## 23FTT204- BIOCHEMISTRY AND NUTRITION

### UNIT IV - METABOLISM OF NUCLEIC ACIDS, VITAMINS AND MINERALS

### Nucleic acids; physicochemical and metabolic functions

Nucleic Acids – Introduction

The first isolation of what we now refer to as DNA was accomplished by Johann Friedrich Miescher 1870. He reported finding a weakly acidic substance of unknown function in the nuclei of human white blood cells, and named this material "nuclein". A few years later, Miescher separated nuclein into protein and nucleic acid components. In the 1920's nucleic acids were found to be major components of chromosomes, small gene-carrying bodies in the nuclei of complex cells. Elemental analysis of nucleic acids showed the presence of phosphorus, in addition to the usual C, H, N & O. Unlike proteins, nucleic acids contained no sulfur. Complete hydrolysis of chromosomal nucleic acids gave inorganic phosphate, 2-deoxyribose (a previously unknown sugar) and four different heterocyclic bases (shown in the following diagram). To reflect the unusual sugar component, chromosomal nucleic acids are called deoxyribonucleic acids, abbreviated DNA. Analogous nucleic acids in which the sugar component is ribose are termed ribonucleic acids, abbreviated RNA. The acidic character of the nucleic acids was attributed to the phosphoric acid moiety.

Their functions include:

1. Serving as energy stores for future use in phosphate transfer reactions. These reactions are predominantly carried out by ATP.

2. Forming a portion of several important coenzymes such as NAD+, NADP+, FAD and coenzyme A.

3. Serving as mediators of numerous important cellular processes such as second messengers in signal transduction events. The predominant second messenger is cyclic-AMP (cAMP), a cyclic derivative of AMP formed from ATP.

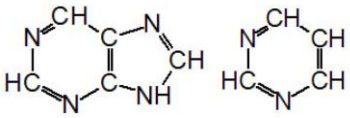
4. Serving as neurotransmitters and as signal receptor ligands. Adenosine can function as an inhibitory neurotransmitter, while ATP also affects synaptic neurotransmission throughout the central and peripheral nervous systems. ADP is an important activator of platelet functions resulting in control of blood coagulation.

5. Controlling numerous enzymatic reactions through allosteric effects on enzyme activity.

6. Serving as activated intermediates in numerous biosynthetic reactions. These activated intermediates include S-adenosylmethionine (S-AdoMet or SAM) involved in methyl transfer reactions as well as the many sugar coupled nucleotides involved in glycogen and glycoprotein synthesis.

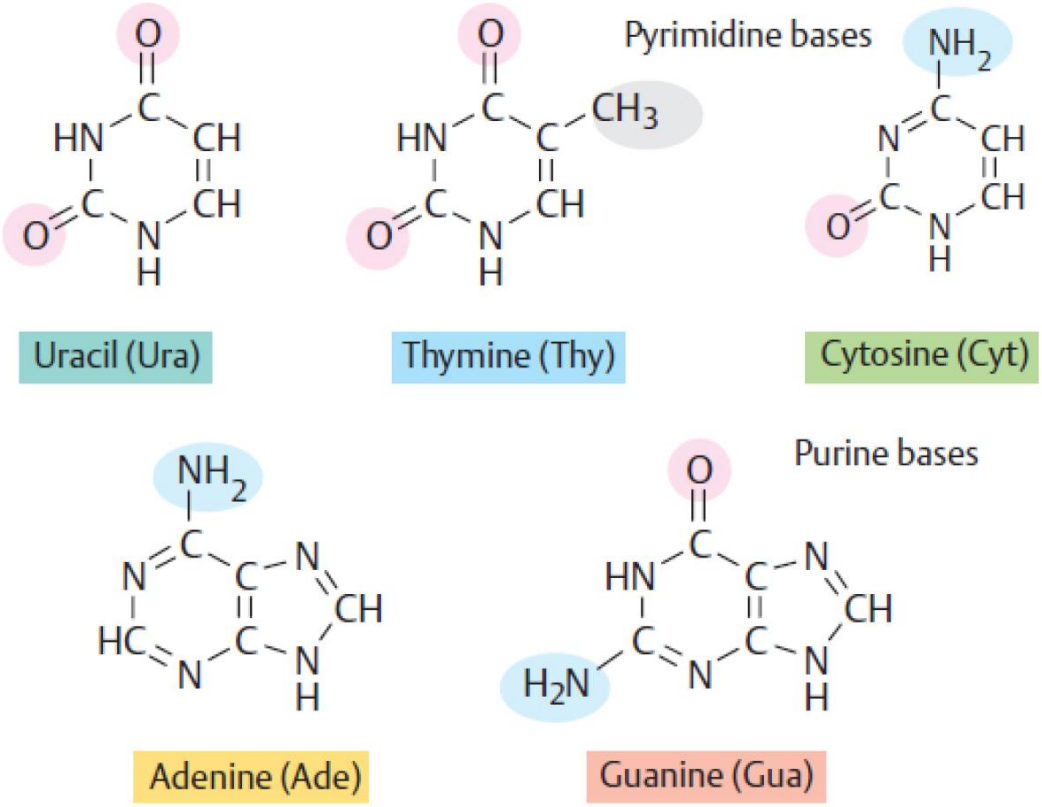
Nucleoside and Nucleotide Structure and Nomenclature:

