BIOLOGICAL AND BIOORGANIC Chemistry

Edited by
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IN 2 BOOKS
2
BOOK

BIOLOGICAL CHEMISTRY

APPROVED
by the Ministry of Education and Science of Ukraine as a textbook for students of higher medical educational establishments

PUBLISHED
pursuant to the Order of the Ministry of Health of Ukraine No. 502 as of 22 June 2010 as a national textbook for students of higher medical educational establishments

RECOMMENDED
by the Academic Council of Bogomolets National Medical University as a textbook for students of higher medical educational establishments

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This textbook contains a systematic presentation of the course of biological chemistry according to the educational program for students of higher medical (pharmaceutical) educational establishments. The core text of this book examines the structure of an enzyme, and the metabolic pathways of the major classes of biomolecules (proteins, amino acids, carbohydrates, lipids, nucleotides, porphyrins); structural features and properties of nucleic acids, DNA and RNA; molecular biology and genetics, biochemical foundations of the physiological functions of the human body and their neurohumoral regulation are highlighted. Considerable attention is paid to the molecular mechanisms underlying the functions of blood cells, liver, kidneys, muscles, connective tissue, immune and nervous systems. The biochemical basis of the pathogenesis of atherosclerosis, diabetes mellitus, obesity, diseases of the endocrine, immune, nervous systems and connective tissue are considered. In addition to informational material, each chapter of the textbook contains tests and tasks for self-control.

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CONTENT

INTRODUCTION

HISTORY OF DEVELOPMENT OF BIOCHEMISTRY

Biochemistry (biological chemistry) is a science that studies a chemical nature of substances forming a part of cells of living organisms, their transformations, relationship of these transformations with the activity of organs and tissues as well as the ways of their regulation.

Biochemistry consists of several sections.

Descriptive biochemistry studies a chemical composition of the organisms and structure of their molecules (proteins, amino acids, nucleic acids, nucleotides, carbohydrates and their derivatives, lipids, vitamins, hormones).

Dynamic biochemistry studies chemical reactions constituting the exchange of substances (metabolism), namely, the pathways of transformation of molecules and mechanisms of reactions, which occur between them.

Bioenergetics is a section of dynamic biochemistry, which studies the regularities of synthesis, accumulation and consumption of energy in biological system.

Functional biochemistry studies biochemical reactions underlying physiological functions. It is studying biochemical bases of digestion of nutrients in the alimentary canal; as well as mechanisms of muscle contraction, conduction of nervous impulse, respiratory function of the blood, regulation of acid-base balance, functions of the liver and kidneys, immune system, etc.

Human biochemistry or ***medical biochemistry*** is a section of biochemistry studying the regularities of metabolism in the human organism, including in diseases.

As the independent science, biochemistry was formed in the second half of the XIX cent. The term “biochemistry” was proposed and introduced into the sciences society by a German chemist Carl Neuberg in 1903.

In the history of biochemistry development as the science, four periods are distinguished:

I period — from ancient times to the Renaissance (15th century). This is the period of practical use of biochemical processes without knowledge of their theoretical bases and the first, at times very primitive, biochemical researches. From ancient times, people knew the technology of such productions based on biochemical processes as bread baking, cheese making, winemaking, leather tanning. The use of plants for food and with therapeutic purposes has led to attempts to understand the properties of certain substances of plant origin.

II period — from the beginning of the Renaissance to the second half of the 19th century, when biochemistry has stood out as the independent science. A great researcher of that time, the author of many masterpieces of art, architect, engineer, anatomist Leonardo da Vinci carried out the experiments, by the results of which he had drawn the important for

those times conclusion that a living organism can exist only in the atmosphere where a flame can burn. It should be also noted the works of such scientists as T. Paracelsus, M.V. Lomonosov, J. Liebig, A.M. Butlerov, A. Lavoisier.

