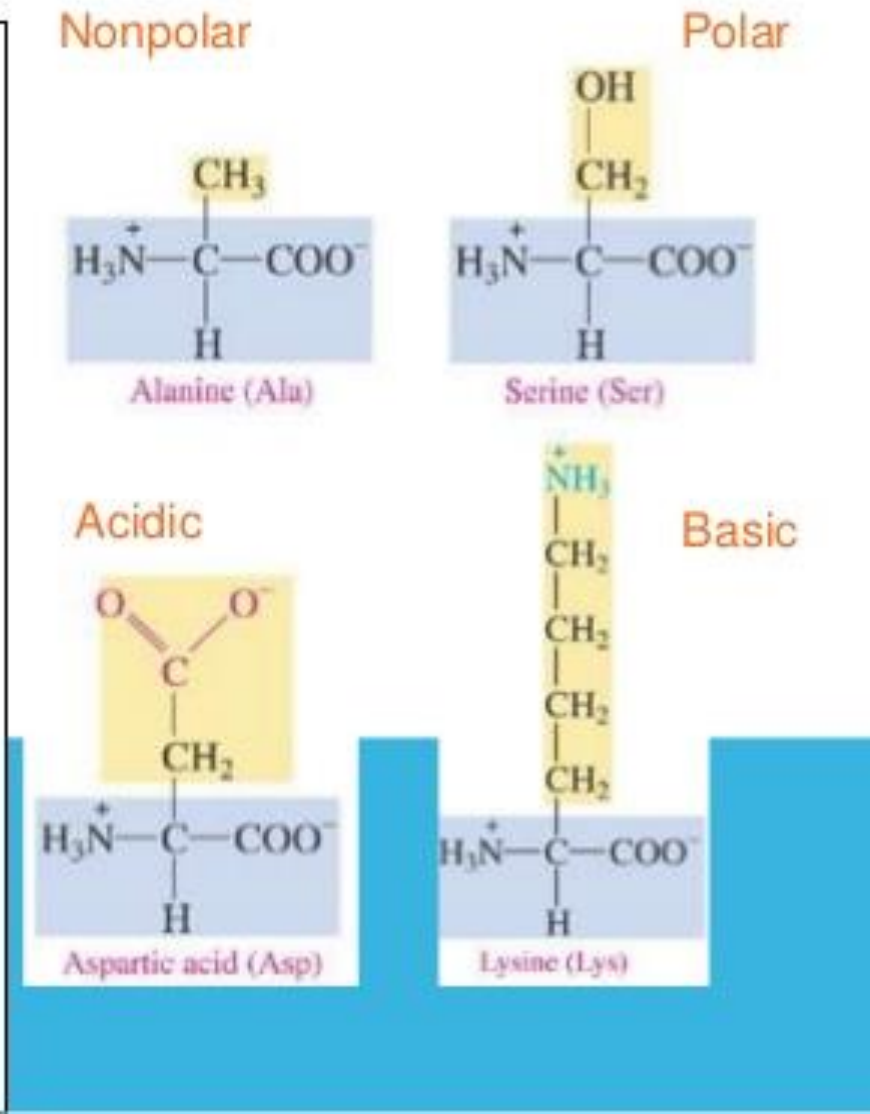
Nonpolar (hydrophobic) with hydrocarbon side chains.

Polar (hydrophilic) with polar or ionic side chains.

Acidic (hydrophilic) with acidic side chains.

Basic (hydrophilic) with

$-NH_2$ side chains.



- non-essential amino acids

  - can be synthesized by an organism

  - usually are prepared from precursors in 1-2 steps

- Essential amino acids

  - cannot be made endogenously

  - must be supplied in diet

    eg. Leu, Phe.....

Nutritionally-Essential amino acids :

Lysine, Leucine, Isoleucine, Valine, Methionine, Phenylalanine,

Threonine, Tryptophan

Nutritionally Nonessential amino acids: Alanine, glycine, aspartate , glutamate, serine, tyrosine, cysteine, proline , glutamine, aspargine

N.B. Histidine & arginine are semi essential. They are essential only for infants growth, but not for old children or adults where in adults histidine requirement is obtained by intestinal flora & arginine by urea cycle

PROTEIN DIGESTION

Digestive Tract of protein

- Proteins are generally too large to be absorbed by the intestine and therefore must be hydrolyzed to the amino acids
- The proteolytic enzymes responsible for hydrolysis are produced by three different organs: the stomach、pancreas and small intestine (the major organ)

Stomach

- HCl (parietal cells) and Pepsinogen (chief cells)
- The pH of gastric juice is around 1.0. Food is retained in the stomach for 2-4 hrs
- HCl kills microorganisms, denatures proteins, and provides an acid environment for the action of pepsin
- **Autocatalysis**: pepsinogen is converted to active pepsin(*Pepsin A)* by HCl

Pancreas and small intestine

- **Endo**peptidase (pancreas)

  Trypsin: carbonyl of arg and lys

  Chymotrypsin: carbonyl of Trp, Tyr, Phe, Met, Leu

  Elastase: carbonyl of Ala, Gly, Ser

  Exopeptidase (pancreas)

  Carboxypeptidase A:amine side of Ala, Ile, Leu, Val

  Carboxypeptidase B: amine side of Arg, lys

- Aminopeptidase (small intestine):

  cleaves N-terminal residue of oligopeptidaes

PROTEIN ABSORPTION

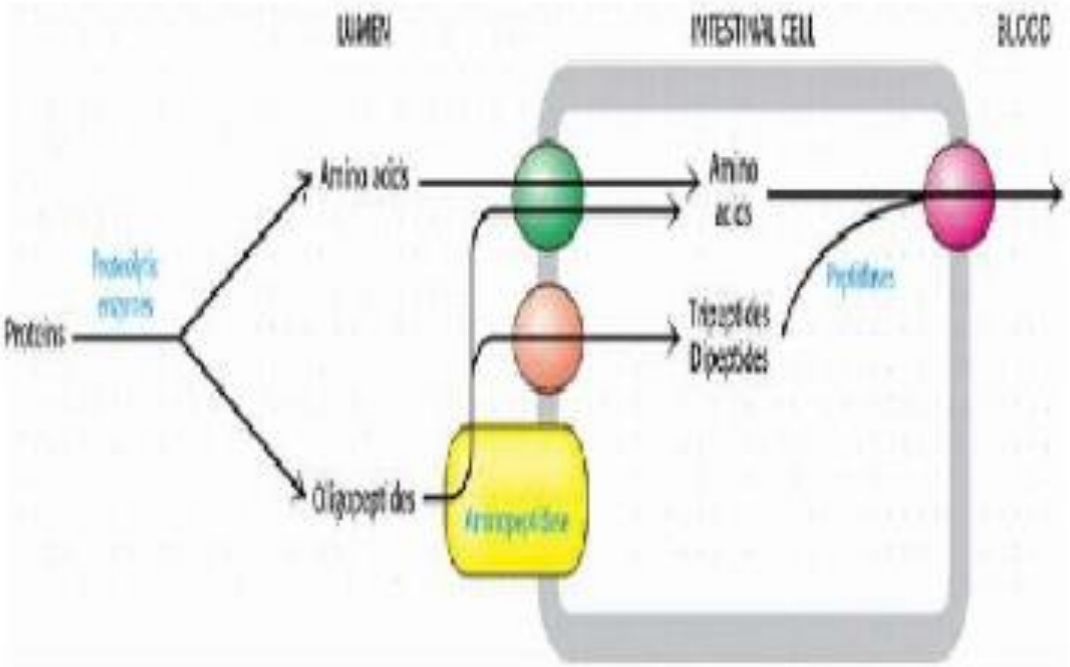
*L-amino acids are actively transported across the intestinal mucosa (need carrier, Na + pump,

Na+ ions, ATP).

Different carrier transport systems are: a) For neut amino acids.
b) For basic amino acid and cysteine.
c) For imino acids and glycine.

d) For acidic amino acids.
e) For B-amino acids (B-alanine & taurine).

*D-isomers transported by simple diffusion.



Nitrogen Balance (NB):

- **Nitrogen balance** is a **comparison between**

  Nitrogen intake (in the form of dietary protein)

  and

  Nitrogen loss (as **undigested protein** in feces ,

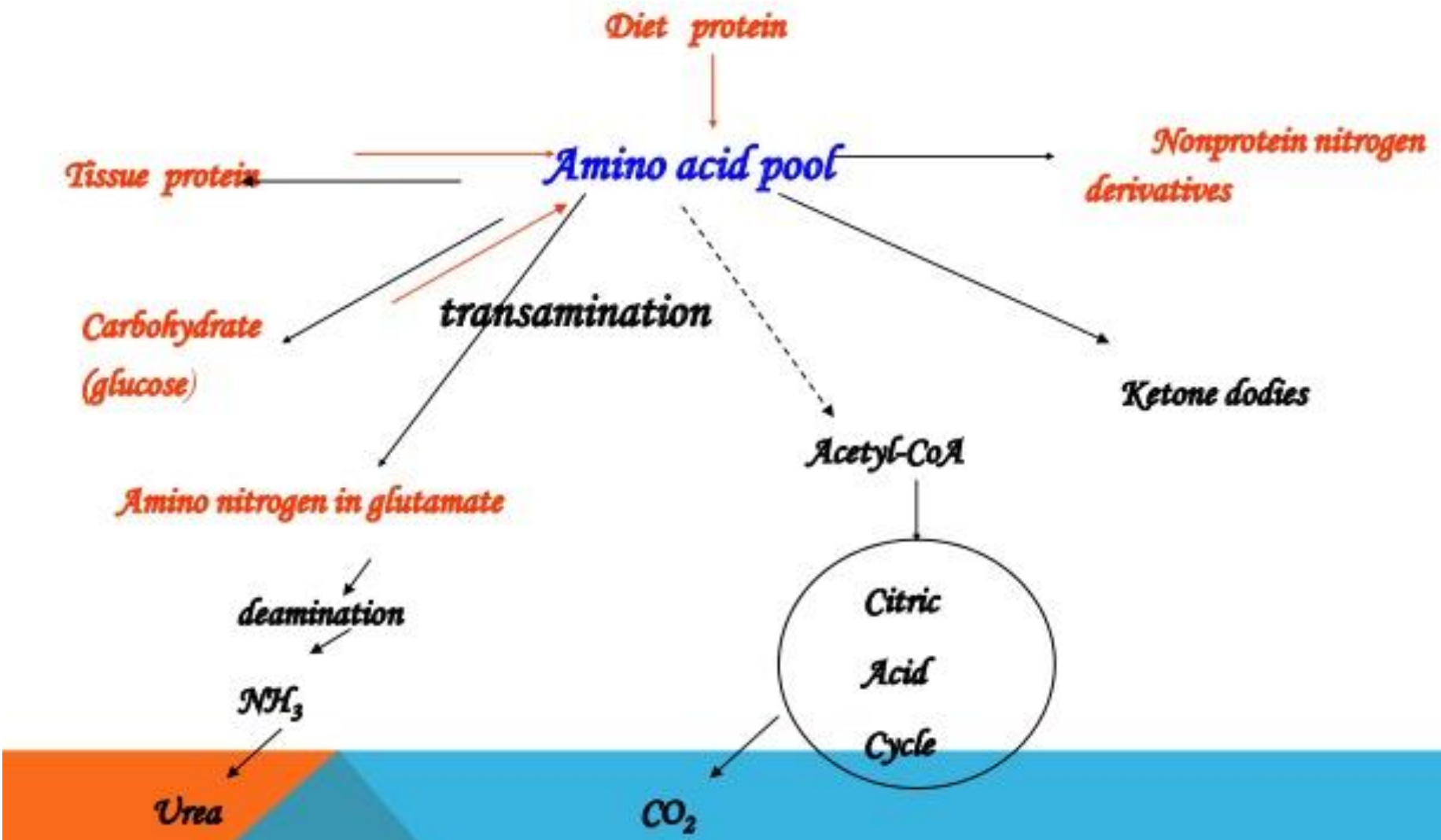
  NPN as urea, ammonia, creatinine & uric acid in urine, sweat & saliva & **losses** by hair, nail, skin).

- NB is important **in** defining

  1.overall protein metabolism of an individual

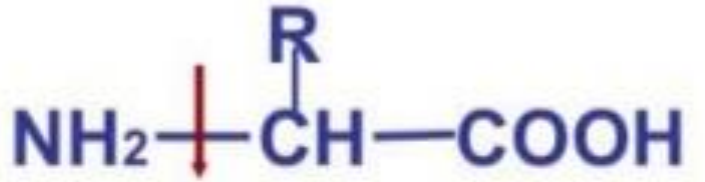
  2.nutritional nitrogen requirement.

AMINO ACID METABOLISM



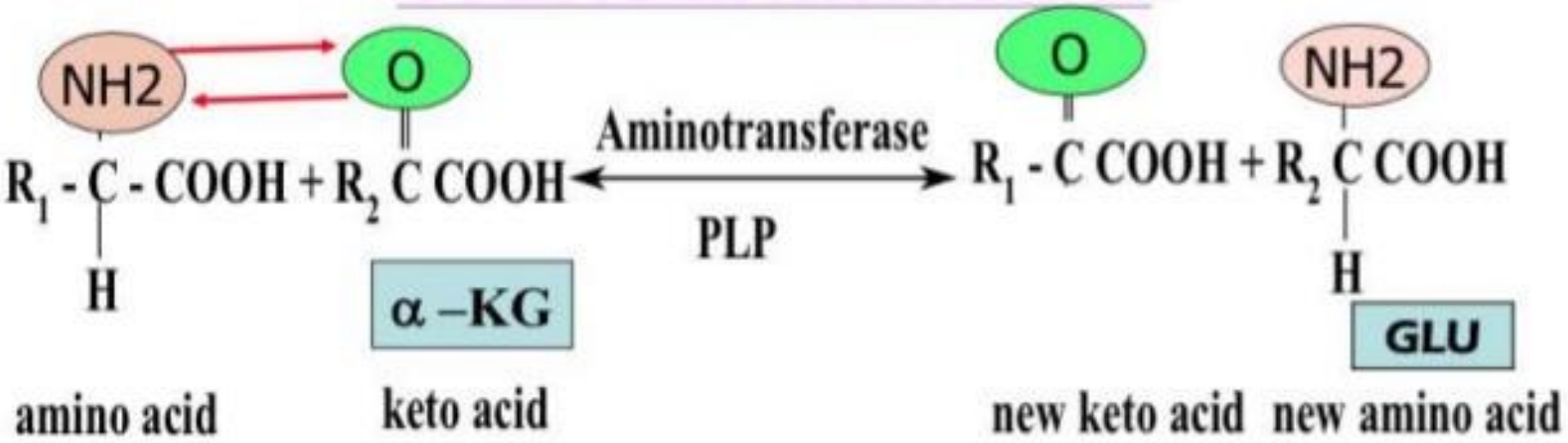
Overview of the protein metabolism

Metabolism OF AMINO ACIDS:



1. **Removal of amonia** by :
   - Deamination → **Oxidative deamination**
     1) glutamate dehydrogenase in mitochondria
     2) amino acid oxidase in peroxisomes
     Direct deamination (nonoxidative)
     1) dea. by dehydration ($-H_2O$)
     2) dea. by desulhydration ($-H_2S$)
   - Transamination (GPT & GOT)
   - and transdeamination.
2. **Fate of carbon-skeletons of amino acids**
3. **Metabolism of ammonia**

Transamination:



Aminotransferases are **active** both in cytoplasm and mitochondria e.g.:

1. **Aspartate aminotransferase (AST)**, Glutamate oxaloacetate transaminase **(GOT),**

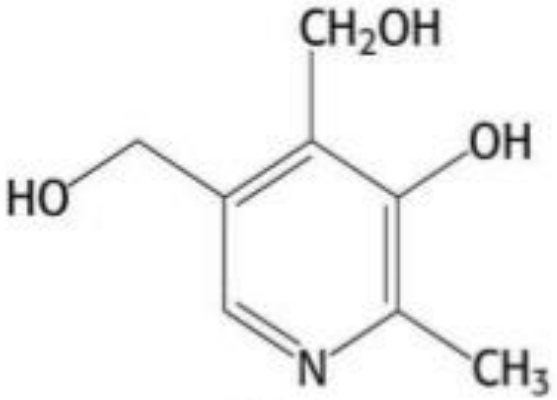
2. **Alanine aminotransferase (ALT)**, Glutamate pyruvate transaminase, **(GPT)**

In all transamination reactions, α-ketoglutarate (α –KG) acts as amino group acceptor.

Most, but not all amino acids undergo transamination reaction with few exceptions **(lysine, threonine and imino acids)**

Mechanism of transamination

All aminotransferases require the prosthetic group ***pyridoxal phosphate (PLP),*** which is derived from ***pyridoxine (vitamin B_6).***

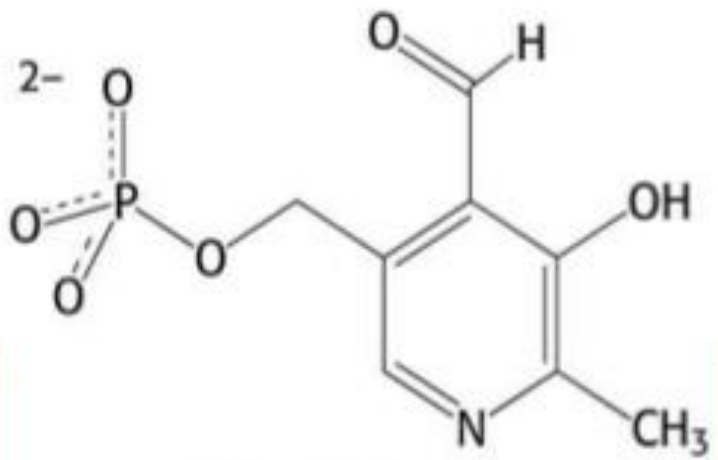


Pyridoxine (Vitamin B_6)

Ping-pong kinetic mechanism

First step: the amino group of amino acid is transferred to pyridoxal phosphate, forming pyridoxamine phosphate and releasing ketoacid.

Second step: α-ketoglutarate reacts with pyridoxamine phosphate forming glutamate



Pyridoxal phosphate (PLP)

B. Oxidative Deamination

- L-glutamate dehydrogenase (in mitochondria)

Glu + NAD^+ (or $NADP^+$) + H_2O ⇆ NH_4^+ + a-ketoglutarate + NAD(P)H +H^+

Requires NAD^+ or $NADP^+$ as a cofactor

Plays a central role in AA metabolism

THE FATE OF CARBON-SKELETONS OF AMINO ACIDS

a) Simple degradation:

(amino acid → Common metabolic intermediate)

Alanine → Pyruvate

Glutamate → α-ketoglutarate

Aspartate → Oxaloacetate

b) Complex degradation:

(amino acid--- Keto acid----- **complex** pathway---- Common metabolic intermediate)

Amino acids whose ketoacids are metabolized via **more complex** pathway **e.g. Tyrosine, Lysine, Tryptophan**

c) Conversion of one amino acid into another amino acid before degradation:

Phenylalanine is converted to **tyrosine** prior to its further degradation.

Metabolism of the Common Intermediates

1. ***Oxidation:*** all amino acids can be oxidized in **TCA** cycle with **energy** production
2. ***Fatty acids synthesis:*** some amino acids provide **acetyl CoA** e.g. leucine and lysine (ketogenic amino acids).
3. ***Gluconeogenesis:*** ketoacids derived from amino acids are used for synthesis of **glucose** (is important in starvation).

Glucogenic	***Ketogenic***	***Glucogenic&Ketogenic***
Ala, Ser, Gly, Cys, Arg, His, Pro, Glu, Gln, Val, Met, Asp, Asn.	Leu , Lys	Phe,Tyr,Trp,Ile,Thr

METABOLISM OF AMMONIA

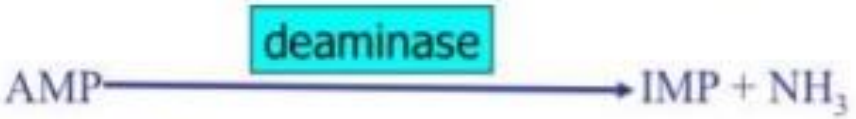
Ammonia is formed in body from:

a) From amino acids: 1.Transdeamination in liver (NOT T.A.)

2.amino acid oxidases and amino acid deaminases in liver and kidney.

b) Deamination of physiological amines: by monoamine oxidase.

c) Deamination of purine nucleotides: especially adenine nucleotides



d) Pyrimidine catabolism.

e) From bacterial action in the intestine **on dietary protein & on urea in the gut.**

NH3 is also produced by glutaminase on glutamine .

TRANSPORT OF AMMONIA TO THE LIVER

Two mechanism are available for the transport of ammonia from peripheral cells to liver for detoxification

The first uses glutamine synthetase to combine glutamate with ammonia

The second , used primarily by muscle, involves transamination of pyruvate to Alanine

GLUTAMATE AND GLUTAMINE RELATIONSHIP

Ammonia Nitrogen can be transported as glutamine.

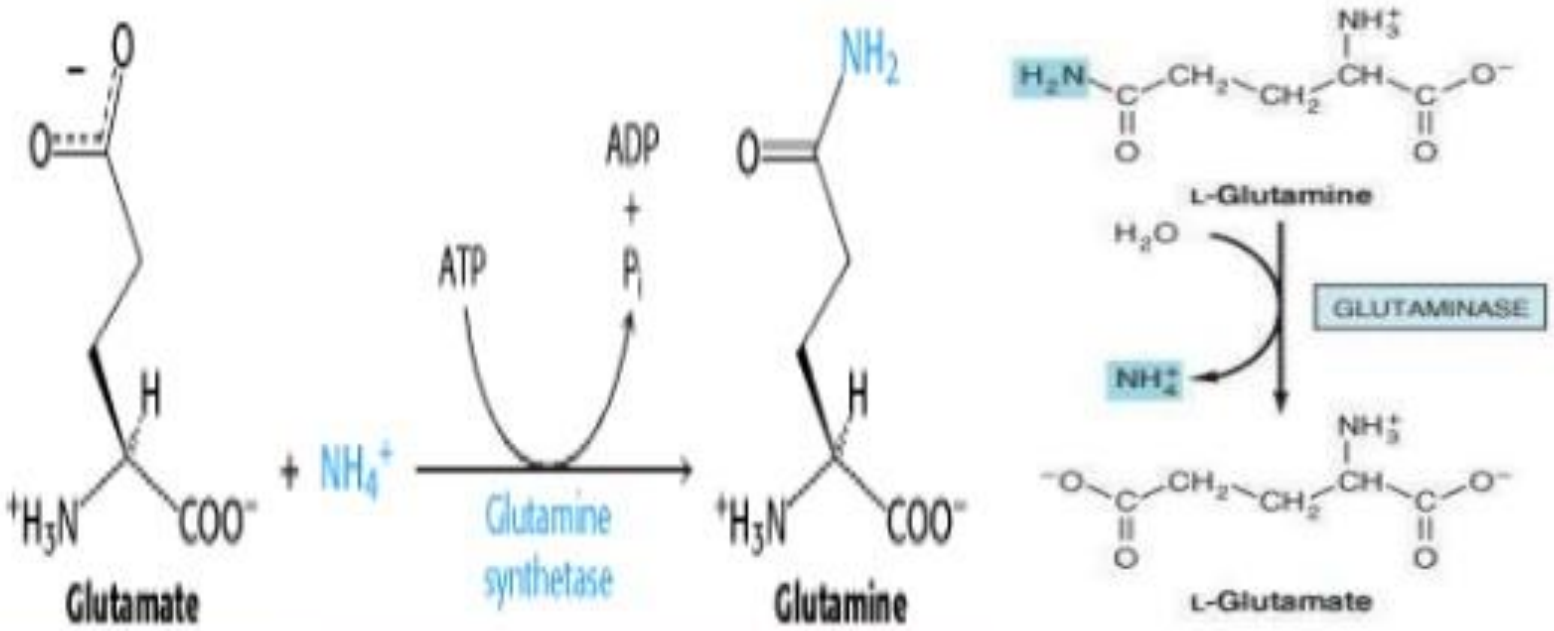
This is the first line of defense in brain cells.

Glutamine synthetase catalyzes the synthesis of glutamine from glutamate and NH_4^+ in an ATP-dependent reaction

The nitrogen of glutamine can be converted to urea in liver by the action of glutaminase in liver

Hydrolytic release of the amide nitrogen of glutamine as ammonia, catalyzed by glutaminase favors glutamate formation.

GLUTAMATE AND GLUTAMINE RELATIONSHIP



The concerted action of glutamine synthase and glutaminase thus catalyzes the interconversion of free ammonium ion and glutamine

GLUCOSE ALANINE CYCLE AND ROLE OF GLUTAMATE

The transport of amino group of amino acids also takes place in the form of Alanine.

Nitrogen is transported from muscle to the liver in two principal transport forms.

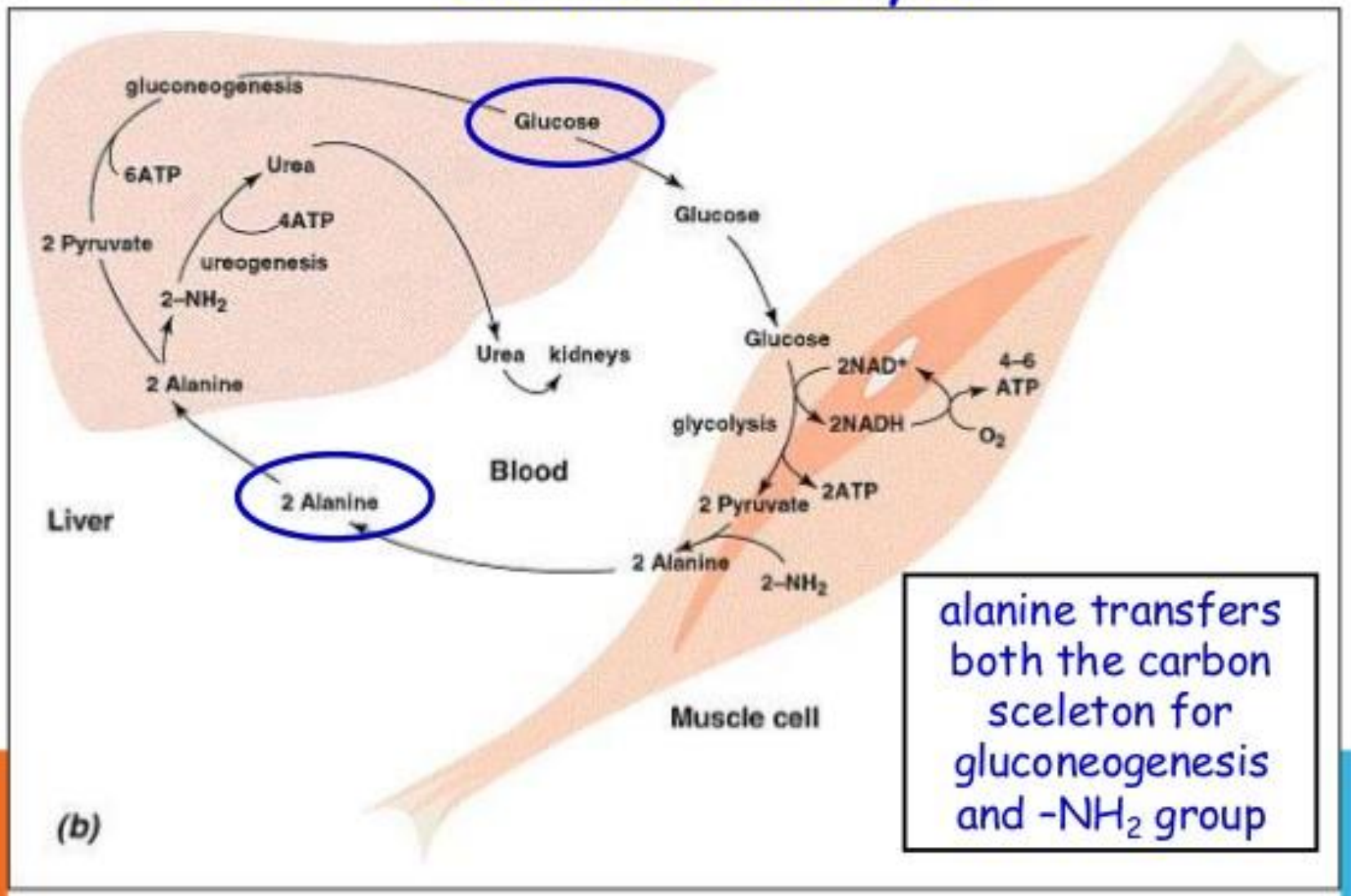
Glutamate is formed by transamination reactions, but the nitrogen is then transferred to pyruvate to form alanine, which is released into the blood.

The liver takes up the alanine and converts it back into pyruvate by transamination.

The pyruvate can be used for gluconeogenesis and the amino group eventually appears as urea.

This transport is referred to as the *alanine cycle.*

Glucose-alanine cycle



alanine transfers both the carbon sceleton for gluconeogenesis and $-NH_2$ group

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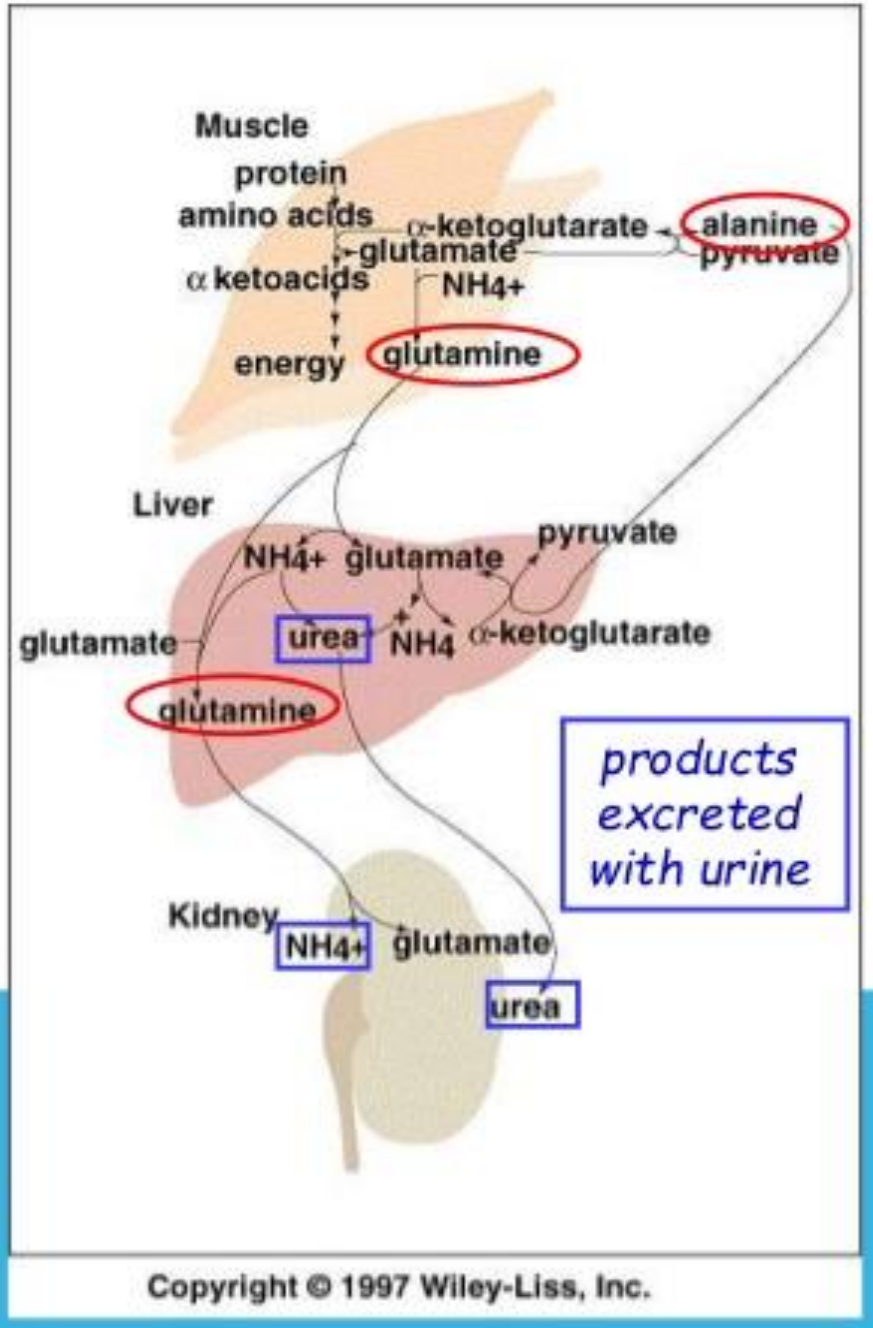
Transport of amino nitrogen

from degraded muscle proteins



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AMMONIA INTOXICATION

The ammonia produced by enteric bacteria and absorbed into portal venous blood and the ammonia produced by tissues are rapidly removed from circulation by the liver and converted to urea.

Thus, only traces (10–20 g/dL) normally are present in peripheral blood.

This is essential, since ammonia is toxic to the central nervous system.

Should portal blood bypass the liver, systemic blood ammonia levels may rise to toxic levels.

This occurs in severely impaired hepatic function or the development of collateral links between the portal and systemic veins in cirrhosis.

AMMONIA INTOXICATION

Excess of ammonia depletes glutamate and hence GABA level in brain

To compensate for glutamate, alpha keto glutarate is used , the decrease concentration of which subsequently depresses TCA and thus deprives brain cells of energy.

Excess Glutamine is exchanged with Tryptophan , a precursor of Serotonin , resulting in hyper excitation.

Symptoms of ammonia intoxication include tremor, slurred speech, blurred vision, coma, and ultimately death.

UREA (ORNITHINE) CYCLE

detoxification pathway (NH_3 is toxic for brain)

proceeds only in the liver

localized in mitochondria /cytoplasm

carbamoyl phosphate synthetase I (= mitoch.)

can acidify an organism (consumes HCO_3^-)

needs energy (3 ATP, but 4 energy rich bonds)

connected with citrate cycle through fumarate

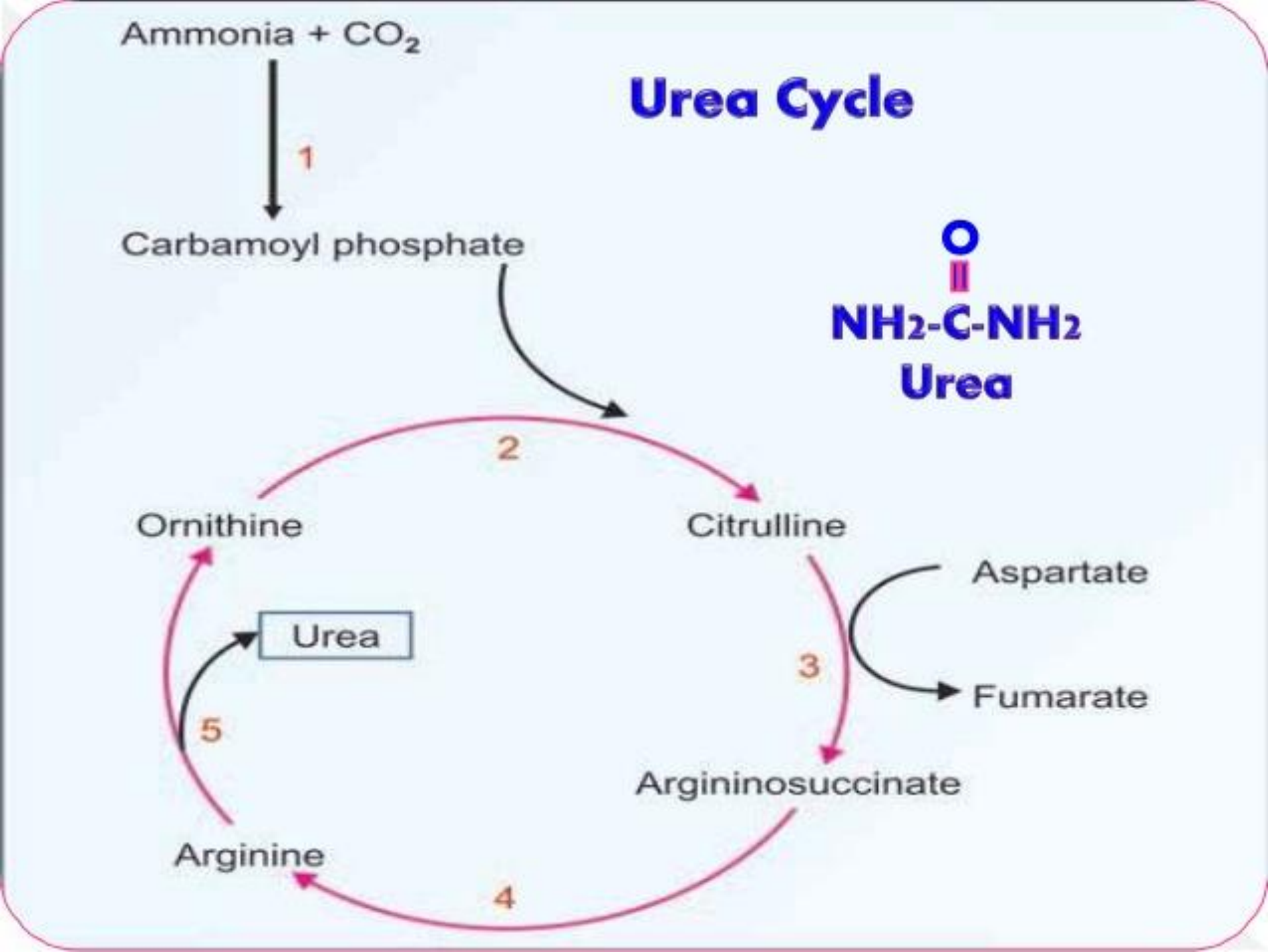
urea is end product of $-NH_2$ metabolism (→ urine)

Urea Cycle

- The urea cycle is the first metabolic pathway to be elucidated.
- The cycle is known as Krebs–Henseleit urea cycle.
- Ornithine is the first member of the reaction, it is also called as Ornithine cycle.
- Urea is synthesized in liver & transported to kidneys for excretion in urine.

- The two nitrogen atoms of urea are derived from two different sources, one from ammonia & the other directly from the a-amino group of aspartic acid.
- Carbon atom is supplied by CO_2
- Urea is the end product of protein metabolism (amino acid metabolism).

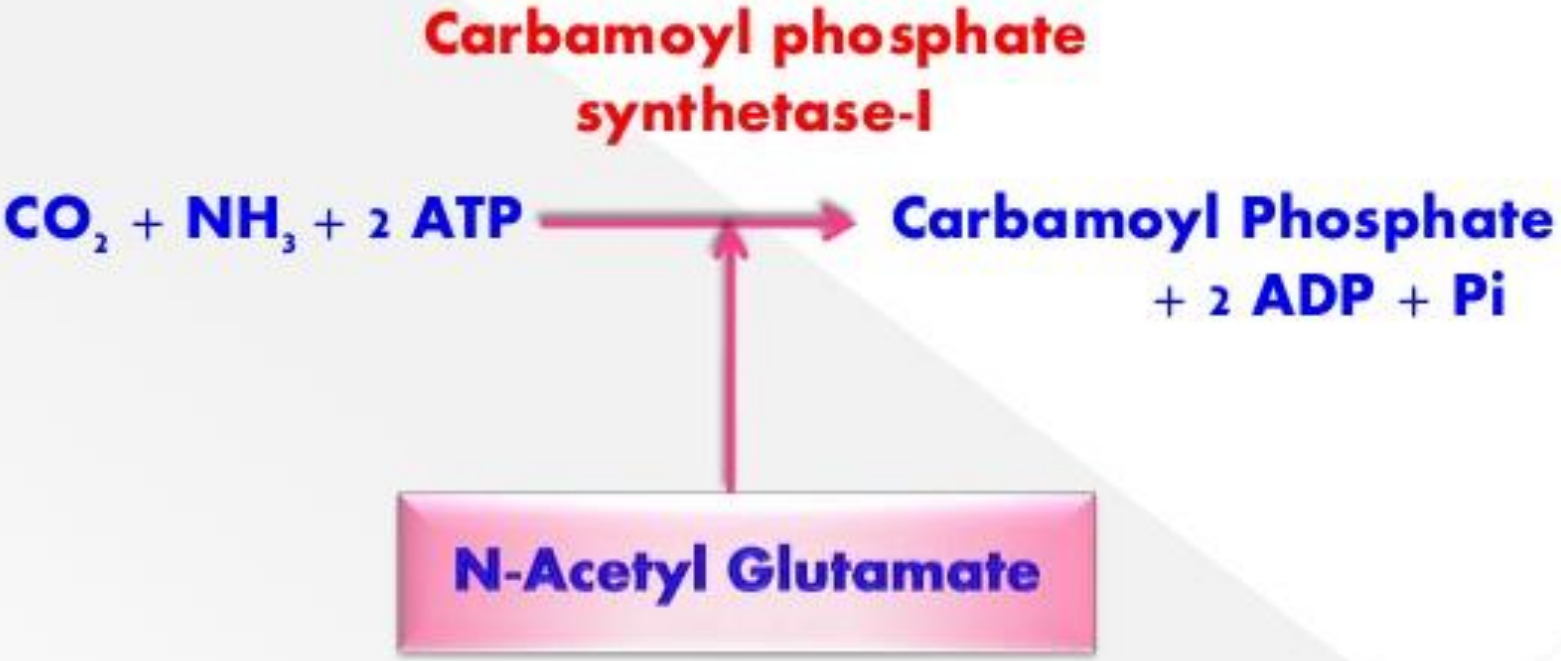
- Urea accounts for 80-90% of the nitrogen containing substances excreted in urine.
- Urea synthesis is a five-step cyclic process, with five distinct enzymes.
- The first two enzymes are present in mitochondria while the rest are localized in cytosol.


Ammonia + CO_2
1
Carbamoyl phosphate
Urea Cycle
NH_2-C-NH_2
Urea
2
Ornithine
Citrulline
Aspartate
Urea
3
Fumarate
5
Argininosuccinate
Arginine
4

Step: 1 Formation of carbamoyl phosphate

- Carbamoyl phosphate synthase I (CPS I) of mitochondria catalyses the condensation of NH_4^+ ions with CO_2 to form carbamoyl phosphate.
- This step consumes two ATP & is irreversible.
- It is a rate-limiting.

Step: 1 Formation of carbamoyl phosphate



Step 2: Formation of Citrulline

- The second reaction is also mitochondrial.
- Citrulline is synthesized from carbamoyl phosphate & ornithine by ornithine transcarbamoylase.
- Ornithine is regenerated & used in urea cycle.

- **Ornithine & citrulline are basic amino acids. (Never found in protein structure due to lack of codons).**
- **Citrulline is transported to cytosol by a transporter system.**
- **Citrulline is neither present in tissue proteins nor in blood; but it is present in milk.**

Step 2: Formation of Citrulline

Step 3: Formation of Arginosuccinate

- Citrulline condenses with aspartate to form arginosuccinate by the enzyme Arginosuccinate synthetase.
- Second amino group of urea is incorporated.
- It requires ATP, it is cleaved to AMP & PPi
- 2 High energy bonds are required.
- Immediately broken down to inorganic phosphate (Pi).

Step:4 Formation of Arginine or cleavage of Arginosuccinate

- The enzyme Argininosuccinase or argininosuccinate lyase cleaves arginosuccinate to arginine & fumarate (an intermediate in TCA cycle)
- Fumarate provides connecting link with TCA cycle or gluconeogenesis.

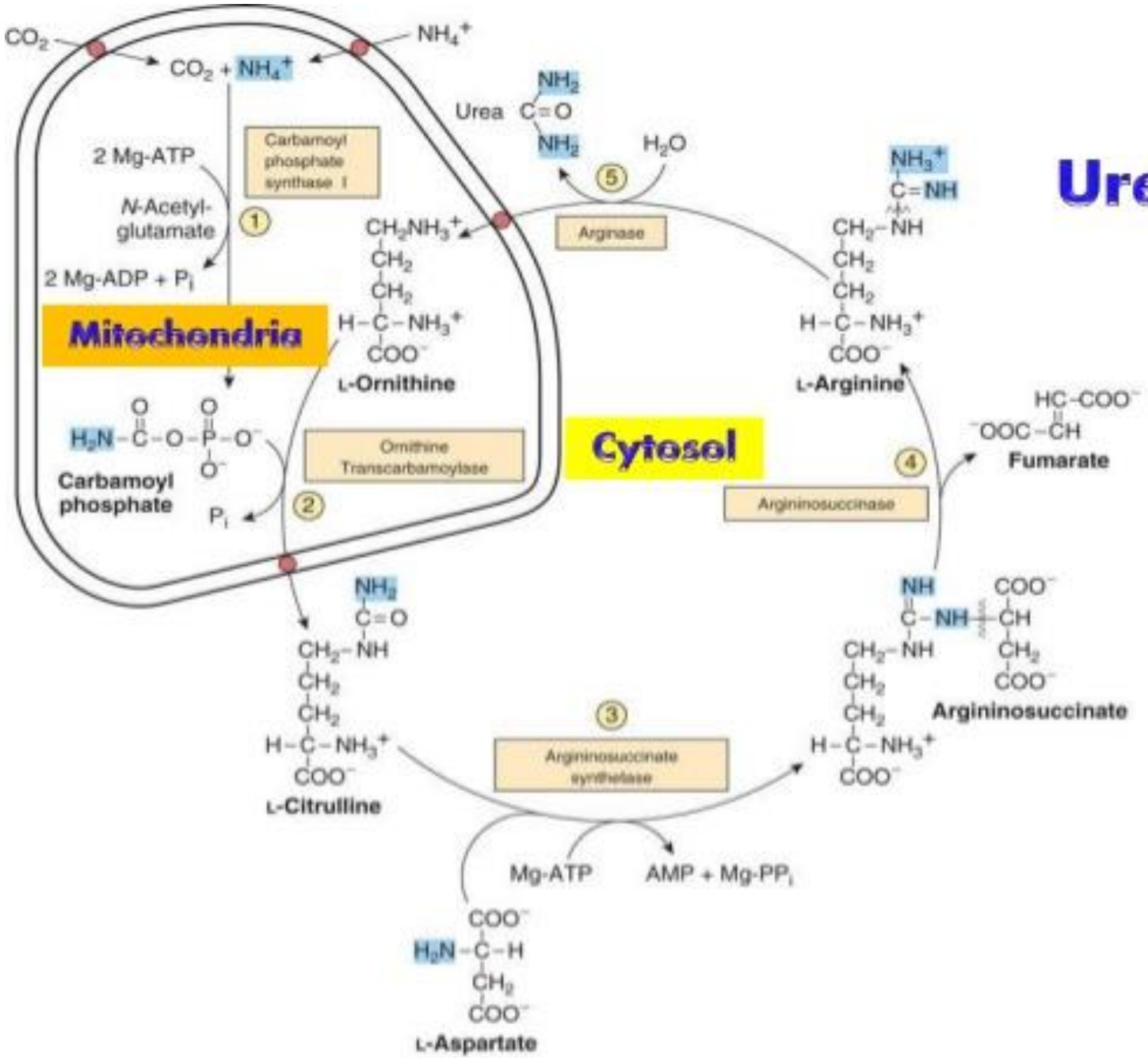
- The fumarate is converted to oxaloacetate via fumarase & MDH & transaminated to aspartate.
- Aspartate is regenerated in this reaction.

Step 5: Formation of Urea

- **Arginase is the 5th and final enzyme that cleaves arginine to yield urea & ornithine.**
- **Ornithine is regenerated, enters mitochondria for its reuse in the urea cycle.**
- **Arginase is activated by Co^{2+} & Mn^{2+}**
- **Ornithine & lysine compete with arginine (competitive inhibition).**

- Arginase is mostly found in the liver, while the rest of the enzymes (four) of urea cycle are also present in other tissues.
- Arginine synthesis may occur to varying degrees in many tissues.
- But only the liver can ultimately produce urea.

Urea Cycle


CO_2
NH_4^+
$CO_2 + NH_4^+$
2 Mg-ATP
Carbamoyl phosphate synthase I
N-Acetyl-glutamate
1
2 Mg-ADP + P_i
Mitochondria
Carbamoyl phosphate
P_i
Ornithine Transcarbamoylase
2
L-Ornithine
Cytosol
Urea
H_2O
5
Arginase
L-Arginine
4
Argininosuccinase
Fumarate
Argininosuccinate
3
Argininosuccinate synthetase
L-Citrulline
Mg-ATP
AMP + Mg-PP_i
L-Aspartate

Energetics of Urea Cycle

- The overall reaction may be summarized as:
- $NH_3 + CO_2 + Aspartate \rightarrow Urea + fumarate$
- 2ATPs are used in the 1st reaction.
- Another ATP is converted to AMP + PPi in the 3rd step, which is equivalent to 2 ATPs.
- The urea cycle consumes 4 high energy phosphate bonds.
- Fumarate formed in the 4th step may be converted to malate.

- Malate when oxidised to oxaloacetate produces 1 NADH equivalent to 2.5 ATP.
- So net energy expenditure is only 1.5 high energy phosphates.
- The urea cycle & TCA cycle are interlinked & it is called as "urea bicycle".

Disposal of urea

- Urea produced in the liver freely diffuses & is transported in blood to kidneys & excreted.
- A small amount of urea enters the intestine where it is broken down to CO_2 & NH_3 by the bacterial enzyme urease.
- This ammonia is either lost in the feces or absorbed into the blood.

Regulation of urea cycle

1. Mitochondrial carbamoyl phosphate synthetase I (CPS I)

CPS I catalyzes the first committed step of the urea cycle

CPS I is also an allosteric enzyme sensitive to activation by N-acetylglutamate（AGA） which is derived from glutamate and acetyl-CoA

Urea Cycle Defects and Hyperammonemia—

(1) Hereditary Hyperammonemia (genetic deficiencies of Urea cycle enzymes)

- Ornithine carbamyl transferase (OTC) deficiency (X linked)
- Carbamyl phosphate synthetase I (CPS I) deficiency
- Citrullinemia (enzyme defect?)
- Arginosuccinic Aciduria (enzyme defect?)
- Argininemia (not severe why?)(enzyme defect?)
- N-acetylGlu synthase deficiency

Urea Cycle Defects and Hyperammonemia

(2) **Acquired Hyperammonemia-------**

a) Liver disease---- (cirrhosis , hepatitis)
b) High protein diet

Clinical significance of blood urea:

- Elevated in renal insufficiency.
- Decreased in hepatic failure.

CHOLESTEROL METABOLISM

By
Dr. Muna M. Yaseen

CHOLESTEROL

→ Cholesterol is a **light yellow crystalline solid**

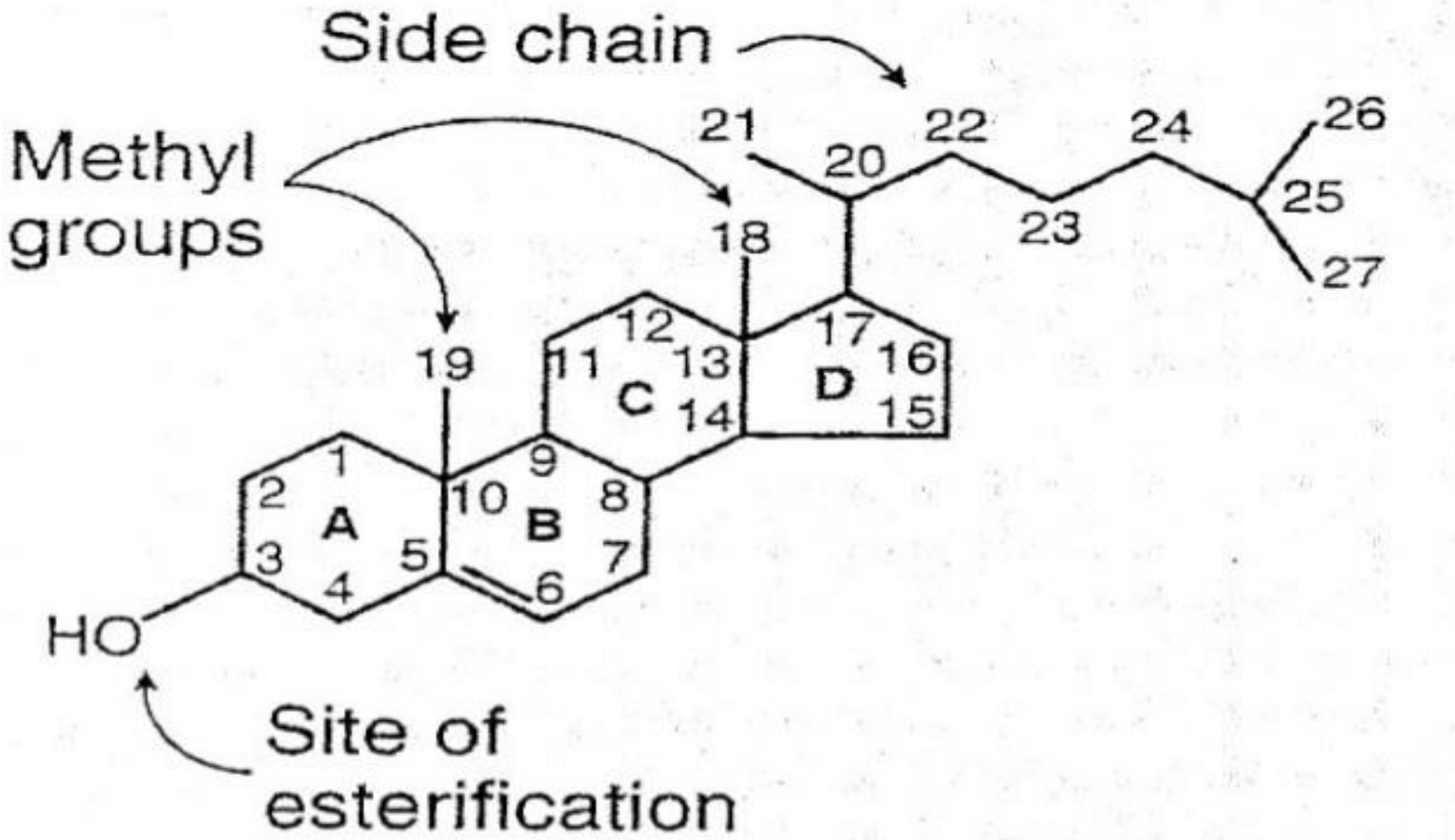
→ It is a **27 Carbon compound**

→ contains ***cyclopentano perhydro phenanthrene*** ring

→ **One hydroxyl group (OH) at 3rd position**

→ **Double bond** between **5 & 6** Carbons

→ **8 Carbon side chain** at 17th Carbon



Cholesterol

Significance of Cholesterol

1) Normal level ***150 – 200 mg/dl*** . Increased levels increases the risk for ***Atherosclerosis***
2) Important ***component of cell membranes*** which affects fluid state of membrane
3) It is used to ***Insulate Nerve fibers***.
4) ***Bile acids*** (24 Carbon) are derived from Cholesterol
5) ***Steroid hormones*** (21 'C' glucocorticoids, 19 'C' androgens and 18 'C' estrogens) are produced from cholesterol
6) ***Vitamin D*** formed from Cholesterol

Biosynthesis of Cholesterol

Major sites – ***Liver, Adrenal Cortex, testis, ovaries*** and ***Intestine***

80% by Liver

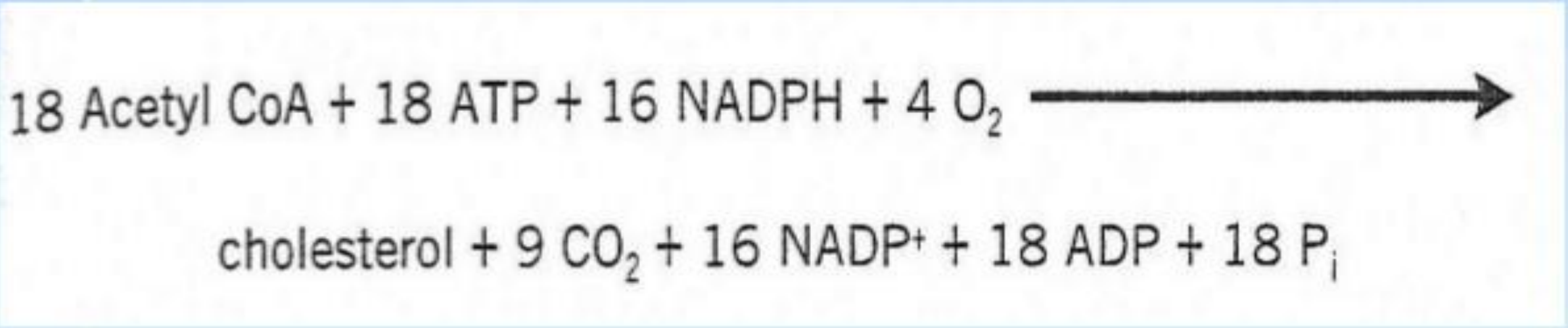
The enzymes involved in synthesis are located partly in ***cytoplasm*** and ***endoplasmic reticulum***.

Requirements:

1) Acetate of **acetyl CoA** provides all the carbon atoms of cholesterol
2) Reducing equivalents by **NADPH**
3) Energy from **ATP**.

De novo Synthesis of Cholesterol

- Primary site: liver (~1g/d)
  - Secondary sites: adrenal cortex, ovaries, testes
- Overall equation:



Cholesterol Synthesis in 5 stages

1) Synthesis of **HMG CoA (6 c)**
2) Formation of **mevalonate (6 C)**
3) Production of **Isoprenoid Units (5 C)**
4) Synthesis of **squalene (30 C)**
5) Conversion of **Squalene to cholesterol (27 C)**

2C ► 6C ► 6C ► 5C ► 10C ► 15C ► 30C ► 27C

Step I : Condensation

Two molecules of Acetyl CoA condense to form **Acetoacetyl CoA**

Enzyme: ***Acetoacetyl CoA Synthase***

Step II : *Production of HMG CoA*

One acetyl CoA condenses with Acetoacetyl CoA to form ***β-hydroxy β-methyl glutaryl CoA*** (HMG CoA)

Enzyme: ***HMG CoA Synthase***

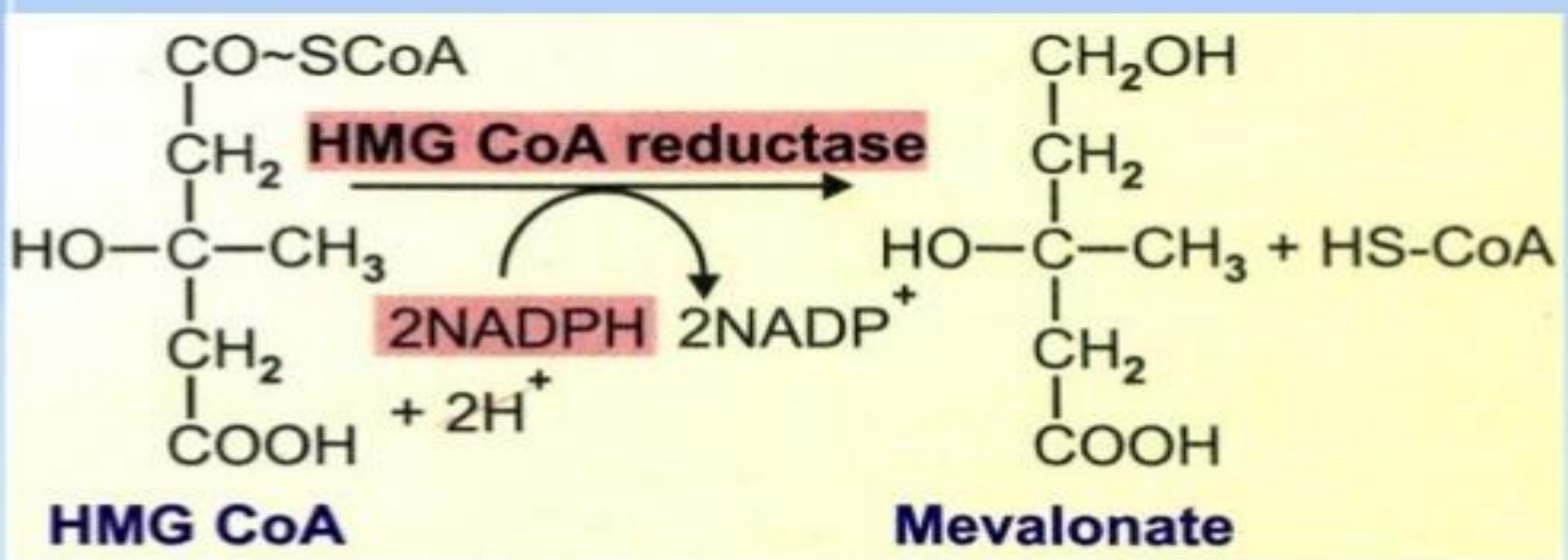
Step III – Regulating Step

Formation of **Mevalonate**

Reduction of HMG CoA to Mevalonate

Enzyme: ***HMG CoA reductase***

requires 2 NADPH



Step 3 of cholesterol synthesis

Step 4 : Formation of Isoprenoid Unit (5 C)

Mevalonate is ***phorphorylated*** three times to form ***3" phospho 5" pyrophospho mevalonate***, requires 3 ATP.

This undergoes **decarboxylation** to form ***Isopentanyl Pyrophosphate*** (5 C)

Step 5: Synthesis of Squalence (30 C)

Isopentanyl pyrophosphate Isomerizes to form

Di methyl allyl pyrophosphate

One molecule of **IPP** (5 C) condenses with **DMP** (5 C) to form **Geranyl pyrophosphate** (10 C)

One molecule of **IPP** (5 C) condenses with **GP** (10 C) to form **Farnesyl pyrophosphate (15 C)**

Two molecules of **Farnesyl pyrophosphate (15 C)** condenses to form **Squalene (30 C)**

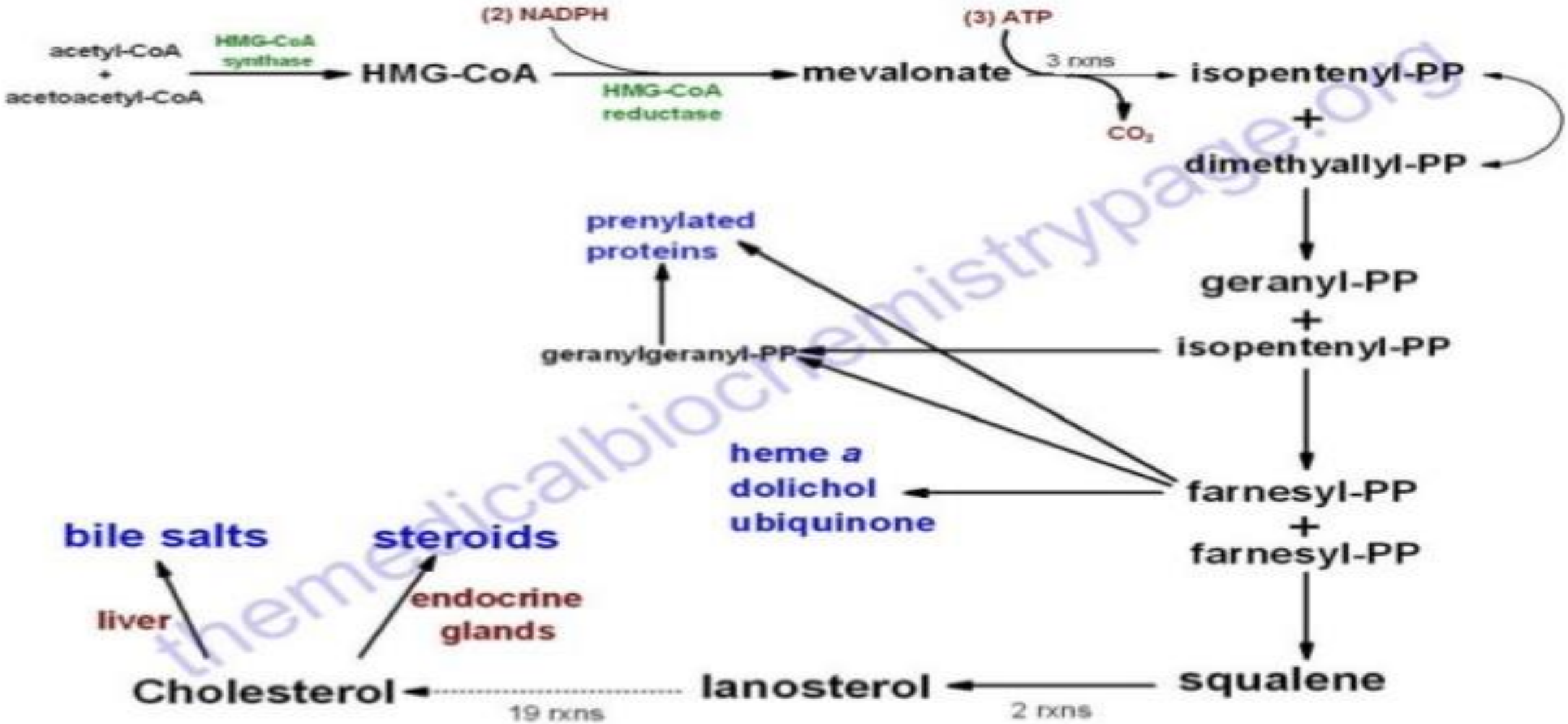
Step 6 : ***Cyclization***

Squalene undergoes oxidation and cyclization to form **Lanosterol**

Lanosterol first formed steroid compound.

