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Scientific Session of the General Meeting of Members of the Russian Academy of Sciences "The Periodic Table of the Chemical Elements as a Universal Language of the Natural Sciences"

Chemical Elements in Medicine

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Abstract—A brief review of chemical elements, compounds from which find application in medicine, ranging from the commonly occurring organogenic elements (carbon, hydrogen, nitrogen, oxygen, sulfur, and phosphorus), composing the structure of proteins and nucleic acids of the cells of living organisms and determining the genetic transmission, to native rarely encountered organic fluorine compounds, synthetic derivatives of which have become firmly ingrained in the arsenal of modern pharmaceutical drugs, is given. Strong emphasis is put on metalloproteins, which play a significant role in the biochemistry of vitally essential processes, as well as metal compounds that are widely used in medicine. Of particular importance are the chemical elements and the isotopes, compounds of which are employed in nuclear medicine for diagnostics and treatment of a wide range of diseases, oncological and cardiovascular in particular.

Keywords: organogenic elements, macro- and microelements, metals essential for life, metalloproteins, radioactive elements, positron emission tomography (PET), boron neutron capture therapy, beta-lactam antibiotics, heterocycles, fluoroquinolones.

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The greatest discovery of Dmitrii Mendeleev, the periodic table, changed the history of science significantly and gave broad leeway in developing novel research directions [1]. The present review discusses the significance of chemical elements in the periodic table, which play a key role in the vital activity of living organisms, as well as elements that are used in medicine.

Medications go back to ancient times. At the early stages of its development, medicine had predominantly the most basic chemical substances in its arsenal (water, spirits of wine, glucose, edible salt, baking soda, potash, mercuric chloride, etc.), as well as water-based extracts or tinctures of natural bio-active compounds with therapeutic action found empirically. Chemical analysis, allowing for reliable determination of the elemental composition, emerged as late as the mid-19th century when data on the chemical elements and their properties were rather limited. At the time of discovery of periodic trends by Mendeleev, his table contained approximately 60 chemical elements, i.e., a little over a half of the elements currently known [1].

Among the 118 elements of the modern periodic table, one (mendelevium) was named after the Russian scientist and another six are directly related to Russian science by the very fact of discovery. The first was the 44th element of the table ruthenium named in honor of Russia. It was discovered by Karl Claus, Professor of Chemistry from Kazan State University, during examination of platinum ore from the Urals in 1844 [1], that is, a quarter century before Mendeleev postulated his periodic table. In 1846 the scientific achievement of Claus was recognized by the Demidov Prize (established in the name of Russian industrialist P.N. Demidov in 1832). A lesser known fact is that Mendeleev was recognized as a Laureate of the Demidov Prize for writing the first Russian textbook in organic chemistry in 1862. As for ruthenium discov-

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Fig. 1. Emblem of the International Year of the Periodic Table.

ered by Claus, at that time nobody could foresee the future significance of coordination compounds both of this unique element analogous to platinum and platinum proper to metal-organic catalysis and medicine [1].

The history of the discovery of another element, samarium, is similarly associated with the Urals. The element was isolated from the mineral samarskite discovered by workers of the engineer V.E. Samarskii-Bykhovets during mining operations in Ilmen Mineralogical Nature Reserve near the city of Miass in 1847 [1].

A series of elements (dubnium 105, flerovium 114, moscovium 115, and oganesson 118) has been discovered as the result of work of the renowned Flerov Laboratory at the Joint Institute for Nuclear Research in Dubna. It is not surprising that the Demidov Science Foundation acknowledged the contribution of Academician Yu.Ts. Oganessyan to the discovery of new transuranic elements by awarding the Demidov Prize in 2019.

The role of elements in vital activities of living organisms: Organogenic elements. We focus now on elements represented in the emblem of the International Year of the Periodic Table. In addition to element 101 (mendelevium), it shows the essential organogenic elements hydrogen, carbon, nitrogen, and oxygen, which additionally entail phosphorus and sulfur (Fig. 1, Table 1).

