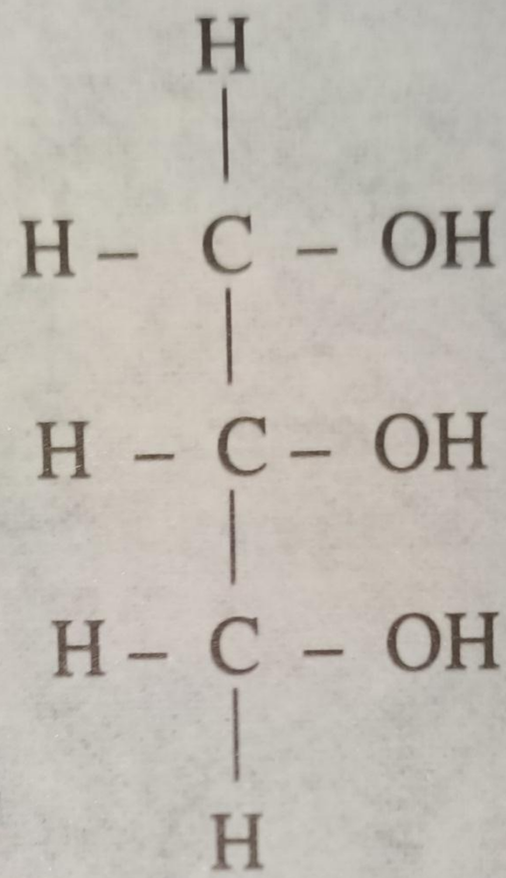
Lecture Series on Biochemistry (Part 4)

Lipids

- The lipids (Gr., *lipos*=fats) are organic compounds which are insoluble in water but are soluble in non-polar organic solvents such as acetone, benzene, chloroform and ether.
- This general property of lipids is due to the predominance of long chains of aliphatic hydrocarbons in their molecules.
- Lipids are non-polar and hydrophobic.
- Common examples of lipids are cooking oil, butter, ghee, waxes, cholesterol etc.

- Lipids are all made of C, H and sometimes O. The number of O atoms in alipid molecule is always small compared to the number of C atoms.
- Sometimes small amounts of P, N and S are also present.
- Natural fats and oils are compounds of glycerol(i.e. glycerine or propane-1,2,3 triol) and fatty acids.
- They are esters which are formed due to resaction of organic acids with alcohols..
- There is only one kind of glycerol: its molecular configuration shows no variation and it is exactly same in all lipids. The formula of glycerol is $C_3H_8O_3$ and its molecular structure is as follows:



Glycerol

Fatty acid

- Fatty acid molecule is amphipathic and has 2 distinct regions or ends:
  - a long hydrocarbon chain, which is hydrophobic and not very reactive chemically.
  - and a carboxylic acid group which is ionised in solution and is extremely hydrophilic and readily forms esters and amides.
- In neutral solutions salts of fatty acids form small spherical droplets or micelles in which the dissociated carboxyl groups occur at surface and the hydrophobic carbon chains project towards the centre.
- In cells, the fatty acids only sparingly occur freely; instead they are esterified to other components and form saponifiable lipids.

Fatty acid molecule may be either saturated or unsaturated.

- The saturated fatty acids consist of long chain hydrocarbon chains terminating in a carboxyl group and conform to the general formula

$$CH_3\text{-}(CH_2)_n\text{-}COOH$$

- In nearly all naturally occurring fatty acids, *n* is an even number from 2 to 22.
- In the saturated fatty acids, most commonly found in animal tissues, n is either 12 (i.e. myristic acid), 14 (i.e. palmitic acid) or 16 (i.e. stearic acid).

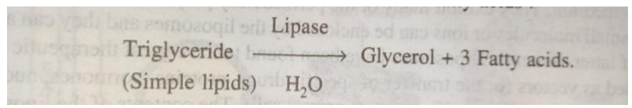
- In unsaturated fatty acids, atleast two but usually no more than six of the C atoms of the hydrocarbon chain are linked together by double bonds (-C=C-). Eg. Oleic acid, linoleic acid, linolenic acid etc.
- The double bonds are important because they increase the flexibility of the hydrocarbon chain, and thereby the fluidity of biological membranes.
- Unsaturated fatty acids predominate in lipids of higher plants and in animals that live at low temperatures.

Types of lipids

- Simple lipids
- Compound lipids
- Derived lipids

Simple lipids

- The simple lipids are alcohol esters of fatty acids :



$$\underset{\text{(Simple lipids)}}{\text{Triglyceride}} \xrightarrow[H_2O]{\text{Lipase}} \text{Glycerol} + 3 \text{ Fatty acids.}$$

- Further classified into following two types:
  - Neutral fats: Triesters of fatty acids and glycerol. It represents the major type of stored lipid and so accumulate in the cytoplasm
  - Waxes: Esters of fatty acids of high molecular weight with the alcohol except glycerol. Most important constituent alcohol of the molecules of waxes is cholesterol.

