In the name of Allah, Most Gracious, Most Merciful.

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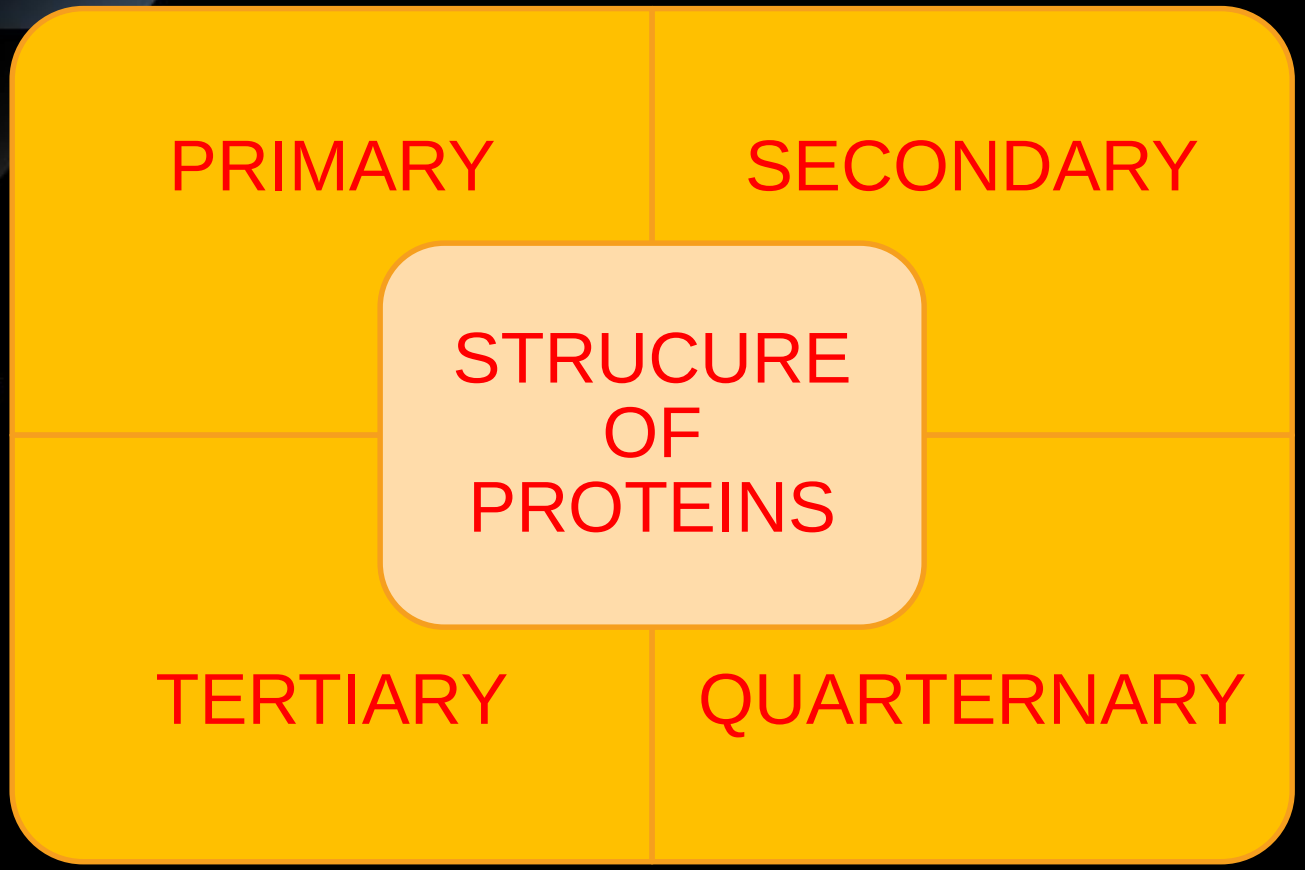
STRUCTURE OF PROTEINS

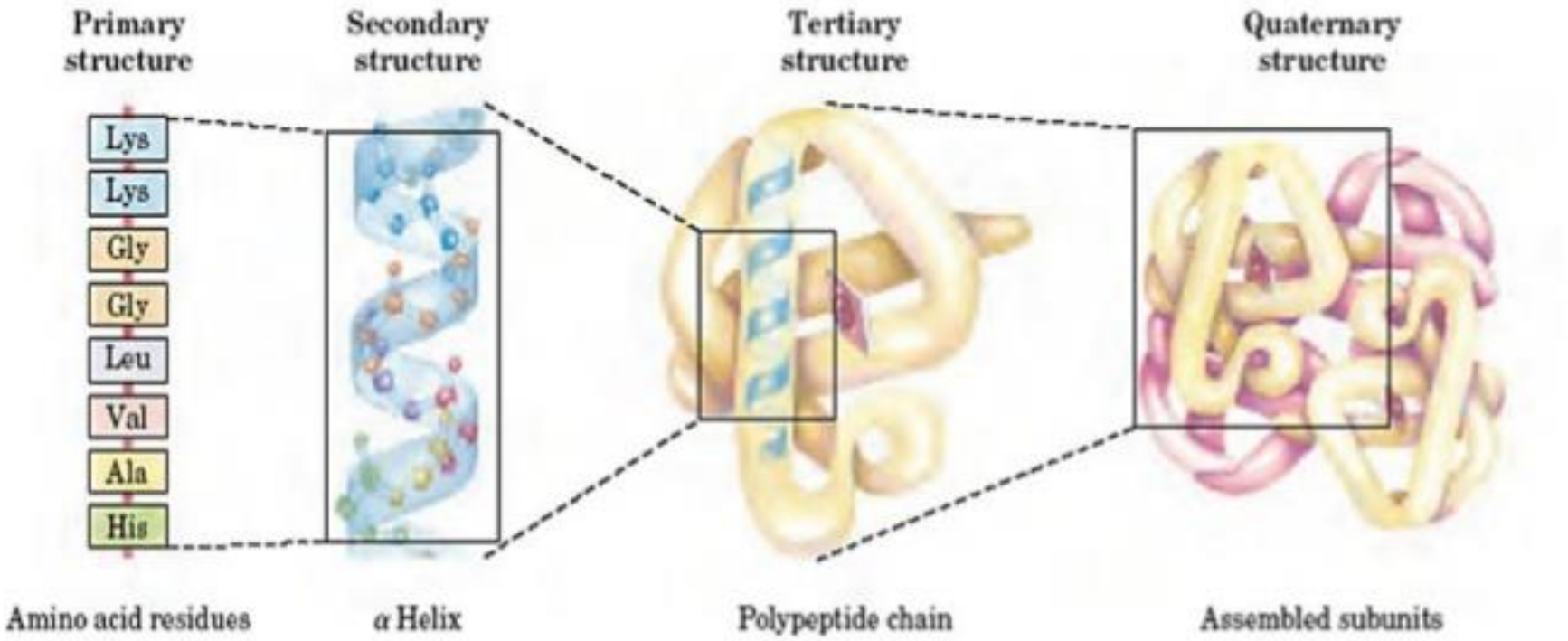
By Dr. Kalsoom Tariq

Learning Objectives:

