Proteins: Structure and Function

Proteins: Structure and Function

Primary Structure

• The **linear sequence** of amino acids in a polypeptide.
• Determined by **peptide bonds (–CO–NH–)** which are strong, planar, and mostly **trans**.
• Sequence dictates higher-order folding and final protein function.
• Even a **single amino-acid mutation** (e.g., Val for Glu in sickle cell anemia) drastically changes structure and function.

Secondary Structure

Local folding patterns stabilized by **hydrogen bonds** between backbone –C=O and –NH groups.

1. ?-Helix

• Right-handed spiral with **3.6 residues per turn**.
• Stabilized by **intrachain hydrogen bonds** every 4th residue.
• Side chains project outward.
• Disrupted by **proline**, **glycine**, and charged residues.

2. ?-Pleated Sheets

• Polypeptide chains arranged side-by-side (parallel or antiparallel).
• Stabilized by **interchain hydrogen bonds**.
• More extended than ?-helix.

3. Turns / Loops

• Sharp bends connecting helices and sheets.
• Often contain **glycine** (flexible) or **proline** (kink-forming).

Description of Secondary Structure

One region forms a helical coil stabilized by hydrogen bonds; another forms zig-zag strands lying side by side, connected by hydrogen bonds.

Tertiary Structure

The **overall 3-dimensional shape** of a single polypeptide chain.

Stabilizing Forces

• **Hydrophobic interactions** – bury nonpolar residues inward.
• **Hydrogen bonds** – stabilize external and internal interactions.
• **Ionic bonds (salt bridges)** – between charged side chains.
• **Disulfide bonds** – covalent S–S links between cysteines.
• **Van der Waals forces** – tight packing in the protein core.

Domains

• Independently folded functional units (e.g., catalytic domains, binding domains).

Description of Tertiary Structure

Hydrophobic residues cluster inward while polar and charged residues orient outward, creating a compact, functional 3D structure.

Quaternary Structure

Association of **two or more polypeptide chains (subunits)** into a functional protein.

Key Features

• Subunits held together by **noncovalent interactions** (H-bonds, ionic, hydrophobic)
• Sometimes by **interchain disulfide bonds**.
• Allows **cooperativity**, **regulation**, and **structural stability**.

Examples

• **Hemoglobin** – ???? tetramer
• **Immunoglobulins** – multiple polypeptide chains linked by disulfide bonds
• **Lactate dehydrogenase** – tetrameric enzyme

Description of Quaternary Structure

Multiple folded subunits assemble into a larger complex, each occupying a precise position and contributing to overall function.

Primary Structure of Insulin

• Human insulin is composed of **two polypeptide chains**:

A-Chain

• **21 amino acids**
• Contains an **intra-chain disulfide bond** between **A6–A11**
• N-terminus begins with **Glycine**, C-terminus ends with **Asparagine**

B-Chain

• **30 amino acids**
• N-terminus begins with **Phenylalanine**, C-terminus ends with **Threonine**

Disulfide Bonds

Insulin contains **three disulfide bridges**:

1. **A7 – B7** (inter-chain)
2. **A20 – B19** (inter-chain)
3. **A6 – A11** (intra-chain)

Proinsulin Processing

• Insulin is synthesized as **preproinsulin ? proinsulin ? insulin**.
• **C-peptide** connects A- and B-chains in proinsulin and is removed during maturation.
• C-peptide is **biologically inactive** but a marker of insulin secretion.

Important Point

• The **primary structure** (specific amino-acid sequence + disulfide pattern) is essential for insulin's ability to bind its receptor.

Structure–Function Relationship of Insulin

1. Disulfide Bonds Are Essential for Activity

• Correct folding of A- and B-chains requires the precise disulfide pattern.
• Any alteration (mutation, reduction, or improper re-oxidation) ? **loss of biological activity**.
• These bonds hold insulin in its functional conformation, enabling receptor binding.

2. A-Chain Provides Stability

• Intra-chain disulfide that stabilizes ?-helical structure.
• Mutations in A-chain regions that stabilize the helix ? **rapid degradation** or poor receptor binding.

3. B-Chain Determines Receptor Binding

• The **N-terminal residues of the B-chain (Phe1, Val2, Asn3)** are critical for insulin receptor recognition.
• B-chain C-terminal residues also participate in the interaction with the receptor.
• Mutations in the B-chain reduce **potency**, **binding**, and **half-life**.