It is the organogenic elements that compose the biosphere of our planet (atmospheric water, oxygen, nitrogen, carbon dioxide, methane, and other natural hydrocarbon sources) and determine photosynthesis and other critical processes in the living cell, leading to the emergence of key classes of organic compounds, such as amino acids, peptides, proteins, carbohydrates (simple and complex), lipids and phospholipids (building blocks for cell membranes), and multiple bio-active heterocyclic compounds [2]. The multiplicity of the world of organic compounds is determined by the unique nature of carbon atoms capable of forming an indefinite number of ordinary (C–C), double (C=C), and triple (C≡C) bonds, cyclic and polyhedral compounds, oligomers and polymers, and bonds with other elements (C–H, C–N, C–O, C–S). To give an example, the structure of the cuddle hormone *oxytocin* consists of multiple amino acid units and the previously mentioned organogenic elements (Fig. 2) [2, 3].

Table 1. Essential organogenic elements

Element	Content in human body, %
Hydrogen (H)	10
Carbon (C)	18
Nitrogen (N)	3
Oxygen (O)	65

The same elements (C, H, N, and O) constitute the molecule of the coenzyme nicotinamide adenine dinucleotide (NAD) and its reduced form (NADH) involved in the essential redox processes in an organism. At this point, another critical element is brought into the spotlight, i.e., phosphorus, in the form of phosphoric acid residue constituting the nucleotide units (Fig. 3) [2, 3].

Ultimately, the acme DNA structure, which opened up a whole new era in biology and medicine, is assembled from the very same organogenic elements (hydrogen, carbon, nitrogen, and oxygen) and phosphorus from phosphoric acid residue into a specific sequence of nucleotides. It is heteroatoms that in the DNA structure determine the ability of heterocyclic bases (adenine, guanine, thymine, and cytosine) to form multiple hydrogen bonds "oxygen–hydrogen" and "nitrogen–hydrogen" and the double helix of DNA [2, 3].

"Metals for life." Among the 118 chemical elements of the periodic table, only 16 qualify as elements essential for life. Above we have noted six non-metals (H, O, N, C, P, and S) that are fundamental building blocks for biologically significant molecules and macromolecules. This should be expanded to include ten vitally essential metals, that is, Na, K, Mg, Ca, Zn, Cu, Co, Mn, Fe, and Mo, which are equally biogenic [4]. Among the ten metals, four belong to macro elements (sodium, potassium, calcium, and magnesium). Each of the elements is critically important; abnormal levels of them require therapeutic correction (Table 2).

Thus, sodium (with a level of 150–200 g in the organism of an adult) works to maintain the acid–base balance, osmotic pressure, pH level in the blood, and transport of amino acids and various anions through the cell membrane. In medicine, sodium salts are used as a basis for a variety of medical compounds to correct abnormalities (chloride, bromide, iodide, sulfate, hydrogen carbonate, nicotinate, benzoate, etc.).

Potassium also falls into the group of macroelements; the potassium content in an adult body is approximately 120 g. The primary biological function of potassium is to create potentials on cell membranes. It is additionally involved in transmission of nerve impulses and regulates cardiac contractions. The available potassium salt-based drugs include, e.g., potassium aspartate and magnesium aspartate, since

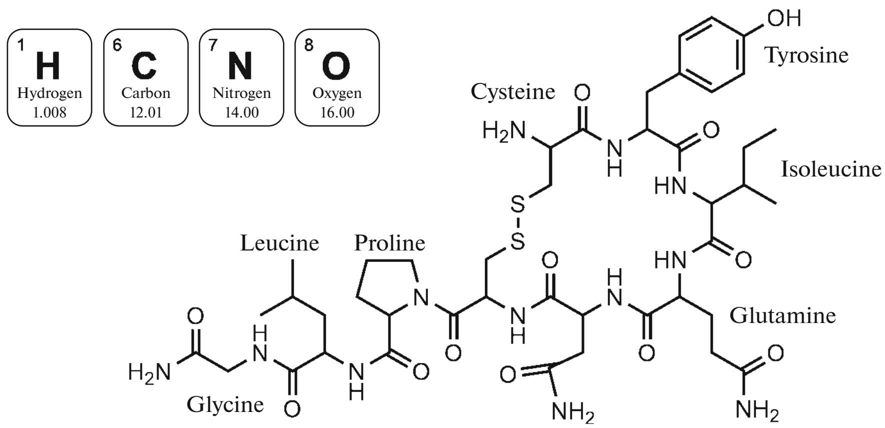


Fig. 2. Structure of the oxytocin enzyme.