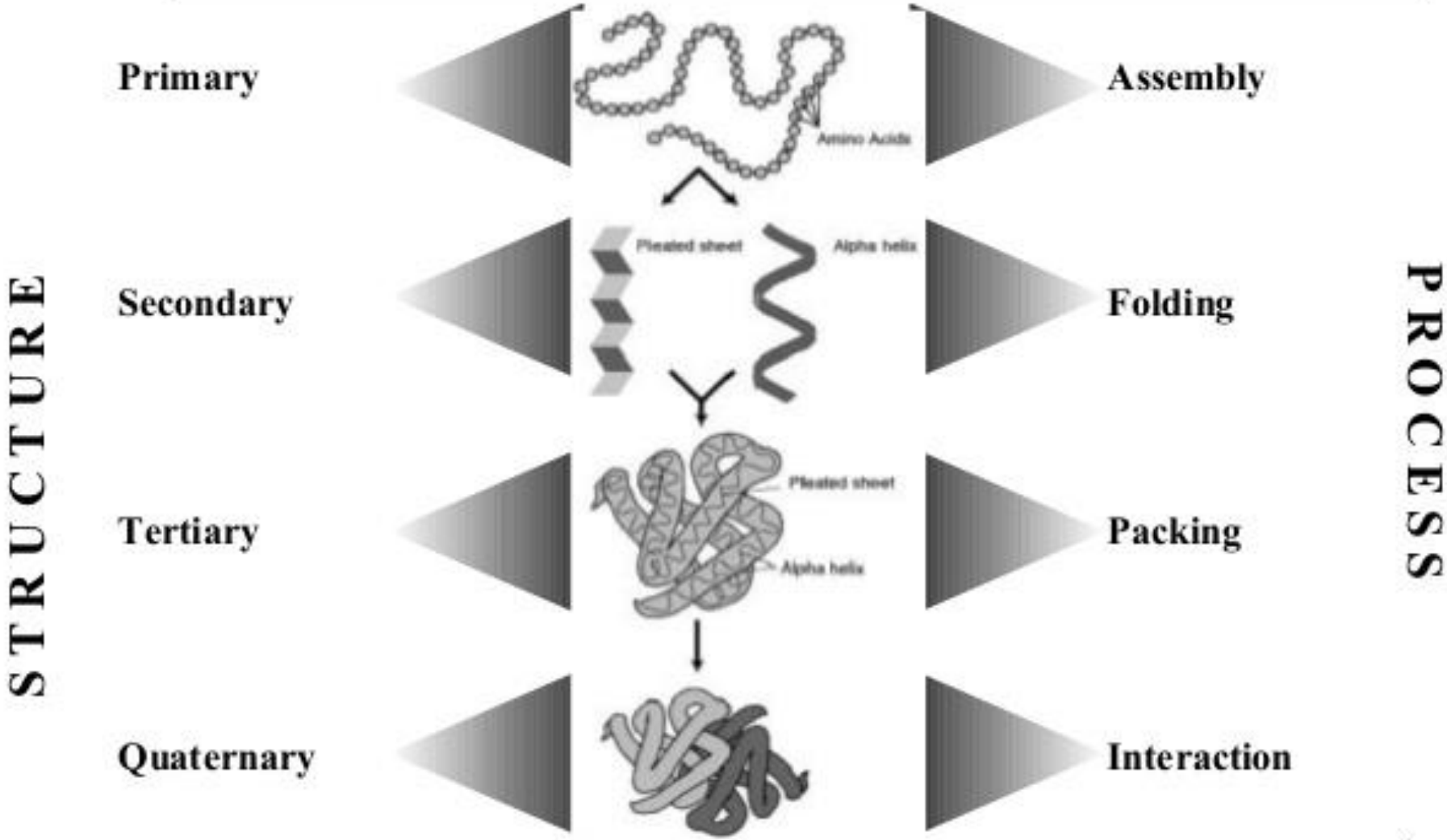


- **Diseases due to altered protein conformation:**
  - **Alzheimer's disease**
  - **Prion disease**

Levels of Protein Structure:



