Virtual University of Pakistan

BIO-202

BioChemistry - I
| Handouts |

Designed & Composed by:

(عمر غفور وٹو)

0335-4232497

Biochemistry

Carbohydrates

- Carbohydrates are polyhydroxy aldehydes or ketones, or substances that yield such compounds on hydrolysis

- Many, but not all, carbohydrates have the empirical formula *(CH2O)n*; some also contain nitrogen, phosphorus or sulfur

Classification

- Carbohydrates are classified into **four** major groups:

–Monosaccharides

–Oligosaccharides

- Disaccharides

–Polysaccharides

- **Monosaccharides** (simple sugars) are those which cannot be hydrolyzed further into simpler forms
- The backbones of common monosaccharides are *unbranched* carbon chains in which all the carbon atoms are linked by single bonds
- In **the open-chain form,** one of the carbon atoms is double-bonded to an oxygen atom to form a *carbonyl group*

- Each of the other carbon atoms has a hydroxyl group
- If the carbonyl group is at an end of the carbon chain (that is, in an aldehyde group) the monosaccharide is an *aldose*

- If the carbonyl group is at any other position (in a ketone group) the monosaccharide is a *ketose*
- **The simplest** monosaccharides are the two three-carbon trioses:
    - Glyceraldehyde,an aldotriose

    - Dihydroxyacetone,a ketotriose
- The carbons of a sugar are numbered beginning at the end of the chain nearest the carbonyl group

- All common monosaccharides and disaccharides have names ending with the suffix —-ose.‖

- Ketoses are designated by inserting "ul" into the name of a corresponding aldose
- For example, ribulose is the ketopentose corresponding to the aldopentose ribose
- There are a few exceptions however, for example, fructose and dihydroxyacetone
- Monosaccharides can be subdivided further depending upon:

- Number of carbon atoms
- Whether aldehyde or ketone groups are present as *aldoses* or *ketoses*

- General formula   Aldosugars   Ketosugars
  Trioses $C_3H_6O_3$ Glyceraldehyde Dihydroxyacetone
  Tetroses $C_4H_8O_4$ Erythrose   Erythrulose
  Pentoses $C_5H_{10}O_5$ Ribose   Ribulose
  Hexoses $C_6H_{12}O_6$ Glucose   Fructose
  - The **hexoses** which include the aldohexose D-glucose and the ketohexose D-fructose, are the most common monosaccharides in nature
  - The **aldopentoses** D-ribose and 2-deoxy-D-ribose are components of nucleotides and nucleic acids

Lesson 2

- **Disaccharides** are those sugars which yield two molecules of the same or different monosaccharides on hydrolysis

  – Maltose - 2 molecules of glucose on hydrolysis
  - Lactose – 1 glucose & 1 galactose on hydrolysis

  - Sucrose – 1 glucose & 1 fructose on hydrolysis
- **Oligosaccharides** are short chains of monosaccharide units or residues (3-10) joined by characteristic linkages called glycosidic linkage

Glycosidic bond

of maltose is formed between the OH of carbon 1 and carbon 4 of 2nd glucose monomers. Thereforer, it forms an alpha (1– 4) glycosidic bond.

Lesson 3

- **Polysaccharides** (Glycans) are those which yield more than 10 molecules of monosaccharides on hydrolysis
- Some have hundreds or thousands of units
- Some polysaccharides, such as *cellulose*, are linear chains; others, such as *glycogen*, are branched
- Both glycogen and cellulose consist of recurring units of D-glucose, but they differ in the type of glycosidic linkage and consequently have strikingly different properties and biological roles
- Polysaccharides are further divided into two groups:

1. Homopolysaccharides (homoglycans): Polymers of same monosaccharide units e.g. starch, glycogen, inulin, cellulose, dextrins, dextrans

2. Heteropolysaccharides (heteroglycans): Polymer of different monosaccharide units or their derivatives e.g. Mucopolysaccharides (glycosaminoglycans)

Biomedical Importance

- Chief source of energy

- Constituents of compound lipids and conjugated proteins

- Lactose , the principal sugar of milk

- Degradation products utilized for synthesis of other substances such as fatty acids, amino acids, cholesterol, etc
- Constituents of mucopolysaccharides which form the ground substance of mesenchymal tissues

- Certain carbohydrate derivatives are used as drugs like **cardiac glycosides.**
- Inherited deficiency of certain enzymes in metabolic pathways of different carbohydrates can cause diseases e.g. **galactosemia, glycogen storage diseases, lactose intolerance,** etc

- Derangement of glucose metabolism is seen in **Diabetes mellitus**

Lesson 4

Isomerism

- The existence of two or more compounds having the same molecular formula but a different arrangement of atoms within the molecule

Enantiomers (mirror images)   **Enantiomers (mirror images)**


Diastereomers (non–mirror images)
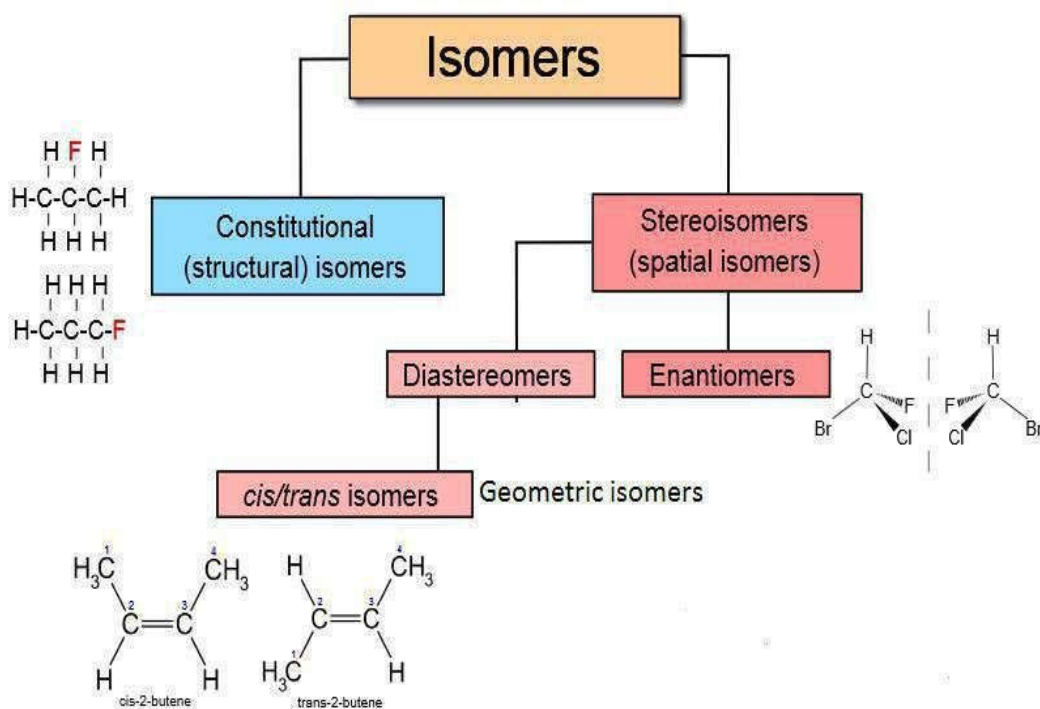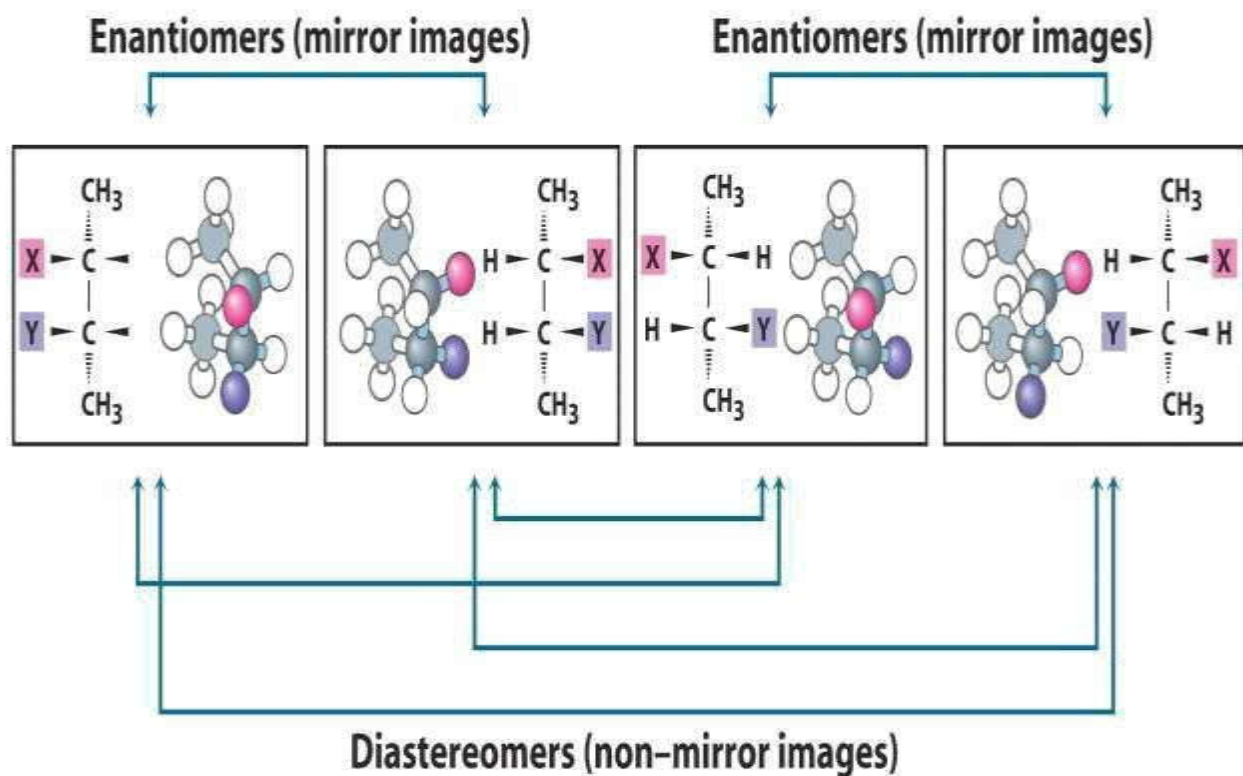
Isomerism

• Compounds which are identical in composition and differ only in configuration (the fixed spatial arrangement of atoms) are called *stereoisomers*

• Stereoisomers that are mirror images of each other are called *enantiomers*

• Pairs of stereoisomers that are not mirror images of each other are called *diastereomers*

• The identifying characteristic of stereoisomers is that they cannot be interconverted without temporarily breaking one or more covalent bonds

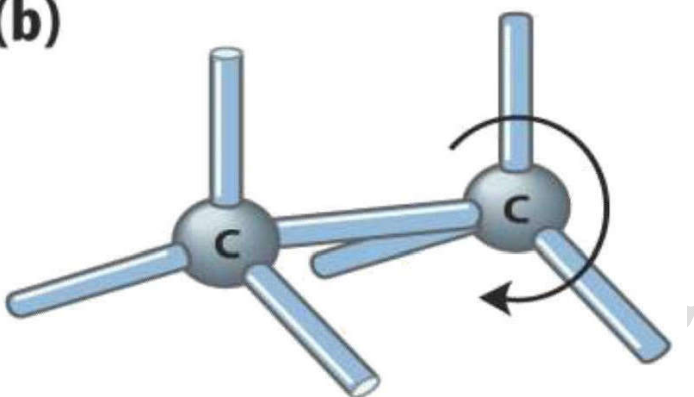• A carbon atom to which four different atoms or groups of atoms are attached is said to be **asymmetric** or *chiral*

Lesson 5
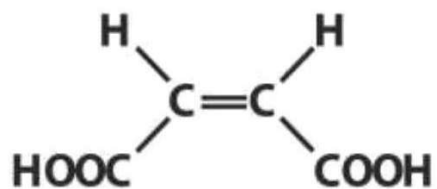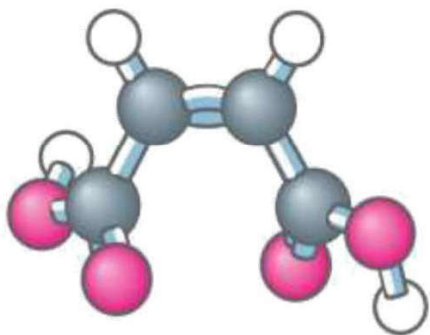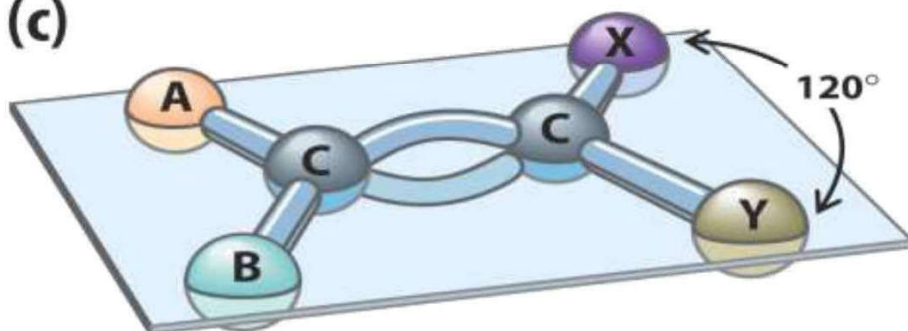
• Configuration is conferred by the presence of either

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(a)

109.5°
C
109.5°

(b)

C C

(c)

A
C
B
X
C
Y
120°

H   H
C=C
HOOC   COOH
Maleic acid (cis)
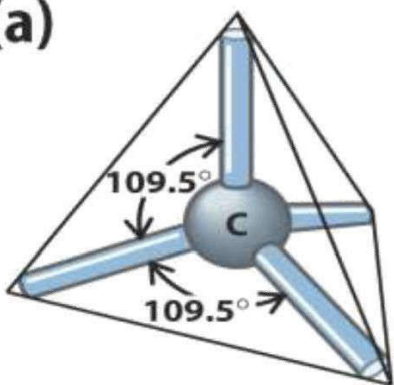
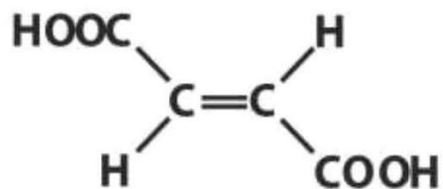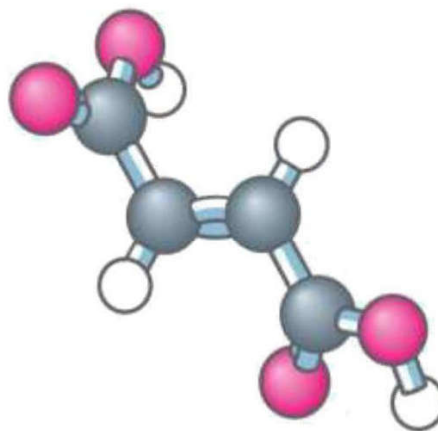HOOC   H
C=C
H   COOH
Fumaric acid (trans)

–(a) **chiral centers,** around which substituent groups are arranged in a specific

orientation –(b) **double bonds,** around which there is no freedom of rotation

• **Geometric isomers;** differ in the arrangement of their substituent groups with respect to the nonrotating double bond (each is a well-defined compound that can be separated from the other, and each has *its own unique chemical properties*)
• The identifying characteristic of configurational isomers is that they cannot be interconverted without temporarily breaking one or more covalent bonds.

The configurations of maleic acid and its isomer, fumaric acid.

These compounds are **geometric,** or **cis-trans, isomers;**

They differ in the arrangement of their substituent groups with respect to the nonrotating double bond

Lesson 6
D and L isomerism:
• The designation of a sugar isomer as the D form or as the L form is determined by its spatial relationship to the parent compound of the carbohydrates, the glyceraldehyde
• The orientation of the —H and —OH groups around the *carbon atom adjacent to the terminal primary alcohol or carbon most distant from the carbonyl carbon – the penultimate carbon*
• *(carbon 5 in glucose)* determines whether the sugar belongs to the D or L series.
• When the —OH group on this carbon is on the right the sugar is the D isomer;
• when it is on the left, it is the L isomer
• Of the 16 possible aldohexoses eight are D forms and eight are L
• Most of the hexoses of living organisms are D isomers and the enzymes responsible for their metabolism are specific for this configuration
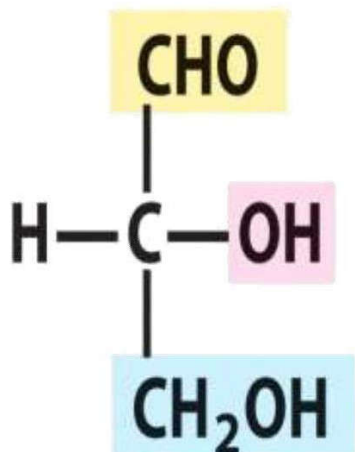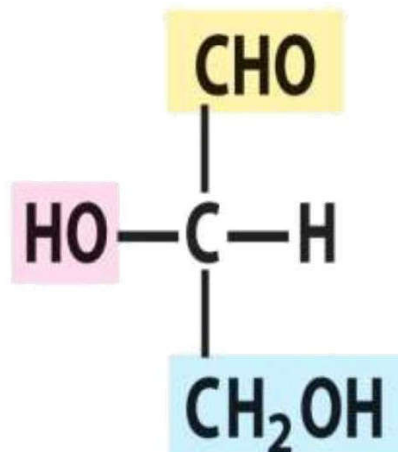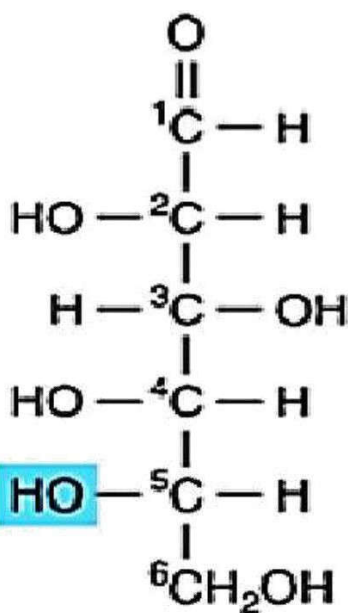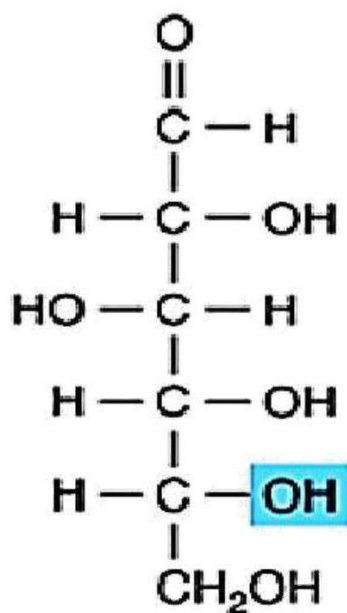
D-Glyceraldehyde   L-Glyceraldehyde

Fischer projection formulas

L-Glucose   D-Glucose

Lesson 7

Four different substituents bonded to a chiral carbon atom may be arranged in two different ways in space, that is, have two stereoisomers (with similar or identical chemical properties *but differing in certain physical and biological properties*)

•   A molecule with only one chiral carbon can have two stereoisomers; when two or more (n) chiral carbons are present, there can be *2^n* stereoisomers

•   **Enantiomers** have nearly identical chemical properties but differ in a characteristic physical property:

-    their interaction with plane-polarized light

•   Thus the presence of asymmetric carbon atoms also confers **optical activity** on the compound

•   When a beam of plane-polarized light is passed through a solution of an **optical isomer,** it rotates either to the right, dextrorotatory (+), or to the left, levorotatory (–)

•   The direction of rotation of plane polarized light is independent of the stereochemistry of the sugar, so it may be designated D(–), D(+), L(–), or L(+)

•   For example, the naturally occurring form of fructose is the D(–) isomer

•   In solution, glucose is dextrorotatory, and glucose solutions are sometimes known as **dextrose**
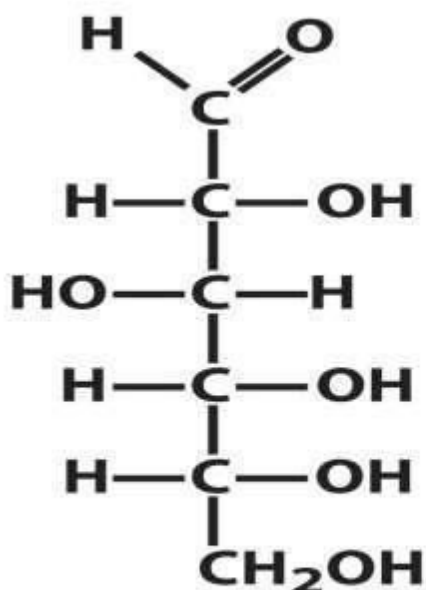
D-Glucose, an aldohexose
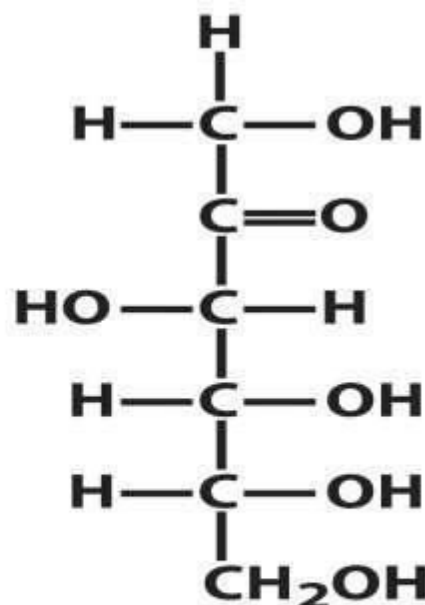
D-Fructose, a ketohexose

Lesson 8

•   When equal amounts of dextrorotatory and levorotatory isomers are present, the resulting mixture has no optical activity

•   Such a mixture is said to be *racemic* and separation of optically active isomers from a racemic mixture is called *resolution*
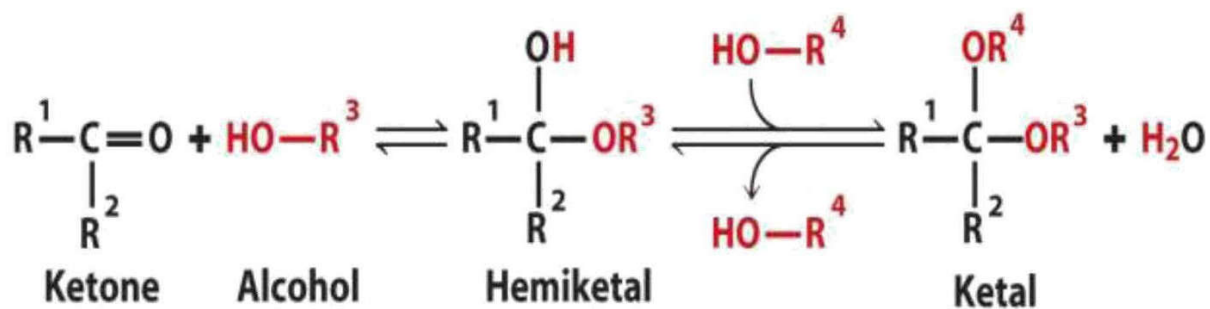
• All the monosaccharides except dihydroxyacetoe contain one or more asymmetric (chiral) carbon atoms and thus occur in optically active isomeric forms

• The simplest aldose, glyceraldehyde contains one chiral center (the middle carbon atom) and therefore has two different optical isomers
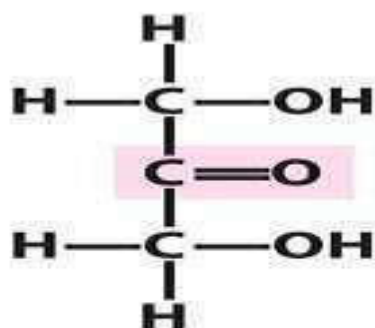
Dihydroxyacetone, a ketotriose

Lesson 9

• In aqueous solution, aldotetroses and all monosaccharides with five or more carbon atoms in the backbone occur predominantly as *cyclic (ring) structures*.

• The formation of these ring structures is the result of a general reaction between alcohols and aldehydes or ketones to form derivatives called *hemiacetals or hemiketals.*

• Which contain an additional *asymmetric carbon atom* and thus can exist in two stereoisomeric forms

• For example,D-glucose exists in solution as an **intramolecular hemiacetal** in which the free hydroxyl group at C-5 has reacted with the aldehydic C-l,

• Therefore rendering the latter carbon (aldehydic C-l) asymmetric

• And producing two stereoisomers, designated *α and β*

• Carbon 1, after cyclization has four different groups attached to it and thus it also becomes _asymmetric'

• *Is*omeric forms of monosaccharides that differ only in their configuration about the hemiacetal or hemiketal carbon atom are called **anomers**

• The carbonyl carbon atom is called the *anomeric carbon*

D-Glucose

Aldehyde   Alcohol   Hemiacetal   Acetal

Ketone   Alcohol   Hemiketal   Ketal

α-D-Glucopyranose   β-D-Glucopyranose
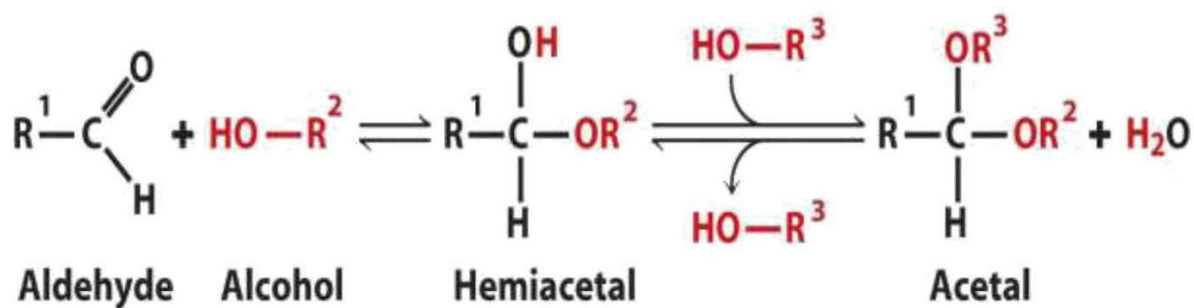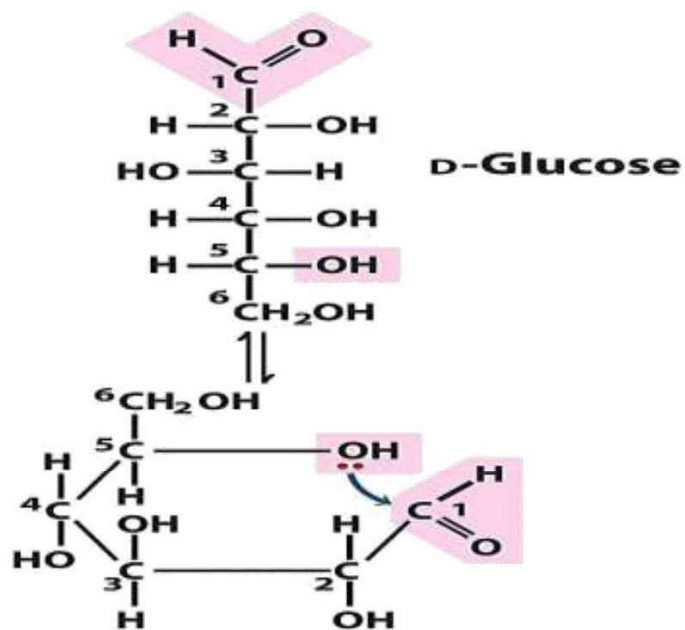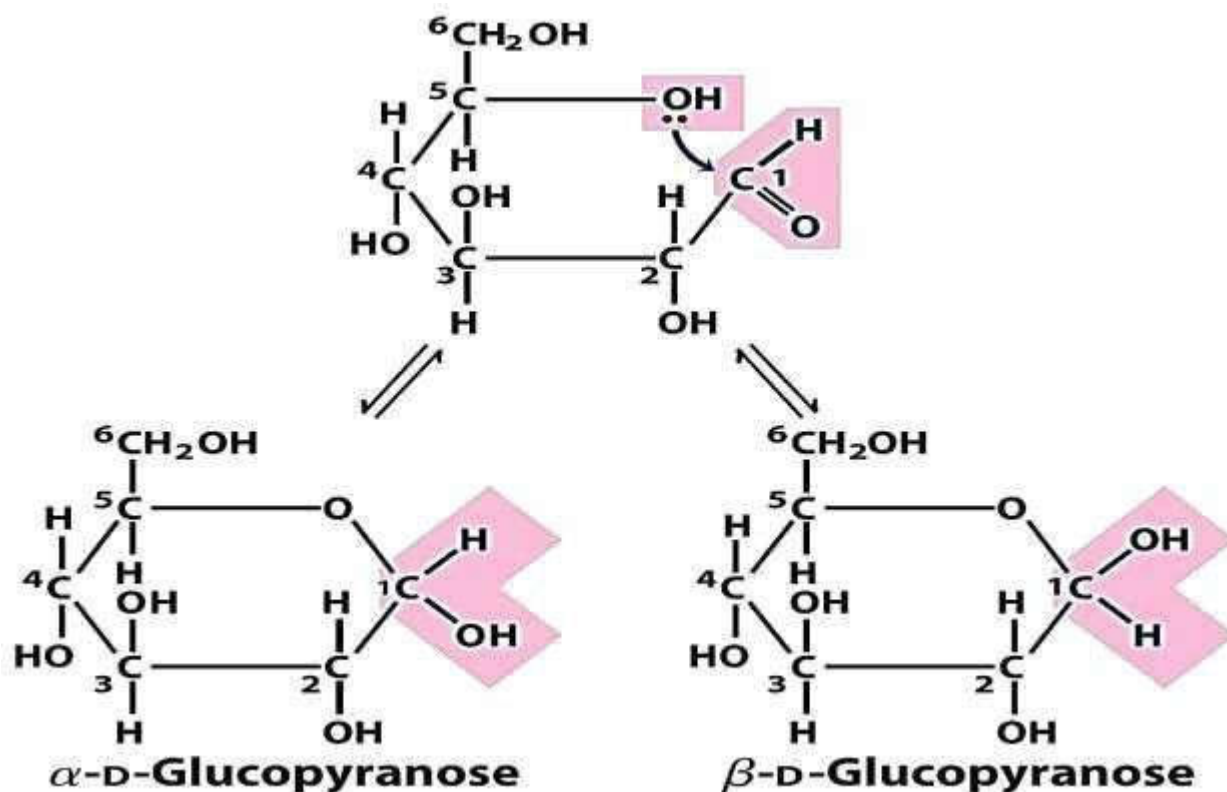
Lesson 10

Ring Structure of Carbohydrates

• For example,D-glucose exists in solution as an **intramolecular hemiacetal** in which the free hydroxyl group at C-5 has reacted with the aldehydic C-l,

• Therefore rendering the latter carbon (aldehydic C-l) asymmetric

• And producing two stereoisomers, designated *α and β*

• Carbon 1, after cyclization has four different groups attached to it and thus it also becomes _asymmetric'

• Isomeric forms of monosaccharides that differ only in their configuration about the hemiacetal or hemiketal carbon atom are called **anomers**

$^6CH_2OH$

^5C

H

^4C
H
OH

HO

^3C

H

OH (highlighted)

H

C^1

O

H

^2C

OH

$^6CH_2OH$

^5C

H

^4C
H
OH

HO

^3C

H

H

^1C
OH
OH

^2C

OH

α-D-Glucopyranose

$^6CH_2OH$

^5C

H

^4C
H
OH

HO

^3C

H

OH

^1C
H

^2C

OH

β-D-Glucopyranose
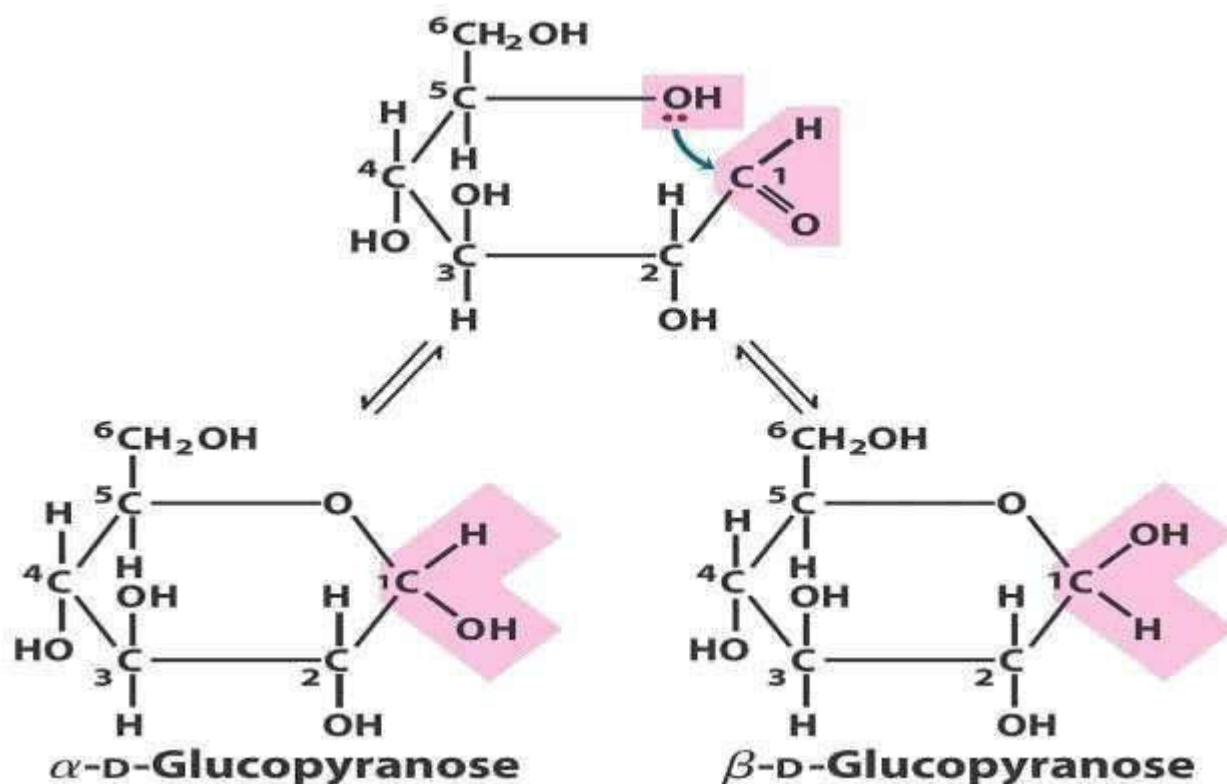
Lesson 11

• The ring structures of monosaccharides are similar to the ring structures of either pyran (six-membered ring) and are called *pyranoses* or furan (a five-membered ring), which are known as *furanoses*

• The six-membered aldopyranose ring is much more stable than the aldofuranose ring

• Therefore predominates in aldohexose and aldopentose solutions

• Similarly Crystalline glucose is **α -D -glucopyranose**

• The α and β anomers of D-glucose interconvert in aqueous solution by a process called **mutarotation.**

• Thus, a solution of α-D-glucose and a solution of β-D-glucose eventually form identical equilibrium mixtures having identical optical properties.

• This mixture consists of about;

• one-third α-D-glucose,

• two-thirds β-D-glucose,

and very small amounts of the linear and five-membered ring (glucofuranose) forms.

• α and β forms are NOT mirror images and are referred to as *diastereomers*

• Enzymes are able to distinguish between these two structures and use one or the other preferentially

• For example, glycogen is synthesized from α-D-glucopyranose, whereas cellulose is synthesized from β-D-glucopyranose

- Ketohexoses also occur in α and β anomeric forms
- In these compounds the hydroxyl group at C-5 (or C-6) reacts with the keto group at C-2, forming a furanose (or pyranose) ring containing a hemiketal linkage
- D-Fructose readily forms the furanose ring ; the more common anomer of this sugar in combined forms or in derivatives is *β*-D-fructofuranose

Pyran

Furan

α-D-Glucopyranose

β-D-Glucopyranose

Pyran
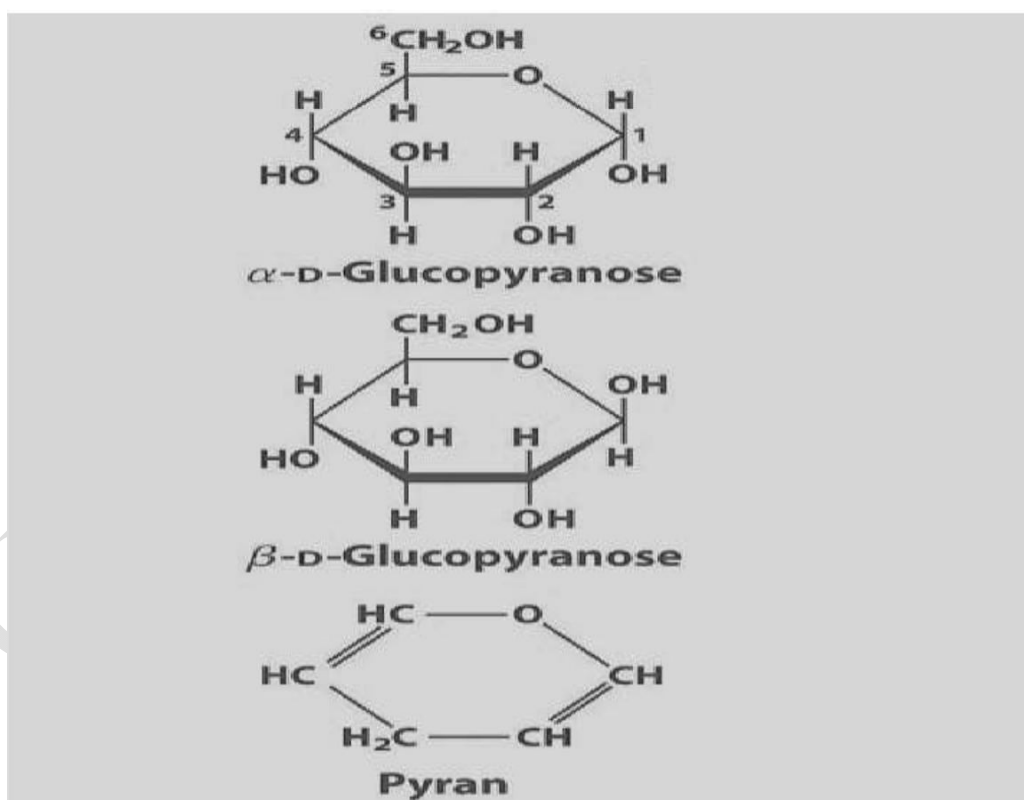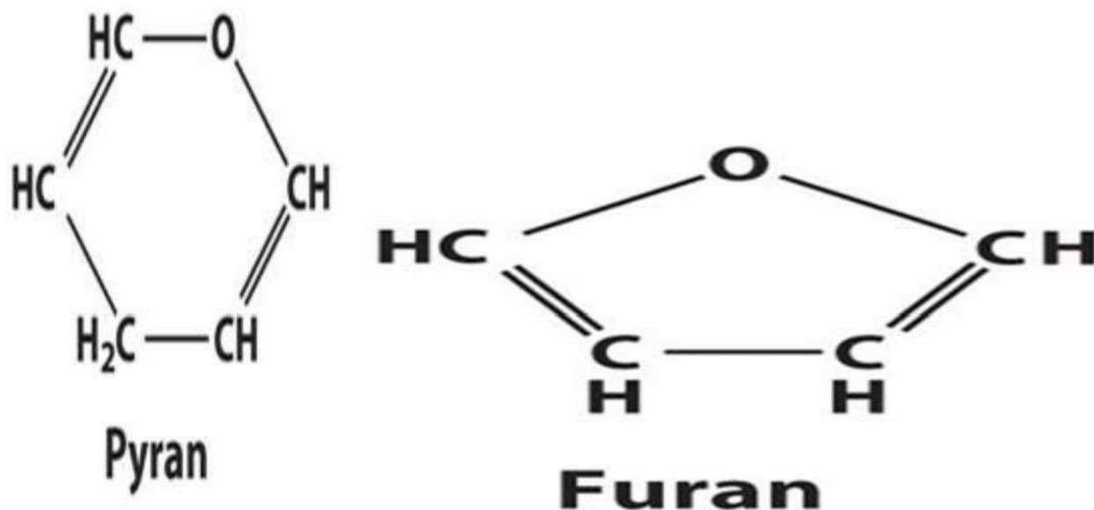
Lesson 23

- **Lactose,** the disaccharide of milk consists of galactose joined to glucose by þ(1→4) glycosidic linkage
- It is dextrorotatory

- As one of the aldehyde group is free, it has reducing properties and exhibits mutarotation

- In lactating mammary gland, the lactose is synthesized from glucose by the duct epithelium
- Many organisms that are found in milk, e.g., *E.Coli* convert lactose of milk to lactic acid (by *β* **galactosidase**) thus causing souring of milk

- **Lactase**, the specific enzyme which hydrolyses lactose is present in the intestinal brush border
- **Lactose intolerance** refers to a condition of pain, nausea, and flatulence after the ingestion of foods containing lactose, most notably dairy products
- Although it is often caused by
  - low levels of lactase
  - it also can because by intestinal injury

- In a **lactase deficient** person, lactose accumulates in the lumen of the small intestine after ingestion of milk
- The large osmotic effect of the unabsorbed lactose leads to an influx of fluid into the small intestine
- Hence, the clinical symptoms of **lactose intolerance** are:
  - abdominal distention,
  - nausea,
  - cramping,
  - pain
  - a watery diarrhea

Lactose (β form)
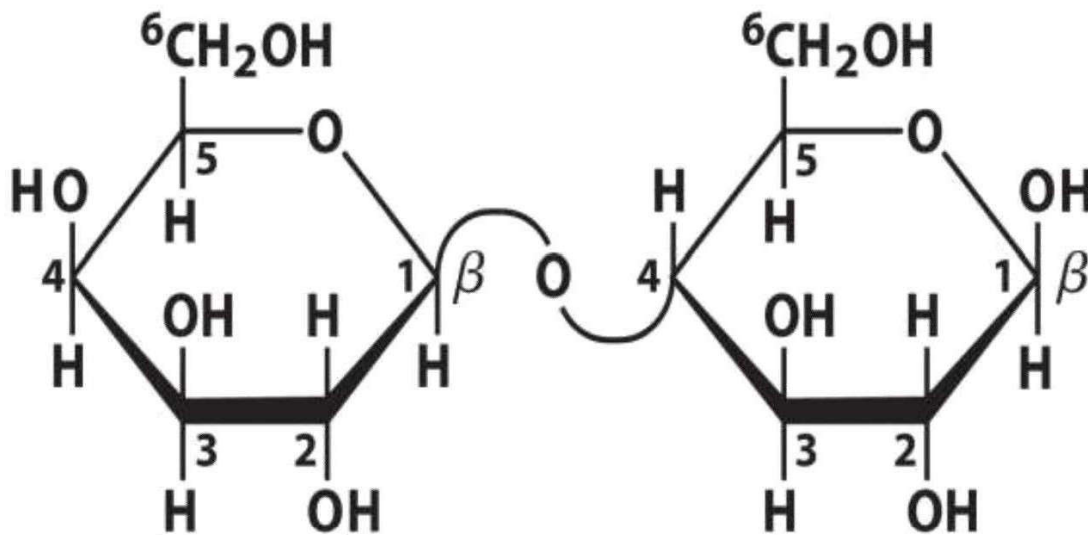
β-D-galactopyranosyl-(1→4)-β-D-glucopyranose

Gal(β1→4)Glc

Lactose Intolerance

- Lactose transits through the small intestine undigested due to insufficient lactase activity on the intestinal surface

- Undigested lactose transits to the large intestine where unadapted colonic bacteria attempts to ferment (metabolize) the lactose

- Lactose fermentation results in large quantities of gas, causing flatulence, distention and acute diarrhea

Lactose Glucose ★ Bacteria in colon Methane Galactose Hydrogen

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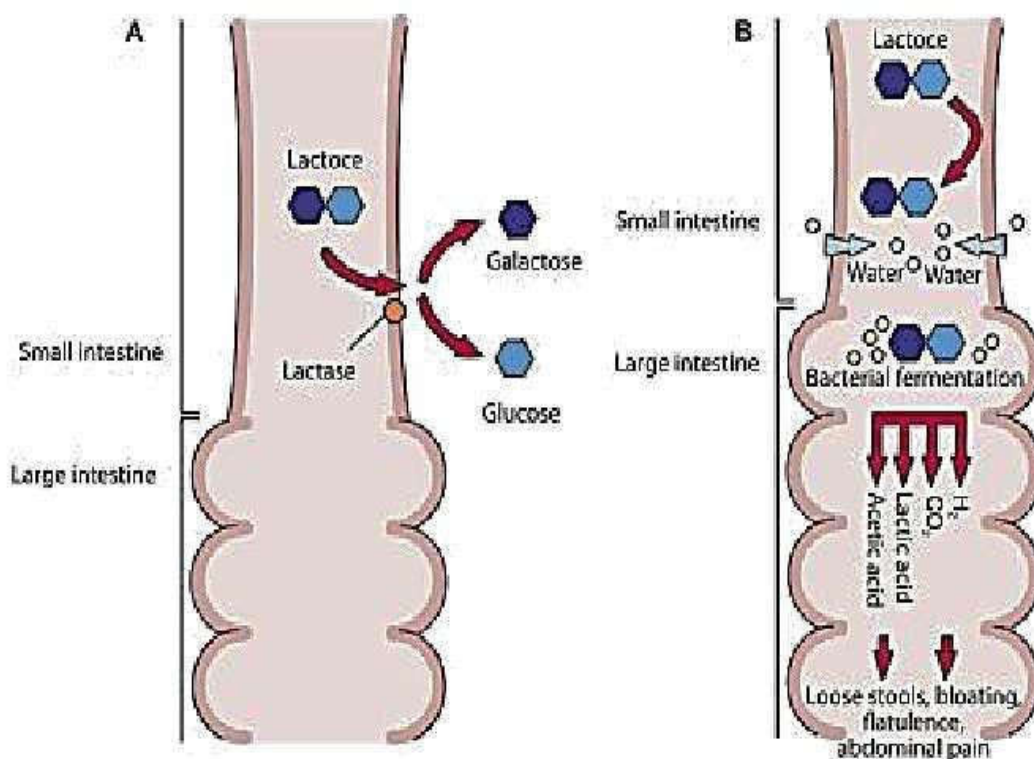
Figure 3. Picture A: Lactase degrades lactose. No symptoms of lactose intolerance.
Picture B: Unabsorbed lactose in the large intestine causes lactose intolerance symptoms.