Compound lipids

- Contain fatty acids, alcohols and other compounds as P, amino-nitrogen carbohydrates, etc., in their molecules.
- Some are important structural components of the cell, in particular of cell membranes.
- Compound lipids of the cell are of following types:
  - Phospholipids (or Glycerophos-phatids)
  - Sphingolipids
  - Glycolipids

Phospholipids

- Forms the major constituent of cell membranes.
- In a molecule of phospholipid, two of hydroxyl group in glycerol are linked to fatty acids, while the third hydroxyl group is linked to phosphoric acid.
- The phosphate is further linked to a hydrophilic compound such as etanolamine, choline, inositol or serine.
- Each phospholipid molecule, therefore, has a hydrophobic or water-insoluble tail which is composed of two fatty acid chains and a hydrophilic or water-soluble polar head group, where the phosphate is located.

- Thus, when a small amount of phospholipid is spread over the surface of water, there forms a monolayer film of phospholipid molecules; in this thin film, tail regions pack together very closely facing the air and their head groups are in contact with the water.
- Two such films can combine tail to tail to make a phopholipid sandwich or self-sealing lipid bilayer, which is the structural basis of cell membranes.

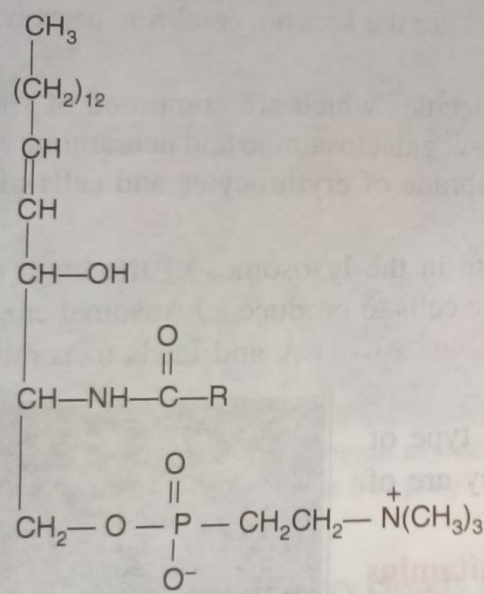


Fig. 4.15. General chemical formula of sphingomyelin.

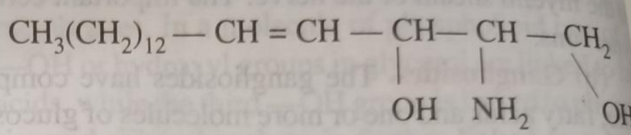


Fig. 4.16. Chemical formula of sphingosine.

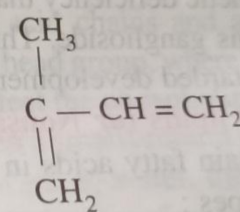


Fig. 4.17. Isoprene.

Sphingolipids

- Occur mostly in the brain cells.
- Structurally, instead of glycerol, they contain in their molecules amine alcohol (sphingol or sphingosine)
- For eg, myelin sheaths of the nerve fibres contain a lipid known as spingomyelin which contains sphingosine and phospholipids in its molecules.

Glycolipids

- They contain in their molecules, carbohydrates and lipids.
- Matrix of animal cells contain two kinds of glycolipids
- Cerebrosides: Contain in their molecules sphingosine, fatty acids and galactose or glucose.
- Cerebrosides are important lipids of white matter of brain and the myelin sheath of the nerve. Eg. Kerasin, cerebron, nervon and oxynervons.

- Gangliosides: Have complex molecules which are composed of sphingosine, fatty acids and one or more molecules of glucose, lactose, galactosamine and neuraminic acid.
- Gangliosides occur in the grey matter of brain, membrane of erythrocytes and cells of the spleen.
- One type of ganglioside, called GM2, may accumulate in the lysosomes of the brain cells because of a genetic deficieincy that results in the failure of the cells to produce a lysosomal enzyme that degrades this ganglioside. This condition is called Tay-Sachs disease and leads to paralysis, blindness and reatarded development of human beings.

Derived lipids (or nonsaponifiable lipids)

- Do not contain fatty acids in their constituents and they are of following 3 types:
  - Terpenes
  - Steroids
  - Prostaglandins

Terpenes

- Include certain fat-soluble vitamins(eg vitamin A, E and K), carotenoids (eg photosynthetic pigments of plants) and certain coenzymes (eg coenzymeQ)
- Terpenes are synthesized from a various number of 5 C building block, called isoprene unit.
- The isoprene units are bonded together in a head-to-tail organisation.
- 2 isoprene units are bonded together to form a monoterpene, 4 form a diterpene etc.

Steroids

- Consist of a system of fused cyclohexane and cyclopentane rings.
- All are derivative of perhydro-cyclopentano-phenanthrene, which consists of 3 fused cyclohexane rings and a terminal cyclopentane ring.
- Alcohols of the steroids are called sterols. Common eg of sterol are cholesterol found in animals and ergosterol and stigmasterol found in plants.