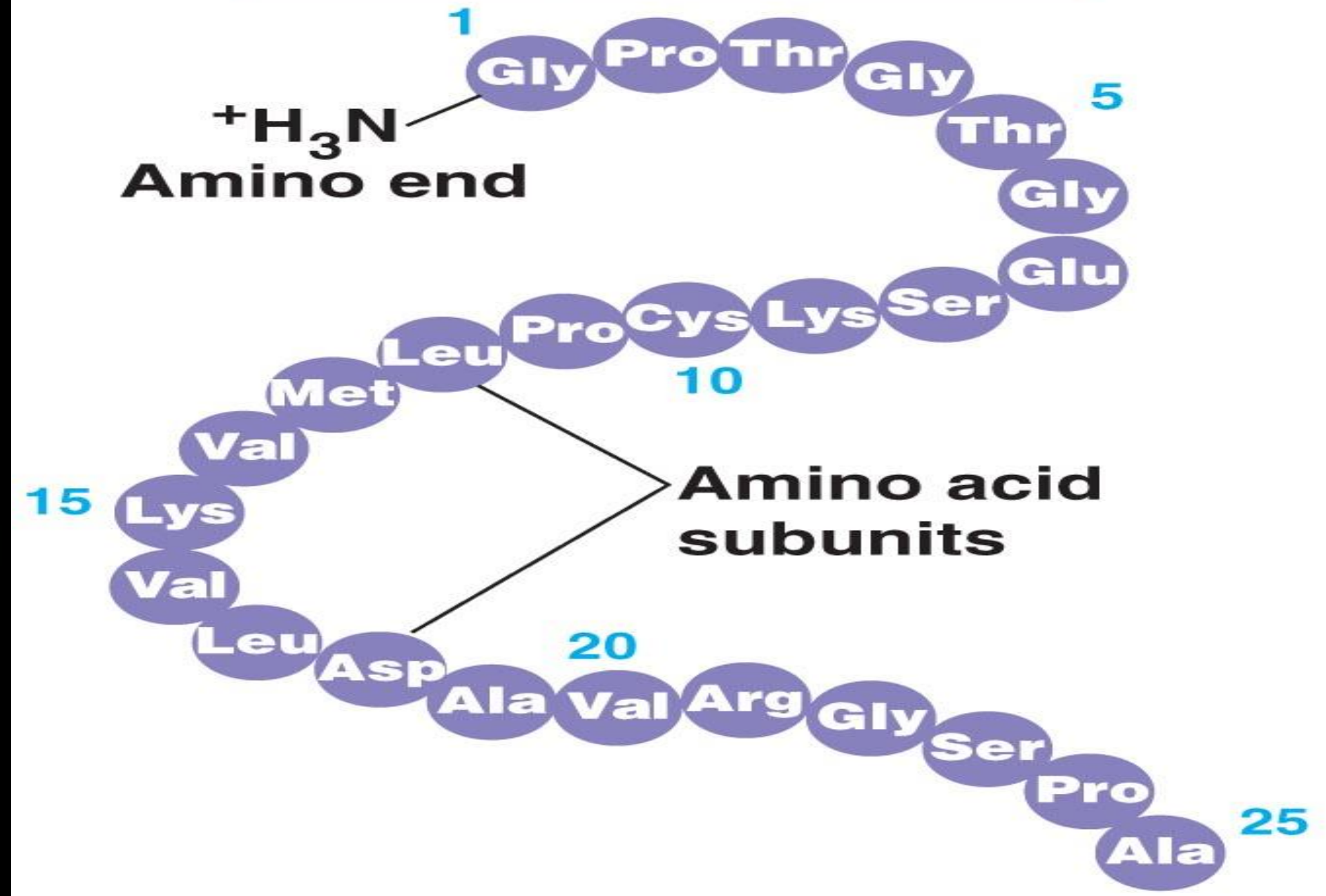
Chemistry of Protein Structure



1. PRIMARY STRUCTURE:

- linear sequence of a. acids, held together by *Peptide Bond.*
- The *Peptide Bonds* form the backbone & the side chains of a. acids residues project outside the peptide back bone

Primary Structure



PEPTIDE BOND

A **peptide bond** is a chemical **bond** formed between two molecules when the carboxyl group of one molecule reacts with the amino group of the other molecule, releasing a molecule of water (H_2O).

- Each component amino acid in polypeptide chain is called ***amino acid residue*** because it's the portion in amino acid left after loss of water molecule during formation of peptide bond

Significance of Primary structure:

- Any change in the sequence is abnormal & may affect the properties and functions of Proteins
- Free -NH_2 end ⟶ N-terminal
- Free –COOH end ⟶ C-terminal

- Small changes in sequence can lead to large change in properties & functions.
- For example:***Sickle Cell Anemia***
  - Valine instead of Glutamic acid at position No. 6 in β – chain of Hb

» Sickle Cell Disease:

Val – His – Thr – Leu – Pro – Glu – Glu – Lys – >>>>> α

Val – His – Leu – Thr – Pro – Val – Glu – Lys – >>>>β

In Deoxygenated state HbS forms long, rope like fibers

↓

Elongated Erythrocytes occlude Blood flow in the Capillaries

↓

Micro infarction produce tissue Anoxia resulting in Tissue damage & Pain

2. SECONDARY STRUCTURE:

- Folding of a Polypeptide chain into a specific coiled or pleated structures, held together by hydrogen bond
- This gives rise to steric relationship between two amino acids located closely in a polypeptide chain

Secondary structures often found in proteins are:

a: α – Helix

b: β – Pleated Sheet

c: β _ bends

d: Triple helix

a: α – Helix:

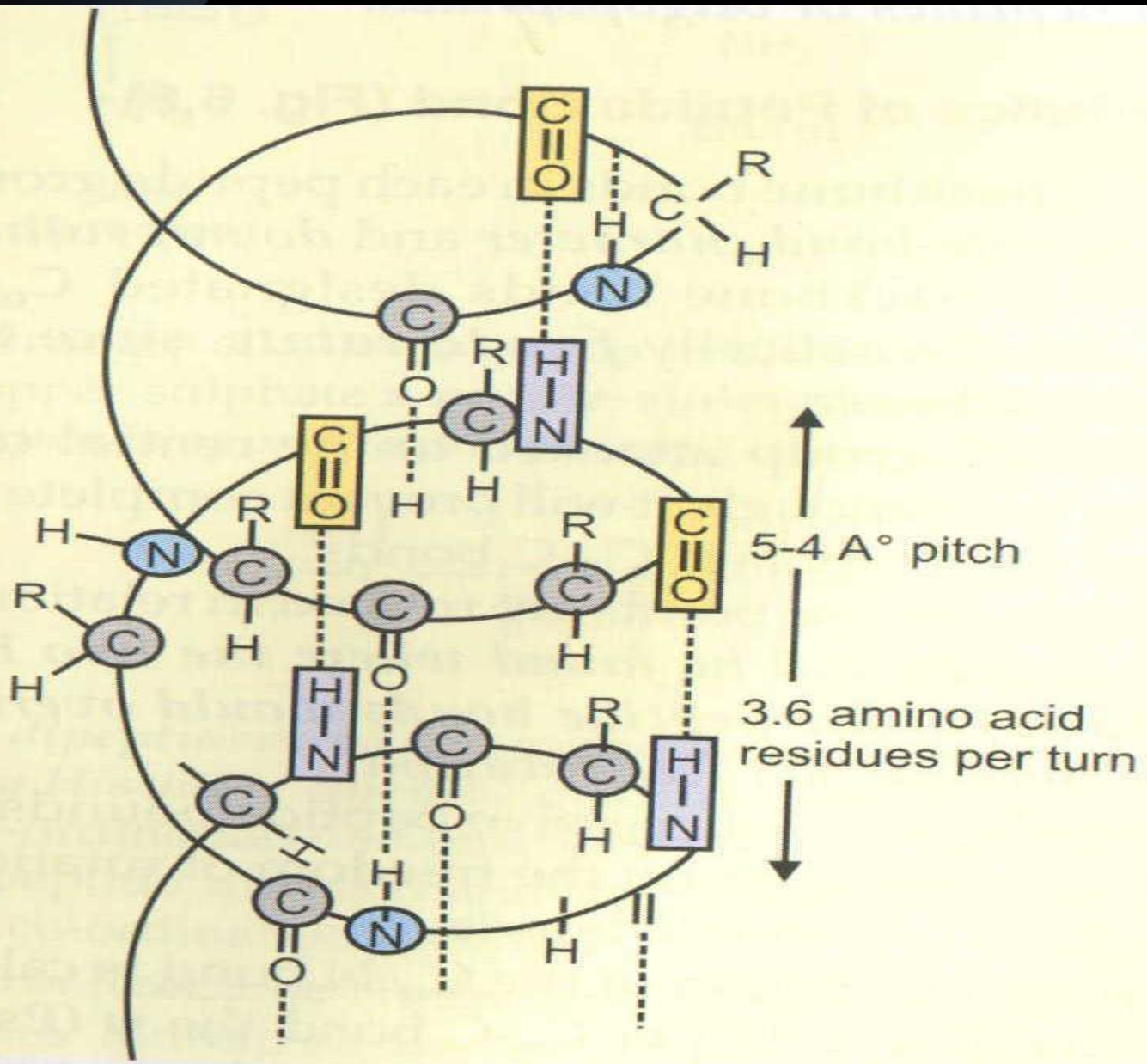
- A peptide chain forms regular helical coils called α – Helix
- Most common helical structure found in proteins e.g; keratin, myoglobin

