Modular Approach of Book

In Pakistan various Universities are still following Conventional System of Study. Although many universities are following newly introduced Integrated Modular System but syllabus of Modular System of different provinces is quite different so to provide a common layout acceptable for all Universities was a hard job but the distinctive feature of this book is that it can be simultaneously used for both Conventional and Integrated Modular System as the book layout is variable. For those students who are studying under institutions where Integrated Modular System is being followed, they are directed to follow the detailed Module Wise Chart (MWC) given before the Learning Outcomes of each module.

Module # 1: Foundation Module

Chapters Included In this Module:

Unit Number and Name	Chapter Number and Name	Topics Included in UHS Modular System 2023
Unit 1: Basic Biochemistry	Chapter 1: Cell and its Organelles	Whole Chapter
Unit 9: Nucleotide Metabolism	Chapter 16: Nucleotide Metabolism	Whole Chapter
Unit 10: Genetics	Chapter 17: DNA replication and repair Chapter 18: Transcription Chapter 19: Genetic Code Chapter 20: Translation	Whole Chapters

Learning Outcomes (LOs)

- Differentiate between different types of cells. Explain the concept of organization of cells to tissue, tissues to organ, organs to system.
- Differentiate between the eukaryotic and prokaryotic cells.
- Describe the composition and structure of cell on biochemical basis and justify it as fluid mosaic model.
- Describe the structure and function of cell membrane with reference to the role of
  - (i) Lipids
  - (ii) Carbohydrates and Proteins
- Explain why the cell membrane is called fluid mosaic model.
- Discuss the various ways of cell-to-cell communication and to the environment.
- Describe cell to cell communications. Cell signaling pathways (only G protein signaling)
- Describe cell to cell adhesion.

CHAPTER 1: CELL AND ITS ORGANELLES

Cell Membrane

Location

Animal: Outermost boundary of animal cells

Chemical composition

- Proteins-------60% to 80%
- Lipids ---------20% to 40%
- Carbohydrates ------ less than 1% (glycoproteins, glycolipids)

Structure

- Two models are being proposed for structure of cell membrane.

1. **Unit membrane model**
   - Proposed by J.D. Robertson in 1959
   - According to this cell membrane contain lipid bilayer.
   - Bilayer is surrounded by proteins on each side.

Lipid Bilayer

- Form central component of cell membrane according to the unit membrane model.
- Composed of **phospholipids**
- Forms a continuous barrier that separates the intracellular and extracellular environments.
- **Hydrophilic** (water-loving) heads of the phospholipids face **outward.**
- **Hydrophobic** (water-repelling) tails face **inward.**

Protein Layers

- Located on the **inner and outer side** of the lipid bilayer.
- Consist of various types of proteins including
  - Integral membrane proteins
  - Peripheral membrane proteins
- **Integral membrane proteins** span the entire width of the lipid bilayer
- **Peripheral membrane proteins** are attached to either the inner or outer surface

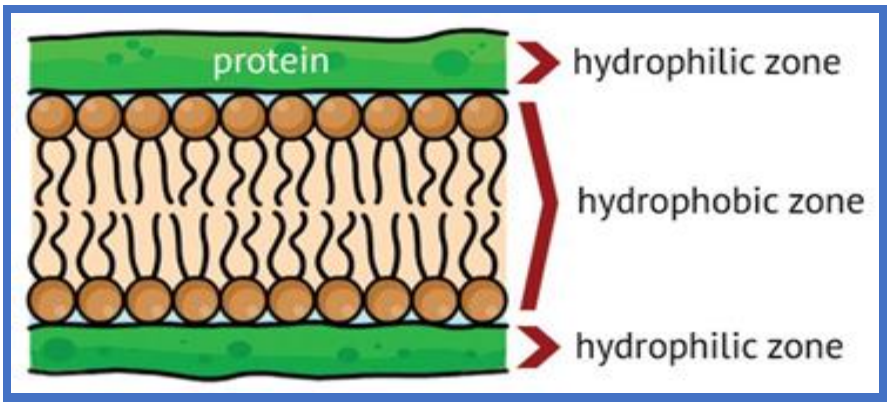


Fig 1.1: Unit Membrane Model

2. Fluid Mosaic Model

- Proposed by Sanger and Nicolson

Statement

- According to this model

  Proteins are present at surface as well as embedded in lipid bilayer in mosaic manner.

- Seems like iceberg (protein) floating in sea (phospholipids)

Types of Lipids in Membrane

1.Phospholipids

- Most abundant type of lipids
- Consist of
  - Glycerol backbone
  - Two fatty acid chains
  - Phosphate group
- Rest of details are given in upcoming chapters.

2.Cholesterol

- Sterol lipid
- Provides stability and **regulates fluidity.**
- Interspersed within the phospholipid bilayer.
- Interact with fatty acid tails.
- Maintain the **integrity** and permeability of the membrane
- Play a crucial role in **cell signaling.**

3.Glycolipids

- Lipids having **carbohydrate** groups attached to them.
- Found on the **outer layer** of the cell membrane.
- Contribute to **cell recognition, cell-cell interactions**, and **immune responses.**
- Have a similar structure to phospholipids but **lack a phosphate group.**
- Have a **carbohydrate** moiety attached to the glycerol backbone.

4.Sphingolipids

- Diverse group of lipids that contain a **sphingosine** backbone.
- Constituents of cell membranes, particularly in **nerve cells**
- Participate in cell **signaling**, membrane structure, and **stability.**
- Examples include **sphingomyelin, cerebrosides, and gangliosides.**

Proteins in Cell Membrane

- Randomly embedded in lipid bilayer
- Consist of various types of proteins including
  - Integral membrane proteins
  - Peripheral membrane proteins
- **Integral membrane proteins** span the entire width of the lipid bilayer
- **Peripheral membrane proteins** are attached to either the inner or outer surface

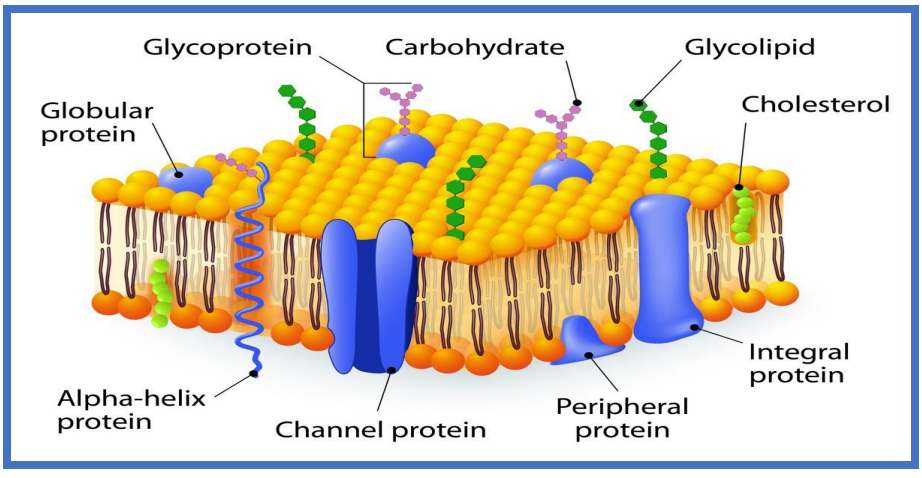


Fig 1.2: Fluid Mosaic Model

Functions

- The primary function of cell membrane is transport of substances.
- Transports are of two types.
  - Passive transport
  - Active transport

1.Passive Transport

- Movement of molecules across the cell membrane **without** the expenditure of **energy**
- Have two major types.
  - Diffusion
  - Osmosis

Diffusion

a) **Simple diffusion**
   - Movement of molecules from an area of **higher concentration** to an area of **lower concentration**
   - Examples include **gases** (e.g., oxygen, carbon dioxide) and **lipid-soluble** molecules.