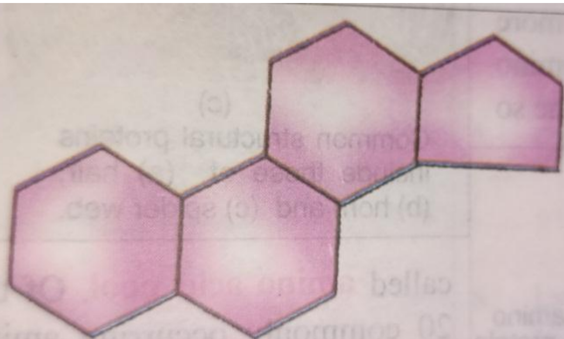


Fig. 4.20. Cyclopentano-perhydro-phenanthrene nucleus of the steroids.

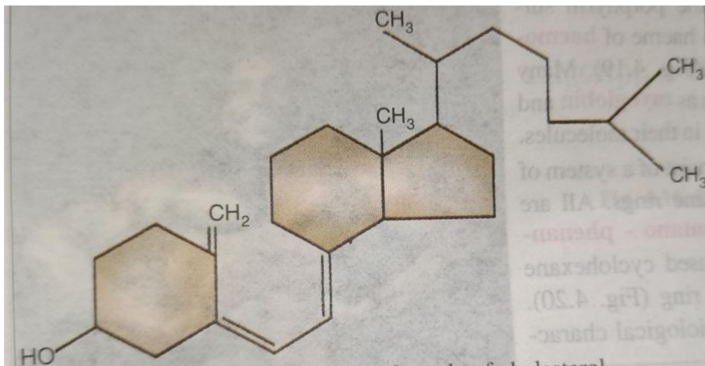


Fig. 4.21. Chemical formula of cholesterol.

Prostaglandins

- Hydroxy derivatives of 20-C polyunsaturated fatty acids.
- Found in human seminal fluid, testis, kidney, placenta, stomach, lung, brain and heart.
- 16 different prostaglandins falling into 9 classes (PGA, PGB, PGC……PGI).
- Main function is binding of hormones to membranes of the target cells.
- Continously synthesised in the membranes from membrane phospholipids by phospholipases.

Proteins

- The term protein was coined by Dutch chemist G.J. Mulder (1802-1880) and is derived from Greek word *proteios* which means "of the first rank"
- Serve as chief structural matetrial of protoplasm and play numerous other essential roles in living systems.
- They form enzymes, antibodies, transport proteins, storage proteins, contractile proteins and some hormones etc.
- In every living organism, there are thousands of different proteins, each fitted to perform a specific functional or structural role.
- Chemically, proteins are polymers of amino acids linked together by peptide bond.

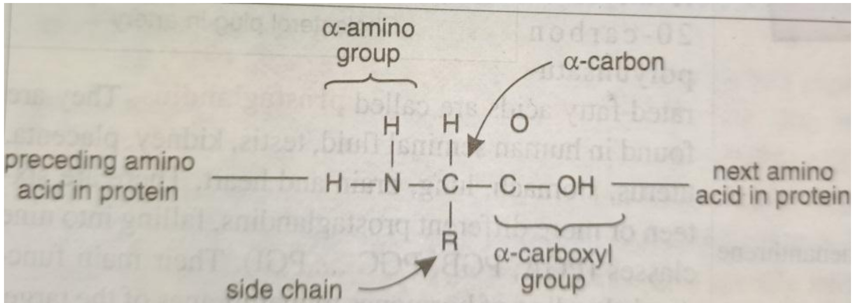


Fig. 4.22. Basic structure of an amino acid.

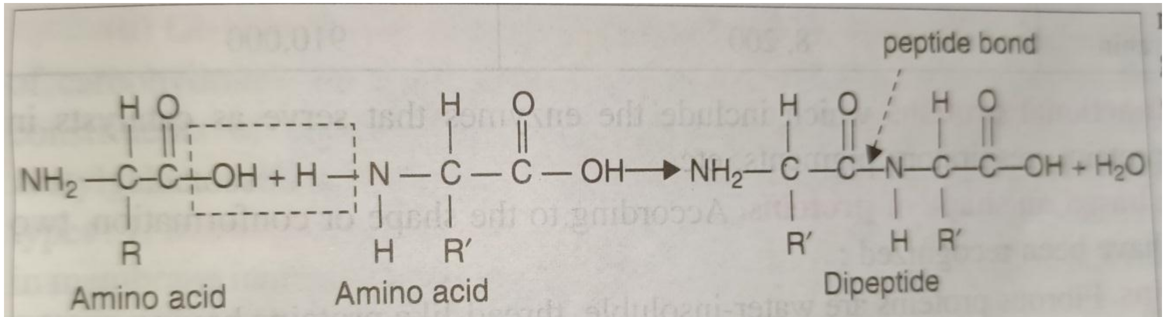


Fig. 4.23. A chemical reaction showing formation of a dipeptide.