Lesson 24
- **Sucrose** (Ordinary table sugar) is obtained commercially from cane or beet
- The anomeric carbon atoms of a glucose unit and a fructose unit are joined in this disaccharide and the configuration of this glycosidic linkage is α for glucose and β for fructose

- Consequently, sucrose lacks a free reducing group (an aldehyde or ketone end), in contrast with most other sugars
- Sucrose is therefore a non-reducing sugar and does not exhibit mutarotation
- Sucrose is dextrorotatory but its hydrolytic products are levorotatory as fructose has a levorotation greater than the dextrorotation of glucose
- As the hydrolytic products invert the rotation, the resulting mixture is called as **invert sugar** and the process is called as **inversion**
- The hydrolysis of sucrose to glucose and fructose is catalyzed by **sucrase** (also called **invertase**), which is also present in the intestinal brush border like lactase and maltase
- Honey is largely invert sugar and the presence of fructose accounts for the greater sweetness of honey

α-D-fructose   open chain   β-D-fructose
                      D-fructose
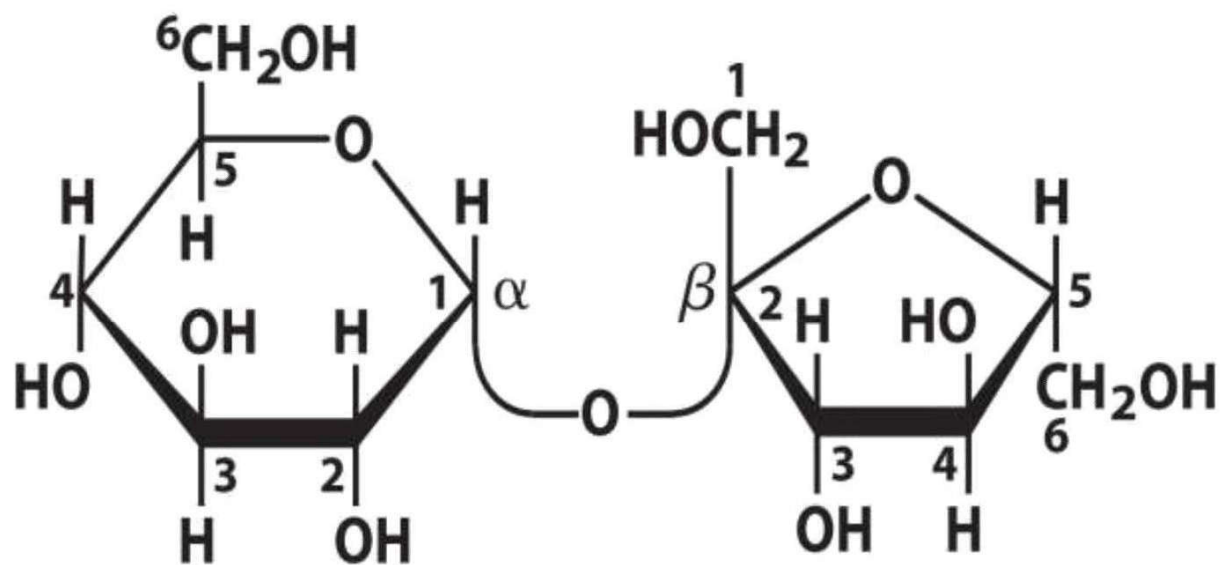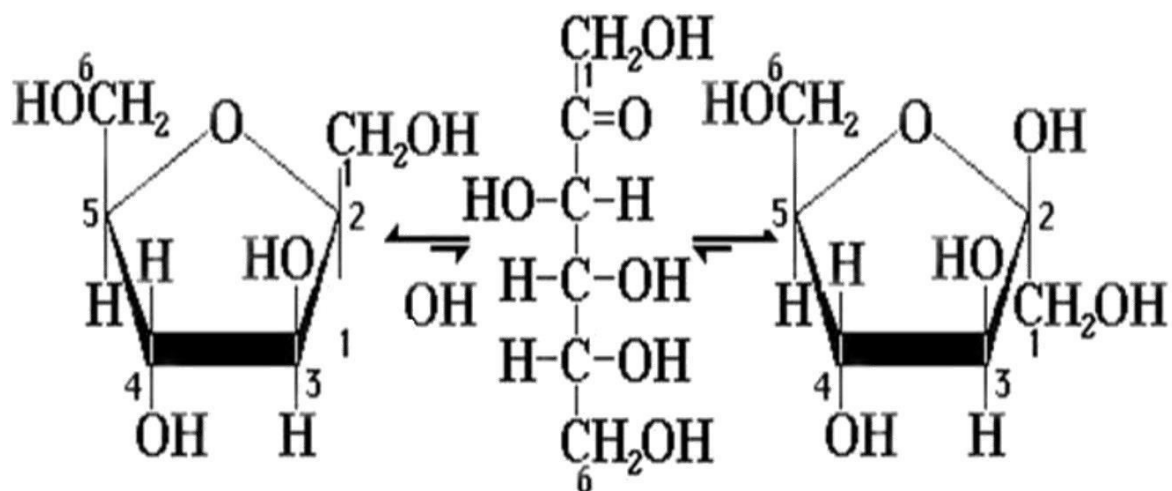
Sucrose

α-D-**glucopyranosyl** β-D-**fructofuranoside**

Glc(α1↔2β)Fru

Lesson 25

- **Oligosaccharides** are short polymers of three to ten monosaccharides joined by glycosidic bonds.
- Most are not digested by human enzymes
- At one end of the chain, the reducing end, is a monosaccharide unit with its anomeric carbon not involved in a glycosidic bond

Biomedical Importance

- Integral membrane proteins contain covalently attached carbohydrate units, oligosaccharides, on their extracellular face
- Many secreted proteins such as antibodies and coagulation factors also contain oligosaccharide units

- The oligosaccharides participate in molecular targeting and cell to cell recognition

- They also mark the passage of time and determine when the proteins should be taken out of circulation

- The human ABO blood groups illustrate the effects of glycosyl- transferases

- Carbohydrates are attached to glycoproteins and glycolipids on the surfaces of red blood cells
- For one type of blood group, one of the three different structures, termed A, B, and O, may be present
- These structures have in common an oligosaccharide foundation called the O (or sometimes H) antigen

- The A and B antigens differ from the O antigen by the addition of one extra monosaccharide, either *N*-acetylgalactosamine (for A) or galactose (for B) through an α-1,3 linkage to a galactose moiety of the O antigen.

Fuc
α-1,2   Gal
         │β-1,3
      GlcNAc
         │β-1,3
        Gal

O antigen

Fuc
α-1,2   Gal   GalNAc
                α-1,3
         │β-1,3
      GlcNAc
         │β-1,3
        Gal

A antigen

Fuc   Gal
α-1,2   Gal α-1,3
         │β-1,3
      GlcNAc
         │β-1,3
        Gal

B antigen
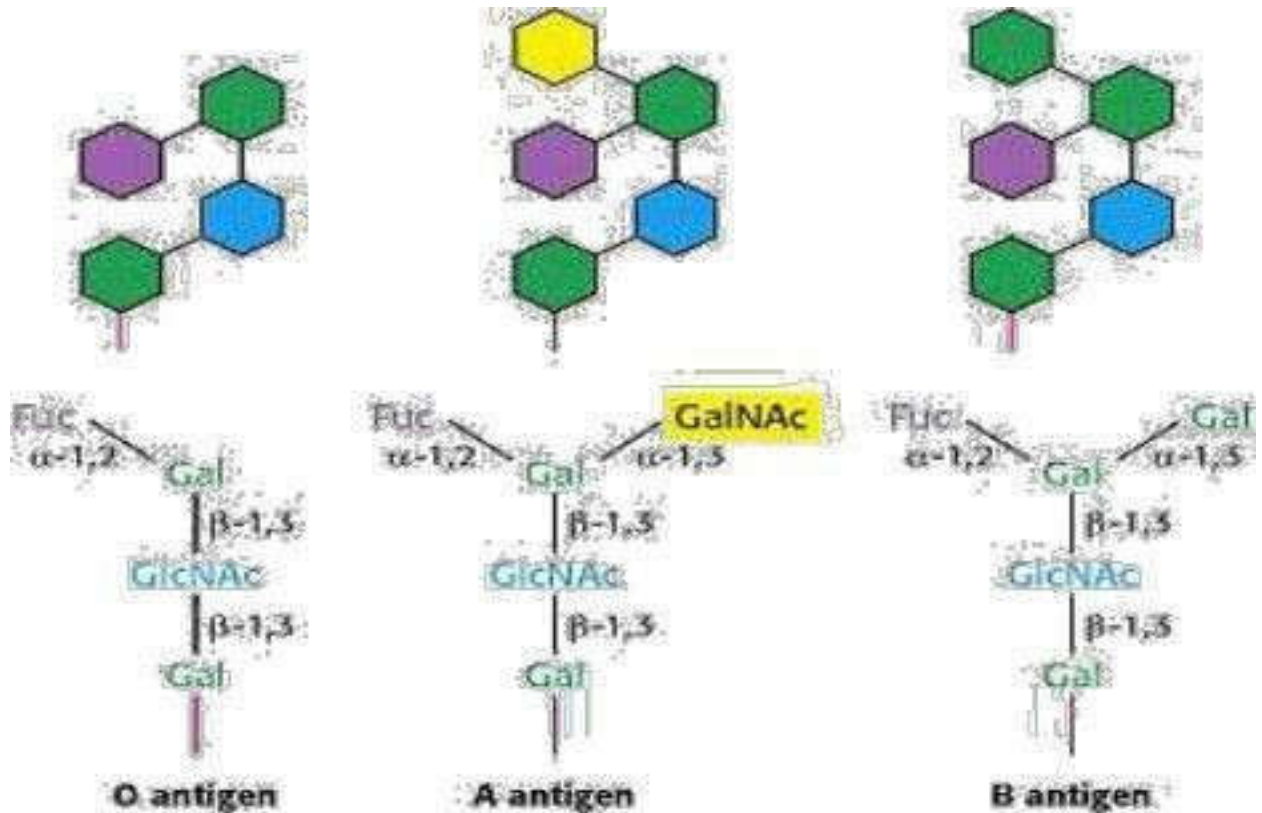
Lesson 26

Polysaccharides

• Most carbohydrates found in nature occur as polysaccharides, polymers of medium to high molecular weight

  Polysaccharides also called **glycans**, differ from each other
  – in the identity of their recurring monosaccharide units
  – in the length of their chains
  – in the types of bonds Iinking the units
  – in the degree of branching
• **Homopolysaccharides** contain only a single monomeric species
• **Heteropolysaccharides** contain two or more different kinds
• Some **homopolysaccharides** serve as storage forms of monosaccharides that are used as fuels
• Other homopolysaccharides (cellulose and chitin) serve as structural elements in plants
• The most important storage polysaccharides are **starch in plant cells and glycogen in animal cells**
• Both polysaccharides occur intracellularly as large clusters or granules
• Most plant cells have the ability to form starch and starch storage is especially abundant in tubers (underground stems), such as potatoes and in seeds

- **Heteropolysaccharides** provide extracellular support for organisms of all kingdoms
- For example, the rigid layer of the bacterial cell envelope (the peptidoglycan) is composed in part of a heteropolysaccharide built from two alternating monosaccharide units

- **Starch** contains two types of glucose polymers:
  – Amylose
  – amylopectin
- It is the most important dietary carbohydrate in cereals, potatoes, legumes, and other vegetables

- **Amylose** (13–20%), consists of long, unbranched helical structure of D-glucose residues connected by (α1‹4) linkages (as in maltose)
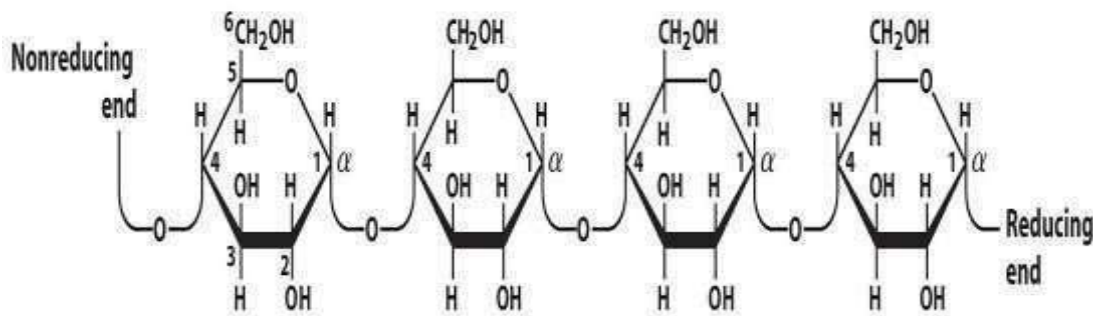
amylose

Lesson 27
- Proteins mediate virtually every process that takes place in a cell, exhibiting an almost endless diversity of functions.
- To explore the molecular mechanism of a biological process, a biochemist almost inevitably studies one or more protein
- Proteins are the most abundant biological macromolecules occurring ; in all cells and all parts of cells
- Proteins also occur in great variety; thousands of different kinds may be found in a single cell
- Moreover, proteins exhibit enormous diversity of biological function and are the most important final products of the information pathways
- Example signal transduction
- Biochemical catalysts known as **enzymes** are proteins
- **Immunoglobulins** that serve as the first line of defense against bacteria and viruses and other foreign agents are proteins
- Several **hormones** are proteins
- **Structural proteins** provide **mechanical support** e.g collagen
- **Contractile proteins** help in the **movement** of muscle fiber and microvilli
- Some proteins present in the cell membrane, cytoplasm and nucleus act as **receptors**

• Certain other proteins in the cell membrane act as **channels and transporters**

• **The transport proteins** carry out the function of transporting specific substances across the membrane or in the body fluids

• **Storage proteins** bind with specific substances and store them

• Under certain conditions, proteins can be catabolized to **provide energy**

• Proteins help in the maintenance of water and electrolyte balance in the body by **exerting osmotic pressure**

• Hence proteins are the most versatile macromolecules in living systems and serve crucial functions in essentially all biological processes

• They function as catalysts, they transport and store other molecules such as oxygen,

• They provide mechanical support and immune protection

• They generate movement, and they control growth and differentiation
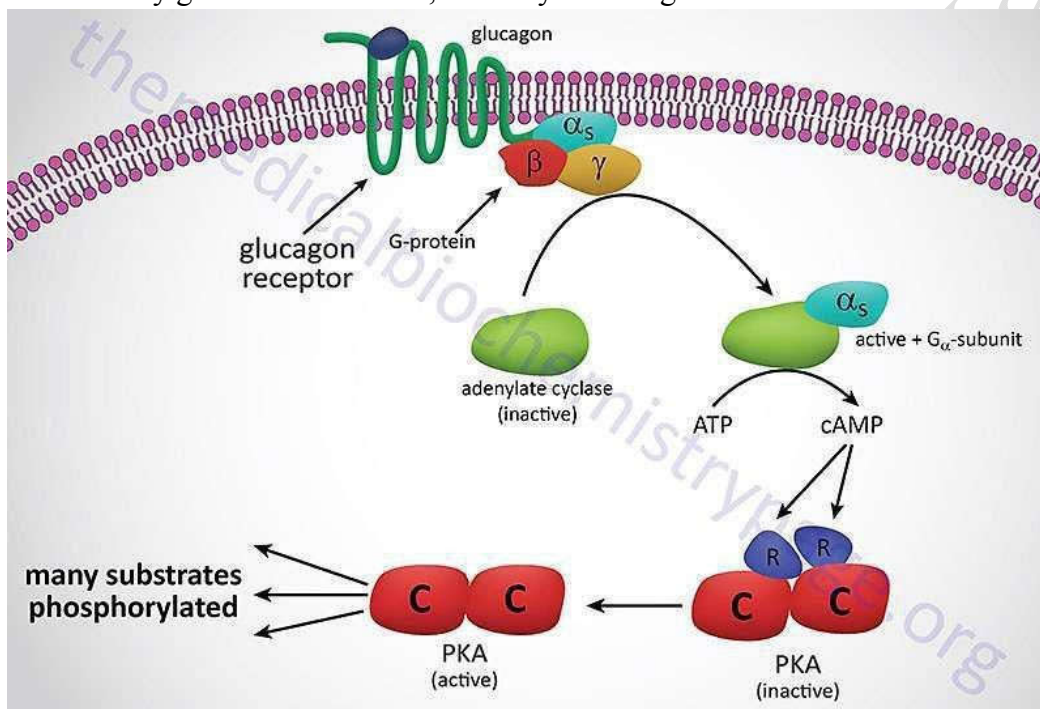
Lesson 28

• Several key properties enable proteins to participate in such a wide range of functions

1. Proteins are linear polymers built of monomer units called amino acids

• The function of a protein is directly dependent on its three dimensional structure

• Remarkably, proteins spontaneously fold up into three-dimensional structures that are determined by the sequence of amino acids in the protein polymer

2. Proteins contain a wide range of functional groups These functional groups include

• alcohols,

• thiols,

• thioethers,

• carboxylic acids,

• carboxamides,

• and a variety of basic groups

• When combined in various sequences, this array of functional groups accounts for the broad spectrum of protein function

3. Proteins can interact with one another and with other biological macromolecules to form complex assemblies

• The proteins within these assemblies can act synergistically to generate capabilities not afforded by the individual component proteins

• These assemblies include macromolecular machines that carry out;

• the accurate replication of DNA,

• the transmission of signals within cells, and many other essential processes

4. Some proteins are quite rigid, whereas others display limited flexibility

• Rigid units can function as structural elements in the cytoskeleton (the internal scaffolding within cells) or in connective tissue

• Parts of proteins with limited flexibility may act as

• hinges,

• springs, and levers

• That are crucial to protein function, to the assembly of proteins with one another and with other molecules into complex units

• And to the transmission of information within and between cells

Lesson 29

• All proteins, whether from the most ancient lines of bacteria or from the most complex forms of life, are constructed from the same set of; 20 amino acids,

• Which are covalently linked in characteristic linear sequence.

• Each of these amino acids has a side chain with distinctive chemical properties

• This group of 20 precursor molecules may be regarded as the alphabet in which the language of protein structure is written

• Proteins are found in a wide range of sizes,

• from relatively small peptides with just a few amino acid residues to huge polymers with molecular weights in the millions

• Cells can produce proteins with strikingly different properties and activities by joining the same 20 amino acids in many different combinations and sequence

• From these building blocks different organisms can make such widely diverse products as

−enzymes,

−hormones,

−antibodies,

−transporters,

−muscle fibers,

– the lens protein of the eye,

– feathers,

– spider webs,

– rhinoceros horn,

– milk proteins,

– antibiotics,

– mushroom poisons etc

•   The light produced by fireflies is the result of a reaction involving the protein luciferin and ATP, catalyzed by the enzyme luciferase
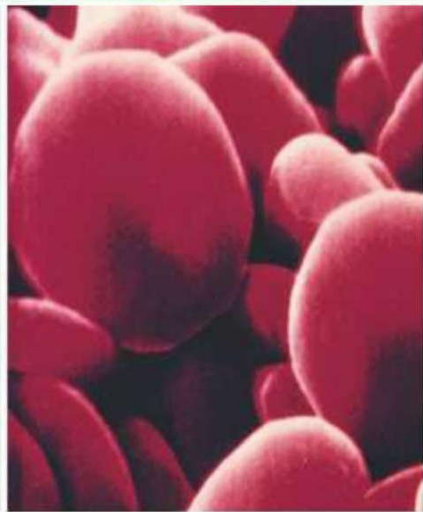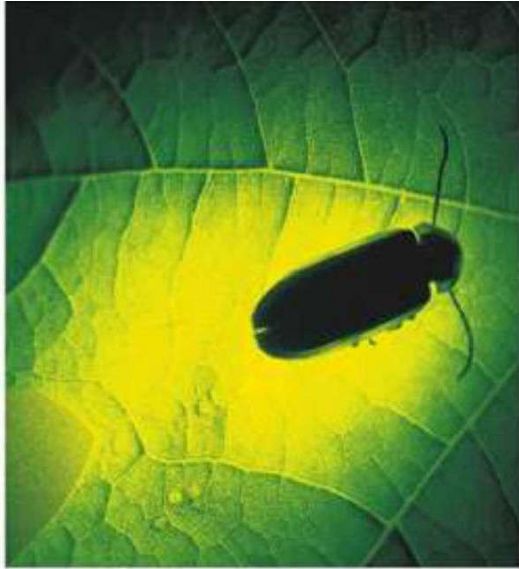
    RBC contain large amounts of the oxygen-transporting protein hemoglobin.
    (c) The protein keratin, formed by all vertebrates, is the chief structural component of hair, scales, horn, wool, nails, and feathers Lesson 30

•   Proteins are polymers of amino acids, with each amino acid residue joined to its neighbor by a specific type of covalent bond termed the **peptide bond**

•   The term "residue" reflects the loss of the elements of water when one amino acid is joined to another

•   Twenty different amino acids are commonly found in proteins

•   All of the 20 common amino acids are **α amino acids**

•   They have a carboxyl group and an amino group bonded to the same carbon atom (the α carbon)

•   They differ from each other in their side chains, or R groups, which vary in –structure,

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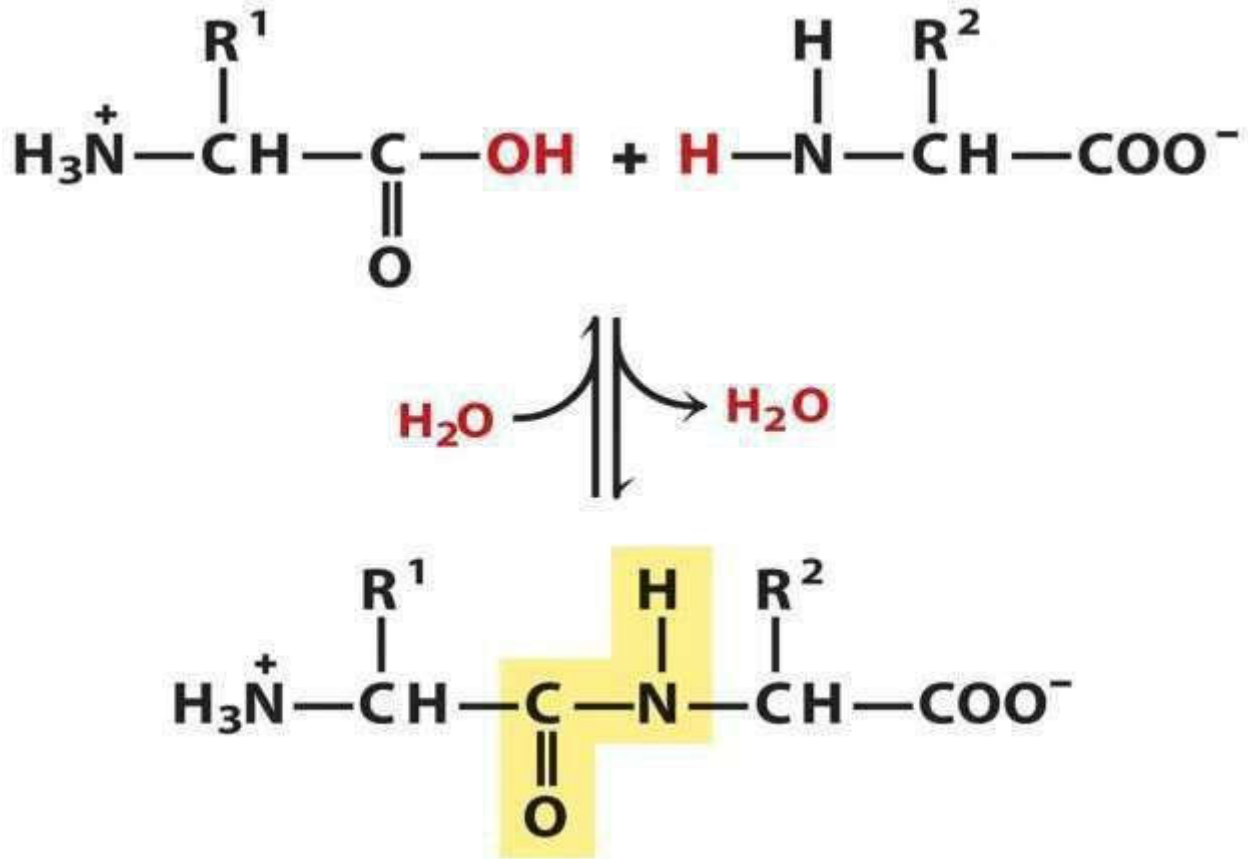–size,

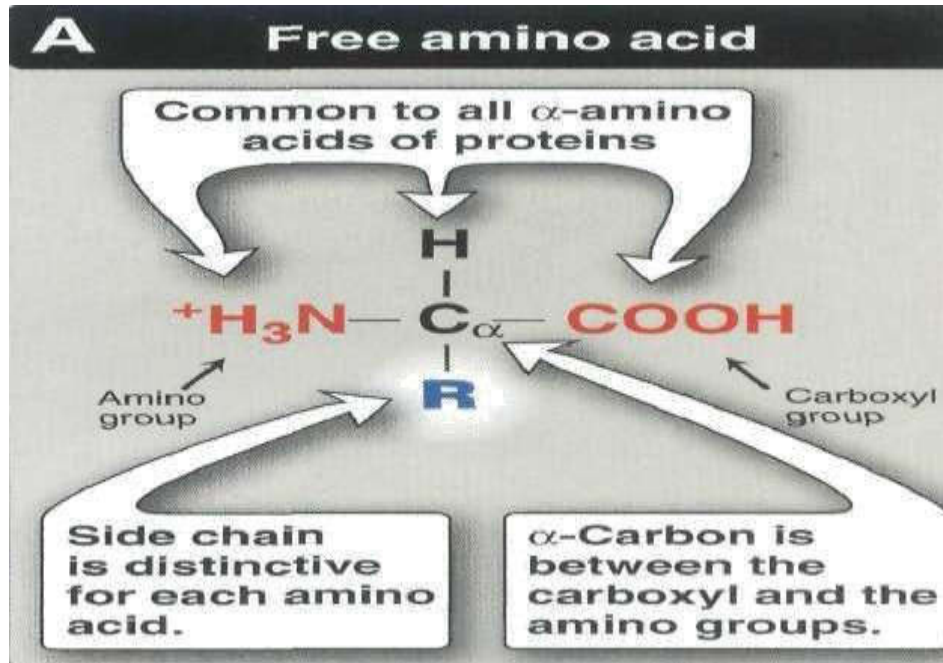−electric charge,
−and which influence the solubility of the amino acids in water

Standard amino acids

• The 20 amino acids that constitute the monomer units of proteins are **the standard amino acids** as the genetic code specifies only these 20 L -α-amino acids

• In addition to these 20 amino acids there are many less common ones i.e., **the non standard amino acids**

A Free amino acid

Common to all α-amino acids of proteins

^+H_3N — $C\alpha$ — COOH

Amino group

Carboxyl group

Side chain is distinctive for each amino acid.

α-Carbon is between the carboxyl and the amino groups.

Lesson 31

• Composition of Proteins

• In addition to the 20 common amino acids, proteins may contain residues created by modification of common residues already incorporated in to a polypeptide

Composition of Proteins

• Some proteins contain additional amino acids that arise by modification of an amino acid already present in a peptide i.e., after the protein has been synthesized
• Examples include
−conversion of peptidyl proline and lysine to
−4-hydroxyproline and
−5-hydroxylysine
−the conversion of peptidyl glutamate to carboxyglutamate the methylation,
• formylation,
• acetylation,
• prenylation, and
• phosphorylation of certain aminoacyl residues

Among these uncommon amino acids
−**4-hydroxyproline**, a derivative of proline
−**5-hydroxylysine**, derived from lysine
• The former is found in plant cell wall proteins, and both are found in collagen

• **6-N-Methyllysine** is a constituent of myosin, a contractile protein

- Another important uncommon amino acid is;
- **y -carboxyglutamate,** found in the blood clotting protein prothrombin and incertain other proteins that bind Ca^{2+} as part of their biological function

- Some 300 additional amino acids have been found in cells but not as constituents of proteins
- Examples include
- Ornithine and citrulline (intermediates in urea cycle)

–Taurine (found in bile acids)
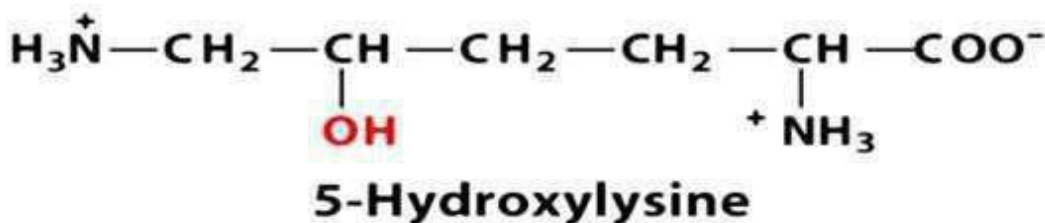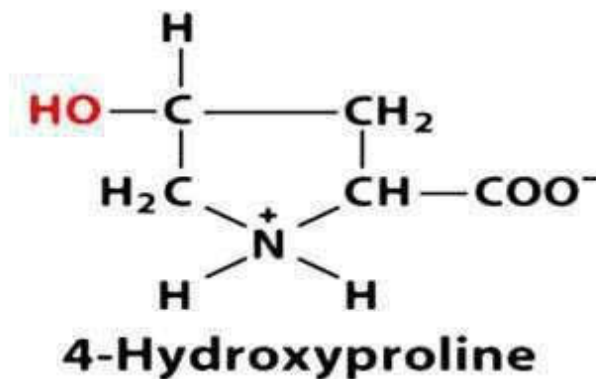–6-Aminolevulinic acid (intermediate in haem synthesis)

D- AMINO ACIDS

•D-amino acids are also non standard amino acids that occur **naturally** and include
–free D- serine, and D-aspartate in brain tissue

–D-alanine & D-glutamate in the cell walls of gram positive bacteria
- D-amino acids are also found in some **antibiotics**

4-Hydroxyproline

5-Hydroxylysine
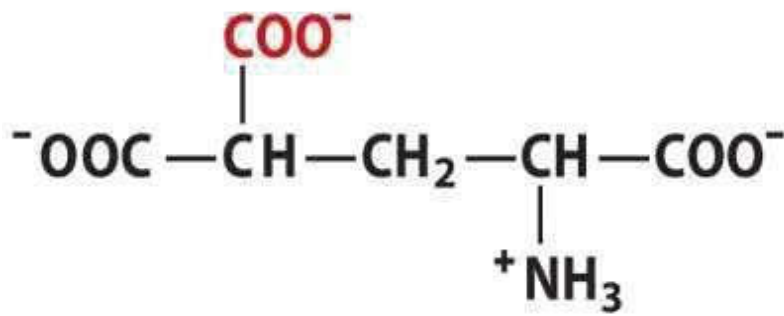
γ-Carboxyglutamate

Lesson 32
Selenocysteine, the 21st L-α-Amino Acid?
- Selenocysteine is an L-α-amino acid found in a handful of proteins, including certain **peroxidases and reductases** where it participates in the catalysis of electron transfer reactions
- Its synthesis is not a post translational modification, but a modification to a **serine** that occurs while the serine is bound to a unique RNA
- The hydroxyl group of serine is replaced by a selenium atom
- The selenocysteine is then inserted into a protein as it is being synthesized

- Since selenocysteine is inserted into polypeptides during translation, it is commonly referred to as the "21st amino acid"
- However, unlike the other 20 genetically encoded amino acids, selenocysteine is not specified by a simple three-letter codon
- **22ⁿᵈ Amino Acid**
- Pyrrolysine (abbreviated as Pyl or O) is a naturally occurring, genetically coded amino acid used by some methanogenic archaea.

serine

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$$HSe-CH_2-CH-COO^-$$
$$\underset{+NH_3}{|}$$
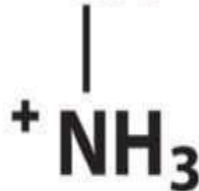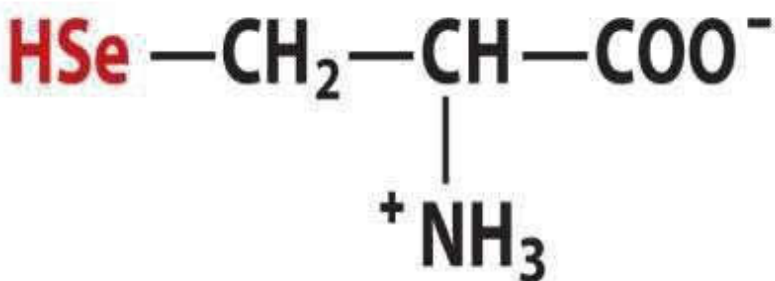
Selenocysteine

Lesson 33

Chiral centers and isomerism

• For all the common amino acids except glycine (the R group is another hydrogen atom), the α carbon is bonded to four different groups:

–a carboxyl group,
–an amino group,
–an R group,
–a hydrogen atom

• The α-carbon atom is thus a chiral center and thus amino acids have two possible stereoisomers

• All molecules with a chiral center are also optically active-that is, they rotate plane polarized light

• Special nomenclature has been developed to specify the absolute configuration of the four substituents of asymmetric carbon atom

• The absolute configurations of simple sugars and amino acids are specified by the D, L system, based on the absolute configuration of the three-carbon sugar glyceraldehyde

• Thus the amino group of L-alanine occupies the same position about the chiral carbon as does the hydroxyl group of L-glyceraldehyde

• Since they are nonsuperposable mirror images of each other, the two forms represent a class of stereoisomers called **enantiomers**

^{1}CHO

HO—^{2}C—H

^{3}CH$_2$OH

L-Glyceraldehyde

CHO

H—C—OH

CH$_2$OH

D-Glyceraldehyde

COO$^-$

H$_3$N$^+$—C—H

CH$_3$

L-Alanine

COO$^-$

H—C—N$^+$H$_3$

CH$_3$

D-Alanine
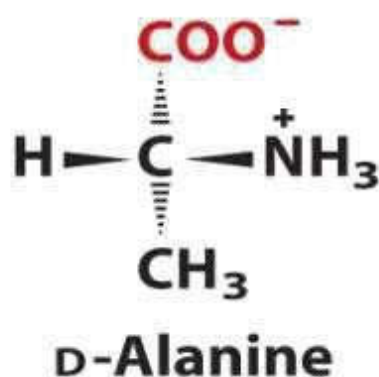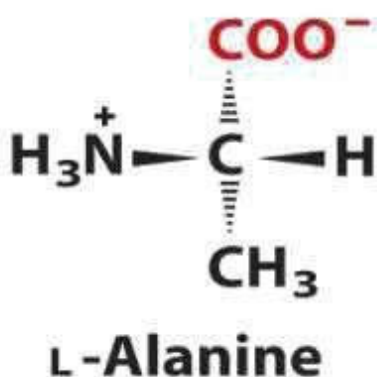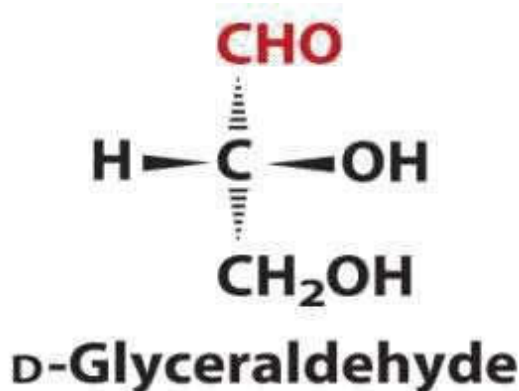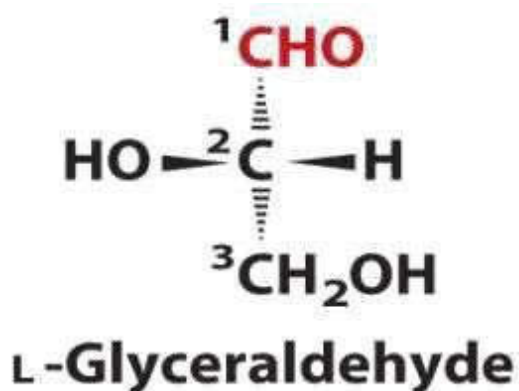
Lesson 34

Two conventions are used to identify the carbons in an amino acid

The additional carbons in an R group are commonly designated **β, γ, δ** and so forth, proceeding out from the **α carbon**

• For most other organic molecules, carbon atoms are simply numbered from one end, giving highest priority (C-1) to the carbon with the substituent containing the atom of **highest atomic number**

• Within this latter convention, the carboxyl carbon of an amino acid would be **C-1** and the **α** carbon would be **C-2**

• In some cases, such as amino acids with heterocyclic R groups (such as histidine), the Greek lettering system is ambiguous and the numbering convention is therefore used

• For branched amino acid side chains, equivalent carbons are given numbers after the Greek letters

• Leucine thus has δ1 and δ2 carbons
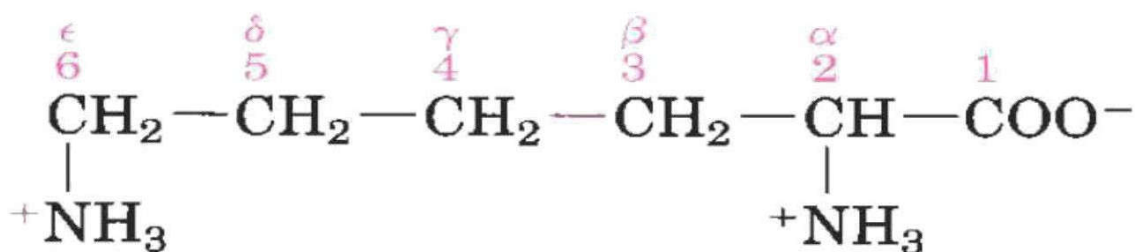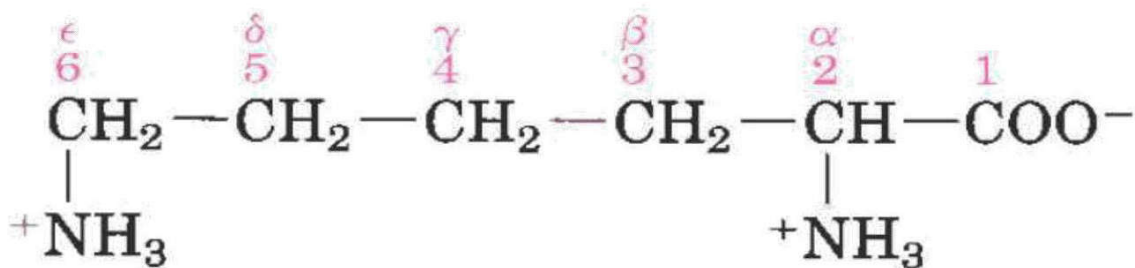
Lysine