The nucleotides found in cells are derivatives of the heterocyclic highly basic, compounds, purine and pyrimidine.



Purine | Pyrimidine

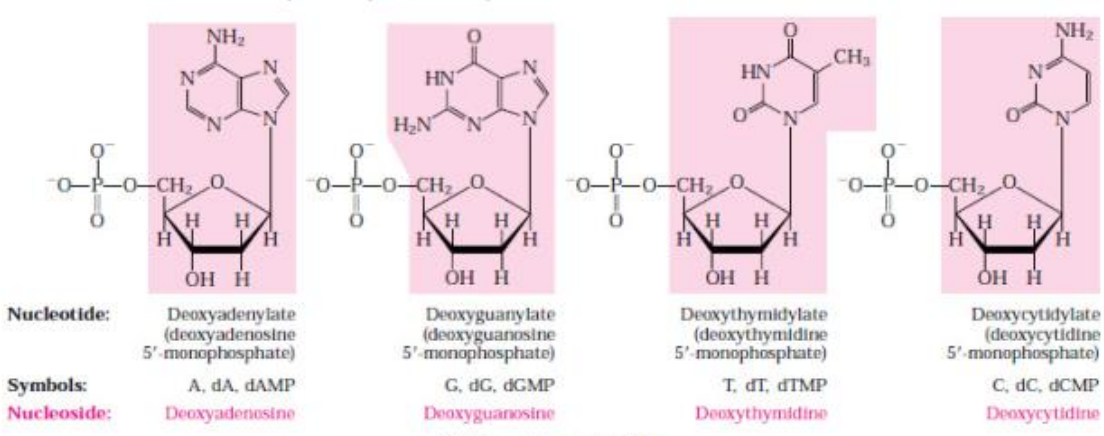
Five of these bases are the main components of nucleic acids in all living creatures. The purine bases adenine and guanine and the pyrimidine base cytosine are present in both RNA and DNA. In contrast, uracil is only found in RNA. In DNA, uracil is replaced by thymine, the 5-methyl derivative of uracil.