2C ► 6C ► 6C ► 5C ► 10C ► 15C ► 30C ► 27C

Biosynthesis of Cholesterol



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Regulation of Cholesterol Synthesis

HMG CoA reductase is the regulating Enzyme

1. **Feed back Inhibition:**

   The end product cholesterol in excess inhibits the gene which is responsible for production of HMG CoA reductase

2. **Hormonal regulation:**

   Glucogon & Glucocorticoids favor the formation of Inactive HMG CoA reductase, thus decreases the cholesterol synthesis

   Insulin increases cholesterol synthesis by enhancing the formation of active HMG CoA reductase.

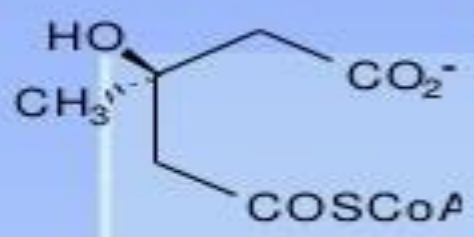
3. **Inhibition by drugs:**

Compactive

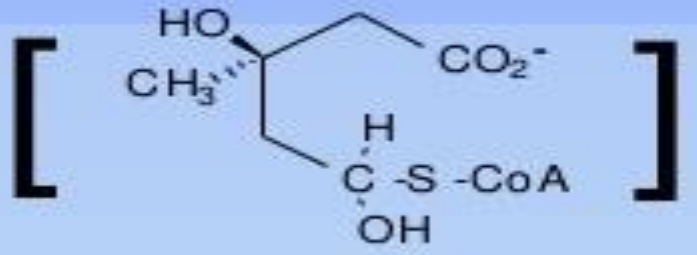
Lovastatin

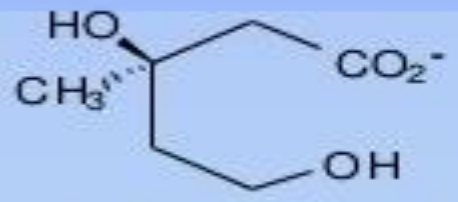
Competitive Inhibitors for HMG CoA reductase.

Inhibition of Cholesterol Biosynthesis

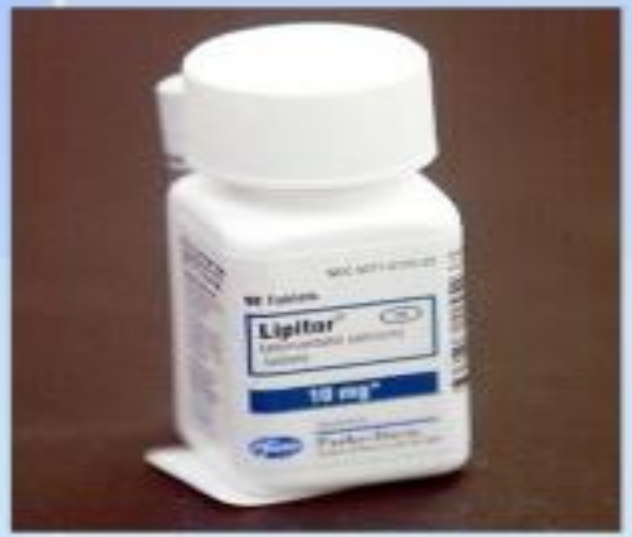


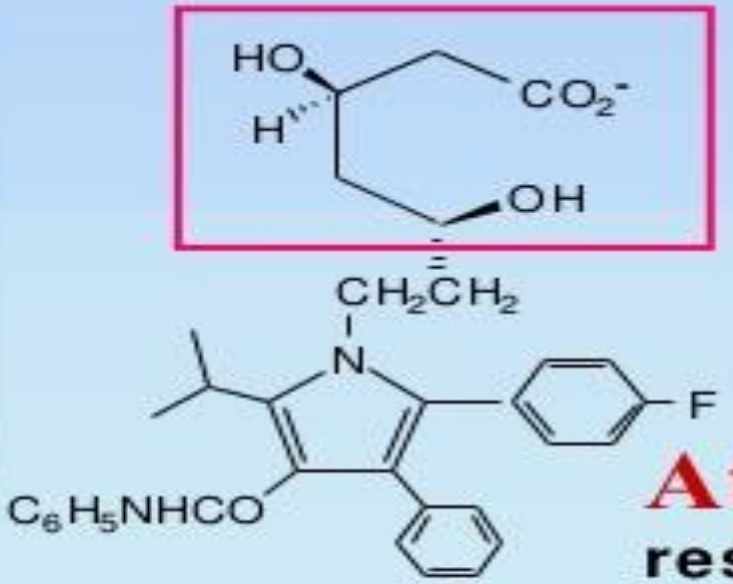
HMGCoA reductase





HMG CoA **Intermediate** **Mevalonate**





Atorvastatin (Lipitor):
resembles intermediate

Degradation of cholesterol

Cholesterol is not completely degraded to Co_2 & H_2o.

It is converted to **Bile acids**
Steroid hormones
Vitamin D

Bile acids:

24 Carbon compounds with steroid ring.

Helps in digestion & absorption of lipids.

Synthesis takes place in **Liver**

7-hydroxylase is the regulating Enzyme

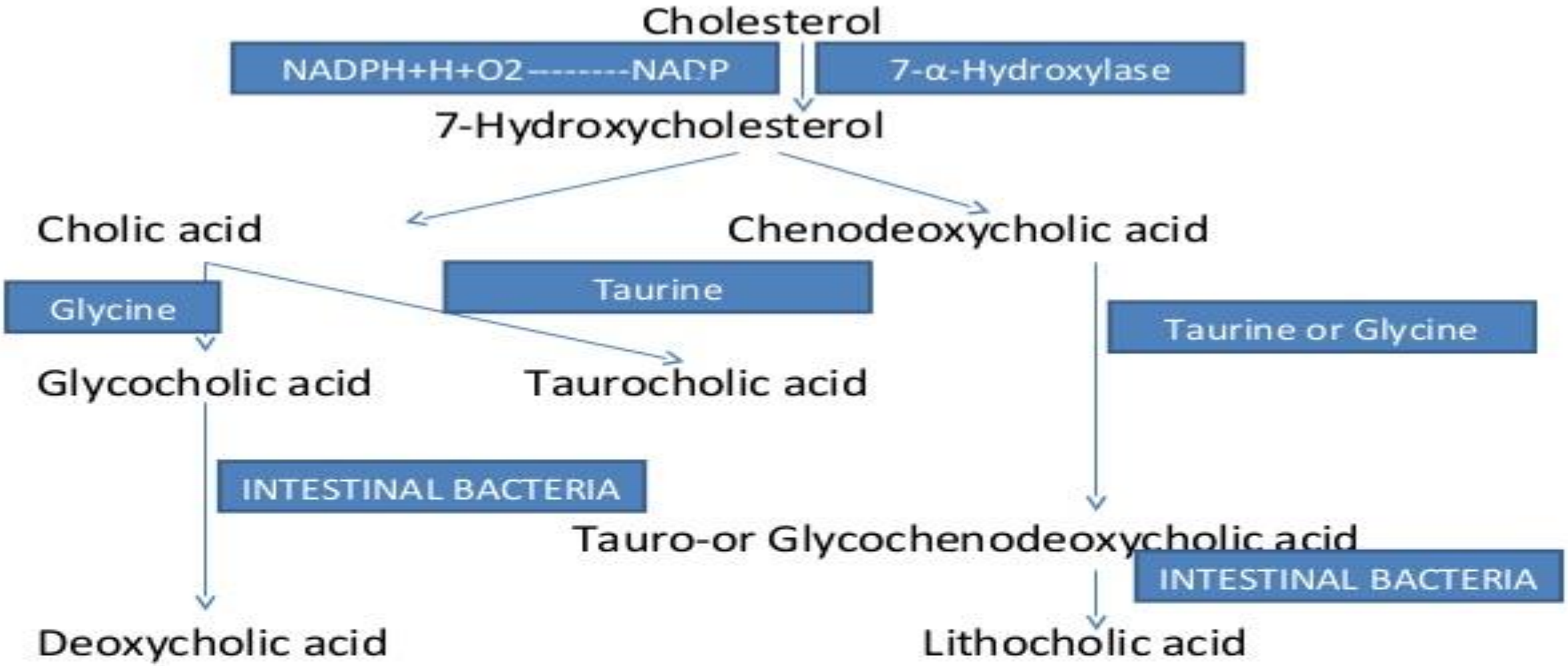
Primary Bile acids –

cholic acid, chenodeoxy cholic acid

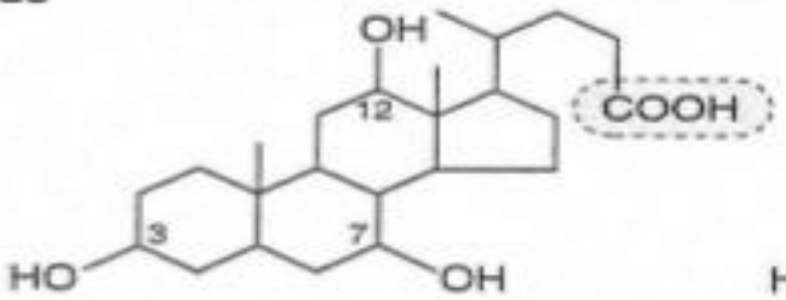
Secondary Bile acids –

deoxycholic acid, Lithocholic acid

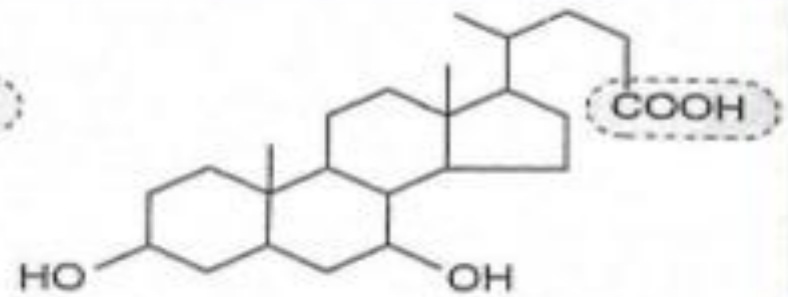
SYNTHESIS OF BILE ACIDS



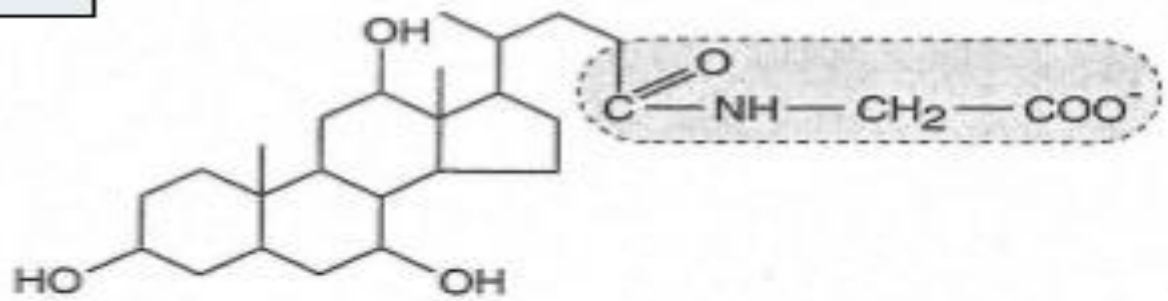
Bile acids



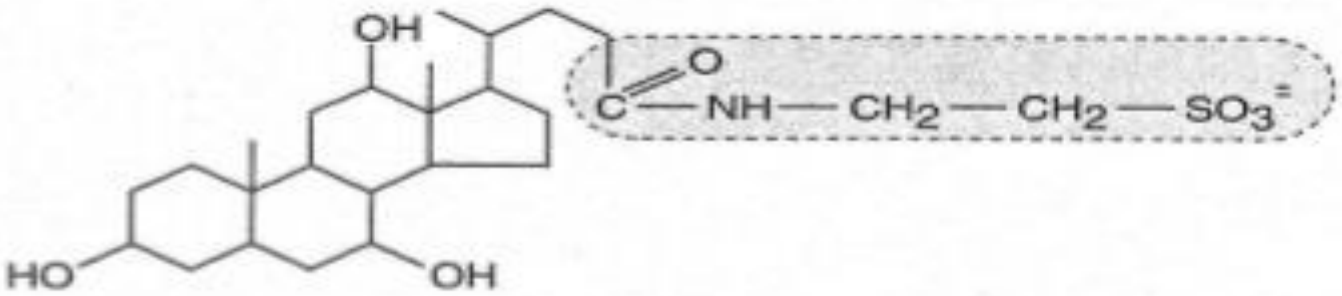
Cholic acid



Chenodeoxycholic acid



Glycholate



Taurocholate

Cholelithiasis: Bile salts and phospholipids are responsible to keep cholesterol in bile in a soluble state.

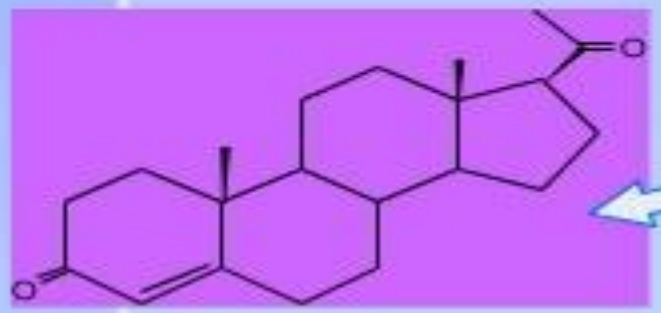
Deficiency of Bile salts, leads to precipitation of cholesterol into crystals in gall bladder resulting in Gall stones or cholelithiasis

Causes:

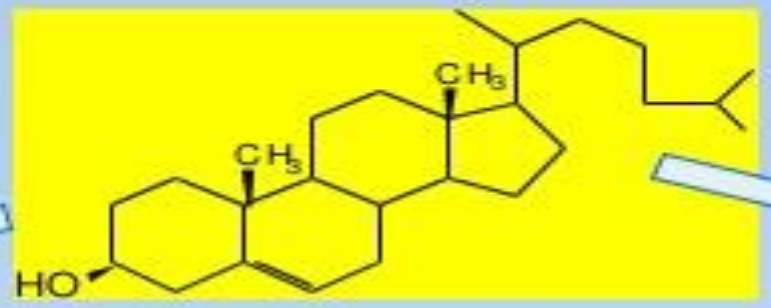
- Impairment in Liver
- Obstruction of biliary tract
- Defect in Enterohepatic circulation of bile salts

Transformations of Cholesterol:

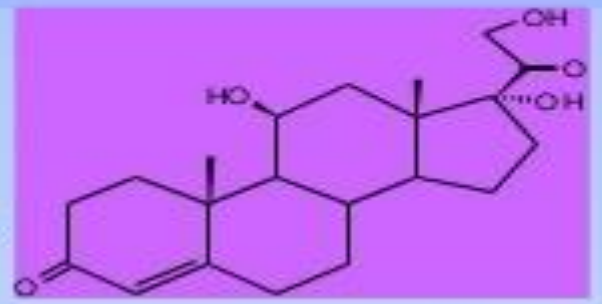
Steroid Hormones



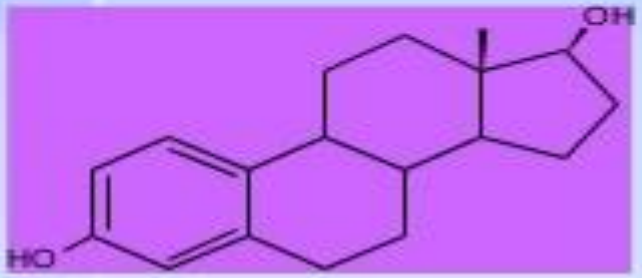
Progesterone



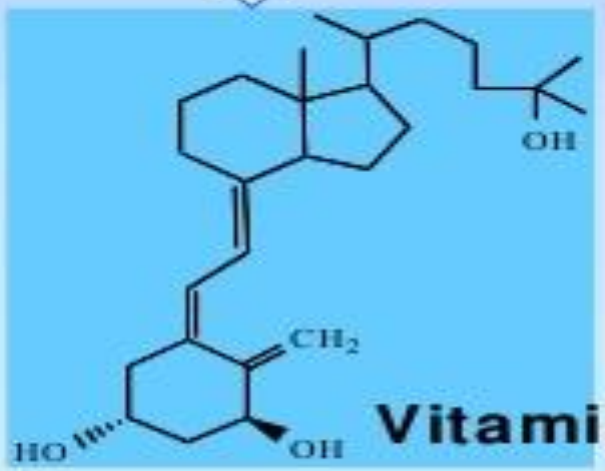
Cholesterol



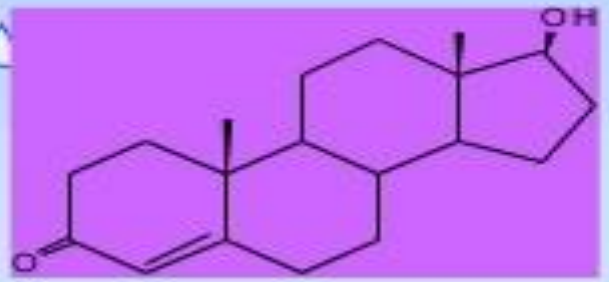
Cortisol



Estradiol



Vitamin D



Testosterone

HYPER CHOLESTEROLEMIA

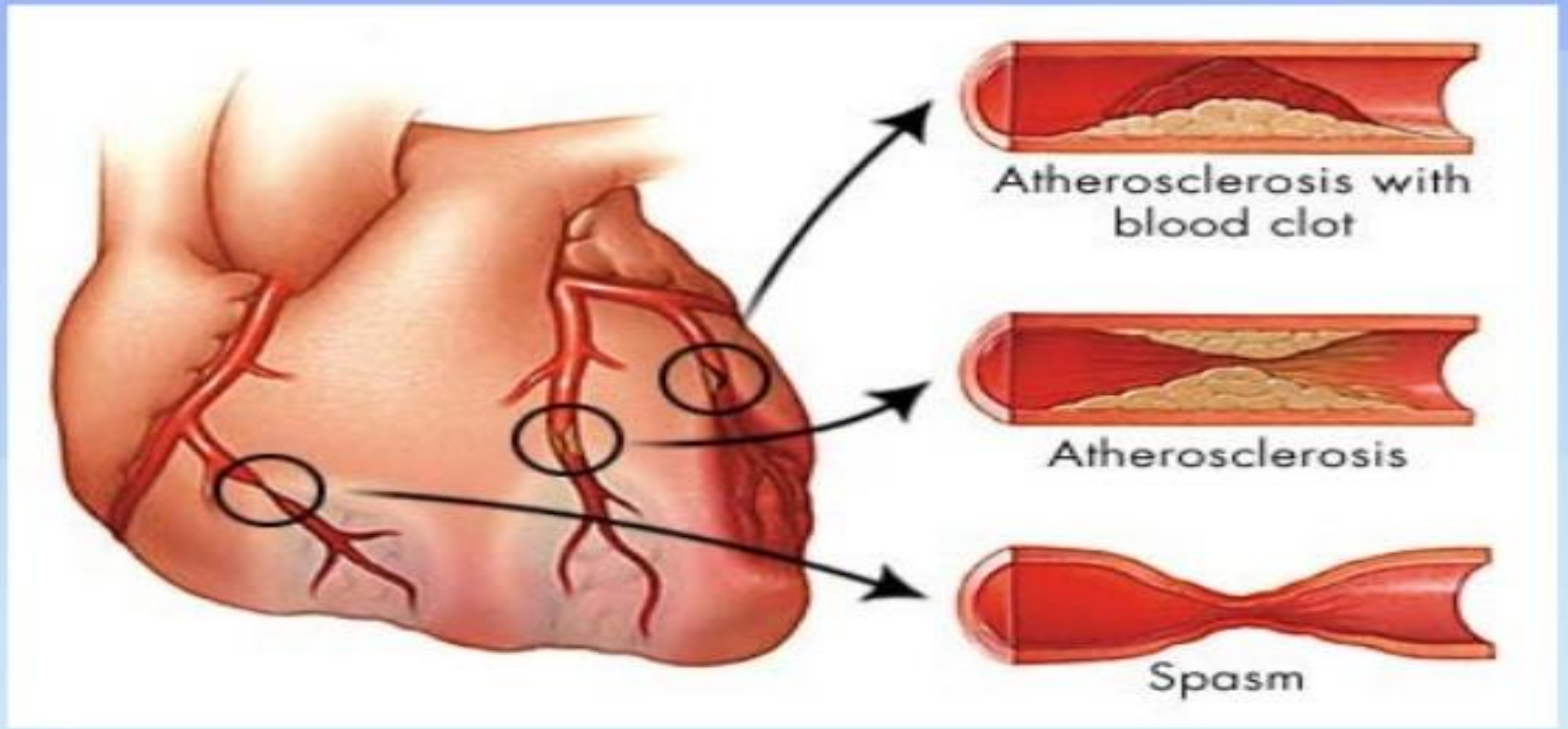
Serum cholesterol level is more than **200mg/dl** it is considered as Hypercholesterolemia

Causes-

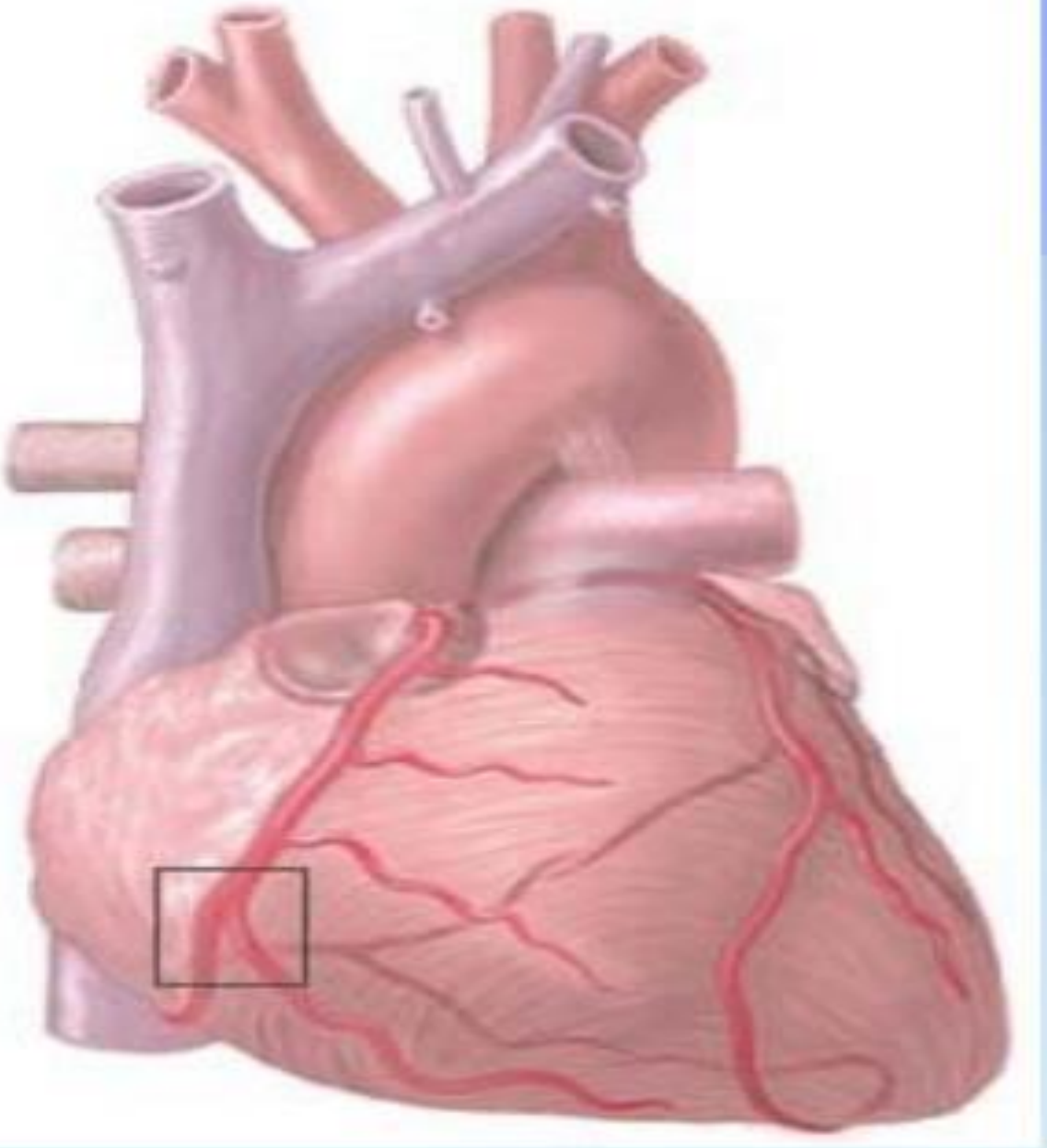
1) **Diabetes mellitus**
2) **Hypothyroidism**
3) **Obstructive jaundice**
4) **Nephrotic syndrome**

Atherosclerosis : Deposition of cholesterol esters and other lipids in the internal layers of arterial walls, leading to hardening and closure of coronary & cerebral arteries

ATHEROSCLEROSIS



Blockage in right coronary artery



Treatment for Hypercholesterolemia

1) Consumption of PUFA
2) Dietary fiber
3) Avoiding high carbohydrate diet
4) Drugs like Lovastatin
   Atorvastatin

} Inhibit HMG CoA reductase

Cholestyramine
Cholestipol

} bind with bile acid decreases Entero hepatic circulation

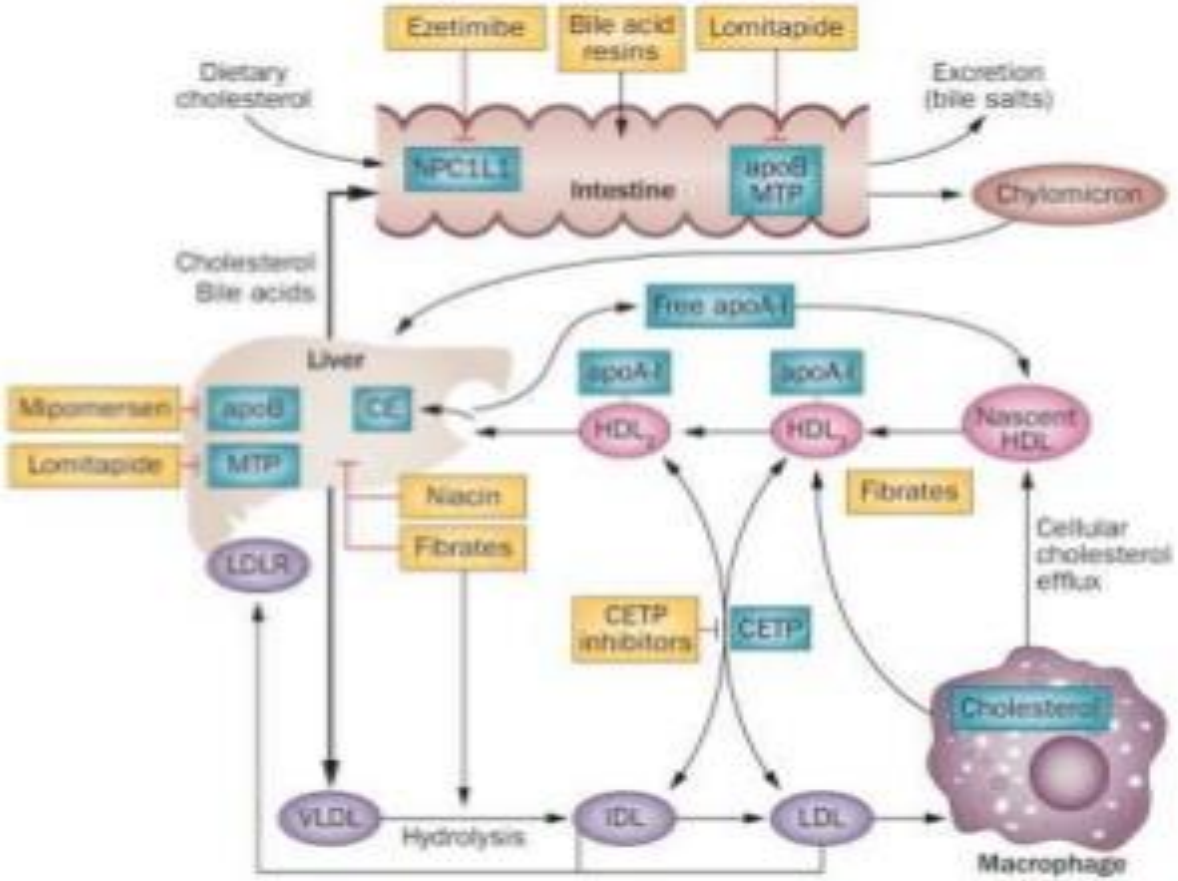
Metabolism of lipids

By

Dr.Muna M. Yaseen

LIPID METABOLISM

- Fats (or triglycerides) within the body are ingested as food or synthesized by adipocytes or hepatocytes from carbohydrate precursors.
- entails the oxidation of fatty acids to either generate energy or synthesize new lipids from smaller constituent molecules.
- associated with carbohydrate metabolism, as products of glucose (such as acetyl CoA) can be converted into lipids.



WHAT IS THE DEFINITION OF LIPID METABOLISM?

- Lipid metabolism is the synthesis and degradation of lipids in cells, involving the break down or storage of fats for energy. These fats are obtained from consuming food and absorbing them or they are synthesized by an animal's liver.

What is the end product of lipid metabolism?

- Just like glucose, the end-products of fatty acid metabolism are carbon dioxide, water and ATP. However, complete combustion of fatty acids to these products also requires glucose, otherwise ketones are produced.

WHAT IS ABNORMAL LIPID METABOLISM?

- Abnormal renal diseases including nephrotic syndrome and chronic renal failure are associated with hyperlipidemia, significance of abnormal lipid metabolism has been thought to be limited in some inherited renal diseases.

WHERE DOES LIPID METABOLISM OCCUR IN THE BODY?

- Triglycerides and lipids, high-energy molecules, are stored in adipose tissue until they are needed. Although lipogenesis occurs in the cytoplasm, the necessary acetyl CoA is created in the mitochondria and cannot be transported across the mitochondrial membrane.

How Lipids are transported in the body?

- Lipid transport function of lipoproteins in blood plasma. Fatty acid and cholesterol transport in plasma lipoproteins evolved in the context of an open circulatory system in which lipoprotein particles are secreted directly into the blood and have ready access to cells in various tissues.

What is a lipid metabolism disorder?

- Lipid metabolism disorders, such as Gaucher disease and Tay-Sachs disease, involve lipids.
- Lipids are fats or fat-like substances. They include oils, fatty acids, waxes, and cholesterol. ... Or the enzymes may not work properly and your body can't convert the fats into energy.

WHERE ARE LIPIDS STORED IN THE BODY?

- Lipids such as cholesterol, cholesteryl esters and triglycerides are stored in your body primarily in specialized fat cells called adipocytes, which comprise a specialized fatty tissue called adipose tissue.
- Stored lipids can be derived from the lipids in your diet or from lipids that your body synthesizes.

WHAT IS THE ROLE OF THE LIVER IN THE USE OF LIPIDS?

- With the help of vitamin K, the liver produces proteins that are important in blood clotting. It is also one of the organs that break down old or damaged blood cells. The liver plays a central role in all metabolic processes in the body. In fat metabolism the liver cells break down fats and produce energy.

How are lipids used in the body?

- Lipids, also known as fats, play many important roles in your body, from providing energy to producing hormones. You wouldn't be able to digest and absorb food properly without lipids. Of course, eating more fat than you need can lead to weight gain, but in proper amounts lipids are a healthy part of your diet.

How do we metabolize fat?

- Fat Metabolism. Almost all fat in your diet comes in the form of triglycerides. These compounds contain three fatty acids held together by a molecule called glycerol. In order to store or use fats for energy, this bond must be broken by pancreatic enzymes released into your stomach acid.

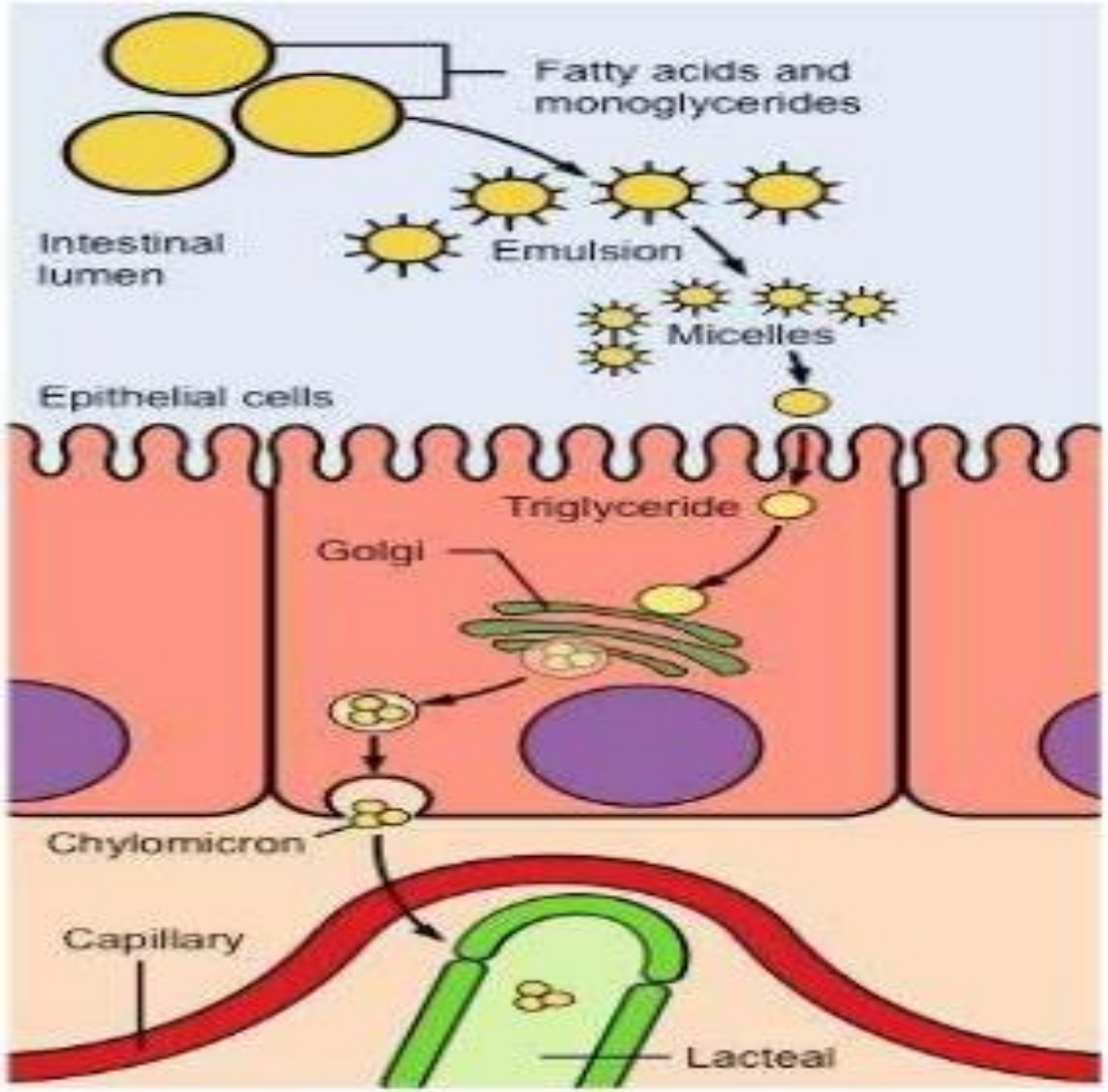
WHAT HAPPENS TO FATTY ACIDS IN THE LIVER?

- The liver is the major site for converting excess carbohydrates and proteins into fatty acids and triglyceride, which are then exported and stored in adipose tissue. The liver synthesizes large quantities of cholesterol and phospholipids.

WHERE ARE LIPIDS ABSORBED IN THE BODY?

- Most lipids that you consume in your diet are fats. Some digestion occurs in your mouth and the stomach, but most takes place in the small intestine. Bile is produced by your liver, stored and released in your gall bladder and emulsifies fat globules into smaller droplets.

Lipid Absorption and Transport



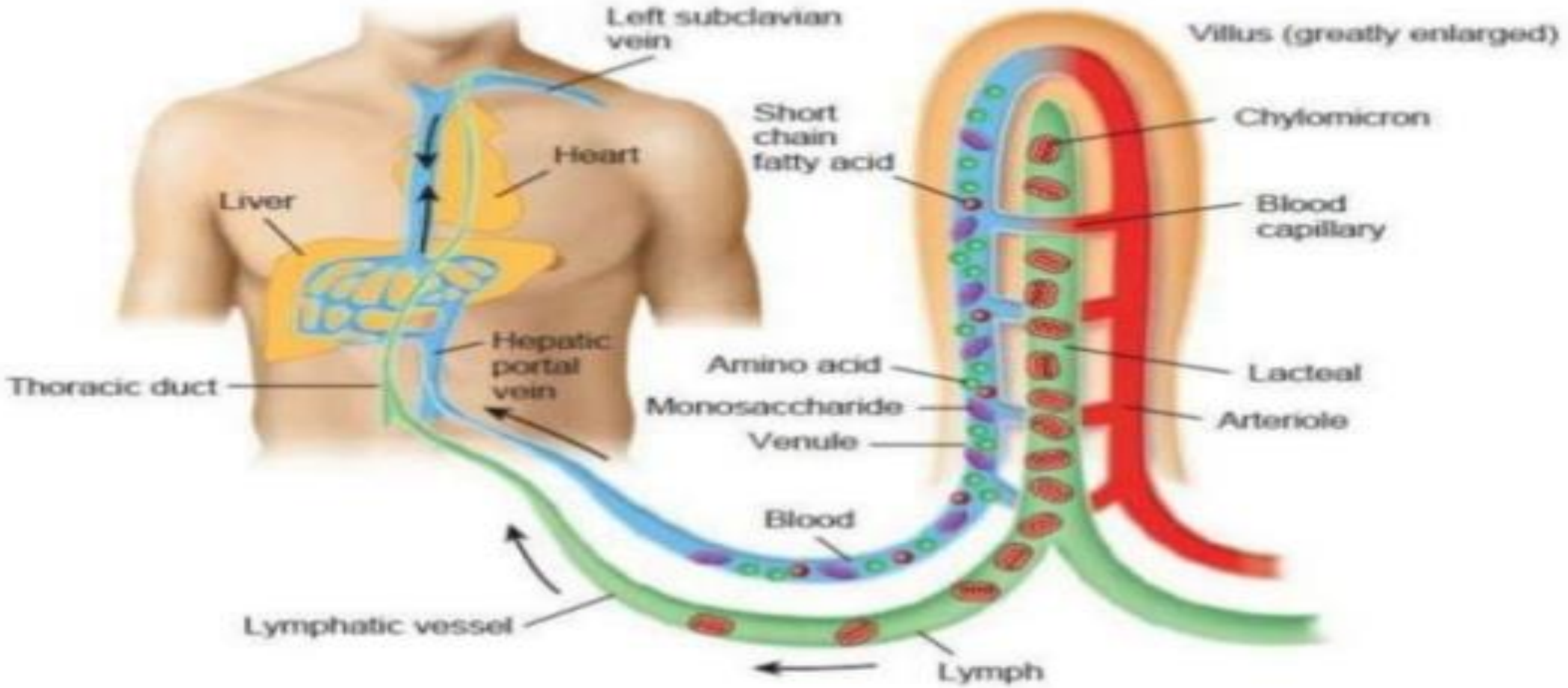
Fatty acids and monoglycerides are emulsified by bile salts to form micelles

Fatty acids enter the epithelial cells and link to form triglycerides

Triglycerides combine with proteins inside the Golgi body to form chylomicrons

Chylomicrons enter the lacteal and are transported away from the intestine

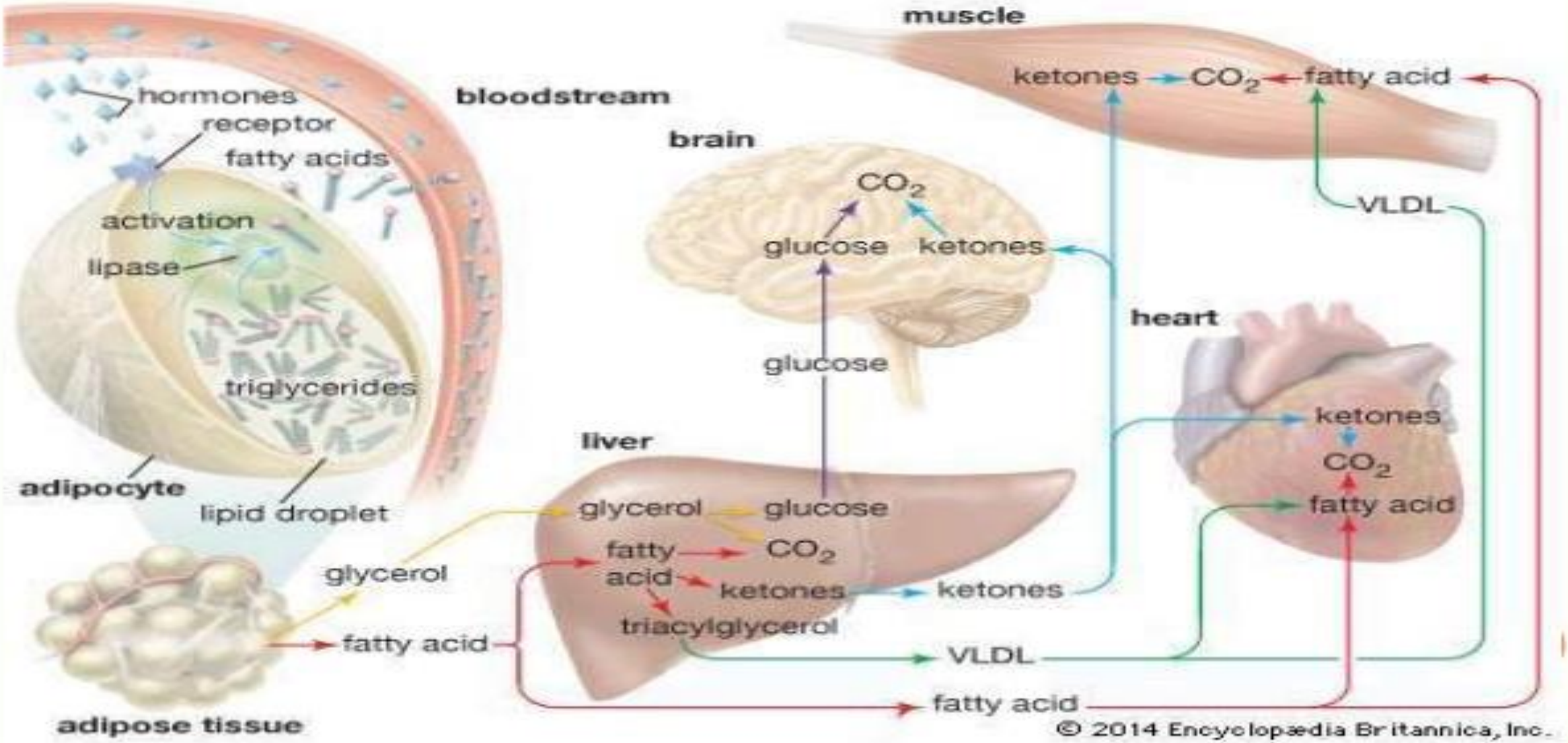
Transport of lipids



Mobilization of fatty acids

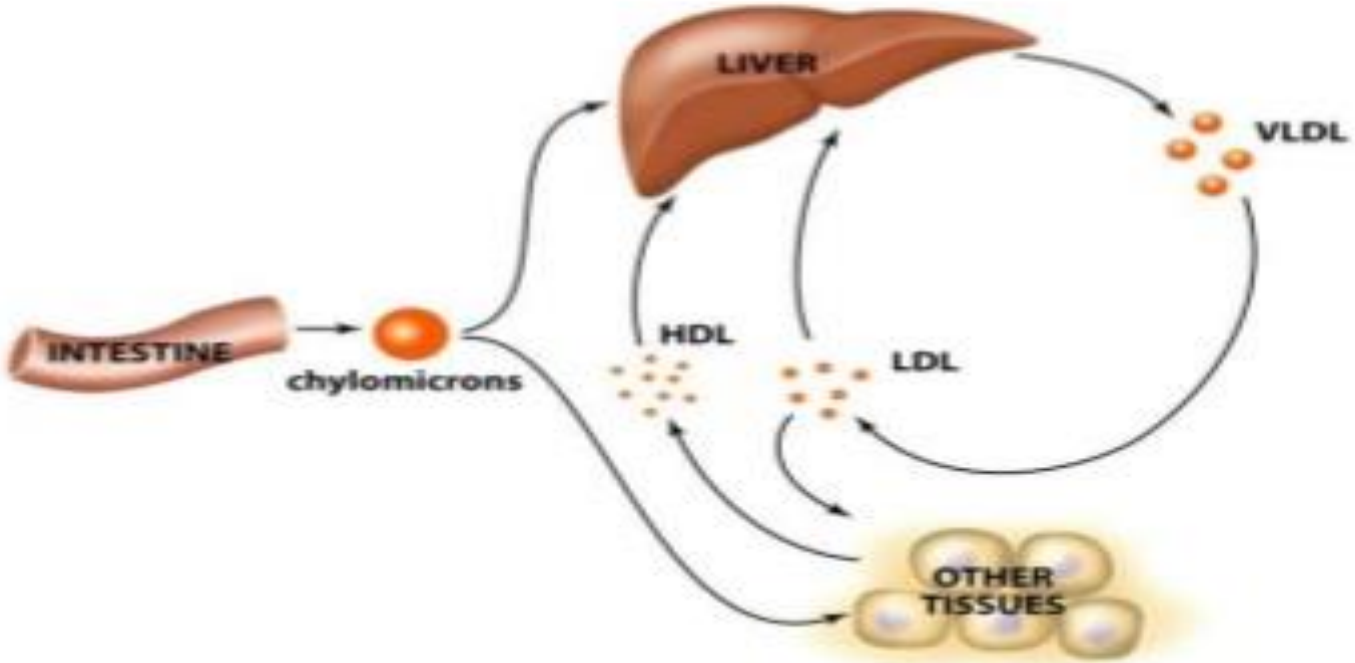
In times of stress when the body requires energy, fatty acids are released from adipose cells and mobilized for use. The process begins when levels of glucagon and adrenaline in the blood increase and these hormones bind to specific receptors on the surface of adipose cells. This binding action starts a cascade of reactions in the cell that results in the activation of yet another lipase that hydrolyzes triglyceride in the fat droplet to produce free fatty acids. These fatty acids are released into the circulatory system and delivered to skeletal and heart muscle as well as to the liver. In the blood the fatty acids are bound to a protein called serum albumin; in muscle tissue they are taken up by the cells and oxidized to carbon dioxide (CO_2) and water to produce energy, as described below. It is not clear whether a special transport mechanism is required for enabling free fatty acids to enter cells from the circulation.

WHEN HORMONES SIGNAL THE NEED FOR ENERGY, FATTY ACIDS AND GLYCEROL ARE RELEASED FROM TRIGLYCERIDES STORED IN FAT CELLS (ADIPOCYTES) AND ARE DELIVERED TO ORGANS AND TISSUES IN THE BODY.



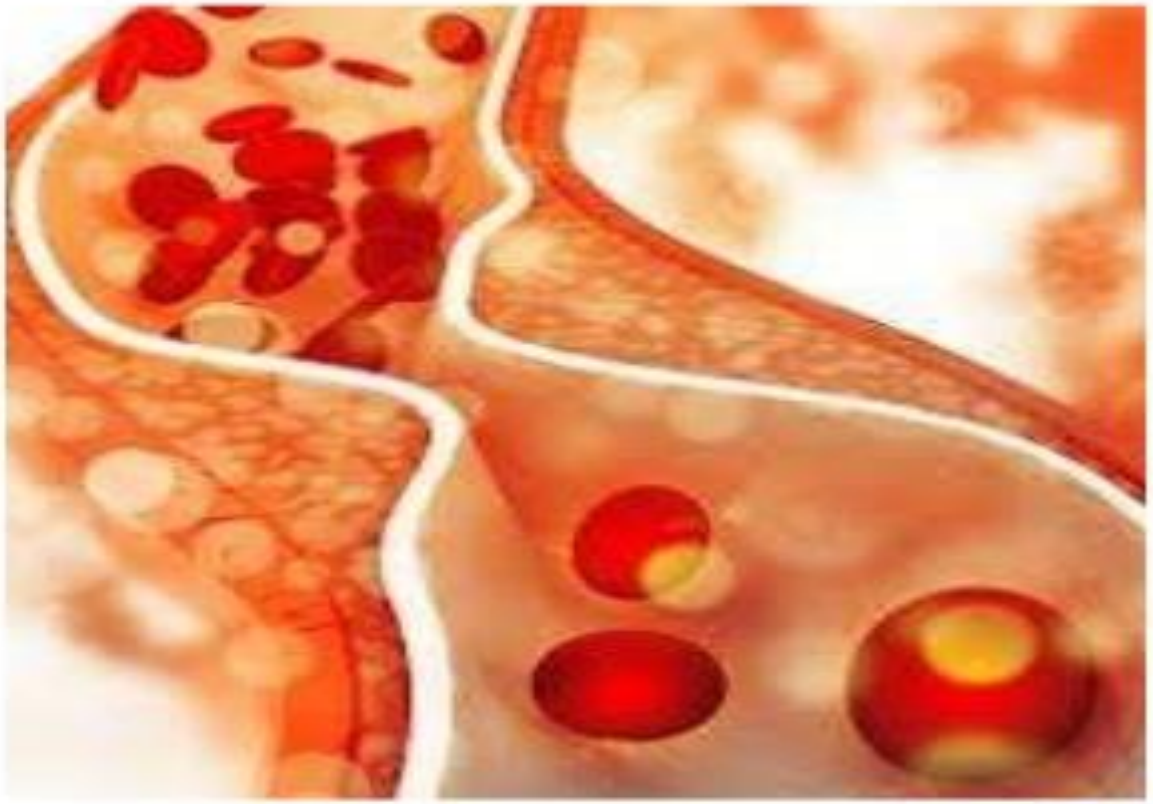
LIVER

- The liver takes up a large fraction of the fatty acids. There they are in part resynthesized into triglycerides and are transported in VLDL lipoproteins to muscle and other tissues. A fraction is also converted to small ketone molecules that are exported via the circulation to peripheral tissues, where they are metabolized to yield energy.



CHOLESTEROL

- Cholesterol is a waxy, fat-like substance that's found in all the cells in your body. Your body needs some cholesterol to make hormones, vitamin D, and substances that help you digest foods. Your body makes all the cholesterol it needs. Cholesterol is also found in foods from animal sources, such as egg yolks, meat, and cheese.



"Good" Cholesterol - HDL

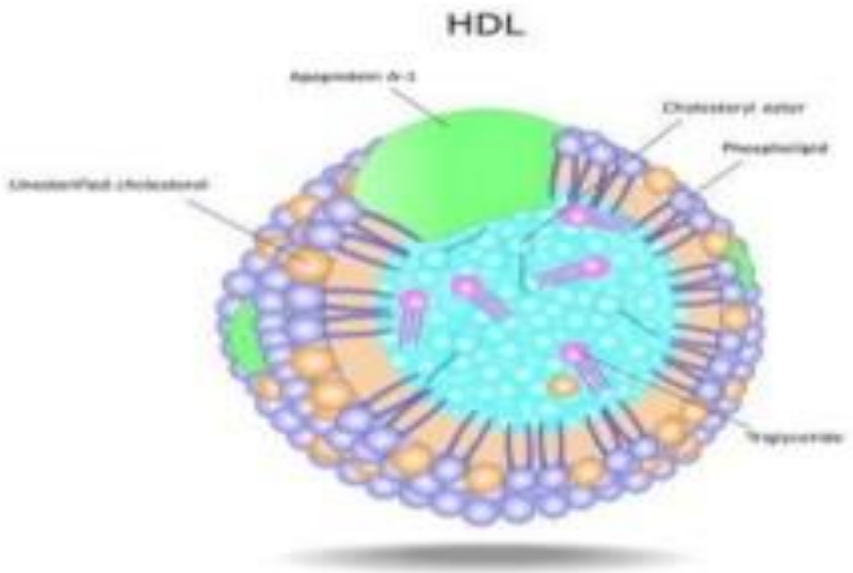
The HDL cholesterol scrapes away necessary LDL from artery walls, preventing the formation of plaques. That's why HDL cholesterol is commonly called "good".

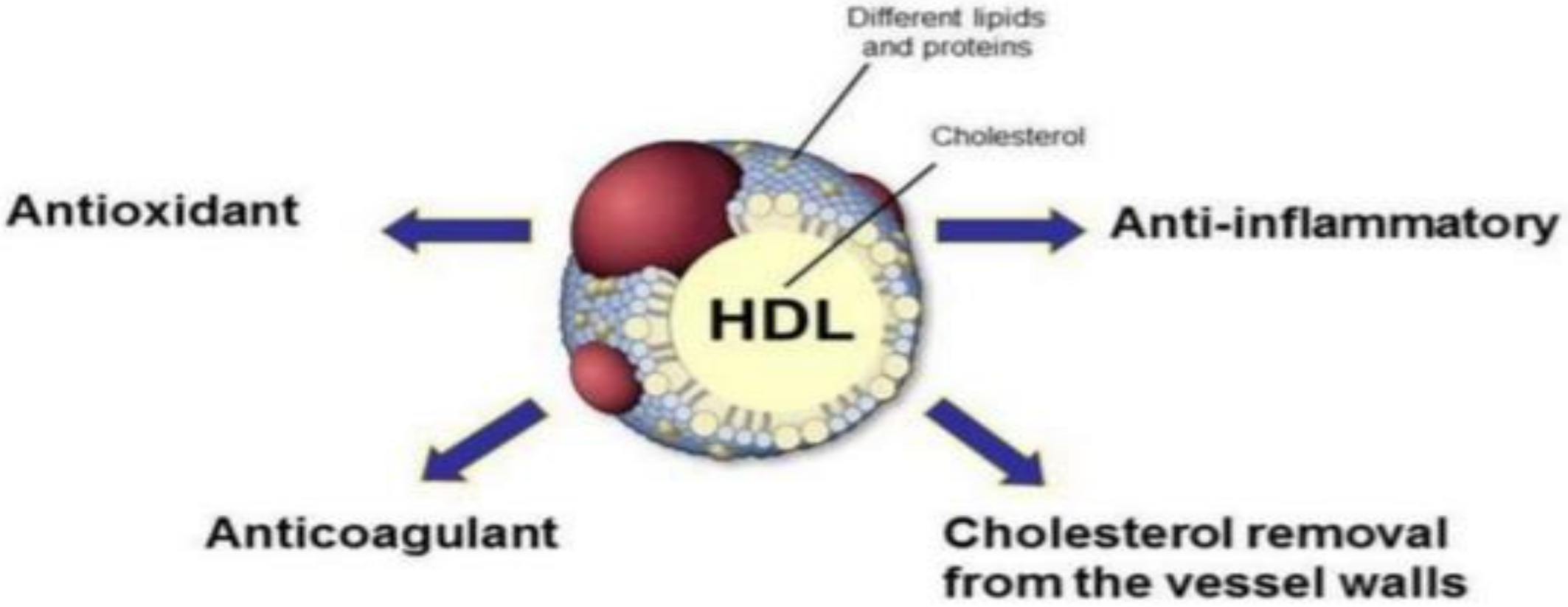
"Bad" Cholesterol - LDL

LDL, on the contrary, deposits excess cholesterol on the artery walls, thus promoting plaque formation. For this reason, the LDL cholestrol is defined as "bad".

HDL : Good cholesterol

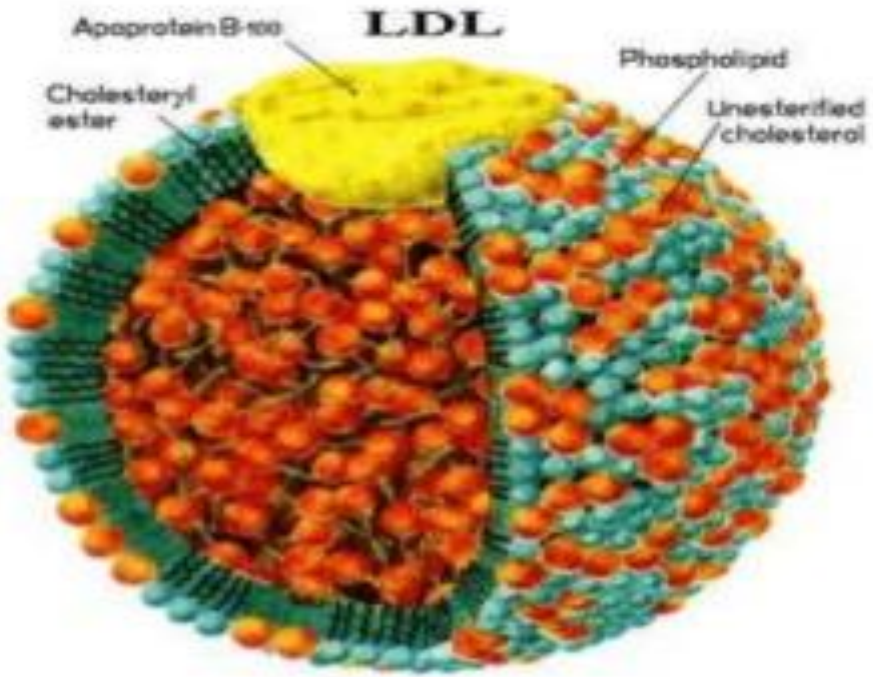
- High-density lipoprotein
- one of the five major groups of lipoproteins. Lipoproteins are complex particles composed of multiple proteins which transport all fat molecules around the body within the water outside cells.





Functions of the HDL particle which protect from coronary heart disease. The amount of antioxidative lipids is decreased so that the antioxidant function of the HDL particle is impaired in subjects with low HDL-cholesterol.

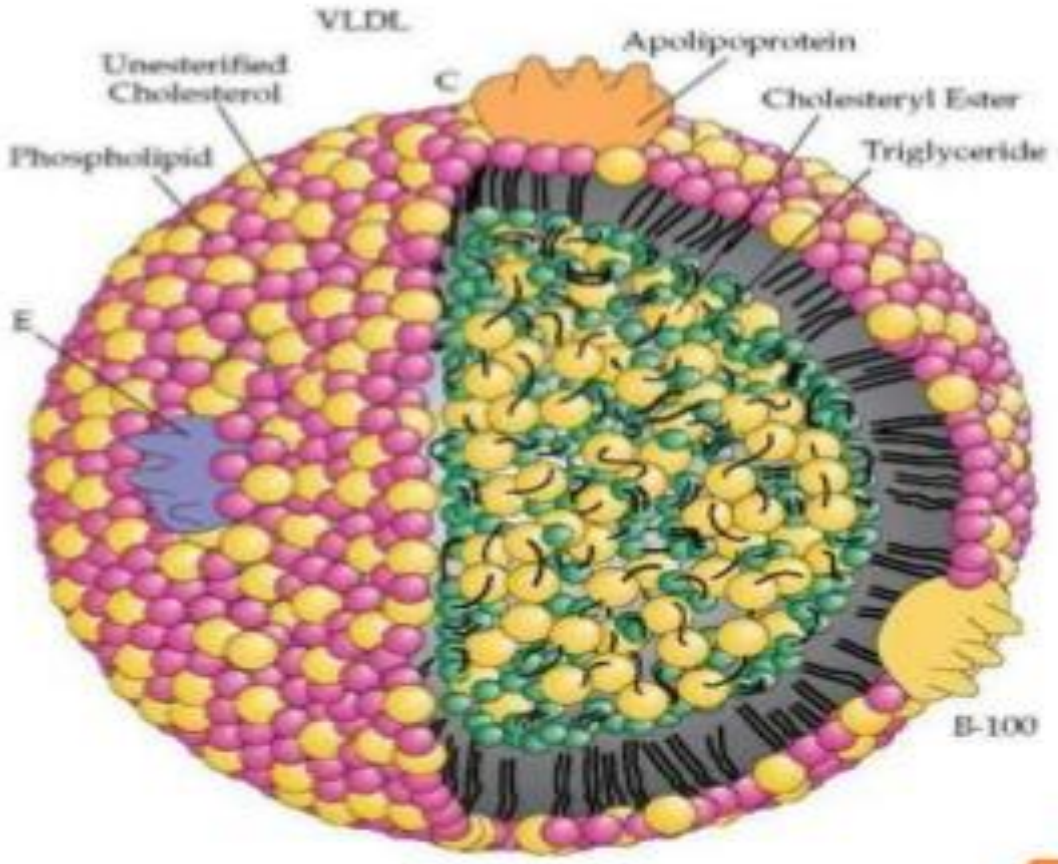
LDL: BAD CHOLESTEROL



- stands for low-density lipoproteins.
- is called the "bad" cholesterol because a high LDL level leads to a buildup of cholesterol in your arteries.

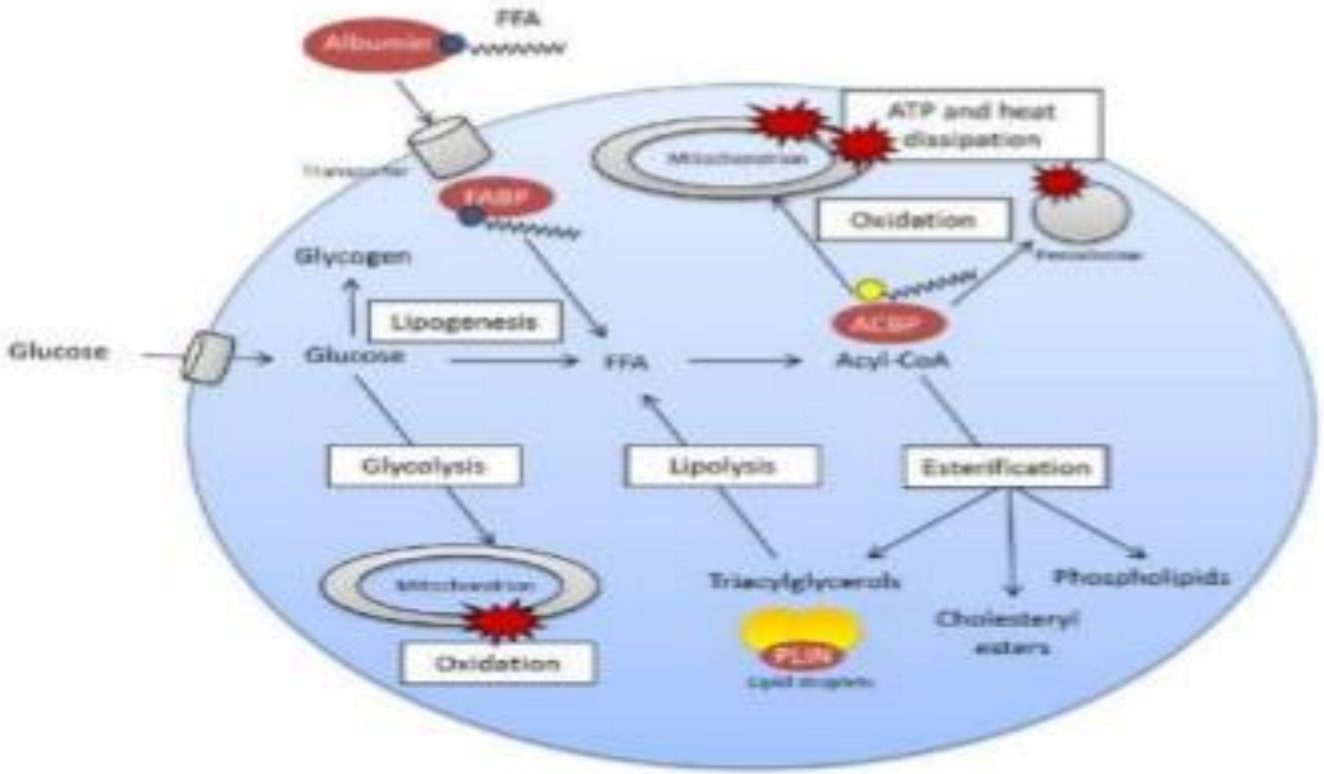
VLDL : VERY LOW-DENSITY LIPOPROTEIN.