Lysine
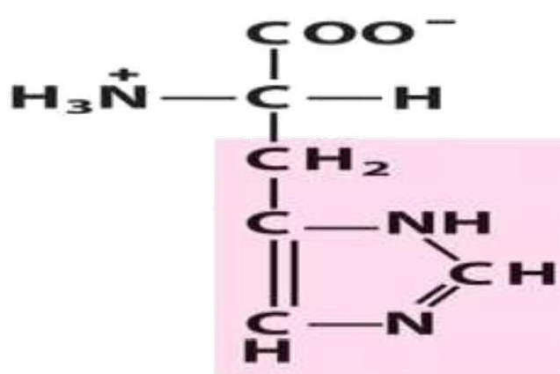
Histidine

pros (in histidine nomenclature).The nitrogen atoms of the imidazole ring of histidine are denoted by pros (_near', abbreviated π) and tele (_far', abbreviated τ) to show their position relative to the side chain. This recommendation arose from the fact that two different systems of numbering the atoms in the imidazole ring of histidine had both been used for a considerable time (biochemists generally numbering as 1 the nitrogen atom adjacent to the side chain, and organic chemists designating it as 3)

Lesson 35
Acid and base properties of amino acids

• The form of an amino acid that has both a positive and a negative charge is called a
zwitterion

• Amino acids in solution at neutral pH exist predominantly as dipolar ions **(zwitterions)**

• In this form, the amino group is protonated ($-NH_3^+$)
• and the carboxyl group is deprotonated
($-COO^-$)
• A zwitterion can act either as an acid (proton donor) or as a base (proton acceptor)
• Substances having this dual nature are **amphoteric** and are often called **ampholytes**
• The ionization state of an amino acid varies with pH
• At physiological pH, the carboxyl group is dissociated , forming the negatively

charged carboxylate ion ($-COO^-$) and the amino group is protonated (NH_3^+)
• A simple monoamino monocarboxylic - amino acid, such as alanine, is a diprotic acid

when fully protonated—it has two groups, the -COOH group and the - NH_3^+ group, that
can yield protons
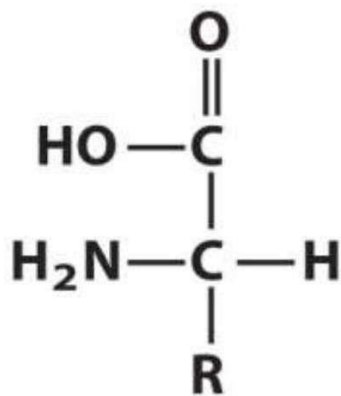
Nonionic form
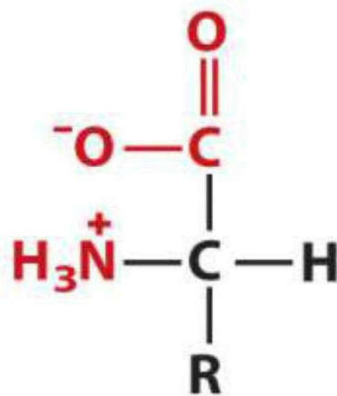
Zwitterionic form

D-Alanine
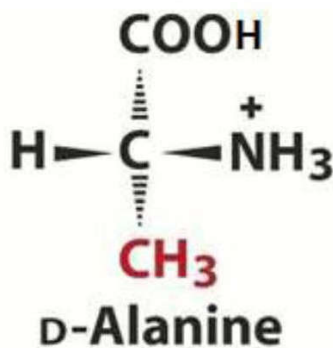
Lesson 36

- Each acid has a characteristic tendency to lose its proton in an aqueous solution
- The stronger the acid, the greater its tendency to lose its proton
- The tendency of any acid (HA) to lose a proton and form its conjugate base (A^-) is defined by the equilibrium constant (K_{eq}) for the reversible reaction
- HA $\rightleftharpoons$ $A^- + H^+$
- Equilibrium constants for ionization reactions are usually called ionization constants or acid dissociation constants, often designated pK_a
- The stronger the tendency to dissociate a proton, **the stronger is the acid and the lower its pKa**
- The pKa expresses, on a logarithmic scale, the relative strength of a weak acid or base:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

-
-
- pKa = log——
- The stronger the acid, the lower its pKa;

-
- At the midpoint of the titration, the concentrations of the proton donor and proton acceptor are equal, and the pH is numerically equal to the pKa.
- The pKa can be determined experimentally;
- it is the pH at the midpoint of the titration curve for the acid or base

-
- At that point, [HA] equals [A], and
- pH = pKa + log 1
- = pKa + 0 = pKa
- At that point, [HA] equals [A], and
- pH = pKa + log 1
- = pKa + 0 = pKa

Lesson 37

- pKa is the measure of the tendency of a group to give up (donate) a proton with the tendency decreasing ten-fold as the pKa increases by one unit
- Each titratable group has a pKa that is numerically equal to the pH at which exactly one half of the protons have been removed from that group
- The pKa for the most acidic group (COOH) is pK1, whereas the pKa for the next most acidic group (NH_3^+) is pK2
- **In acid solution** (e.g., pH 1), the amino group is protonated ($-NH_3^+$) and the carboxyl group is not dissociated (–COOH)

- As the pH is raised, the carboxylic acid is the first group to give up a proton, as its p*Ka is near 2*
- The dipolar form persists until the pH approaches 9, when the protonated amino group loses a proton

Lesson 38

Titration of an amino acid Dissociation of the carboxyl group:

- The titration curve of an amino acid can be analyzed
- Consider alanine, for example, which contains both an α-carboxyl and an α-amino group
- At a low (acidic) pH, both of these groups are protonated
- As the pH of the solution is raised, the -COOH group of form I can dissociate by donating a proton to the medium
- The release of a proton results in the formation of the carboxylate group – COO$^-$
- This structure is shown as form II, which is the **dipolar form of the molecule**
- This form, also called a **zwitterion,** is the **isoelectric form** of alanine
- That is, it has an overall charge of zero
- The dissociation constant of the carboxyl group of an amino acid is called K1 rather than K2 because the molecule contains a second titratable group

Dissociation of the amino group:

- The second titratable group of alanine is the amino group
- This is a much weaker acid than the -COOH group and, therefore, has a much smaller dissociation constant, K2
- Release of a proton from the protonated amino group of form II results in the fully deprotonated form of alanine, form III

H
|
^+H_3N _ C _ COO$^-$
|
CH$_3$

FORM II

Alanine in neutral solution
(pH approximately 6)

Net charge = 0
(isoelectric form)

H
|
^+H_3N _ C _ COO**H**
|
CH$_3$
FORM I

OH$^-$ H$_2$O

pK$_1$=2.3

H
|
^+H_3N _ C _ COO$^-$
|
CH$_3$
FORM II

OH$^-$ H$_2$O

Pk$_2$=9.1

H
|
H$_2$N _ C _ COO$^-$
|
CH$_3$
FORM III
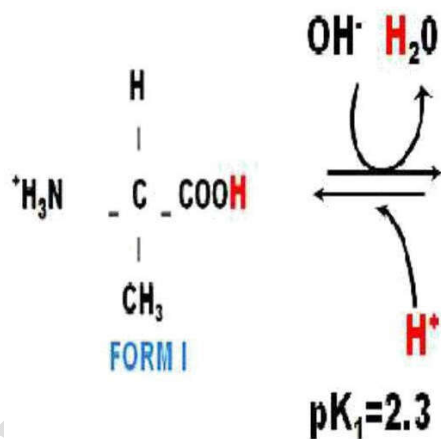
Alanine in acid solution
(pH less than 2)

Net charge = + 1
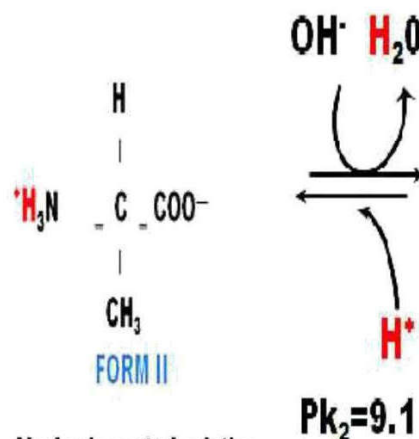
Alanine in neutral solution
(pH approximately 6)

Net charge = 0
(isoelectric form)
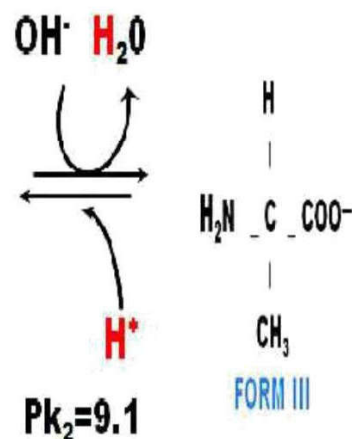
Alanine in basic solution
(pH greater than 10)

Net charge = - 1

Lesson 39

- A simple amino acid e.g. **glycine** is a diprotic acid when fully protonated

- This means that it has two groups, the COOH and the NH_3^+ group that can yield protons • Figure shows the titration curve of the diprotic form of glycine

- The two ionizable groups of glycine, the carboxyl group and the amino group, are titrated with a strong base

- The plot has two distinct stages, corresponding to deprotonation of two different groups on glycine

- At very low pH, the predominant ionic species of glycine is **the fully protonated form**, $^+H_3N\text{-}CH_2\text{-}COOH$

- **At the midpoint** of any titration, a point is reached where the **pH is equal to the pKa** of the protonated group being titrated

- At the midpoint in the first stage of the titration, in which the --COOH group of glycine loses its proton, equimolar concentrations of the protonated ($^+H_3N\text{-}CH_2\text{-}COOH$) and the deprotonated ($^+H_3N\text{-}CH_2\text{-}COO^-$) species are present

- As the titration proceeds, another important point is reached at pH 5.97

- This is a point, at which removal of the first proton is essentially complete and removal of the second has just begun

- At this pH glycine is present largely as the dipolar ion (zwitterion) $^+H_3N\ CH_2\text{-}COO^-$

- The second stage of the titration corresponds to the removal of a proton from the $-NH_3^+$ group of glycine

- The pH at the midpoint of this stage is 9.60, equal to the pKa for the $-NH_3$ group

- The titration is essentially complete at a pH of about 12, at which point the predominant form of glycine is

- $H_2N\text{-}CH_2\text{-}COO^-$
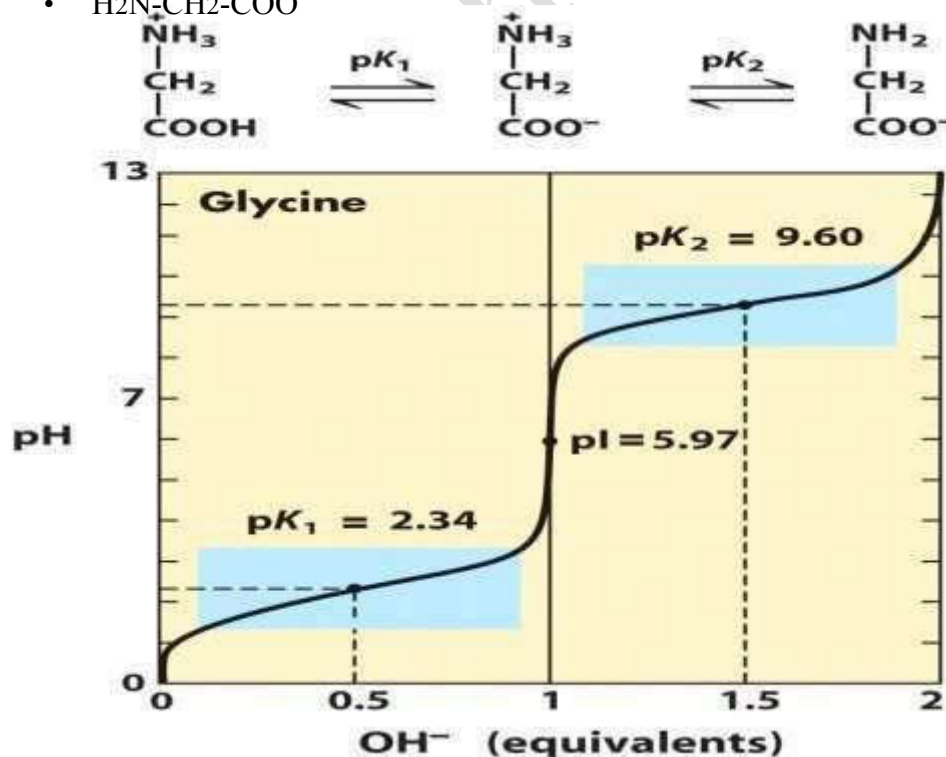
Lesson 40

- From the titration curve of glycine we can derive several important pieces of information
  - First, it gives a quantitative measure of the pK_a, of each of the two ionizing groups:
    2.34 for the -COOH group
    9.60 for the $-NH_3^+$ group
    The second piece of information is that this amino acid has **two regions of buffering power**
- One of these is the relatively flat portion of the curve, extending for approximately 1 pH unit on either side of the first pK_a, of 2.6, indicating that glycine is a good buffer near this pH
- The other buffering zone is centered around pH 9.60
- Note that glycine is not a good buffer at the pH of intracellular fluid or blood, about 7.4
- Another important piece of information derived from the titration curve of an amino acid is the relationship between its net charge and the pH of the solution
- At pH 5.97, glycine is present predominantly as its dipolar form, fully ionized but with no net electric charge
- The characteristic pH at which the net electric charge is zero is called the **isoeleetric point or isoelectric pH, designated pI**
- For glycine, which has no ionizable group in its side chain;
- the pI is simply the arithmetic mean of the two pK_a values
- pI = ½ (pK1+pK2)
- = ½ (2.34+9.60) = 5.97
- The farther the pH of a glycine solution is from its pI, the greater the net electric charge of the population of glycine molecules
- At any pH below its pI, glycine has a **net positive charge** and will move toward the negative electrode (cathode)
- At any pH above its pI, glycine will have a net negative charge and thus will move towards the positive electrode (anode)

Lesson 41

- All amino acids with a
- single α-amino group,
- a single α-carboxyl group, and
- an R group that does not ionize
- have titration curves resembling that of glycine
- These amino acids have very similar, although not identical, pK_a values:
- pK_a of the –COOH group in the range of 1.8 to 2.4
- pK_a of the $-NH_3^+$ group in the range of 8.8 to 11
- The differences in these pK_a values reflect the effects of the R groups
- Alanine has only two dissociable hydrogens (one from α carboxyl & one from α amino group)
- Its pI can be calculated as follows:
- pI = pK1 + pK2 ÷ 2
- pK1 = 2.3 (for carboxyl group)
- pK2 = 9.1 (for amino group)
- pI = 2.3 + 9.1 ÷ 2 = 5.7

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- Amino acids with an ionizable R group have more complex titration curves, with three stages corresponding to the three possible ionization steps and thus they have **three pKa values**
- The additional stage for the titration of the ionizable R group merges to some extent with the other two
- In addition, each of the acidic and basic amino acids contains an ionizable group in its side chain
- Thus, both free amino acids and some amino acids combined in peptide linkages can act as **buffers**
- A buffer is a solution that resists change in pH following the addition of an acid or base
- The isoelectric points reflect the nature of the ionizing R groups present
- For example, glutamate has a pI of 3.22, considerably lower than that of glycine
- This is due to the presence of two carboxyl groups, with an average of their pKa values of 3.22
- Histidine has got 3 dissociable hydrogens
    - one from carboxyl, pK1=1.8,
    - one from imidazole group,   pK2=6.0
    - one from amino group,   pK3=9.2
- The pI of Histidine, with two groups that are positively charged when protonated, is 7.59 (the average of the pKa values of the amino and imidazole groups)
- Only histidine has an R group (pKa = 6.0) providing significant buffering power near the neutral pH usually found in the intracellular and extracellular fluids of most animals
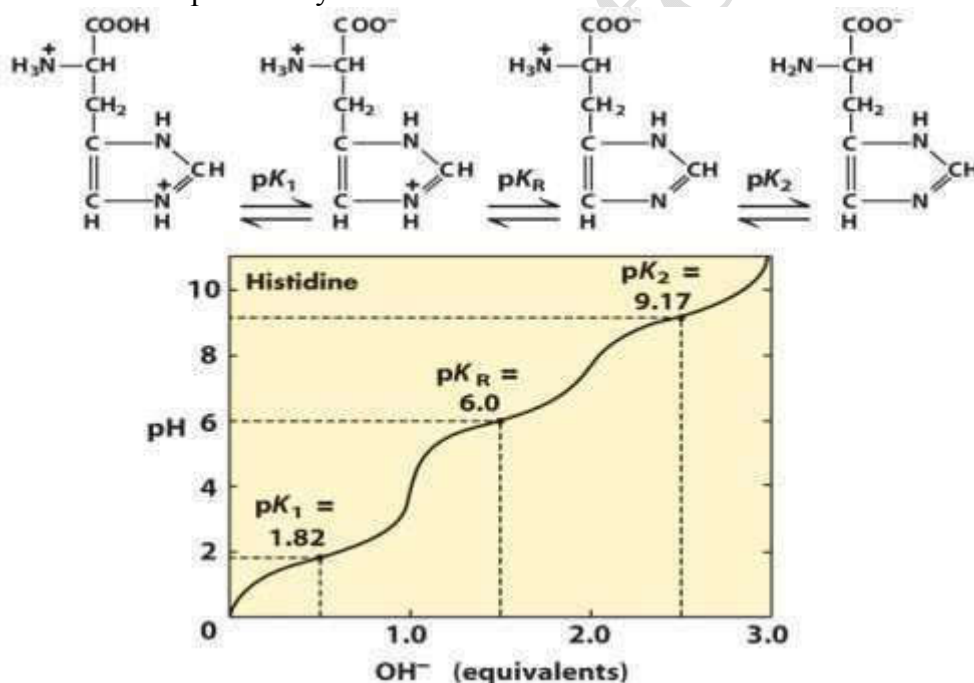
Lesson 42,43,44,45 are not available

Lesson 46
Classification of amino acids
B. Aromatic Amino Acids

- The aromatic amino acids have been grouped together because they all contain ring structures with similar properties, **but their polarity differs**
- The aromatic ring is a six-membered carbon–hydrogen ring with three conjugated double bonds (the benzene ring or phenyl group)
- Benzene is an organic chemical compound with the chemical formula C6H6. Its molecule is composed of 6 carbon atoms joined in a ring, with 1 hydrogen atom attached to each carbon atom
- The substituents on this ring determine whether the amino acid side chain engages in polar or hydrophobic interactions
- This group includes
  - Phenylalanine
  - Tyrosine
  - Tryptophan
  - with their aromatic side chains, are relatively nonpolar (hydrophobic).
  - All can participate in hydrophobic interactions.

Aromatic R groups
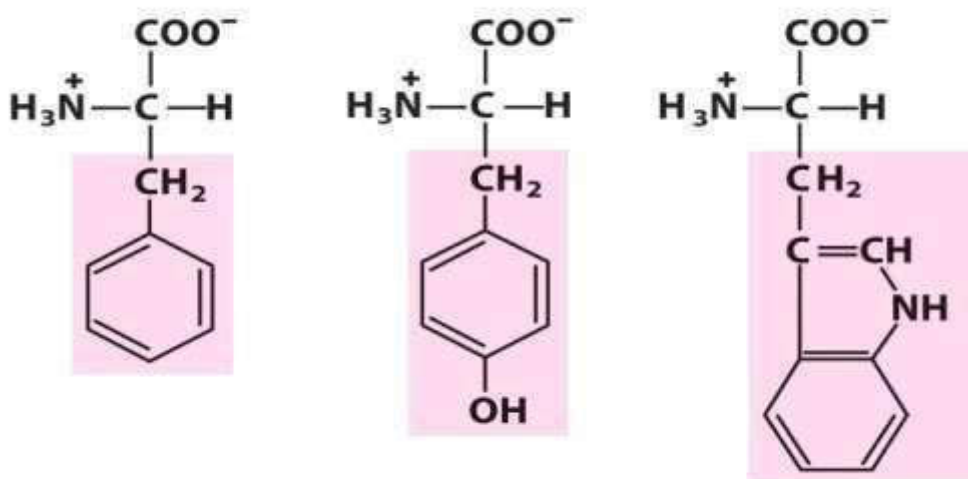
Phenylalanine Tyrosine Tryptophan

- In the amino acid **phenylalanine**, the ring contains no substituents, and the electrons are shared equally between the carbons in the ring, resulting in *a very* **nonpolar hydrophobic** structure in which the rings can stack on each other
- In **tyrosine**, a hydroxyl group on the phenyl ring engages in hydrogen bonds, and the side chain is therefore more polar and **more hydrophilic**
- The more complex ring structure in **tryptophan** is an indole ring with a nitrogen that can engage in hydrogen bonds
- Tryptophan is therefore also more polar than phenylalanine
- Tyrosine and tryptophan are significantly more polar than phenylalanine, because of the tyrosine hydroxyl group and the nitrogen of the **tryptophan** indole ring

Lesson 47
C. Aliphatic, Polar, Uncharged R Groups

- The R groups of these amino acids are more soluble in water, or more hydrophilic, than those of the nonpolar amino acids.
- Because they contain functional groups that form hydrogen bonds with water.

- This class of amino acids includes
- **serine,**
  threonine,
- **cysteine,**
- **asparagine,** and
- **glutamine.**
- These Amino acids have zero net charge at neutral pH
  - **Serine & threonine** of this class contain a polar hydroxyl group
  - Similarly side chains of **asparagine & glutamine** contain a carbonyl group & amide group, both of which can participate in hydrogen bonding
    -
- These side chains are sites of attachment for other compounds
- The polar hydroxyl groups of **serine & threonine** serve as a site of attachment for phosphate groups
- The amide group of **asparagine** & the hydroxyl group of **serine & threonine** serve as a site of attachment for oligosaccharide chains in glycoproteins
- Amino acids with side chains that contain an amide group (asparagine and glutamine) or a hydroxyl group (serine and threonine) can be classified as **aliphatic, polar, uncharged amino acids**
- Asparagine and glutamine are amides of the amino acids aspartate and glutamate
- As a consequence of their hydrophilicity, these amino acids are frequently found on the surface of water-soluble globular proteins
- Cysteine, which is sometimes included in this class of amino acids, has been separated into the class of sulfur-containing amino acids

Polar, uncharged R groups
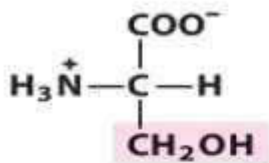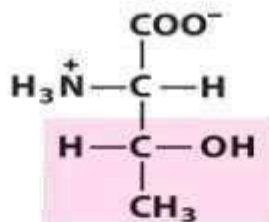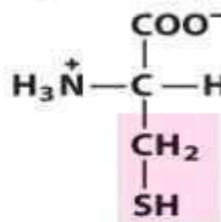
Serine   Threonine   Cysteine
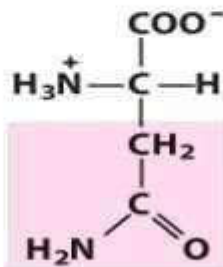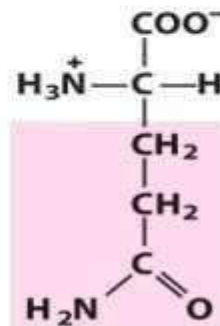
Asparagine   Glutamine

Lesson 48

D. Positively Charged (Basic) R Groups

- The side chains of these amino acids are proton acceptors
- The amino acids in which the R groups have significant **positive charge** at pH 7.0 are:
  - **Lysine**, which has a second primary amino group at the s position on its aliphatic chain
  - **Arginine,** which has a positively charged guanidinium group
  - **Histidine,** which has an aromatic imidazole group
- The side chains of the two basic amino acids, arginine and lysine, have pKa values above 10, so that the positively charged form always predominates at physiologic pH
- The side chain of histidine (pKa ~ 6.0) dissociates near physiologic pH, so only a portion of the histidine side chains carry a positive charge
- **Histidine** is therefore weakly basic & the *free* amino acid is mainly uncharged at physiologic pH
- The amino acid side chains might have very different pKas than those of the free amino acids if they are involved in hydrogen or ionic bonds with other amino acid sidechains
- Therefore, when histidine is incorporated into a protein, its side chain can be either positively charged or neutral depending on the ionic environment provided by the polypeptide chains of the protein

Positively charged R groups
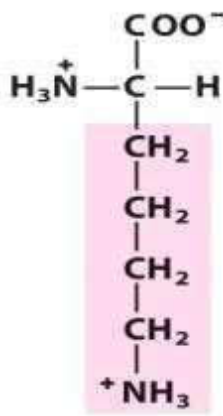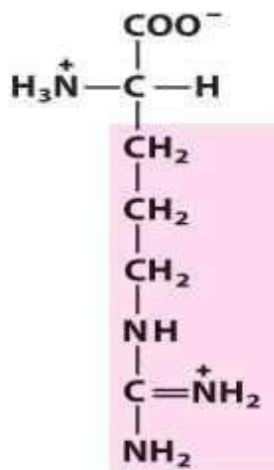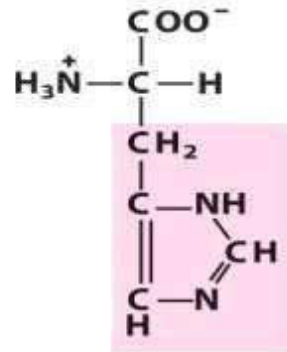
Lysine   Arginine   Histidine

Lesson 49

E. Negatively Charged (Acidic) R Groups

- These amino acids are proton donors
- At neutral pH, the side chains of these amino acids are fully ionized, containing a negative_ly charged carboxylate group
- (--COO)
- Therefore these amino acids are negatively charged at phyisologic pH
- The two amino acids having R groups with a net negative charge at pH 7.0 are **aspartate and glutamate**, each of which has a second carboxyl group
- Humans have no dietary requirement for protein, per se, but, the protein in food does provide essential amino acids.
- Nine of the twenty amino acids needed for the synthesis of body proteins are essential-that is, they cannot be synthesized in humans at an adequate rate
- **Essential amino acids** can not be made by the body. As a result, they must come from food. The nine **essential amino acids** are: histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine.
- Of these nine, some amino acids are essential at all times, whereas some are required only during periods of rapid tissue growth characteristic of childhood or recovery from illness
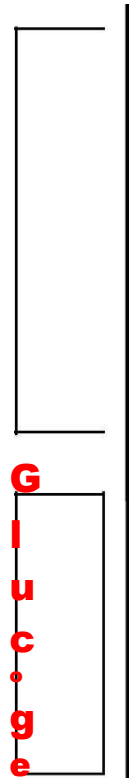
Glucogenic

Alanine

Arginine

Asparagine

Cysteine

Glutamate

Glutamine

Glycine

Proline

Serine

Tyrosine

Negatively charged R groups
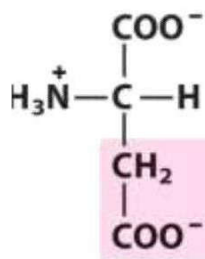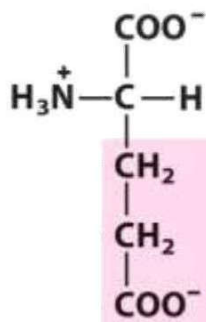
Aspartate   Glutamate

Essentia	Histidine Methionine Valine	

Essential	Conditionally Non-Essential	Non-Essential
Histidine	Arginine	Alanine
Isoleucine	Asparagine	Asparatate
Leucine	Glutamine	Cysteine
Methionine	Glycine	Glutamate
Phenylalanine	Proline	
Threonine	Serine	
Tryptophan	Tyrosine	
Valine		
Lysine		

(fastbleep)

Lesson 50

- Amino acids can be classified as **glucogenic or ketogenic** based on what intermediates are produced during their catabolism

A. Glucogenic amino acids

- Amino acids whose catabolism yields **pyruvate are termed glucogenic or glycogenic**
- These intermediates are substrates for **gluconeogenesis** and, therefore, can give rise to the net formation of glucose or glycogen in the liver and glycogen in the muscle

B. Ketogenic amino acids

- Amino acids whose catabolism yields either **acetoacetate or its precursor, (acetyl CoA or acetoacetyl CoA)** are termed **ketogenic**
- Acetoacetate is one of the ketone bodies which also include 3-hydroxybutyrate and acetone
- **Leucine and lysine** are the only exclusively ketogenic amino acids found in proteins
- Their carbon skeletons are not substrates for gluconeogenesis and, therefore, cannot give rise to the net formation of glucose or glycogen in the liver, or glycogen in the muscles

Glucogenic	Glucogenic And Ketogenic	Ketogenic
Alanine Arginine Asparagine Cysteine Glutamate Glutamine Glycine Proline Serine	Tyrosine	
Histidine Methionine Valine	Threonine Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

TABLE 14-4 Glucogenic Amino Acids, Grouped by Site of Entry

Pyruvate
Alanine
Cysteine
Glycine
Serine
Threonine
Tryptophan*

α-Ketoglutarate
Arginine
Glutamate
Glutamine
Histidine
Proline

Succinyl-CoA
Isoleucine*
Methionine
Threonine
Valine

Fumarate
Phenylalanine*
Tyrosine*

Oxaloacetate
Asparagine
Aspartate

Note: All these amino acids are precursors of blood glucose or liver glycogen, because they can be converted to pyruvate or citric acid cycle intermediates. Of the 20 common amino acids, only leucine and lysine are unable to furnish carbon for net glucose synthesis. *These amino acids are also ketogenic (see Fig. 18-21).

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Lesson 51

- Different classifications of proteins are based on their:
- Shape and Size
- Biological actions/ Functions
- Solubility and physical properties
- Quality

Catalytic Proteins:

These specialized proteins are called **enzymes** which catalyze the biochemical reactions

- **Protective Proteins**
- **Immunoglobins (Igs)**
- These freely circulating proteins protect the body from invading microbes such as bacteria or viruses by inactivating or killing them through various mechanisms.

- **Fibrinogen**
  This forms fibrin clot and stops bleeding from wounds
  - **Regulatory Proteins:**
    Hormones control genetic expression, cellular signalling *and* biochemical reactions catalyzed by enzymes. Enzymes are either activated or inactivated through modification of their structure.
    Examples of protein hormones are
    - growth hormone
    - Insulin
    - Glucagon
    - Somatostatin
- **Structural Proteins:**
  These proteins form various body structures e.g.
  - Collagen
  - Elastin
  - Keratin
- **Transport Proteins:**
  These proteins transport various substances from one part of the body to the other e.g.
  - Hemoglobin transport O_2 from lungs to tissues and CO_2 from tissues to lungs
  - Transferrin transports iron
  - **Contractile Proteins:**
  - These proteins are involved in muscle contraction and
  relaxation − Myosin of thick filaments
  - Actin of thin filaments of skeletal muscles

Lesson 52 is not available Lesson 53

PEPTIDE BOND
- We now turn to polymers of amino acids, the peptides and proteins
- Biologically occurring polypeptides range in size from small to very large, consisting of two or three to thousands of linked amino acid residues
- Two amino acid molecules can be covalently joined through **an amide linkage,** termed **a peptide bond**
- This linkage is formed by removal of the elements of water from the α-carboxyl group of one amino acid and the α-amino group of another
- Two configurations are possible for a planar peptide bond
- In the trans configuration, the two -carbon atoms are on opposite sides of the peptide bond
- In the cis con-, these groups are on the same side of the peptide bond.
- *Almost all peptide bonds in proteins are trans*
- This preference for trans over cis can be explained by the fact that steric clashes between groups attached to the -carbon atoms hinder formation of the cis form but do not occur in the trans configuration

Amino R—N with H, H

Amido R—C—N with H, H (C double bonded to O)

$$H_3\overset{+}{N}-CH(R^1)-C(=O)-OH + H-N(H)-CH(R^2)-COO^-$$

$$H_2O \rightleftharpoons H_2O$$

$$H_3\overset{+}{N}-CH(R^1)-C(=O)-N(H)-CH(R^2)-COO^-$$

Trans   Cis

Figure 2.20
Biochemistry, Seventh Edition
© 2012 W. H. Freeman and Company
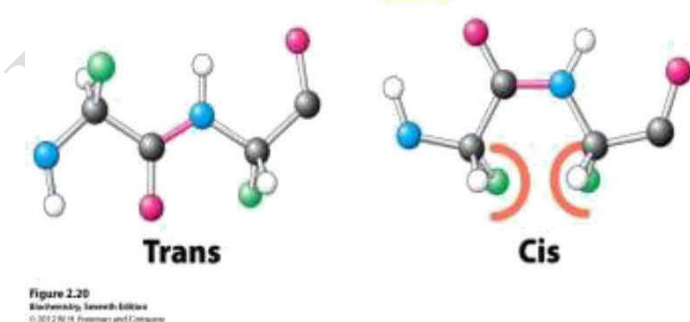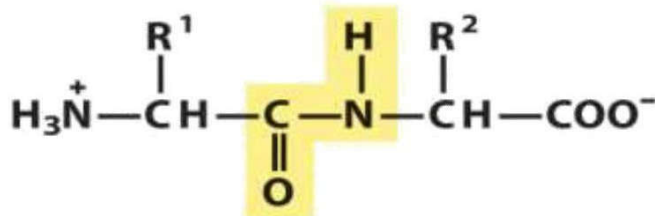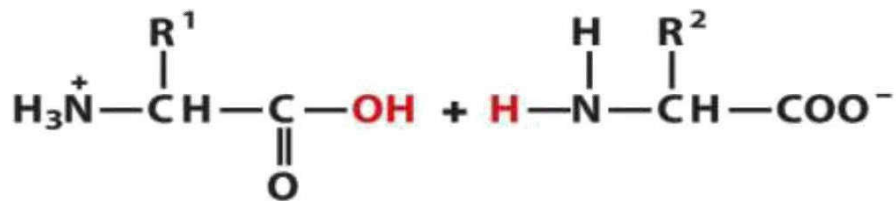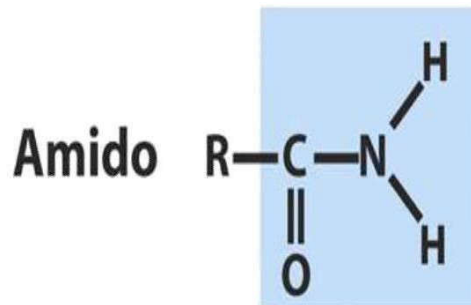
Lesson 54
The Structure of Proteins
Four levels of protein structure are commonly defined
The Primary Structure
A description of all covalent bonds (mainly **peptide bonds** and **disulfide bonds**) linking amino acid residues in a polypeptide chain is its primary structure
The most important element of primary structure is the **sequence** of amino acid residues **Secondary structure**
Secondary structure refers to **particularly stable arrangements** of amino acid residues giving rise to recurring structural patterns
Tertiary structure
Tertiary structure describes all aspects of the **three-dimensional** folding of a polypeptide
Quaternary structure
When a protein has **two or more polypeptide** subunits, their arrangement in space is referred to as quaternary structure
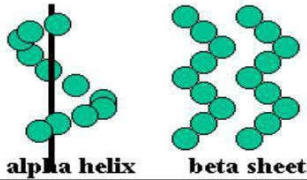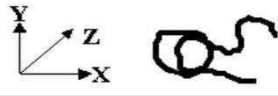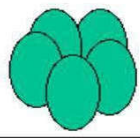
Primary structure — **Secondary structure** — **Tertiary structure** — **Quaternary structure**

Amino acid residues — α Helix — Polypeptide chain — Assembled subunits
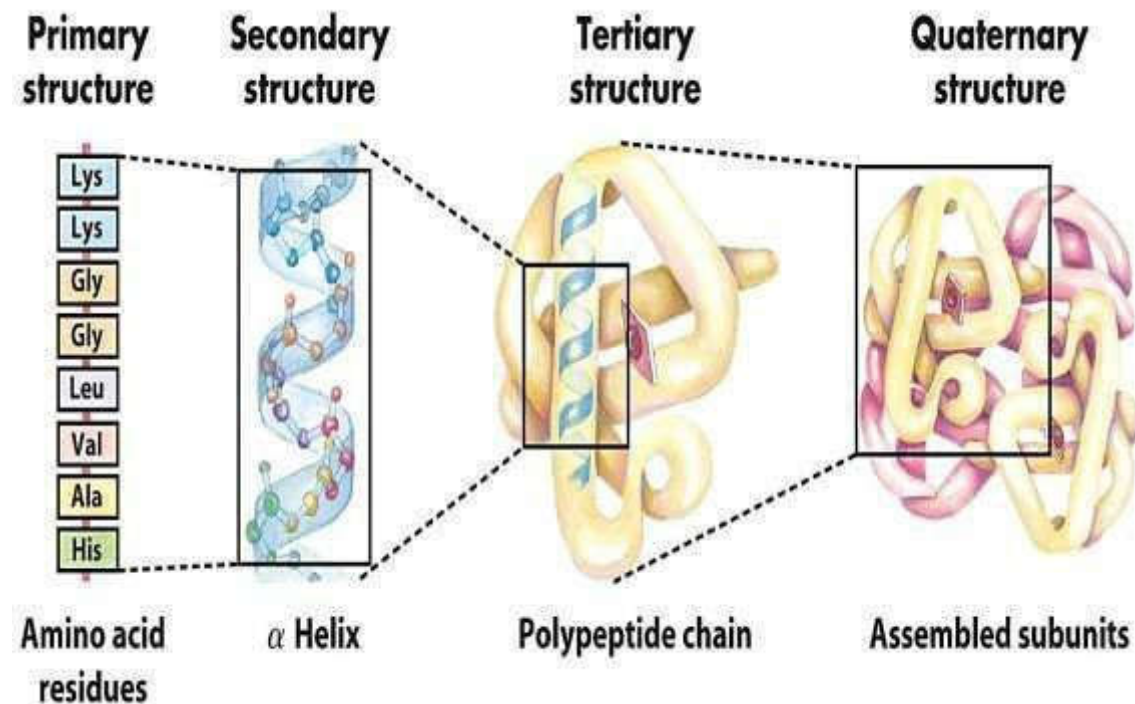
Protein Structure(Summary)

•Primary	The amino acid sequence	Glu-Arg-Phe-Gly
•Secondary	Characteristic structures that occur in many proteins (E.g. alpha helix , beta sheets)	alpha helix beta sheets
•Tertiary	Three dimensional structure of proteins	
•Quaternary	Three dimensional structure of proteins composed of multiple subunits	

Primary structure
amino acid sequence

Secondary structure
regular sub-structures

Tertiary structure
three-dimensional structure

Quaternary structure
complex of protein molecules
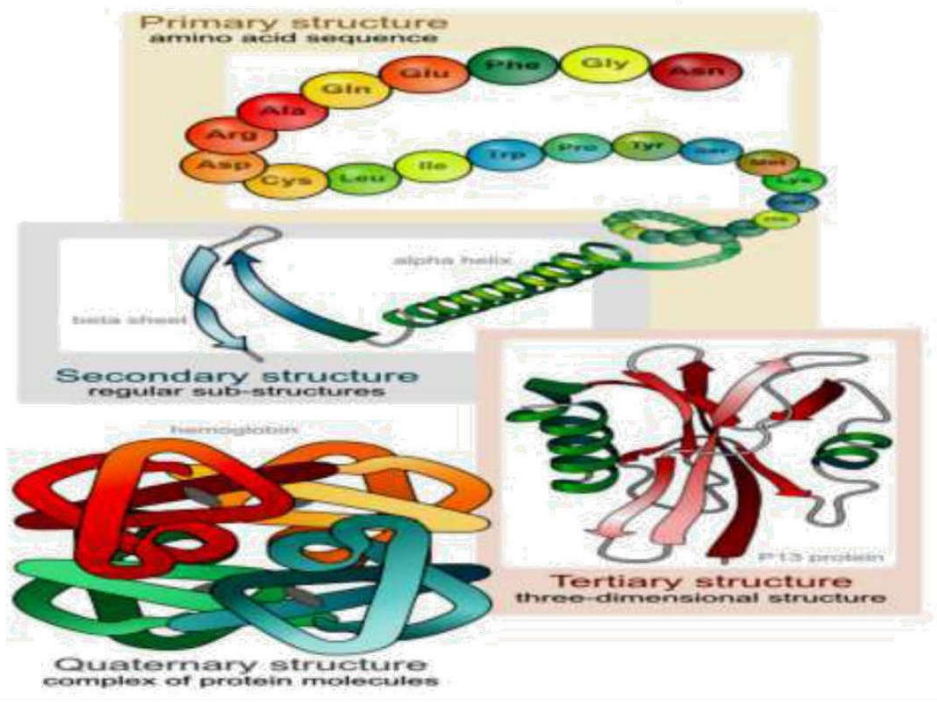
Lesson 55
Primary structure

- The primary structure of a protein refers to the **linear sequence** of amino acids in the polypeptide chain.
- The primary structure is held together by covalent bonds such as peptide bonds, which are made during the process of protein biosynthesis or translation.

