Course Title:

Biochemistiy

كلية العلوم

الفرقة الثانية علوم

شعبة بيوتكنولوجى

كود المقرر : 201

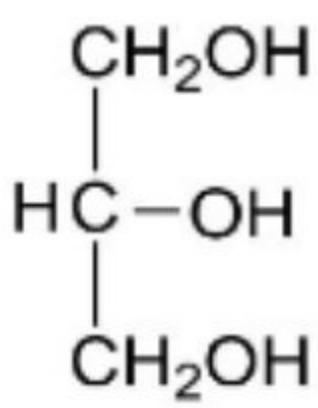
اعداد :

ا. م . د / حسين تميرك

Carbohydrates Definition

C : H : O

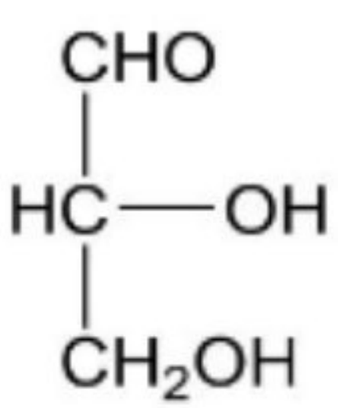
1 : 2 : 1



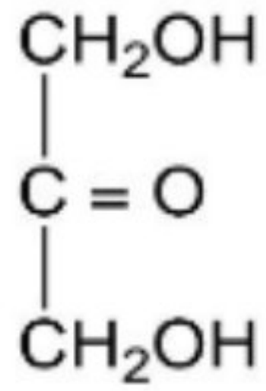
Glycerol

C : H_2O

1 : 1



Glyceraldehde



Dihydroxyacetone

Carbohydrates classifications

- 1) **Monosacchrides:** simplest carbohydrates may be:

  a) Polyhydroxyaldhydes (aldoses)

  b) Polyhydroxyketones (ketoses)
- 2) **Disacchrides** : contain 2 monosacchride
- 3) **Oligosacchrides**: 3-10 monosacchride units bound by glycosidic bonds
- 4) **Polysacchrides:** larger, containing hundreds monosacchrides

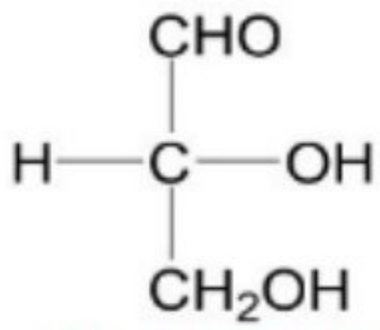
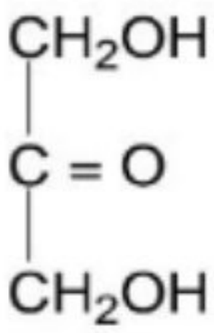
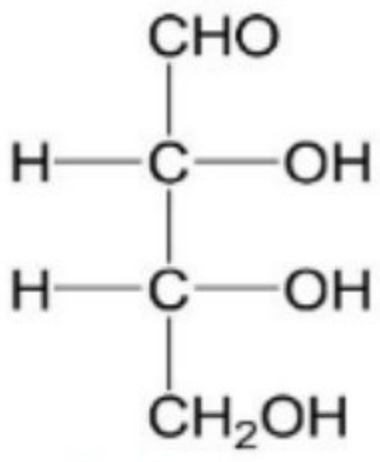
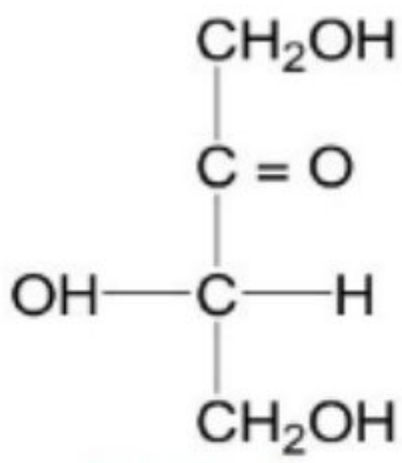
Carbohydrates structure

- The OH groups in CHO allows interaction with aqueous environment
- Derivatives of CHO contain N, S and P
- CHO can also combine with lipids to form glycolipids or proteins to form glycoproteins (Glycoconjugates)

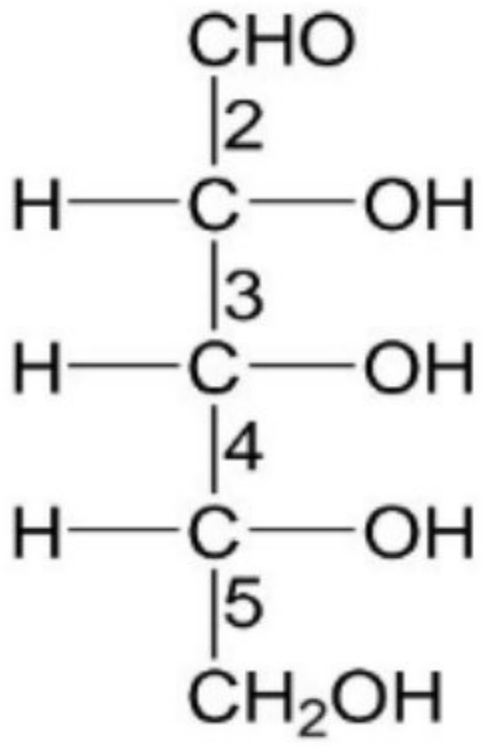
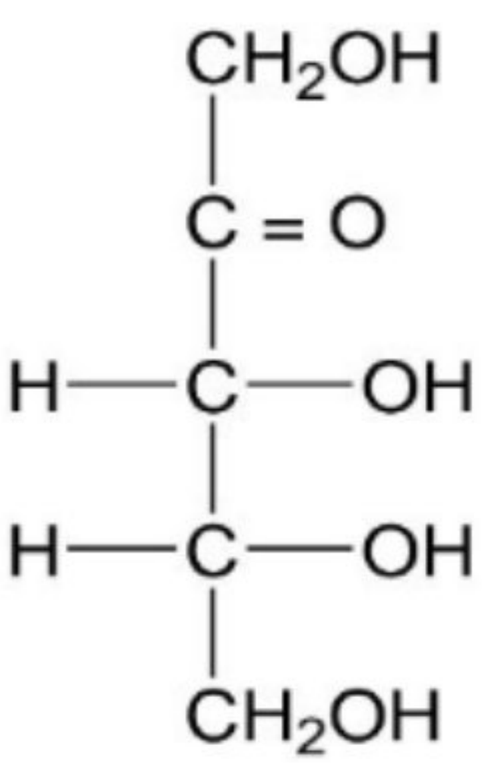
Monosaccharides

No. of carbons		Aldehyde (Aldose)	Ketone (Ketose)
3	Trioses	Glyceraldehyde	Dihydroxyacetone
4	Tetroses	Erythrose	Erythulose
5	Pentoses	Ribose	Ribulose
6	Hexoses	Glucose, Galactose, Mannose	Fructose

Monosaccharides

	Aldehyde	Ketone
Trioses	 Glyceraldehde	 Dihydroxyacetone
Tetroses	 Erythrose	 Erythrulose

Monosaccharides

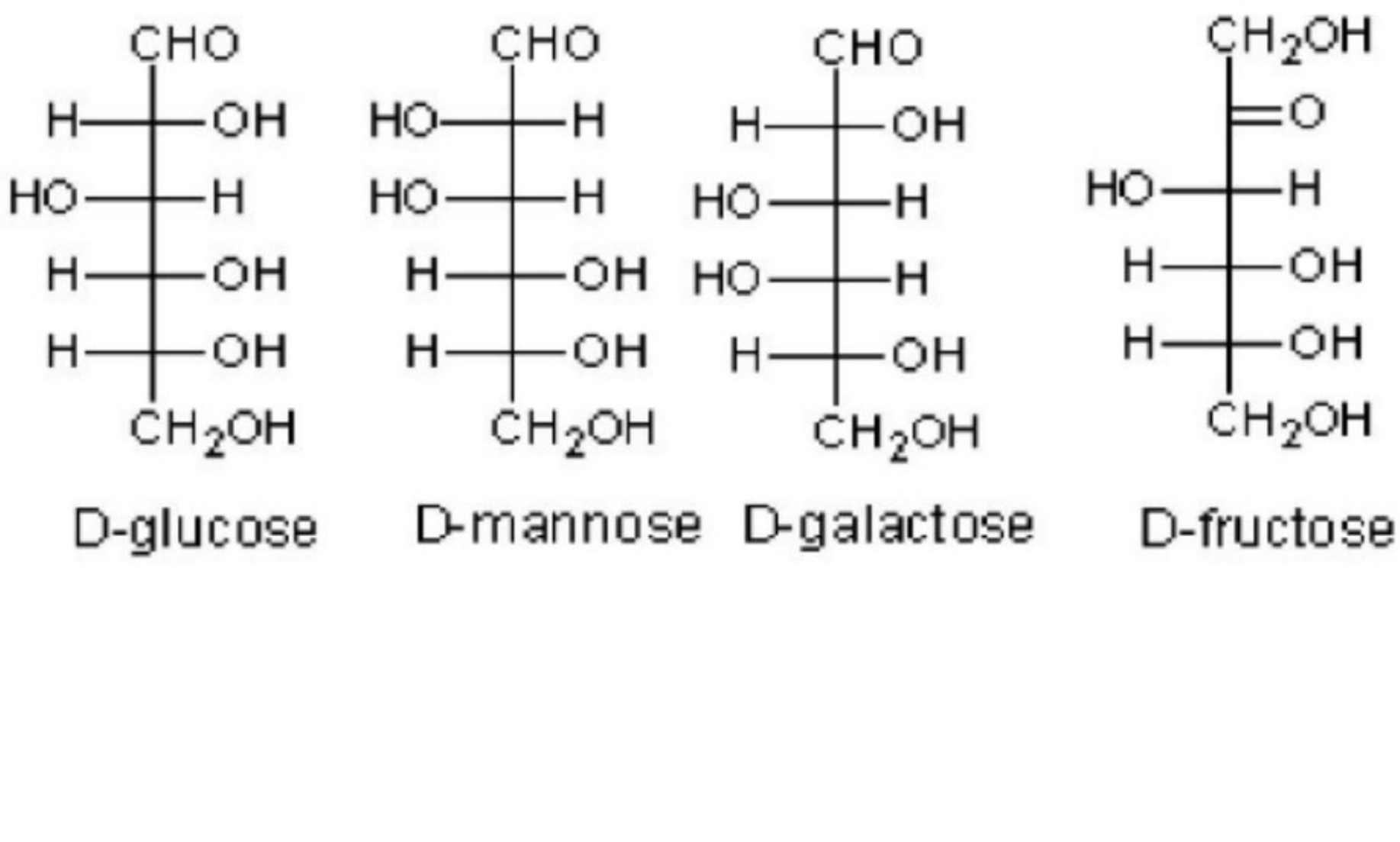
	Aldehyde	Ketone
Pentoses	 Ribose	 Ribulose

Monosaccharides

Aldehydes

Ketone

Hexoses



Properties of Monosaccharides

Physical Properties	Chemical Properties
1. Soluble in water	1. Oxidation
2. Show optical activity	2. Reduction
3. Ring or Cyclic structure	3. Reaction with H_2SO_4
4. Show optical isomerism	4. Osazone formation

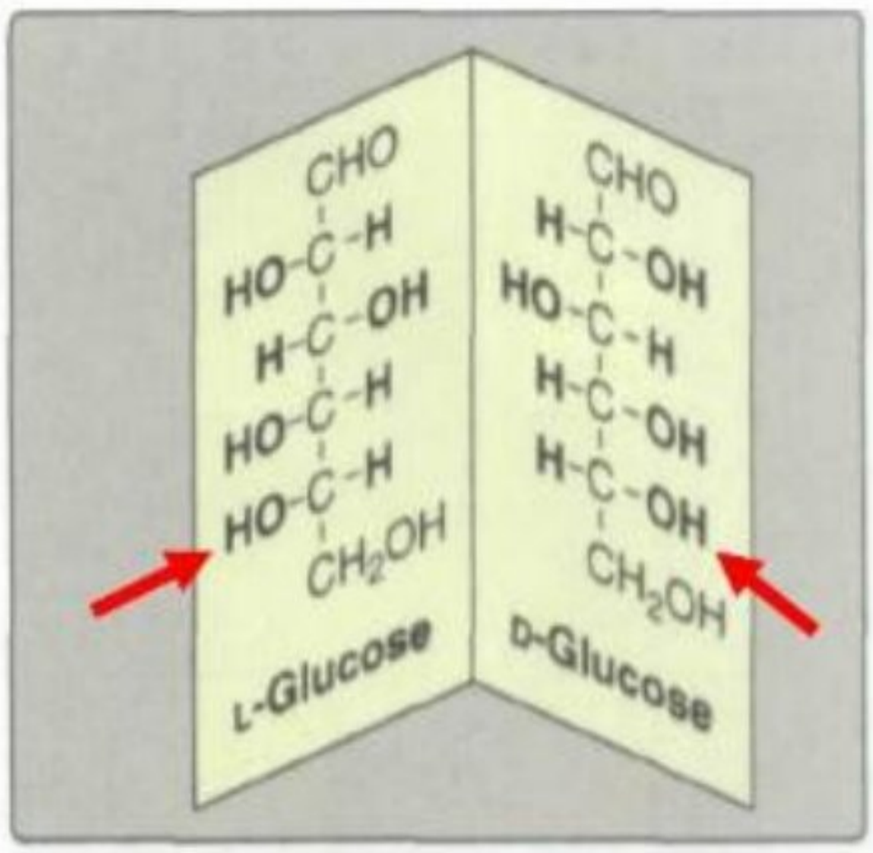
Monoscchrides

- Optically active (rotate polarized light), contain **at least 1** asymmetric carbon (chiral center)
- Stereoisomers (Isomers): cpds with same chemical formula but different structures. CHO have:

  1- Enantiomers

  2- Epimers

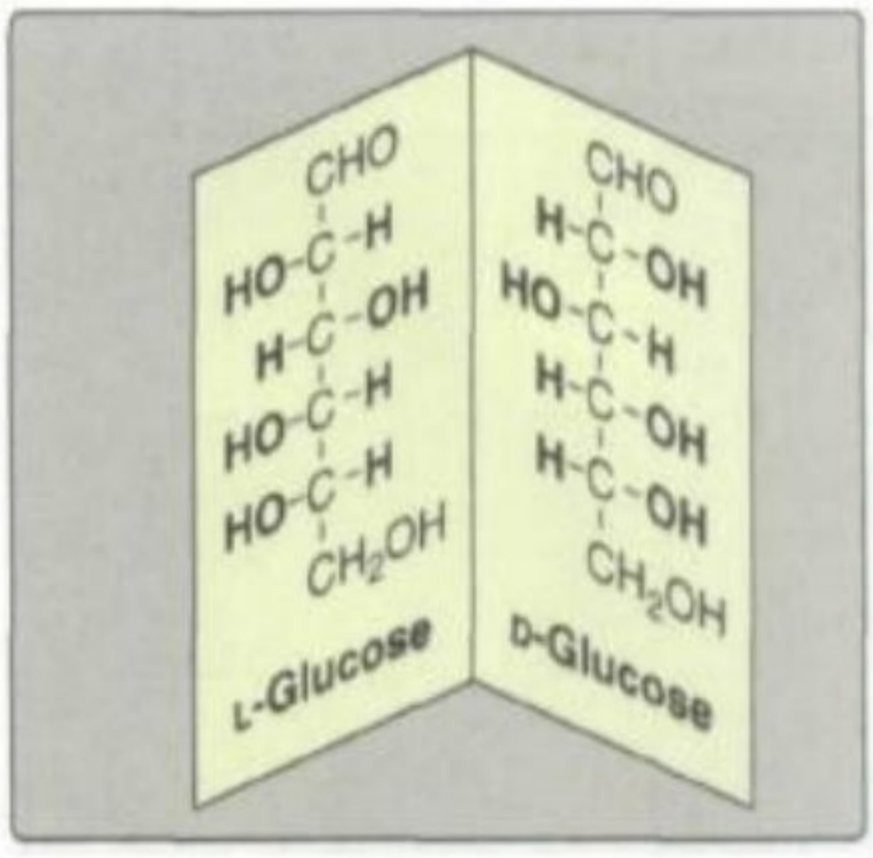
  3- Anomers



Monosacchrides

Enantiomers:

- They can exist in D, L conformation according to OH-orientation of farthest chiral carbon from carbonyl
- D, L forms are ENANTIOMERS (mirror images)
- D-form is physiologically important



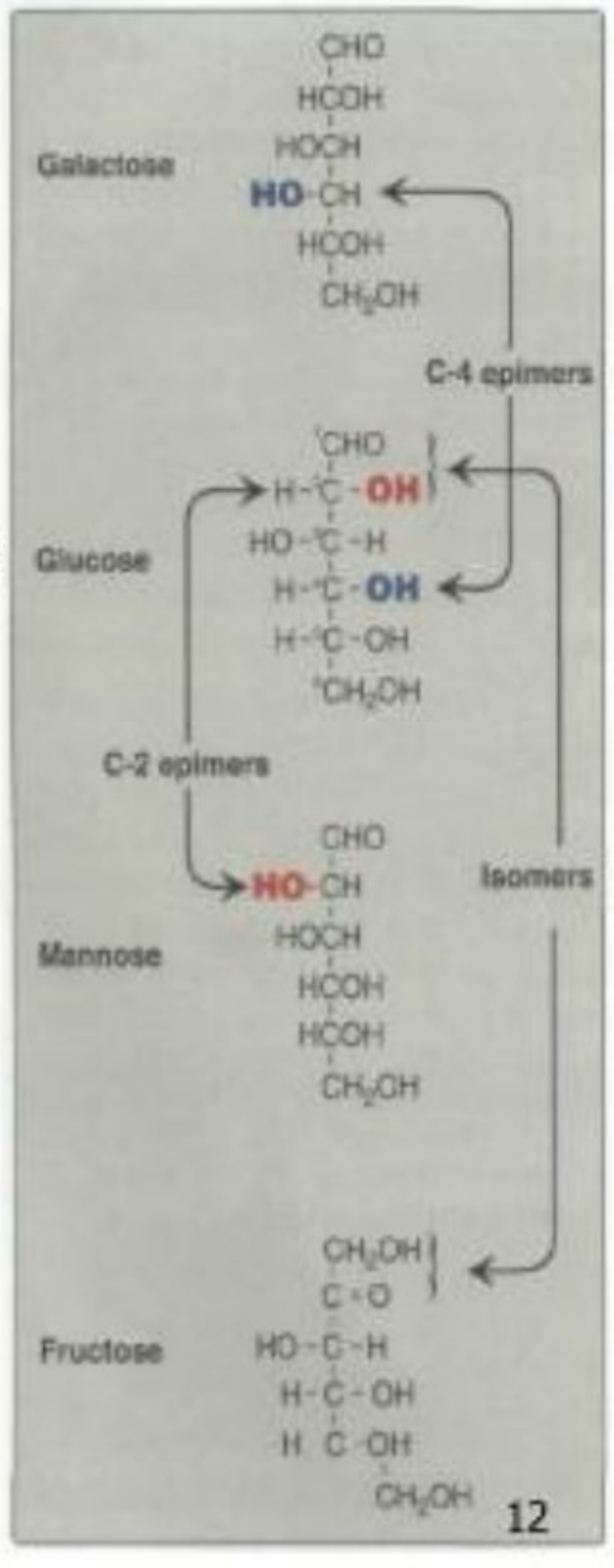
Monoscchrides

Epimers:

- Sugar molecules that differ in configuration a **only one** of several chiral centers are called epimers.
- For example,

D-mannose **C2** epimer of D-glu

D-galactose **C4** epimer of D-glu



Monosacchrides

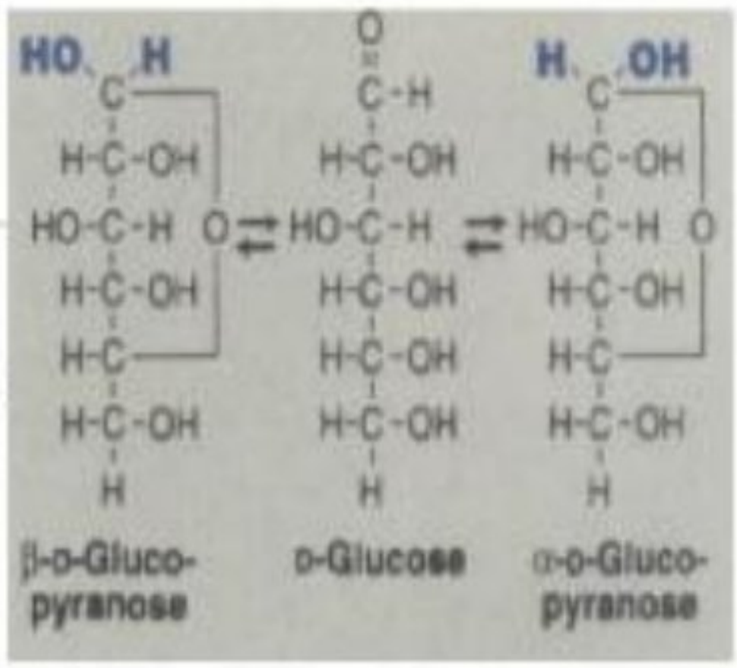
Anomers:

- The aldhyde or ketone will form a cyclic ring either:

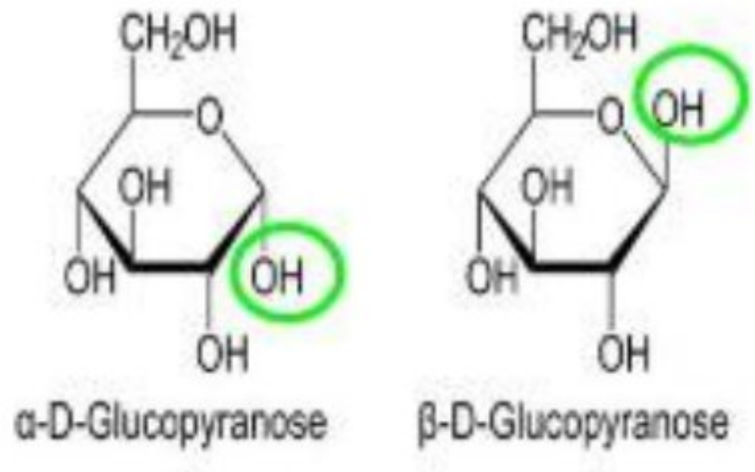
a) five member ring called furanose

b) six membered ring called pyranose

- These rings can reopen and close allowing rotation to occur, leading to 2 configuration α and β
- This carbon is anomeric carbon and α and β are anomers



Fisher projections



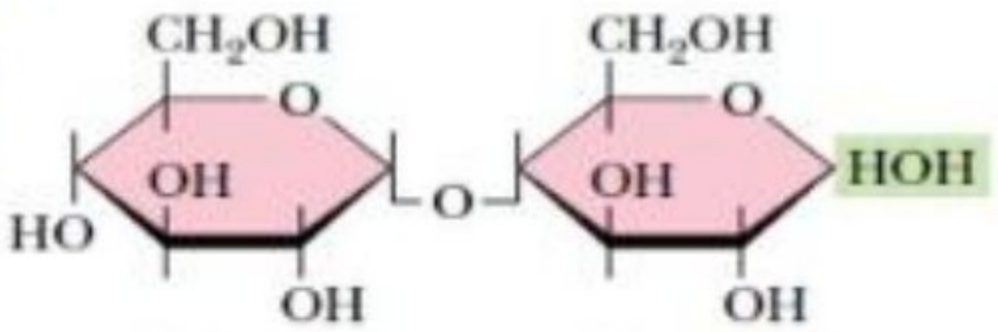
Haworth projectons

Right downwards

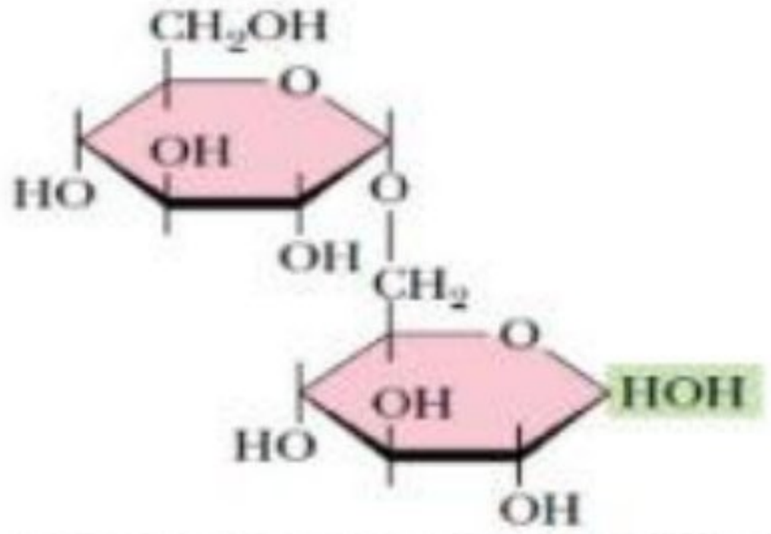
Left upwards

Disaccharides

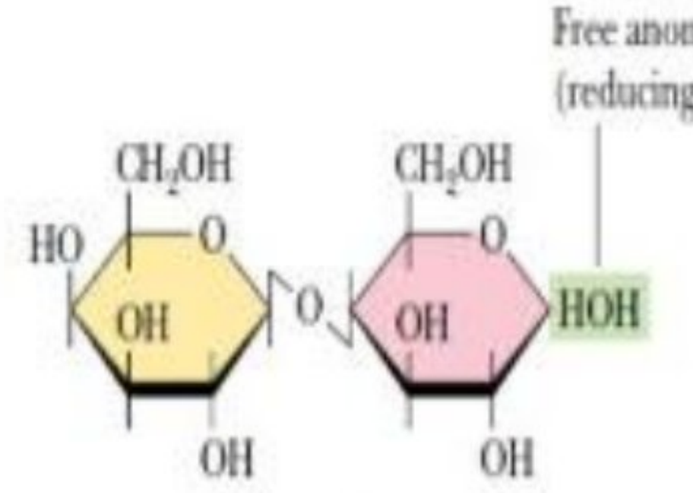
- 2 monosaccrides will form disacchrides by glycosidic bond e.g.
- 1- Sucrose: glucose + fructose,
- 2-Lactose: galactose + glucose.
- 3-Maltose: glucose + glucose.



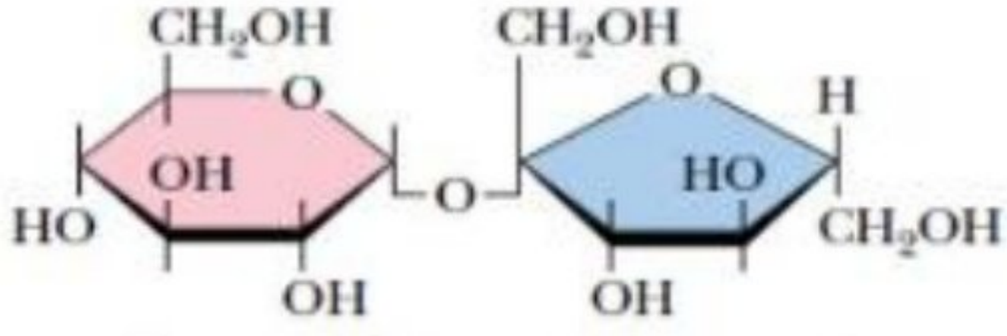
Maltose (glucose-α-1,4-glucose)



Isomaltose (glucose-α-1,6-glucose)



Lactose (galactose-β-1,4-glucose)



Sucrose (glucose-α-1,2-fructose)

Reducing and non-reducing sugars

- Reducing sugars:

contain a reactive carbonyl group, they are readily oxidized to diverse products.

Reduce metal ions as Cu+2 to insoluble products

e.g. Glucose, maltose, and lactose

- Non-reducing sugars:

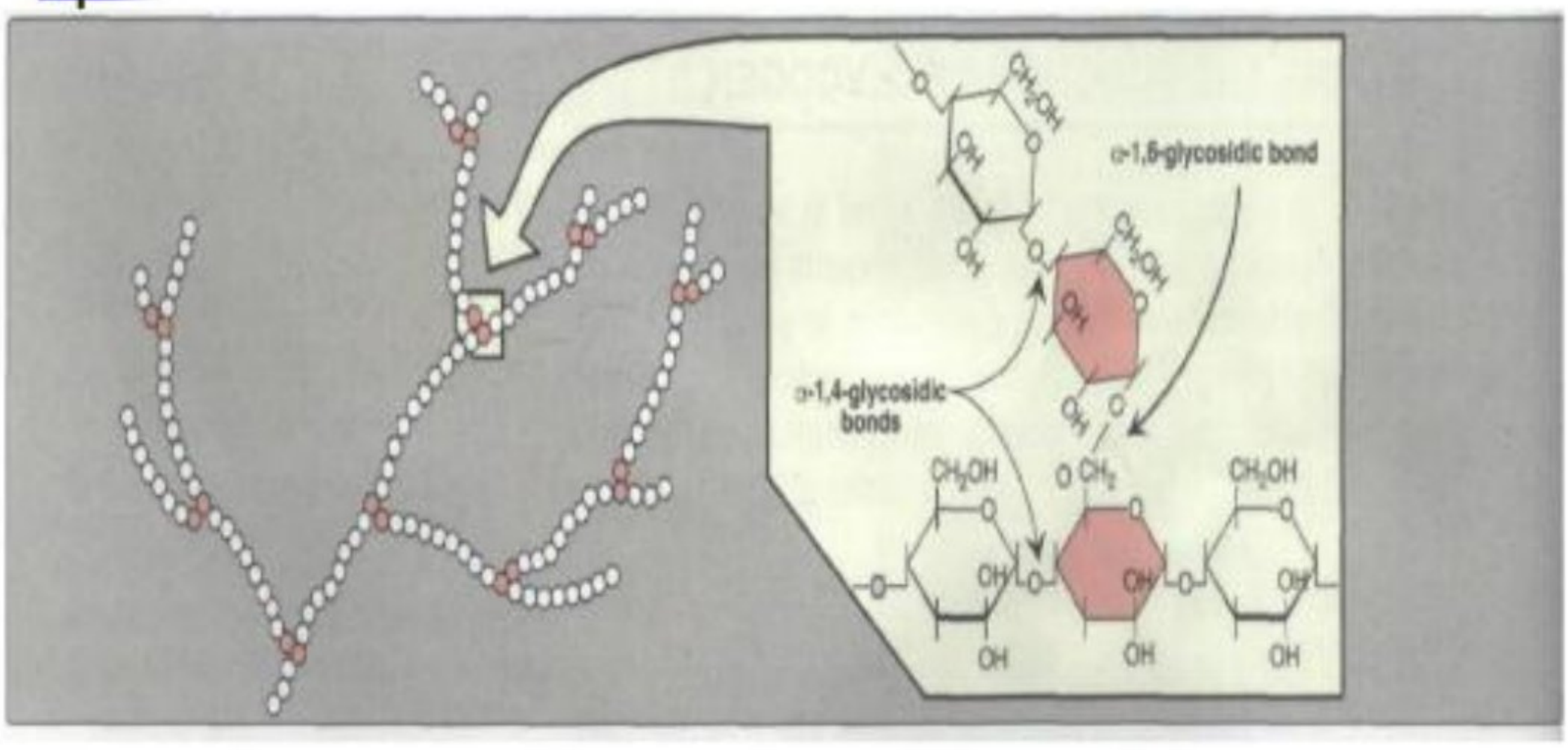
Sucrose, which are not readily oxidized because both anomeric carbon atoms are fixed in a glycosidic linkage

Polysacchrides

- Homopolysacchrides: composed of single monosacchride building block e.g glycogen
- Heteropolysacchride: different building blocks e.g glycosaminoglycans
- Glycogen
- Starch
- GAGs

Glycogen

- Major form of stored CHO in animals
- Polymer of α(1,4) glucose linkage
- Highly branched by α(1,6) linkage every 8-10 residues
- Very compact, allow storage of energy in small volume, low osmolarity

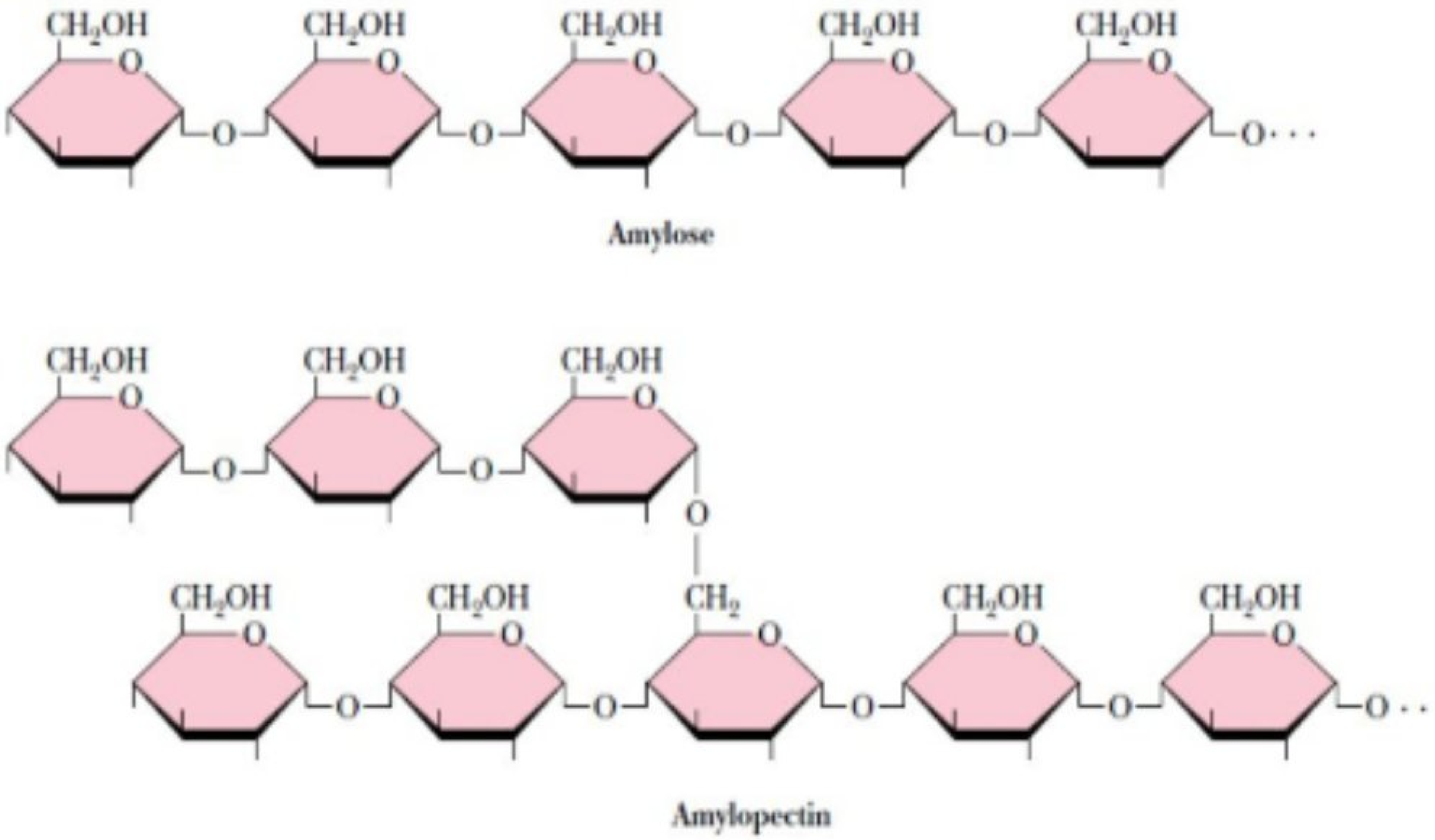


Glycogen

Starch

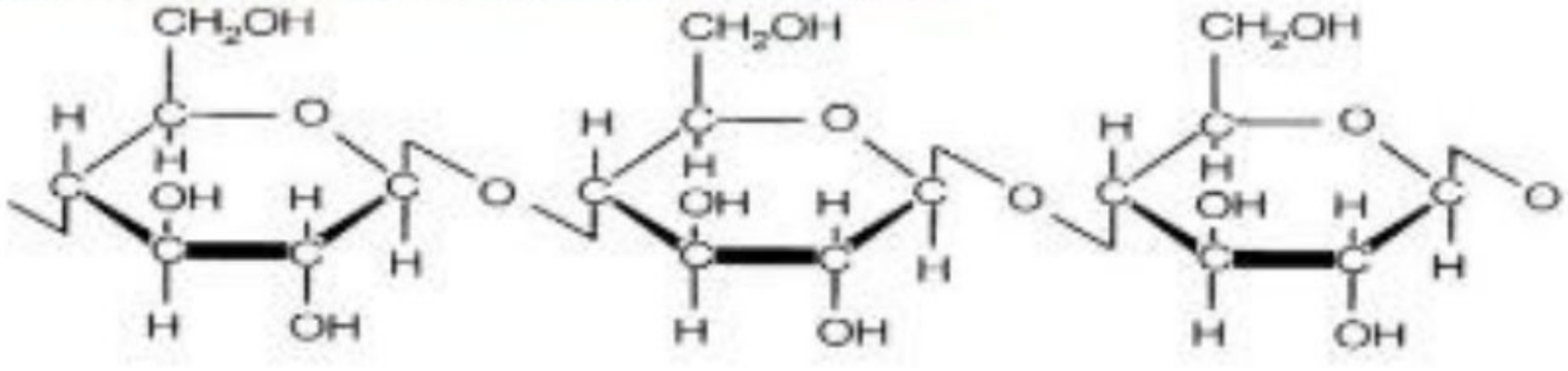
- Major form of storage in plant
- Similar structure as glycogen but less extensively branched (20-30 residues)
- Unbranched starch called amylose
- Branched called amylopectin

Starch



Cellulose (structural polysaccharide)

- Structure: Long straight non-branching chains of b-D-glucose linked by b-(1-4) glucosidic bond.
- Properties: insoluble in water & cannot be digested by humans due to absence of hydrolase enzymes that can attack b-linkage.
- Its presence in diet is important, because it cannot be digested, so it will increase the bulk of stool & stimulate the intestinal movement & prevent constipation.



Proteoglycans

- Also called glycosaminoglycans. These molecules are long unbranched **polysaccharides** containing a *repeating disaccharide unit +* specific **protein** called core proteins.
- These are predominantly in ECM, CT of multicellular animals
- The disaccharide units contain either of two modified sugars:

A) N-acetylgalactosamine (GalNAc) or N-acetylglucosamine (GlcNAc)

B) uronic acid such as glucuronate

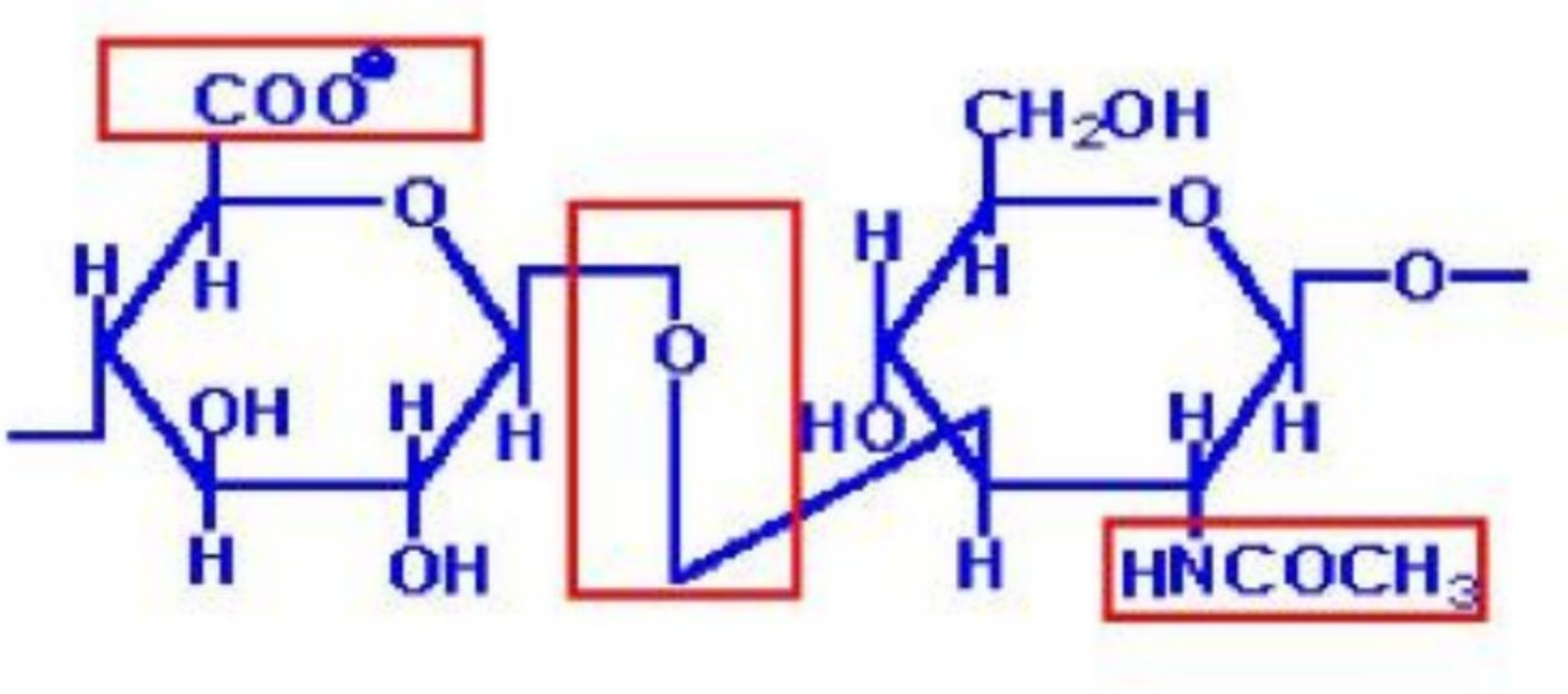
C) some contain sulphate groups

Examples of GAGs

- Hyaluronan
- Chondroitin sulphate
- Heparin

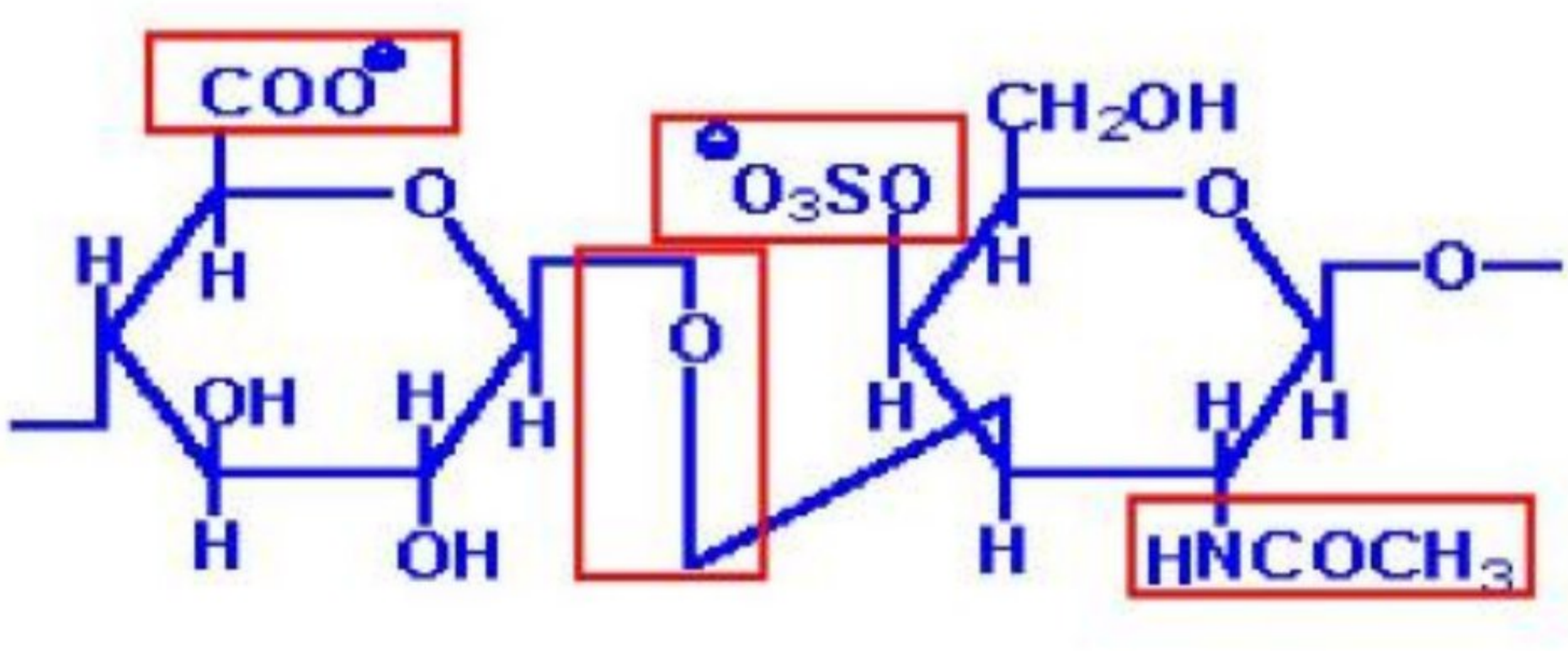
Hyaluronan:

- Composed of D-glucuronate + GlcNAc linkage is b(1, 3)
- Localization: synovial fluid, vitreous humor, ECM of loose connective tissue



Chondroitin 4- and 6-sulfates

- Composed of D-glucuronate + GalNAc-4- or 6-sulfate linkage is b(1, 3) (the figure contains GalNAc 4-sulfate
- Cartilage, bone, heart valves



Macromolecular Structures

Contents

- Amino acids and their structure
- Structure of proteins
- Globular proteins: Hemoglobin structure and functions
- Fibrous proteins (collagen and elastin)
- Enzymes
- Nucleotides: DNA & RNA
- Carbohydrate chemistry
- Lipid chemistry

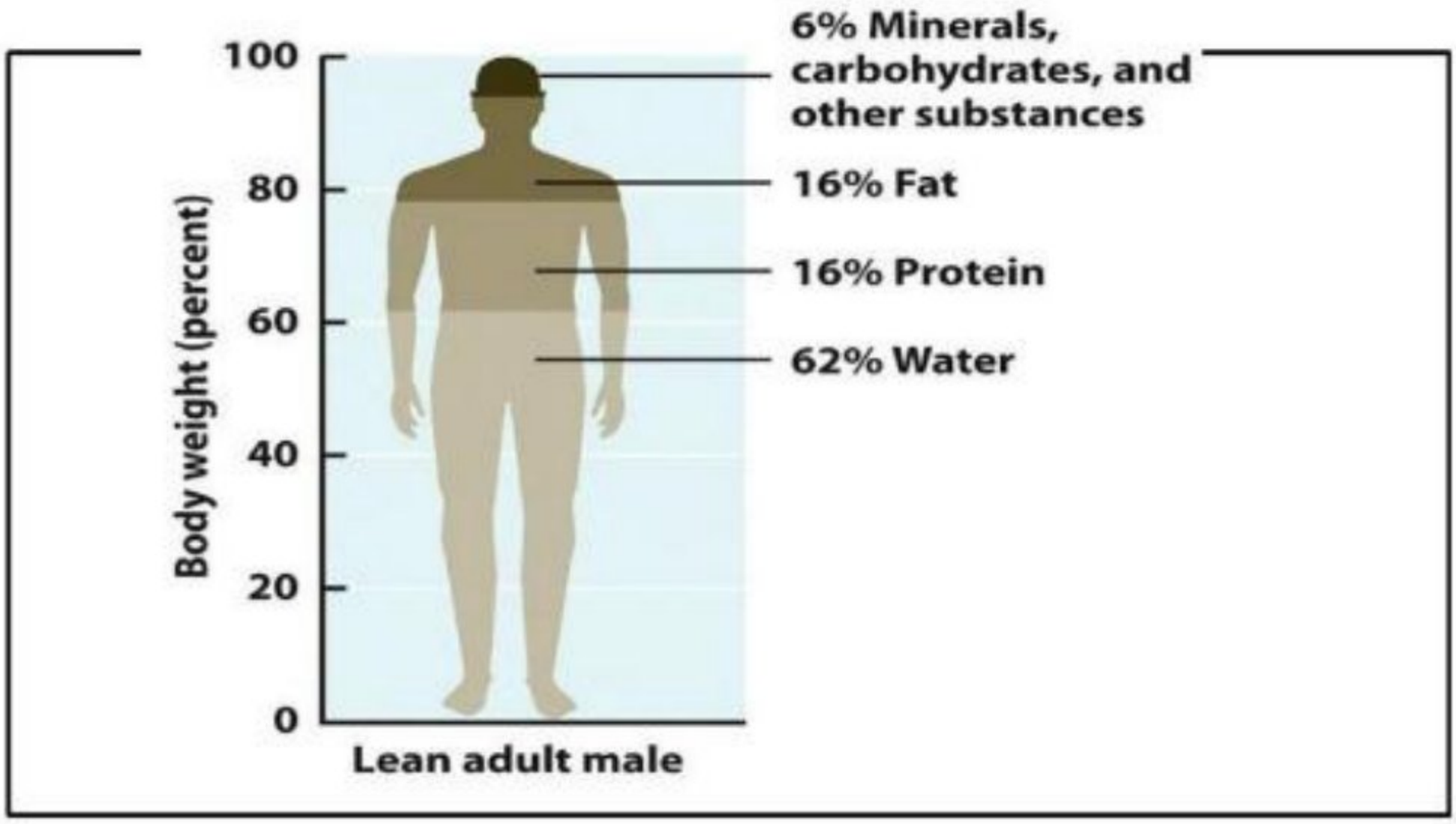
Biochemistry

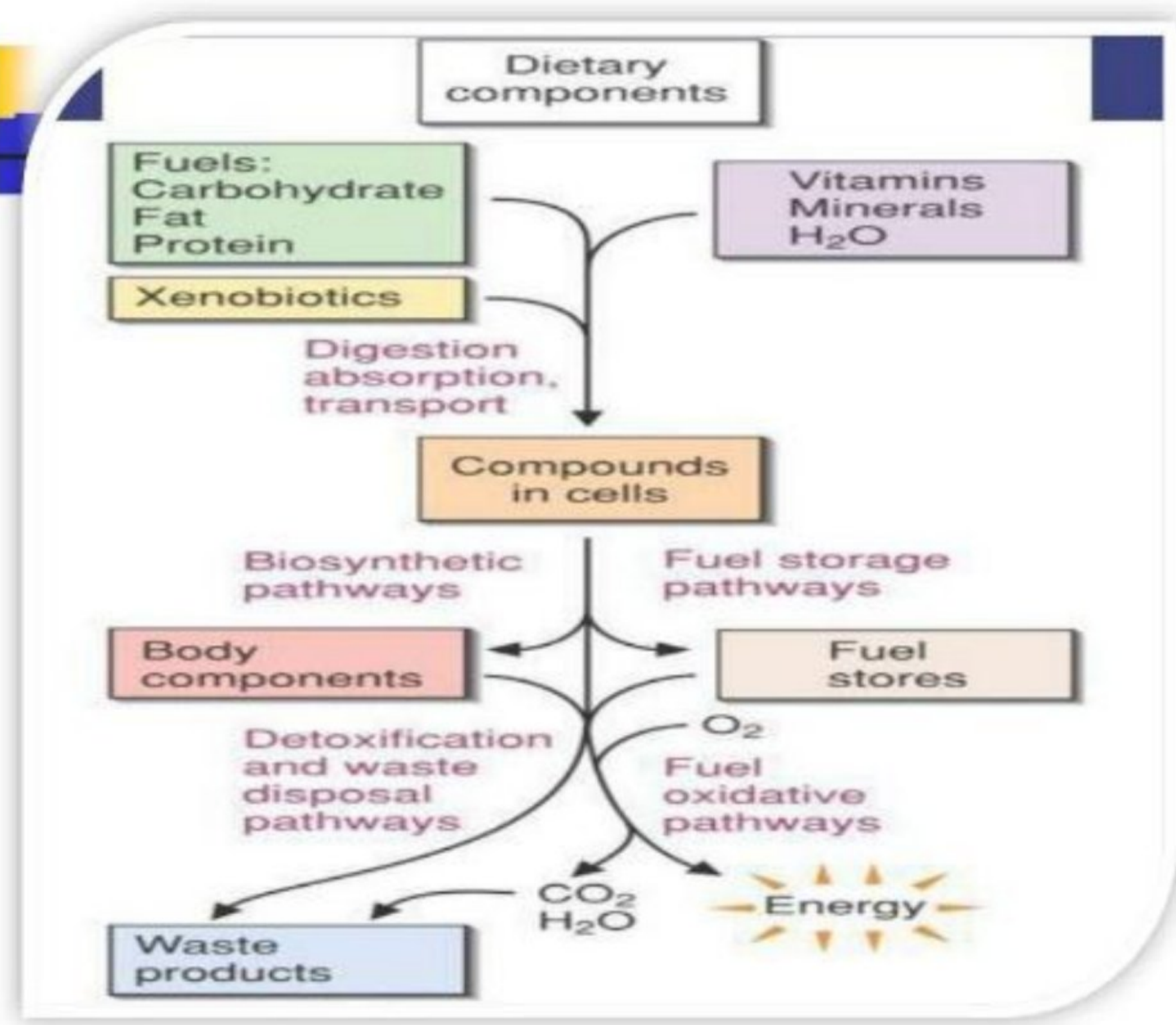
- **What is biochemistry?**
  - It is the chemistry of life.
  - describe the structure, organization and functions of living matter
  - The biological levels of organization of living things arranged from the simplest to most complex are: organelle, cells, tissues, organs, organ systems, organisms
  - It is also the science concerned with study of biomolecules

Biomolecules

- **Biomolecules:**
  - an organic compound made in a living system
- **Four major classes of biomolecules:**
  - Carbohydrates
  - Lipids
  - Proteins
  - Nucleic acids

Composition of human body





Nutrition

- **Nutrition** is the science of how the body uses food.
- **Nutrition** is about **why** you eat, **what** you eat and **how** the food affects your body and your health.
- **Nutrition** is the science concerned with the study of nutrients and other substances in foods and the body's handling of them (including ingestion, digestion, absorption, transport, metabolism, and excretion).
- **Dietetics**: the science concerned with the diet and its effects on health

Nutrients

- **Nutrients** divided into two categories:

1. **Macronutrients : Protein, fat, carbohydrates, (*dietary fuels or energy-yeilding nutrients*) and water.**
2. **Micronutrients : Vitamins and minerals.**

Energy from food

- The amount of energy a food provide depends on how much carbohydrate, fat, and protein contains.
- When completely broken down in the body,

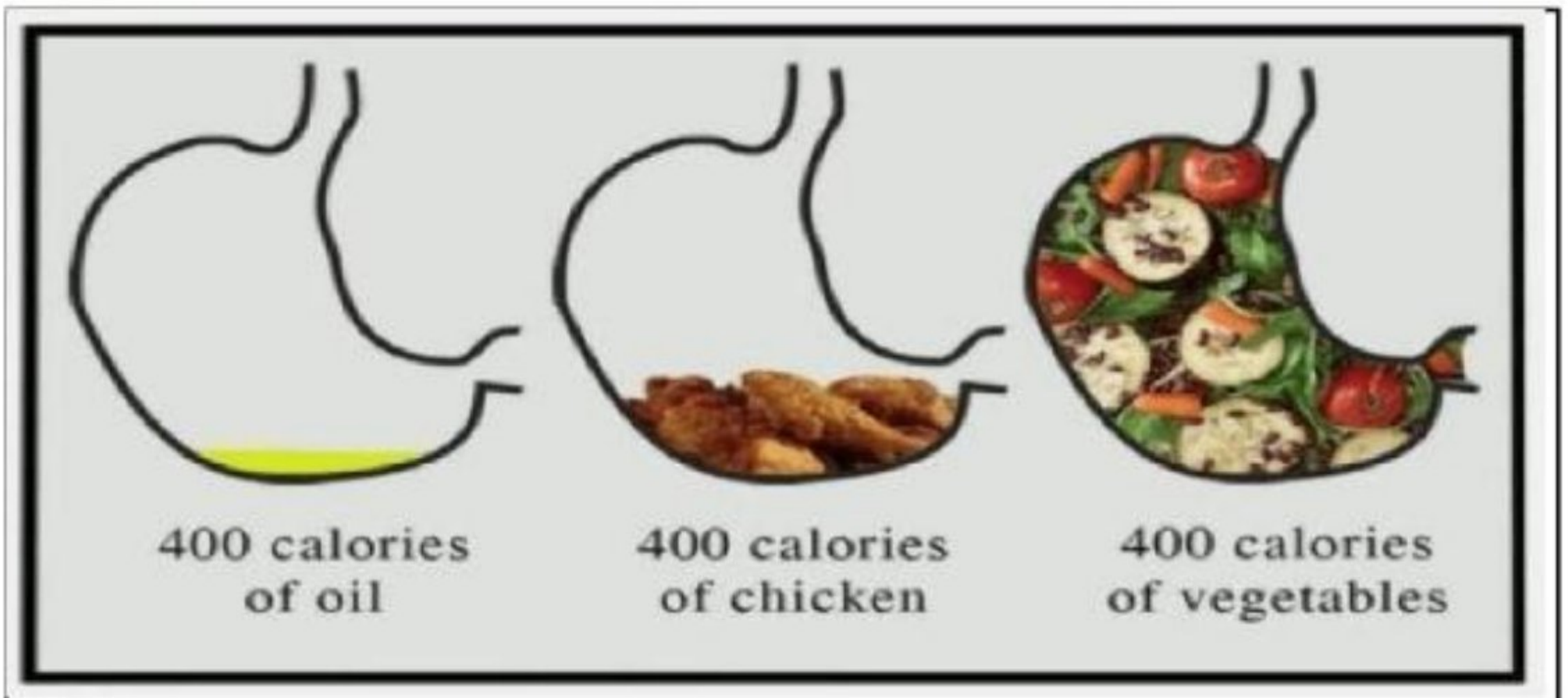
1 gm carbohydrate →4 kcal of energy

1 gm protein → 4 kcal of energy

1 gm of fat → 9 kcal of energy

- therefore fat has the greater energy density than either carbohydrate or protein.

Energy density



Calorie Needs

- **According to the Dietary Guidelines for Americans 2015,**
  - **Women generally need 2000 calories (1,600 to 2,400) calories (kilocalorie) per day to maintain a healthy body weight**
  - **Men usually need 2500 calories (2,000 to 3,000 calories) each day.**
- **If you're overweight,**
  - **Women should aim for 1,200 to 1,500 calories daily**
  - **Men should aim for 1,500 to 1,800 calories daily**

Weight Maintained

Isocaloric Balance

Energy In = Energy Out

Weight Loss

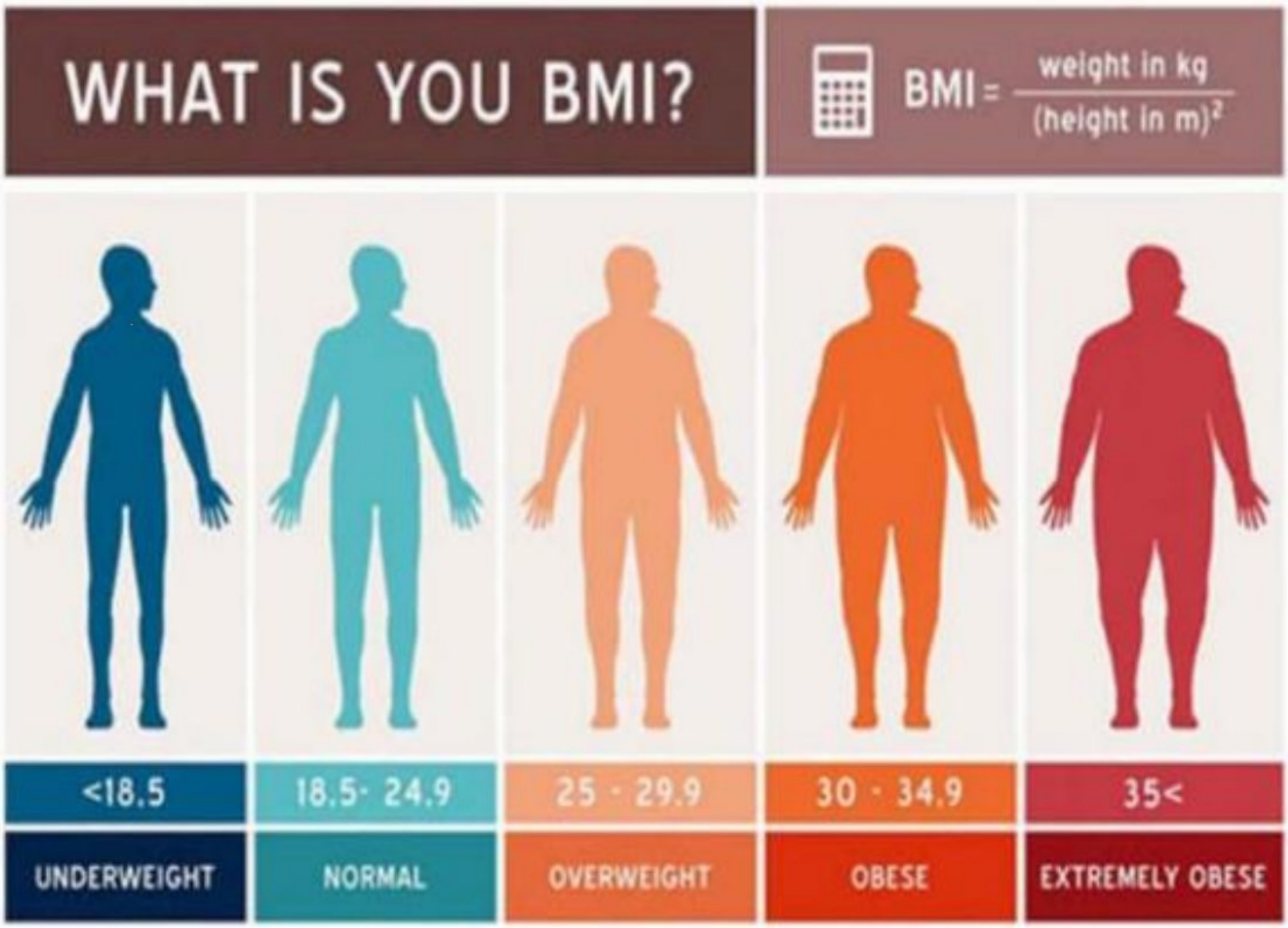
Negative Caloric Balance

Energy In < Energy Out

Weight Gain

Positive Caloric Balance

Energy In > Energy Out



Chapter 1: Amino acids

Overview of proteins

- most abundant and functionally diverse molecules in living systems.
- Enzymes and hormones: direct and regulate metabolism in the body
- Muscles: contractile proteins permit movement.
- Bones: the protein collagen forms a framework for the deposition of calcium phosphate crystals,
- Blood: proteins, such as hemoglobin and plasma albumin, shuttle molecules essential to life,
- Immunoglobulins fight infectious bacteria and viruses.

Structure: linear polymers of amino acids.