Formation of protein

- Amino acids are amphoteric molecules.
- They unite with one another to form complex and large protein molecules.
- When two amino acid molecules are combined, then the basic group (-NH2) of one amino acid molecule combines with the carboxylic group (-COOH) of other amino acid and the loss of water molecule takes place.
- This sort of condensation of two amino acid molecules results in the formation of peptide linkage.

Types of protein

- Classification based on biological functions
  - Structural proteins
  - Dynamic or functional

- Classification based on shape of protein
  - Fibrous proteins
  - Globular proteins

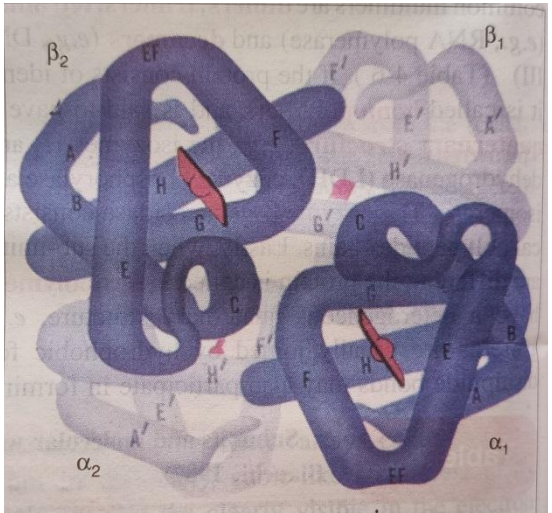
Classification based on solubility characteristics

- Simple proteins
  - Albumins
  - Globulins
  - Glutelins
  - Prolamines
  - Scleroproteins
  - Histones
  - Protamines

- Conjugated proteins
  - Chromoproteins
  - Glycoproteins
  - Lipoproteins
  - Nucleoproteins
  - Metalloproteins

Haemoglobin

- It is one of the fully sequenced protein
- M.F. Perutz got the Nobel Prize in 1962, along with J.C. Kendrew for their studies on haemoglobin and myoglobin.

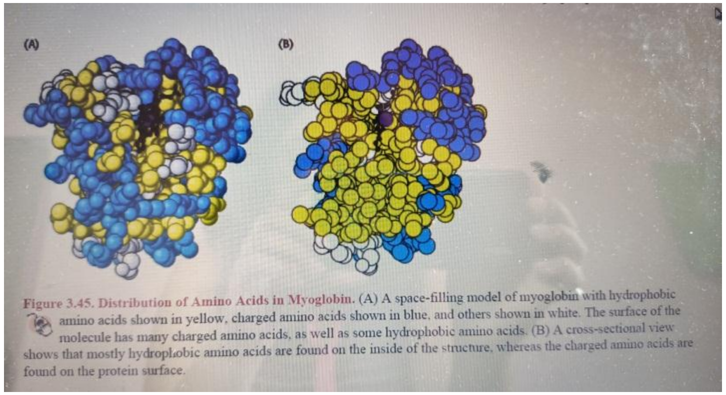


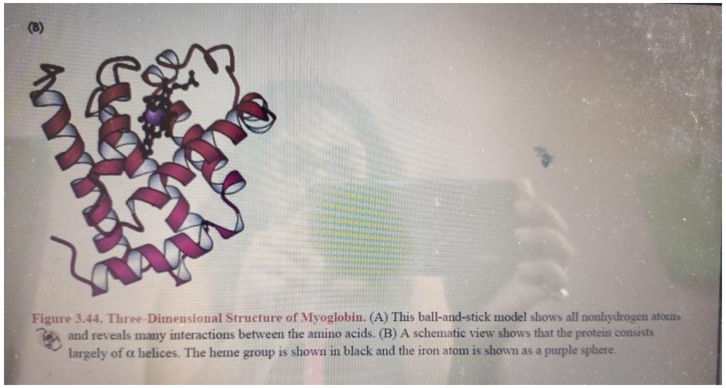
Haemoglobin molecule.

- Haemoglobin is a conjugated globular protein, i.e. it contains some non-protein part.
- In humans, most common type of Hb is HbA, which consists of 574 amino acid residues and has a molecular weight of 64,500.
- The protein portion of Hb molecule globin is composed of 4 polypeptide chains, each of which is also globular in shape.
- The 4 globin chains consist of 2 identical pairs: 2 alpha chains (141 amino acids each) and 2 beta chains (146 amino acids each)

- The non-protein portion of Hb consists of 4 iron containing haem groups, one associated with each of the 4 globin chains.
- Nineteen of the 20 biologically important amino acids are included in the globin of Hb.
- Hb molecule is highly symmetric and can be divided into 2 equal halves, each consisting of a αβ-dimer.
- Complete tetramer is similar to a mildly flattened sphere having a maximum diameter of about 5.5 nm
- A cavity of about 2.5 nm long and varying in width from about 5 to 10 angstrom passes through the molecule along the axis.
- Each globin chain envelops its haem group in a deep cleft.