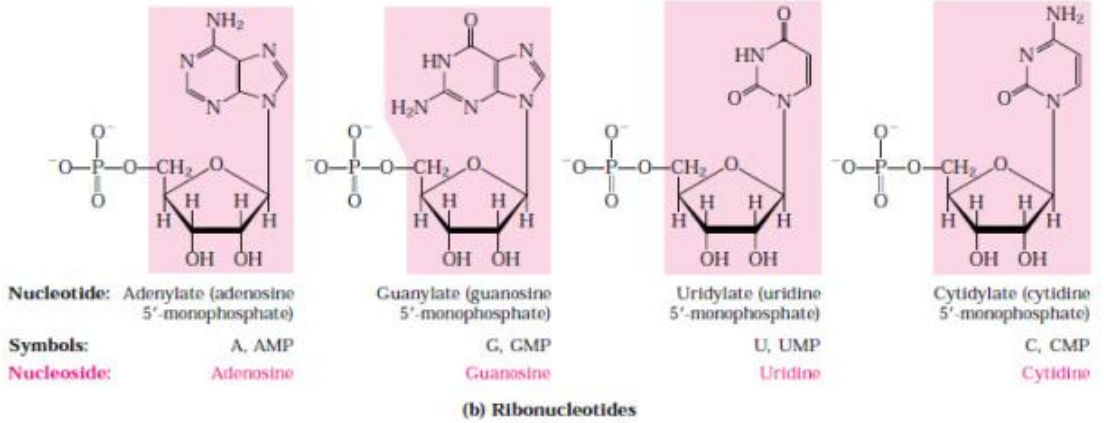

When a nucleic acid base is N-glycosidically linked to ribose or 2-deoxyribose, it yields a nucleoside. The nucleoside adenosine (abbreviation: A) is formed in this way from adenine and ribose, for example. The corresponding derivatives of the other bases are called guanosine (G), uridine (U), thymidine (T) and cytidine (C). When the sugar component is 2-deoxyribose, the product is a deoxyribonucleoside.

In the cell, the 5' OH group of the sugar component of the nucleoside is usually esterified with phosphoric acid. If the 5' phosphate residue is linked via an acid–anhydride bond to additional phosphate residues, it yields nucleoside diphosphates and triphosphates—e. g., ADP and ATP, which are important coenzymes in energy metabolism. All of these nucleoside phosphates are classified as nucleotides. In nucleosides and nucleotides, the pentose residues are present in the furanose form. The sugars and bases are linked by an N-glycosidic bond between the C-1 of the sugar and either the N-9 of the purine ring or N-1 of the pyrimidine ring. This bond always adopts the β-configuration. 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 bases. The base of a nucleotide is joined covalently (at N-1 of pyrimidines and N-9 of purines) in an N-β-glycosyl bond to the 1_ carbon of the pentose, and the phosphate is esterified to the 5_ carbon. The N-β-glycosyl bond is formed by removal of the elements of water (a hydroxyl group from the pentose and hydrogen from the base), as in O-glycosidic bond formation.

Both DNA and RNA contain two major purine bases, adenine (A) and guanine (G), and two major pyrimidines. In both DNA and RNA one of the pyrimidines is cytosine (C), but the second major pyrimidine is not the same in both: it is thymine (T) in DNA and uracil (U) in RNA. Only rarely does thymine occur in RNA or uracil in DNA.




(a) Deoxyribonucleotides



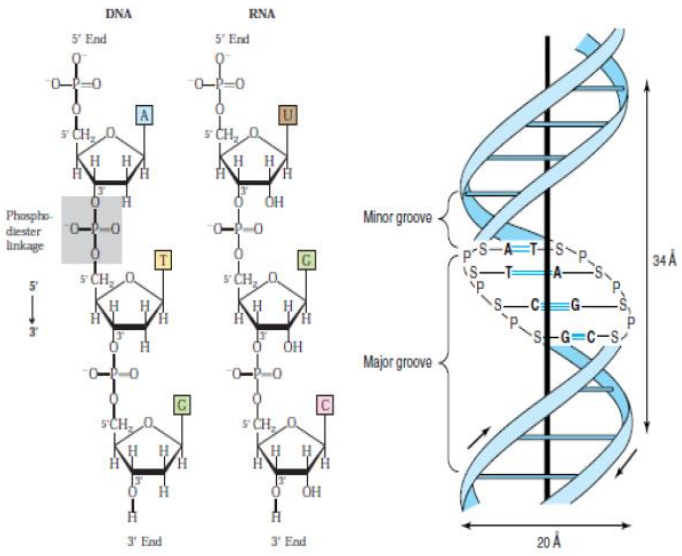

(b) Ribonucleotides

**Nucleotide and Nucleic Acid Nomenclature**

| *Base* | *Nucleoside* | *Nucleotide* | *Nucleic acid* |
|---|---|---|---|
| **Purines** | | | |
| Adenine | Adenosine | Adenylate | RNA |
| | Deoxyadenosine | Deoxyadenylate | DNA |
| Guanine | Guanosine | Guanylate | RNA |
| | Deoxyguanosine | Deoxyguanylate | DNA |
| **Pyrimidines** | | | |
| Cytosine | Cytidine | Cytidylate | RNA |
| | Deoxycytidine | Deoxycytidylate | DNA |
| Thymine | Thymidine or deoxythymidine | Thymidylate or deoxythymidylate | DNA |
| Uracil | Uridine | Uridylate | RNA |