Amino acids

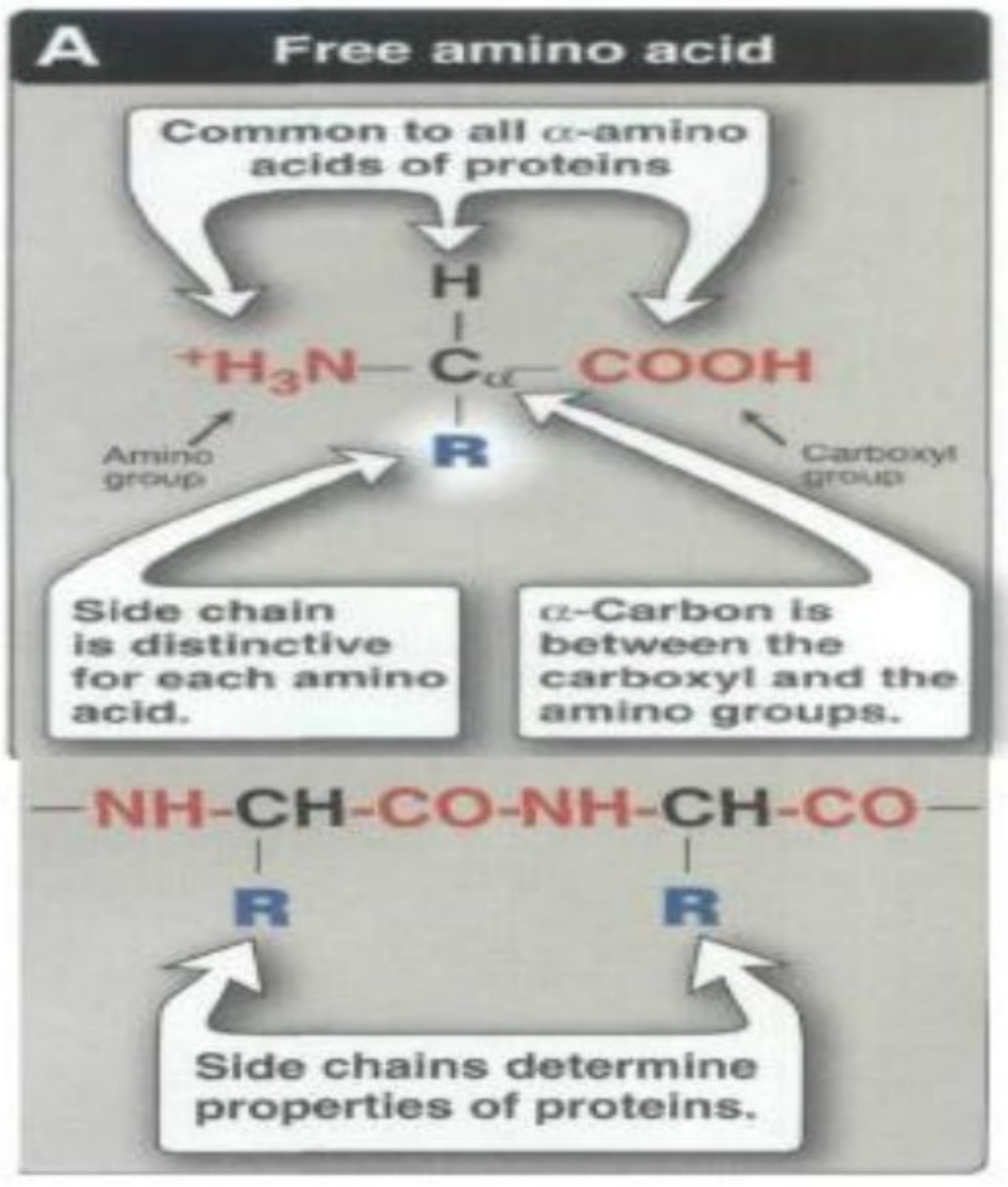
- 20 aa in protein structure (coded by genetic code)
- Each aa:

a) NH3 group

b) COOH group

c) R-group

- aa in proteins form peptide bond
- R-group determines role of aa in protein



Amino acids classification

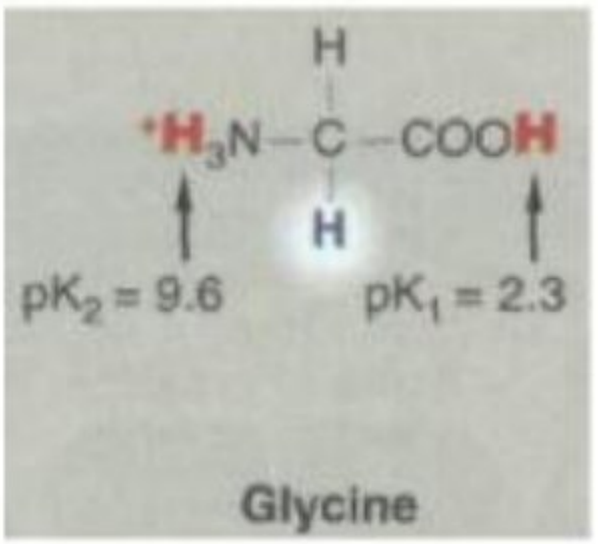
- AA with non-polar side chain (Hydrophobic)
- AA with polar side chains:

a) Uncharged polar side chains: e.g sulphur and OH

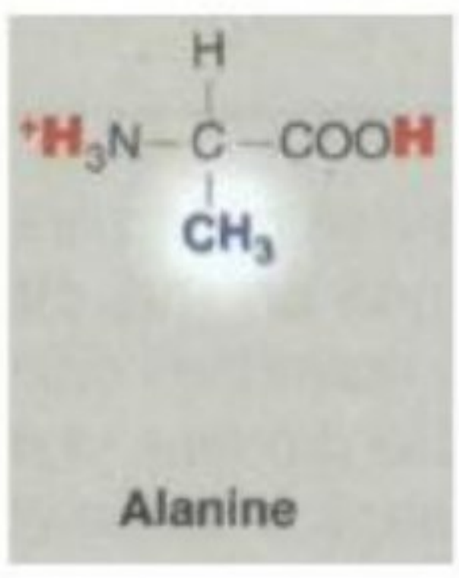
b) Charged polar side chains: e.g. acidic and basic side chains

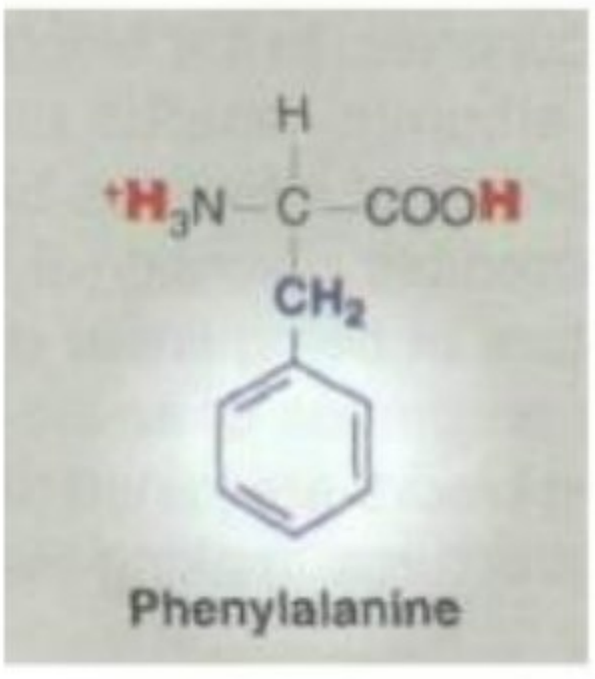
c) Proline: cyclic or secondary NH3 group

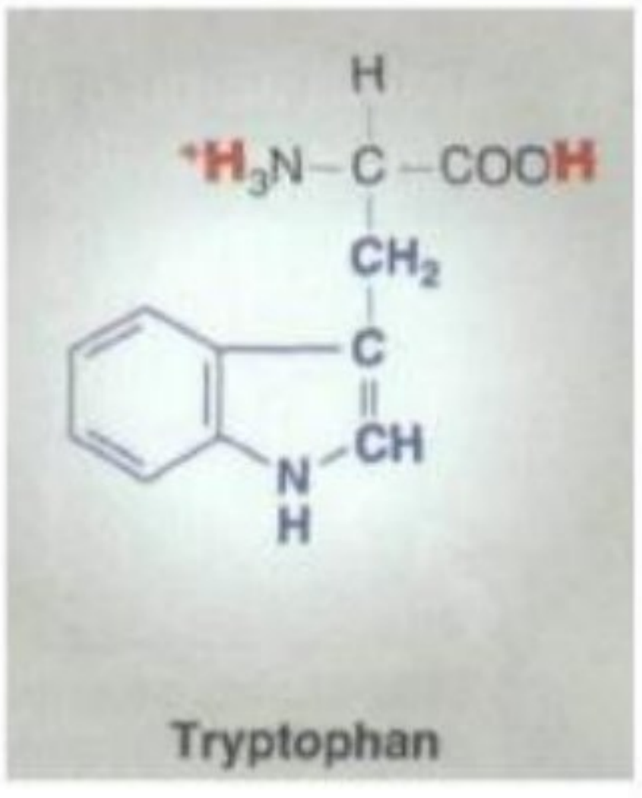
AA with non-polar side chain



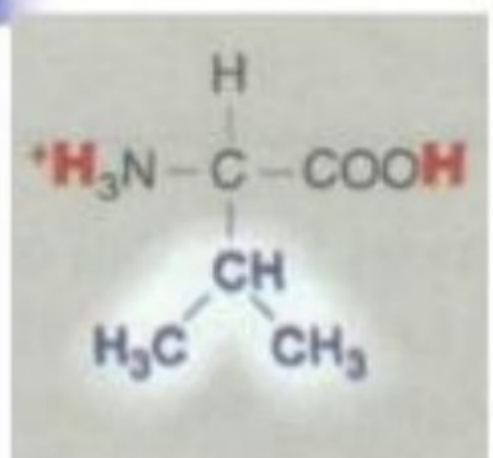
smallest aa
non chiral

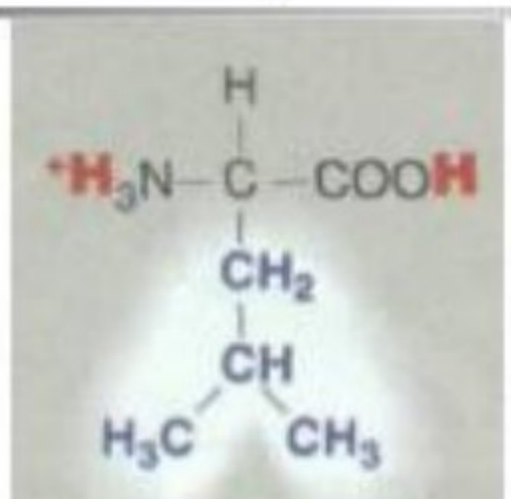


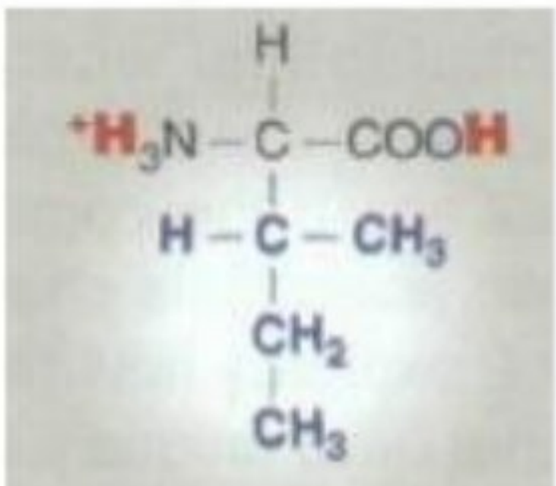


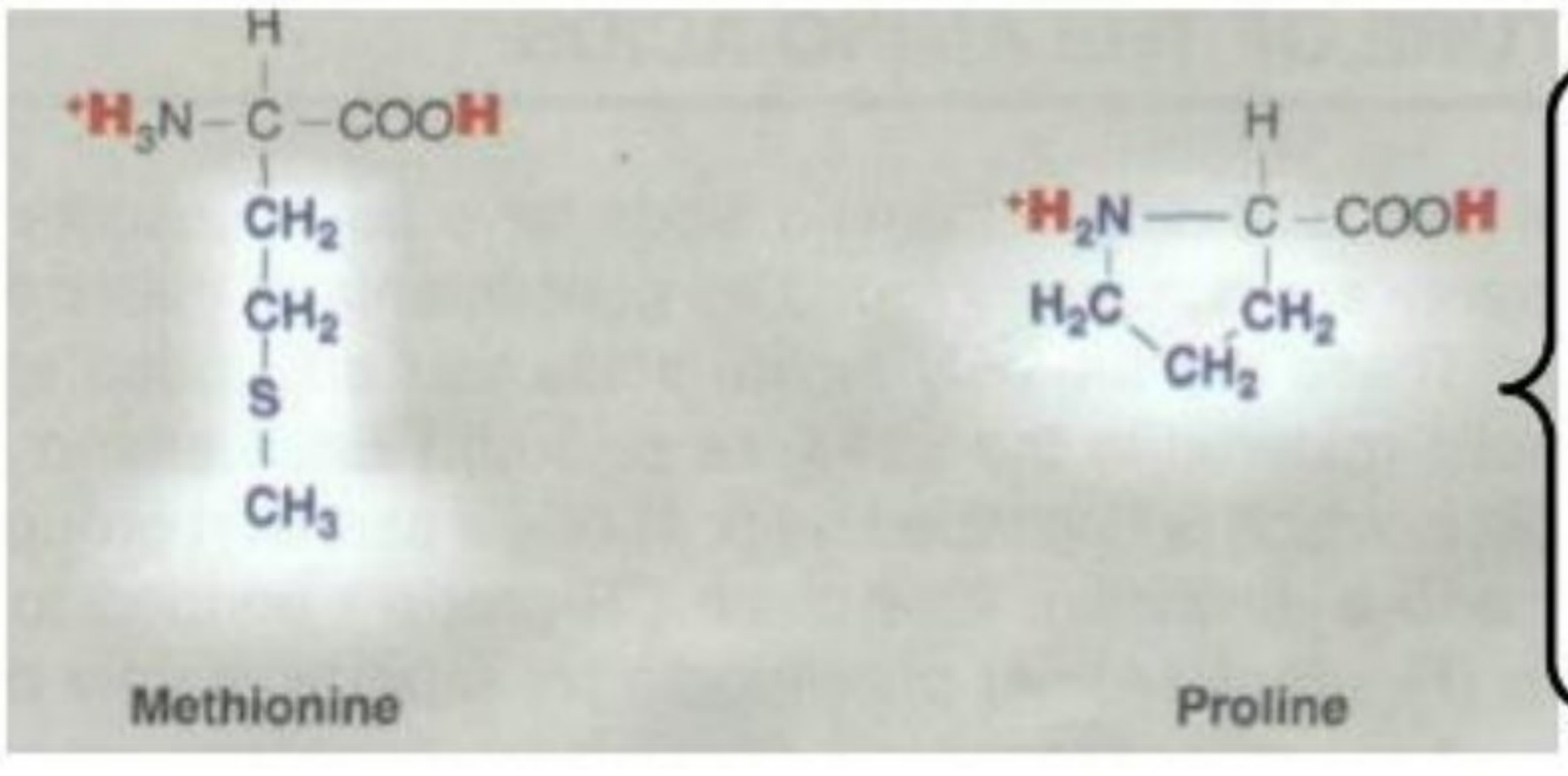


AA with non-polar side chain









- side chain and NH3 form a 5-membred ring
- 2ry NH3 group not 1ry called IMINOacid

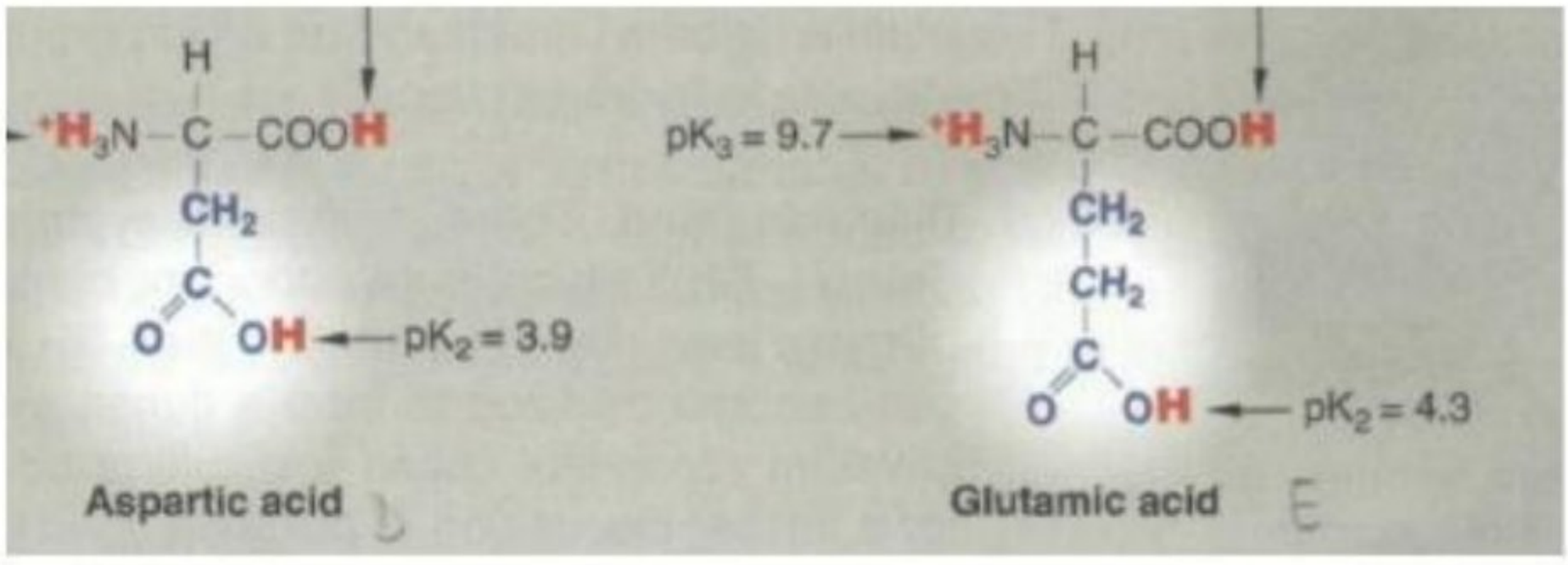
AA with non-polar side chains

- The nonpolar R-groups thus fill up the interior of the folded protein and help give it its three-dimensional shape.
- Membrane proteins:

the non polar aa are found on the outside surface of the protein

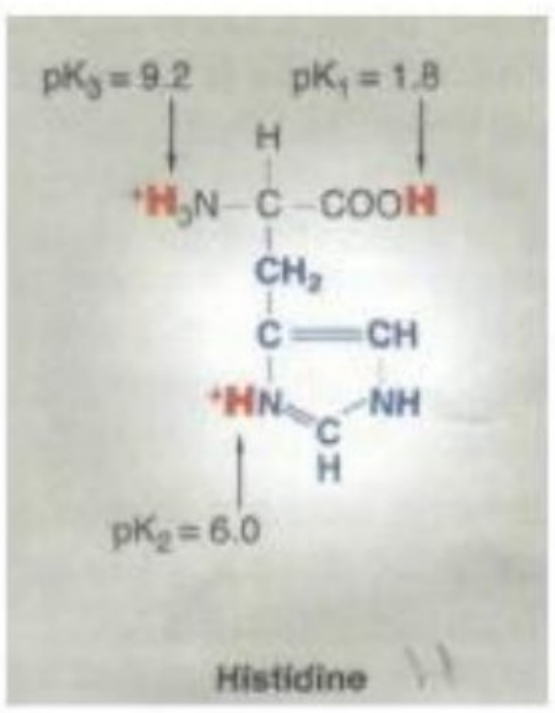
AA with acidic R

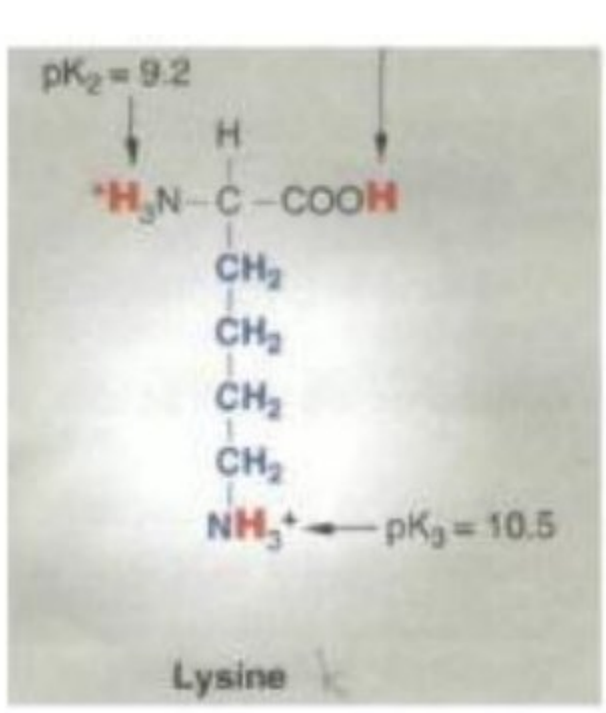
- The amino acids aspartic and glutamic acid are **proton donors.**
- At neutral pH the side chains of these amino acids are fully ionized, containing a negatively charged **carboxylate group** (-C00"). They are, therefore, called aspartate or glutamate

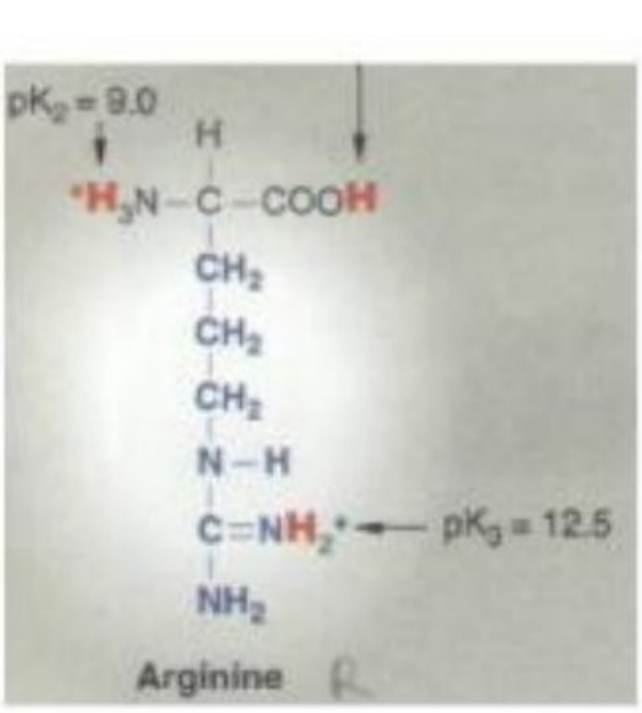


AA with basic R

- accepts protons
- Lysine and Arginine fully ionized at physiological pH
- Histidine weakly basic (+ve charged or neutral depending on the ionic environment

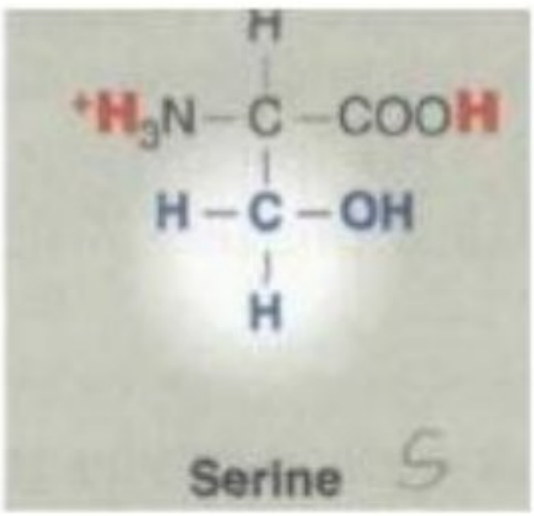


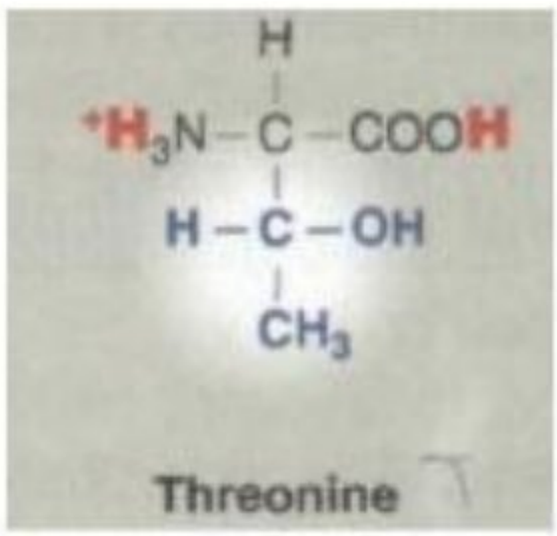


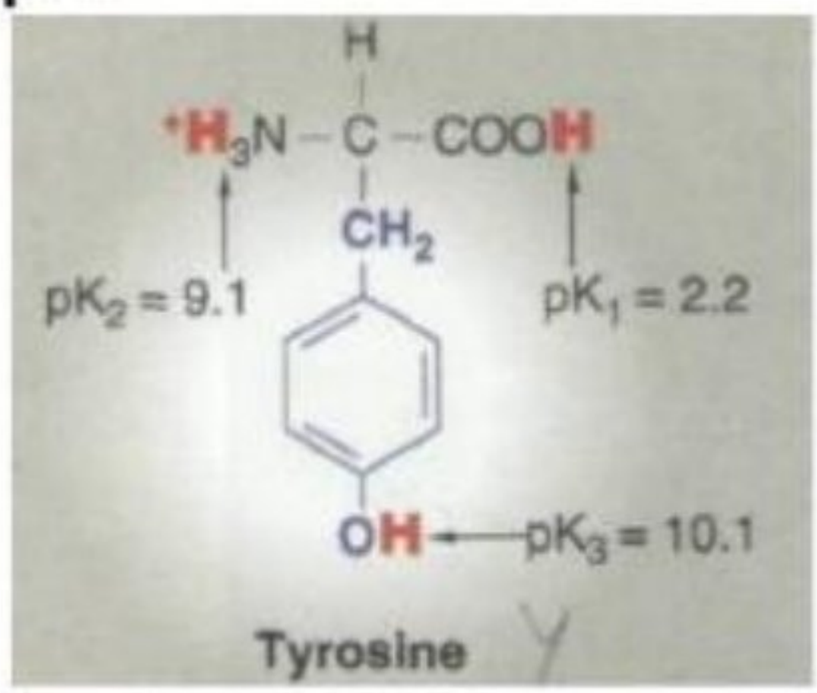


AA with uncharged polar AA

- zero net charge at neutral pH

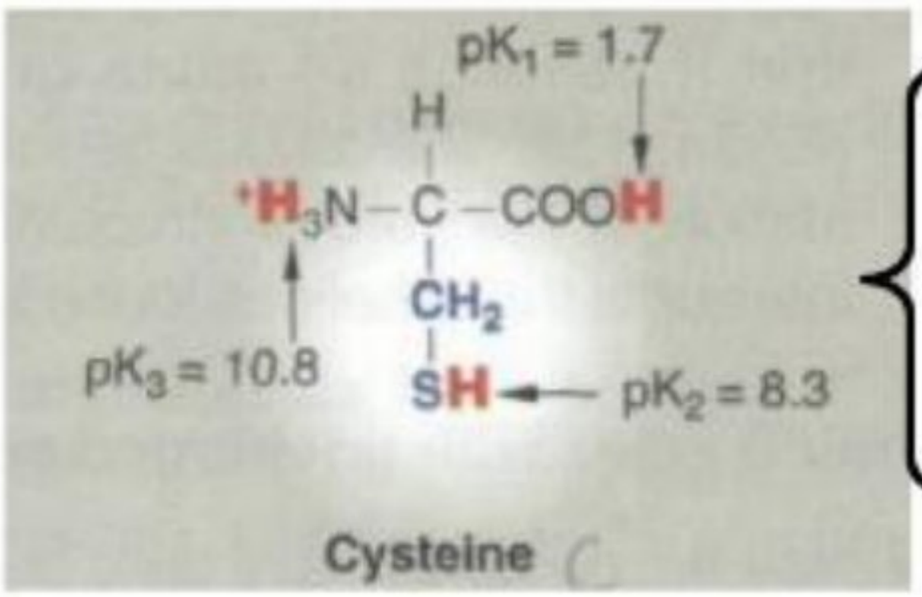




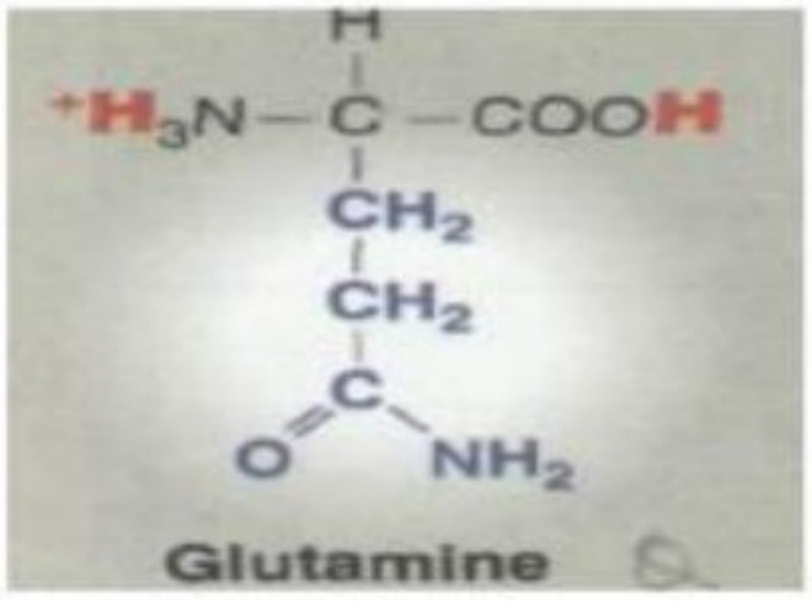


- polar OH group participate in H-bond formation
- site of attachment of phosphate groups or oilgosacchrides in glycoproteins

AA with uncharged polar AA



- **sulphhydryl group (SH)**
- **active sites of many enzymes**
- **form disulphide bond (S-S) forming *CystIne***



	Name	Abb	One letter
1	Alanine	Ala	A
2	Arginine	Arg	R
3	Asparagine	Asn	N
4	Aspartate	Asp	D
5	Cysteine	Cys	C
6	Glutamate	Glu	E
7	Glutamine	Gln	Q
8	Glycine	Gly	G
9	Histidine	His	H
10	Isoleucine	Ile	I
11	Leucine	Leu	L
12	Lysine	Lys	K
13	Methionine	Met	M
14	Phenylalanine	Phe	F
15	Proline	Pro	P
16	Serine	Ser	S
17	Threonine	Thr	T
18	Tryptophan	Trp	W
19	Tyrosine	Tyr	Y
20	Valine	Val	V

1 Unique first letter:

Cysteine	=	Cys	= C
Histidine	=	His	= H
Isoleucine	=	Ile	= I
Methionine	=	Met	= M
Serine	=	Ser	= S
Valine	=	Val	= V

2 Most commonly occurring amino acids have priority:

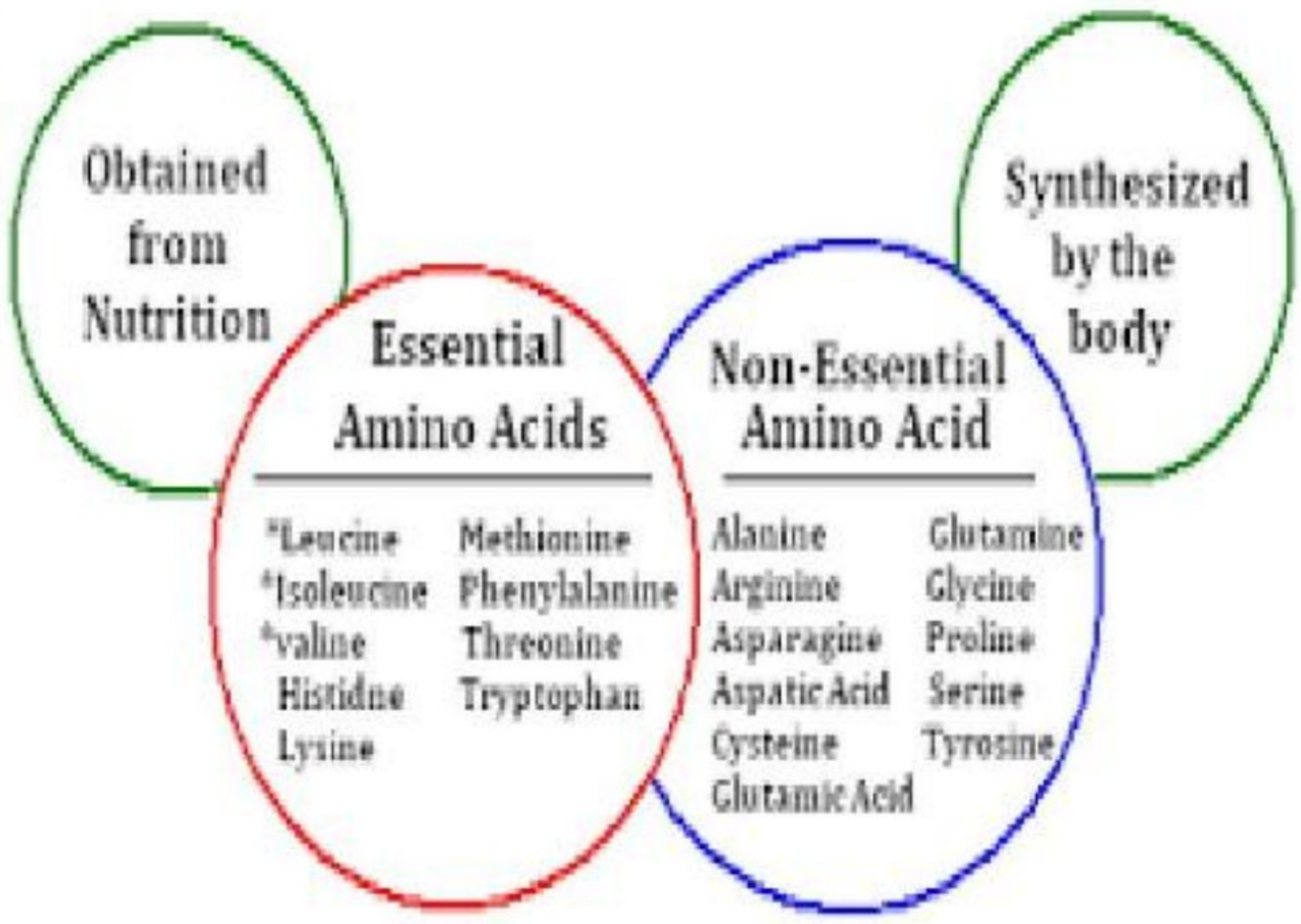
Alanine	=	Ala	= A
Glycine	=	Gly	= G
Leucine	=	Leu	= L
Proline	=	Pro	= P
Threonine	=	Thr	= T

3 Similar sounding names:

Arginine	= Arg	= R	("aRginine")
Asparagine	= Asn	= N	(contains N)
Aspartate	= Asp	= D	("asparDic")
Glutamate	= Glu	= E	("glutEmate")
Glutamine	= Gln	= Q	("Q-tamine")
Phenylalanine	= Phe	= F	("Fenylalanine")
Tyrosine	= Tyr	= Y	("tYrosine")
Tryptophan	= Trp	= W	(double ring in the molecule)

4 Letter close to initial letter:

Aspartate or asparagine	=	Asx	= B (near A)
Glutamate or glutamine	=	Glx	= Z
Lysine	=	Lys	= K (near L)
Undetermined amino acid	=		X



Amino acid in human body

Optical properties of aa

- The α-carbon of each amino acid is **chiral** or **optically active** carbon atom (attached to four different chemical groups)

- Glycine is is optically inactive (α-carbon has two hydrogen substituents).

- All amino acids found in proteins are of the **L-configuration**. However, **D-amino acids** are found in some antibiotics and in bacterial cell walls.

Acidic and basic properties of aa

- Amino acids in aqueous solution contain
  a) weakly acidic α-carboxyl groups
  b) weakly basic α-amino groups.
  c) an ionizable group in its side chain (acidic or basic).
- Both free amino acids and some amino acids combined in peptide linkages can act as **buffers.**

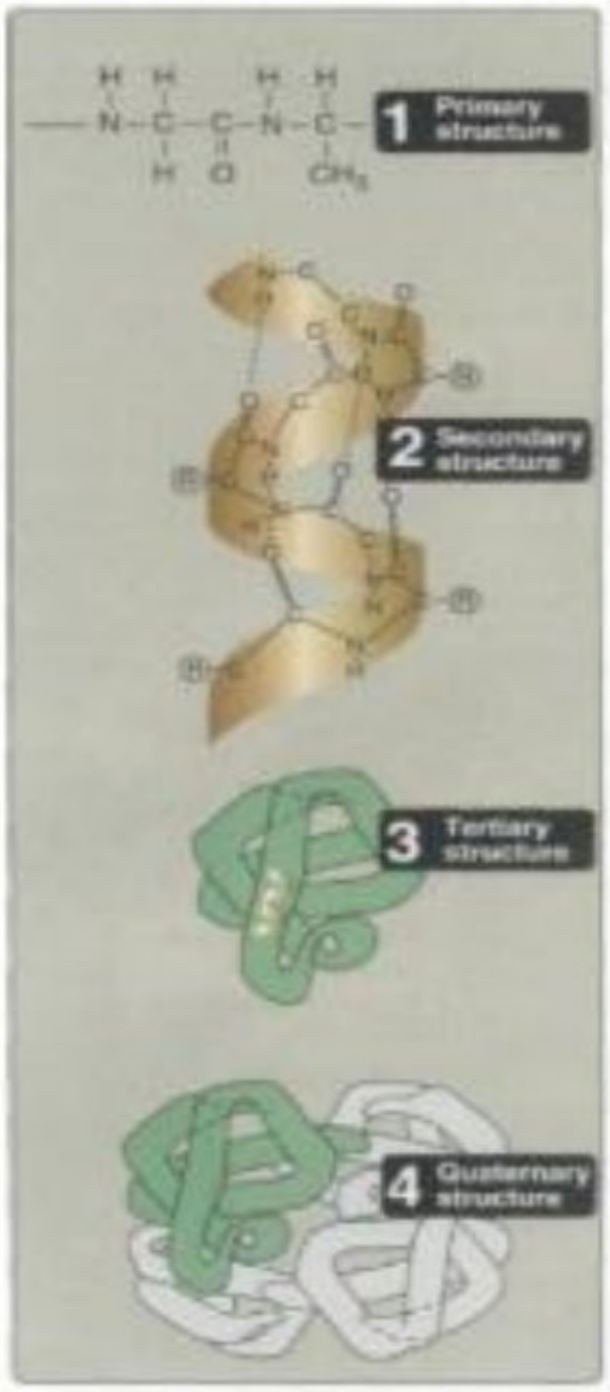
Net charge

- At physiologic pH, all amino acids have a negatively charged group COO- and and a positively charged group NH3+
- Substances, such as amino acids, that can act either as an acid or a base are defined as **amphoteric,** and are referred to as **ampholytes (amphoteric electrolytes).**

Structure of Protein

Protein structure

- The twenty amino acids commonly found in proteins are joined together by peptide bonds.
- The sequence of the amino acids contains the information necessary to generate a protein molecule with a unique three dimensional shape



Chapter 2: Protein structures

1) Primary structure:

- Linear sequence of amino acids
- Peptide bond: amide linkage between COOH of aa and NH2 of another

not broken by denaturation conditions (heating or high concentration of urea)

broken by strong bases or acids at high temp

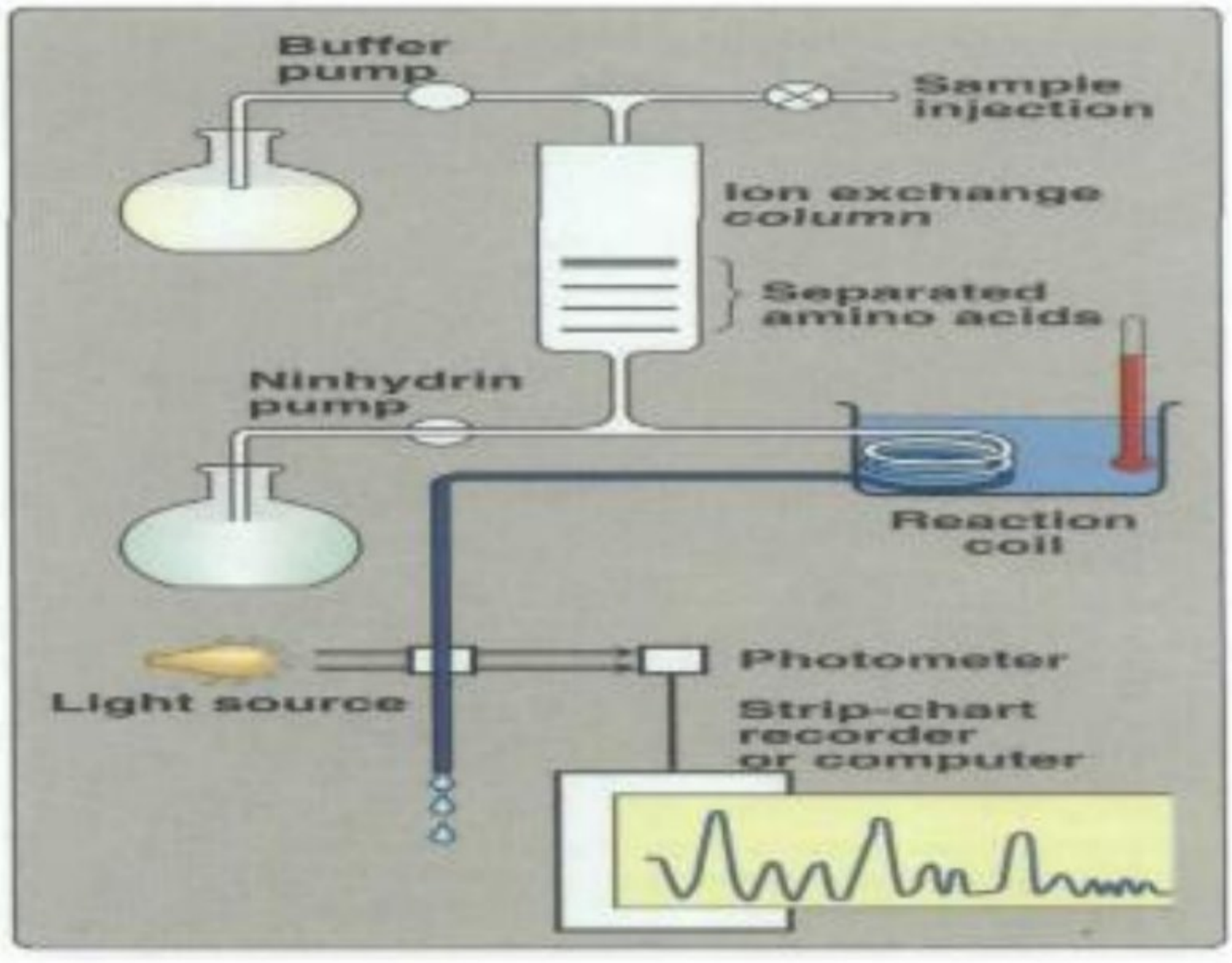
- Naming:

a) N-terminal (free NH2 group) to left and C-terminal (free COOH group) to right

B) NH2 end residues have suffix ----yl, the COOH is not e.g glutamylcysteinylglycine NH2-glu-cys-glycine-COOH

Sequencing of the peptide

Cation exchange chromatography



Determination of aa composition

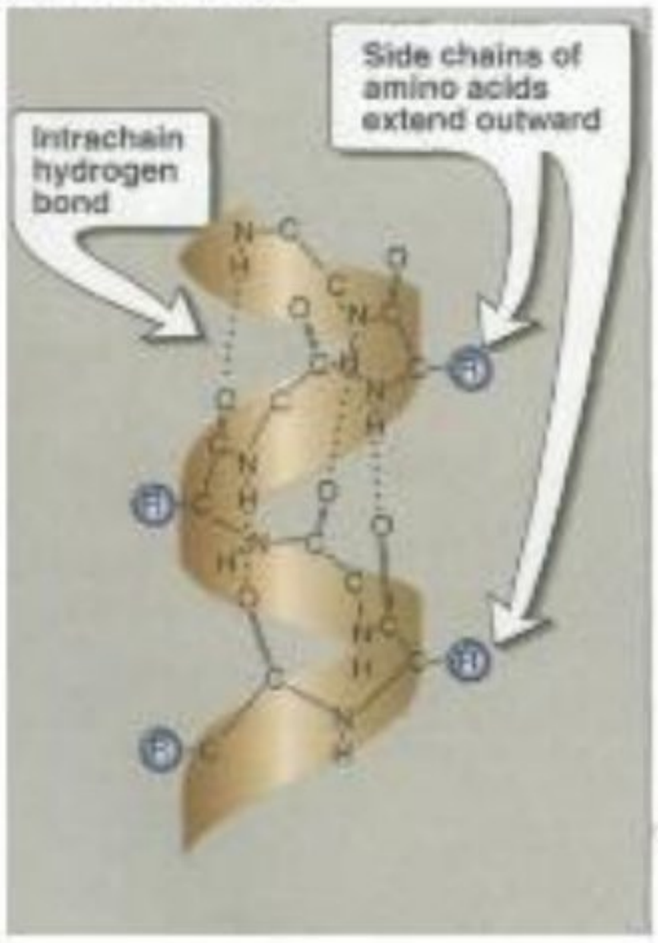
Cation exchange chromatography

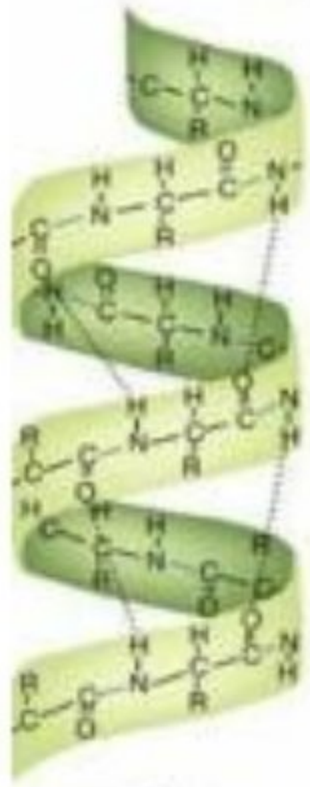
- **The first step in determining the primary structure of a polypeptide is to identify and quantitate its constituent amino acids.**
- **A purified sample of the polypeptide to be analyzed is first hydrolyzed by strong acid at 110°C for 24 hours, so release individual aa**
- **AA are separated by Cation exchange column**
- **Each aa will be sequentially released by eluting with solutions of increasing ionic strengths or pH.**
- **The separated amino acids contained in the eluate from the column are quantitated by heating them with NINHYDRIN reagent that forms a purple compound with most amino acids, ammonia, and amines and the amount is detected spectrophotometrically**
- **The analysis described above is performed using an amino acid analyser**

Secondary Structure

1. α-helix

- **It is a Spiral structure consisting of a tightly packed, coiled polypeptide backbone core with side chains extending outward from the central axis to avoid interfering sterically with each other.**





α-helix

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Secondary Structure (cont.)

- **Characteristics of α-helix**
  1. It is stabilized by extensive parallel hydrogen bonds between carbonyl oxygen of one peptide bond with amide hydrogen of a peptide linkage **four** residues ahead (intrachain hydrogen bond).

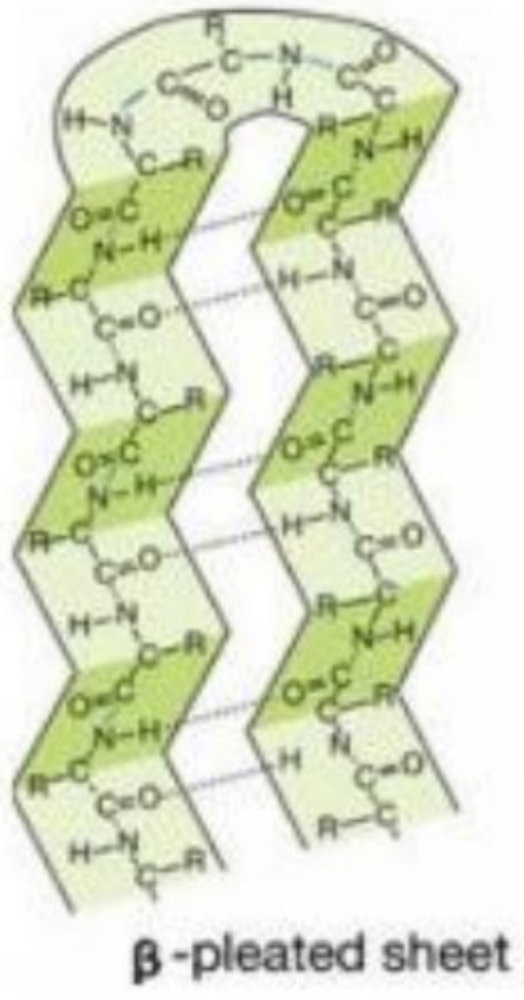
  2. Amino acids that disrupt an α-helix are:

❖ Proline.
❖ Charged amino acids e.g. lysine.
❖ Amino acids with bulky side chains, e.g. tryptophan.
❖ Amino acids that branch at ß-carbon, e.g. isoleucine.

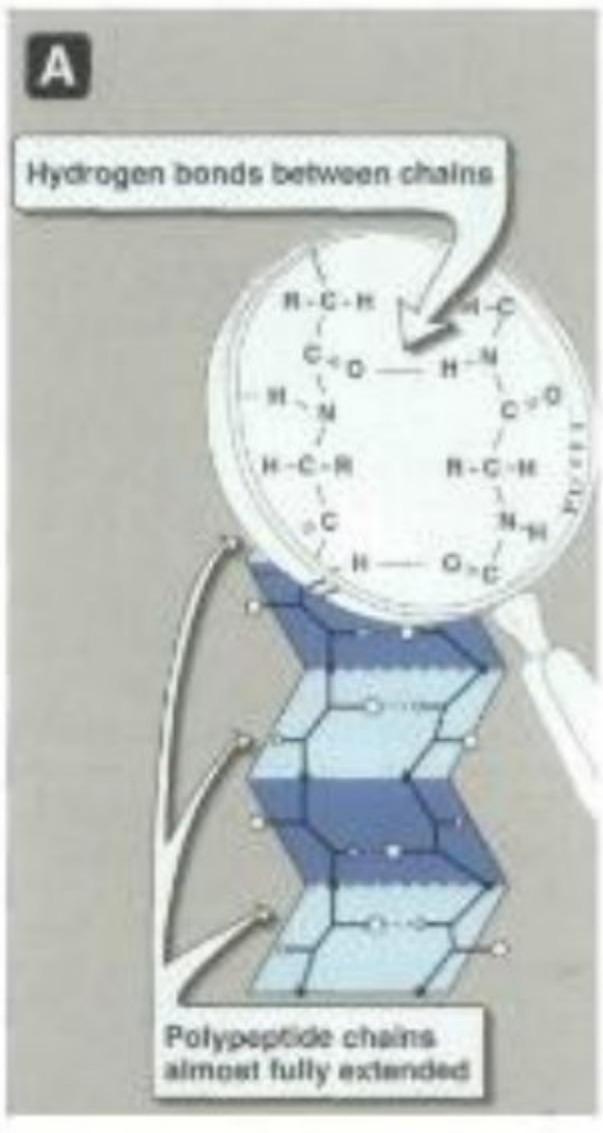
Secondary Structure (cont.)

2. ß-pleated sheet:

It is composed of two or more peptide chain sheet or segments of polypeptide chains, (ß-strands) which are almost fully extended stabilized by H bond.



β -pleated sheet



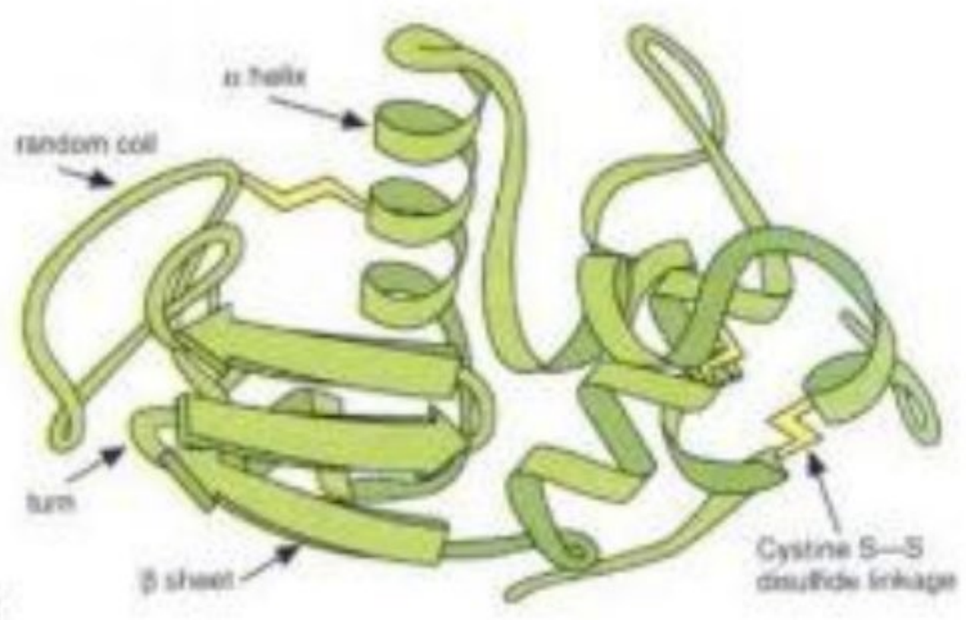
Secondary Structure (cont.)

3.ß-bends (reverse turns, ß-turns):

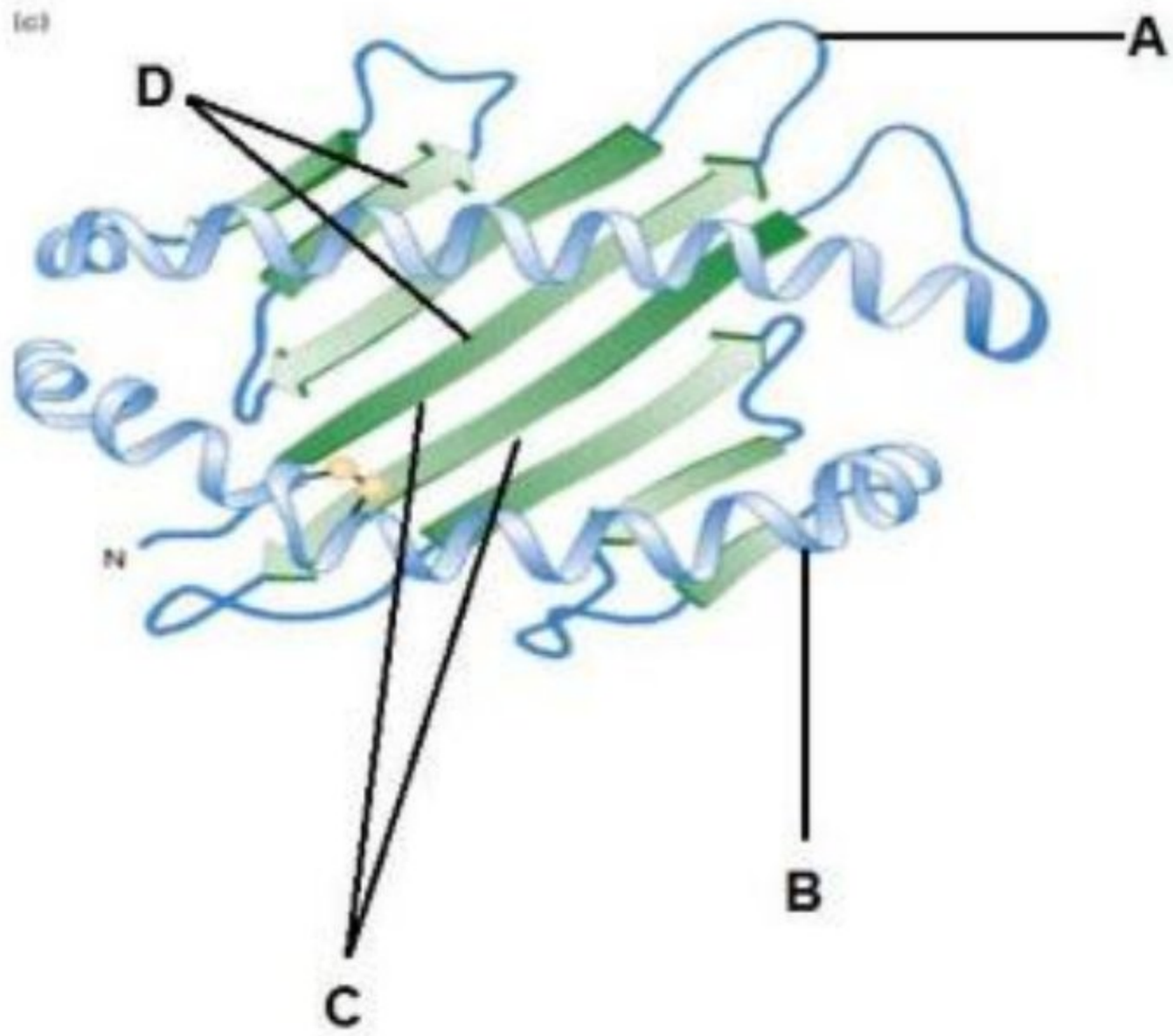
ß-bends reverse the direction of a polypeptide chain

- **Characteristics of ß-bends**

1. Found on the surface of proteins
2. Composed of:
   - ❑ Proline that causes a kink.
   - ❑ Acidic amino acids
   - ❑ Basic amino acids.
3. ß-bends are stabilized by hydrogen and ionic bonds.

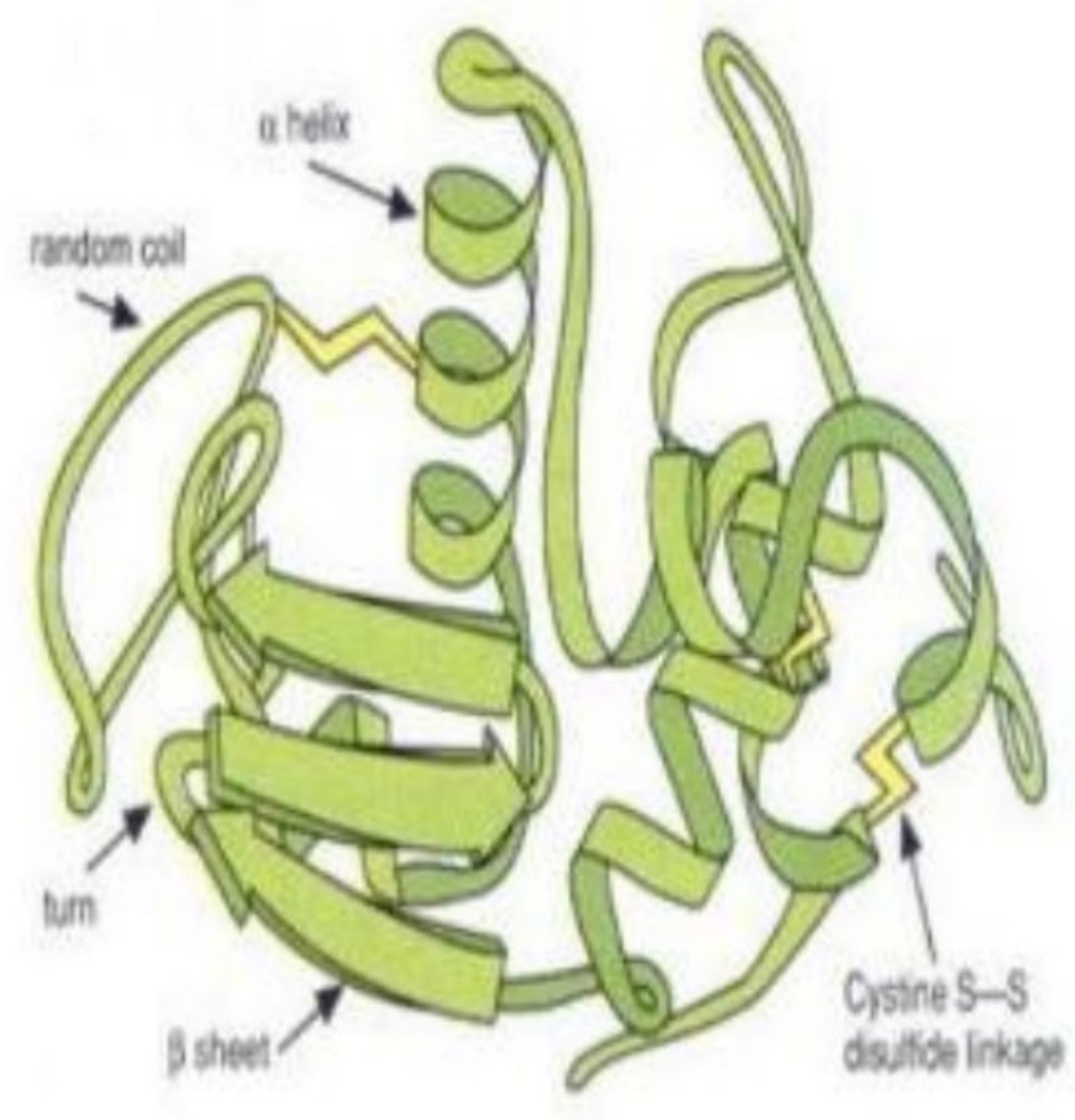


Identify the 2ry protein structure

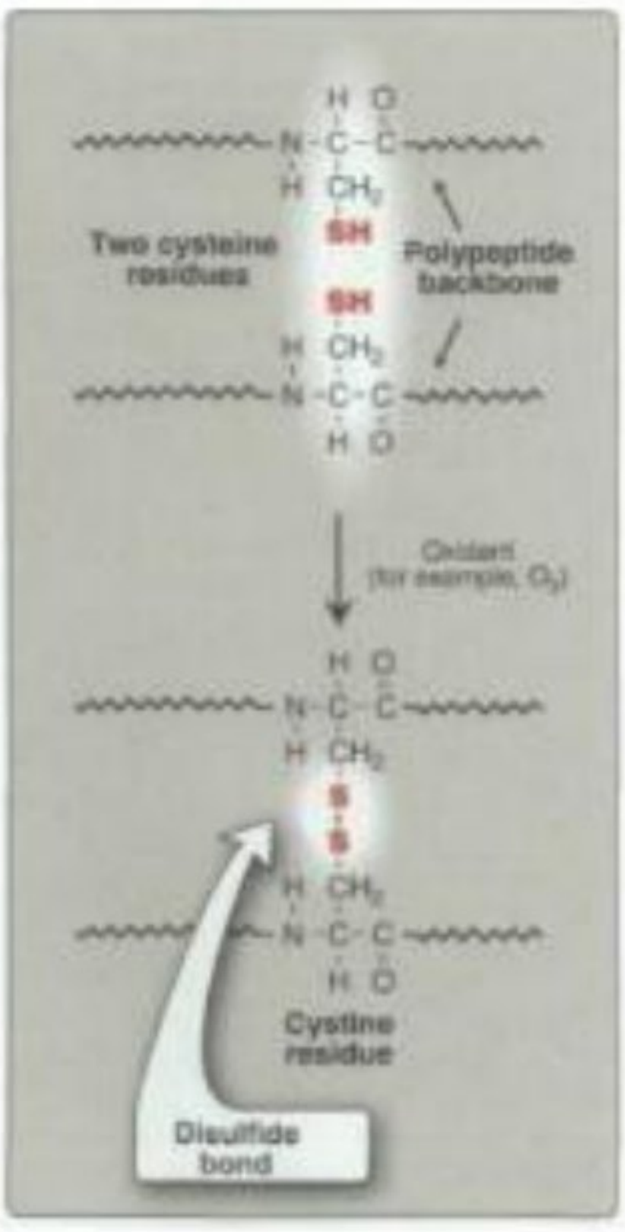


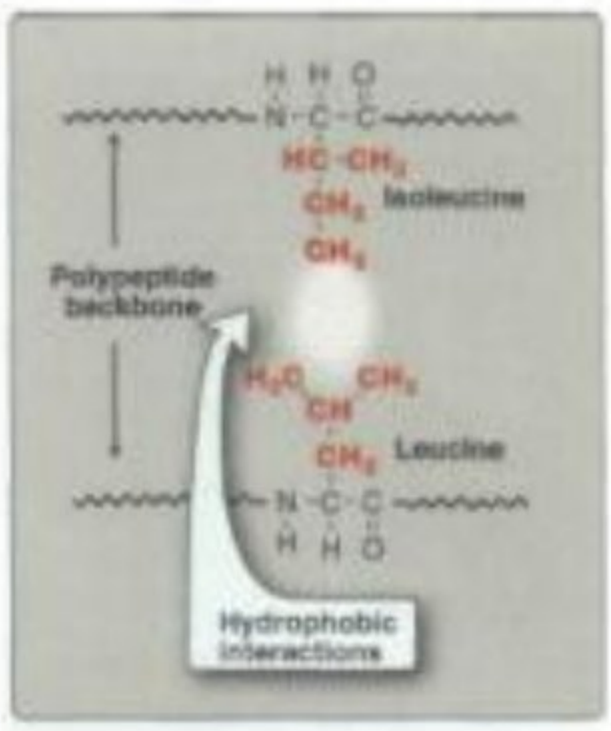
Tertiary Structure

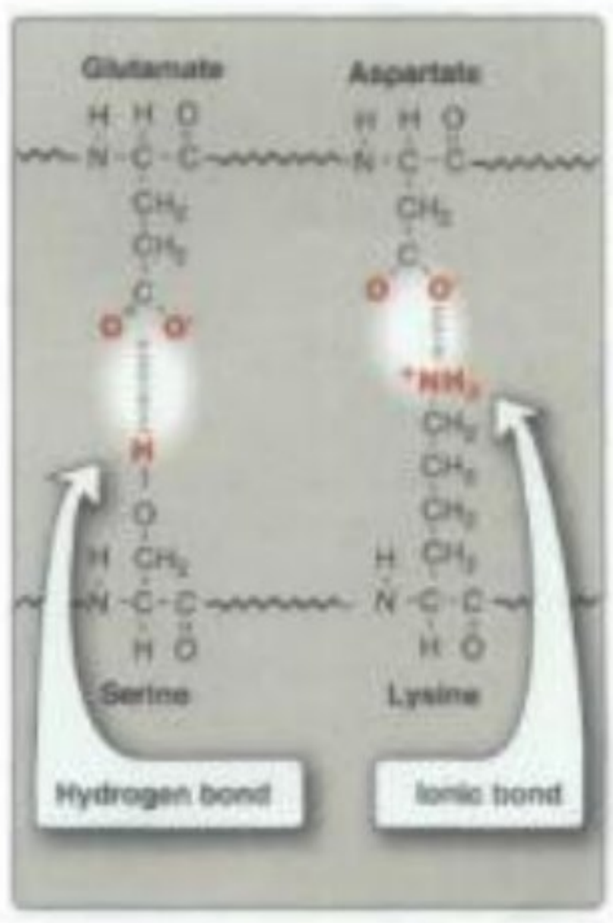
- The final arrangement of single polypeptide chain in the space. Resulting from spatial relationship of more distant amino residues.



Bonds stabilizing tert structure







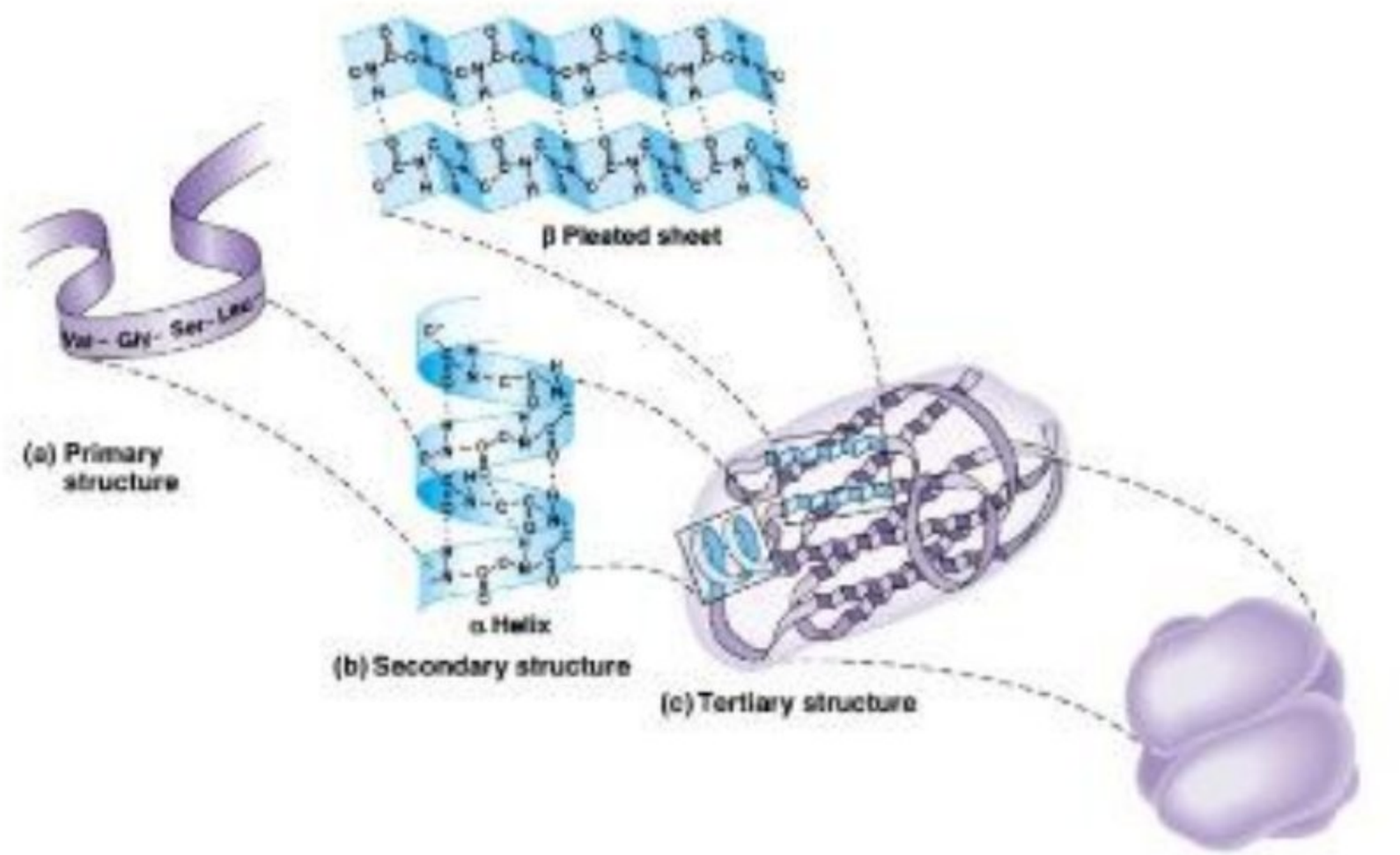
Quaternary Structure

➢**the arrangement of two or more polypeptide chains or subunits that may be structurally identical or totally unrelated.**

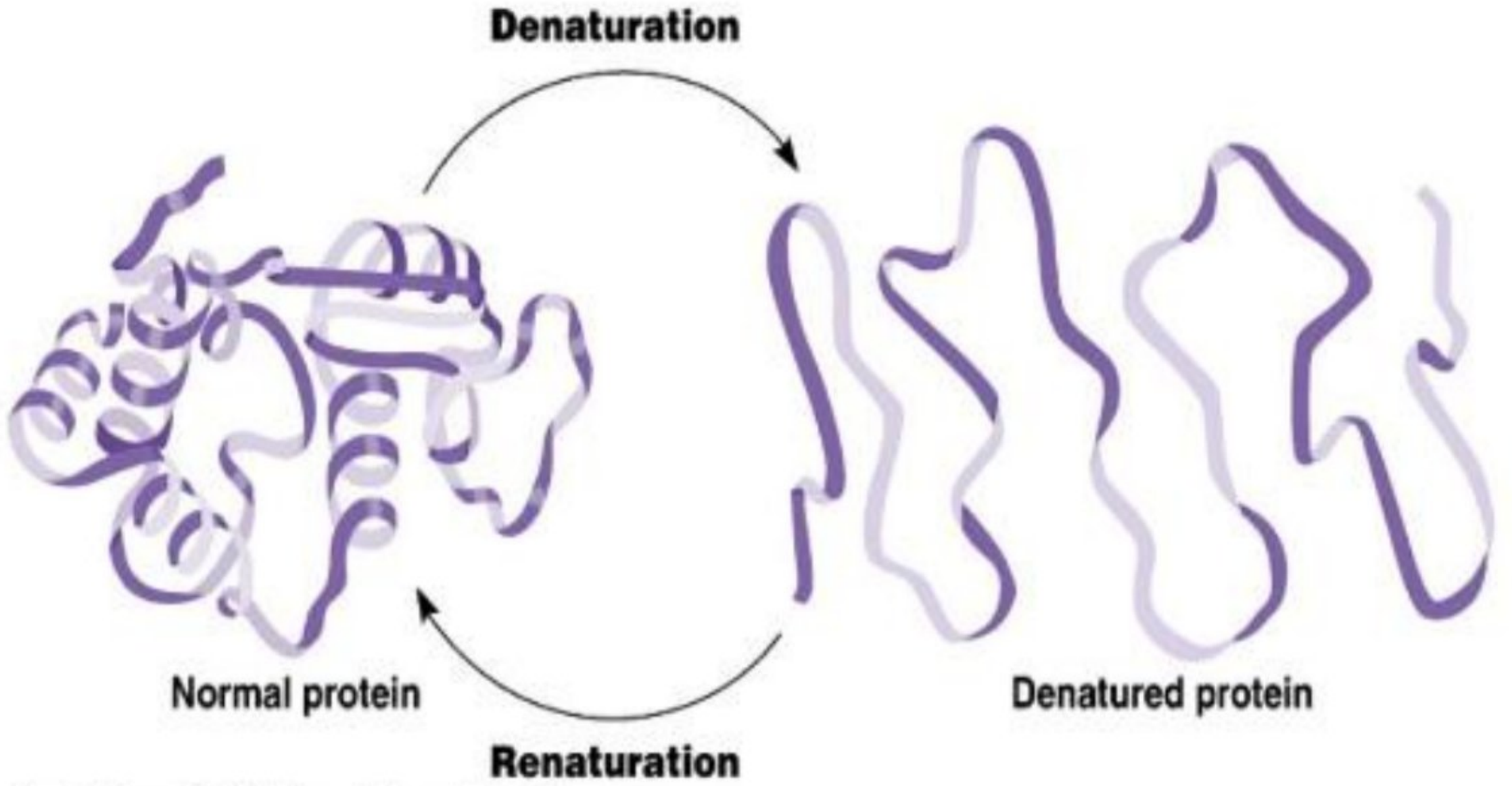
➢**Characteristics of subunits:**

1. They are held together by (hydrogen, hydrophobic and ionic bonds).

2. They are defined as **dimeric** when they consist of two polypeptide chains, **trimeric** and **tetrameric** when they consist of three and four polypeptide chains respectively.