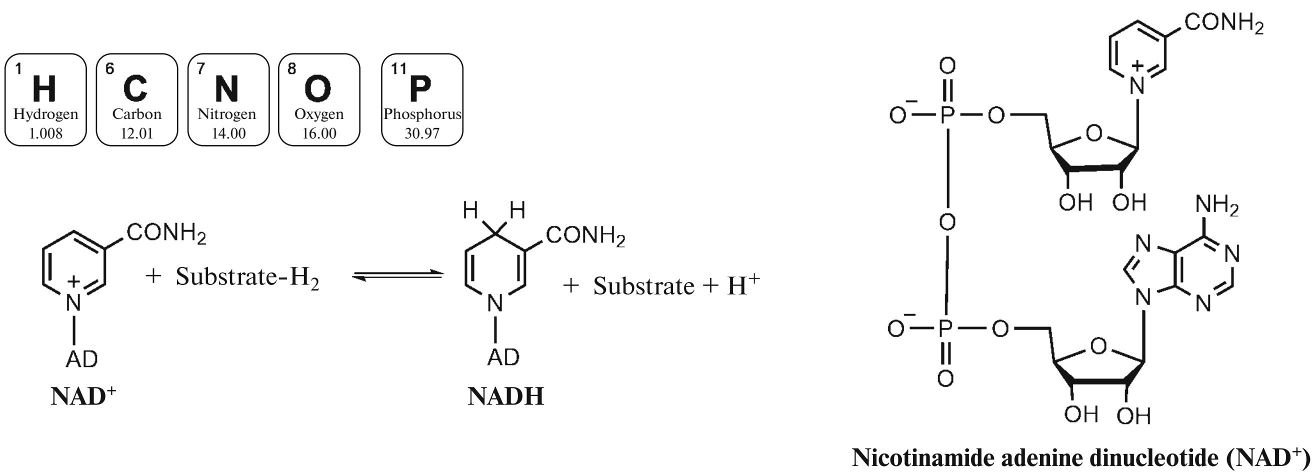


Fig. 3. Structure of NAD and NADH coenzymes.

magnesium is equally essential to heart rhythm and signal transmission in nervous and muscle tissues.

Among metals essential for life, magnesium also belongs to the macroelements; the content in the adult body amounts to approximately 25 g. A considerable amount of magnesium is contained in bone tissue (magnesium depot). There are preparations available based on magnesium citrate and orotate, e.g., *Magnerot,* for muscle spasm and pain treatment.

The most abundant macroelement of inorganic nature in the human body is calcium, which plays a key role in cellular physiological and biochemical processes. Ions of calcium (Ca^{2+}) are involved in coagulation and regulate a large variety of intracellular processes, such as muscle contraction, exocytosis, and secretion of hormones and neurotransmitters. An adult body contains approximately 1.2 kg of calcium (2% of the weight), 99% of which are in the human skeleton and teeth. Its deficiency directly causes osteoporosis and other physiological abnormalities. The role of calcium in stomatology cannot be overstated.

Equally important are microelements, which are keys to the catalysis of biochemical processes [5]. The most significant of them are represented by a series of six metals (Fe, Cu, Zn, Mn, Co, and Mo) and four nonmetals (fluorine, bromine, iodine, and selenium)

Table 2. Macroelements

Element	Content in human body, %
Sodium (Na)	0.15
Magnesium (Mg)	0.05
Potassium (K)	0.35
Calcium (Ca)	2.00
Phosphorus (P)	1.10
Sulfur (S)	0.25
Chlorine (Cl)	0.15

Table 3. Essential microelements

Element	Daily requirement, mg
Manganese (Mn)	5
Iron (Fe)	18
Cobalt (Co)	0.2
Copper (Cu)	2
Zinc (Zn)	15
Molybdenum (Mo)	0.18
Fluorine (F)	3
Bromine (Br)	1
Iodine (I)	0.15
Selenium (Se)	0.04

(Table 3). Notwithstanding the low content of microelement-metals in the organism, they fulfill essential functions and, therefore, are referred to the metals essential for life and are generally present in the body in the form of cations coordinated with heteroatoms of amino acid units or with heterocycles.