Myoglobin


(A)
(B)
Figure 3.45. Distribution of Amino Acids in Myoglobin. (A) A space-filling model of myoglobin with hydrophobic amino acids shown in yellow, charged amino acids shown in blue, and others shown in white. The surface of the molecule has many charged amino acids, as well as some hydrophobic amino acids. (B) A cross-sectional view shows that mostly hydrophobic amino acids are found on the inside of the structure, whereas the charged amino acids are found on the protein surface.


(B)
Figure 3.44. Three-Dimensional Structure of Myoglobin. (A) This ball-and-stick model shows all nonhydrogen atoms and reveals many interactions between the amino acids. (B) A schematic view shows that the protein consists largely of α helices. The heme group is shown in black and the iron atom is shown as a purple sphere.

- Myoglobin, the oxygen carrier in muscle, is a single polypeptide chain of 153 amino acids
- The capacity of myoglobin to bind oxygen depends on the presence of *heme,* a nonpolypeptide *prosthetic (helper) group* consisting of protoporphyrin IX and a central iron atom.
- *Myo-globin is an extremely compact molecule*. Its overall dimensions are 45 × 35 × 25 Å, an order of magnitude less than if it were fully stretched out.

- About 70% of the main chain is folded into eight a helices, and much of the rest of the chain forms turns and loops between helices.
- The folding of the main chain of myoglobin, like that of most other proteins, is complex and devoid of symmetry.
- The overall course of the polypeptide chain of a protein is referred to as its *tertiary structure*.

- A unifying principle emerges from the distribution of side chains.
- The striking fact is that *the interior consists almost entirely of nonpolar residues* such as leucine, valine, methionine, and phenylalanine.
- Charged residues such as aspartate, glutamate, lysine, and arginine are absent from the inside of myoglobin.
- The only polar residues inside are two histidine residues, which play critical roles in binding iron and oxygen.
- The outside of myoglobin, on the other hand, consists of both polar and nonpolar residues. The spacefilling model shows that there is very little empty space inside.

Enzymes

- Enzymes are specialised proteins and they have the capacity to act as catalysts in chemical reaction.
- Enzymes are catalysts of biological world and they influence the rate of a chemical reaction, while themselves remain quite unchanged at the end of the reaction.
- Play a vital role in various metabolic and metabolic activities of the cell

Classification of enzymes

- Oxidoreductases
- Transferases
- Hydrolases
- Lyases
- Isomerases
- Ligases or synthetases

Vitamins

- Organic compounds of diverse chemical nature.
- Required in minute amounts for normal growth, functioning and reproduction of cells.
- Plays important role in cellular metabolismand act as enzymes or other biological catalysts in variuos chemical activities of the cell.
- Its importance for animals has been reported by Hopkins, Osborne, Memdal and McCollum (1912-1913).
- Funk (1912) demostrated the presence of basic nitrogen in its chemical structure and gave the name "vitamins" meaning " vital amines"

Table 4-7. Vitamins and their characteristics.

Vitamin	Daily requirement	Sources	Functions	Diseases and symptoms caused by lack of vitamin
Fat Soluble Vitamins 1. Vitamin A (Retinol)	750 µ gm	Animal fats (fish liver oil, egg-yolk, milk, butter, cheese); palm oils; red peppers; dark green leafy vegetables (spinach, methi, cabbage); yellow vegetables (carrot, pumpkin) and yellow fruits (mango, papaya).	Stored in liver; maintain general health and vigour of epithelial cells.	1. Skin becomes dry and scaly and so does cornea of eyes causing **xerophthalmia** or 'dry eye'; 2. **Night blindness or nyctalopia** (inability to see in dimlight).
2. Vitamin D (Calciferol)	200 IU (5 µ gm)	Fish liver oils, liver, egg-yolk, butter, fresh milk; also produced by our body when skin-cholesterol is exposed to ultra-violet rays of sunlight.	Involved in intestinal absorption of calcium and phosphorus and in calcium metabolism and bone formation.	1. **Rickets** in children; 2. **Osteomalacia** in adults.
3. Vitamin E (Tocopherol)	Trace amounts (15 IU)	Vegetable oils (especially polysaturated fatty acids); wheat germ oil; egg-yolk; green leafy vegetables; tomato; milk and butter.	Inhibit catabolism (*i.e.*, oxidation) of certain fatty acids of cellular membranes.	**Hemolytic anemia** due to oxidation of unsaturated fats resulting in abnormal structure and function of mitochondria, lysosomes and plasma membrane of cells.
4. Vitamin K (Naphtoquinone)	Trace amounts	Naturally produced by intestinal bacteria; liver; fresh green vegetables (spinach, cabbage, cauliflower).	Required for the formation of prothrombin (an essential component of blood-clotting).	**Haemorrhage or bleeding** in new-born infants; scurvy-like symptoms (blood takes longer to clot).
Water Soluble Vitamins 5. Vitamin B (Thiamine)	1.3 mg (boys) 1.2 mg (girls)	Yeast; whole cereals (*e.g.*, unpolished rice); pulses; oil-seeds, soyabean; nuts (especially groundnut); liver, pork, sea food, green leafy vegetables.	1. Essential for synthesis of acetylcholine; 2. Rapidly destroyed by heat. 3. Carbohydrate metabolism.	1. **Beriberi**. Partial paralysis of smooth muscle of gastrointestinal tract; paralysis of skeletal muscles, atrophy of limbs. 2. **Polyneuritis**.
6. Vitamin B_2 (Riboflavin)	1.6 mg (boys) 1.4 mg (girls)	Peas, beans, milk, egg-white, liver, kidney, germinated cereals and pulses, growing green leafy vegetables.	Forms the coenzyme FAD which is involved in metabolism of carbohydrates and proteins.	1. Blurred vision, cataract and corneal ulceration; 2. **Dermatitis** (inflammation of skin); 3. **Cheilosis** (cracking of skin at the corners of mouth and scaling of lips).