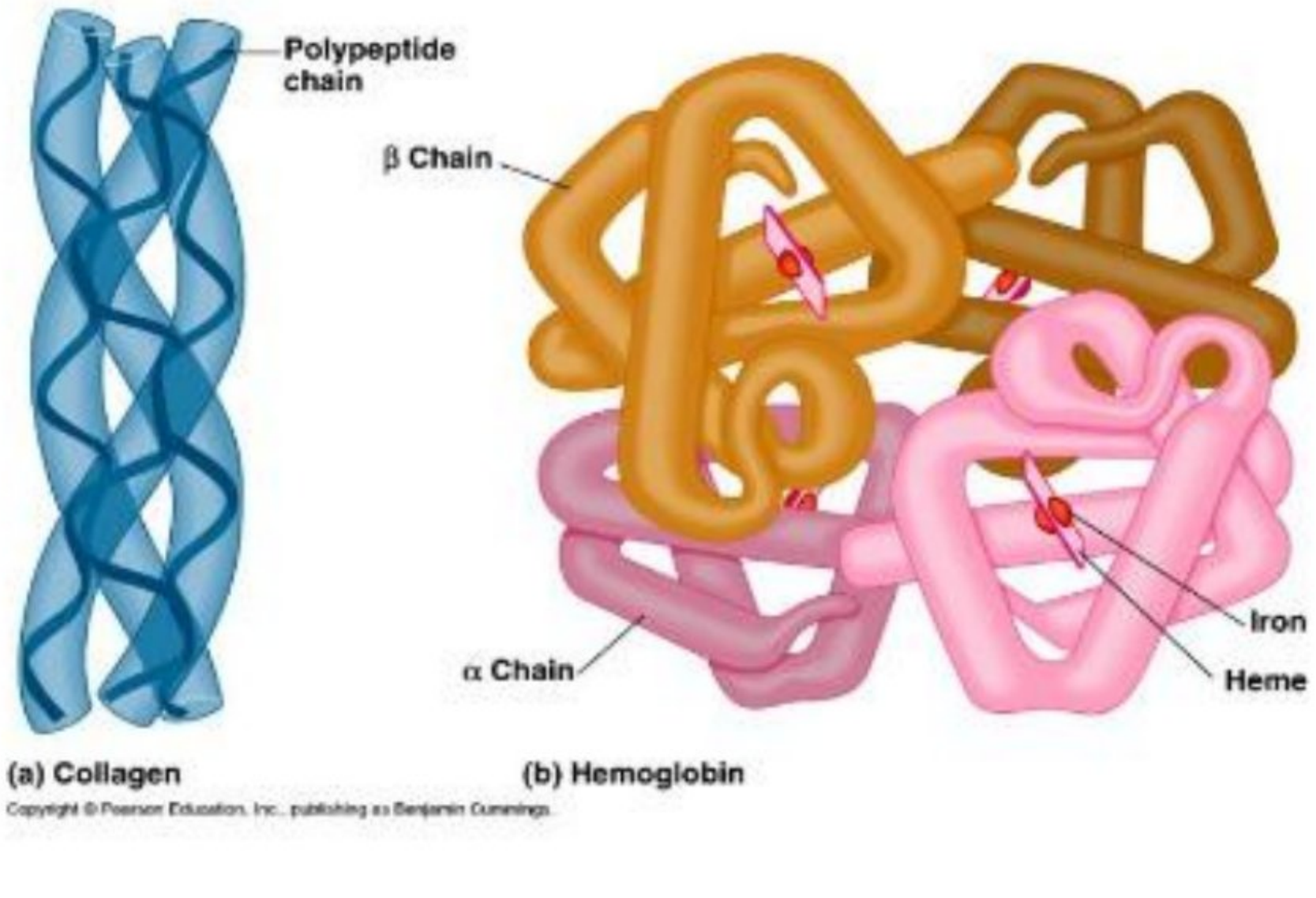


Protein denaturation

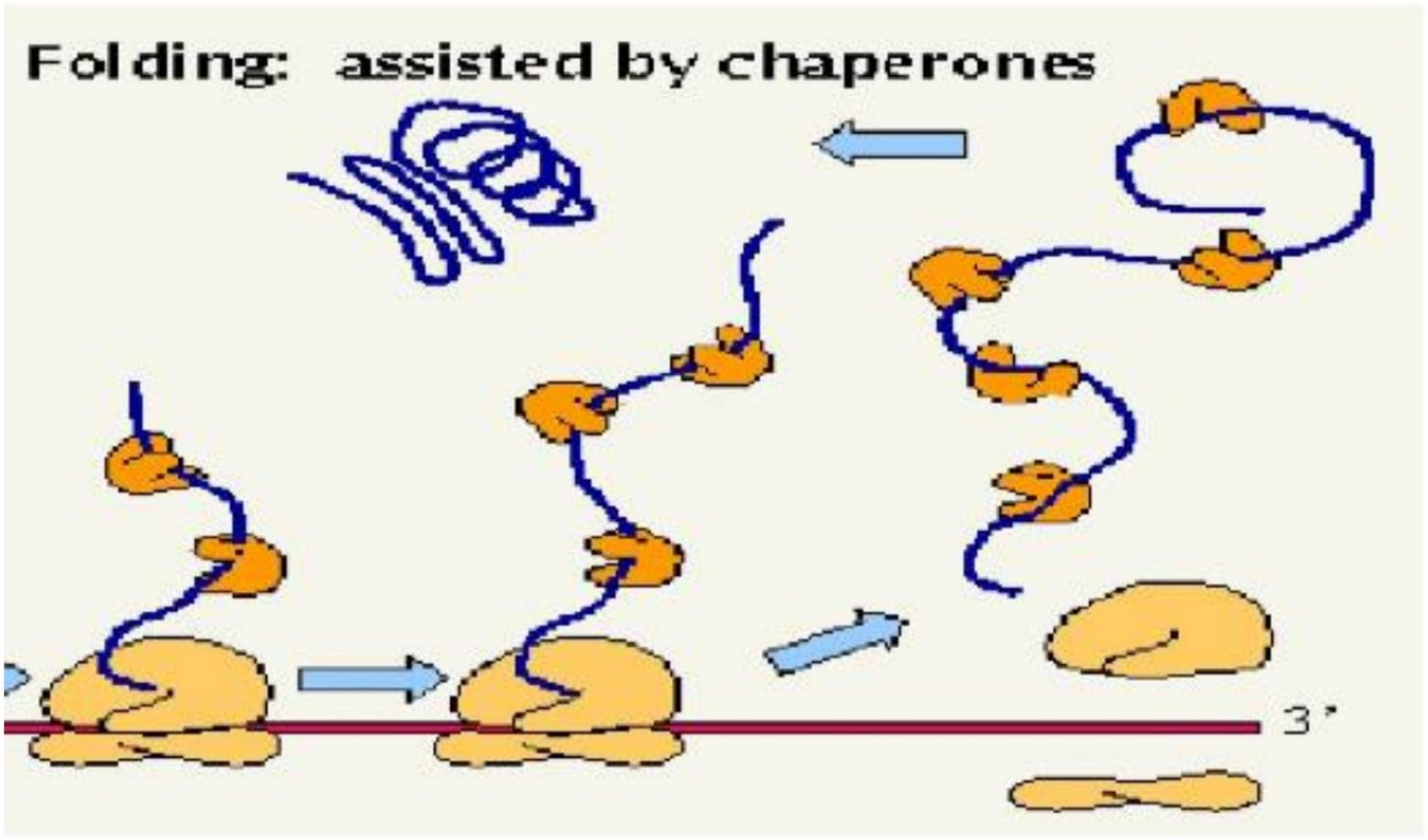


Protein folding

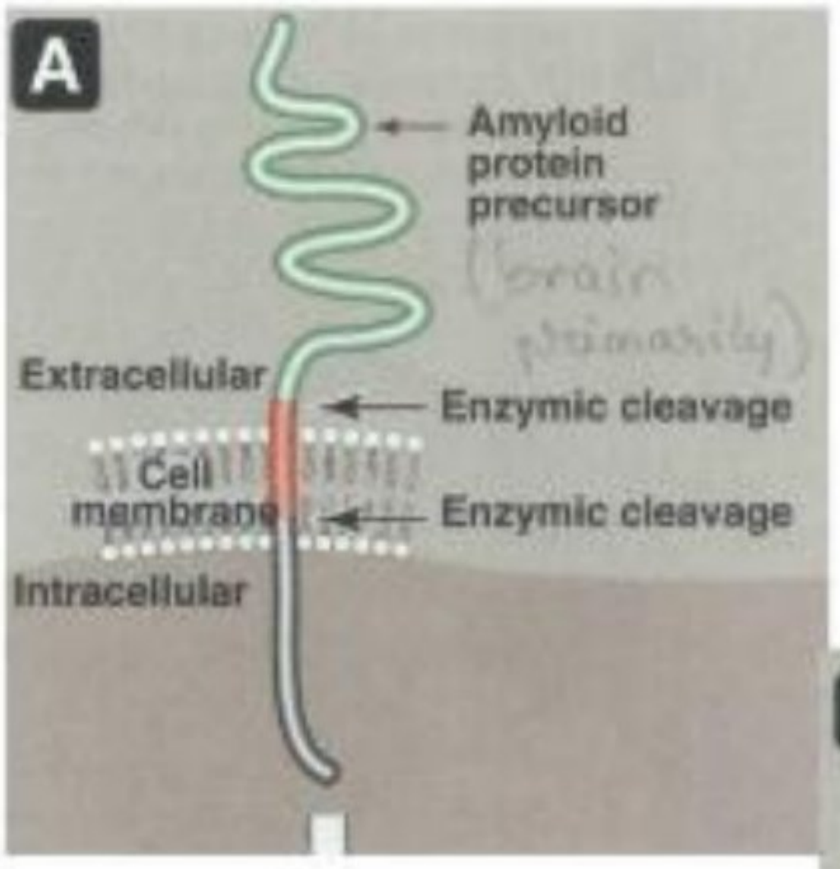
- Proteins are classified according to the folding process into:
  1. Fibrous proteins: axial ratio L / W more than 10, e.g. collagen
  2. Globular proteins: axial ratio L / W less than 10, e.g. hemoglobin

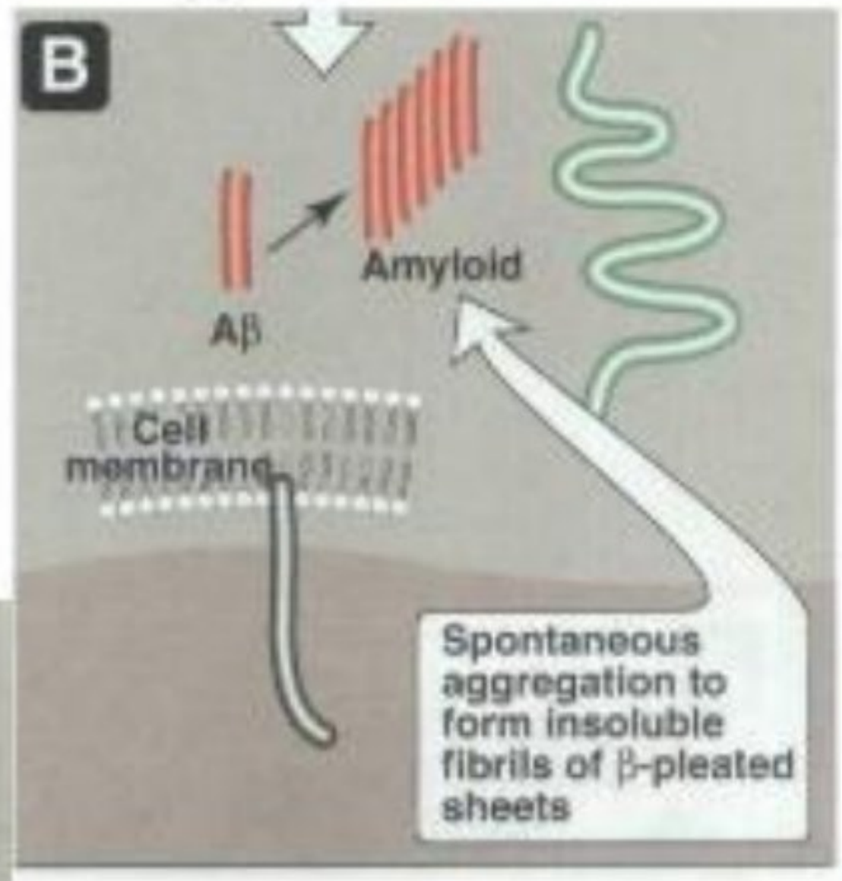


Heat shock proteins

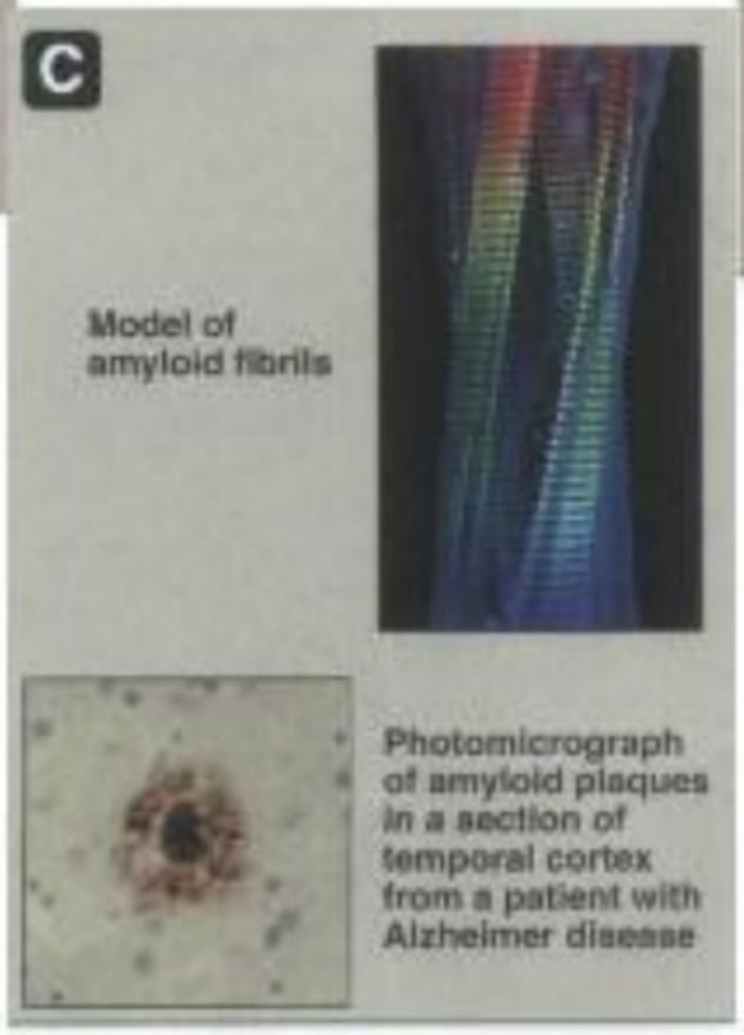


Protein misfolding



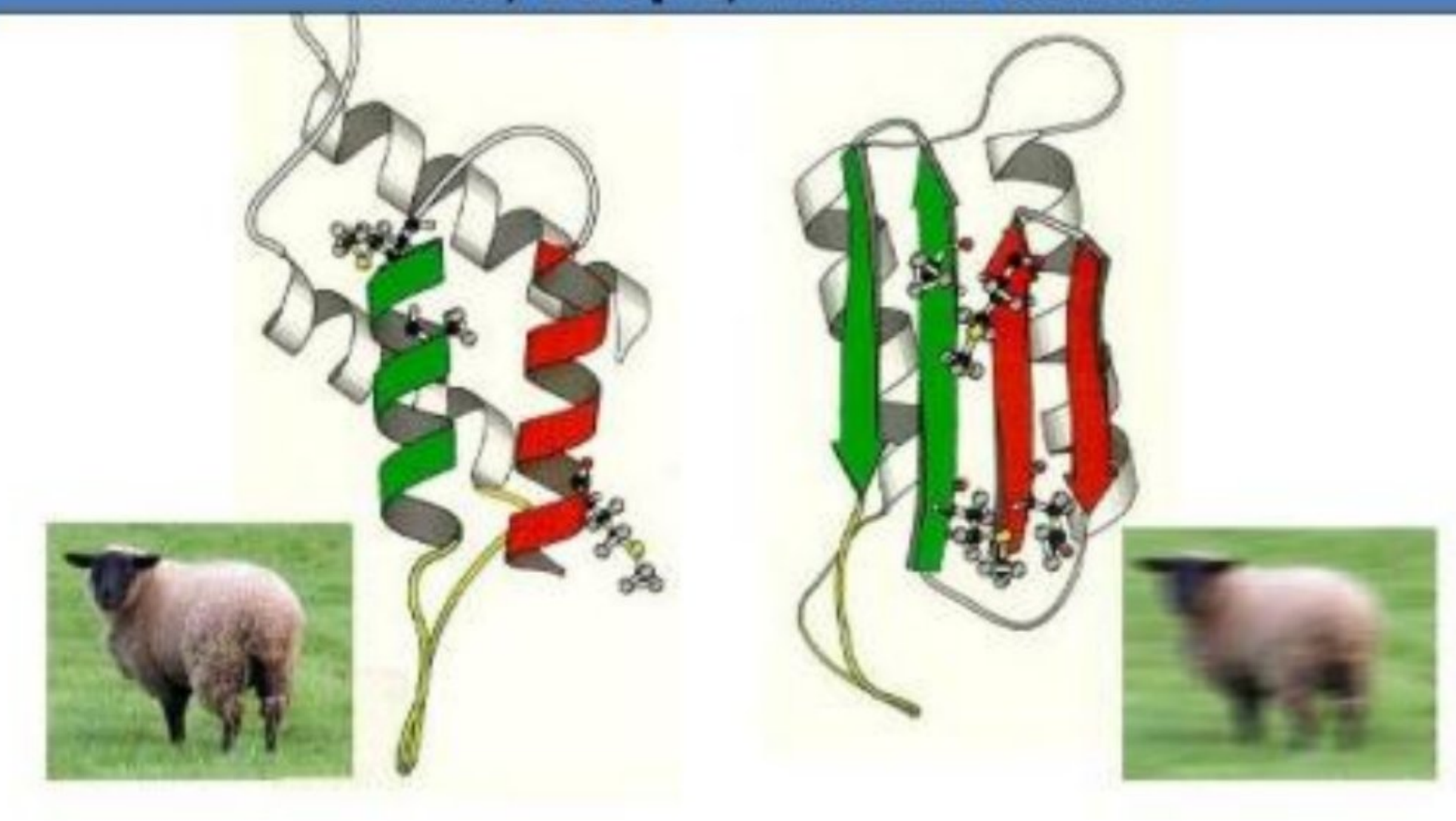


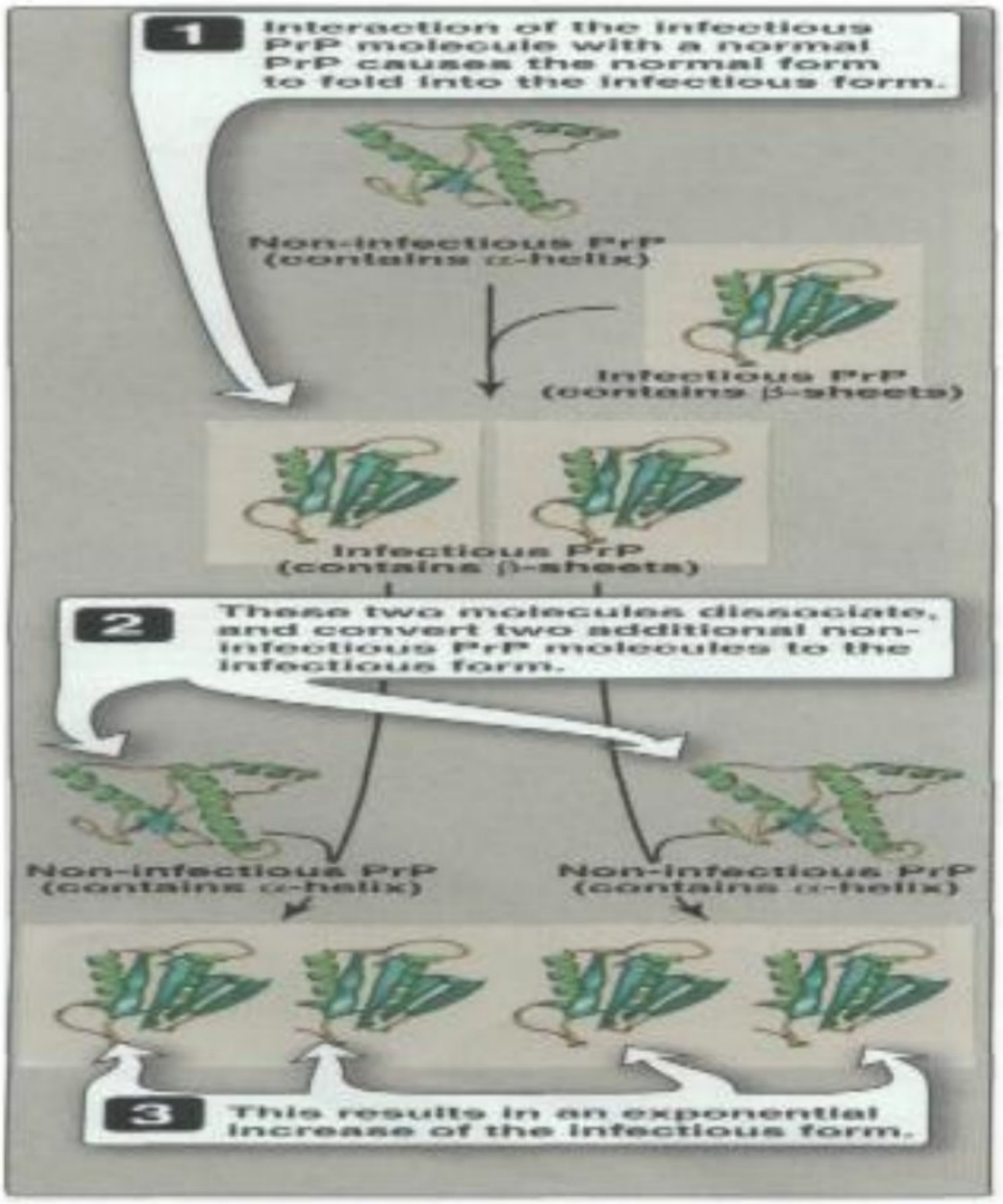
Alzheimer disease

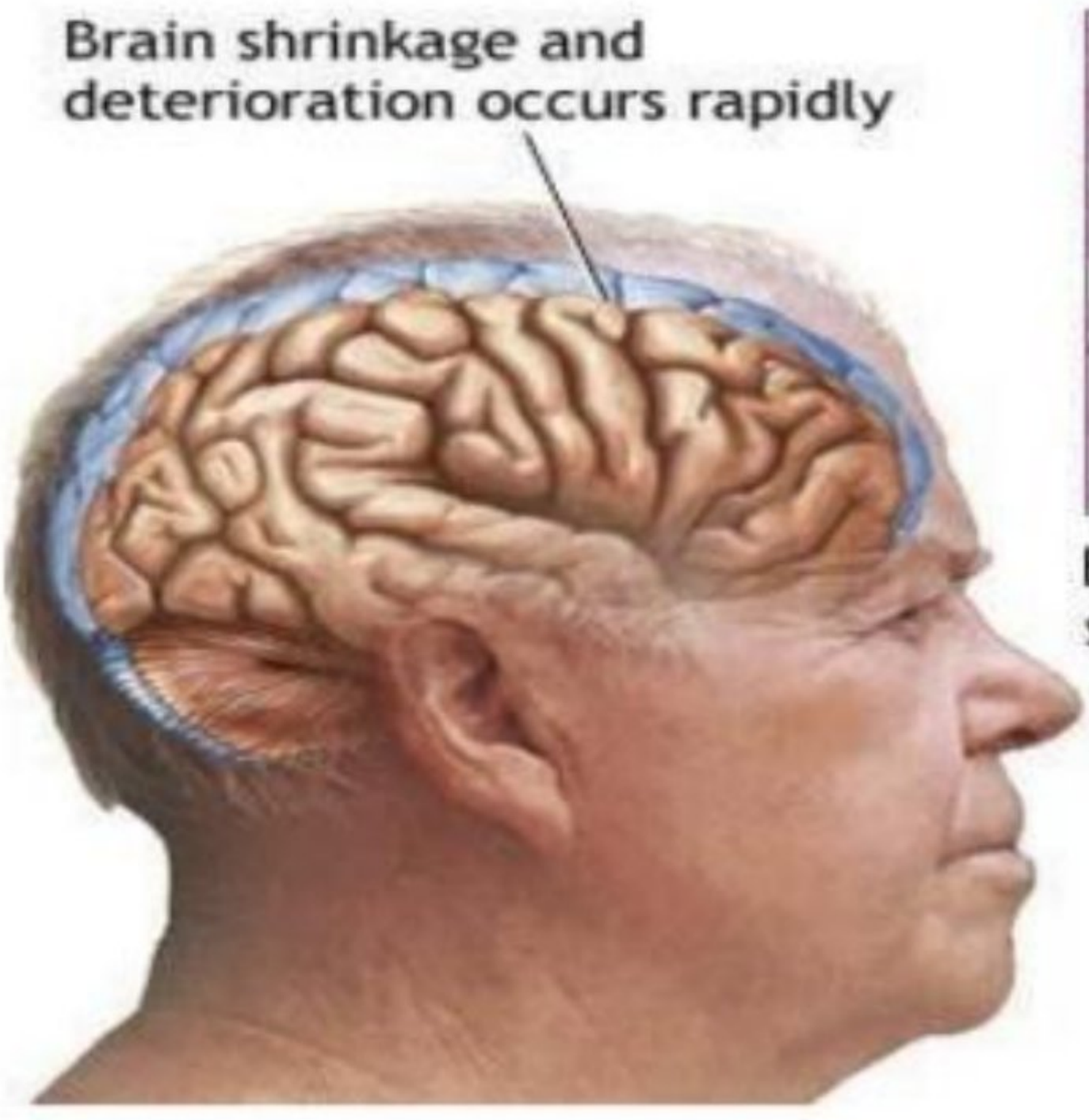


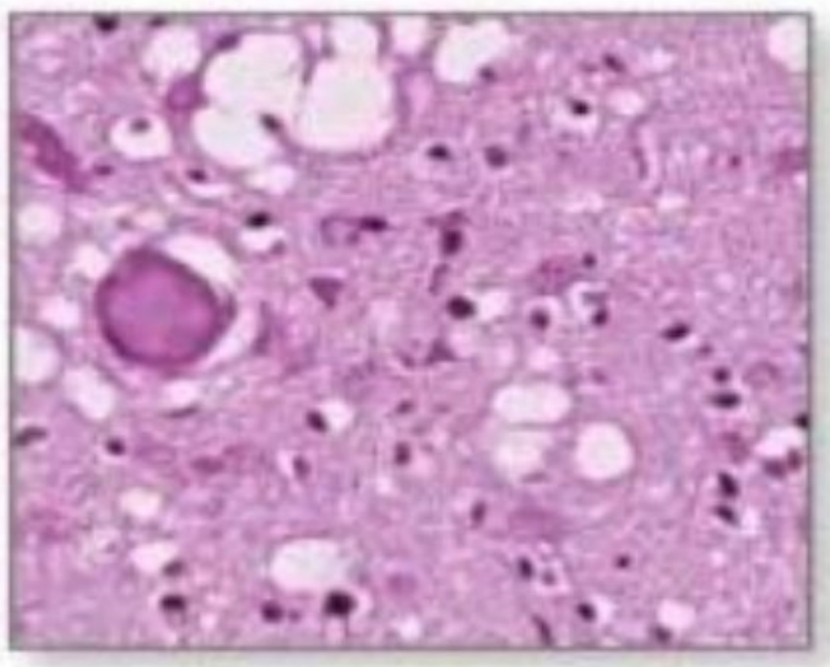
Prion diseases:

Transmissible spongiform encephalopathies: Creutzfeldt-Jakob, Scrapie, mad cow disease









Brain section showing spongiform pathology characteristic of Creutzfeldt-Jakob

I- Fibrous proteins

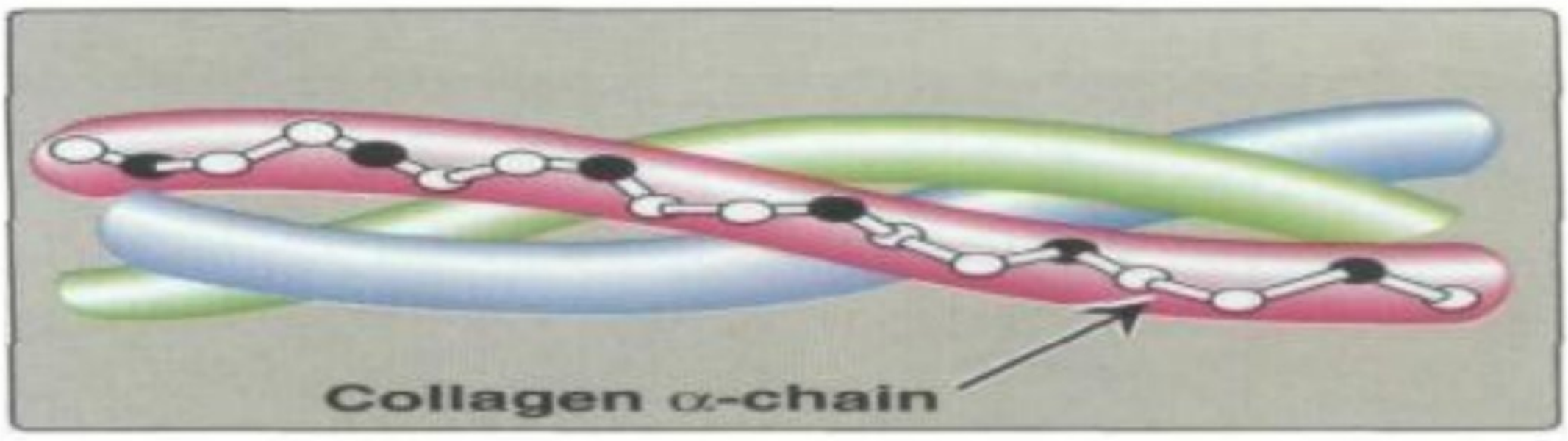
- **They include: Keratin, collagen, elastin.**

1-Keratins: They alpha-helical polypeptide chains, rich in cysteine.

- They found in hair, nail, enamel of teeth and outer layer of skin.

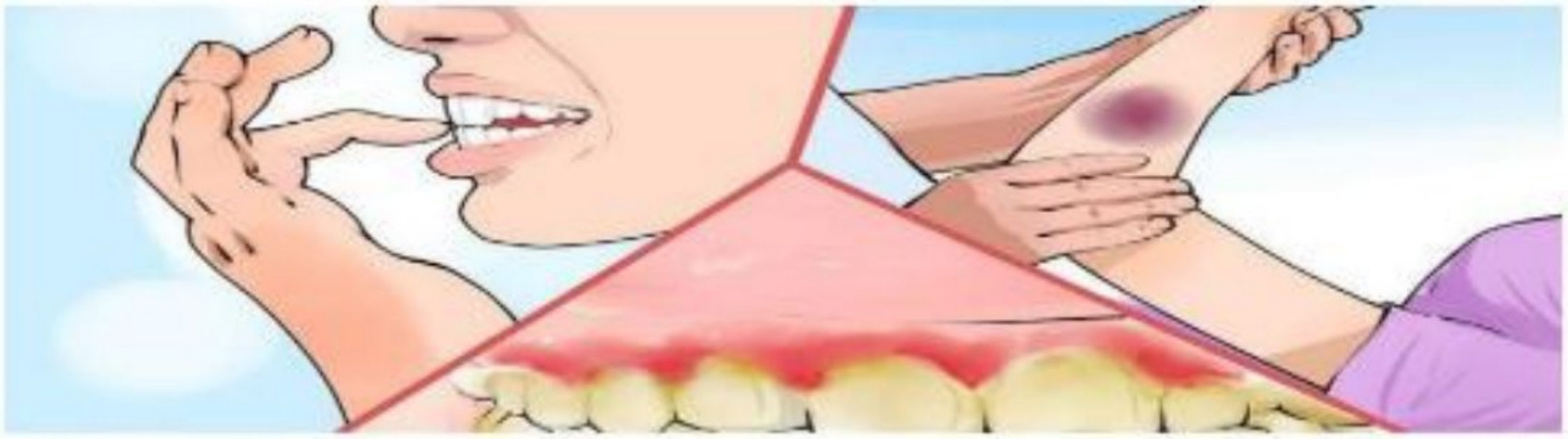
2-Collagen

- Is 3 alpha polypeptide, forming triple helix.
- Found in all tissues and organs providing the tissues their form and structural strength.
- Skin collagen is comparatively very high in glycine (33%), proline, the derived aa hydroxyproline, and hydroxylysine.



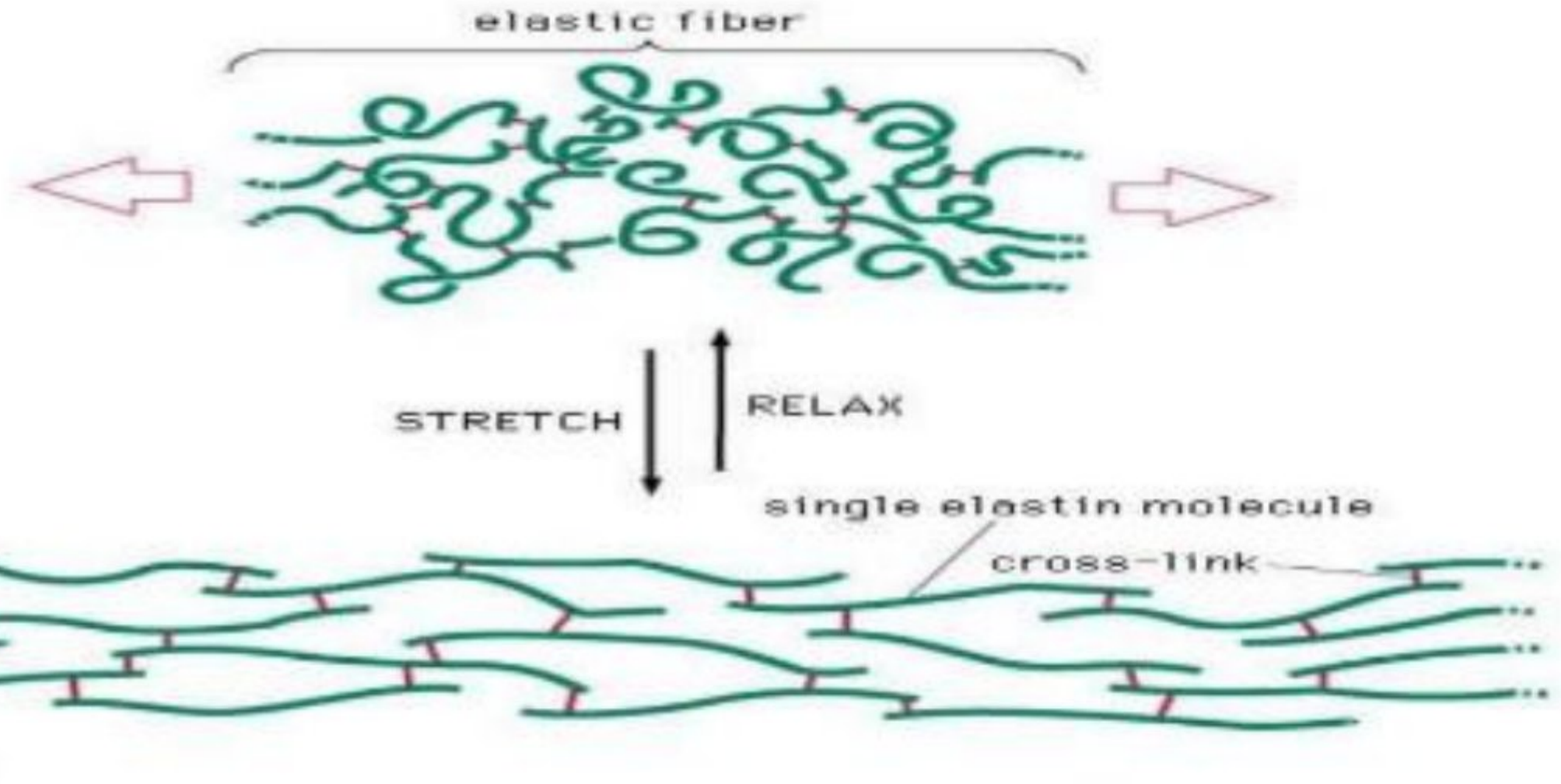
- The enzymatic hydroxylation of proline requires <u>ascorbic acid (vitamin C)</u>; (vit C deficiency=poor synthesis of new collagen) <u>(Scurvy):</u>

- Collagen fibers are weakened, skin and gums develop lesions and blood vessels are weakened.
- The condition is quickly improved by administration of vitamin C.



3-Elastin

- Fibrous protein in ligaments and arterial blood vessels.
- The polypeptide chain of elastin is rich in glycine and alanine and is very flexible and easily extended.



- However, the sequence also contains frequent lysine side chains, which can be involved in cross-links:

- 4 lysine residue are linked together to form a cyclic structure termed, Desmosine.
- These cross-links prevent the elastin fibers from extending indefinitely and allow them to "snap back" on removal of tension as would a piece of rubber.

Globular Proteins

Overview

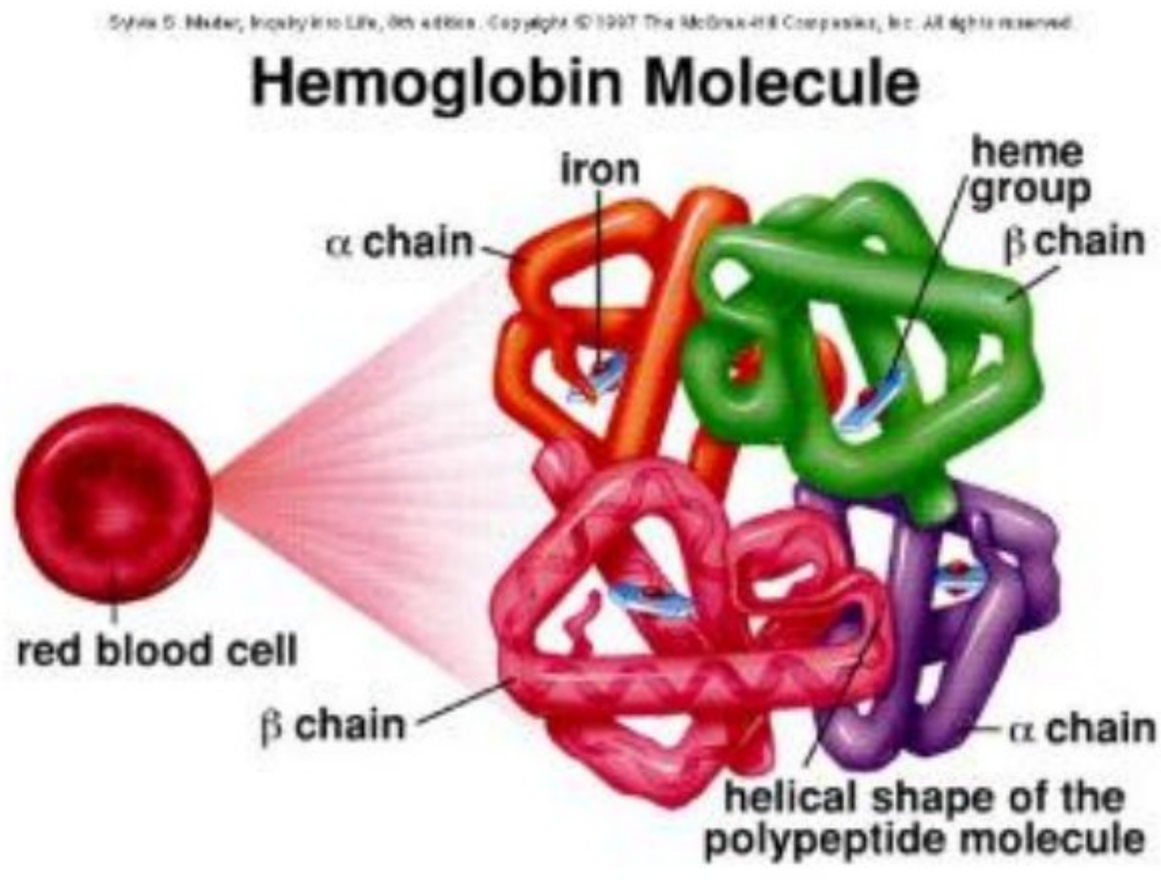
➢ Globular protein characterized by their axial ratio L/W <10

➢ **Hemeproteins are a group of specialized complex proteins that contain heme as a tightly bound as a prosthetic group.**

➢ Role of heme group is dictated by the environment (the 3-dimensional structure of protein):

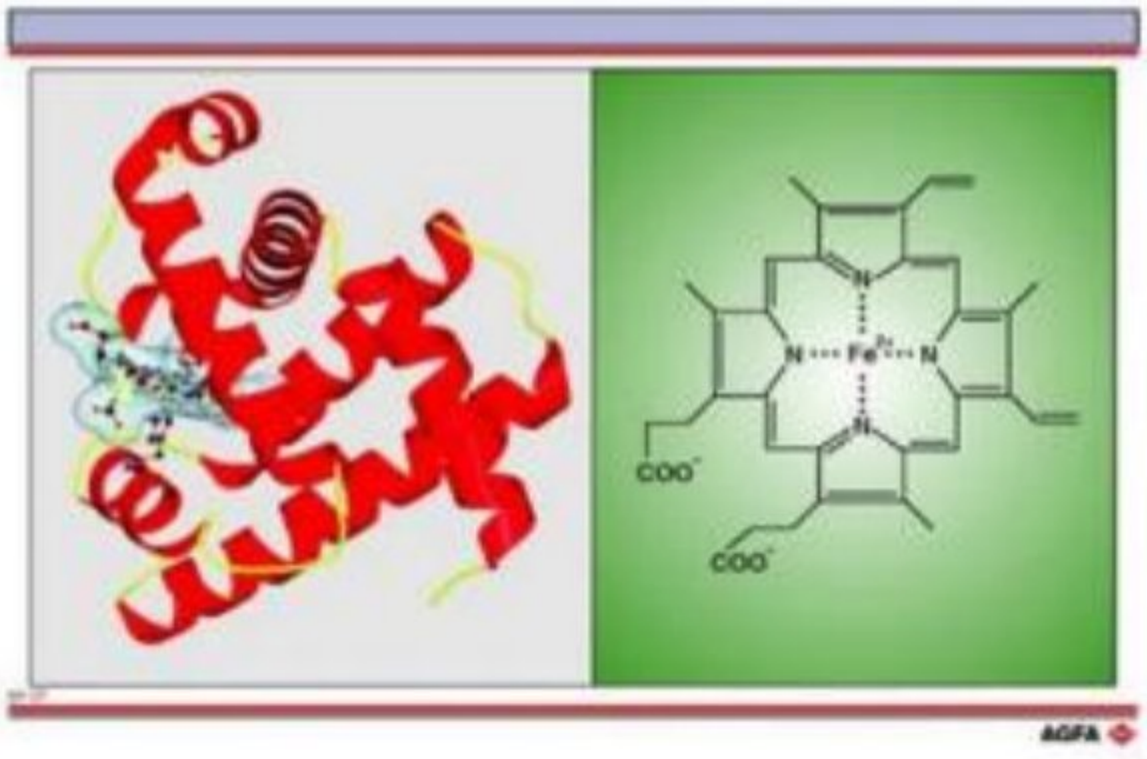
- ❖**Cytochrome:** functions as an electron transport.
- ❖**Catalase enzyme**: catalyzes breakdown of H_2O_2.
- ❖**Hemoglobin and myoglobin:** reversibly bind O_2.

Hemeproteins



Structure of heme

- **Heme is a complex of protoporphyrin IX and ferrous iron (Fe^{2+}).**
- The **iron** is held in the center of the heme molecule by:
  - **4 bonds** to the 4 nitrogens of the protoporphyrin ring.
  - **2 additional bonds** (one on each side of the planar ring):one to the side chain of a histidine residue of the globin molecule and other one to bind O_2.

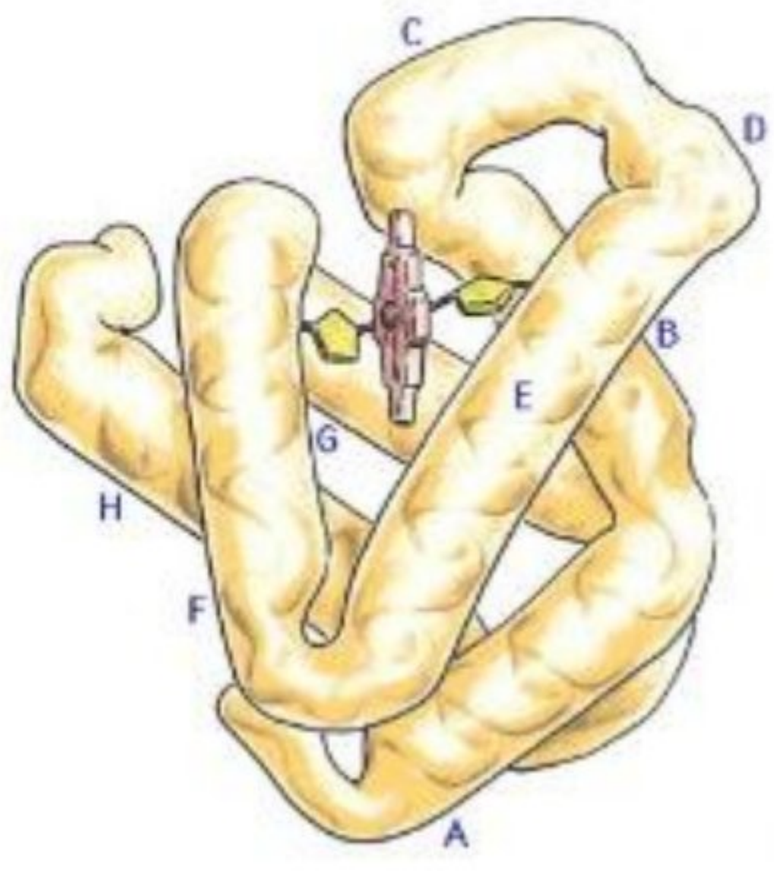


Structure of Myoglobin

- **Single polypeptide chain (monomer)** composed of:
  - 8 stretches of α-helix labeled **A to H**
  - **One** Heme group sitting in a cleft.

composed of:

- Charged amino acids on the surface of molecule.
- Non polar amino acids in the interior of the molecule. Except: histidine binds directly to iron



Structure of Hemoglobin

- **4 polypeptide chains (tetramer)** composed of **identical: Dimer $(\alpha\beta)_1$ & Dimer $(\alpha\beta)_2$.**
- **Quaternary structure**
- **Interchain** hydrophobic interactions form strong associations between α & ß subunits in a dimer.
- Weak ionic &H interactions occur between 2 dimers.

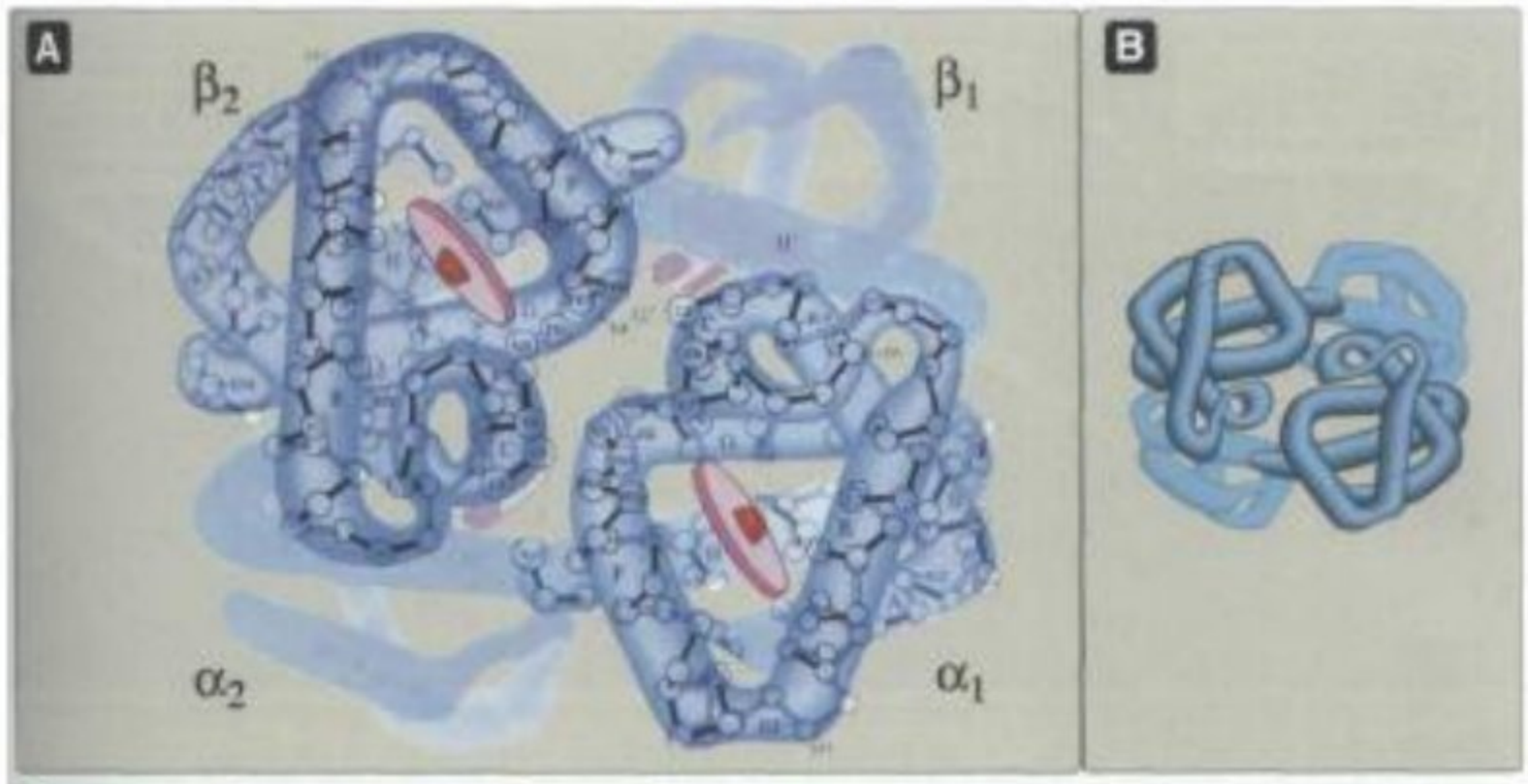


Figure 3.3
A. Structure of hemoglobin showing the polypeptide backbone. B. Simplified drawing showing the helices.

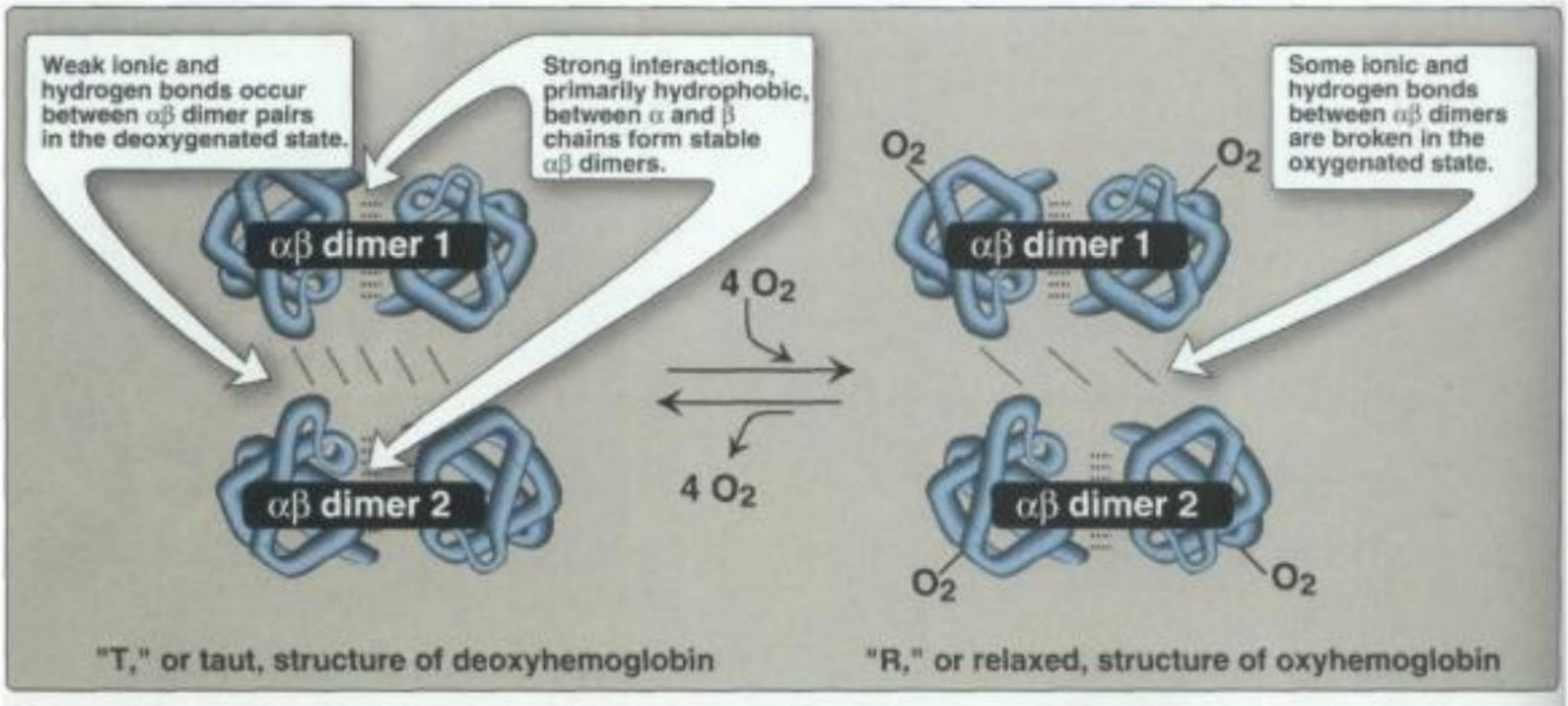


Figure 3.4
Schematic diagram showing structural changes resulting from oxygenation and deoxygenation of hemoglobin.

Functional difference between myoglobin and Hb

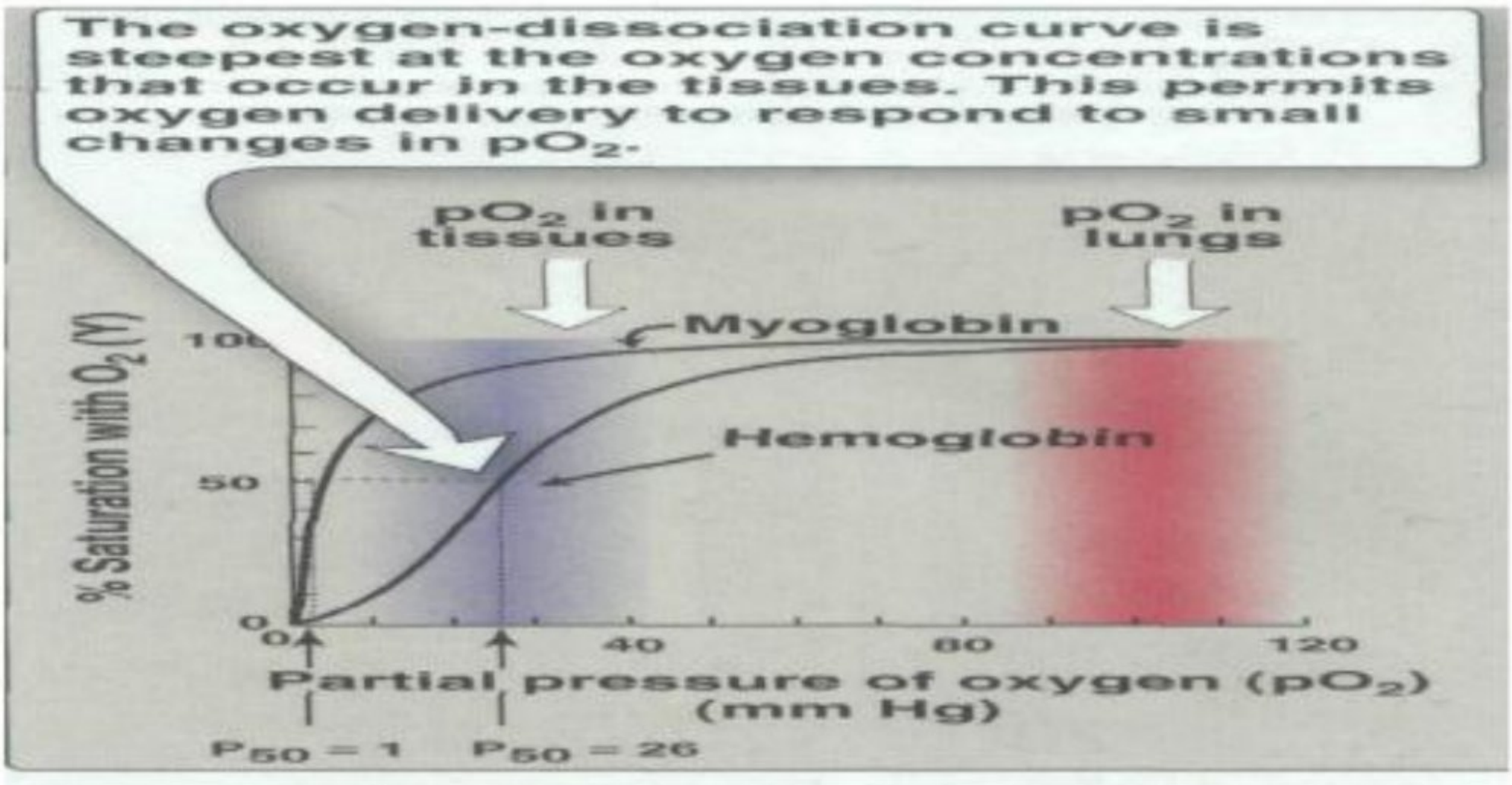


Figure 3.5
Oxygen dissociation curves for myoglobin and hemoglobin.

Oxygen Dissociation Curve (cont.)

Item	Myoglobin (Mb)	Hemoglobin (Hb)
P_{50}	1 mmHg	26 mmHg
Shape	▪ Hyperbolic ▪ binds a single O_2 molecule. ▪ Mb + O_2 ↔ MbO_2	▪ Sigmoid ▪ 4 Subunits cooperate in binding O_2 ▪ Binding of an O_2 molecule at one heme, increases O_2 affinity of remaining groups in the same Hb.

Oxygen Dissociation Curve (cont.)

Item	Myoglobin (Mb)	Hemoglobin (Hb)
Significance	▪Releases O_2 within the muscle cell in response to O_2 demand(delivers no O_2 to tissues).	▪Steep slope permits delivery of O_2 efficiently from sites of high pO_2 (lungs) to sites of low pO_2 (tissues) in response to relatively small changes in the partial pressure of O_2.

Allosteric Effectors

- **The ability of Hb to reversibly bind O_2 is affected by:**
  - **pO_2 (through heme-heme interaction)**
  - **pH of the environment**
  - **pCO_2**
  - **Availability of 2,3-bisphosphoglycerate**

- These are collectively called allosteric ("other site") effectors.

Allosteric Effectors(cont.)

➢ **pO_2 (through heme-heme interaction)**

The last O_2 bound is ~ **300 times** greater than its affinity for the first O_2 bound. This effect is referred to as heme-heme interaction where the specific structural changes initiated at one heme group are transmitted to the other groups in the Hb tetramer.

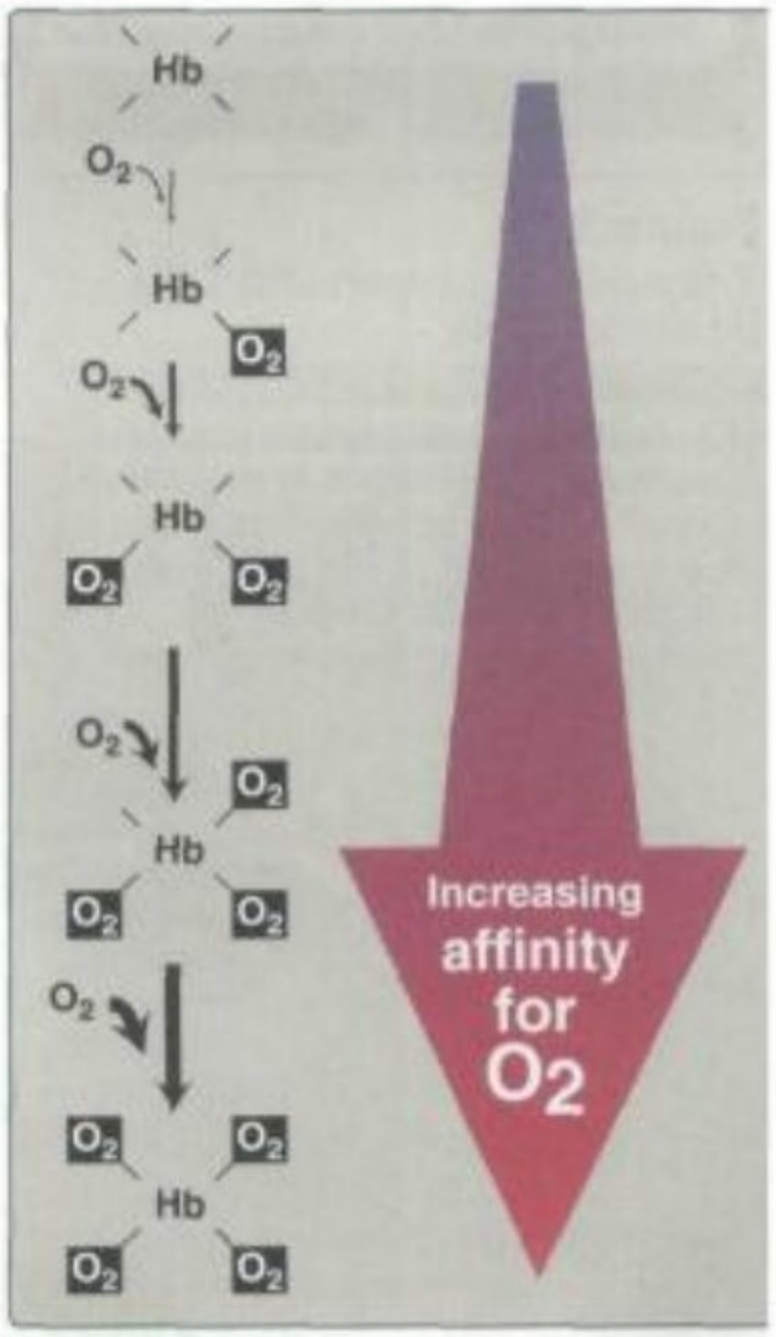


Figure 3.6
Hemoglobin binds oxygen with

Allosteric Effectors(cont.)

➢ **Bohr effect (pCO_2 and pH of the environment)**

❖Metabolizing cells produce CO_2 which diffuses into the blood and enters the circulating red blood cells (RBCs).

❖Most of the CO_2 produced in metabolizing cells is transported to the lungs in this way.

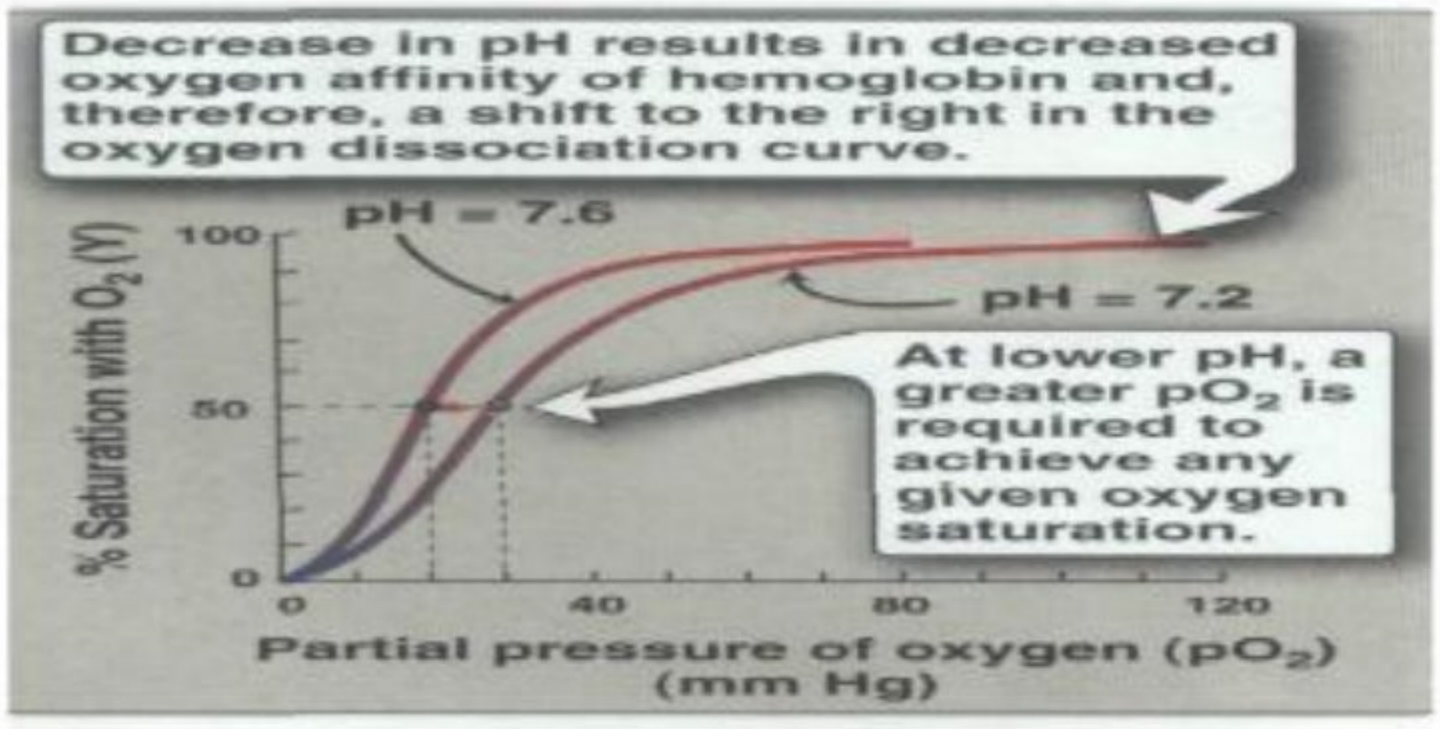


Figure 3.8
Effect of pH on the oxygen affinity of hemoglobin.

Allosteric Effectors(cont.)

➢ **Mechanism of Bohr effect:**

❖Protons (H^+) cause ionizable groups in Hb to become protonated and able to form ionic bonds.

❖ These bonds preferentially stabilize the deoxy form of hemoglobin (T-form), producing a decrease in O_2 affinity, favoring the unloading of O_2 in the peripheral tissues.

$HbO_2 + H^+ \longrightarrow HbH+ + O_2$

Oxyhemoglobin deoxyhemoglobin

The differential pH gradient (lungs having a higher pH, tissues a lower pH) favors the unloading of O_2 in peripheral tissues, and loading of O_2 in the lung. Thus, the oxygen affinity of the Hb molecule responds to small shifts in pH between the lungs and tissues, making Hb a more efficient transporter of O_2.

Allosteric Effectors (cont.)

❖As much as CO_2 is transported to the lungs bound to N-terminal amino groups of the T form of hemoglobin.

❖The reaction, depicted below, forms what is called carbamino-hemoglobin.

❖H^+, produced lowers the pH in tissues where the CO_2 concentration is high. The binding of CO_2 stabilizes the "T" form, resulting in decrease in O_2 affinity. In the lungs, CO_2 dissociated from the Hb, and is released in the breath.

$CO_2 + Hb\text{-}NH_2 <\text{-----}> H^+ + Hb\text{-}NH\text{-}COO^-$

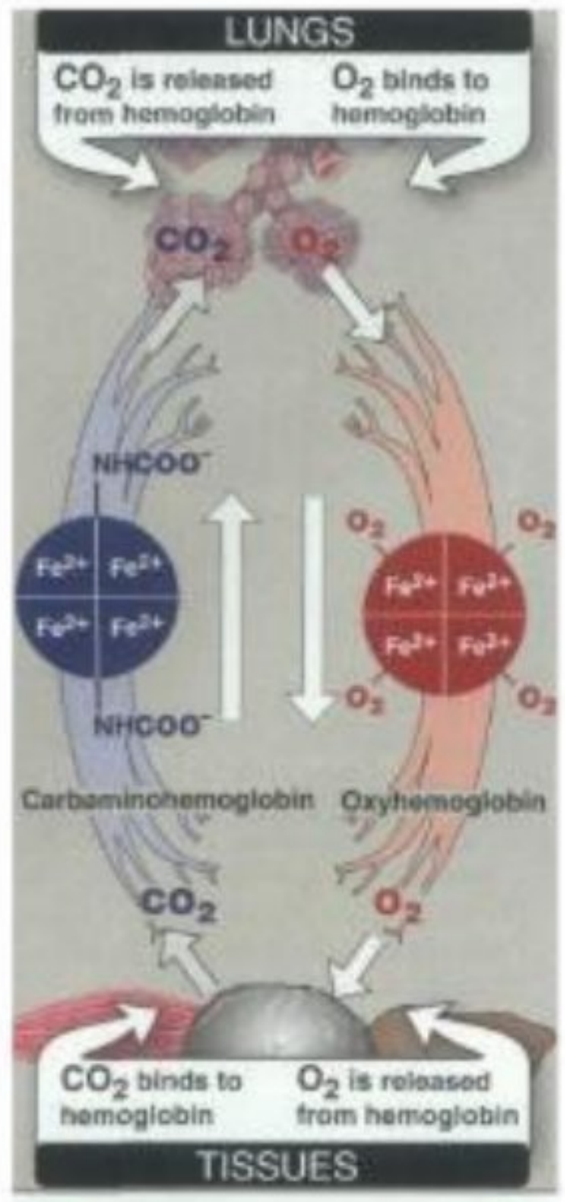


Figure 3.7
Transport of oxygen and CO_2 by hemoglobin.

Allosteric Effectors (cont.)

4. Availability of 2,3-bisphosphoglycerate (most abundant organic phosphate in the RBCs).

- It is obtained from glucose
- The concentration of 2, 3-BPG in the RBCs increases in response to chronic hypoxia, such as high altitudes or obstructive pulmonary obstruction and anemia.

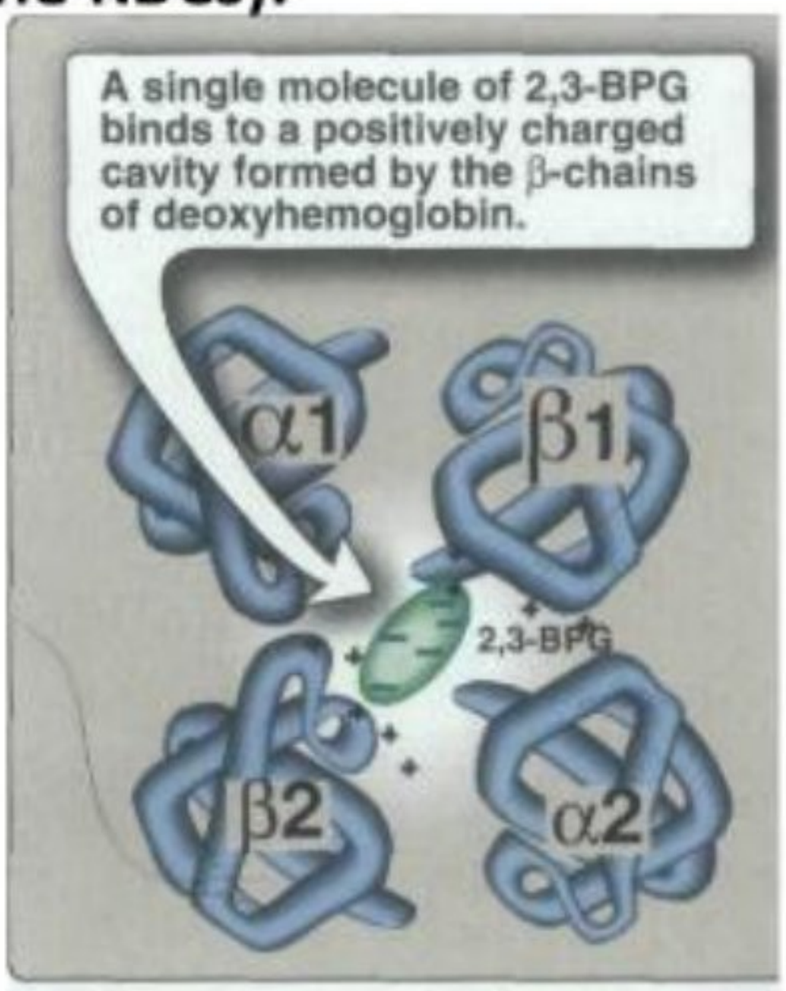


Figure 3.10
Binding of 2,3-BPG by deoxy-hemoglobin.

http://themedicalbiochemistrypage.org/images/23bpg.jpg

Allosteric Effectors (cont.)