III period — from the second half of the 19th century to the 50-ties of the 20th century. This period was marked by a sharp increase of the intensity and depth of biochemical researches, volume of received information, use of the achievements of biochemistry in the industry, medicine, agriculture. Main discoveries of that period are as follows:

1904 — F. Knoop discovered the mechanism of β-oxidation of fatty acids;

1926 — J. Sumner isolated the enzyme urease in the crystalline form having proved that the enzymes are proteins;

1930 — V.A. Engelgardt discovered the process of oxidative phosphorylation;

1930 — L. Pauling successfully predicted the secondary structure of protein;

1933 — G.A. Krebs studied in detail the ornithine cycle of urea formation and in 1937 discovered a tricarboxylic acid cycle (TCA cycle);

1933 — D. Keilin isolated cytochrome *c* and reproduced the process of transfer of electrons along the respiratory chain on the example of cardiac muscle;

1938 — A.E. Brownstein and M.G. Kritsman for the first time described transamination reactions that are the key ones in the nitrogen metabolism.

IV period — from the beginning of the 50-ties of the 20th century and until now, is characterized by a wide use of physical, physicochemical, mathematic methods, active and successful study of basic biological processes (biosynthesis of proteins and nucleic acids) at the molecular and super-molecular levels in biochemical researches.

Main discoveries in biochemistry of this period were the following:

1953 — J. Watson and F. Crick proposed a spatial structure of DNA molecule;

1953 — F. Sanger established the amino acid sequence of the protein insulin;

1961 — M. Nirenberg deciphered a genetic code;

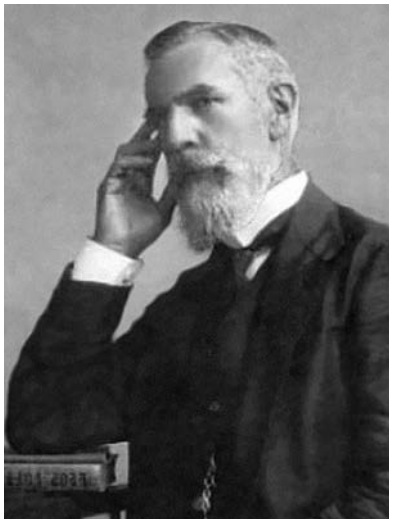
1966 — P. Mitchell formulated a chemiosmotic theory of a coupling between the respiratory chain and oxidative phosphorylation;

1967 — A. Kornberg synthetized a viral DNA *in vitro*.

In 2006 E. Fire and K. Mello were jointly awarded the Nobel Prize in Physiology and Medicine for the discovery of RNA interference — suppression of gene expression by the double-stranded RNA. In 2013, the most prestigious scientific prize was granted to R. Scheckman, J. Rothman and T. Südhof for the discovery of mechanisms of vesicular transport —the main transport system in the cells.

Currently, basic problems that are being solved by biochemistry are the following: relationship between the structure and biological function, pathways of the information transfer, spatial and time distribution of biomolecules in the cells and in the whole organism, problem of deciphering mechanisms of evolution as a biochemical process.

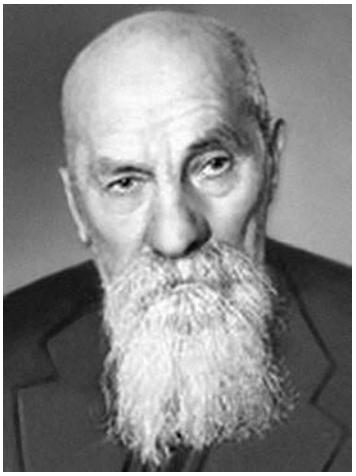
WELL-KNOWN SCIENTISTS-BIOCHEMISTS



Ivan Yakovlevich Horbachevsky (1854—1942) — Ukrainian biochemist, hygienist and epidemiologist, political and public figure. He is a native of the village Zarubintsy (now Ternopolskaya region), graduated from a medical faculty of Medical University of Vienna. He was one of the organizers of the Ukrainian university courses, which in 1921 were reorganized into the Ukrainian Free University in Vienna, from October 23, the same year — in Prague. Since 1923 he was repeatedly elected the rector of this university, from 1937 — the honorary professor. In 1922—1923, he was also a professor of the Ukrainian Technical and Economic Institute, Ukrainian Economic Academy in the city Podebrady (Czechia), in 1927—1928 — the Chairman of chemical nomenclature commission at this academy, which developed the principles of Ukrainian chemical terminology.

I.Ya. Horbachevsky first synthetized uric acid, established the sources and pathways of its formation in the body, discovered enzyme xanthine oxidase. He prepared a two-volume textbook on organic and inorganic chemistry in Ukrainian laying the foundations for Ukrainian scientific terminology. He is an author of the four-volume textbook of medicinal chemistry in the Czech language (1904—1908). In 1898, the scientist was decorated with the highest award of Austro-Hungary — Order of the Iron Crown. In 1992, by the decision of the Cabinet of Ministers of Ukraine, Ternopil State Medical Institute (now — the university) was named after academician I.Ya. Horbachevsky (now — the university) and memorial plaque was installed.