» These coils are stabilized by Hydrogen bonds between *Carboxyl group* of 1st a. acid & *Amino group* of 4th a. acid in linear sequence

- Each turn of α – Helix contain 3.6 a. acids
- In α – Helix the H – bonding is *Intra chain*
- H-bonds lie parallel to the spiral
- Looks like a coiled "Telephone Cord

- *Can be right handed or left handed, right handed more stable and found in proteins*

a: α – Helix:



Properties of α – Helix:

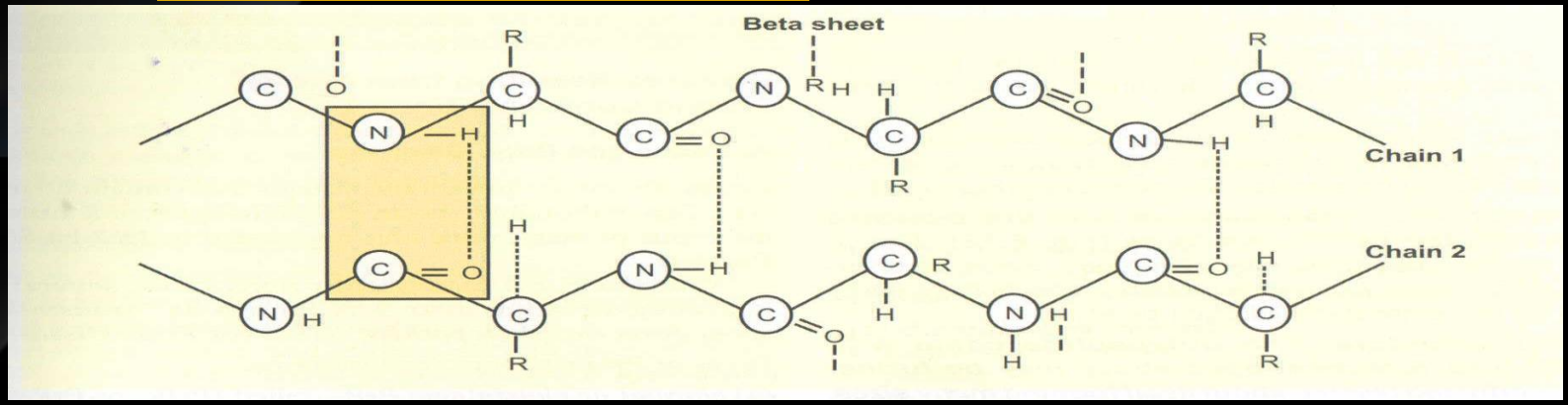
- It gives stability to peptide molecule because each peptide bond participates in H – Bonding.
- Proteins containing α–Helix shows great strength & elasticity and can be easily stretched because they are in the form of tight coil

- Following amino acids disrupt α – Helix structure;

1. Proline (secondary amino group)
2. Glycine
3. A. acids with charged R – Group (forms ionic bonds or repels each other)
4. A.acids with bulky R – Group (due to steric clashes)

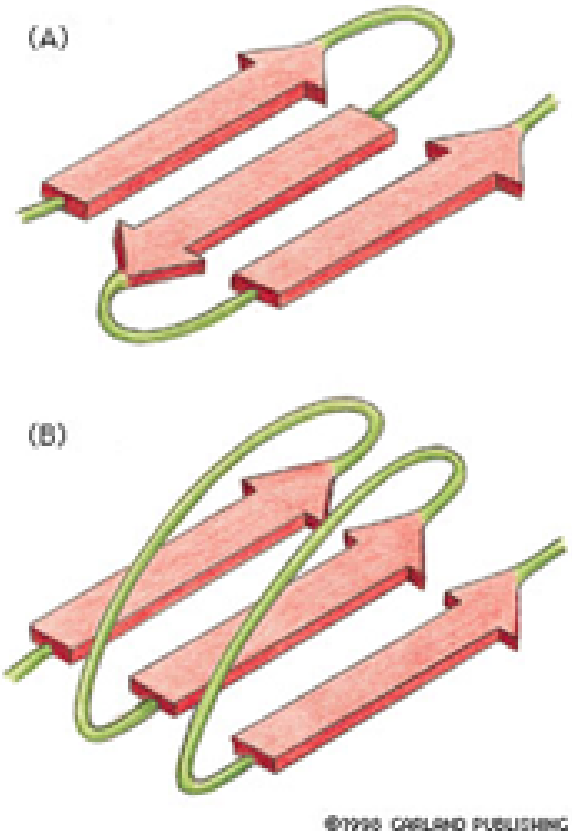
Small or uncharged amino acid residues are found in alpha helix e.g., Alanine, Leucine, Phenylalanine

b: β – Pleated Sheets:



- H – bonds exist between Peptide chains running parallel & closer to each other i.e., *Inter chain H – Bonds*
- Surfaces of β-sheets appear pleated
- β –sheet can be formed by single Polypeptide chain folding upon itself ,in this case H-bonds are intra chain

β Sheets



- Core of many proteins is the β sheet
- Form rigid structures with the inter chain H-bond
- Can be of 2 types
  - Anti-parallel – run in an opposite direction of its neighbor (A)
  - Parallel – run in the same direction with longer looping sections between them (B)

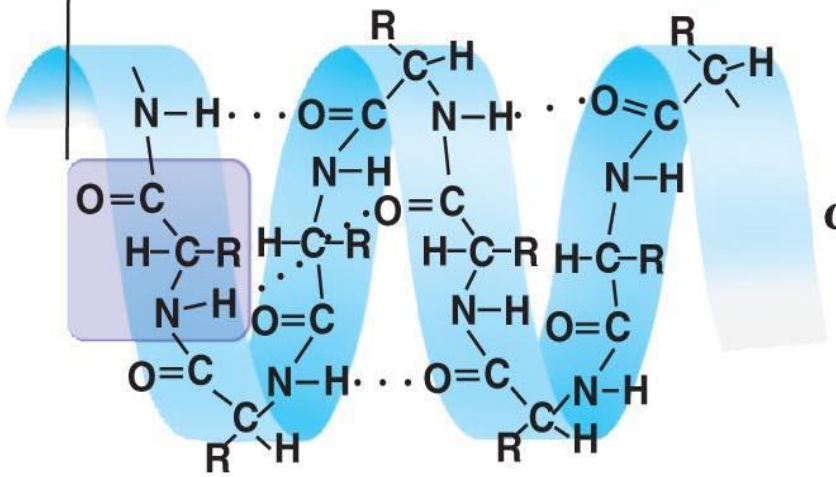
β -sheets VS α -helix

- β–sheets may be composed of two or more peptide chains(β –strands)
- H-bonds are perpendicular to polypeptide backbone
- The axial distance between a.a is 3.5A^{o}
- 3 to 10 a.a are present in the polypeptide chains of β–sheets .