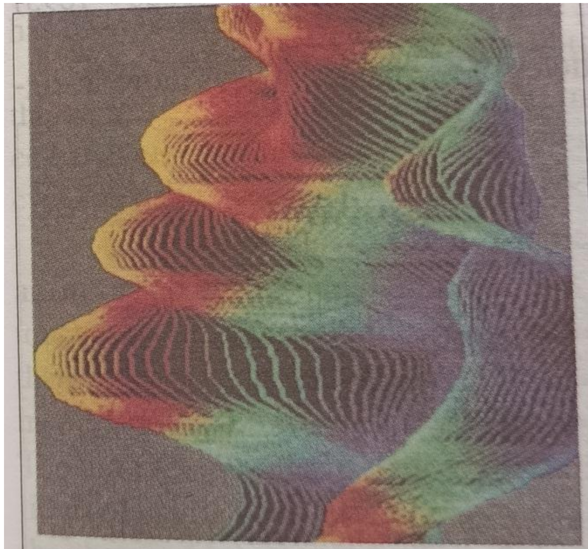
Vitamin	Daily requirement	Sources	Functions	Diseases and symptoms caused by lack of vitamin
7. Niacin (Nicotinic acid)	18 mg (boys) 15 mg (girls)	Meat, liver, fish, chicken, yeast, whole grain, peas, beans, pulses, nuts (groundnuts) potato, tomato, green vegetables, germinated seeds and milk (Maize is deficient in niacin).	1. Forms the coenzyme NAD which is involved in energy-releasing reactions; 2. In lipid metabolism inhibits production of cholesterol and help in fat breakdown.	**Pellagra**, a disease characterised by three D's-dermatitis, diarrhoea and dementia (psychological disturbance).
8. Vitamin B_6 (Pyridoxin)	1.5–2 mg	Liver, meat, fish (salmon), whole cereals, yellow corn, legumes, tomatoes, yoghurt.	1. Forms coenzymes involved in amino acid metabolism in brain; 2. Involved in fat metabolism.	1. Convulsions; 2. Dermatitis of eyes, nose and mouth; 3. Retarded growth.
9. Folic acid	50–100 mg	Green leafy vegetables, germinated pulses, eggs, liver.	1. Essential for synthesis of DNA. 2. Overcooking destroys it.	**Macrocytic anaemia** (production of abnormally large red blood cells).
10. Biotin (Vitamin H)	0.3 mg	Yeast, liver, egg-yolk, milk, kidneys.	Acts as coenzyme in metabolism of carbohydrates, fatty acids and nucleic acid.	1. Mental depression; 2. Muscular pain, fatigue; 3. Dermatitis; 4. Nausea.
11. Vitamin B_{12} (Cyanocobalamin)	0.2–1.0 μ gm	Liver, kidney, meat, fish, eggs, milk, cheese	Acts as coenzyme necessary for DNA synthesis, red blood cell formation, growth and nerve function.	1. **Pernicious anaemia**; 2. Malfunctioning of nervous system.
12. Vitamin C (Ascorbic acid)	40 mg	Amla, guava, citrus fruits (lime, lemon, orange), tomatoes, green leafy vegetables (cabbage, *chauli* and cauliflower).	1. Promotes protein synthesis (collagen), wound healing and iron absorption; 2. Protects body against infections; 3. Rapidly destroyed by heat.	**Scurvy**. A disease characterised by swelling of gums, multiple haemorrhages, anaemia and weakness.