Aleksey Nikolayevich Bach (1857—1946) — the founder of soviet biochemical school, academician of the USSR Academy of Sciences. He studied at the Saint Vladimir's University (now – Taras Shevchenko National University of Kyiv). He had taken the initiative to found Physico-chemical Institute named after L. Karpov, later on— the Institute of Biochemistry of the USSR Academy of Sciences. The main trends of his researches are associated with the study of photosynthesis, oxidative processes in the living cells and enzymes. A.N. Bach explained the chemism of the process of carbon dioxide assimilation by chlorophyll-containing plants with formation of organic substance, having established that this process is based on a reaction with participation of water. The scientist came to the conclusion that peroxides play an important role in the process of respiration. He is the author of peroxide theory.



Aleksandr Vladimirovich Palladin (1885—1972) — one of the founders of the Ukrainian scientific biochemical school, academician of the All-Ukrainian Academy of Sciences, academician of the Academy of Sciences of Ukr. SSR, academician of the USSR Academy of Sciences, full member of the USSR Academy of Sciences, President of the Academy of Sciences of Ukr. SSR, Honored worker of Science and Technology of Ukraine, Hero of Socialist Labor, Laureate of the V.I. Lenin Prize. He is the son of academician V.I. Palladin and was a student of N.E. Vvedensky and I.P. Pavlov.

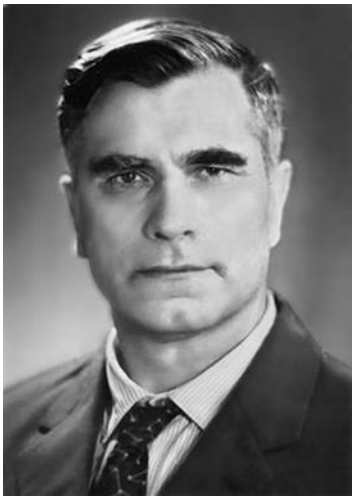
A.V. Palladin studied the biochemical processes of the nervous system and muscle activity, vitamins and nutrition. He is the founder of Ukrainian functional neurochemistry. He showed the difference of chemical composition and biochemical characteristics of morphologically and functionally different parts of the central and peripheral nervous systems, peculiarities of metabolism of proteins, carbohydrates, mediators and other biologically active substances in the nervous tissue in excitation and inhibition. He established regularities of the intracellular localization and age changes in the activity of the proteolytic enzyme systems, found out molecular mechanisms of ion transport through cellular membranes.

He studied some features of metabolism in the muscles (in the process of work, rest and training) that became the base of the theory of physical culture. He was the first in the USSR to begin biochemical studies of vitamins and revealed a relationship between metabolic disturbances and vitamin deficiency in the experimental scurvy and polyneuritis. He synthetized a new water-soluble analogue of vitamin K — vicasol that is widely used in medical practice.

Rostislav Vsevolodovich Chagovets (1904—1982) — doctor of biological sciences, professor, academician of the Academy of Sciences of Ukr. SSR, Honored worker of Science and Technology of Ukr. SSR, professor, academician-secretary of the Department of biochemistry, physiology and theoretical medicine of the Academy of Sciences of Ukr. SSR.

He was born in Kiev, graduated from a biological faculty of Kiev Institute of Public Education (now— Taras Shevchenko National University of Kiev). In 1932—1950, he worked at Kiev Medical Institute, at the same time since 1933 — a research assistant of the Institute of Biochemistry of Academy of Sciences of Ukr. SSR (in 1948—1976 — Head of the laboratory of vitamins). He is one of the founders of formation of scientific school and main trends of fundamental researches in the biochemistry of vitamins in Ukraine.

Main directions of his studies are associated with the biochemistry of muscles, experimental bases of vitaminotherapy, biochemistry of vitamin-containing enzymes and history of vitaminology.