Secondary Structure

β pleated sheet

Examples of amino acid subunits



α helix

Properties of β – Pleated Sheets:

- Inelastic, because H – Bonds are at right angle to the direction of stretching
- May be parallel or anti parallel
- Silk fiber, is rich in β – Pleated Sheets (a portion of Silk Worm)

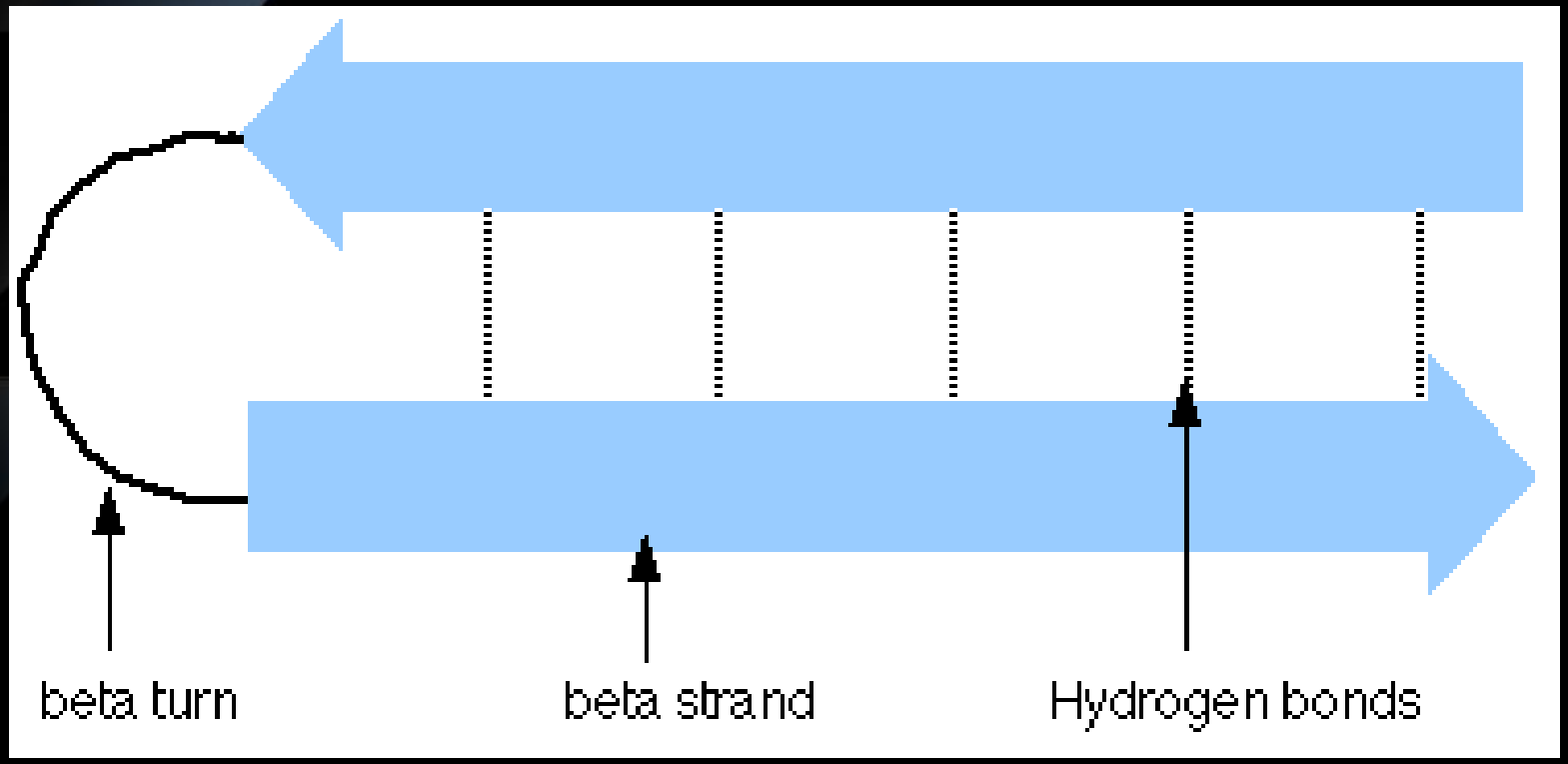
- Silk fiber is rich in β – Pleated Sheets. This makes the silk fiber mechanically strong, but resist to stretch. It breaks on application of force.

- Wool is flexible & extensible without breaking because of presence of α – Helical structure.

» Alpha helix and beta sheet account for 50% of protein structure

c: β – Bends (Reverse Turn or β- Turn):

- β – Bends reverse the direction of a polypeptide chain, helping it to form a compact, globular shape
- They connect successive strands of anti–parallel β – sheets.
- It has 4 amino acid residues(beta loop has more amino acids)
- Usually contain proline and glycine


beta turn
beta strand
Hydrogen bonds

d: Triple helix:

- In protein like collagen , which are rich in proline & hydroxy proline can not form α–helix & β–pleated structures so these form triple helix .It is stabilized by covalent & non covalent bonds in addition to hydrogen bonds between different peptide chains which are almost perpendicular to the long axis .In addition 2^0 amide bonds of peptide bonds are present.

e: Super Secondary Structure (Motif):

Motif means ‘structure’. Its a part of domain.