Nucleic acids

- Nucleic acids are complex macromolecular organic compounds of immense biological importance.
- Polymers of nucleotides (nucleoside + phosphoric acid)
- Nucleoside is composed of pentose sugars and nitrogenous bases (purines and pyrimidine)
- Purines are A and G
- Pyrimidines are C, T and U

Types of nucleic acid

- Deoxyribonucleic acid (DNA)
- Ribonucleic acid (RNA)



Photograph of DNA made by tunneling microscopy.

- DNA and RNA are long linear polymers, called nucleic acids, that carry information in a form that can be passed from one generation to the next.
- These macromolecules consist of a large number of linked nucleotides, each composed of a sugar, a phosphate, and a base.
- Sugars linked by phosphates form a common backbone, whereas the bases vary among four kinds.

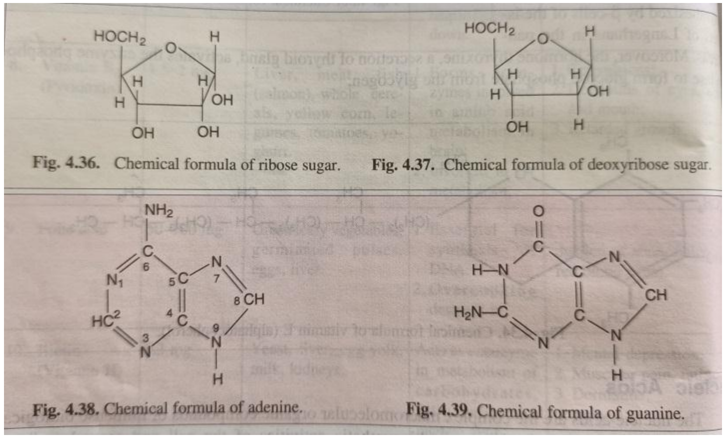


Fig. 4.36. Chemical formula of ribose sugar.
Fig. 4.37. Chemical formula of deoxyribose sugar.
Fig. 4.38. Chemical formula of adenine.
Fig. 4.39. Chemical formula of guanine.

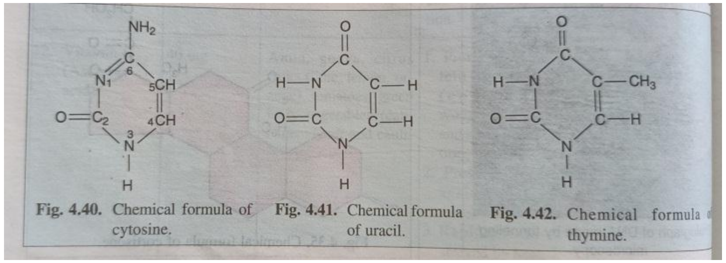


Fig. 4.40. Chemical formula of cytosine.
Fig. 4.41. Chemical formula of uracil.
Fig. 4.42. Chemical formula of thymine.

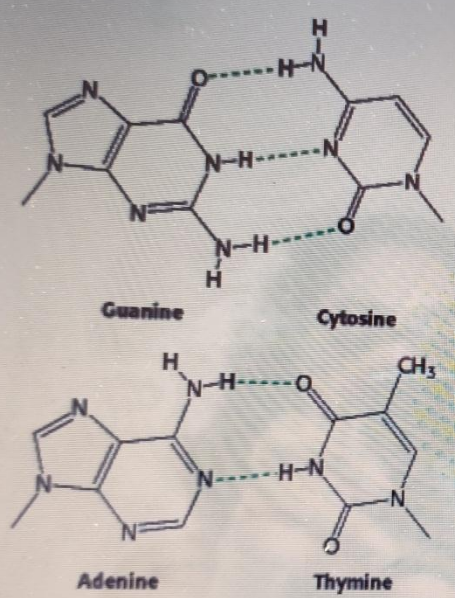
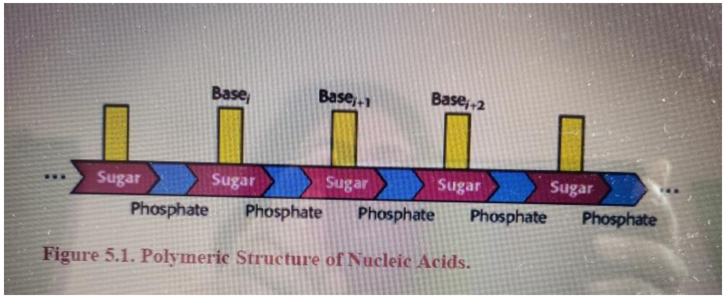


Figure 5.12. Structures of the Base Pairs Proposed by Watson and Crick.


Base$_i$
Base$_{i+1}$
Base$_{i+2}$
Sugar
Sugar
Sugar
Sugar
Sugar
Phosphate
Phosphate
Phosphate
Phosphate
Phosphate
Figure 5.1. Polymeric Structure of Nucleic Acids.


