MEDICAL EDUCATION RESOURCE

Biochemical Perspective to Medicine

Historical Background — Concise Exam Notes

• Biochemistry evolved from organic chemistry and physiology to explain life processes at the molecular level.

• Ancient Indian medicine recognized metabolic basis of disease — **Charaka** described diabetes (madhumeha) as a disorder of carbohydrate and fat metabolism.

• Term **“Biochemistry”** coined by **Neuberg in 1903** (bios = life, chymos = juice).

• Early foundational books:
– **Liebig (1842):** introduced concept of metabolism.
– **Hoppe-Seyler (1877):** published *Textbook of Physiological Chemistry*.

• Key early discoveries:
– **Rouelle (1773):** isolated urea.
– **Wöhler (1828):** synthesized urea ? disproved “vital force.”
– **Pasteur (1860):** fermentation as biological process.
– **Buchner (1897):** extracted enzymes ? cell-free fermentation.

• Major biochemical milestones:
– **ATP isolated** (Fiske & Subbarow, 1926).
– **Creatine phosphate** discovered (Lohmann, 1932).
– **TCA cycle** described (Krebs, 1937).
– **DNA proved genetic material** (Avery & MacLeod, 1944).
– **DNA structure** elucidated (Watson & Crick, 1953).
– **Genetic code** cracked (Nirenberg, 1961).
– **Gene synthesis** (Khorana, 1965).

• Modern breakthroughs:
– **Recombinant DNA** (Paul Berg, 1972).
– **PCR** (Kary Mullis, 1985).
– **Human Genome Project** (1990–2003).

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• Present-day importance:
– Central to understanding metabolism, genetics, enzymology, disease mechanisms.
– Basis of modern diagnostics, biomarkers, molecular medicine, and therapeutics.

Biomolecules

Major elements of the human body

• Six elements form >99% of body composition: **O, C, H, N, Ca, P**.
• Body composition: **60% water**, **15% proteins**, **15% lipids**, **2% carbohydrates**, **8% minerals**.

Molecular precursors

• All major biomolecules arise from ~30 basic precursors (“alphabet of biochemistry”).
• Includes **20 amino acids**, **2 purines**, **3 pyrimidines**, **glucose**, **ribose**, **palmitate**, **glycerol**, **choline**.

Hierarchy of molecular complexity

• **Monomers ? Macromolecules ? Supramolecular assemblies ? Organelles ? Cell ? Tissue**.
• Examples:
– Glucose ? glycogen
– Amino acids ? proteins
– Nucleotides ? nucleic acids

Covalent linkage & macromolecule formation

• Biomolecules join by **covalent bonds** (strong, stable).
• Examples:
– Glycosidic bonds (carbohydrates)
– Peptide bonds (proteins)
– Phosphodiester bonds (nucleic acids)
• Covalent assembly forms large macromolecules essential for structure and function.

Supramolecular systems

• Macromolecules interact via **noncovalent forces** (hydrogen bonds, ionic bonds, van der Waals, hydrophobic interactions).
• Examples:
– Ribosomes (RNA + proteins)
– Lipoproteins (lipids + proteins)
– Chromatin (DNA + protein)

Prokaryotes vs Eukaryotes (Table 1.2)

• **Prokaryotes:**
– Small size
– No true nucleus
– No membrane-bound organelles
– Rigid cell wall
• **Eukaryotes:**
– Large size (1000–10,000× larger)
– True nucleus with nuclear membrane
– Organelles present (mitochondria, ER, Golgi, lysosomes)
– Plasma membrane with lipid bilayer

Study of Metabolic Processes

Digestion – Primary Metabolism

• Dietary carbohydrates, fats, and proteins are broken down into **monosaccharides, fatty acids/glycerol, and amino acids**.
• Takes place in the **gastrointestinal tract** by enzymatic hydrolysis.
• Produces small absorbable molecules that enter circulation.

Intermediary / Secondary Metabolism

• Absorbed nutrients undergo **further oxidation** inside cells.
• Generates **NADH and FADH?**.
• Includes pathways like **glycolysis, ?-oxidation, deamination, and TCA cycle**.
• Main purpose: extraction of reducing equivalents and metabolic intermediates.

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Tertiary Metabolism – ETC & ATP

• NADH and FADH? feed electrons to the **electron transport chain** in mitochondria.
• Electron flow creates a proton gradient used by **ATP synthase** to form ATP.
• **Oxygen** acts as the final electron acceptor, producing water.

Anabolism and Catabolism

• **Catabolism:** Breakdown of complex molecules, energy-releasing, exergonic (e.g., glycolysis, ?-oxidation).
• **Anabolism:** Synthesis of biomolecules, energy-requiring, endergonic (e.g., glycogen, protein, and fatty acid synthesis).
• Together they maintain overall **metabolic balance** in the body.