USMLE/UKMLA Questions

1. A 45-year-old man with a history of chronic alcohol abuse presents to the emergency department with severe vomiting and diarrhea. His arterial blood gas analysis shows a pH of 7.29, PCO2 of 40 mmHg, and HCO3- of 20 mEq/L. Which of the following is the most likely acid-base disturbance?

A) Metabolic acidosis
B) Respiratory acidosis
C) Metabolic alkalosis
D) Respiratory alkalosis

Answer: A) Metabolic acidosis
The patient's pH is low, indicating acidosis. The HCO3- level is also low, suggesting a primary metabolic acidosis.

2.A 30-year-old woman with a history of type 1 diabetes presents to the clinic with deep and rapid breathing. Her arterial blood gas analysis reveals a pH of 7.50, PCO2 of 30 mmHg, and HCO3- of 24 mEq/L. What is the most likely acid-base imbalance in this patient?

A) Respiratory alkalosis
B) Metabolic alkalosis
C) Respiratory acidosis
D) Metabolic acidosis

Answer: A) Respiratory alkalosis
The patient's pH is high, indicating alkalosis. The low PCO2 level suggests a primary respiratory alkalosis.

Question: A 65-year-old woman with chronic obstructive pulmonary disease (COPD) is brought to the emergency department with worsening shortness of breath. Her arterial blood gas analysis reveals a pH of 7.30, PCO2 of 60 mmHg, and HCO3- of 32 mEq/L. Which acid-base disturbance is most likely present?

A) Metabolic alkalosis
B) Respiratory alkalosis
C) Metabolic acidosis
D) Respiratory acidosis

Answer: D) Respiratory acidosis
The patient's pH is low, indicating acidosis. The elevated PCO2 level suggests a primary respiratory acidosis.

4.A 50-year-old man presents to the clinic with muscle weakness and tingling in his extremities. His arterial blood gas analysis shows a pH of 7.55, PCO2 of 42 mmHg, and HCO3- of 34 mEq/L. Which acid-base disturbance is most likely present?

A) Respiratory alkalosis
B) Metabolic alkalosis
C) Respiratory acidosis
D) Metabolic acidosis

Answer: B) Metabolic alkalosis
The patient's pH is high, indicating alkalosis. The elevated HCO3- level suggests a primary metabolic alkalosis

5. A 20-year-old woman is brought to the emergency department after ingesting a large quantity of aspirin. Her arterial blood gas analysis shows a pH of 7.50, PCO2 of 30 mmHg, and HCO3- of 20 mEq/L. Which acid-base disturbance is most likely present?

A) Respiratory alkalosis
B) Metabolic alkalosis
C) Respiratory acidosis
D) Metabolic acidosis

Answer: A) Metabolic acidosis
The patient's pH is low, indicating acidosis. The HCO3- level is also low, suggesting a primary metabolic acidosis.

Polysaccharides

Definition

- Consist of **repeating units** of monosaccharides
- Held together by **glycosidic** bonds.
- Functions + structural role and storage of energy.
- Linear as well as branched

Types of Polysaccharides

Homopolysaccharides

- Contain single type of monosaccharide.
- Named based on nature of the monosaccharide.

Heteropolysaccharides

- Mixture of a few monosaccharides or their derivatives
- Also called heteroglycan.

Homopolysaccharides

Starch

- Reserve of **plants**
- Found in cereals, roots, tubers, vegetables etc.
- Composed of **D-glucose** units held by **alpha-glycosidic** bonds.

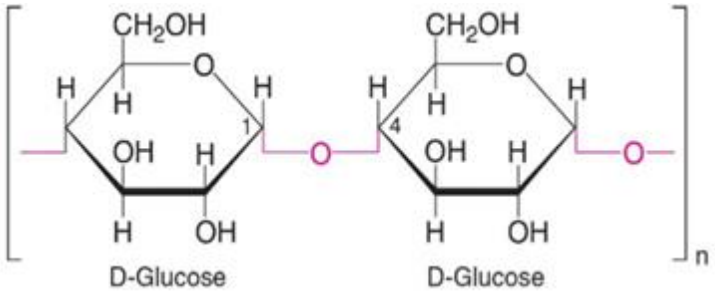


Fig 4.7: Structural unit of polysaccharides

Types of Starch

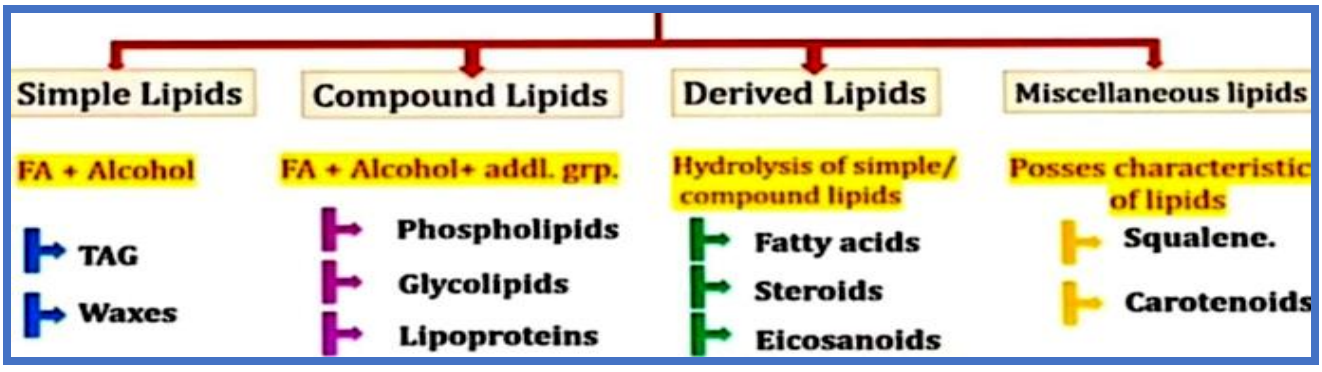
Amylose

- Water soluble
- 15-20%
- long unbranched chain
- 200–1,000 D-glucose units
- Held by alpha (1→4) glycosidic linkages.

Amylopectin

- Water insoluble amylopectin
- 80-85%
- Branched
- More than thousand glucose units
- Contain both alpha (1→4) and alpha (1→6) glycosidic linkage.

Classification of Lipids



Simple Lipids

- Esters of fatty acids with alcohols.

Types

Fats/Oils (triacylglycerols)

- Esters of fatty acids with glycerol.,
- Examples are fats and Oils
- Differ in physical Properties
- Oil is liquid at room temperature
- Fats are solid at room temperature

Waxes

- Esters of fatty acids (usually long chain) with alcohols other than glycerol.
- Alcohols may be aliphatic or alicyclic.
- Cetyl alcohol is most common
- Used in the preparation of candles, lubricants, cosmetics, ointments, polishes

Complex/Compound Lipids

- Esters of fatty acids with alcohols
- Contain **additional groups such as phosphate, nitrogenous base**

Subdivision

1.Phospholipids:

- Contain **phosphoric acid** and frequently a nitrogenous base.
- Have a hydrophilic "head" containing a phosphate group and two hydrophobic "tails" derived from fatty acids, joined by an alcohol residue.
- Component of cellular membranes.
- **Example:** Phosphatidylcholine
- Have two types

Glycerophospholipids

- Phospholipids contain glycerol
- e.g., lecithin, cephalin.