Motif is produced in globular proteins at sites where two β – Sheets are connected by α – Helix. This is called *β – α – β Super Sec. Motif*

- Several α–strands may connect several β–sheets

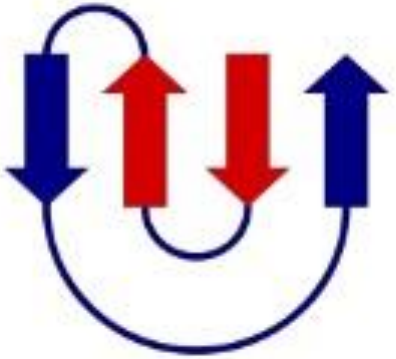
Domains:

- Functional & structural units of Polypeptide
- Polypeptide chains that are > than 200 a. acids in length generally consists of two or more domains
- Independent of other domains

SUPER SECONDARY STRUCTURES (MOTIFS)

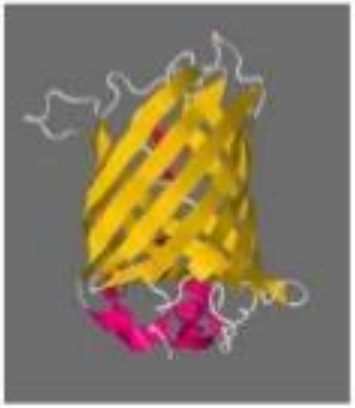
Certain groupings of secondary structural elements are called **motifs.**

beta-alpha-beta motif



Greek key motif

β-meander motif



Beta barrel

- In Greek Key; Several α – strands connect

Several β – sheets.

- β – α – β Structure; Two β – sheets are connected to each other by α – Helix
- β – Meander:5 β -pleated sheets connected by reverse turns

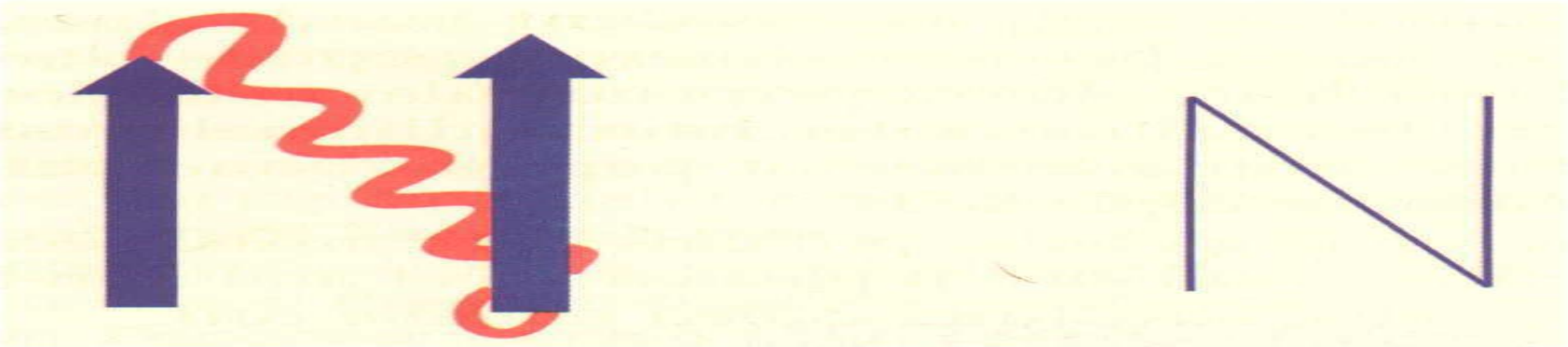


FIG. 6.11: β-α-β UNIT

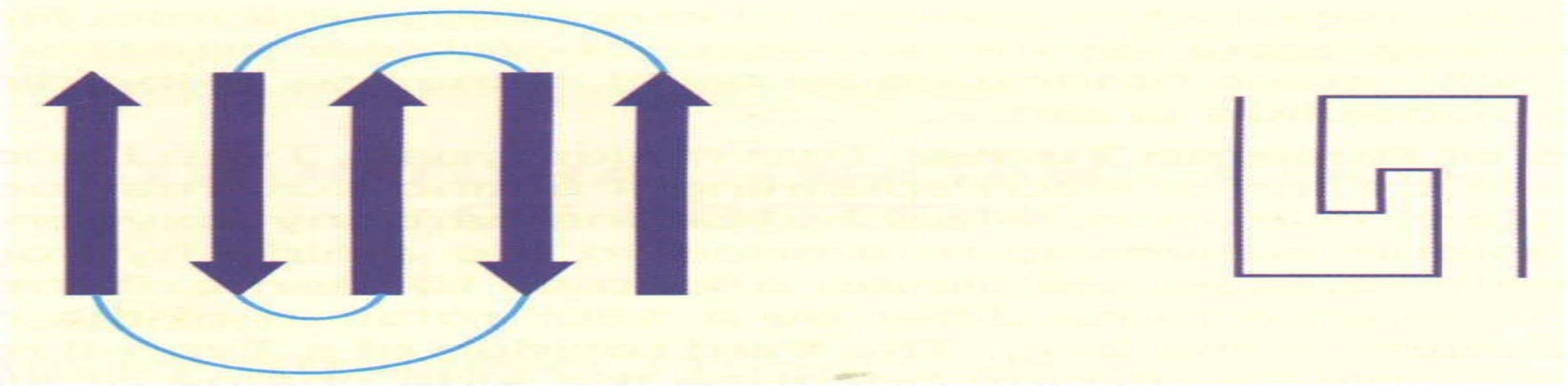


FIG. 6.12: GREEK KEY

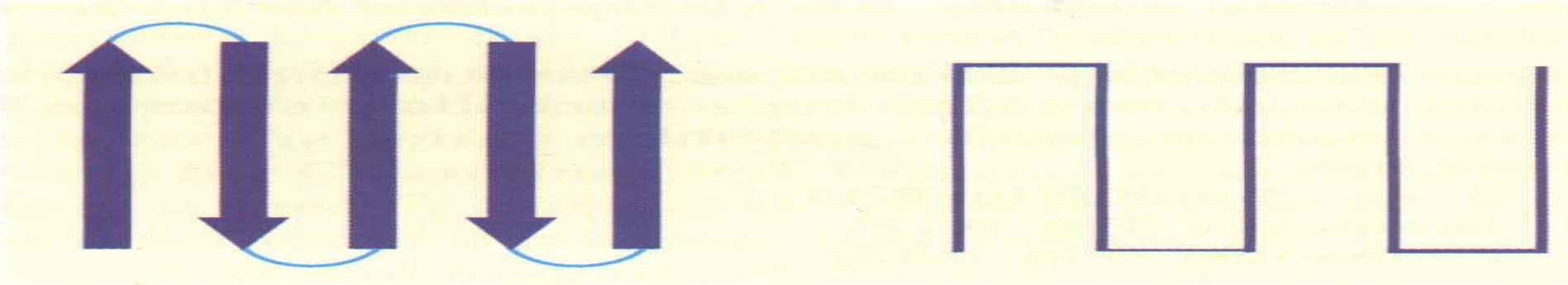
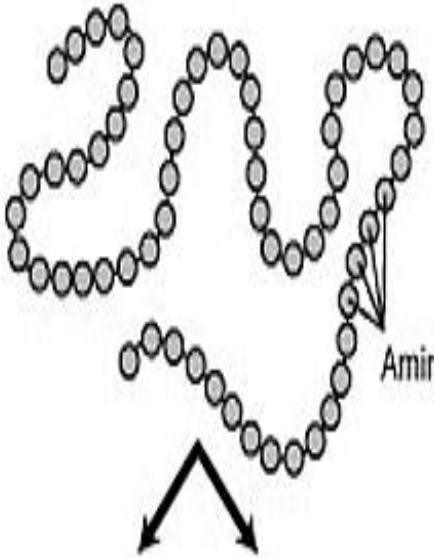