- The two ends of the polypeptide chain are referred to as the **carboxyl terminus** (C-terminus) and the **amino terminus** (N-terminus) based on the nature of the free group on each extremity.
- The primary structure of a protein determines **how it folds up** into its unique three-dimensional structure, and this in turn determines the function of the protein
- The function of a protein therefore depends on its amino acid sequence
- Proteins have unique amino acid sequences, that are specified by genes**.**
- Each of the 20 amino acids incorporated in the proteins is encoded by one or more *specific* sequences of three nucleotides in DNA or RNA.
- Understanding of the primary structure of proteins is important because many genetic diseases result in proteins with abnormal amino acid sequences which cause loss or impairment of normal function.
- The defect can range from a single change in the amino acid sequence (as in **sickle cell anemia**) to deletion of a larger portion of the polypeptide chain (as in most cases of **Duchenne** muscular dystrophy)
- In Sickle cell anemia a **Glutamate** residue is replaced by **Valine** at position 6 of beta chain of Hemoglobin, resulting in decreased functioning and increased fragility of Hb.
- Duchenne Muscular dystrophy results from a large segment of gene deletion in X chromosome, resulting in small truncated **dystrophin** protein.
- Thus we know that if the primary structure is altered, the function of the protein may also be changed
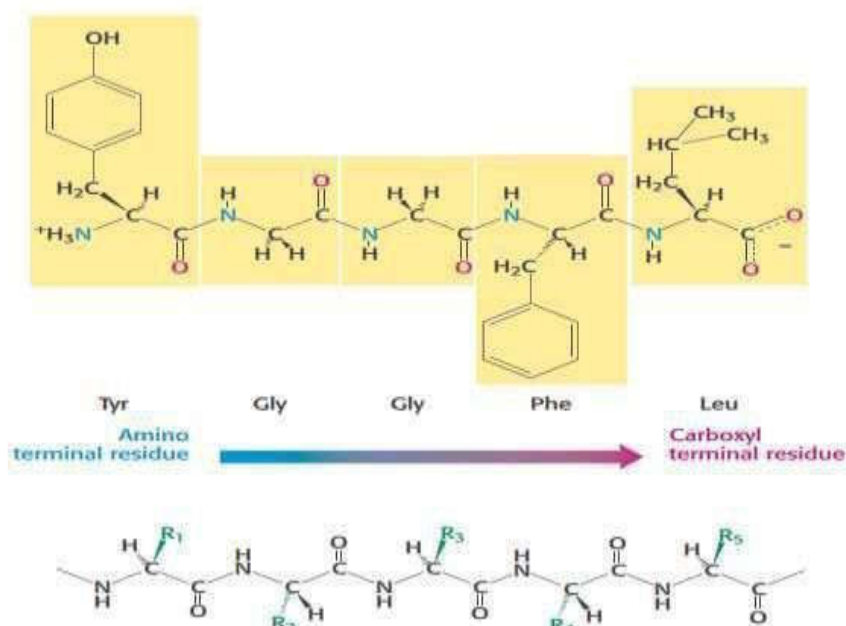
Lesson 56

Secondary structure**,** the folding of short (3- to 30-residue), contiguous segments of polypeptide into **geometrically ordered units**

The term secondary structure refers to any chosen segment of a polypeptide chain and describes the local spatial arrangement of its main-chain atoms, without regard to its relationship to other segments

There are a few types of secondary structure that are particularly stable and occur widely in

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proteins

The most prominent are the **α helix and þ conformations**

 The α Helix is a   common protein secondary structure

The simplest arrangement the polypeptide chain can assume, given its rigid peptide bonds (but free rotation around its other, single bonds), is a helical structure, called the α helix

Within the α helix, every peptide bond (except those close to each end of the helix) participates in such hydrogen bonding
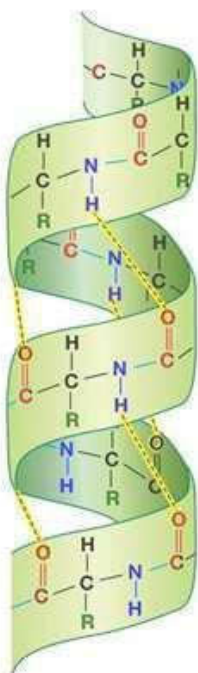
                The structure is stabilized by a hydrogen bond between the hydrogen atom attached to the electronegative nitrogen atom of a peptide linkage and the electronegative carbonyl oxygen atom of the fourth amino acid on the amino-terminal side of that peptide bond

Lesson 57

- Amino acid residues included in alpha helix have an **intrinsic propensity** to form an alpha helix, reflecting the properties of the R group.
- Amino acids most commonly found in alpha helices are **non-polar** with aliphatic side chains
- **Alanine** shows the greatest tendency to form α helices in most experimental model systems.
- Amino acids most commonly found in alpha helices are **non-polar** with aliphatic side chains
- **Alanine** shows the greatest tendency to form α helices in most experimental model systems.
- The bulk and shape of **Ser, Thr**, and **Cys** residues can destabilize an α helix if they are close together in the chain.
- The bulk and shape of **Ser, Thr**, and **Cys** residues can destabilize an α helix if they are close together in the chain.
- Amino acids with charged R groups such as **Aspartate, Lysine** residues can also disrupt the helix.

- Amino acids with charged R groups such as **Aspartate, Lysine** residues can also disrupt the helix.
- In **proline**, the nitrogen atom is part of a rigid ring, and rotation about the N-C bond is not possible
- Thus, a proline residue introduces a destabilizing kink in an α helix
- **Glycine** occurs infrequently in α helices for a different reason.
- It has more conformational flexibility than the other amino acid residues

Polymers of glycine tend to take up coiled structures quite different from an α helix

Negatively charged R groups

Aspartate	Glutamate

Positively charged R groups

Lysine	Arginine	Histidine
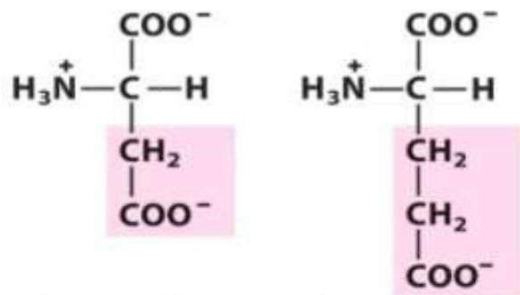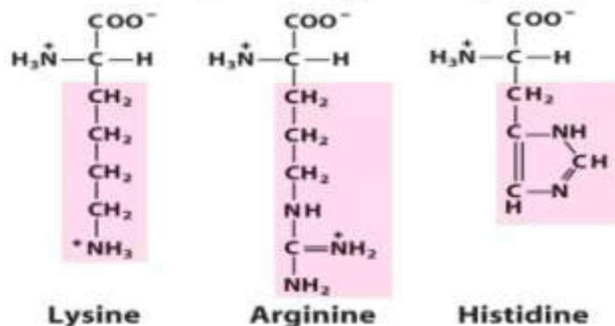
Lesson   58

The Secondary Structure

- **A very diverse group of proteins contains α-helices**
- The alpha-helical content of proteins ranges widely, from nearly none to almost 100%
- For example, the **keratins** are a family of closely related, fibrous proteins whose structure is nearly entirely α-helical.
- They are a major component of tissues such as hair, nails, hoofs and skin.
- In contrast to keratin, myoglobin, whose structure is also highly α-helical, is a globular, flexible molecule.
- Nearly all trans membrane proteins contain alpha helices in their membrane spanning domains.
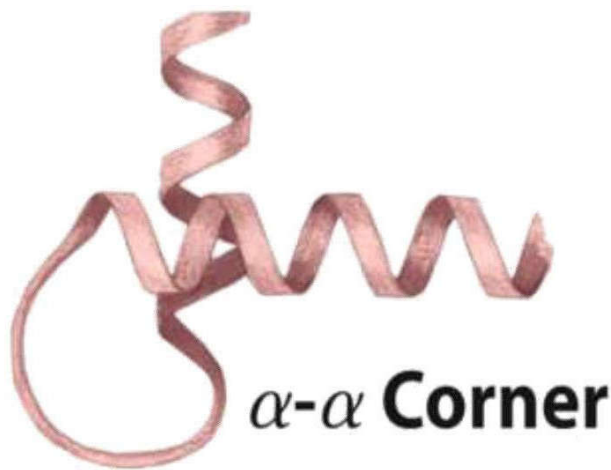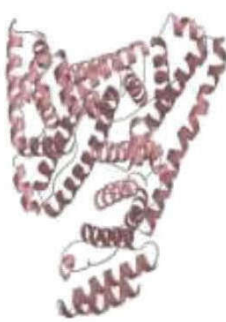
α-α **Corner**

All α

1AO6	1BCF	1GAI	1ENH
Serum albumin	Ferritin-like	α/α toroid	DNA-binding 3-helical bundle
Serum albumin	Ferritin-like	Glycosyltransferases of the superhelical fold	Homeodomain-like
Serum albumin	Ferritin	Glucoamylase	Homeodomain
Serum albumin	Bacterioferritin (cytochrome b₁)	Glucoamylase	engrailed Homeodomain
Human (Homo sapiens)	Escherichia coli	Aspergillus awamori, variant x100	Drosophila melanogaster

Lesson 59

The β Conformation organizes polypeptide Chains in β sheets

• Sheets are a second type of regular secondary structure that maximizes hydrogen bonding between the peptide backbones.
The backbone of the polypeptide chain is extended into a zigzag rather than helical structure
The zigzag polypeptide chains can be arranged side by side to form a structure resembling a series of pleats

In this arrangement called a β sheet, hydrogen bonds form between adjacent segments of polypeptide chain
The -pleated sheet is described as parallel if the polypeptide strands run in the same direction (as defined by their amino and carboxy terminals) and anti-parallel if they run in opposite direction

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Antiparallel strands are often the same polypeptide chain folded back on itself, with simple hairpin turns or long runs of polypeptide chain connecting the strands
The amino acid side chains(R groups) of each polypeptide strand alternate between extending above and below the plane of the β-sheet. Most sheets are not perfectly flat but tend to have a twist.
The individual segments that form a β sheet are usually nearby on the polypeptide chain, but can also be quite distant from each other in the linear sequence of the peptide and may even be in different polypeptide chains.
Clusters of twisted strands of sheet form the core of many globular proteins.

(a) Antiparallel

Top view

Side view

(b) Parallel

Top view

Side view

All β
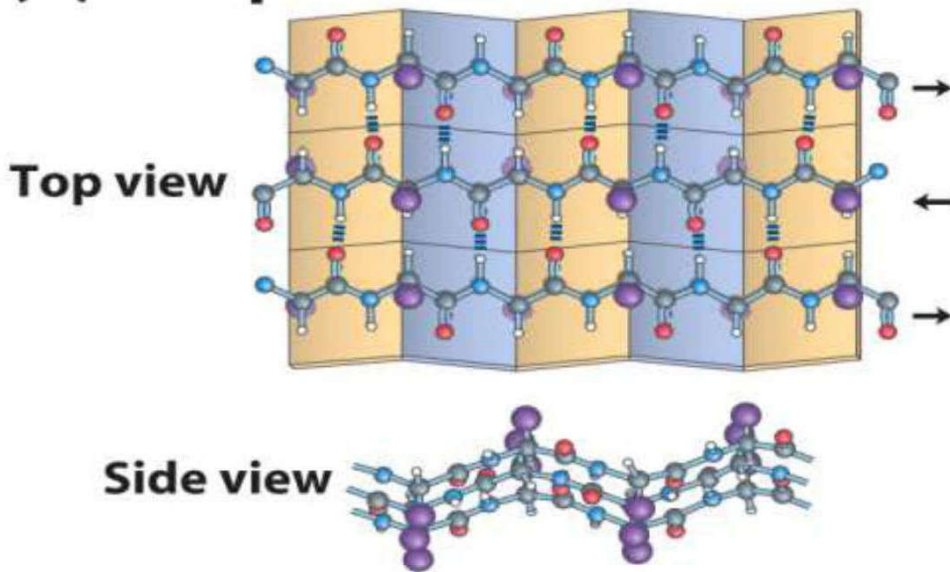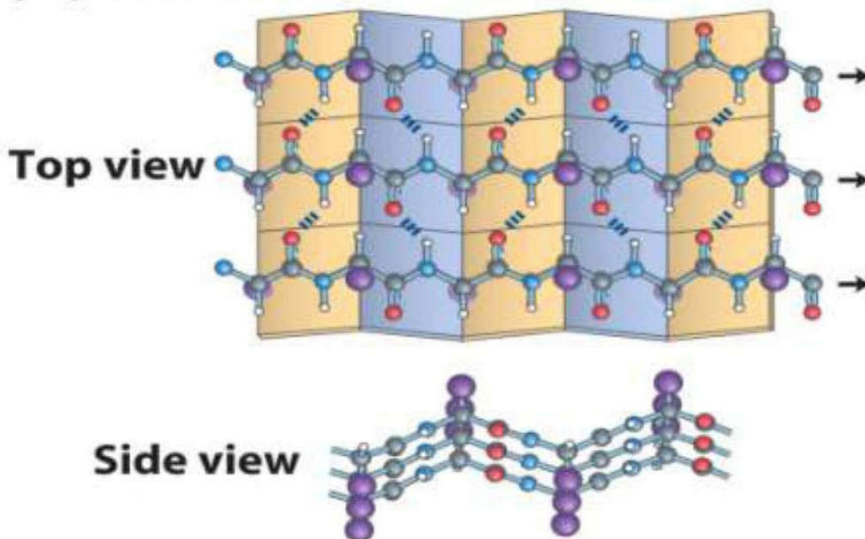
1HOE
α -Amylase inhibitor
α -Amylase inhibitor
α -Amylase inhibitor
HOE-467A
Streptomyces tendae 4158
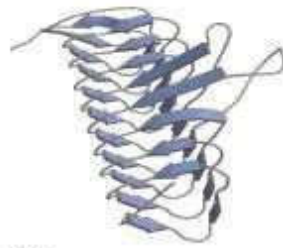
1LXA
Single-stranded left-handed β helix
Trimeric LpxA-like enzymes
UDP N-acetylglucosamine acyltransferase
UDP N-acetylglucosamine acyltransferase
Escherichia coli

1PEX
Four-bladed β propeller
Hemopexin-like domain
Hemopexin-like domain
Collagenase-3 (MMP-13),
carboxyl-terminal domain
Human (*Homo sapiens*)

1JPC
β-Prism II
α-ᴅ-Mannose-specific plant lectins
α-ᴅ-Mannose-specific plant lectins
Lectin (agglutinin)
Snowdrop (*Galanthus nivalis*)
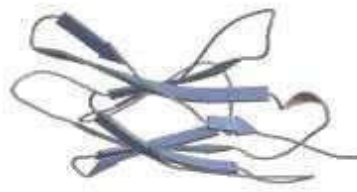
1CD8
Immunoglobulin-like β sandwich
Immunoglobulin
Antibody variable domain-like
CD8
Human (*Homo sapiens*)

Lesson 60

- In contrast to regular repeating element in the twist of an alpha Helix or a pleat of Beta sheet, **bends, loops,** and **turns are** non- regular secondary structures that do not have a repeating element.
- **Beta-bends** are short regions usually involving four successive amino acid residues.
- They often connect strands of antiparallel beta-sheets.

- β-Bends reverse the direction of a polypeptide chain, helping it form a compact, globular shape.
- The structure is a 180 degree turn involving four amino acid residues

- The carbonyl oxygen of the first residue forms a hydrogen bond with the amino-group hydrogen of the fourth residue.
- β-Bends were given this name because they often connect successive strands of antiparallel β-sheets
- Glycine and Proline residues often occur in β turns
- Glycine because it is small and flexible
- Proline because peptide bonds involving the imino nitrogen readily assume the cis configuration, a form that is particularly amenable to a tight turn

Lesson 61

- A **motif** also called a **super secondary structure** is simply a recognizable folding pattern involving two or more elements of secondary structure and the connection(s) between them.

- Structural motifs are intermediate between secondary and tertiary structures.

- A motif can be very simple, such as two elements of secondary structure folded against each other, and represent only a small part of a protein
- An example is a þ-α-þ loop.
- A motif can also be a very elaborate structure involving scores of protein segments folded together, such as the þ barrel

β-α-β **Loop**

α-α **Corner**

β **Barrel**

Twisted β **sheet**
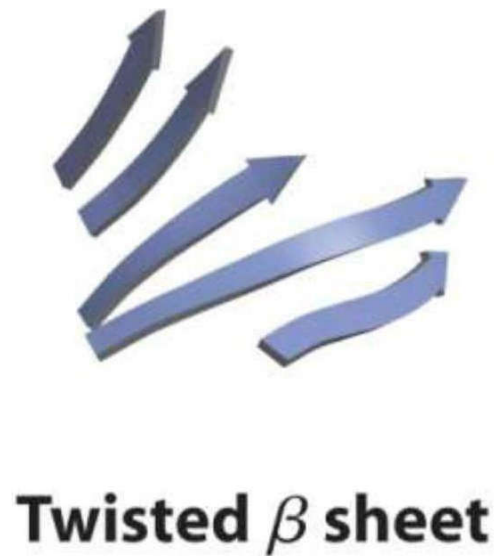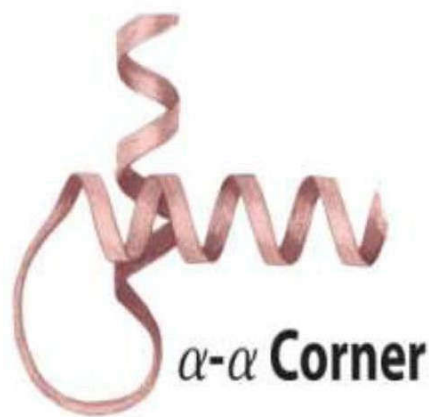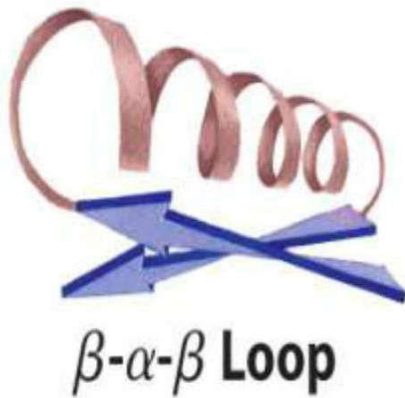
Lesson 62
The tertiary structure

- The tertiary structure of a protein is the folding pattern of the secondary structural elements into a three-dimensional conformation.
- It indicates, in three-dimensional space, how secondary structural features—helices, sheets, bends, turns, and loops—assemble to form domains and how these domains relate spatially to one another.

Domains in the Tertiary Structure

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- The tertiary structure of large complex proteins is often described in terms of physically independent regions called structural domains.
- A domain is a section of protein structure sufficient to perform a particular chemical or physical task such as binding of a substrate or other ligand.
- Each domain is formed from a continuous sequence of amino acids in the polypeptide chain that are folded into a three-dimensional structure independently of the rest of the protein.
- Two domains are connected through a simpler structure like a loop.
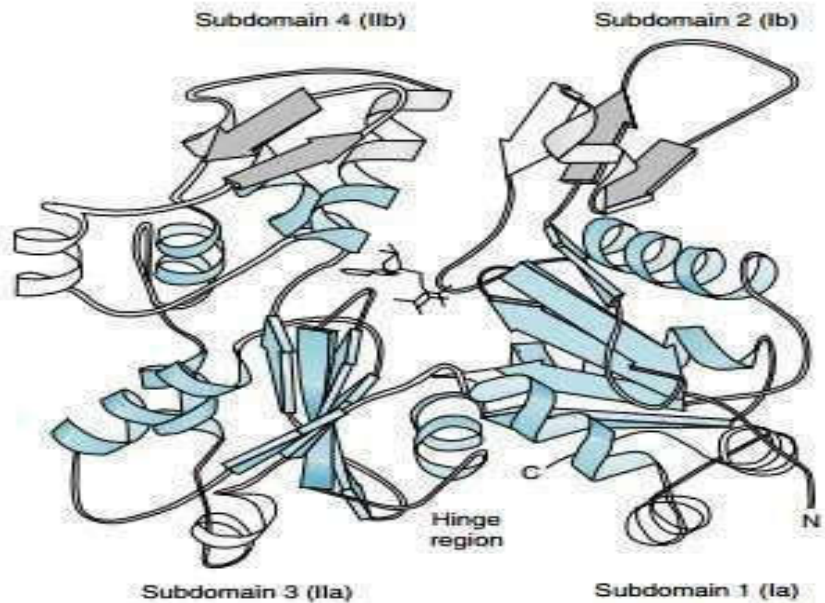
G-Actin. ATP binds in the center of the cleft. The two domains that form the cleft are further subdivided into subdomains 1–4. The overall structure is found in many ATPbinding proteins and is called the actin fold.

Lesson 63
- The Tertiary Structure
- Molecular forces that stabilise three dimensional tertiary structure include:
- Electrostatic Interactions
- Hydrophobic interactions
- Disulphide bridges
- Hydrogen bonding
- The Tertiary Structure
- The **positive** charges on the basic amino acids enables them to form ionic bonds (electrostatic bonds) with **negatively** charged groups, such as the side chains of acidic amino acids.
- The Tertiary Structure
- **Electrostatic Interactions**
- The **positive** charges on the basic amino acids enables them to form ionic bonds (electrostatic bonds) with **negatively** charged groups, such as the side chains of acidic amino acids.
- The Tertiary Structure
- The Tertiary Structure

62 | Page

- The positive charges on the basic amino acids enables them to form ionic bonds (electrostatic bonds) with negatively charged groups, such as the side chains of acidic amino acids.
- The Tertiary Structure
- The positive charges on the basic amino acids enables them to form ionic bonds (electrostatic bonds) with negatively charged groups, such as the side chains of acidic amino acids.
- The Tertiary Structure
- The positive charges on the basic amino acids enables them to form ionic bonds (electrostatic bonds) with negatively charged groups, such as the side chains of acidic amino acids.
- The Tertiary Structure
- **Hydrophobic Interactions**
- Hydrophobic Interactions occur between non-polar uncharged side chains such as between aromatic groups of phenylalanine side chains.
- The Tertiary Structure
- Hydrophobic interactions occur between non-polar uncharged side chains such as between aromatic groups of phenylalanine side chains.
- The Tertiary Structure
- **Disulfide Bridges**
- The amino acid cysteine in a protein can form a covalent disulfide bond with another cysteine molecule through spontaneous (nonenzymatic) oxidation of their sulfhydryl groups.
- The Tertiary Structure
- The amino acid cysteine in a protein can form a covalent disulfide bond with another cysteine molecule through spontaneous (nonenzymatic) oxidation of their sulfhydryl groups.
- The Tertiary Structure
- **Hydrogen bonds**
- Hydrogen bonds in which a hydrogen atom is shared by a nitrogen (or oxygen) in the peptide backbone and an oxygen atom in an amino acid side chain.
- The Tertiary Structure
- Hydrogen bonds in which a hydrogen atom is shared by a nitrogen (or oxygen) in the peptide backbone and an oxygen atom in an amino acid side chain.

charged R groups

Lysine   Arginine   Histidine

Glutamate   Aspartate
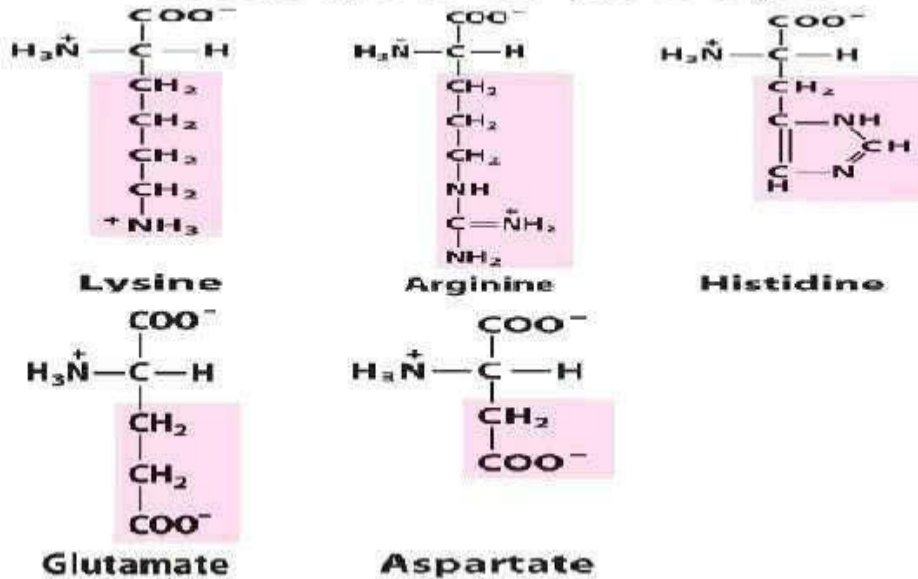
Lesson   64

The Quaternary Structure

- Some proteins contain two or more separate polypeptide chains, or subunits, which may be identical or different.
- The arrangement of these protein subunits in three-dimensional complexes constitutes **quaternary structure.**

- Many proteins have multiple polypeptide subunits (from two to hundreds)
- The association of polypeptide chains can serve a variety of functions
- A multisubunit protein is also referred to as a **multimer,** with the prefixes ―homo‖ or ―hetero‖ used to describe identical or different subunits, respectively.
- Most multimers have identical subunits
- or repeating groups of nonidentical subunits, usually in symmetric arrangements.
- The repeating structural unit in such a multimeric protein is **protomer**
- Assembly into a multisubunit structure increases the stability of a protein.

(a)   (b)
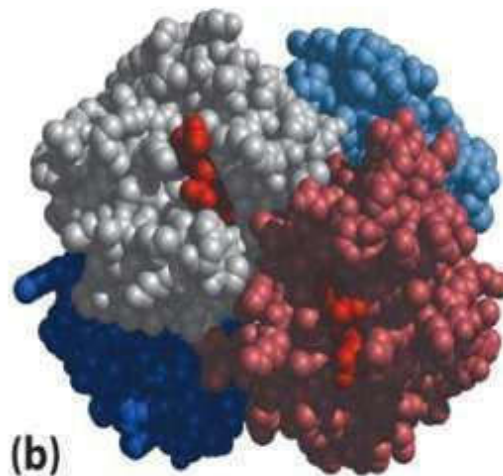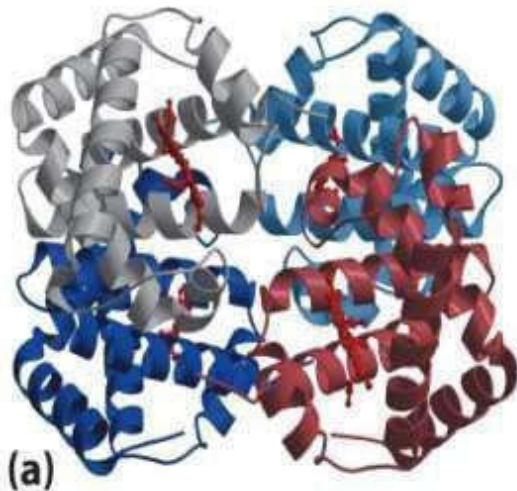
X-ray diffraction analysis of deoxyhemoglobin shows how the four polypeptide subunits are packed together. (a) A ribbon representation. (b) A space-filling model. The alpha subunits are shown in gray and light blue; the beta subunits in pink and dark blue. Note that the heme
groups (red) are relatively far apart.
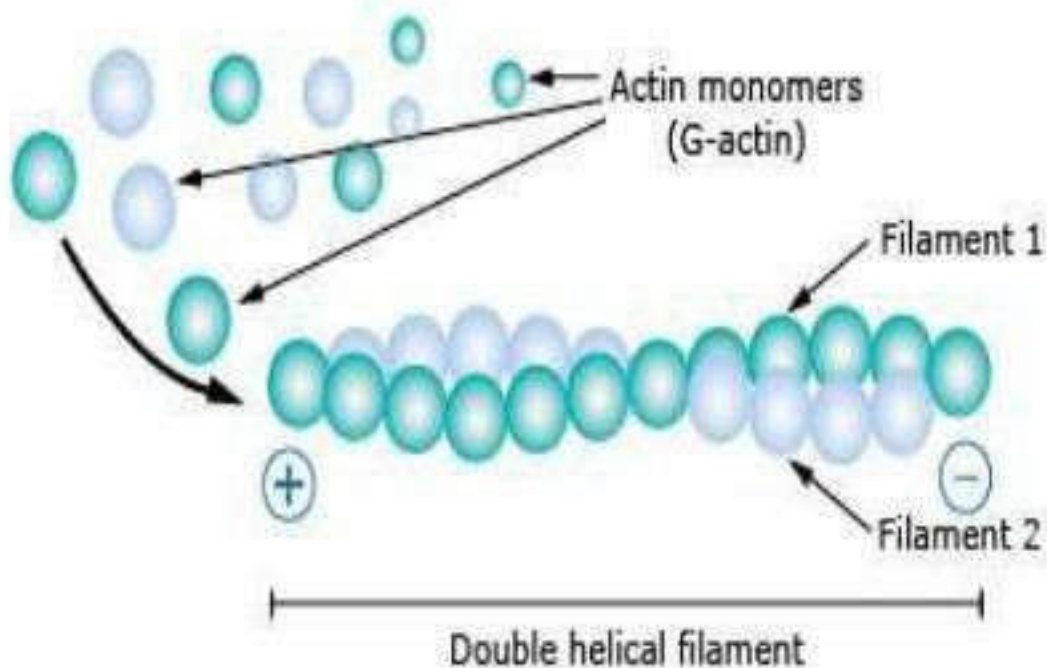
Actin filament is a homo polymer. G-actin, forms the basic unit for actin filaments. Actin filaments together with their associated motor proteins (e.g. myosin superfamily) form an elaborate network known as the actin cytoskeleton involved inn functions including cell motility, muscle contraction, cell division, cytokinesis, vesicle and organelle movement and cell signaling.

Lesson 65
Perks of The Quaternary structure
- The increase in size increases the number of possible interactions between aminoacid residues and therefore makes it more difficult for a protein to unfold and refold.
- A multisubunit structure has many advantages besides increased stability.
- It may enable the protein to exhibit cooperativity between subunits in binding ligands (illustrated later with hemoglobin)
- Or it may form binding sites with a high affinity for large molecules (illustrated with antigen binding to the immunoglobulin molecule IgG).
- An additional advantage of a multi-subunit structure is that the different subunits can have different activities and cooperate in a common function.
- For example enzymes that have regulatory subunits or exist as multiprotein complex, such as Pyruvate Dehydrogenase.
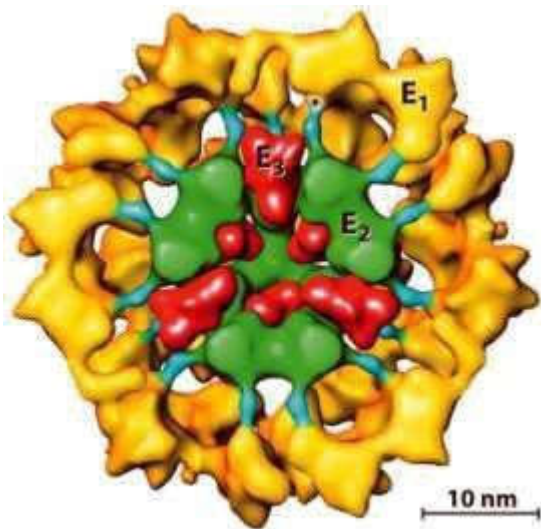
- **E1 , pyruvate dehydrogenase;**

- **E2, dihydrolipoyl transacetylase; and**

- **E3,dihydrolipoyl dehydrogenase**
  (PDC) is a complex of three enzymes that convert pyruvate into acetyl-CoA by a process called pyruvate decarboxylation

Lesson 66

Protein Folding

Protein folding is the process by which a protein structure assumes its functional shape or conformation.

- Protein Folding

It is the physical process by which a polypeptide folds into its characteristic and functional three-dimensional structure from random coil

- Protein Folding

- Protein Folding
- The overall three-dimensional structure of a protein must meet certain requirements to enable the protein to function in the cell or extracellular medium of the body.
- Protein Folding
- The first requirement is the creation of a binding site that is specific for just one molecule, or a group of molecules with similar structural properties.
- The specific binding sites of a protein usually define its functional role.
- Protein Folding
- Moreover, The three dimensional structure must have an external surface appropriate for its environment (e.g., plasma proteins contain polar amino acids on the surface to remain soluble in an aqueous environment.)
- Protein Folding
- Protein Folding
- Proteins are dynamic molecules that can fold into their functionally competent conformation in milliseconds

- Protein Folding
- A protein is called a native protein if its amino acid composition and molecular conformation are unchanged from that found in natural states.
- Protein Folding
- Folding into the native state does not involve a haphazard search of all possible structures.
- The native conformation of a Protein is dictated thermodynamically.
- Protein Folding
- The number of potential conformations of even a relatively small—15-kDa—polypeptide is unbelievably vast
- Proteins are guided through this vast labyrinth of possibilities by thermodynamics
- Protein Folding
- Thermodynamic stability is not evenly distributed over the structure of a protein molecule.
- It has regions of high and low stability;

variations in the stability of regions within a protein are often essential for protein to function.

The regions of low stability allow a protein to alter its conformation between two or more states, such as an inactivated and activated enzyme.
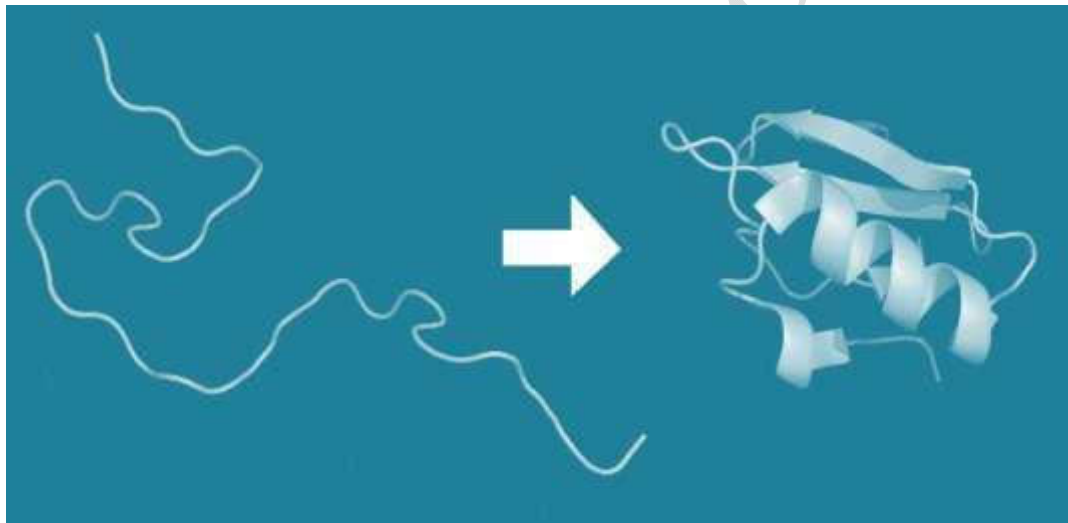
Such as binding site for substrates in enzymes, ligands in receptors, for extracellular matrix in cytoskeletal proteins and for antigens in immunoglobins and so forth.

Lesson 67

- Proteins are dynamic molecules that can fold into their functionally competent conformation in milliseconds
- A protein is called a native protein if its amino acid composition and molecular conformation are unchanged from that found in natural states
- And which is operative and functional
- Folding into the native state does not involve a haphazard search of all possible structures.
- Protein folding in cells takes place in an orderly and guided fashion.

- Protein folding generally occurs via a stepwise process.
- In the first stage, as the newly synthesized polypeptide emerges from the ribosome, short segments fold into secondary structural units that provide local regions of organized structure
- Then, each element of secondary or super-secondary structure facilitates proper folding by directing the folding process toward the native conformation and away from unproductive alternatives.
- This step-wise folding of the proteins is dictated by thermodynamics resulting in a formation of native form, which is also the most energetically favoured form.

Computer simulated Protein folding showing *local assembly* **followed by** *global protein folding.*

Lesson 68
- Protein Folding
- The native conformation of a protein is dictated thermodynamically.
- The biologically relevant—or native—conformation of a protein generally is that which is most energetically favored
- The three dimensional structure of a native protein in its normal physiological state is the one in which the Gibbs free energy of the whole system is lowest.
- The free energy change for a process at constant pressure is:
- **G = H – T ΔS**
- **G = Free Energy**
- **H = Enthalpy**
- **S= Entropy**
- Folding of a globular protein is a thermodynamically favored process, i.e. G must be negative.
- **G = H – T ΔS**

- The folding process involves going from a multitude of random-coil conformations to a single folded structure.
- The folding process involves a decrease in randomness and thus a decrease in entropy - **S** and an overall positive contribution to G. This decrease in entropy is termed ―conformational entropy‖.
- Difference in energy (free energy) between folded (native) and unfolded (denatured) state is small, 5-15 kcal/mol.
- Protein Folding
- It is very difficult to determine how all factors blend together to give overall DGfolding

  Use of averages contributions, but

  Each protein is unique Large

  stabilization factors, Large

  destabilization factors,

  But small difference between them

     G = H – T ΔS
- Small **G** is necessary because too large a free energy change would mean a very stable protein, one that would never change.
- However, structural flexibility is important to protein function, and proteins need to be degraded.
- Enthalpy and entropy differences balance each other, and   **G** is a small positive number.
- Enthalpy is the total energy of the system. **Entropy** is a measure of the randomness or disorder in a system. **Entropy of a system always tend to increase to a maximum** value.

Lesson 69

Protein Folding

- The native state has a smaller Gibbs free energy than the denatured state. The stability of the protein depends on the solvent–solvent, protein–solvent, and protein–protein interactions.

- The free energy of a protein molecule is influenced by

- (1) the hydrophobicity,

- (2) hydrogen bonds,

- (3) electrostatic interactions, and

- (4) the conformational entropy due to the restricted motion

- **Entropy** is a measure of the randomness or disorder in a system.

- According to Second Law of Thermodynamics: **The entropy of a system will tend to increase to a maximum** value.

The folding process involves a decrease in randomness and thus a decrease in entropy - **S** and an overall positive contribution to G. This decrease in entropy is termed —conformational entropy‖.

- the hydrophobic effect and hydrogen bonds are the major stabilizing contributions which counteract entropy.

- Starting from the unfolded protein, the polypeptide chain has to fold partially in order to bring together the residues that need to form the contacts stabilizing the native structure.

- The constrained polypeptide chain has smaller entropy, which means higher Gibbs free energy.

- As native contacts form, the enthalpy term decreases, the protein is stabilized.

- Thermodynamic stability is not evenly distributed over the structure of a protein molecule.

- It has regions of high and low stability; variations in the stability of regions within a protein are often essential for protein to function.

- The rate limiting step in the folding process is the formation of the transition state, i.e., the conformation that has the highest Gibbs free energy on the folding pathway
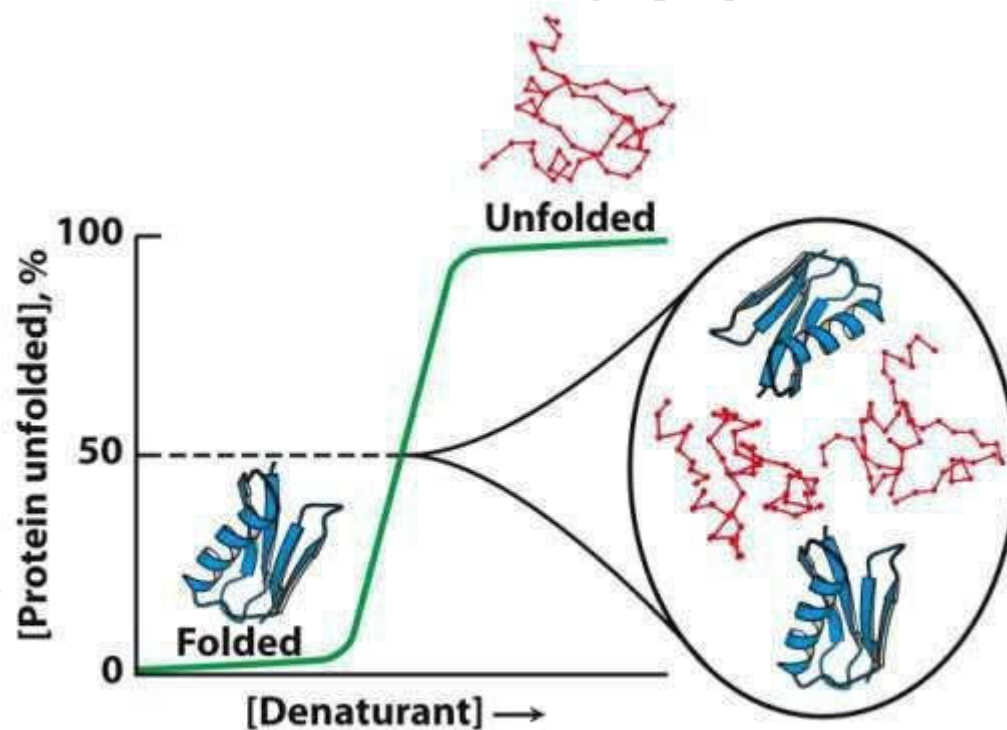
Figure 2.57
Biochemistry, Seventh Edition
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Entropy is maximum at unfolded state

The regions of low stability allow a protein to alter its conformation between two or more states, such as an inactivated and activated enzyme.
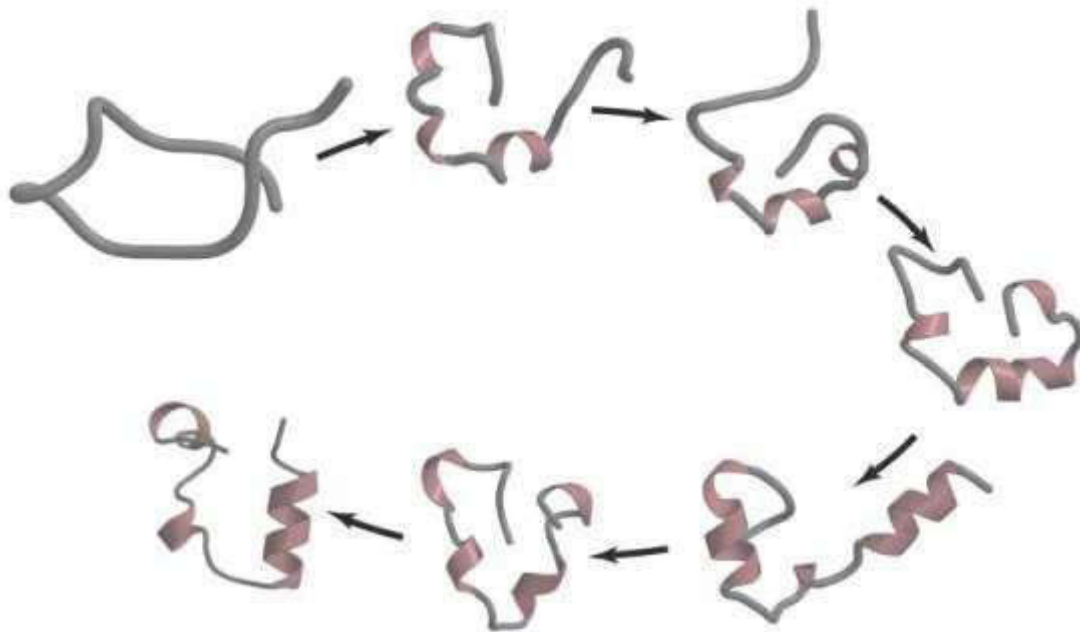
Lesson 70

- Protein Folding

- In the cell, not all proteins fold into their native conformation on their own.

- As the protein folds and refolds while it is searching for its native low energy state, it passes through many high-energy conformations that slow the process

- These high energy conformations are called kinetic barriers.

- Cells employ auxiliary proteins to overcome these kinetic barriers.

- These auxillary proteins are called chaperones.

- Chaperone use energy provided by ATP hydrolysis to assist in the folding process

- **Chaperones** participate in the folding of over half of mammalian proteins.

- They prevent immature folding of the nascent polypeptide and help in the final native protein formation.

- The hsp70 family of chaperones binds short sequences of hydrophobic amino acids in newly synthesized polypeptides.

- Protein Folding

- Chaperones prevent aggregation, thus providing an opportunity for the formation of appropriate secondary structural elements.

- Protein Folding

- Protein Folding

- They also unfold proteins prior to their insertion through the membrane of mitochondria and other organelles.