4. Zinc Stabilizes Storage, Not Action

• In pancreatic ?-cells, insulin forms **hexamers** with zinc.
• Hexamer ? storage form
• Monomer ? biologically active form
• Rapid-acting insulin analogs are designed to **prevent hexamer formation**, improving

absorption.

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5. C-Peptide Does Not Affect Function

• Removed before secretion.
• Its presence prevents early folding and aggregation during insulin synthesis.
• Used as a **clinical marker** for endogenous insulin production.

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6. Mutations Affect Structure and Diabetes

• Point mutations in the insulin gene can disturb folding ? “**insulinopathies**.”
• Examples include improper disulfide pairing or disrupted receptor domains leading to early-onset diabetes.

Sequence Analysis

Definition

• Sequence analysis determines the **exact order of amino acids** in a protein.
• Essential for understanding protein structure, function, and genetic mutations.

Methods

1. Edman Degradation
• Sequential removal of **N-terminal amino acids** one at a time.
• Each residue is identified ? gives **primary structure**.
• Useful for peptides up to ~50 residues.

2. Enzymatic Cleavage
• Proteases like **trypsin**, **chymotrypsin**, **pepsin** cut proteins at specific residues.
• Fragments are analyzed and assembled into the full sequence.

3. Chemical Cleavage
• Cyanogen bromide cleaves at **methionine** residues.

4. Mass Spectrometry

• Modern method for rapid **peptide sequencing**.
• Identifies amino acids based on mass/charge ratios.
• Detects post-translational modifications (phosphorylation, acetylation, disulfide patterns).

Applications

• Identification of mutations (e.g., sickle cell anemia: Glu?Val).
• Protein engineering & recombinant insulin design.
• Quality control in biotech proteins.

Iso-electric pH (Iso-electric Point, pI)

Definition

• pI is the **pH at which an amino acid or protein has zero net charge**.
• Exists predominantly as a **zwitterion**.

Importance

• **Minimum solubility** at pI ? proteins precipitate easily.
• No movement in an electric field ? basis of **isoelectric focusing**.
• Proteins with a high content of acidic residues ? low pI.
• Proteins rich in basic residues ? high pI.

Determination

• For neutral amino acids:
pI = (pK? + pK?) / 2
• For acidic and basic amino acids: all three pKs considered.

Clinical Relevance

• Abnormal pI helps detect protein variants in diseases (e.g., HbS, HbC).
• Used in separation of serum proteins (albumin, globulins).

Precipitation Reactions

Proteins precipitate when their **solubility decreases**, caused by pH, salts, organic solvents, or heat.

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1. Precipitation at Iso-electric Point (pI)

• Proteins have **minimum solubility** at pI.
• Used to isolate casein from milk at pH 4.6.
• Used in laboratory protein purification.

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2. Salting Out

• High salt concentration (ammonium sulfate) removes water from proteins.
• Protein–protein interactions increase ? precipitation.
• Common in protein purification and enzyme isolation.

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3. Organic Solvent Precipitation

• Alcohols (ethanol, acetone) reduce dielectric constant ? protein denaturation ? precipitation.
• Used in **plasma protein fractionation**.

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4. Heavy Metal Precipitation

• Hg^{2}?, Pb^{2}?, Ag? bind –COO? and –SH groups ? protein precipitation.
• Used in poisoning treatment (egg white protects gut mucosa).
• Basis of some diagnostic tests.

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5. Heat Coagulation

• High temperature disrupts hydrogen bonds and hydrophobic interactions ? coagulation.
• Example: egg white becoming solid on heating.

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6. Acid and Alkali Precipitation

• Extreme pH denatures proteins.
• Used in **gastric digestion** (HCl).
• Used to precipitate casein or remove proteins from solutions.

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7. Denaturation-Induced Precipitation

• Mild denaturing agents (urea, guanidinium chloride) disrupt tertiary structure.
• Leads to exposure of hydrophobic groups and aggregation.

Denaturation of Proteins

Definition

• Denaturation is the **loss of secondary, tertiary, or quaternary structure** of a protein **without breaking peptide bonds**.
• The primary structure **remains intact**, but the protein loses shape and function.

What Happens During Denaturation?