FIG. 6.13: β-MEANDER

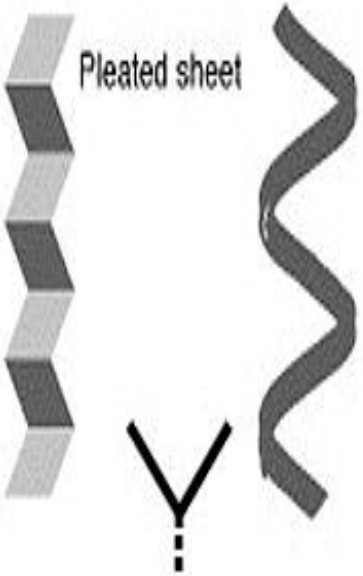
3. TERTIARY STRUCTURE:

- The polypeptide chain with secondary structure may be further folded, super folded, twisted about itself forming many sizes. Such a structural conformation is called tertiary structure.

- It is only such conformation which is biologically active and protein in this conformation is called **“Native Protein”**
- In Tertiary structure the Secondary structure of protein is packed, to reduce its size & make the molecule compact

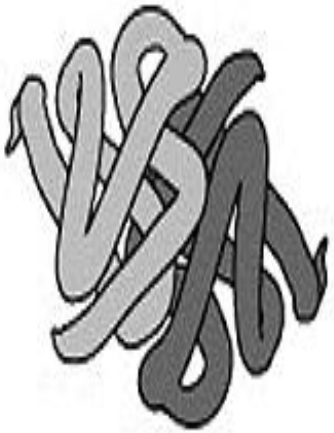


Primary protein structure
is sequence of a chain of amino acids



Secondary protein structure
occurs when the sequence of amino acids are linked by hydrogen bonds

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



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

» FORCES STABILIZING TERTIARY STRUCTURE:

- Hydrophobic interactions
- Hydrogen bonds
- Electrostatic interactions
- Van der Waal forces
- Disulphide bonds

- **Hydrophobic interactions**: Normally occu between nonpolar side chains of amino acids such as alanine, leucine, methionine, isoleucine and phenylalanine. They constitute the major stabilizing forces for tertiary structure forming a compact three-dimensional structure.
- **Hydrogen bonds**: Normally formed by the polar side chains of the amino acids.

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» • **Ionic or electrostatic interactions**: These are formed between oppositely charged polar side chains of amino acids, such as basic and acidic amino acids.

» • **Van der Waal Forces**: Occur between nonpolar side chains.

» • **Disulfide bonds**: These are the S–S bonds between-SH groups of distant cysteine residues

4. QUARTERNARY STRUCTURE:

- Not seen in all proteins
- Seen in those cases where protein molecules is made up of more than one Peptide chain subunit
- Each of which has its own Primary, Secondary & Tertiary Structure.

Hb has 4 Polypeptide Chains (Tetramer)

Two identical α & two identical β

These four subunits aggregate together to form

Quaternary structure of Hb

Pyruvate dehydrogenase has 3 subunits(Trimer)

CPK has 2 monomers(Dimer)

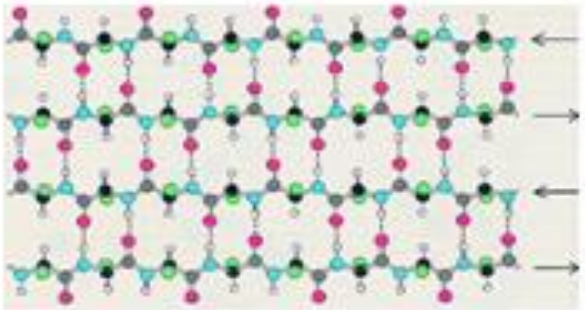
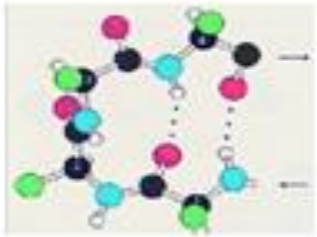
The subunits usually held together by non covalent bonds

- Hydrogen bonds
- Hydrophobic interactions
- Ionic bonds

The Hierarchical nature of protein architecture

- **Primary structure**
  - Proteins are first synthesized as linear sequences of amino acids

- **Secondary structure**
  - The linear sequence can undergo simple packing in regions of local regularity
    - *i.e.*, α-helices, β-strands, -sheets & -turns

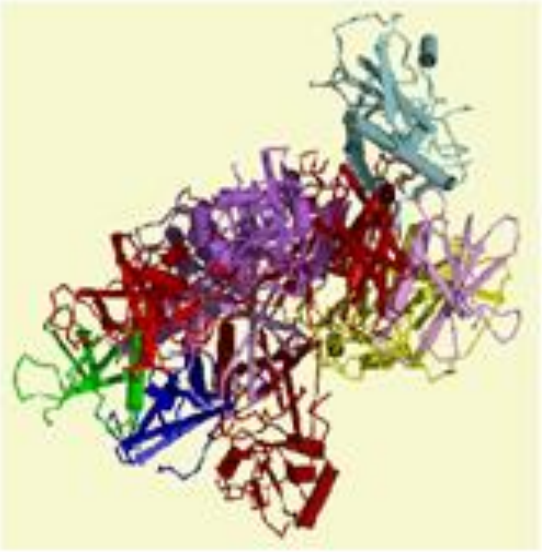




- Most of the secondary structured proteins are folded to protect hydrophobic regions (Tertiary structures)

- Tertiary structure
  - The complex folding of packed secondary structures give the tertiary structure of the protein

- Some proteins work as multi-complex machines and have to undergo a quaternary level of folding.