- **Binding of CO**

forming **carboxyhemoglobin.**

When CO binds to one or more of the four heme sites, the Hb shifts to the relaxed conformation, causing the remaining heme sites to bind O_2 with **high affinity**.

This shifts the O_2 dissociation curve to the left.

The affinity of Hb for CO is 220 times greater than for O_2. Consequently, even minute concentrations of CO in the environment produce toxic concentrations of carboxyhemoglobin in blood.

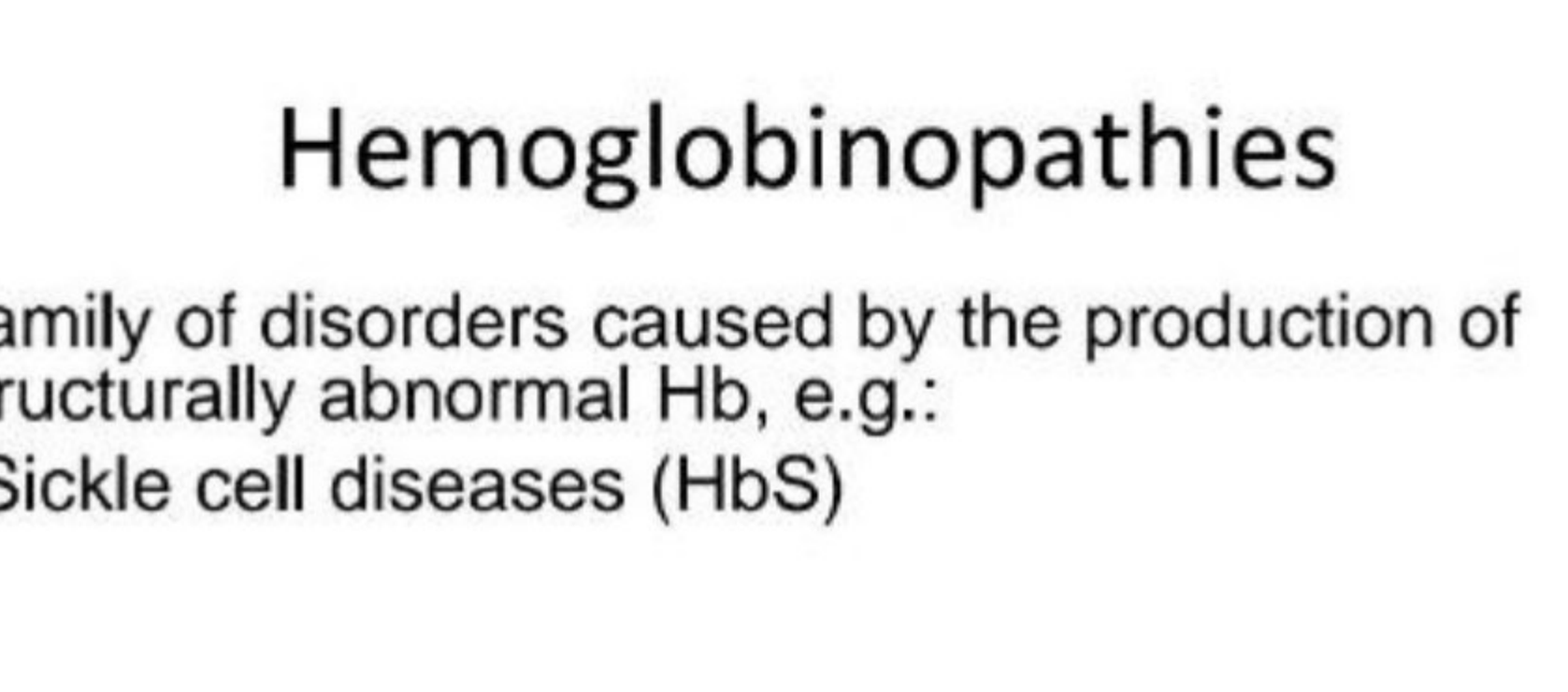
CO poisoning is treated with 100% O_2 therapy, which facilitates the dissociation of CO from the Hb.

Normal adult human hemoglobins

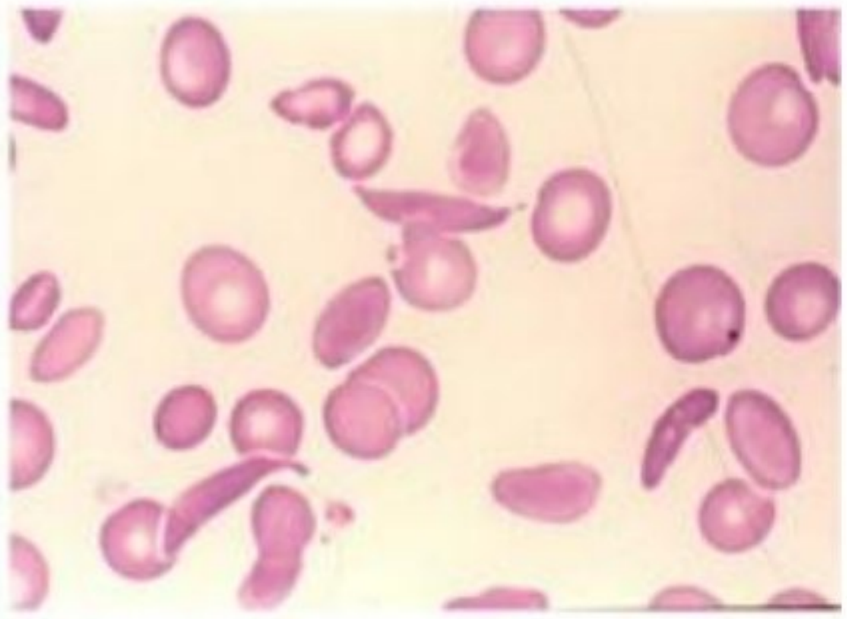
Form	Chain composition	Fraction of total hemoglobin
HbA	$\alpha_2 ß_2$	90%
HbF	$\alpha_2 \gamma_2$	<2%
HbA_2	$\alpha_2 \varsigma_2$	2-5%
HbA_{1c}	$\alpha_2 ß_2$-glucose	3-9%

Hemoglobinopathies

- Family of disorders caused by the production of structurally abnormal Hb, e.g.:
  Sickle cell diseases (HbS)



Sickle cell anemia (HbS)



❖**Molecular Evidence**

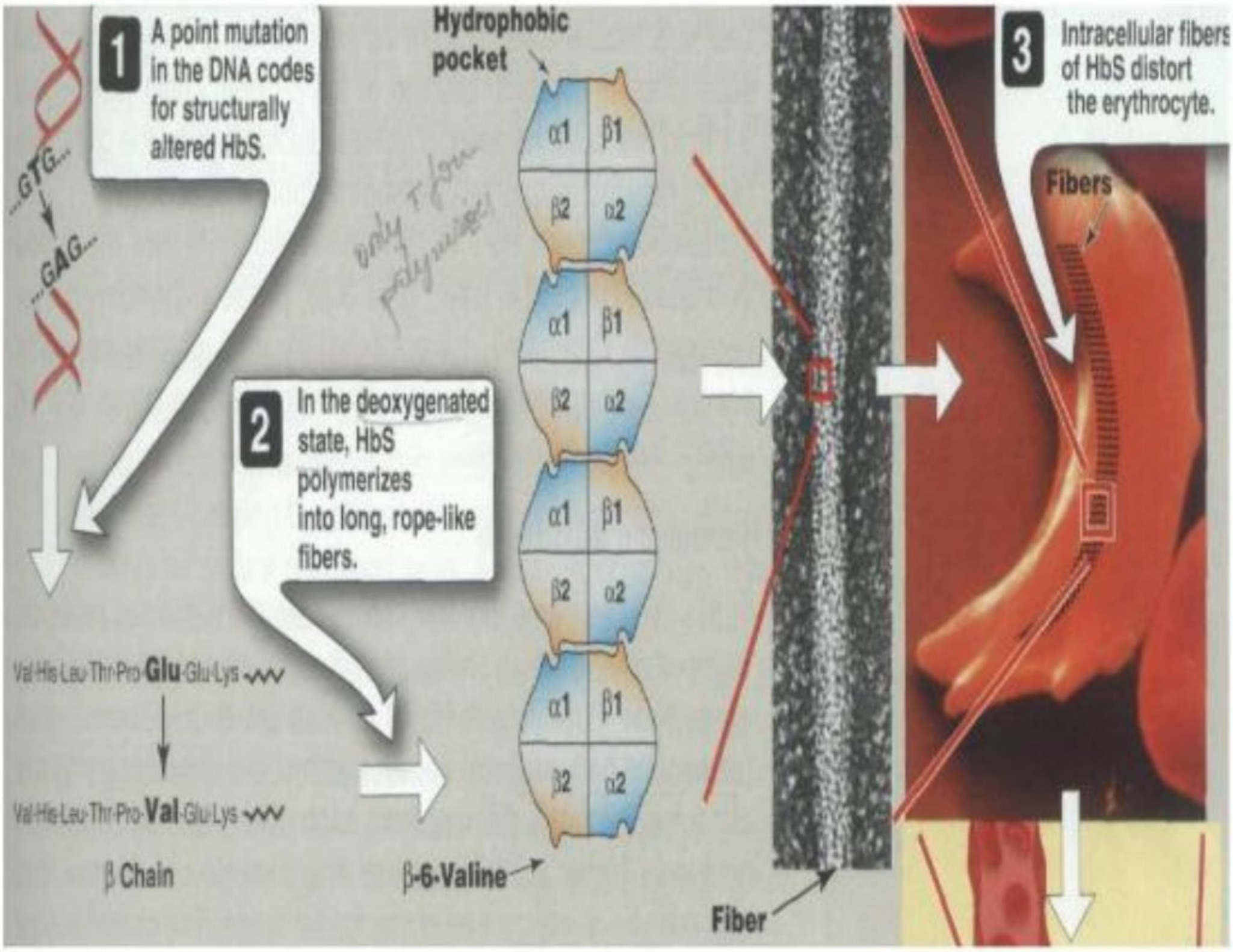
single point mutation in the ß-globin gene, where glutamate (-vely) at position 6 is replaced with valine (neutral).

❖**Cellular Evidence**

- Valine forms a protrusion on the ß-globin that fits on a complementary site on another Hb in the cell.

Deoxyhemoglobin S polymerizes inside the RBCs, that stiffen and distort the cell, producing rigid, misshapen erythrocytes.

- Such sickled cells frequently block the flow of blood in the narrow capillaries.



Hemoglobinopathies (cont.)

❖**Symptoms:**

▪Lifelong episodes of pain: localized anoxia (oxygen deprivation) in the tissue, causes pain and death (infarction) of cells.

▪Chronic hemolytic anemia. The lifetime of an erythrocyte in sickle cell disease is less than 20 days .The tapering sharp ends of the sickled cells rupture each other during flow.

▪Increased susceptibility to infections

▪Acute chest syndrome, Stroke

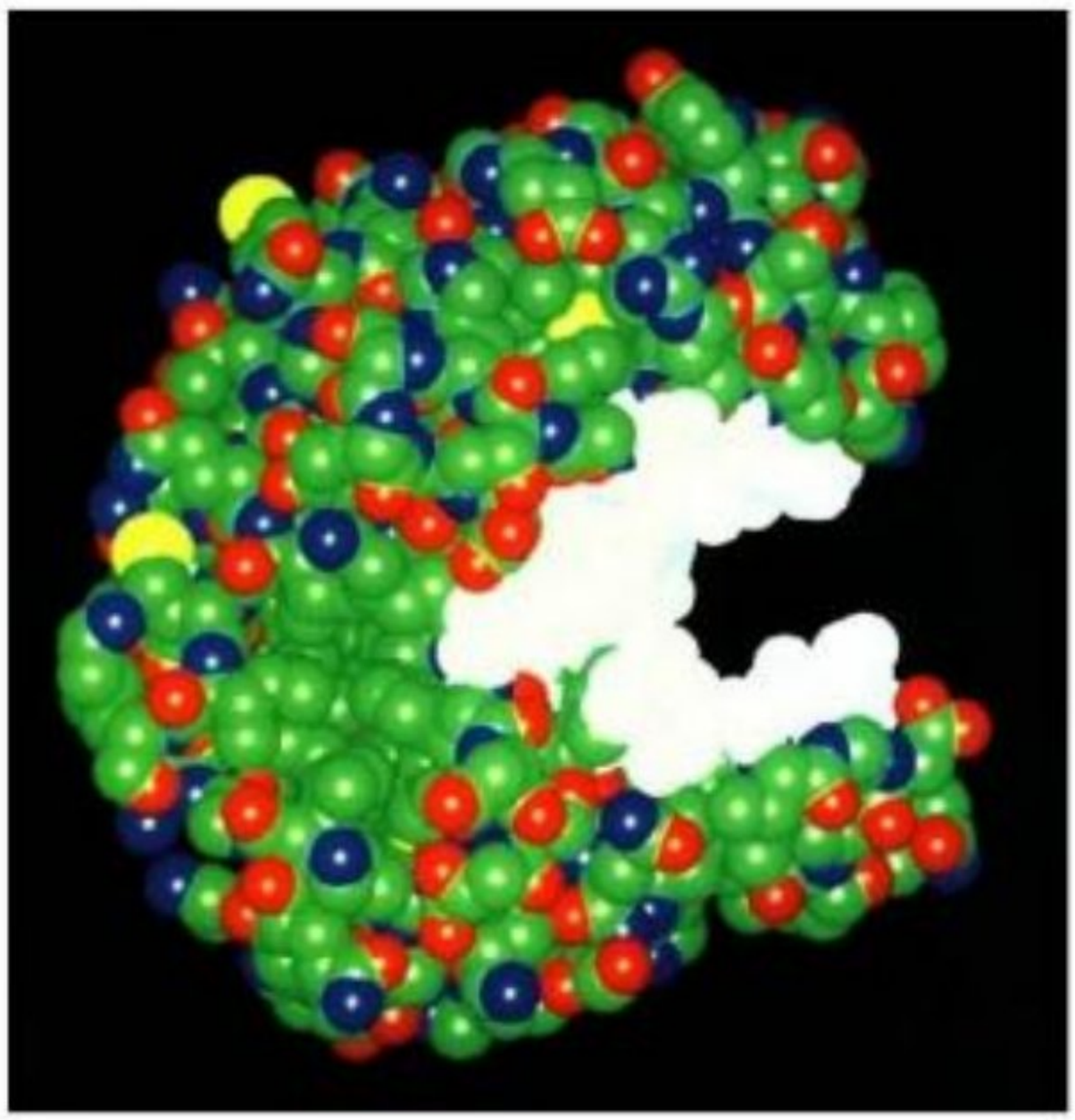
❖**Treatment:** Analgesics & Blood transfusion

Enzymes

What Are Enzymes?

Definition:

They are protein catalysts that increase the rate of a chemical reaction without being changed in the overall process.



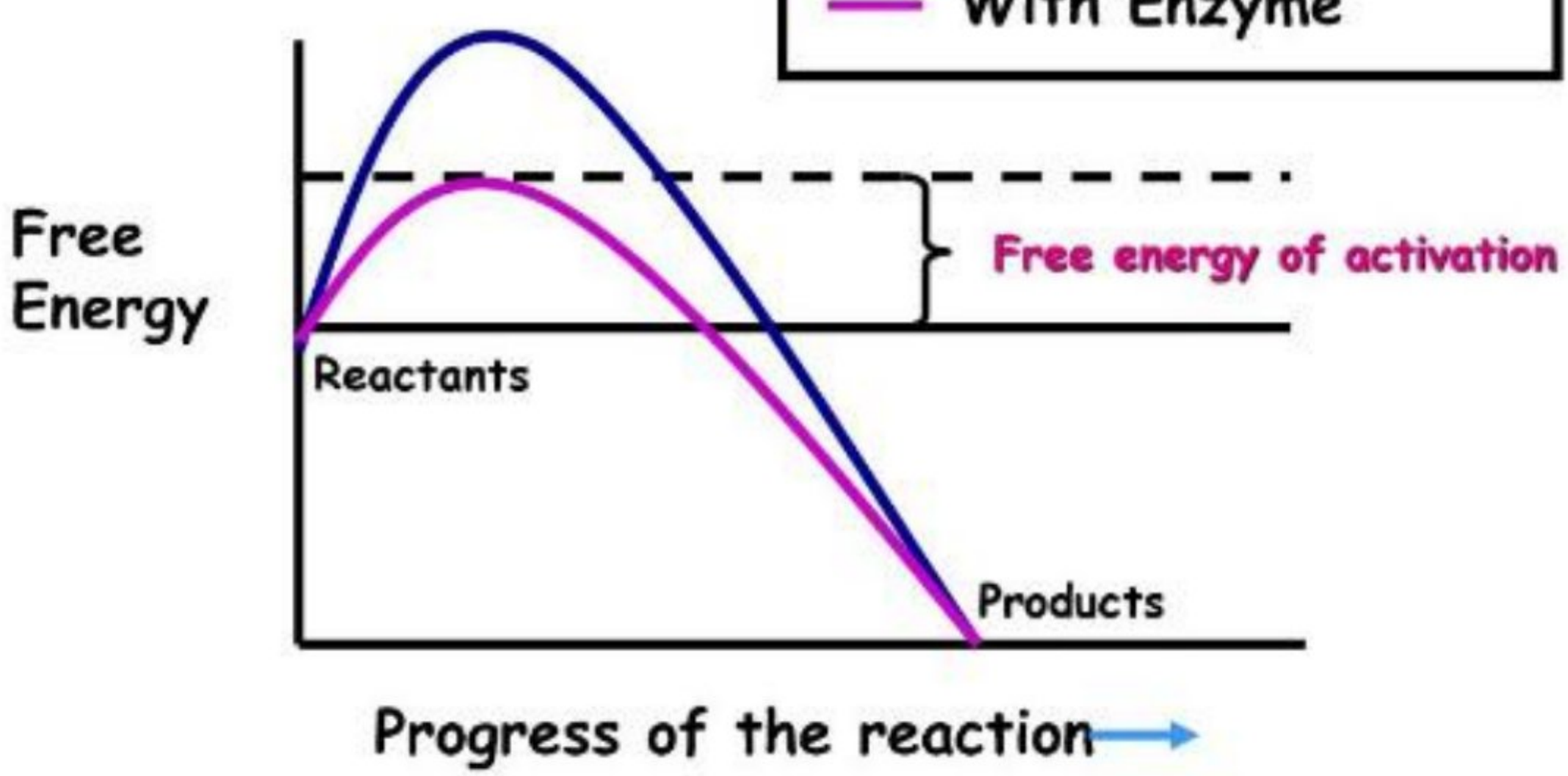
- Most enzymes are Proteins

Classification of Enzymes

1. **Oxidoreductases:** Catalyze oxidation-reduction reactions
2. **Transferases:** Catalyze transfer of C-, N- or P- containing groups.
3. **Hydrolases:** Catalyze cleavage of bonds by addition of water.
4. **Lyases:** Catalyze cleavage of C-C, C-S and certain C-N bonds.
5. **Ligases:** Catalyze joining of two chemical groups
6. **Isomerases:** Catalyze racemization of optical or geometric isomers

How do enzymes Work?

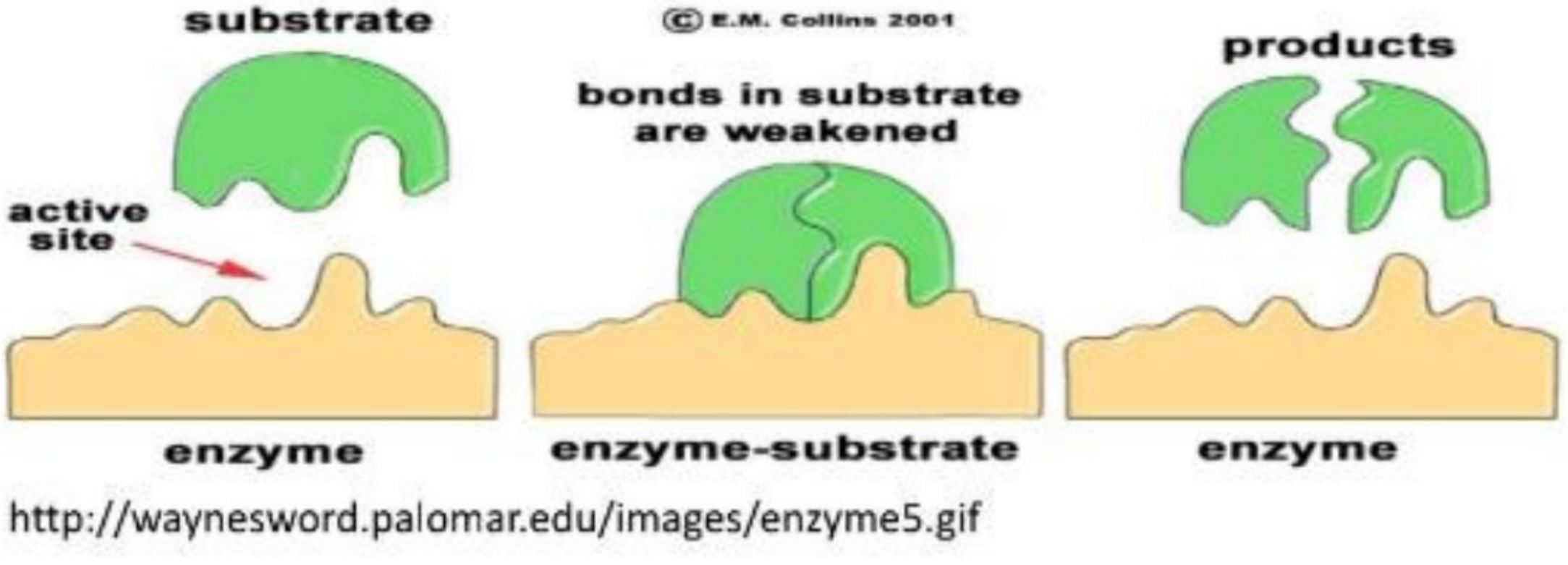
Enzymes work by lowering activation energy



Properties of enzymes

1. **Active site**

- A special pocket or cleft containing amino acid side chains that create a 3-dimensional surface complementary to the substrate.



http://waynesword.palomar.edu/images/enzyme5.gif

Properties of enzymes (cont.)

2. Cofactors and coenzymes

Protein (Apoenzyme) + non-protein = Holoenzyme

➢ **Non protein are:**

❖ **Cofactor: e.g. metal ions as Zn^{2+}, Fe^{2+}.**

❖ **Coenzyme (organic molecule)**

Properties of enzymes (cont.)

3. Catalytic efficiency

Enzyme-catalyzed reactions proceed 10^3 to 10^8 times faster than uncatalyzed ones.

4. Specificity

Enzymes are highly specific, interacting with one or few substrates.

5. Regulation

Enzymes can be: Activated / Inhibited in response to cellular need.

6. Location within the cell

Enzymes are localized in specific organelles within the cell to isolate the reaction substrate or product from other competing reactions.

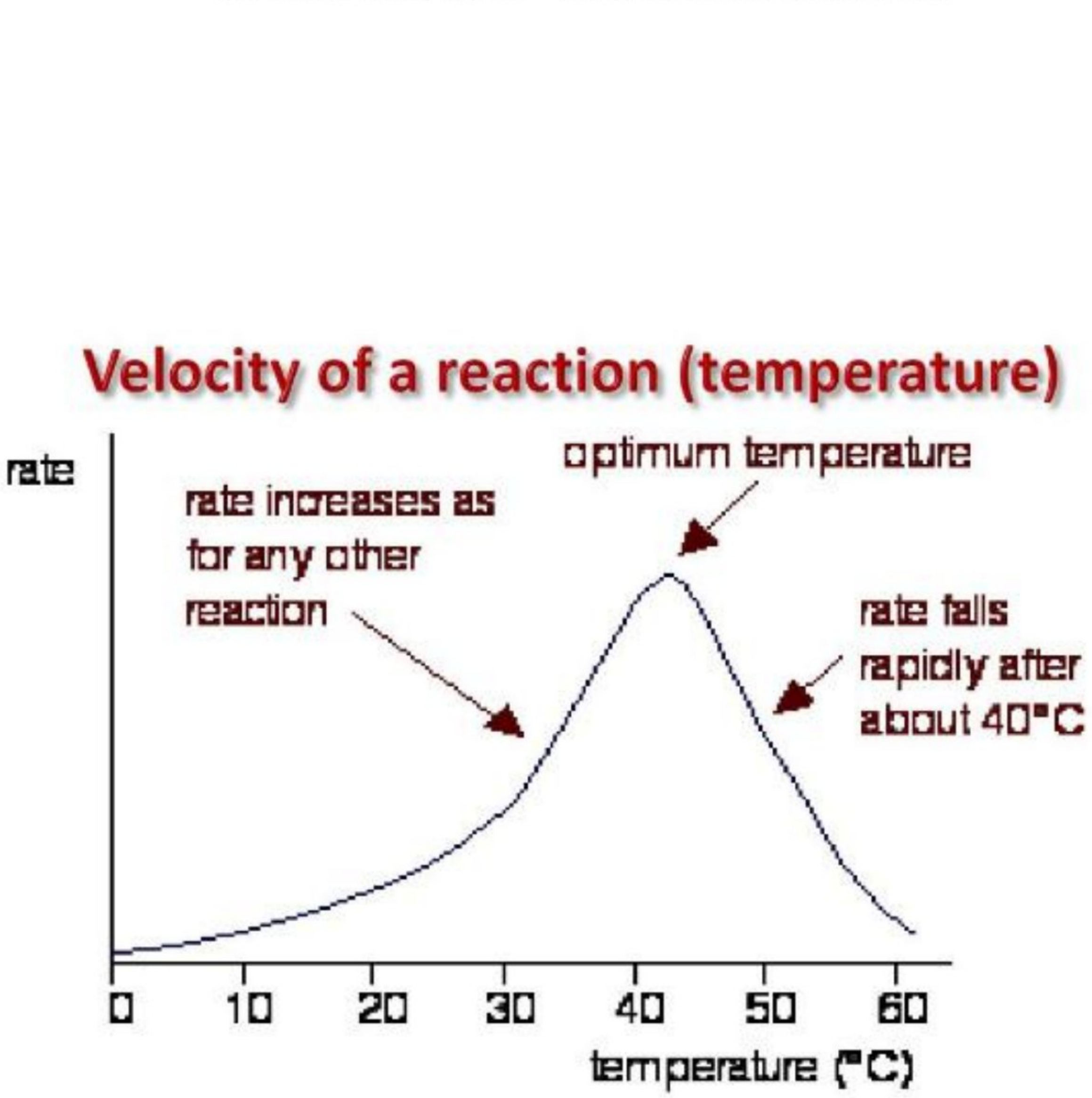
Factors affecting reaction velocity

1-Temperature

2-pH

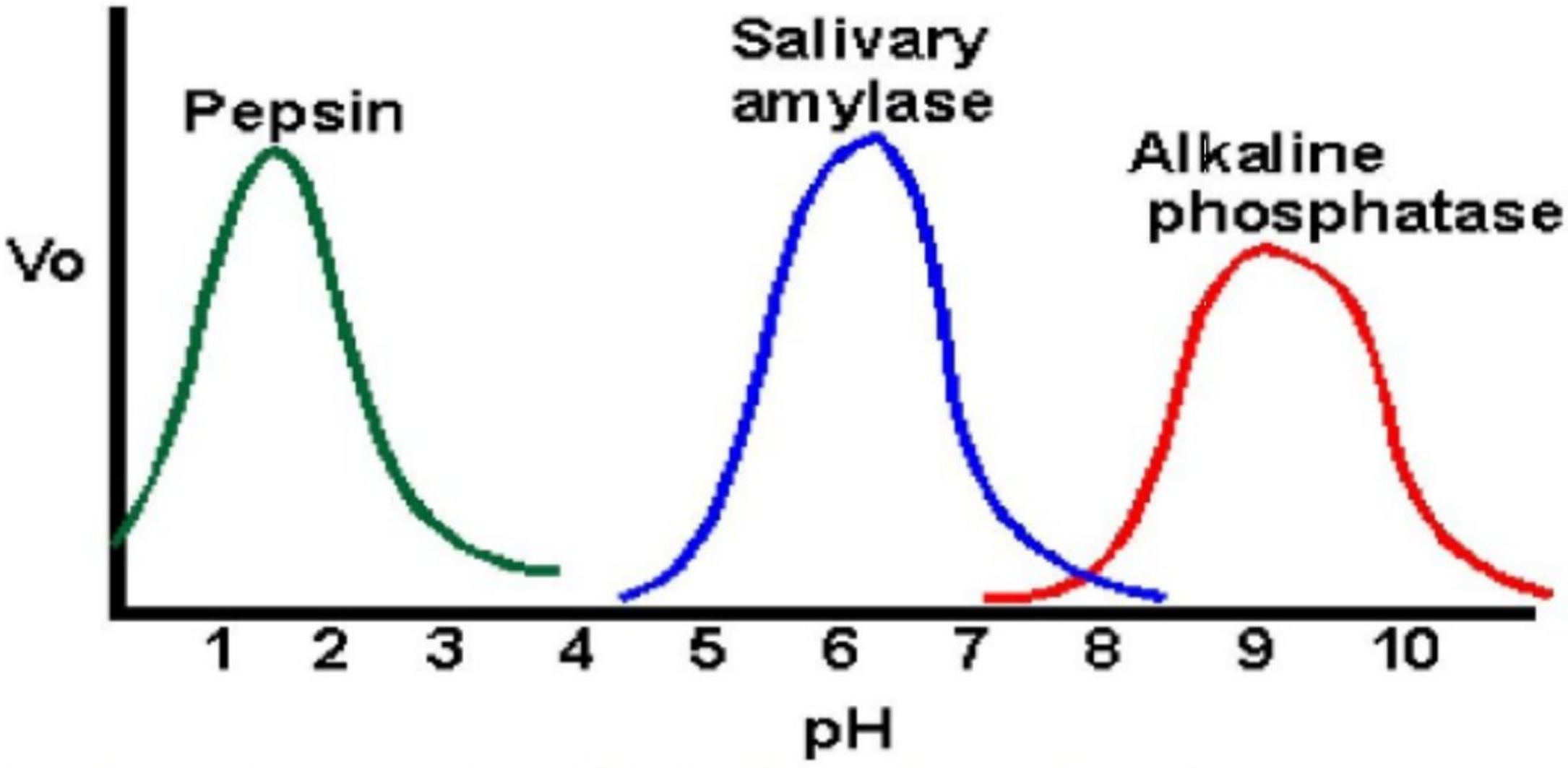
3- Substrate concentrations

Velocity of a reaction (temperature)



Velocity of a reaction (pH)

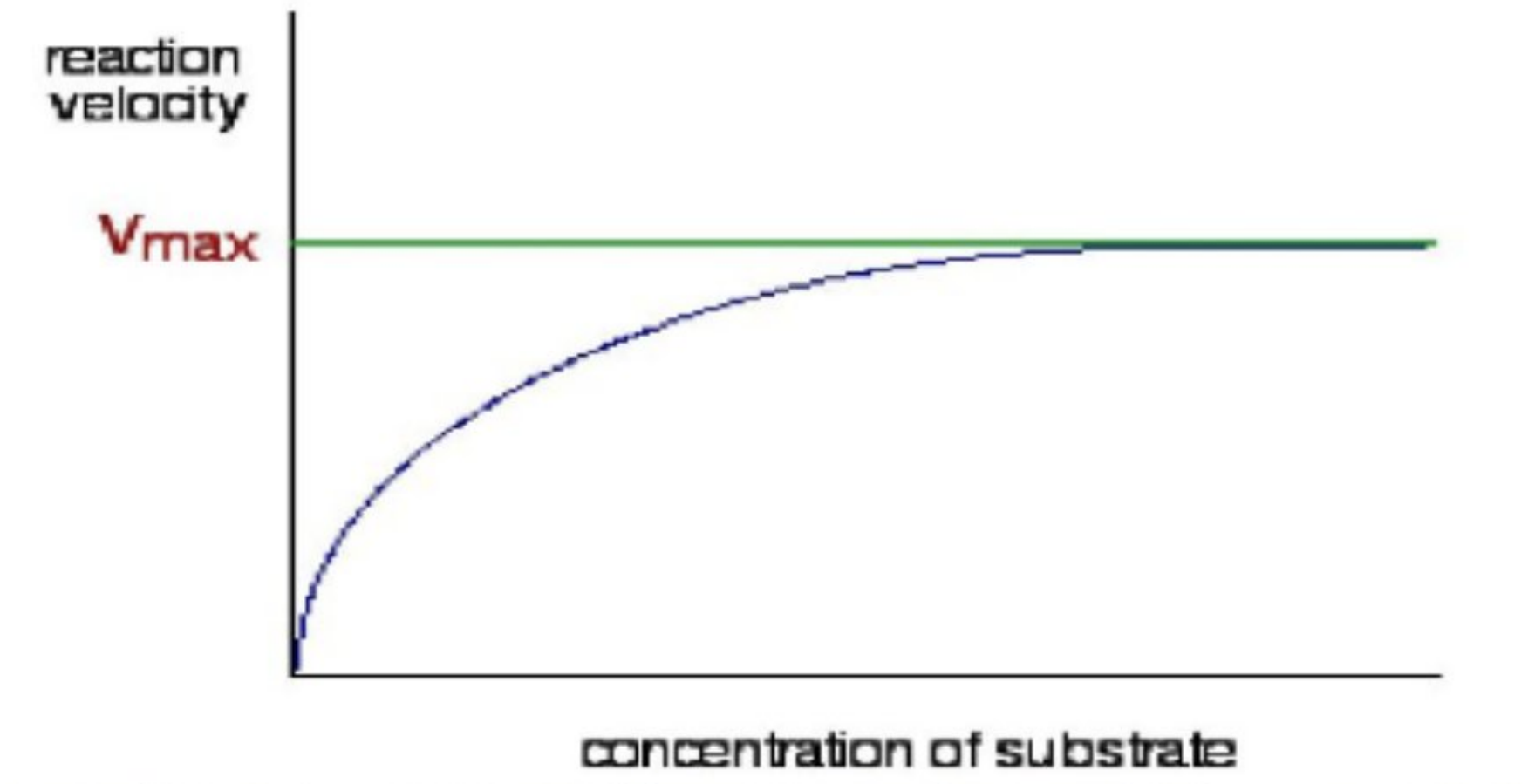
Catalysis needs the enzyme and the substrate chemical groups to be either ionized or non-ionized to interact.



http://www.dentistry.leeds.ac.uk/biochem/lecture/enzymes/fig6.gif

Velocity of a reaction (Substrate conc)

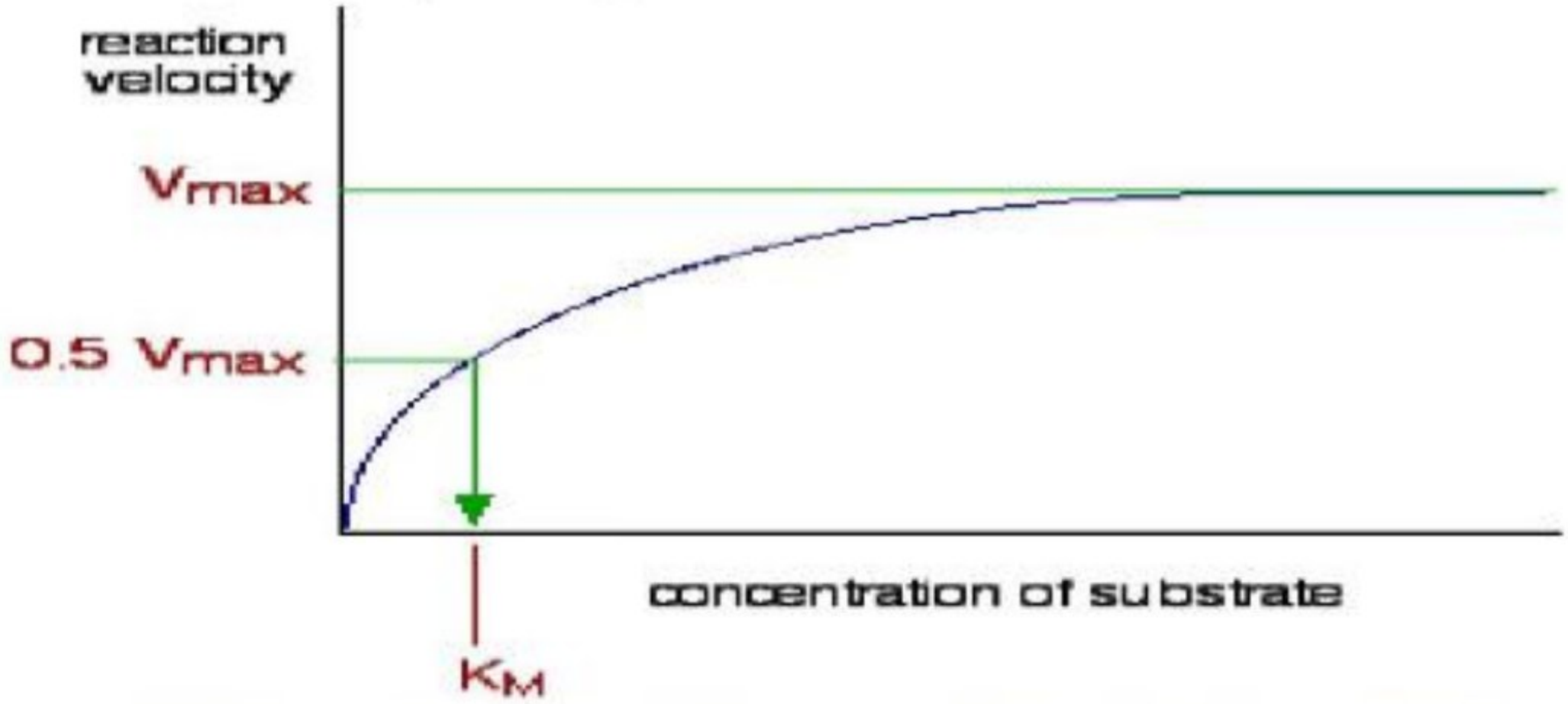
- The maximum rate for a particular enzyme reaction is known as V_{max}.
- Most enzymes show a **hyperbolic shape** of kinetics curve. In contrast, allosteric enzymes frequently show a sigmoidal curve.



http://www.chemguide.co.uk/organicprops/aminoacids/enzymeratet.gif

Velocity of a reaction (cont.)

- **Michaelis constant K_m** is characteristic of an enzyme and its particular substrate.
- **K_m** is numerically equal to the substrate concentration at which the reaction velocity **is equal to half V_{max}**.
- It reflects affinity of enzyme for its substrate



http://www.chemguide.co.uk/organicprops/aminoacids/enzymeratet.gif

Lineweaver – Burk plot

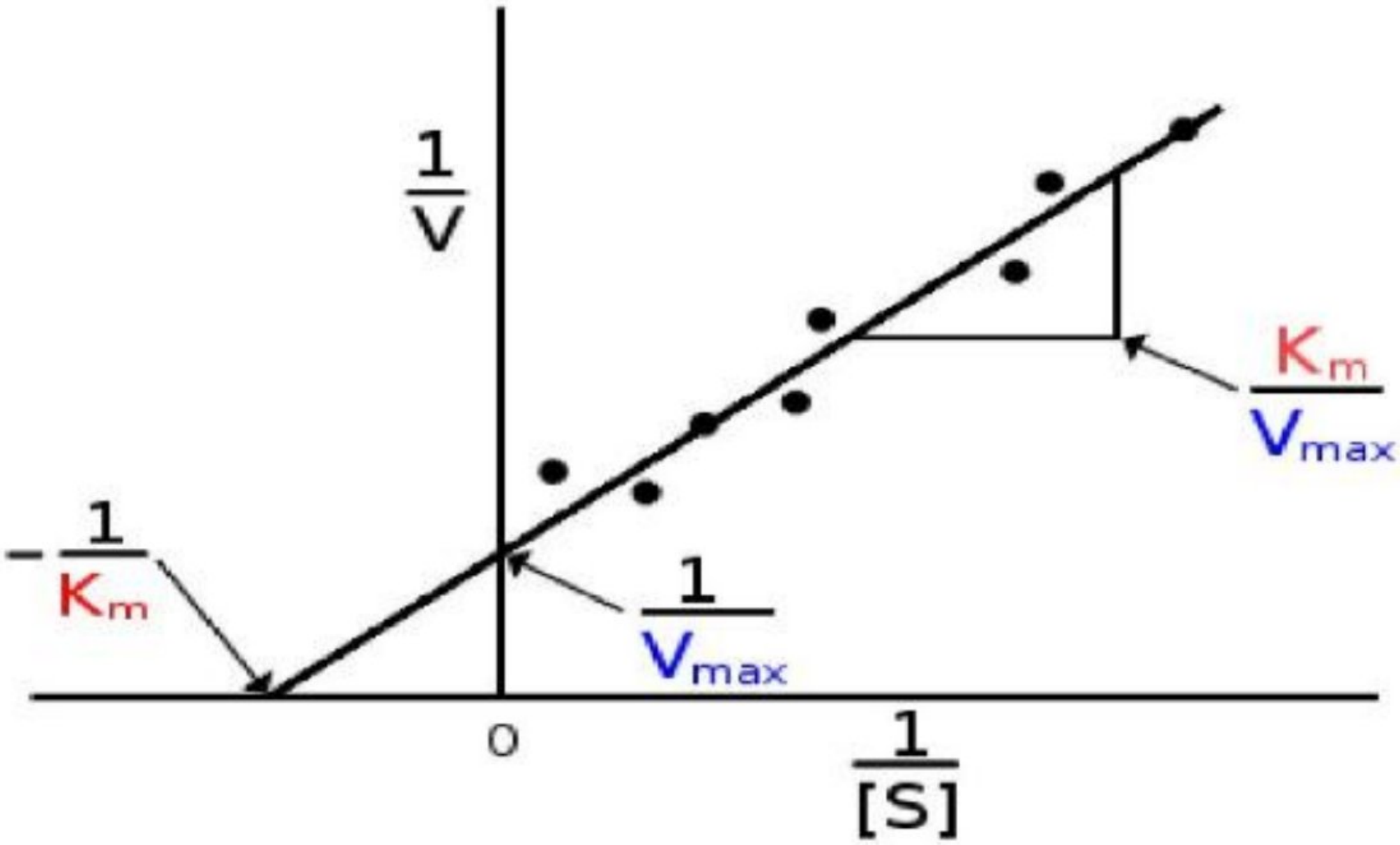
- When V_0 is plotted against **[S]**, it is not always possible to determine when **V_{max}** has been achieved, because of the gradual upward slope of the hyperbolic curve at high substrate concentrations.

- If $1 / V_0$ is plotted versus $1 / [S]$, a straight line is obtained.

- The Lineweaver – Burk plot **(also called a double-reciprocal plot)** can be used to:

  - Calculate K_m and $V_{max.}$
  - Determine the mechanism of action of enzyme inhibitors.

Lineweaver – Burk plot



http://upload.wikimedia.org/commons/thumb/7/70/Lineweaver-Burke_plot.svg/350px

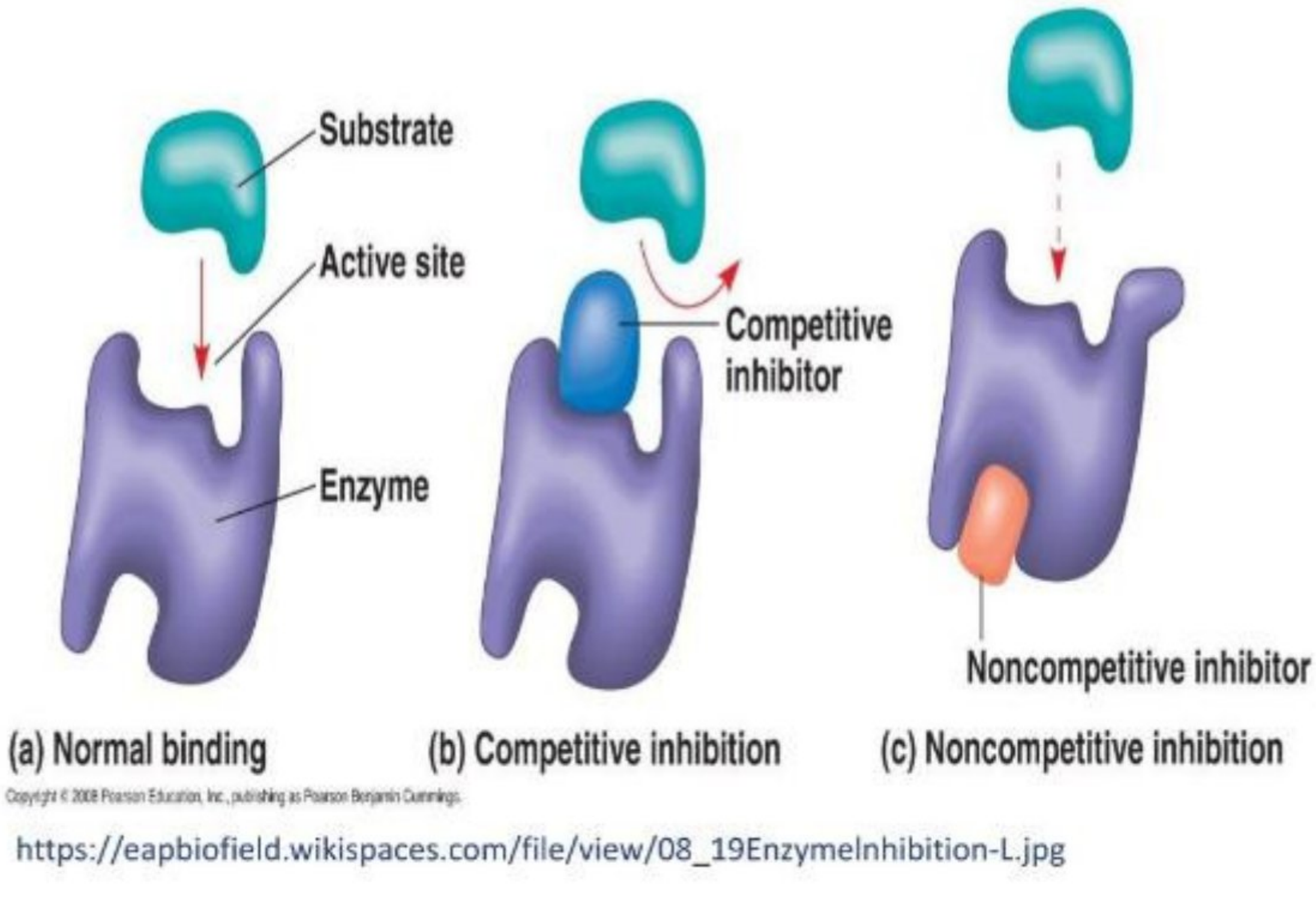
Inhibition of enzyme activity

Any enzyme that can diminish the velocity of an enzyme- catalyzed reaction is called an inhibitor.

- There are 2 types of inhibitors:

  - **Irreversible inhibitors:** lead & ferrochelatase
  - **Reversible inhibitors**: competitive & uncompetitive

Inhibition of enzyme activity



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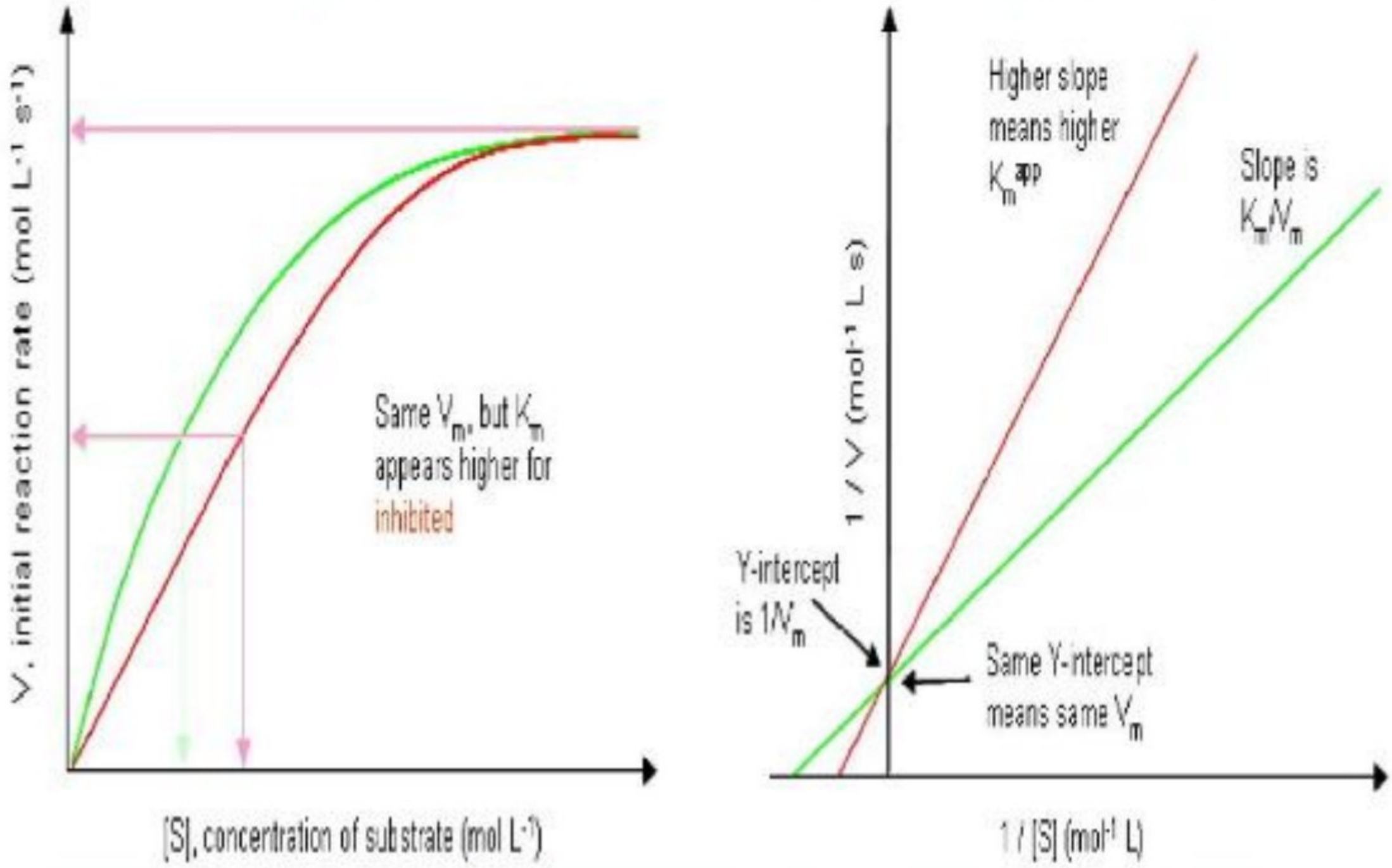
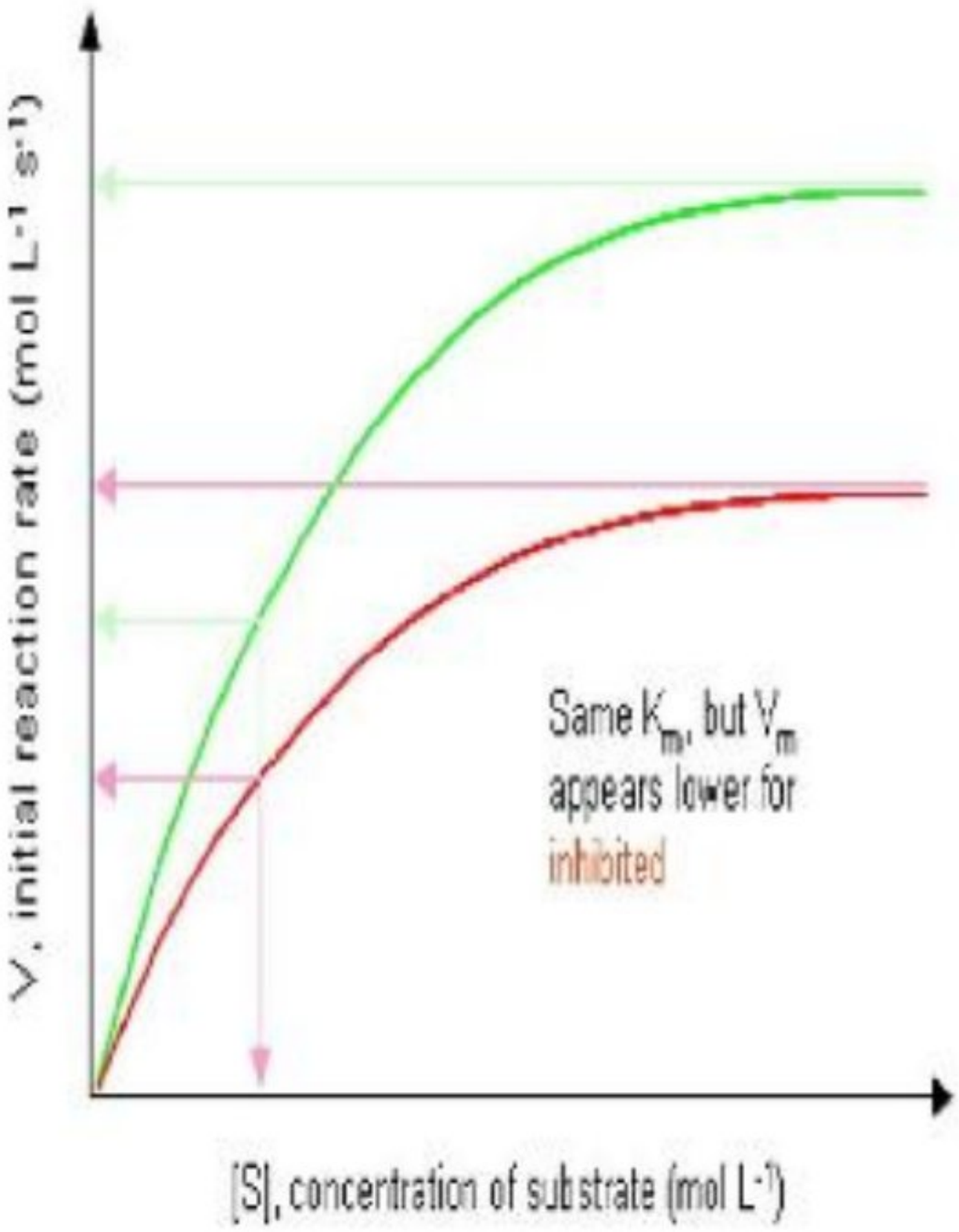
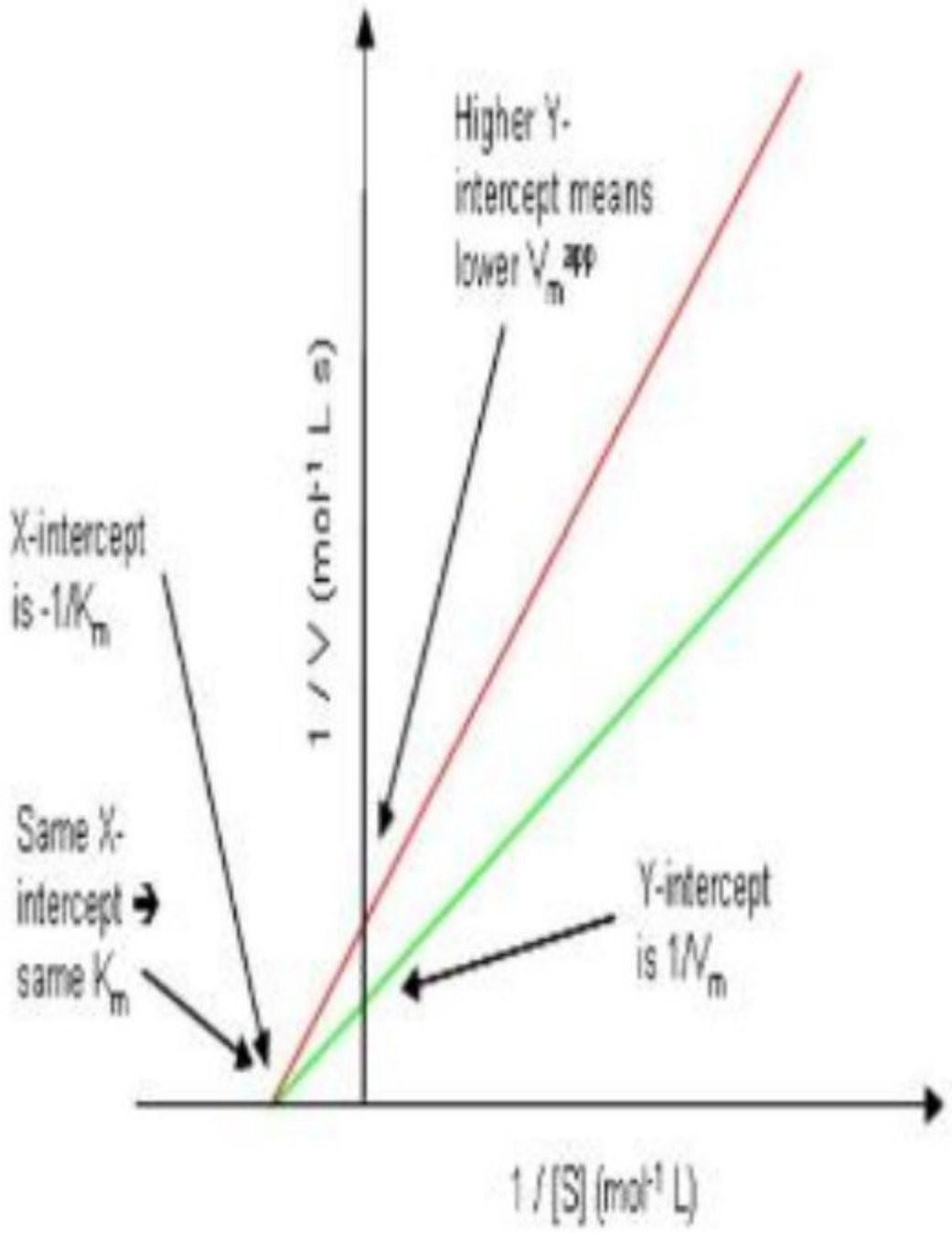
Competitive Inhibition (cont.)



http://www.steve.gb.com/images/science/competitive_inhibition_lineweaver_burk.png

Noncompetitive Inhibition (cont.)





http://www.steve.gb.com/images/science/competitive_inhibition_lineweaver_burk.png

Examples of Enzyme Inhibitors Used As Drugs

Used in treatment of	*Type of Inhibition*	*Target enzyme*	*Drug used as enzyme inhibitor*
Gout	Competitive	Xanthine oxidase	Allopurinol e.g. Zyloric , Nouric
Cancer chemotherapy	Competitive	Dihydrofolate reductase	Methotrexate
Anticoagulant	Competitive	Vitamin K carboxylase	Dicumarol
Bacterial chemotherapy	Competitive	Enzymes of bacterial Folic acid synthesis	Sulfanilamide
Antibiotics	Non-Competitive	Enzymes of bacterial cell wall synthesis	Lactam antibiotics .e.g. Amoxicillin and penicillin
Anti-hypertensive	Non-Competitive	Angiotensin converting enzyme (ACE)	ACE-Inhibitors e.g. Captopril

Regulation of enzyme activity

A. **Short term regulation**

1. Allosteric regulation
2. Covalent modification (phosphorylation/dephosphorylation)

B. **Long term regulation**

1. Induction and repression

Regulation of enzyme activity (cont.)

1. Allosteric binding site:

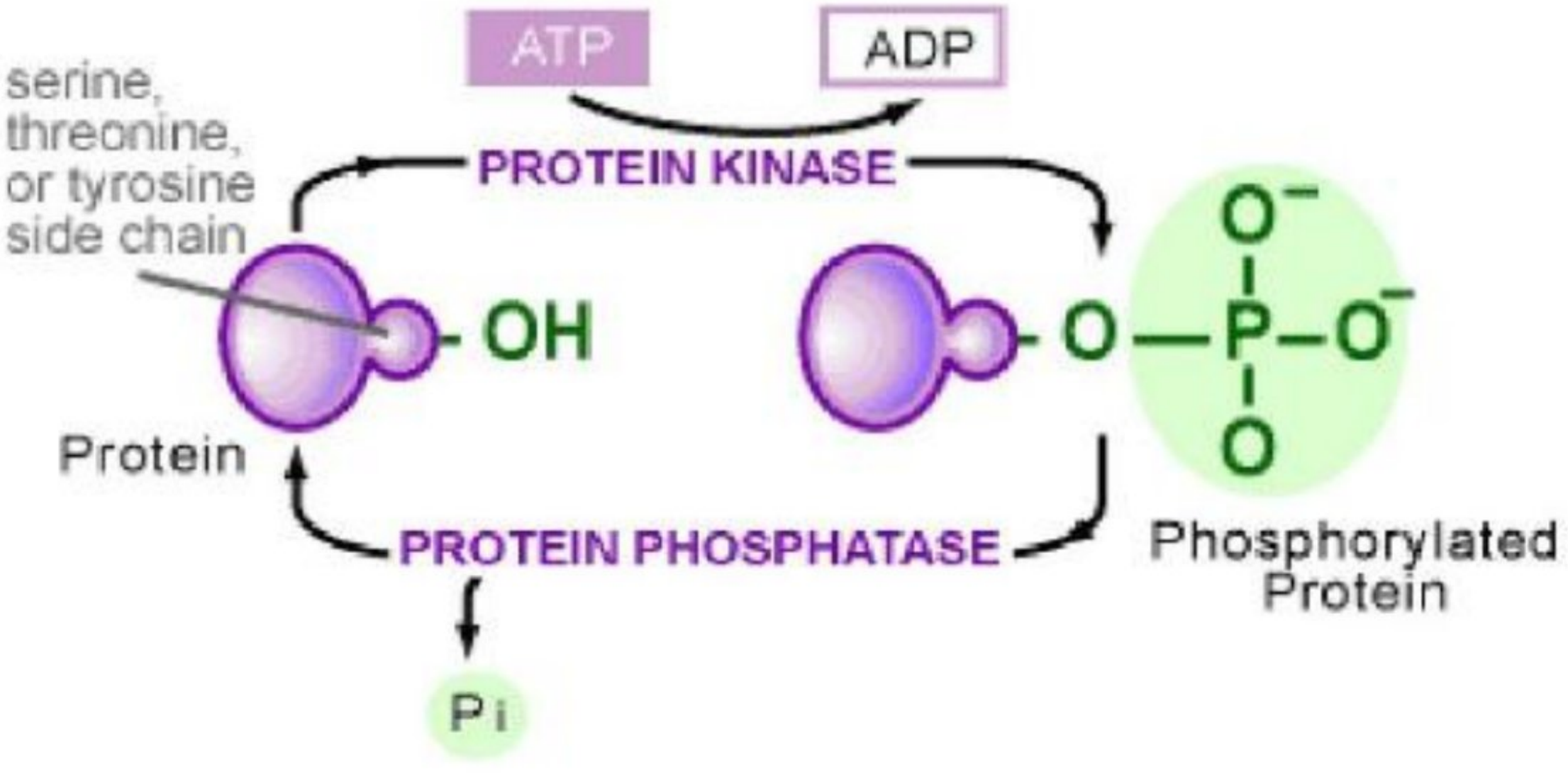
- **An allosteric effector can:**
  - ❖ Modify maximal catalytic activity of the enzyme
  - ❖ Alter the affinity of the enzyme for its substrate
  - ❖ Both

- **Types of effectors**
  - ❖ **Positive effectors:** increase enzyme activity.
  - ❖ **Negative effectors:** inhibit enzyme activity.

Regulation of enzyme activity (cont.)

2. Covalent modification

- Addition or removal of phosphate groups from specific serine, threonine, or tyrosine residues of the enzyme.



Regulation of enzyme activity (cont.)

B- Long term:

Induction and repression

- Regulation of the amount of enzyme present by altering the rate of enzyme synthesis (alter total population of active sites).

- Alterations in enzyme levels are slow (hours to days).

- For example, elevated levels of insulin as a result of high blood glucose levels cause an increase in the synthesis of key enzymes involved in glucose metabolism.

Lipid Chemistry

Biological importance of lipids

- Components of biological membranes.
- Energy reserves
- Serve as vitamins and hormones.
- Lipophilic bile acids aid in lipid solubilization.
- Used for the synthesis of prostaglandins, leukotrienes

CLASSIFICATION OF LIPIDS

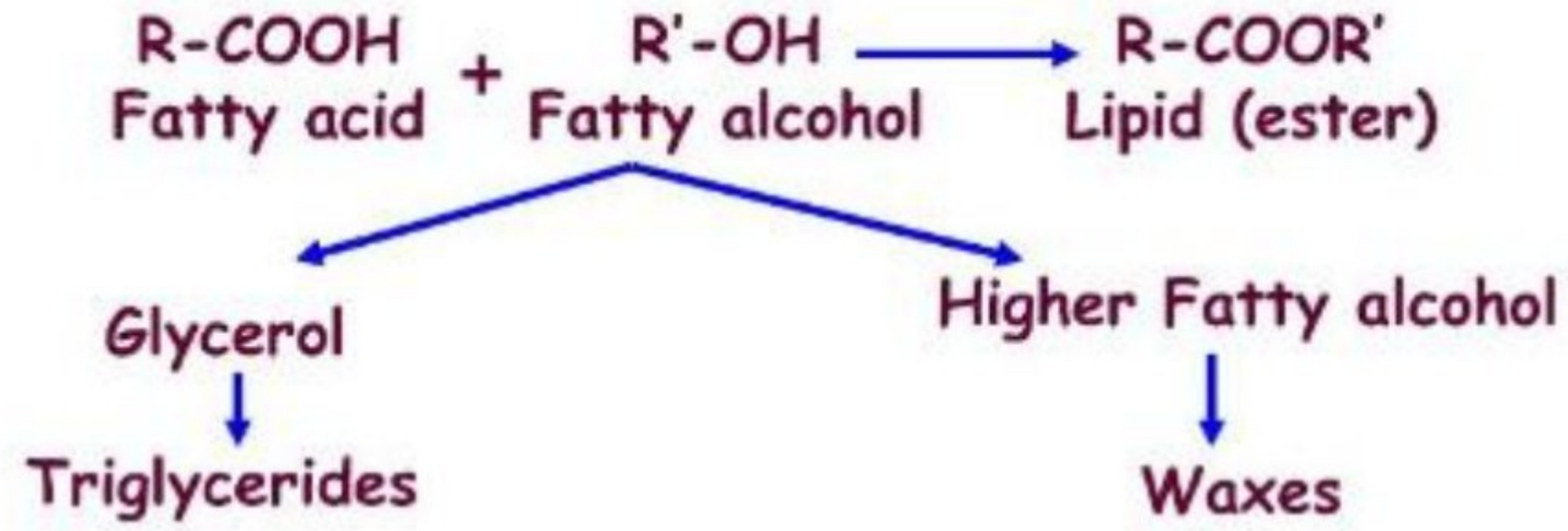
I-Simple Lipids

II-Compound Lipids

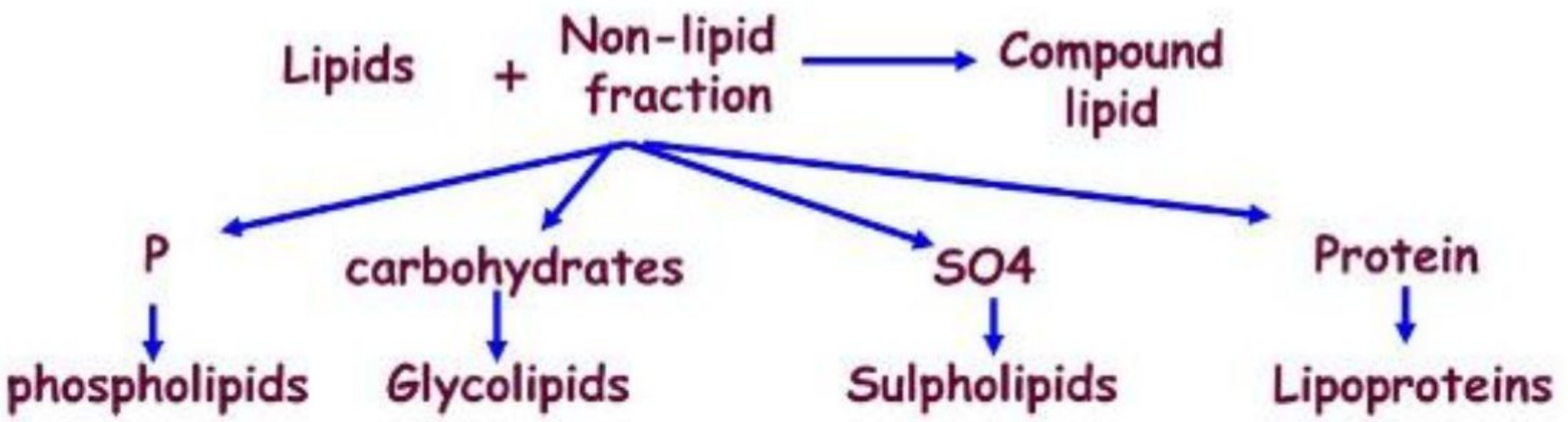
III-Derived Lipids

I) Simple lipids

These are esters of fatty acids + alcohol



II) Compound lipids



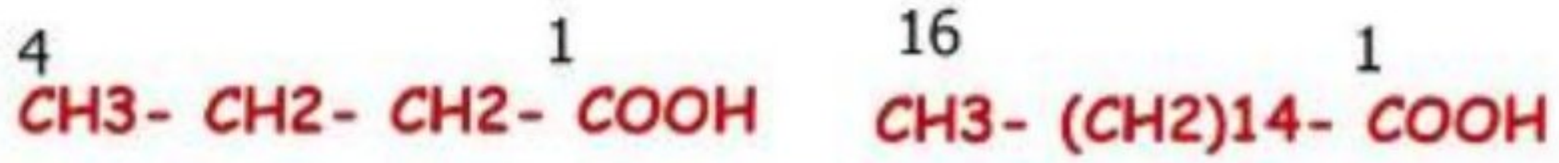
III) Derived Lipids:

These are substances produced from simple and compound lipids by hydrolysis or digestion.

a- Fatty acids b- Alcohols.