Vladimir Aleksandrovich Belitser (1906—1988) — academician of Academy of Sciences of Ukr. SSR, doctor of biological sciences, professor. He graduated from the physico-mathematical faculty of Lomonosov Moscow State University in the specialty "physicochemical biology". He studied the relationship between a respiratory system and glycolytic reactions in the animal tissues and established effect of creatine on muscular respiration and role of creatine phosphate in this process. He first showed that aerobic phosphorylation is coupled with respiration. He studied stoichiometric ratio between a conjugated binding of phosphate and oxygen absorption, and estimated a thermodynamic significance of this process, having demonstrated that the energy of transfer of electrons from a substrate to oxygen is used for the formation of three ATP molecules per one atom of absorbed oxygen.

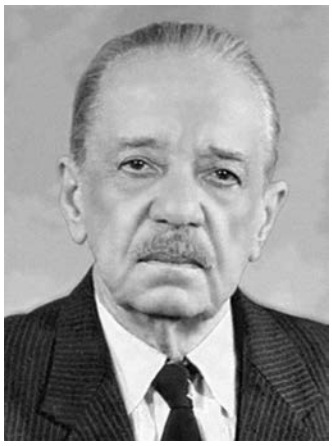
From 1944 to 1988, he worked at the Institute of Biochemistry of Academy of Sciences of Ukraine, where he headed the laboratory of enzymes, since 1966 — department of structure and function of proteins; in 1969—1972 — Director of the Institute. He studied properties of native and denatured protein, produced a blood substitute BK-8 from proteins of the serum of cattle. Representatives of V.A. Belitser's school have studied a molecular mechanism of one of the main reactions of blood coagulation — transformation of fibrinogen into fibrin. They described the structure and function of fibrinogen and fibrin, experimentally proved that for the fibrin network formation, specific centers of polymerization are of substantial significance, and transformation of fibrinogen into fibrin proceeds in two stages – enzymatic and polymerization. V.A. Belitser proposed his own conception for the mechanism of transformation of fibrinogen into fibrin, substantiated a kinetic theory of this reaction and studied a domain structure of fibrinogen. A number of diagnostic tests for differential diagnosis of cardiovascular diseases was developed and introduced into medical practice under the guidance of V.A. Belitser.

Aron Mikhaylovich Utevsky (1904—1988) — doctor of biological sciences, professor, corresponding member of NASU. He graduated from Kharkov State University (now — Karazin Kharkov National University) in 1924. In 1925—1931 he worked under A.V. Palladin's scientific supervision. Since 1931 he headed the newly established department of biochemistry of Ukrainian Institute of Endocrinology and department of biochemistry of Kharkov Medical Institute.

Scientific works of the professor A.M. Utevsky, devoted to the study of metabolism of epinephrine and other biogenic amines, have laid the foundation for further investigations of pathways of transformation of hormones into mediators and catalysts of processes of intracellular metabolism, the study

of the role of hormone metabolism in the mechanism of their action and the expanding understanding of biochemical factors of neurotrophic processes. Methods of investigation developed by him and theoretical conceptions of functional significance of the direction of processes of hormone metabolism were used in many clinical investigations while studying endocrine and non-endocrine diseases.

German Vasilyevich Troitsky (1913—1992) — doctor of biological sciences, candidate of medical sciences, professor, a corresponding member of Academy of Sciences of Ukr. SSR, Honored worker of Scince and Technology of Ukr. SSR. In 1951—1988 he headed the department of biological chemistry of Crimean Medical Institute, was the founder of Crimean biochemical school.



Main works of the professor G.V. Troitsky are devoted to the study of vitamin A metabolism, changeability of the structure of blood proteins in pathology. G.V. Troitsky first proved the presence of β- sheet structure in globular proteins, developed a method of isoelectric focusing in borate-polyol systems. With the help of this method and method of electrophoresis, highly purified preparations of proteins were obtained under the zero-gravity state at the space station “Salyut”.