- very low-density lipoprotein.
- also a "bad" cholesterol because it too contributes to the buildup of plaque in your arteries. But VLDL and LDL are different; VLDL carries triglycerides and LDL carries cholesterol.



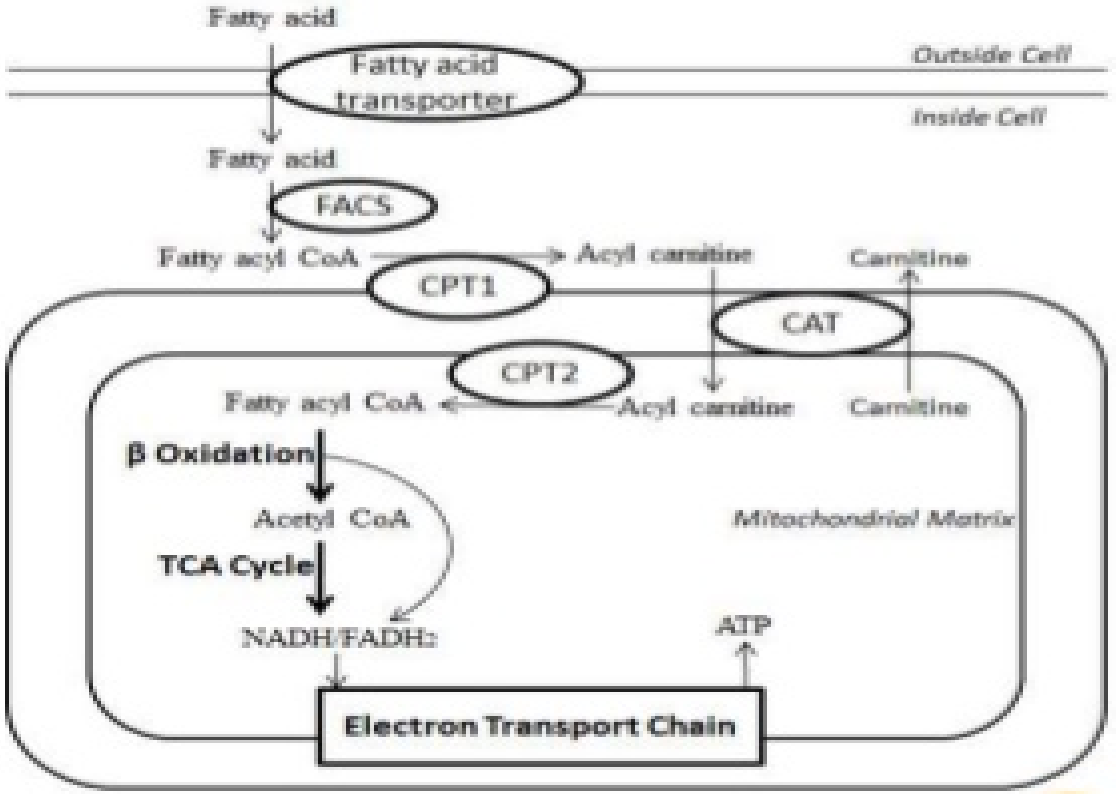
Fatty Acid Metabolism

- Fatty acid metabolism consists of catabolic processes that generate energy, and anabolic processes that create biologically important molecules. Fatty acids are a family of molecules classified within the lipid macronutrient class.



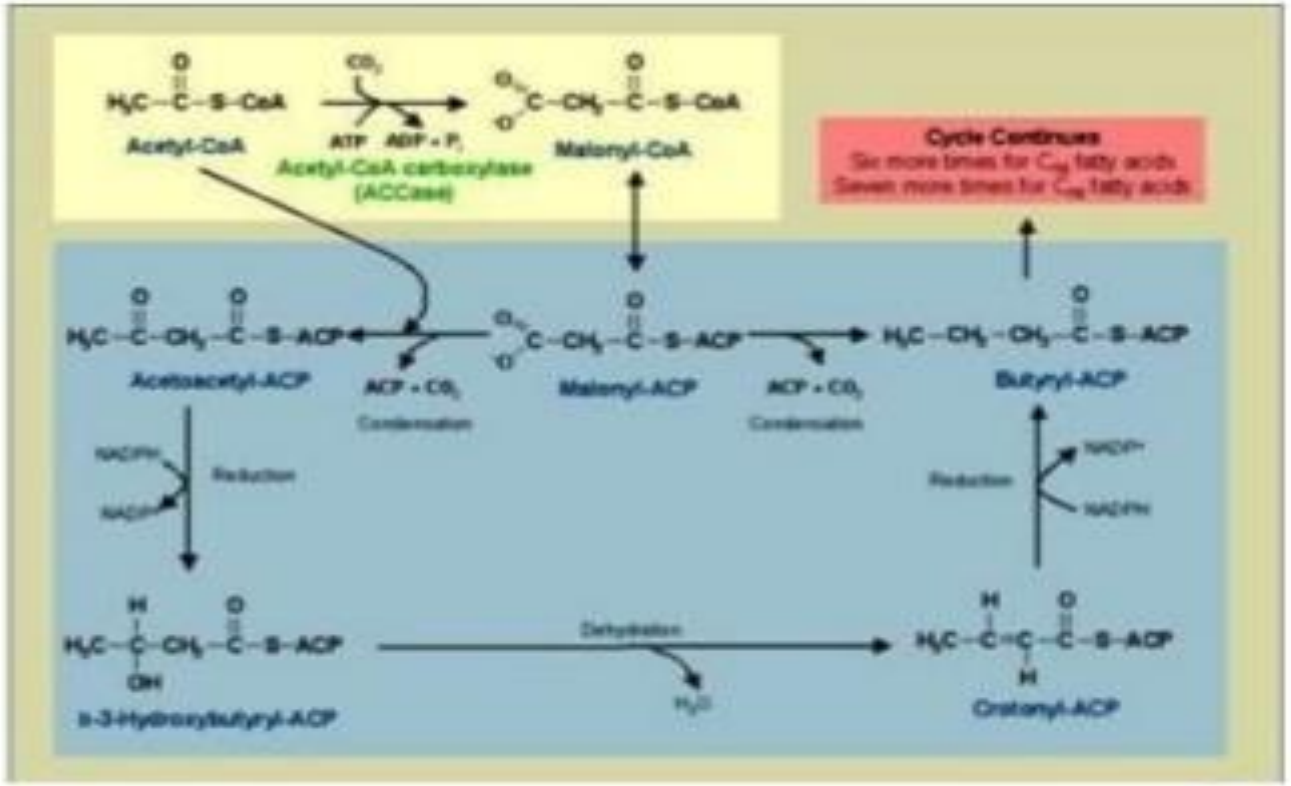
- a multistep process by which fatty acids are broken down by various tissues to produce energy. Fatty acids primarily enter a cell via fatty acid protein transporters on the cell surface [1]. Fatty acid transporters include fatty acid translocase (tissue specific fatty acid transport proteins and plasma membrane bound fatty acid binding protein Once inside the cell, a CoA group is added to the fatty acid by fatty acyl-CoA synthase (FACS), forming long-chain acyl-CoA. Carnitine palmitoyltransferase 1 (CPT1) conversion of the long-chain acyl-CoA to long-chain acylcarnitine allows the fatty acid moiety to be transported across the inner mitochondrial membrane via carnitine translocase (CAT), which exchanges long-chain acylcarnitines for carnitine. An inner mitochondrial membrane CPT2 then converts the long-chain acylcarnitine back to long-chain acyl-CoA. The long-chain acyl-CoA enters the fatty acid β-oxidation pathway, which results in the production of one acetyl-CoA from each cycle of fatty acid β-oxidation. This acetyl-CoA then enters the mitochondrial tricarboxylic acid cycle. The NADH and FADH2 produced by both fatty acid β-oxidation and the TCA cycle are used by the electron transport chain to produce ATP.

FATTY ACID BETA - OXIDATION

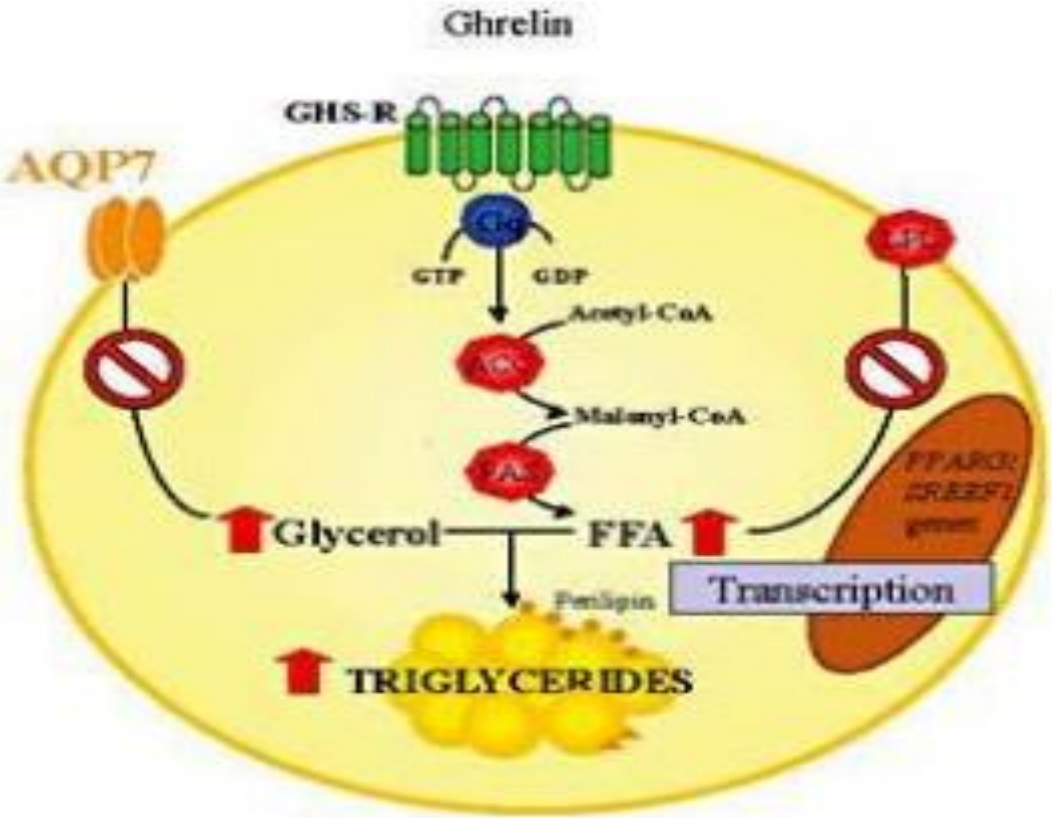


Fatty Acid Synthesis

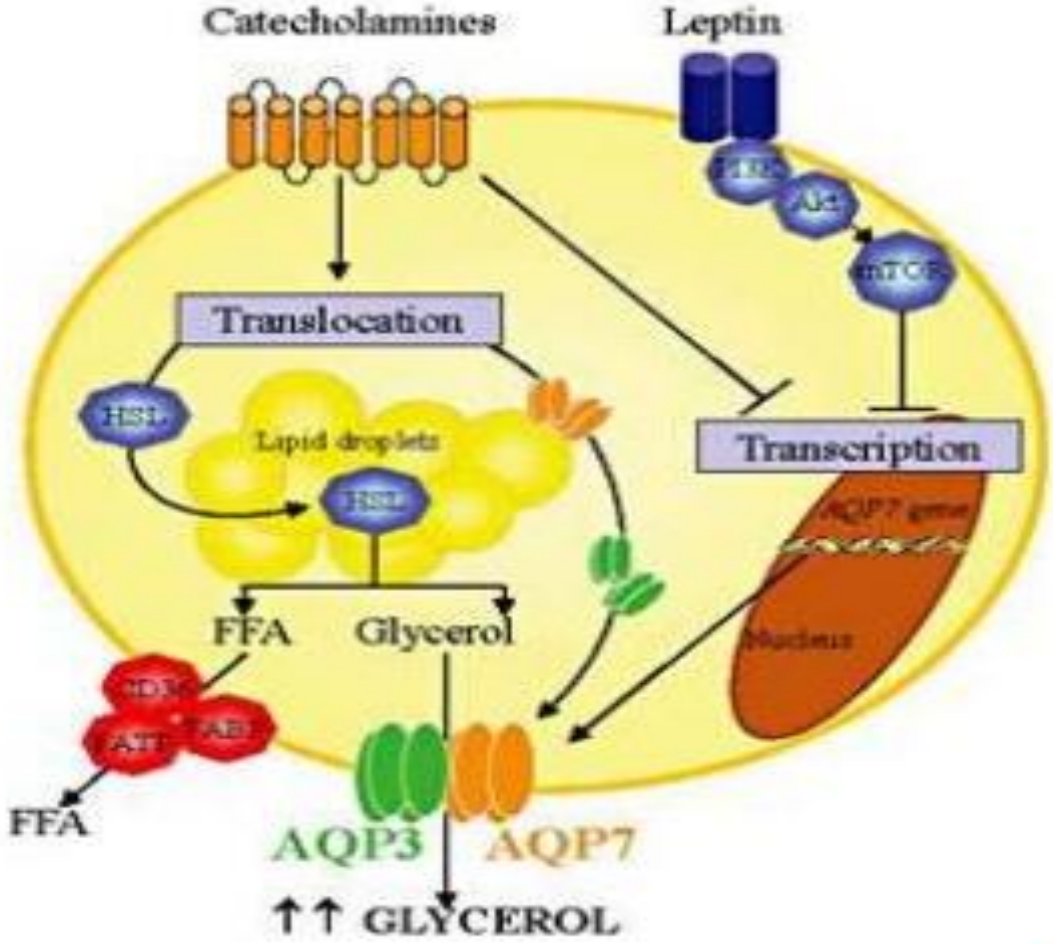
- Fatty acid synthesis is the creation of fatty acids from acetyl-CoA and NADPH through the action of enzymes called fatty acid synthases.
- This process takes place in the cytoplasm of the cell. Most of the acetyl-CoA which is converted into fatty acids is derived from carbohydrates via the glycolytic pathway.



Lipogenesis

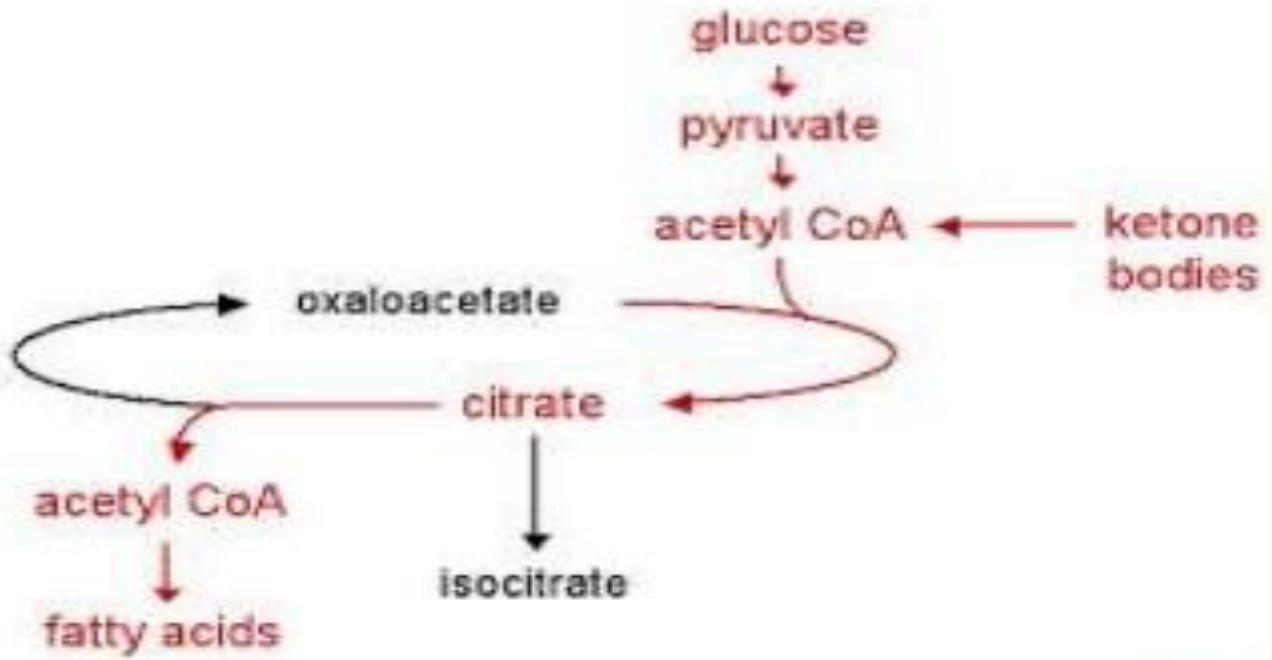


Lipolysis



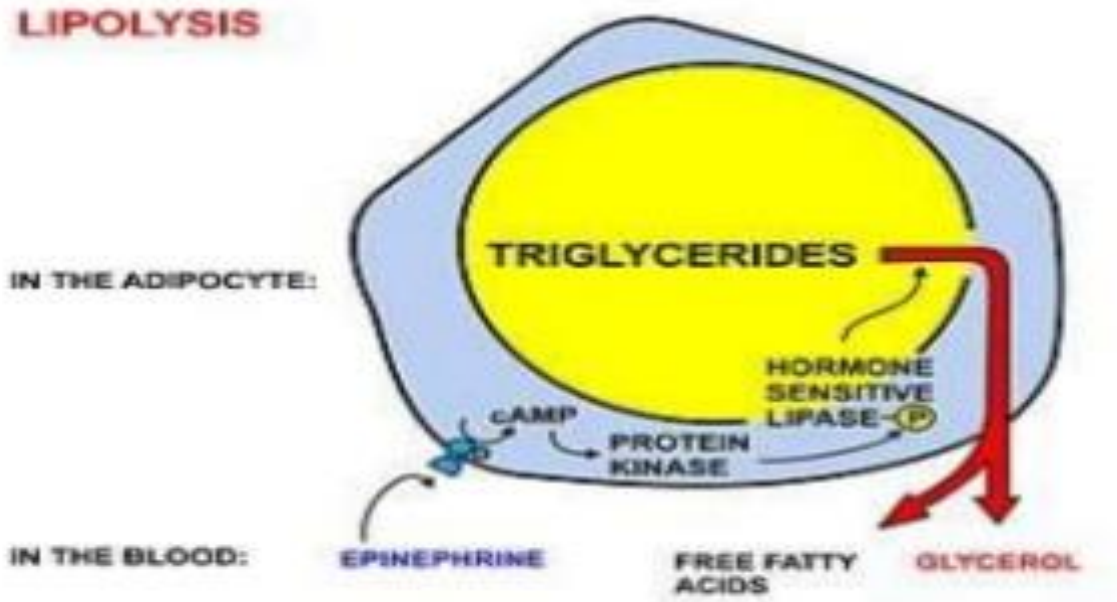
LIPOGENESIS

- Lipogenesis is the process your body uses to convert carbohydrates into fatty acids, which are the building blocks of fats.
- Fat is an efficient way for your body to store energy.



LIPOLYSIS

- the breakdown of lipids and involves hydrolysis of triglycerides into glycerol and free fatty acids.
- Predominantly occurring in adipose tissue, lipolysis is used to mobilize stored energy during fasting or exercise.



Putting Lipids to Use

- essential to good health, not only for humans but also for other animals and even plants.
- a poor conductor of heat, lipids also can function as effective insulators
- Act as chemical messengers in the body, while others serve as storage areas for chemical energy. There is a good reason why babies are born with "baby fat" and why children entering puberty often tend to become chubby: in both cases, they are building up energy reserves for the great metabolic hurdles that lie ahead, and within a few years, they will have used up those excessive fat stores

Thank you

Enzymes

Luc. 1

By

Dr. Muna M. Yaseen

Objective

- Definition
- Nomenclature
- Classification of enzymes
- Factors affecting enzyme activity.
- Application of enzyme inhibition.
- Isoenzymes.
- Enzyme in the Diagnosis of Pathology

- ***Definition***

Enzyme : It is a protein, catalyst, synthesized in all living cells that regulate a biochemical reaction without being changed.

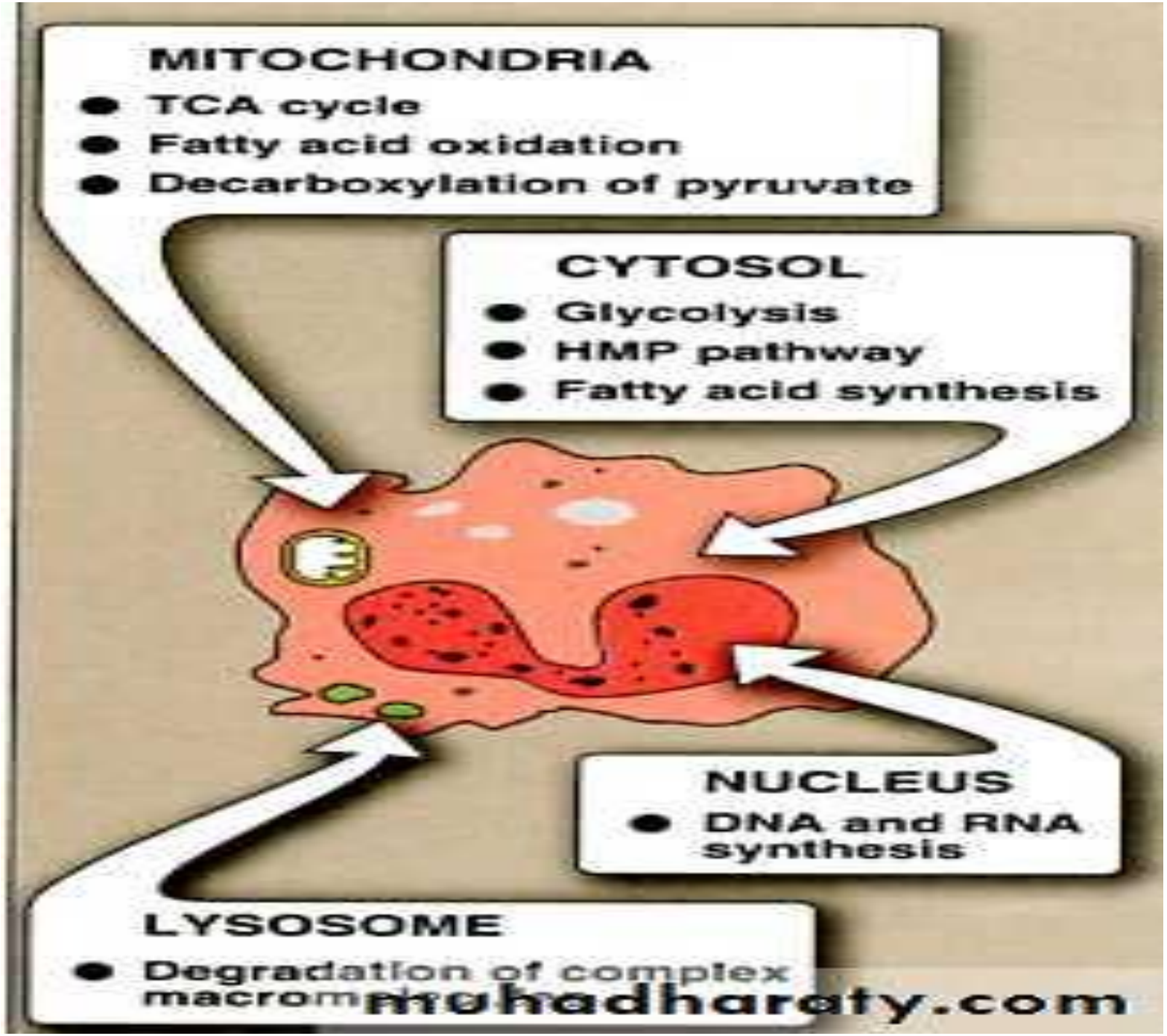
- ***Characteristics***

They are high catalytic rate.

They catalyze reaction without being changed.

They are very specific .

Enzyme distribution


MITOCHONDRIA
TCA cycle
Fatty acid oxidation
Decarboxylation of pyruvate
CYTOSOL
Glycolysis
HMP pathway
Fatty acid synthesis
NUCLEUS
DNA and RNA synthesis
LYSOSOME
Degradation of complex
macrom
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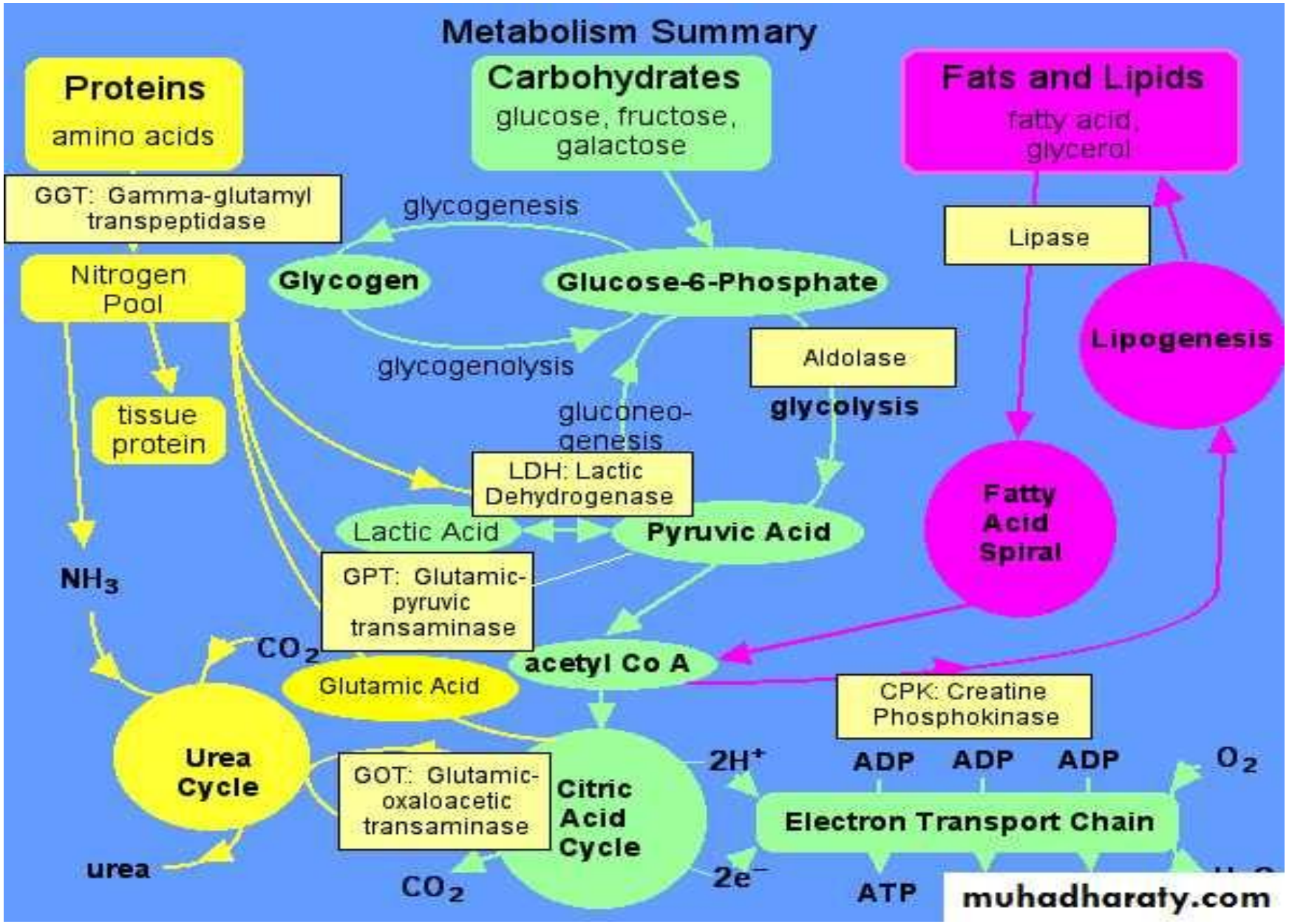
Metabolism Summary
Proteins
amino acids
Carbohydrates
glucose, fructose, galactose
Fats and Lipids
fatty acid, glycerol
GGT: Gamma-glutamyl transpeptidase
glycogenesis
Lipase
Nitrogen Pool
Glycogen
Glucose-6-Phosphate
Lipogenesis
glycogenolysis
Aldolase
tissue protein
gluconeo-genesis
glycolysis
LDH: Lactic Dehydrogenase
Fatty Acid Spiral
Lactic Acid
Pyruvic Acid
NH3
GPT: Glutamic-pyruvic transaminase
CO2
acetyl Co A
Glutamic Acid
CPK: Creatine Phosphokinase
Urea Cycle
2H+
ADP ADP ADP
O2
GOT: Glutamic-oxaloacetic transaminase
Citric Acid Cycle
Electron Transport Chain
urea
CO2
2e−
ATP
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Cofactor

Definition: A non-protein unit ,its presence is important in many enzymes.

Types:

1-Inorganic metals: Mn ,Zn ,Fe ,Cu.

2-Organic Complex (Coenzyme) .

Cofactors

Metal-activated enzymes:

- active in the presence of metal ions as K+, Mg+ or Ca++.

- Example: Kinase uses Mg++ , ATP.

Metalloenzyme:

- Firmly bound metal ion in the active site as Iron , copper , Zn & Co.

Examples:

1-Carbonic Anhydrase Zn.

2- Cytochrome oxidaseFe2+.

COENZYMES

Many enzymes require for their action on substrate, specific ,heat stable ,low M. wt.

and organic substance called ***coenzymes***

Enzyme which requires a coenzyme for its catalytic action is called ***apoenzyme*** and complete catalytic unit which

contain enzyme and its coenzyme is called ***holoenzyme.***

Catalytic unit (Apoenzyme + Coenzyme ==== Holoenzyme)

Apoenzyme: *inactive protein part.*

Cofactor: *Non protein part.*

Holoenzyme: *Active enzyme .*

Coenzyme itself may covalently or non covalently bound to enzyme and when coenzyme is covalent linked to its enzyme it will be then called ***PROSTHETIC GROUP.***

Majority of enzyme in the body required coenzyme in their action

(Nomenclature)

Unsystematic nomenclature:

1- Enzyme is named by adding (ase) to the name of the substrate e.g. (Urease).

2-Some other enzymes as (Trypsin ,pepsin) are known by their historic names.

one enzyme has one name or many enzymes have the same name.

Systematic Nomenclature

Adopted by **(IUB)** ; According to the type of reaction which is catalyzed.

It divided the enzymes into **6 classes.**

Classification of enzymes

Class no I Oxidoredoctase

Class no II Transferase

Class no III Hydrolases

Class no IV Lyases

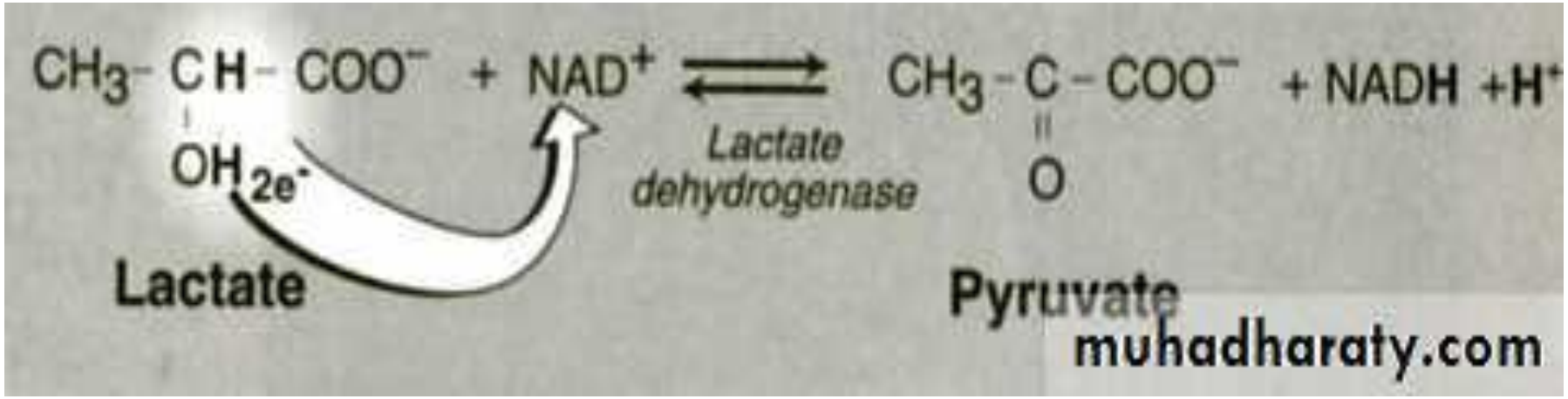
Class no V Isomerases cis and Trans

Class no VI Ligases

Class 1: Oxido-Reductase:

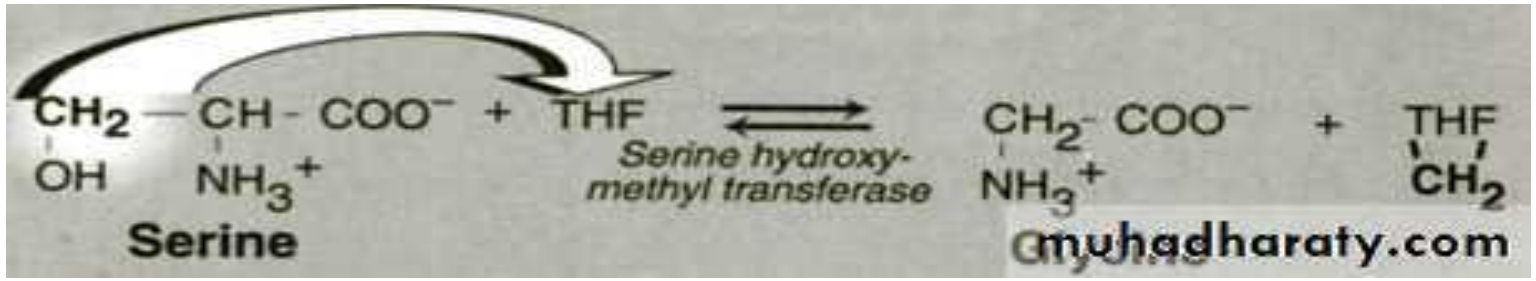
Catalyses Oxidation ,reduction reactions as : Dehydrogenase ,Oxidase ,Hydroxylase ,Peroxidase.

Usually they require coenzymes as : (NAD+,NADP+,FAD,FMN).



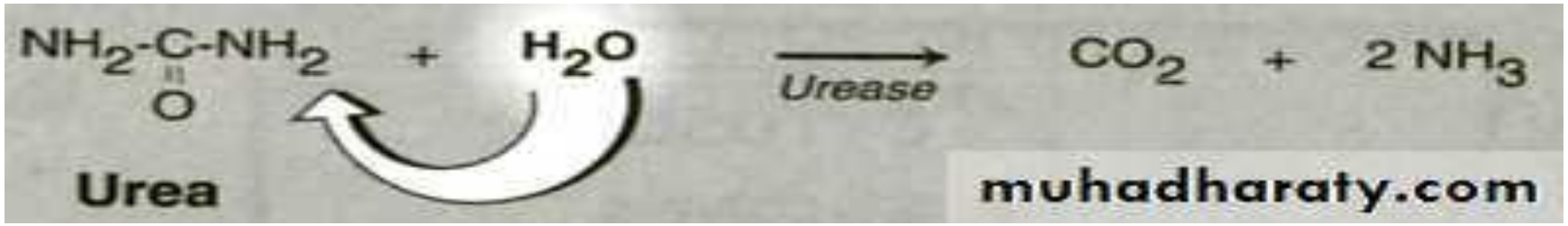
Class 2: Transferase

Catalyze transfer of functional group between donor & acceptor molecule as methyl , formyl ,carboxyl ,nitrogenous, phosphorus & sulfur containing groups



Class 3: Hydrolases

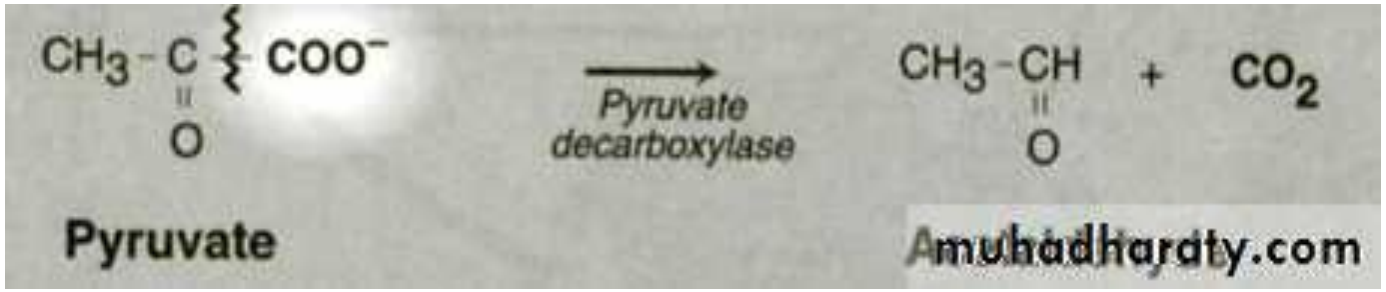
Catalyze hydrolytic reaction by adding H2Ocleavage of bond between C & others as : C-O , C-N & C-S.



Class 4 : Lyases

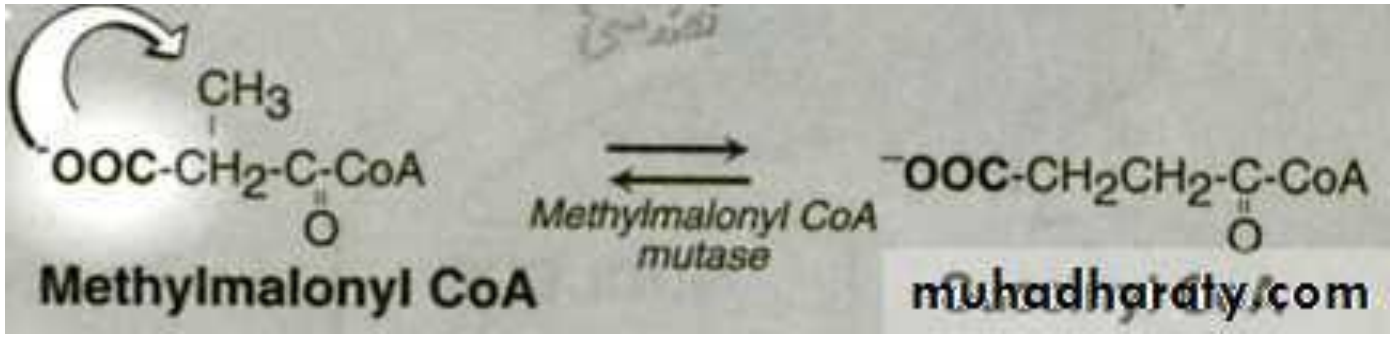
Catalyze non-hydrolytic reaction

Examples: Decarboxylase .



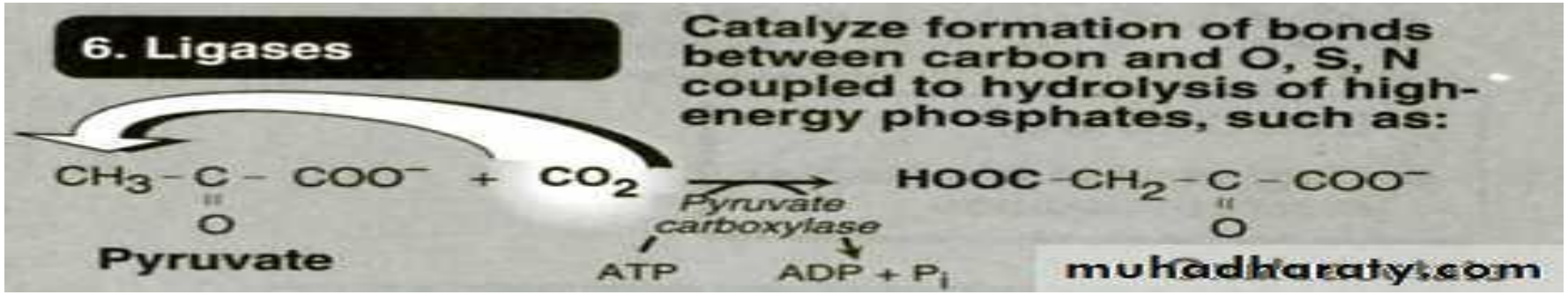
Class 5 : Isomerase

Catalyze transfer of groups within a molecule (rearrange).



Class 6:Ligase

Catalyze bond formation coupled to ATP-hydrolysis joining 2 molecules.



Substrate

The molecule being utilized and/or modified by a particular enzyme at its active site

Enzyme Specificity

The most significant properties in the enzyme catalytic reaction is the ability of the enzyme in catalyze one specific reaction and no other that is a characteristic of enzyme and when these enzyme is absent the respective reaction will not occur and this behavior is called ***specificity*** of enzyme and this behavior is usually appear in the following **TWO** properties:

I-optical specificity

II- Selective group

I-optical specificity

The enzyme has an absolute specificity in particular optical region of the substrate. Almost all human enzyme are being specific for an optical part of substrate . ex: enzyme acting on CHO. Metabolism (sugar breakdown)are usually specific for D-sugar not act on L-sugar or other enzyme acting on amino acid metabolism are usually acting on L- amino acid (not D-amino acid) with exception of D- amino acid oxidase in the kidney .

II- Selective group:

In this properties enzyme is usually affective on specific chemical group that is present in the structure of substrate. ex: glycosidase, glycosidase catalyze hydrolysis of Glycosidic bond between sugar and alcohol are highly specific for sugar portion not specific for alcohol.

Trypsin and pepsin act on peptide bond.

Some enzymes have a higher degree of specificity ex: amino peptidase act on amino group , carboxypeptidase act on carboxy end of peptide bond .

Chymotrypsin will act on peptide bond on which carboxy terminal end of peptide bond is being contributed to an aromatic a.a. Which may be phenyl alanine , tyrosine and tryptophan split of a.a one at a time from the carboxy or amino terminal end of polypeptide chain respectively.

Tyrosine

Tyrosine

CH NH2COOH

CH NH2COOH

CH2

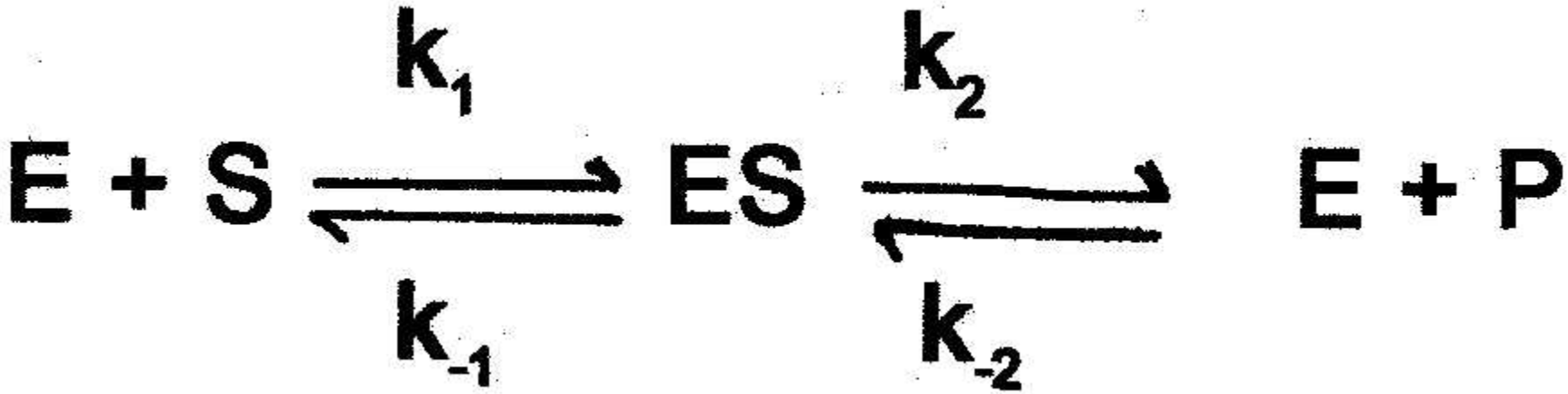
CH2

-HO

-HO

Enzyme velocity (V)

It is moles of product (P) appearing or substrate (S) disappearing per unit of time. (Mole / liter /sec.)



S = substrate P = product

E = enzyme

ES = enzyme-substrate complex

k_1, k_{-1}, k_2, k_{-2} are rate constants

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Enzyme units

International unit (IU): a mount of enzyme that converts one micromole (µmol) of substrate per minute at 25°C under the optimal conditions of the measurement.

Katal: amount of enzyme that converts one mole of substrate to product/sec

(Active site)

Active site: is an important structural feature to recognize and to bind substrates.

It is very specific.

Catalytic Site:

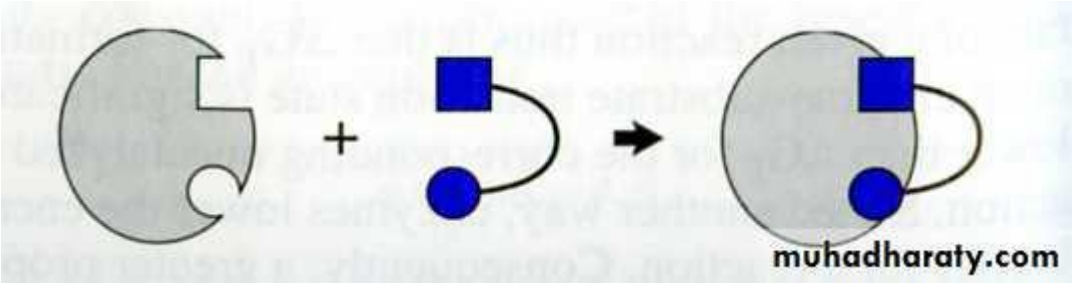
The large size of the enzyme molecule in comparison with substrate size that a small part or limited number of amino acids in the enzyme molecule is being responsible for the catalytic reaction these size is called ***CATALYTIC SITE*** or ***ACTIVE SITE*** or ***ACTIVE CENTER*** of the enzyme.

There are two theory or mode or type to explain the interaction between the substrate and enzyme.

Type I

The lock & key model:

- Enzyme fits substrate as a lock & key .
- Its rigid type.

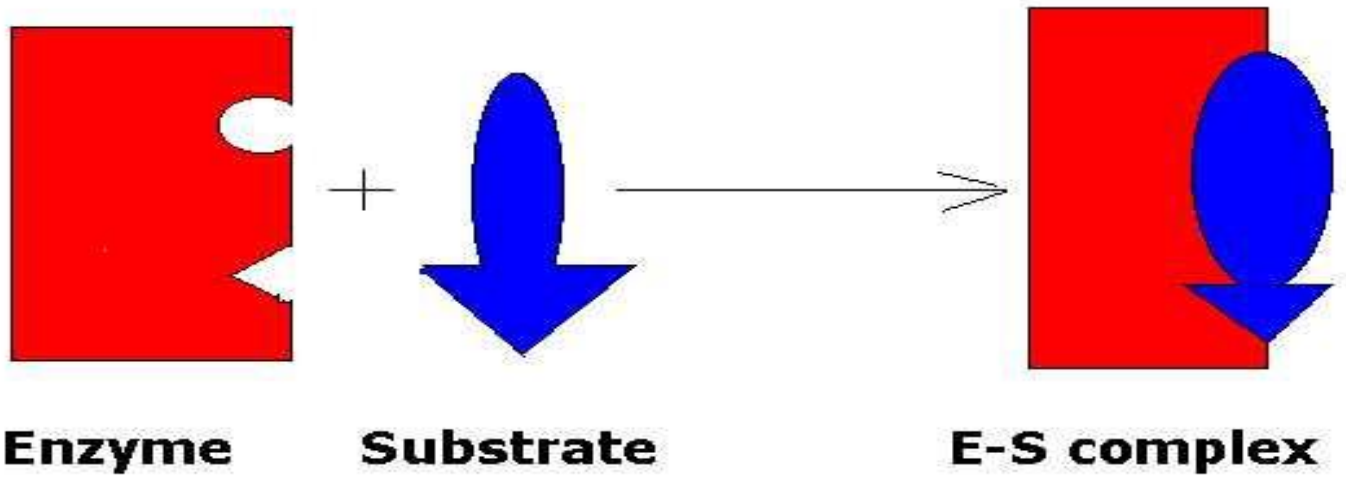


Type II Induced fit (Koshland model):

the substrate induces conformational changes in the active site rearrangement of the A.A Enzyme fits substrate exactly.

This type discovered by Koshland in which there is a source of flexibility in substrate – enzyme binding in which certain physical changes take place in the enzyme that include arrangement of certain (a.a)s both to the substrate binding site and at catalytic site.

These changes are called ***(conformational changes)*** and the site in which these changes take place are called ***Allosteric site*** being important for the enzyme catalytic reaction. This type is more flexible than the lock and key type and it has wide application in explainin



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Catalytic efficiency

Most enzyme-catalyzed reactions are highly efficient, proceeding from 103 to 108 times faster than uncatalyzed reactions.

Factors affecting Enz. Activity

1.Enzyme concentration.

2.Temperature.

3.PH

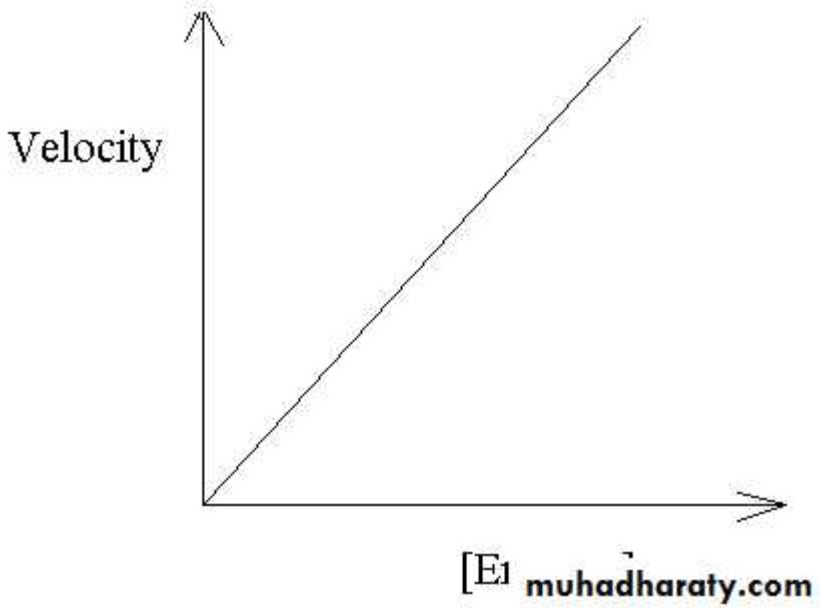
4.Substrate concentration.

5. Inhibiters

6. Activators

Enzyme concentration:

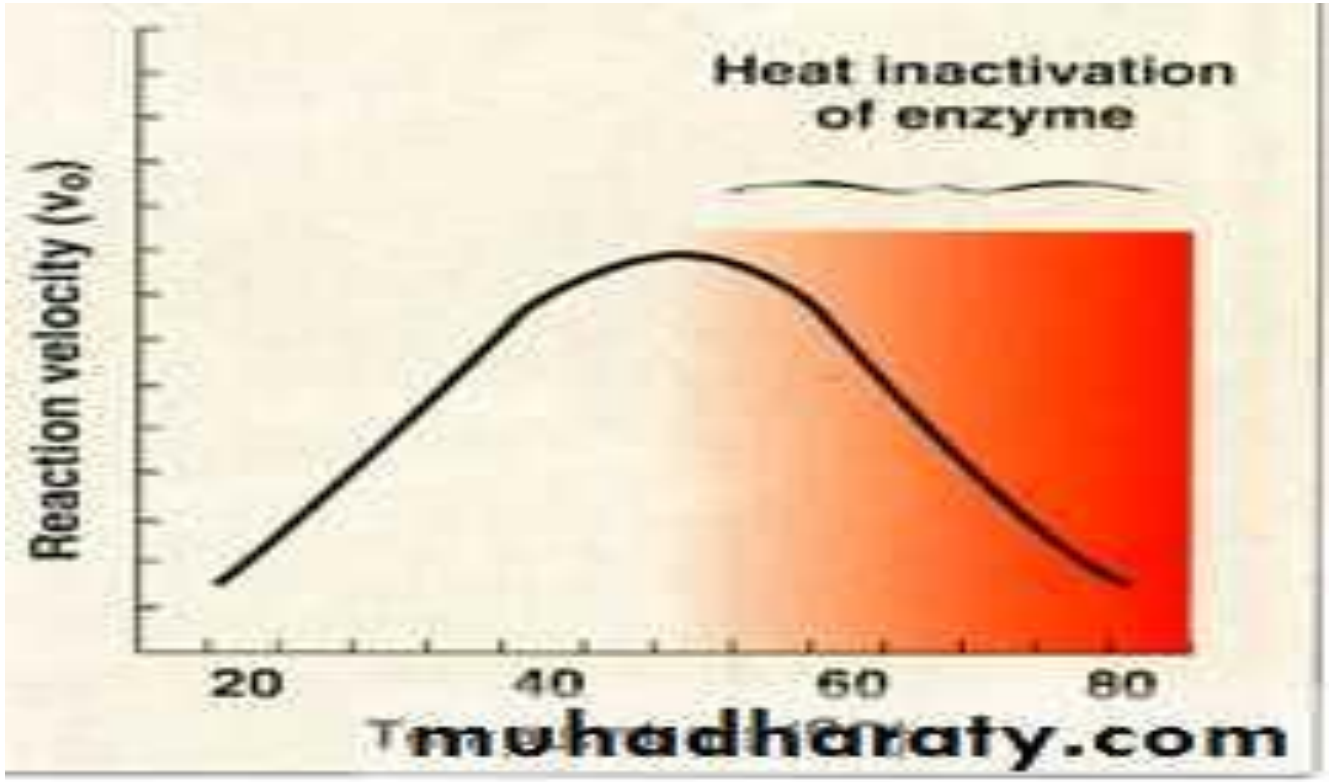
The rate of the reaction is directly proportional to [enzyme]



Temperature

The rate of the reaction increases with the temperature increasing until reaching the (Maximal velocity) at the (Optimal temperature) . Increasing of the temperature after the optimal temperature decreasing in the reaction velocity.

The velocity decreases due to (enzyme denaturation)

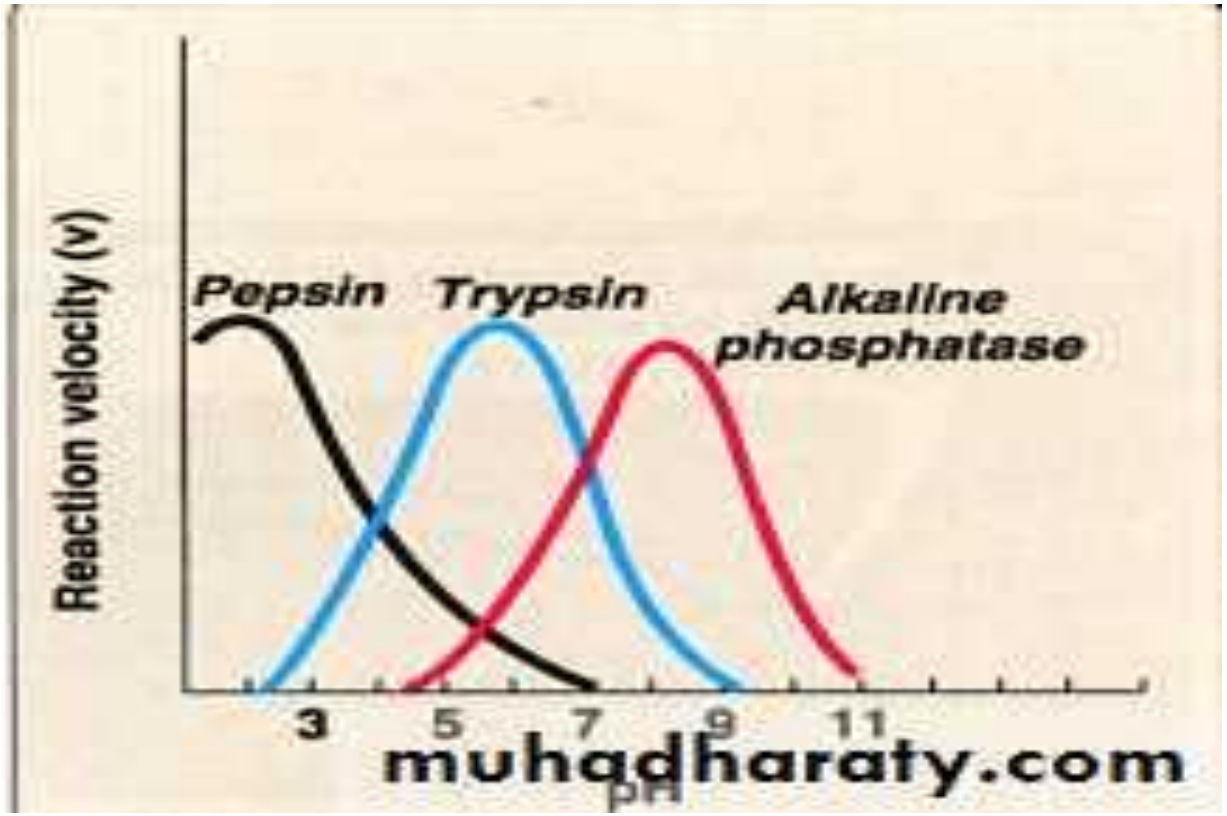


Effect of PH

Each enzyme has its own (Optimal PH).

Any change in the PH decreasing in the reaction velocity due to change in the ionization of the active site A.A.

This ionization inactivation of the active site decrease in enzyme activity.



Substrate concentration

Rate of the catalytic enzyme increases rapidly constant.

1-low [S] active sites are not saturated rapid reaction .

2-High [S] Saturated active sites slow reaction.

Substrate concentration

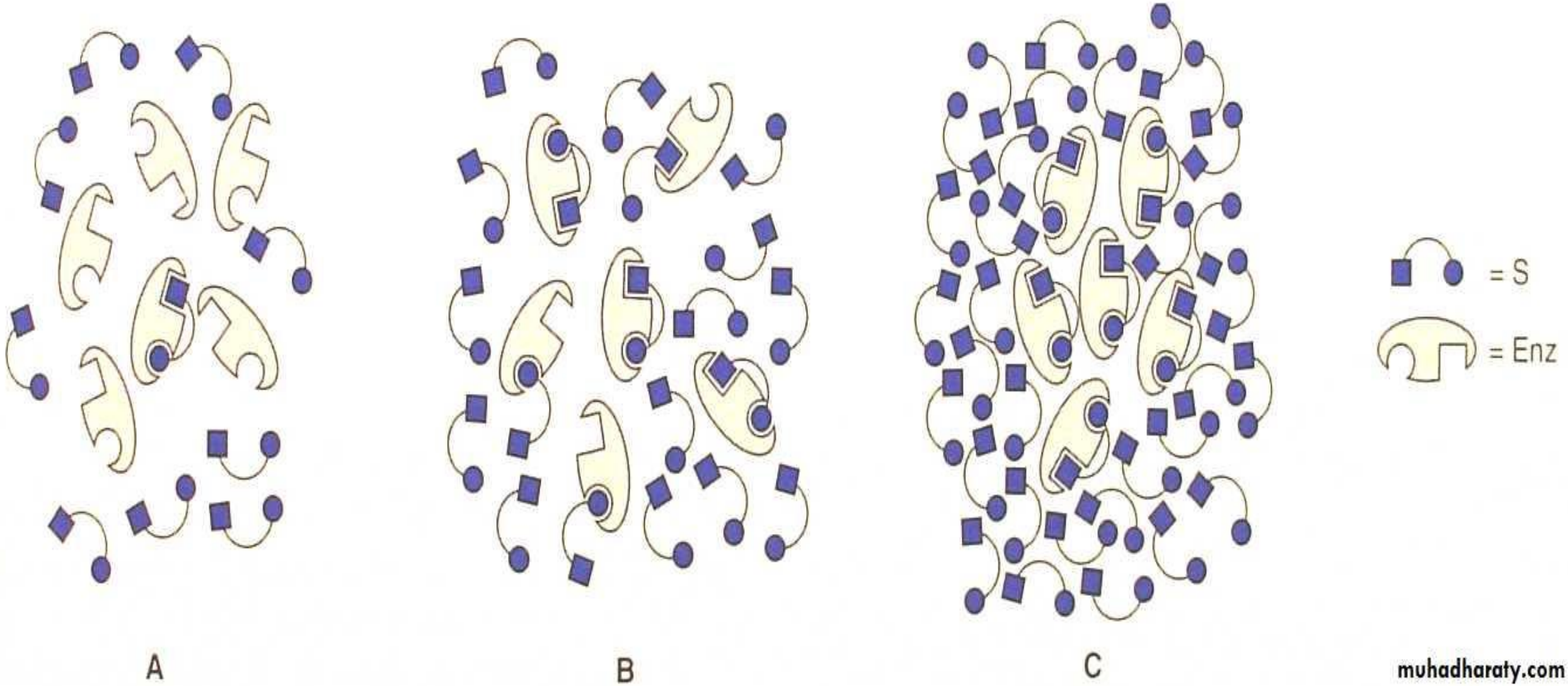
The rate or velocity of a reaction (v) is the number of substrate molecules converted to product per unit time and is usually expressed as µmoles product formed per minute.

The rate of an enzyme-catalyzed reaction increases with substrate concentration until a maximal velocity (Vmax) is reached.

A. Low [S]

B. 50% [S] or Km

C. High, saturating [S]



The Michaela's- menten constant (Km).

The quantitative relationship between substrate concentration and Vmax. For different enzymes, it is defined as that substrate conc. at which a given enzyme give one – half it maximum velocity . In many cases the Km is an inverse measure of the affinity of the enzyme for its substrate : the lower the Km the higher the affinity .

$$v_o = \frac{[V_{max}][S]}{Km + [S]}$$

v_o = initial reaction velocity

V_{max} = maximal velocity

[S] = substrate concentration

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Characteristics of Km

The Michaelis constant is characteristic of an enzyme and a particular substrate, and reflects the affinity of the enzyme for that substrate.

Km does not vary with the concentration of enzyme. A numerically small (low) Km reflects a high affinity of the enzyme for substrate because a low concentration of substrate is needed to half-saturate the enzyme.

Large Km:

A numerically large (high) Km reflects a low affinity of enzyme for substrate because a high concentration of, substrate is needed to half-saturate the enzyme.