Sphingophospholipids

- Phospholipids contain Sphingosine
- e.g., sphingomyelin.

3.Basis of Nature of Chain

Monounsaturated fatty acid Contain one double bond.

- **Polyunsaturated fatty acid** Contain 2 or more double bonds

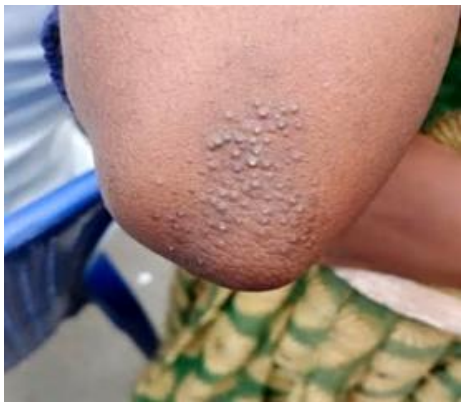
4.Basis of Synthesis in Body

Essential Fatty Acid (EFA)

- Cannot be synthesized by the body
- Should be supplied in the diet
- **Chemical Nature** → Polyunsaturated fatty acids
- **Examples**
    1. Linoleic acid
    2. Linolenic acid
    3. Arachidonic acid becomes essential, if its precursor linoleic acid is not provided in the diet in sufficient amounts.
- **Biochemical basis for essentiality** :
- Linoleic acid and Linolenic acid are essential since **humans lack the enzymes that can introduce double bonds beyond carbons 9 to 10.**
- **Functions of EFA :**
- Required for the membrane structure and function
- Transport of cholesterol
- Formation of lipoproteins and eicosanoids
- Prevention of fatty liver

Deficiency of EFA

- Cause **Phrynoderma** or toad skin
- **Symptom**
- Horny eruptions on the posterior and lateral parts of limbs, on the back and buttocks
- Loss of hair
- Poor wound healing



Non Essential Fatty acids:

- Can be synthesized in body
- All fatty acid except Linoleic and Linolenic acid

High Yield Past Paper SEQs of all Universities

1.Classify phospholipids and write down their four important biological functions.

2-Draw the structure of cholesterol. Give its three physiochemical properties and functions in the body.

3(a)- How are dextrans obtained and what is their biomedical significance? Describe the phenomenon of mutarotation with reference to glucose.

b)Name the nutritionally essential fatty acid for humans. Describe important functions of cholesterol and lecithin in human body

4-Describe oxidation and reduction of monosaccharides with examples. What is the biological significance of leukotriene B4 and prostaglandin PG1s (prostacyclin)?

5(a)- What ate the principle biological functions of Thrombaxane A2? Enumerate the components of SRS-A (slow reacting substance of anaphylaxis) along with their main biological function.

b)What are omega-3 fatty acids along with biomedical importance of their dietary use?

6-Classify unsaturated acids along with examples of biologically important unsaturated fatty acids. Write down principle biological functions of leukotriene B4 ad prostacyclin.

7(a)- Five omega 3 fatty acids of dietary importance and mention which of them undergoes peroxidation resulting in the formation of toxic free radicals.

b) Give structure components and tissue location of plasminogen.

8(a)- Enumerate the unsaturated fatty acids of dietary importance which does not undergo autoxidation to generate dangerous free radicals.

b) Give beneficial functions of cholesterol.

9-What is phosphatidic acid and its derivatives? What is meant by lipid peroxidation?

10(a)- Write down the principle biological functions of prostacycline and leukotriene B4. Describe the structural characteristics of plasminogens.

b) A 52 years old man presented in OPD with severe chest pain in his chest radiating to his left arm. Angiography revealed atherosclerotic plaques in the arteries Laboratory tests showed raised levels of cholesterol and LDL in his blood. Give three important functions of cholesterol and mention to total number of carbon atom found in the structure of cholesterol.

ii)-Why excessive dietary intake of trans-fats is associated with increased coronary heart disease (CHD?)

11-Define and classify phospholipids. What is their biological importance?

12-Classify phospholipids & write down their four important functions?

13-Draw the structure of cholesterol. Give its three physiochemical properties and functions in the body?

14(a)- What do you understand by Omega Fatty acids? Differentiate Omega 3 and omega 6 fatty acids quoting suitable examples.

b) What are harmful effects of Lipid Peroxidation on bio-membranes? Enumerate vitamins and minerals with Antioxidant activity?

Standard Amino Acids	Non-Standard Amino Acids
Amino acids that **take part in synthesis of proteins.**	Amino acids that **do not take part in synthesis of proteins**
About 25 amino acids are standard amino acids	All amino acids other than 25 standard amino acid
Examples Proline, Lysine, Arginine etc.	**Examples** Valinomycin, Actinomycin, Gramicidin etc.

Classification of Standard Amino Acids

- Amino acids can be classified on four bases. They include.
    1. On basis of Structure and Chemical Nature
    2. On basis of Polarity or Solubility
    3. On basis of Metabolic Fate
    4. On basis on nutritional requirements

1.Classification on basis of Structure or Chemistry

- Amino acids can be further classified in 7 groups:

1.Aliphatic Amino Acids (**Mnemonic**: GAVLI)

- Glycine, Alanine, Valine, Leucine, Isoleucine

2.Aromatic Amino Acids (**Mnemonic**: Tahreek Taliban Pakistan TTP)

- Tyrosine, Tryptophan, Phenylalanine

3.Acidic Amino Acids (**Mnemonic**: Word **acid** in name & their amides)

- Glutamic acid, Aspartic acid , Glutamate, Aspartate

4.Basic Amino Acids (**Mnemonic**: HLA – test done before blood transfer)

- Histidine, Lysine Arginine

5.Sulpher Containing (**Mnemonic**: Chief Minister -CM)

- Cysteine, Methionine

6.Hydroxyl Group Containing (**Mnemonic**: TeST- no AA starts with e)