• **Hydrogen bonds**, **ionic bonds**, **hydrophobic interactions**, and **disulfide bonds** are disrupted.
• Protein unfolds ? **loss of biological activity**.
• Hydrophobic groups become exposed ? aggregation or precipitation.

Causes of Denaturation

• **Heat**
• **Strong acids or alkalis**
• **Organic solvents** (alcohol, acetone)
• **Heavy metals** (Hg^{2}?, Pb^{2}?)
• **Detergents** (SDS)
• **Reducing agents** (?-mercaptoethanol)
• **Radiation** or **ultrasonic vibration**

Consequences

• Loss of **enzymatic activity**
• Loss of **solubility** ? precipitation
• Change in **physical properties** (viscosity, optical rotation)
• Sometimes reversible, but usually **irreversible** in biological systems

Examples

• Cooking an egg (albumin coagulation)
• Denaturation of enzymes during fever
• Alcohol-based hand sanitizers denature viral proteins
• HCl in the stomach denatures dietary proteins

Importance

• Essential in **digestion**, **diagnostics**, **food processing**, and understanding protein folding diseases.

Heat Coagulation

Definition

• Coagulation is **precipitation of proteins due to heat**, caused by irreversible denaturation and aggregation.

Mechanism

• Heat breaks **weak non-covalent bonds** (hydrogen bonds, hydrophobic interactions).
• Protein unfolds ? exposed hydrophobic regions stick together ? **insoluble coagulum** forms.

Examples

• Egg white (albumin) turning solid when boiled
• Coagulation of milk proteins when heated
• Clotting of serum proteins during diagnostic heat tests
• Heat-labile enzymes losing activity at high temperatures

Clinical Relevance

• **Heat coagulation test** for detecting proteins in urine or cerebrospinal fluid.
• Fever can partially denature heat-sensitive enzymes, affecting metabolism.
• Heat instability in certain genetic enzyme deficiencies.

Difference from Simple Denaturation

• Denaturation = unfolding
• Coagulation = **unfolding + aggregation + precipitation**

Description of Heat Coagulation Process

A protein heated above its stability range begins to unfold, exposing hydrophobic inner residues. These residues stick to one another, forming large aggregates that become insoluble and appear as a solid mass or cloudy precipitate.

Classification of Proteins

Proteins can be classified based on **composition**, **shape**, and **function**.

A. Based on Composition

1. Simple Proteins

• Yield **only amino acids** on hydrolysis.
• Examples:
– **Albumins** (serum albumin)

– **Globulins** (IgG)
– **Histones**

2. Conjugated Proteins

• Protein + **non-protein (prosthetic) group**.
Examples:
• **Glycoproteins** ? carbohydrate
• **Lipoproteins** ? lipids
• **Metalloproteins** ? metal ions (hemoglobin, cytochromes)
• **Phosphoproteins** ? phosphate (casein)
• **Nucleoproteins** ? nucleic acids

3. Derived Proteins

• Formed by partial hydrolysis or denaturation.
• Examples: **metaproteins**, **proteoses**, **peptones**, **polypeptides**.

B. Based on Shape

1. Fibrous Proteins

• Long, thread-like
• Structural role
• Low solubility
• Examples: **Collagen, Keratin, Elastin**

2. Globular Proteins

• Spherical, compact
• Functional role (enzymes, hormones)
• Soluble in water
• Examples: **Enzymes, Hemoglobin, Albumin**

C. Based on Function

• Enzymatic (lipase, trypsin)
• Structural (collagen, keratin)
• Transport (hemoglobin)
• Storage (ferritin)
• Regulatory (insulin)
• Protective (antibodies)

Quantitative Estimation of Proteins

Common biochemical methods used to measure protein concentration:

1. Biuret Method

• Based on **violet complex** formed between $Cu^{2?}$ and **peptide bonds** in alkaline medium.
• Requires **two or more peptide bonds** ? minimum tripeptide.
• Used for plasma proteins.

2. Lowry Method

• More sensitive than Biuret.
• Combines Biuret reaction + reduction of **Folin–Ciocalteu reagent** ? blue color.
• Sensitive to aromatic amino acids.

3. Bradford Method

• Uses **Coomassie Brilliant Blue dye**.
• Dye binds to basic and aromatic residues ? blue color.
• Very sensitive, widely used for micro-assays.