The rate of the reaction is directly proportional to the enzyme concentration at all substrate concentrations.

When [S] is much less than Km, the velocity of the reaction is proportional to the substrate concentration.

Uses of Km

Experimentally, Km is a useful parameter for characterizing the number and/or types of substrates that a particular enzyme will utilize. It is also useful for comparing similar enzymes from different tissues or different organisms. Also, it is the Km of the rate-limiting enzyme in many of the biochemical metabolic pathways that determines the amount of product and overall regulation of a given pathway. Clinically, Km comparisons are useful for evaluating the effects mutations have on protein function for some inherited genetic diseases

Enzymes

Luc. 2

By

Dr. Muna M. Yaseen

Effect of activator:

Some enzymes require certain inorganic metallic action, Mg+2,Mn+2,Zn+2,Ca+2. for their optimum activity, these metals function as activator of the enzyme velocity through various mechanism

Each enzyme has own optimum PH at which the velocity maximum.

Most of the enzyme showed optimum activity around neutral PH , PH(6-8)

Enzyme Inhibition:

a substrate which binds with enzyme and bring about a decrease in catalytic activity of that enzyme.

Enzyme Inhibitor **3 groups**

Reversible **Irreversible** **Allosteric**

Inhibitors are chemicals that reduce the rate of enzymic reactions.

They are usually specific and they work at low concentrations.

They block the enzyme but they do not usually destroy it.

Many drugs and poisons are **inhibitors** of enzymes in the nervous system.

Meaning of enzyme inhibitors

Irreversible inhibitors : Inhibition of enzyme activity by combining with active site.

Reversible inhibitors : Inhibitors binds non-covalently with the enzyme and the enzyme can be reversed if the inhibitor is removed.

a-Competitive inhibitors : Inhibition of enzyme activity by competing with active site .

b-Un Competitive inhibitors : Inhibition of enzyme activity by combining with allosteric site.

c-Non Competitive inhibitors : Inhibition of enzyme activity by combining with both to free enzyme and ES at allosteric site.

The inhibitor competes with the substrate and binds at the active site of the enzyme but doesn't undergo any catalysis.

Ex. Of clinical &pharmacological inhibition.

xanthine

Uric Acid

Xanthine oxidase

Allopurinol

Hypoxanthine

Allopurinol acts as competitive inhibitor to xanthine oxidase , it competes with enzyme xanthine oxidase and prevent or block the reaction. so control **Gout** (decrease uric acid production).

Allopurinol is a classified as a **xanthine oxidase** inhibitor. This means that it stops the enzyme xanthine oxidase from functioning correctly.

Xanthine oxidase converts oxypurines (hypoxanthine and xanthine) to uric acid. It is found in many organs such as the liver, stomach, heart, brain, kidneys, and blood plasma.

Xanthine oxidase converts hypoxanthine to xanthine and then xanthine to uric acid. Uric acid is a product of broken down foods and cells that are excreted by the kidneys. A decreased level of xanthine oxidase, an increased amount of hypoxanthine and xanthine, or a decreased kidney function can all increase the level of uric acid in the blood. Too much uric acid in the blood builds up around joints and causes the pain and swelling associated with gout. An increase in uric acid is also associated with organ damage and failure

Allopurinol reaches its peak in thirty to sixty minutes once ingested and has a relatively short half-life. As it inhibits xanthine oxidase from converting enzymes to uric acid, it also helps to stop tophi (uric acid crystals) from forming. Tophi are responsible for causing gouty arthritis. Allopurinol decreases the function of xanthine oxidase when there is too much hypoxanthine and xanthine in the body which lowers the level of uric acid

Diagnostic importance of Enzymes:

Measurement of enzyme activities in biological fluid (plasma/serum) is of great clinical importance.

Enzymes in the circulation is divided into two groups:

1/ plasma specific or plasma functional enzymes:

Certain enzymes are normally present in the plasma and they have specific function.

Generally these enzymes activities are higher in plasma than in tissues. They are mostly synthesized in the liver and enter the circulation.

Ex: lipoprotein lipase plasmin, choline esterase.

Impairment of liver function or genetic disorders leads to fall in the activities of plasma function enzyme.

2/Non –plasma specific: these enzymes are either totally absent or present at a low concentration in plasma compared to their level found in the tissues. All GIT enzymes ,amylase, pepsin, trypsin present in the plasma are known as **secretary enzymes**. Measurement of the activities of non plasma specific is important in the diagnosis and prognosis of several diseases

Isoenzymes

- Multiple forms of an enzyme which differ in physical and chemical properties and catalyze the same reaction as an enzyme.
- **Isoenzymes** are produced by a single gene and some may result from more than one gene.
- Isoenzymes can be separated by:

1-Heat inactivation

2-Chemical inhibition

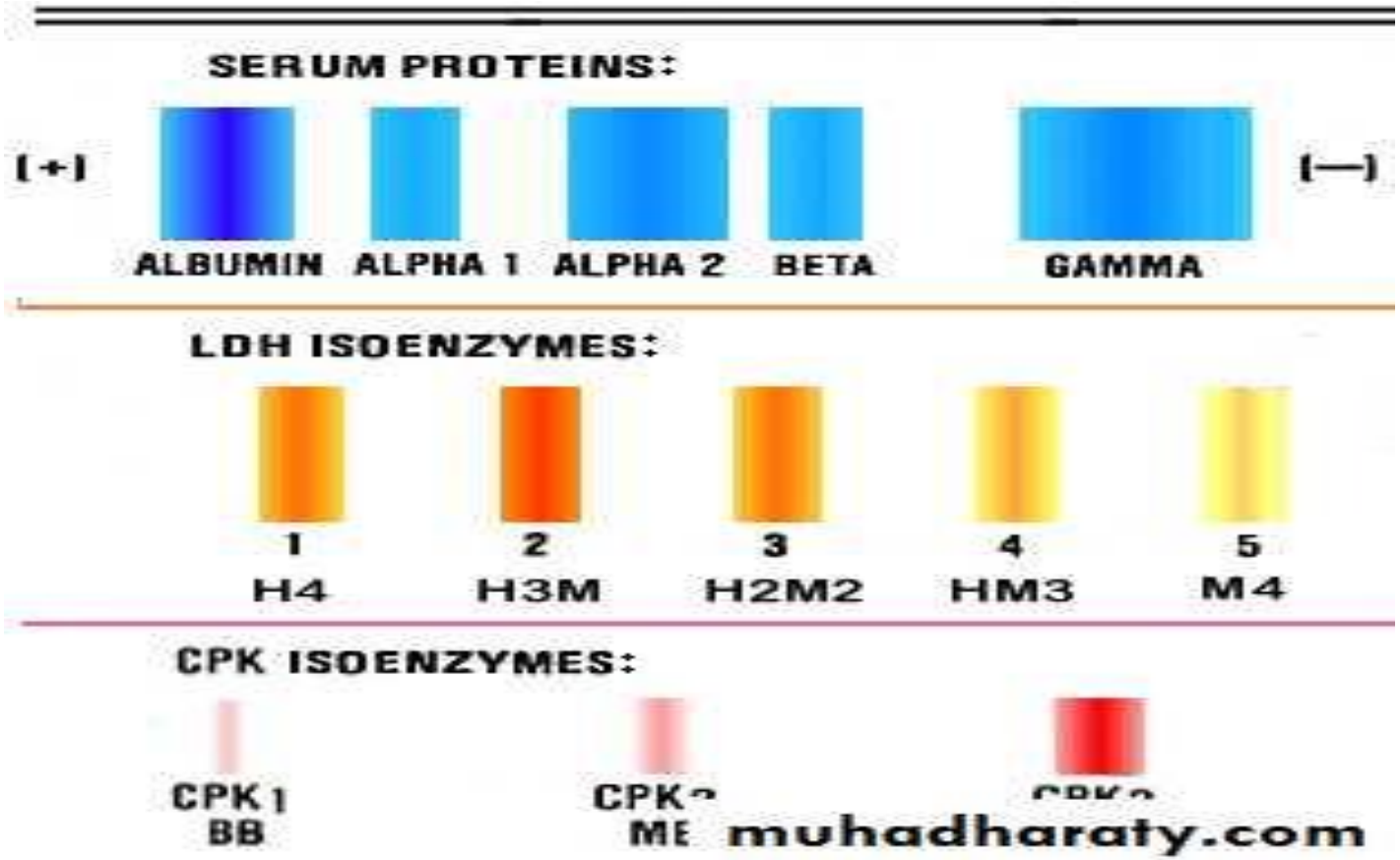
3-Electrophoretic techniques (specific method)

Differ in AA sequence and physical properties.

- Different Isoenzymes may arise from different tissues and their specific detection may give clues to the site of pathology

Electrophoresis

Is a technique by which separation of Movement of charged particles through an electrolyte when subjected to electrical field.



Advantages of Isoenzyme measurement

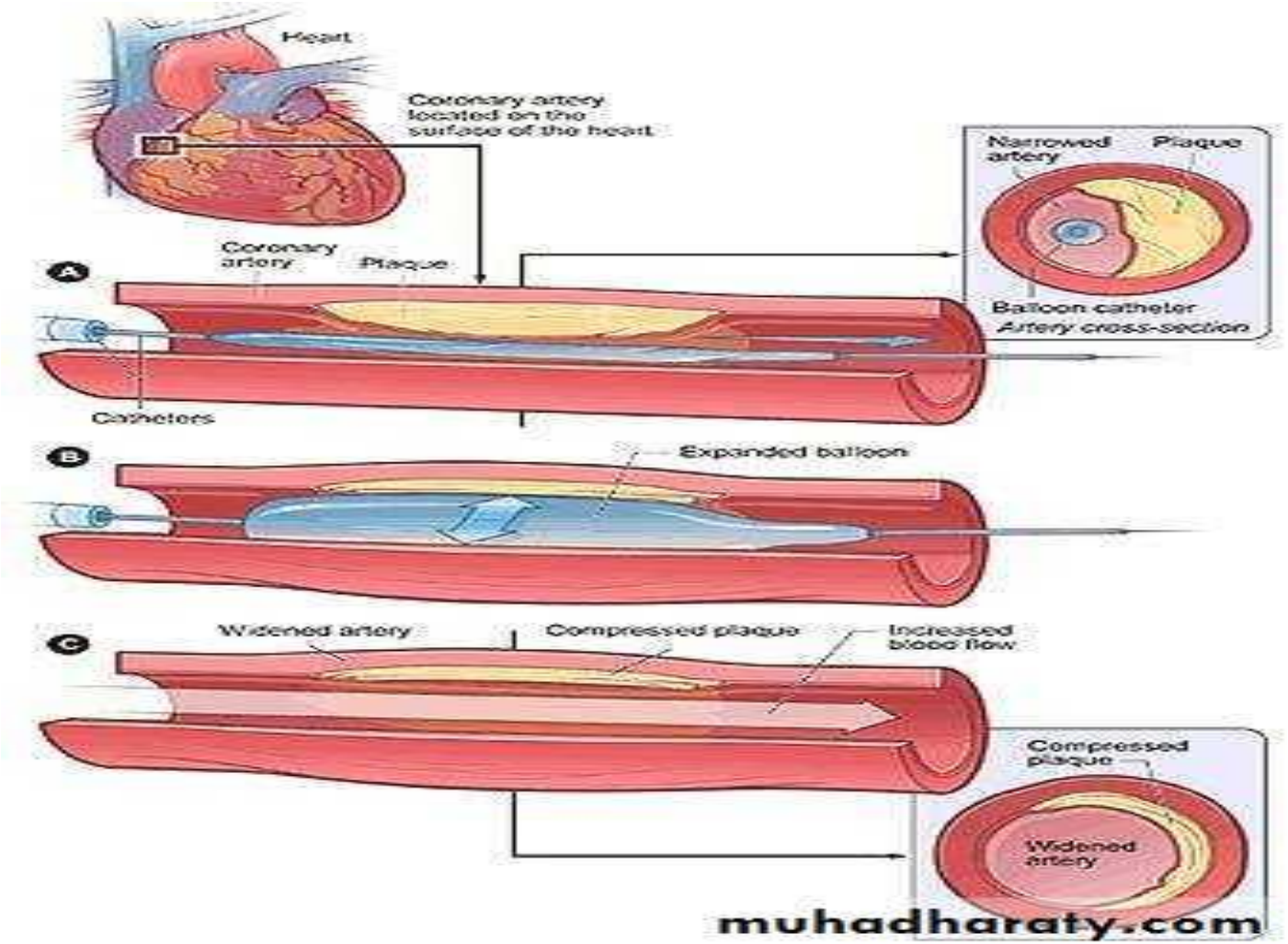
- Isoenzyme variants are derived from different tissue sources.
- So separation renders increased specificity to enzyme analysis.
- Tissue or organ effected can be detected (where isoenzyme elevation occurs)

Types

- **CPK** (creatinine Phospho Kinase)
- Troponin
- **LDH** (Lactate Dehydrogenase)
- **ALP** (Alkaline phosphatase)
- Aldolase
- Amylase

Atherosclerosis

Is a condition in which arteries are blocked to a greater or lesser extent by deposition of cholesterol plaques , leading most commonly to coronary heart disease by blocking of coronary arteries i.e (myocardial infarction MI).



Creatine kinase

is a dimer made of 2 monomers occurs in the tissues Skeletal muscle contains M subunit, Brain contains

B subunits . **Three different isoenzymes are formed**

CREATINE KINASE (CK)

CPK (CK)

Creatinine Phospho kinase or Creatinine Kinase Catalyses the conversion of creatinine to creatinine Phosphate.

Creatinine +ATP Creatinine kinase creatinine phosphate +ADP Creatinine Phospho kinase

Normal level: 15-100U/L (males) : 10-80 U/L (females)

Sample: in serum it is estimated and not increased in hemolysis

Isoenzyme name	Composition	Present in	Elevated in
CK-1	BB	Brain	CNS diseases
CK-2	MB	Myocardium/ Heart	Acute myocardial infarction
CK-3	MM	Skeletal muscle	Myocardium

CPK-Creatinine Phospho kinase

CPK Isoenzymes are performed when the total CPK level is elevated.

Isoenzyme testing can help differentiate the source of the damaged tissue.

CPK is an enzyme found predominantly in the heart, brain, and skeletal muscle.

CPK is composed of **3 Isoenzymes** that differ slightly in structure:

CPK is a dimer made up of 2 subunits called B for brain and M for muscle

CPK- Isoenzymes

CPK-1 (also called CPK-BB) is concentrated in the brain and lungs

CPK-2 (also called CPK-MB) is found mostly in the heart

CPK-3 (also called CPK-MM) is found mostly in skeletal muscle

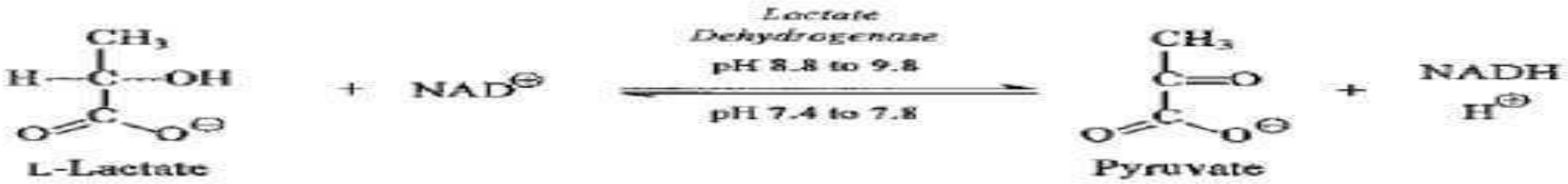
Because the **CPK-1** isoenzyme is predominately found in the brain and lungs, injury to either of these organs (for example, stroke or lung injury due to a pulmonary embolism) are associated with elevated levels of this isoenzyme

LACTATE DEHYDROGENASE (LDH)

LDH is elevated in myocardial infarction, blood disorders It is a tetrameric protein and made of two types of subunits namely

H = Heart, M = skeletal muscle It exists as 5 different isoenzymes with various combinations of H and M subunits

Lactate dehydrogenase (LDH)



Normal values
Serum -100 -200 U/L
CSF - 7 -30 U/L
Urine - 40 -100 U/L

muhadharaty.com

Description LDH

LDH is found in the cells of almost all body tissues.

Because this enzyme is actually composed of five different Isoenzymes, however, analysis of the different LDH isoenzyme levels in the blood can help in the diagnosis of some diseases.

LDH

LDH is an Oxidoredoctase enzyme whose activity is necessary for the reversible reaction in which Pyruvate and lactate are inter converted. It is important in glycolysis.

LDH Isoenzyme is a tetramer with 4 subunits. The subunit may be either H (heart) or M (muscle) .

Clinical significance

- MI (Myocardial infarction)
- Acute infective hepatitis
- Muscular dystrophy
- Leukemia

LDH-Isoenzymes

The LDH has five Isoenzymes which are:

LDH-1 (H4) is found mainly in the heart.

LDH-2 (H3M1) Reticuloendothelial system.

LDH-3 (H2M2) is found in the lungs.

LDH-4 (H1M3) in the kidney, placenta, and pancreas, and

LDH-5 (M4) in liver and striated (skeletal) muscle.

Normally, levels of LDH-2 are higher than those of the other Isoenzymes

LDH and Heart Attack

One of the most important diagnostic uses for the LDH Isoenzymes test is in the differential diagnosis of myocardial infarction or heart attack.

The total LDH level rises within 24-48 hours after a heart attack, peaks in two to three days, and returns to normal in approximately five to ten days. The **LDH-1** isoenzyme level, however, is more sensitive and specific than the total LDH.

Normally, the level of LDH-2 is higher than the level of LDH-1. An **LDH-1** level higher than that of LDH-2, a phenomenon known as "flipped LDH," is strongly indicative of a myocardial infarction. The flipped LDH usually appears within 12-24 hours after a heart attack. A normal **LDH-1/LDH-2 ratio** is considered reliable evidence that a heart attack has not occurred.

Alkaline Phosphatase (ALP)

- Isoenzymes are five:
- ALP-1 present in liver increased in obstructive jaundice, biliary cirrhosis.
- ALP-2 in bone increased in rickets
- ALP-3 in placenta increase in 2nd and 3rd trimester of pregnancy and decrease indicates placental insufficiency and foetal death.

Alkaline Phosphatase (ALP)

- 4. ALP-4 in intestine increased in intestinal disease and after gastrectomy surgery
- 5. ALP-5 in kidney increases in kidney disorders.

In normal serum liver and bone fractions are present.
Abnormal ALP Isoenzymes Regan are present in carcinomas and metastasis.
Normal level: 40-125 U/L

Enzymes in Liver diseases

The following enzymes when elevated are useful in the diagnosis of liver diseases and dysfunction due to viral hepatitis, toxic hepatitis, cirrhosis and hepatic necrosis

1.Alanin transaminas(ALT).
2. Aspartate transaminase (AST).
3.Lactate dehydrogenase (LDH).

The enzymes that markedly increase in **intrahepatic** and **extra hepatic** cholestasis are

Alkaline Phsphatase.
5- Nucleotidase.

HORMONES

It is a chemical substance which is produced in one part of the body, enters the circulation and is carried to distant target organs and tissues to modify their structures and functions.

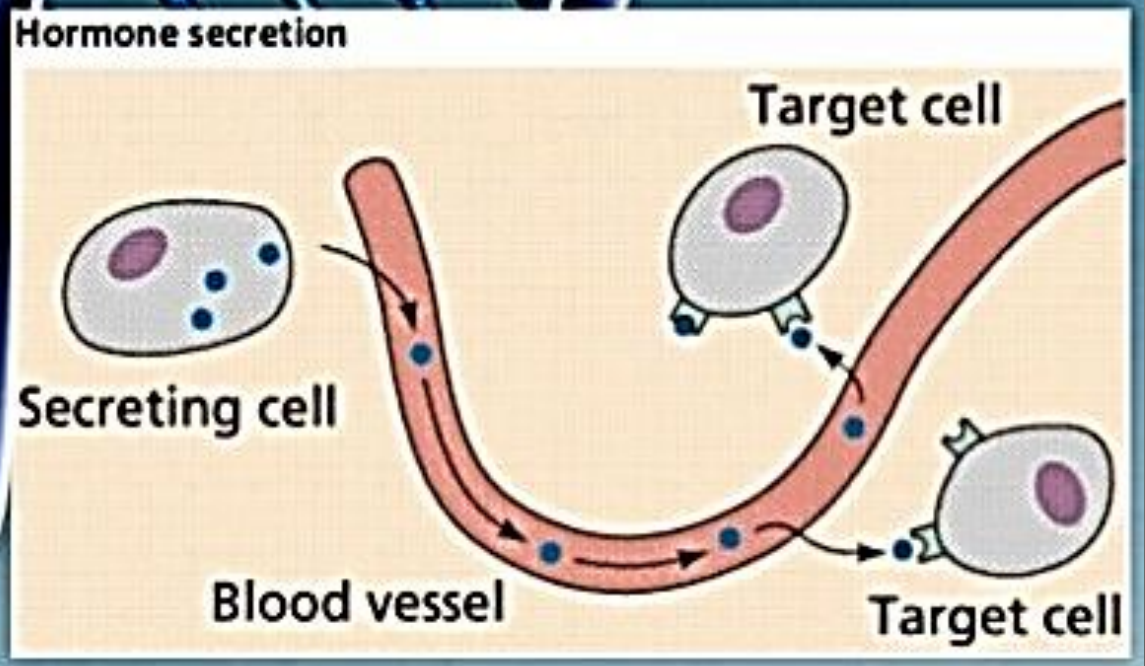
The word hormone is derived from a Greek word "Hormacin" which means to "Excite". Hormones are strictly speaking stimulating substances and act as body catalysts. The hormones catalyse and control diverse metabolic processes, despite their varying actions and different specifities depending on the target organ.

HORMONE SECRETION

Hormones in animals are often transported in the blood. Endocrine hormone molecules are secreted (released) directly into the bloodstream, while exocrine hormones (ecto-hormones) are secreted directly into a duct, and from the duct they either flow into the bloodstream or they flow from cell to cell by diffusion

Hormone secretion can be stimulated and inhibited by:

- Other hormones (stimulating or releasing hormones)
- Plasma concentrations of ions or nutrients
- Neurons and mental activity
- Environmental changes, E.g. Change in light or temperature.



EFFECT OF HORMONES

Hormones have the following effects on the body:

- Stimulation or inhibition of growth
- Mood swings
- Activation or inhibition of the immune system
- Regulation of metabolism
- Preparation of the body for fighting, fleeing, mating, and other activities
- Preparation of the body for a new phase of life, such as puberty, parenting, and menopause
- Control of the reproductive cycle
- Hunger cravings
- Hormone may also regulate the production and release of other hormones.
- Hormone signals control the internal environment of the body through homeostasis.

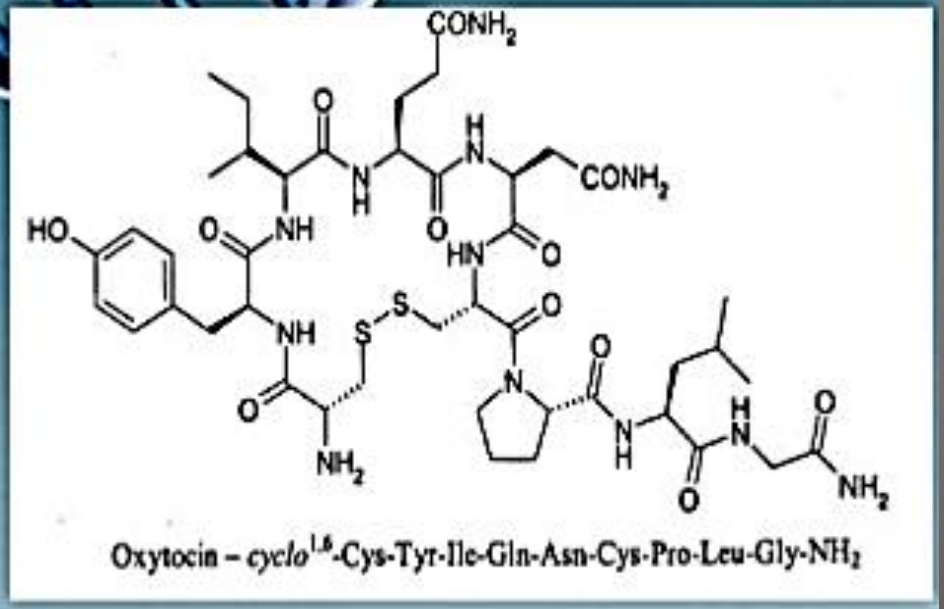
CLASSIFICATION OF HORMONES

Most commonly, hormones are categorized into four structural groups, with members of each group having many properties in common:

- Peptides and proteins
- Amino acid derivatives
- Steroids

1. PEPTIDES AND PROTEINS:

Peptide and protein hormones are products of translation. They vary considerably in size and post-translational modifications, ranging from peptides as short as three amino acids to large, multi-subunit glycoproteins. Peptide hormones are synthesized in endoplasmic reticulum, transferred to the Golgi and packaged into secretory vesicles for export. E.g. Oxytocin.



Oxytocin – *cyclo*[1,6]-Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2

2. AMINO ACID DERIVATIVES:

There are two groups of hormones derived from the amino acid, tyrosine:

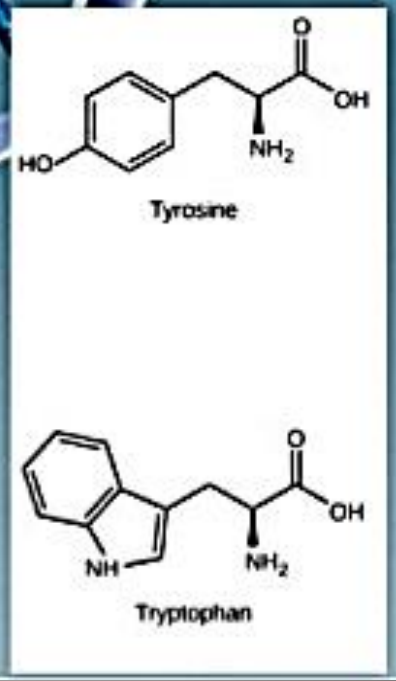
· Thyroid hormones are basically a "double" tyrosine with the critical incorporation of 3 or 4 iodine atoms.

· Catecholamine include epinephrine and norepinephrine, which are used as both hormones and neurotransmitters.

Two other amino acids are used for synthesis of hormones:

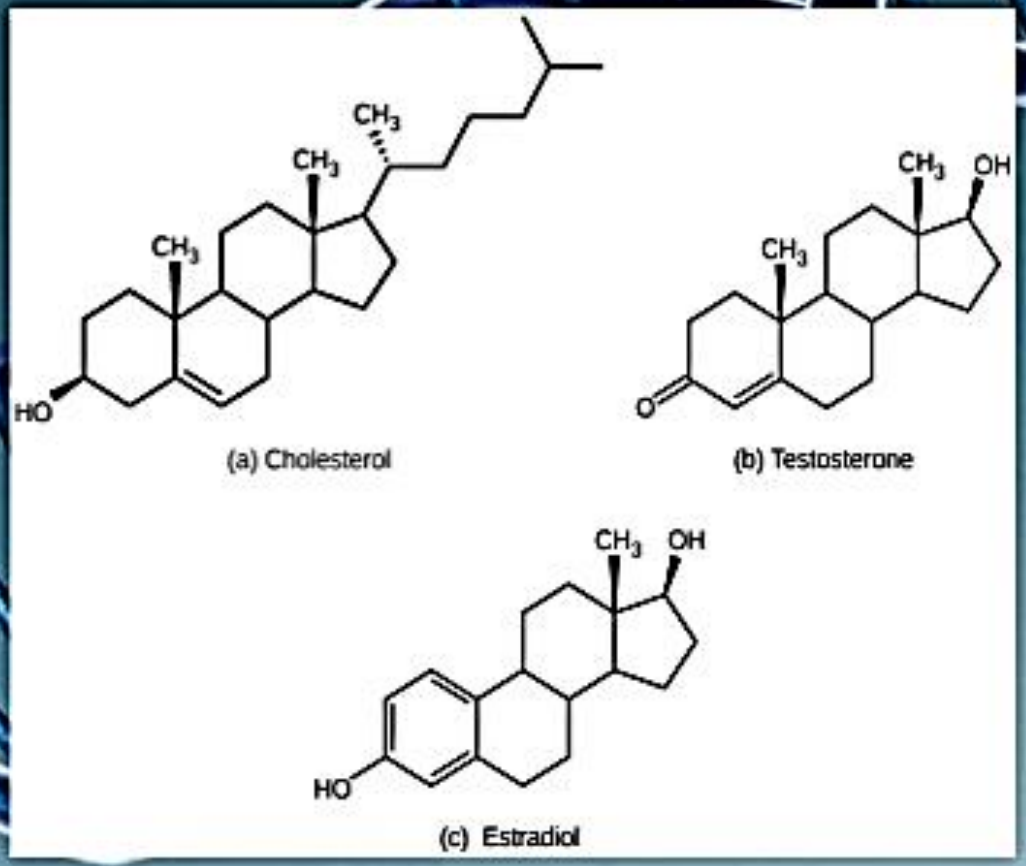
· Tryptophan is the precursor to serotonin and the pineal hormone melatonin.

· Glutamic acid is converted to histamine.



3. STEROIDS:

Steroids are lipids and, more specifically, derivatives of cholesterol. Examples include the sex steroids such as testosterone and adrenal steroids such as cortisol.



ACTION OF MECHANISIM

Understanding mechanism of action is not only of great interest to basic science, but critical to understanding and treating diseases of the endocrine system and in using hormones as drugs.
There are two fundamental mechanisms by which a hormone can change its target cell. These mechanisms are:

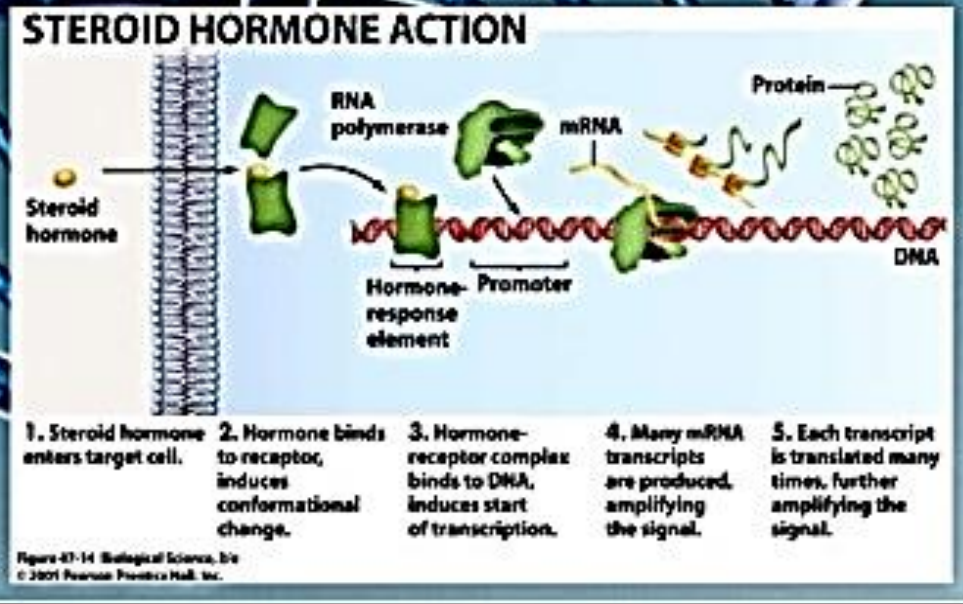
1. ACTIVATION OF ENZYMES AND OTHER DYNAMIC MOLECULES:

Most enzymes fluctuate between conformational states that are catalytically active versus inactive. Many hormones affect their target cells by inducing such transitions, usually causing an activation of one of more enzymes. Because enzymes are catalysts and often serve to activate additional enzymes, a seemingly small change induced by hormone receptor binding can lead to widespread consequences within the cell.

2. MODULATION OF GENE EXPRESSION:

Stimulating transcription of a group of genes clearly can alter a cell's phenotype by leading to a burst of synthesis of new proteins. Similarly, if transcription of a group of previously active genes is shut off, the corresponding proteins will soon disappear from the cell.

More specifically, when a receptor becomes bound to a hormone, it undergoes a conformational change which allows it to interact productively with other components of the cells, leading ultimately to an alteration in the physiologic state of the cell.



HORMONE RECEPTORS

Despite the molecular diversity of hormones, all hormone receptors can be categorized into one of two types, based on their location within the cell:

LOCATION OF RECEPTOR	CLASSES OF HORMONES	PRINCIPLE MECHANISM OF ACTION
Cell surface receptors (plasma membrane)	Proteins peptides, catecholamine and eicosanoids (water soluble)	Generation of second messengers which alter the activity of other molecules, usually Enzymes, within the cell.
Intracellular receptors (cytoplasm and/or nucleus)	Steroids and thyroids hormones (lipid soluble)	Alter transcriptional activity of responsive Genes.

THE FINAL EFFECTS OF HORMONES ACTION

1. Change the permeability of cell membrane.
2. Accelerate the penetration of substrates, enzymes, coenzymes into the cell and out of cell.
3. Acting on the allosteric centers, affect the activity of enzymes (Hormones penetrating membranes).
4. Affect the activity of enzymes through the messengers (cAMP). (Hormones that can not penetrate the membrane).
5. Act on the genetic apparatus of the cell (nucleus, DNA) and promote the synthesis of enzymes (Steroid and thyroid hormones).

FACTORS REGULATING HORMONE ACTION

Action of a hormone at a target organ is regulated by four factors:

1. Rate of synthesis and secretion: The hormone is stored in the endocrine glands.
2. In some cases, specific transport systems in plasma.
3. Hormone-specific receptors in target cell membranes which differ from tissue to tissue.
4. Ultimate degradation of the hormones usually by the liver or kidneys.

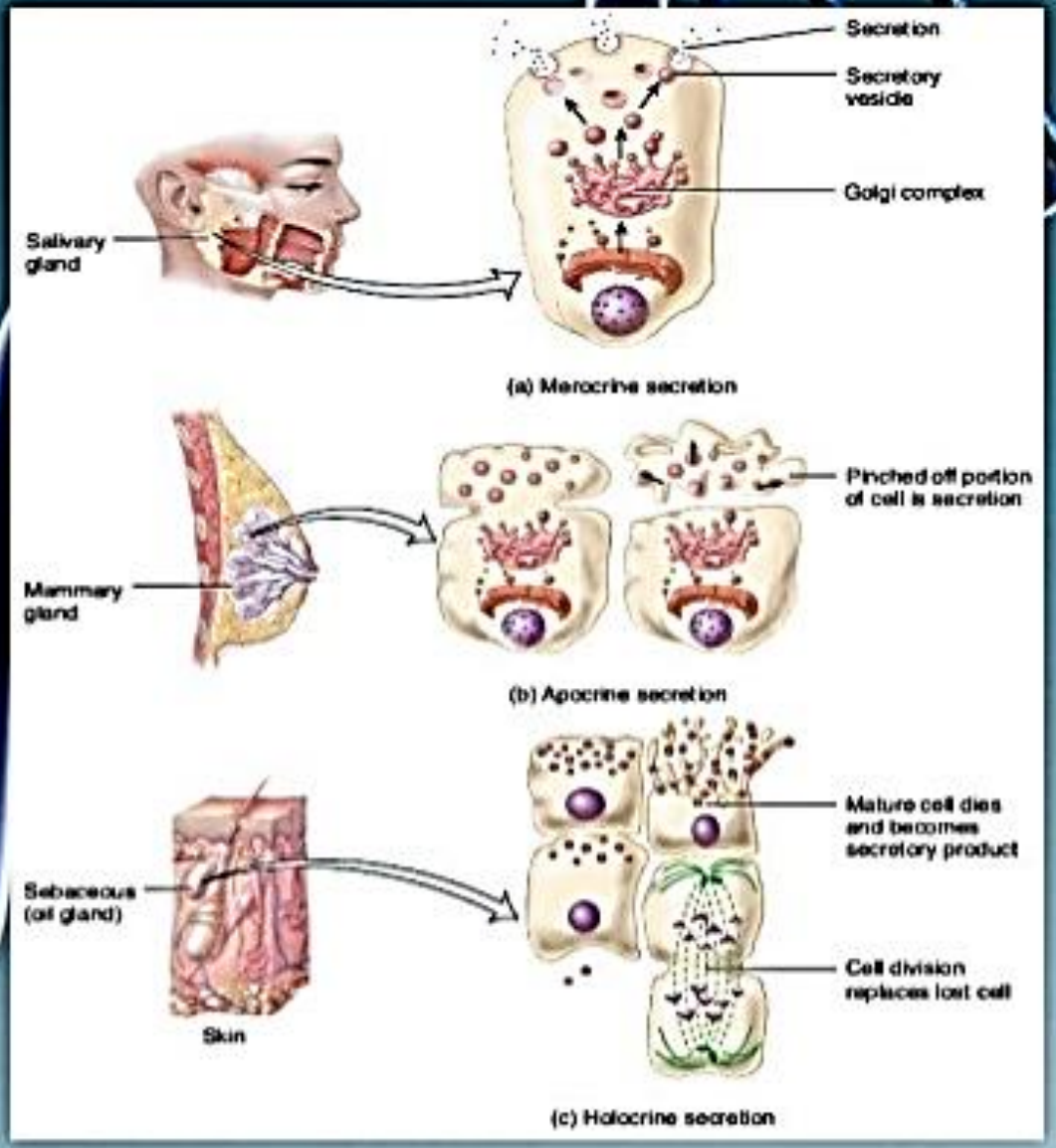
ENDOCRINE HORMONES

Endocrine glands produce endocrine hormones which have certain effects on our bodies.

Gland	Hormones produced	Effect of Hormone
Pineal gland	Melatonin	Affects reproductive development and daily physiologic cycles.
Pituitary gland	Growth hormone	Controls growth of bones and muscles.
	Anti-diuretic hormone	Increases reabsorption of water in kidneys.
	Gonadotrophins	Controls development of ovaries and testes.
Thyroid gland	Thyroxine	Controls rate of metabolism and rate that glucose is used up in respiration, and promote growth.
Adrenal gland	Adrenaline	Prepares the body for emergencies: increases heart rate and rate and depth of breathing, raises blood sugar level so more glucose is available for respiration, diverts blood from gut to limbs.
Pancreas	Insulin	Converts excess glucose into glycogen in liver.
	Glucagon	Converts glycogen back to glucose in liver.
Ovaries	Oestrogen	Controls ovulation and secondary sexual characteristics.
	Progesterone	Prepares the uterus lining for receiving an embryo.
Testes	Testosterone	Controls sperm production and secondary sexual characteristics.
Thymus	Thymosin	Promotes production and maturation of white blood cells.

EXOCRINE HORMONES

These are exocrine glands in which exocrine hormones are present:



GLUCAGON
(PROTEIN HORMONE)

INTRODUCTION:

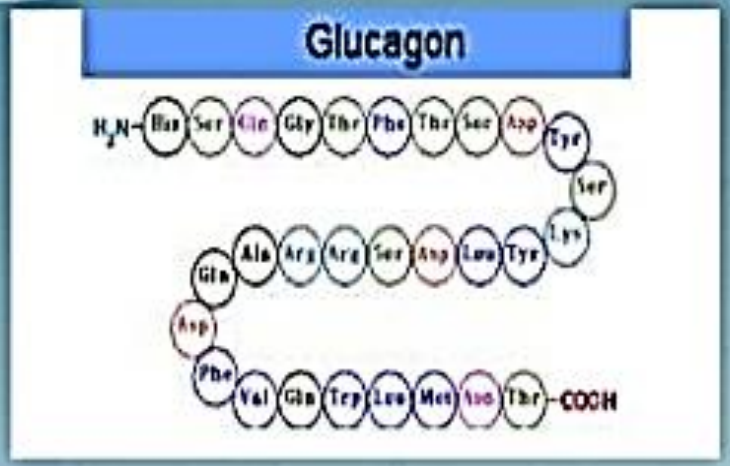
Glucagon is a hormone produced by α-cells of islets of Langerhans of pancreas and is an important hormone involved in:

- Rapid mobilization of hepatic glycogen to give glucose by glucogenolysis
- To a lesser extent FA from adipose tissue.

Thus, it act as a hormone required to mobilise metabolic substrates from storage depots.

CHEMISTRY:

Glucagon has been purified and crystallized from pancreatic extracts and also the hormone has been synthesized. It is a polypeptide containing 29 amino acids.



ESTROGEN
(STEROID HORMONE)

INTRODUCTION:

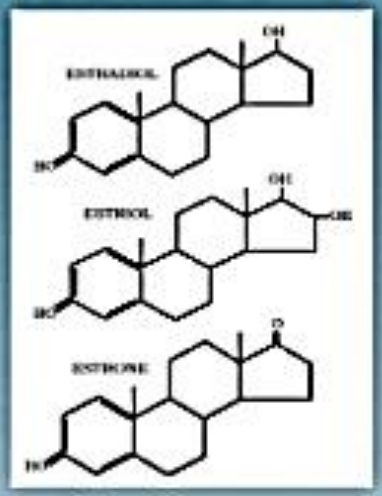
Estrogen are hormones capable of producing certain biological effects. They include:

- Growth of female genetic organs
- The appearance of female secondary sex characteristics
- Growth of the mammary duct system and numerous other phenomena which vary some what in different species.

CHEMISTRY:

The naturally occurring estrogens in humans are:

- β-Estradiol
- Estrone
- Estriol



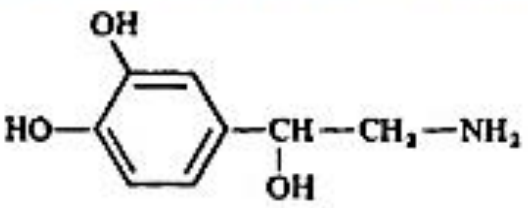
EPINEPHRINE & NOREPINEPHRINE (AMINO ACID DERIVATIVE)

INTRODUCTION:

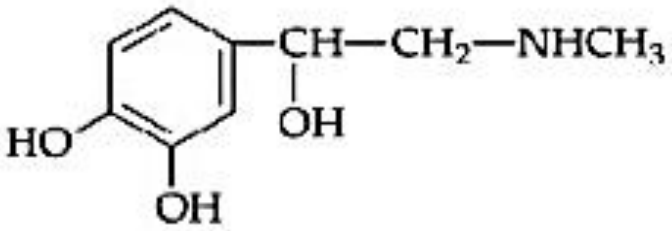
They are the hormones secreted from adrenal gland from adrenal medulla. They help in fight and flight responses.

CHEMISTRY:

- The naturally occurring forms are levorotatory.
- They don't have -COOH group.
- They act as neurotransmitters.
- They are stored in the form of granules.



NOREPINEPHRINE



EPINEPHRINE

SIMILARITIES & DISSIMILARITIES OF HORMONES & ENZYMES

SIMILARITIES:

- Both act as body catalysts.
- Both are required only in small quantities.
- Both are not used up during the reaction.

DISSIMILARITIES:

- Hormones are produced in an organ other than that in which they ultimately perform their action.
- They are secreted in blood prior to use.
- Structurally they are not only proteins. Few hormones are protein in nature, few are small peptides. Some are derived from amino acids while some are steroids in nature.

IMPORTANCE OF HORMONES

- Our bodies rely on hormones to function properly. Any problems affecting hormonal balance will affect our lives. Some things hormones are responsible for include: simulation of growth, control of cell's life span, control of **immune system**, metabolism regulation, control of phases of life, self preservation reactions, sexual functions, reproductive cycle.

- Hormones are chemical messengers in the body which control certain processes in the body, such as reproduction and homeostasis.

For example, insulin is a hormone in homeostasis which controls the concentration of glucose in the blood by causing its conversion into a insoluble substance. Without it (as in Type 1 diabetes), the blood sugar level would rise uncontrollably.


THANKYOU ☺

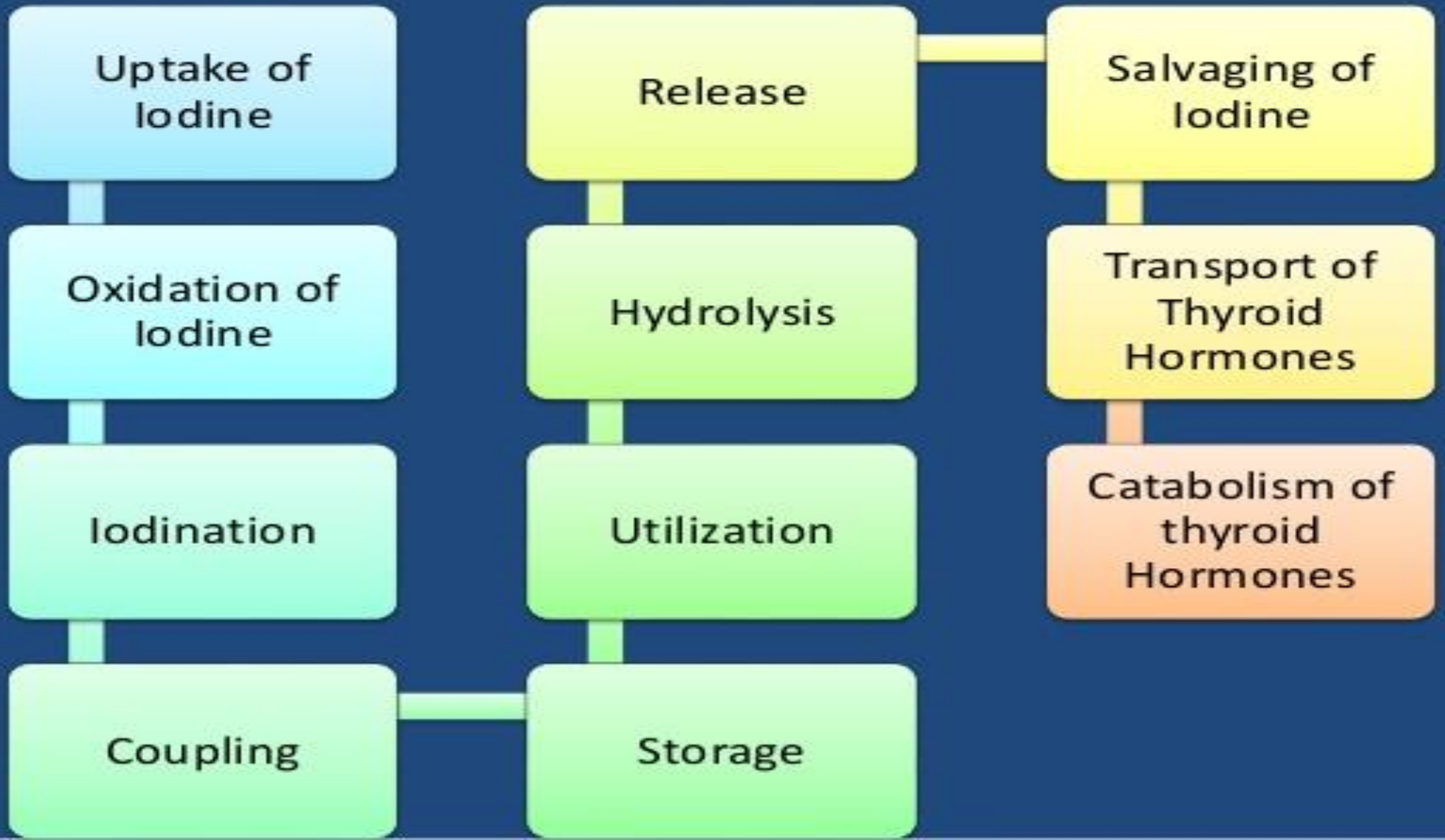
Thyroid Hormone

- Secreted by the thyroid gland
- Gland secret major hormone;
  - Thyroxine (T4)
  - Triiodothyronine (T3)
- Controlled by the primarily TSH (Thyroid stimulating hormone) secreted by the ant Pituitary gland.
- Gland also secrete calcitonin (imp hormone in calcium metabolism).

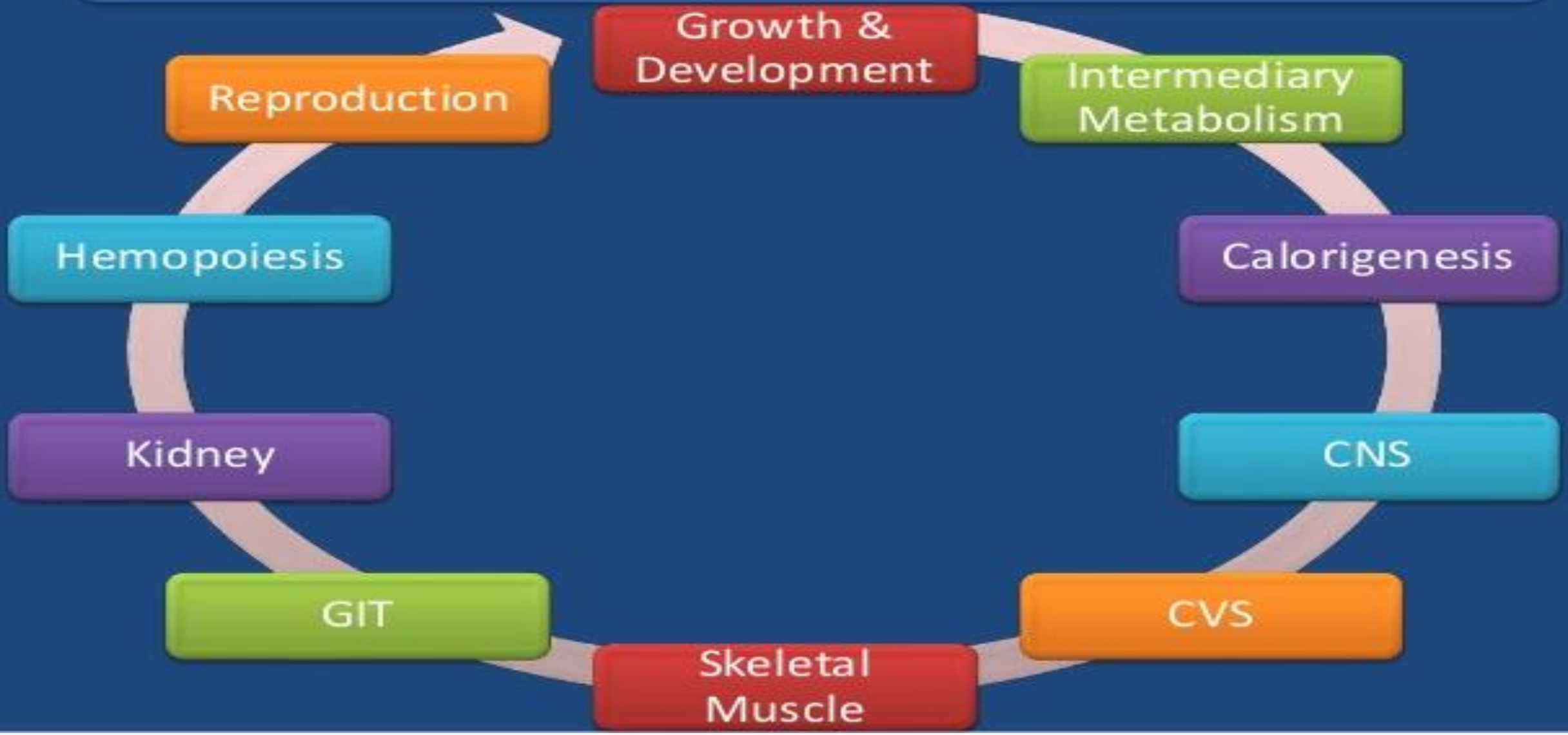
Iodine metabolism

- Iodine is required for the formation of thyroid (150-200µg/day) (sr 5-10 µg/dL)
- About 80% is stored in Thyroid gland.
- Ingredients which prevent the utilization of Iodine are called as Goitrogens.

Synthesis & secretion of Thyroxin



Effect of Thyroid Hormones



Effect of Thyroid Hormones

Lipid metabolism

- Fat mobilization.
- Oxidation of FA
- Inversely related to hormone levels.

Carbohydrate metabolism

- Enhance insulin dependent glucose entry
- Increased gluconeogenesis & glycogenolysis.

Growth

- For normal growth.

Development

- Physical and mental development in fetal, neonatal, young and adult.

Other effect

- Cardiovascular
- Central nervous system
- Reproductive system
- Hemopoiesis
- Skeletal, GIT, Kidney

Thyroid Disorders

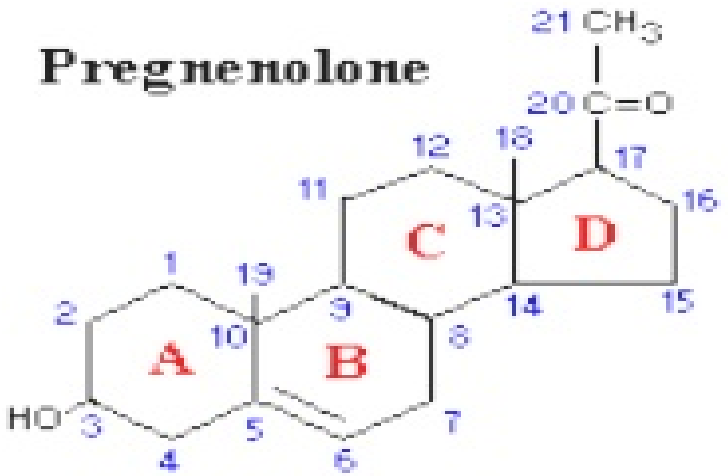
- Cretinism
- Hyperthyroidism
- Hypothyroidism
- Euthyroid Goiter

Steroid Hormones

- Steroid hormones: produced in the adrenal cortex, testis, ovary, and some peripheral tissues (adipose tissue, the brain!)
- All steroid hormones share a typical (but not identical) ring structure.

Steroid hormones

- All steroid hormones are derived from cholesterol and differ only in the ring structure and side chains attached to it.
- All steroid hormones are lipid soluble



Types of steroid hormones

- **Glucocorticoids**; cortisol is the major representative in most mammals
- **Mineralocorticoids**; aldosterone being most prominent
- **Androgens** such as testosterone
- **Estrogens**, including estradiol and estrone
- **Progestogens** (also known a progestins) such as progesterone

Steroid hormones

- Steroid hormones are not water soluble so have to be carried in the blood complexed to specific binding globulins.
- Corticosteroid binding globulin carries cortisol
- Sex steroid binding globulin carries testosterone and estradiol
- In some cases a steroid is secreted by one cell and is converted to the active steroid by the target cell: an example is androgen which secreted by the gonad and converted into estrogen in the brain

Functions of Steroid Hormones

- Steroid hormones play important roles in:
  - carbohydrate regulation (glucocorticoids)
  - mineral balance (mineralocorticoids)
  - reproductive functions (gonadal steroids)

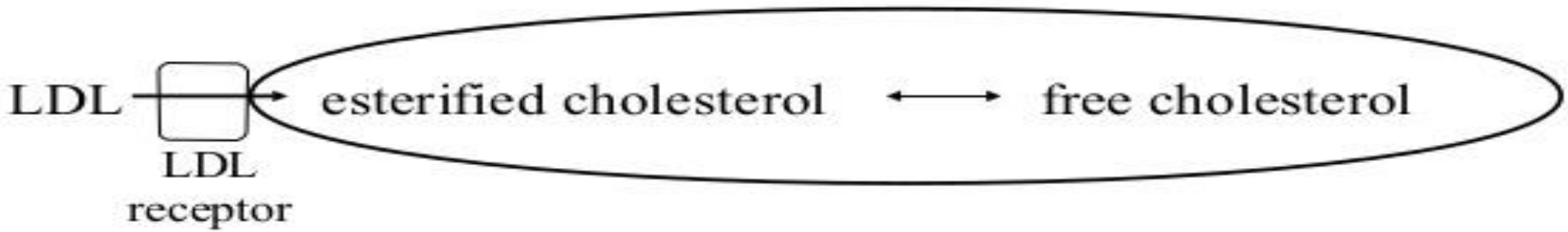
- Steroids also play roles in inflammatory responses, stress responses, bone metabolism, cardiovascular fitness, behavior, cognition, and mood.

Sources of Cholesterol for Steroid Synthesis

- Cholesterol is also taken up by the cell in the form of low density lipoprotein (LDL).

  - LDL is a complex composed of cholesterol, phospholipids, triglycerides, and proteins (proteins and phospholipids make LDL soluble in blood).

  - LDL is taken into cells via LDL receptors, and broken down into esterified cholesterol, and then free cholesterol:



Adrenal Steroids

- The adrenal glands are located immediately superior to the kidneys.
- There are three classes of adrenal steroids:
  - mineralocorticoids,
  - glucocorticoids, and
  - androgens

Parathyroid Hormone

- provides a powerful mechanism for controlling extracellular calcium and phosphate concentrations by regulating:

- ✓ intestinal reabsorption
- ✓ renal excretion
- ✓ exchange between the extracellular fluid and bone of these ions.

- **Excess activity** of the parathyroid gland causes rapid **absorption of calcium salts** from the bones, with resultant **hypercalcemia** in the extracellular fluid;

- conversely, **hypofunction** of the parathyroid glands causes **hypocalcemia**, often with resultant **tetany**.

Chemistry of Parathyroid Hormone

- synthesized in the form of a **preprohormone**
- cleaved to a **prohormone**
- then to the **hormone itself with 84 amino acids** by the endoplasmic reticulum and Golgi apparatus
- finally is **packaged in secretory granules** in the cytoplasm of the cells.

Effect on Ca^+ and Phosphate Concentrations in the ECF

- suddenly infusing PTH

- ✓ **calcium** ion concentration begins to **rise** and reaches a plateau in about 4 hours.

- ✓ the **phosphate** concentration, however, **falls** more rapidly than the calcium rises and reaches a depressed level within 1-2 hours.

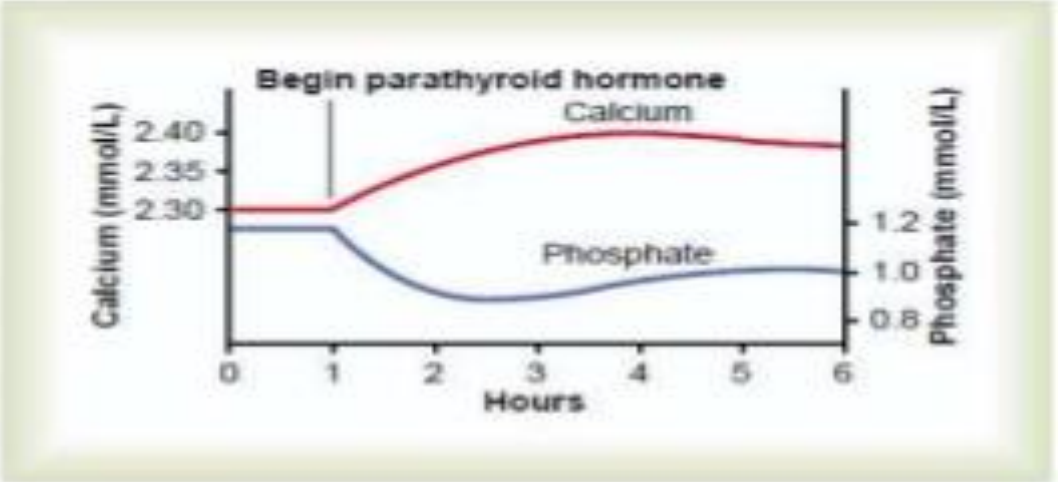


Figure 79–10

Approximate changes in calcium and phosphate concentrations during the first 5 hours of parathyroid hormone infusion at a moderate rate.

- PTH ↑calcium and phosphate absorption from the bone
- PTH ↓excretion of calcium by the kidneys.
- PTH ↑renal phosphate excretion **

** an effect that is usually great enough to override increased phosphate absorption from the bone.

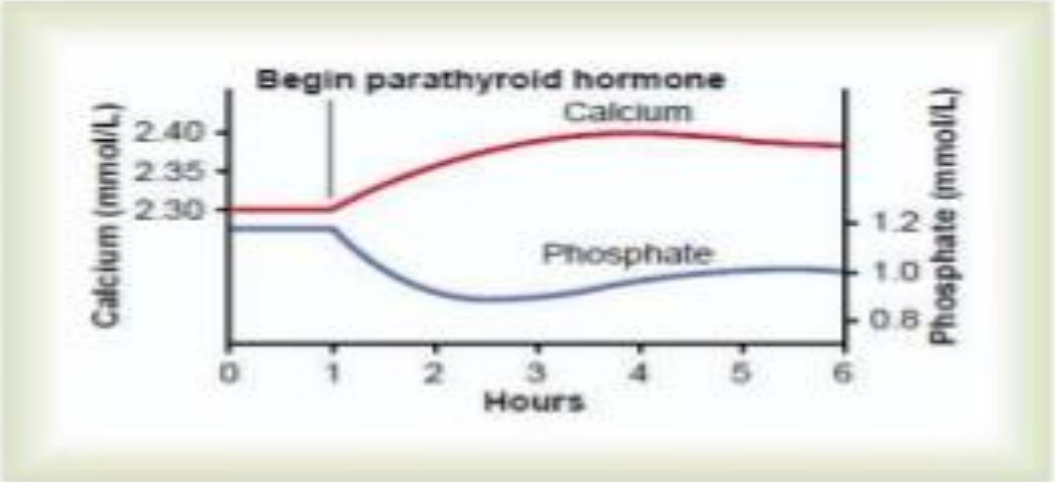


Figure 79–10

Approximate changes in calcium and phosphate concentrations during the first 5 hours of parathyroid hormone infusion at a moderate rate.

PTH ↑calcium and phosphate absorption from the bone

First phase	Second phase
rapid	**slow**
Minutes-hours	Days-weeks
Activation of already existing **osteocytes /osteoblasts**	Proliferation of **osteoclasts**
Receptor protiens on octeocytes/osteoblasts that bind PTH and activate calcium pump	Activated osteocytes/osteoblasts send **secondary signals** to osteoclasts
Promote **calcium and phosphate** absorption	Osteoclastic absorption of **bone** itself

Disorders of PTH

- hypoparathyroidism
- Primary hyperparathyroidism
- Secondary hyperparathyroidism

Hypoparathyroidism

- ↓PTH→↓Ca^+ reabsorption from bone→↓ Ca^+ level in body fluids

- Bone remains strong

- If parathyroid glands are suddenly removed:
  - ✓ Ca^+ levels fall from 9.4mg/dl to 6-7 within few days
  - ✓ **Phosphate** concentration may **double**
  - ✓ **↓Ca^+→tetany**

- **Laryngeal muscles tetany**→obstructs respiration →death

Hypoparathyroidism

- Treatment

- ✓ hypoparathyroidism is usually **not treated with PTH** administration.
- ✓ large quantities of **vitamin D** daily
- ✓ 1-2 grams of **Calcium**
- ✓ **1,25-dihydroxycholecalciferol**

Primary Hyperparathyroidism

- **Osteoblastic activity** in the bones also **increases** greatly in attempt to make up for the old bone absorbed by the osteoclastic activity.

- When the osteoblasts become active, they secrete large quantities of **alkaline phosphatase**. Therefore, one of the important diagnostic findings in hyperparathyroidism is a high level of plasma alkaline phosphatase.

Primary Hypeparathyroidism

- **Tumor in parathyroid glands** (females mainly)→ excess PTH → **↑Ca concentration in ECF. ↓Phosphate**
- In severe hyperparathyroidism the bone may be eaten away entirely.
- Indeed, the reason a hyperparathyroid person seeks medical attention is often a broken bone.

Kidney stones

- **Mild hyperparathyroidism** leads to formation of kidney stones(calcium phosphate, calcium oxalate stones)

- Kidney stones are more common in alkaline urine(low solubility in alkaline media)→**treatment include acidotic diet & acidic drugs.**

Secondary hyperparathyroidism

- high levels of PTH occur as a compensation for **hypocalcemia**
- this contrasts with primary hyperparathyroidism, which is associated with hypercalcemia.
- caused by **vitamin D deficiency** or **chronic renal disease** in which the damaged kidneys are unable to produce sufficient amounts of the active form of vitamin D

Introduction to Biochemistry

MACROMOLECULES

Building Blocks

All large molecules (macromolecules) in our bodies are created from monomers. The building and deconstruction of these macromolecules are done by two processes.