Fatty acids

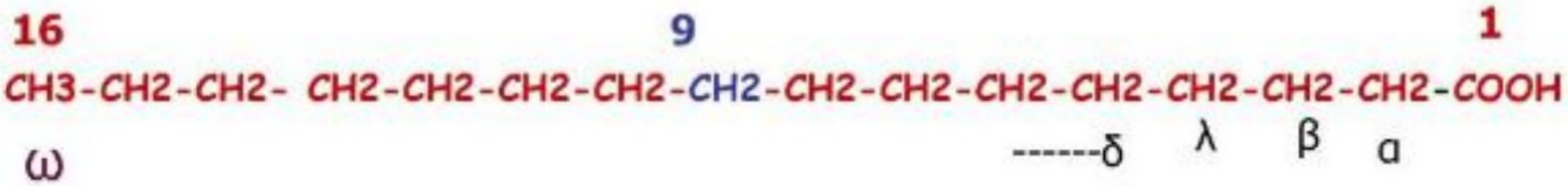
Fatty acids are long-chain hydrocarbon molecules containing a carboxylic acid moiety at one end.



Almost all fatty acids present in mammalian tissues are straight chain.

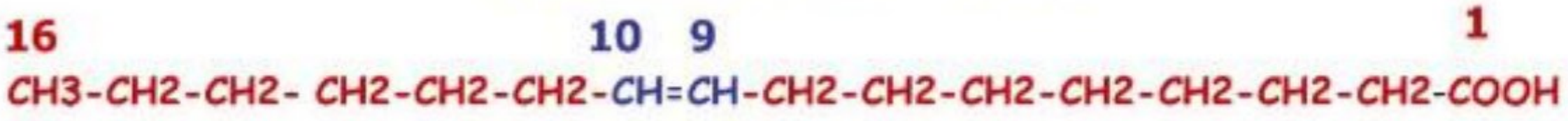
Nomenclature of fatty acids:

It comes from the number of carbon atoms, followed by the number of sites of unsaturation



16C: Palmitic acid

No double bonds 16:0



16C: Palmitoleic acid

1 double bond $16:1^{\Delta 9}$

$18:3^{\Delta 9,12,15}$ w3,6,9

Physiologically Relevant Saturated FA

- Saturated fatty acids *(nonessential fatty acids)*

1-Short chain

▪ 2: 0	Acetic	CH3-COOH
▪ 3: 0	Propionic	CH3-CH2-COOH
▪ 4: 0	Butyric	CH3-CH2-CH2-COOH
▪ 5: 0	Valeric	CH3-(CH2)3- COOH
▪ 6: 0	Caproic	CH3-(CH2)4- COOH
▪ 8: 0	Caprylic	CH3-(CH2)6- COOH

2-Long chain

▪ 14: 0	Myristic	CH3-(CH2)12- COOH
▪ 16: 0	Palmitic	CH3-(CH2)14- COOH
▪ 18: 0	Stearic	CH3 - (CH2)16- COOH

Unsaturated FAs (Essential FA)

- Essential fatty acids include those which contain more than one double bond (polyunsaturated fatty acids) e.g. lenoleic, lenolenic and arachidonic acids.

- This is because there are no human enzyme systems that can introduce a double bond except between the ninth carbon and COOH carbon (not beyond C9)

- N.B: monounsaturated FA are nonessential

Physiologically Relevant Unsaturated FA

MonoUnsaturated Fatty Acids (Nonessential fatty acids)

Sat FA	Unsat FA
Palmitic (16:0)	Palmitoleic ($16:1^{\Delta 9}$)
Stearic (18:0)	Oleic ($18:1^{\Delta 9}$)
	Linoleic ($18:2^{\Delta 9,12}$)
	Linolenic ($18:3^{\Delta 9,12,15}$)
	Arachidonic ($20:4^{\Delta 5,8,11,14}$)

Derivatives of fatty acids

Eicosanoids:

- These compounds derived from (20) carbons (polyunsaturated) fatty acids e.g. arachidonic

- They comprise:

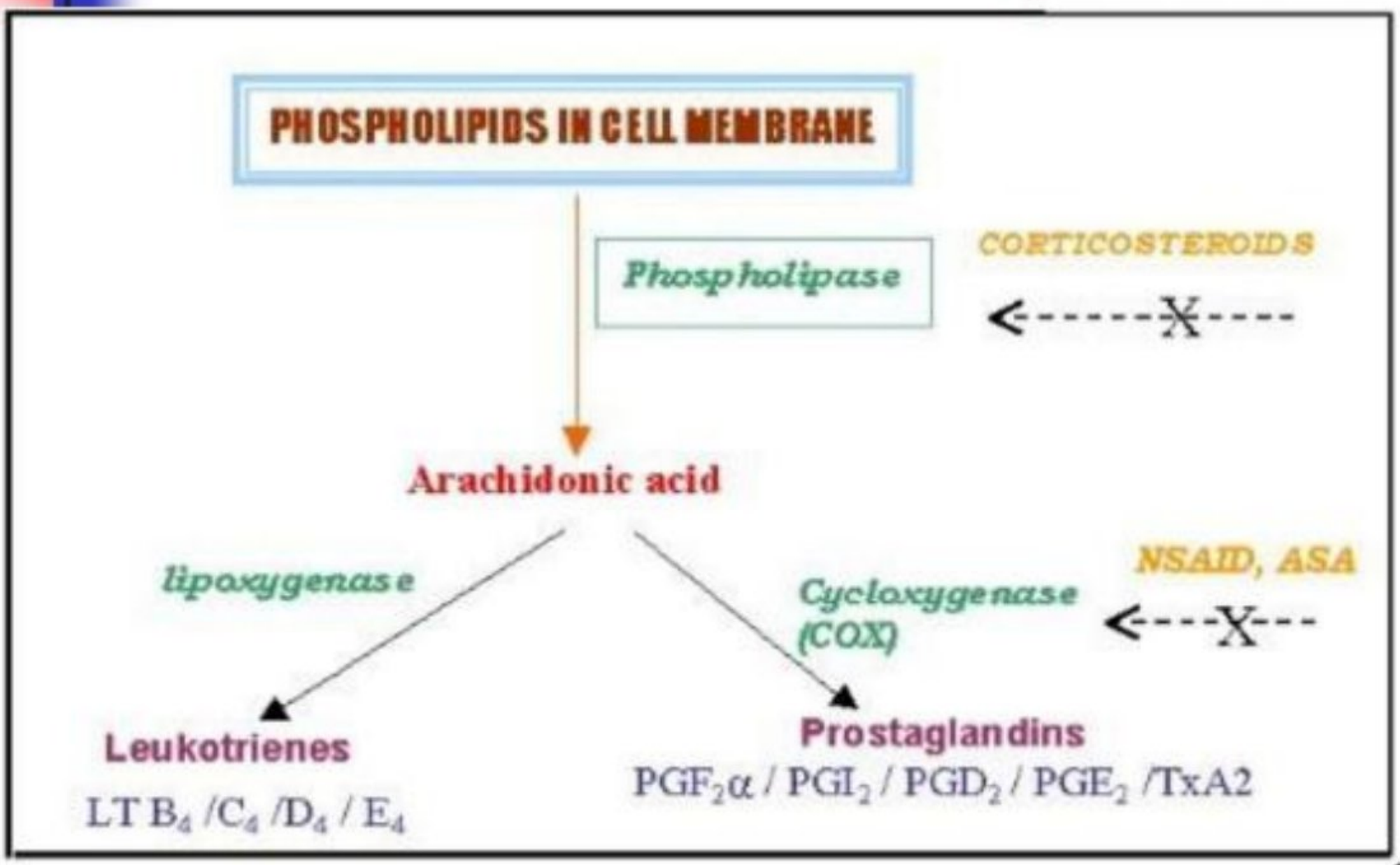
A) Prostanoids include prostaglandins (PGs), prostacyclins (PGI) and thromboxanes (TX)

B) Leukotrienes

Biosynthesis of Prostaglandins

- PGs are produced and released by nearly <u>all mammalian cells</u> and tissues except RBc's
- PGs have a very <u>short half-life</u>. Soon after release, they are rapidly taken up by cells and <u>inactivated</u> in the liver and lungs.
- The immediate precursor of PG is arachidonic acid (20 : 4) which is derived from: Phospholipids present in cell membrane by the action of phospholipase A2.

Inhibition of PG Biosynthesis:



Physiological effects of Prostaglandins

[1] Inflammation: natural mediators of inflammation.

[2] Gastric secretion and peptic ulcer:

- PGs inhibit gastric acid secretion in patients with peptic ulcers.

[3] Decrease blood pressure:

- PGs decrease blood pressure due to vasodilatation.

[4] Platelet aggregation and thrombosis:

- Prostacyclin inhibits platelet aggregation.
- PGE2 and thromboxane A2 (TXA2) stimulate platelet aggregation.

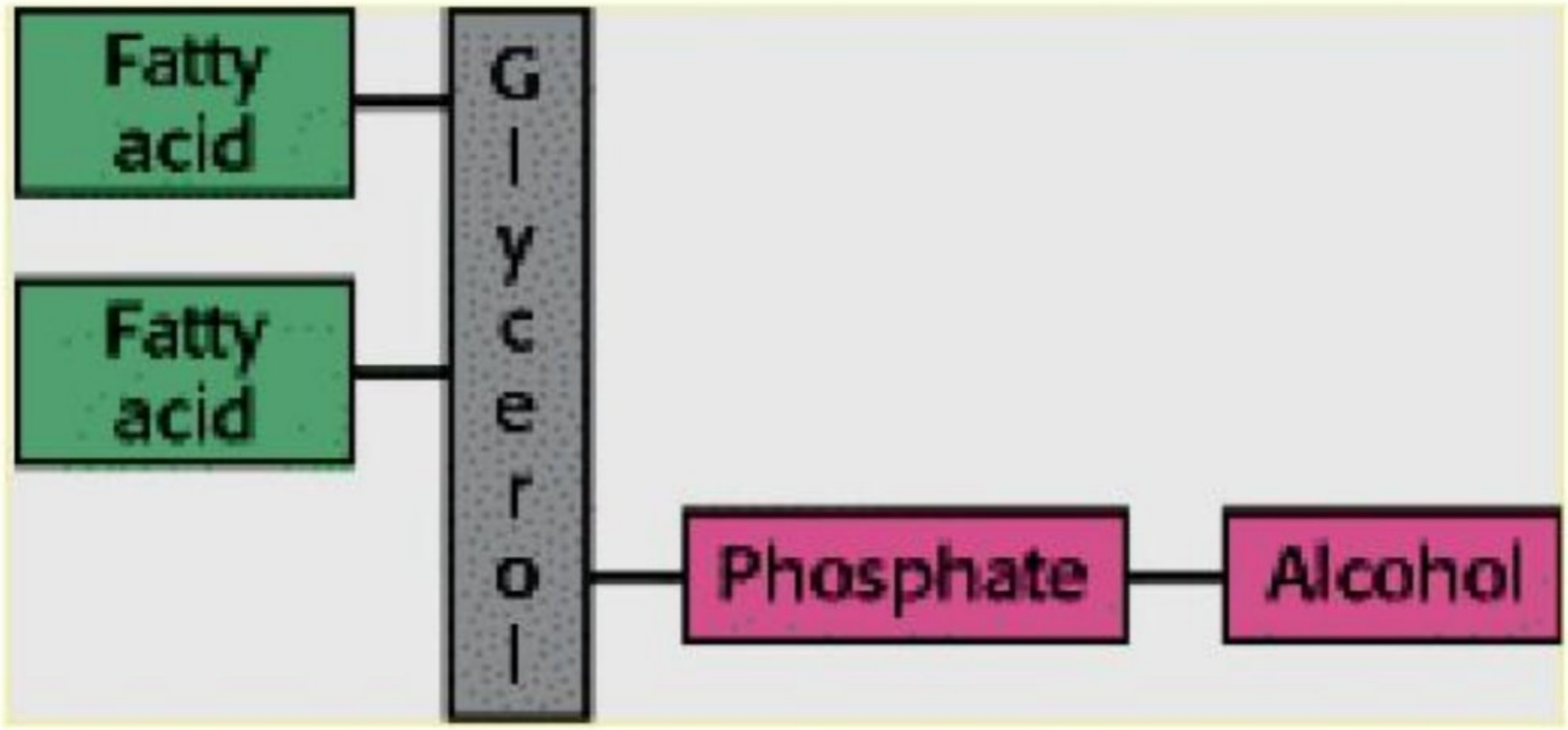
[5] Leukotrienes are mainly involved in allergic reactions

II- COMPOUND LIPIDS

- These consist of a lipid part and prosthetic group. They include:-
- A) Phospholipids
- B) Glycolipids
- C) Lipoproteins
- D) Slufolipids

A-Phospholipids

- abundant in cell membranes have glycerol or sphingosine backbone



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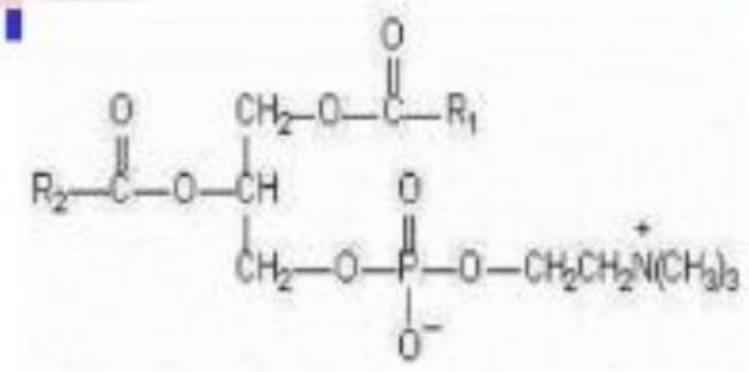
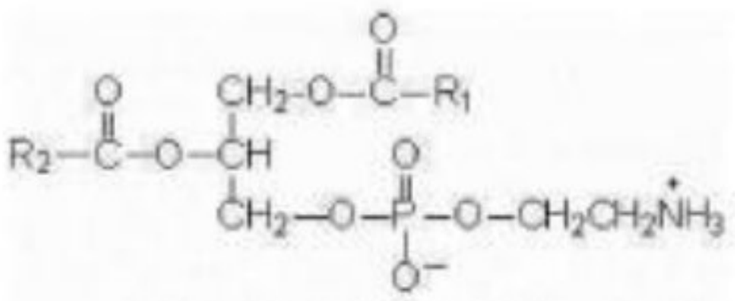
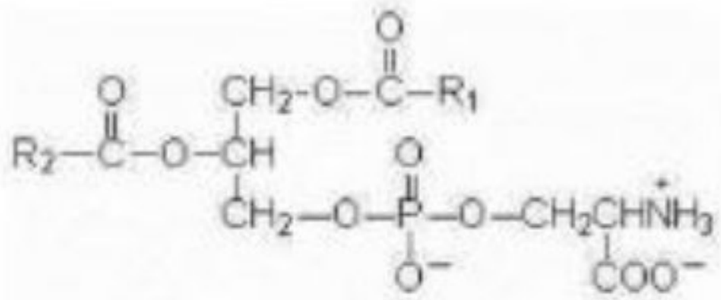
Lecithin (Phosphatidylcholine)



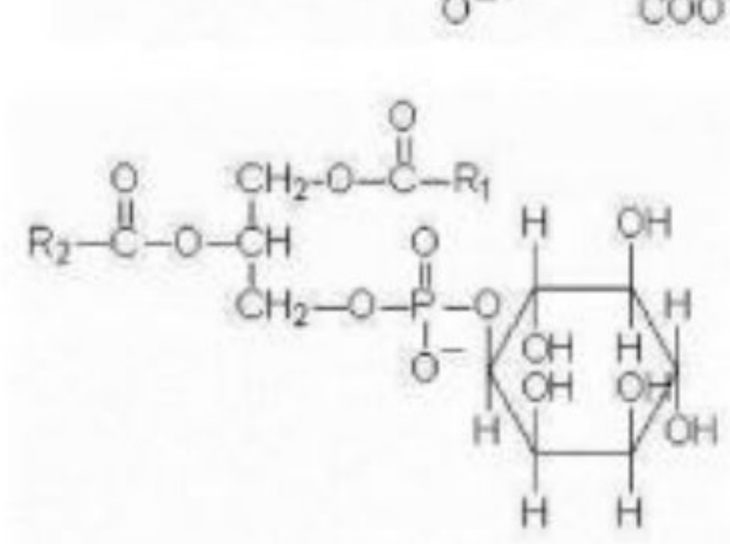
phosphatidylcholine



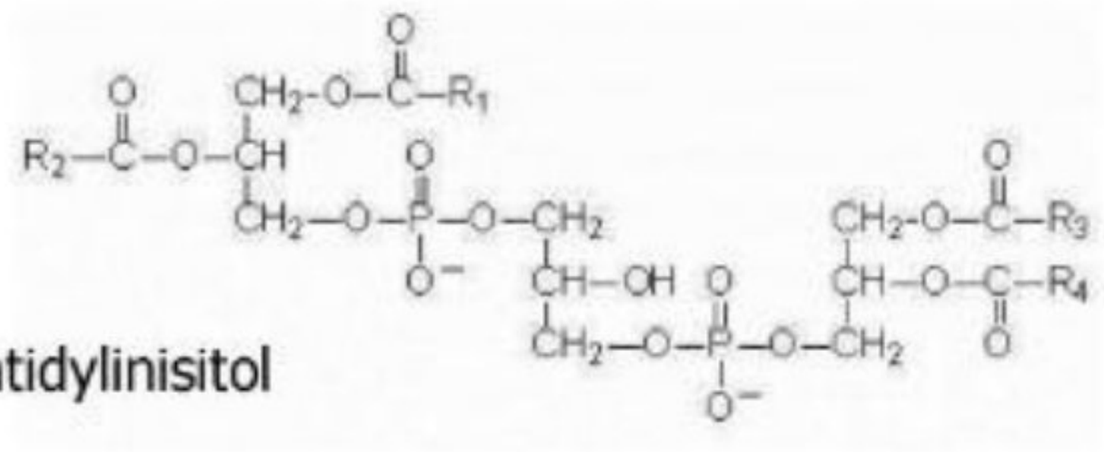
phosphatidylethanolamine



phosphatidylserine



phosphatidylinisitol



Cardiolipin

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B- Glycolipids

- These are complex lipids containing carbohydrates.
- Glycolipids include:

A-Cerebrosides: brain

B-Gangliosides: brain

C-Lipoproteins

- They are composed of *lipids and proteins.*
- They serve for the transport of lipids in blood. & have a role in lipid metabolism.

Lipoproteins types

1-Chylomicrons

2- VLDL (pre-B-lipoprotein)

3- LDL (B-lipoprotein)

4-HDL (alpha-lipoprotein)

Steroids and sterols

a-Cholesterol

b-Vitamin D.

c-Bile salts.

d-Steroid hormones:

(1) Testosterone

(2) Estrogen and progestrone

(3) Cortisol.

Cholesterol

- - It founds in the blood in 2 forms:
- (1) Free form.
- (2) Esterified (combined to fatty acids to form ester).

Functions

a-It enters in the structure of every body cell.

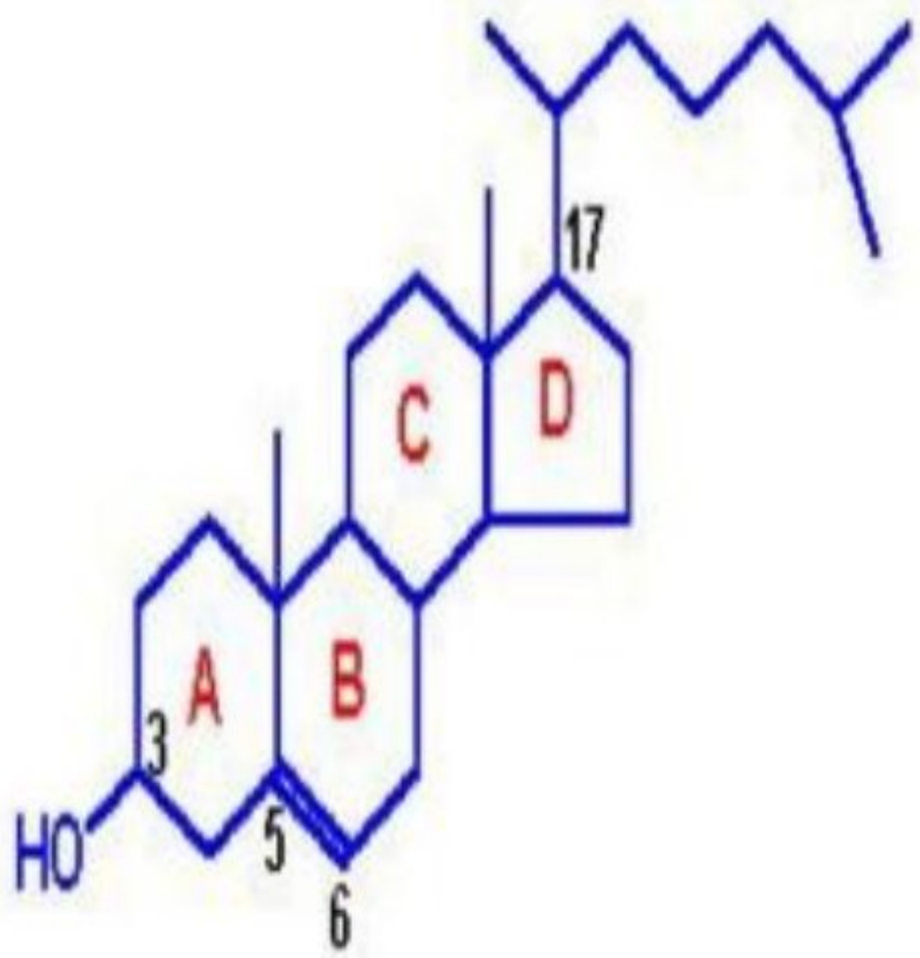
b-It is the precursor of all steroid hormones.

c-It is the precursor of bile salts.

Structure

It contains

- -OH group at C3 (site of estrification).



Metabolism

The biochemical reactions that happen inside the body.

Metabolism divided into to process

1- Catabolim

2- Anabolism

Catabolism

The biochemical processes of metabolism by which large molecules are breakdown to small molecules or oxidizing to producing energy.

Anabolism

The biochemical processes of metabolism by which molecules are synthesized or built up.

Note

Catabolism and anabolism are separated process, catabolism process occur to produce energy, but anabolism need energy.

INTRODUCTION

The carbohydrates are source of energy for animal nutrition. The

monosaccharides and oligosaccharides are efficiently metabolized by simple stomach animals. On the other hand, ruminants contain microbes, which secrete enzymes capable of degrading cellulose. Glycogen is a polysaccharide found in animal and fungal cells. Glycogen is a storage form of carbohydrate and is readily utilized when there is deficiency of energy.

Digestion

The dietary carbohydrates that are most important nutritionally are polysaccharides and disaccharides, since free monosaccharides are not commonly present in the diet in significant quantities. There is, however, some free glucose and fructose in honey, in certain fruits, and in the carbohydrates that are added to processed foods. The cellular use of carbohydrates depends on their absorption from the Gastrointestinal (GI) tract into the blood stream, a process normally restricted to monosaccharides. Therefore, poly saccharides and disaccharides must be hydrolyzed to their constituent monosaccharide units. The hydrolytic enzymes involved are collectively called glycosidases, or, alternatively, carbohydrases.

1 Disaccharides

Virtually no digestion of disaccharides or small oligo saccharides occurs in the mouth or stomach. In the human it takes place entirely in the upper small intestine. Unlike amylase, disaccharidase activity is associated with the mucosal cells of the microvilli or brush border rather than with the intestinal lumen. Among the types of enzyme activities located in the mucosal cells are lactase, invertase (sucrase), and isomaltase. The latter is not a disaccharidase but instead hydrolyses branched dextrins, as mentioned in an earlier section. Lactase catalyses the cleavage of lactose to equimolar amounts of galactose and glucose, and sucrase hydrolyses sucrose to yield glucose and one fructose residue; sucrase also hydrolyses maltose and maltotriose to free glucose.

2 Polysaccharides

The glycosidase, a-amylase, assumes a particularly important role in polysaccharide digestion because of its specific hydrolytic action on the α-1,4 bonds of the starches. Resistant to the action of this enzyme, therefore, are the β-1,4 bonds of cellulose and the α -1,6 linkages that form branch points in the starch amylopectin. The a-amylase hydrolyses the unbranched amylose rapidly into units of the disaccharide maltose and into the trisaccharide malltotriose, the latter subsequently undergoing slower hydrolysis to maltose and glucose. The enzyme's hydrolytic action on amylopectin produces, in addition to glucose, maltose, and maltotriose, a mixture of branched oligo saccharides, or dextrins, the smallest of which are tetrasaccharides and pentasaccharides. Together with the complementary activity of another glycosidase, α-dextrinase, which hydrolyses the α-1, 6 bonds at the branches, the dextrins are consequently hydrolysed to free glucose.

Metabolism of carbohydrates

- تحليل الجلوكوز	Glycolysis
- دورة كربس	Krebs Cycle
- بناء الجلايكوجين	Glycogenesis
- إستحداث الجلايكوجين	Gluconeogenesis
- تحليل الجلايكوجين	Glycogenolysis

Glycolysis

Glycolysis is, by definition, the pathway by which glucose is converted into two units of lactic acid, a triose. The pathway can function anaerobically, and in situations in which oxygen debt is in effect, as in times of strenuous exercise, lactate accumulates in the muscle cells, causing the aches and

pains associated with overexertion. The importance of glycolysis in energy metabolism is that it provides the initial sequence of reactions necessary for glucose to be oxidized completely to CO_2 and H_2O via the citric acid cycle. In cells that lack mitochondria, such as the erythrocyte, the pathway of glycolysis is the sole provider of ATP by substrate level phosphorylation of ADP. The glycolytic enzymes function within the cytoplasmic matrix of the cell, while the enzymes catalyzing the citric acid (Krebs) cycle reactions are located within the mitochondrion (pp. 8, 9). Further metabolism of the products of glycolysis in the Krebs cycle allows complete oxidation of glucose to CO_2 and H_2O, with maximal energy production. Some of the energy liberated is salvaged as ATP, while the remainder maintains body temperature. Many cell types are involved in glycolysis, but most of the energy derived from carbohydrates originates in liver, muscle, and adipose tissue. The pathway of glycolysis, showing the entry of dietary fructose and galactose, the following are comments on selected reactions:

1 .The hexokinase/glucokinase reaction consumes 1mol ATP/mol glucose. Hexokinase (not glucokinase) is negatively regulated by the product of the reaction, glucose 6-phosphate.

2 .Glucose phosphate isomerase catalyses this inter-conversion of isomers.

3 .The phosphofructokinase reaction, an important regulatory site, is modulated negatively by ATP and citrate and positively by AMP.

Another ATP is consumed in the reaction.

3 .The aldolase reaction results in the splitting of a hexose bisphosphate into two triose phosphates.

4 .The isomers glyceraldehyde 3-phosphate and dihydroxyacetone phosphate (DHAP) are interconverted by the enzyme triosephosphate isomerase. In an isolated system the equilibrium favors DHAP formation. However, in the cellular environment it is shifted completely toward the production of glyceraldehyde 3- phosphate, since this metabolite is being continuously removed from the equilibrium by the subsequent reaction catalysed by glyceraldehyde 3-phosphate dehydrogenase.

5 .In this reaction, glyceraldehyde 3-phosphate is oxidised to a carboxylic acid, while inorganic phossphate is incorporated as a high-energy anhydride bond. The enzyme is glyceraldehyde 3-phosphate dehydrogenase, which uses NAD as its hydrogen accepting substrate. Under aerobic conditions, the NADH formed is deoxidized to NAD by O_2 via the electron transport chain in the mitochondria. The reason the O_2 is not necessary to sustain this reaction under anaerobic conditions is that the NAD consumed is restored by a subsequent reaction

6 .This reaction, catalyzed by phosphoglycerate kinase, exemplifies a substrate level phosphorylation of ADP. Do a little extensive reading, for a more detailed review of this mechanism by which ATP can be formed from ADP by the transfer of a phosphate from a high-energy donor molecule.

7 .Phosphoglyceromutase catalysis the transfer of the phosphate group from the carbon-3 to carbon-2 of the glyceric acid.

8 .Dehydration of 2-phosphoglycerate by the enzyme enolase introduces a double bond that imparts high energy to the phosphate bond.

9 .The product of reaction (9), phosphoenolpyruvate (PEP), donates its phosphate group to ADP in a reaction catalysed by pyruvate kinase. This is the second site of substrate level phosphorylation of ADP in the glycolytic pathway.

10 .The lactate dehydrogenase reaction transfers two hydrogen from NADH and H+ to pyruvate, reducing it to lactate. NAD is formed in the reaction and can replace the NAD consumed in reaction (6) under anaerobic conditions. It must be emphasized that this reaction is most active in situations of oxygen debt, as in prolonged muscular activity. Under normal, aerobic conditions, pyruvate enters the mitochondrion for complete oxidation. A third important option available to pyruvate is its conversion to the amino acid alanine through trans-amination with the amino group donor glutamate. This, together with the fact that pyruvate is also the product of the catabolism of various amino acids, makes it an important link between protein and carbohydrate metabolism.

11 .These two reactions provide the means by which dietary fructose enters the glycolytic pathway. Fructose is an important factor in the average American diet, since nearly half of the carbohydrate consumed is sucrose, and high fructose corn sugar is becoming more popular as a food sweetener. Reaction 12 functions in extrahepatic tissues and involves the direct phosphorylation by hexokinase to form fructose 6-phosphate. This is a relatively unimportant reaction. It is slow and occurs only in the presence of high levels of the ketose. Reaction 13 is the major means by which fructose is converted to glycolysis metabolites.

The phosphorylation occurs at carbon-l and is catalysed by

fructokinase, an enzyme found only in hepatocytes. The fructose lphosphate is subsequently split by aldolase, designated aldolase B to distinguish it from the enzyme acting on fructose 1,6-bisphosphate, forming DHAP and glyceraldehyde. The latter can then be phosphorylated by glyceraldehyde kinase (or triokinase) at the expense of a second ATP to produce glyceraldehyde 3-phosphate. Fructose is therefore converted to glycolytic intermediates and as such can follow the pathway to pyruvate formation and Krebs cycle oxidation. Alternatively, they can be used in the liver to produce free glucose by a reversal of the first part of the pathway through the action of gluconeogenic enzymes.

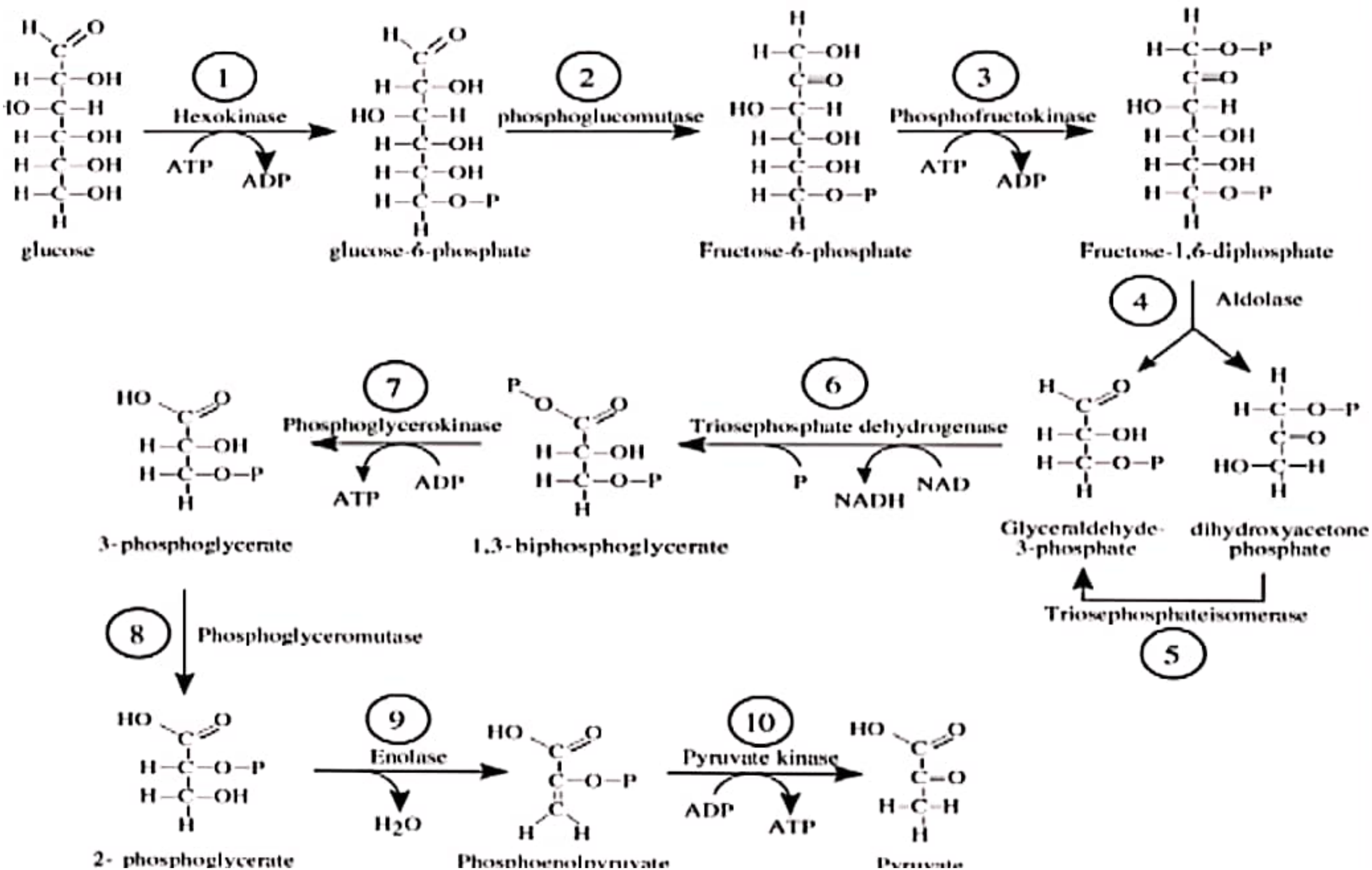
Glucose formation from fructose would be particularly important

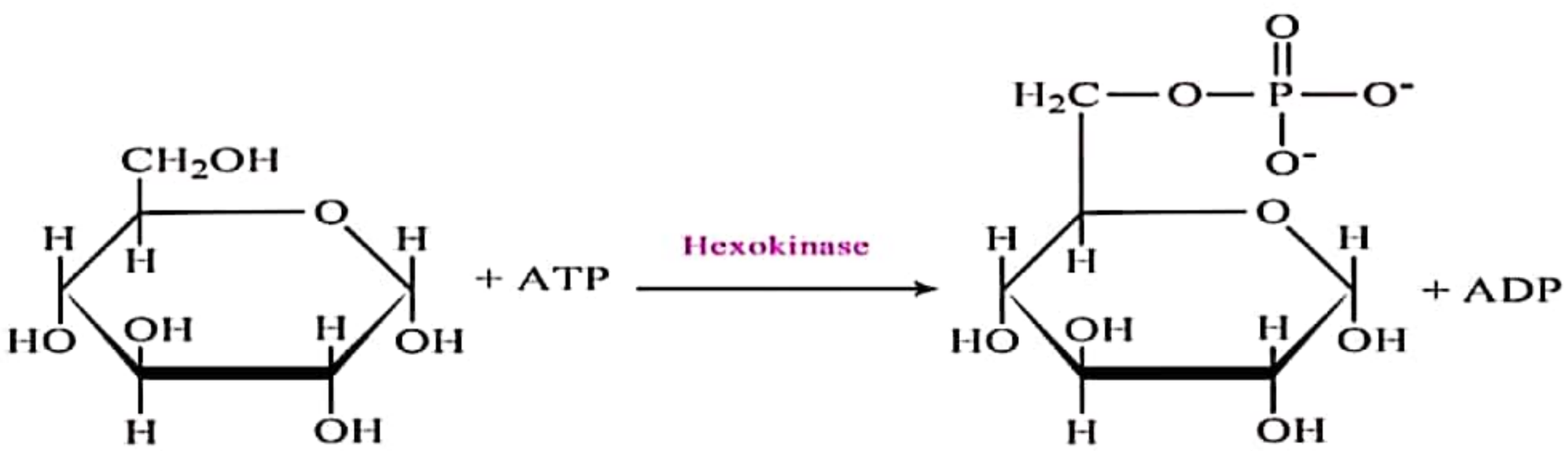
if fructose provides the major source of carbohydrate in the diet.

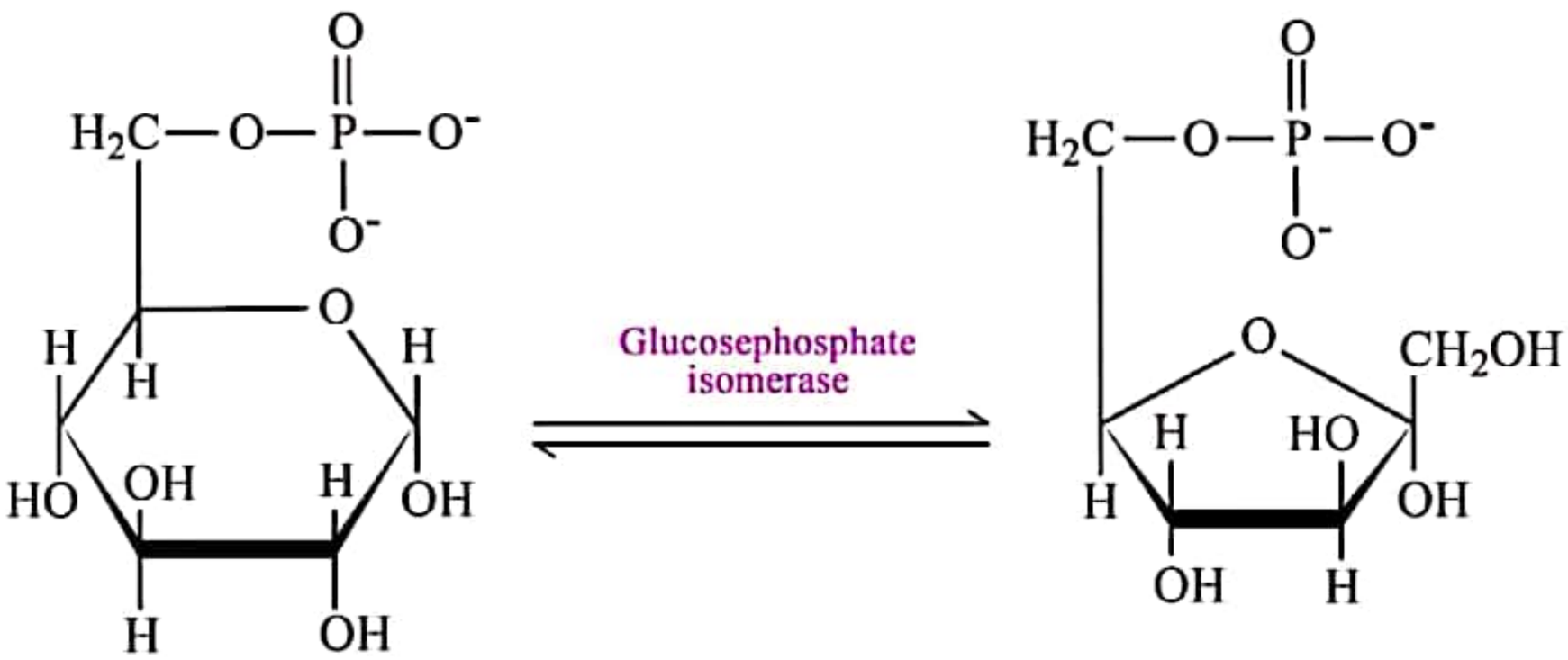
Since the phosphorylation of fructose is essentially the responsibility of the liver, the ingestion of large amounts of the ketose can cause a depletion of hepaatocyte ATP, leading to reduction in the rate of various biosynthetic processes such as protein synthesis.

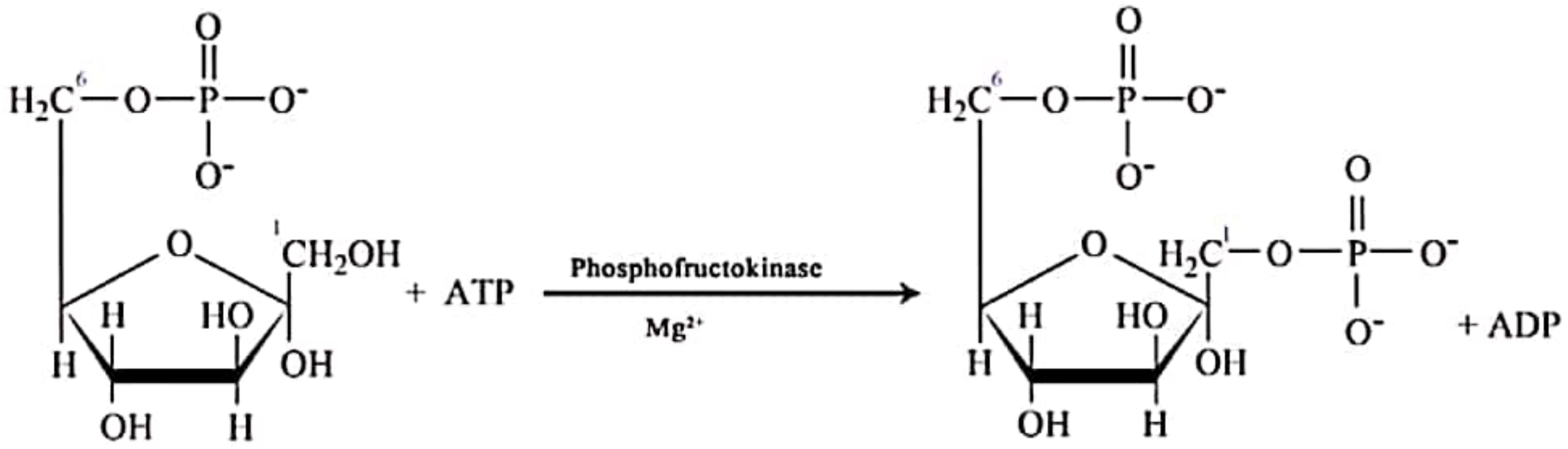
12 Like glucose and fructose, galactose is first phosphorylated. The transfer of the phosphate from ATP is catalysed by galactokinase and the resulting phosphate ester is at carbon-l of the sugar. The major dietary source of galactose is lactose, from which the monosaccharide is hydrolytically released by lactase.

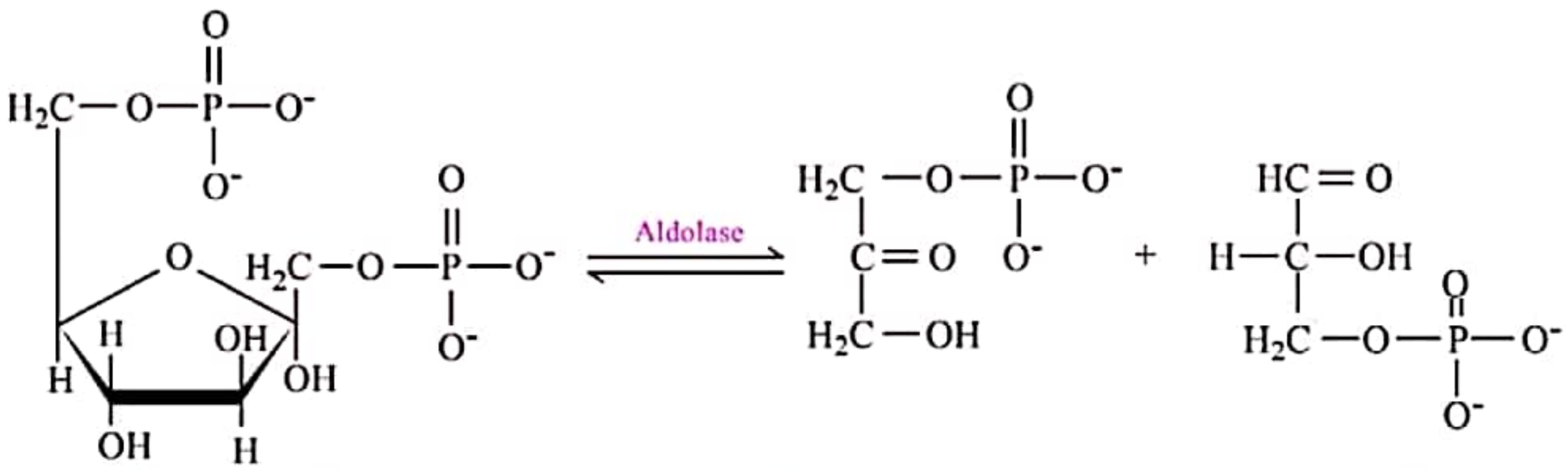
13 .Galactose 1-phosphate can be converted to glucose l phosphate by the enzyme galactose 1-phosphate uridyl transferase. The reaction involves the transfer of a uridyl phosphate residue from UDP glucose to the galactose l-phosphate, yielding glucose 1-phosphate and UDP galactose. As glucose 1-phosphate, galactose can be incorporated into glyycogen through reactions discussed previously. It can enter the

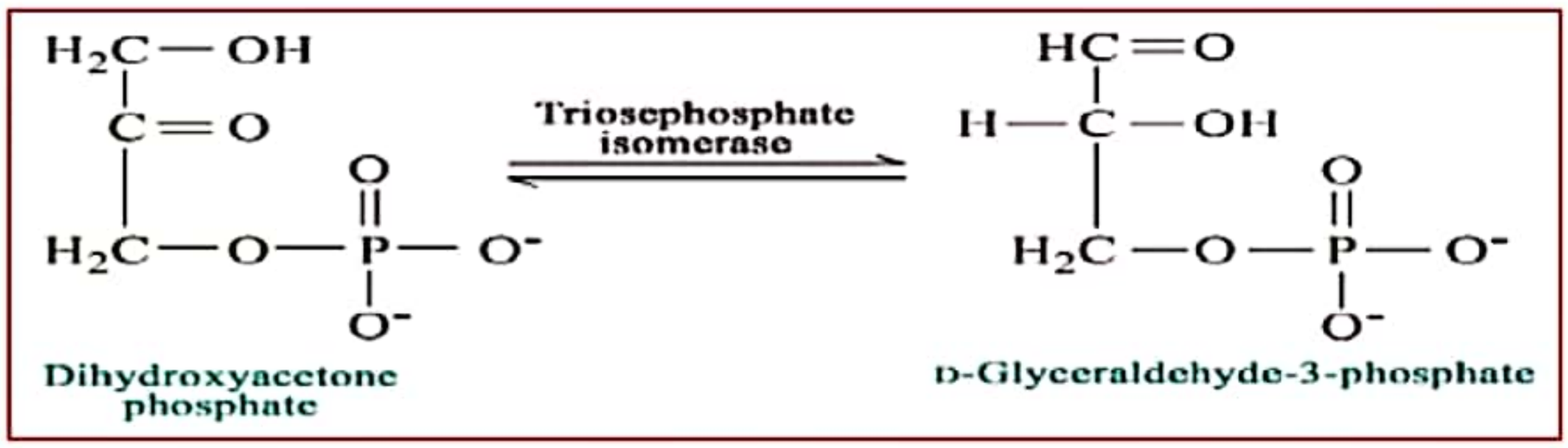


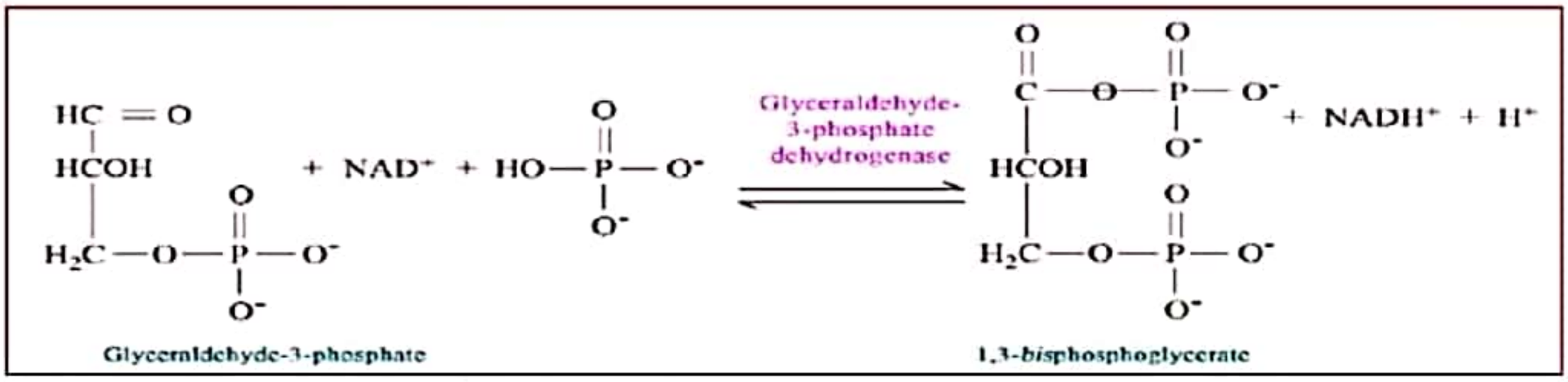


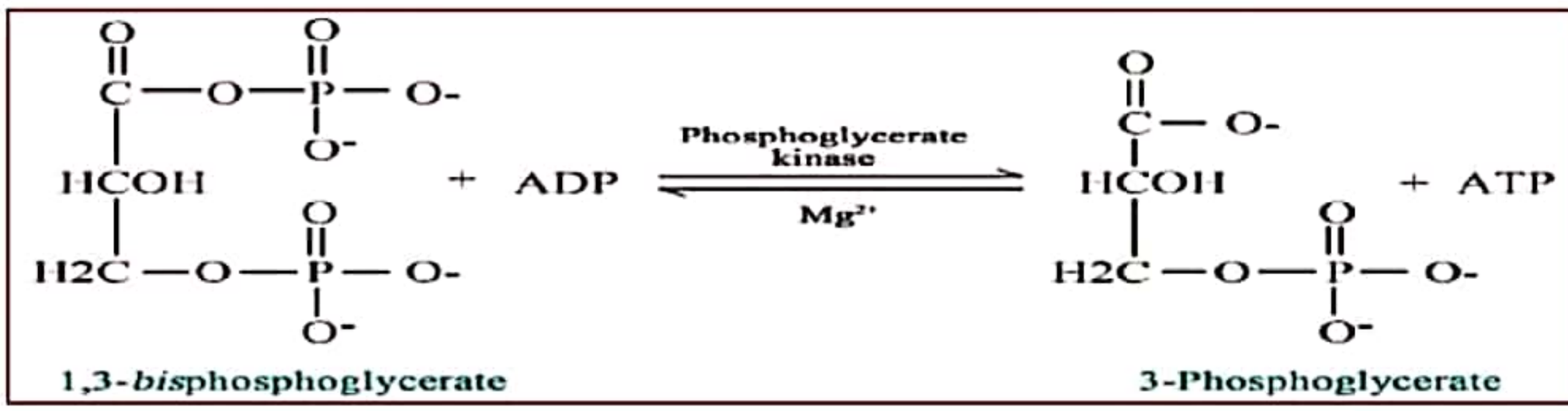


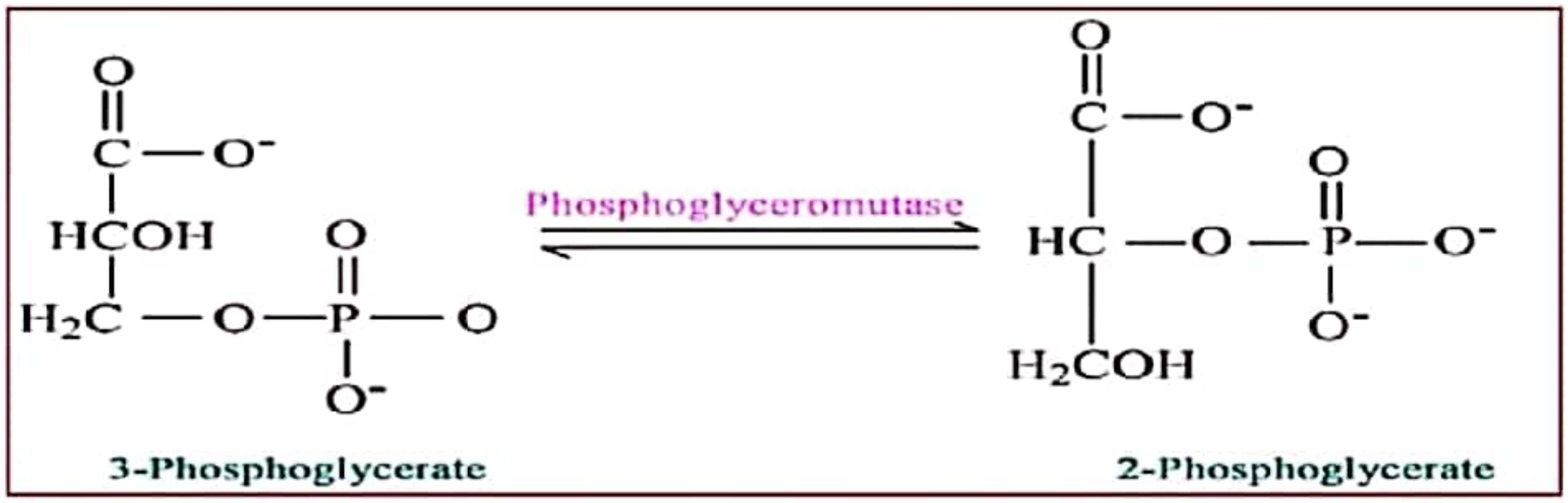


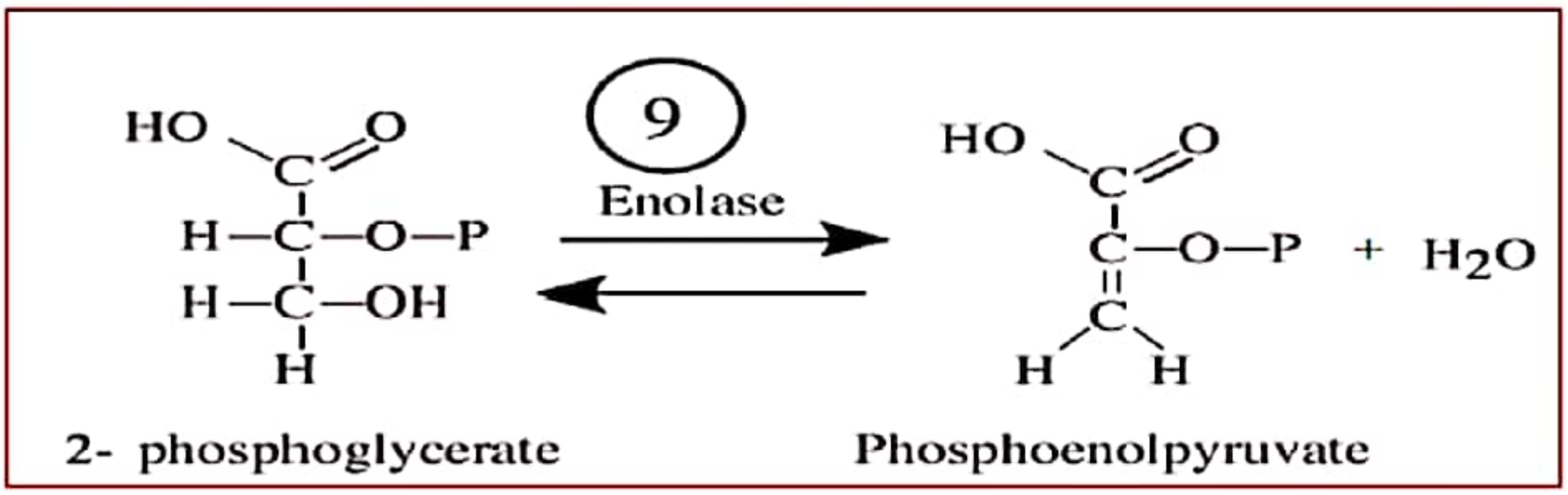


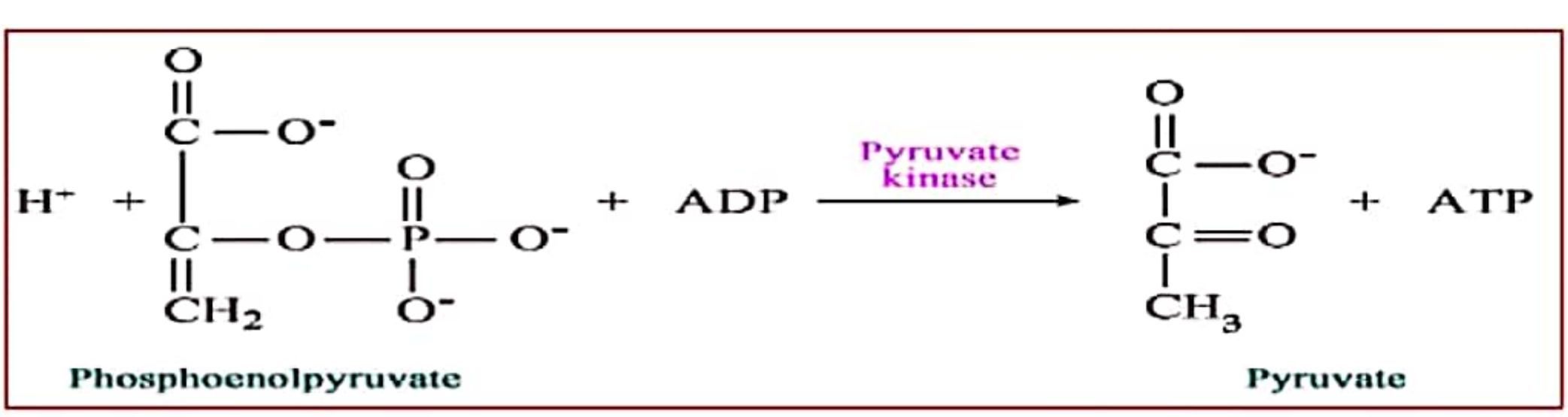


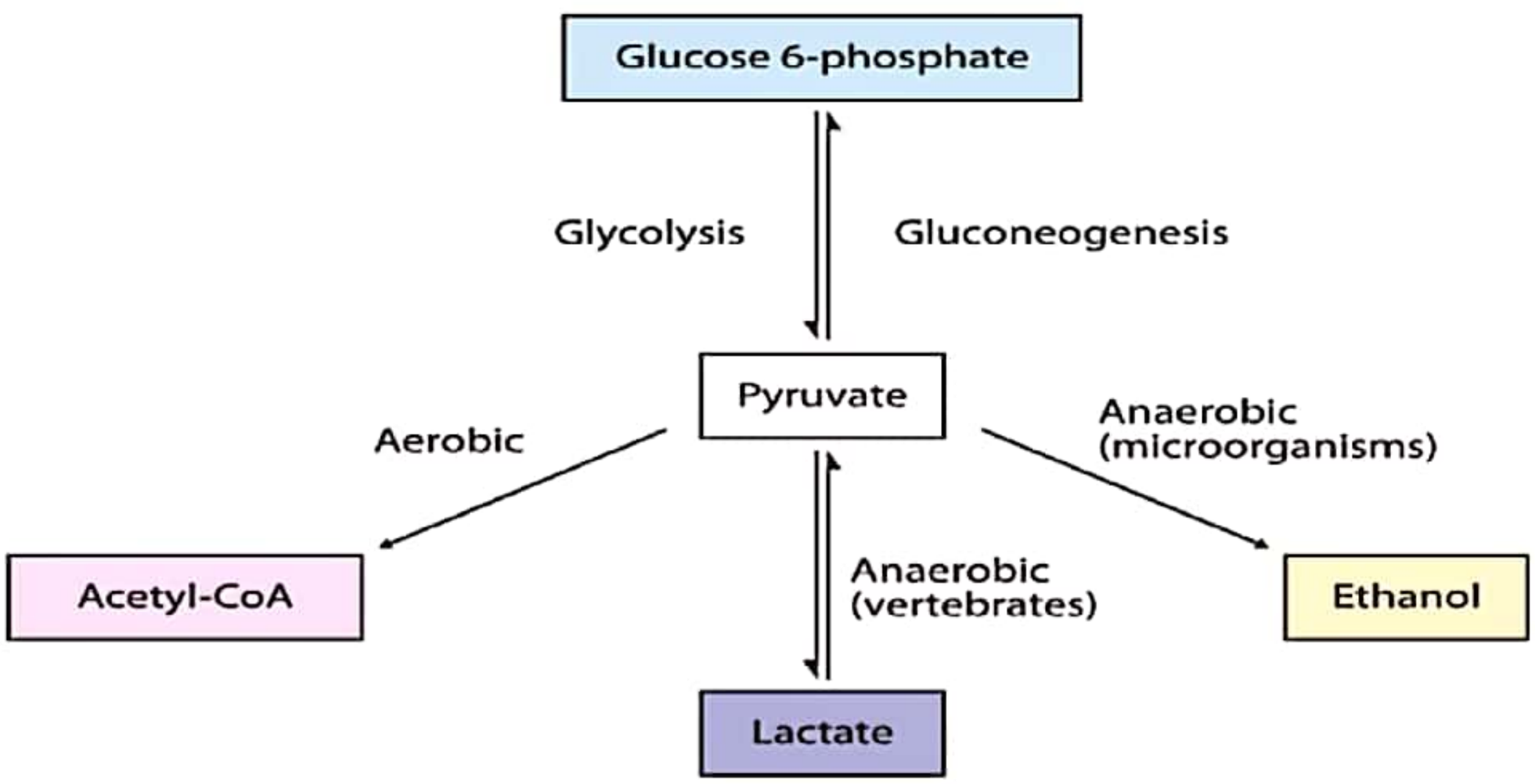


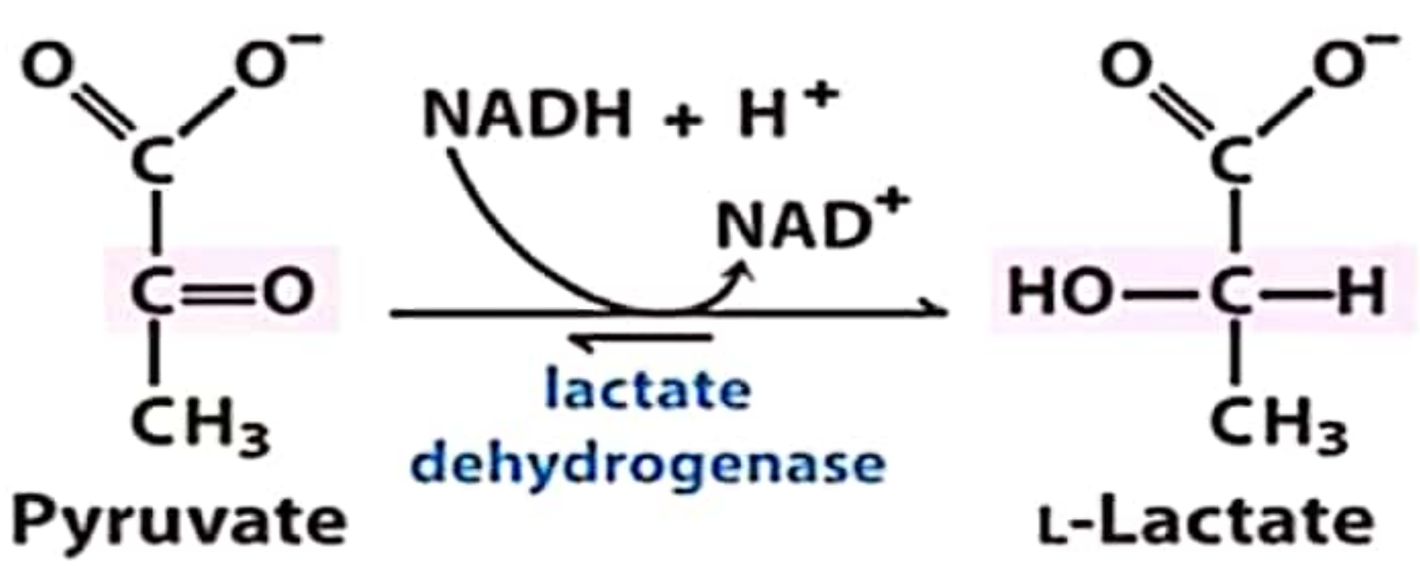


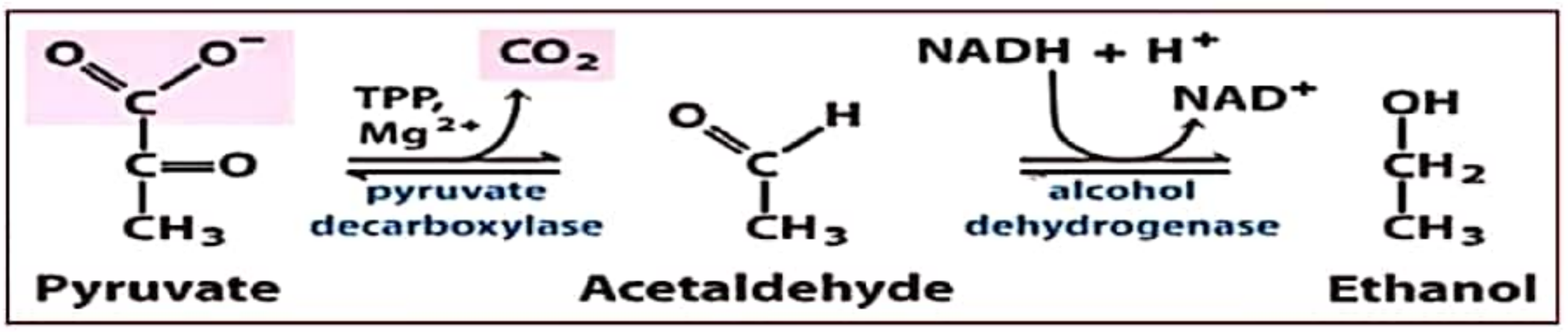


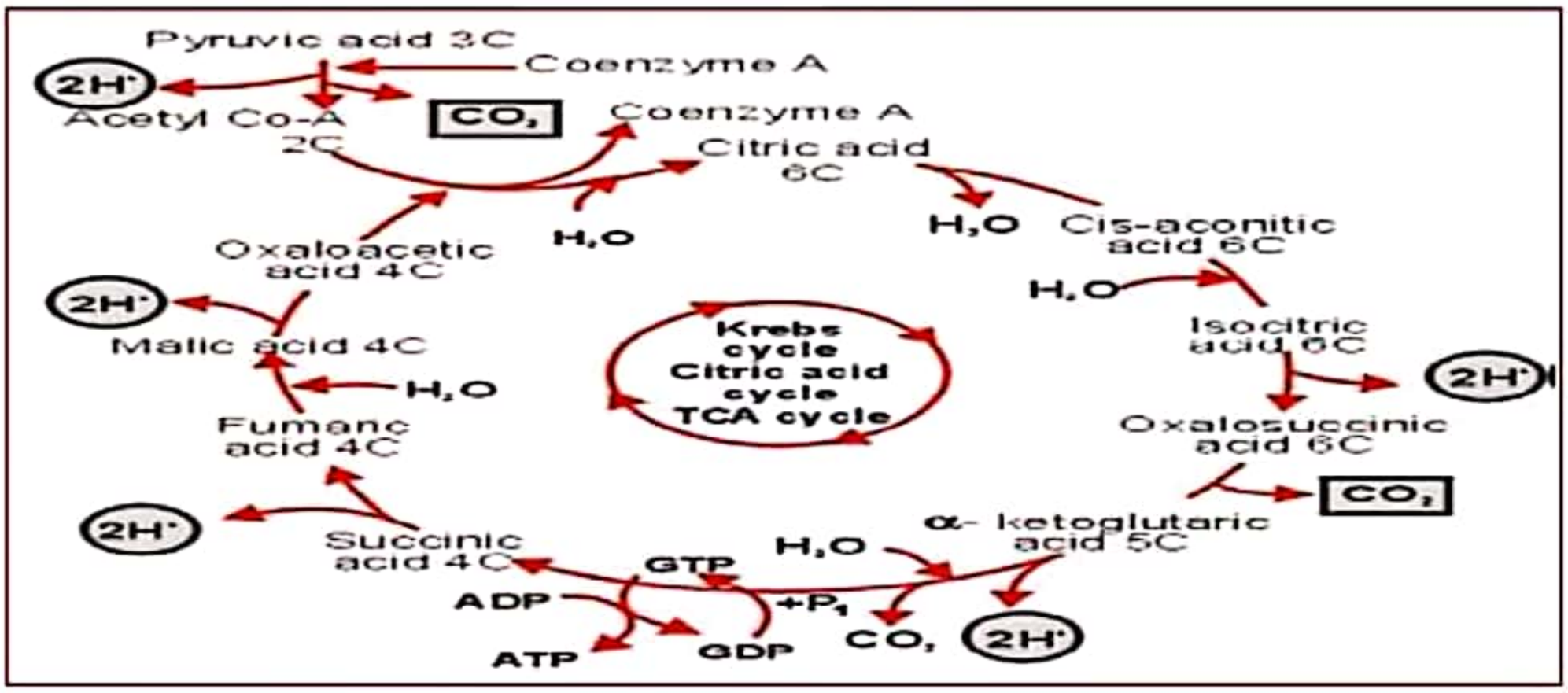












Krebs Cycle

Alternatively designated the tricarboxylic acid cycle or the citric acid cycle, this sequence of reactions represents the forefront of energy metabolism in the body. It can be thought of as the common and final catabolic pathway because products of carbohydrate, fat, and amino acids feed into the cycle where they can be totally oxidised to CO_2 and H_2O, with the accompanying generation of large amounts of ATP. Not all entrant substances are totally oxidised. Some Krebs cycle intermediates are used to form glucose by the process of gluconeogenesis, which will be discussed in the next section, and some can be converted to certain amino acids by transamination. However, the importance of the cycle as the nucleus of energy production is evidenced by the estimation that over 90 per cent of energy released from food occurs here.