4. UV Absorption (280 nm)

• Aromatic residues (Phe, Tyr, Trp) absorb UV at 280 nm.
• Rapid method for pure proteins.

5. Kjeldahl Method

• Measures **total nitrogen content**; indirectly measures total protein.
• Used in food analysis.

Protein Folding & Chaperones

Protein Folding

• Folding converts a linear polypeptide into its **functional 3D conformation**.
• Driven by:
– Hydrophobic interactions
– Hydrogen bonds
– Ionic interactions
– Disulfide bonds
– Van der Waals forces

Energy Landscape

• Folding follows a path toward a **stable low-energy state** (native structure).
• Incorrect folding ? aggregation ? diseases (Alzheimer’s, Parkinson’s).

Molecular Chaperones

• Specialized proteins that **assist in proper folding** without becoming part of the final protein.

Types

• **Hsp60 (Chaperonins)** — barrel-shaped; provide isolated environment for folding.
• **Hsp70** — binds hydrophobic regions and prevents aggregation.
• **Protein disulfide isomerase (PDI)** — rearranges disulfide bonds.
• **Peptidyl-prolyl isomerase** — converts cis/trans proline bonds.

Functions

• Prevent misfolding
• Promote refolding
• Assist in transport across membranes
• Prevent aggregation during stress

Renaturation

Definition

• Some denatured proteins can **regain their native structure and function** when denaturing agents are removed.

Features

• Works only if the **primary structure is intact**.
• Demonstrates that **all information for proper folding lies in the amino-acid sequence**.

Classic Example

• **Ribonuclease** regains full activity after denaturation by urea and ?-mercaptoethanol when reagents are removed.

Limitations

• Not all proteins renature easily.
• Aggregated proteins generally **cannot** renature.
• In cells, chaperones are required to guide renaturation.

Protein Functions

Proteins perform diverse biological roles essential for life.

1. Enzymatic Function

• Proteins act as **biocatalysts** (enzymes).
• Increase reaction rate without being consumed.
• Examples: amylase, lipase, DNA polymerase.

2. Structural Function

• Provide strength, shape, and support.
• Examples: **collagen**, **keratin**, **elastin**, **actin**, **tubulin**.

3. Transport Function

• Carry molecules across membranes or in blood.
• Examples: hemoglobin (O?), transferrin (iron), albumin (fatty acids & drugs).

4. Regulatory Function

• Hormonal and signaling proteins regulate metabolism.
• Examples: insulin, glucagon, growth hormone.

5. Protective / Immune Function

• Immunoglobulins defend against infection.
• Complement proteins help destroy pathogens.
• Fibrinogen involved in clot formation.

6. Storage Function

• Ferritin stores iron.
• Casein stores amino acids in milk.

7. Contractile / Motor Function

• Actin and myosin enable muscle contraction.
• Dynein and kinesin move organelles inside cells.

8. Buffering Function

• Proteins help maintain acid–base balance due to amphoteric nature.

9. Receptor Function

• Membrane-bound receptors bind hormones, neurotransmitters, and antigens.

Plasma Proteins

Plasma proteins include **albumin, globulins, and fibrinogen**.

1. Albumin

• Major plasma protein (~60%).
• Maintains **oncotic pressure** ? prevents edema.
• Transports fatty acids, bilirubin, calcium, drugs.
• Reduced in malnutrition, liver disease, nephrotic syndrome.

2. Globulins

• **? and ? globulins**
– Transport proteins (transferrin, ceruloplasmin, lipoproteins).
• **?-globulins (Immunoglobulins)**
– Antibodies: IgG, IgA, IgM, IgE, IgD.

3. Fibrinogen

• Precursor of **fibrin** for blood clot formation.
• Synthesized in liver.

A/G Ratio

• Normal: **1.2–1.8**.
• Low ratio ? increased globulins (infection), low albumin (liver disease).

Clinical Significance

• Used in diagnosing liver disease, kidney disease, malnutrition, inflammation.
• Electrophoresis helps detect multiple myeloma.

Collagen & Elastin

Collagen

Structure

• Most abundant protein in the body.
• Triple-helical structure: **three polypeptide chains** wound into a rope-like helix.
• Rich in **glycine**, **proline**, and **hydroxyproline**.