Lesson 71

Protein Folding

- The hsp60 family of chaperones, sometimes called **chaperonins,** differ in sequence and structure from hsp70 and its homology

- Hsp60 acts later in the folding process, often together with an hsp70 chaperone

- Hsp60 chaperonins form a multi-subunit barrel-shaped structure

- The unfolded protein fits into the barrel cavity that excludes water and serves as a template for the folding process.

- Chaperone proteins can also "rescue" unfolded proteins that have become thermodynamically trapped in a misfolded dead end by unfolding hydrophobic regions and providing a second chance to fold productively

- Finally, the folding pathways of some proteins require two enzymes that catalyze isomerization reactions.

- Protein disulfide isomerase (PDI) is a widely distributed enzyme that catalyzes the interchange, or shuffling, of disulflde bonds until the bonds of the native conformation are formed.
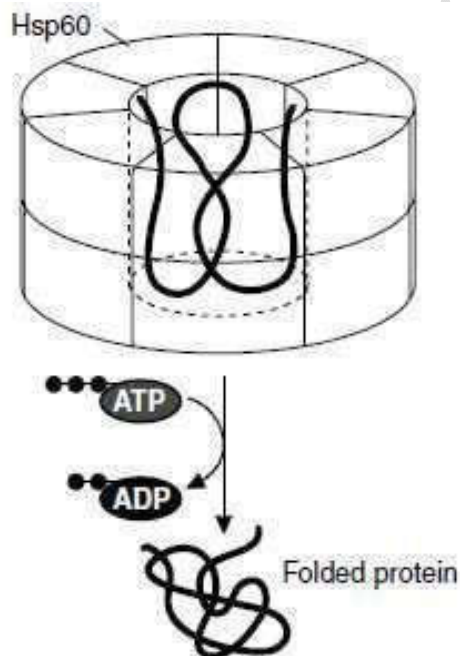
The Hsp60 class of protein has a barrel shape into which the protein fits. It acts as a template, binding and rebinding portions of the unfolded protein until folding is completed. It hydrolyzes many ATP bonds to provide energy for the process.

Lesson 72

Protein Misfolding

- Despite the many processes that assist in protein folding, misfolding does occur.

- Misfolding of proteins may occur spontaneously

- or caused by a mutation in a particular gene, producing an altered protein.

- In addition some apparently normal proteins can, after abnormal proteolytic cleavage, take on a unique conformational state

- That leads to the formation of long fibrillar protein assemblies consisting of β pleated sheets

- Many conditions, including

- Alzheimer's disease

- Type 2 diabetes,

- Huntington's disease and

- Parkinson's disease, arise from a common misfolding mechanism.

- In most cases, a soluble protein that is normally secreted from the cell is secreted in a misfolded state

- and converted into an insoluble extracellular amyloid fiber.

- The diseases are collectively referred to as amyloidoses.

- Amyloidosis is a generic term that refers to the extracellular tissue deposition of fibrils composed of low molecular weight of a variety of proteins..

- Amyloidoses may be

- organ specific or

- generalized (systemic).

- Primary systemic amyloidosis is caused by deposition of fibrils consisting of misfolded immunoglobulin light chain

- Examples of organ-specific amyloidoses include:

- **Alzheimer's disease** due to deposition of amyloid-b protein cleaved from amyloid precursor protein (APP).

- Islet amyloid polypeptide (IAPP) is commonly seen in diabetes mellitus type 2 and is caused by deposition of amylin in pancreatic islets.

- It has been suggested that the disease-causing mechanism in Huntington's disease (and the other polyglutamine disorders) is the ability of polyglutamine to undergo a conformational change that can lead to the formation of very stable anti-parallel beta-sheets; more specifically, amyloid structures
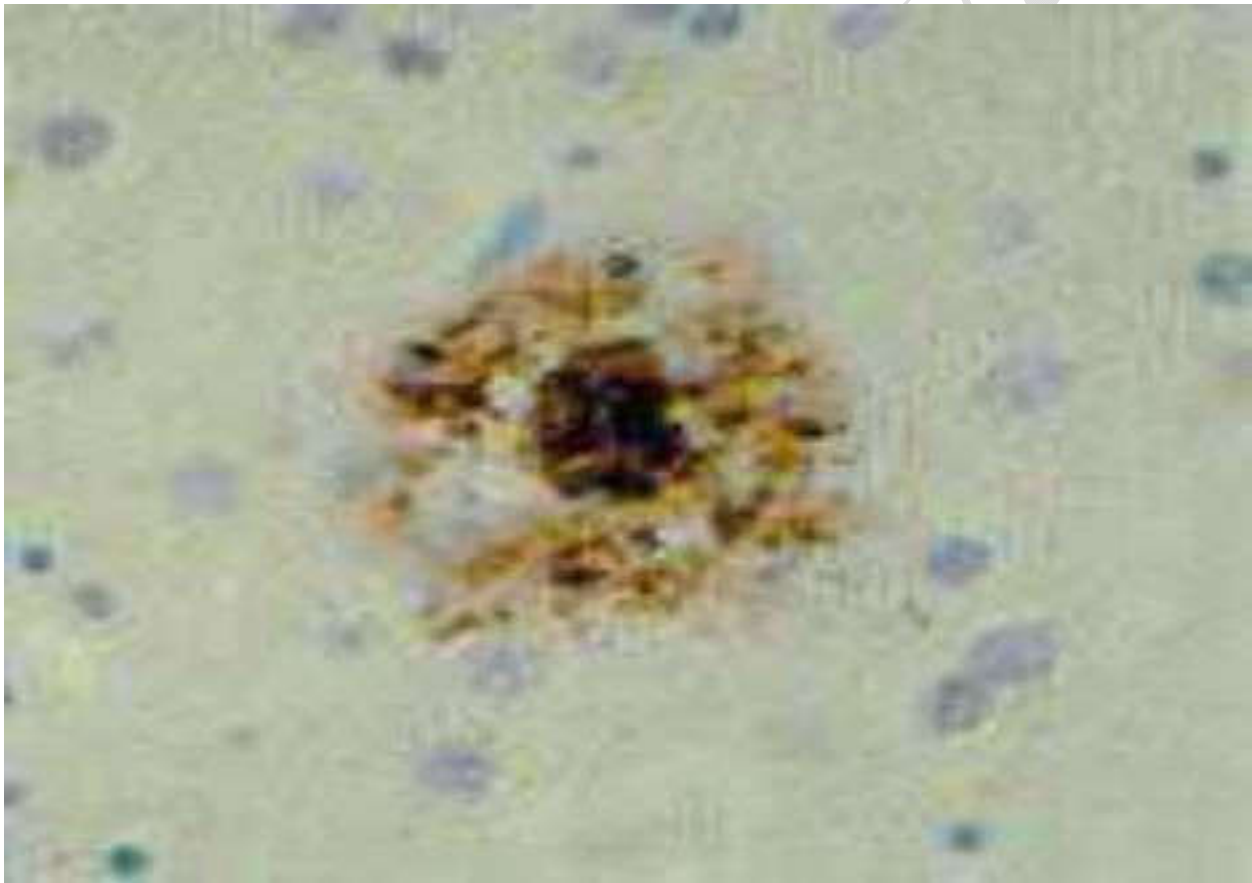
Photomicrograph of amyloid plaques in a section of temporal cortex from a patient with Alzheimer's disease

Alzheimer's is a type of dementia that causes problems with memory, thinking and behaviour. In August 1994, at the age of 83, Reagan was diagnosed with <u>Alzheimer's disease.</u> Died in 2004.

Topic 73

Protein Denaturation

- A loss of three-dimensional structure sufficient to cause loss of function is called denaturation

(Electrostatic bonds, disulfide bonds, Specific hydrogen bonding, Hydrophobic bonds)

- The denatured state does not necessarily equate with complete unfolding of the protein and randomization of conformation

- Under most conditions, denatured proteins exist in a set of partially folded state

Denaturing agents can disrupt the tertiary and secondary structure of a protein and destroy the protein's biological functions.

Denatured protein

Native protein
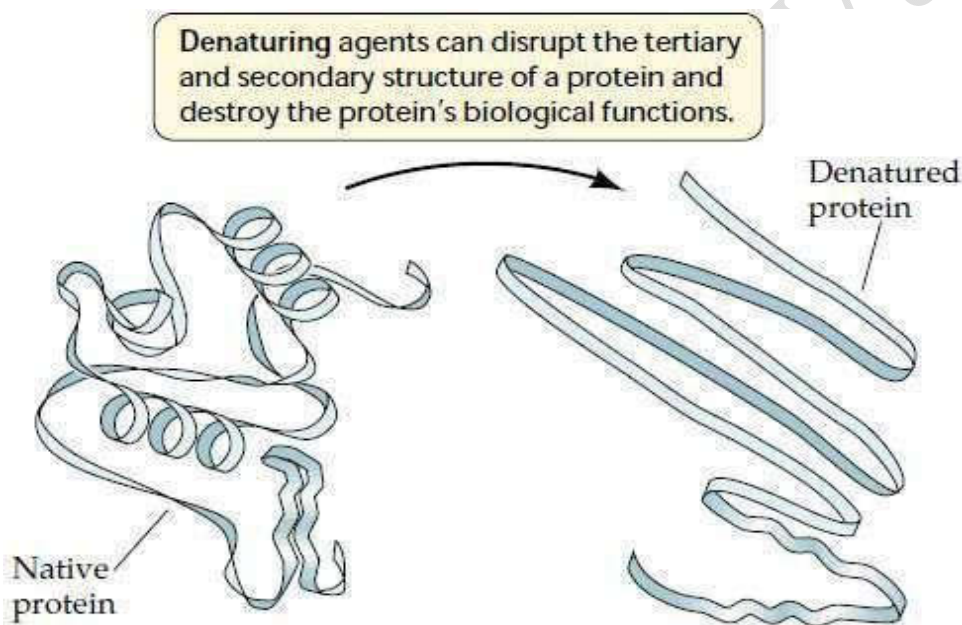
- Most proteins can be denatured by heat,

- which has complex effects on the weak interactions in a protein (primarily hydrogen bonds).

- Organic solvents, urea, and detergents act

- primarily by disrupting the hydrophobic interactions that make up the stable core of globular proteins;

- Extremes of pH alter the net charge on the protein, causing disruption of electrostatic interactions

- And the disruption of some hydrogen bonding.

- Protein Denaturation

- When milk curdles, the acidity increases.

- Thermal denaturation by cooking.

- Mechanical denaturation when whisking an egg.

- Perming hair breaks then reforms the disulphide bonds.

- The main purpose of beating an egg is to "denature" the protein within the egg. Proteins are long chains of amino acids and they have lots of internal chemical bonds, which hold them together into tightly contained units. When a protein is denatured, those internal bonds break and the amino acid chains unravel and become elongated. At the same time, atoms that were previously bonded (as part of the internal bonds I mentioned) become available to bond with other molecules

Topic 74

- Certain proteins denatured by heat, extremes of pH, or denaturing reagents

- Regain their native structure and their biological activity if returned to conditions in which the native con-formation is stable.

- At Very High or Low pH. At Very High Temperatures.By Heavy Metal Ions.By Small Polar Molecules

-

- This process is called renaturation

- Unfolded proteins generally retain a number of contacts and regions of secondary structure that facilitate the refolding process

- A classic example is the denaturation and renaturation of ribonuclease A

- Purified ribonuclease A denatures completely in a concentrated urea solution in the presence of a reducing agent.

Native state; catalytically active.

addition of urea and mercapto-ethanol

Unfolded state; inactive. Disulfide cross-links reduced to yield Cys residues.
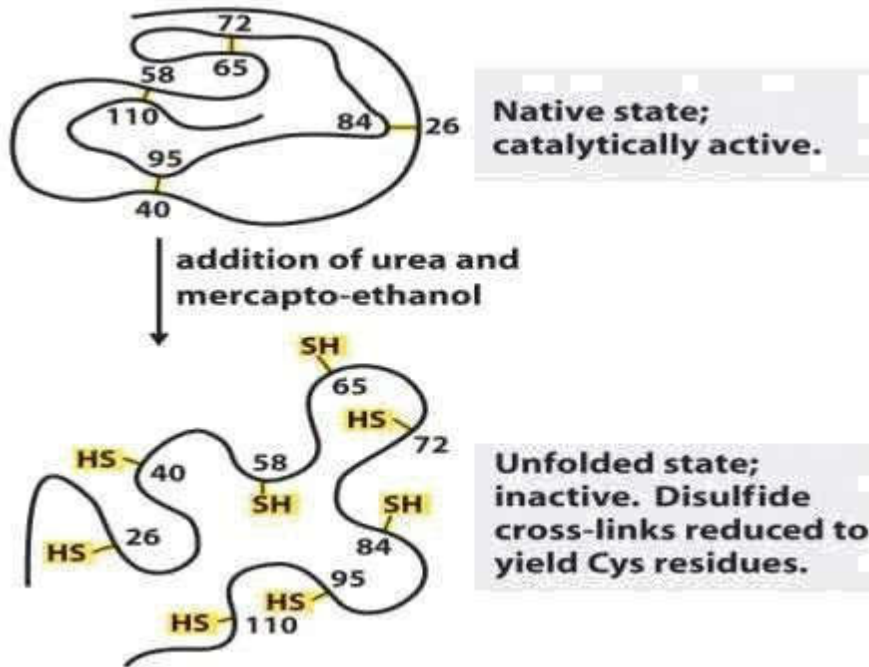
- When the urea and the reducing agent are removed, the randomly coiled, denatured ribonuclease spontaneously refolds into its correct tertiary structure, restoring its catalytic activity

Unfolded state; inactive. Disulfide cross-links reduced to yield Cys residues.

removal of urea and mercapto-ethanol

Native, catalytically active state. Disulfide cross-links correctly re-formed.
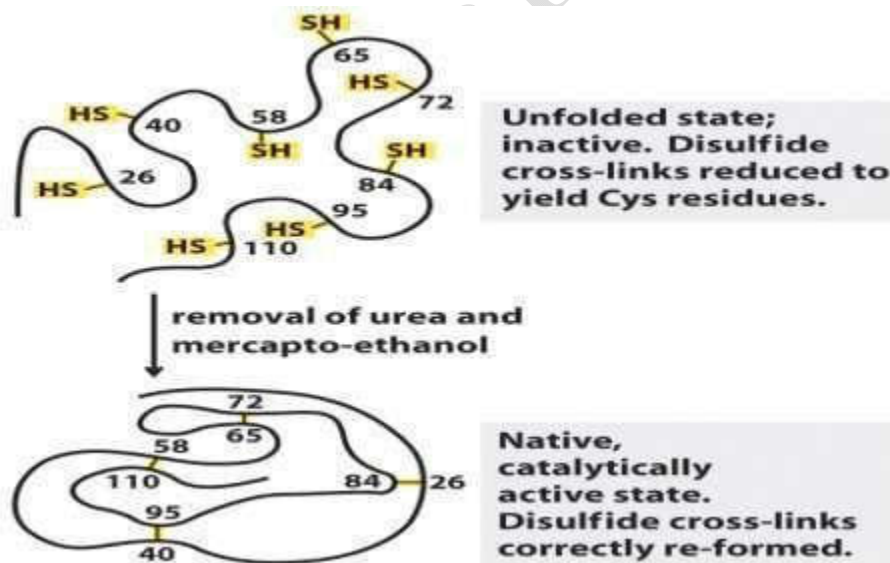
denatur   renatur

Incubate   100-fold
protein   dilution of
in protein
guanidine

- This proofs that denaturation of some proteins is reversible.

- Which tells us that primary structure of a protein determines its three-dimensional conformation.

Topic 75

Reversible binding of a protein to a ligand **Oxygen-Binding Proteins**

- The functions of many proteins involve the reversible binding of other molecules.

- A molecule bound reversibly by a protein is called a **ligand.**

- A ligand may be any kind of molecule, including another protein.

- The transient nature of protein ligand interactions is critical to life, allowing an organism to respond rapidly and reversibly to changing environmental and metabolic circumstances.

- A ligand is a small molecule that is able to bind to proteins by weak interactions such as ionic bonds, hydrogen bonds, Van der Waals interactions, and hydrophobic effects. In some cases, a ligand also serves as a signal triggering molecule. A ligand can be a substrate inhibitor, activator or a neurotransmitter.

- A ligand binds at a site on the protein called **the binding site**, which is complementary to the ligand in

  - size,

  - shape,

  - charge,

عمر غفور

- hydrophobicity

– This *complementarity* of protein ligand binding gives the interaction a great deal of specificity.

- **Binding of IgG to an antigen**
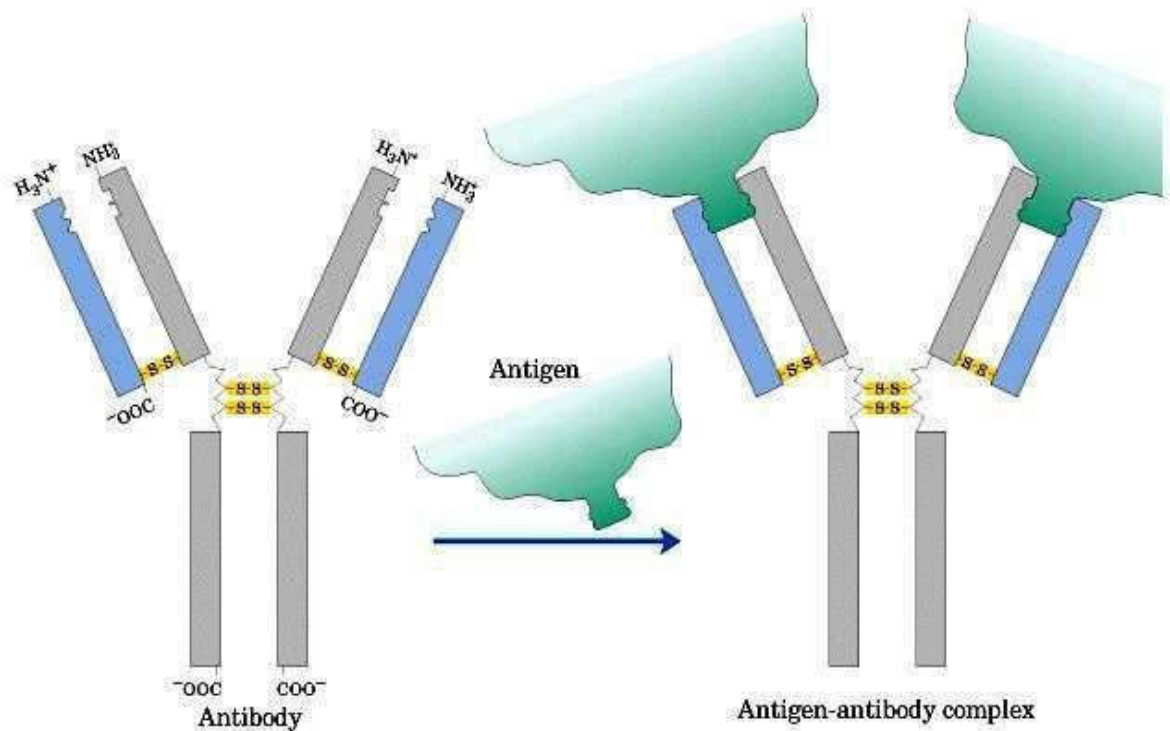
- The protein can discriminate among thousands of different molecules in its environment and selectively bind only one or a few similar compounds.

- A given protein may have separate binding sites for several different ligands

- The binding of a protein and Iigand is often coupled to a conformational change in the protein that makes the binding site more complementary to the ligand, permitting tighter binding

- The structural adaptation that occurs between protein and Iigand is called **induced fit.**

- Reversible binding of ligands is essential for the function of gloubular proteins

    – Specificity of ligands and binding sites

    – Ligand binding is often coupled to conformational changes, sometimes quite dramatic (Induced Fit)

- In multisubunit proteins, conformational changes in one subunit can affect the others (Cooperativity)

– Interactions can be regulated

- Illustrated by:

  – Hemoglobin, antibodies, and muscle contraction

Topic 76

- **Oxygen-Binding Proteins**

- **Myoglobin and hemoglobin**

- These two molecules illustrate almost every aspect of that most central of biochemical processes:

- The reversible binding of a ligand to a protein

- Oxygen is poorly soluble in aqueous solutions and cannot be carried to tissues in sufficient quantity if it is simply dissolved in blood plasma.

- Diffusion of oxygen through tissues is also ineffective over distances greater than a few millimeters

- The evolution of larger, multicellular animals depended on the evolution of proteins that could transport and store oxygen

- Myoglobin is composed of a single polypeptide chain that has one O_2 binding site.

- Hemoglobin is a tetramer in which each subunit has a strong sequence homology to myoglobin and contains an O_2 binding site.

- Myoglobin and hemoglobin are two oxygen-binding proteins with a very similar

- primary structure

- Hemoglobin is a tetramer composed of two different types of subunits (2α and 2β polypeptide chains, referred to as two $\alpha\beta$ protomers

Heme group

Myoglobin   β subunit of hemoglobin
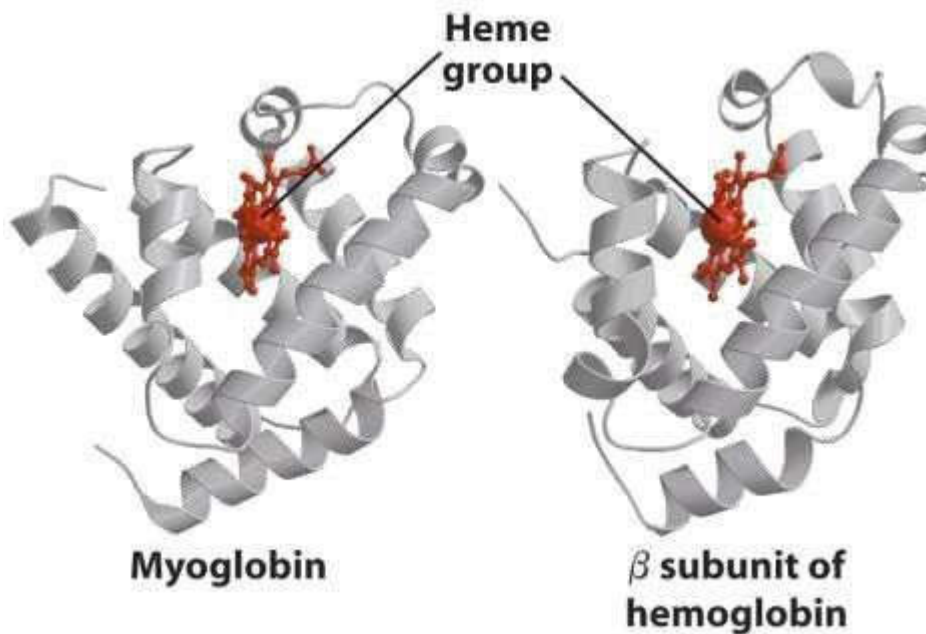
- Each subunit has a strong sequence homology to myoglobin.

- We will compare the;

- structure and

- functional relation of each protein in the subsequent discussion to see how both these proteins are suited to perform their required function in their relative sites in the body.

Topic 77

Reversible binding of a protein

- The tertiary structure of oxygen binding globins consists of;

- Eight α-helices.

- The helices create a

hydrophobic O_2

binding pocket containing;

- tightly bound heme with an iron atom **Ferrous** (Fe^{2+}) in its center.

- 1.Globin. 2.Prosthetic group i.e heme composed of protoporphyri IX ring containing iron as ferrous

- This iron bound heme is an example of prosthetic group.

- **A prosthetic group** is a compound permanently associated with a protein and contributes to the protein's function.

- **Prosthetic group** is a tightly bound, specific non-polypeptide unit required for the biological function of some proteins. The **prosthetic group** may be organic (such as a vitamin, sugar, or lipid) or inorganic (such as a metal ion), but is not composed of amino acids.

- Heme consists of a complex organic ring structure, **protoporphyrin IX**, to which is bound a single iron atom in its **ferrous (Fe^{2+}) state**

- The iron atom has six bonds,

- four to nitrogen atoms that are part of the flat porphyrin ring system

- and two perpendicular to the porphyrin
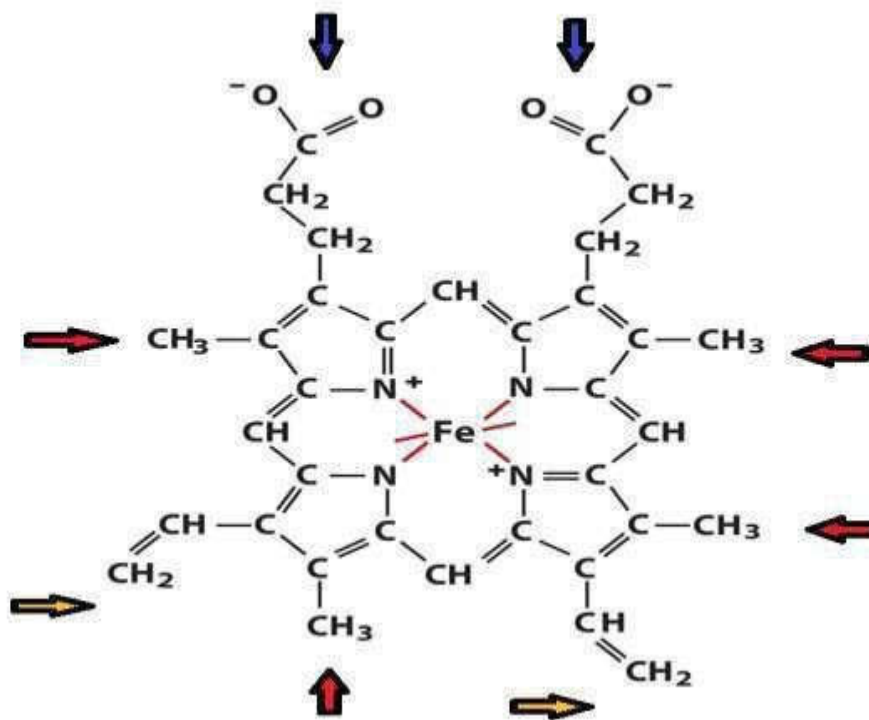
Negatively charged propionate (blue) groups on the porphyrin ring interact with arginine and histidine side chains from the hemoglobin, and the hydrophobic methyl(red) and vinyl(yellow) groups that extend out from the porphyrin ring interact with hydrophobic amino acid side chains from hemoglobin. All together, there are approximately 16 different interactions between myoglobin.

ht
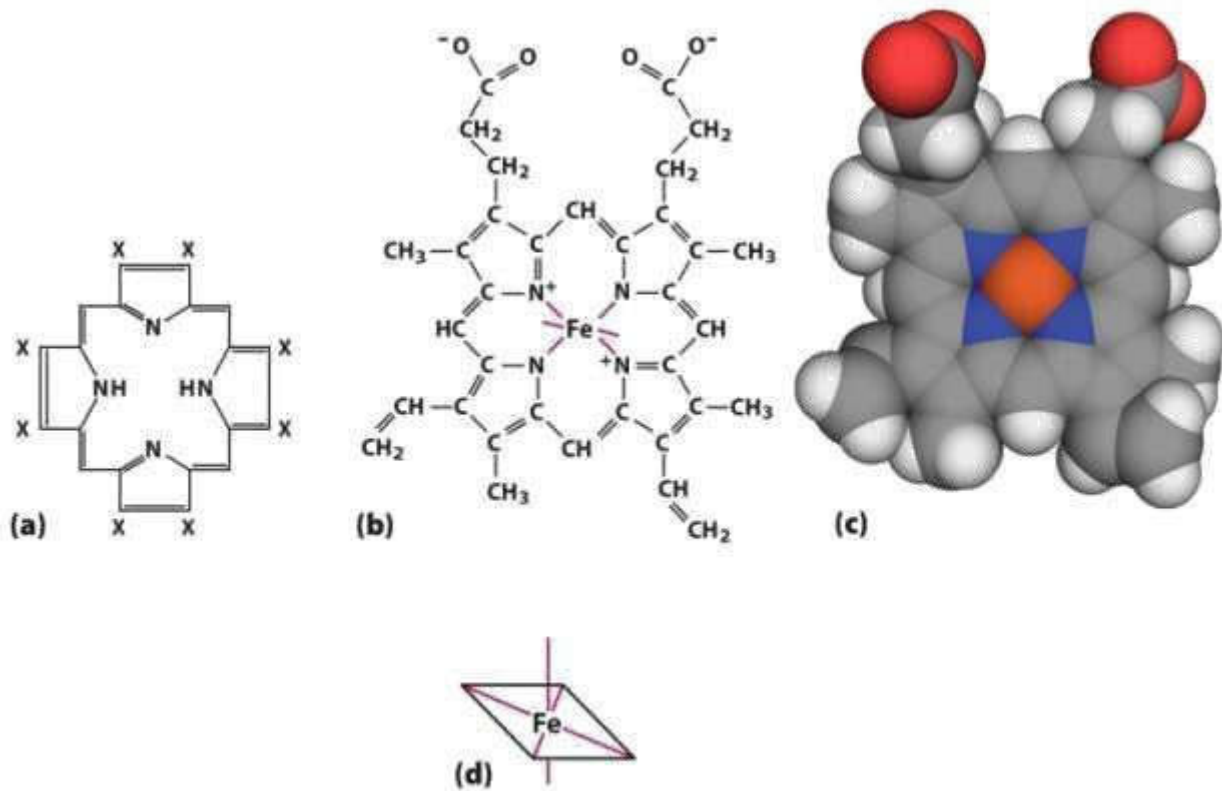
Figure 5-1
Lehninger Principles of Biochemistry, Sixth Edition
© 2013 W. H. Freeman and Company

FIGURE 5–1 Heme. The heme group is present in myoglobin, hemoglobin, and many other proteins, designated heme proteins. Heme consists of a complex organic ring structure, protoporphyrin IX, with a bound iron atom in its ferrous (Fe^{2+}) state.

- Porphyrins, of which protoporphyrin IX is only one example, consist of four pyrrole rings linked by methene bridges, with substitutions at one or more of the positions denoted X.(b,

     Two representations of heme (derived from PDB ID 1CCR). The iron atom of heme has six coordination bonds: four in the plane of, and bonded to, the flat porphyrin ring system, and (d) two perpendicular to it.

     Negatively charged propionate groups on the porphyrin ring interact with;

     Arginine and

     Histidine side chains from the hemoglobin.

     The hydrophobic;

methyl and

vinyl groups

- interact with hydrophobic amino acid side chains from hemoglobin.

Topic 78

- Iron in the Fe^{2+} state binds oxygen reversibly
- But in the Fe^{3+} (Ferric) state it does not bind oxygen
- The iron atom of heme has six coordination bonds four in the plane of, and bonded to, the flat porphyrin ring system with Nitrogen

- Where as two perpendicular to it.

- A coordinate bond (also called a dative covalent bond) is a covalent bond (a shared pair of electrons) in which **both** electrons come from the same atom.
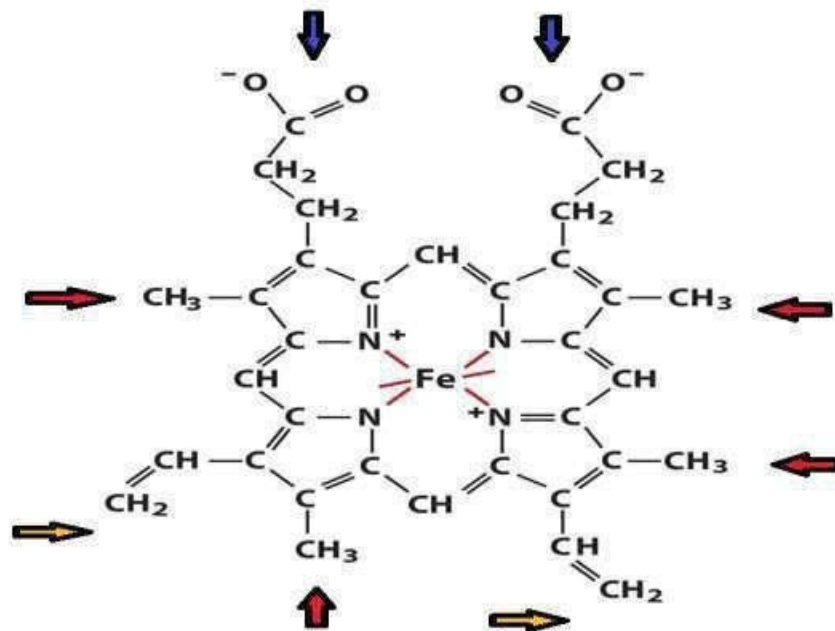
Negatively charged propionate (blue) groups on the porphyrin ring interact with arginine and histidine side chains from the hemoglobin, and the hydrophobic methyl(red) and vinyl(yellow) groups that extend out from the porphyrin ring interact with hydrophobic amino acid side chains from hemoglobin. All together, there are approximately 16 different interactions between myoglobin.

Heme:

protoporphyrin

(a)

Edge view

(c)

(d)   Histidine residue   Plane of porphyrin ring system
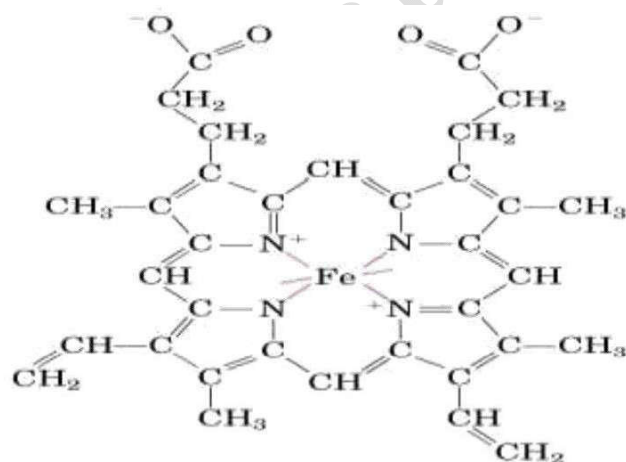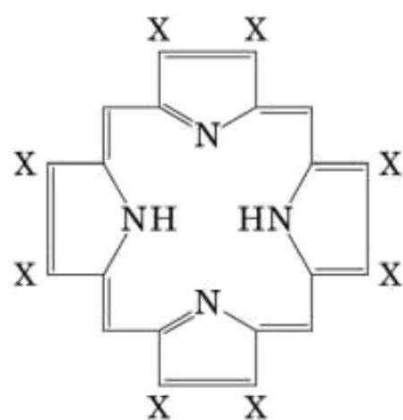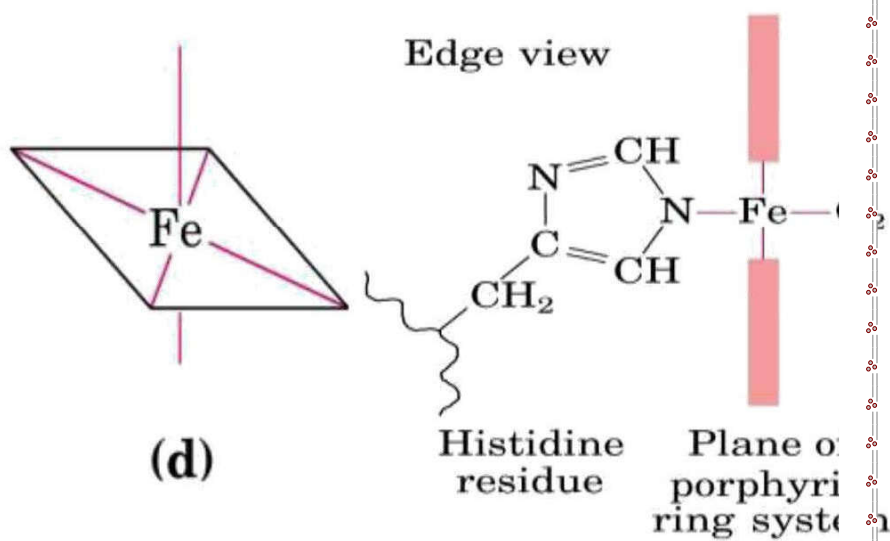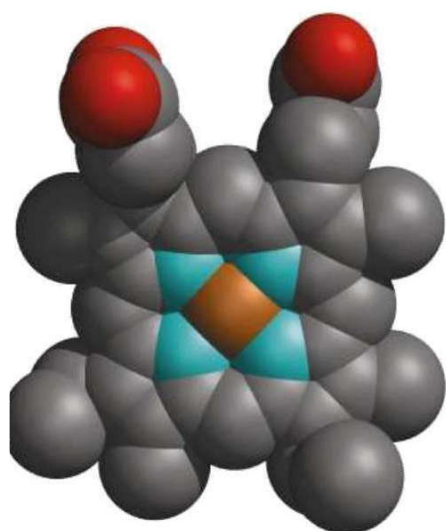
- Therefore free heme molecules (heme not bound to protein) leave Fe^{2+} with two "open" coordination bonds

- **One** of these two coordination bonds is occupied by a side chain nitrogen of a **His residue**

- The **other** is the binding site for molecular oxygen **(O)$_2$**

- **One** of these two coordination bonds is occupied by a side chain nitrogen of a **His residue**

- The **other** is the binding site for molecular oxygen **(O)$_2$**

Positively charged R groups

Lysine, Arginine, Histidine structures
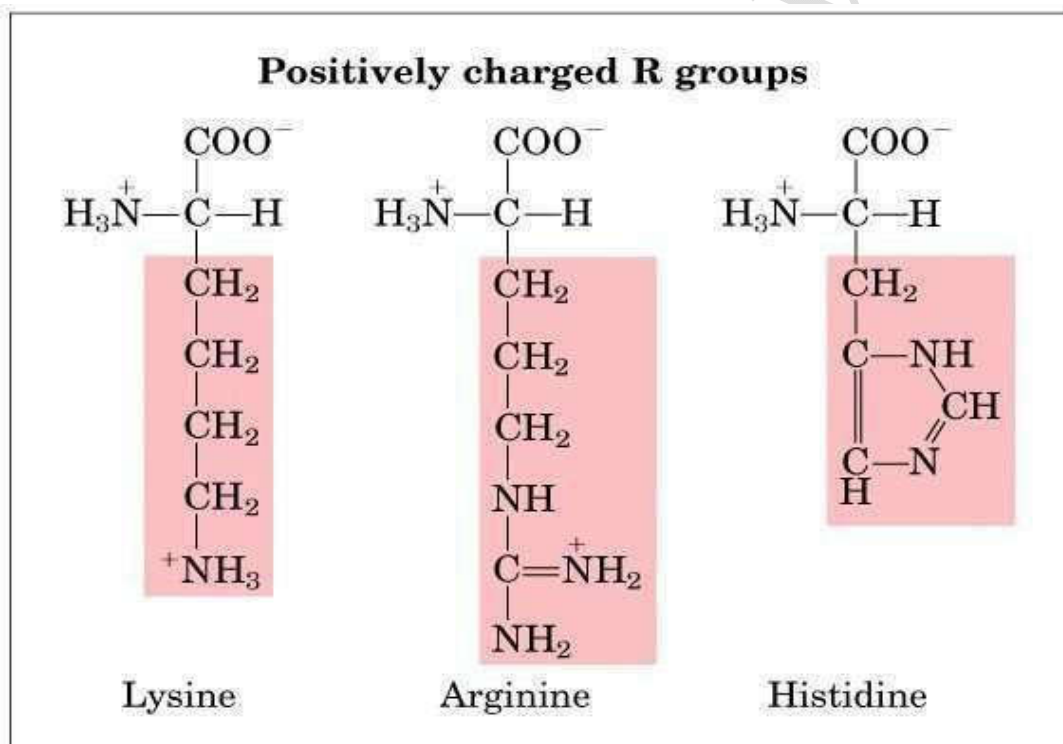
Negatively charged propionate (blue) groups= arginine and histidine side

Topic 79

- Iron in the Fe^{2+} state binds oxygen reversibly

- But in the Fe^{3+} (Ferric) state it does not bind oxygen

- The coordinated nitrogen atoms (which have an electron-donating character) help in **preventing** the conversion of the heme iron to the ferric (Fe^{3+}) state

small part of a protein molecule globin

N

Fe

N

N

H_2O

This water molecule can be replaced by an oxygen molecule, O_2.
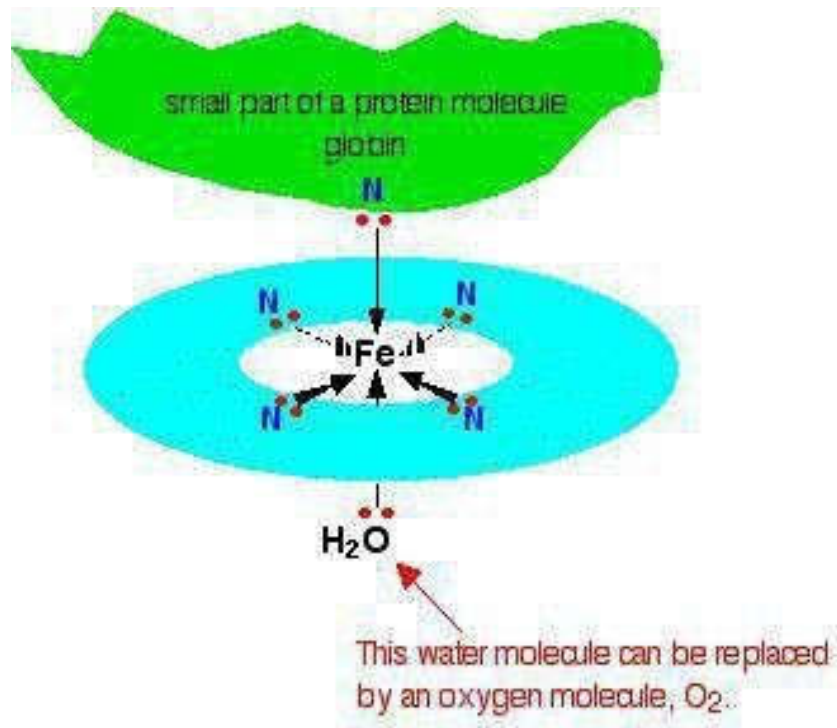
- The conversion Fe^{2+} to Fe^{3+} is much more likely in *free* heme,

- Sequestering each heme deep with in the protein structure further helps to prevent this reaction.
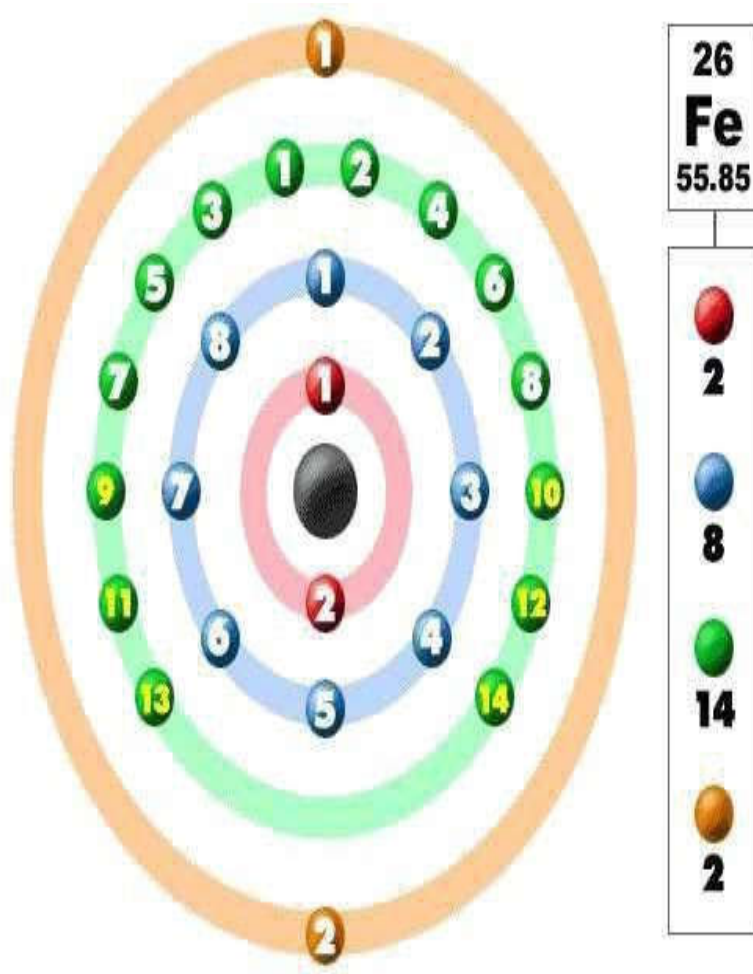
Iron is a transition metal & because its orbitals are so close energy wise they tend to give up either 2 or 3 electrons at time

Problem of Octet rule

- Octet rule cannot be used for type II cations (most of the transition
  and inner transition elements).