(A)
34Å

- The bases have an additional special property: they form specific pairs with one another that are stabilized by hydrogen bonds.
- The base pairing results in the formation of a double helix, a helical structure consisting of two strands.
- *These base pairs provide a mechanism for copying the genetic information in an existing nucleic acid chain to form a new chain.*

A Nucleic Acid Consists of Four Kinds of Bases Linked to a Sugar-Phosphate Backbone

- The nucleic acids DNA and RNA are well suited to function as the carriers of genetic information by virtue of their covalent structures.
- These macromolecules are *linear polymers* built up from similar units connected end to end
- Each monomer unit within the polymer consists of three components: a sugar, a phosphate, and a base. The sequence of bases uniquely characterizes a nucleic acid and represents a form of linear information.

RNA and DNA Differ in the Sugar Component and One of the Bases

- The sugar in *deoxyribonucleic acid (DNA)* is *deoxyribose*. The deoxy prefix indicates that the 2 carbon atom of the sugar lacks the oxygen atom that is linked to the 2 carbon atom of *ribose* (the sugar in *ribonucleic acid*, or *RNA*).
- The sugars in nucleic acids are linked to one another by phosphodiester bridges.
- Specifically, the 3 - hydroxyl (3 -OH) group of the sugar moiety of one nucleotide is esterified to a phosphate group, which is, in turn, joined to the 5 -hydroxyl group of the adjacent sugar.

- Whereas the backbone is constant in DNA and RNA, the bases vary from one monomer to the next. Two of the bases are derivatives of *purine* adenine (A) and guanine (G) and two of *pyrimidine* cytosine (C) and thymine (T, DNA only) or uracil (U, RNA only), as shown in RNA, like DNA, is a long unbranched polymer consisting of nucleotides joined by 3 5 phosphodiester bonds.
- Each phosphodiester bridge has a negative charge. This negative charge repels nucleophilic species such as hydroxide ion; consequently, phosphodiester linkages are much less susceptible to hydrolytic attack than are other esters such as carboxylic acid esters. This resistance is crucial for maintaining the integrity of information stored in nucleic acids.

- The absence of the 2 -hydroxyl group in DNA further increases its resistance to hydrolysis. The greater stability of DNA probably accounts for its use rather than RNA as the hereditary material in all modern cells and in many viruses.

The Double Helix Is Stabilized by Hydrogen Bonds and Hydrophobic Interactions

- The existence of specific base-pairing interactions was discovered in the course of studies directed at determining the three-dimensional structure of DNA.
- Maurice Wilkins and Rosalind Franklin obtained x-ray diffraction photographs of fibers of DNA
- The characteristics of these diffraction patterns indicated that DNA was formed of two chains that wound in a regular helical structure.

- From these and other data, James Watson and Francis Crick inferred a structural model for DNA that accounted for the diffraction pattern and was also the source of some remarkable insights into the functional properties of nucleic acids

Features of the Watson-Crick model of DNA deduced from the diffraction patterns

1. Two helical polynucleotide chains are coiled around a common axis. The chains run in opposite directions.

2. The sugar-phosphate backbones are on the outside and, therefore, the purine and pyrimidine bases lie on the inside of the helix.

3. The bases are nearly perpendicular to the helix axis, and adjacent bases are separated by 3.4 Å. The helical structure repeats every 34 Å, so there are 10 bases (= 34 Å per repeat/3.4 Å per base) per turn of helix. There is a rotation of 36 degrees per base (360 degrees per full turn/10 bases per turn).

4. The diameter of the helix is 20 Å.

- How is such a regular structure able to accommodate an arbitrary sequence of bases, given the different sizes and shapes of the purines and pyrimidines?
- In attempting to answer this question, Watson and Crick discovered that guanine can be paired with cytosine and adenine with thymine to form base pairs that have essentially the same shape

Table 4-8. Comparison of DNA and RNA.

DNA	RNA
1. It contains pentose sugar known as deoxyribose.	1. It contains pentose sugar called the ribose.
2. The molecule contains the phosphoric acid (phosphate) molecule which connects various sugars with one another.	2. The molecule contains the phosphoric acid (phosphate) molecule which connects various sugars with one another.
3. The nitrogen bases are : (i) Purines—adenine and guanine. (ii) Pyrimidine—cytosine and thymine.	3. The molecule contains following nitrogen bases in its molecule: (i) Purines—adenine and guanine. (ii) Pyrimidines—cytosine and uracil.
4. Molecules have four nucleotides as deoxyadenosine monophosphate, deoxyguanosine monophosphate, deoxycytidine monophosphate and thymidine monophosphate.	4. Molecules have four nucleotides as adenosine monophosphate, guanosine monophosphate, cytidine monophosphate and uridine monophosphate.
5. The molecule contains a double stranded helix structure in which many nucleotides remain arranged in pair.	5. The molecules consist of single chain of polynucleotides.
6. DNA is a genetic material and occurs in chromosomes, nucleoplasm and mitochondria, etc.	6. RNA is a carrier of genetic informations and it plays very significant role in the mechanism of protein synthesis. It mostly occurs in nucleolus, nucleoplasm and cytoplasm.