Dehydration Synthesis

Simply put, we take small things and make one big thing.

Dehydration = removing water

Synthesis = put together

Hydrolysis

Simply put, we use water to break a big thing apart.

Hydro = water

lysis = break apart

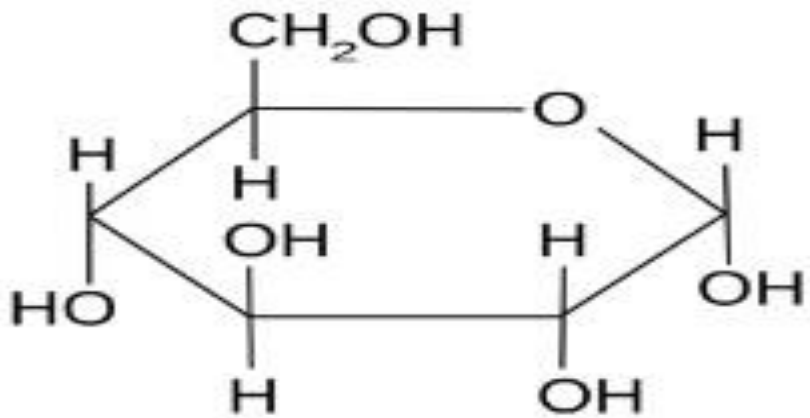
CARBOHYDRATES

Structure

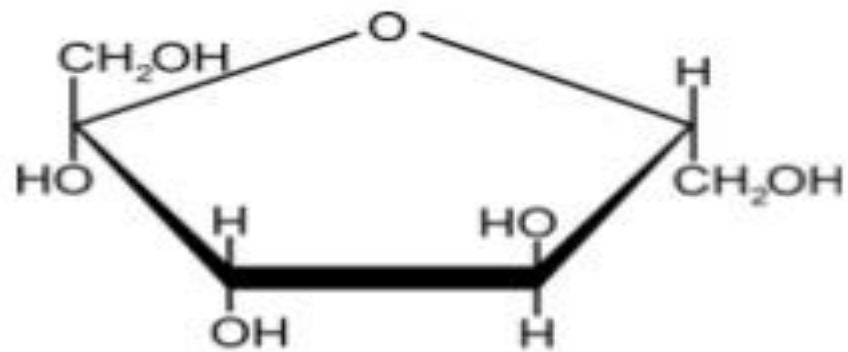
The building blocks of carbohydrates are **monosaccharides**.

All carbohydrates follow the generic formula of $C_nH_{2n}O_n$

Examples of monosaccharides include:



Glucose ($C_6H_{12}O_6$)

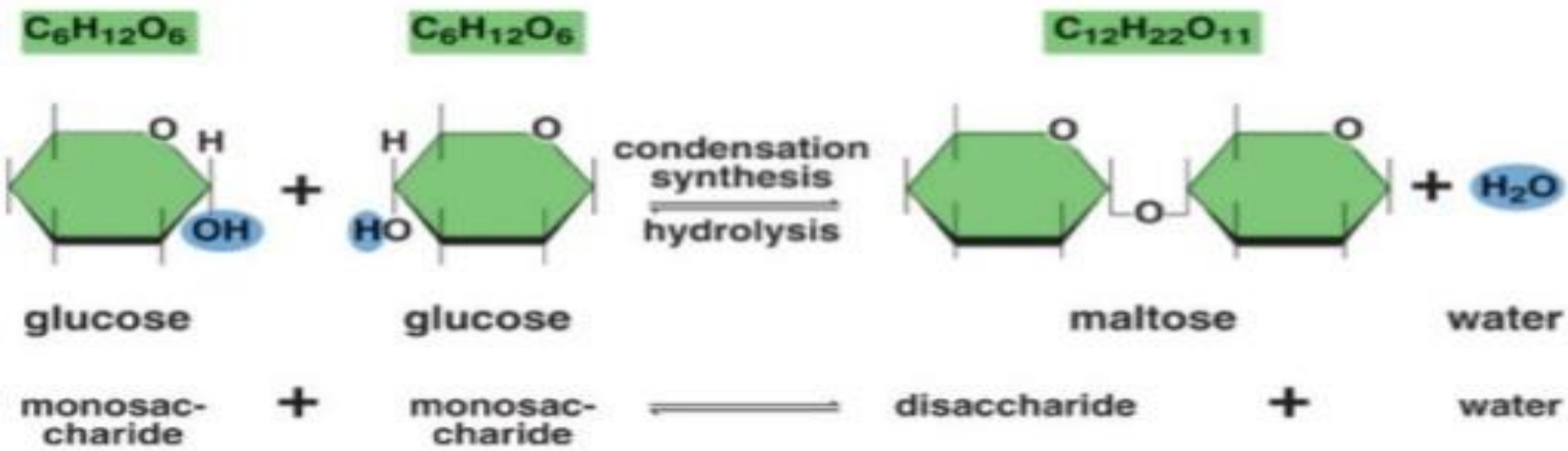


Fructose ($C_6H_{12}O_6$)

CARBOHYDRATES

Polymers

Disaccharides: When two monosaccharides are joined together in a dehydration synthesis reaction they form a disaccharide.



CARBOHYDRATES

Polymers

Examples of Disaccharides:

Maltose = Glucose + Glucose

Sucrose = Glucose + Fructose

Lactose = Glucose + Galactose

CARBOHYDRATES

Polymers

Polysaccharide: When very long chains of monosaccharides are arranged into a complex molecule we call this a polysaccharide.

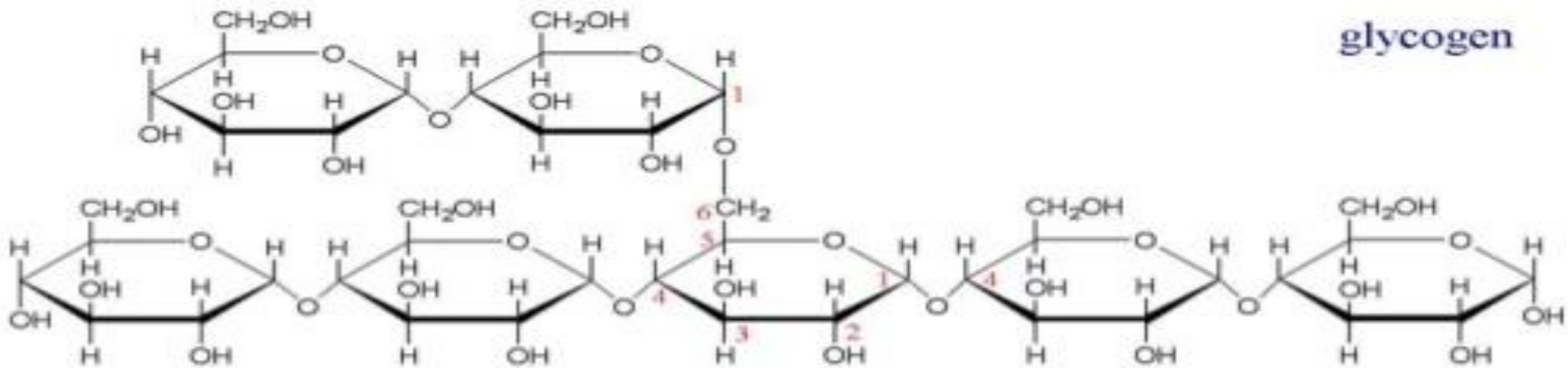
Polysaccharides have different structures and functions depending on the monomers that produce them.

CARBOHYDRATES

Polymers

Glycogen: Produced when very long chains of the monomer glucose are bonded together.

Function: Long term energy storage in animals.



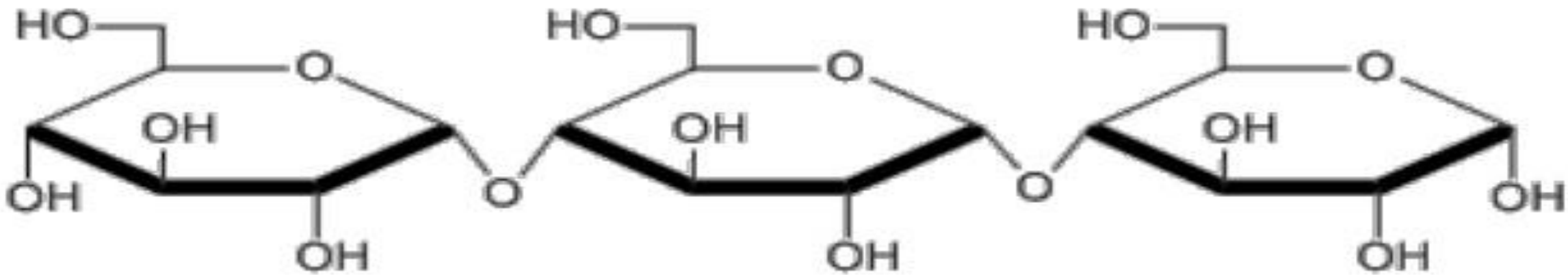
glycogen

CARBOHYDRATES

Polymers

Starch: Produced when very long chains of the monomer glucose are bonded together.

Function: Long term energy storage in plants.

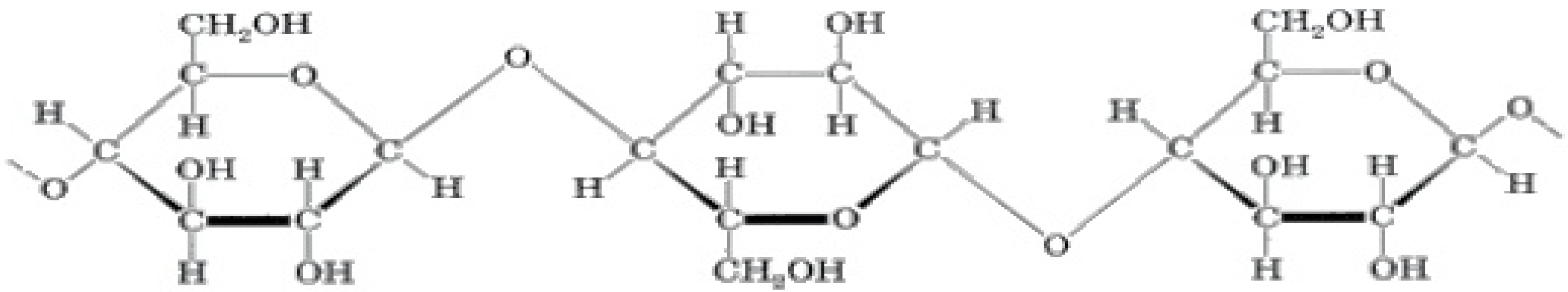


CARBOHYDRATES

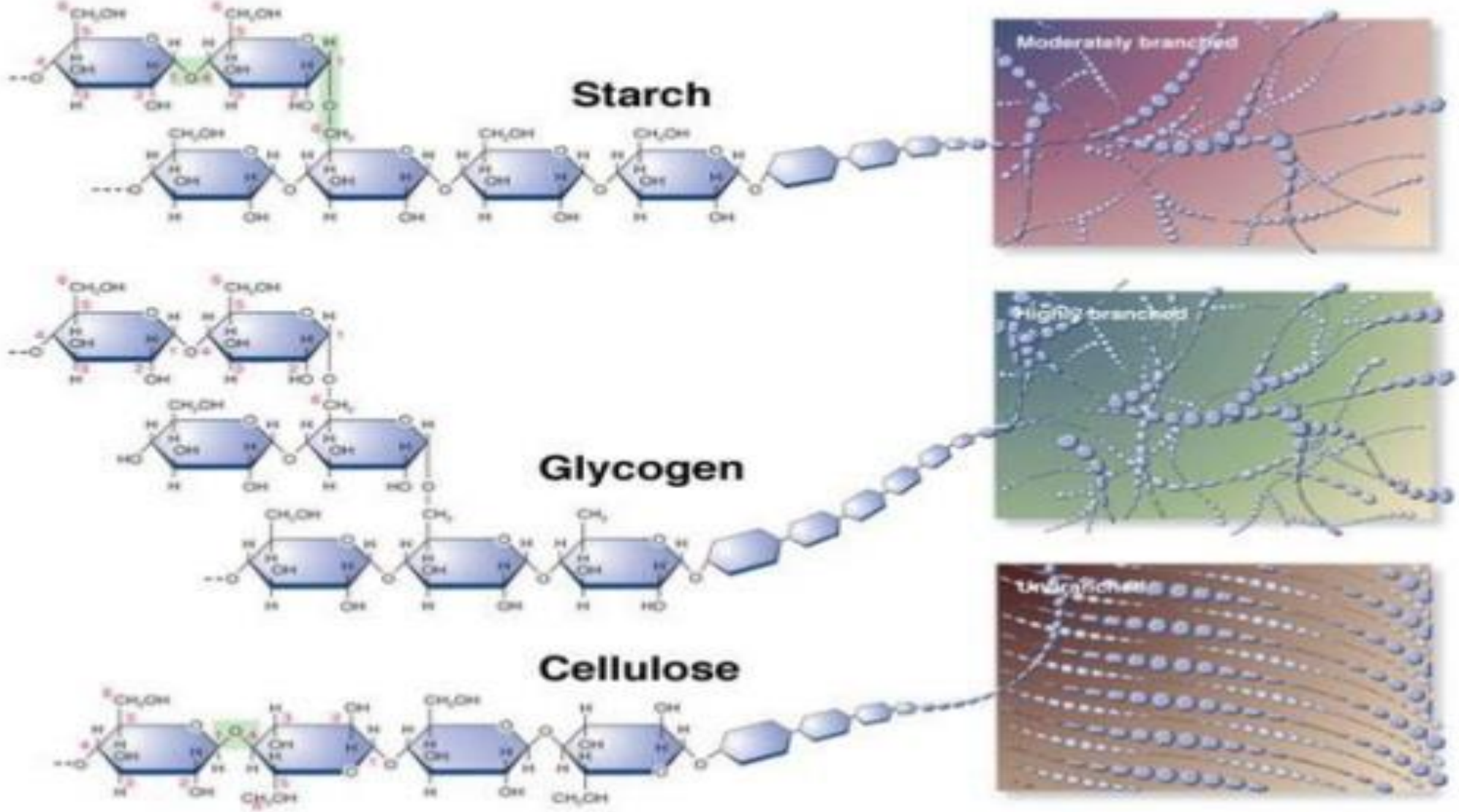
Polymers

Cellulose: Produced when very long chains of the monomer glucose are bonded together. The difference between starch and cellulose is the monomer glucose is reversed 180 degrees each time in cellulose.

Function: Structural compound found in plants.



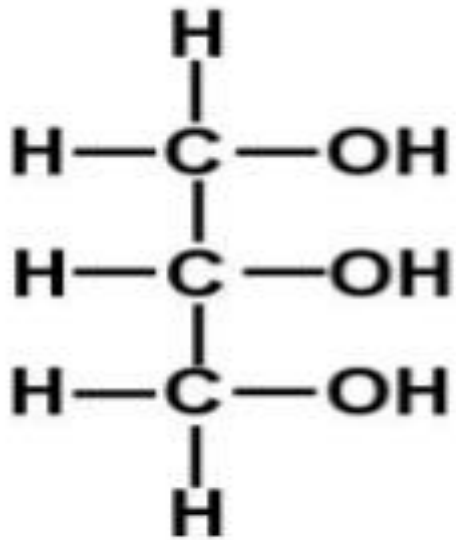
CARBOHYDRATES



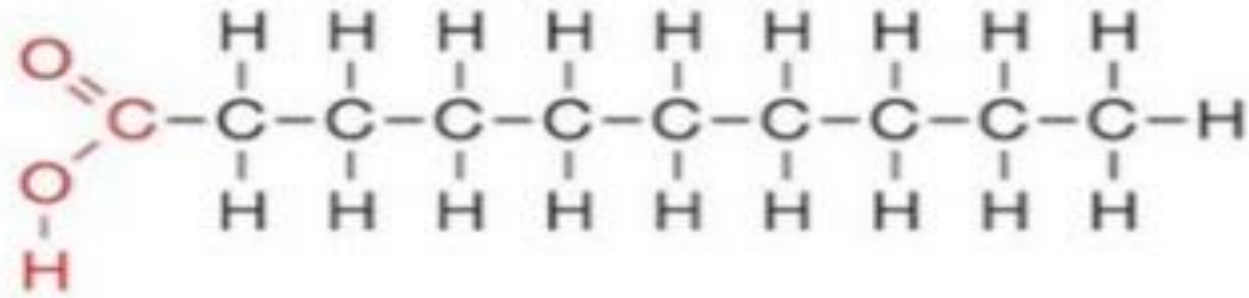
LIPIDS

Structure

All lipids are insoluble in water. The building blocks of lipids are **glycerol and fatty acids.**



Glycerol



fatty acid (saturated)

LIPIDS

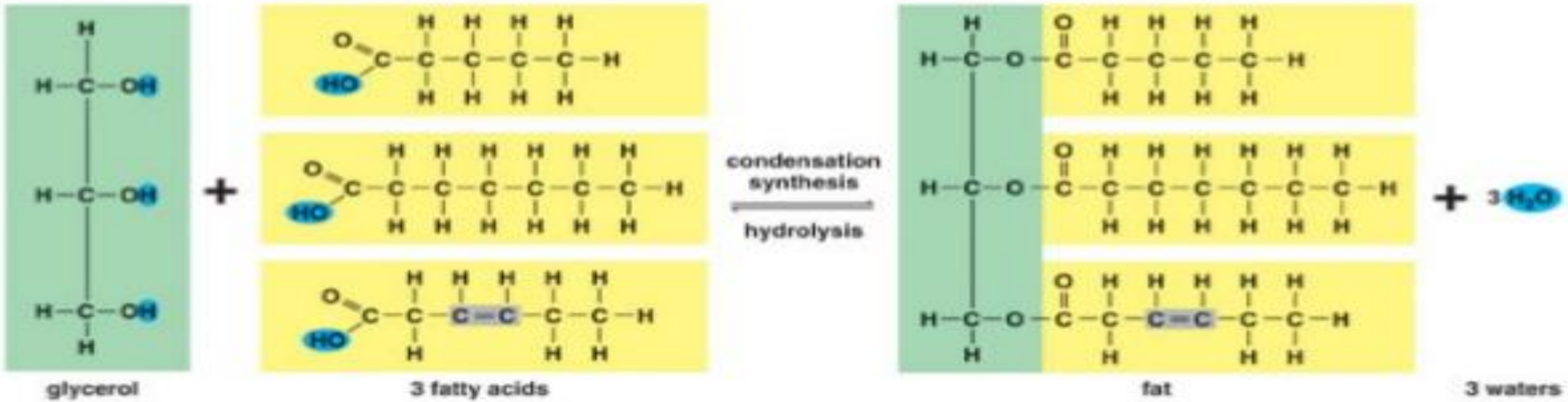
Function

- Long term energy stores
- Membrane formation
- Serve as hormones
- Provide insulation
- Protection of internal organs

LIPIDS

Polymers

Triglycerides: fats and oils that are formed by synthesizing a glycerol molecule with 3 fatty acids.



LIPIDS

Polymers

Triglycerides: the fatty acids (10-30 carbon chains) are what provide the variability in fats and oils.

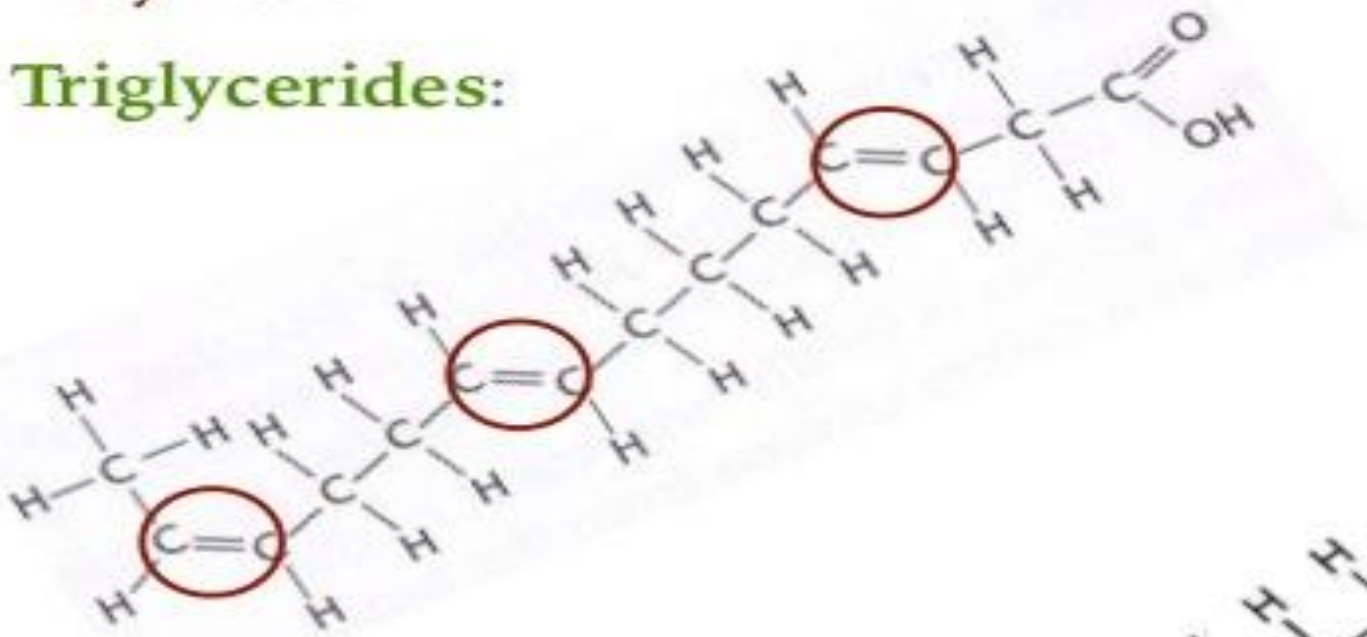
Saturated fatty acids: all the carbon atoms in the chain contain the maximum number of hydrogen atoms. Usually solid at room temperature

Unsaturated fatty acids: one or more double bonds between carbon atoms in the chain. Usually liquid at room temperature.

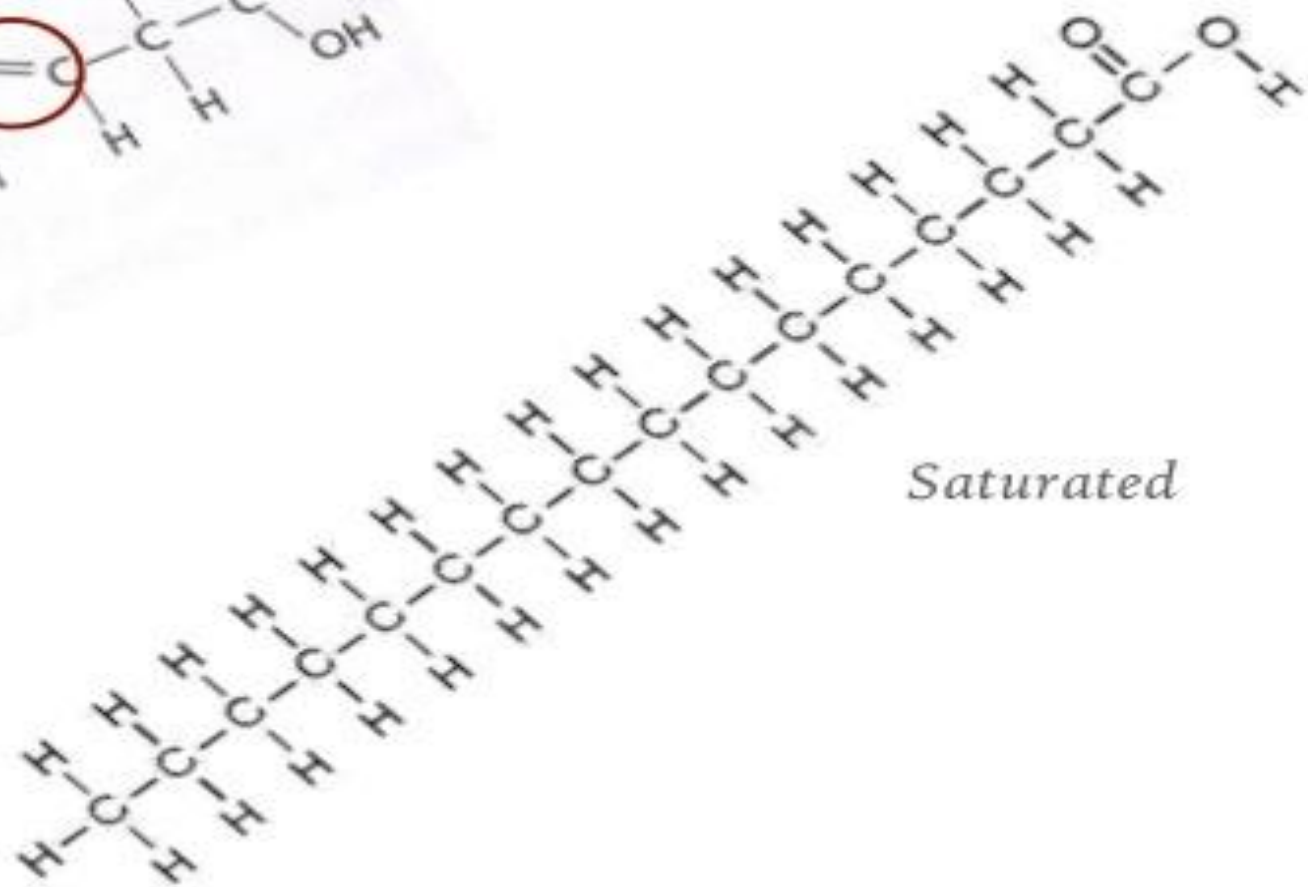
LIPIDS

Polymers

Triglycerides:



Unsaturated

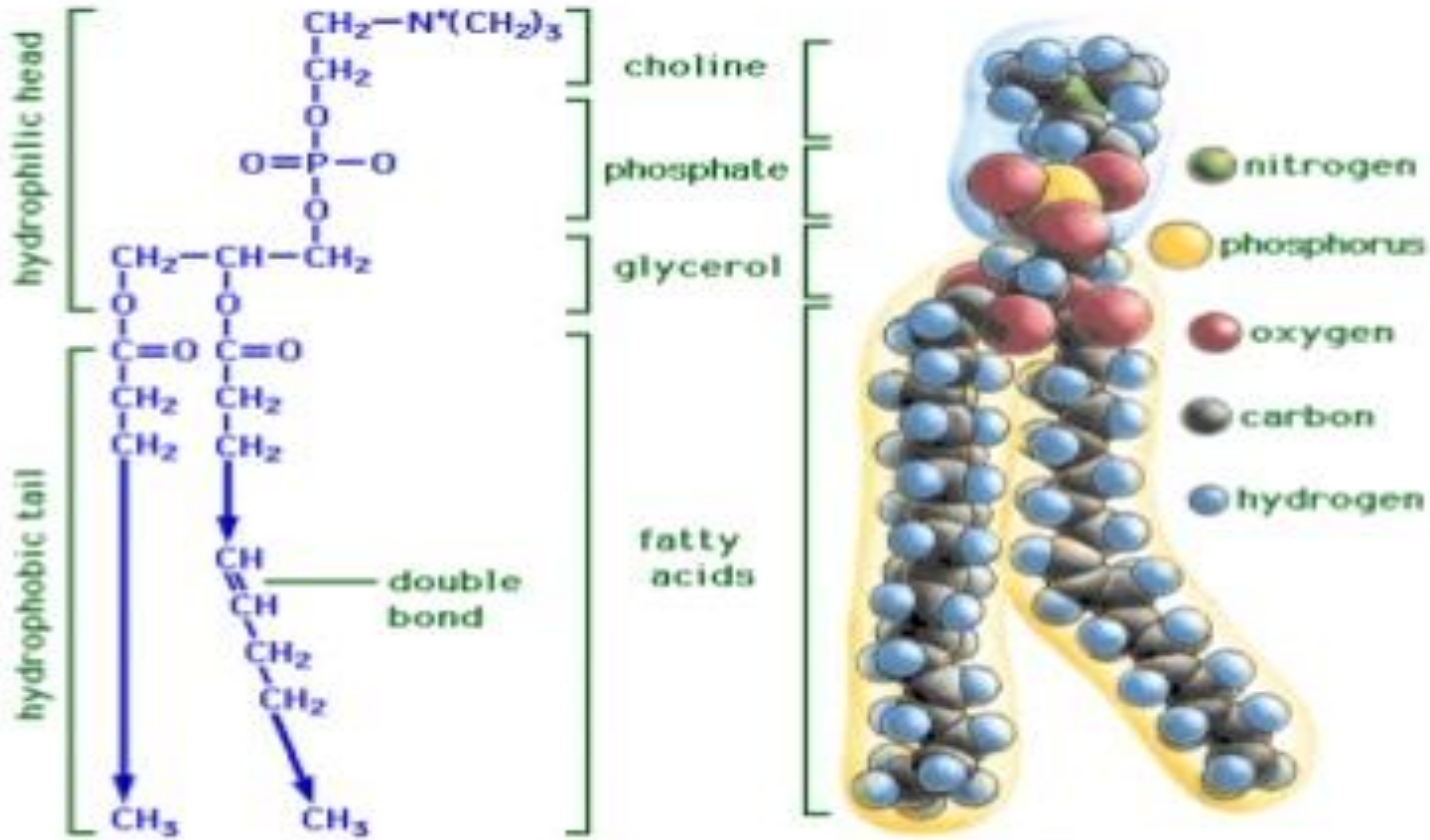


Saturated

LIPIDS

Polymers

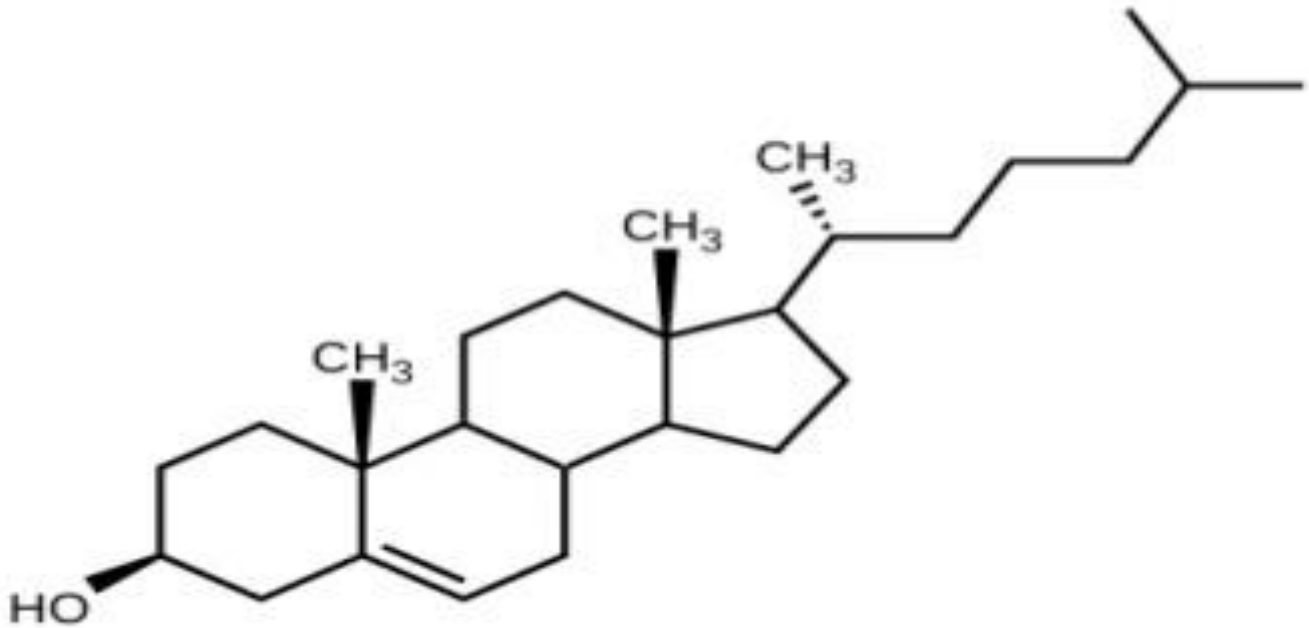
Phospholipids: A modified triglyceride. One fatty acid is removed and replaced with a phosphate group. This creates a polar molecule. One end hydrophilic (water loving) and the other is hydrophobic (water hating)



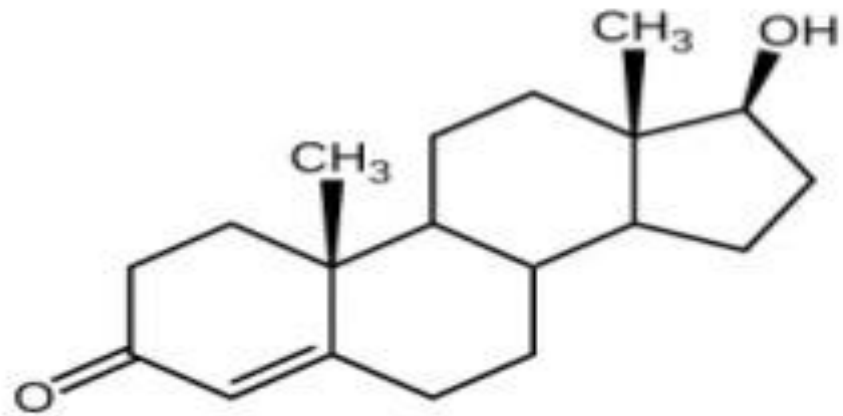
LIPIDS

Polymers

Cholesterol and Derivatives: found in many areas of the body such as cell membranes. Also include steroids and bile acid.



(a) Cholesterol



(b) Testosterone

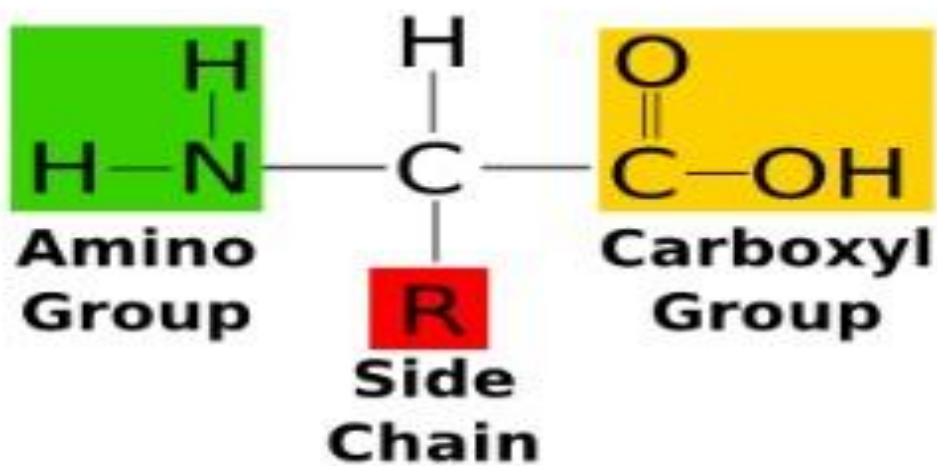
PROTEINS

Structure

The building blocks of proteins are **amino acids**. One end contains an amine group and one end contains a carboxyl group.

There are 20 amino acids, of which 9 can not be produced by your body.

The generic amino acid molecule looked like this:



PROTEINS

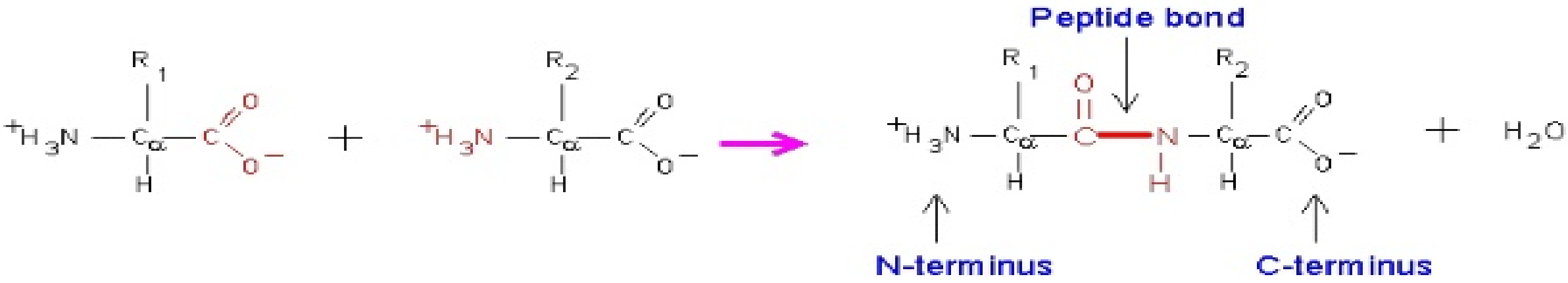
Function

- Structural Proteins
- Enzymes - speed reactions (end in ase)
- Antibodies
- Transport carriers
- Allow materials to cross cell membrane

PROTEINS

Polymers

Peptide chains: amino acids are bonded together via dehydration synthesis. The bond formed between amino acids are called peptide bonds.



PROTEINS

Polymers

Levels of Organization: The more amino acids that are added to the structure, the more complex it becomes. We group proteins structures into 4 classifications.

Primary: polypeptide chain.

Secondary: α helix and β sheets

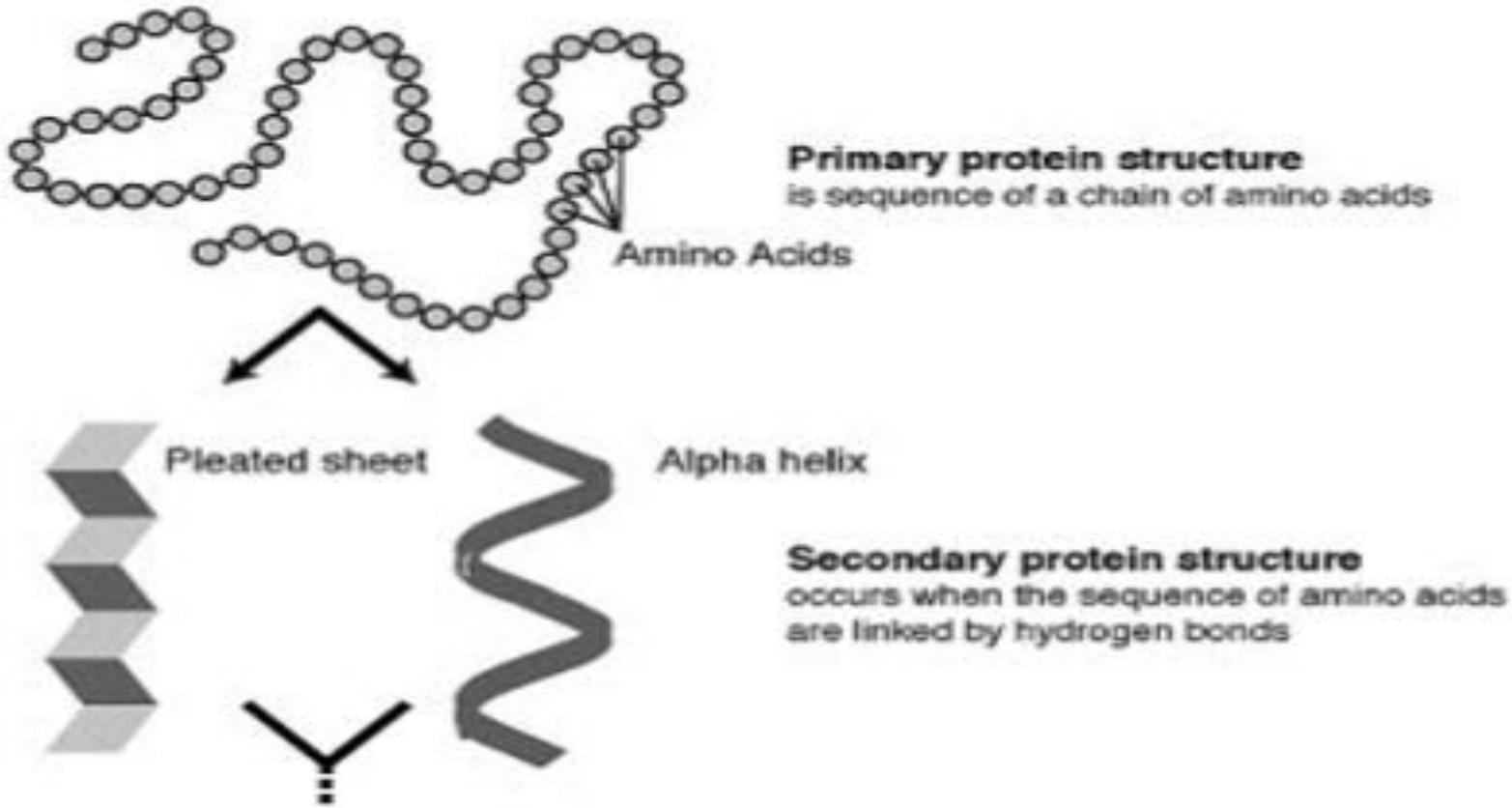
Tertiary: Globular Structures

Quaternary: Multiple polypeptide chains.

PROTEINS

Polymers

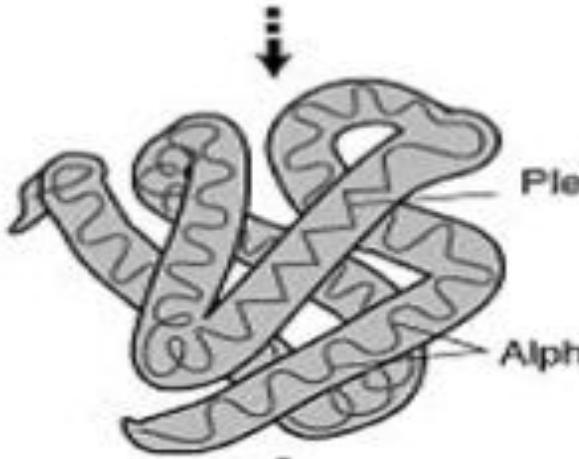
Levels of Organization:



PROTEINS

Polymers

Levels of Organization:



Tertiary protein structure
occurs when certain attractions are present between alpha helices and pleated sheets.

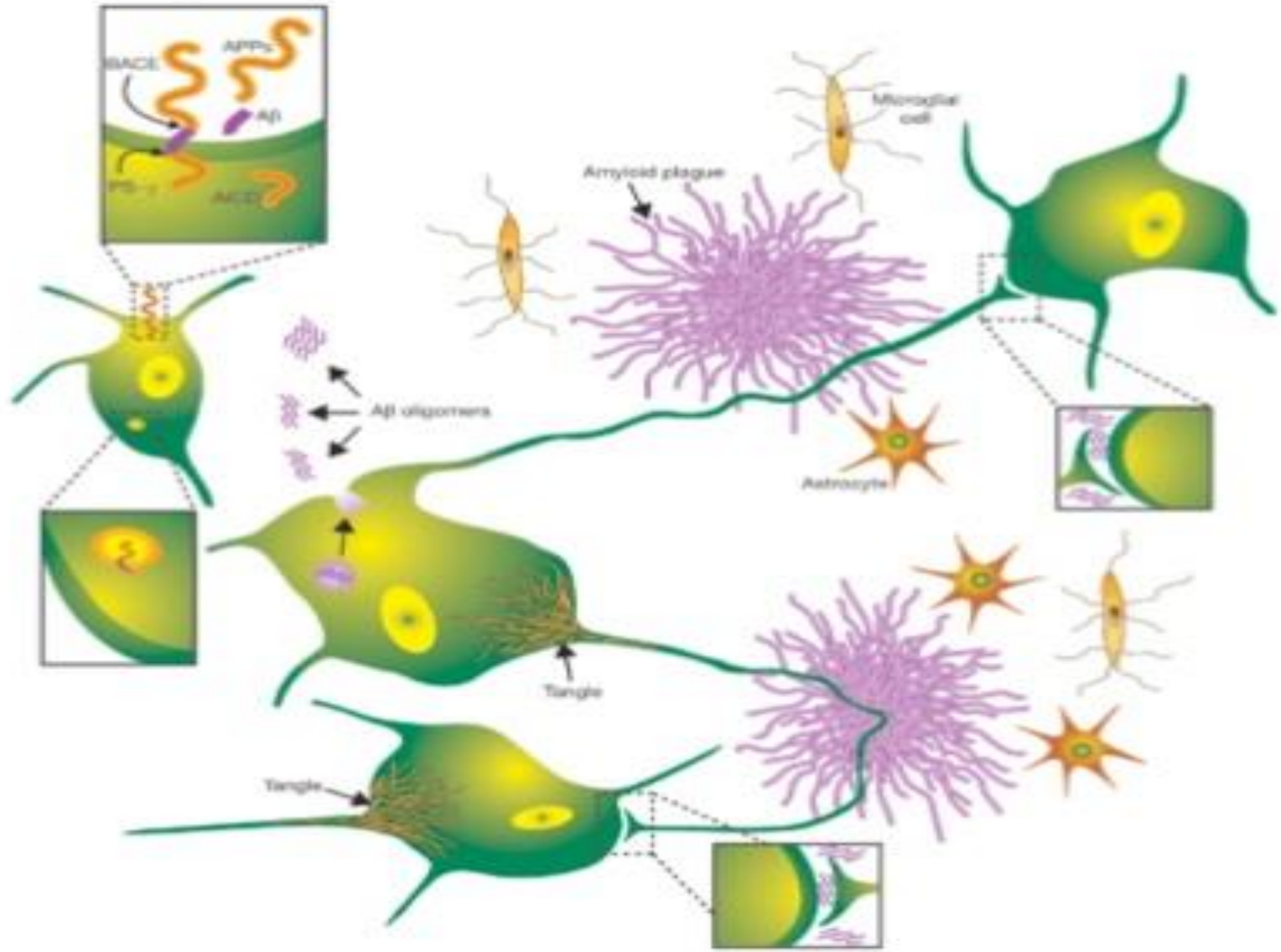
Quaternary protein structure
is a protein consisting of more than one amino acid chain.

PROTEINS – DISEASE

Alzheimer's

Amyloid plaque made of protein envelops axons

Tau changes shape and stick together causing tangles inside cell bodies.



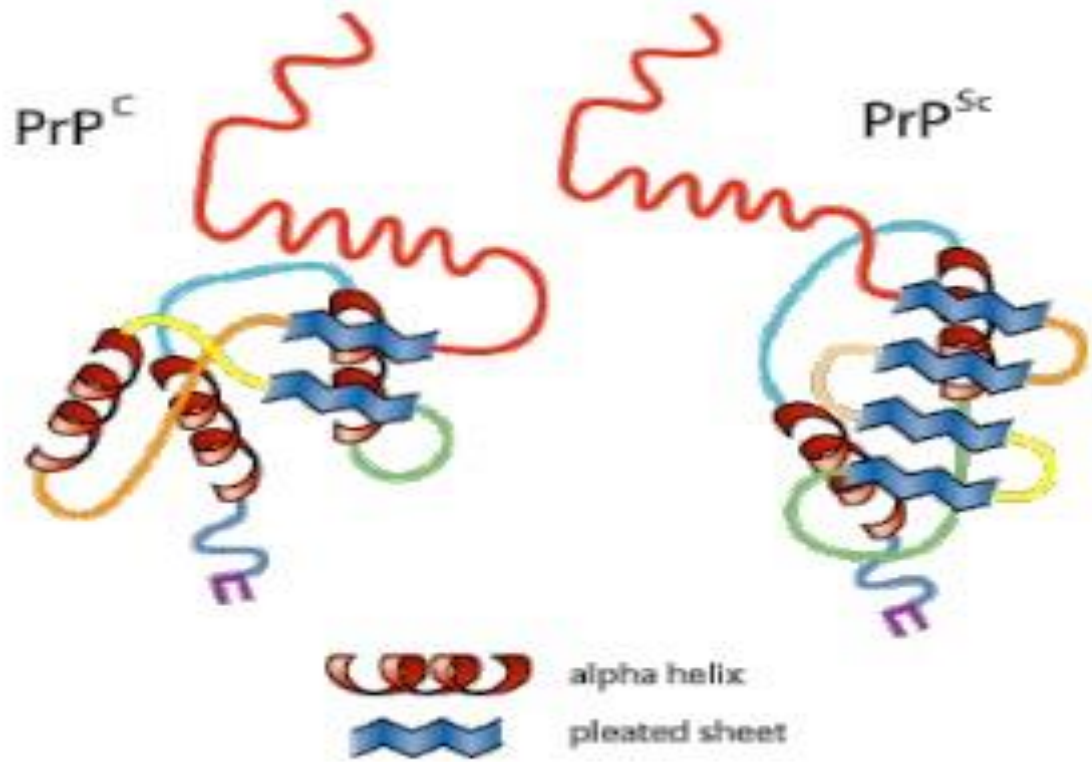
PROTEINS – DISEASE

Creutzfeld-Jacobs disease

Normally soluble prion proteins become insoluble

These proteins become insoluble in the presence of other insoluble prions

Insoluble prions damage brain tissue causing disease



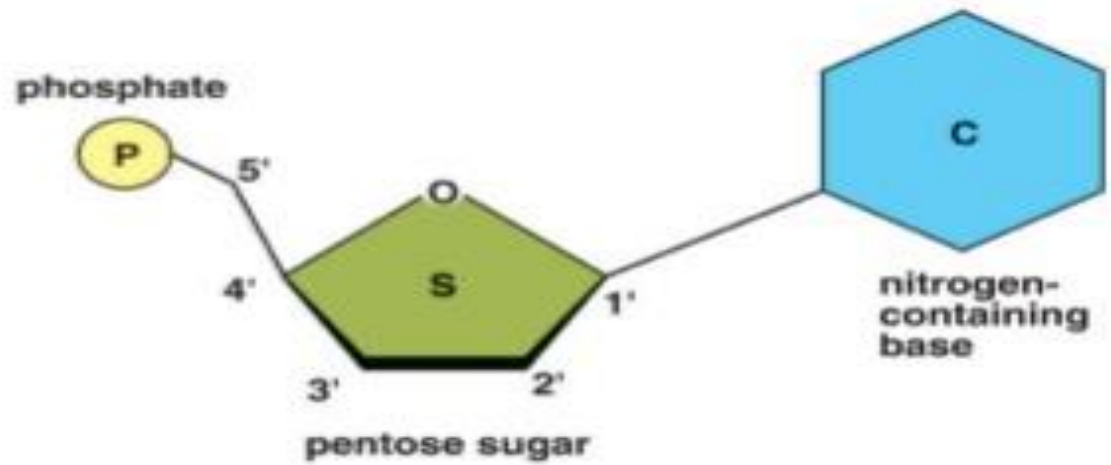
NUCLEIC ACIDS

Structure

The building blocks of nucleic acids are **nucleotides**.

Nucleotides consist of a phosphate group, a 5 sided sugar, and a nitrogenous base.

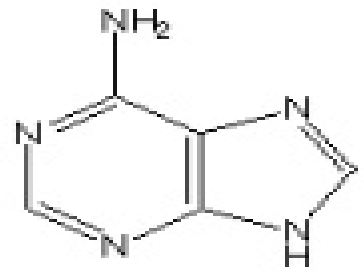
The generic nucleotide molecule looked like this:



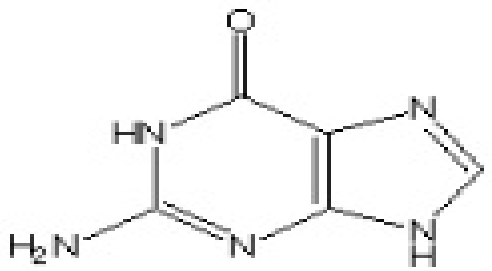
NUCLEIC ACIDS

Structure

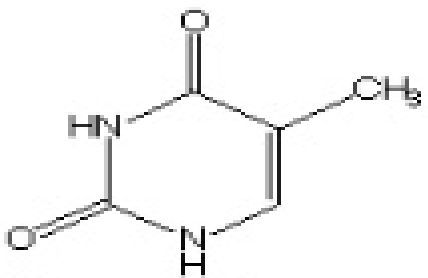
There are 5 nitrogenous bases that are used to create the polymers DNA and RNA.



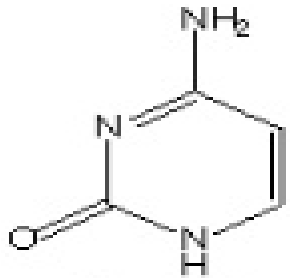
adenine



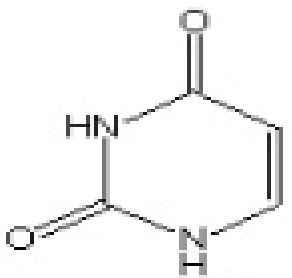
guanine



thymine



cytosine



uracil

NUCLEIC ACIDS

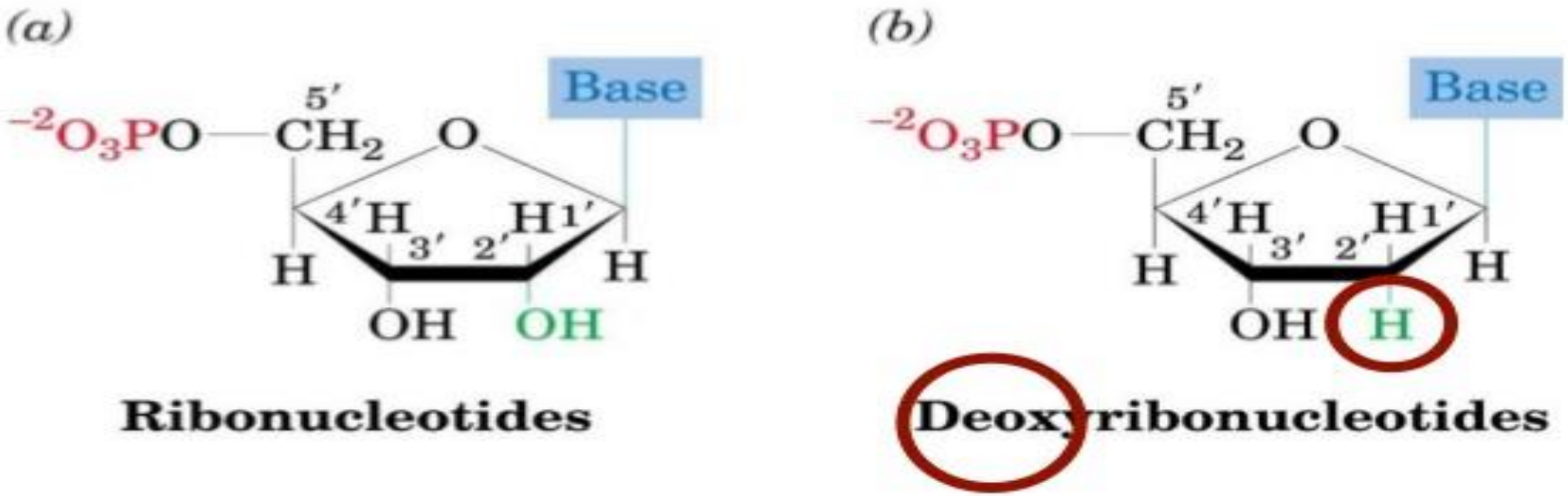
Function

- Energy
- Storage and transfer of genetic information

NUCLEIC ACIDS

Polymers

DNA and RNA:



NUCLEIC ACIDS

Polymers

DNA and RNA:

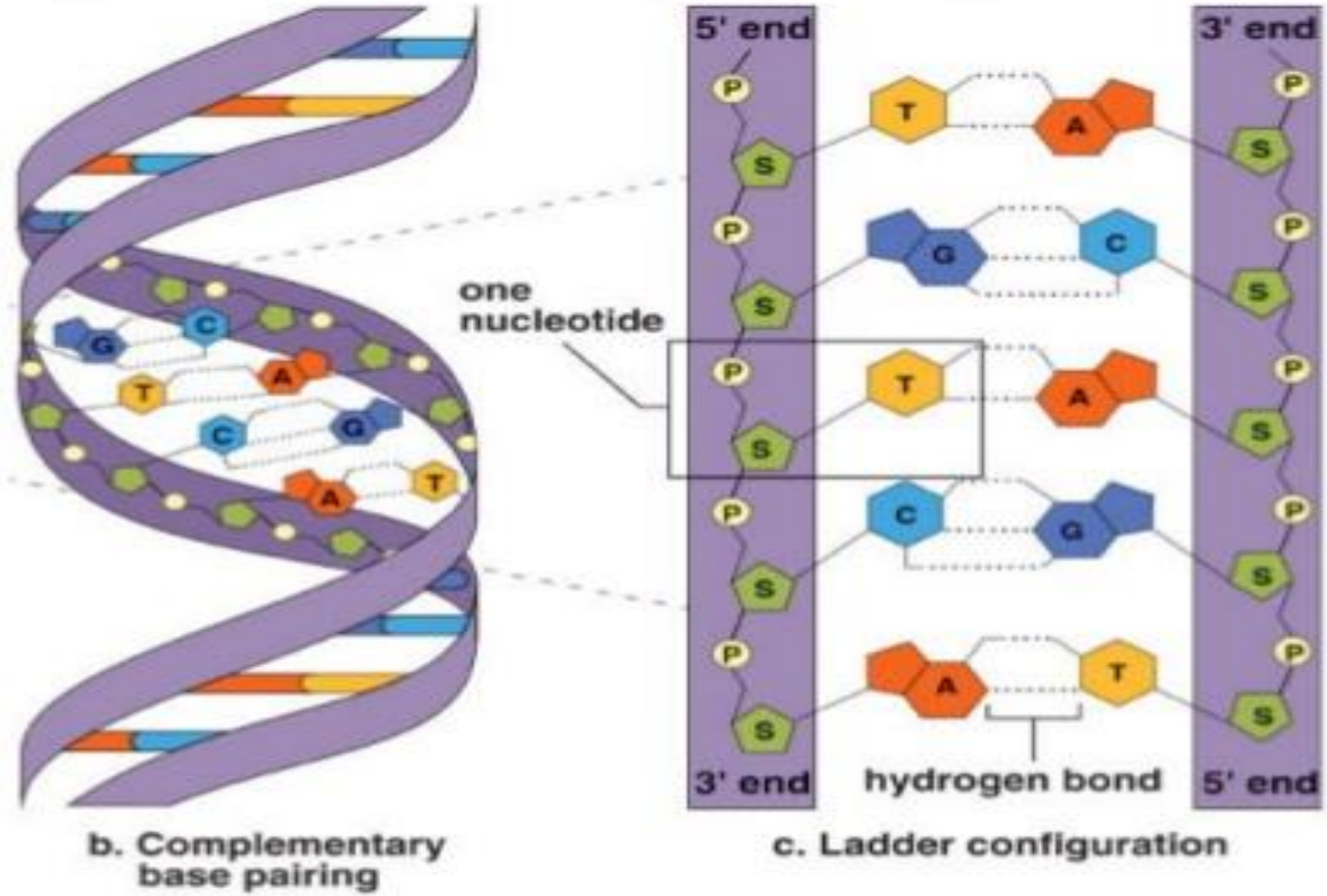
Table 2.3 DNA Structure Compared to RNA Structure

	DNA	RNA
Sugar	Deoxyribose	Ribose
Bases	Adenine, guanine, thymine, cytosine	Adenine, guanine, uracil, cytosine
Strands	Double stranded with base pairing	Single stranded
Helix	Yes	No

NUCLEIC ACIDS

Polymers

DNA:



NUCLEIC ACIDS

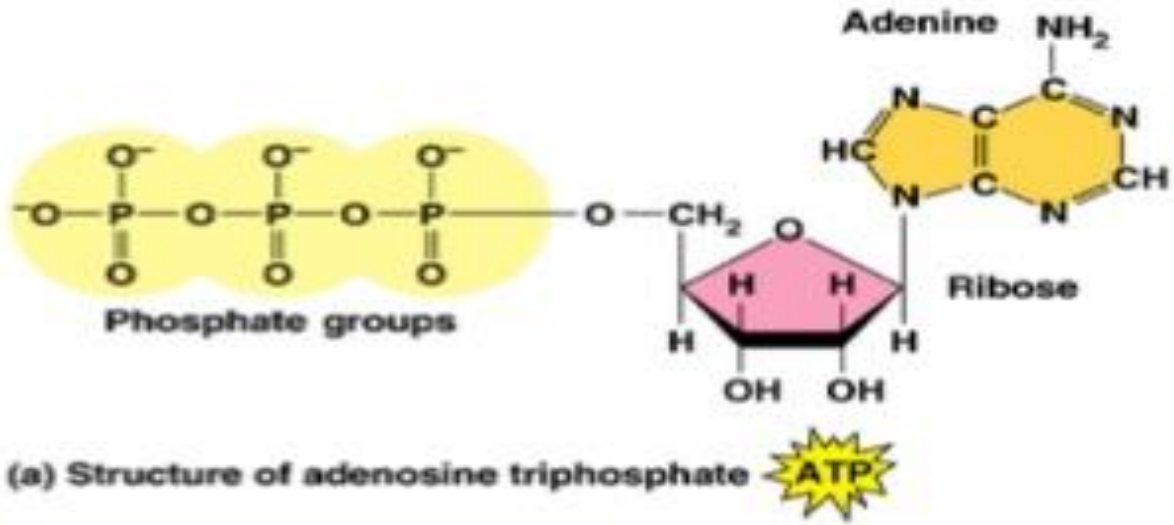
Special Nucleotide: ATP

Adenosine triphosphate (ATP) contains the nucleic acid adenine. It has 3 high energy phosphates attached.

ATP is the energy currency for the cell. When phosphates are removed, energy is released that allow for reactions to occur in the cell.

NUCLEIC ACIDS

Special Nucleotide: ATP



(a) Structure of adenosine triphosphate

Adenosine triphosphate (ATP)

Inorganic phosphate

Adenosine diphosphate (ADP)

(b) Hydrolysis of ATP

CLINICAL SIGNIFICANCE of Proteins in Blood and urine

Lac.3

By
Dr. Muna M. Yaseen

Objective

1. Type of proteins in blood
2. Clinical Diagnostic & Utility

of Proteins Measurements in blood

3. Causes of Proteinuria

- **Proteins** are Polypeptide group of nutrients in human body. All enzymes, receptors, membrane channels such as those of Na-K, Ca channels, coagulation factors and peptide hormones

(GH, prolactin,...),..., etc. are proteins in nature.

- All proteins are synthesized in the liver, with exception of complement systems

(C1-C9 these are components of immune system synthesized by liver and macrophages), and Immunoglobulin's (Igs) (by plasma cells of immune system).

- Proteins may be linear structural (such as collagen component of connective tissue) or globular functional such as enzymes & peptide hormones.

Amounts of proteins in blood depend on balance:

rate of synthesis ↔ (rate of catabolism + rate of clearance).

However, protein distribution between the Intravascular (IV) and Extra vascular compartments is also important and therefore blood protein concentrations are affected by dehydration & over hydration.