Fe^{2+} Fe^{3+}

Cu^{1+} Cu^{2+}
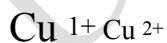
- The physiological oxidation state of an iron atom has a positive two charge (**ferrous ion**) instead of three charge (**ferric ion**)

- And it is too large to fit into the plane of protoporphyrin

- However, when iron oxidized from ferrous ion (Fe^{2+}) to ferric ion (Fe^{3+}), there is loss of one extra electron, forces between protons and electrons increases so that the electron cloud will penetrate more towards to the nucleus

- As a result, the ferric ion (Fe^{3+}) has a smaller size then ferrous ion (Fe^{2+}) and fits into the protoporphyrin plane

- This deep impregnation of Fe^{3+} in the protoporphyrin results in inability of Fe^{3+} to bind with oxygen.

- Some small molecules, such as carbon monoxide **(CO)** and nitric oxide **(NO),** coordinate to heme iron with greater affinity than does **O_2**

- When a molecule of CO is bound to heme, O_2 is excluded, that is why CO is highly toxic to aerobic organisms

- By surrounding and sequestering heme, oxygen-binding proteins regulate the access of CO to the heme iron.

Topic 80

- About 78% of the amino acid residues in the **myoglobin** are found in **α helices** with bends in between.

- The helical segments are named A through H.(eight)

- The bends are designated AB, CD, EF, and so forth.

- An individual amino acid residue is designated either by its position in the amino acid sequence

- or by its location in the sequence of a particular α-helical segment

- For example, the His residue coordinated to the heme in myoglobin, **His^{93}** (the 93rd residue from the amino-terminal end of the myoglobin polypeptide sequence), is also called **His F8** (the 8th residue in a helix F)

- Oxygen stored in red muscle myoglobin is released during O_2 deprivation (eg, severe exercise) for use in muscle mitochondria for aerobic synthesis of ATP.

- The surface of myoglobin is polar, important for interacting with polar aqueous environment of cytosol.

- The interior contains only nonpolar residues such as

- Leu,

- Val,

- Phe, and

- Met.

- with two notable exceptions—

- The exceptions are **His E7** and **His F8**, the seventh and eighth residues in helices E and F,

- Which lie close to the heme iron, where they stabilize heme and help in O2 binding.
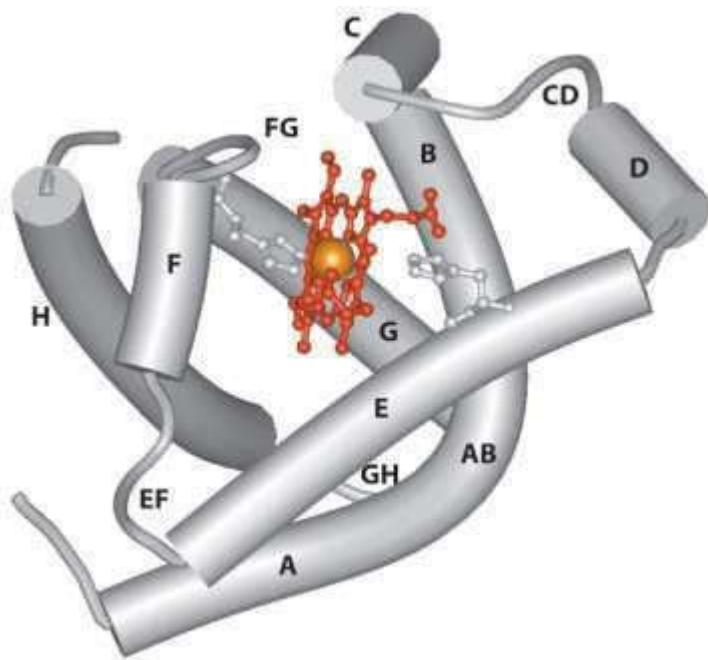
Topic 81

- The cervice (Pocket)created by nonpolar amino acids in the interior of myoglobin create a binding pocket for heme.

- **The proximal histidine F8**, binds directly to the iron of heme

- Whereas **distal histidine E7**, does not directly interact with the heme, but helps stabilize the binding of oxygen to the ferrous iron.

- In myoglobin and hemoglobin, heme is covalently linked with **histidine F8**(eighth residue of F helix). because of covalent bond this histidine is **closer to heme** iron and named as proximal histidine (closer histidine),

- While other key histidine which responsible for stabilization of oxygen in **E7** (seventh residue of E helix) is **far from heme iron** so named as distal

- The protein, or globin portion of myoglobin thus creates a special microenvironment for the heme that permits the reversible binding of one oxygen molecule (oxygenation)

- The physiological importance of oxygen stabilization of the distal histidine (E7) lies in the fact that it prevents the binding of CO which is a low level product of cellular metabolism.

(c)

r
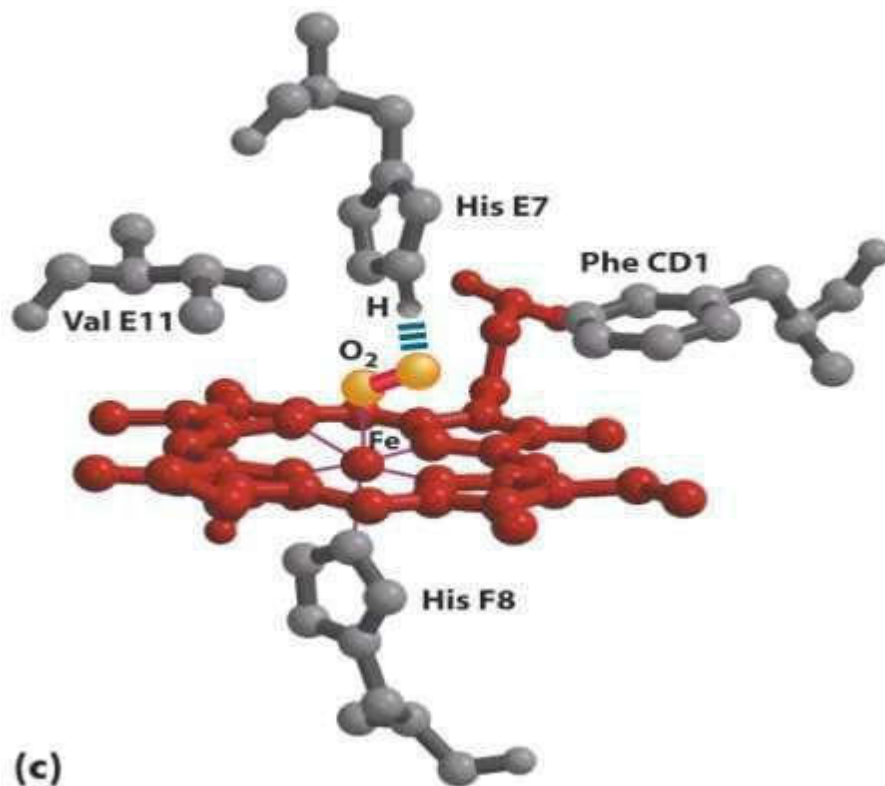
Topic 112 and 113 and 114

Polyunsaturated Fatty Acids Of Biological Importance

Polyunsaturated fatty acids contain more than one double bond

These include:

Linoleic acid (18: 2 $^{9, 12}$)

α-Linolenic acid (18 : 3 $^{9, 12, 15}$)

Arachidonic acid series (20 : 4 $^{5, 8, 11, 14}$)

Of these

Linoleic acid and

α-Linolenic acid are essential fatty acids.

Whereas, arachidonic acid is synthesized from both Linoleic acid and α-Linolenic acid.

Arachidonic acid becomes essential if linoleic acid is deficient in the diet

Arachidonic acid is the precursor of paracrine hormones called **Eicosanoids.**

Eicosanoids are chemical messengers which act over a short distance and include:

Prostaglandins

Leukotrienes and

Thromboxanes

These eicosanoids are semi cyclic structures.

They exert complex control over many bodily systems;

in inflammation

immunity, and as messengers in the central nervous system.

Topic 115

- **Polyunsaturated Fatty Acids Of Biological Importance** (Cont.)

- Eicosanoids are derived from either omega-3 (ω-3) or omega-6 (ω-6) fatty acids.

- In general, the ω-6 eicosanoids are **pro-inflammatory.**

- **Imbalance of omega-6 and omega-3** PUFAs in the diet is associated with:
  - an increased risk of cardiovascular disease.
- Long chain omega-3 fatty acids such as alpha-linolenic acid and their derivatives such as
- eicosapentaenoic acid (EPA) and
- docosahexaenoic acid (DHA) have
- anti-inflammatory effects
- In addition, docosahexaenoic acid (DHA) is selectively incorporated into
- retinal cell membranes and
- postsynaptic neuronal cell membranes
- suggesting it plays important roles in vision and nervous system function.
- Current evidence suggests that diet rich in omega 3 fatty acids are beneficial particularly for
- cardiovascular disease and also to some extent for
- Alzheimer's disease,
- Cancer and
- Rheumatoid Arthritis.
- This disease preventing role is due to the
- anti-inflammatory action of these
- omega-3 derivatives.
- Classically, ω-3 PUFAs mediate some of these effects by antagonizing ω-6 PUFA (arachidonic acid)-induced pro-inflammatory prostaglandin E_2 (PGE_2) formation

Topic 116

- **Unsaturated Fatty Acids of Physiologic and Nutritional Significance**
- In this module we will talk about unsaturated fatty acid in a tabulated form.

Number of C Atoms and Common Double Bonds	Family	Common Name	Systematic Name	Occurrence
Monoenoic acids (one double bond)				
16:1;9	ω7	Palmitoleic	*cis*-9-Hexadecenoic	In nearly all fats.
18:1;9	ω9	Oleic	*cis*-9-Octadecenoic	Possibly the most common fatty acid in natural fats; particularly high in olive oil.

Number of C Atoms and Common Double Bonds	Family	Common Name	Systematic Name	Occurrence
Monoenoic acids (one double bond)				
18:1;9	ω9	Elaidic	*trans*-9-Octadecenoic	Hydrogenated and ruminant fats.

Number of C Atoms and Common Double Bonds	Family	Common Name	Systematic Name	Occurrence
Dienoic acids				
18:2;9,12	ω6	Linoleic	all-*cis*-9,12-Octadecadienoic	Corn, peanut, cottonseed, soy bean, and many plant oils.

Number of C Atoms and Common Double Bonds	Family	Common Name	Systematic Name	Occurrence
Trienoic acids				
18:3;6,9,12	ω6	γ-Linolenic	all-*cis*-6,9,12-Octadecatrienoic	Some plants, eg, oil of evening primrose, borage oil; minor fatty acid in animals.
18:3;9,12,15	ω3	α-Linolenic	all-*cis*-9,12,15-Octadecatrienoic	Frequently found with linoleic acid but particularly in linseed oil.

Topic 117

Other Common Fatty Acids
- Other Fatty acids commonly found in body which are worth knowing are:
- Palmitic Acid (16:0)

- Stearic Acid (18:0) and Oleic acid (18:1)
- Palmitic Acid(16:0) Palmitic acid, or hexadecanoic acid, is the
- most common saturated Fatty Acid found in animals, plants and microorganisms •
  Palmitic acid mainly occurs as its ester in triglycerides (fats), especially palm oil.
- It is also found in high amounts in

- Butter,
- Cheese,
- milk and
- meat
- Excess carbohydrates in the body are converted to palmitic acid.
- Palmitic acid is the first fatty acid produced during fatty acid synthesis and the precursor to longer fatty acids
- As a consequence, palmitic acid is a major body component of fats found in the animals.
- Stearic Acid (18:0)
- As its ester, stearic acid is one of the most common saturated fatty acids found in nature following palmitic acid.
- Fats and oils rich in stearic acid are
- more abundant in animal fat (up to 30%)
- than in vegetable fat (typically <5%)
- Oleic Acid(18:1)
- Possibly the most common fatty acid in adipose tissue • It is particularly high in olive oil
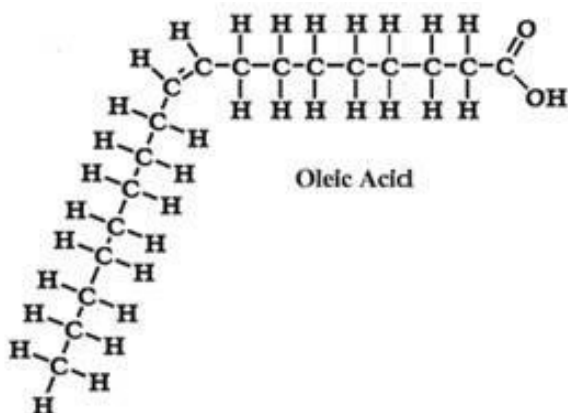
Oleic Acid

- Oleic acid in olive oil accounts for the blood pressure lowering effect of olive oil. • In addition, because of cis configuration and the kink produced due to the
- cis configuration.
- It is also highly abundant in membrane lipids, providing
- fluidity to membrane.
- Saturated Fatty Acids

Common name	Number of carbons	
Acetic	2	Major end product of carbohydrate fermentation by rumen organisms
Butyric	4	In certain fats in small amounts (especially butter). An end product of carbohydrate fermentation by rumen organisms. Also formed in the cecum of herbivores and to a lesser extent in the colon of humans.
Valeric	5	
Caproic	6	

Saturated Fatty Acids

Common name	Number of carbons	
Lauric	12	Spermaceti, cinnamon, palm kernel, coconut oils, laurels, butter
Myristic	14	Nutmeg, palm kernel, coconut oils, myrtles, butter
Palmitic	16	Common in all animal and plant fats
Stearic	18	

- Spermaceti by the sperm whale. Palm saeed. evergreen tree *(Laurus nobilis)* of the
- Mediterranean region valued for its aromatic ovate leaves. Nutmeg Jorenk, Jefal

Topic 118

- **Glycerol and Sphingosine**

- Glycerol and Sphingosine are the two types of **alcohols** most commonly found in lipids.

- **Glycerol**

- It is a simple poly hydroxy alcohol (also called polyol or sugar alcohol)

- and part of a class of lipids: glycolipids

- It contains 3 carbons and 3 hydroxyl (OH) groups.

- Glycerol is synthesized from

- Dihydroxyacetone Phosphate (an intermediate of the glycolytic pathway)

- Dihydroxyacetone phosphate is acted upon by two enzymes to form glycerol, namely

- Glycerol Phosphate Dehydrogenase and

- Glycerol Kinase respectively.

- Glycerol is a precursor for synthesis of triacylglycerols and of phospholipids in the liver and adipose tissue.

- When the body uses stored fat as a source of energy, glycerol and fatty acids are released into the bloodstream.

- And enter the glycolysis pathway directly

- Sphingosine is an amino alcohol,

- which is a component of the class of lipids known as sphingolipids

- Sphingosine is synthesized in the body in the form of ceramide,

- to which different moieties are added to form sphingolipids.

- Serine and palmitoyl CoA condense to form a product (ketosphinganine) that is reduced.

- A very long-chain fatty acid forms an amide with the amino group.

- a double bond is generated, and ceramide is formed.

There is no direct route of synthesis from sphinganine (dihydrosphigosine) to sphingosine;

it has to be acylated

first to dihydroceramide,

which is then dehydrogenated to **ceramide.**

Sphingosine is formed via degradation of sphingolipid in the lysosome.

Therefore ceramide is the structural parent of all sphingolipids.

In short,

Serine+ Palmitate

• Sphingosine

Sphingosine +

FA = ceramide
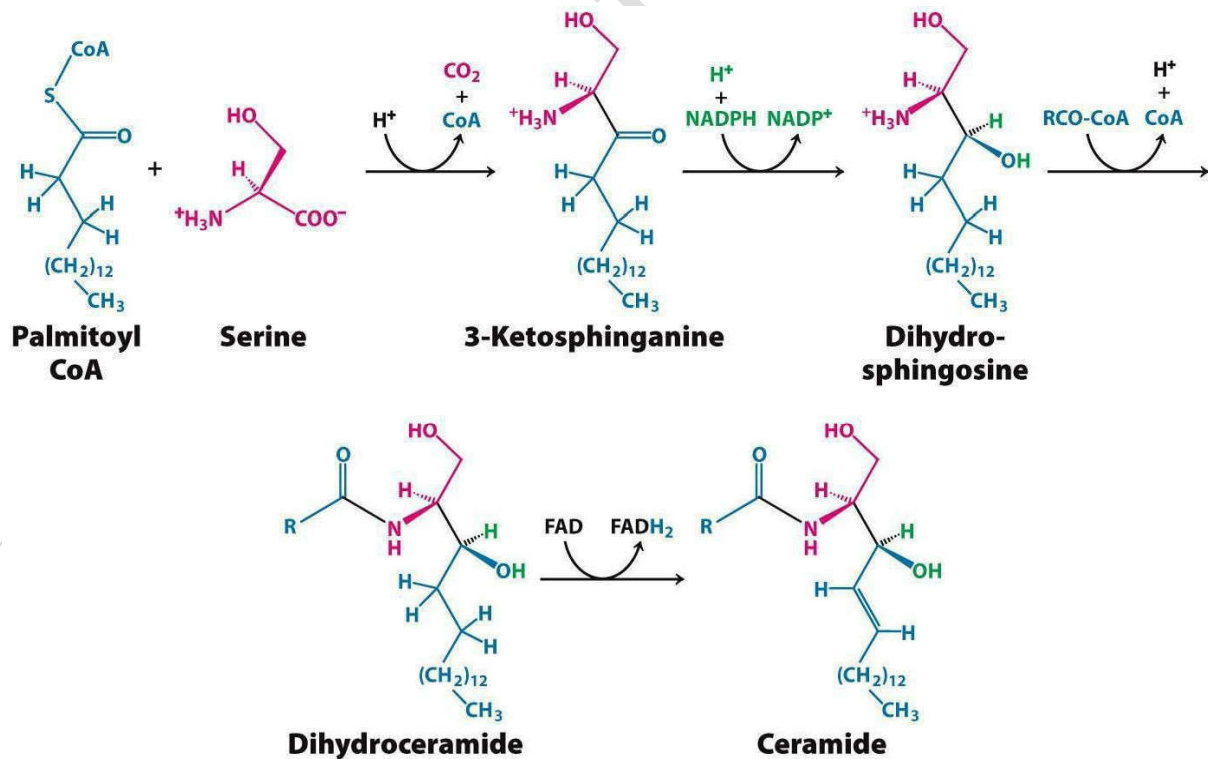
Figure 26.3
Biochemistry, Seventh Edition
© 2012 W. H. Freeman and Company

SPHINGOSINE

CH3 -(CH2)12-CH=CH-CH-CH-CH2OH

         OH NH2
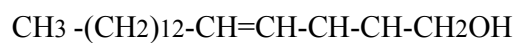
Carbon atoms 1 and 2 arise from the amino acid

serine Carbon atoms 3 to 18 arise from palmitic acid

CERAMIDE

Sphingosine

CH3 -(CH2)12-CH=CH-CH-CH-CH2OH

         OH NH

CH3 - (CH2)22 - C = 0
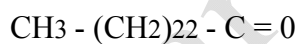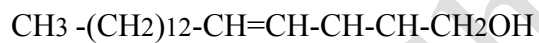
Long Chain Fatty Acid

Topic 120

Properties of Glycerol

Popularly known as glycerin,

Glycerol is widely used in pharmaceutical and cosmetic preparations.

It has the following properties:

Colorless

Viscous oily liquid with

sweet taste.

Acrolein Test

On heating with sulfuric acid or KHSO4 (dehydration)

it gives acrolein that

has a bad odor.

used for detection of free glycerol or any compound containing glycerol.

In contrast to glycerol

Sphingosine does not show positive acrolein test.

Therefore glycerolipids and shingolipids can be differentiated on the basis of acrolein test.

Glycerol combines with three molecules of nitric acid to form Glycerol trinitrate that is

used as explosive and

vasodilator

On **esterification** with fatty acids it gives:

monoacylglycerol: one fatty acid + glycerol.

diacylglycerol: two fatty acids + glycerol.

triacyl-glycerol: three fatty acids + glycerol.

Gluconegenic substrate

Glycerol can form dihydroxyacetone phosphate

which can convert into glucose or

glyceraldehyde phosphate

to enter into gluconeogenic pathway.

Topic 121

Simple lipids:

Esters of fatty acids with various alcohols

These contain:

Fats (and Oils) and

Waxes.

- **Fats:** Esters of fatty acids with glycerol (**Oils** are fats in the liquid state)

- **Waxes:** Esters of fatty acids with higher molecular weight monohydric alcohols.

(having one OH group)

- **Triacylglycerols (TAGs)**

- The simplest lipids constructed from fatty acids are the triacylglycerols**,**

- Also referred to as;

- triglycerides,

- fats, or

- neutral fats or

- storage lipids.

- Triacylglycerols are composed of

- three fatty acids

- in ester linkage with

- a single glycerol

- **Structure of triacylglycerols**

- The three fatty acids esterified to a glycerol molecule are usually **not** of the same type

- The fatty acid on **carbon 1** is typically saturated,

- Whereas that on **carbon 2** is unsaturated,

- and that on **carbon 3** can be either

- Simple triglycerides:

- Fatty acids connected to glycerol are of the same type

- e.g., tripalmitin.

- Mixed triglycerides:

- Fatty acids are of different types, e.g.,

- stearo-diolein and palmito-oleo-stearin.

- The main difference between fats and oils is for oils being liquid at room temperature, whereas, fats are solids.

- This is mainly due to presence of larger percentage of unsaturated fatty acids in oils than fats that has mostly saturated fatty acids.

- TAGs containing saturated fatty acids are solid at room temperature such as butter whereas

- TAGs containing unsaturated fatty acids are liquid at room temperature such as olive oil.(Olic acid, 18:1,9)

Topic 122

- **Triacylglycerols (TAGs)**

- Because the polar hydroxyls of glycerol

- and the polar carboxylates of the fatty acids are

- bound in ester linkages

- Therefore the triacylglycerols are nonpolar, hydrophobic molecules, essentially insoluble in water

- Triacylglycerols provide

- Stored Energy

- and Insulation.

- In vertebrates, specialized cells called **adipocytes, or fat cells**, store large amounts of triacylglycerols as fat droplets that nearly fill the cell

- Triacylglycerols are also stored as oils in the **seeds** of many types of plants.

- Thus providing energy and biosynthetic precursors during seed germination

- Adipocytes and germinating seeds contain lipases, enzymes that catalyze the hydrolysis of stored triacylglycerols.

- Therefore releasing fatty acids for export to sites where they are required

ADIPOCYTES

MATRIX

NUCLEUS PUSHED AGAINST CELL MEMBRANE.
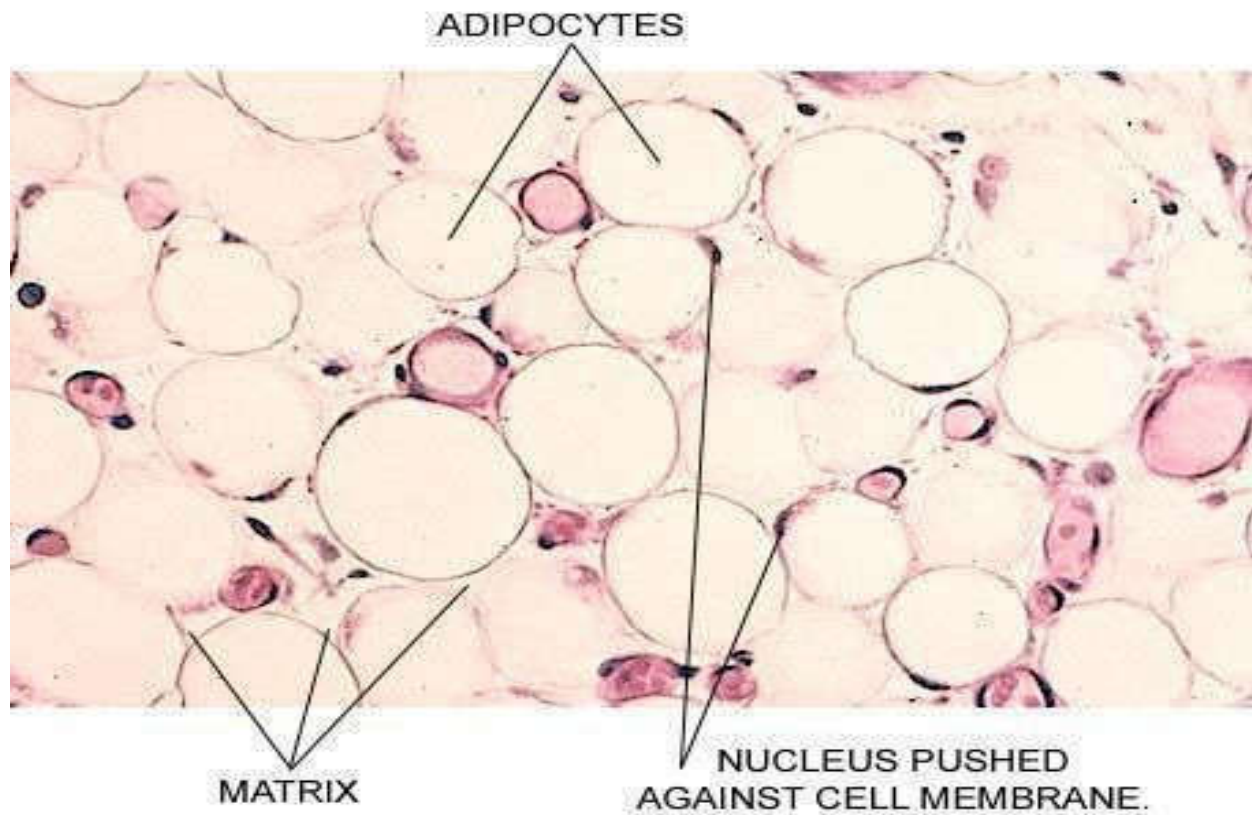
Topic 123

Triacylglycerols (TAGs) Cont.

There are two significant advantages to using triacylglycerols as stored fuels, rather than polysaccharides such as glycogen and starch.

First, the carbon atoms of fatty acids are more reduced than those of sugars, and oxidation of triacylglycerols yields more than twice as much energy, as the oxidation of carbohydrates

Second, because triacylglycerols are hydrophobic and therefore unhydrated.

The organism that carries fat as fuel does not have to carry the extra weight of water of hydration that is associated with stored polysaccharides

(2 g per gram of polysaccharide)

Moderately obese people with 15 to 20 kg of triacylglycerols deposited in their adipocytes could meet their energy needs for months by drawing on their fat stores

In contrast, the human body can store less than a day's energy supply in the form of glycogen (the polymer of glucose)

In some animals, triacylglycerols stored under the

skin serve as insulation against low temperatures.

Seals, penguins, bears and other warm-blooded polar animals

are amply padded with triacylglycerols Topic 124

Properties of TAGs

Physical properties

Neutral fats are

colourless,

odorless and

tasteless substances

- **Solubility**:

They are insoluble in water but

soluble in organic fat solvents(e.g., ether, benzene, acetone, chloroform)

5. Specific gravity:

The specific gravity of all fats is less than 1.0,

consequently all fats float in water

6. Emulsification:

Emulsions of fat may be made by shaking vigorously in water and by emulsifying agents such as gums and soaps

The emulsification of dietary fats in intestinal canal, brought about by bile salts, is

a prerequisite for digestion and absorption of fats.

The **bile salts**, act to break apart the fat globules in the small intestines and allow them to become more "soluble" for absorption.

The hydrophobic fat molecules will clump together into globules in the watery mixture in the digestive system.

The emulsifiers break them down to smaller "globules" and allow them to become more soluble.
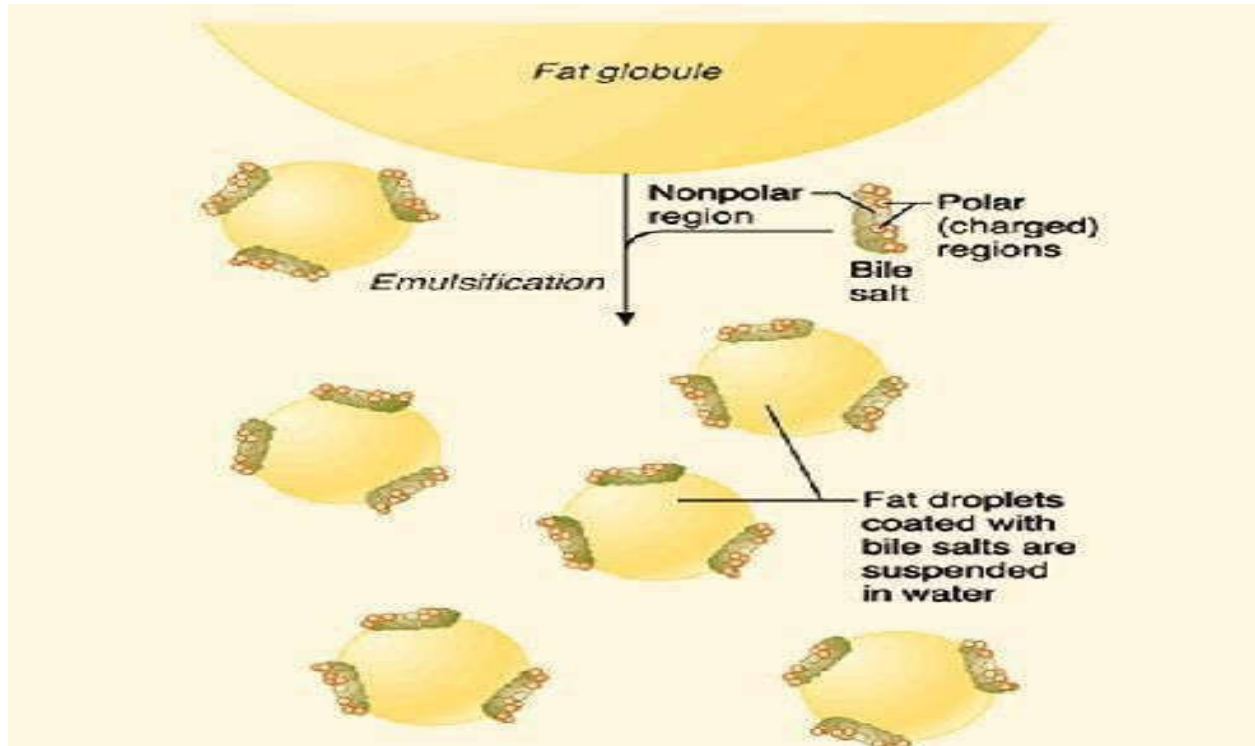
In Mustard variety of chemicals in the mucilage surrounding the seed hull act as emulsifiers
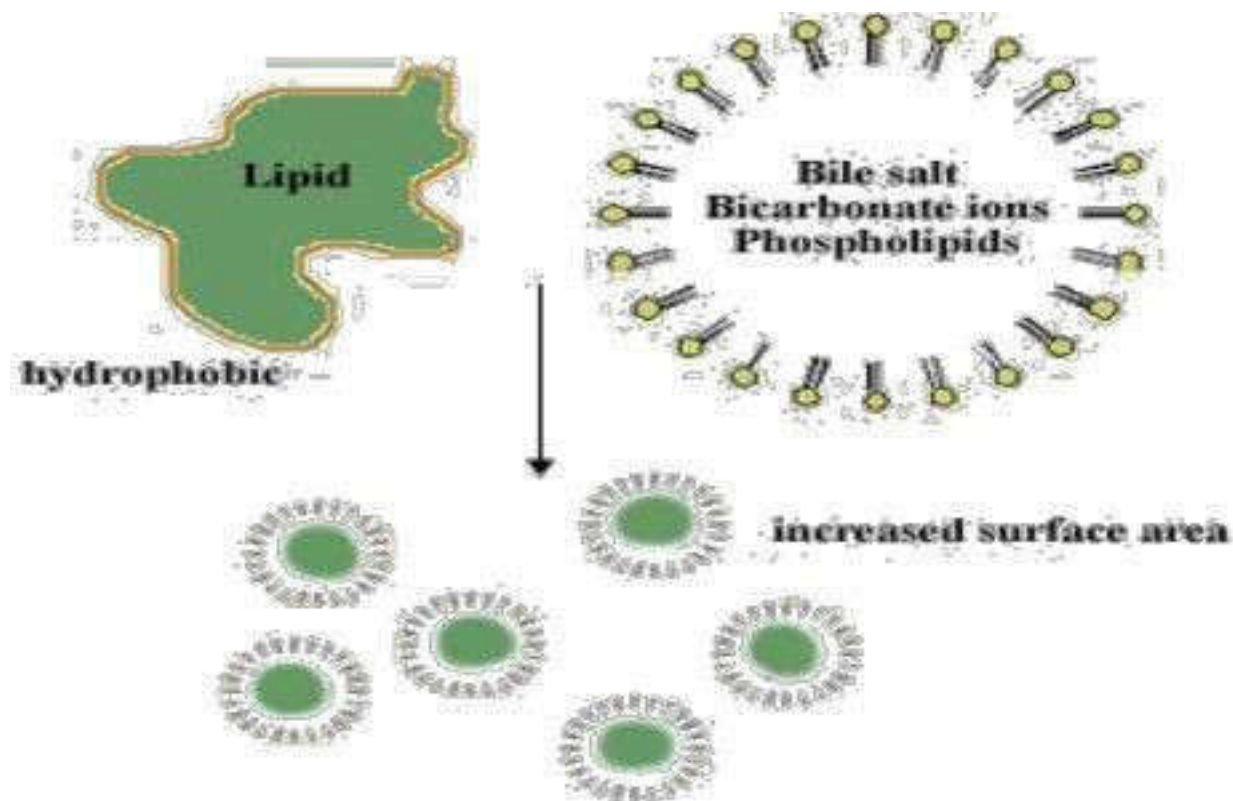
Topic 125

Chemical Properties of TAGs

• Hydrolysis

The fats may be hydrolysed with super heated steam, by acids, or alkalies, by the specific fat splitting enzymes lipases to

– free fatty acids

– glycerol

Saponification

• Hydrolysis of a fat by an alkali is called **saponification**

• The resultant products are;

• glycerol and

• the alkali salts of the fatty acids, which are called "soaps"

• The number of mgs of NaOH/KOH required to saponify the free and combined FA in one gram of a given fat is called its **saponification number**

- The amount of **alkali** needed to saponify a given quantity of fat will depend upon the number of carboxylic (–COOH) group present

- Thus fats containing short chain fatty acids will have more –COOH groups per gram than long- chain fatty acids and this will take up more alkali

- And hence will have higher saponification number

- Butter containing a larger proportion of short- chain fatty acids, such as butyric (C4) acid and caproic (C6) acid etc.

- Therefore it has relatively high saponification number from 220 to 230

- In contrast, Olive Oil (which contain Oleic acid (C18), a longer chain FA),

- has saponification number of 195 or less.
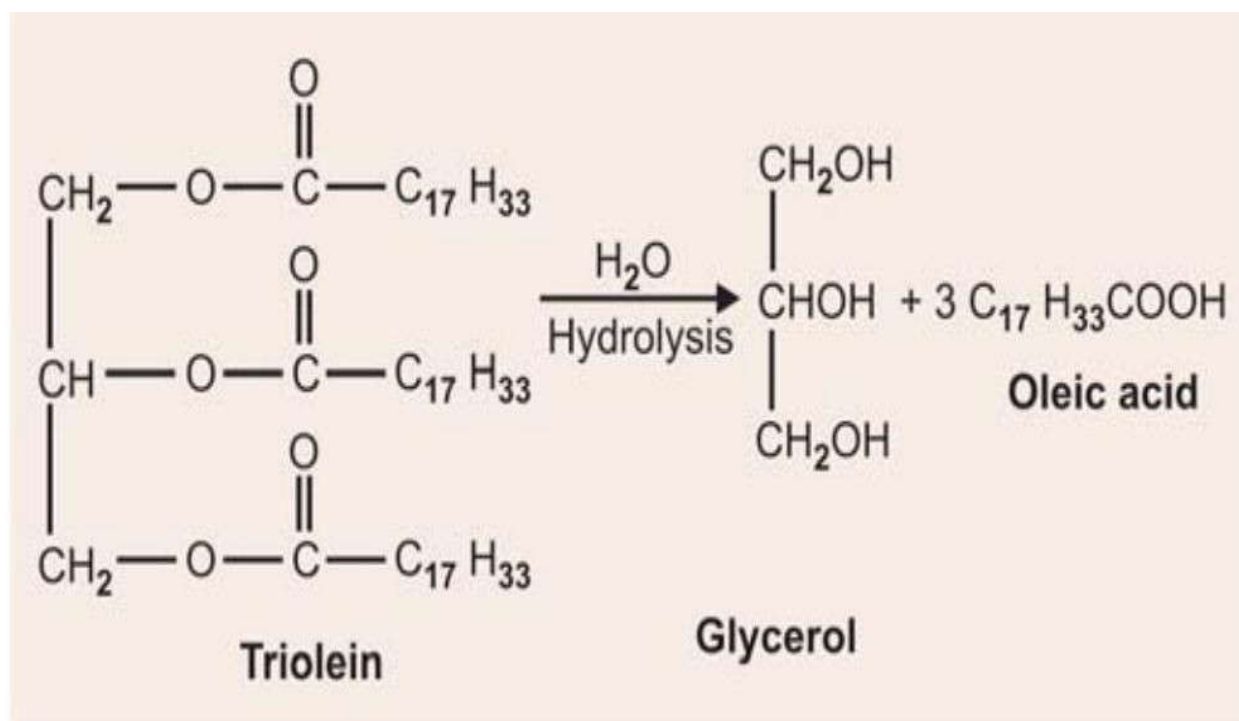
Triolein is another example of simple TAG.

عمر غفور

Triglyderide + 3NaOH → Glycerol + Sodium Plamitate

(a) A soap

(b) Cross section of a soap micelle in water

Na⁺

Polar "head"

Nonpolar "tail"
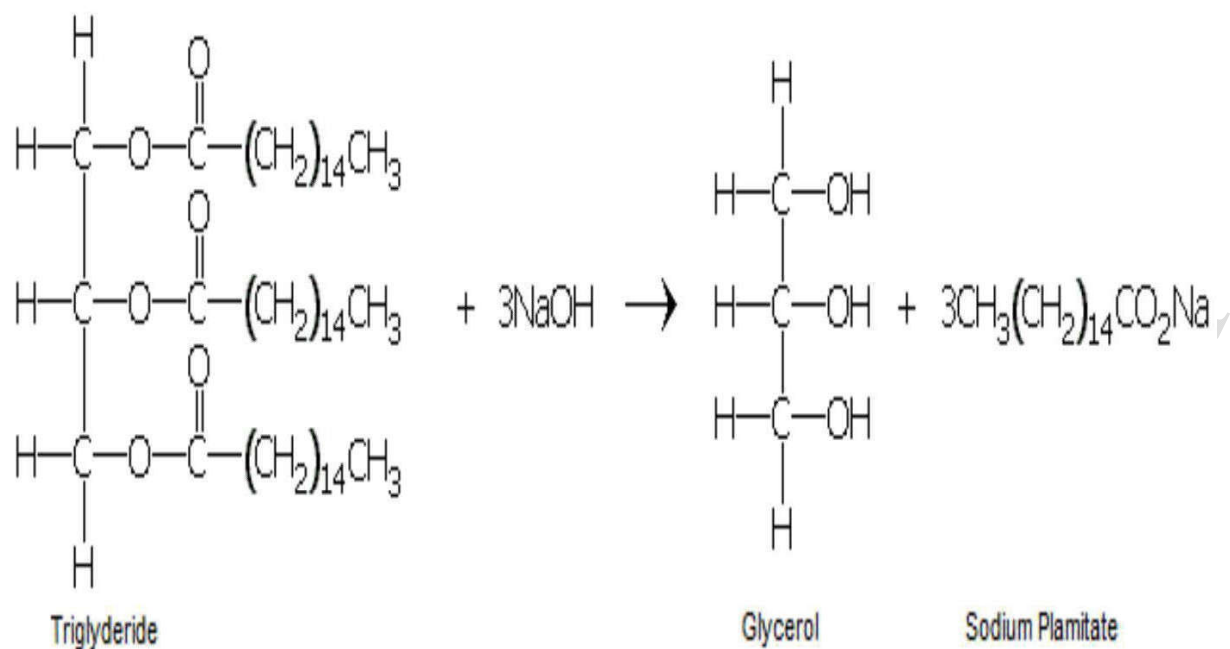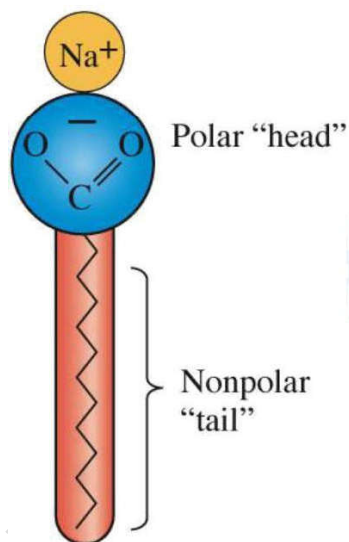
© Brooks/Cole, Cengage Learning

Na⁺ ions
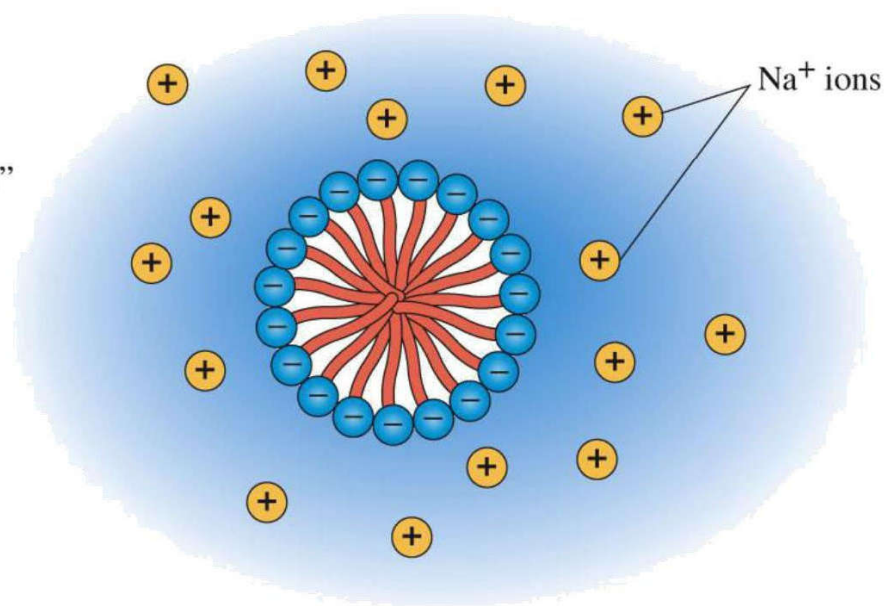
Lipid properties

Table 1. Examples saponification and iodine numbers

Fat or oil	Saponification #	Iodine #
Beef tallow	194 – 200	34 – 43
Cocoa butter	192 – 198	32 – 42
Coconut oil	245 – 262	6 – 10
Cottonseed oil	192 – 196	103 – 112
Lard	193 – 200	50 – 80
Milk fat	210 – 233	26 – 35
Peanut oil	186 – 194	89 – 98

Tallow is the fat obtained from cattle used in soap industry.