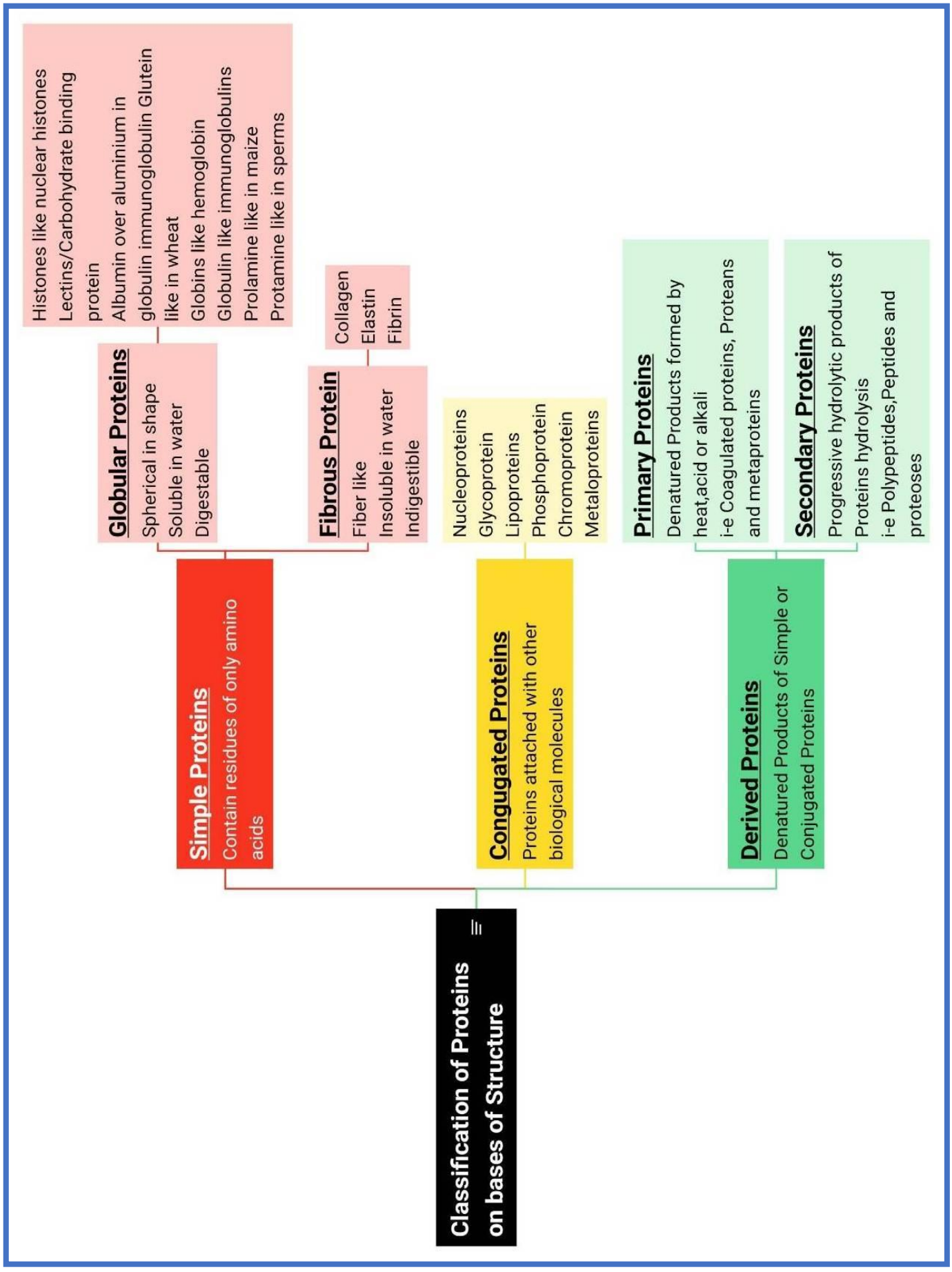
- Tyrosine, Threonine, Serine

7.Imino group Containing

- Proline

2.Classification on basis of Polarity

- Can be broadly classified into two groups.
    1. Hydrophobic -water insoluble
    2. Hydrophilic – water Soluble


Classification of Proteins on bases of Structure
Simple Proteins
Contain residues of only amino acids
Globular Proteins
Spherical in shape
Soluble in water
Digestable
Histones like nuclear histones
Lectins/Carbohydrate binding protein
Albumin over aluminium in
globulin immunoglobulin Glutein like in wheat
Globins like hemoglobin
Globulin like immunoglobulins
Prolamine like in maize
Protamine like in sperms
Fibrous Protein
Fiber like
Insoluble in water
Indigestible
Collagen
Elastin
Fibrin
Conjugated Proteins
Proteins attached with other biological molecules
Nucleoproteins
Glycoprotein
Lipoproteins
Phosphoprotein
Chromoprotein
Metaloproteins
Derived Proteins
Denatured Products of Simple or Conjugated Proteins
Primary Proteins
Denatured Products formed by heat,acid or alkali
i-e Coagulated proteins, Proteans and metaproteins
Secondary Proteins
Progressive hydrolytic products of Proteins hydrolysis
i-e Polypeptides,Peptides and proteoses

USMLE /UKMLA Questions

1.A new drug is developed which selectively cleaves covalent bonds between two sulfur atoms of non-adjacent amino acids in a polypeptide chain. Which level of protein structure in affected molecules would be most directly affected by the drug?

a) Primary structure

b) Secondary structure

c) Tertiary structure

d) Quaternary structure

Correct Answer: c) Refer to Topic tertiary structure of protein

2.The major protein component of human hair is α-keratin. Hair 'straighteners' are commonly used tools which use heat to iron hair into temporarily lying flat and straight. What is the best biological explanation for this phenomenon?

a) Hair straightener denatures protein by pH

b) Hair straightener disrupt hydrogen bonds in alpha keratin

c) Hair straightener disrupt the ionic bond in alpha keratin

d) Hair straightener cause misfolding of protein

Correct Answer: b) Refer to Topic secondary structure of protein

3.Creutzfeldt-Jakob Disease (CJD) is a degenerative neurological disorder. Biopsy of the the brains of affected individuals reveals aggregations of a "prion protein"—a protein which is capable of folding into multiple, structurally distinct forms. What is basic pathology behind this?

a) Variant form has significant beta structure

b) Variant has significant alpha helix structure

c) Variant form is less stable

d) Variant form is prone to denaturation

Correct Answer: a) Refer to Topic Prions in misfolding of protein

4.Certain bacteria synthesize toxic proteins which are responsible for many of the problems they cause in humans. If you were to develop a drug designed to inhibit bacterial protein synthesis without interfering with normal human protein synthesis, what might be a logical target for the drug?

a) RNA

b) Ribosomes

c) DNA

d) Golgi apparatus

Correct Answer: b) Ribosomes are the site of protein synthesis so drug can be synthesized in protein factory i-e Ribosomes

5. Mr. Wingfoot comes to a neurologist and present his wife who has complaint of memory loss that has disrupts her daily life.She had poor judgment along with loss of spontaneity and sense of initiative. She used to ask same question again and again.The neurologist diagnose it to be the case of

a) Alzheimer disease

b) Wernicke's Karskoff Syndrome

c) Mad Cow disease

d) Transmissible spongioform encephalopathy

Correct Answer: a) Refer to Topic Amyloidosis in misfolding of protein

Michalis-Menten Kinetics

Michelis and Menton proposed a simple model that explains all features of the enzyme- catalyzed reactions. The reaction models involve one substrate which reversibly combines with enzyme to forms ES and then converted to product.

$$E + S \quad K1 \rightleftharpoons K-1 \quad \text{ES complex} \quad K2 \rightarrow \quad E + P$$

Where K_1,K-1, K_2 are rate constant.