The high energy output of the Krebs cycle is attributed to mitochondrial electron transport, with oxidative phosphorylation providing the means for ATP formation. The oxidation reactions occurring in the cycle are actually dehydrogenations in which an enzyme catalyses the removal of two hydrogens to an acceptor co-substrate such as NAD or FAD. Since the

enzymes of the cycle and the enzymes and electron carriers of electron transport are both compartmentalised within the mitochondria,

the reduced cosubstrates, NADH and FADH2 are readily reoxidised by O_2 via the electron transport chain. In addition to its production of the reduced co-substrates NADH and FADH2, which furnish the energy through their oxidation via electron transport, the Krebs cycle produces most of the carbon dioxide through decarboxylation reactions. Viewing this in its proper perspective with regard to glucose metabolism, it must be recalled that two pyruvates are produced from one glucose during cytoplasmic glycolysis. These pyruvates are in turn transferred into the mitochondria, where decarboxylation leads to the formation of two acetyl CoA units and two molecules of CO_2. The two carbons represented by the acetyl CoA are additionally lost as CO_2 through Krebs cycle decarboxylations. Most of the CO_2 produced is exhaled through the lungs, although some is used in certain synthetic reactions called carboxylation. The Krebs cycle is shown in figure below. It is usually visualized as beginning with the condensation of acetyl CoA with oxaloacetate to form citrate. The acetyl CoA is formed from numerous sources, including the breakdown of fatty acids, glucose (through pyruvate), and certain amino acids. Its formation from pyruvate will be considered now, since this compound links cytoplasmic glycolysis to the mitochondrial Krebs cycle activity. The reaction shown below is generally referred to as the pyruvate dehydrogenase reaction. However, the reaction is a complex one requiring a multienzyme system and various cofactors. The enzymes

and cofactors are contained within an isolable unit called the pyruvate dehydrogenase complex. The cofactors include coenzyme A (CoA)thiamine diphosphate (TDP), Mg+2, NAD, FAD, and lipoic acid. Four

vitamins are therefore necessary for the activity of the complex pantothenic acid (a component of CoA), thiamine, niacin, and riboflavin.

The role of these vitamins and others as precursors of coenzymes will be discussed in another unit. The enzymes include pyruvate decarboxylase, dihydroolipoyl dehydrogenase, and dihydrolipoyl transacetylase. The net effect of the complex results in decarboxylation and dehydrogenation of pyruvate with NAD serving as the terminal hydrogen acceptor. This reaction therefore yields energy, since the reoxidation by electron transport of the NADH produces three mol of ATP by oxidative phosphorylation. The reaction is regulated negatively by ATP and by NADH. The condensation of acetyl CoA with oxaloacetate initiates the Krebs cycle reactions. The following are comments on reactions:

1 .The formation of citrate from oxaloacetate and acetyl CoA is catalysed by citrate synthetase. The reaction is regulated negatively by ATP. The isomerisation of citrate to isocitrate involves cis aconitate as an intermediate. The isomerisation, catalysed by aconitase, involves dehydration followed by sterically reversed hydration, resulting in the repositioning of the-OH group onto an adjacent carbon. The first of four

dehydrogenation reactions within the cycle, the isocitratede hydrogenase reaction supplies energy through the respiratory chain reoxidation of the NADH. Note that the first loss of CO_2 in the cycle occurs at this site. It arises from the spontaneous decarboxylation of an intermediate compound, oxalosuccinate. The reaction is positively modulated by ADP and negatively modulated by ATP and NADH.

2 .The decarboxylation/dehydrogenation of aglutarate is mechanistically identical to the pyruvate dehydrogenase complex reaction in its multi-enzyme/cofactor requirement. In the reaction, referred to as the α

ketoglutarate dehydrogenase reaction, NAD serves as hydrogen acceptor, and a second carbon is lost as CO_2 The pyruvate dehydrogenase, isocitrate dehydrogenase, and aglutarate dehydrogenase reactions account for the loss of the three-carbon equivalent of pyruvate as CO_2.

3 .Energy is conserved in the thioester bond of succcinyl CoA. The hydrolysis of that bond by succinyl thiokinase releases enough energy to drive the phosphorylation of guanosine diphosphate (GDP) by inorganic phosphate. The resulting GTP is a high energy phosphate anhydride compound like ATP; as such, GTP can serve as phosphate donor in certain phosphorylation reactions. One such reaction occurs in the gluconeogenesis pathway.

4 .The succinate dehydrogenase reaction uses FAD instead of NAD as hydrogen acceptor. The FADH2 is reoxidised by electron transport to O_2, but only two ATPs are formed by oxidative phosphorylation instead of three.

5 .Fumarase incorporates the elements of H_2O across the double bond of fumarate to form malate.

6 .The conversion of malate to oxaloacetate completes the cycle. NAD acts as a hydrogen acceptor in this dehydrogenation reaction catalysed by malate dehydrogenase. It is the fourth site of reduced co substrate formation and therefore of energy release in the cycle.

In summary the complete oxidation of glucose to CO_2 and H_2O can be shown by the equation:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6\ CO_2 + 6\ H_2O + \text{energy}.$$

This is achieved by the combined reaction sequences of the glycolytic and Krebs cycle pathways. The amount of released energy conserved as ATP under aerobic conditions is as follows:

The glycolytic sequence, glucose →2 pyruvates, produces two ATPs by substrate level phosphoryllation and either four or six by oxidative phosphoorylation, depending on the shuttle system for NADH-reducing equivalents. Generally, six will be formed due to the overall greater activity of the malate shuttle system. The intra mitochondrial pyruvate dehydrogenase reaction yields two mol of NADH, one for each pyruvate oxidised and therefore six additional ATPs by oxidative phosphorylation.

The oxidation of 1 mol of acetyl CoA in the Krebs cycle yields a total of

12 ATPs. The sites of formation, indicated by reaction number, follow.

3 - 3 .ATP

4 -3 .ATP

5 -1 .ATP (as GTP)

6 -2 .ATP

8-3 .ATP

Total 12 ATP

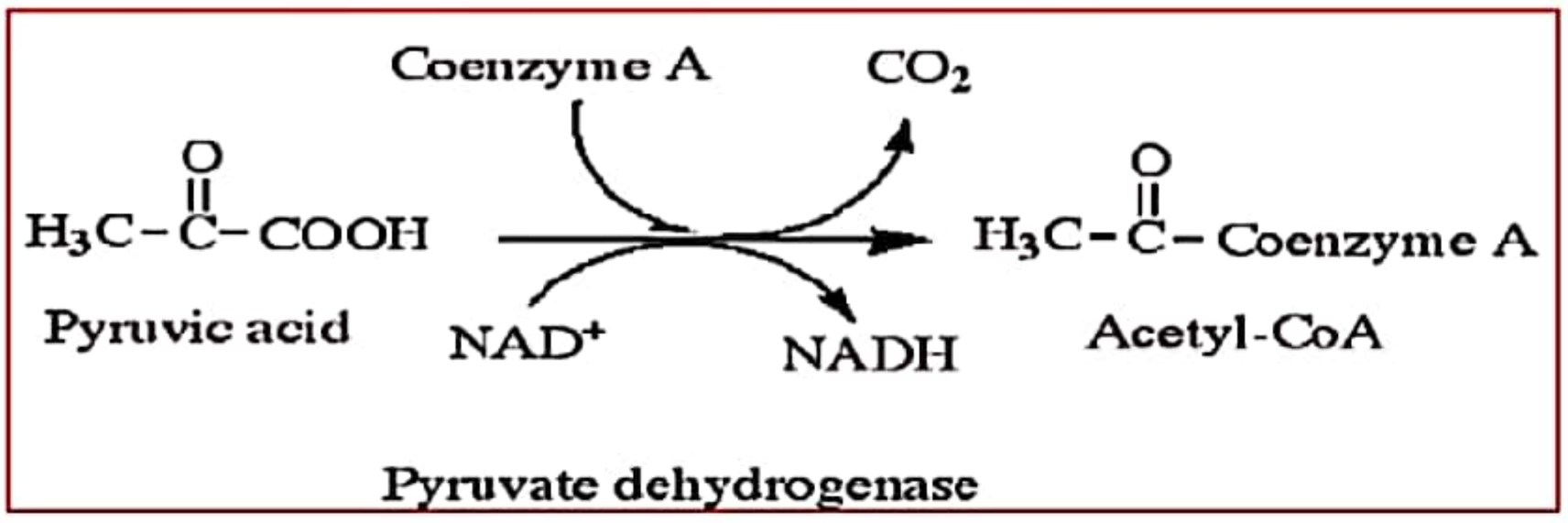
Since 2 mol acetyl CoA derived from one glucose, however, the actual

total is 24 ATPs. The total number of ATPs realized for the complete oxidation of 1 mol of glucose is therefore 38, equivalent to 262.8 kcal. It will be recalled that this figure represents only about 40% of the total energy released by mitochondrial electron transport. The remaining 60 per cent, or approximately 394 kcal, is released

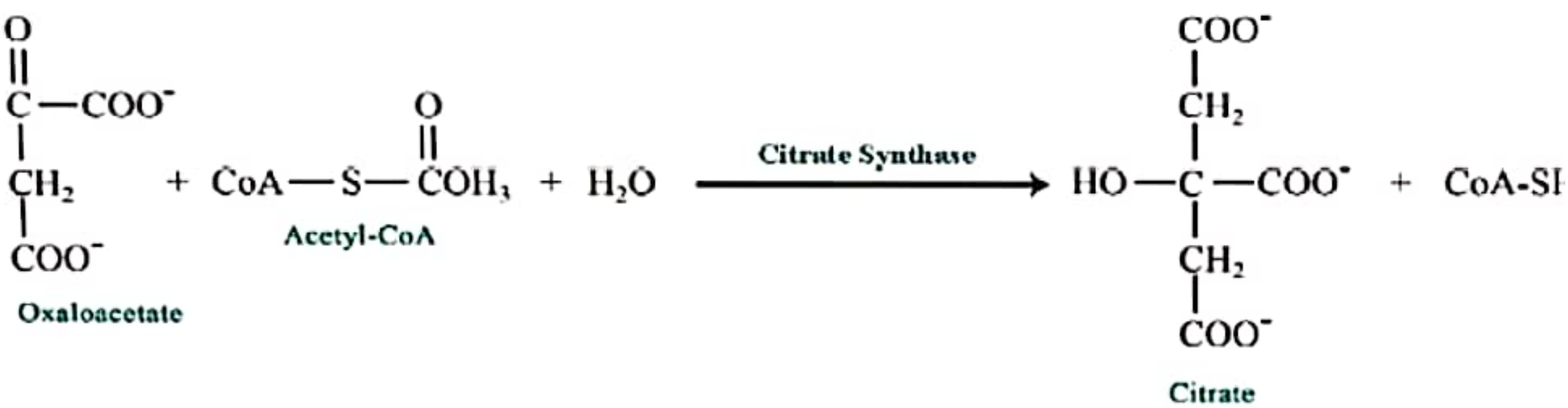
as heat to maintain body temperature has already been mentioned that acetyl CoA is produced by fatty acid oxidation and amino acid catabolism as well as from the glycolytically

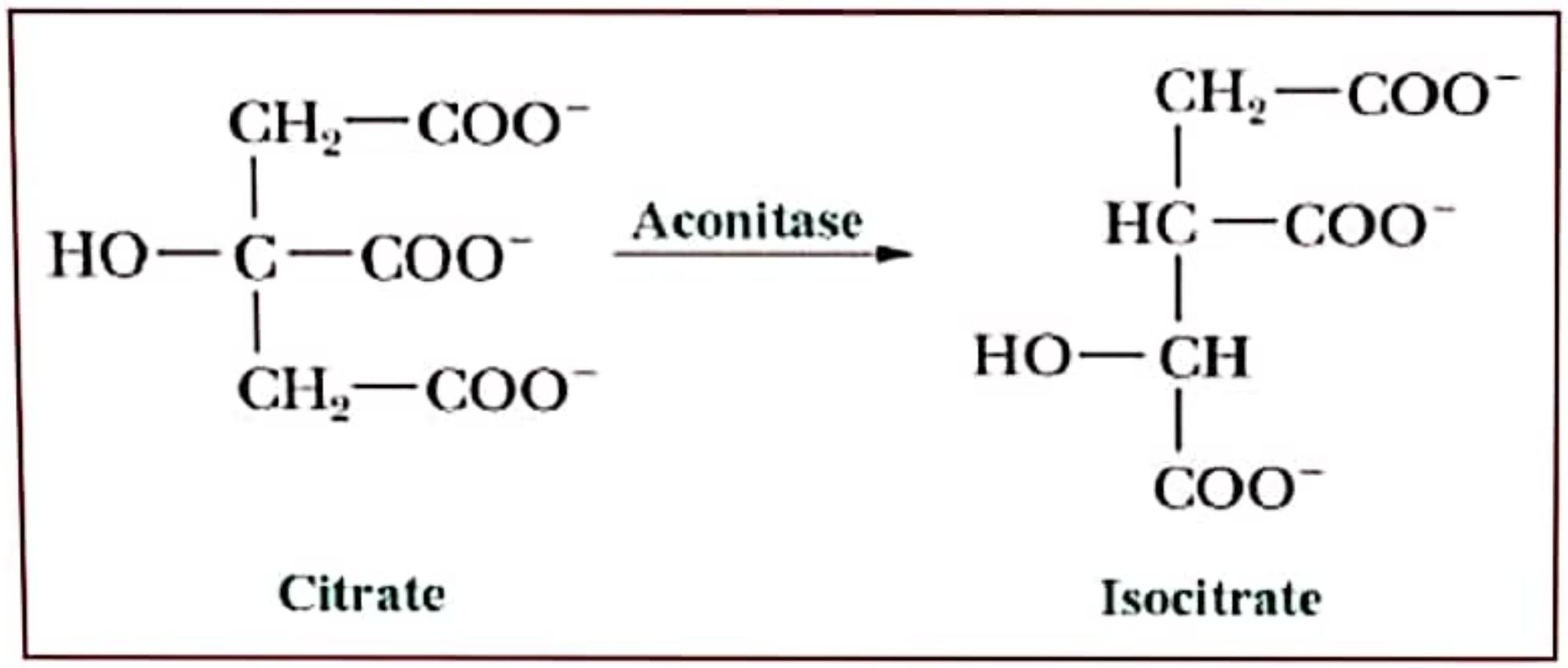
derived pyruvate. This clearly leads to an imbalance between the amount of acetyl CoA and oxaloacetate, which condense one to one stoichiometrically in the citrate synthetase reaction. It is therefore important that oxaloacetate and/or Krebs cycle intermediates, which can form oxaloacetate, be replenished in the cycle. Such a mechanism does indeed exist. Oxaloacetate, fumarate, succinyl CoA, and a rate can all be formed from certain amino acids, but the single most important mechanism for ensuring an ample supply of oxaloacetate is the reaction

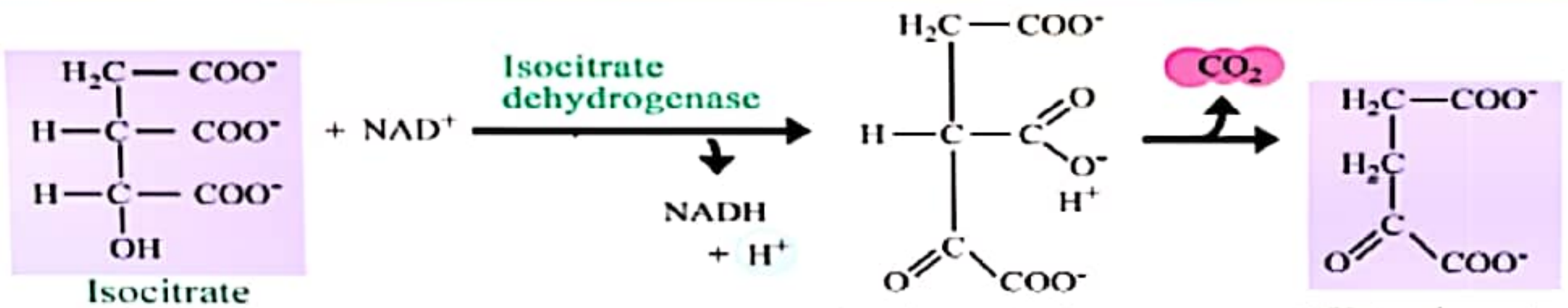
by which it is formed directly from pyruvate. This reaction, shown below, is catalysed by pyruvate carboxxylase. The "uphill" incorporation of CO_2 is accomplished at the expense of ATP, and the reaction requires the participation of biotin. The diversion of pyruvate into oxaloacetate is called an anaplerotic (filling up) process because of its role in restoring oxaloacetate to the cycle. It is of interest that pyruvate carboxylase is regulated positively by acetyl CoA, thereby accelerating oxaloacetate formation in answer to increasing levels of acetyl CoA.

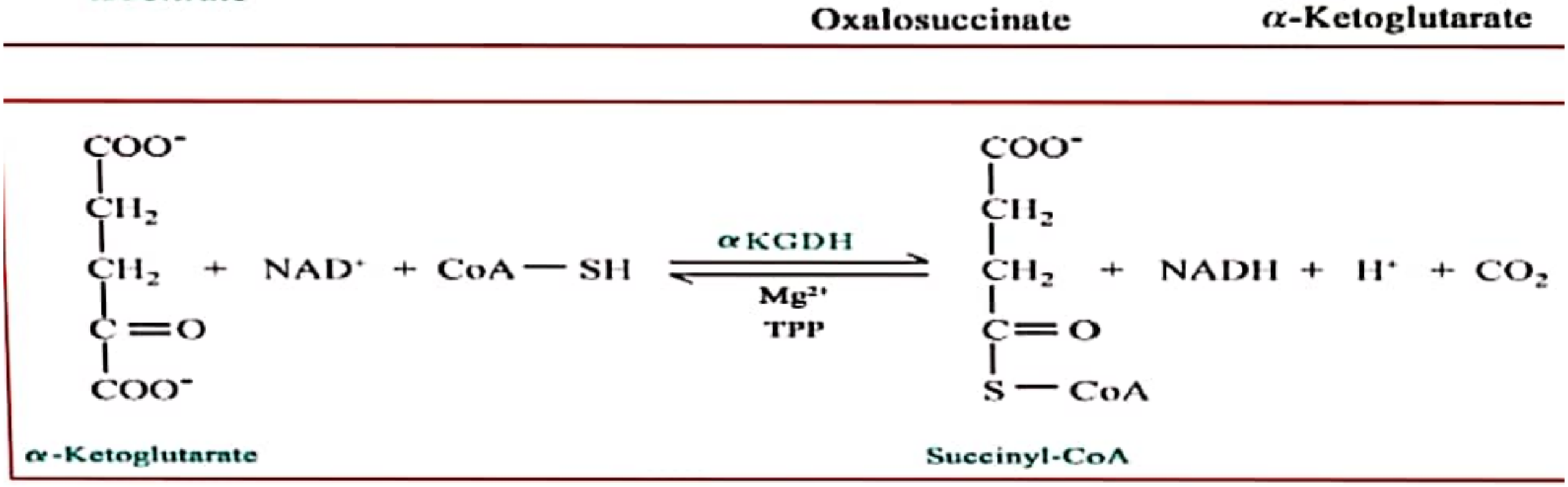


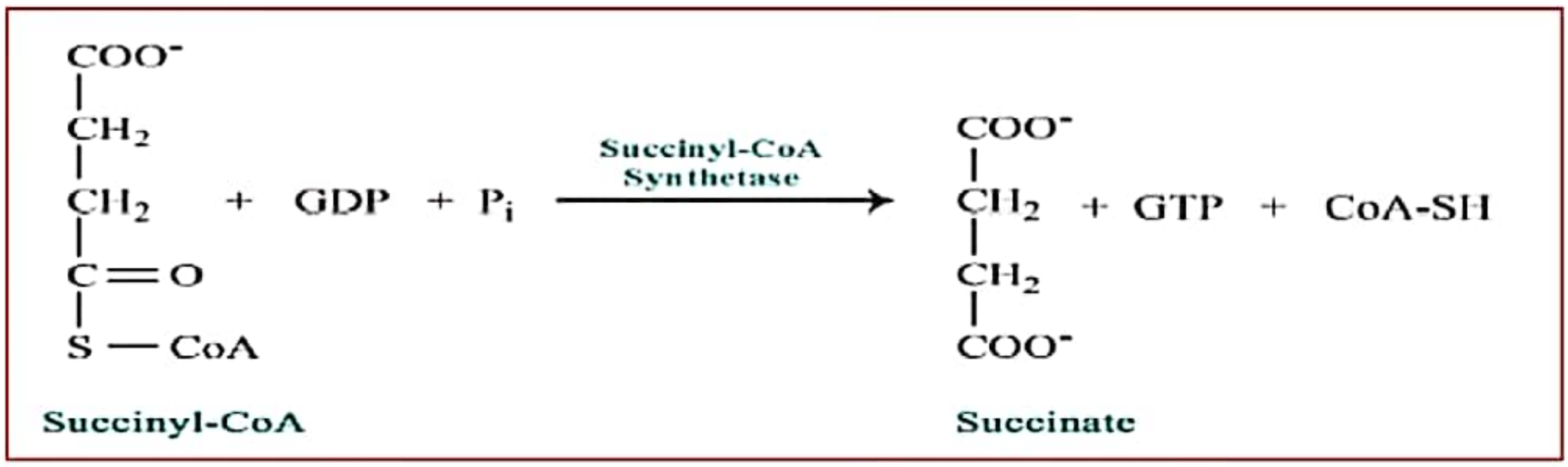
خطوات دورة كربس

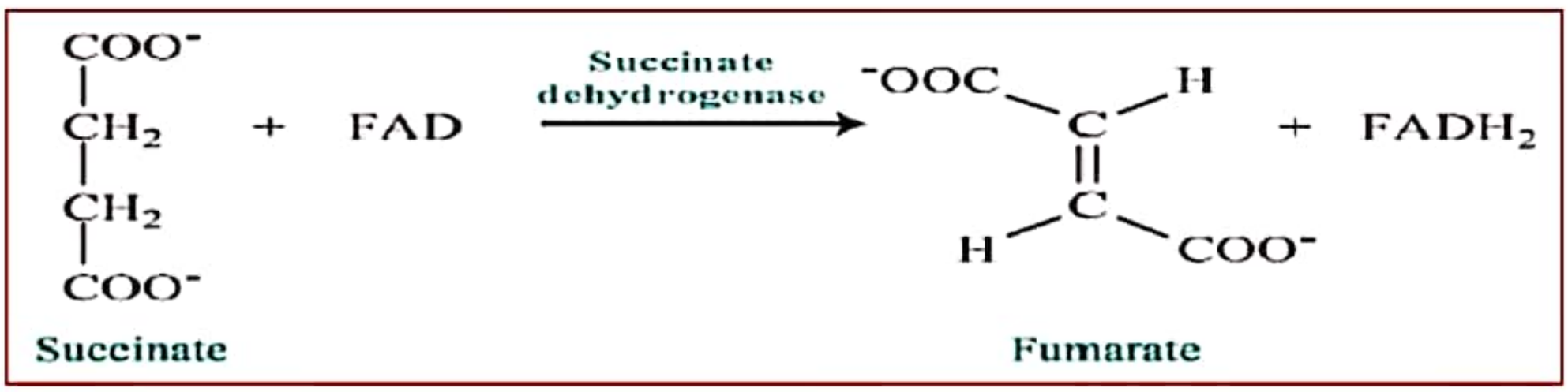


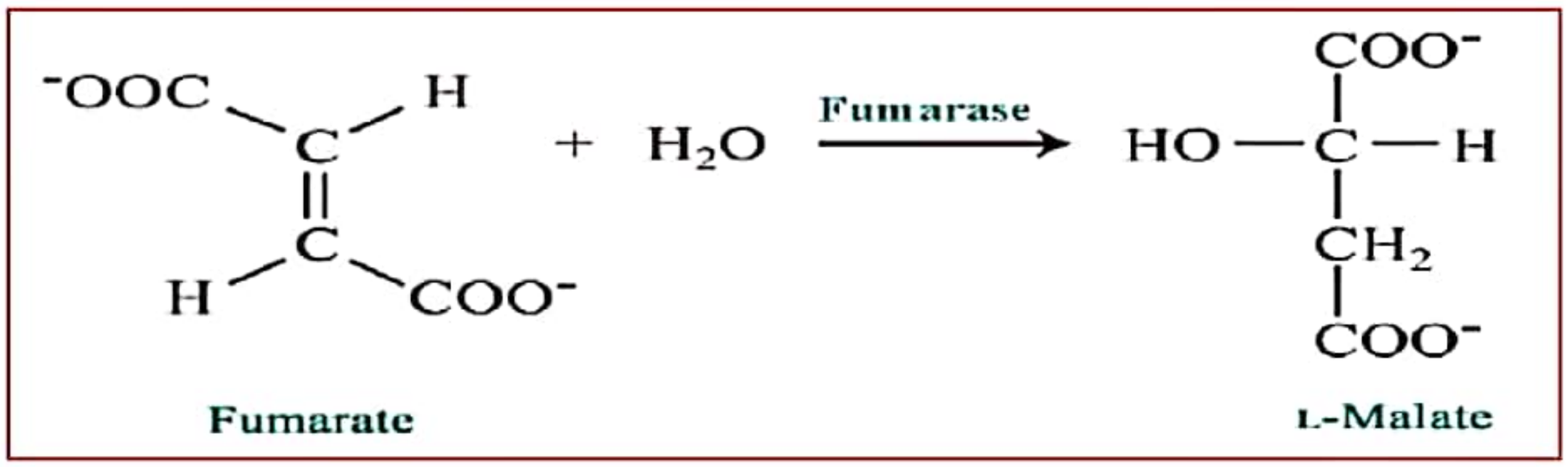


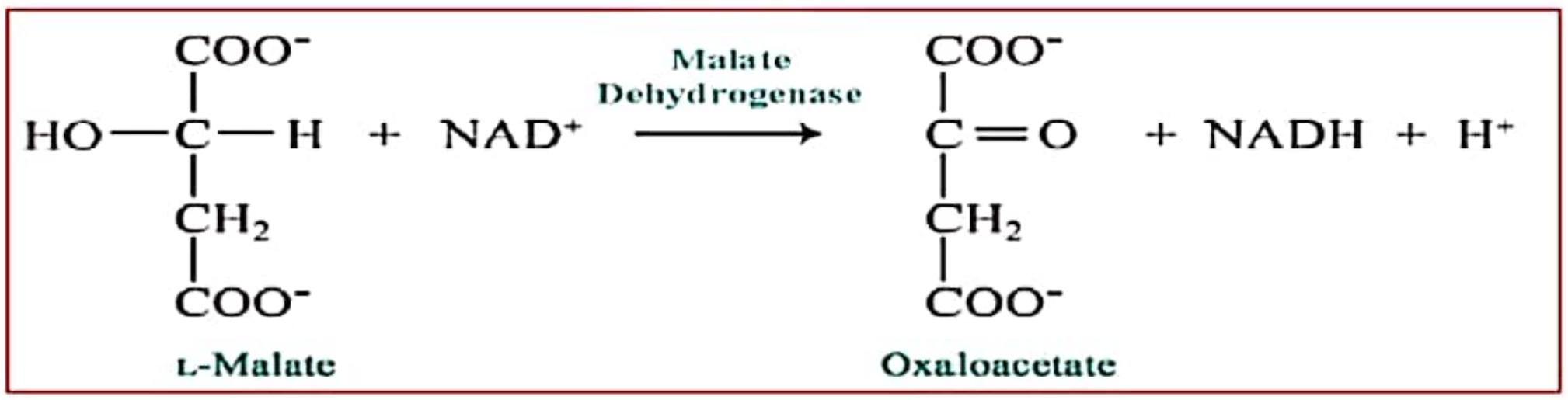




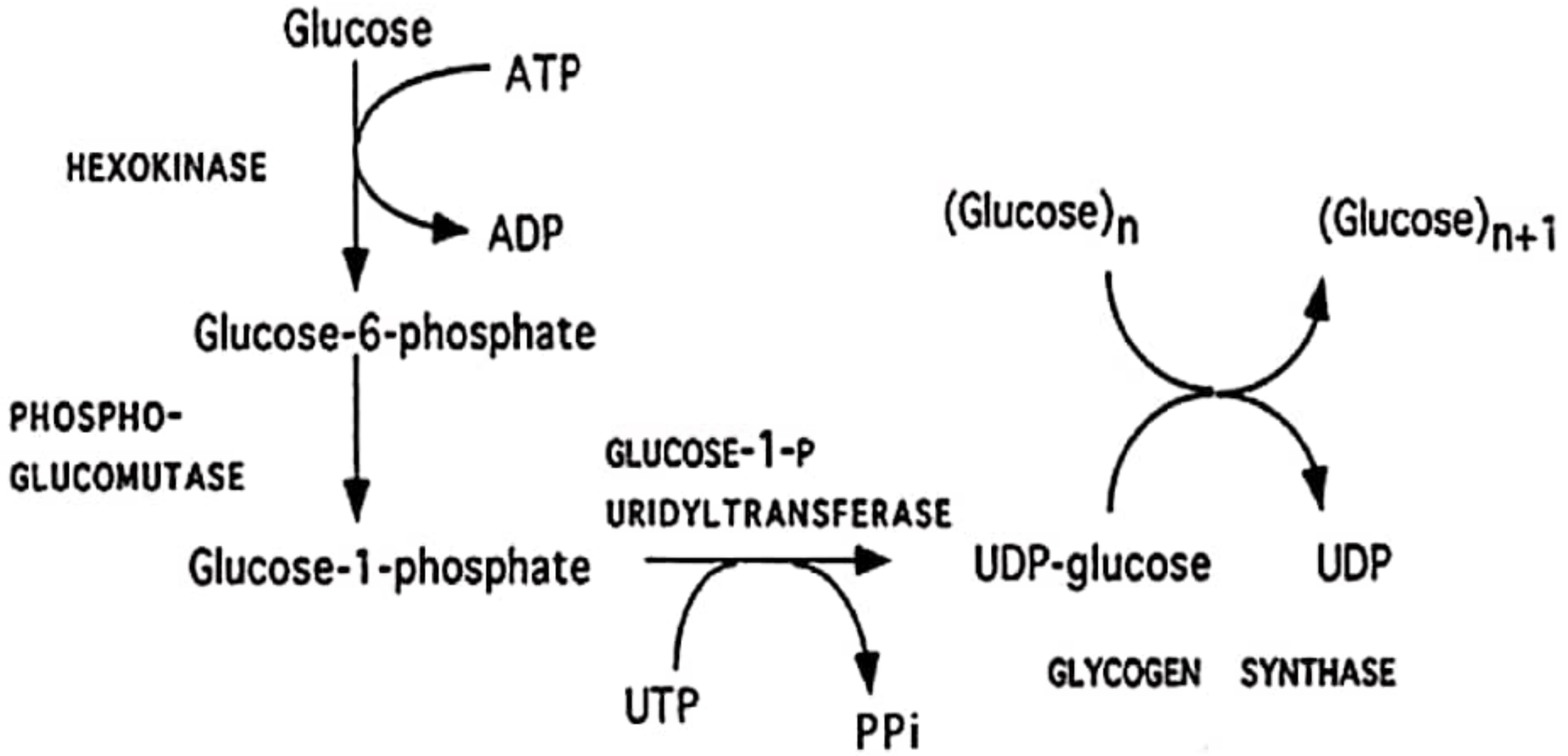




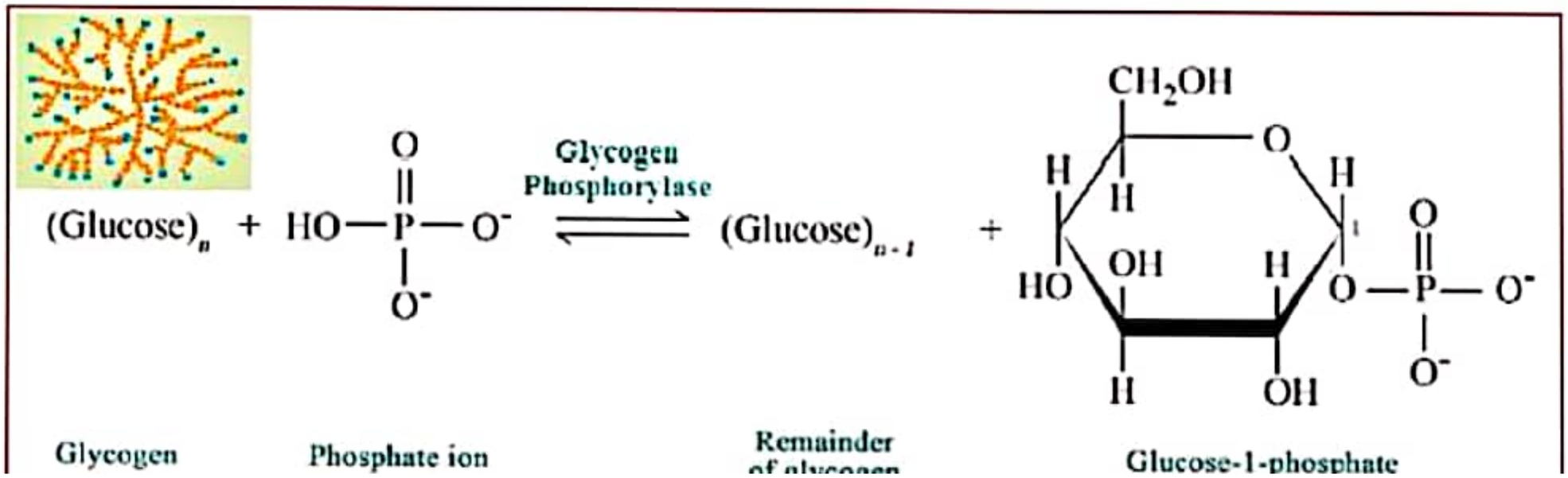


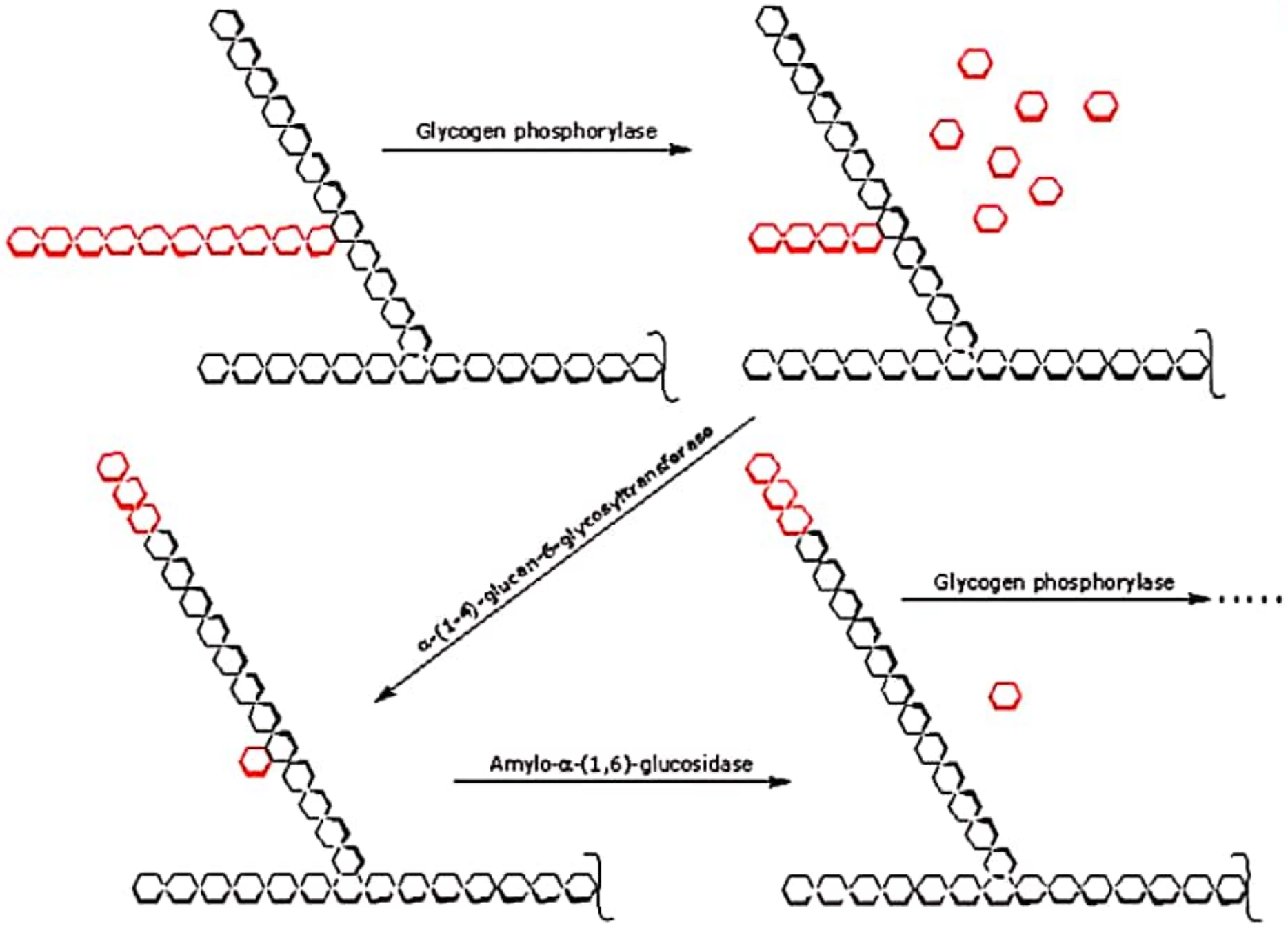


بناء الجلايكوجين (Glycogenesis)



إستحداث الجلايكوجين (Gluconeogenesis)

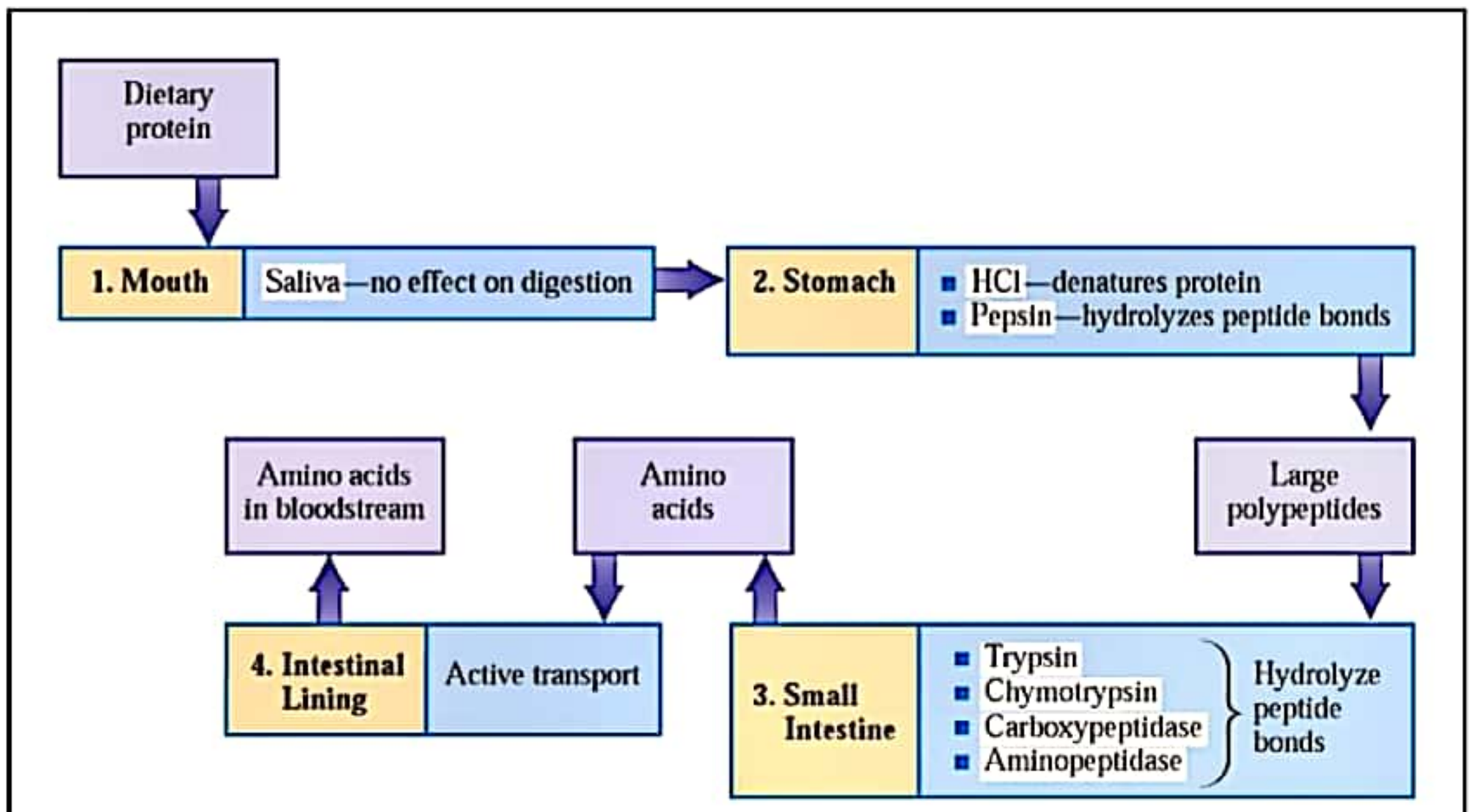


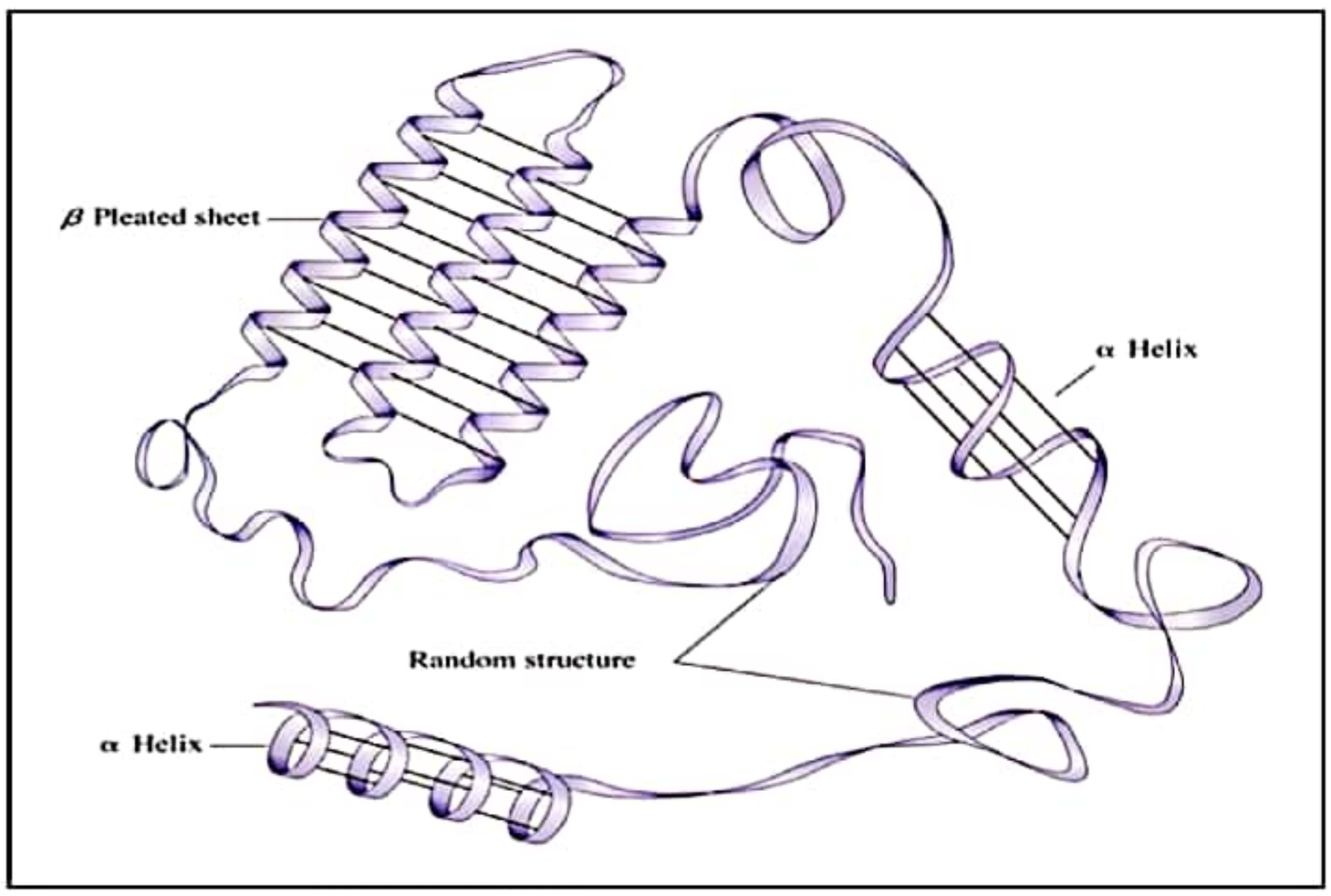


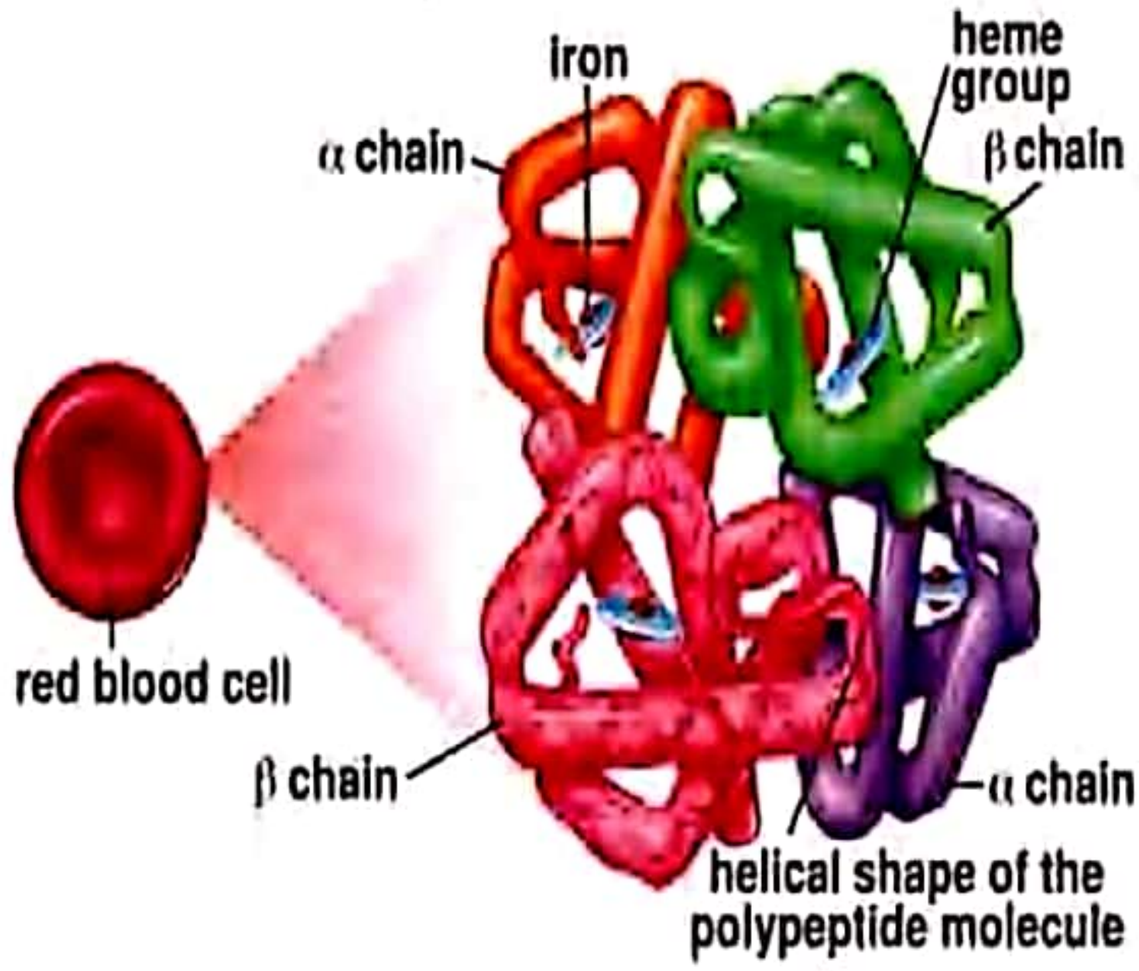
Protein Digestion

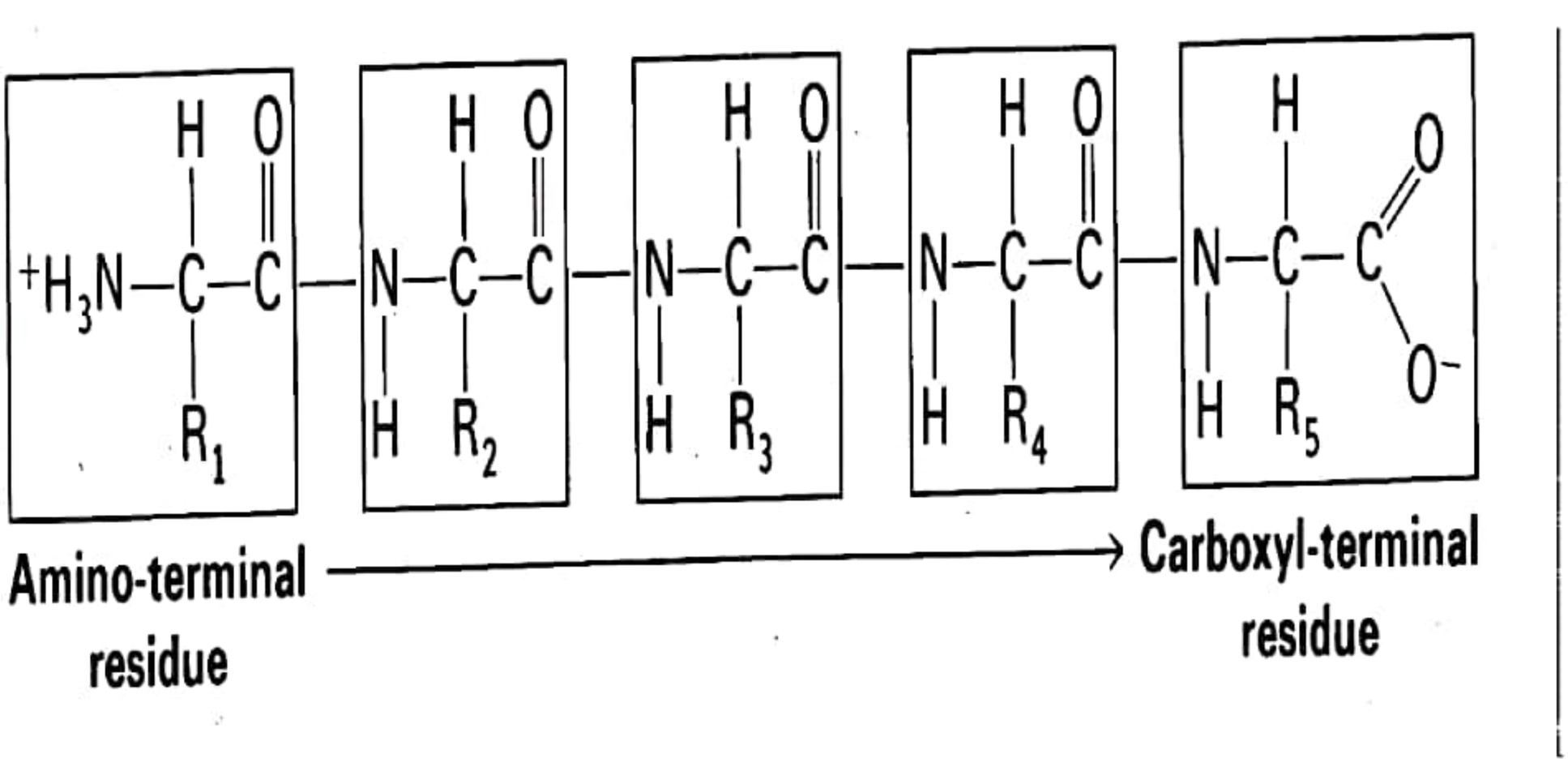
Protein breakdown begins in the **stomach**.

No protein hydrolyzing enzymes are found in saliva.









Hydrolysis (10% of peptide bonds) & **denaturization** by pepsin enzyme & HCl acid produce **short chain polypeptides** in the stomach.

Trypsin, chymotrypsin, & carboxypeptidase from Pancreatic juices, and **Aminopeptidase** from cells in the small intestine Brush Zone create "free" **amino acids**.

Free amino acids are absorbed thru intestinal wall via active transport.

Enter bloodstream and are brought to cells.

The total supply of free amino acids available is called: the **Amino Acid Pool**.

<u>3 sources of "free" amino acids:</u>

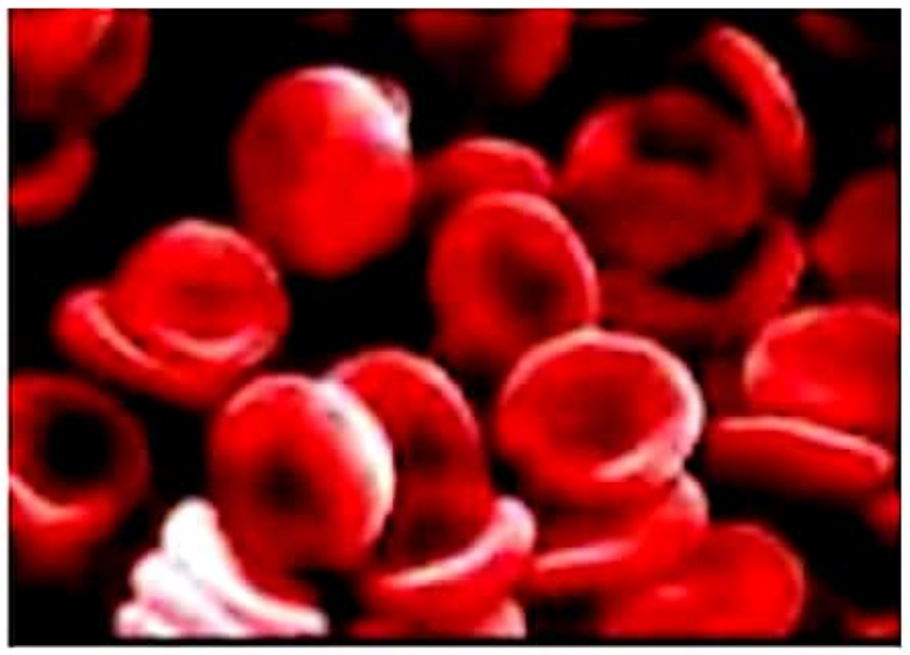
1. Dietary protein breakdown
2. Biosynthesis of amino acids in the Liver
3. Protein turnover (I prefer apple turnovers)

Protein turnover is the breakdown & re-synthesis of body protein:

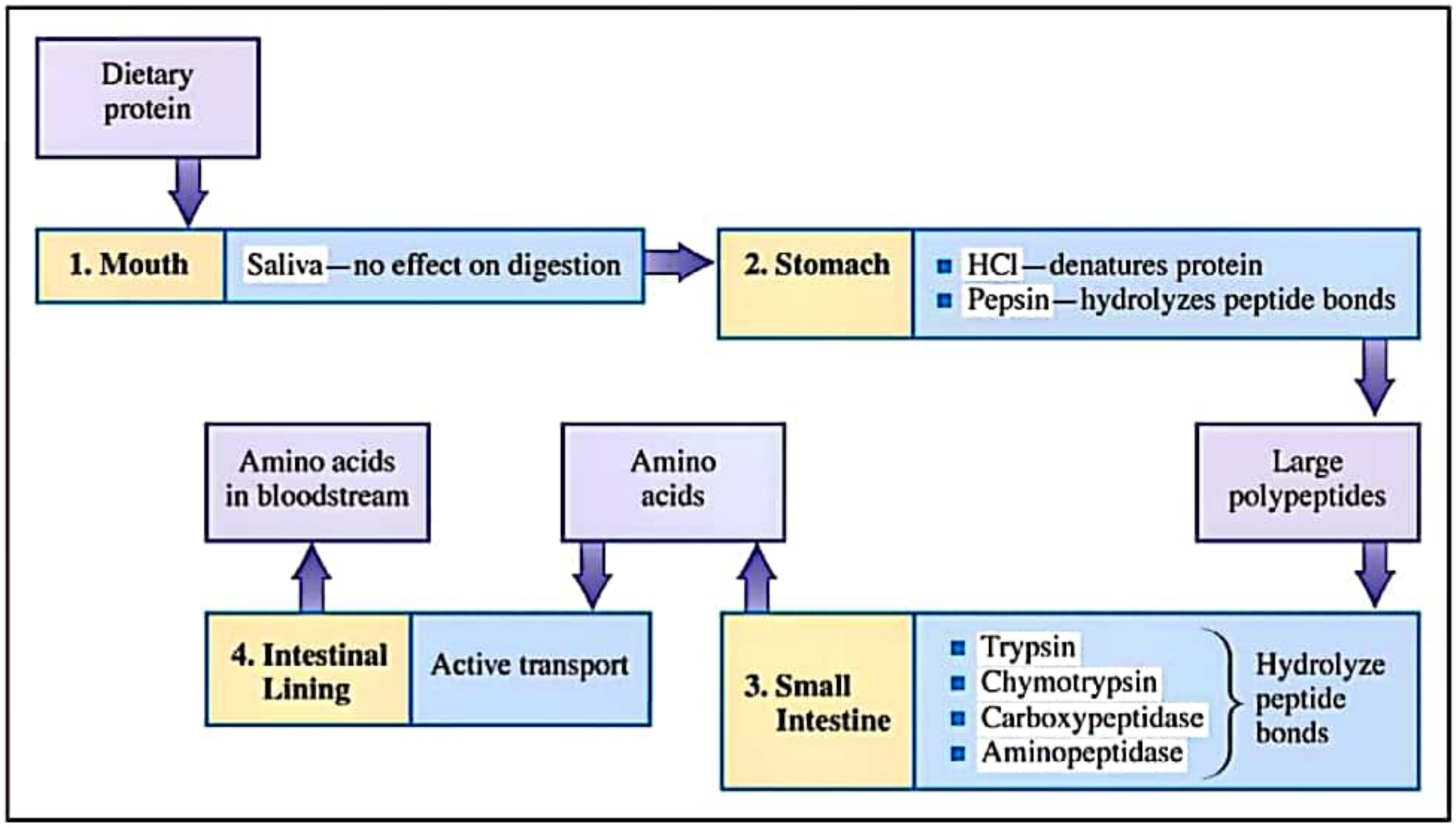
Old tissues

Damage

Recycling enzymes & hormones



Summary of protein digestion in the human body. Possible fates for amino acid degradation products.



Transamination and Oxidative Deamination:

Two steps in degrading amino acids

1) remove a-amino group

2) breakdown & process carbon skeleton

Release of an **amino group** is also two steps:

1) **Transamination**

2) **Oxidative deamination**

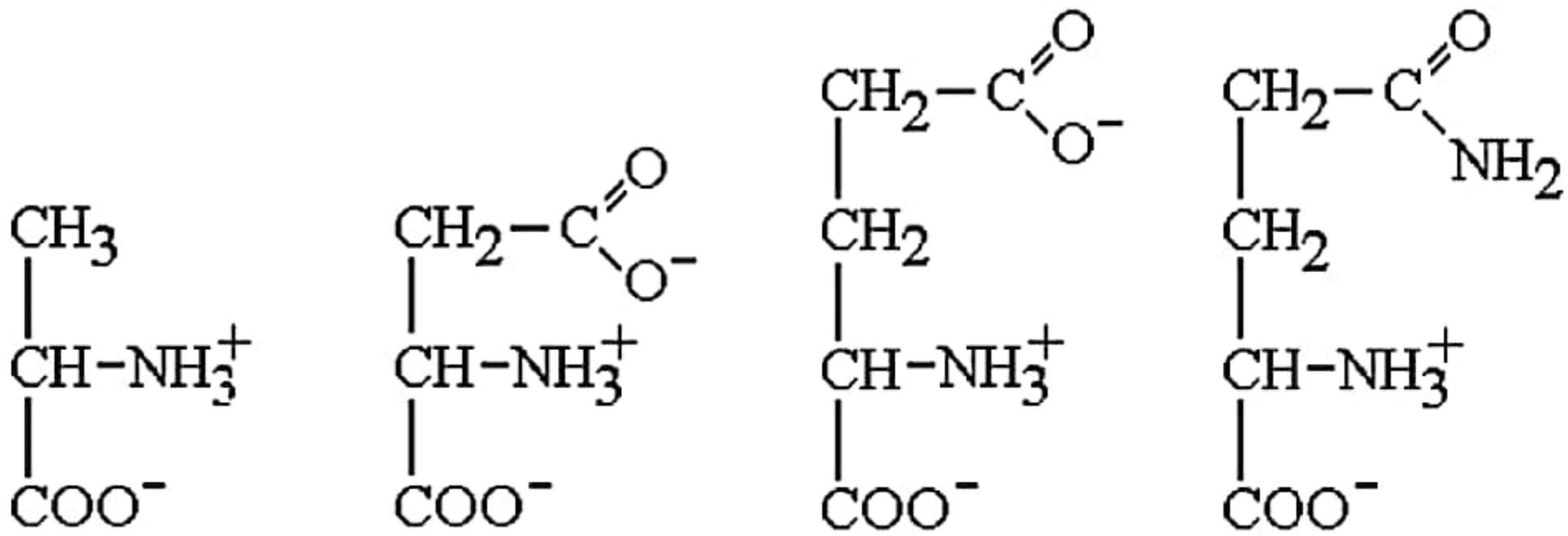
Central role of glutamate:

Amino acids:

Glutamate, **aspartate**, **alanine** & **glutamine**

present in higher concentrations in mammalian cells. Have metabolic functions as well as roles in proteins.

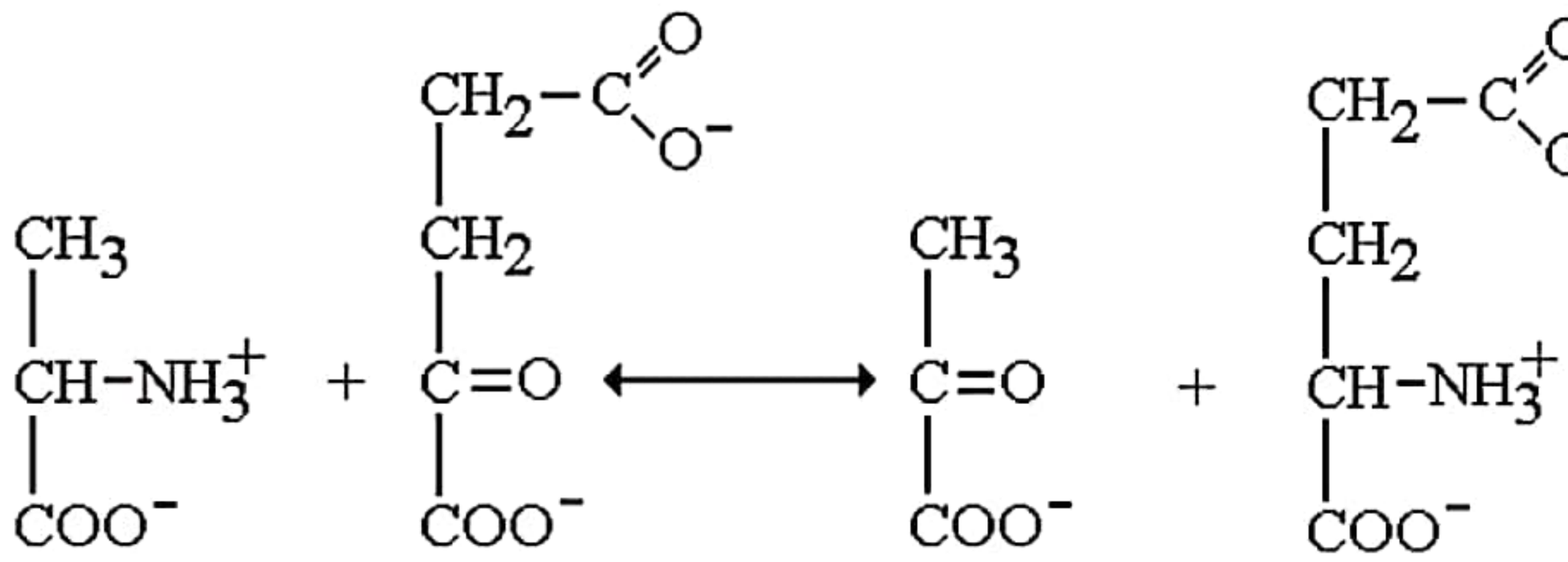
Glutamate is the most important, metabolically



Alanine Aspartate Glutamate Glutamine

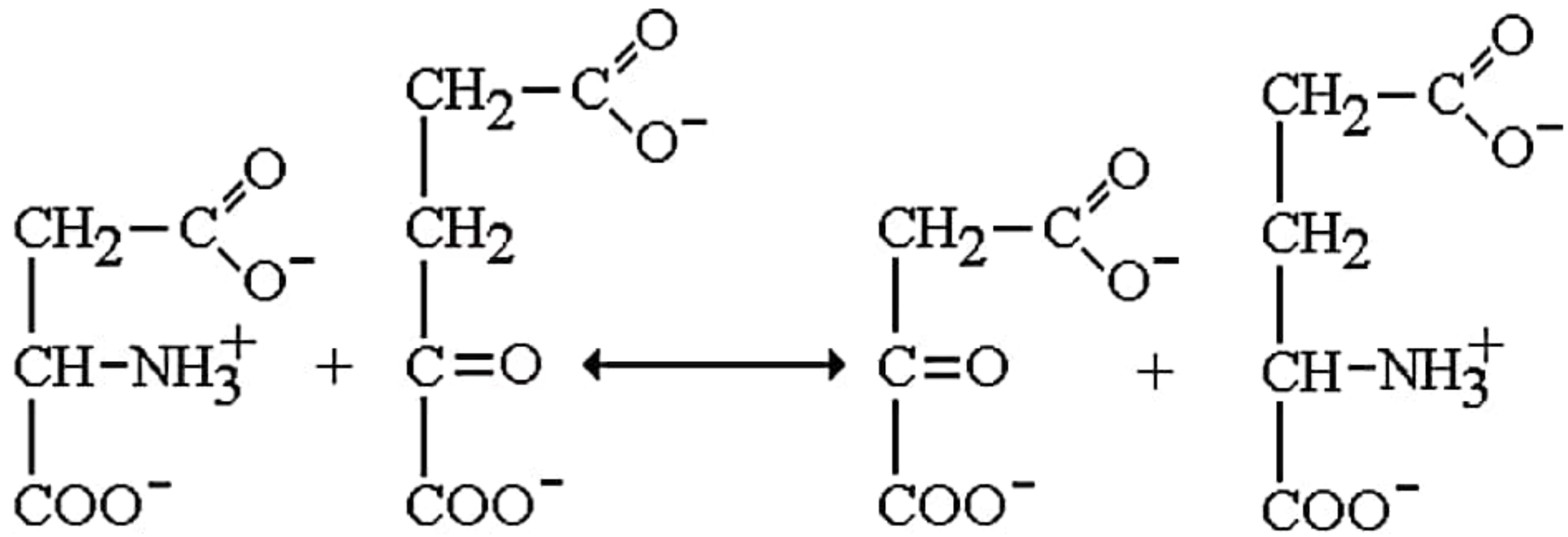
Some **transaminases** are used for diagnosing disorders:

enzyme **alanine aminotransferase**. Escapes in large amounts from dead or dying liver tissue. Measured in blood samples for diagnostic purposes.



Alanine Oxoglutarate Pyruvate Glutamate

Transaminase enzyme **aspartate aminotransferase** very active enzyme inside heart cells. Also escapes in large amounts from dead or dying heart tissues & enters bloodstream. Measured in blood for diagnosing myocardial infarction.

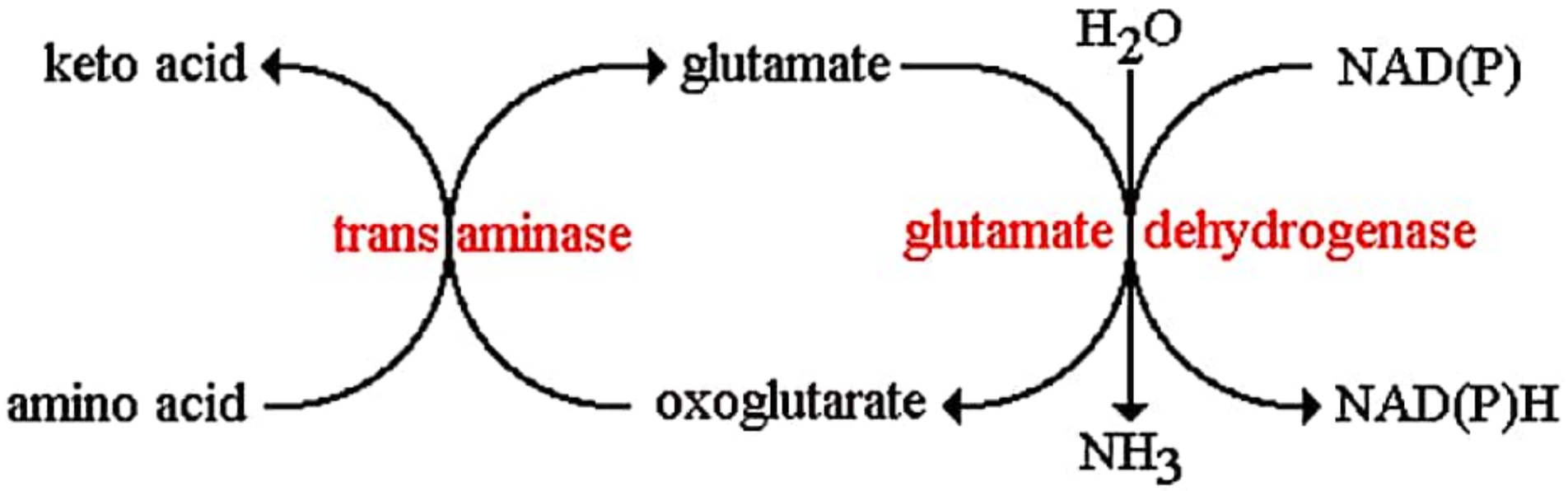


Trans-deamination (sum it up)

Most **transaminases** share a common substrate and product (oxoglutarate and glutamate) with the enzyme **glutamate dehydrogenase**.