Topic 126

- **Chemical Properties (Contd.)**

- **2.** Additive Reactions

- The unsaturated fatty acids present in neutral fat exhibits all the additive reactions, i.e.

    - hydrogenation,

    - halogenation.

- **Hydrogenation**

- A hydrogenation reaction involves conversion of a carbon-carbon double bond to a carbon-carbon single bond through the addition of hydrogen

- **Hydrogenation**

    - As you continue to hydrogenate your molecule

        Melting point increases

Fat becomes more solid at room temp

- **Hydrogenation**

- Oils which are liquid at ordinary room temperature, on **hydrogenation** become solidified

- This is the basis of Banaspti ghee manufacturing.

- Where inedible and cheap oils like cotton seed oil are hydrogenated and converted to edible solid fats.

- The hydrogenation is done

- under high pressure of hydrogen and is catalyzed by finely divided nickel or copper and heat.

- It is the base of hardening of oils (margarine manufacturing), e.g.

- change of oleic acid of fats (liquid)

- into stearic acid (solid).
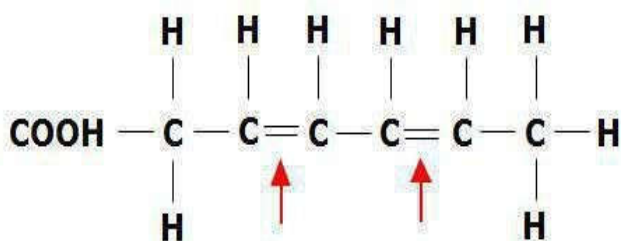
Polyunsaturated Fat
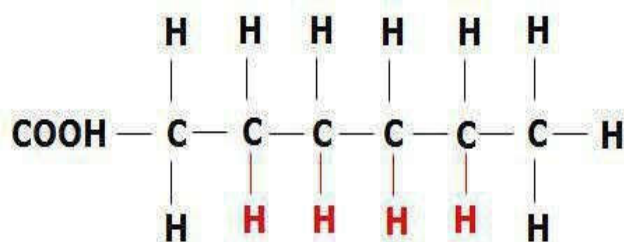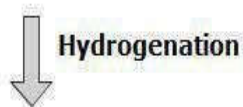
Hydrogenation
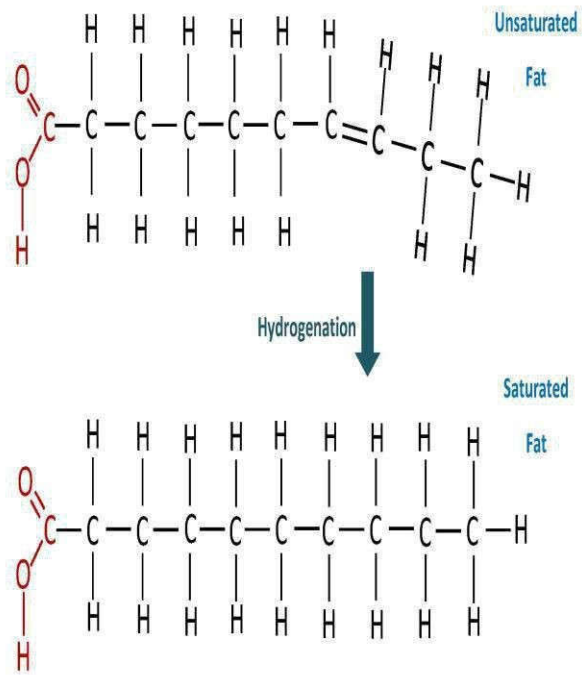
Hydrogenated Fat

unsaturated fats have lower melting points, stearic (SFA) melts at 70°C, oleic (PUFA) at 26°C
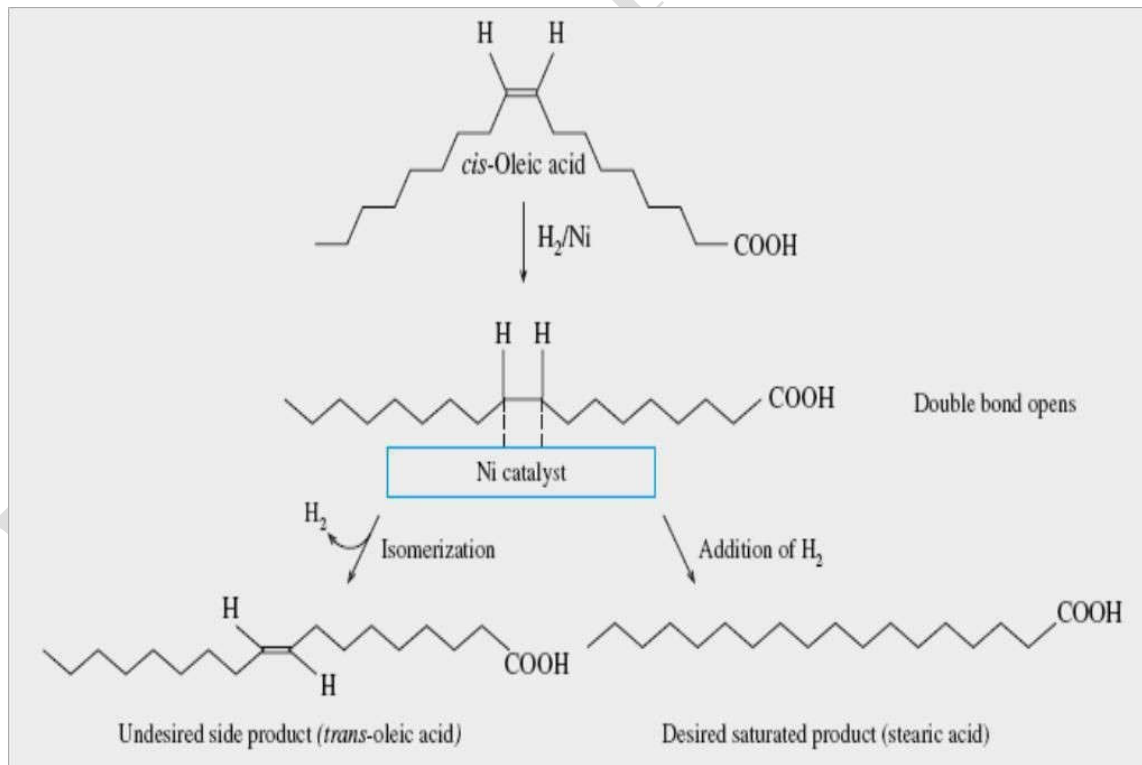
Topic 127

Chemical Properties (Contd.)

Halogenation

Similar to hydrogenation,

Halogens such as chlorine, bromine and iodine can also be added to double bonds in

unsaturated fatty acids.

It is a very important property to determine the degree of unsaturation of the fat or oil
that determines its biological value.

The degree of unsaturation is reflected by Iodine number.

Iodine number is defined as the number of grams of iodine absorbed by 100 gm of fat.

The more the iodine number, the greater the degree of unsaturation.

Fats rich in saturated fatty acids have low iodine numbers,

while fats rich in unsaturated fatty acids have high iodine numbers

The determination of iodine number is useful to the chemist in determining the quality of an oil
or its freedom from adulteration

Iodine number of cotton seed oil varies from 103 to 111.

That of olive oil from 79 to 88,

And that of linseed oil from 175 to 202

A commercial lot of olive oil which has iodine number higher than 88 might
have been adulterated with cotton seed oil

The higher is the iodine number, the more reactive, less stable, more susceptible to oxidation
and rancidification is the oil or fat.

Comparison of Dietary Fats

DIETARY FAT

Oil/Fat	Saturated (red)	Linoleic (blue)	Alpha-linolenic (orange)	Oleic (yellow)
Canola oil	7	21	11	61
Safflower oil	8	14	1	77
Flaxseed oil	9	16	57	18
Sunflower oil	12	71	1	16
Corn oil	13	57	1	29
Olive oil	15	9	1	75
Soybean oil	15	54	8	23
Peanut oil	19	33	*	48
Cottonseed oil	27	54	*	19
Lard	43	9	1	47
Palm oil	51	10	*	39
Butter	68	3	1	28
Coconut oil	91	2		7
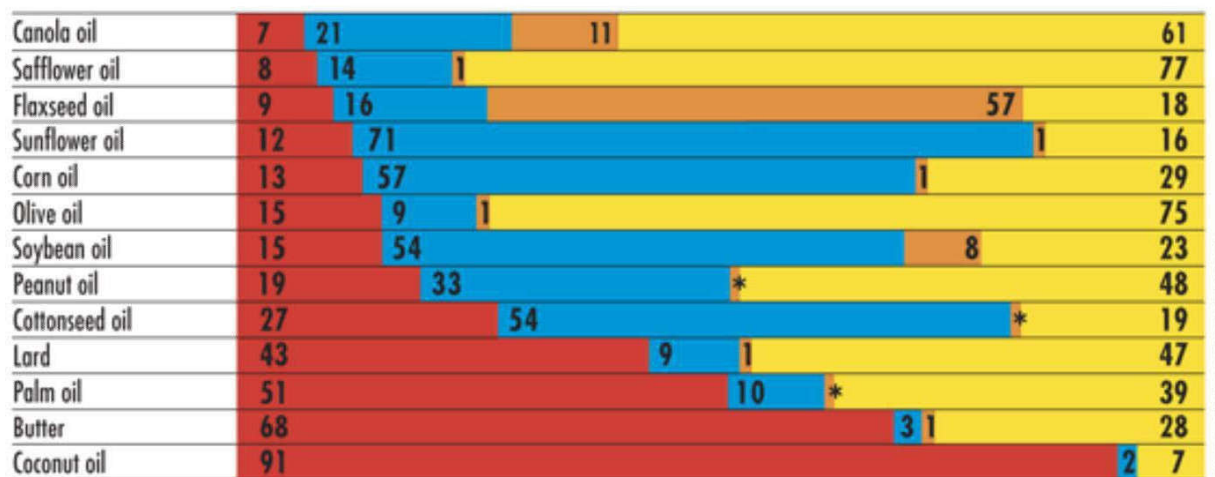
SOURCE: POS PILOT PLANT CORPORATION

SATURATED FAT ■ (red)

POLYUNSATURATED FAT
- ■ linoleic acid (an omega-6 fatty acid)
- ■ alpha-linolenic acid (an omega-3 fatty acid)

MONOUNSATURATED FAT
- ■ oleic acid (an omega-9 fatty acid)

*Trace   Fatty acid content normalized to 100%

Oil/Fat	16:0	16:1	18:0	18:1	18:2	18:3	20:1	22:1	24:0	Average Unsaturation Per Triglyceride
soybean	11	0.1	4	23.4	53.2	7.8				4.6
palm	44.4	0.2	4.1	39.3	10	0.4				1.8
rapeseed	3	0.2	1	13.2	13.2	9	9	49.2	1.2	3.8
sunflower	6		5	20	60					1.4
tallow	27	11	7	48	2					0.6
cottonseed	21.6	0.6	2.6	18.6	54.5	0.7				3.9
olive	13.7	1.2	2.5	71.1	10	0.6				2.8
corn	10.9	0.2	2	25.4	59.6	1.2				4.5
canola	4.1	0.3	1.8	60.9	21	8.8	1	0.7	0.2	3.9
linseed	5.5		3.5	19.1	15.3	56.6				6.6

Topic 128

- **Chemical Properties (Contd.)**

- Rancidity

- The chemical deterioration of fats.

- When lipid-rich foods are exposed too long to the oxygen in air, they may spoil and become foul smelling**.**

- **Rancidity**

- **Definition:**

- It is a physico-chemical change in the natural properties of the fat leading to the development of

- unpleasant odor or

- taste or

- abnormal color

It occurs particularly

- on aging

- after exposure to atmospheric oxygen,

- light,

- moisture,

- bacterial or fungal contamination

- and/or heat.

- Saturated fats resist rancidity more than unsaturated fats that have unsaturated double bonds.

- **Rancidity**

is due to

- Oxidation

- Hydrolysis

- **Oxidative Rancidity**

Oxidation of the fat molecules give rise to some short

chain aldehydes, ketones and dicarboxylic acids

which have objectionable taste and odor.

The unpleasant taste and smell associated with rancidity result from
the *oxidative cleavage of double bonds in unsaturated fatty acids*

The oxygen of the air is necessary for this type of

rancidity. This can be prevented by addition of anti-

oxidants such as vitamin E to foods.

II. Hydrolytic Rancidity

It is due to the slow hydrolysis of fats,

which in case of fats like butter results in the

liberation of short chain fatty acids which are volatile and have rancid taste and odor.

Topic 129

Waxes

A second group of neutral lipids that are of physiological importance.

Although they are a minor component of biological systems.

Properties of waxes

Waxes are insoluble in water, but

soluble in fat solvents and are

negative for acrolein test.

very resistant to rancidity.

Waxes are not easily hydrolyzed as the fats

and are indigestible by lipases (enzymes responsible for fat digestion in body)

Thus they are of no nutritional value

Waxes are of two types:

- True waxes

- Other Waxes or

Non true waxes or

Wax-like compounds

- **True Waxes**

- Waxes are solid simple lipids containing a monohydric alcohol (with a higher molecular weight than glycerol)

- esterified to long-chain fatty acids.

- Waxes are widely distributed in nature such as the secretion of certain insects as;

- **Bees-wax,**

- **Spermaceti** of the sperm whale

- Waxes also form protective coatings of the skins and furs of animals and

- leaves and fruits of plants.

Myricyl alcohol (30C)

Triacontanol is a _fatty alcohol_ of the general formula C30H62O, also known as **melissyl alcohol** or **myricyl alcohol.**

It is found in plant _cuticle waxes_ and in _beeswax_.
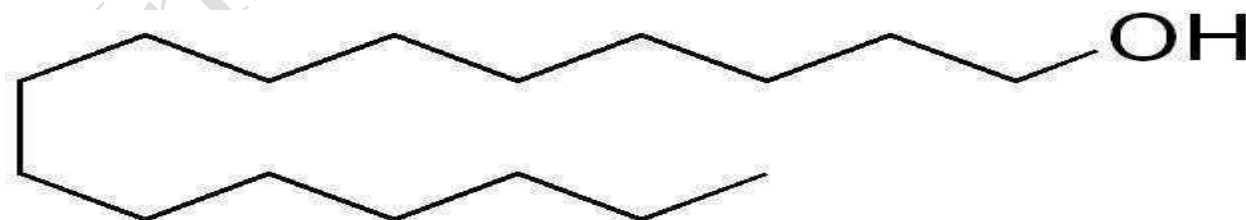
Cetyl Alcohol (16 C)

The name cetyl derives from the whale oil (Latin: cetus) from which it was first isolated

Cetyl Alcohol can be found in mooisturizer,facial moisturizer,conditioner,anti-aging,hair color,hair bleaching,facial cleanser. hand cream,shampoo,lipstic,eye cream.

Topic 130

1.True Waxes

Bees-wax is secreted by the honeybees that use it to form the combs.

It is a mixture of waxes

chief constituent is myricyl palmitate

(30C)   (16C)

2.Spermaceti

 is a wax that is most often found in the head cavities of the sperm whale.

Fatty esters are formed essentially of

cetyl palmitate and

cetyl myristate.

It was used in cosmetics, pharmacy and also in candles

recent international regulation concerning whale captures, has stopped its use.

It is now replaced by synthetic cetyl palmitate.

2.Other Waxes or Non true waxes

include esters of:

Cholesterol

Vitamin A

Vitamin D

Cholesterol esters: Lanolin (or wool fat) is secreted by sheep sebaceous glands

and It contains both free and esterified cholesterol, e.g., cholesterol-palmitate

Lanolin secretion helps sheep in reducing water evaporation from the skin.

It is used as

industrial lubricant and in

cosmetics.
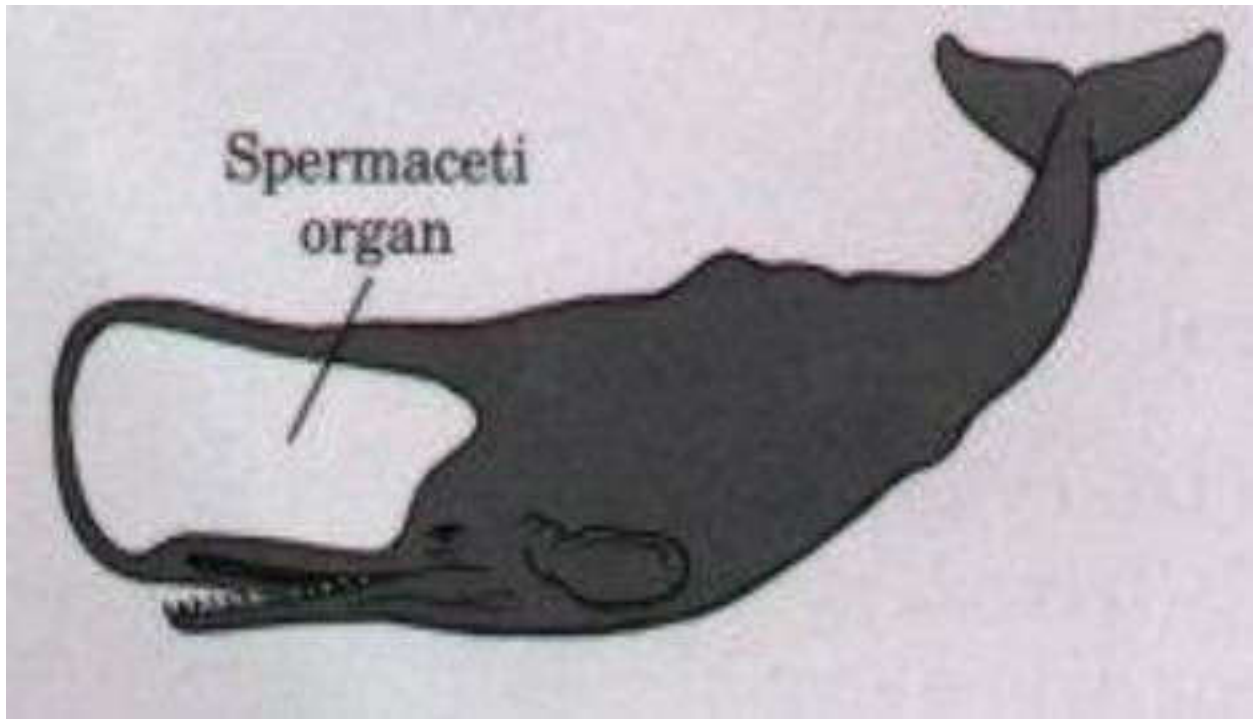
Topic 131

Lipids and Nutrition

- Dietary fats strongly influence the incidence of coronary heart disease (CHD).

- In the past, dietary recommendations emphasized decreasing the total amount of fat in the diet.

- Research now indicates that the type of fat is more important than the total amount of fat consumed

To gauge the effect of these dietary fats on CHD, we measure different biochemical parameters, which include:

- LDL-Cholesterol

- HDL-Cholesterol

- Total Cholesterol

1

- TAG

- LDL and HDL stand for

- Low Density Lipoprotein and

- High Density Lipoprotein respectively

- they are included in the class of complex lipids and serve to

- transport lipids in the blood.

- Serum Cholesterol and TAGs are a risk factor for CHD among others.

- The risk increases progressively with higher values for serum total cholesterol and that of LDL cholesterol.

- Association of TAGs is weaker than that of LDL cholesterol with CHD.

- A much stronger correlation exists between the levels of blood LDL cholesterol and heart disease.

- In contrast, high levels of HDL cholesterol have been associated with a decreased risk for heart disease

- In order to understand the influence of these parameters on CHD, we must first understand biochemical role of Lipoproteins:

- Lipoprotein particles are spherical aggregates with hydrophobic lipids at the core and hydrophilic protein side chains and lipid head groups at the surface.

- These proteins are called apolipoproteins.

- Lipoproteins function is to keep their component lipids soluble as they transport them in the aqueous environment of plasma.

- Due to imbalanced metabolism of these lipoproteins there can be a gradual deposition of lipid—especially **cholesterol**—in tissues, which in arteries of the heart, can lead to CHD.

Topic 132

Lipoproteins

- The lipoprotein particles include

- chylomicrons (CM),

- very-low-density lipoproteins (VLDL),

- low-density lipoproteins (LDL), and

- high-density lipoproteins (HDL).

- They differ in

- lipid and protein composition,

- size,

- density and

- site of origin

- Different combinations of lipids and proteins produce particles of different densities

- ranging from chylomicrons to high-density lipoproteins

- these particles can be separated by ultracentrifugation and HPLC

- Chylomicrons are formed and assembled in intestinal mucosal cells after a fatty meal

- And carry dietary triacylglycerol, cholesterol, and cholesteryl esters to the **peripheral tissues.**

- As the chylomicron circulates and most of its dietary TAG are degraded and taken up by peripheral tissues in the form of fatty acids,

- the particle size decreases and density increases.

- The remaining particle, called Chylomicron Remnant, is removed from the circulation by the liver.
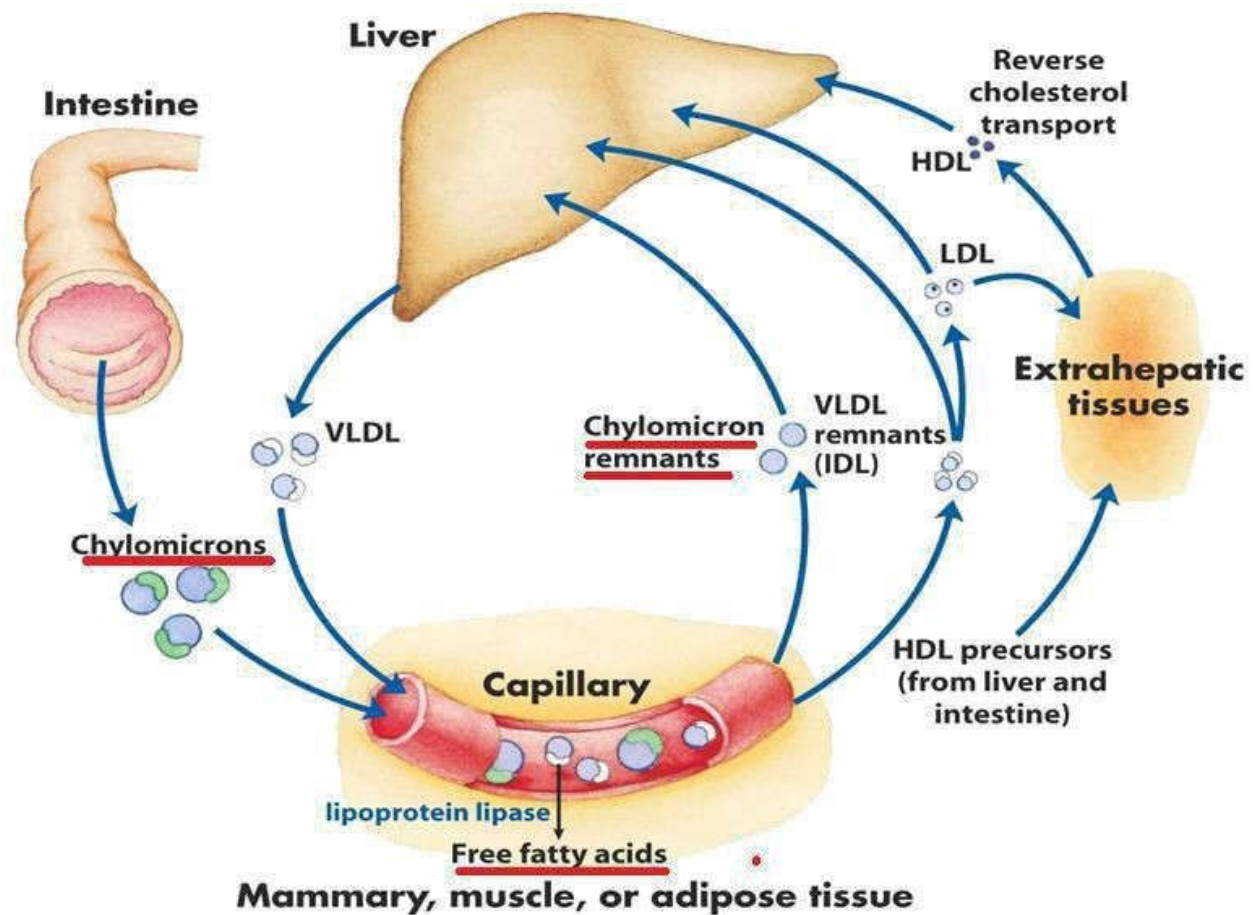
Topic 133

- **Lipoproteins (Contd.)**

- **VLDLs** are assembled in the liver.

- composed predominantly of TAGs synthesized in liver and

- contain some cholesterol and cholesteryl esters

- As VLDL pass through the circulation, TAG is degraded and taken up by peripheral tissues in the form of fatty acids,

- causing the VLDL to decrease in size and become denser,

- called VLDL remnant.

- further removal of triacylglycerol

- from these remnants produces low-density lipoprotein (LDL)

- LDL particles contain much less triacylglycerol than their VLDL predecessors,

- and have a high concentration of cholesterol and cholesteryl esters

- LDLs contain apoB-100 as their major apolipoprotein

- they carry cholesterol to extra hepatic tissues that have specific plasma membrane receptors that recognize apoB-100.

- apoB-100 receptors internalize the LDL into the cell.

- Remaining LDL is endocytosed by Liver cells.

- Oxidized LDL can also accumulate in the macrophage cells lining the arteries

- resulting in the formation of atherosclerosis.

Topic 134

Lipoproteins (Contd.)

- **HDL** The fourth major lipoprotein type, high-density lipoprotein,

- originates in the liver and small intestine

- as small, protein-rich particles that contain little cholesterol and no cholesteryl esters

- They take up cholesterol from non-hepatic (peripheral) tissues and **return** it to the liver as cholesteryl esters

- When cholesterol is taken up by HDL, it is immediately esterified and becomes hydrophobic and

- which is sequestered in the core of the HDL,

- This transforms the nascent HDL to a mature HDL particle.

- Mature HDL then returns to the liver, where the cholesterol is unloaded in a process called reverse cholesterol transport pathway

- This is the basis for the inverse relationship seen between plasma HDL concentration and atherosclerosis, and for HDL's designation as the "good" cholesterol carrier.

- A much stronger correlation exists between the levels of blood LDL cholesterol and heart disease

- In contrast, high levels of HDL cholesterol have been associated with a decreased risk for heart disease

- Abnormal levels of plasma lipids (dyslipidemias) act in combination with smoking, obesity, sedentary lifestyle, insulin resistance, and other risk factors to increase the risk of CHD

- Clinical studies have demonstrated that dietary or drug treatment of hyper - cholesterolemia is effective in decreasing LDL, increasing HDL, and reducing the risk for cardiovascular events.

Topic 135

Is not available

Topic 136

Role of dietary Lipids (Contd.)

- Unhealthy Fat contains

- Trans fat

- Saturated Fat

- Increased cholesterol content

Trans fat

- elevate serum LDL (but not HDL),

- Therefore they increase the risk of CHD

- Fatty acids of *trans* configuration in our food come from two different sources:

- industrially produced partially hydrogenated fat (IP-TFA) and

- ruminant produced Trans Fatty acid (RP-TFA)

- Industrially produced trans fatt (IP-TFA)

- These are made by partial hydrogenation of vegetable fat, and to a lesser extent, of fish oils by heating to about 400°C under high pressure and with the addition of different catalysts such as Nickel

- Ruminant produced Trans Fatty acid (RP-TFA)

- are made by bacterial metabolism of polyunsaturated fatty acids in the rumen of ruminants, such as cow & sheep

- And are consequently present in all fats from these animals

- The concentration of IP-TFA in partially hydrogenated fat may be as high as 60%.

- Whereas the maximum content of RP-TFA in ruminant fat is about 6%.

- In milk, RP-TFA is 4–6% of the fat.

- Recent studies suggest that with equal amounts of intake

- IP-TFA is more harmful than RP-TFA when compared on a gram-to-gram basis.

- The deleterious effects of trans fats occur at intakes of 2 to 7 g/day

- A single serving of French fries in a restaurant may contain this amount of trans fatty acids!

- Therefore, to reduce the harmful effects of trans fats, one should

- limit intake of foods prepared in IP-TFA containing oils such as baked goods and fast foods etc.

- instead of limiting fat intake from dairy sources.

Topic 137

Role of dietary Lipids (Contd.)

- Unhealthy Fat contains

- Trans fat

- Saturated Fat

- Increased cholesterol content

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Topic 137

Role of dietary Lipids (Contd.)

- Saturated fats —

Consumption of saturated fats is associated with high levels of

- total plasma cholesterol
  and

- LDL cholesterol.

- Saturated fats —

- butter,

- hard cheeses,

- whole milk,

- animal fats,

- palm oil, and

- coconut oils.

- Among the SFAs, stearic acid (18:0) appears to have a neutral effect on LDL-C.

- While lauric (12:0), myristic (14:0), and palmitic (16:0) acids are considered to be hypercholesterolemic

- Saturated FAs increase plasma LDL-C by;

- increasing the formation of LDL in the plasma compartment

- and by decreasing LDL turnover.

- The lowering of plasma LDL-C observed with PUFAs is likely due to;

- redistribution of cholesterol between plasma and tissue pools

- and up regulation of the LDL receptor

- In contrast, monounsaturated fatty acids (MUFAs) and PUFAs of the (n-6) family have been shown to;

- decrease plasma cholesterol concentrations in clinical studies

- **Dietary cholesterol:** Cholesterol is found only in animal products.

- dietary cholesterol has little effect on plasma cholesterol.

- Therefore, effect of dietary cholesterol on plasma cholesterol is less important than the amount and types of fatty acids consumed.

- A further reduction in dietary cholesterol seems to be unnecessary in those people;

- who have already reduced their intake of saturated fat

- and increased the ratio of polyunsaturated to saturated fatty acids

- **The Mediterranean Diet**

- Mediterranean cultures, show a low incidence of coronary heart disease

- The Mediterranean diet is an example of a

- diet rich in monounsaturated fatty acids (from olive oil) and ω-3 fatty acids (from fish oils and some nuts),

- but low in saturated fat

- The Mediterranean diet contains

- seasonally fresh food, with

- an abundance of plant material,

- low amounts of red meat, and

- olive oil as the principal source of fat

    - The Mediterranean diet is associated with decreased serum total cholesterol and LDL cholesterol—but

- little change in HDL cholesterol—when compared with a typical Western diet higher in saturated fats

Topic 138

STRUCTURE OF PHOSPHOLIPIDS

There are two classes of phospholipids:

- those that have glycerol as a backbone: glycerophospholipids

- those that contain sphingosine: sphingphospholipids

    Phospholipids are the predominant lipids of cell membranes

- Membrane Iipids are **amphipathic** i.e. one end of the molecule is hydrophobic, the other hydrophilic

- Their hydrophobic interactions with each other and their

- hydrophilic interactions with water direct their

- packing into sheets called membrane bilayers

- The formation of membrane bilayers

- help in partitioning the cellular environment from extracellular environment.

- Non-membrane-bound phospholipids serve additional functions in the body, for

    example, as components of lung surfactant

    essential components of bile.

- In contrast to triacylglycerol which is essentially synthesized only in liver, adipose tissue, lactating mammary glands, and intestinal mucosal cells

- essentially all cells except mature erythrocytes can synthesize phospholipids.

Topic 139

Glycerophospholipids
  ●

    Phosphatidic acid

- It is the simplest phosphoglyceride,

- It is a diacylglycerol with a phosphate group on the third carbon of glycerol.

- Phosphatidic acid is the precursor of the other members of this group.

- Further esterification with a low-molecular weight alcohol gives a glycerophospholipid

In general, glycerophospholipids contain

- a C_{16} or C_{18} saturated fatty acid at **C-1** and

- a C_{18} or C_{20} unsaturated fatty acid at **C-2** in addition to

- a phosphate group on **C-3**

- The phosphate group on phosphatidic acid (PA) can be esterified to another compound containing a hydroxyl group

- Serine + PA → phosphatidylserine

- Ethanolamine + PA → phosphatidylethanolamine

- Choline+ PA → phosphatidylcholine (lecithin)

- Inositol + PA → phosphatidylinositol

• The molecule is both a <u>primary amine</u> and a <u>primary alcohol</u>

• The fatty acids in glycerophospholipids can be any of a wide variety, so a given phospholipid (phosphatidylcholine, for example) may consist of several *molecular species,* each with its unique complement of fatty acids.
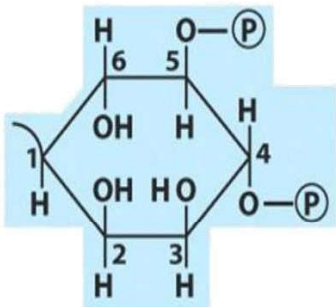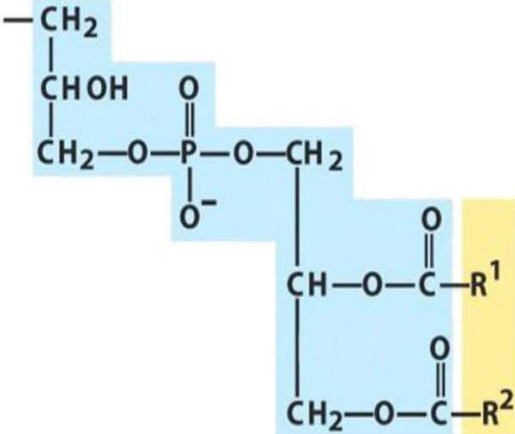
For instance,

• Dipalmatoyl phosphatidyl choline

and

• Palmitoyl-oleyl-phosphatidylcholine

are two different examples of Lecithins.

عمر غفور

Name of glycerophospholipid	Name of X	Formula of X
Phosphatidic acid	—	$-H$
Phosphatidylethanolamine	Ethanolamine	$-CH_2-CH_2-\overset{+}{N}H_3$
Phosphatidylcholine	Choline	$-CH_2-CH_2-\overset{+}{N}(CH_3)_3$
Phosphatidylserine	Serine	$-CH_2-CH-\overset{+}{N}H_3$ $\quad\quad\quad\; COO^-$
Phosphatidylglycerol	Glycerol	$-CH_2-CH-CH_2-OH$ $\quad\quad\quad OH$
Phosphatidylinositol 4,5-bisphosphate	*myo*-Inositol 4,5-bisphosphate	
Cardiolipin	Phosphatidyl-glycerol	

Topic 140

Glycerophospholipids

(Contd.)

Phosphatidylcholines (Lecithins)

- the most abundant phospholipids of the cell membrane

- represent a large proportion of the body's store of choline- important in nervous transmission, as acetylcholine.

- Dipalmitoyl phosphatidyl choline (DPPC or dipalmitoylecithin),

is also the major lipid component of lung surfactant

- Alveoli are the structural and functional unit of respiratory system in which gaseous exchange takes place.

- A thin fluid layer lines the alveoli for efficient gas exchange.

- When the water forms a surface with air, the water molecules on the surface (in contact of air) are strongly attracted to each other trying to reduce the surface area of contact. This is called **"surface tension"**.

- **surface tension** might result in alveolar collapse

- it requires a certain inflation pressure to maintain expanded alveoli

- the higher the surface tension, the more pressure required to inflate the bubble, especially in small alveoli.

- made and secreted by lung cells, surfactant serves to decrease the surface tension of this fluid layer.

- It scatters among the fluid molecule decreasing the attraction between them.

- surfactant have both hydrophilic and hydrophobic regions

- by adsorbing to the air-water interface of alveoli hydrophilic head groups in the fluid and the hydrophobic tails facing towards the air (DPPC) reduces surface tension.

عمر غفور

Nasal cavity

Nostril

Pharynx

Epiglottis

Glottis

Larynx

Trachea

Right lung

Left lung

Left bronchus

Blood flow

Smooth muscle

Bronchiole

Pulmonary arteriole

Pulmonary venule

Capillary network on surface of alveolus

Alveolar sac

Alveoli
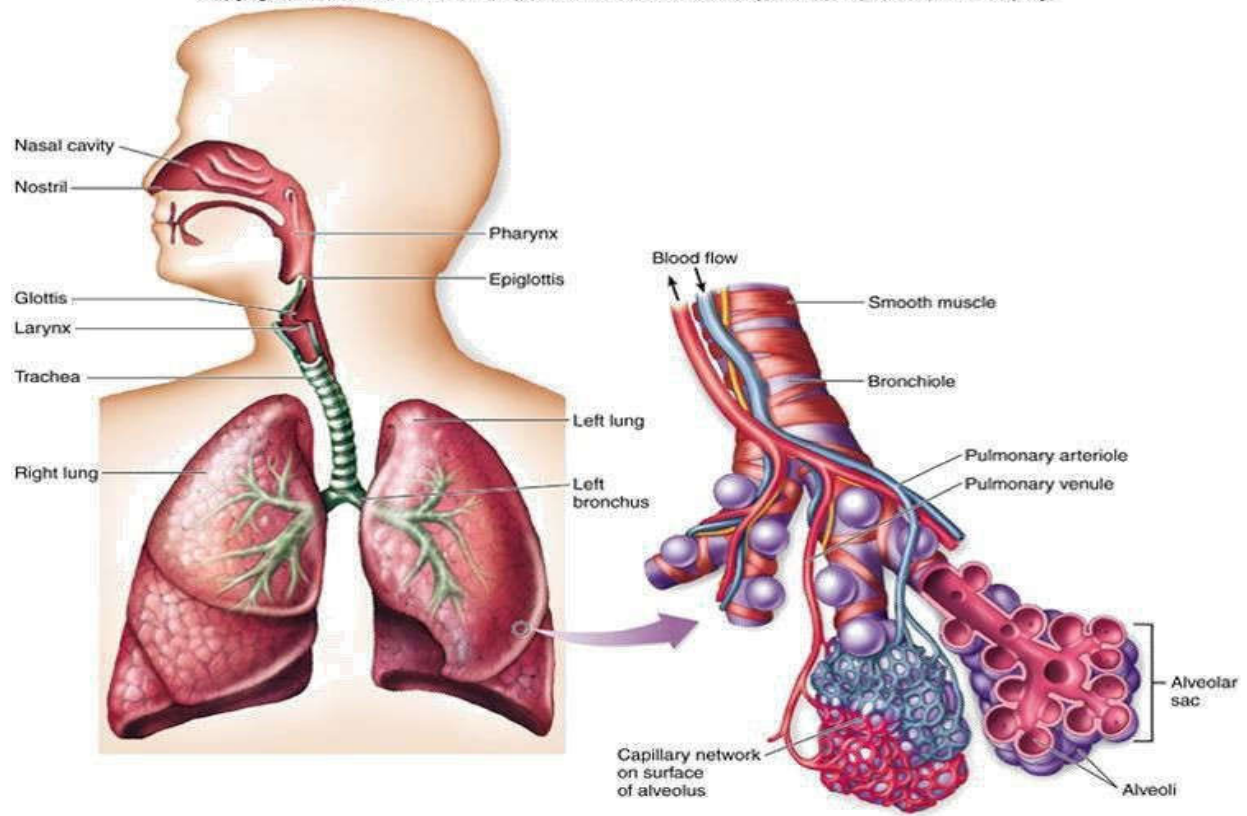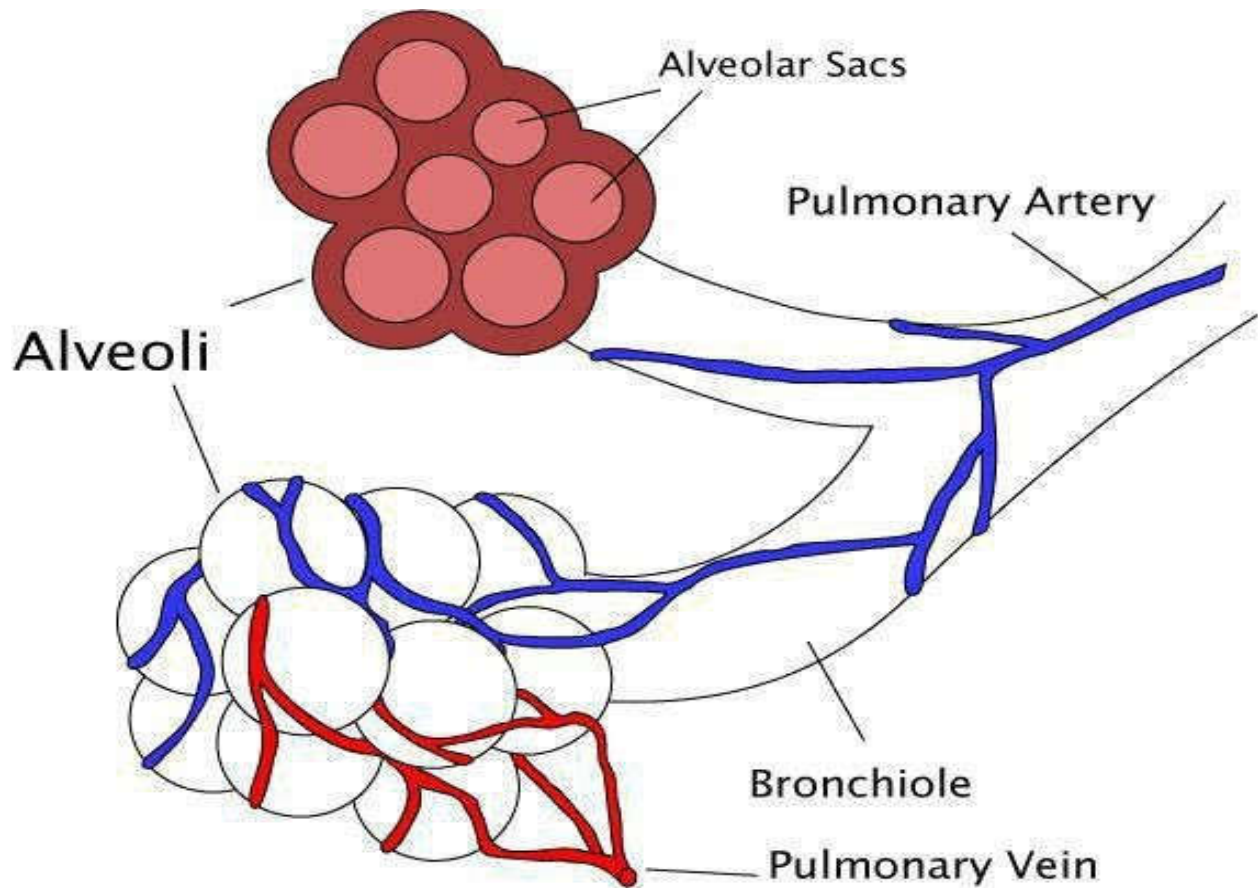
Topic 141

Glycerophospholipids

(Contd.)