Michalis-Menten Kinetics

The equation which tells us how reaction velocity relates with substrate concentration.

$$V_0 = V_{max}\frac{Vmax[S]}{Km+[S]}$$

Derivation

Using model Equation

$$E + S \quad K1 \rightleftharpoons K-1 \quad \text{ES complex} \quad K2 \rightarrow \quad E + P$$

Steps

Calculate Km → Calculate [E] using E_0 concept→ Calculate [ES] putting [E] in Km equation → Using velocity concept calculate Vmax → Use initial velocity Vo concept and rearrange to get desired form

Initially when:

Rate of formation of ES = Rate of breakdown of ES

K_1 [E][S] = K -1[ES]

Helden modified it as

K_1 [E][S] = K-1 [ES] +K_2 [ES]

K_1 [E][S] = [ES] (K-1 +K_2)

$$\frac{[E][S]}{[ES]} = \frac{K\text{-}1 + K2}{K1}$$

We know that:

$$\frac{K\text{-}1 + K2}{K1} = Km \text{ (MICHELIS- MENTON CONSTANT)}$$

Km refers to substrate concentration when velocity of reaction is equal to half of Vmax (maximum velocity).

$$\frac{[E][S]}{[ES]} = Km - \text{(equation 1)}$$

Let us consider total enzyme = E_0 which is equal to sum of enzyme in freeze state and enzyme in the form of enzyme substrate complex.

$$[E_0] = [E] + [ES]$$

$$[E] = [E_0] - [ES] \text{ -----(equation 2)}$$

Putting equation 2 in equation 1 we get

$$\frac{([E_0] - [ES])([S]}{[ES]} = Km$$

$$\frac{[E_0][S] - [ES][S]}{[ES]} = Km$$

$$[E_0][S] - [ES][S] = Km[ES]$$

$$[E_0][S] = Km[ES] + [ES][S]$$

$$[E_0][S] = [ES](Km + [S]$$

$$\frac{[E_0][S]}{Km + [S]} = [ES] \text{----- equation 3}$$

Now velocity of reaction at any time is equal to amount of product formed which depends on K2 and ES complex converted to product. So,

$$V_0 = K_2 [ES] \text{ ----- equation 4}$$

Putting equation 3 in equation 4 we get

$$Vo = K_2 \frac{[E_0][S]}{[S] + Km} \text{ ------ equation 5}$$

We know that velocity of reaction will be maximum when the total enzyme E is being used and on the rate of second reaction i.e K2

$$V_{max} = K_2 [E_0] - \text{equation 6}$$

Putting equation 6 in equation 5

$$\mathbf{V_0 = V_{max}} \frac{Vmax[S]}{Km + [S]}$$

Assumption

1- Substrate Relative Concentration

- Substrate concentration[s]>>> enzyme conc.
- % age of substrate bound to enzyme at any time is very small.

2. Steady-state assumption: -

- The conc. of [ES] does not change. i-e
- [Rate of formation of ES complex] = [Rate of breakdown of ES complex into E+S and E+P]
- Steady states mean rate of synthesis= rate of degradation.

3. Initial velocity (Vo). -

- During enzymatic analysis initial velocity (Vo) is used.
- Initial velocity is velocity of reaction when substrate and enzyme are just mixed. At V_0 rate of reverse reaction is very slow so it can be ignored.

Competitive Inhibition

- Inhibitor binds reversibly with active site
- Compete with substrate to bind site so called competitive inhibition

Effect on Vmax

- Competitive inhibition can be reversed by increasing substrate conc so later or earlier Vmax (saturation) can be achieved.
- Vmax remains **unchanged**.

Effect on Km

- To achieve Km (Vmax/2) we need more substrate conc. to reverse effect of inhibitor.
- Km (substrate conc at Vmax/2) is **increased**.

Effect on Lineweaver Burk Plot

- Vmax will remain same
- -1/Km will move toward origin (0 value) indicating that Km is increased

Example

- **Malonate** is competitive inhibitor for **succinate dehydrogenase.**

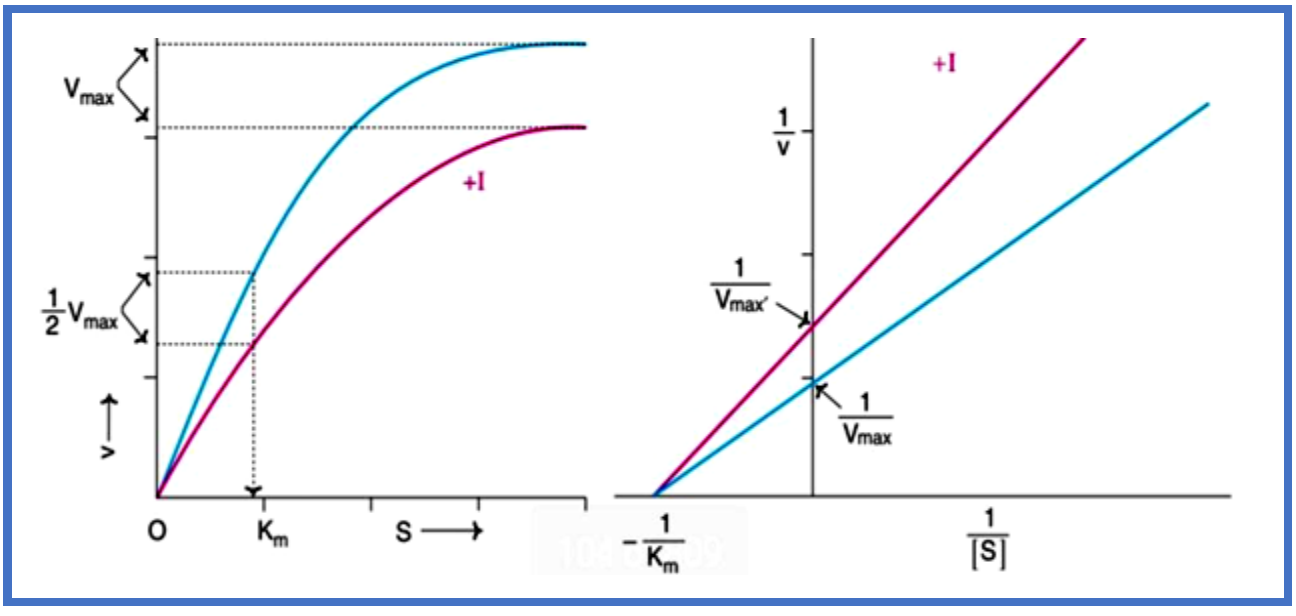


Fig 10.6 Effect of Competitive Inhibition on Michalis Menten and Lineweaver Burk Plot

Non-Competitive Inhibition

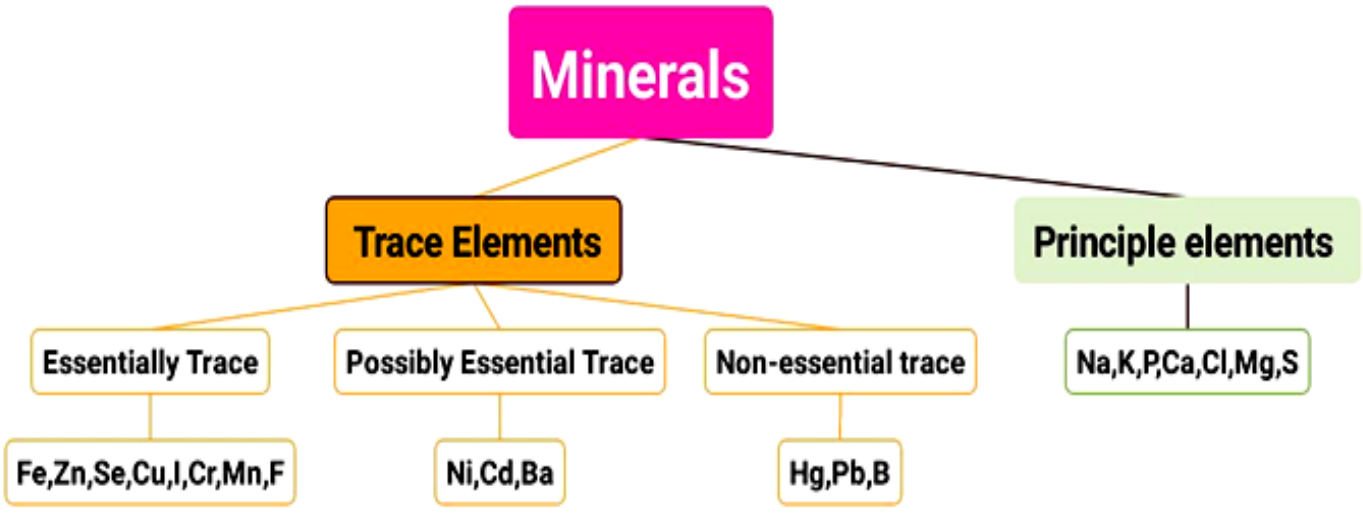
- Inhibitor binds at any site **other than active site**
- **Change enzyme activity** in such a way that prevent reaction to occur.
- **Cannot be overcome** by increasing substrate concentration