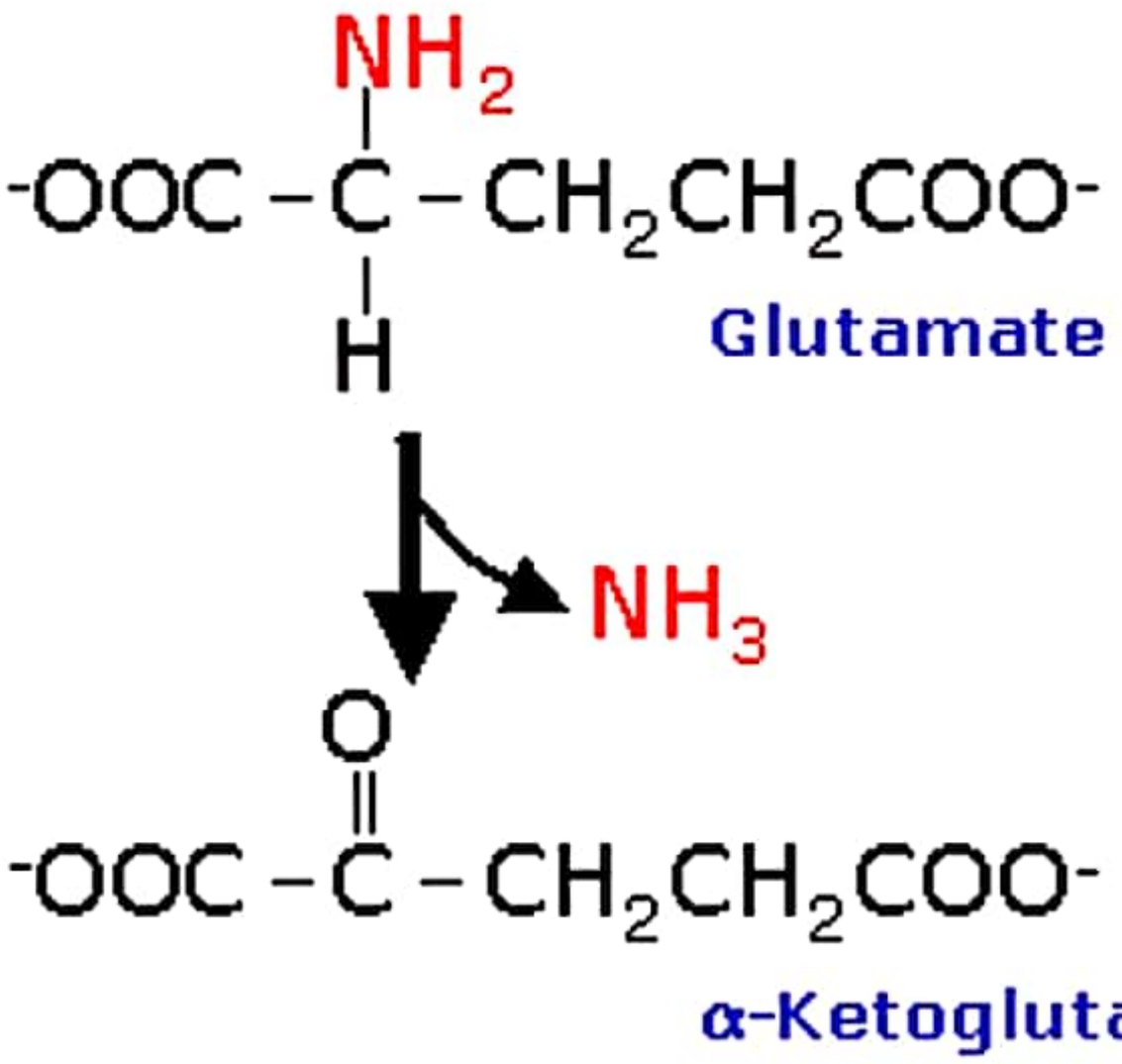
This permits a ***combined*** N excretion pathway for individual amino acids: "trans-deamination."

Glutamate has a central role in the overall control of nitrogen metabolism.



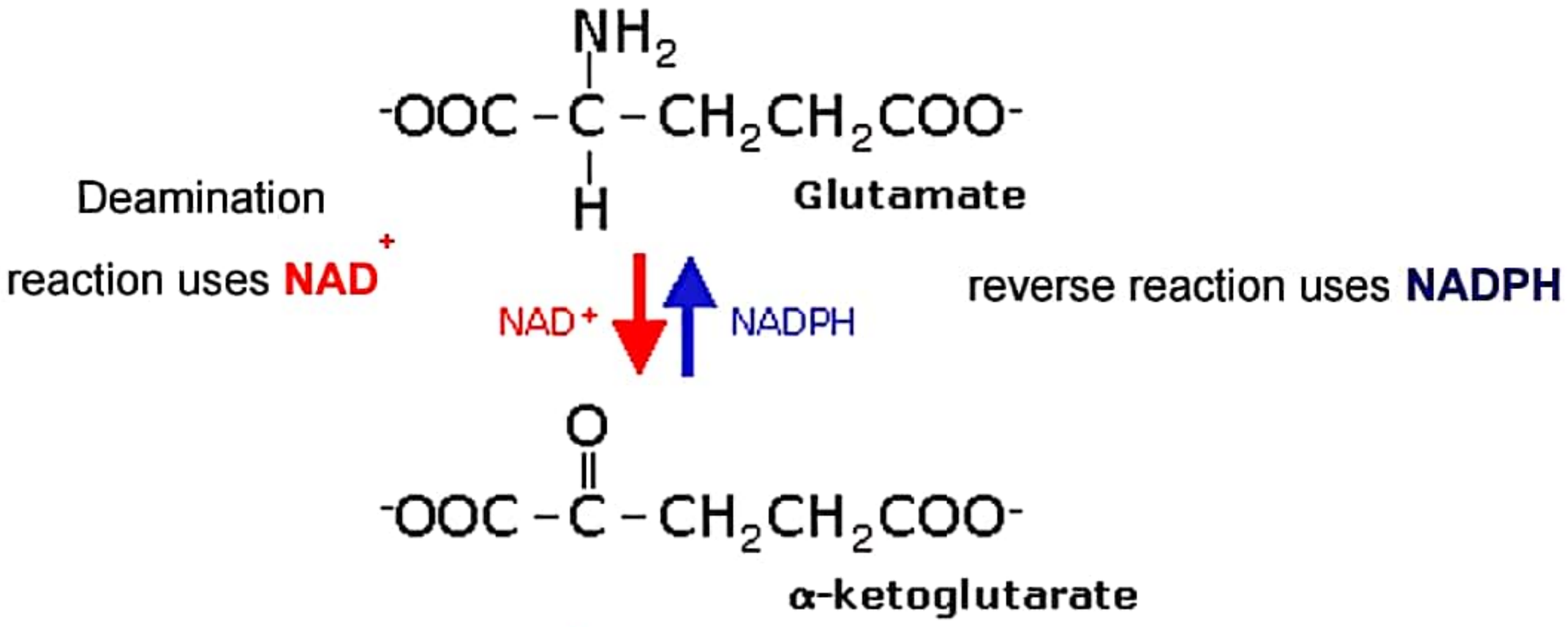
Oxidative Deamination

The **glutamate** produced from the transamination step is then deaminated by **oxidative deamination** using the enzyme **glutamate dehydrogenase**



Recycles back to a ketodiacid & releases ammonia

Glutamate dehydrogenase [GluDH] will reversibly convert **glutamate** to **a-ketoglutarate** and **a-ketoglutarate** to **glutamate**.



Uses ***both*** **NAD**$^+$ and **NADPH** – how to regulate it?

Urea cycle:

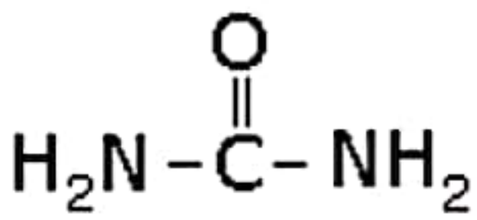
Ammonium salts (NH_4^+) are toxic compounds.

Oxidative deamination converting glutamate to a-ketoglutarate is an easily shifted equilibrium reaction.

Ammonium ions building up favors the synthesis of excessive amounts of glutamate, decreasing the Krebs cycle intermediate **a-ketoglutarate**.

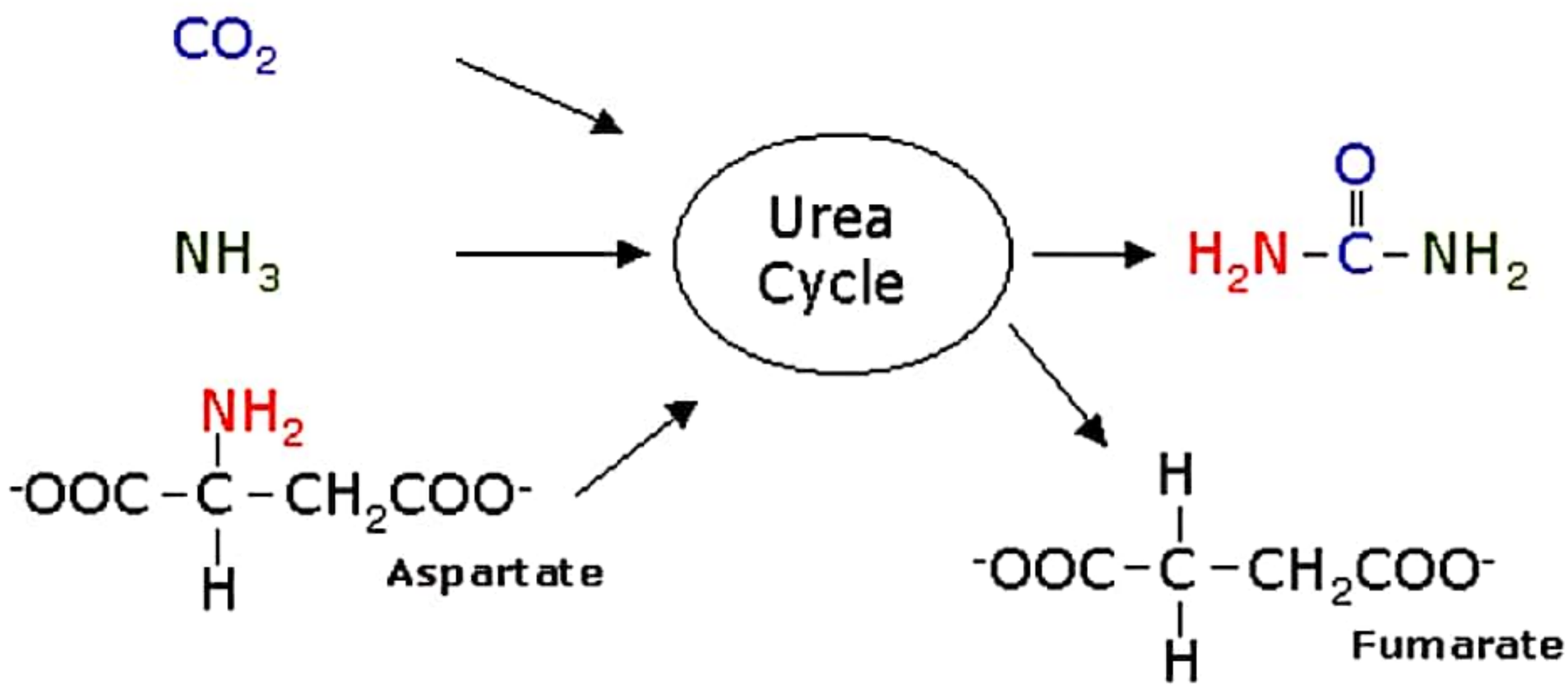
This in turn decreases **ATP production**, and that affects the nervous system.

The answer is Urea:

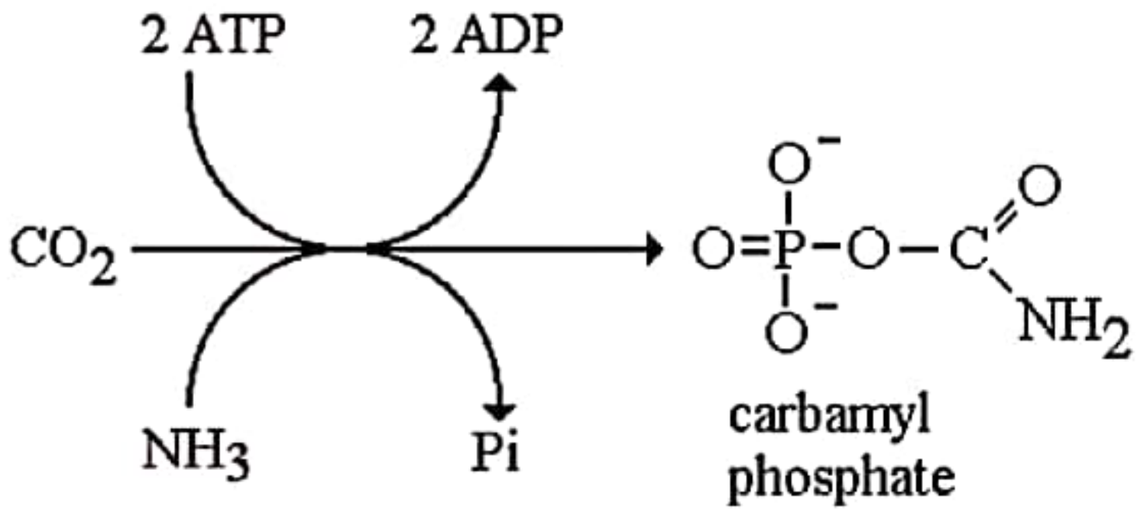


The **inputs** to the urea cycle are NH_3, CO_2 and aspartic acid and ATP.

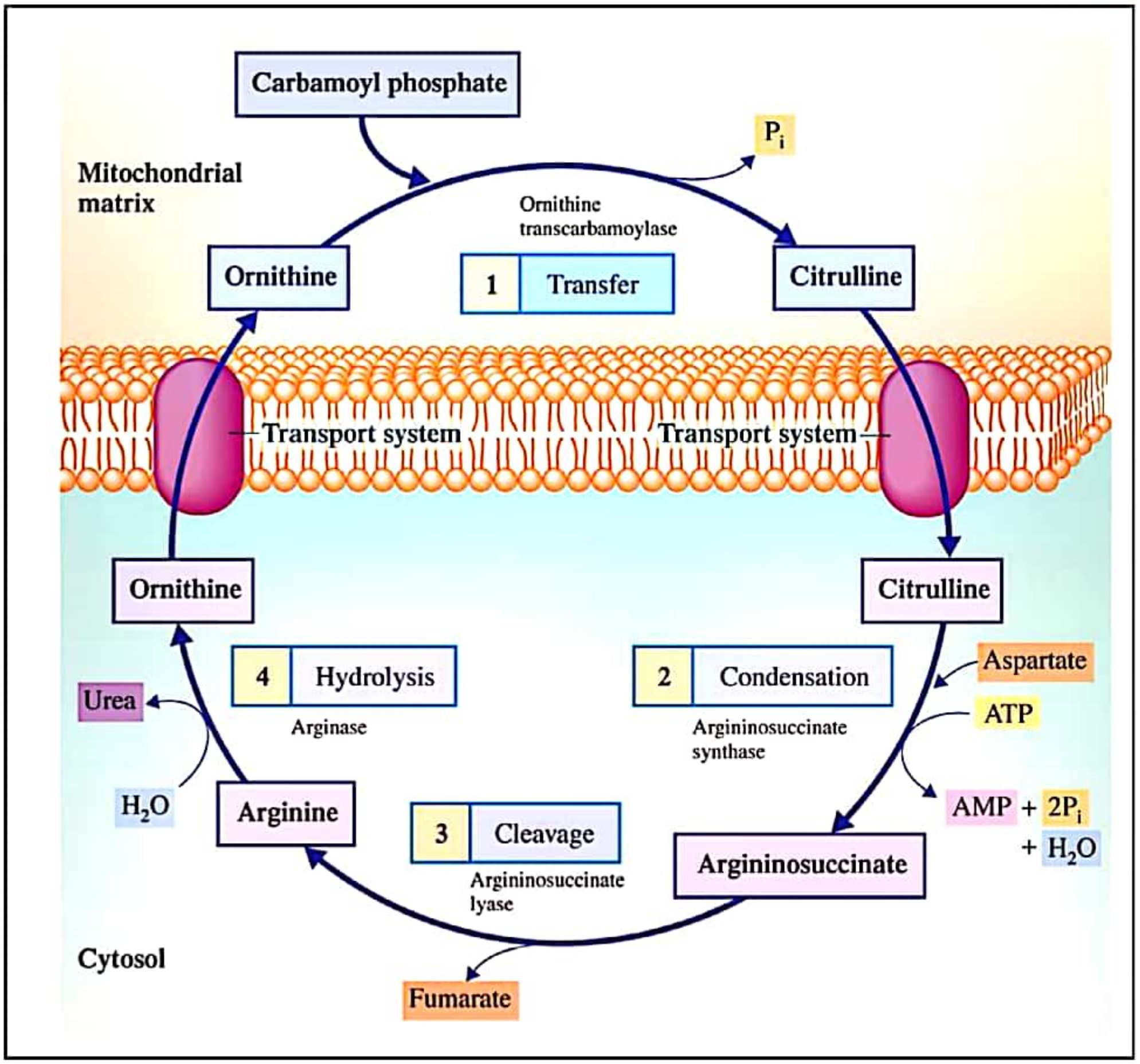
The **outputs** are urea, ADP and fumaric acid.



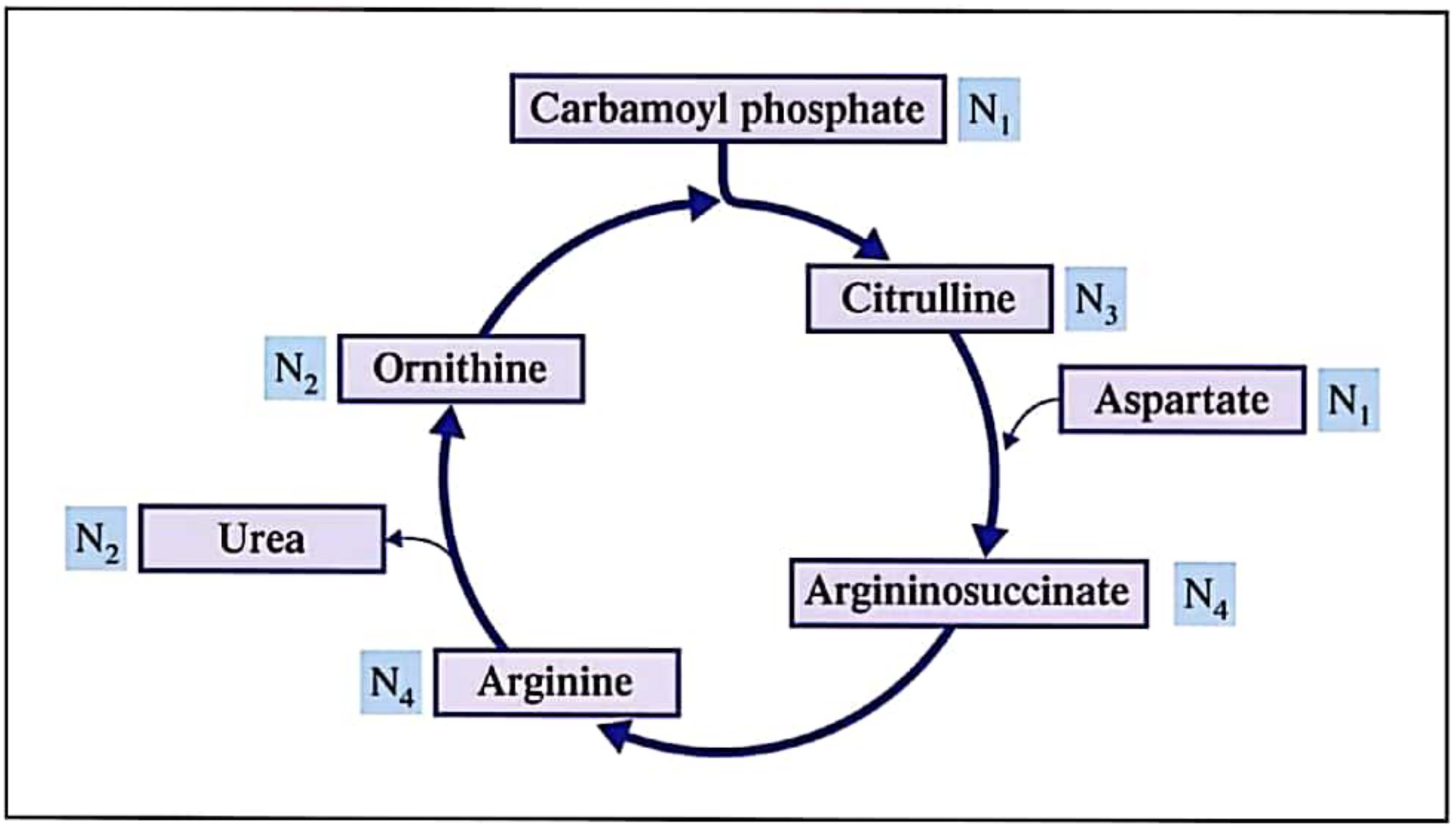
The carbonyl group of urea is derived from **CO_2** , **Ammonia** contributes one of the amine groups on urea



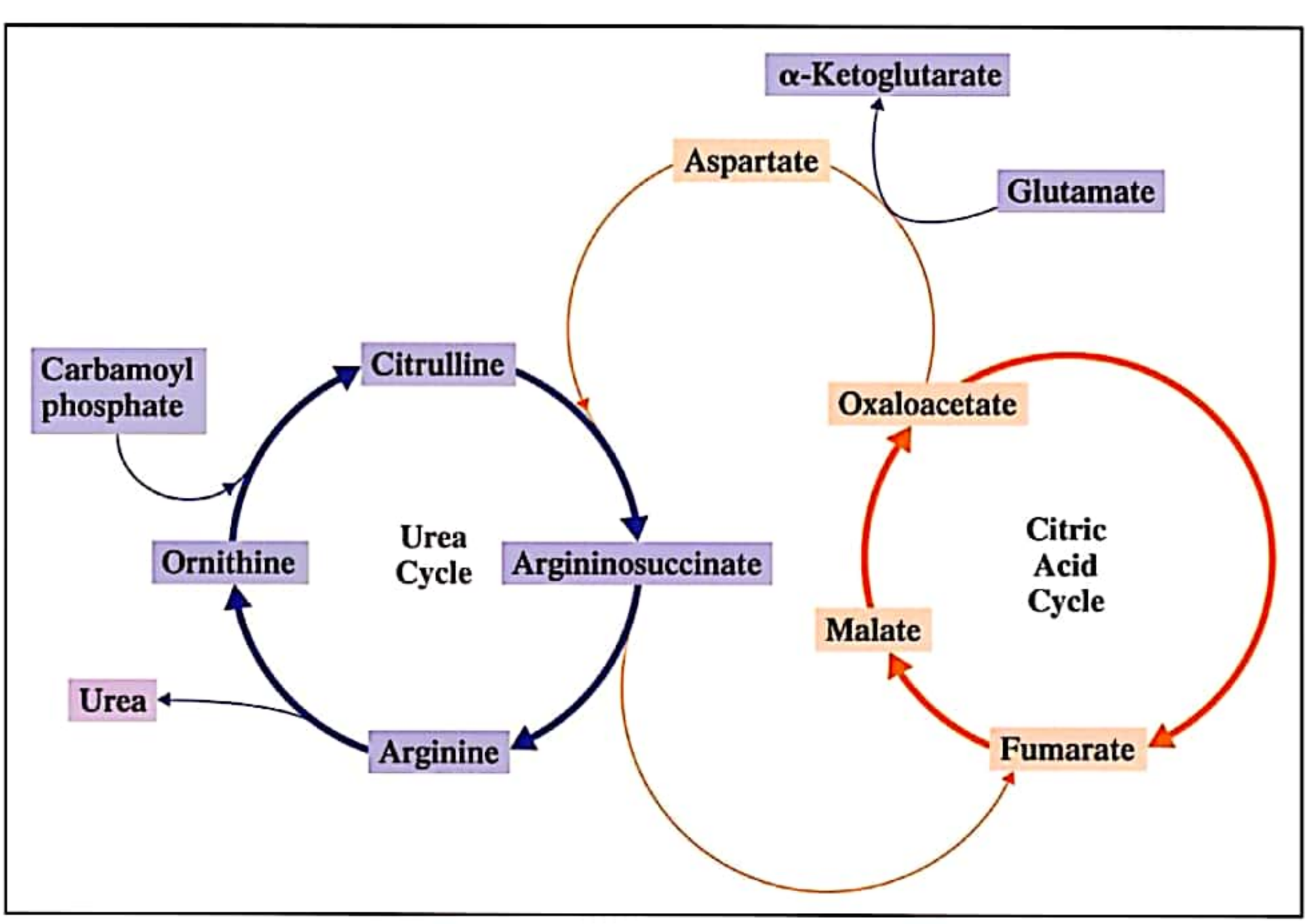
The **four-step** urea cycle in which **carbamoyl phosphate** is converted to **urea**.



The nitrogen content of the various compounds that participate in the urea cycle



Fumarate from the urea cycle enters the Krebs cycle. **Aspartate** produced from **oxaloacetate** of the Krebs cycle enters the urea cycle.



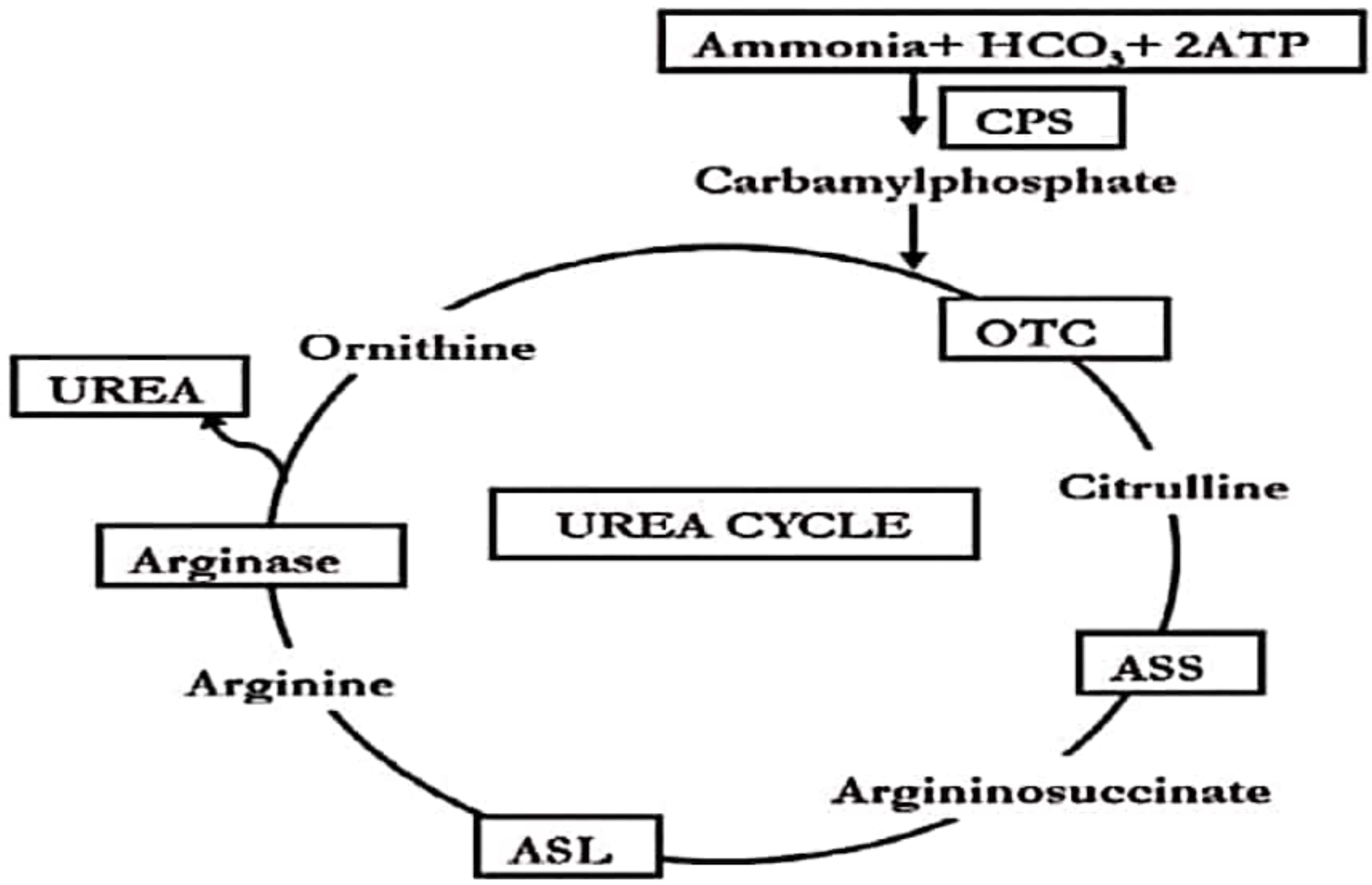
Oxaloacetate has 4 potential fates: transamination; conversion to glucose; formation of citrate; conversion to pyruvate

Summary:

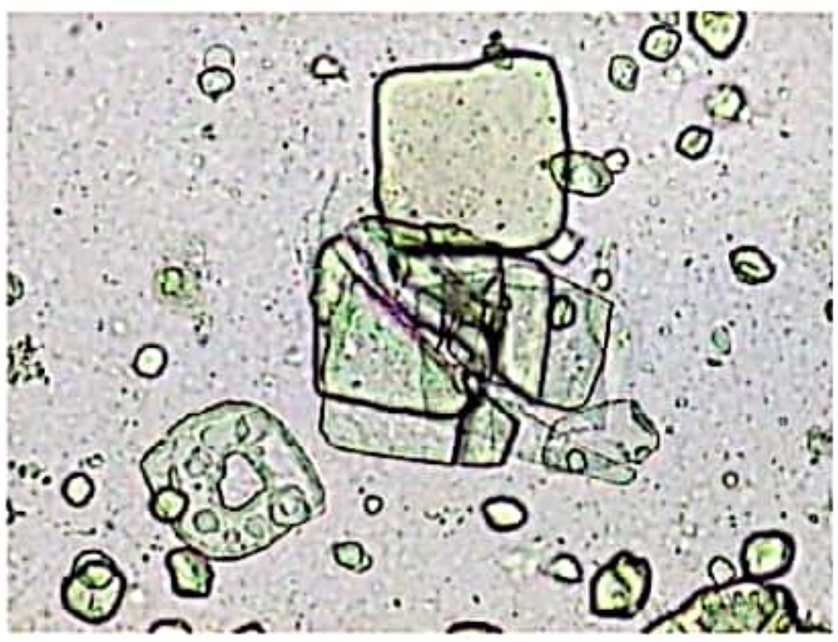
Transamination takes off amine groups from amino acids and forms **glutamate**
(ionized glutamic acid)

Amine groups form **ammonia** when removed in **deamination**
This combines with **CO_2** & **Aspartate**.

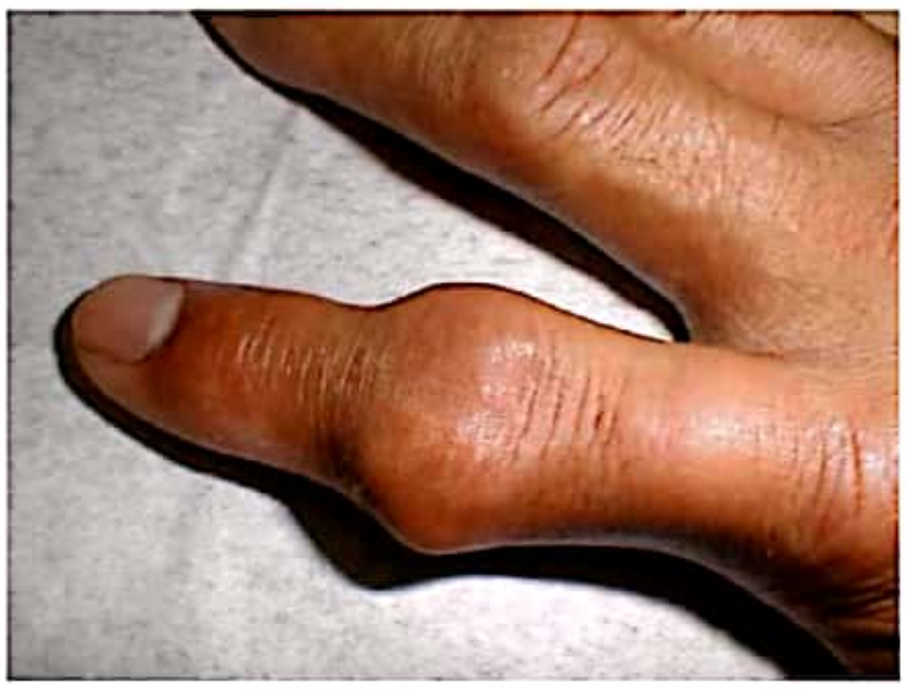
Forms **urea**, **Arginine**,
& Fumarate

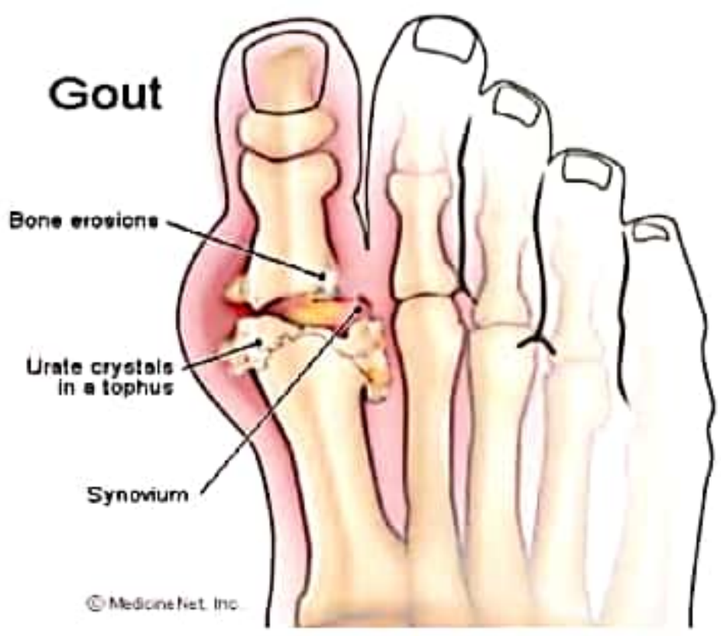


Reptiles & birds excrete **uric acid** – very ***insoluble*** purine compound – forms supersaturated solutions. Concentrated urine, supersaturated with uric acid, goes from cloaca into hindgut – uric acid crystalizes & water is reabsorbed.



In humans uric acid deposits crystals & causes gout





Processing Amino Acid Carbon Skeletons

Transamination or Oxidative deamination both produce a-keto acids

Degradation of these carbon skeletons may take several different pathways:

Amino acid C skeletons that degrade to form a Krebs cycle intermediate can then be used to make glucose via **gluconeogenesis**.

These are called **Glucogenic Amino Acids**.

Amino acid C skeletons that degrade to form **acetyl CoA** or **Acetoacetyl CoA** can form fatty acids or ketone bodies.

These are called **Ketogenic Amino Acids**.

Amino Acid Biosynthesis

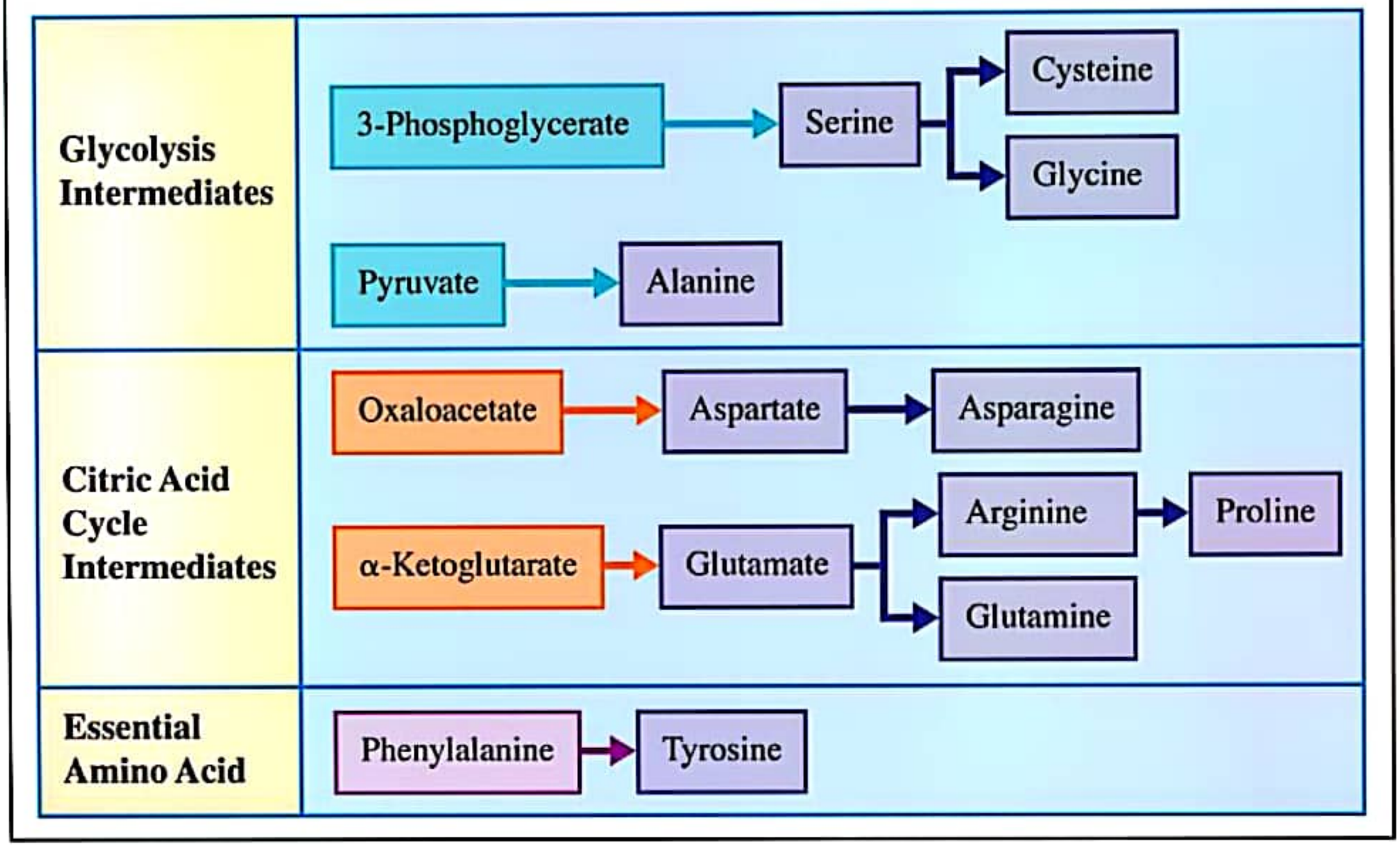
Essential amino acids can be made by plants & bacteria in 7 to 10 steps.

We obtain these amino acids by eating plants.11 Non-essential amino acids synthesized in 1 to 3 steps. Use glycolysis intermediates:

3-phosphoglycerate & pyruvate Krebs cycle intermediates:

Oxaloacetate & **a-ketoglutarate**.

Starting materials for biosynthesis of 11 **nonessential** amino acids: 1 step, 2 steps, or 3 steps

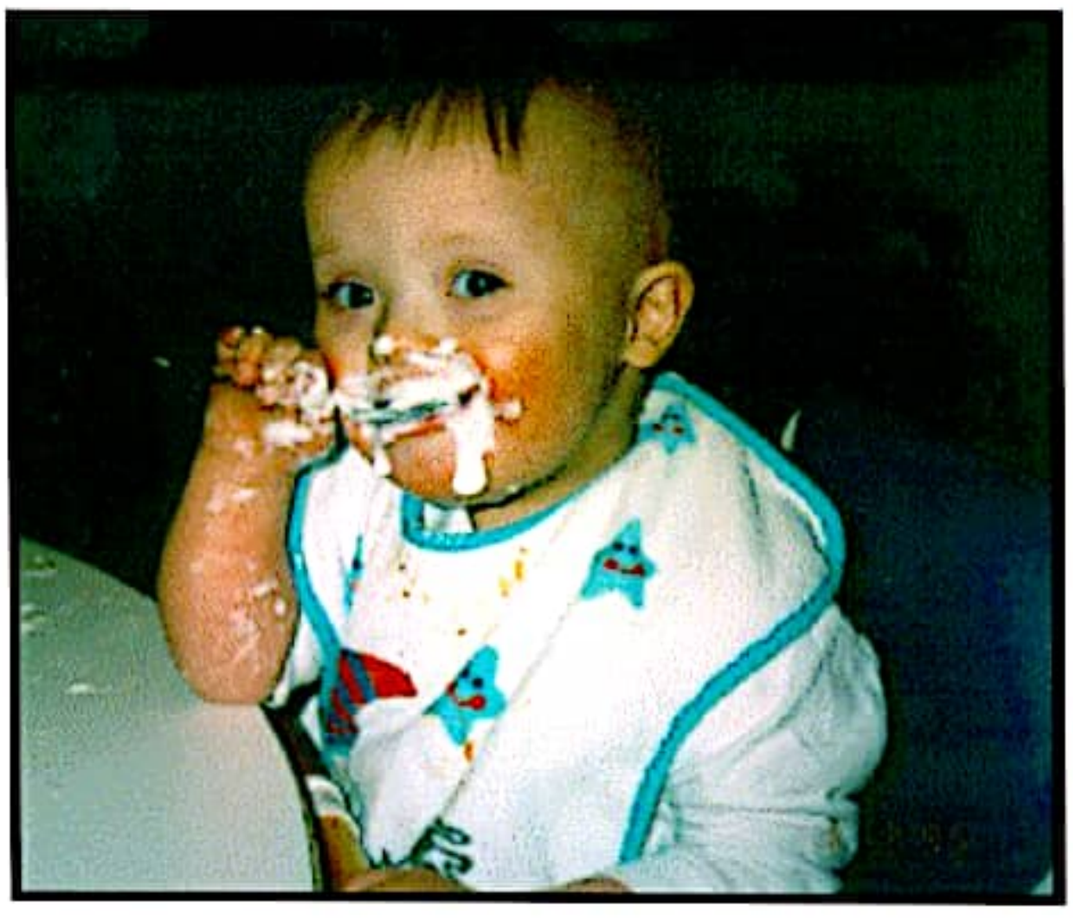


Alanine, aspartate, & glutamate use transamination

Phenylketonuria (PKU):

Defective phenylalanine hydroxylase – **phenylalanine** accumulates in body. Phenylalanine is transaminated to **phenylpyruvate**.

Accumulation of phenylpyruvate leads to severe mental retardation in infants. Persons suffering from phenylketonuria should not consume foods containing high levels of phenylalanine, such as aspartame.



Hemoglobin catabolism

Red blood cells contain oxygen carrying pigments of a conjugated protein: Protein part is ***Globin*** Non-protein prosthetic group is ***Heme***. **Heme** contains four pyrrole (**tetrapyrrole**) groups held together by an **iron** atom. Old red blood cells degraded in the spleen. Globin is hydrolyzed into amino acids. Iron atom stored in a protein (***ferritin***) **Tetrapyrrole** degraded to **bile pigments**.

Review: can you…

- Describe the steps in Protein digestion & absorption
- Explain how Amino Acids are utilized in the body
- Explain **Transamination** and **Oxidative De-amination**
- Describe **The Urea Cycle** – purpose and steps
- Describe how a.a. Carbon Skeletons are processed
- Define and explain Amino Acid Biosynthesis.
- Describe the chemical composition of urine.

Lipid Metabolism

Fatty acids (F.A.s) are taken up by cells.

They may serve as:

- precursors in synthesis of other compounds
- fuels for energy production
- substrates for ketone body synthesis.

Ketone bodies may be exported to other tissues: used for **energy production**. Some cells **synthesize fatty acids** for storage or export.

Energy

Fats are an important source of calories. Typically 30-40% of calories in American diet are from **fat**. Fat is the major form of **energy storage**.

Typical body fuel *reserves* are:

fat: **100,000 kcal.**

protein: **25,000 kcal.**

carbohydrate: **650 kcal.**

Provides 60% of energy needs for body at restTAG reserves would enable someone to survive starvation for ~30 days.

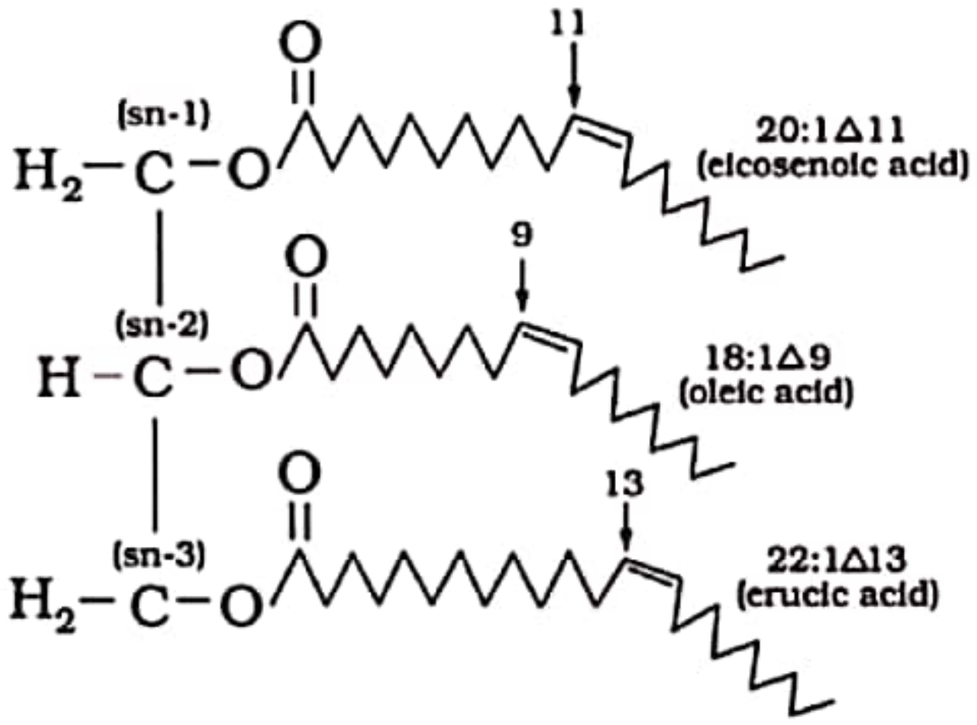
Digestion and Absorption of Lipids

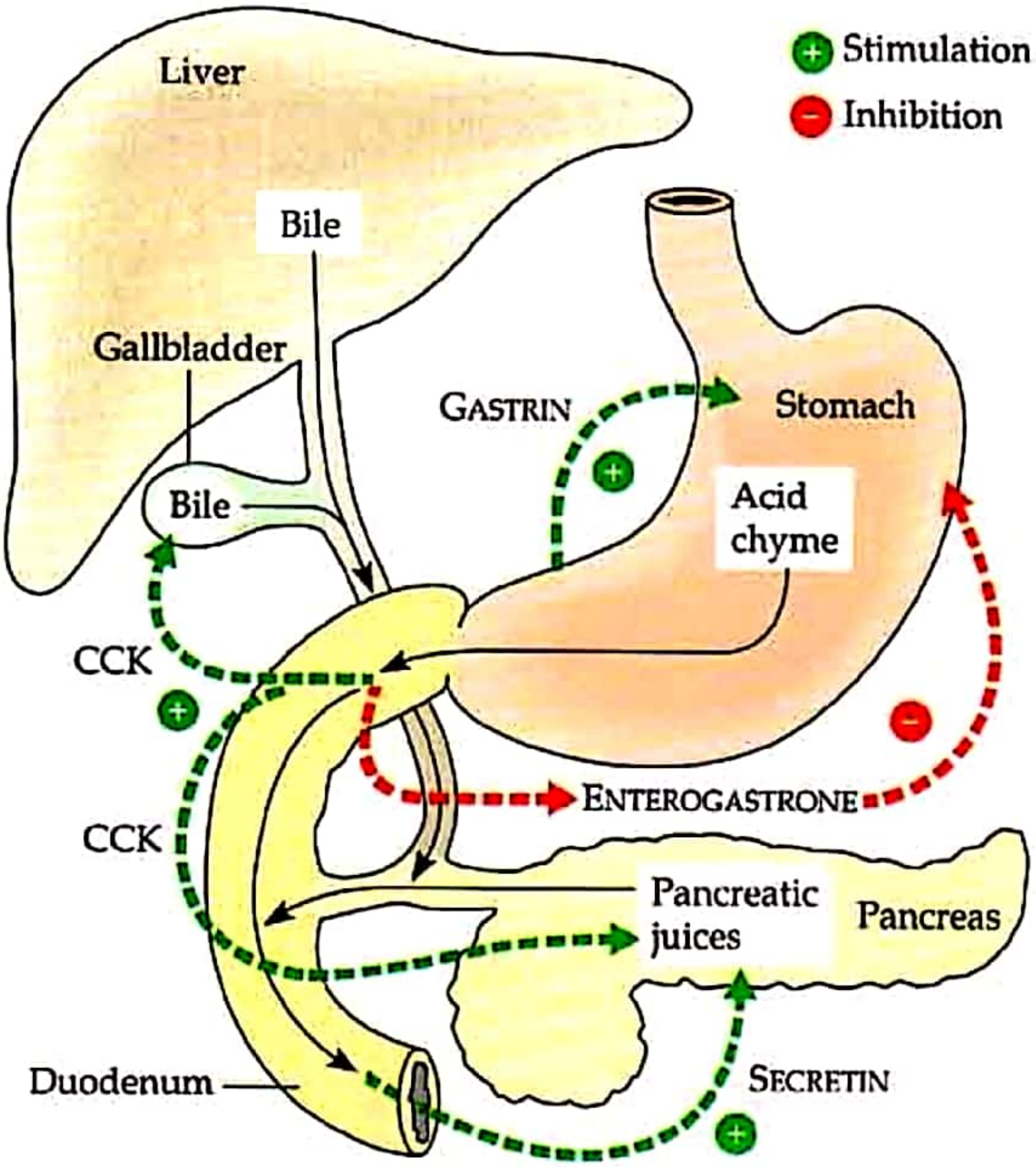
- 98% of ingested lipids are triacylglycerols (TAGs)
- Digestion in the Mouth: enzymes are **aqueous**-little effect on lipids
- Digestion in the Stomach:causes a large ***physical*** change-

  Churned into droplets:

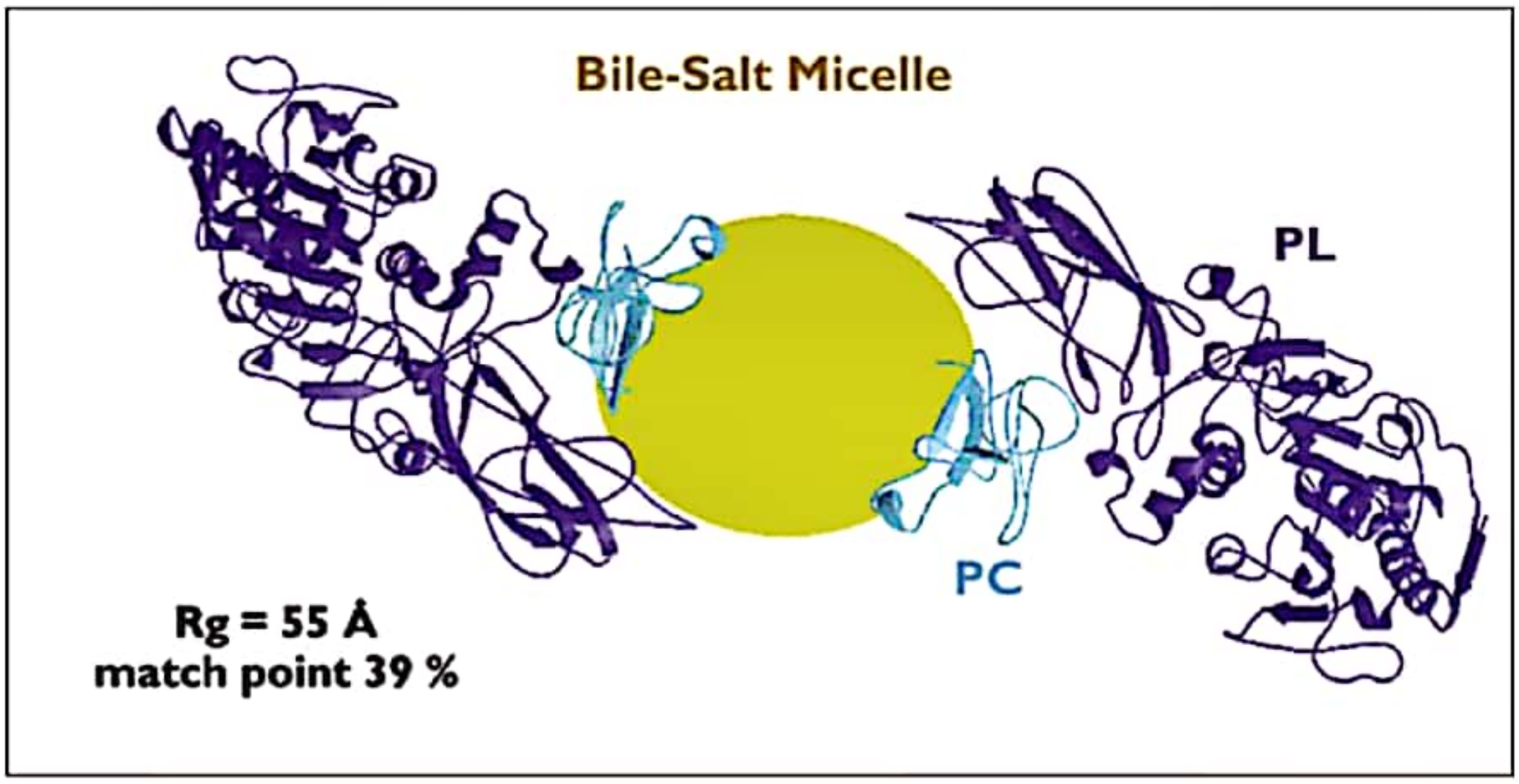
  "Chyme"

TRIACYLGLYCEROL



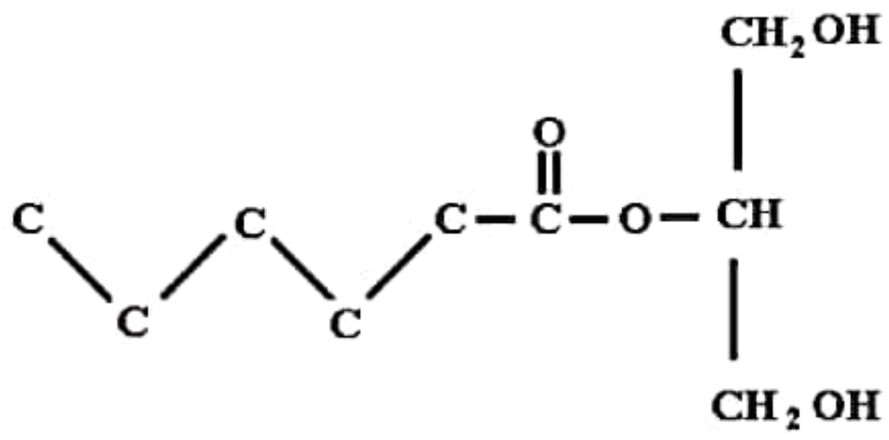


Gastric Lipase: Begins actual lipid digestion.~10% of TAGs are hydrolyzed in the **stomach**.Chyme stimulates **cholecystokinin** (CCK) to release **bile** from gallbladder.Bile is an emulsifier

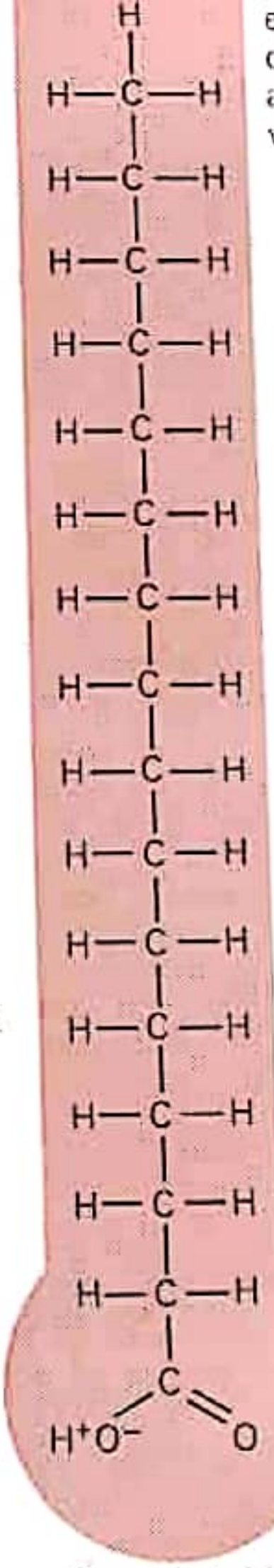


Pancreatic lipase (PL) hydrolyzes insoluble triglyceride by binding to the **bile-salt micelles**TAGs are ***partially*** hydrolyzed: 2 of the 3 F.A.s have ester linkages hydrolyzed and are released.

Monoacylglycerol remains = glycerol and 1 fatty acid



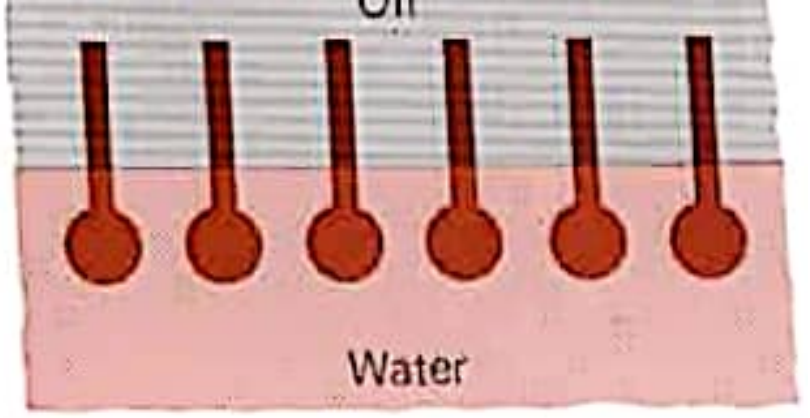
Oil droplets will form spherical **micelle** shapes.Bile salts aid this process clumping fatty acids and monacylglycerols.



end orients away from water

Ionic end is soluble in water

Palmitic acid



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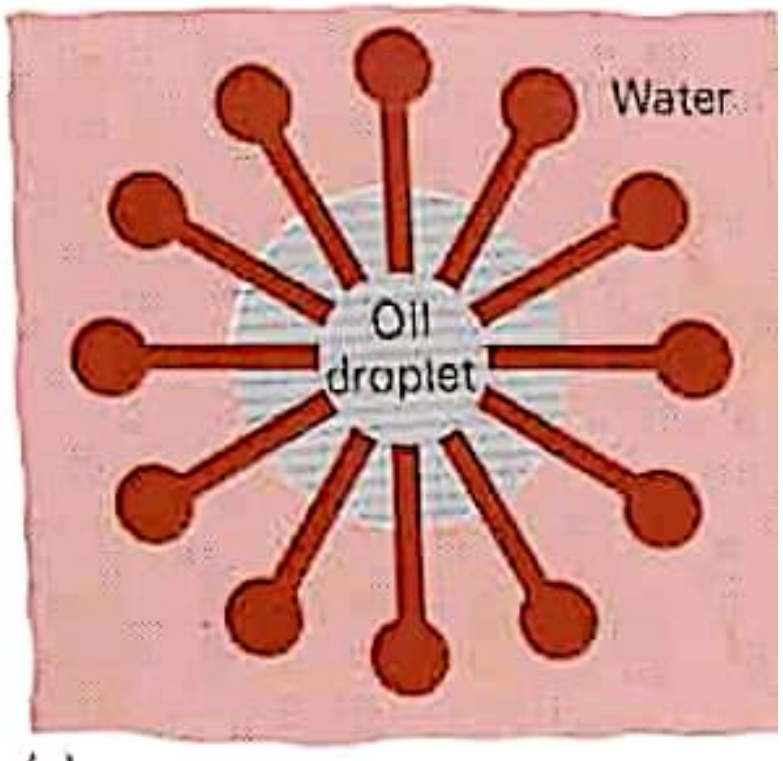
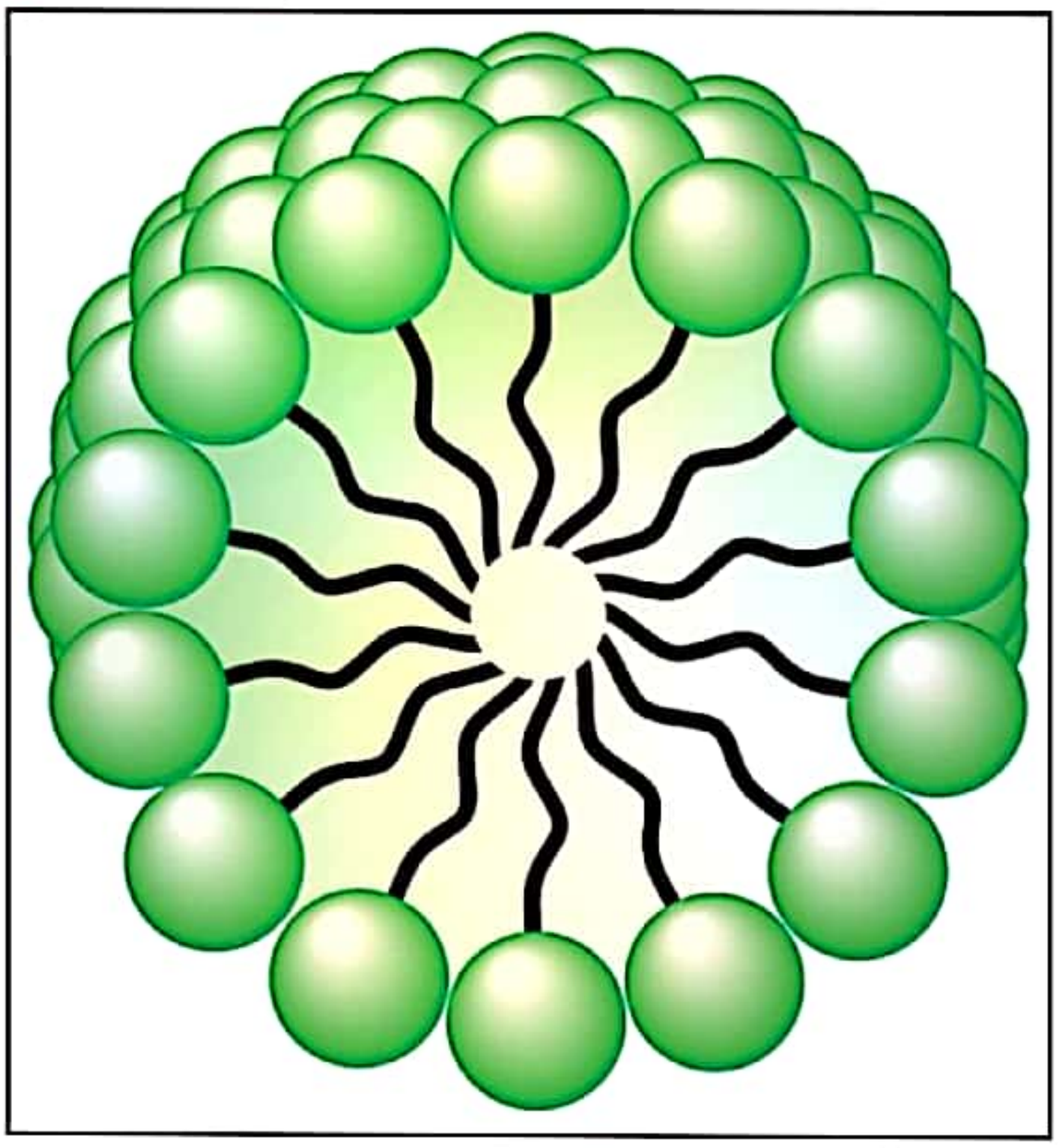


(c)

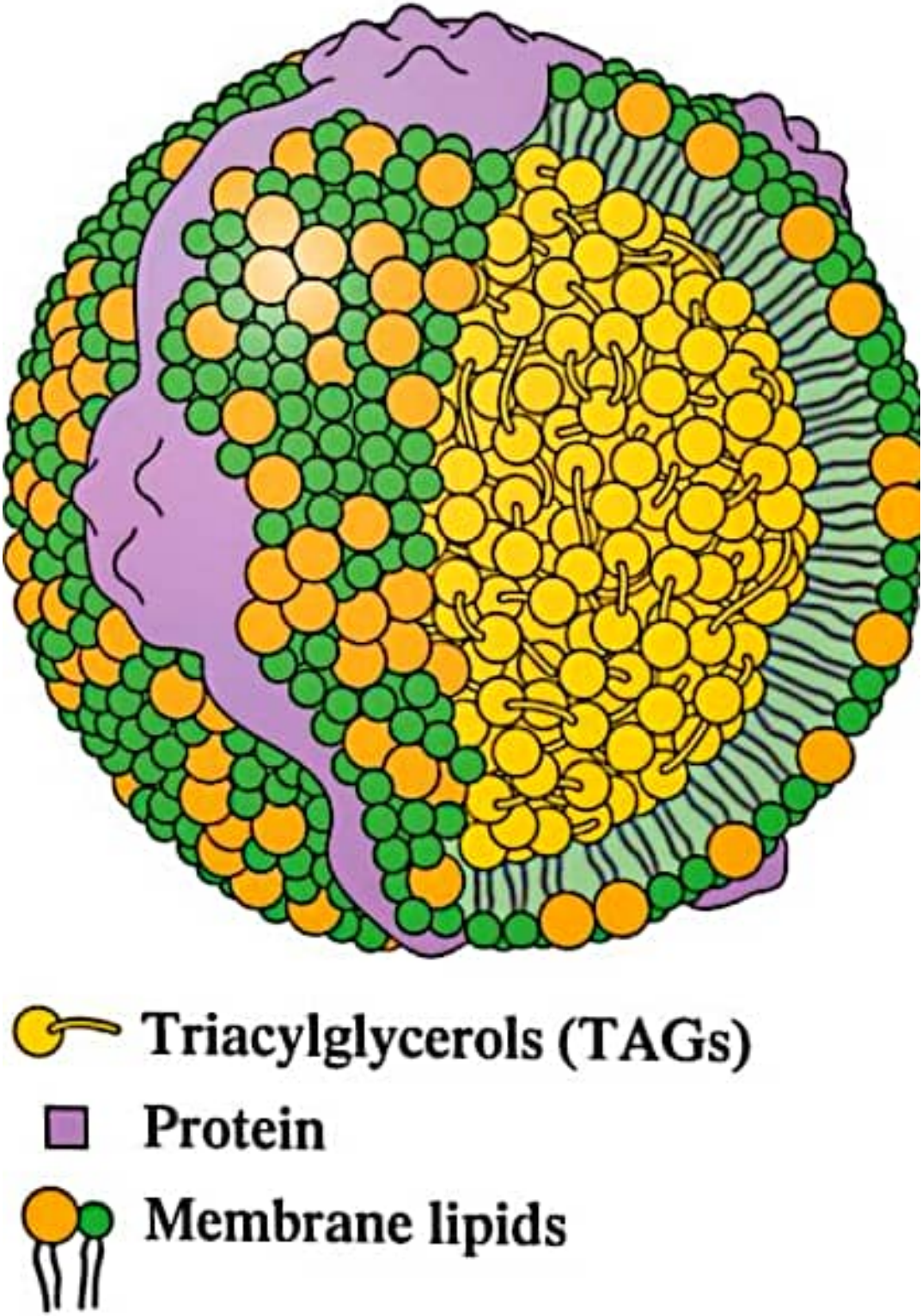
Fatty acid micelle: **hydrophobic** fatty acids & monoacylglycerols are in the interior. Bile salts on exterior.

Micelles are small enough to penetrate membrane of intestinal cells.
Free fatty acids & monoacylglycerols are reformed into **triacylglycerols**.