- Quaternary structure
  - the arrangement of separate chains within a protein that has more than one subunit
    - *e.g.*, haemoglobin



Alzheimer's Disease

- Chronic neurodegenerative disorder
- Due to elevated levels of β -amyloid(a polypeptide produced by cleavage of amyloid precursor protein; APP)
- APP is trans membrane protein critical for neuronal growth, survival and post injury repair

- APP is acted upon by enzymes producing β -amyloid
- β –amyloid undergoes conformational change from soluble α -helix to β -sheet that are prone to self aggregate
- Deposits outside neurons and forms neurofibrillary tangles or neuritic plaques

- Aggregated proteins induce apoptosis
- SIGNS AND SYMPTOMS

  usually manifests above age 65 yrs, dementia ,dis orientation, mood swings, problems with language, social withdrawal, aggression, exhaustion

Prion and prion disease

- Prion diseases are caused by conversion of normal prion protein(PrPc,α-helical) present in neurons to β-pleated form(PrPsc)
- TRANSMISSION:
  - acquired(inoculation eg corneal graft, neuronal surgery)
  - familial/sporadic/genetic

- PrPsc is resistant to degradation and facilitates conversion of more PrPc to PrP sc
- Accumulation results in spongiform encephalopathy, dementia and death
- Other features include visual disturbances, ataxia.

Two types

1 :Normal or physiological PrPc/PrP-sen.:

- Consist of 253a.a found in leucocytes and nerve cells.
- Gene of this PrPc is located in short arm of chromosome 20 .
- This protein is heat sensitive and protease sensitive.

2 :Abnormal or pathologic PrPsc/PrP-res.:

- This form is associated with transmissible spongiform encephalopathies.
- This form is heat resistant and protease resistant.

Prion disease:

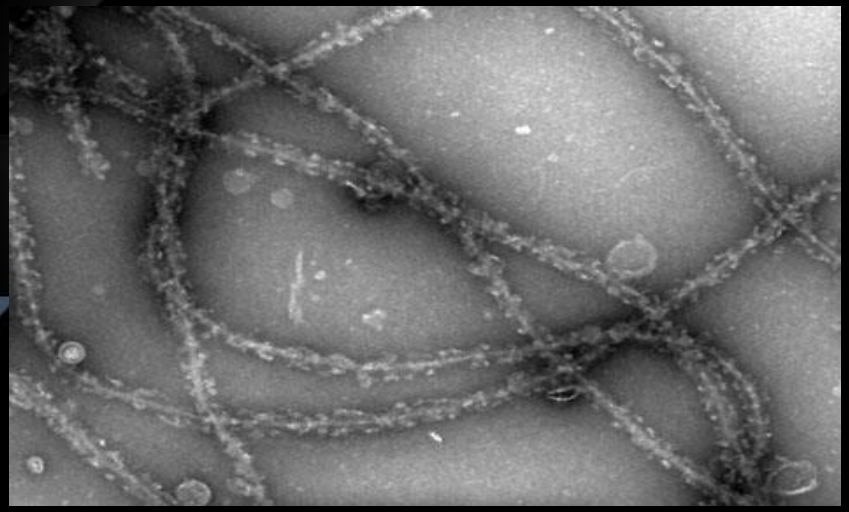
- Characterized by ataxia, dementia and paralysis and is almost fatal(4 to 6 months in creutz feldt-jakob disease)
- Pathological examination shows amyloid plaques and spongiform(vacuolar) degeneration.

Prion disease:

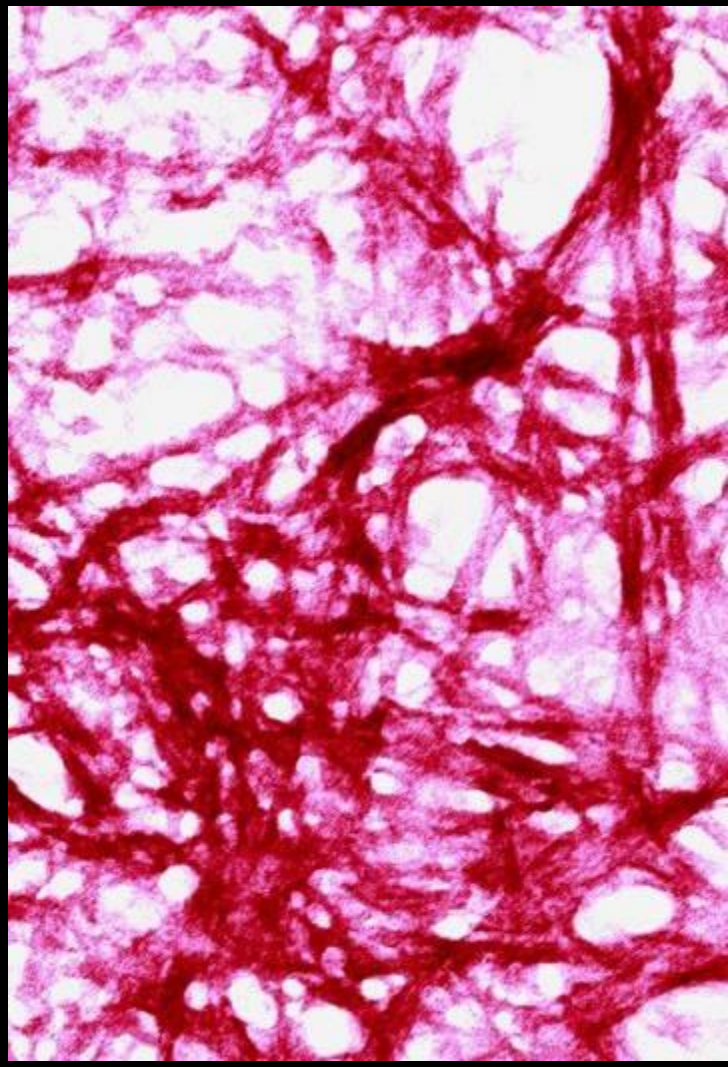
- In humans :creutzfeldt-Jakob disease(CJD),fatal familial insomnia, kuru
- In animals scrapie in sheep,bovine spongiform encephalopathy also called mad cow disease

Structural studies

- PrPc is soluble
- PrPsc forms insoluble filaments



45,000X magnification electron micrograph of yeast prion protein fibers formed in the test tube. The rigid fibers are similar to those observed in amyloid diseases of mammals.



Applying Your Knowledge

1. Primary
2. Secondary
3. Tertiary
4. Quaternary

A. Which structure results exclusively from hydrogen bonding?
B. Which structure involves an association of two or more protein chains?
C. Which structure describes the linear sequence of amino acids?
D. Which structure depends upon interactions between the R groups of the amino acids?

TAKE HOME MESSAGE

- Four levels of protein structural organization
- Primary protein represents sequence of amino acids in linear structure
- Force stabilizing secondary structure is mainly H-bonding
- H-bonds lie parallel to spiral in α -helix while perpendicular to polypeptide backbine in β-pleated sheet

- Forces stabilizing tertiary structure:H-bonds, electrostatic interactions, hydrophobic interactions,Van der waals forces, disulphide bonds
- Quarternary structure consist of two or more polypeptide subunits held together by non covalent forces

THANK YOU