Effect on Vmax

- As non-competitive inhibition cannot be overcome (no matter how much substrate is increased)
- Actual Vmax in case of non-inhibited reaction can **never be achieved**
- In other words, in case of inhibition Vmax is **decreased**.

CHAPTER 13: MINERALS

- Inorganic compound
- Essential for proper functioning of body



Sodium

RDA:

- Normal 5 – 10 g/day
- If hypertension →Less than normal

Sources

- NaCl , Ingested foods, whole grains (Bread), Leafy vegetables ,Nuts , Egg & Milk etc

Absorption → GIT i.e very little in feces

Transport→ Through CF (plasma) chief cation

Excretion→ Controlled by Aldosterone (99% reabsorbed)

Storage

- Plasma Level **135 – 145 mEq/L**
- Storage Bones = **50%**
- ECF = **40%**
- Soft tissues = **10%**

Biochemical function

- Regulate Body's **acid-base balance**
- Maintain **Osmotic pressure**
- Normal **muscle irritability**
- Cell **Permeability**

α-Helical content

- Approximately **80%** of its polypeptide chain folded into **eight stretches of α-helix.**
- α-helical regions, are **terminated** either by
    1. Presence of **proline**, whose five-membered ring cannot be accommodated in an α-helix
    2. **β-bends** and loops stabilized by hydrogen bonds and ionic bonds

Location of polar and nonpolar amino acid residues

- **Interior** of the myoglobin molecule is composed almost entirely of **nonpolar amino acids.**
- Stabilized by **hydrophobic interactions** between these clustered residues
- **Charged amino acids** are located almost exclusively on the **surface** of the molecule,
- Form **hydrogen bonds**, both with each other and with water

Fig 14.2: Structure of Myoglobin

Binding of the heme group

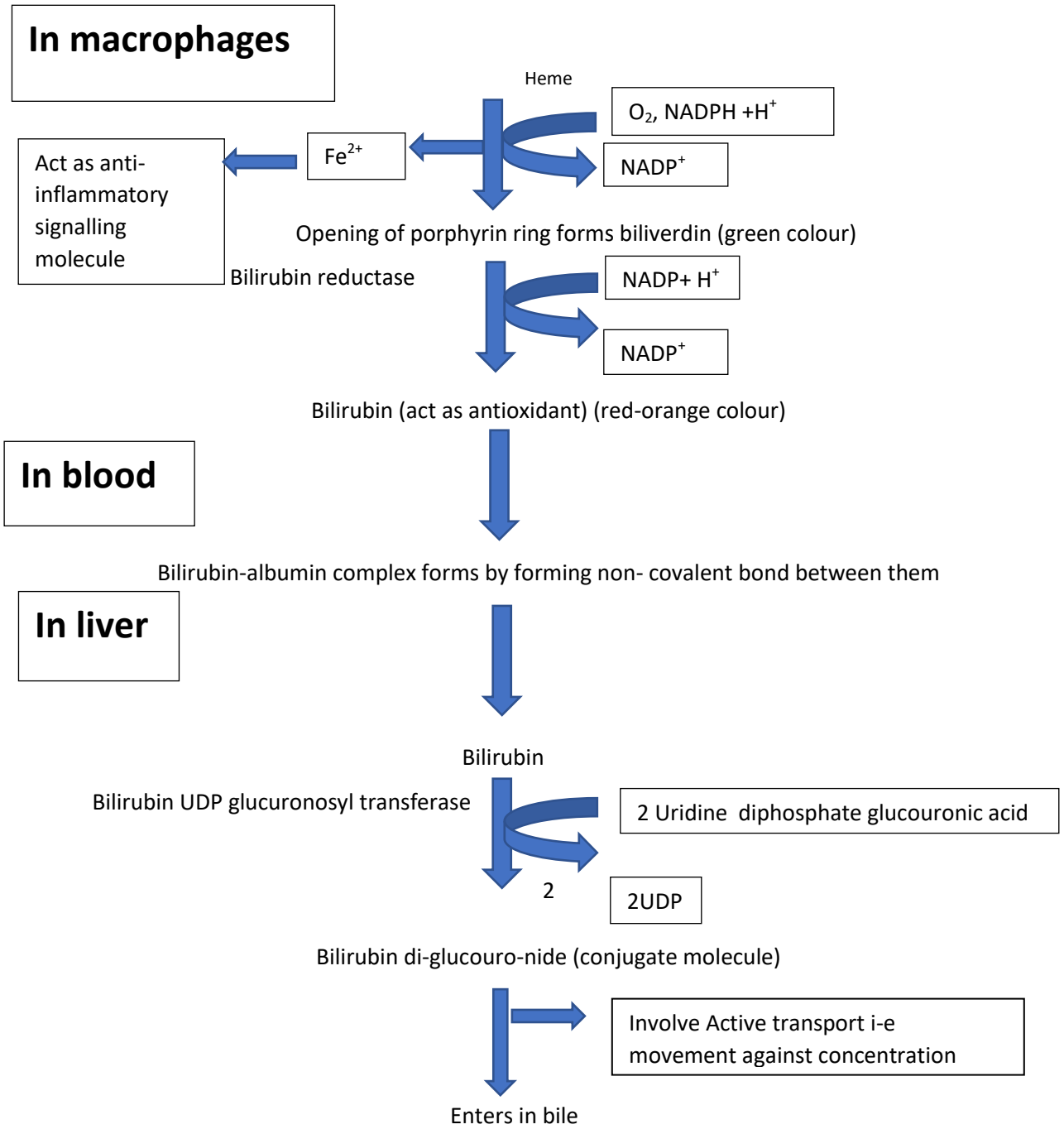
- The heme group of myoglobin sits in a **crevice**
- Lined with **nonpolar amino acids**
- Surrounded by **two histidine residues.**
- **Proximal** histidine binds directly to the **iron** of heme.
- **Distal** histidine stabilize the binding of **oxygen** to the ferrous iron

Hemoglobin

- Found in Red Blood Cells (RBCs)
- Function is to
    1. Transport (O2) from lungs to tissues
    2. Transport H+& CO2 from tissues to lungs
- **Hemoglobin A** major hemoglobin in adults
- Composed of four polypeptide chains
    - Two α chains
    - Two β chains
    - Held together by non-covalent interactions.
- More **complex** than myoglobin
- Carry four molecules of O_2

Heme Degradation

Degraded by mononuclear phagocyte system (MPS)



MCQs

- Salicylate, sulfonamides separate bilirubin from albumin→Bilirubin accumulate in CNS→cause neuropathy

- Coordinate the complex patterns of gene expression required for **development** and **homeostasis**.
- Play a role in chromatin remodeling, by **recruiting histone-modifying** enzymes to specific regions of DNA.