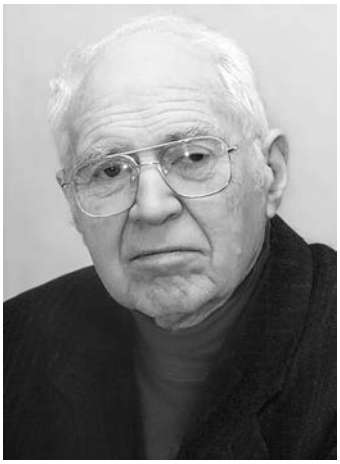
Vladimir Petrovich Vendt (1906—1993) — doctor of biological sciences, professor, laureate of State Prize of Ukraine. He graduated from Odessa Physico-pharmaceutical Institute. Since 1930 he worked at the Ukrainian Institute of Pathology and Occupational Hygiene in Kharkov, then — a research assistant of Ukrainian Institute of Experimental Medicine. Since 1946 — higher research assistant of the Institute of Biochemistry of Ukr. SSR Academy of Sciences. In 1963, V.P. Vendt headed the laboratory, later — the department of photo-biochemistry and department of biochemistry of sterols (1976—1983). He was the first to carry out the wide-scale studies of biochemistry of sterols, first of all, vitamins of D group (showed the possibility of the formation of sterol complexes with proteins and clarified to the nature of chemical bonds between them). This has allowed develop methods of obtaining the artificial protein-vitamin complexes with the high activity on the base of casein (or other proteins) with preparations of vitamins D_2, D_3, E and carotene. These developments are used for the industrial production of vitamin D_3 (videin D_3), which is used in poultry farming and medicine. He proposed a method of the early diagnosis of D-hypovitaminosis, developed and introduced into medical practice methods of the early diagnosis of rickets in children and the estimation of degree of risk of disease by the analysis of umbilical cord blood.

V.P. Vendt and R.I. Yakhimovich first received a crystalline vitamin D_3 and its complex with cholesterol (videchol), which is successfully used for prophylaxis and treatment of rickets.

Evgeny Fedorovich Shamray (1911—1980) — doctor of biological sciences, professor, Honored worker of Science and Technology of Ukr. SSR. In 1938, after graduation of biological faculty of Taras Shevchenko Kiev State University, he worked at the first Kiev Medical Institute (KMI). In 1947—1953, he headed the department of biological chemistry of Stanislavsky (Ivano-Frankovsky) Medical Institute, then again returned to KMI. E.F. Shamray's research activity was devoted to the study of biological action of plant polyphenols, vitamins C and P, substantiation of vitamin clinical application as well as creation and introduction of new vitamin preparations. "Galascorbin" invented by him is used in medical practice in burns, in the complex operative and radiation therapy and also used abroad (France, USA, Japan).

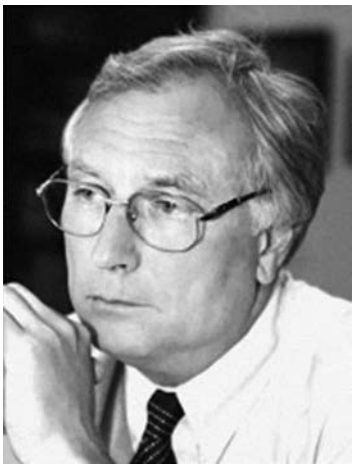
Maksim Fedotovich Guly (1905—2007) — doctor of biological sciences, professor, academician of the Ukr. SSR Academy of Sciences, laureate of State prizes of the USSR and Ukr. SSR, Honored worker of Science and Technology of Ukr. SSR, Hero of Ukraine, Director of Palladin Institute of Biochemistry of Academy of Sciences of Ukr. SSR (1972—1977).

He graduated from Kiev Veterinary-zootechnical Institute and since 1932 worked at the Institute of Biochemistry, since 1944 — at the Ukrainian Agricultural Academy. The main direction of his researches was the study of problems of modern functional biochemistry and molecular biology metabolic regulation of physiological state of human and animals. M.F Guly proved that carbon dioxide is the active regulator of metabolism; developed methods of diagnosis, prophylaxis and treatment of diseases associated with pathogenesis of acid-base homeostasis. He developed a clinical method of glucose determination, biotechnology of molecular oxygen production, pharmaceutical preparation of antimicrobial action "Microcid". The author of conception of mechanisms of development of alcohol and narcotic addiction, new pharmaceutical preparation "Medichronal" and agent for treatment or prophylaxis —"Corectin" that can be used in the orthopedics, oncology, gerontology and metabolic therapy.



Yury Vladimirovich Khmelevsky (1930—2014) — doctor of medical sciences, professor, laureate of A.V. Paladin prize of Academy of Sciences of Ukr. SSR. He graduated from Kiev Medical Institute (1952). In 1969—1976, professor of the department, from 1976 to 1988 — Head of the department of biochemistry, in 1985—1988 — a Dean of the 2-nd medical faculty of Kiev Medical University named after O.O. Bogomolets (now— Bogomolets National Medical University).