Stabilizing Forces in Molecules

Covalent Bonds

• Strong bonds formed by **sharing of electron pairs** between atoms.
• Responsible for basic structure of biomolecules (peptide, glycosidic, phosphodiester bonds).
• High bond strength ? stable macromolecular backbones.

Ionic / Electrostatic Bonds

• Formed by **attraction between oppositely charged ions**.
• Occur when an electron is transferred from an electropositive atom to an electronegative atom.
• Strength decreases in aqueous environments but is important for protein folding and interactions.

Example: NaCl, KBr, NaF

• Na?–Cl?, K?–Br?, Na?–F? represent classical ionic compounds.
• Demonstrate electron transfer and electrostatic attraction between the resulting ions.

Positive & Negative Charges in Amino Acids

• **Positive (basic) groups:**
– Lysine: ?-amino group
– Arginine: guanidinium group
– Histidine: imidazolium group

• **Negative (acidic) groups:**
– Aspartate: ?-carboxyl group
– Glutamate: ?-carboxyl group

• These charged groups form ionic interactions that stabilize **protein tertiary and quaternary structure**.

Hydrogen Bonds

Hydrogen Donors

• Atoms or groups that supply a hydrogen already covalently attached to an electronegative atom.
• Common donors in biological molecules include:
– **–NH** groups (as in peptide bonds, indole ring of tryptophan, imidazole ring of histidine)
– **–OH** groups (serine, threonine, tyrosine)
– **–NH?** groups (lysine, arginine side chains)

Hydrogen Acceptors

• Electronegative atoms with lone pairs of electrons capable of accepting a hydrogen.
• Major acceptors in biomolecules:
– **Carbonyl oxygen (C=O)** of peptide bonds
– **Carboxylate groups (COO?)** of aspartate and glutamate
– **Sulfur atoms in disulfide linkages** may participate weakly
– **Nitrogen or oxygen atoms** in nucleic acid bases

Role in Proteins & DNA

• In proteins:
– Hydrogen bonds stabilize **?-helices**, **?-sheets**, and **turns** of secondary structure.

– Occur between the carbonyl oxygen of one amino acid and the amide hydrogen of another along the peptide backbone.
– Side-chain hydrogen bonds help fine-tune folding and maintain the tertiary structure.

• In DNA:
– Hydrogen bonds hold complementary bases together:
– **A–T** pairs form **two** hydrogen bonds.
– **G–C** pairs form **three** hydrogen bonds.
– These bonds allow the double helix to be **stable yet separable**, enabling replication and transcription.
– Provide specificity in base pairing and maintain the geometry of the helix.

Hydrophobic Interactions

Nonpolar Residues Clustering

• Nonpolar amino-acid side chains (like leucine, isoleucine, valine, phenylalanine) tend to **avoid water**.
• In an aqueous environment, these nonpolar groups move closer together, reducing their contact with water.
• This clustering forms the **hydrophobic core** of proteins and is a major driving force behind protein folding.

Description of Hydrophobic Interaction

Nonpolar side chains come together and pack tightly in the interior of a protein while water molecules remain on the outside. This minimizes the exposure of hydrophobic residues to the surrounding water, helping the protein fold into a stable three-dimensional structure.

Van der Waals Forces

• Very weak, short-range attractive forces arising from temporary dipoles formed when electrons fluctuate around atoms.
• Occur between **all atoms**, whether polar or nonpolar.

• Individually weak (?1 kcal/mol), but collectively significant because they act throughout the protein interior.
• Essential for **tight packing of amino acids** within the folded structure and stabilizing the nonpolar core.

Water: The Universal Solvent

Hydrogen Bonding Network

• Each water molecule can form up to **four hydrogen bonds** due to its bent structure and polarity.
• These dynamic bonds constantly **form and break**, creating a flexible network in liquid water.
• This network gives water its unique physical and chemical properties essential for life.

Ice vs Liquid Water Density

• In ice, water molecules arrange in a **fixed tetrahedral structure**, creating more open space.
• This makes ice **less dense** than liquid water, allowing it to float.
• When ice melts, hydrogen bonds collapse partially, and molecules pack more tightly ? **higher density**.

Thermal Motion & Temperature Effects

• As temperature increases, water molecules move faster, breaking hydrogen bonds more frequently.
• At **0–4°C**, collapsing hydrogen bonds increase density.
• Above 4°C, thermal expansion dominates ? density decreases.
• At **100°C**, kinetic energy exceeds hydrogen bonding ? water becomes vapor.

Hydrophilic & Hydrophobic Effects

• **Hydrophilic molecules** (polar or charged) dissolve easily because they can form hydrogen bonds or ionic interactions with water.
• **Hydrophobic molecules** (nonpolar) cannot form bonds with water, causing them to **cluster together**, a key principle in protein folding and membrane formation.

Description of Hydrogen-Bonded Water Molecules

Water molecules are shown connected through multiple hydrogen bonds: the oxygen atom of one molecule attracts the hydrogen atom of a neighboring molecule. These repeated interactions create a loosely organized yet constantly shifting network that explains water's high cohesion, surface tension, and solvent capacity.