4. DNA helicases and topoisomerases

- Play a critical role in DNA replication and transcription, by **unwinding** and **untangling** the double helix of DNA.
- Helicases use ATP to **break the hydrogen bonds** between the two strands of DNA
- Create a **replication fork** that can be used by other proteins to synthesize new DNA strands.
- **Topoisomerases** help to **relieve the torsional stress** that builds up ahead of the replication fork, by creating transient breaks in the DNA backbone and allowing the strands to rotate.

5. DNA repair proteins

- Diverse group of enzymes
- Play a critical role in maintaining the **integrity of the genome**
- Recognize and repair various types of DNA damage, such as breaks, cross-links, and base modifications
- **Prevent mutations** and other genomic abnormalities.
- Play a role in **recombination**, the process by which homologous chromosomes exchange genetic information during meiosis

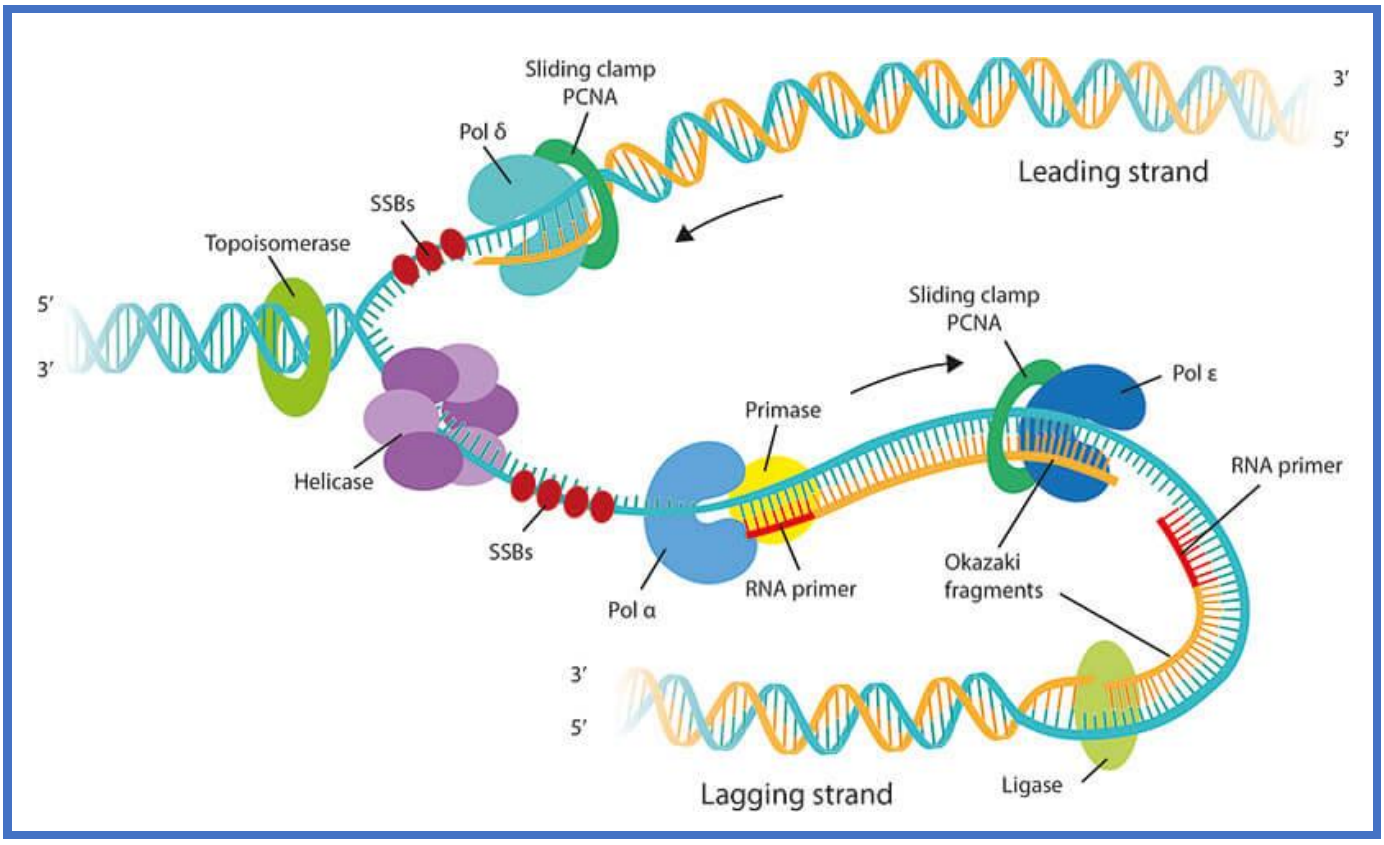


Fig 16.12: Proteins and Enzymes of DNA Replication

Formation of 80S Initiation Complex

- 48S initiation complex now binds to 60S which was free after ribosomal dissociation, forms **80S initiation complex**.
- **This requires hydrolysis of GTP for energy.**
- **eIF-2 carries GTP and eIF-5 GTPase activity**, both interact to bring about hydrolysis.
- Reaction then results in release of all the initiation factors bound to the 48S initiation complex, which are then recycled.
- Occurs rapid association of 40S and 60S subunits to **form the 80S ribosomal complex ready for protein synthesis.**
- The 80S complex has **two receptor sites**:
  1. **'P' site or peptidyl site**
     - At this point, the mett-RNA *is* on the 'P' site. On this site, the growing peptide chain will grow.
  2. **'A' site** or **aminoacyl site**
     - At this point it is free, the new incoming t-RNA with the amino acid to be added next is taken up, at this site.
- The **t-RNA binds** with **ribosome** through the pseudo uridine arm
- Key differences between the initiation of translation in prokaryotes and eukaryotes is given in table and illustrated in diagram

Aspect	Prokaryotes	Eukaryotes
Ribosome Binding Site (RBS)	Consists of Shine-Dalgarno sequence, located upstream of the start codon.	Initiator codon (AUG) is typically preceded by a 5' untranslated region (UTR).
Initiation Factors	Initiation factors IF1, IF2, and IF3 are involved.	Initiation factors eIF1, eIF1A, eIF2, eIF3, and eIF4 complex are involved.
Initiation Complex Formation	Small ribosomal subunit (30S) binds to mRNA at the RBS, guided by the Shine-Dalgarno sequence.	Small ribosomal subunit (40S) binds to mRNA at the 5' cap structure.
Start Codon Recognition	AUG start codon is recognized directly by IF2.	AUG start codon is recognized by eIF2-GTP-Met-tRNAiMet complex.
Kozak Sequence	Not applicable.	Kozak consensus sequence (e.g., GCCRCCAUGG) can enhance start codon recognition.
GTP Hydrolysis	GTP hydrolysis occurs upon start codon recognition, releasing initiation factors.	GTP hydrolysis occurs after start codon recognition, releasing initiation factors.
Large Ribosomal Subunit	Large ribosomal subunit (50S) joins the small subunit (30S) to form the complete ribosome.	Large ribosomal subunit (60S) joins the small subunit (40S) to form the complete ribosome.