Proteins in blood involved two types:

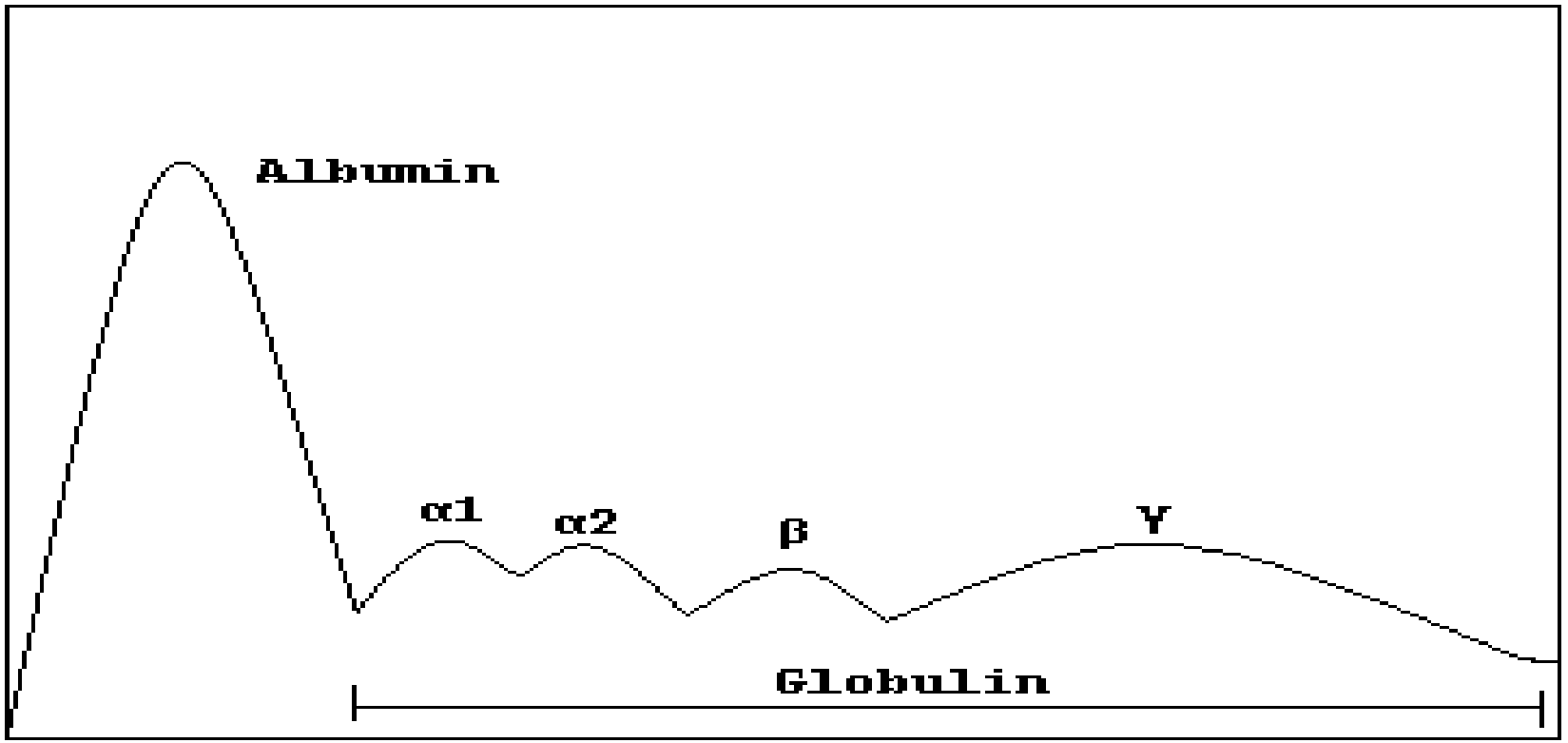
Albumin & total Globulin.

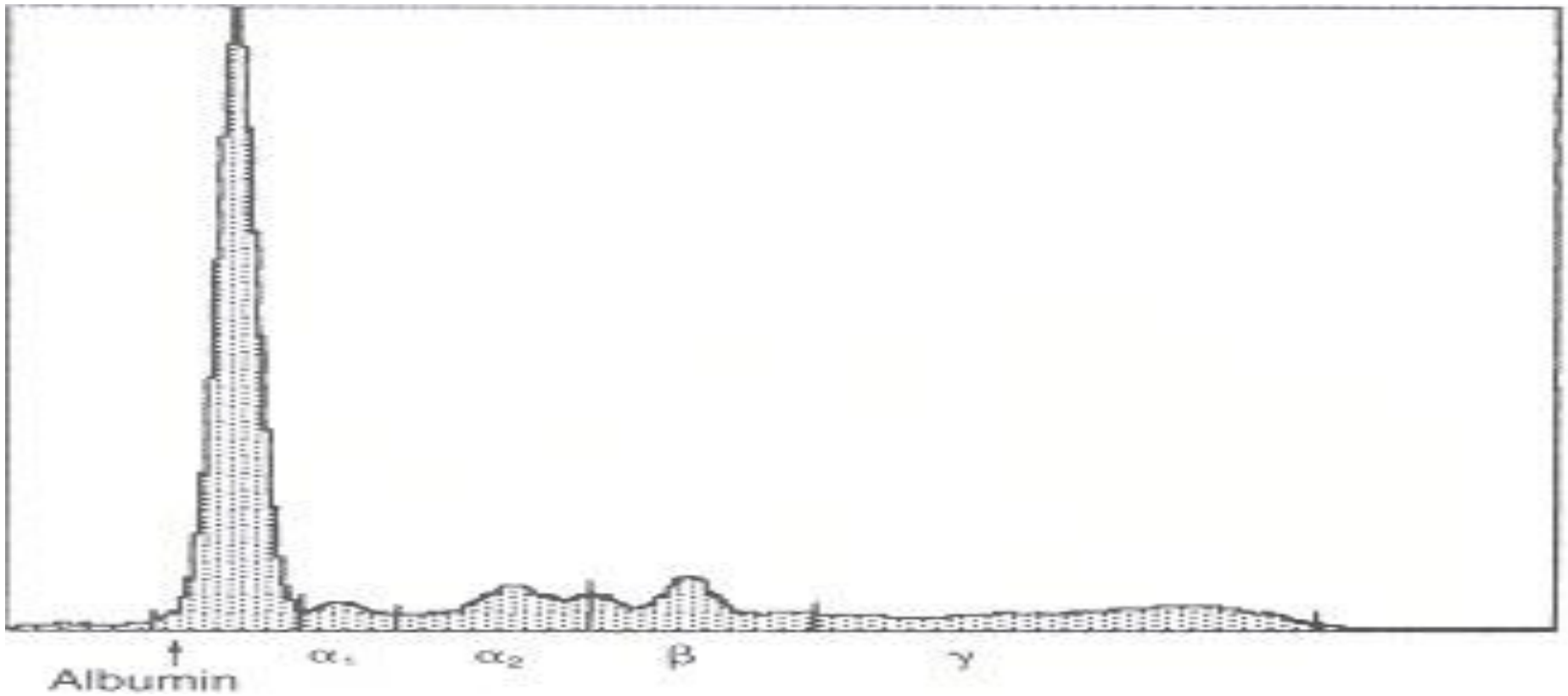
Albumin is the major single protein accounts to 60 % of total serum protein,

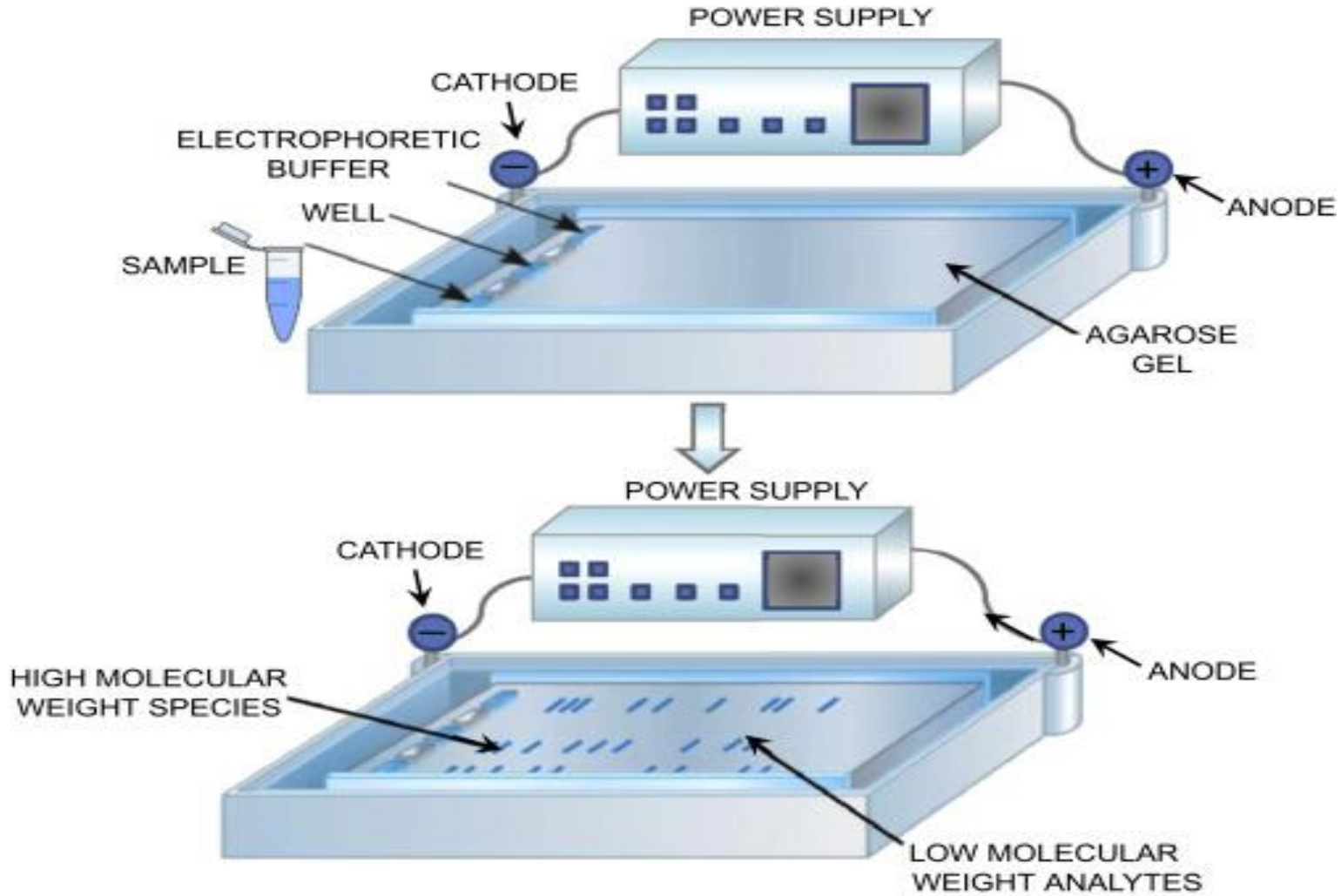
while globulin is consisted of 4-5 fractions**; α 1, α 2, β 1, β 2, and γ globulins**.

These Proteins components are separated by **electrophoresis technique** in which serum is introduced to filter paper in a media of PH 8.6 to make protein which are polar substances negatively charged. Then electrical current is passed into media and the serum proteins are separated **according to their MW and charge intensity** into five–six fractions or bands: **albumin, α1- globulin, α2-globulin, β-globulin (may be β1 & β2), and γ globulin**.

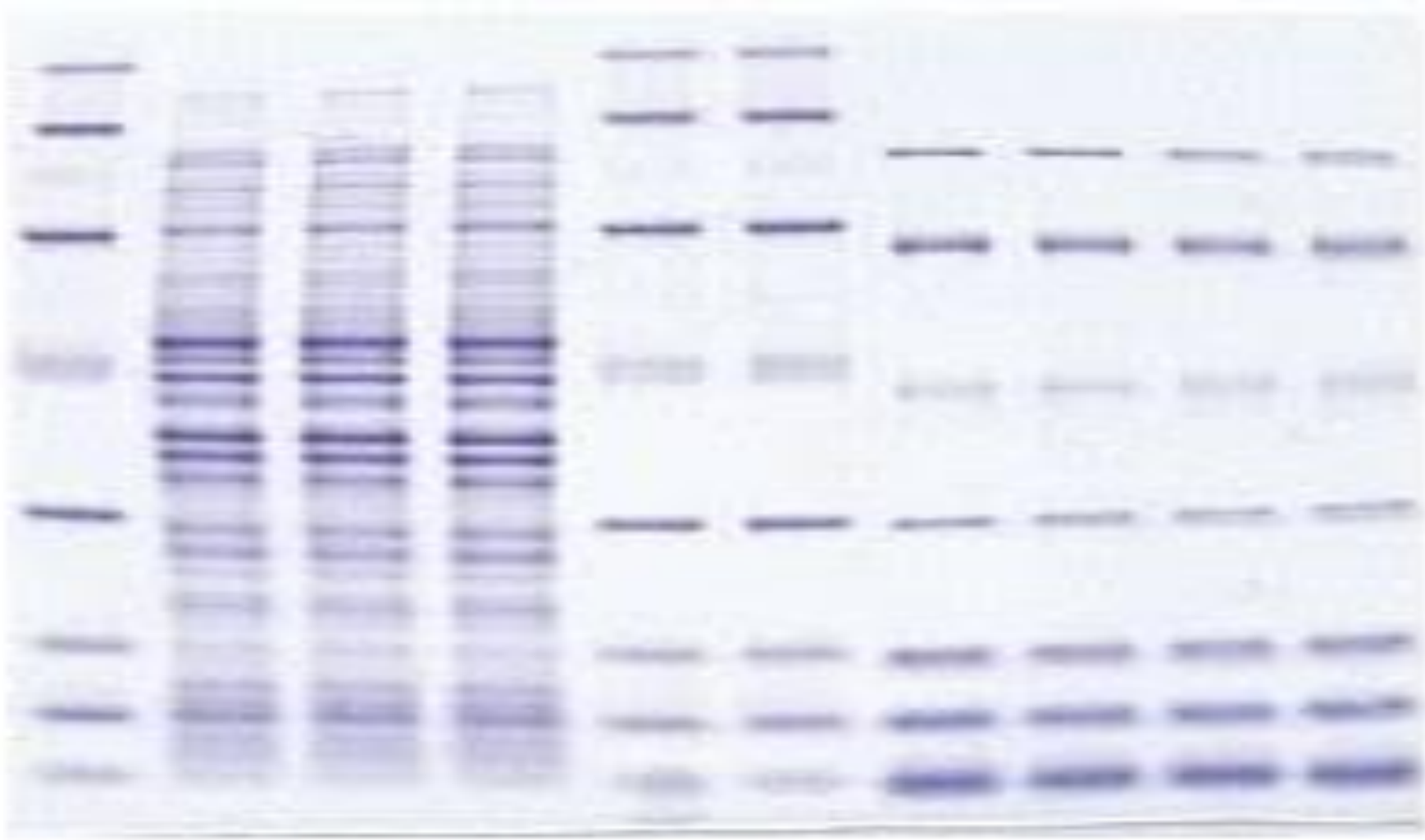
Total Serum Protein=S. albumin + total serum globulin.

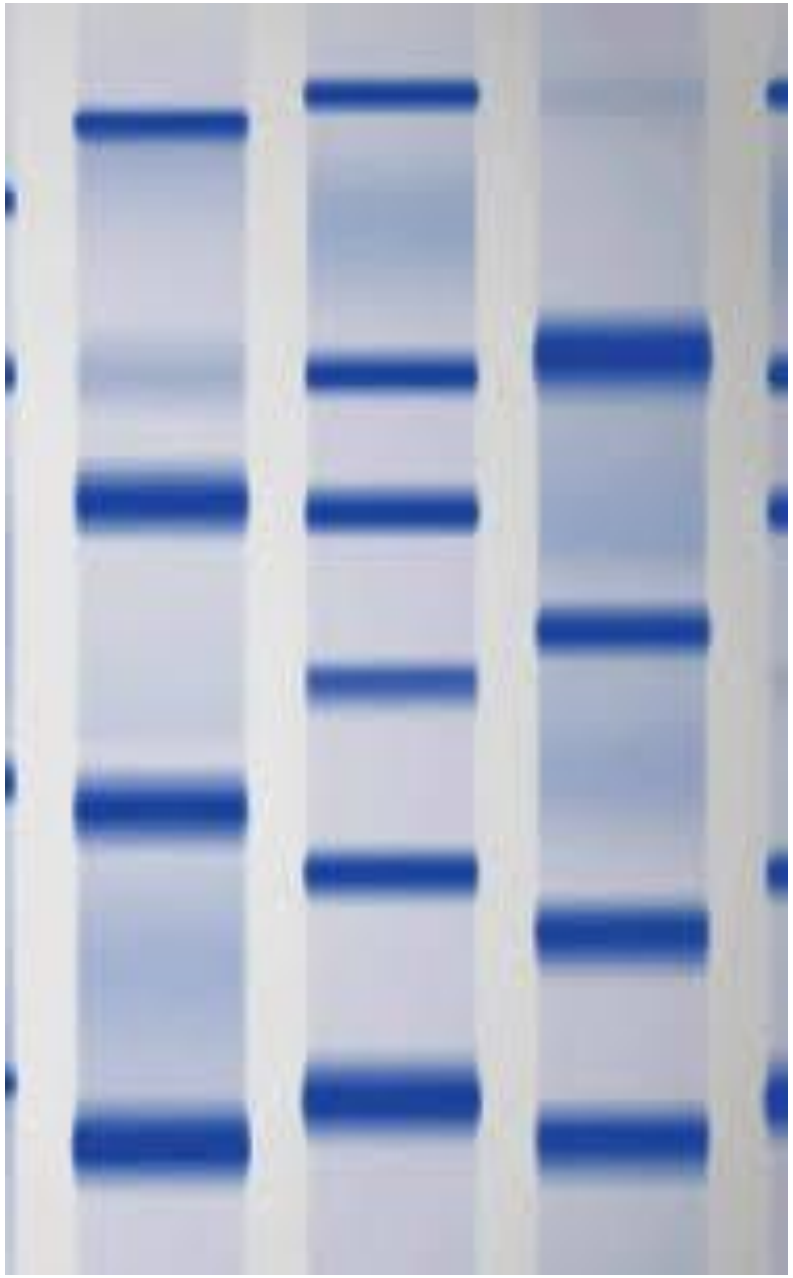

Albumin
α1
α2
β
γ
Globulin

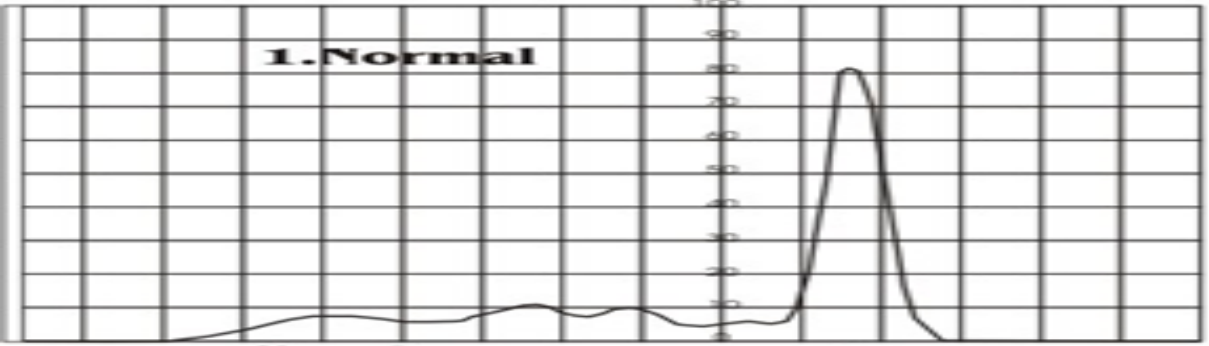

Albumin
α1
α2
β
γ

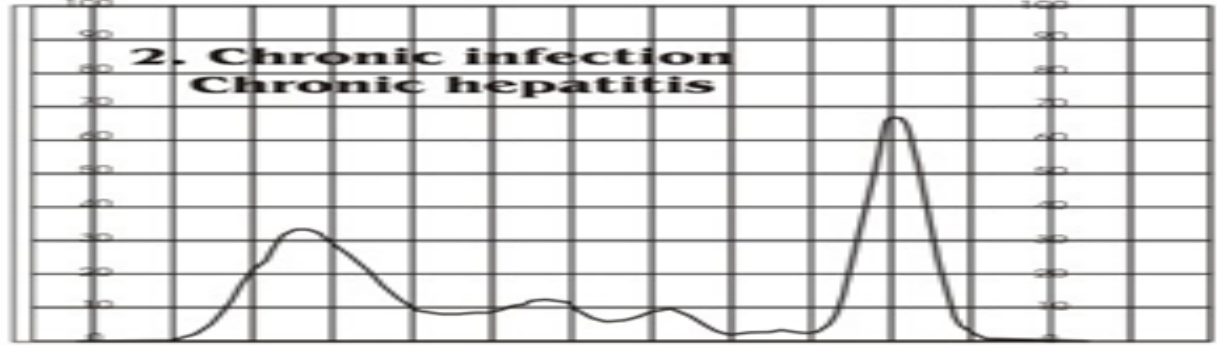

POWER SUPPLY
CATHODE
ELECTROPHORETIC BUFFER
WELL
SAMPLE
ANODE
AGAROSE GEL
POWER SUPPLY
CATHODE
ANODE
HIGH MOLECULAR WEIGHT SPECIES
LOW MOLECULAR WEIGHT ANALYTES

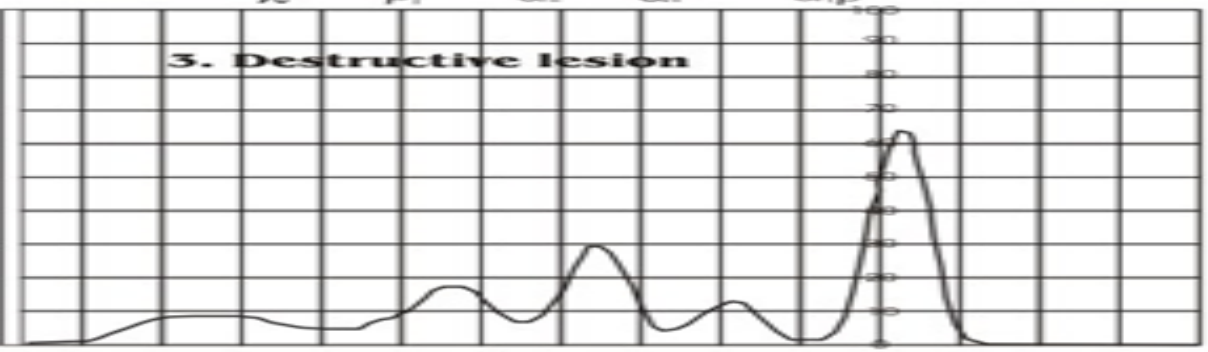

depositphotos

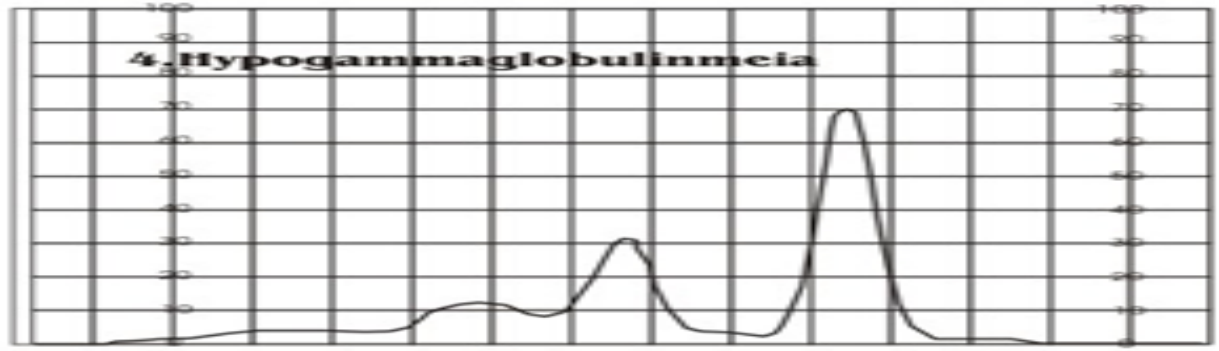


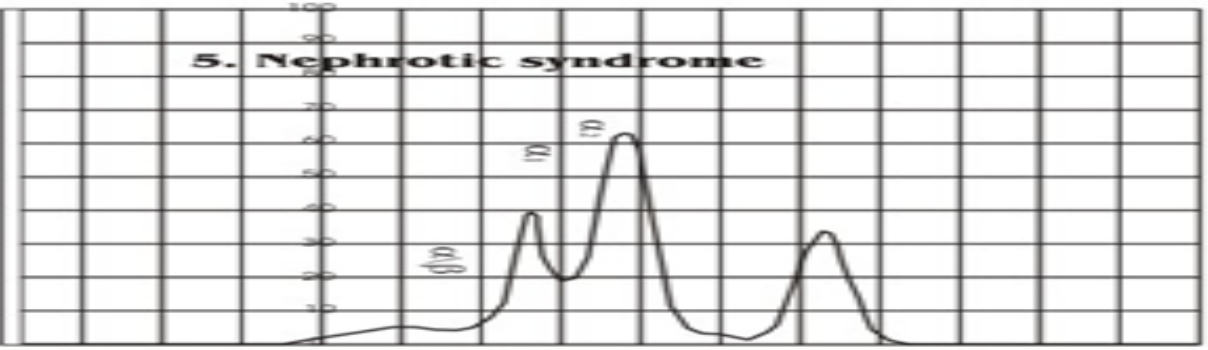


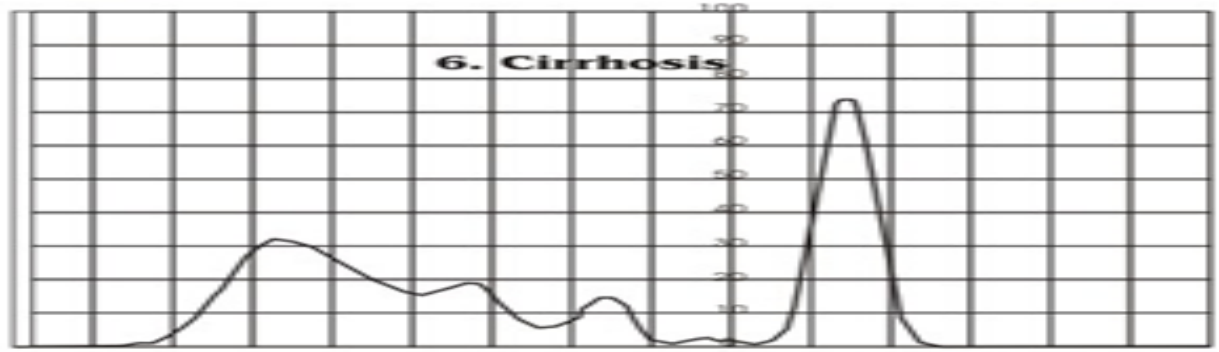

1.Normal
χ
β
α2
α1
α\β

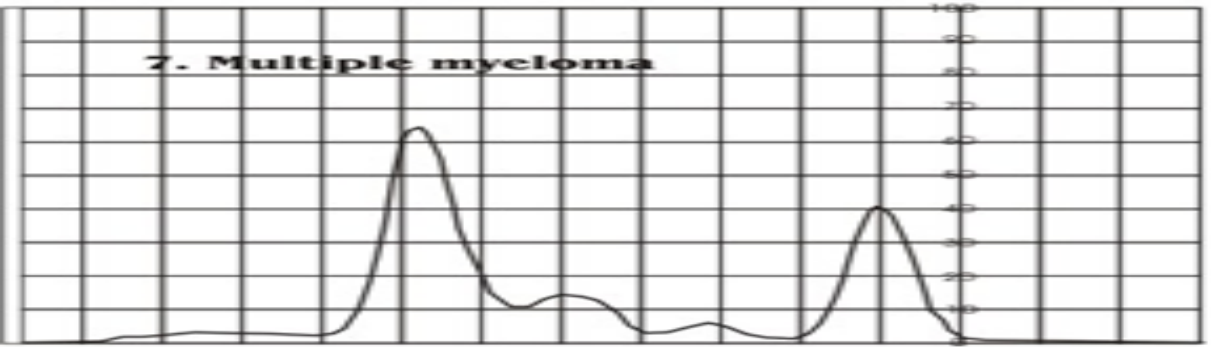

2. Chronic infection
Chronic hepatitis

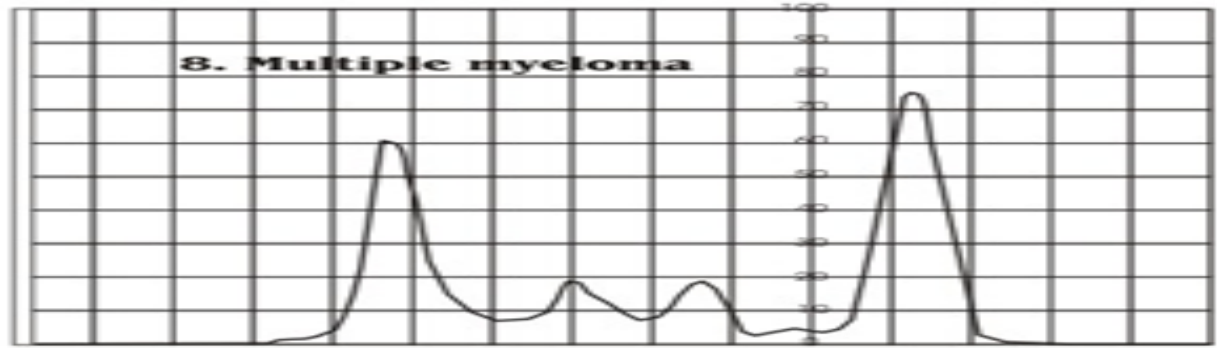

3. Destructive lesion


4.Hypogammaglobulinmeia


5. Nephrotic syndrome
α\β
α1
α2


6. Cirrhosis


7. Multiple myeloma


8. Multiple myeloma

Hyperproteinemia

are rare and are of no clinical significance value and may obtained from prolonged vein stasis during blood collection, posture (due to fluid redistribution) and from excessive dehydration.

Hypoalbuminemia:

It is clinically an important condition because albumin is one of the major components of osmotic colloid pressure of blood vessels and involved in normal fluid distribution between the Intravascular and Extra vascular compartments and in maintenance of normal blood pressure.

Albumin is also the major transporter substance in the blood; transporting bilirubin, fatty acids, steroid drugs, steroid & thyroid hormones,

Hypoalbuminemia

1. Chronic liver disease ; liver cirrhosis

2. Advanced kidney disease; Nephroteic syndrome &Chronic renal failure

3. Malnutrition (Kwashiorkor & Marasmus diseases) and Malabsorption like in Tropical intestinal diseases; Celiac disease

4. Loss through Enteropathy

5. skin lesions; extensive burns.

Clinical consequences Hypoalbuminemia :

1. edema due to migration of fluid from IV to interstitum compartment

2. transporting and binding capacity defects; such as for fatty acids, bilirubin, steroid Hs and drugs which may leads to toxicity with appropriate dose.

Analbuminemia is a rare disorder characterized by low blood albumin (s. albumin 10 gram/l; but of no edema or other symptoms and signs).

Globulin

This include 4-5 fractions (alpha 1, alpha 2, beta, and gamma fractions).

Increased in globulin may be due to increased in one or more of its fractions;α,β, and γ.

The α-1 and -2 include :

α1 -Antitrypsin,

haptoglobin,

ceruloplasmin,

C- reactive protein(CRP),

α2- macroglobulin.... etc.

α1-Antitrypsin(AAT)

- Protease inhibitor that binds to, and inactivates macrophage enzymes like trypsin, limit their actions during infection, and protects the body.
- **Deficiency** is associated with

– Pulmonary emphysema.

– Liver Cirrhosis (direct hyperbilirubinemia; Jaundice is one of tests used in investigation of prolonged neonatal)

•α1 -Fetoprotein(AFP)

– Principal fetal protein, used in screening for fetal abnormalities (neural tube defects) and in adult for liver
carcinoma investigation.

α2 -Macroglobulin

- Largest non-immunoglobulin in blood ~750 KD
- Protease inhibitor
- Increased in Nephrotic syndrome (largest in size)

(α -globulin) Ceruloplasmin (Cp)

- Copper transporting protein
- Participates in plasma redox reactions like Fe+2 Fe+3.
- serum CP measurement is used in investigation of Wilson's disease (Liver cirrhosis-Copper storage disease) in

which serum Cp level is decreased due to genetic defect in incorporation of Cu with apoceruloplasmin in the liver,

leading to precipitation of toxic Cu ion and damage of liver .

(α2) Haptoglobin

- Binds to, and preserves hemoglobin and its content of iron during hemolysis.
- Hemolytic diseases can deplete haptoglobin levels (α2) .

(β) Transferrin

- Iron transporting protein
- Transferrin is increased in iron deficiency anemia.

Apotransferrin + Fe+3=Transferrin

B2 -Microglobulin BMG

- Smallest blood protein (MW=11.8K)

- BMG is filtered through the glomerulus, but is reabsorbed by

renal tubules.

- Urinary BMG levels are a sensitive measure of renal tubular function

γ -Region

- Includes Immunoglobulin's (IgG, IgM, IgA, IgD & IgE).

They are involved in specific immune system.

- CRP is the most sensitive indicator of Acute Phase Reaction (non specific early immune defense system)

– Serum CRP (high sensitive -CRP) increased in Inflammation, trauma, infection, etc.

Protein in urine

normally less than 100 mg/day of proteins appears in urine,

in kidney disease this value increased according to degree of kidney damage which

reflect mainly the glomerular damage.

Normally glomerulus is permeable to

proteins of MW < 60 KD (D Dalton unit of

MW.

In kidney damage(mainly of glomerulus) excess amounts of proteins of large MW>60 KD will pass in the urine and may reach 5-50 gr/day.

Presence of low MW of proteins, like BMG in the urine

indicates the renal tubules damage as these tubules normally catabolize and reabsorbed the low MW proteins. In tubules damage these proteins will escape from the damaged tubules and appear in the urine(Low MW).

LIPID

By

Dr. Muna M. Yaseen

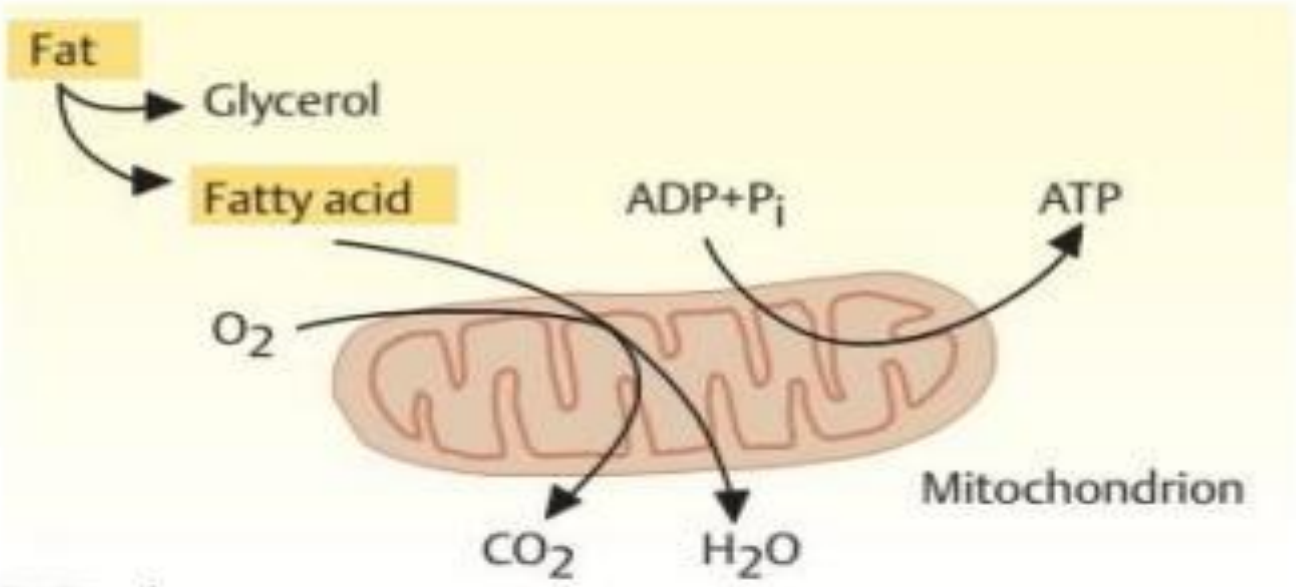
Introduction

- *Any member of a large and diverse group of oils, fats, and fat like substances that occur in living organisms and that characteristically are soluble in* ***organic solvents*** *but only sparingly soluble in aqueous solvents.*
- Lipids are not polymers, but mostly small molecules.
- Chief cellular storage form of energy
- Role in cellular structure and biochemical functions

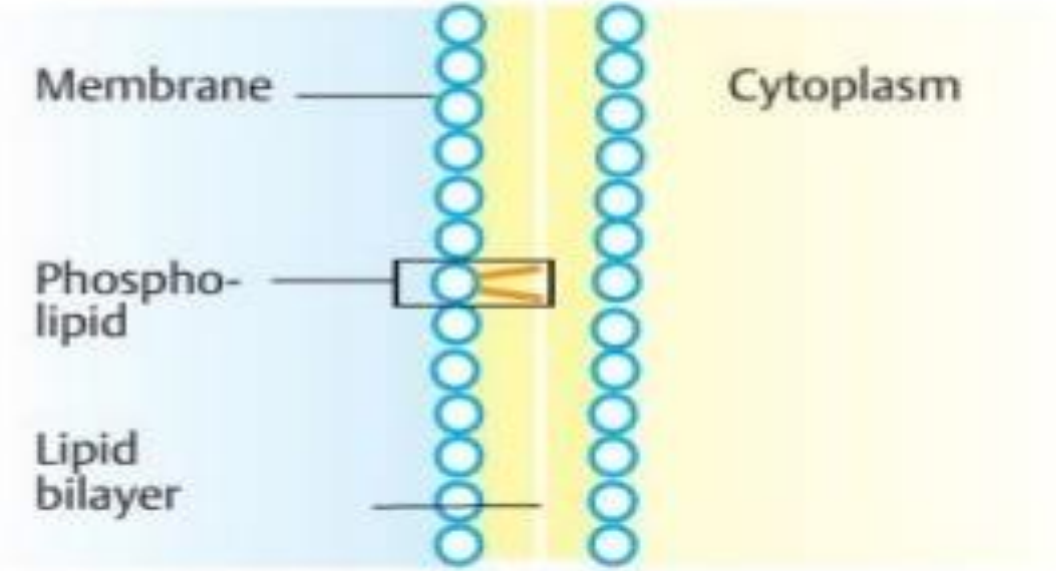
Biological Importance

- Fat-soluble vitamins
- Essential fatty acids contained in the fat of natural foods
- Stored in **adipose tissue,**
  - thermal insulator in the subcutaneous tissues and around certain organs
- **Myelinization : electrical insulators,** allowing rapid propagation of depolarization waves along **myelinated nerves.**
- **Lipoproteins** : Combinations of lipid and protein - important cellular constituents, occurring both in the cell **membrane** and **mitochondria**.
- Means of **transporting lipids** in the blood.
- **Obesity, diabetes mellitus, atherosclerosis**
- Role of various **polyunsaturated fatty acids** in nutrition and health.

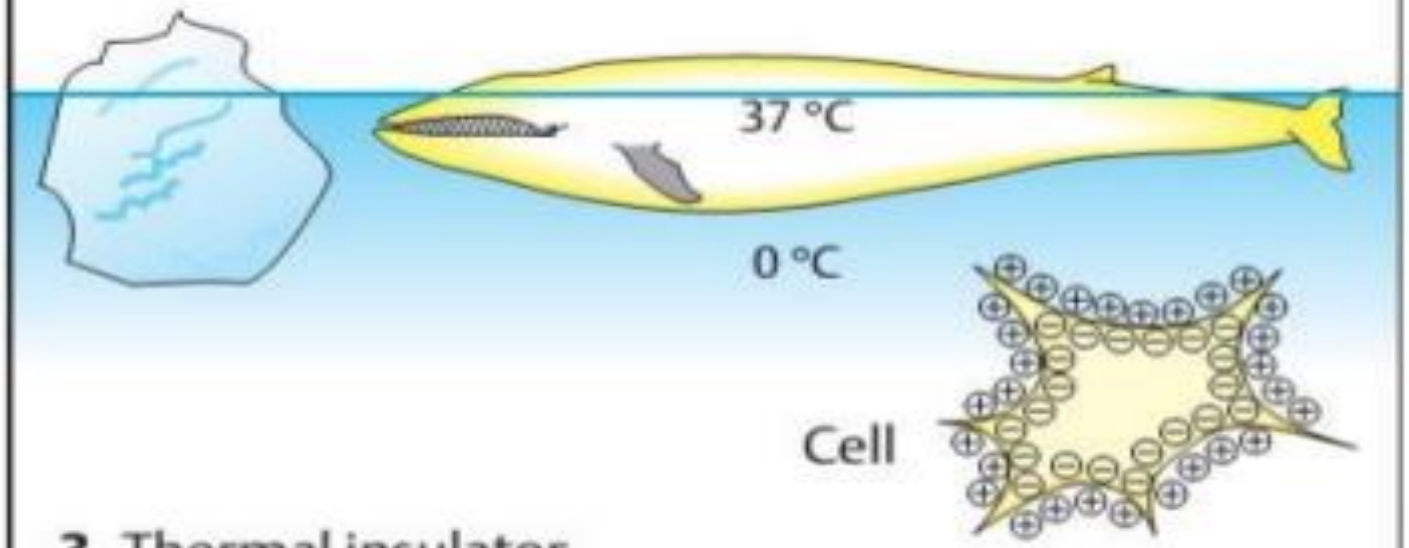
B. Biological roles



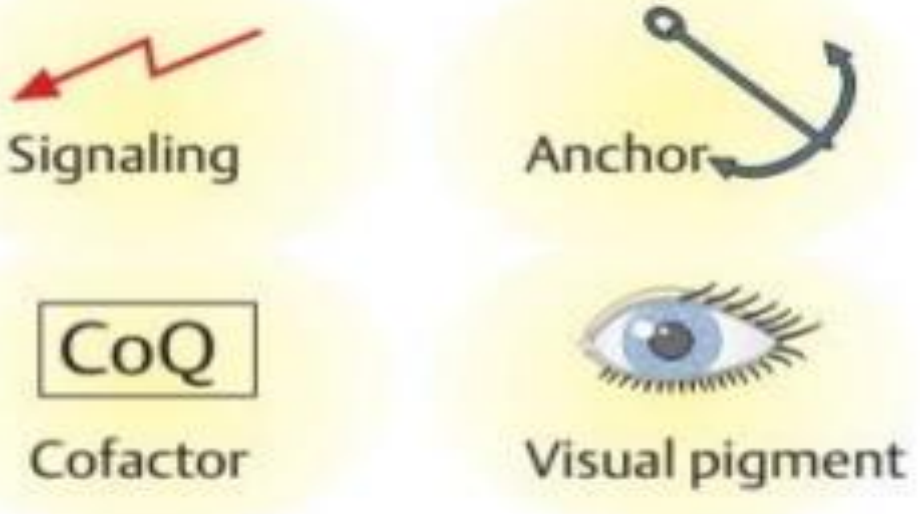
1. Fuel



2. Building block

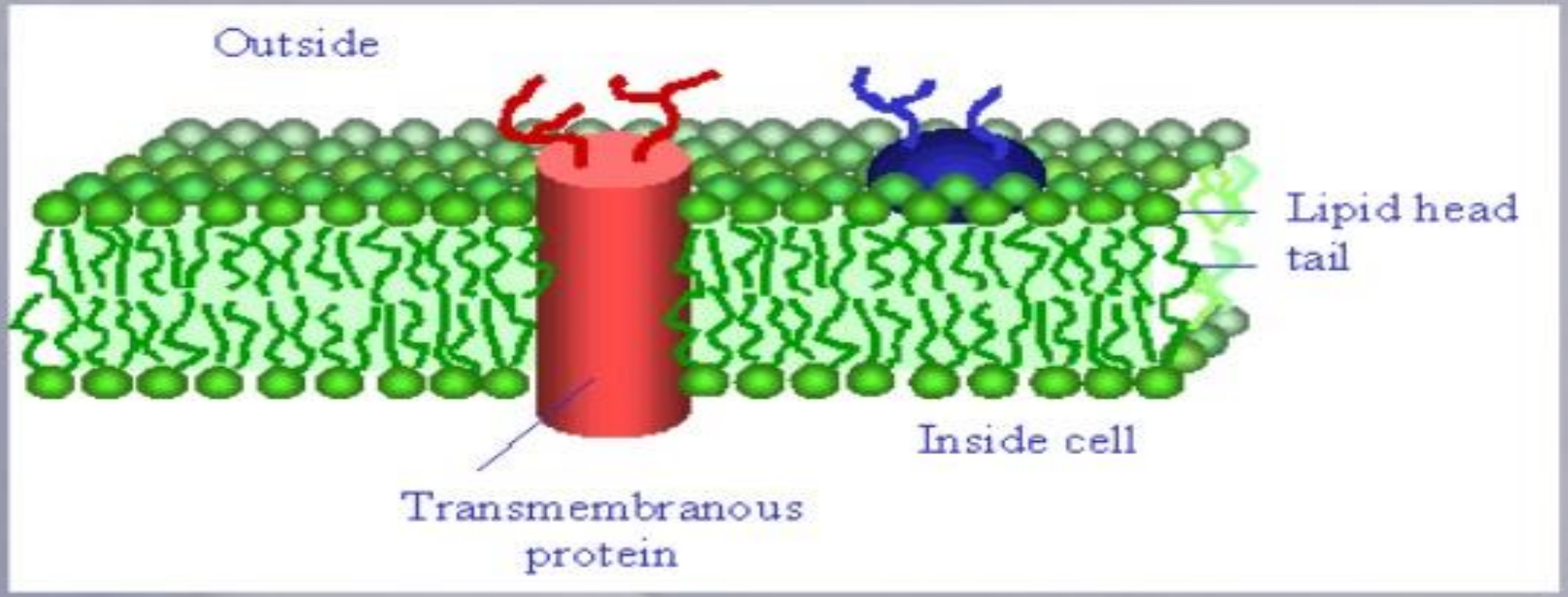


3. Thermal insulator



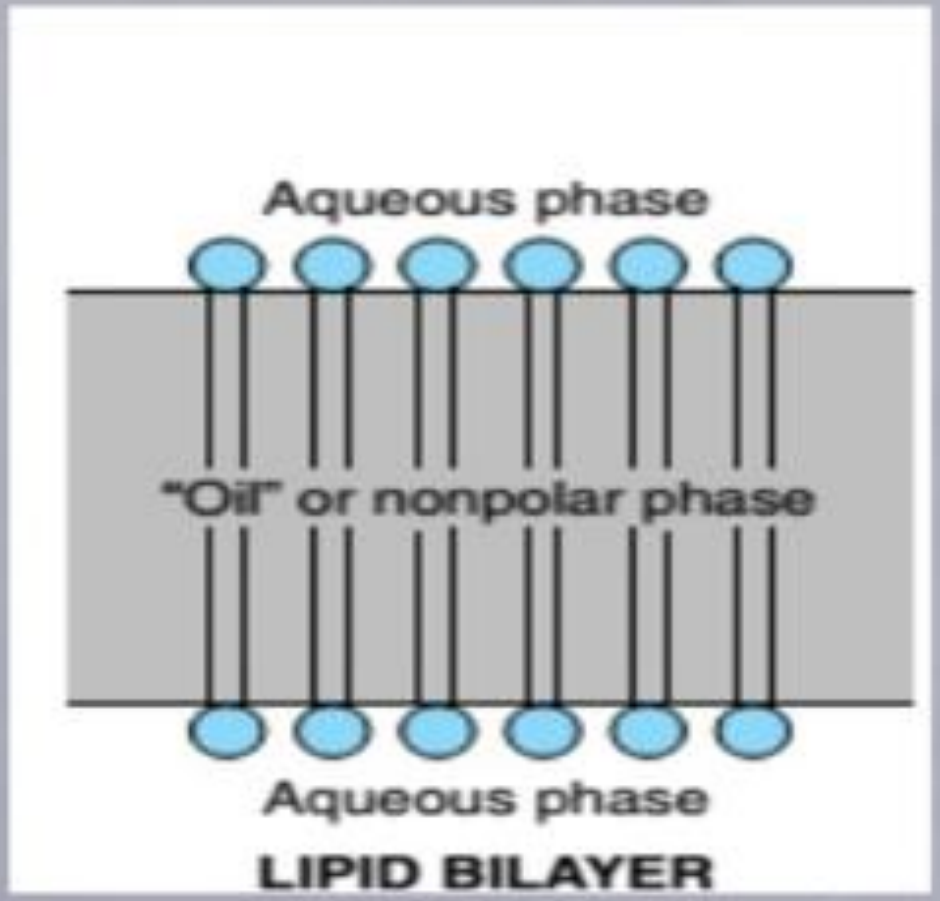
4. Special tasks

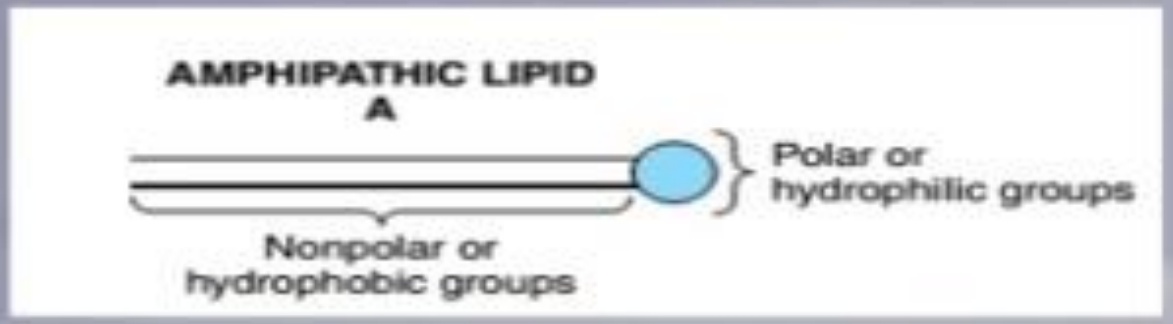
Lipids Bilayer Plasma Membrane



Micelle

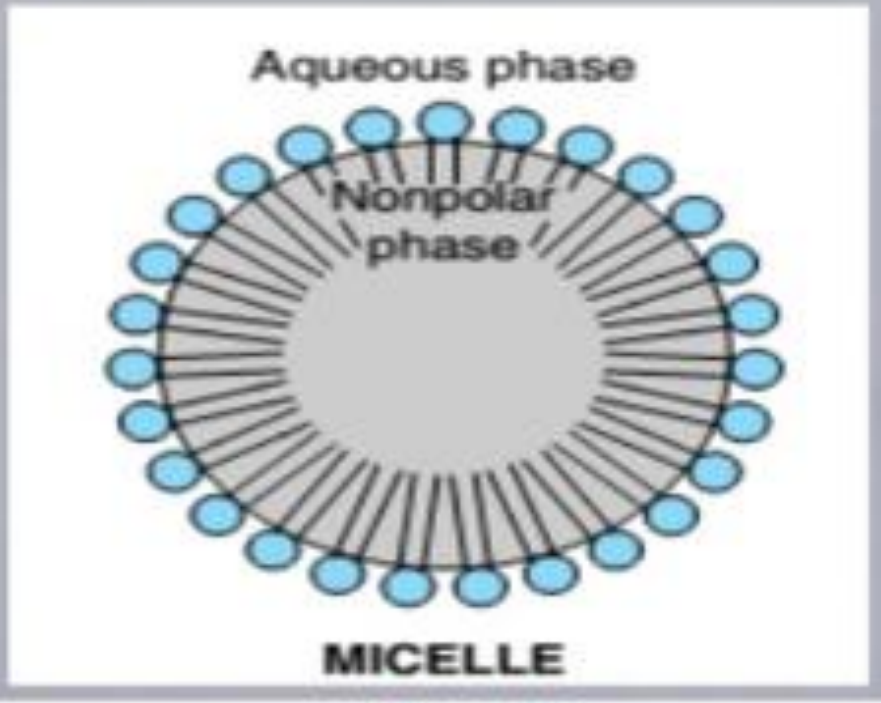
- Lipids are **insoluble in water** - predominance of nonpolar (hydrocarbon) groups.
- Fatty acids, phospholipids, sphingolipids, bile salts, and, to a lesser extent, cholesterol contain **polar group** i.e both polar and non-polar group.
- Such molecules are described as **Amphipathic.**

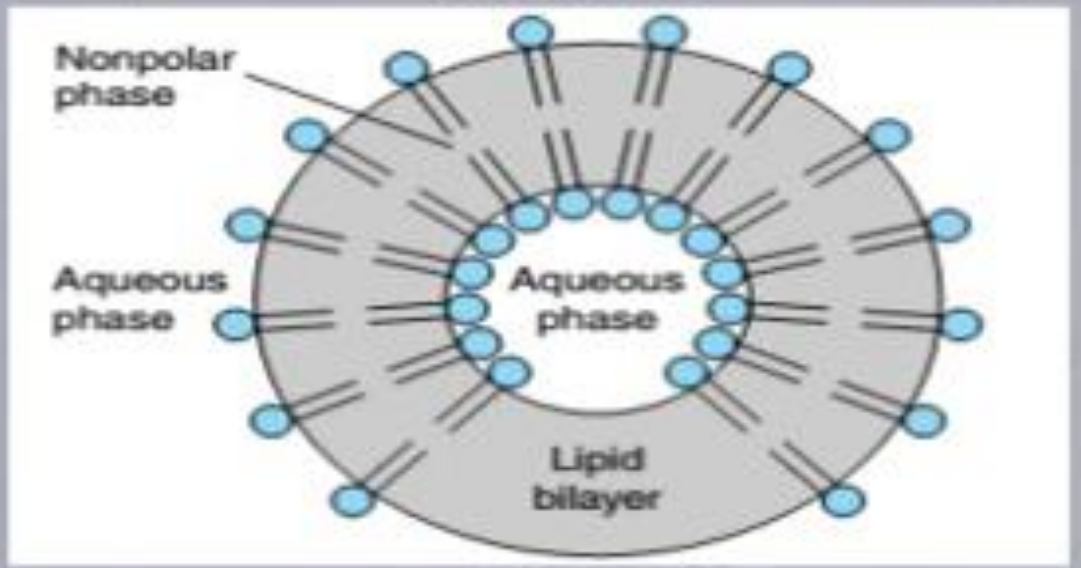




Micelle

- They become oriented at oil : water interfaces with the **polar group** in the **water phase** and the **nonpolar group** in the **oil phase**.
- basic structure in biologic membranes
- When a critical concentration of these lipids is present in an aqueous medium, they form **micelles**
- Micelle further forms liposomes
- It can be used for drug delivery – emulsion ointments, cancer therapy (targeted drug delivery)





Classification

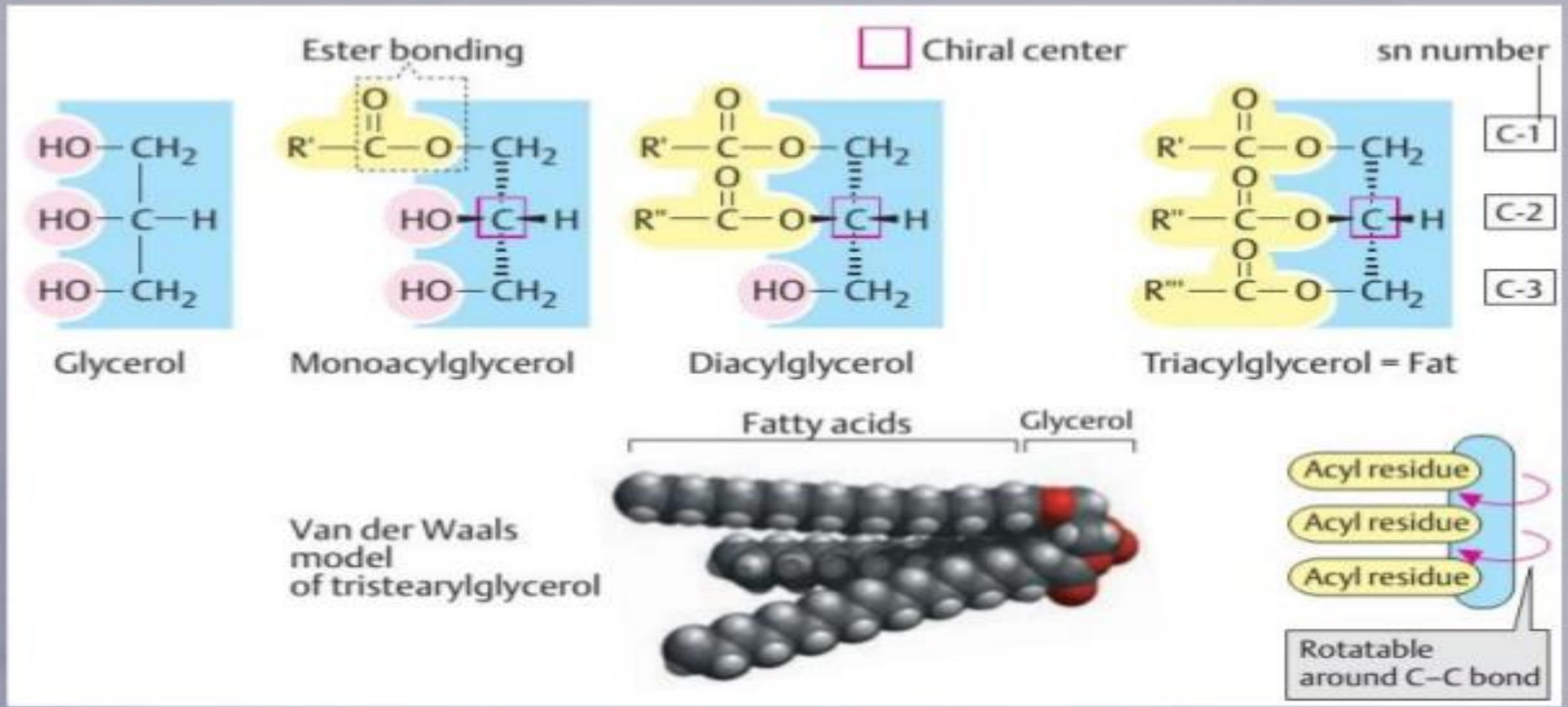
- The lipids are classified as
  - Simple lipid
  - Complex lipid
  - Precursor and derived lipid

Simple lipids

- Esters of fatty acids with various alcohols.
  - **Fats:** Esters of fatty acids with glycerol. **Oils** are fats in the liquid state.
  - **Waxes:** Esters of fatty acids with higher molecular weight monohydric alcohols.

FATTY ACIDS

- Simplest form of lipids
- Carboxylic acids with HC side chain
- Usually contains an **even number** of carbon atoms (**14C- 20C**) – biosynthesis of fatty acid occurs with sequential addition of 2 carbon atom.
- Chain may be **saturated** (containing no double bonds) or **unsaturated** (containing one or more double bonds)
- It occurs mainly in esterified form.
- Fats of animal origin are more simple than that of plant origin.
- **Palmitic acid** and **stearic acid** – most common


Ester bonding
Chiral center
sn number
C-1
C-2
C-3
Glycerol
Monoacylglycerol
Diacylglycerol
Triacylglycerol = Fat
Fatty acids
Glycerol
Van der Waals model of tristearylglycerol
Acyl residue
Acyl residue
Acyl residue
Rotatable around C–C bond

Major Saturated Fatty Acids

Common Name	Number of C Atoms	
Acetic	2	Major end product of carbohydrate fermentation by rumen organisms[1]
Propionic	3	An end product of carbohydrate fermentation by rumen organisms[1]
Butyric	4	In certain fats in small amounts (especially butter). An end product of carbohydrate fermentation by rumen organisms[1]
Valeric	5	
Caproic	6	
Lauric	12	Spermaceti, cinnamon, palm kernel, coconut oils, laurels, butter
Myristic	14	Nutmeg, palm kernel, coconut oils, myrtles, butter
Palmitic	16	Common in all animal and plant fats
Stearic	18	

Major Unsaturated Fatty Acids

Number of C Atoms and Number and Position of Double Bonds	Family	Common Name	Systematic Name	Occurrence
Monoenoic acids (one double bond)				
16:1;9	ω7	Palmitoleic	*cis*-9-Hexadecenoic	In nearly all fats.
18:1;9	ω9	Oleic	*cis*-9-Octadecenoic	Possibly the most common fatty acid in natural fats.
18:1;9	ω9	Elaidic	*trans*-9-Octadecenoic	Hydrogenated and ruminant fats.
Dienoic acids (two double bonds)				
18:2;9,12	ω6	Linoleic	all-*cis*-9,12-Octadecadienoic	Corn, peanut, cottonseed, soybean, and many plant oils.
Trienoic acids (three double bonds)				
18:3;6,9,12	ω6	γ-Linolenic	all-*cis*-6,9,12-Octadecatrienoic	Some plants, eg, oil of evening primrose, borage oil; minor fatty acid in animals.
18:3;9,12,15	ω3	α-Linolenic	all-*cis*-9,12,15-Octadecatrienoic	Frequently found with linoleic acid but particularly in linseed oil.
Tetraenoic acids (four double bonds)				
20:4;5,8,11,14	ω6	Arachidonic	all-*cis*-5,8,11,14-Eicosatetraenoic	Found in animal fats and in peanut oil; important component of phospholipids in animals.
Pentaenoic acids (five double bonds)				
20:5;5,8,11,14,17	ω3	Timnodonic	all-*cis*-5,8,11,14,17-Eicosapentaenoic	Important component of fish oils, eg, cod liver, mackerel, menhaden, salmon oils.
Hexaenoic acids (six double bonds)				
22:6;4,7,10,13,16,19	ω3	Cervonic	all-*cis*-4,7,10,13,16,19-Docosahexaenoic	Fish oils, phospholipids in brain.

Unsaturated Fatty Acids

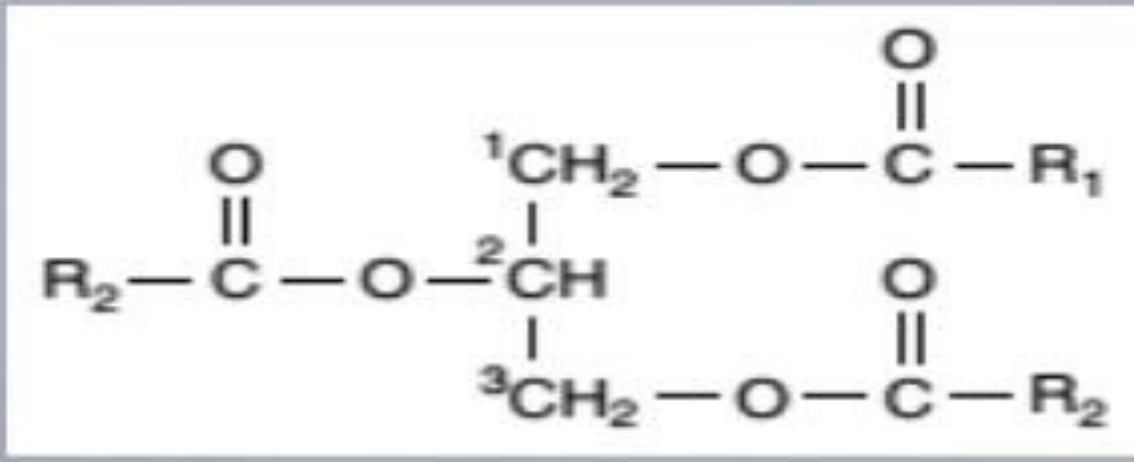
- Fatty acids may be further subdivided as follows
  - **Monounsaturated** (monoethenoid, monoenoic) acids, containing one double bond.
  - **Polyunsaturated** (polyethenoid, polyenoic) acids, containing two or more double bonds.
  - **Eicosanoids:** These compounds, derived from eicosa- (20-carbon) polyenoic fatty acids, comprise the **prostanoids, leukotrienes (LTs)** and **lipoxins (LXs).** Prostanoids include **prostaglandins (PGs), prostacyclins (PGIs),** and **thromboxanes (TXs).**

Essential fatty acids

- The fatty acid cant be synthesized by the body and therefore has to be supplied in the diet.
- Ex: **Linoleic Acid, Linolenic Acid**
- **Archidonic acid** becomes essential – **precursor linoleic acid** is not provided in the diet
- Functions of EFA
  - Membrane structures and functions
  - Transport of cholesterol
  - Formation of lipoprotein
  - Prevention of fatty liver
- Deficiency of EFA : Phrynoderma – toad skin

TRIACYLGLYCEROLS

- Also known as triglycerides
- Main storage of fatty acids
- Esters of the trihydric alcohol glycerol and fatty acids
- Phosphorylated on *sn*-3 by **glycerol kinase** to give **glycerol 3-phosphate** and not glycerol 1-phosphate.



Complex Lipids

Complex lipids

- It contains groups in addition to an alcohol and a fatty acid.

  a. **Phospholipids:** in addition to fatty acids, phospholipid contains

  – an alcohol,

  – a phosphoric acid residue.