- **Phosphatidyl ethanol amine** and **phosphatidylserine**

- are also found in cell membranes and

- differ from phosphatidylcholine only in that ethanolamine or serine, respectively, replaces choline

- Serine is a standard amino acid

- which on decarboxylation produces ethanolamine:

- a primary alcohol and a primary amine.

- Phosphatidylserine also plays a role in apoptosis (programmed cell death)

Cardiolipin

diphosphatidylglycerol

- Two molecules of phosphatidic acid esterified through their phosphate groups to an additional molecule of glycerol

- In eukaryotes, cardiolipin is virtually exclusive to **the inner mitochondrial membrane**, where it appears to be required for the maintenance of certain respiratory complexes of the electron transport chain.

- Decreased cardiolipin levels or alterations in its structure or metabolism cause mitochondrial dysfunction in **aging** and in **pathological conditions** including **heart failure**

- Cardiolipin is antigenic, and is recognized by antibodies raised against Treponema pallidum, the bacterium that causes syphilis

- The VDRL test measures immunoglobulin G (IgG) and IgM antibodies to lipoidal material released from damaged host cells as well as to lipoprotein-like material

- and possibly cardiolipin released from the treponemes

- Anti-cardiolipin antibodies may also be found non-specifically in certain auto-immune diseases.

Topic 142

Glycerophospholipids

(Contd.)

Phosphatidylinositol

- consists of phosphatidic acid and

- Inositol in an

- ester linkage

- Inositol is a polyol synthesized in the body from glucose

- and have the same chemical formula as glucose

Phosphatidylinositol (PI) is an unusual phospholipid in that it often contains

- stearic acid on carbon 1 and

- arachidonic acid on carbon 2 of the glycerol

- PI, therefore, as a reservoir of arachidonic acid, serves as precursor for prostaglandin synthesis

- Specific proteins can be covalently attached via a carbohydrate bridge to membrane-bound PI.

- Phosphatidylinositol is a precursor of second messengers

- The phosphorylation of membrane-bound phosphatidylinositol produces phosphatidylinositol 4,5-bisphosphate (PIP2)

- The degradation of PIP2 by phospholipase C occurs in response to the binding of a variety of neurotransmitters, hormones, and growth factors to receptors on the cell membrane

- The products of this degradation are

- inositol 1,4,5 trisphosphate (IP3) and

- diacylglycerol (DAG)

- These products mediate the

- mobilization of intracellular calcium and

- the activation of protein kinase C, respectively, which act synergistically to evoke specific cellular responses

Topic 143

Glycerophospholipids

(Contd.)

- **Ether lipids**

They are type of Glycerophospholipids,

in which one acyl chains is attached to glycerol in ether linkage, rather than ester linkage

- Ether lipids with an unsaturated group (alkenyl) at the 1st position on the glycerol chain are called Plasmalogens

- In some instances serine, or inositol may be substituted for ethanolamine or choline

- These compounds constitute as much as 10% of the phospholipids of brain and muscle

- Vertebrate heart tissue is uniquely enriched in ether lipids

- About half of the heart phospholipids are plasmalogens

- The membranes of halophilic bacteria, ciliated protists, and certain invertebrates also contain high proportions of ether lipids.

- The functional significance of ether lipids in these membranes is unknown;

- perhaps their resistance to the phospholipases that cleave ester-linked fatty acids from membrane lipids is important in some roles

- **Platelet-activating factor (PAF)**

- This is an unusual ether glycero phospholipid, with a **saturated** alkyl group in an ether link to carbon 1 and an acetyl residue (rather than a fatty acid) at carbon 2 of the glycerol backbone

- PAF is synthesized and released by a variety of cell types

- It binds to surface receptors, triggering potent thrombotic and acute inflammatory events

- It causes platelets to aggregate and degranulate (required for clotting), and neutrophils and alveolar macrophages to generate superoxide radicals (required for microbial killing)

Topic 144

SPHINGOLIPIDS

- Sphingolipids, like other membrane lipids, are composed of a

- hydrophobic portion, (ceramide) and

- a polar head group

- The first three carbons at the polar end of sphingosine are analogous to the three carbons of glycerol in glycerophospholipids

- The amino group at C-2 bears a fatty acid in amide linkage

- The fatty acid is usually saturated or monounsaturated, with

- 16, 18, 22, or 24 carbon atoms.

- Ceramide is the parent compound for this group

SPHINGOLIPIDS

- There are two subclasses of sphingolipids:

  – Sphingomyelins

  – Sphingoglycolipids

- **Sphingomyelins**

contain phosphocholine or phosphoethanolamines as their polar head group and are therefore classified along with glycerophospholipids as phospholipids

Sphingoglycolipids

are molecules that contain both

- carbohydrate and

- lipid (in the form of ceramide) components

- When the alcohol group at carbon 1 of sphingosine is, esterified to **phosphorylcholine**, **sphingomyelin,** the only significant sphingophospholipid in humans, is produced

Sphingomyelins are

- present in the plasma membranes of animal cells and are especially prominent in nerve tissue including myelin, -thus the name "sphingomyelins

- Sphingomyelin of the **myelin sheath** contains predominant longer-chain fatty acids such as lignoceric acid and nervonic acid (24 carbon)

- whereas **gray matter of the brain** has sphingomyelin that contains primarily stearic acid(18 carbon)

Topic 145

Glycosphingolipids are molecules that contain both

- carbohydrate and

- lipid components

- Like the phospholipid sphingomyelin, they are derivatives of ceramide

- They are also an important component of membrane bilayers.

- They occur largely in the outer face of plasma membranes have polar head groups with

- one or more sugars connected directly to the -OH at

- C-1 of the ceramide moiety by an O-glycosidic bond

Cerebrosides

- have a single sugar linked to ceramide;

- galactocerebrosides are found in the plasma membranes of **neural cells**,

- glucocerebrosides in the plasma membranes of **non neural cells**

- **Galactosylceramide** is a major glycosphingolipid of brain and other nervous tissue,

- It contains a number of characteristic C24 fatty acids, eg, cerebronic acid

- **Globosides**

are glycosphingolipids

- with two or more sugars, usually

- D -glucose,

- D- galactose, or

- N-acetyl-D-galactosamine.

- A glycosphingolipid that has only one sugar as the side chain is called a cerebroside

- Globosides are highly abundant in RBCs.

- Globosides are also found in human serum, spleen and liver.

Topic 146

Glycosphingolipids

(Contd.)

- **Gangliosides**

- They have oligosaccharides as their polar head groups and

- one or more residues of N-acetylneuraminic acid (a sialic acid), at the termini.

- Sialic acids are acidic sugars with a nine-carbon backbone, of which the most common is

- *N*-acetylneuraminic acid

- Sialic acid gives gangliosides the negative charge at pH 7.

- Gangliosides with one sialic acid residue are in the GM (M for mono-) series,

- those with two are in the GD (D for di-) series,

- and so on (GT three sialic acid residues; GQ, four)

- About 6% of **brain** lipids are gangliosides and were first isolated from the ganglion of brain cells

- They act as specific receptors for glycoprotein hormones in the cells.

- Some gangliosides also serve as receptors for some bacterial protein toxins e.g.

- Cholera toxin binds to the GM1 gangliosides on the surface of target cells

- Gangliosides also help in

- cell-cell recognition and thus have a significant role in

- growth and

- differentiation of tissues and also in

- carcinogenesis

Sulfatides

Sulfoglycosphingolipids (sulfatides) are cerebrosides that contain sulfated galactosyl residues, and are therefore negatively charged at physiologic pH

- Sulfatides are found predominantly in nerve tissue and kidney

Topic 147

ABO Blood Groups and Glycosphingolipids

- The basis of blood groups depend on expression of different antigens on RBCs.

- These antigens are found in cell membranes as oligosaccharide components of

- glycosphingolipids

OR

- glycoproteins

- Different compositions of carbohydrate (oligosaccahride chains) in different antigens.

- These oligosaccharides are attached to proteins through a serine or threonine residue

- or to ceramide lipid intermediate

- The precursor to the ABO blood group antigens, present in people of all common blood types, is the O antigen (also referred to as H antigen.)

- Modification of this O antigen then

- results in A, B or AB blood groups respectively.

- These antigens are present on other cells of the body as well.

Topic 148

Glyceroglycolipids

These are the predominant membrane lipids of the plants, such as those of chloroplast.

They include

- Galactolipids and

- Sulfolipids

As the name indicates these glycolipids contain glycerol instead of sphingosine as their backbone.

Galactolipids

In galactolipids, the C3 of the glycerol moiety is connected to one or more galactose residues by glycosidic linkages.

The head groups of these galactolipids are uncharged but polar.

عمر غفور

Galactolipids are localized in the internal membranes of chloroplast

They constitute about 70% to 80 % of plant membrane lipids and

thus are the most abundant lipids in the biosphere.

Sulfolipids

They are membrane glycolipids with **sulfur** containing functional

groups Sulfonated glucose is joined to the **C3** of diacylglycerol in

glycosidic linkage

Topic 149

- **Steroids and Cholesterol**

- A **steroid** is a lipid whose structure is based on the tetracyclic (four-ring)

structure consists of

- 3 cyclohexane rings.

- 1 cyclopentane ring.

- Steroids with eight to ten carbon atoms in the side chain at C-17 and a hydroxyl group at C-3 are classified as **sterols**

- Cholesterol is the major sterol in animal tissues

- Cholesterol has an eight carbon branched hydrocarbon chain attached to **C-17** of the D ring

- Ring A has a hydroxyl group at C-3, and ring B has a double bond between C-5 and C-6

- Cholesterol is an amphipathic lipid

- Cholesterol is a structural component of all cell membranes, modulating their fluidity

- Cholesterol is a precursor of

> bile acids
>
> steroid hormones
>
> vitamin D

All tissues containing nucleated cells are capable of cholesterol synthesis, which occurs in the

endoplasmic reticulum and the

cytosol

- **Cholesterol** is present in tissues and in plasma either as free cholesterol or combined with a long-chain fatty acid as cholesteryl ester

- In plasma, both forms are transported in lipoproteins

- in esterified form, with a FA attached at C-3,

- the structure becomes more hydrophobic than free cholesterol

- Cholesteryl esters are not found in membranes, and are normally present only in low levels in most cells

- The ring structure of cholesterol cannot be metabolized to CO_2 and H_2O in humans

- Therefore humans cannot utilize cholesterol for energy.

- Cholesterol is excreted from the body via the bile either in the

- unesterified form or

- after conversion into bile acids in the liver

Topic 150

BILE ACIDS AND BILE SALTS

- Bile is a fluid that is made and released by the liver and stored in the gallbladder

- Bile helps with lipid digestion

- Bile can either pass directly from the liver into the duodenum, or

- be stored in the gallbladder when not immediately needed for digestion

- Bile consists of a watery mixture of organic and inorganic compounds

- Phosphatidylcholine (lecithin) and

- bile salts (conjugated bile acids) are quantitatively the most important organic components of bile

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- The primary bile acids are synthesized in the liver from cholesterol

- These are cholic acid and

- chenodeoxycholic acid

- The bile acids contain 24 carbons, with two or three hydroxyl groups and a side chain that terminates in a carboxyl group

The carboxyl group has a pKa of about 6 and, is not fully ionized at physiologic pH- hence the term "bile acid"

- The bile acids are amphipathic molecules

- They therefore can act as emulsifying agents in the intestine

- They emulsify

- dietary triacylglycerol and other complex lipids

- for degradation by pancreatic digestive enzymes.
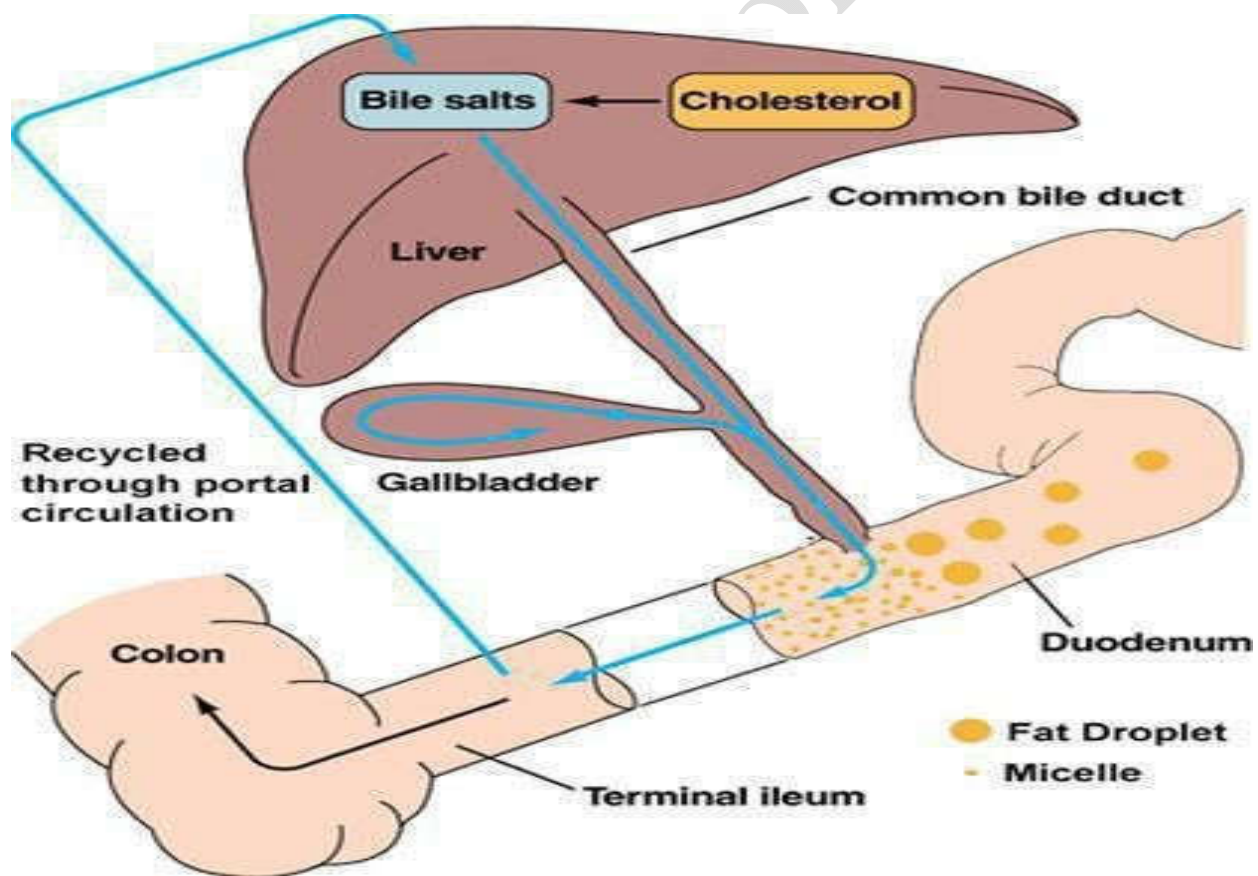
Topic 151

EICOSANOIDS

Eicosanoids are a large group of lipid messengers with potent effects on every tissue in the body

Eicosanoids are derived from metabolism of 20-carbon, polyunsaturated fatty acids **(eicosanoic acids)**

- **Eicosanoids** include (but not limited to)

    Prostanoids consisting of

    Prostaglandins

    Prostacyclins

    Thromboxanes

    Leukotrienes

    Lipoxins

    Epoxides

    These extremely potent compounds acting through their specific receptors

- elicit a wide range of physiologic and pathologic responses.

- particularly important in eliciting inflammatory response that occurs after infection or injury and

- produce symptoms such as pain, swelling, and fever.

- they also control bleeding through forming blood clots

- Eicosanoids are derived from either omega-3 (ω-3) or omega-6 (ω-6) fatty acids.

- Arachidonic acid is the most common precursor of the eicosanoids.

- Three major pathways for the metabolism of arachidonic have been discovered sofar.

- Cyclooxygenase pathway; prostaglandins and thromboxanes.

- lipoxygenase pathway; leukotrienes, HETEs, and lipoxins.

- cytochrome P450 pathway epoxides and HETEs

- There are different series of eicosanoids

- depending on the precursor 20 C FA. derived from the essential fatty acids **linoleic**

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acid and **linolenic,** OR

- directly from dietary **arachidonic acid** and **eicosapentaenoic acid**

- Depending on the precursor different numbers of double bonds are present in these eicosanoids reflecting the parent 20C FA.

Topic 152

CYCLOOXYGENASE PATHWAY

- **Prostaglandins**

- Prostaglandins are fatty acids containing 20 carbon atoms, including

- an internal 5-carbon ring.

- **Nomenclature** of prostaglandins (PGs) involves the

- assignment of a capital letter (PGE),

- a numeral subscript (PGE$_1$), and

- for the PGF family, a Greek letter subscript (PGF$_{2\alpha}$).

- The capital letter refers to the ring substituents at positions X and Y.

- The numeral subscript that follows the capital letter(e.g. PGE$_1$) refers to the PG series 1, 2, or 3, determined by the number of unsaturated bonds present in the linear portion of the hydrocarbon chain.

- It does not include double bonds in the internal ring.

- The double bonds between carbons 13 and 14 are *trans*; the others are *cis*

- The Greek letter subscript, found only in the F series, refers to the position of the hydroxyl group at carbon 9.

- This hydroxyl group primarily exists in the α position, i.e. it lies below the plane of the ring.
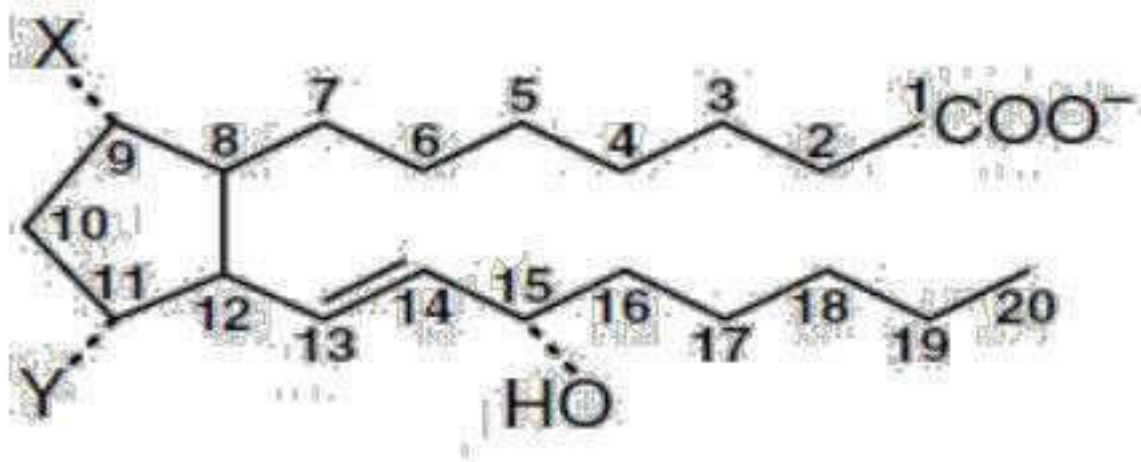
Prostaglandins have a hydroxyl group at C 15, a double bond between C 13 and C 14, and various substituents on 5 membered ring at C9 and C11

Double bonds also may be present between carbons 5 and 6 and between carbons

17 and 18 in case of series 2 and 3

Topic 153

CYCLOOXYGENASE PATHWAY (Contd.)

- Thromboxanes (TX)

- also formed via the cyclooxygenase pathway,

- differ from PGs in that they contain a 6-membered ring that includes an oxygen atom

Biosynthesis of the PGS and TX

- Those derived from arachidonic acid, the 2-series, (such as PGE**2**,TXA**2**), are described here

- because the 1-series and the 3-series are present in very small amounts in humans.

- The initial step, which is catalyzed by a cyclooxygenase (COX), forms the five-membered ring and

- adds four atoms of oxygen (two between C 9 and C11, and two at C 15) to

- form the unstable PGG**2**.

- The hydro-peroxy group at carbon 15 is

- quickly reduced to a hydroxyl group by a peroxidase to form PGH**2**

- PGH**2** is the precursor of all other PGs and TXAs

- The next step is tissue specific

- For example, PGH**2** may be reduced to PGE**2** or PGD**2** by specific isomerases (PGE synthase or PGD synthase respectively).

- For example, TXA Synthase is present in high concentration in platelets and forms TXA**2**.

- In the vascular endothelium, however, PGH**2** is converted to the PGI**2** by action of Prostacyclin Synthase.

- The beneficial effect of cold water fish (e.g., salmon), with a high content of eicosa-pentaenoic(TX**3**) acid (EPA), and docosa-hexaenoic acid (DHA) comes from the fact that they lead to formation of more TXA**3** relative to TXA**2**.

- TXA**3** is less effective in stimulating platelet aggregation than its counterpart in the 2-series, TXA**2**.

- Platelet aggregation is the culminating step in the cardiovascular diseases due to atherosclerosis.

Topic 154 and 155

Lipoxygenase Pathway:

Synthesis of the Leukotrienes, and Lipoxins (Count.)

- In addition to serving as a substrate for the cyclooxegenase pathway,

- arachidonic acid and other 20 C FAs also act as substrate for the lipoxygenase pathway.

- In contrast to products of the cyclooxegenase pathway which are cyclical.

- Products of lipoxygenase pathway are linear.

- Similar nomenclature rules are followed for Leukotrienes and Lipoxins,

- except that there are no series of 1 and 2.

- The series starts from 3.

- the eicosanoids synthesized in lipoxygenase pathway from;

- Eicosa-tri-enoic acid (ETA) have 3 double bonds

- from; Arachidonic acid have 4 double bonds

- From; Eicosa-pentaenoic acid (EPA) have 5 double bonds .

- The lipoxygenase enzymes catalyze the incorporation of an oxygen molecule on to a carbon of one of several double bonds of arachidonic acid, forming a hydro-peroxy (– OOH) group at these positions

- The double bonds at which oxygen is added are between C5 & C6, between C11 and C12 and between C14 and C15.

Topic 156

Lipoxygenase Pathway:

Synthesis of the Leukotrienes, and Lipoxins

(Contd.)

- HPETEs (Hydro-per-oxy-eicosa-tetra-enoic acids) are the precursors of leukotrienes and lipoxins

- The major leukotrienes are produced by 5-lipoxygenase

- 5-HPETE is converted to leukotriene A$_4$ (LTA$_4$).

- Other functional leukotrienes are formed from LTA$_4$ for example,

- LTA$_4$ is converted to LTB$_4$, as a 5,12-dihydroxy derivative.

- the addition of reduced glutathione to carbon 6 forms LTC$_4$

- Removal of glutamate residue from LTC$_4$ forms LTD$_4$

- LTD$_4$ on removal of glycine becomes LTE$_4$

- Leukotrienes were so named because they were first discovered in leukocytes(white blood cells)
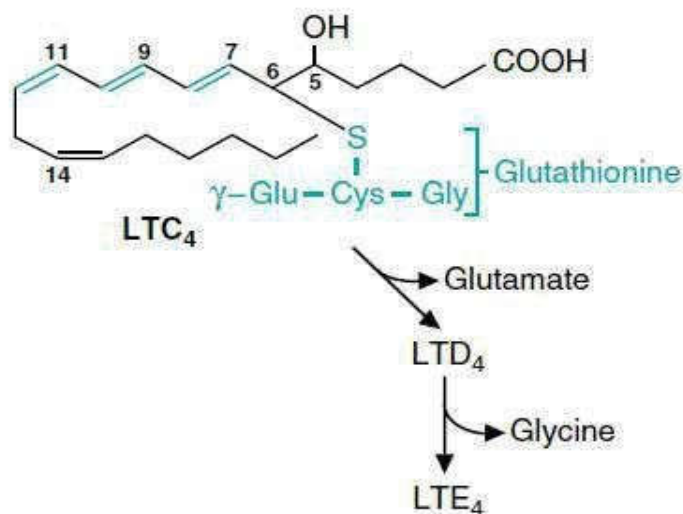
Topic 157

Lipoxygenase Pathway:

Synthesis of the Leukotrienes, and Lipoxins

(Contd.)

- The lipoxins are formed through the action of 15-lipoxygenase followed by the action of 5-lipoxygenase on arachidonic acid.

- A series of reductions of the resultant hydro-per-oxy groups leads to the formation of tri-hydroxy derivatives of arachidonic acid known as the lipoxins.

- Lipoxins induce chemotaxis and

- stimulate superoxide radicals for killing of microorganisms

- Prostaglandins, thromboxanes, leukotrienes and lipoxins have very short half lives and rapidly degraded in the body.

- In summary, Eicosanoids are derived from C20 (eicosanoic) fatty acids synthesized from the essential fatty acids and make up important groups of physiologically active compounds.

Topic 158

Biomedical importance of nucleotides

- **Precursors of nucleic acids:** Nucleotides are the building blocks of nucleic acids.

- Without them, DNA or RNA can not be produced.

- **Transmission of genetic information;**

- This gives them the ability to store and transmit genetic information from;

- one generation to the next which is a fundamental condition for life

- **Protein synthesis,**

- the ultimate expression of this information, is therefore dependent on nucleotides.

- **Energy currency:** Nucleotides play an important role as "energy currency" in the cell.

- Nucleoside tri- and diphosphates such as **ATP and ADP** are the principal donors and acceptors of phosphoryl group in metabolism.

- By doing this, they play a key role in the energy transduction.

    This energy is used in almost every energy requiring process in the body, such as;

    Muscle contraction,

    Transmission of nerve impulse,

    Transports of nutrients across cell membrane

    Motility of spermatozoa

    And many more energy dependent processes

Topic 159

- The sugar derivatives UDP-glucose and UDP-galactose participate in sugar inter conversions

- And in the biosynthesis of starch and glycogen

- Similarly, nucleoside-lipid derivatives such as CDP acylglycerol are intermediates in lipid biosynthesis.

- **Co-enzymes:**

- When linked to vitamins nucleotides are structural components of several essential coenzymes, for example,

- coenzyme A,

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- FAD, (Flavin Adenine Dinucleotide)

- **Co-enzymes:**

- NAD$^+$ (Nicotinamide adenine Dinucleotide) and

- NADP$^+$ (Nicotinamide adenine Dinucleotide Phosphate)

- **Regulatory compounds:** Nucleotides are important regulatory compounds for many of the pathways of intermediary metabolism, inhibiting or activating key enzymes.

- Roles that nucleotides perform in metabolic regulation include:

- ATP-dependent enzyme phosphorylation in key metabolic reactions.

- Allosteric regulation of enzymes by ATP, AMP, and CTP

- Phosphorylation can either activate or inhibit ATP-dependent enzyme depending on the type of enzyme.

- Similar is the case with dephosphorylation.

Topic 160

Biomedical importance

of nucleotides (Contd.)

- **Sulfate group donor:** Adenosine 3'-phosphate-5'-phosphosulfate is the sulfate donor for

    sulfated proteoglycans

    sulfate conjugates of drugs.

- **Methyl group donor:**

    S-adenosylmethionine is a methyl group donor

- e.g Nor-adrenaline ‹ Adrenaline by methylation.

- **Second messengers:** Nucleotides, such as *cyclic AMP (cAMP)* and *cyclic GMP (cGMP)*,

- serve as second messengers in signal transduction pathways.

- **Signal Transduction**: GTP and GDP play key

- roles in activating or inhibiting proteins in

- various cellular signaling cascades.

- **Medical applications** Specifically medical applications include the

- use of synthetic purine and pyrimidine analogs

- that contain halogens, thiols, or additional nitrogen atoms;

   There use include chemotherapy for cancer

   as suppressors of the immune response during organ transplantation.

   as anti-viral drugs such as in the treatment of AIDS

Topic 161

Composition of Nucleotides

Nucleotides are composed of

- A nitrogenous base (purine or pyrimidine)

- A pentose monosaccharide

- One, two, or three phosphate groups

- **Nitrogenous Bases**

- The nitrogen-containing bases belong to two families of compounds:

- Purines

- Pyrimidines

- By the attachment of different groups to the rings, different types of pyrimidine and purine are generated.

- The suffix "ine" in these bases denotes the presence of nitrogen (amine) in the ring.

- However, there are some exceptions such as naming of uracil

- The utility of these nitrogen-containing ring structures lies in the ability of the nitrogen to form hydrogen bonds and to

- accept and donate electrons while still part of the ring.

Topic 162

Composition of Nucleotides (Contd.)

- **Purines**

- Both DNA and RNA contain the same purine bases:

- Adenine (A)

- Guanine (G)

- Adenine when combines with pentose the structure is known as Adenosine or deoxyadenosine

- Guanine when combines with pentose the structure is known as Guanosine or deoxyguanosine

- Adenine is 6-aminopurine

- Guanine is 2-amino,6-hydroxypurine

- Minor Purine Bases: Inosine (I) & methyl guanine (7mG)

- Unnatural: Mercaptopurine, Allopurinol & 8-Azaguanine

- Other purines include: hypoxanthine and xanthine

- Uric acid is the catabolic end product of purines in human beings.

Topic 163

Composition of Nucleotides (Contd.)

- **Pyrimidines:**

- Pyrimidines include:

- Cytosine (C)—in both DNA and RNA

- Thymine (T)—only in DNA

- Uracil (U) —only in RNA

- Cytosine when combines with

 pentose it becomes deoxycytidine and cytidine

- Thymine becomes thymidine and deoxythymidine

- Uracil (U) becomes uridine and deoxyuridine

- depending on the type of sugar.

- Cytosine is 2-oxy-4-amino-pyrimidine

- Thymine is 2,4-dioxy-5-methyl-pyrimidine

- Uracil is 2,4-dioxy-pyrimidine

- T and U differ by only one methyl group, which is present on T but absent on U

- Minor Pyramidine Bases:

- Dihydrouridine (DHU) ,

- 5-Methyl Cytadine &

- 5-Hydroxy-Methyl Cytadine

- Unnatural Pyramidine Bases:

- Fluorouracil (5FU) &

- 6-Aza Cytosine (AZC)

- Unlike the purine ring, which is not cleaved in human cells, the pyrimidine ring is opened and degraded

- to highly soluble products, β-alanine and β-amino-iso-butyrate,

- with the production of NH_3 and CO_2.

Topic 164

Composition of Nucleotides (Contd.)

- **Pentose Sugar**

- D-ribose and 2-deoxy D-ribose are the only sugars so far found in the nucleic acids.

- These aldo pentoses belong to D-family

- They are present as Furanose (ring) in the form of β-Anomer

- The addition of a pentose sugar to a base produces a **nucleoside**

    If the sugar is D-ribose, a ribonucleoside is produced

    If the sugar is 2-deoxy D- ribose, a deoxyribonucleoside is produced

- **Phosphate group**

- There may be one, two, or three phosphate groups present in nucleotides.

- **Nucleotides** are monophosphate, diphosphate, or triphosphate esters of nucleosides

- These phosphate groups give an over all negative charge to the nucleotides.

Topic 165

Properties of Nitrogenous Bases

- **Aromatic:** The Nitrogen containing bases are aromatic i.e. they have alternate double bonds

- **Heterocyclic:**

- They are heterocyclic i.e. structures that contain other atoms in addition to carbon, such as nitrogen in the ring structure

- The six-atom rings of purines and pyrimidines are numbered in opposite directions.

- **Weak Bases:** Purines or pyrimidines with an $-NH_2$ group are weak bases

- **Functional Groups:** The most important functional groups of pyrimidines and purines are

- ring nitrogens

- carbonyl groups

- exocyclic amino groups

- **Hydrophobicity:**

- The purine and pyrimidine bases are hydrophobic and relatively insoluble in water at the near-neutral cell pH

- **Stacking Interaction:** Hydrophobic stacking interactions in which two or more bases are positioned with the planes of their rings parallel (like a stack of coins) are one of two important modes of interaction between bases in nucleic acids.

- Base stacking helps to minimize contact of the bases with water, and these interactions are very important in stabilizing the three-dimensional structure of nucleic acids.

Topic 166

**Properties of Nitrogenous Bases** (Contd.)

- **UV light absorbance:** The conjugated double bonds of purine and pyrimidine derivatives absorb ultraviolet light.

- Nucleic acids are characterized by a strong absorption at wavelengths near 260 nm.

- The mutagenic effect of ultraviolet light is due to its absorption by nucleotides that results in chemical modifications in DNA.

- This property is also utilized in quantitative and qualitative analysis of nucleotides and nucleic acids.

- **Tautomerism:**

- All these bases can exist in keto-enol or amine-imine form.

- At physiologic pH keto and amine form is predominant.

- Note that the smaller pyrimidine molecule has the *longer* name and

- the larger purine molecule the *shorter* name.

Topic 167

N-glycosidic bond

- Sugars are linked to the heterocycle by a β -N-glycosidic bond, almost always to the

- N-1 of a pyrimidine

- N-9 of a purine

- The N-glycosyl bond is formed by removal of the elements of water

- a hydroxyl group from the pentose and

- hydrogen from the base

ATP
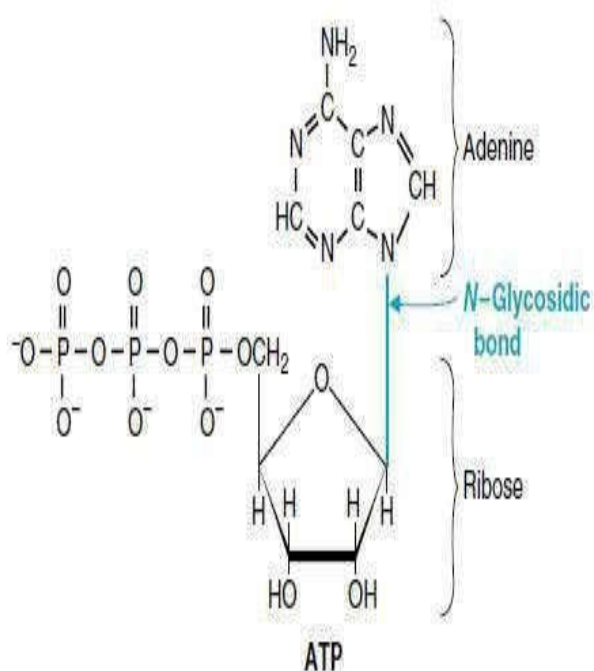
- Thus it is a condensation reaction.

- Similar to O-glycosidic bond formation in carbohydrates

- However, N-glycosidic bonds, have Nitrogen atom instead of oxygen linking the two residues.

- the addition of the glycosidic bond to nitorgenous base is indicated by the name change

- such as from adenine to aden**osine** for the gly**cosidic** bond

Topic 168

Numbering of Carbon and Nitrogen Atoms

- The carbon and nitrogen atoms in the rings of the base and the sugar are numbered separately.

- The atoms in the rings of the **bases** are numbered

- 1 to 6 in pyrimidines &

- 1 to 9 in purines

- In the pentoses of nucleotides and nucleosides the carbon numbers are given a prime (')

designation to distinguish them from the numbered atoms of the nitrogenous base.

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- The carbons in the **pentose** are numbered 1' to 5'.

- Numerals with a prime (e.g., 2' or 3') distinguish atoms of the sugar from those of the heterocycle.

- Thus, when the 5'-carbon of a nucleoside (or nucleotide) is referred to, a carbon atom in the pentose, rather than an atom in the base, is being specified.

Topic 169

Phosphodiester Bond

- When two or more nucleotides combine together a phosphodiester bond is formed.

- This bond is formed mainly between the 3´OH group of sugar of one nucleotide and

- 5´PO4 group of sugar of another nucleotide creating a phosphodiester linkage.

- By definition, the 5´ end lacks a nucleotide at the 5´ position and the

- 3´ end lacks a nucleotide at the 3´ position.

- The sugar and phosphate group is called the backbone of the nucleic acid.

- The backbones of both DNA and RNA are hydrophilic.

- The hydroxyl groups of the sugar residues form hydrogen bonds with water.

- The phosphate groups, are completely ionized and negatively charged at pH 7

- The negative charges are generally neutralized by ionic interactions with positive charges which are present on proteins, metal ions, and polyamines.

- Depending on the number of nucleotides

- mono- di-, tri-, oligo- and polynucleotides are formed

- as a result of phosphodiester bond formation.

Topic 170

Cyclic Nucleotides

- There are two important cyclic nucleotides:

- Cyclic AMP cAMP

- Cyclic GMP cGMP

Cyclic AMP is a cyclic nucleotide

- cAMP is synthesized in tissues from ATP

- chemically it is 3´-5´ adenosine monopohosphate.

Functions of c-AMP

- Acts as second messenger in the cell

- It has role in glycogen metabolism

- ‡cAMP, ‡glycogenolysis

- ‡cAMP ‡TAG metabolism

- ‡cAMP ‡ lipolysis

- It decreases cholesterol synthesis

- It causes activation of protein kinases which in turn;

- activate or deactivate other enzymes.

- It regulates the cell membrane permeability, by increasing permeability of cell membrane to H_2O, Na^+, K^+ & Ca^{+2}

- Moreover, it regulates

- insulin secretion,

- catecholamine biosynthesis &

- Melatonin synthesis

Cyclic GMP is synthesized from GTP

- It serves as a second messenger in response to nitric oxide during relaxation of smooth muscle (especially blood vessels) so it has role in smooth muscle relaxation and vasodilatation.

It also has role in

- Protein phosphorylation

- Neurotransmission

- Insulin action

- Regulation of sodium channels

Topic 171

DNA

- It stands for Doeoxyribonucleic acid

- DNA is present in nuclear chromosomes of eukaryotes

- mitochondria

- chloroplasts and

- plasmids of prokaryotes

- DNA is a polymer of deoxyribonucleoside monophosphates

- covalently linked by 3'   5'-phosphodiester bonds.

- DNA is a repository of genetic information

- In eukaryotic cells, DNA is present in the chromosomes in the nucleus.

- It is found associated with basic proteins HISTONES and also various other proteins present in nucleus (nucleoproteins)

- Prokaryotic cells lack nuclei, and have a single chromosome.

- The protein-DNA complex is present in a non membrane bound region known as nucleoid.

- It also contain non-chromosomal DNA in the form of plasmids.

- Nucleic acid structure can be described in terms of hierarchical levels of complexity (primary, secondary, tertiary)

- The primary structure of a nucleic acid is its

- covalent structure and

- nucleotide sequence.

- Any regular, stable structure taken up by some or all of the nucleotides in a nucleic acid can be referred to as secondary structure

- In DNA double **helix**, the two strands of DNA are held together by hydrogen bonds.

- The nucleotides on one strand base pairs with the nucleotide on the other strand.

- The secondary structure is responsible for the shape that the **nucleic** acid assumes.

- The complex folding of large chromosomes within eukaryotic chromatin and bacterial nucleoids is generally considered tertiary structure

Topic 172

DNA Interactions

- The purine and pyrimidine bases are hydrophobic and relatively insoluble in water at the near-neutral pH of the cell.

- Hydrophobic stacking interactions in which bases are positioned with the planes of their rings parallel

- Hydrophobic stacking are an important interaction between bases in nucleic acids.

- The stacking also involves a combination of van der Waals and dipole-dipole interactions between the bases.

- Base stacking helps to minimize contact of the bases with water.

- Therefore base-stacking interactions are very important in stabilizing the three-dimensional structure of nucleic acids.

- The most important functional groups of pyrimidines and purines are

- ring nitrogens,

- carbonyl groups, and

- exocyclic amino groups.

- Hydrogen bonds involving the amino and carbonyl groups are the second important mode of interaction between bases in nucleic acid molecules.

- The most important hydrogen-bonding patterns are those defined by James D. Watson and Francis Crick, in which

- A bonds specifically to T (or U) and

- G bonds to C.

- These two types of base pairs predominate in double-stranded DNA and RNA.

Topic 173

DNA Primary Structure

- The primary structure of a nucleic acid is its

- covalent structure and

- nucleotide sequence.

- The back bone of the primary structure is the linear strand made by sugar phosphate residues, linked together, while the bases project laterally.

- This way a long, un-branched chain is formed.

- The resulting long, un-branched chain has polarity.

- Both 5'-end and 3'-end are free.

- at 5'-end there is a free phosphate.

- at 3'-end there is a free OH that are not attached to other nucleotides.

- Purines and pyrimidines project laterally from the backbone and forms a variable part.

- The variable part is concerned with the expression of genetic information.

- By convention, the structure of a single strand of nucleic acid is always written with the 5´ end at the left and the 3´ end at the right

- that is, in the 5´ to 3´ direction.

- Some simpler representations of this penta deoxy ribonucleotide are

- pA-C-G-T-A OH,

- pApCpGpTpA, and

- finally 5´-ACGTA-3´.