Types

• **Type I** – bone, skin, tendon
• **Type II** – cartilage
• **Type III** – blood vessels
• **Type IV** – basement membrane (network-forming)

Synthesis Highlights

• Requires **vitamin C** for hydroxylation of proline and lysine.
• Cross-linking via lysyl oxidase requires **copper**.

Disorders

• Scurvy (impaired hydroxylation)
• Osteogenesis imperfecta (defective Type I collagen)
• Ehlers–Danlos syndrome (defective cross-linking)

Elastin

Structure

• Highly elastic protein allowing tissues to stretch and recoil.
• Rich in **glycine, alanine, valine**.
• Contains unique amino acids **desmosine** and **isodesmosine** ? cross-links.

Location

• Found in ligaments, lungs, skin, arterial walls.

Properties

• Random coil structure ? elasticity.
• Cross-linking provides resilience and recoil.

Disorders

• **Marfan syndrome** — defective fibrillin (scaffolding protein for elastin).
• Leads to hyperelastic joints, lens dislocation, aortic aneurysm.

Frequently Asked Questions (FAQs)

1. What is the primary structure of a protein?

It is the **linear sequence of amino acids** linked by peptide bonds.

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2. Why is the peptide bond planar?

Because it has **partial double-bond character** due to resonance, restricting rotation.

---

3. What forces stabilize secondary structure?

Hydrogen bonds between the carbonyl oxygen and amide hydrogen of the peptide backbone.

---

4. What is an ?-helix?

A right-handed helical structure with **3.6 residues per turn**, stabilized by intrachain hydrogen bonds.

---

5. What breaks ?-helices?

Proline, **glycine**, and clusters of charged residues.

---

6. What is a ?-pleated sheet?

A stretched peptide arrangement stabilized by **interchain hydrogen bonds**; can be **parallel or antiparallel**.

---

7. What stabilizes tertiary structure?

Hydrophobic interactions, hydrogen bonds, ionic bonds, van der Waals forces, and **disulfide bonds**.

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8. What is a protein domain?

A compact, independently folded, functional region within a protein.

---

9. What is quaternary structure?

Association of **two or more polypeptide subunits** into a functional protein.

---

10. Give examples of quaternary proteins.

Hemoglobin, immunoglobulins, LDH (tetramer).

---

11. What are simple proteins?

Proteins that yield **only amino acids** on hydrolysis (e.g., albumin, globulin).

---

12. What are conjugated proteins?

Proteins with a **prosthetic group** (e.g., hemoglobin, lipoproteins, glycoproteins).

---

13. What is the main function of albumin?

Maintains **oncotic pressure** and transports fatty acids, bilirubin, and drugs.

---

14. What is the A/G ratio?

Albumin–globulin ratio; normal is **1.2–1.8**.

---

15. What amino acids are abundant in collagen?

Glycine, **proline**, and **hydroxyproline**.

---

16. What does vitamin C do in collagen synthesis?

Required for **hydroxylation** of proline and lysine.

---

17. What is the major defect in scurvy?

Impaired hydroxylation ? unstable collagen.

---

18. What is unique about elastin?

Contains **desmosine** and **isodesmosine**, which provide elasticity.

---

19. What is the main defect in Marfan syndrome?

Defective **fibrillin**, which is required for elastin scaffolding.

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20. What is heat coagulation?

Denaturation and precipitation of proteins on heating (e.g., cooking an egg).

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21. How is protein concentration estimated most commonly?

Biuret method (violet complex with peptide bonds).

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22. What is the basis of Bradford assay?

Binding of **Coomassie Blue dye** to basic and aromatic residues.

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23. What is renaturation?

Recovery of native protein structure after removal of denaturing agents—possible only if the **primary structure remains intact**.

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24. What proteins assist in folding?

Chaperones, including Hsp70, Hsp60 (chaperonins), and PDI.

---

25. What happens if a protein misfolds?

It may aggregate and cause diseases like **Alzheimer's, Parkinson's**, and prion diseases.