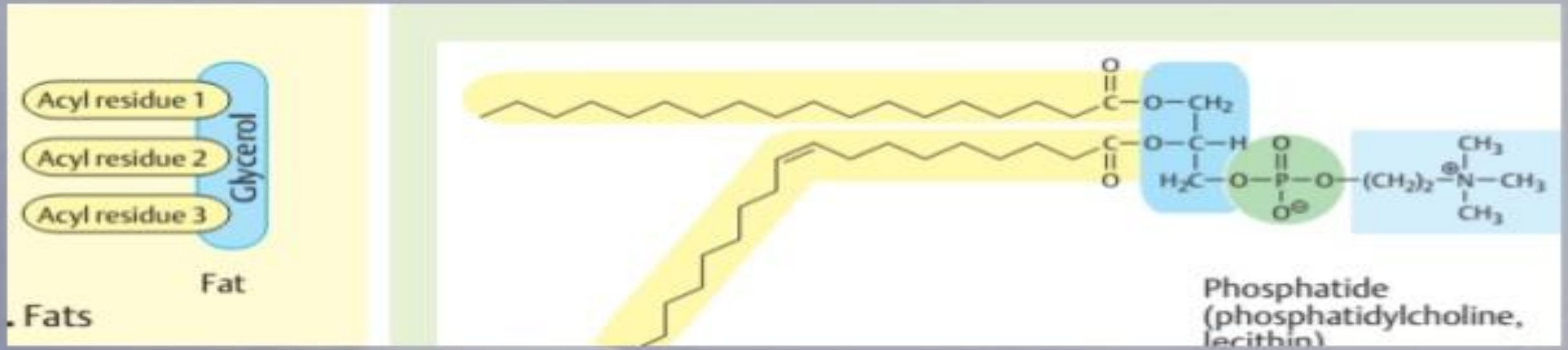
  – May have nitrogen containing bases and other substituent

  Ex: glycerophospholipids the alcohol is *glycerol* and in **sphingophospholipids** the alcohol is *sphingosine*.

  b. **Glycolipids (glycosphingolipids)**: Lipids containing a fatty acid, sphingosine, and carbohydrate.

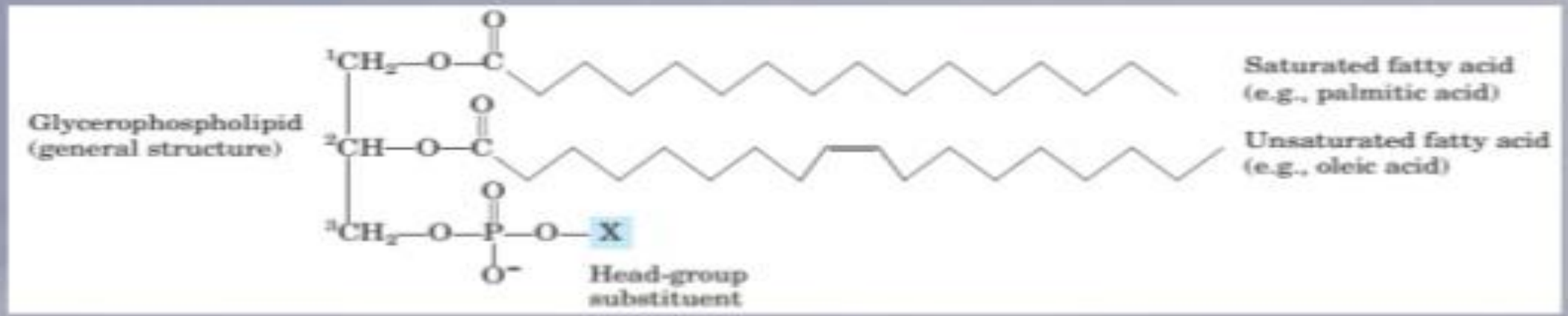
  c. **Other complex lipids**: Lipids such as sulfolipids and aminolipids. Ex: **Lipoproteins**

Phospholipids



Glycerophospholipids

- also called phosphoglycerides
- membrane lipids in which two fatty acids are attached in ester linkage to the first and second carbons of glycerol
- a highly polar or charged group is attached through a phosphodiester linkage to the third carbon



Glycerophospholipids

- Glycerol is prochiral
  - no asymmetric carbons
  - But attachment of phosphate at one end converts it into a chiral compound.
- Various important types of glycerophopholipids
  - Phosphatidic acid
  - Lecithin
  - Cephalin
  - Phosphatidylinositol
  - Phosphatidylserine
  - Plasmalogens
  - Cardiolipin

Phosphatidylcholines

- Also known as lecithins
- Present in phospholipids of the cell membrane.
- Choline (part of neurotransmittor) – component of lecithin
- **Dipalmitoyl lecithin** is a very effective surface active agent - major constituent of the S**urfactant**
  - Absence - premature infants causes **respiratory distress syndrome**

Phosphatidylinositol

- Precursor of Second Messengers
- **Phosphatidylinositol 4,5-bisphosphate -** constituent of cell membrane phospholipids.
- upon stimulation by a suitable hormone agonist
- cleaved into **diacylglycerol** and **inositol trisphosphate**

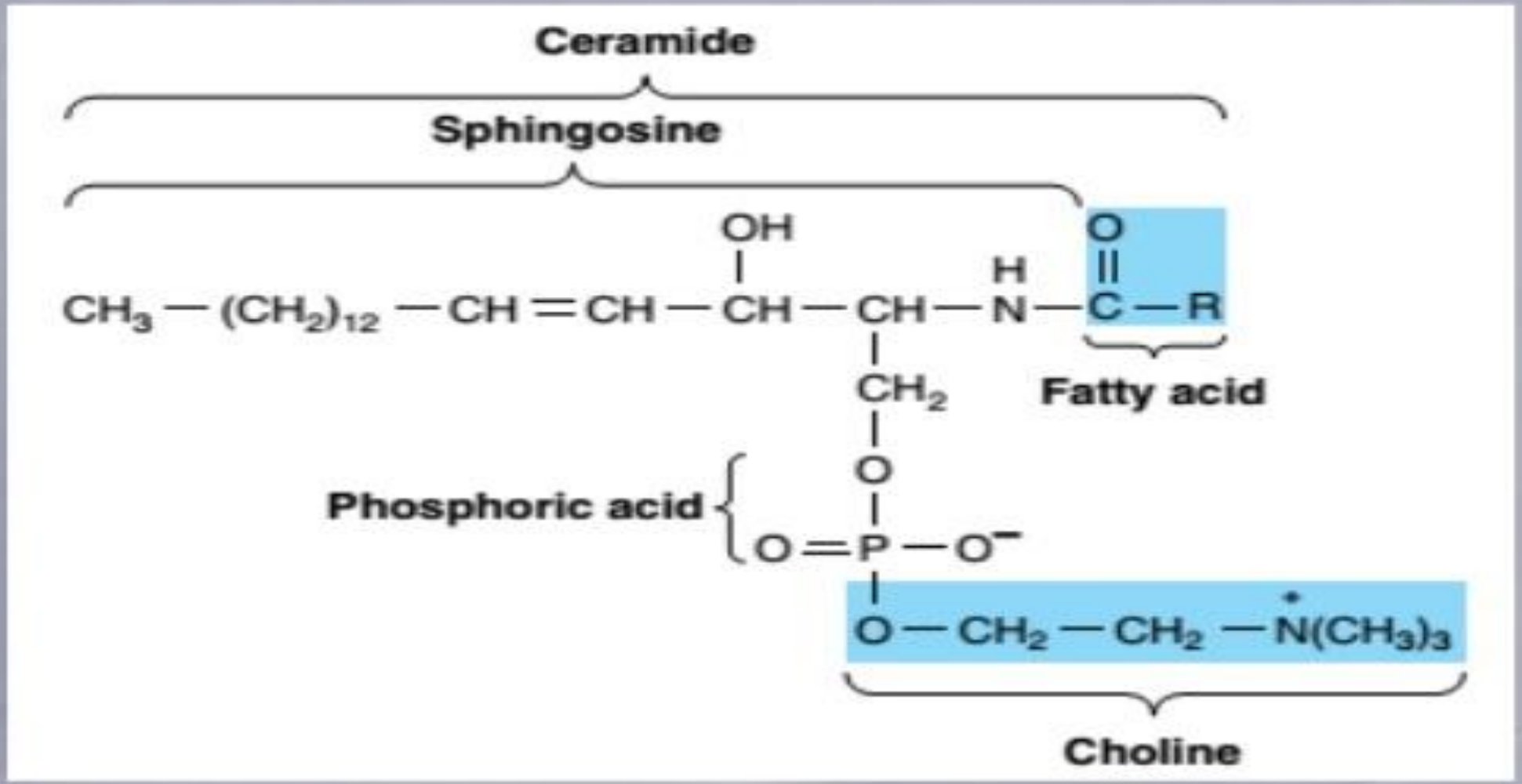
Function of phospholipid

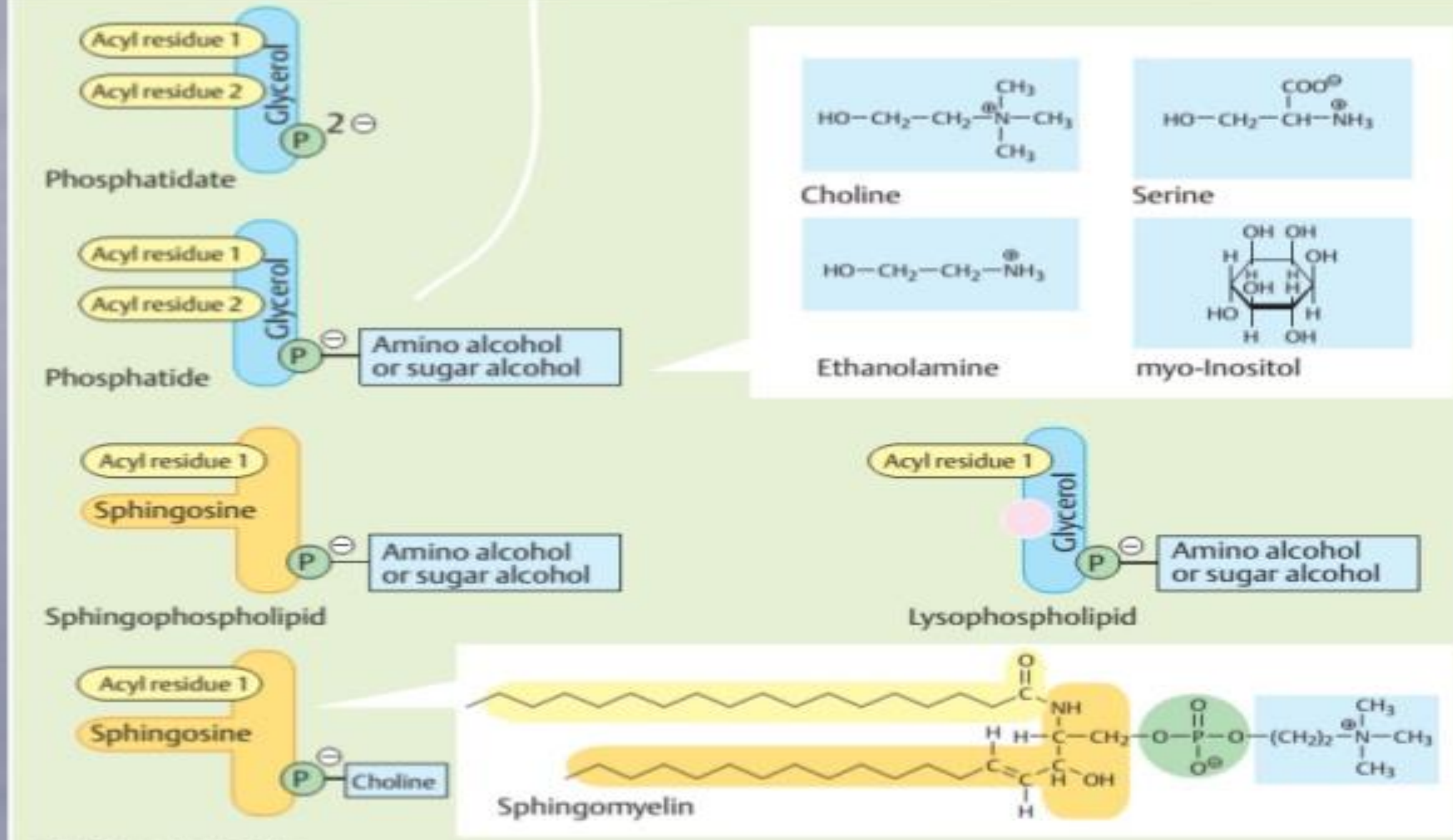
- Component of cell membrane – **both structural and regulatory** functions.
- Phospholipid in mitochindria – lecithin, cephalin and cardiolipin – maintain ETC
- Absorption of fat
- Transport of lipids
- Arachidonic acid – serves as a precursor of various eicosanoids
- Cephalin – Blood clotting

Sphingophospholipids

- Found in large quantities in brain and nerve tissue.
- fatty acid, phosphoric acid, choline, and a complex amino alcohol, **sphingosine**
- No glycerol is present.
- The combination of sphingosine plus fatty acid is known as **ceramide** – found in glycosphingolipids

Sphingophospholipids





2. Phospholipids

GLYCOLIPIDS

- widely distributed in every tissue of the body,
- particularly in nervous tissue such as brain
- outer leaflet of the plasma membrane, where they contribute to **cell surface carbohydrates.**
- **Ex: glycosphingolipid** :ceramide and one or more sugars.
  - **Galactosylceramide**
  - **Gangliosides**

Lipoproteins

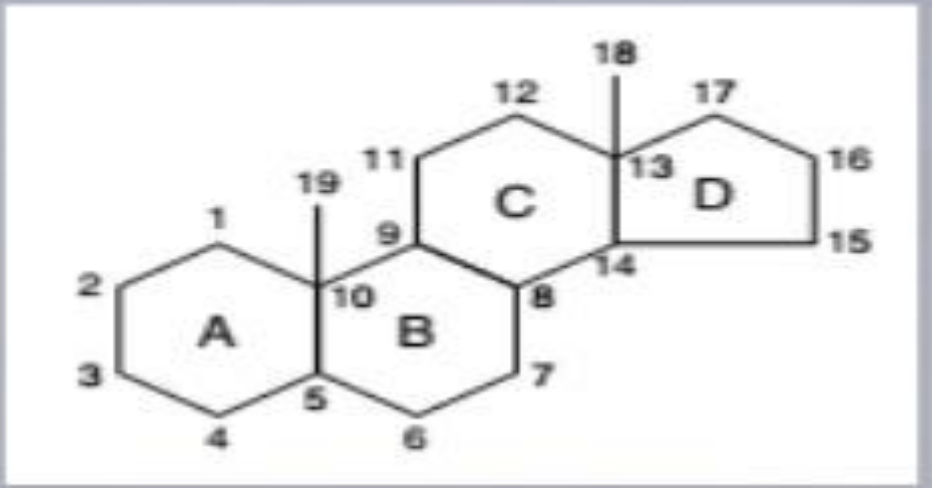
- Complexes of lipid with protein
- Transport vehicle for lipids
- Five types
  - Chylomicron
  - Very low density lipoprotein (VLDL)
  - Low density lipoprotein (LDL)
  - High Density lipoprotein (HDL)
  - Free fatty acid complexes

Precursor and derived lipids

- These include fatty acids, glycerol, **steroids**, other alcohols, fatty aldehydes, and ketone bodies, hydrocarbons, lipid-soluble vitamins, and hormones.

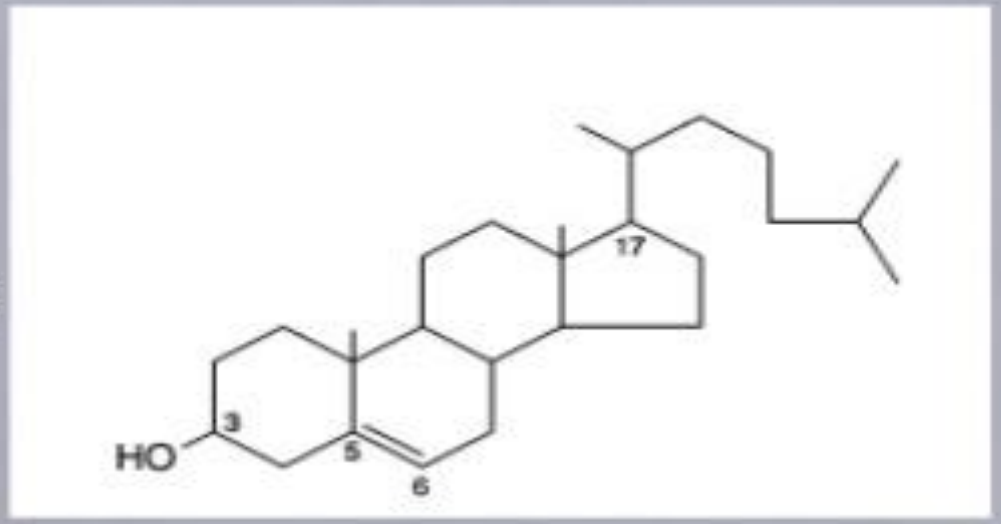
Steroids

- Compound containing cyclic steroid nucleus
- Phenanthrene nucleus – A,B,C
- Cyclopentane ring – D
- Several steroids in biological systems
  - Cholestrol
  - Bile acids
  - Vitamin D
  - Sex Hormone
  - Adrenocortical hormones
  - Cardiac glycosides
  - Alkaloids



Cholesterol

- Best known steroid
- Association with **atherosclerosis.**
- Precursor of a large number of equally important steroids
  - bile acids,
  - adrenocortical hormones,
  - sex hormones,
  - D vitamins - **Ergosterol**
  - cardiac glycosides



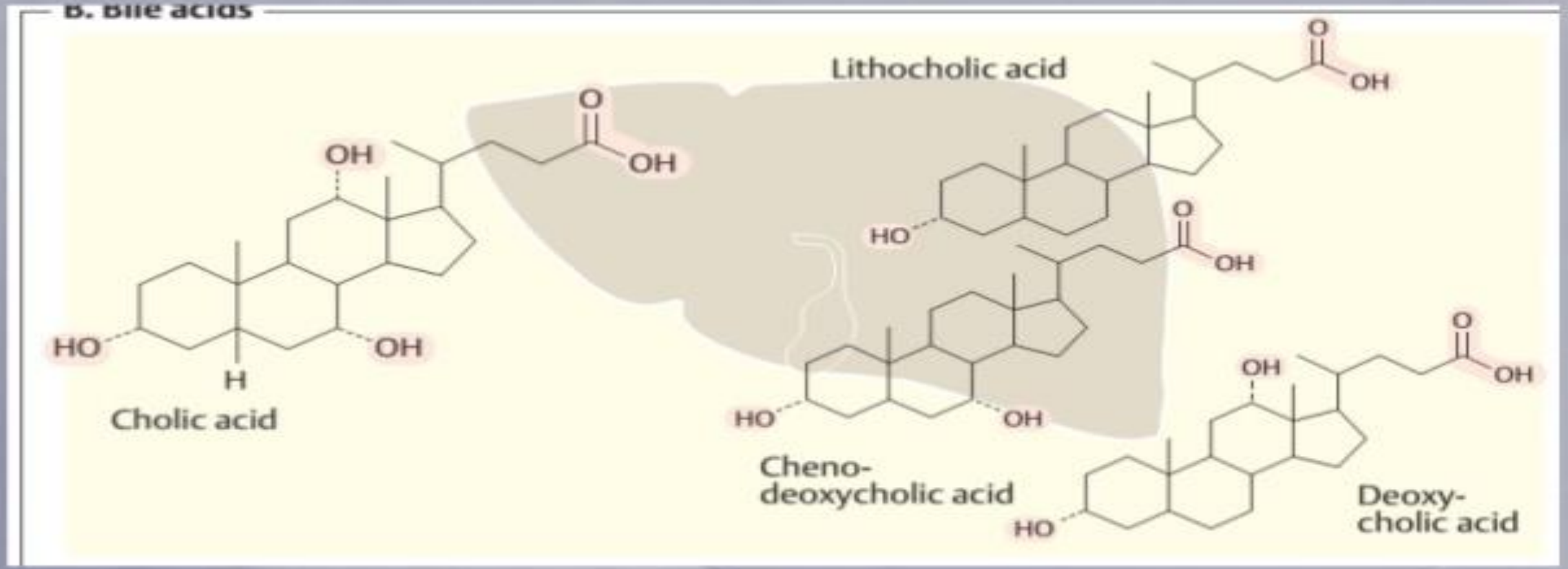
Cholesterol

- **Properties**
  - Yellowish crystalline solid
  - Insoluble in water and soluble in organic solven
- **Function**
  - Present in nervous tissues – insulating cover
  - Biochemical function – precursor for many biochemical substances and component of cell membrane

Bile acids

- synthesized from cholesterol in the liver
- It keep bile cholesterol in a soluble state as micelles and promote the digestion of lipids in the intestine.
- Primary bile acids *:* **Cholic acid** and **chenodeoxycholic acid**
- Secondary bile acids *:* **lithocholic acid** and **deoxycholic acid**.

Bile acids


B. Bile acids
Lithocholic acid
Cholic acid
Cheno-
deoxycholic acid
Deoxy-
cholic acid

Thank you

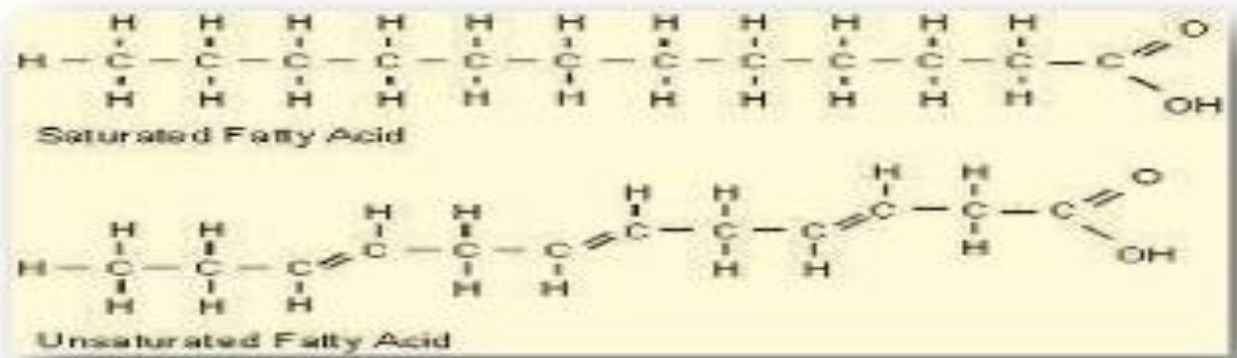
Oxidation of Fatty acids

by

Dr. Muna M. Yaseen

FATTY ACIDS

A fatty acid contains a long hydrocarbon chain and a terminal carboxylate group. The hydrocarbon chain may be saturated (with no double bond) or may be unsaturated (containing double bond).



- Fatty acids can be obtained from-
- Diet
- Adipolysis
- De novo synthesis

FUNCTIONS OF FATTY ACIDS

Fatty acids have four major physiological roles.

1) Fatty acids are **building blocks of phospholipids and glycolipids.**

2) Many proteins are modified by the **covalent attachment of fatty acids, which target them to membrane locations**

3) Fatty acids are **fuel molecules**. They are stored as triacylglycerols. Fatty acids mobilized from triacylglycerols are oxidized to meet the energy needs of a cell or organism.

4) Fatty acid **derivatives serve as hormones and intracellular messengers** e.g. steroids, sex hormones and prostaglandins.

TRIGLYCERIDES

- Triglycerides are **a highly concentrated** stores of energy because they are ***reduced* and *anhydrous*.**
- The yield from the complete oxidation of fatty acids is about 9 kcal g-1 (38 kJ g-1)
- Triacylglycerols are nonpolar, and are stored in a nearly anhydrous form, whereas much more polar proteins and carbohydrates are more highly

TRIGLYCERIDES V/S GLYCOGEN

- ***A gram of nearly anhydrous fat stores more than six times as much energy as a gram of hydrated glycogen,*** which is likely the reason that triacylglycerols rather than glycogen were selected in evolution as the major energy reservoir.
- The glycogen and glucose stores provide enough energy to sustain biological function for about 24 hours, whereas the **Triacylglycerol stores allow survival for several weeks.**

TRANSPORTATION OF FREE FATTY ACIDS

- Free fatty acids—also called unesterified (UFA) or nonesterified (NEFA) fatty acids—are fatty acids that are in the **unesterified state.**
- In plasma, longer-chain FFA are combined with **albumin,** and in the cell they are attached to a **fatty acid-binding protein.**
- **Shorter-chain fatty acids are more water-soluble and exist as the un-ionized acid or as a fatty acid anion.**
- By these means, free fatty acids are made accessible as a fuel in other tissues.

TYPES OF FATTY ACID OXIDATION

Fatty acids can be oxidized by-

1) **Beta oxidation-** Major mechanism, occurs in the mitochondria matrix. 2-C units are released as acetyl CoA per cycle.

2) **Alpha oxidation**- Predominantly takes place in brain and liver, one carbon is lost in the form of CO2 per cycle.

3) **Omega oxidation-** Minor mechanism, but becomes important in conditions of impaired beta oxidation

4) **Peroxisomal oxidation-** Mainly for the trimming of very long chain fatty acids.

BETA OXIDATION

Overview of beta oxidation

A saturated acyl Co A is degraded by a recurring sequence of four reactions:

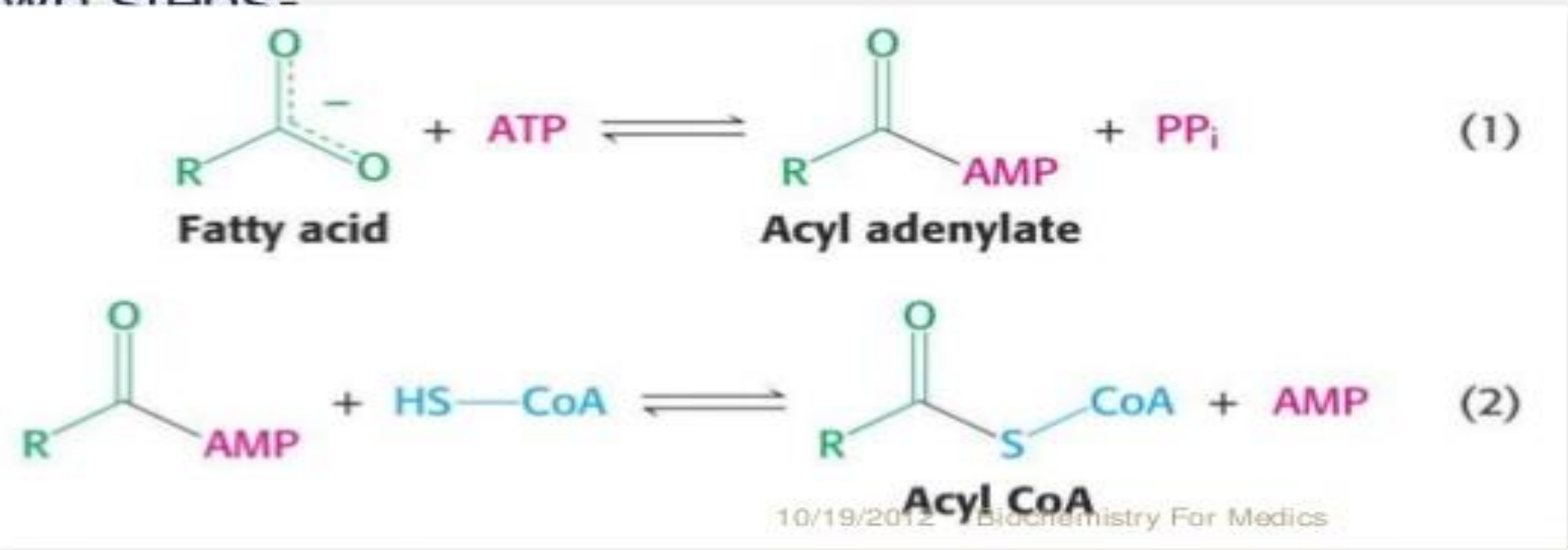
1) **Oxidation** by flavin adenine dinucleotide (FAD)
2) **Hydration,**
3) **Oxidation** by NAD^+, and
4) **Thiolysis** by Co ASH

BETA OXIDATION

- The fatty acyl chain is shortened by two carbon atoms as a result of these reactions,
- FADH2, NADH, and acetyl Co A are generated.
- Because oxidation is on the β carbon and the chain is broken between the α (2)- and β (3)-carbon atoms—hence the name – β oxidation .

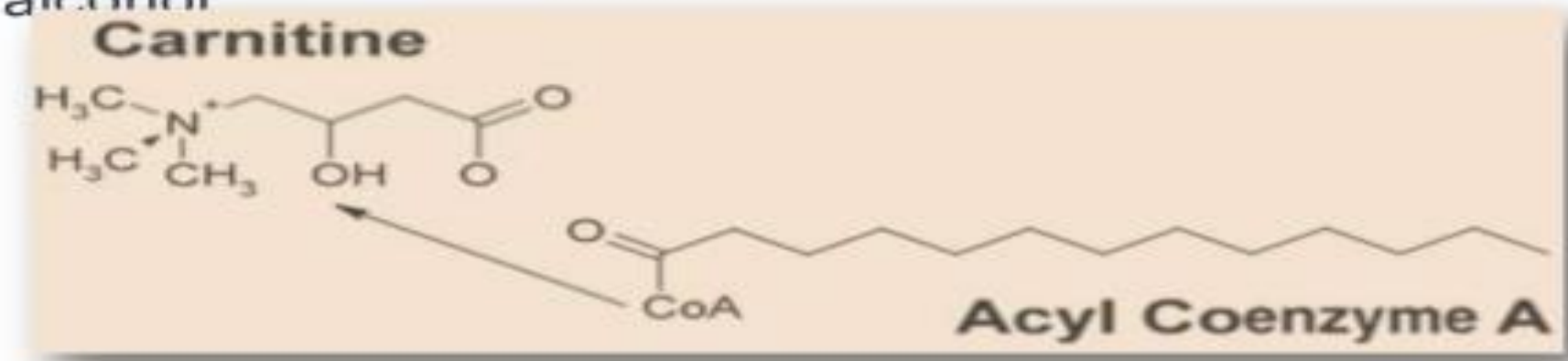
ACTIVATION OF FATTY ACIDS

Fatty acids must first be converted to an active intermediate before they can be catabolized. This is the only step in the complete degradation of a fatty acid that requires energy from ATP. The activation of a fatty acid is accomplished in two steps-



TRANSPORT OF FATTY ACID IN TO MITOCHONDRIAL MATRIX

- Fatty acids are activated on the outer mitochondrial membrane, whereas they are oxidized in the mitochondrial matrix.
- Activated long-chain fatty acids are transported across the membrane by conjugating them to *carnitine*, a zwitterionic alcohol



Carnitine (ß-hydroxy-Y-trimethyl ammonium butyrate), $(CH_3)_3N^+—CH_2—CH(OH)—CH_2—COO^-$, is widely distributed and is particularly abundant in muscle. Carnitine is obtained from foods, particularly animal-based foods, and via endogenous synthesis.

ROLE OF CARNITINE

1) The acyl group is to the hydroxyl group of carnitine to form *acyl carnitine*. This reaction is catalyzed by ***carnitine acyl transferase I***

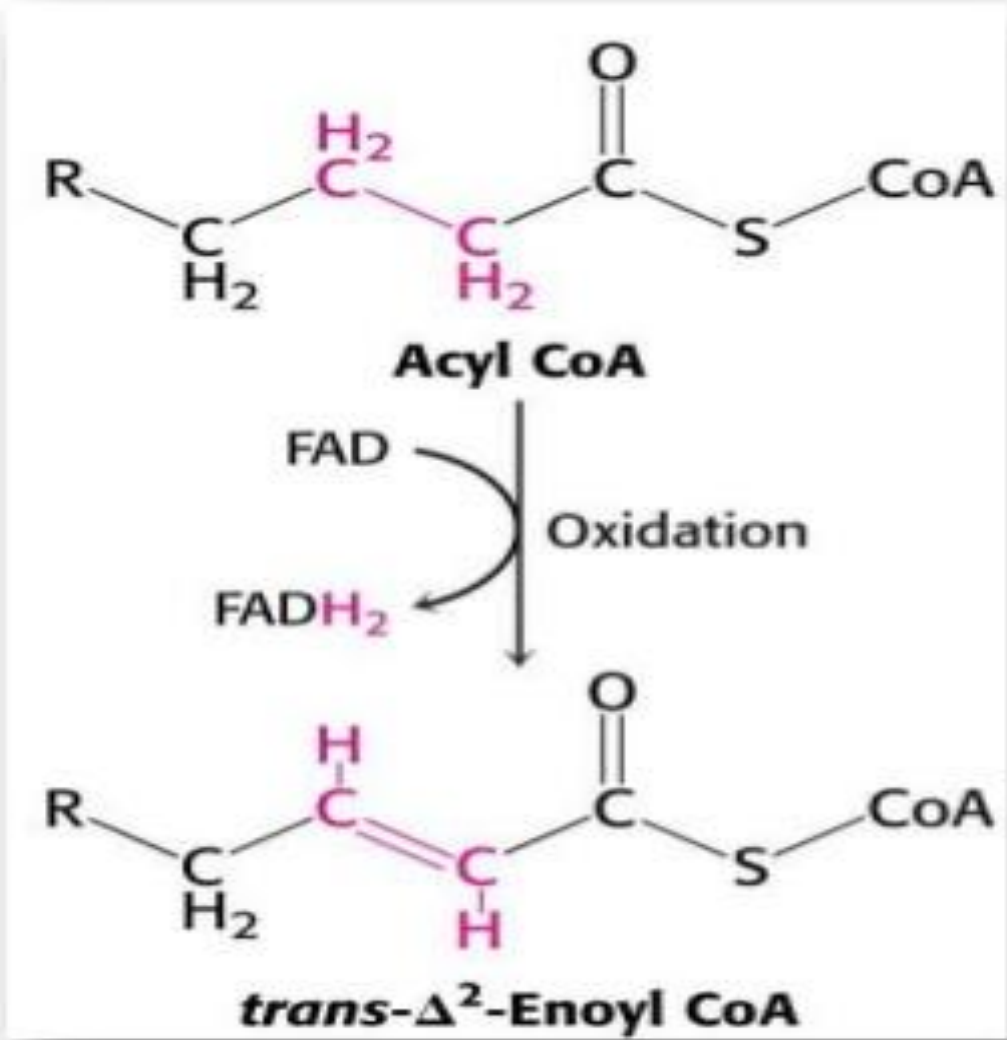
2) Acyl carnitine is then shuttled across the inner mitochondrial membrane by a **translocase.**

3) The acyl group is transferred back to CoA on the matrix side of the membrane. This reaction, which is catalyzed by ***carnitine acyl transferase II.***

Finally, the translocase returns carnitine to the cytosolic side in exchange for an incoming acyl carnitine

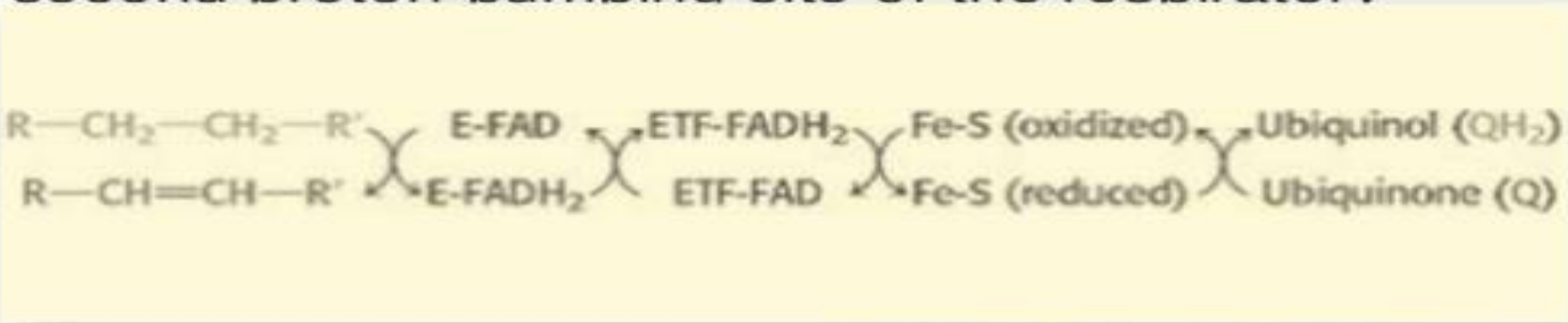
STEPS OF BETA OXIDATION

Step-1
Dehydrogenation-
The first step is the removal of two hydrogen atoms from the 2(α)- and 3(β)-carbon atoms, catalyzed by **acyl-CoA dehydrogenase** and requiring FAD. This results in the formation of Δ^2-*trans*-enoyl-CoA and $FADH_2$.

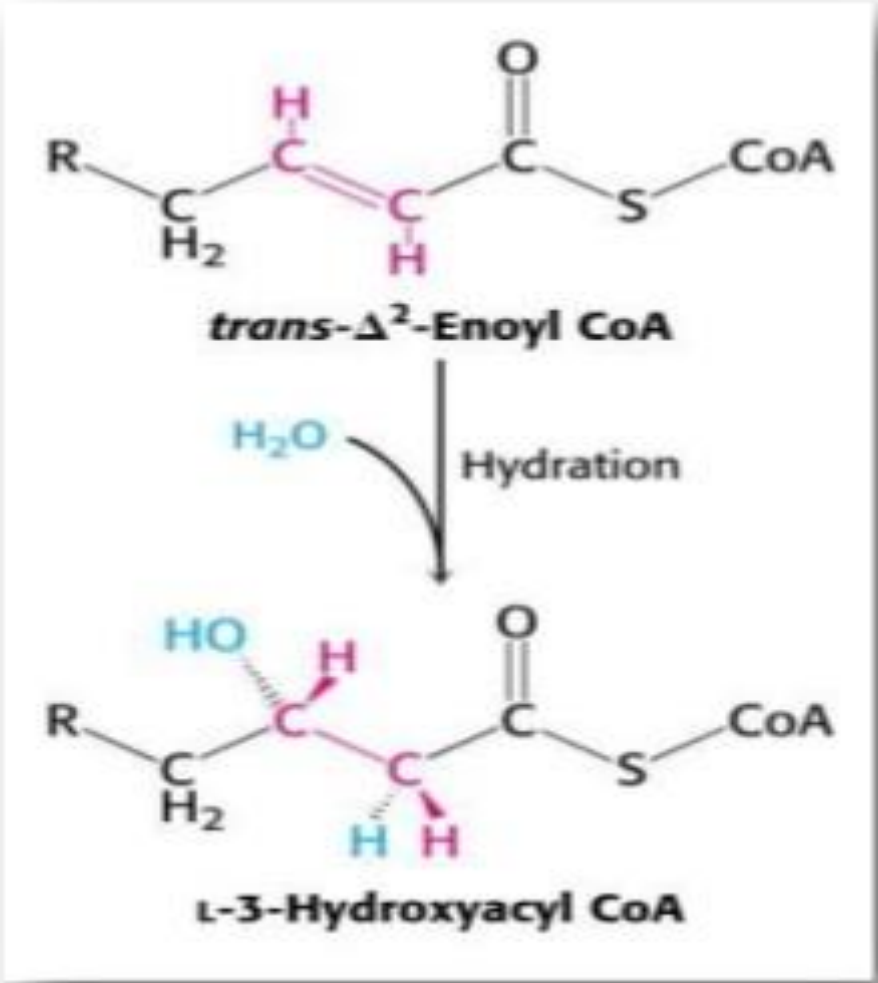


STEPS OF BETA OXIDATION

- Electrons from the FADH2 prosthetic group of the reduced acyl CoA dehydrogenase are transferred to ***electron-transferring flavoprotein*** **(ETF).**
- ETF donates electrons to ***ETF: ubiquinone reductase*****, an iron-sulfur protein.**
- Ubiquinone is thereby reduced to ubiquinol, which delivers its high-potential electrons to the second proton-pumping site of the respiratory



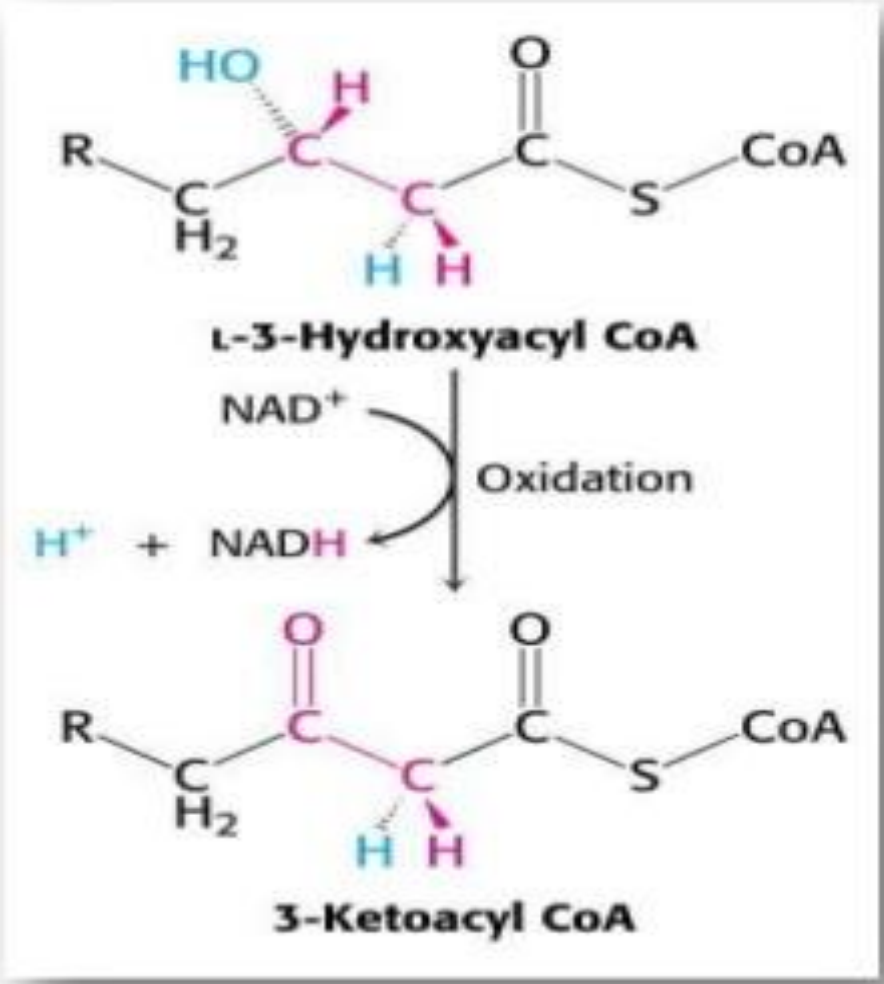
STEPS OF BETA OXIDATION



Step-2- Hydration

Water is added to saturate the double bond and form 3-hydroxyacyl-CoA, catalyzed by **Δ ²-enoyl-CoA hydratase.**

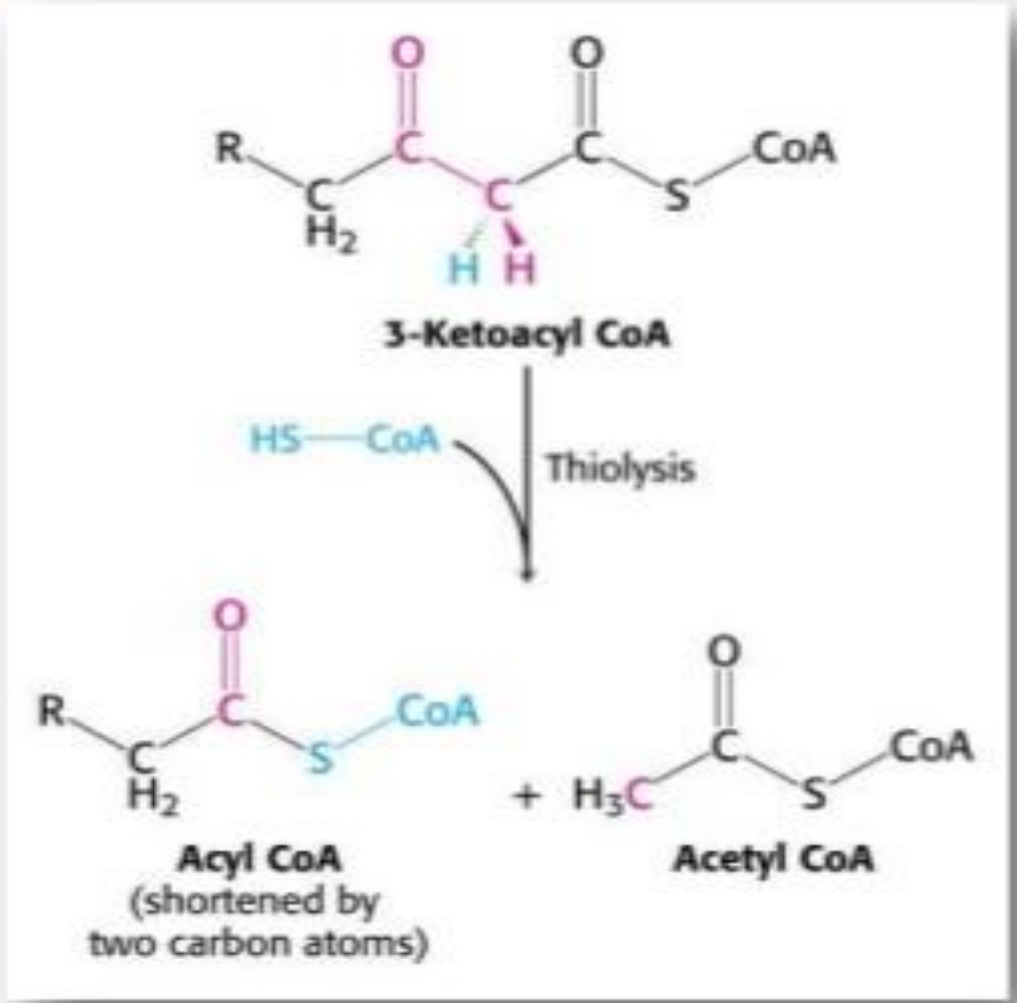
STEPS OF BETA OXIDATION



Step-3-dehydrogenation-

The 3-hydroxy derivative undergoes further dehydrogenation on the 3-carbon catalyzed by **L(+)-3-hydroxyacyl-CoA dehydrogenase** to form the corresponding 3-ketoacyl-CoA compound. In this case, NAD^+ is the coenzyme involved.

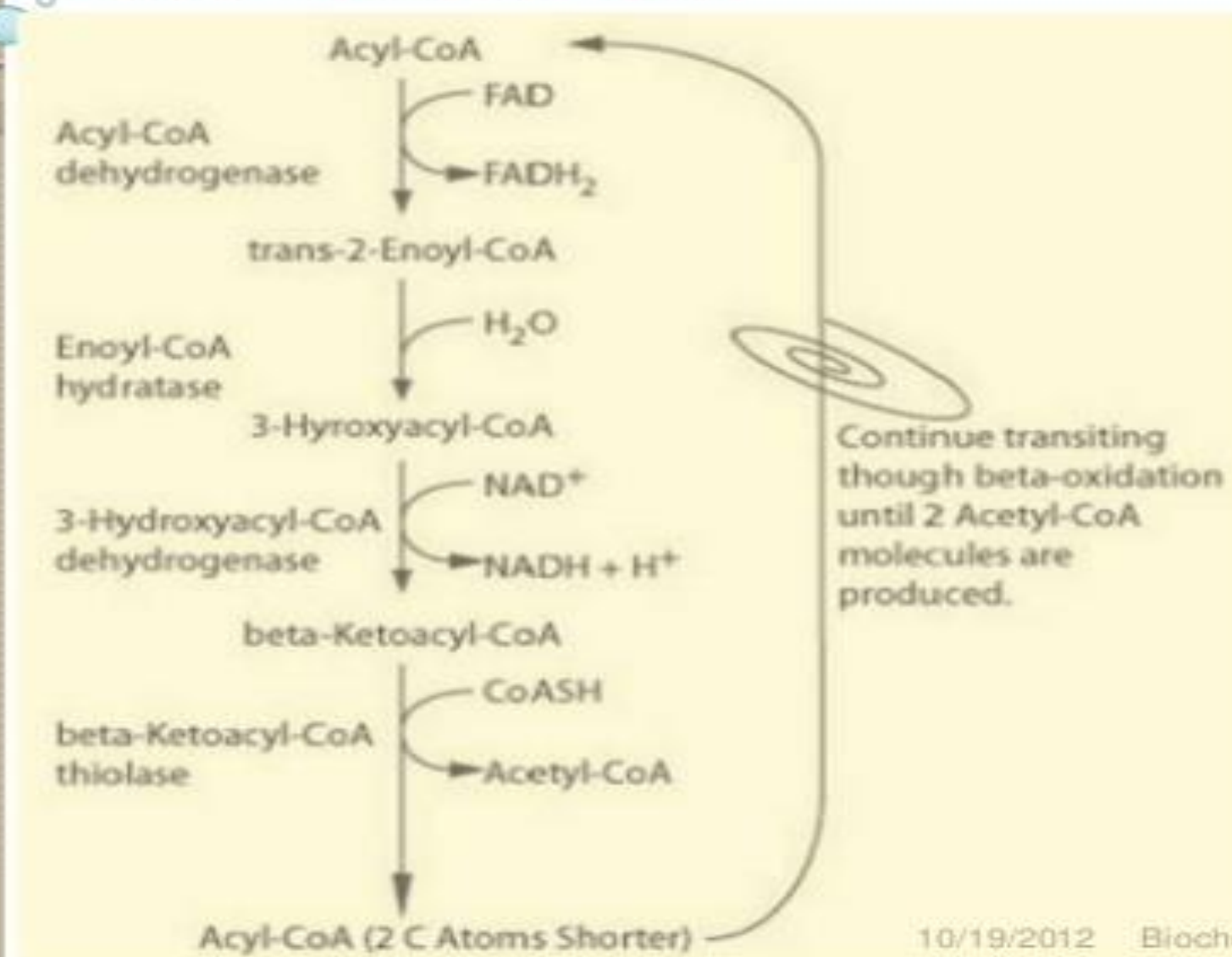
STEPS OF BETA OXIDATION



Step-4-
Thiolysis-

3-ketoacyl-CoA is split at the 2,3-position by **thiolase** (3-ketoacyl-CoA-thiolase), forming acetyl-CoA and a new acyl-CoA two carbons shorter than the original acyl-CoA molecule.

STEPS OF BETA OXIDATION



- The acyl-CoA formed in the cleavage reaction reenters the oxidative pathway at reaction 2.
- Since acetyl-CoA can be oxidized to CO_2 and water via the citric acid cycle the complete oxidation of fatty acids is achieved

BETA OXIDATION

The overall reaction can be represented as follows-

$$C_n\text{-acyl CoA} + FAD + NAD^+ + H_2O + CoA \longrightarrow C_{n-2}\text{-acyl CoA} + FADH_2 + NADH + \text{acetyl CoA} + H^+$$

BETA OXIDATION- ENERGY YIELD

Energy yield by the complete oxidation of one mol of Palmitic acid-

The degradation of palmitoyl CoA (C16-acyl Co A) requires seven reaction cycles. In the seventh cycle, the C4-ketoacyl CoA is thiolyzed to two molecules of acetyl CoA.

$$\text{Palmitoyl CoA} + 7\,\text{FAD} + 7\,\text{NAD}^+ + 7\,\text{CoA} + 7\,\text{H}_2\text{O} \longrightarrow 8\,\text{acetyl CoA} + 7\,\text{FADH}_2 + 7\,\text{NADH} + 7\,\text{H}^+$$

106 (129 As per old concept) ATP are produced by the complete oxidation of one mol of Palmitic acid.

BETA OXIDATION- ENERGY YIELD

2.5 ATPs per NADH = 17.5

1.5 ATPs per FADH2 = 10.5

10 ATPs per acetyl-CoA = 80

Total = 108 ATPs

2 ATP equivalents (ATP $\longrightarrow$ AMP + PPi

PPi $\longrightarrow$ 2 Pi)

consumed during activation of palmitate to Palmitoyl CoA

Net Energy output- 108-2 = 106 ATP

DISORDERS ASSOCIATED WITH IMPAIRED BETA OXIDATION

1) Deficiencies of carnitine or carnitine transferase or translocase

- Symptoms include muscle cramps during exercise, severe weakness and death.
- Muscle weakness related to importance of fatty acids as long term energy source
- Hypoglycemia and hypo ketosis are common findings
- Diet containing medium chain fatty acids is recommended since they do not require carnitine shuttle to enter mitochondria.

DISORDERS ASSOCIATED WITH IMPAIRED BETA OXIDATION

2) Jamaican Sickness- Jamaican vomiting sickness is caused by eating the unripe fruit of akee tree, which contains the toxin hypoglycin, that inactivates medium and short-chain acyl-CoA dehydrogenases, inhibiting β oxidation and thereby causing hypoglycemia.

3) Dicarboxylic aciduria is characterized by-

i) Excretion of C_6–C_{10} -dicarboxylic acids and

ii) **Nonketotic hypoglycemia** which is caused by lack of mitochondrial **medium chain acyl-CoA dehydrogenases.**

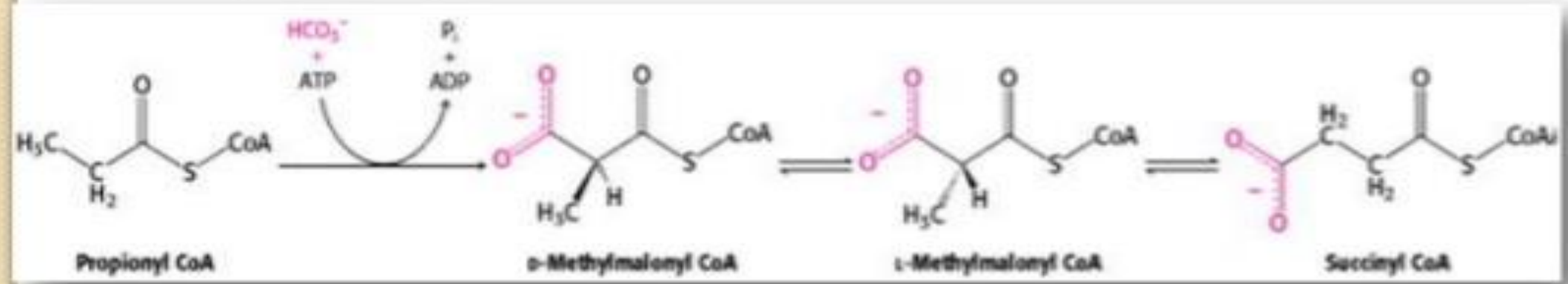
DISORDERS ASSOCIATED WITH IMPAIRED BETA OXIDATION

4) Acute fatty liver of pregnancy

- Manifests in the second half of pregnancy, usually close to term, but may also develop in the postpartum period.
- The patient developed symptoms of hepatic dysfunction at 36 weeks of gestation.
- Short history of illness, hypoglycemia, liver failure, renal failure, and coagulopathy are observed.
- Diagnosis is made based on an incidental finding of abnormal liver enzyme levels.
- Affected patients may become jaundiced or develop encephalopathy from liver failure, usually reflected by an elevated ammonia level.
- Profound hypoglycemia is common.

BETA OXIDATION OF ODD CHAIN FATTY ACIDS

Fatty acids with an odd number of carbon atoms are oxidized by the pathway of β-oxidation, producing acetyl-CoA, until a three-carbon (propionyl-CoA) residue remains. This compound is converted to Succinyl-CoA, a constituent of the citric acid cycle



The propionyl residue from an odd-chain fatty acid is the only part of a fatty acid that is glucogenic. Acetyl CoA cannot be converted into pyruvate or Oxaloacetate in animals.

Vitamins

By

Dr.Muna M. Yaseen

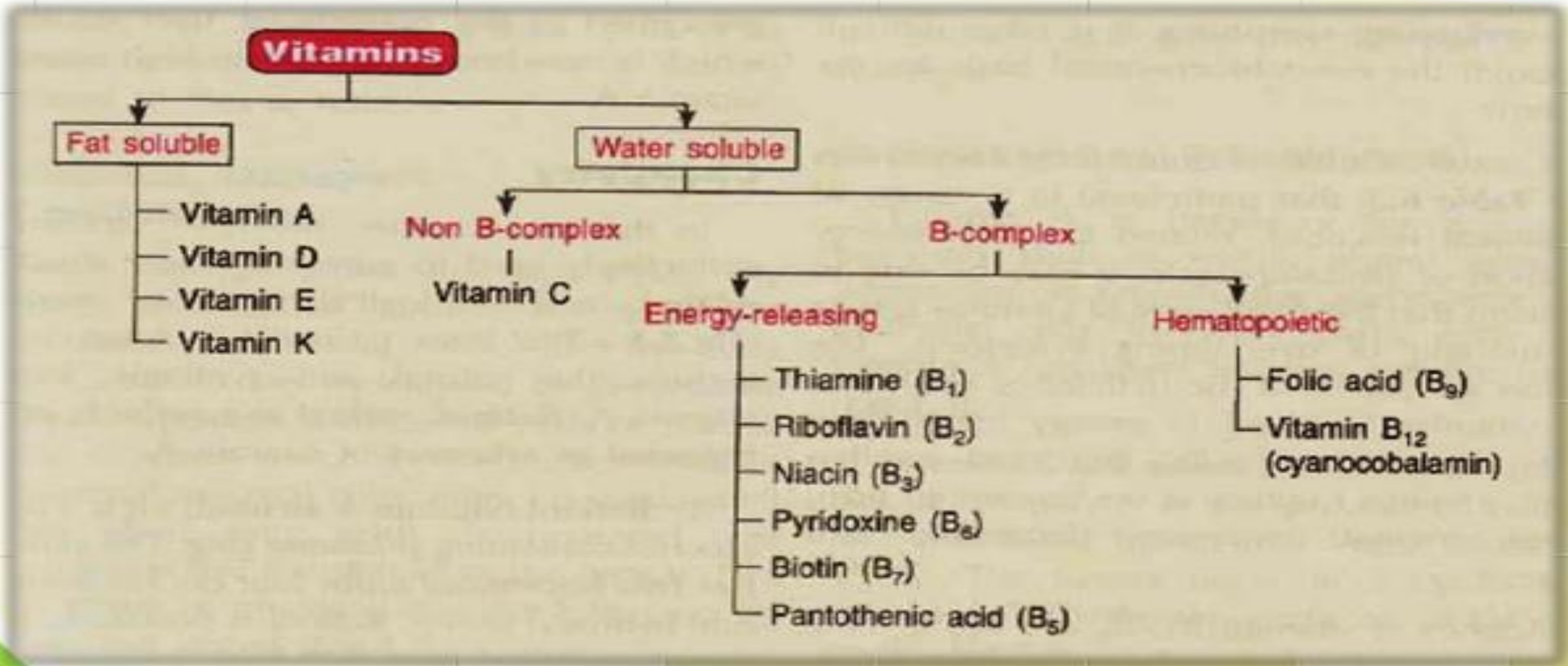
What are vitamins?

- Organic molecules with a wide variety of functions
- Cofactors for enzymatic reactions
- Essential, supplied in the diet
- **Two distinct types: Fat soluble (A, D, E, K)**
- **Water soluble (B – complex, C)**

Vitamins are organic molecules that are essential for normal health and growth. They are required in trace amounts and must be obtained from the diet because they are not synthesized in the body. Before vitamins were discovered, it was known that lime juice prevented the disease scurvy in sailors and that cod liver oil could prevent rickets. In 1912, scientists found that, in addition to carbohydrates, fats, and proteins, certain other factors called vitamins must be obtained from the diet.

Why are they good for us?

- Greater need due to worse environment
- Improve immunity
- Prevent ilnesses
- Slower aging


Vitamins
Fat soluble
Vitamin A
Vitamin D
Vitamin E
Vitamin K
Water soluble
Non B-complex
Vitamin C
B-complex
Energy-releasing
Thiamine (B_1)
Riboflavin (B_2)
Niacin (B_3)
Pyridoxine (B_6)
Biotin (B_7)
Pantothenic acid (B_5)
Hematopoietic
Folic acid (B_9)
Vitamin B_{12} (cyanocobalamin)

- Soluble in aqueous solutions
- Used as cofactors by many enzymes
- Not stored in the body

Table 21.9 Vitamins and Function

Water-Soluble Vitamins	Coenzyme	Function
Thiamine (vitamin B_1)	Thiamine pyrophosphate	Decarboxylation
Riboflavin (vitamin B_2)	Flavin adenine dinucleotide (FAD); Flavin mononucleotide (FMN)	Electron transfer
Niacin (vitamin B_3)	Nicotinamide adenine dinucleotide (NAD^+); Nicotinamide adenine dinucleotide phosphate ($NADP^+$)	Oxidation–reduction
Pantothenic acid (vitamin B_5)	Coenzyme A	Acetyl group transfer
Pyridoxine (vitamin B_6)	Pyridoxal phosphate	Transamination
Cobalamin (vitamin B_{12})	Methylcobalamin	Methyl group transfer
Ascorbic acid (vitamin C)	Vitamin C	Collagen synthesis, healing of wounds
Biotin	Biocytin	Carboxylation
Folic acid	Tetrahydrofolate	Methyl group transfer

Fat-Soluble Vitamins

Are A, D, E, and K.