Elongation

- **Cyclic process on the ribosome** in which one amino acid is added to the nascent peptide chain.
- Peptide sequence is determined by the **codons** present in the m-RNA.
- It requires **elongation factors—EF-IA, EF-2.**

Steps

The steps are mainly **three:**

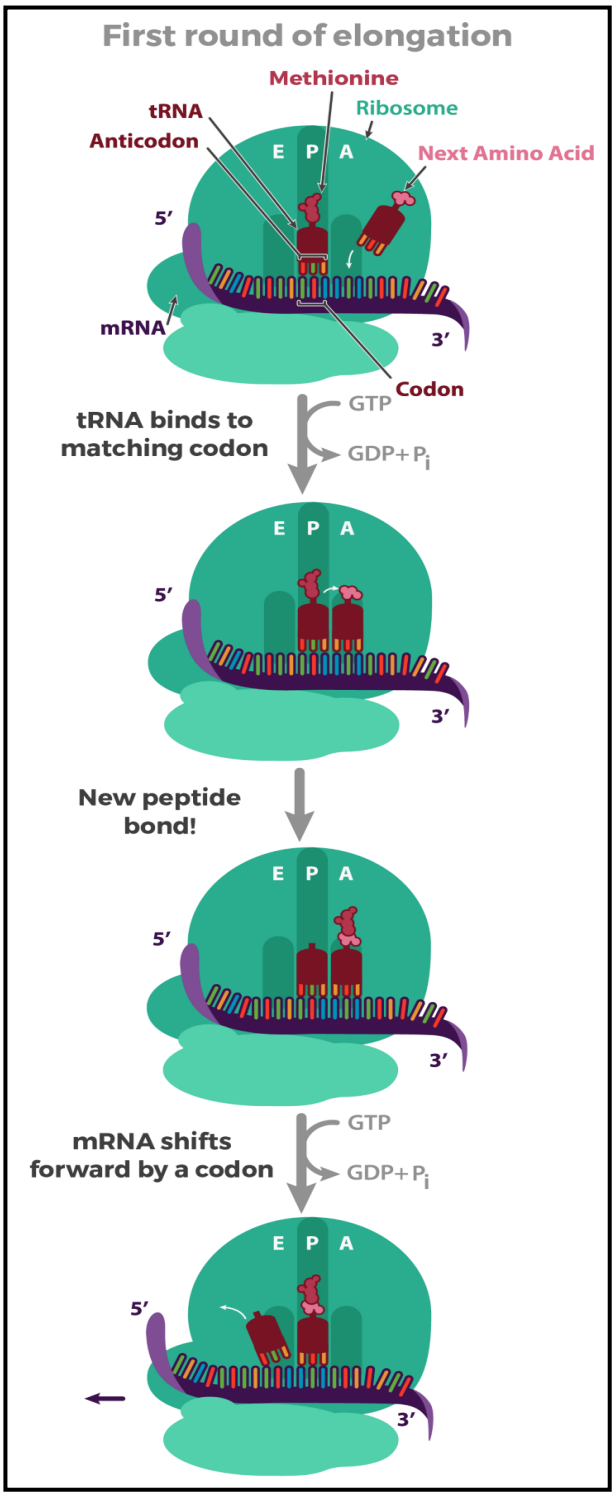
1.Binding of new aminoacyl-tRNA to 'A' site

2.Peptide bond formation

3.Translocation process

Binding of Aminoacyl-tRNA to the A Site

- In the 80S ribosomal initiation complex, the 'P' site is occupied by **met-tRNA** and **'A' site** is free.
- Fidelity of protein synthesis depends on having correct **aminoacyl-tRNA** in the 'A' site as per codon reading.
- Elongation factor **EF-IA** forms a ternary complex with **GTP** and the entering **aminoacyl-tRNA (A_1).**
- This complex allows the amino acyl-tRNA to **enter** the **'A' site.**
- **GTP** is hydrolysed to give energy and this is catalysed by an active site on the ribosome. This releases the EF-IA-GDP and Pi.
- **EF-IA-GDP** is converted again to **EF-IA-GTP** by other soluble protein factors and GTP
- It is further **recycled**



Peptide Bond Formation

- **α-NH_2** group of the new aminoacyl-tRNA (A_1) in the 'A' site combines with the **–COOH** group of **MettRNA** (m) occupying the **'P' site**
- Reaction is catalysed by the enzyme **Peptidyl transferase**, a component of the 28S RNA of the 60S ribosomal subunit.
- Because the amino acid on the aminoacyl-tRNA is already "activated", the reaction does not require any further energy

BIBLIOGRAPHY

Chapter 1: Cell and its Organelles

Bain DL, Heneghan AF Connaghan-Jones KD, Miura MT: Nuclear receptor structure: implications for function. Annu Rev Physiol 2007;69:201-220.

Bartalina L: Thyroid hormone-binding proteins: update 1994.

Endocr Rev 1994:13:140-142. Cristina Casals-Casas C, Desvergne B: Endocrine disruptors:from endocrine to metabolic disruption. Annu Rev Physiol 2011:73:135-162.

DeLuca HR: The vitamin D story: a collaborative effort of basic science and clinical medicine. FASEB J 1988; 2:224-236.

Douglass J, Civelli O, Herbert E: Polyprotein gene expression: generation of diversity of neuroendocrine peptides. Annu Rev

Biochem 1984;53:665-715. Farooqi IS, O'Rahilly S: Monogenic obesity in humans. Annu Rev

Med 2005;56:443-458. Fan W, Atkins AR, Yu RT, et al: Road to exercise mimetics: targeting nuclear receptor in skeletal muscle. J Mol Endocrinol 2013:51:T87-T100.

Hah N, Kraus WL: Hormone-regulated transcriptomes: lessons learned from estrogen signaling pathways in breast cancer cells.

Mol Cell Endocrinol 2014;382:652-664.

Miller WL: Molecular biology of steroid hormone biosynthesis.Endocr Rev 1988;9:295-318.

Russell DW, Wilson JD: Steroid 5 alpha-reductase: two genes/two enzymes. Annu Rev Biochem 1994;63:25-61. Steiner DF, Smeekens SP, Ohagi S, et al: The new enzymology of precursor processing endoproteases. J Biol Chem 1992;267 :23435-23438.

Taguchi A, White M: Insulin-like signaling, nutrient homeostasis and life span. Annu Rev Physiol 2008;70:191-212.

Weikum ER, Knuesel MT, Ortlund EA, Yamamoto KR:

Glucocorticoid receptor control of transcription: precision and plasticity via allostery. Nat Rev Mol Cell Biol 2017;18:159-174. Xu Y, O'Malley BW, Elmquist JK: Brain nuclear receptors and body weight regulation. J Clin Invest 2017;127:1172-1180.

Chapter 2: Physiochemical Aspects

Cooper GM, Hausman RE: The Cell: A Molecular Approach, 7th ed. Palgrave, 2015. (An excellent textbook of cell biology, with comprehensive coverage of trafficking and sorting.)

Hebert DN, Molinari M: In and out of the ER: protein folding, quality control, degradation and related human diseases. Physiol Rev 2007;87:1377.