Principles of Thermodynamics

First Law of Thermodynamics

• Total energy of a system and its surroundings remains constant.
• Energy can be transformed but not created or destroyed.

?E = Q – W

• **?E:** Change in internal energy
• **Q:** Heat absorbed by the system
• **W:** Work done by the system
• If heat is absorbed and no work is done, internal energy increases.

Second Law of Thermodynamics

• Spontaneous processes increase the **entropy** (randomness/disorder) of a system + surroundings.
• Systems naturally move from **ordered ? disordered** states unless energy is added.

Entropy Concepts

• Entropy (**S**) reflects randomness; higher entropy means greater disorder.
• At equilibrium, entropy reaches its **maximum**.
• Biological systems maintain order by increasing entropy in surroundings.

Q = T × ?S

• **Q:** Heat absorbed
• **T:** Absolute temperature
• **?S:** Change in entropy
• Shows that entropy changes depend on heat flow and temperature.

Gibbs Free Energy

• Determines whether a reaction can occur spontaneously.
• Combines enthalpy (heat) and entropy (disorder) effects.

?G = ?H – T?S

• **?G:** Free energy change
• **?H:** Change in enthalpy
• **T?S:** Temperature × entropy change
• Negative ?G ? reaction proceeds spontaneously.
• Positive ?G ? requires energy input.

Exergonic & Endergonic Reactions

• **Exergonic:** ?G negative ? energy-releasing ? spontaneous.
• **Endergonic:** ?G positive ? energy-requiring ? non-spontaneous unless coupled.

Coupled Reactions

• Unfavorable reactions (positive ?G) can proceed when paired with favorable reactions (negative ?G).
• The combined ?G becomes negative, allowing the pathway to move forward.

Example: Glucose ? G6P

• Glucose + Pi ? Glucose-6-phosphate is **endergonic** (positive ?G).
• Coupled with ATP hydrolysis (strongly exergonic).
• Net ?G becomes **negative**, enabling phosphorylation of glucose.

Standard Free Energy Change (?G°)

• Free energy change under standard conditions (1 M concentration, pH 7).
• Indicates reaction tendency but actual ?G depends on concentrations inside cells.

Near-Equilibrium vs Far-From-Equilibrium Reactions

• **Near-equilibrium reactions:**
– ?G ? 0
– Easily reversible
– Direction depends on substrate/product concentration.

• **Far-from-equilibrium reactions:**
– Large negative ?G
– Irreversible
– Usually catalyzed by key regulatory enzymes.

Irreversible Steps in Metabolism

• Pathways contain a few strongly exergonic steps that **drive the entire sequence forward**.
• These irreversible steps determine pathway direction, regulate metabolic flow, and prevent backward cycling.

Donnan Membrane Equilibrium

Ion Distribution Across Semipermeable Membranes

• When two solutions are separated by a membrane permeable to **water and small ions** but not to **large charged molecules** (e.g., proteins), ions redistribute unevenly.
• The side containing **non-diffusible ions** develops a predictable imbalance of diffusible ions.

Donnan Product Rule: [Na?]L × [Cl?]L = [Na?]R × [Cl?]R

• At equilibrium, the **product of concentrations** of diffusible cations and anions on one side equals the product on the other side.
• This rule explains why ion distribution becomes **asymmetric** when large fixed ions are present.

Electrical Neutrality Rule

• Each compartment must maintain **overall neutrality**:
– Total cations = total anions.
• Even if ions shift across the membrane, each side still balances charge internally.

Conservation of Diffusible Ions

• The **total amount** of each diffusible ion (e.g., Na? or Cl?) remains equal before and after equilibrium.
• Only the **distribution** between the two sides changes.

Description of Donnan Equilibrium Illustration

One side of the membrane contains a salt with a **non-diffusible anion** (such as a protein), while the other side contains only diffusible ions. As equilibrium is reached, more **cations accumulate** on the side with the non-diffusible anion, and fewer anions remain there. The other side shows the complementary pattern. Despite this imbalance, the equations for neutrality, product rule, and conservation all remain satisfied.

Clinical Applications

Plasma Osmotic Concentration

• Plasma proteins (non-diffusible anions) cause an uneven distribution of small ions.
• This contributes to the **oncotic pressure** that helps maintain plasma volume.

Tissue pH Difference

• Cells contain negatively charged proteins ? attract more H? ions.
• This leads to **slightly lower pH inside tissues** compared to extracellular fluid.

RBC pH (Hemoglobin Effect)

• Hemoglobin carries strong negative charges.
• This causes increased H? concentration inside red cells ? **lower RBC pH** than plasma.

Chloride Shift (Hamburger Phenomenon)

• When CO? enters RBCs and is converted to HCO??, chloride ions move into RBCs to maintain electrical neutrality.
• This unequal movement of Cl? is partly explained by the **Donnan effect**.