The successive nucleotides of both DNA and RNA are covalently linked through phosphate-group "bridges," in which the 5_-phosphate group of one nucleotide unit is joined to the 3_-hydroxyl group of the next nucleotide, creating a phosphodiester linkage. Thus the covalent backbones of nucleic acids consist of alternating phosphate and pentose residues, and the nitrogenous bases may be regarded as side groups joined to the backbone at regular intervals. The backbones of both DNA and RNA are hydrophilic.

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' n 3' direction. Some simpler representations of this penta deoxyribonucleotide are pA-C-G-T-AOH, pApCpGpTpA, and pACGTA. A short nucleic acid is referred to as an oligonucleotide. The definition of "short" is somewhat arbitrary, but polymers containing 50 or fewer nucleotides are generally called oligonucleotides. A longer nucleic acid is called a polynucleotide.



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.

The features of the Watson-Crick model of DNA deduced from the diffraction patterns

are:

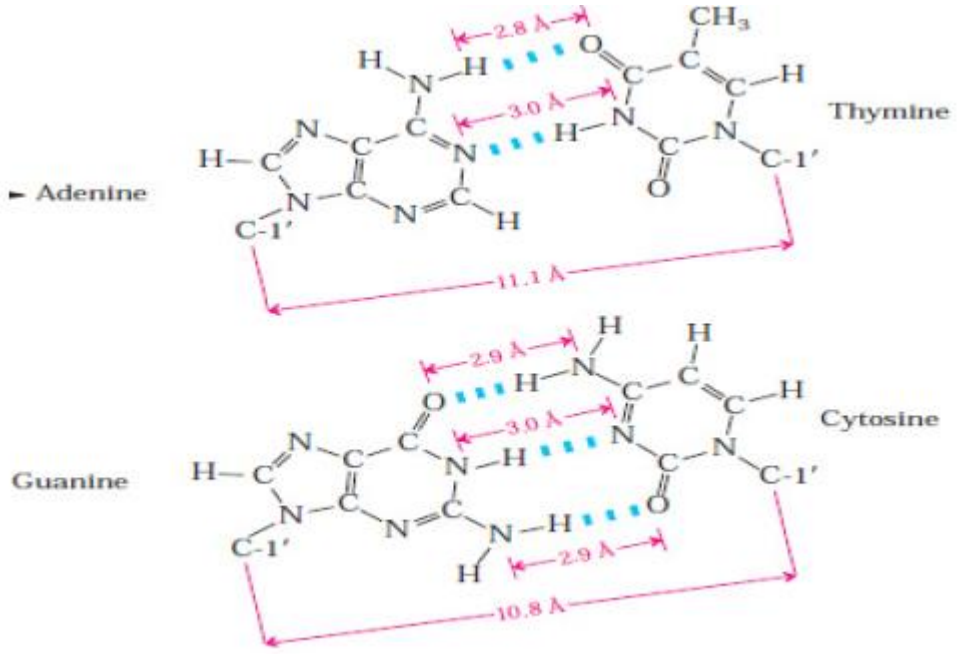
1. Two helical polynucleotide chains are coiled around a common axis. The chains run in opposite directions.

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.

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. These base pairs are held together by specific hydrogen bonds. This base-pairing scheme was supported by earlier studies of the base composition of DNA from different species. In 1950, Erwin Chargaff reported that the ratios of adenine to thymine and of guanine to cytosine were nearly the same in all species studied.



The meaning of these equivalences was not evident until the Watson-Crick model was proposed, when it became clear that they represent an essential facet of DNA structure. The spacing of approximately 3.4 Å between nearly parallel base pairs is readily apparent in the DNA diffraction pattern. The stacking of bases one on top of another contributes to the stability of the double helix.