MCQs

1. The peptide bond is planar due to:

A. Ionic bonding
B. Hydrogen bonding
C. Resonance causing partial double-bond character
D. Hydrophobic interactions
Answer: C

---

2. Which amino acid disrupts ?-helix formation?

A. Alanine
B. Proline
C. Valine
D. Cysteine
Answer: B

---

3. ?-pleated sheets are stabilized mainly by:

A. Disulfide bonds
B. Hydrogen bonds between different segments
C. Hydrophobic interactions
D. Van der Waals forces
Answer: B

---

4. Which is an example of quaternary structure?

A. Single chain of myoglobin
B. Triple helix of collagen
C. ???? arrangement of hemoglobin
D. ?-helix in keratin

Answer:

---

5. Which protein is most abundant in plasma?

A. Globulin
B. Fibrinogen
C. Albumin
D. Transferrin
Answer: C

---

6. Which plasma protein maintains oncotic pressure?

A. IgG
B. Albumin
C. Fibrinogen
D. Ceruloplasmin
Answer: B

---

7. Glycine, proline, and hydroxyproline are abundant in:

A. Elastin
B. Keratin
C. Collagen
D. Albumin
Answer: C

---

8. Vitamin C is essential for which step in collagen synthesis?

A. Glycosylation
B. Hydroxylation
C. Disulfide bond formation
D. Cleavage of propeptides
Answer: B

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9. Elastin contains which unique amino acid cross-links?

A. Hydroxylysine
B. Desmosine and isodesmosine
C. Selenocysteine
D. Ornithine
Answer: B

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10. Defect in fibrillin is seen in:

A. Scurvy
B. Marfan syndrome
C. Osteogenesis imperfecta
D. Ehlers–Danlos syndrome
Answer: B

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11. The Biuret test detects proteins based on:

A. Reaction with aromatic rings
B. Copper binding to peptide bonds
C. Reaction with sulfhydryl groups
D. Reduction of Folin reagent
Answer: B

---

12. Bradford assay is based on:

A. Ninhydrin binding
B. Protein absorption at 280 nm
C. Coomassie Blue dye binding to proteins
D. Reduction of metal ions
Answer: C

---

13. Chaperones assist in:

A. Peptide bond formation
B. Proper protein folding
C. DNA replication

D. Protein degradation

Answer: B

---

14. Renaturation is possible only when:

A. Disulfide bonds break

B. Primary structure remains intact

C. Protein is heat-coagulated

D. Aggregates are present

Answer: B

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15. Which of the following is a simple protein?

A. Hemoglobin

B. Lipoprotein

C. Albumin

D. Glycoprotein

Answer: C

---

16. Collagen triple helix contains how many chains?

A. One

B. Two

C. Three

D. Four

Answer: C

---

17. Radioimmunoelectrophoresis is mainly used to detect:

A. Plasma albumin

B. Immunoglobulins

C. Fibrinogen

D. Transferrin

Answer: B

---

18. Which factor causes heat coagulation of proteins?

A. Peptide bond hydrolysis
B. Breaking of weak non-covalent interactions
C. Increased hydrogen bonding
D. Enhanced tertiary folding
Answer: B

---

19. Which enzyme stabilizes disulfide bonds during folding?

A. Hsp70
B. PDI (Protein disulfide isomerase)
C. Peptidyl-prolyl isomerase
D. Trypsin
Answer: B

---

20. Which protein fraction increases in chronic infection?

A. Albumin
B. Fibrinogen
C. ?-Globulins
D. ?-Globulins only
Answer: C

Viva Voce

1. What is the primary structure of a protein?

The linear sequence of amino acids linked by peptide bonds.

---

2. Why is the peptide bond rigid?

Because resonance gives the –CO–NH– bond **partial double-bond character**, restricting rotation.

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Proline (kink-forming) and glycine (too flexible).

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Extended strands arranged side-by-side, stabilized by **interchain hydrogen bonds**.

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Hemoglobin (????).

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The albumin–globulin ratio (normal 1.2–1.8).

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Cross-linking via **desmosine** and **isodesmosine**.

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Disruption of weak non-covalent bonds by heat ? unfolding + aggregation.

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Copper ions bind to peptide bonds in alkaline medium ? violet color.

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Assist correct protein folding and prevent aggregation.

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Protein disulfide isomerase (PDI).

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A protein that yields only amino acids on hydrolysis (e.g., albumin).

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24. What is a conjugated protein?

Protein + prosthetic group (e.g., hemoglobin, lipoprotein, glycoprotein).

---

25. What property allows proteins to act as buffers?

They are **amphoteric**, containing both acidic and basic groups.