Soluble in lipids, but not in aqueous solutions

Important in vision, bone formation, antioxidants, and blood clotting

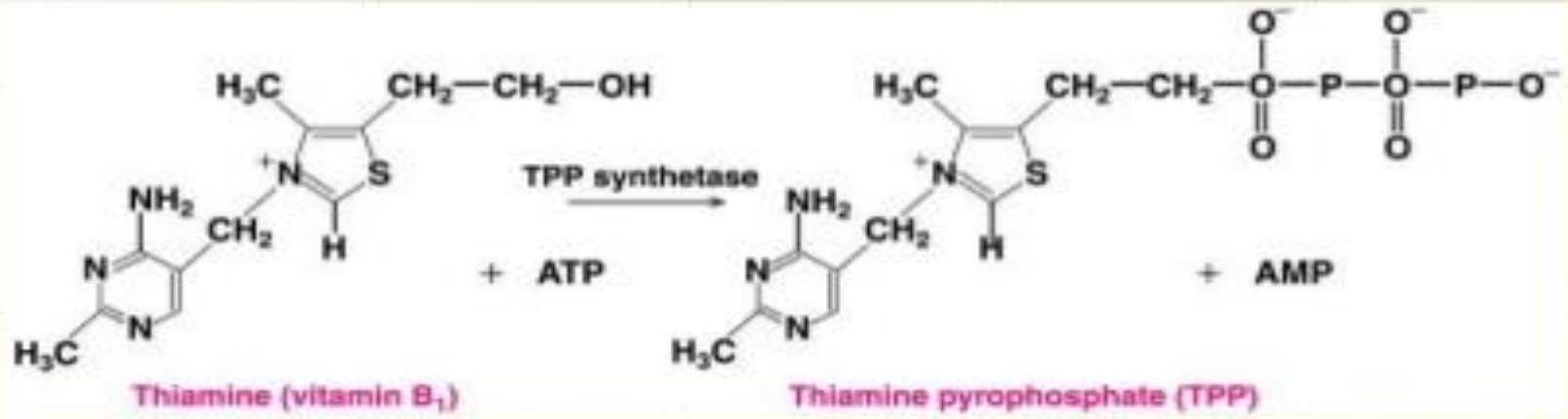
Stored in the body

Fat-Soluble Vitamins

Fat-Soluble Vitamins	
Vitamin A	Formation of visual pigments; development of epithelial cells
Vitamin D	Absorption of calcium and phosphate; deposition of calcium and phosphate in bone
Vitamin E	Antioxidant; prevents oxidation of vitamin A and unsaturated fatty acids
Vitamin K	Synthesis of prothrombin for blood clotting

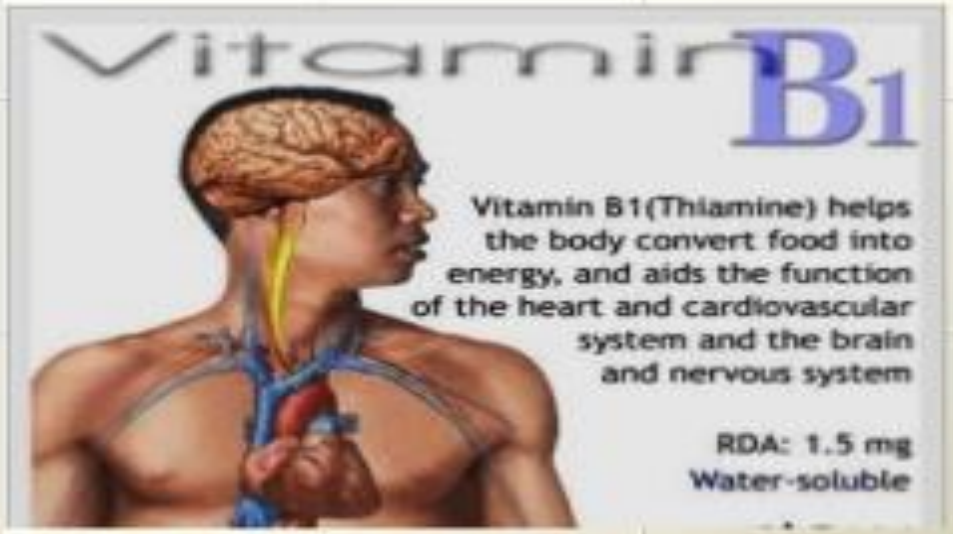
Thiamine (Vitamin B_1)

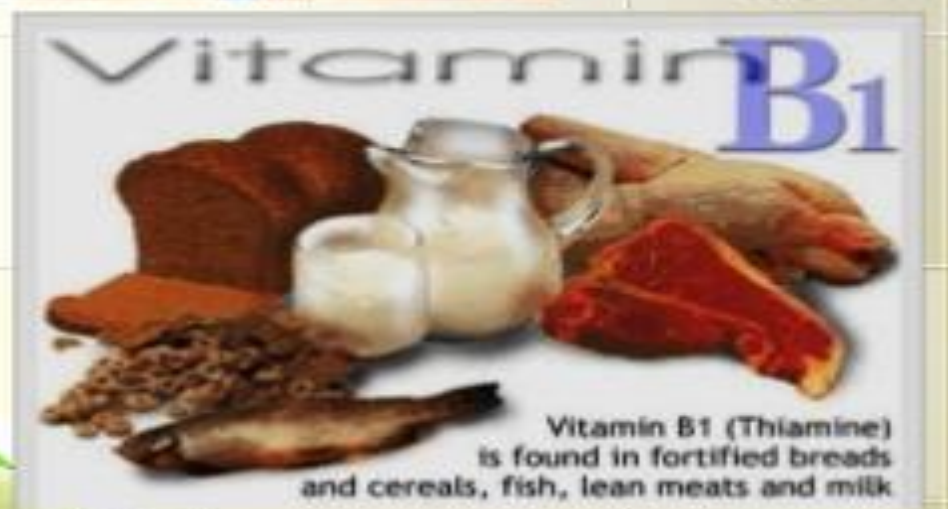
- Was the first B vitamin identified.
- Is part of the coenzyme thiamine pyrophosphate(TPP).



- TPP coenzyme is required by enzymes in the decarboxylation of α-keto carboxylic acids.
- Deficiency results in beriberi (fatigue, weight loss, and nerve degeneration).

Thiamine





- Influences sacharide metabolism
- Helps against tiredness
- Is destroyed by severe washings of rice and vegetables
- Severe deficiency leads to beri-beri
- Sources: yeasts, cereals,rice, liver, legumes

Riboflavin

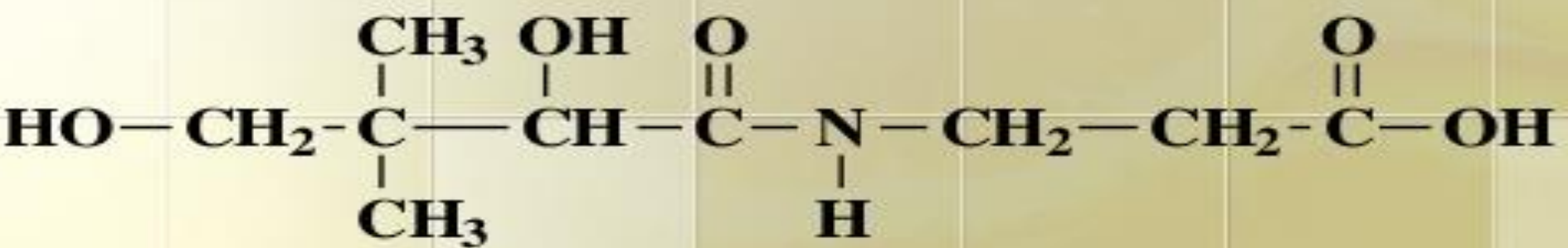
- Sacharide and lipids metabolism
- Curing of skin diseases
- Support of sight function
- Light sensitive
- Sources: cerals, eggs, vegetables, dairy products, yeast, liver

Niacin (Vitamin B_3)

- Is part of the coenzyme nicotinamide adenine dinucleotide (NAD^+) involved in oxidation-reduction reactions.
- Deficiency can result in dermatitis, muscle fatigue, and loss of appetite.
- Is found in meats, rice, and whole grains.

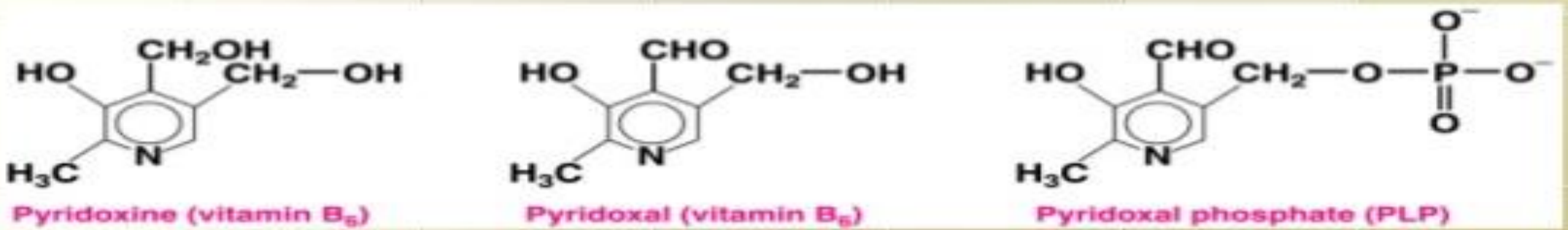
Pantothenic Acid (Vitamin B_5)

- Is part of coenzyme A needed for energy production as well as glucose and cholesterol synthesis.
- Deficiency can result in fatigue, retarded growth and anemia.
- Part of coenzyme A
- Reduces stress, prevents tiredness
- Necessary for formation of glycogen, fatty acids, steroid hormones
- Sources: whole grains, and vegetables ,eggs,liver, heart, yeast



Pyridoxine (Vitamin B_6)

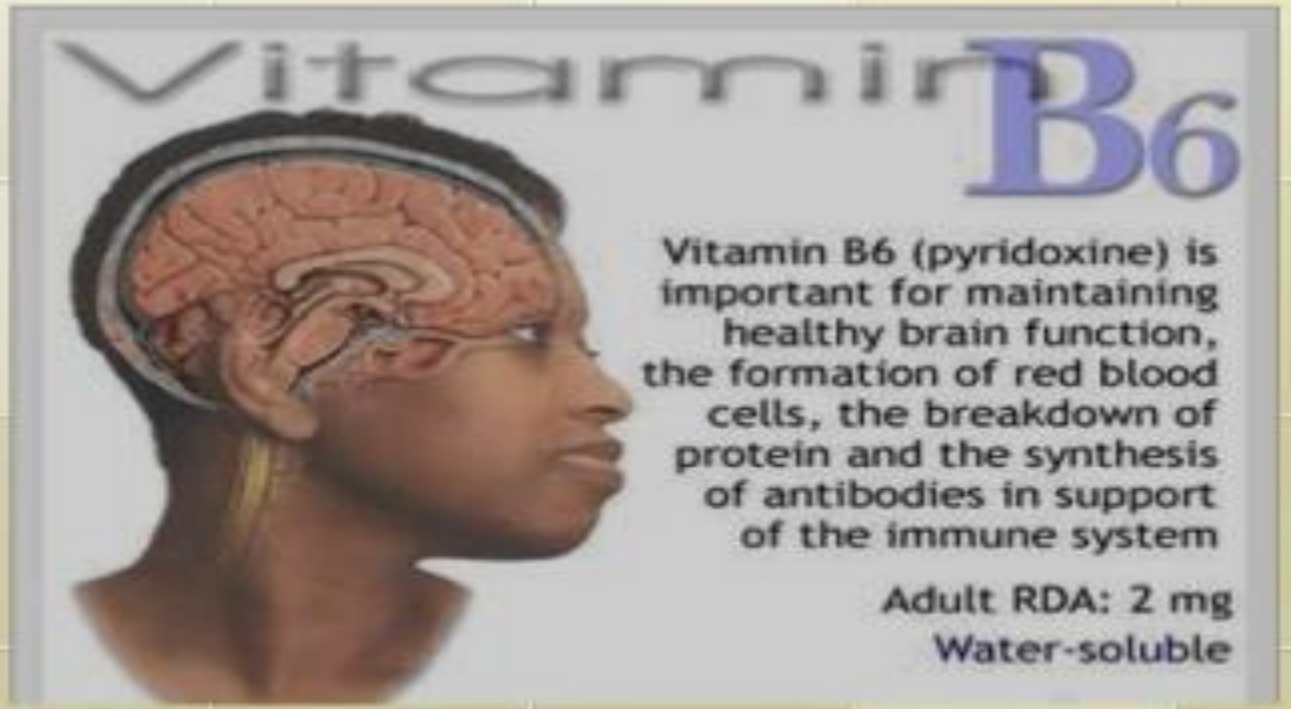
- Pyridoxine and pyridoxal are two forms of vitamin B_6, which are converted to the coenzyme pyridoxal phosphate (PLP).



- PLP is required in the transamination of amino acids and decarboxylation of carboxylic acids.
- Deficiency of pyridoxine may lead to dermatitis, fatigue, and anemia.

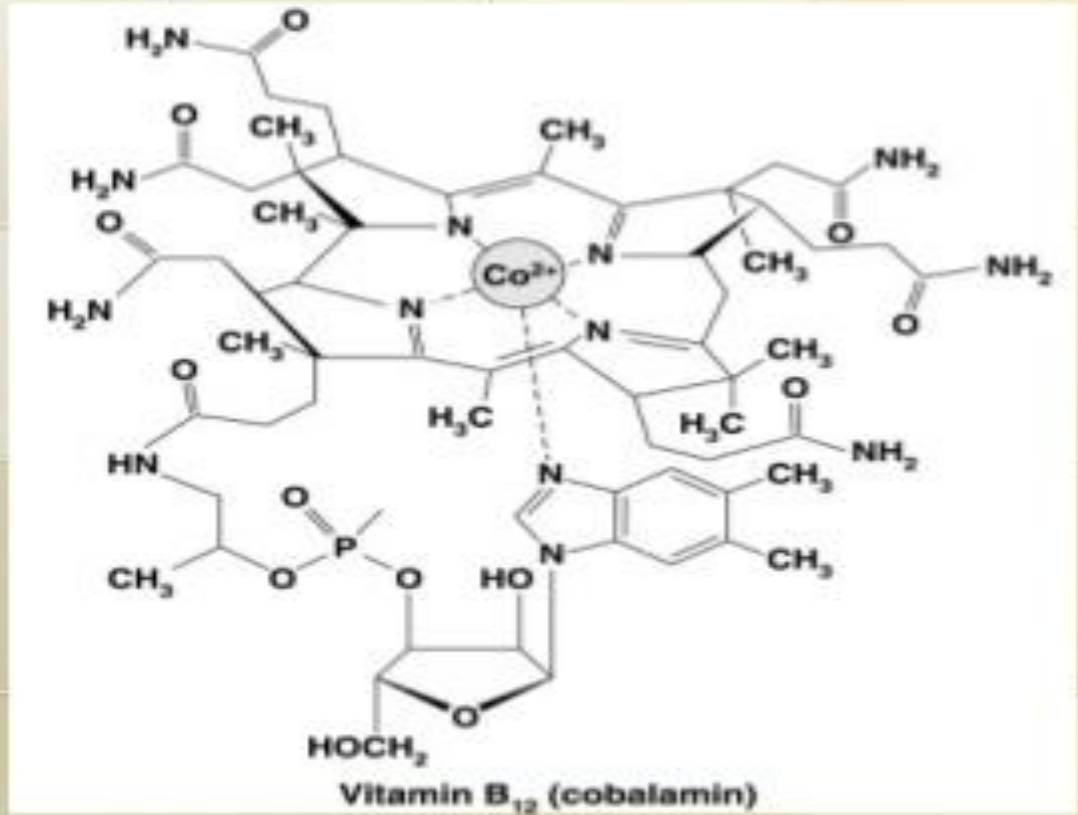
Pyridoxine

- Aminoacids and protein metabolism
- Cure of anemy
- Formation of red blood cells
- Sources: meat, fish, liver, vegetables, cerals, yolk, legumes



Cobalamin (Vitamin B_{12})

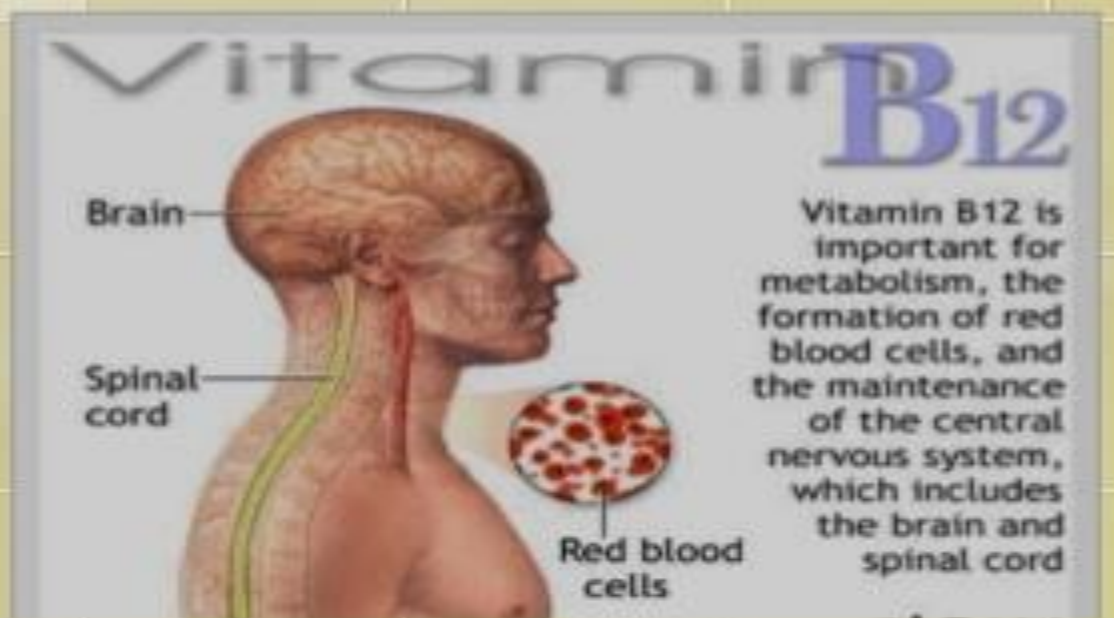
- Consists of four pyrrole rings with a Co^{2+}.
- Is a coenzyme for enzymes that transfer methyl groups and produce red blood cells.
- Deficiency can lead to pernicious anemia and nerve damage.



Vitamin B_{12} (cobalamin)

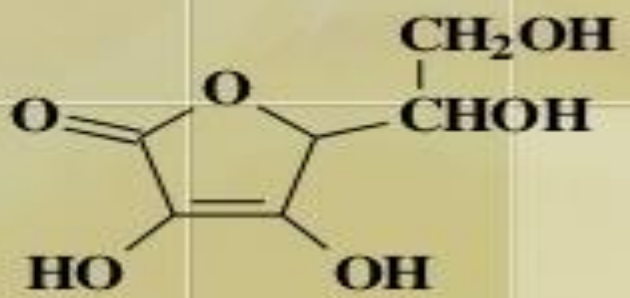
Cyanocobalamin

- Formation of red blood cells
- Maintenance of neuro tissue
- Cure of neuro diseases, anemia
- Sources: dairy products, meat, poultry, sea products



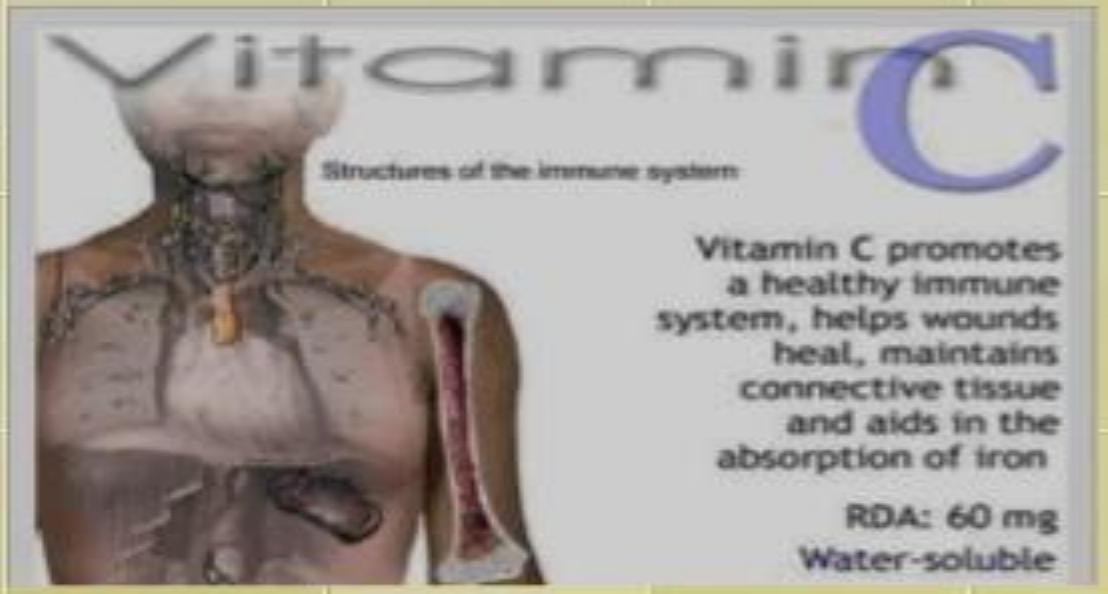
Ascorbic Acid (Vitamin C)

- Is required in collagen synthesis.
- Deficiency can lead to weakened connective tissue, slow-healing wounds, and anemia.
- Is found in Indian gooseberries, blueberries, citrus fruits, tomatoes, broccoli, red and green vegetables.



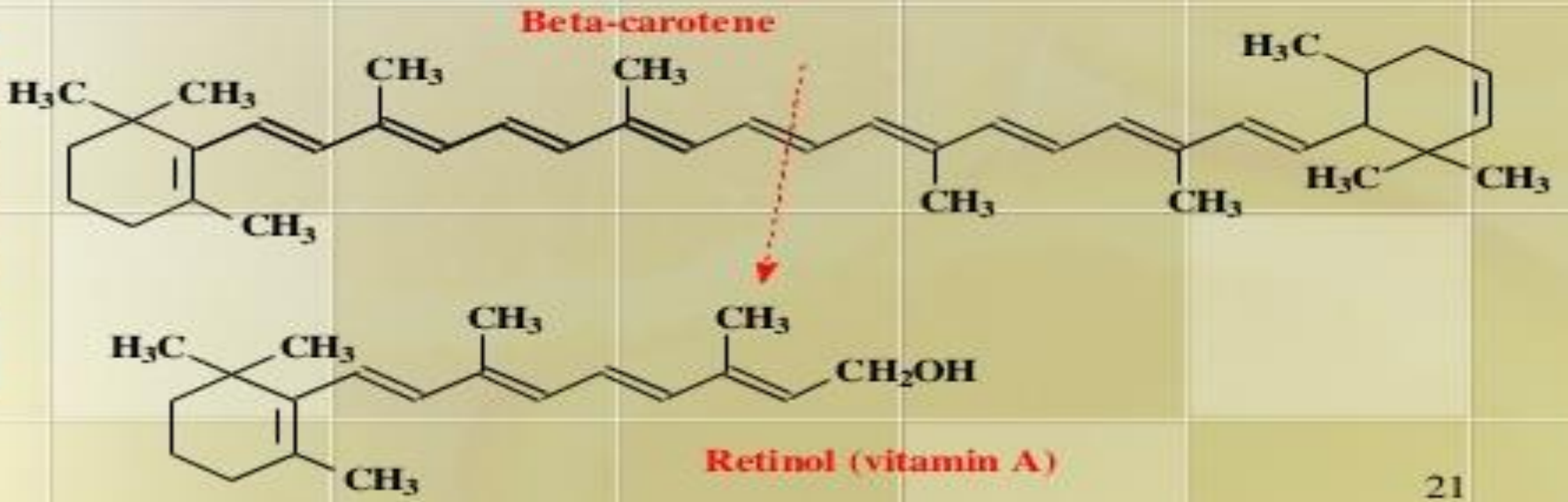
Vitamin C

- Hormone, collagen synthesis
- Infection resistance, cure of cuts
- Hypervitaminosis: addiction, diarrhea
- Hypovitaminosis: scurvy
- Source: fruits,vegetables



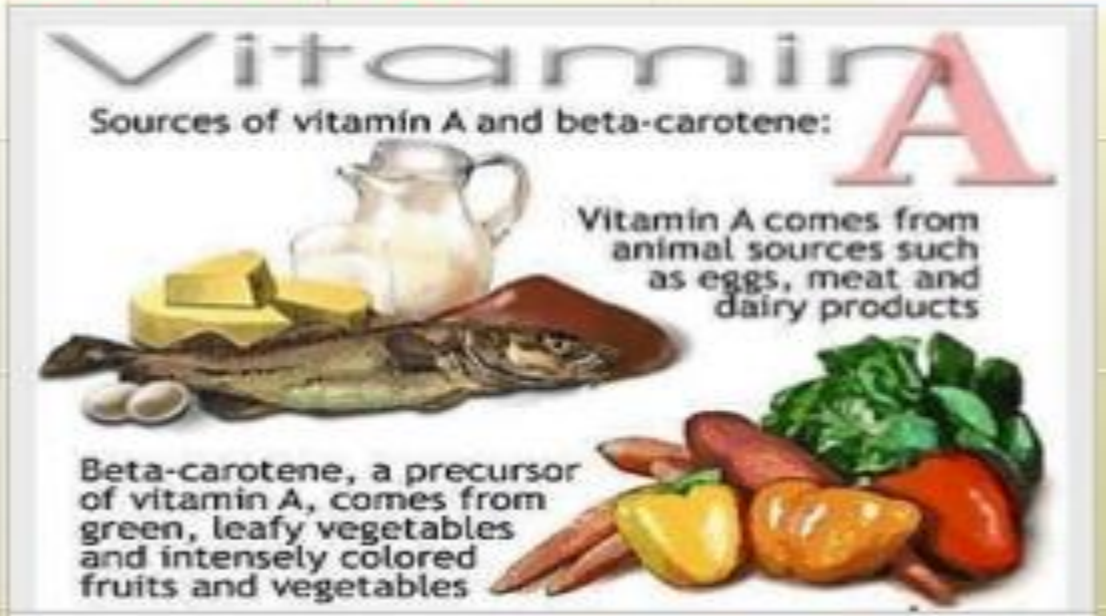
Vitamin A

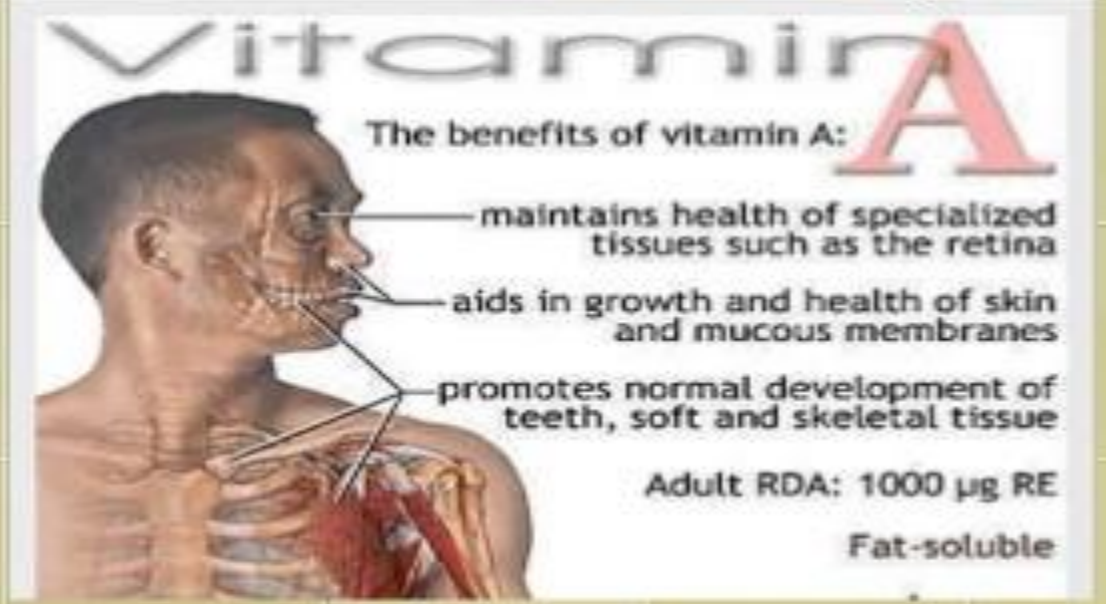
- **Vitamin A** is obtained from meats and beta-carotenes in plants.
- Beta-carotenes are converted by liver enzymes to vitamin A (retinol).



Vitamin A and provitaminA

- **Retinol**
- Cancer cure and prevention
- Skin, eyes, genital glands
- Provitamin changes to A vitamin in liver
- Sources: liver, egg yolks, dairy products
- provitamin: carrots, pepper, spinach, yellow fruits





Compiled & Edited by
Dr.Syed Ismail,MAU, Parbhani

Beneficial effects of β-carotene

Increased consumption of β-carotene is associated with decreased incidence of heart attacks, skin and lung cancers. This is attributed to the antioxidant role of β-carotene which is independent of its role as a precursor of vitamin A. Ingestion of high doses of β-carotene for long periods are not toxic like vitamin A.

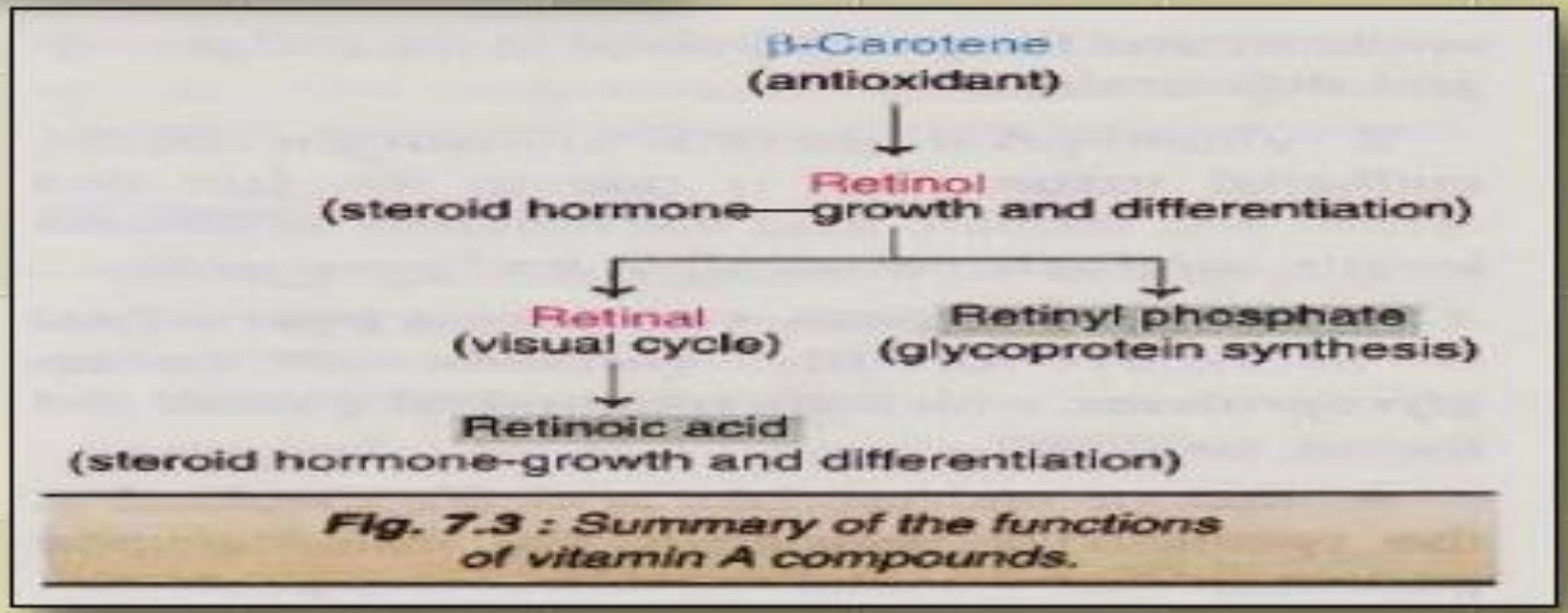
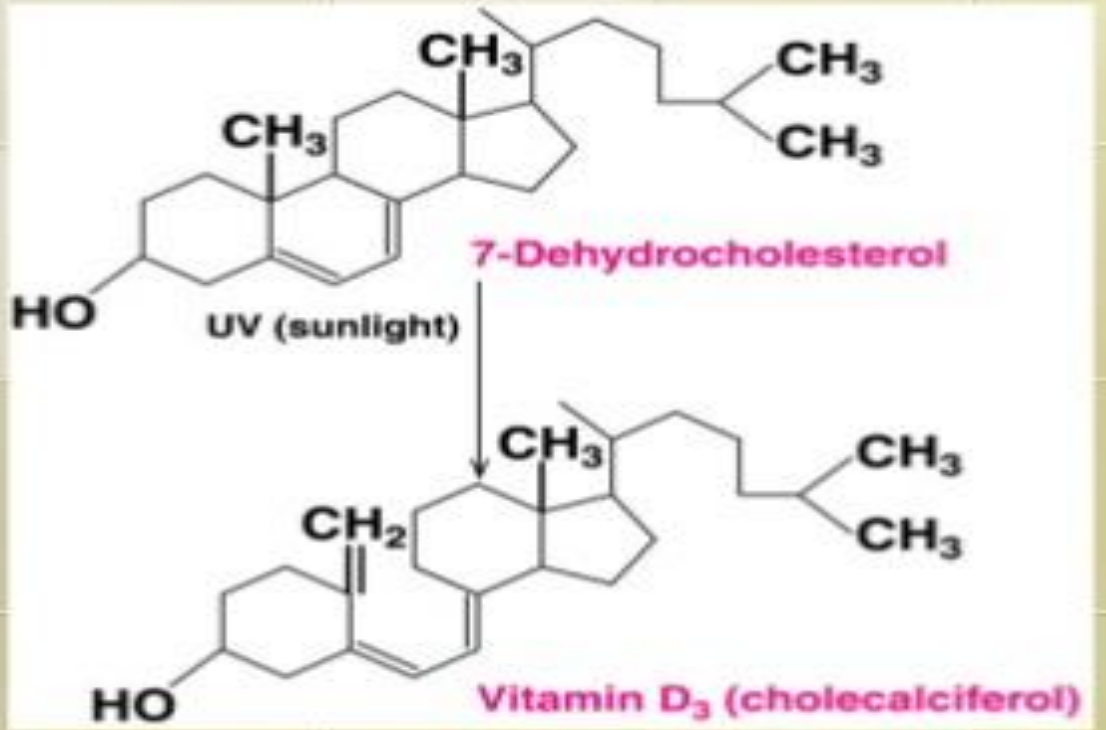


Fig. 7.3 : Summary of the functions of vitamin A compounds.

Vitamin D

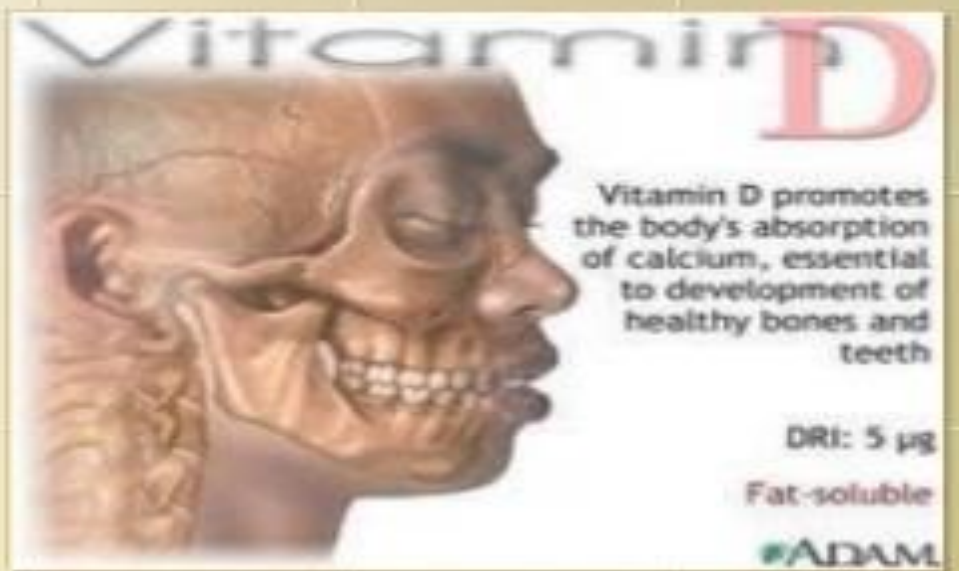
Vitamin D (D_3):

- Is synthesized in skin exposed to sunlight.
- Regulates the absorption of phosphorus and calcium during bone growth.
- Deficiency can result in weakened bones.
- Sources include cod liver oil, egg yolk, and enriched milk.



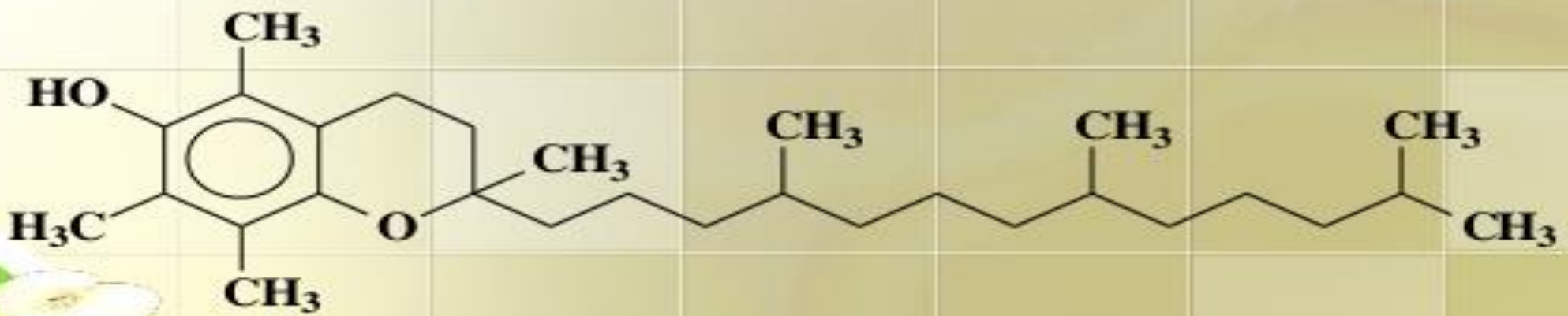
Vitamin D

- **Calciferols**
- the sun vitamin (UV rays)
- regulation of calcium metabolism
- sources: yeasts, fish, yolks, dairy products



Vitamin E

- Is an antioxidant in cells.
- May prevent the oxidation of unsaturated fatty acids.
- Is found in vegetable oils, whole grains, and vegetables.



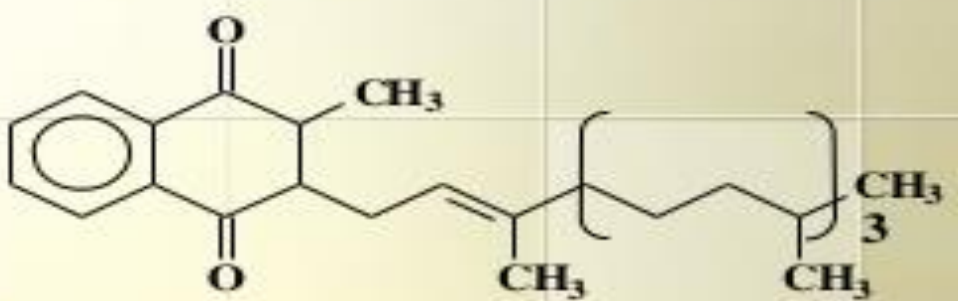
Vitamin E

Tocoferols

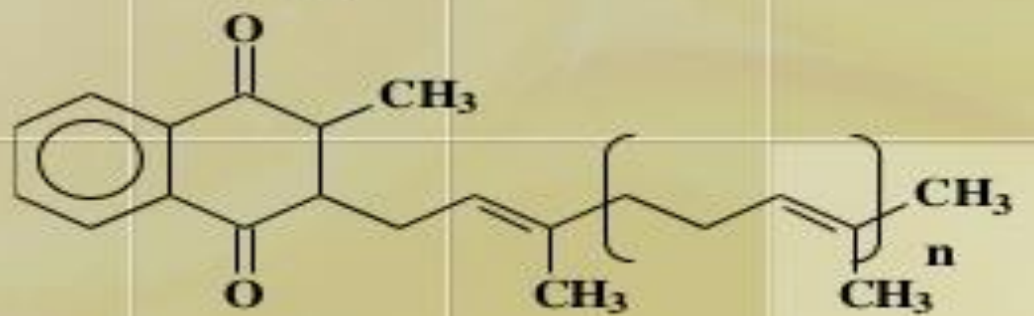
- Antioxidant (lipid protection)
- improves immunity
- Cures muscle, heart and skin diseases, burns
- Sources: green vegetables, vegetable oil, corn, eggs, bread, dairy products, peas, beans

Vitamin K

- Vitamin K_1 in plants has a saturated side chain.
- Vitamin K_2 in animals has a long unsaturated side chain.
- Vitamin K_2 is needed for the synthesis of zymogens for blood clotting.



Vitamin K_1 (phylloquinone)



Vitamin K_2 (menaquinone)

Vitamin K

- Blood clotting
- Higher need by newborns, people with liver diseases, or fat malabsorbtion
- Sources: green fruits and vegetables, tomatoes, soy, beef liver, yolks, wheat, butter, cheese

Daily values:

Vitamin:	Daily values [mg]:
A (retinol)	1-3
B1 (thiamine)	30 - 200
B2 (riboflavin)	25 - 200
B3 (niacin, niacinamid)	30 - 100
B5 (Pantothenic acid)	20 - 500
B6 (pyridoxine)	10 - 15
B12 (Cynocobalamine)	5 - 8
H (Biotin)	300 - 5000
C (Ascorbic acid)	2 - 12 g
D (cholecalciferol)	10
E (tokoferol)	400 - 2000
K	80

Thank You!

Vitamins

By

Dr.Muna M. Yaseen

VITAMINS

- Vitamins are made up of carbon, hydrogen and oxygen.
- Vitamins are called micronutrients because they are needed in only very small quantities. They all have chemical names but they are usually referred to by letters.

1.They differ from other organic food stuffs in that:

- They do not enter into tissue structures, unlike proteins.
- Do not undergo degradation for providing energy unlike carbohydrates and lipids.
- Several B complex vitamins play an important role as **coenzymes** in several energy transformation reactions in the body.

2. They differ from hormones: In not being produced within the organism, and most of them have to be provided in the diet.

MAIN FUNCTIONS

- Vitamins are essential to the body:
  - To maintain health
  - To help prevent deficiency diseases such as Beriberi (weakened muscles, heart, nerves and digestive system) and rickets (softening of the bones)
  - To regulate the repair of body cells
  - To help combat the ageing process
  - To help to process carbohydrates and release energy in the body

VITAMINS - Two main categories

Water soluble

B

C

Fat Soluble

A

D

E

K

Water soluble	Fat Soluble
• Cannot be stored in body - regular supply needed	• Can be stored in body - regular supply not needed
• Excess is excreted in urine - no danger of toxic levels	• Can accumulate to toxic levels if large amounts ingested
• Unstable to heat and light, leach into cooking liquids	• Fairly stable at normal cooking temperatures

Vitamin A – 2 forms; Retinol and Beta-Carotene

Retinol

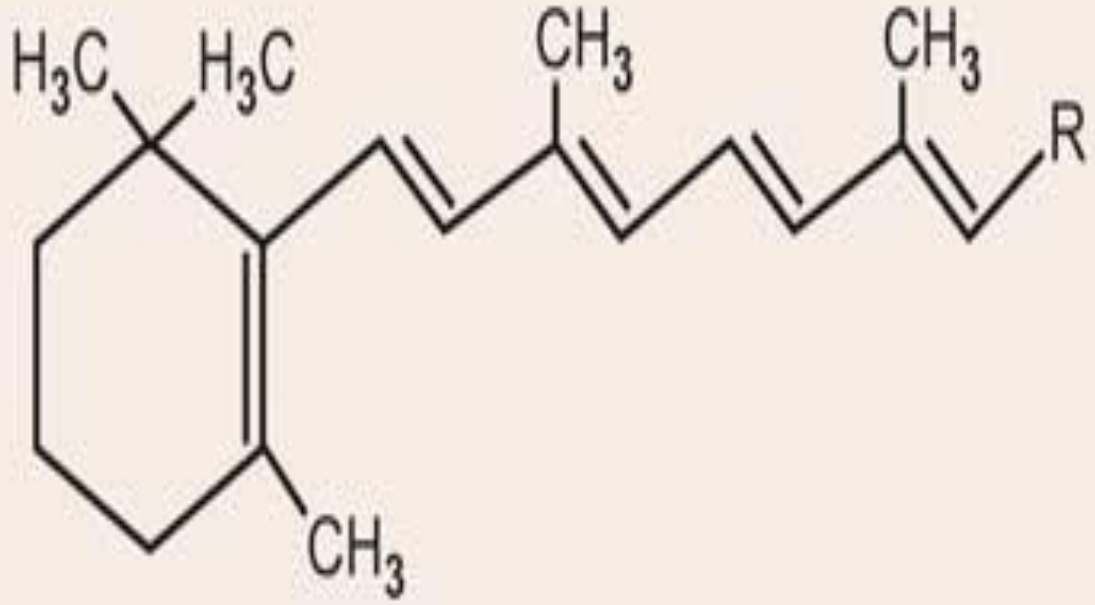
Named because of its concern with retina of eye

Only found in animal foods

Beta-Carotene

Plant sources

Present with chlorophyl
in plants, converted t
Vitamin A in gut wall



When

R = –CH_2OH Retinol or vitamin A alcohol

R = –CHO Retinal or vitamin A aldehyde

R = –COOH Retinoic acid or vitamin A acid

Vitamin A - Retinol and Beta-Carotene

Functions

- Regulates growth
- Promotes healthy skin
- Maintenance of healthy tissues
- Helps eye adapt to dim light

The moisturising

Sources

Retinol - Cod liver oil, Liver, Dairy products, Herrings, Egg yolk

Beta-Carotene

Dark green leafy vegetables, Broccoli, Carrots, Deep orange fruits and vegetables

Vitamin A - Retinol and Beta-Carotene

Effects of deficiency

- Retarded growth, malformed bones
- Long term-may lead to night blindness
- Susceptibility to infection
- Excess beta-carotene may lead to liver and bone damage

Vitamin D -Calciferols

Functions

- Absorption and laying down of calcium and phosphorous in bones and teeth
- Regulates calcium balance between bones and blood
- Prevents rickets

Sources

Sunlight conversion

Fish liver oils

Dairy products

Oily fish

Margarine

Vitamin D -Calciferols

Effects of deficiency

- *Rickets in children and *osteomalacia in adults

> * Conditions where bones are soft and cannot take weight of body

- **Osteoporosis

> **Bones become light, less dense and prone to fractures

- Dental caries

Vitamin E - Tocopherol

Functions

- Protects tissues against damage
- Promotes normal growth and development
- Helps in normal red blood cell formation

Sources

Pure vegetable oils

Wheat

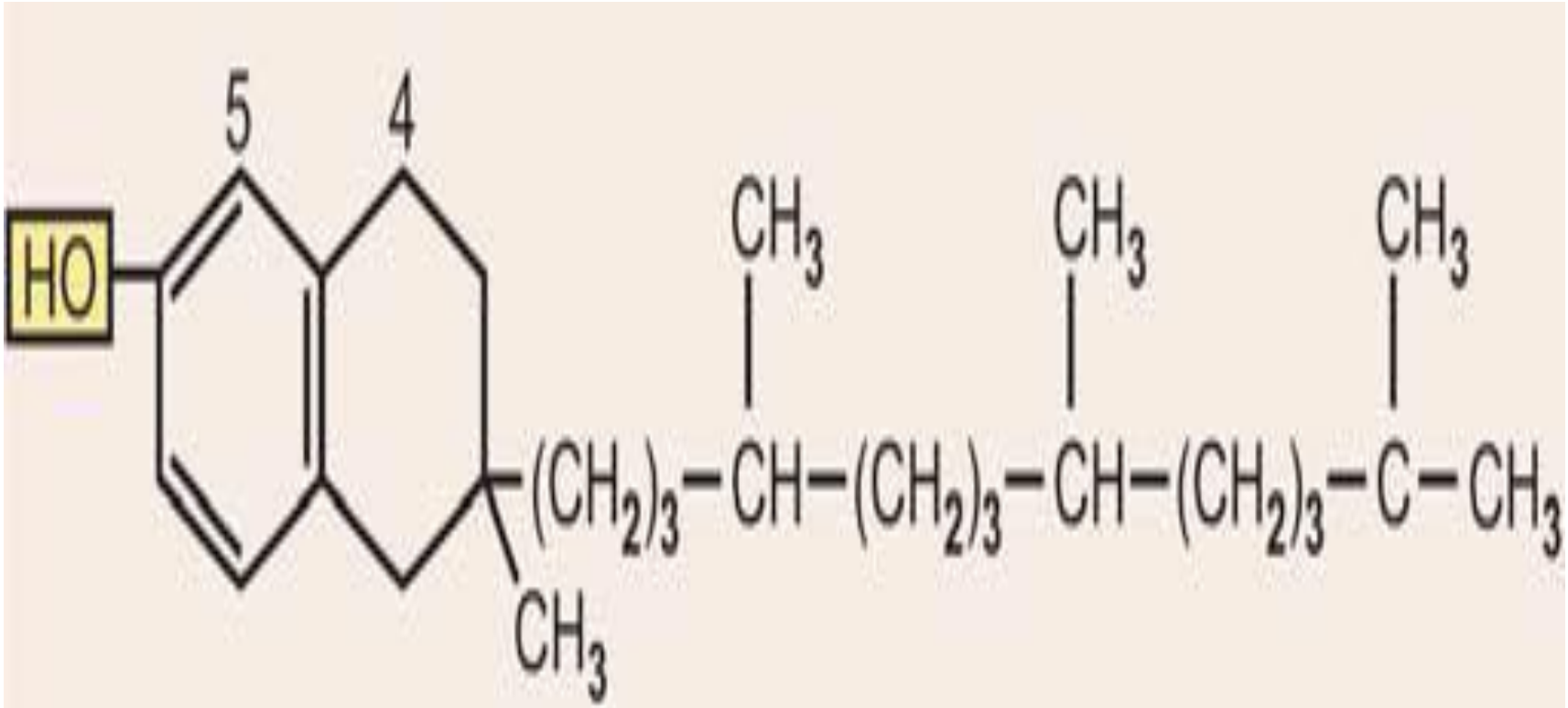
wholemeal bread and

Cereals

egg yolk

nuts

sunflower seeds



Structure of vitamin E

Vitamin E - Tocopherol

Effects of deficiency

Deficiency is very rare but it could affect the central nervous system

Vitamin K - Napthoquinone

Functions

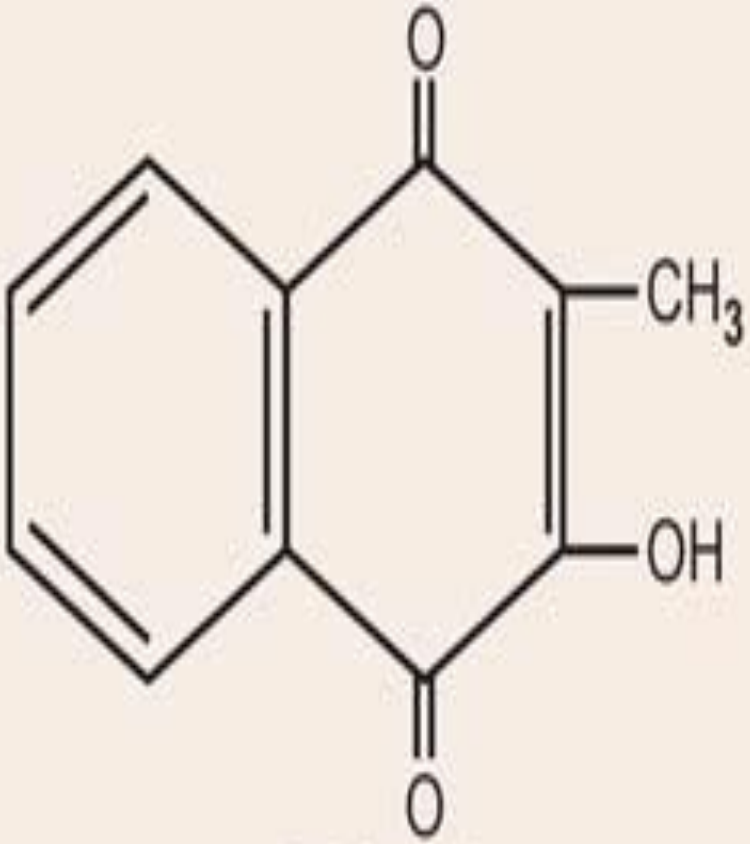
- Needed for blood clotting, which means it helps wounds heal properly.
- There is increasing evidence that vitamin K is also needed to help build strong bones.

Sources

Green leafy veg

Vegetable oil

Cereals



Pthiocol

(2-methyl, 3-hydroxy, 1,4-naphthoquinone)

Vitamin K - Napthoquinones

Effects of deficiency

Deficiency is very rare but individuals with liver damage and new born infants are at a higher risk

Vitamin B_1 - Thiamin

Functions

- Essential for release of energy from carbohydrates
- Necessary for appetite and good health
- Needed for normal functioning of nervous system

Sources

Meat
Oatmeal
Breakfast cereals
Wheat
Fortified white flour
Milk
Eggs
Vegetables

Vitamin B_1 - Thiamin

Deficiency

- Fatigue, depression, irritability
- Beri-beri - disease of nervous system

Vitamin B_2 -Riboflavin

Functions

- Metabolism of carbohydrates, proteins and fats
- Growth, repair, development of body tissues - healthy skin, eyes and tongue
- The principal growth promoting factor in the vitamin B complex

Sources

Offal
Milk
Cheese
Eggs
Yeast extracts
Green Vegetables

Vitamin B_2 -Riboflavin

Deficiency

- Loss of appetite
- Swollen tongue, cracked lips, eye infection,

Vitamin B3 -Niacin

Functions

- Metabolism of carbohydrates, proteins and fats
- Needed for normal functioning of nervous system

Sources

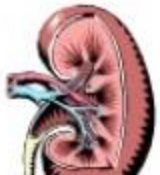
Meat, Offal

Yeast extracts

Yeast

Bran, wheat, flour

Some pulses, dried fruit

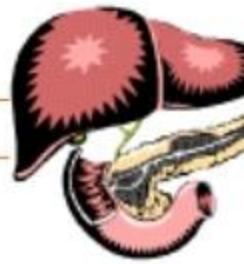


Vitamin B3 -Niacin

Deficiency

- Fatigue, depression, irritability
- Beri-beri - disease of nervous system

Vitamin B9 -Folic Acid



Functions

- Red blood cell formation
- Development of brain, spinal cord and skeleton in foetus
- Reduces risk of neural tube defects e.g. spina bifida
- May play role preventing heart attacks, strokes and cancer

Sources

- Fortified cereals
- Green leafy vegetables
- Potatoes
- bread
- Milk
- Wheat

Vitamin B9 -Folic Acid

Deficiency

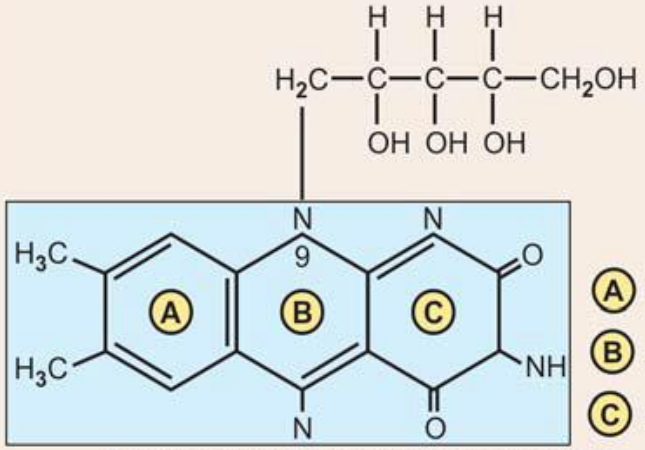
- Fatigue in mild cases
- Anaemia in severe cases
- Neural tube defects

Important to take folic acid prior to conception and vital during first 3 months pregnancy

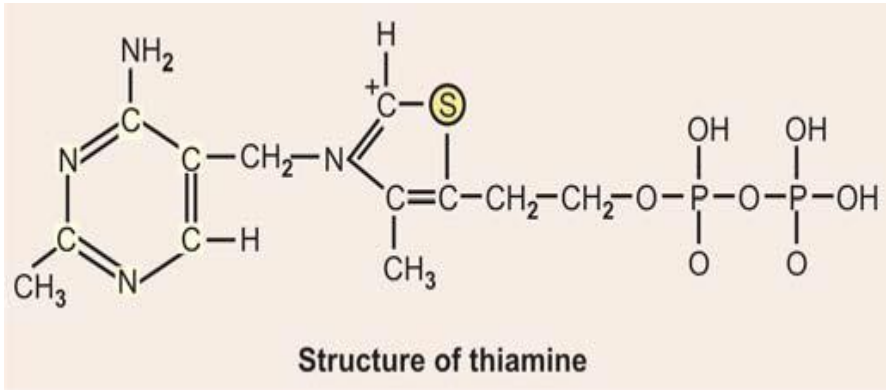
Folic acid fortification

Folic acid is a B vitamin. It is called folate when it is found in foods in its natural form. Folic acid is used in supplements or added to food.

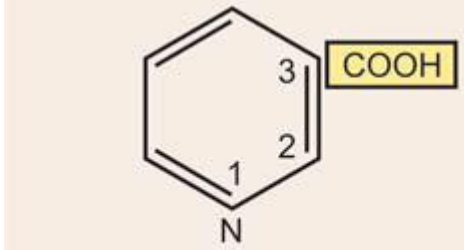
Some foods, such as many breakfast cereals and spreads, are already fortified with folic acid and other vitamins and minerals. But recently there have been discussions about whether it should be compulsory to add folic acid to bread or flour in the UK.



6,7-dimethyl-9 D-ribityl isoalloxazine
(Riboflavin (Vitamin B_2))

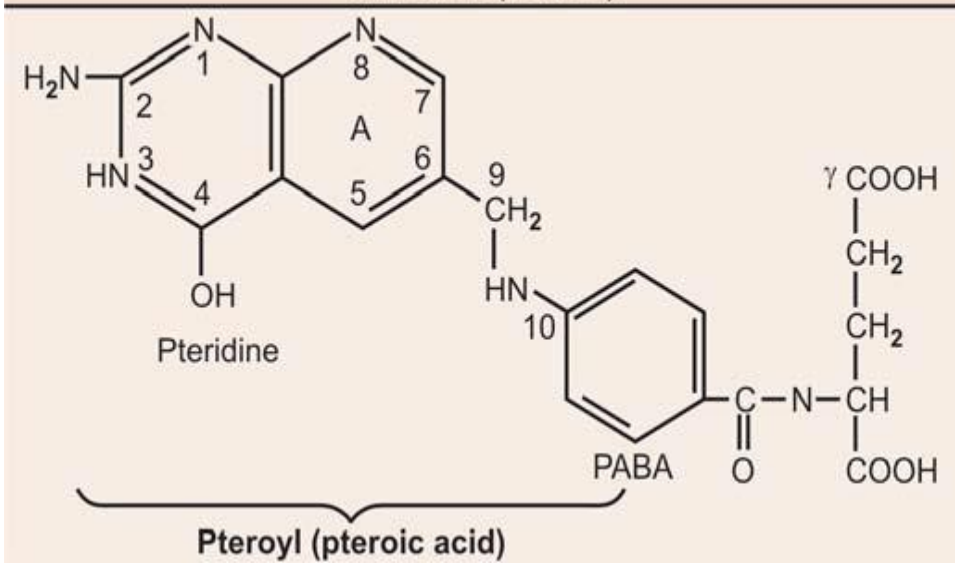


Structure of thiamine



Niacin

Folic acid (folacin)



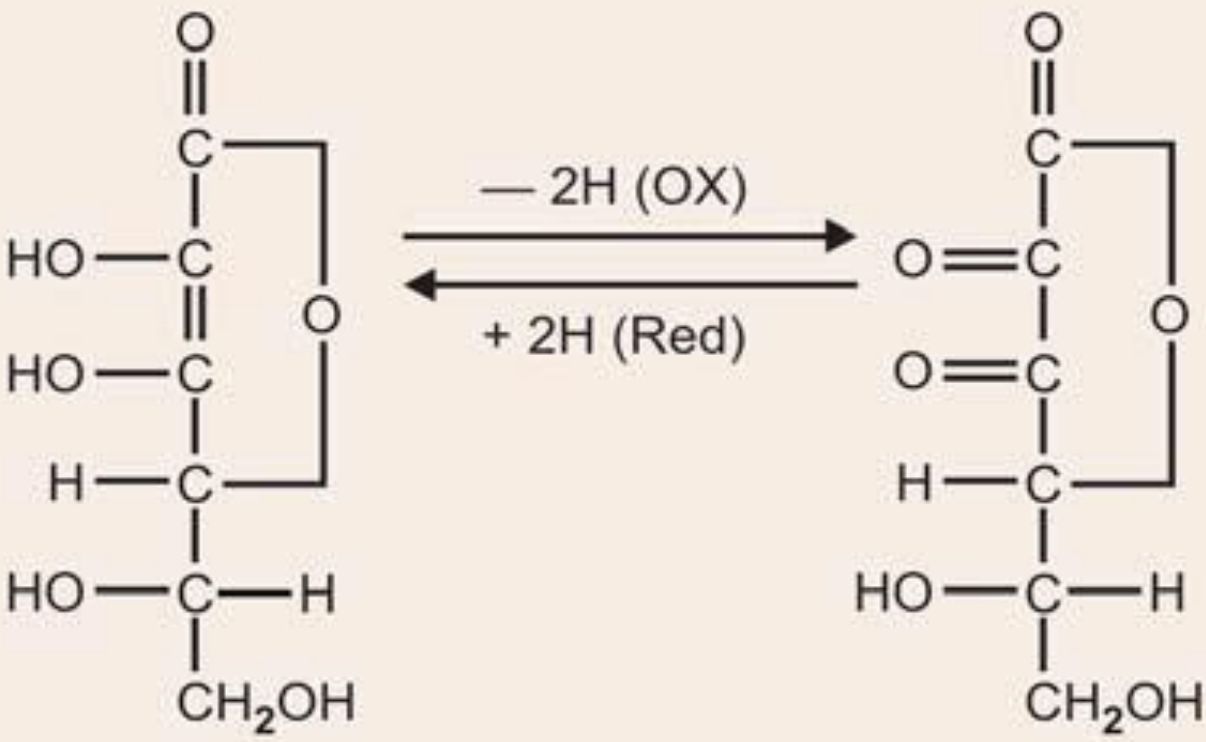
Vitamin C -Ascorbic Acid

Functions

- Critical to immune system
- Formation of connective tissue, collagen
- Helps absorption of iron
- Prevents scurvy
- Promotes healing of wounds and healthy blood vessels
- Acts as antioxidant, protects cholesterol

Sources

- Rosehips, blackcurrants,
- green peppers, kiw citrus
- fruits, strawberries,
- spinach, cabbage,
- broccoli



L-ascorbic acid
(Reduced form)

L-dehydroascorbic acid
(Oxidised form)

Vitamin C -Ascorbic Acid

Deficiency

- Weakening of connective tissue
- Susceptibility to infection
- Incomplete iron absorption
- Delayed healing of wounds
- Prevent scurvy - pale skin with spots, bleeding, soft gums.

KEY FACTS:

- Micronutrients are essential for a healthy body
- Water soluble vitamins must be eaten every day
- It is easy to improve the micronutrient content of your diet by eating more fruit and vegetables, enough red meat and wholegrain cereals.

MINERALS

- Our body requires mineral elements for a variety of functions. They are also known as micronutrients.

MINERALS

- Unlike vitamins, which are organic substances minerals are inorganic and are found in rocks and soil. Vegetables absorb minerals as they grow, while animals digest it through their diet.
- Minerals can be divided into two groups - those needed in larger quantities (major minerals) and those only required in tiny amounts (trace elements).

MINERALS

- **Trace Minerals** - are iron, zinc and iodine.

- **Major Minerals** - are sodium, potassium, calcium and phosphorus.

MINERALS

- Minerals have 4 major functions:
- Body building – teeth and bones
- Control of body processes, especially the nervous system
- Essential part of body fluids and cells
- Form part of enzymes and other proteins necessary for the release of energy

Iron

- **Functions**
- Production of haemoglobin in red blood cells to carry oxygen in the blood

Deficiency

- Anaemia

- **Sources**
- Red meat
- Kidney
- Liver
- Eggs
- Bread
- Green veg

Calcium

- **Functions**
- Teeth and bones.
- Blood clotting.
- Nerve and muscle contraction.
- Heart regulation

Deficiency

Stunted growth can cause rickets, osteoporosis.

- **Sources**
- Dairy products
- fortified white bread
- oily fish
- green veg
- nuts and seeds
- citrus fruits.

Phosphorus

- **Functions**
- Bones and teeth with calcium.
- Muscle contraction

- **Sources**
- Dairy products
- Nuts
- Meat
- Fish
- foods rich in calcium

Deficiency

Rarely deficient but could cause tiredness and depression

Sodium

- **Functions**
- Maintains water balance in the body and controls body temperature, helps you sweat when body temp rises.

Deficiency

Deficiency is highly unlikely

- **Sources**
- Cheese
- Bacon
- smoked meats
- Fish
- processed foods
- table salt.
- Government advice says on average you should be eating no more than 6g of salt a

Potassium

- **Functions**
- Muscle contraction and in maintaining fluid. It is necessary for the building of muscle and for normal body growth.

- **Sources**
- Banana
- Celery
- Turnips

Deficiency

Dry skin, acne,

Muscle spasms

Zinc

- **Functions**
- Everything from acne to diabetes. Aids the immune system. Needed for the senses of smell and taste.

- **Sources**
- Meat (lamb)
- Oats
- Eggs
- Nuts

Deficiency

Dry skin, acne,

Muscle spasms

Iodine

- **Functions**
- Thyroid gland function (controls how quickly the body uses energy) and body metabolism

Deficiency

Particularly in children,
fall in the production of thyroid hormones

- **Sources**
- Animal and plat life from the sea
- Milk
- Eggs
- Yogurt

THANK YOU