DNA: structure

Deoxyribonucleic acids (DNAs) are polymeric molecules consisting of nucleotide building blocks. Instead of ribose, however, DNA contains 2'-deoxyribose, and the uracil base in RNA is replaced by thymine. The spatial structure of the two molecules also differs. The first evidence of the special structure of DNA was the observation that the amounts of adenine and thymine are almost equal in every type of DNA. The same applies to guanine and cytosine. The model of DNA structure formulated in 1953 explains these constant base ratios: intact DNA consists of two polydeoxynucleotide molecules ("strands").

Each base in one strand is linked to a complementary base in the other strand by H-bonds. Adenine is complementary to thymine, and guanine is complementary to cytosine. One purine base and one pyrimidine base are thus involved in each base pair. The complementarity of A with T and of G with C can be understood by considering the H bonds that are possible between the different bases. Potential donors are amino groups (Ade, Cyt, Gua) and ring NH groups. Possible acceptors are carbonyl oxygen atoms (Thy, Cyt, Gua) and ring nitrogen atoms. Two linear and therefore highly stable bonds can thus be formed in A–T pairs, and three in G–C pairs. Base pairings of this type are only possible, however, when the polarity of the two strands differs—i. e., when they run in opposite directions.

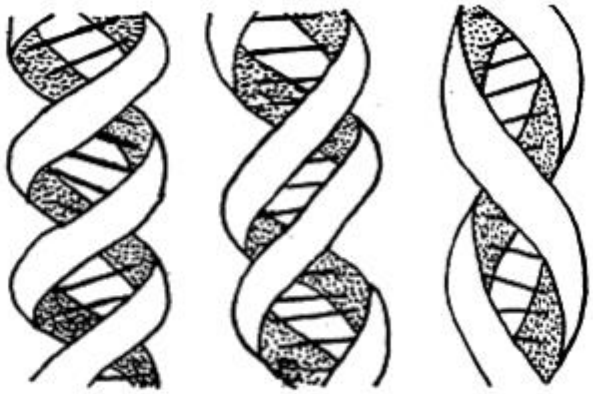
In addition, the two strands have to be intertwined to form a double helix. Due to steric hindrance by the 2'-OH groups of the ribose residues, RNA is unable to form a double helix. The structure of RNA is therefore less regular than that of DNA. The conformation of DNA that predominates within the cell is known as B-DNA. Along the whole length of the DNA molecule, there are two depressions—referred to as the "minor groove" and the "major groove"—that lie between the strands.

DNA: conformation

Investigations of synthetic DNA molecules have shown that DNA can adopt several different conformations. All of the DNA segments shown consist of 21 base pairs (bp) and have the same sequence. By far the most common form is B-DNA. This consists of two antiparallel polydeoxynucleotide strands intertwined with one another to form a righthanded double helix. The "backbone" of these strands is formed by deoxyribose and phosphate residues linked by phosphoric acid diester bonds. In the B conformation, the aromatic rings of the nucleobases are stacked at a distance of 0.34 nm almost at right angles to the axis of the helix. Each base is rotated relative to the preceding one by an angle of 35°. A complete turn of the double helix (360°) therefore contains around 10 base pairs (abbreviation: bp), i. e., the pitch of the helix is 3.4 nm. Between the backbones of the two individual strands there are two grooves with different widths. The major groove is visible at the top and bottom, while the narrower minor groove is seen in the middle. DNA-binding proteins and transcription factors usually enter into interactions in the area of the major groove, with its more easily accessible bases. In certain conditions, DNA can adopt the A conformation. In this arrangement, the double helix is still

right-handed, but the bases are no longer arranged at right angles to the axis of the helix, as in the B form. As can be seen, the A conformation is more compact than the other two conformations. The minor groove almost completely disappears, and the major groove is narrower than in the B form. A-DNA arises when B-DNA is dehydrated. It probably does not occur in the cell.

In the Z-conformation, which can occur within GC-rich regions of B-DNA, the organization of the nucleotides is completely different. In this case, the helix is left-handed, and the backbone adopts a characteristic zig-zag conformation (hence "Z-DNA"). The Z double helix has a smaller pitch than B-DNA. DNA segments in the Z conformation probably have physiological significance, but details are not yet known.



| Form | A | B | Z |
|---|---|---|---|
| helical twist | right | right | left |
| base pairs per turn | 11 | 10 | 12 |
| occurrence | RNA, DNA | DNA | DNA |