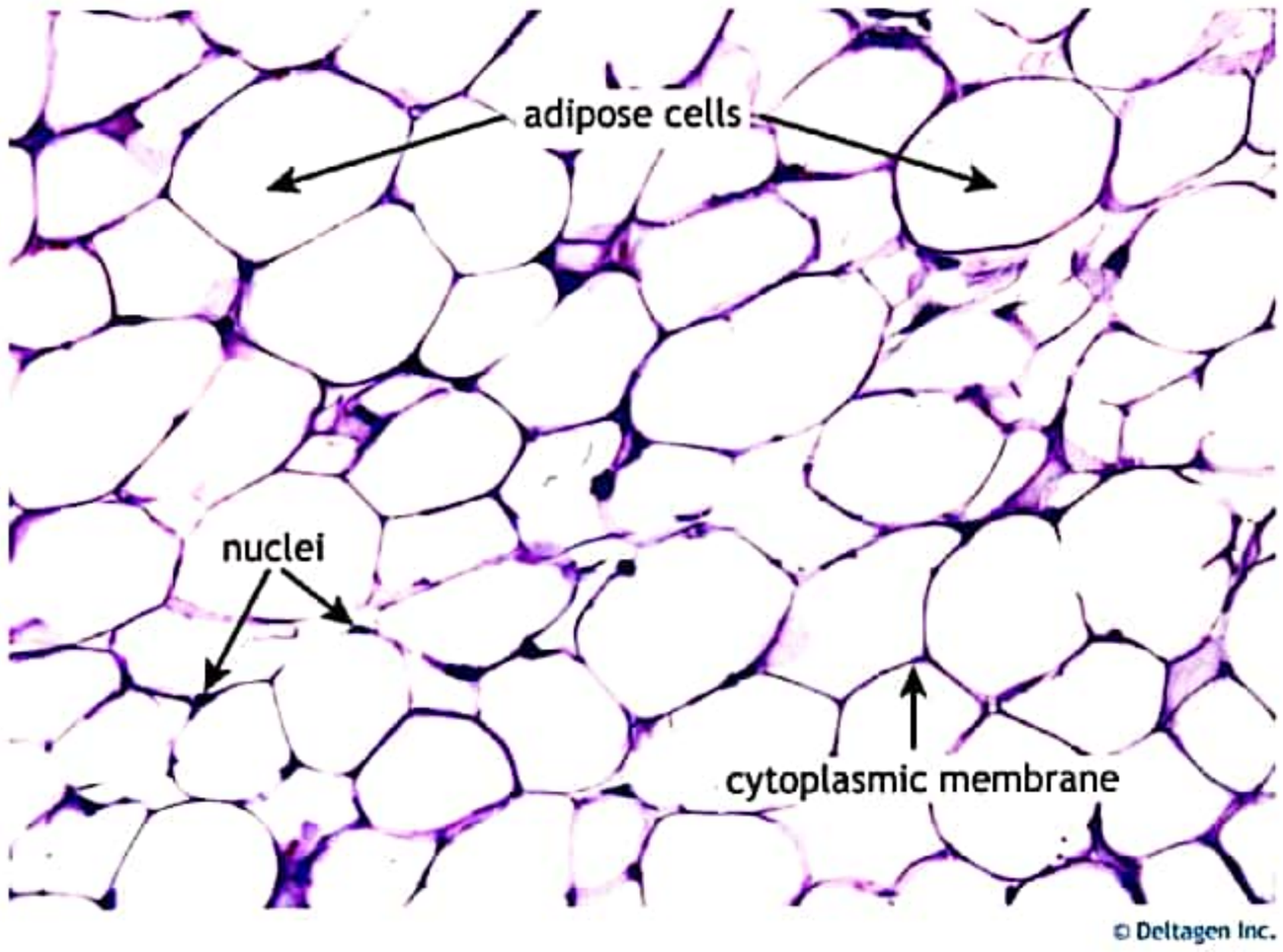


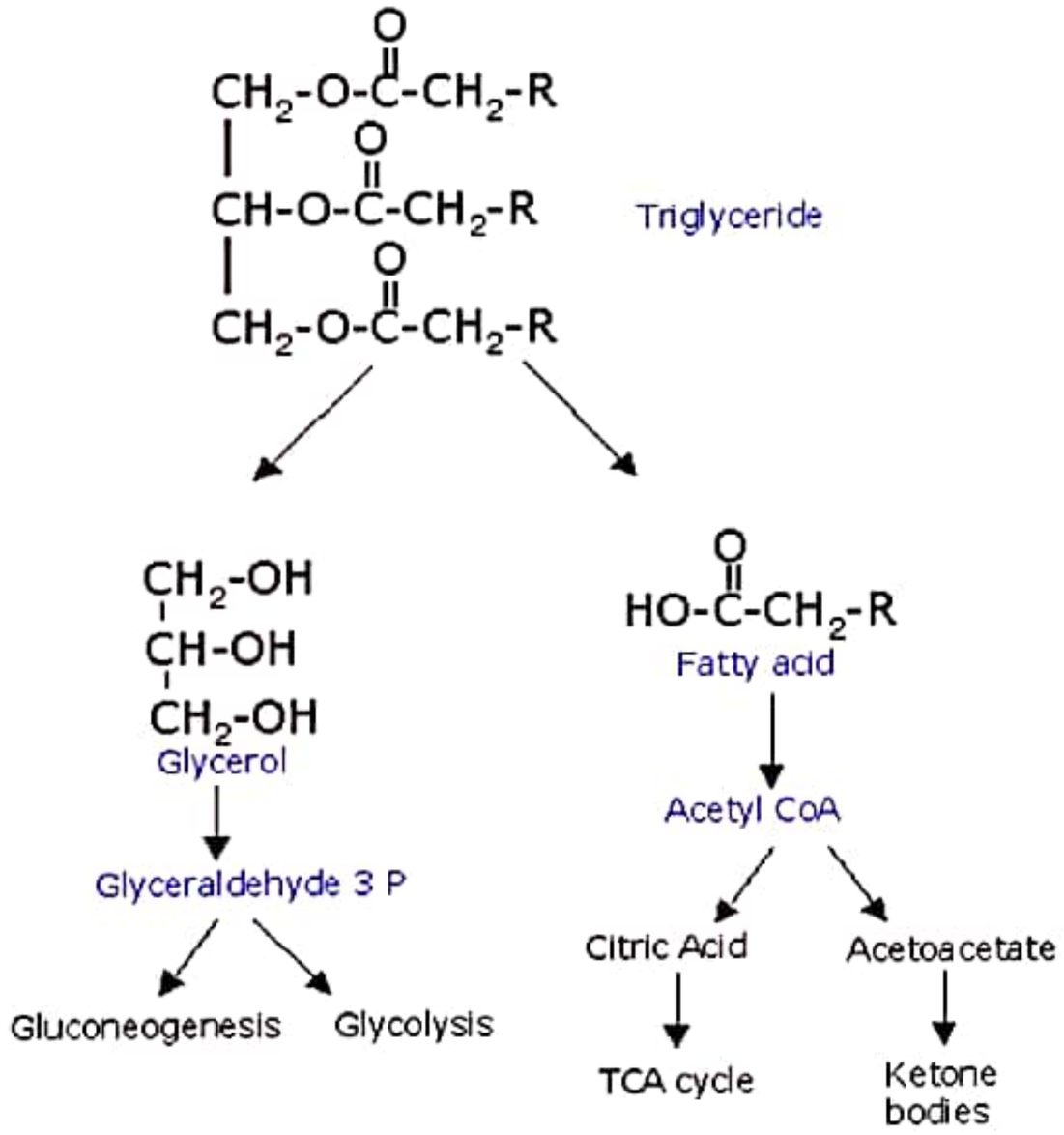
TAGs are combined with membrane & water soluble proteins to form a **chylomicron**, a lipoprotein.

Chylomicrons carry TAGs from intestinal cells into bloodstream via the **lymph system**.

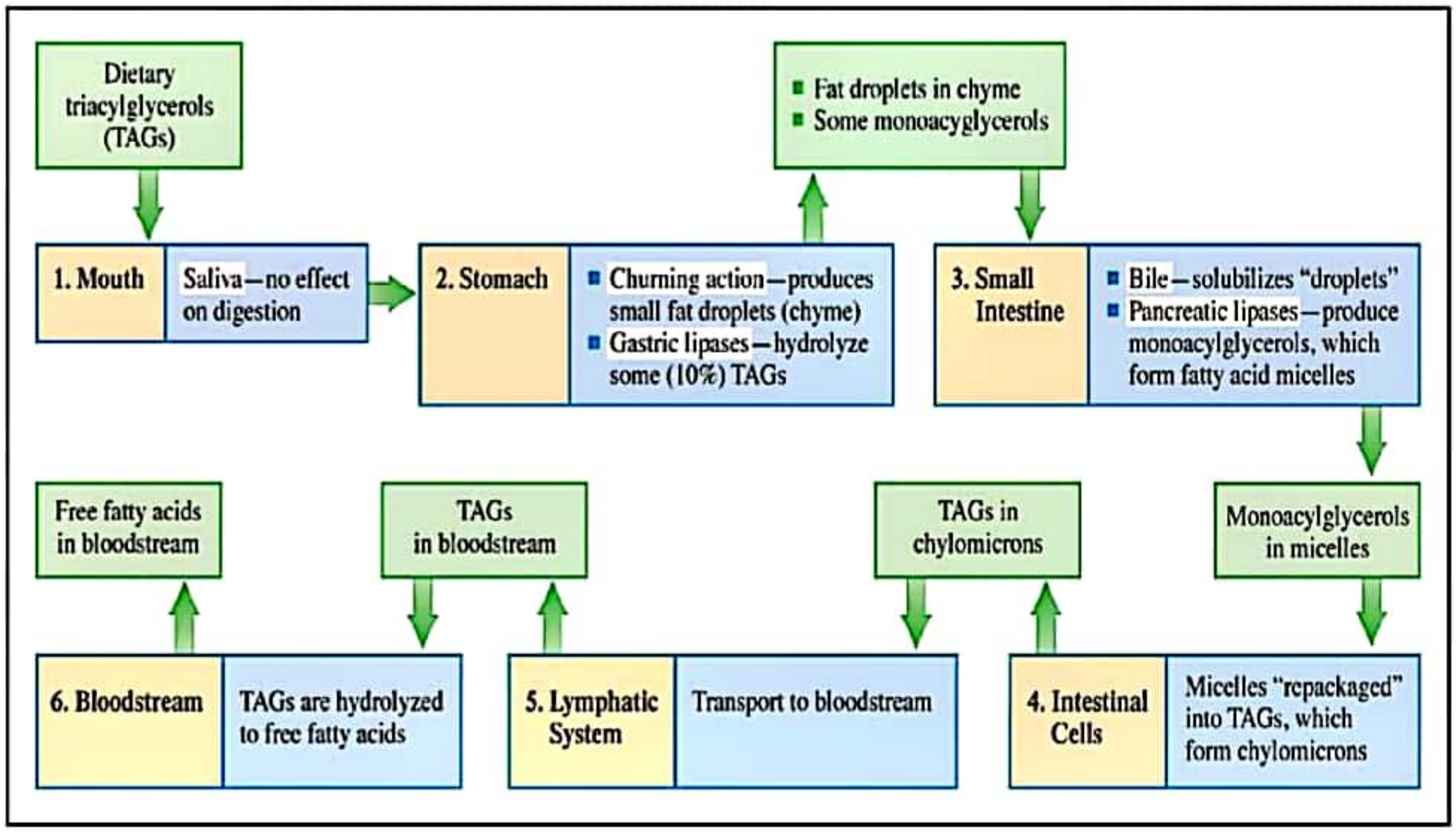


Triacylglycerols reach bloodstream & are hydrolyzed down to **glycerol** and **fatty acids**.These are absorbed by cells and processed further for energy by forming **acetyl CoA**. Or Stored as lipids in fat cells (adipose tissue.



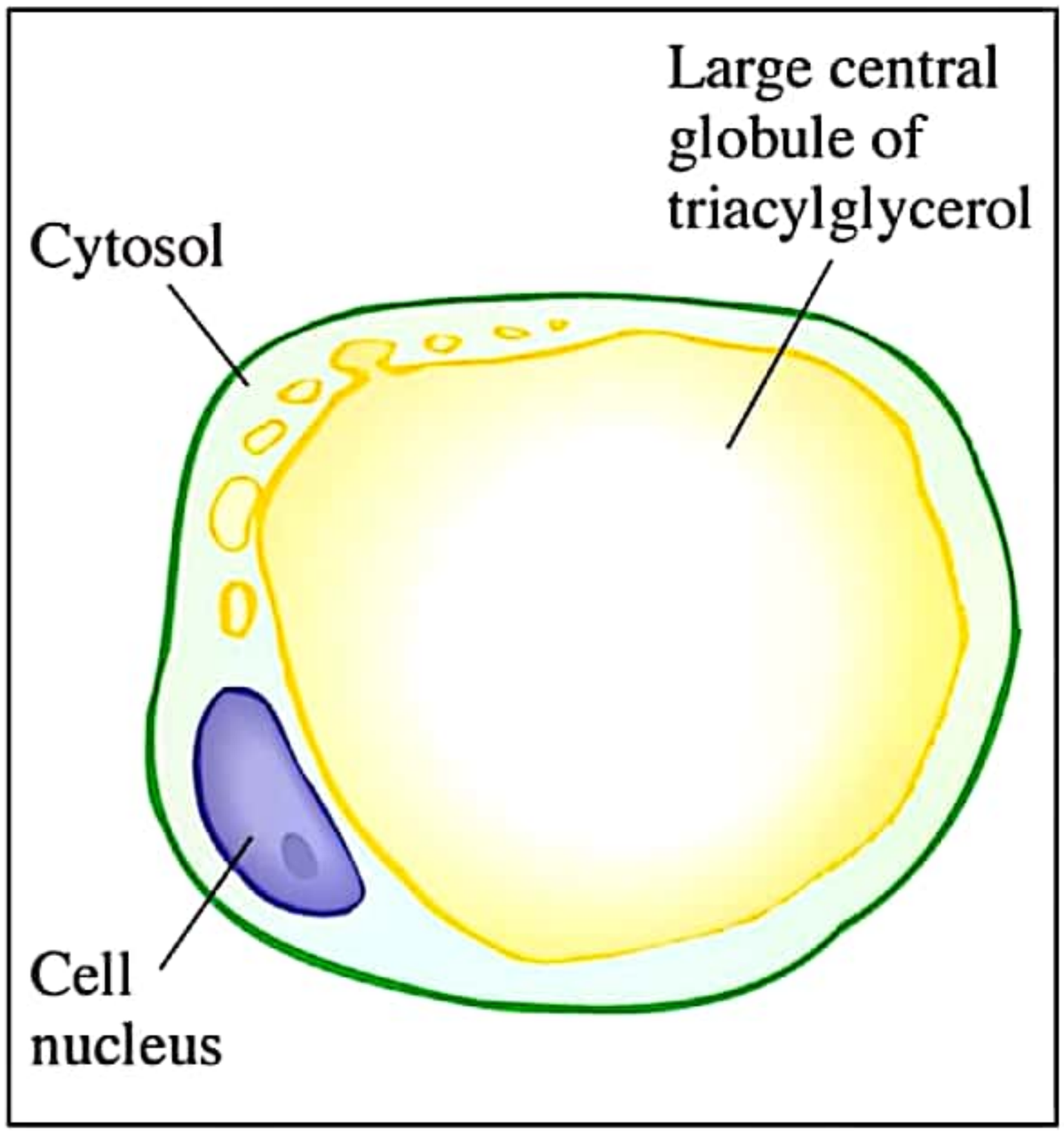


Summary of events that must occur before triacyglycerols (TAGs) can reach the bloodstream through the digestive process.



Triglyceride Storage & Mobilization

Storage of triacylglycerol is in **adipocytes** Fatty acids stored primarily as triacylglycerol.Triacylglycerol is **hydrolyzed** to release **fatty acids** when needed.



Hormonal control of lipolysis

The breakdown of triglycerides by lipases is under hormonal control.

Hormones involved are:

Epinephrine, glucagon, and insulin.

Epinephrine & glucagon:

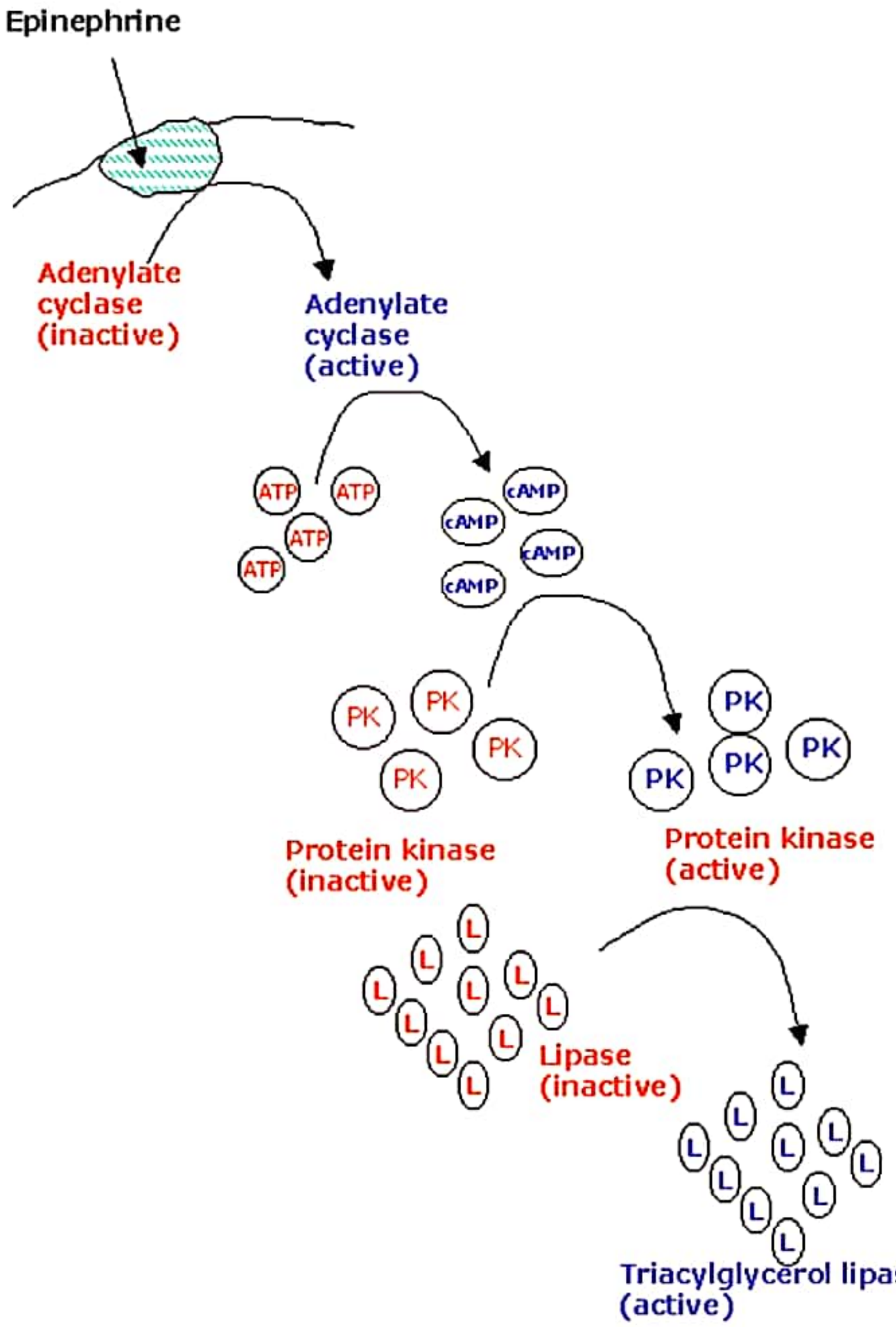
promote breakdown of fat (lipolysis)

Insulin:

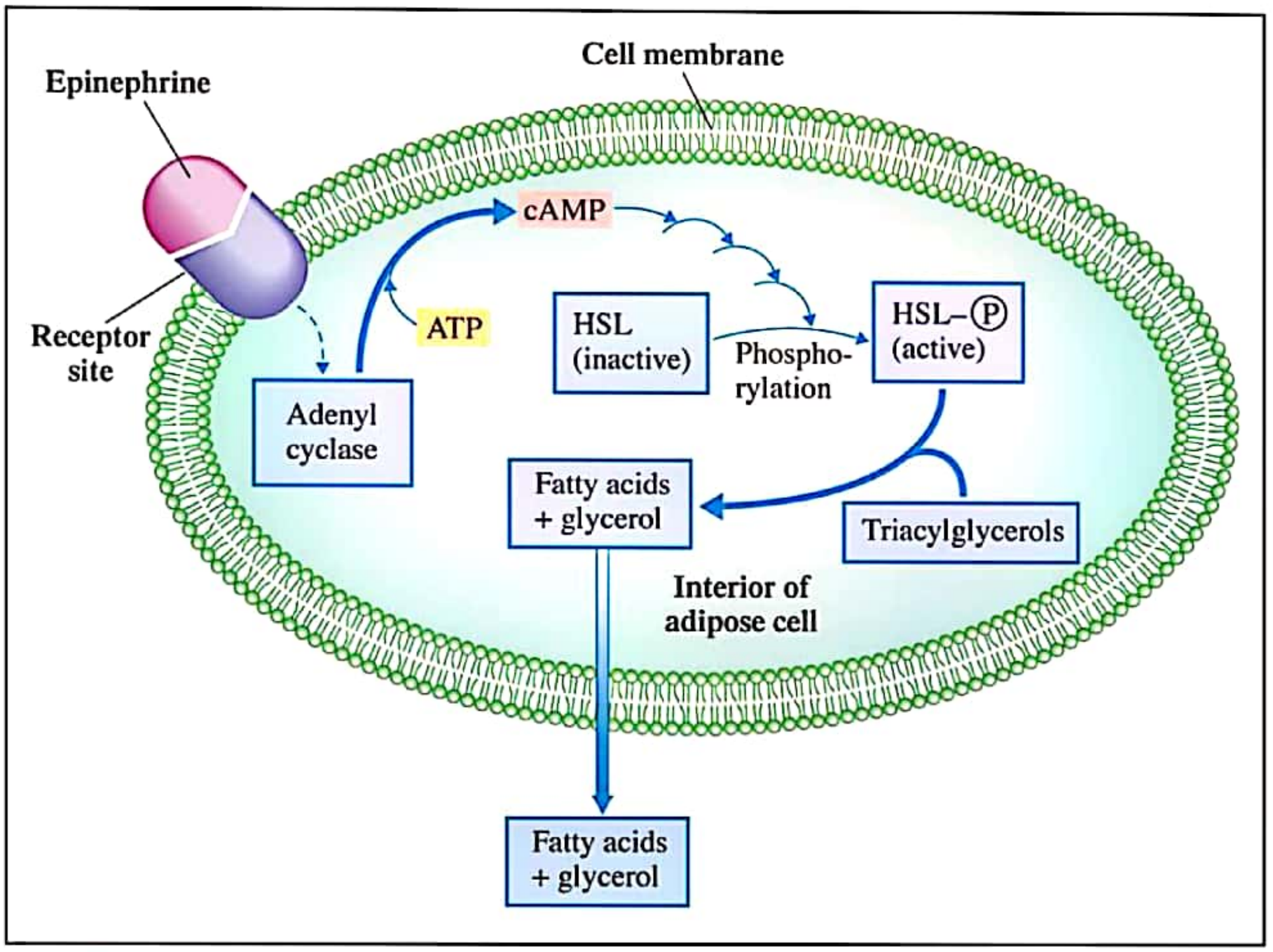
inhibits lipolysis.

Triacylglycerol Mobilization:

Hydrolyzing lipid reserves in adipose tissue for **energy**.Triggered by hormones~10% TAGs replaced in adipose tissue daily as they get used up for energy.



Hydrolysis of stored triacylglycerols in adipose tissue is triggered by hormones that stimulate cAMP production within adipose cells.

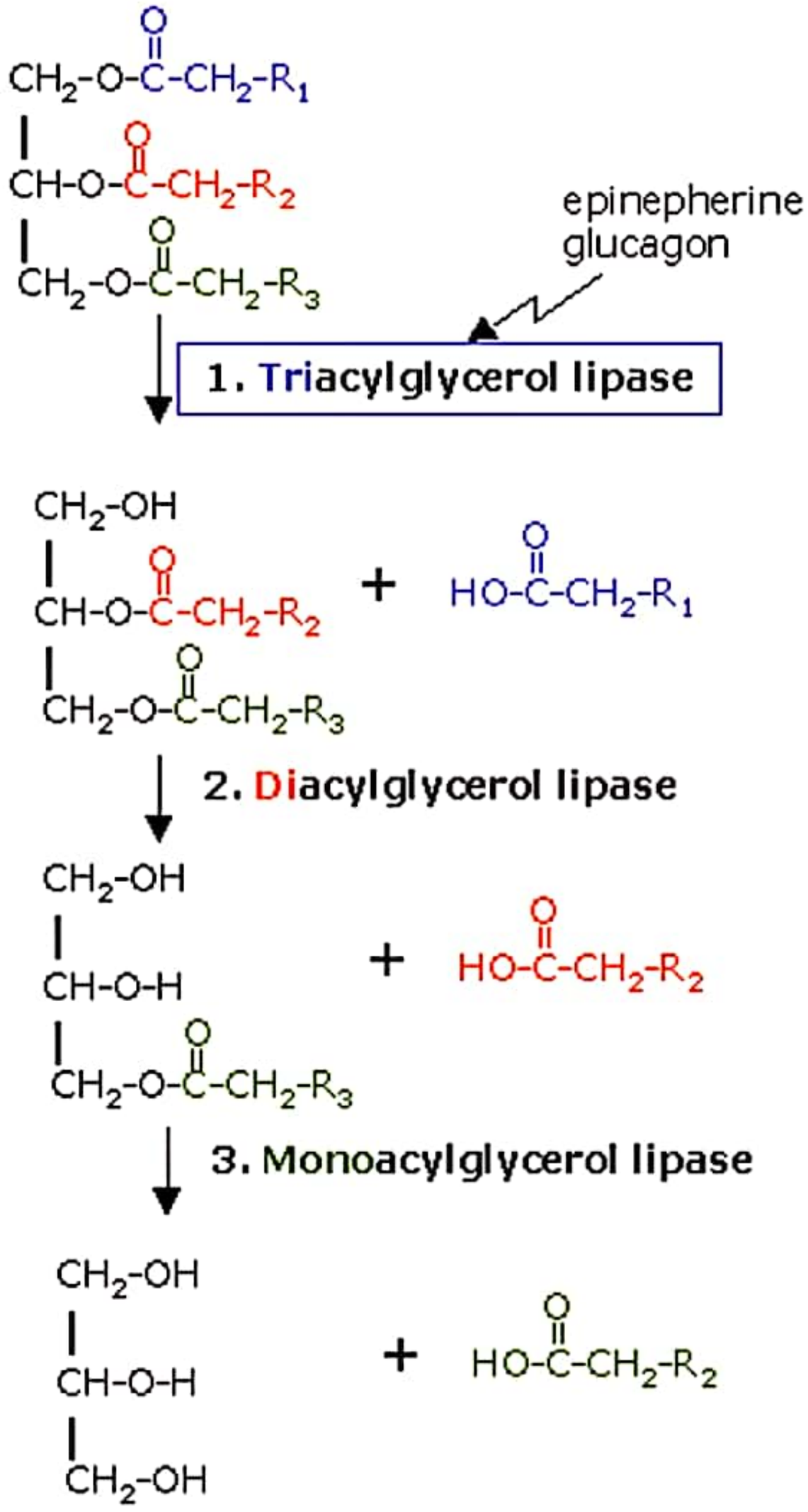


rd

Third time is a charm! TAGs hydrolyzed a 3 time to form fatty acids.

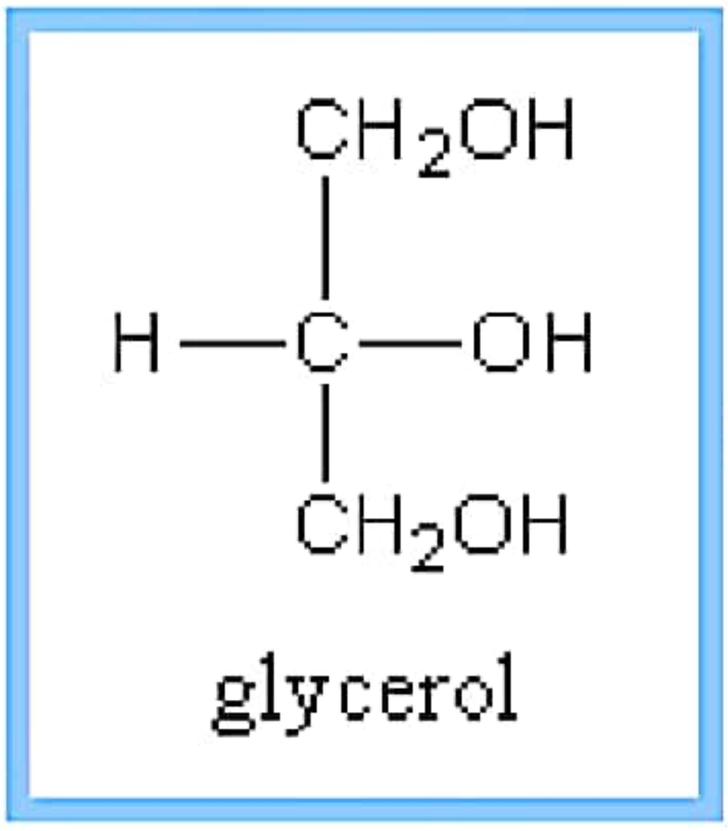
Triacylglycerol lipase **Di**acyclglycerol lipase **Mono**acylglycerol lipase

Only triacylglycerol lipase is activated by epinephrine.

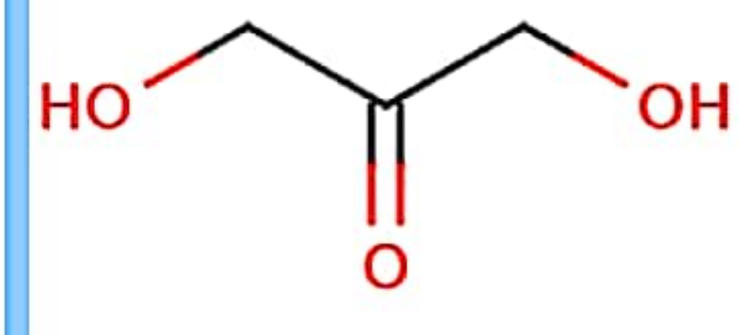


One glycerol formed for each TAG hydrolyzed. Enter bloodstream & go to liver or kidneys for processing. Converted in 2 steps to

Dihydroxyacetone phosphate

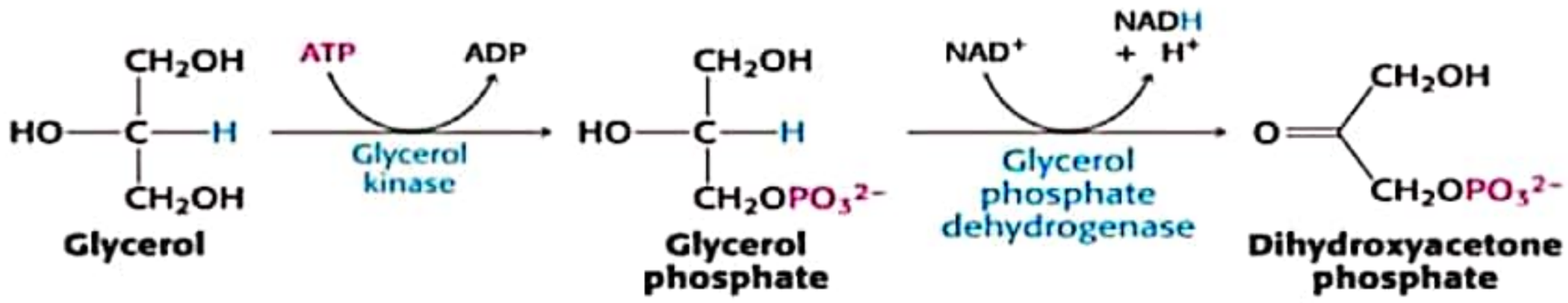


glycerol



Where will the phosphate be attached?

Uses up one ATP.Reduces one NAD^+ to NADH



Primary hydroxyl group is phosphorylated

Dihydroxyacetone phosphate

is an intermediate for both

Glycolysis:

converted to Pyruvate, then to Acetyl CoA, & eventually to CO_2,

releasing its energy.

Gluconeogenesis:

creates Glucose from **non-carbohydrate** source

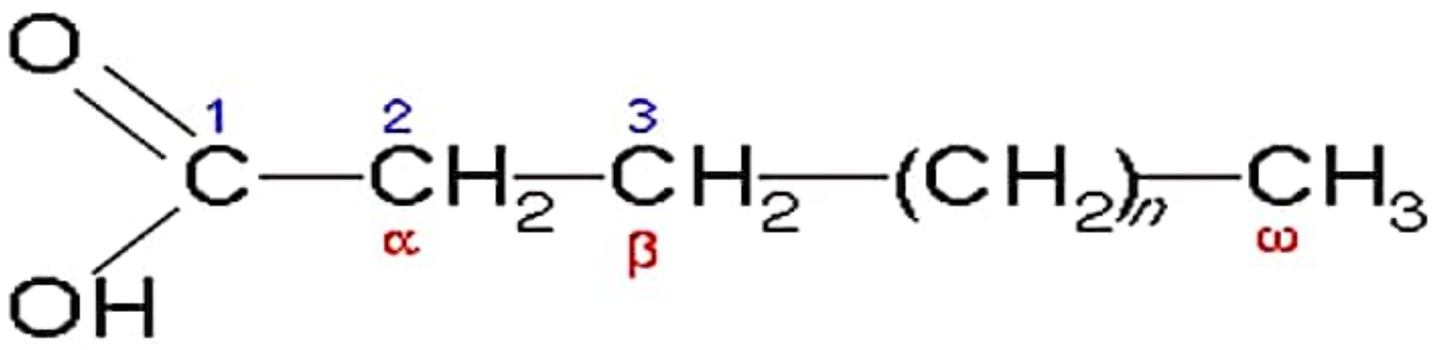
Lipid metabolism & carbohydrate metabolism

are connected.

Fatty acids can also be broken down for energy. What kind of reaction is needed?

Oxidation!

Quick review first on fatty acid numbers & letters:



Fatty acid numbering system

Review Important fatty acids:

Name	# Carbons: (saturation)
Palmitate	16:0
Stearate	18:0
Palmitoleate	16:1 - cis at C9
Oleate	18:1 - cis at C9
Linoleate	18:2 - cis at C9 and C12
Linolenate	18:3 - cis at C9, C12 & C15

Lipid Metabolism

Lipid nomenclature

•Oxidation of Fatty acids

•β-oxidation

•Ketone Bodies

Lipid nomenclature

Fatty acids

•triacylglycerols: know structure

•phospholipids

•waxes

•sphingolipids

•Glycosphingolipids

•Isoprenoids

•Steriods

•Nomenclature

•saturated: palmitate, stearate, no double bonds

•unsaturated: palmitoleate, Oleate: double bond at cis9 position

•polyunsaturated

•Melting points: saturated vsunsaturated

Oxidation of Fatty acids

•Know equation for palmitate: $C_{16}H_{32}O + O_2 \dashrightarrow CO_2 + H_2O$

•Comparison of glucose with palmitatefor ATP production and energy yield

•Mobilization of Triacylglycerols from adipose tissue

–hormonal control: glucagon, epinephrine

–lipases

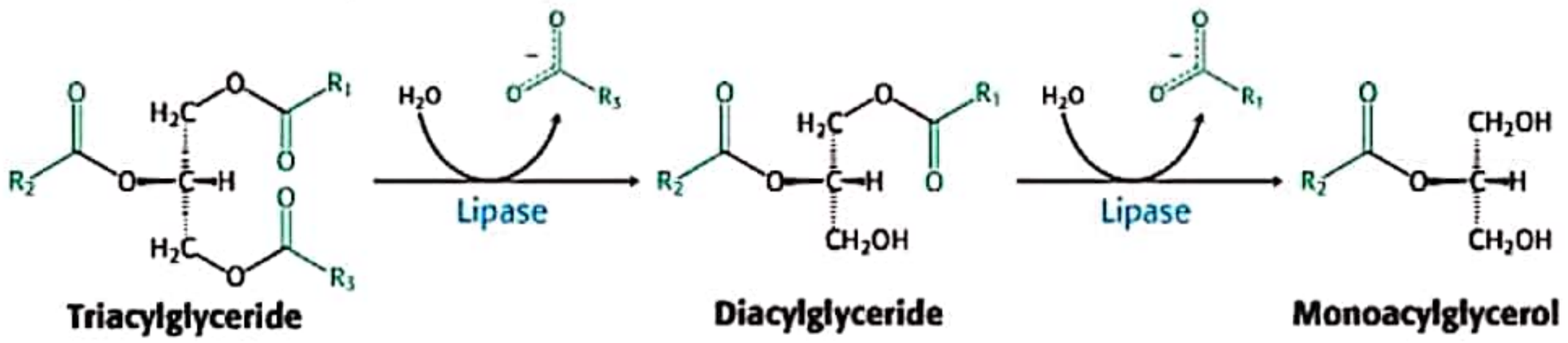
–transport by lipoproteins

–fate of glycerol

•transport into cytoplasm of cell

Digestion of lipid in diet

•Triacylglycerolsfrom diet
•broken down in small intestine
•lipases
•bile salts
•transport to adipose tissue

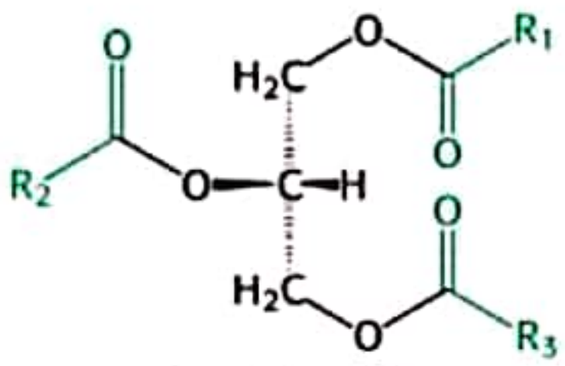


Triacylglyceride **Diacylglyceride** **Monoacylglycerol**

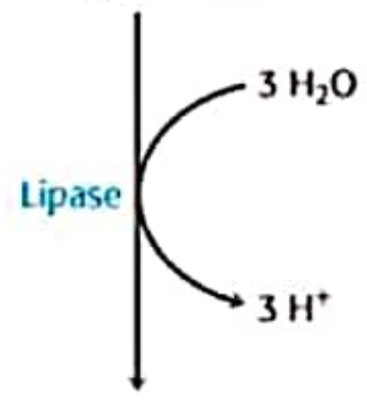
Mobilization of Triacylglycerols

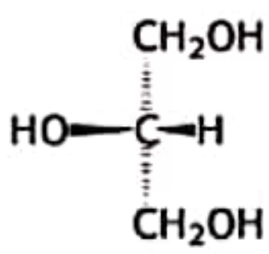
–hormonal control of lipolysis: glucagon, epinephrine
–lipases
–transport by lipoproteins
–transport into cytoplasm of cell
–Insulin inhibits lipolysis

Breakdown of triacylglycerides



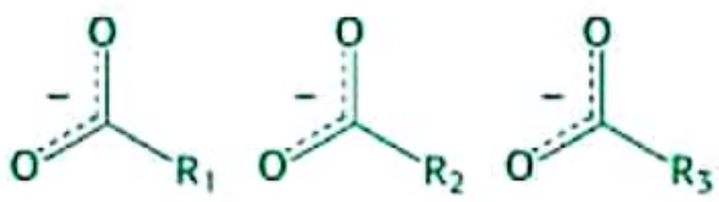
Triacylglyceride



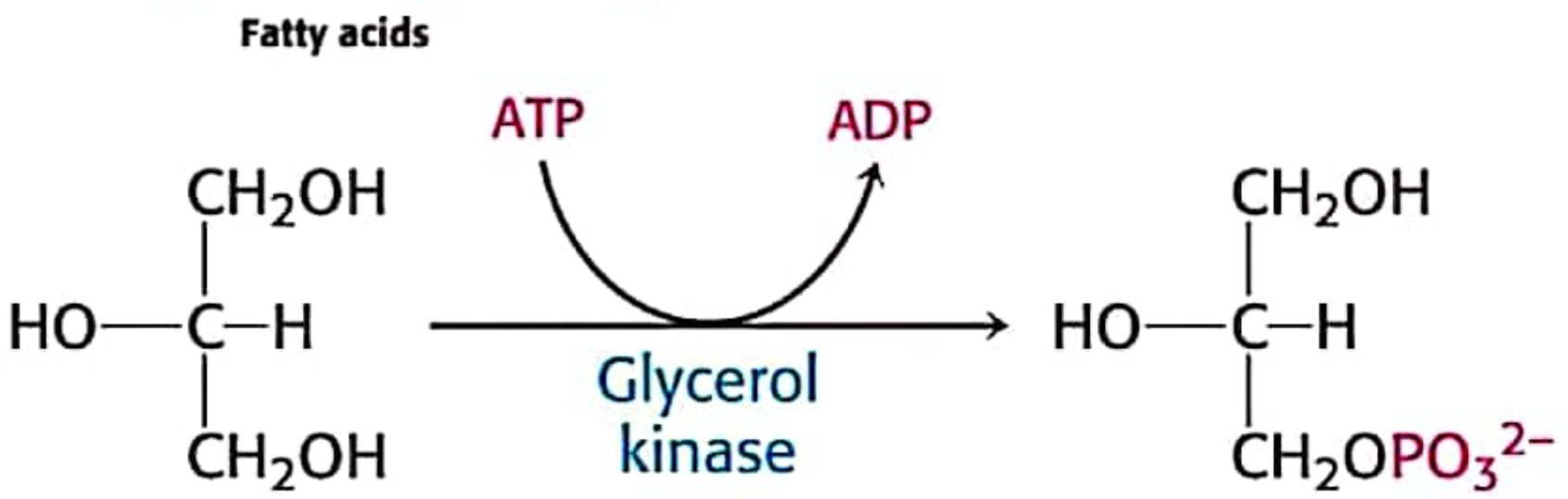


Glycerol

+

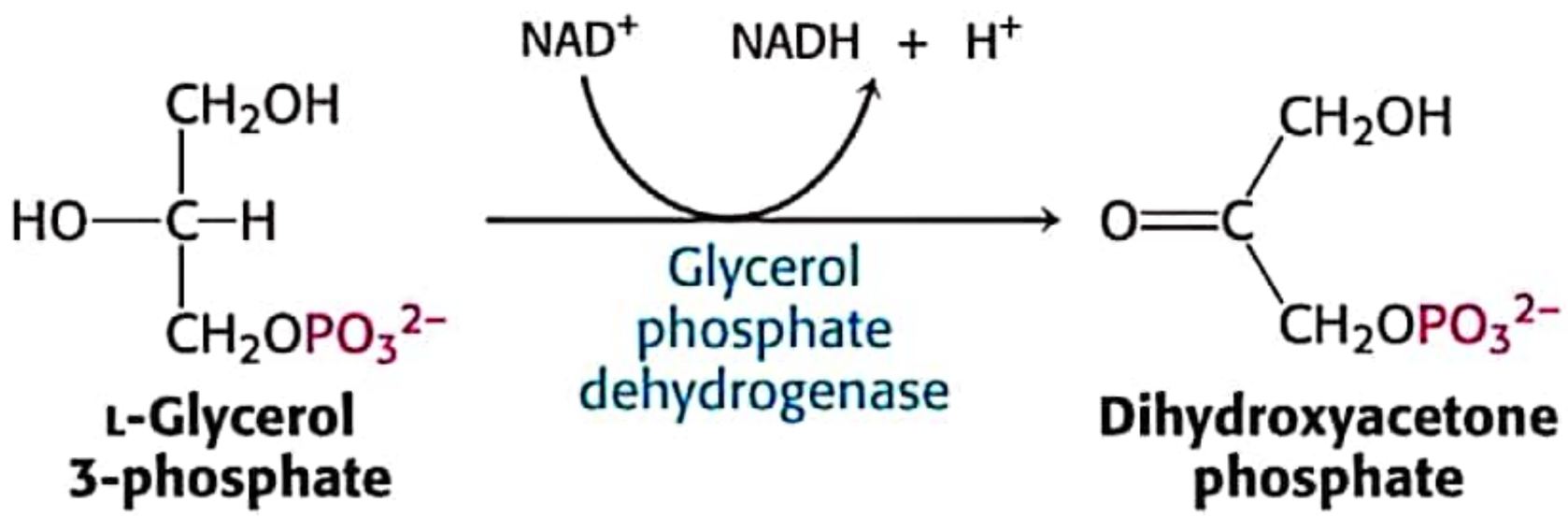


Fatty acids



Glycerol

L-Glycerol 3-phosphate



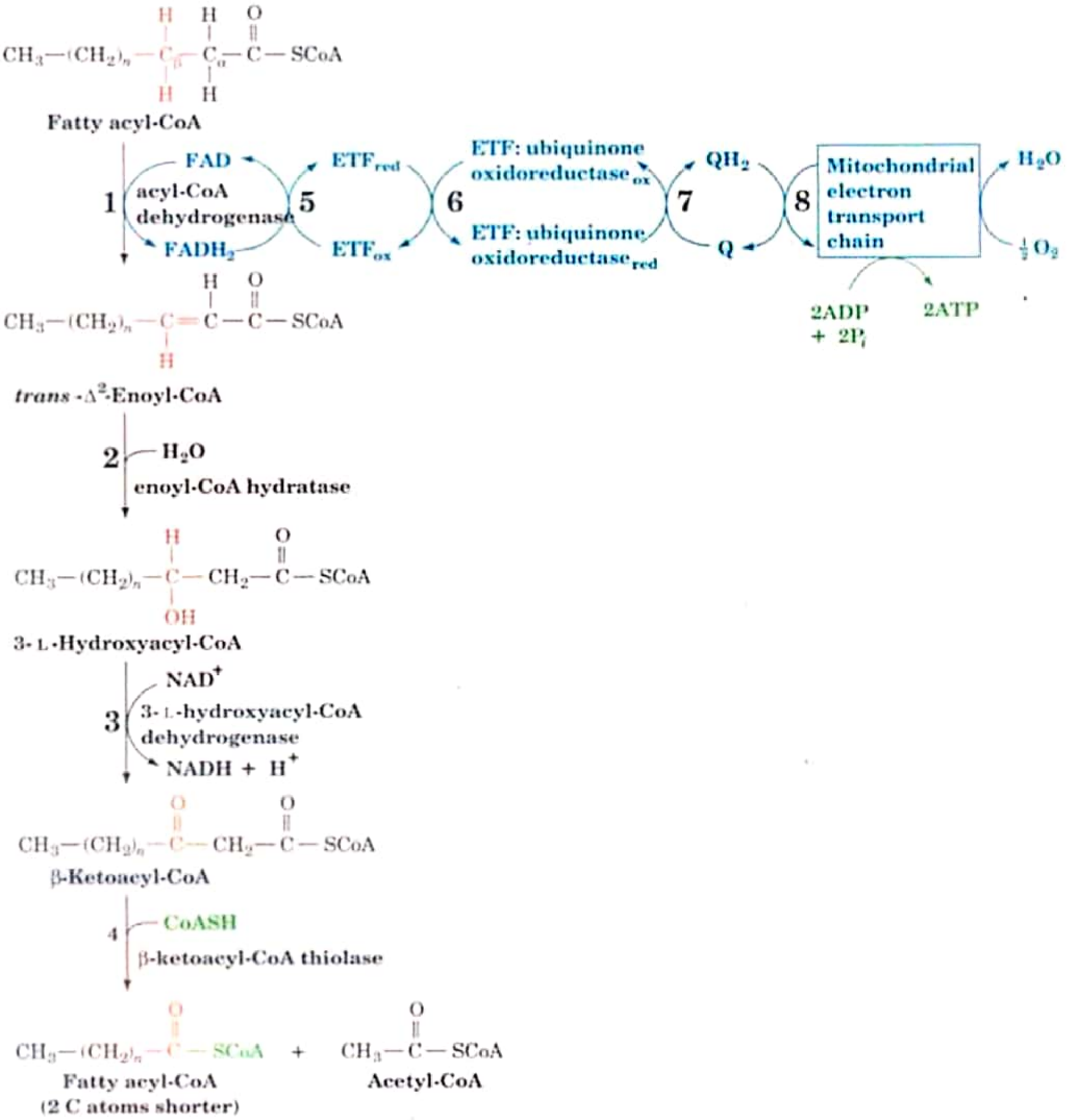
L-Glycerol 3-phosphate

Dihydroxyacetone phosphate

fate of glycerol

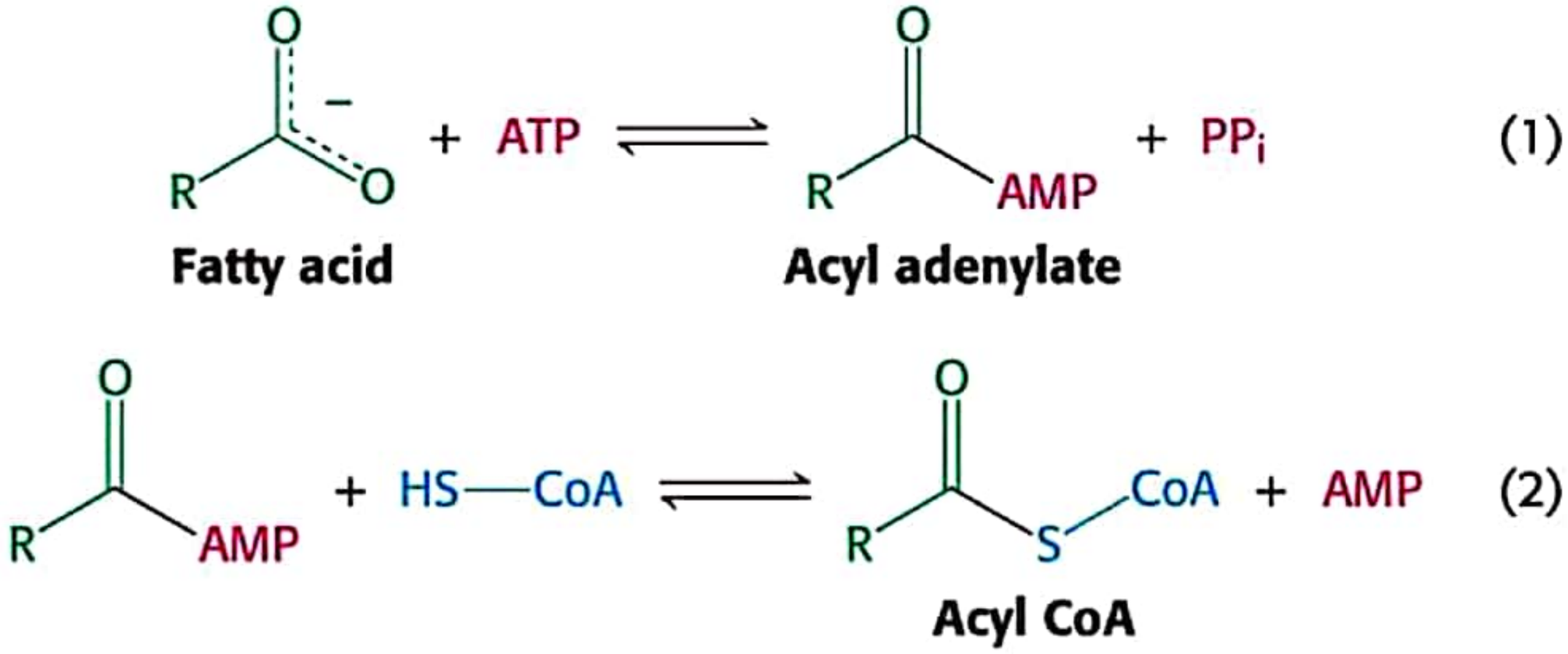
β-oxidation

- occurs in mitochondria
- uses FAD and NAD
- produces acetyl CoA



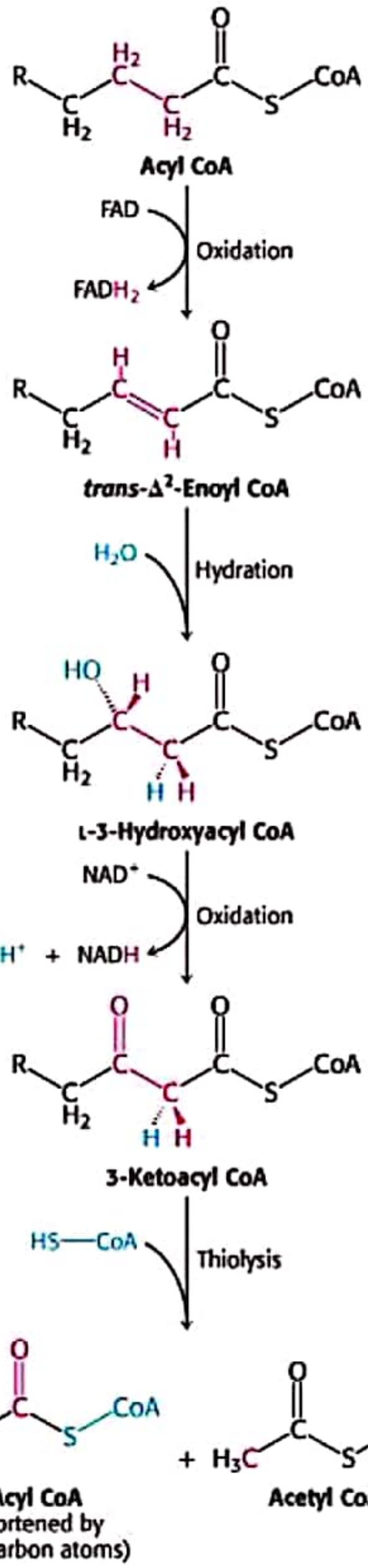
acylCoA synthetase

•two step reaction
•ATP + FA ---> AMP-FA
•AMP-FA + CoASH------> FA-CoA + AMP



β-oxidation

AcylCoA dehydrogenase
•enoyl-CoA hydratase
•L-hydroxyacyldehydrogenase
•ketoacyl-CoA thiolase
•Repeat steps



Summary of Reactions

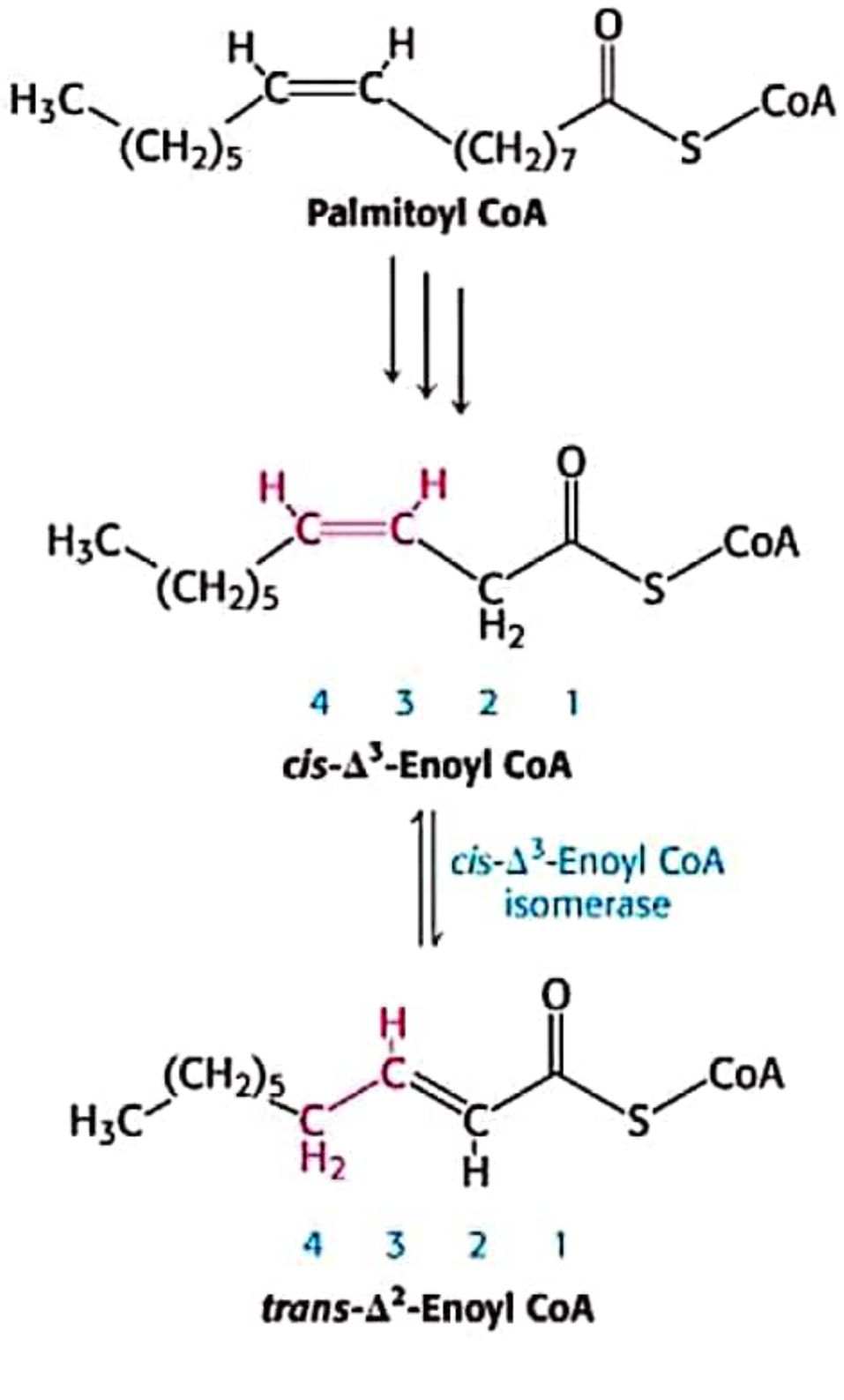
TABLE 22.1 **Principal reactions in fatty acid oxidation**

Step	Reaction	Enzyme
1	Fatty acid + CoA + ATP $\rightleftharpoons$ acyl CoA + AMP + PP_i	Acyl CoA synthetase [also called fatty acid thiokinase and fatty acid:CoA ligase (AMP)]
2	Carnitine + acyl CoA $\rightleftharpoons$ acyl carnitine + CoA	Carnitine acyltransferase (also called carnitine palmitoyl transferase)
3	Acyl CoA + E-FAD $\longrightarrow$ *trans*-Δ^2-enoyl CoA + E-$FADH_2$	Acyl CoA dehydrogenases (several isozymes having different chain-length specificity)
4	*trans*-Δ^2-Enoyl CoA + H_2O $\rightleftharpoons$ L-3-hydroxyacyl CoA	Enoyl CoA hydratase (also called crotonase or 3-hydroxyacyl CoA hydrolyase)
5	L-3-Hydroxyacyl CoA + NAD^+ $\rightleftharpoons$ 3-ketoacyl CoA + NADH + H^+	L-3-Hydroxyacyl CoA dehydrogenase
6	3-Ketoacyl CoA + CoA $\rightleftharpoons$ acetyl CoA + acyl CoA (shortened by C_2)	β-Ketothiolase (also called thiolase)

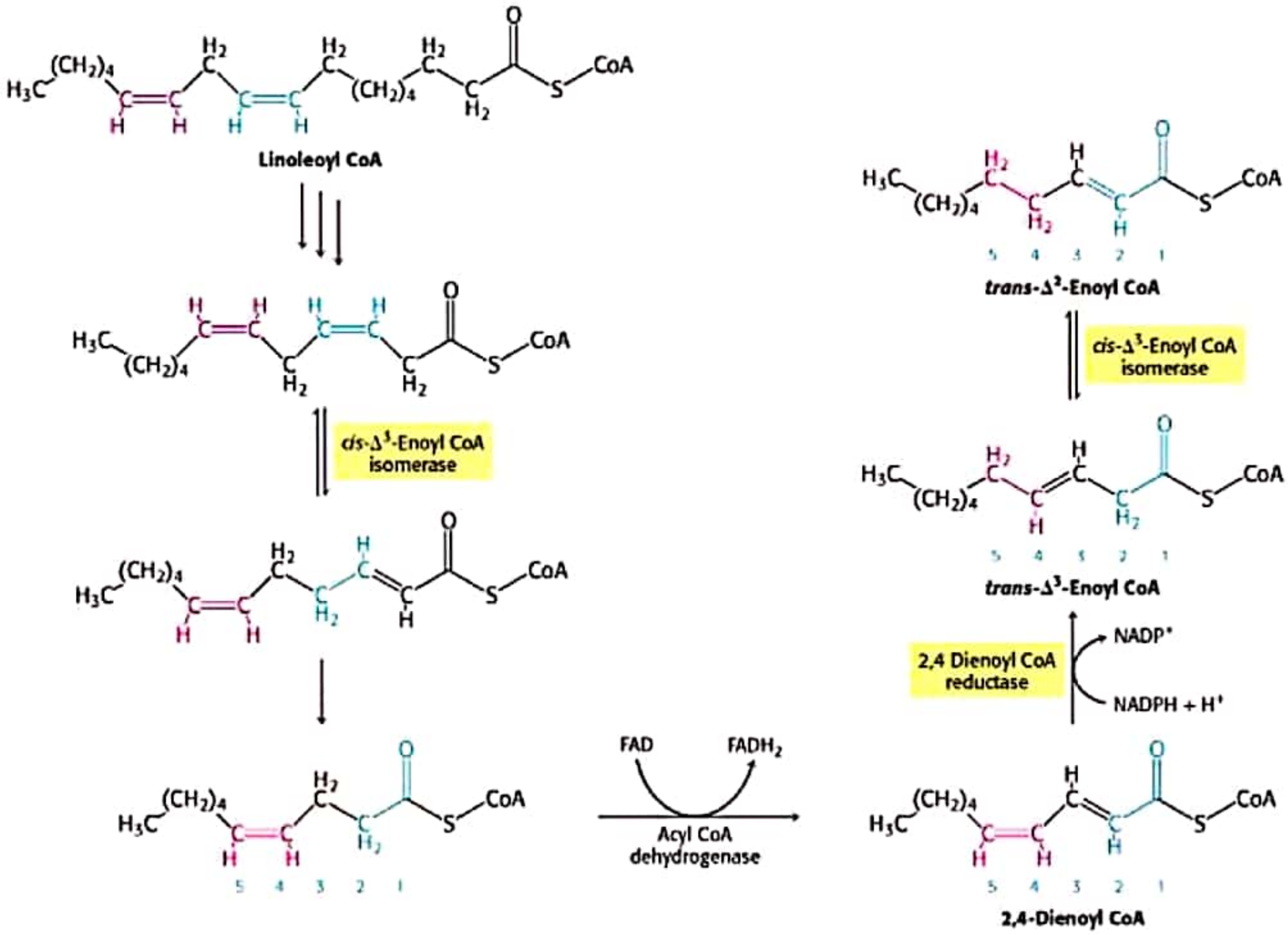
Energy production

- NADH and FADH from B-oxidation
- TCA cycle from acetyl CoA
- Total net yield is minus 2 ATP from activation

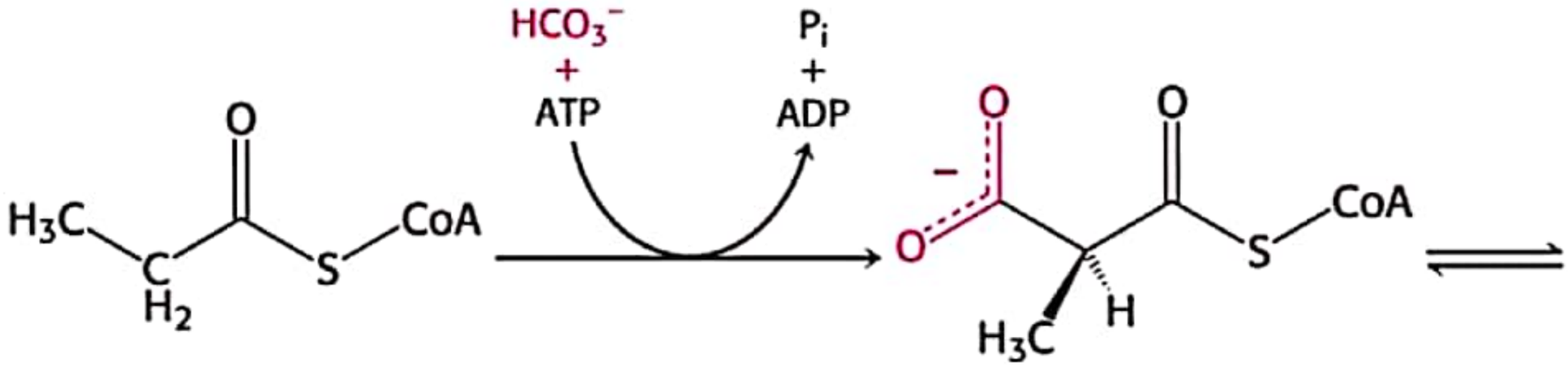
Oxidation of Unsaturated Fatty acids



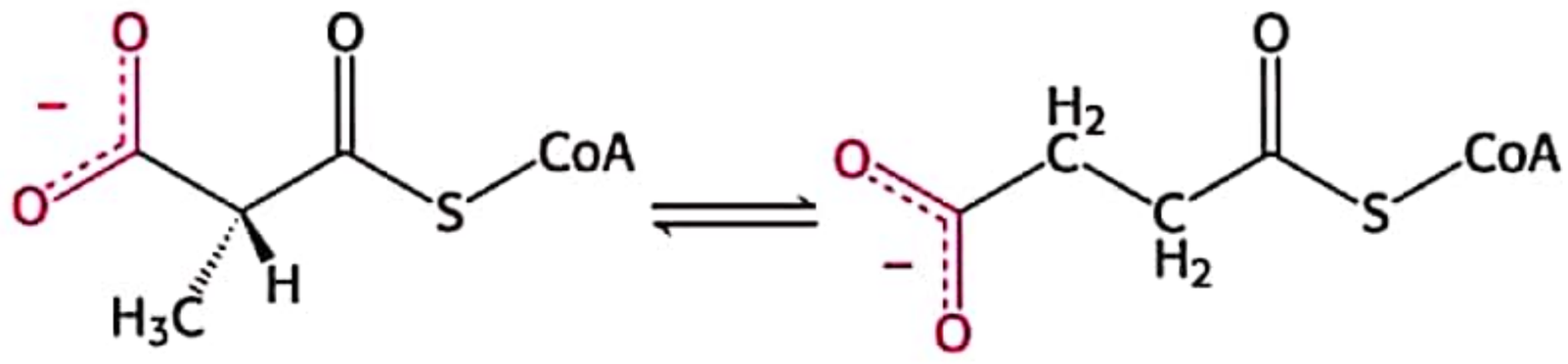
Unsaturated Fatty acids



Oxidation of odd chain fatty acids



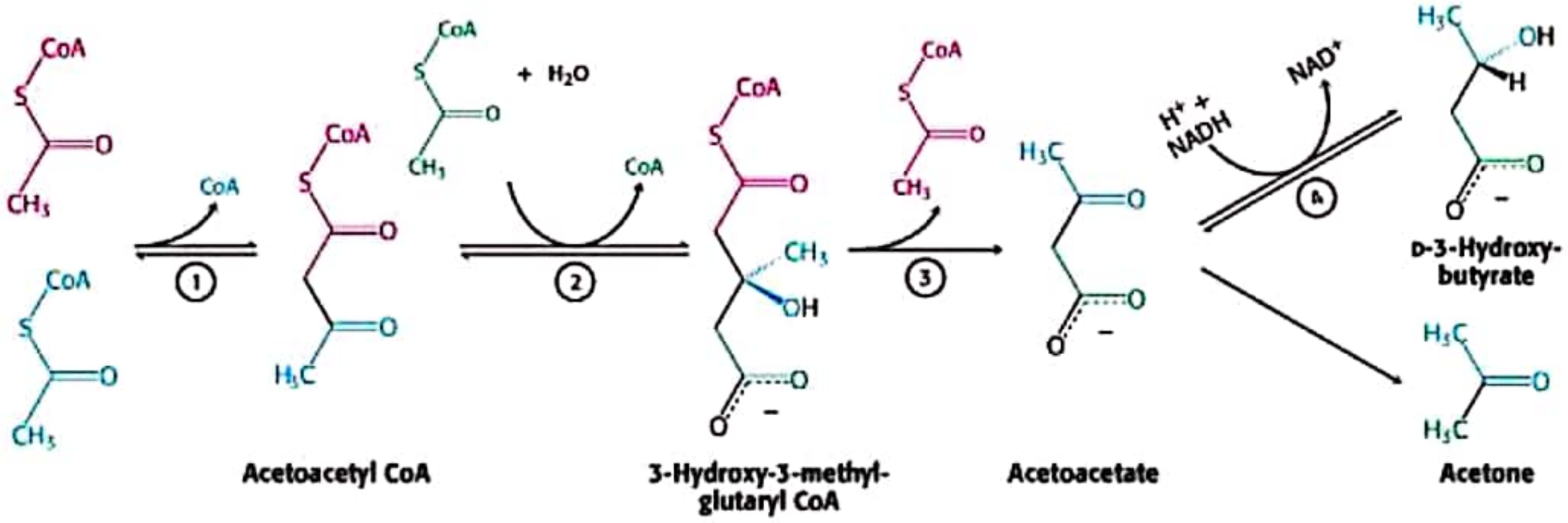
Propionyl CoA **D-Methylmalonyl CoA**



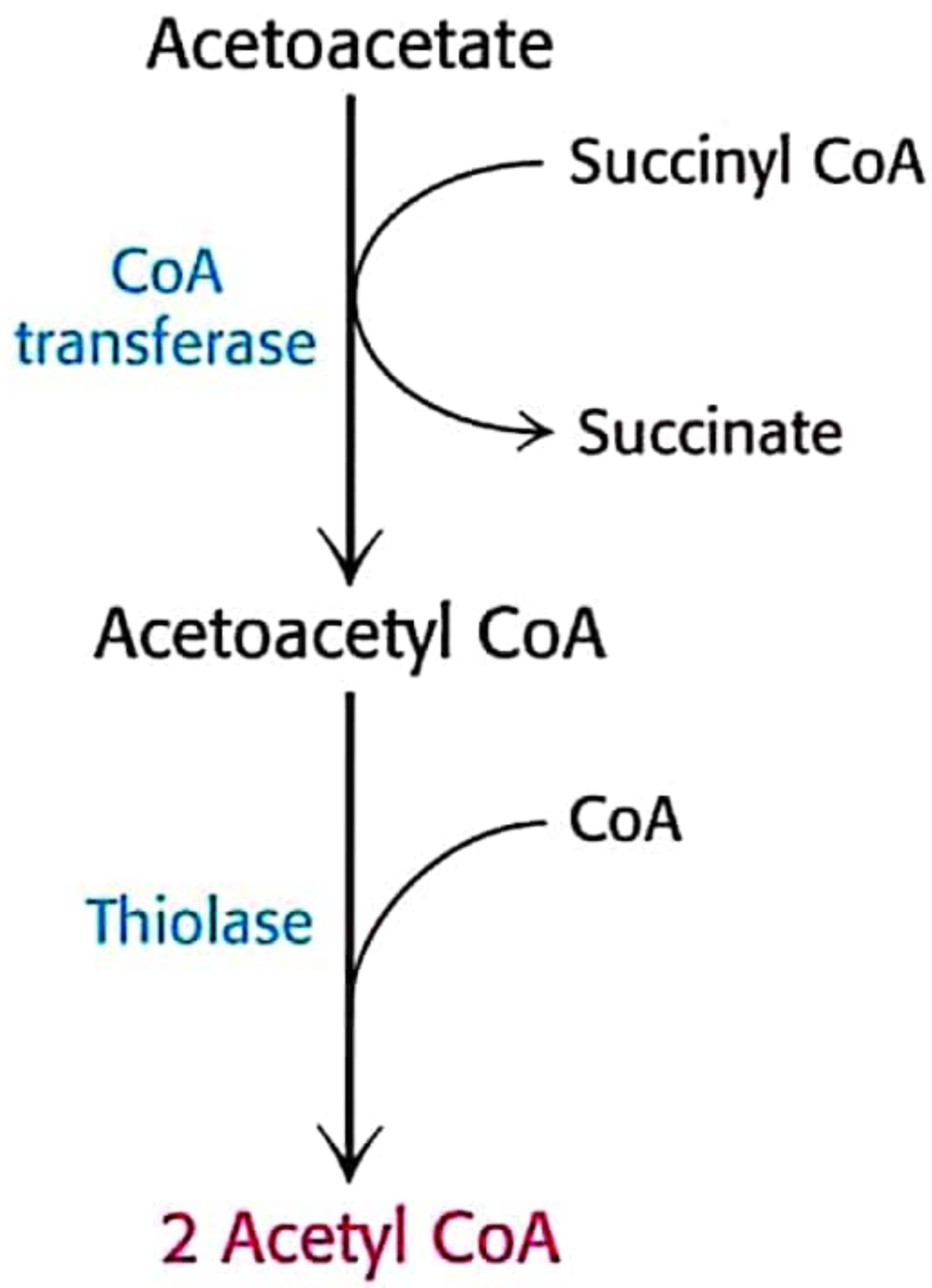
L-Methylmalonyl CoA **Succinyl CoA**

- form propionylCoA
- produce succinylCoA

Ketone Bodies



Acetoacetyl CoA **3-Hydroxy-3-methyl-glutaryl CoA** **Acetoacetate** **Acetone**



- Acetoacetate
- Acetone
- B-hyroxybutyrate
- HMG CoA synthase

Referances

Available online

1-BIOCHEMISTRY IN PERSPECTIVE

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