Main researches of professor Yu.V. Khmelevsky are devoted to the problems of pathobiochemistry of metabolism in modeling of different hypoxic states, biochemistry of coenzyme vitamins, in particular, thiamine and pyridoxine, vitamin E and short-chain tocopherols in the experimental damage of myocardium and radiation sickness.



Sergey Vasilyevich Komissarenko (born in 1943) — a leading scientist in the field of biochemistry and molecular immunology. Academician of NASU and Academy of Medical Sciences of Ukraine, Honored master of sciences and engineering of Ukraine, laureate of State prize of Ukr. SSR. Academician-secretary of the Department of biochemistry, physiology and molecular biology of NASU. Director of A.V. Palladin Institute of Biochemistry of NASU. Editor-in-chief of "Ukrainian biochemical journal". President of Ukrainian biochemical society.

He was born in the family of well-known Ukrainian scientist-pathophysiologist academician V.P. Komissarenko. He graduated from medical faculty of Kiev Medical Institute and the postgraduate studies at the Institute of Biochemistry of Academy of Sciences of Ukr. SSR.

Scientific works of academician S.V. Komissarenko are devoted to the problems of biochemistry and molecular immunology, main directions of the his scientific activities are associated with immunochemical study of antigenic structure of proteins and peptides. He introduced methods of immunoenzymatic studies and flow cytofluorometry, a hybridoma technology to obtain monoclonal antibodies. He studied the immunity in the liquidators of the Chernobyl disaster; found out new centers of fibrin polymerization, developed a complex of immunoenzymatic test-systems for a control of the antidiphtheritic immunity in the population, for diagnosis and monitoring of treatment of blood coagulation system disorders and diagnosis of tuberculosis. He revealed the antineoplastic and immunomodulatory activity of methylenebisphosphoric acid, on the base of which the antineoplastic agents are created for treatment of oncologic diseases.

Part I

GENERAL PRINCIPLES OF REGULATION OF METABOLISM

Chapter 1
BIOMOLECULES AND CELLULAR STRUCTURES

1.1. CHEMICAL COMPOSITION OF LIVING ORGANISM

Living organisms, by their composition, differ from the objects of inorganic nature. Less than half of the 92 inorganic chemical elements are necessary for the vital activity of living organisms. The most prevalent chemical elements in the living organisms are the following: the first place by the amount is taken by hydrogen H (63 % of the total number of atoms), the second — oxygen O (25.5 %), the third — carbon C (9.5 %) and the fourth — nitrogen N (1.4 %). Thus, more than 99 % of atoms account for the share of these elements. In addition to carbon, oxygen, hydrogen and nitrogen, human body also contains a great amount of phosphorus P and sulfur S.

Among chemical elements that are necessary for a vital activity of a human organism, there are ***macroelements*** (content of which in the organism constitutes more than 0.001 %, a recommended daily dose of consumption — more than 200 mg), and ***microelements*** (less than 0.001 %, a recommended daily dose of consumption — less than 200 mg).

Six macroelements (C, O, H, N, P, S) have got the name of ***organogens***, or ***bioelements***. The most of organic molecules in human body just consist of them. The macroelements also include sodium, potassium, magnesium, calcium and chlorine, which are contained in the body in the form of ions (Na^+, K^+, Mg^{2+}, Ca^{2+}, Cl^-). More than 30 microelements are known, among them are iron, zinc, silicon, copper, fluorine, iodine, manganese, chrome, selenium, aluminum, brome, molybdenum, cobalt, vanadium, nickel et al.

1.2. BIOMOLECULES AND THEIR FUNCTIONS

Biomolecules are organic substances of living organisms performing plastic (building), metabolic (participation in the metabolism) and regulatory functions. Nucleic acids, proteins, carbohydrates, lipids, vitamins, hormones and intermediate products of metabolism (metabolites) are referred to biomolecules.

Nucleic acids (deoxyribonucleic acid (DNA) and ribonucleic acid (RNA)) are polymers consisting of nucleotides. In the composition of each nucleotide, there are nitrogenous base (derivatives of pyrimidine or purine), pentose (ribose or deoxyribose) and phosphoric acid. In the molecule of nucleic acid, nucleotides are connected linearly by phosphodiester

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