Iron is one of the most important biogenic metals. Despite the inconsiderable quantitative content in the human body (4.5 g), iron fulfills multiple functions, while being a part of protein transporters and enzymes. Thus, the complex of iron ions with porphyrin composes the basis for hemoglobin active sites capable of reversibly binding to oxygen, while coordinating four O_2 molecules and ensuring its passage in tissue through the circulatory system (Fig. 4). The hemoglobin content in the human body varies within the range of 120–180 g/L (normal).

Multicenter metalloenzymes occur widely. Enzyme cytochrome c oxidase critical for respiration contains both iron and copper; it performs the conversion of molecular oxygen O_2 to water. Another example is vitamin B_{12} (Fig. 5), which in terms of structure is a complex coordination compound of cobalt and corrin. In 1955 the British chemist and biochemist Dorothy Crowfoot-Hodgkin determined the spatial configuration, as well as the chemical structure, of a molecule of vitamin B_{12}, for which she was awarded the Nobel Prize in 1964. Vitamin B_{12} is essential for a healthy brain and nervous system and DNA synthesis.

Metalloproteins and metalloenzymes, in particular, are of key importance in biochemistry. Thus, carboxypeptidase A enzyme, which in addition to 307 amino acids comprises zinc ions, assists in catalysis of peptide bond hydrolysis (Fig. 6). Oxidation of xanthine to uric acid effectively occurs with the involvement of xanthine oxidase enzyme, which contains atoms of iron and molybdenum (Fig. 7); while ascorbic acid oxidation takes place in the presence of the corresponding oxidase, containing copper (Fig. 8).

Elements used in medicine as compounds. There are several million organic substances currently known in the world; tens of thousands among them are biologically active [6–8]. However, there are precisely four elements (hydrogen, carbon, nitrogen, and oxygen) that constitute the structure of the majority of synthesized medicines, ranging from the simple, such as *aspirin, analgin,* and *phthivazidum,* to the considerably more complex, containing asymmetric (chiral) carbon atoms or enantiomerically pure substances, such as the natural-source anticancer drug of natural origin *Taxol* (Fig. 9) [6–8].

The astounding fact is that such a limited number of chemical elements from the periodic table (hydrogen, carbon, oxygen, nitrogen, phosphorus, sulfur, and silicon) have proved to be sufficient for derivation of the sizeable variety of organic substances, including medications, diagnostic agents, polymers, and medical devices intended for various uses. The presence of heteroatoms (nitrogen, oxygen, and sulfur) in this series is critically important, inasmuch as the compounds comprising a heterocyclic unit are of the utmost importance to medicinal chemistry. They make the most significant contribution (at least 60%)

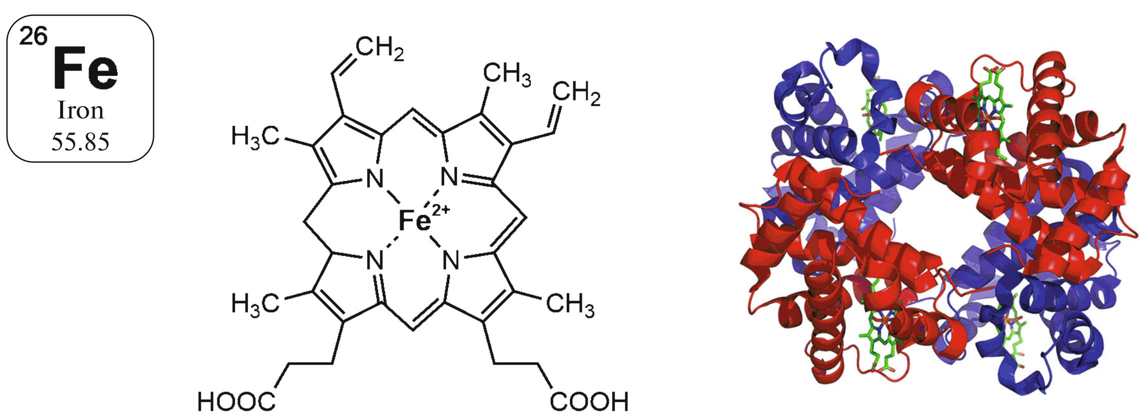


Fig. 4. Iron compound with protoporphyrin and hemoglobin, which is a metal-containing protein, playing a major role in oxygen transport.

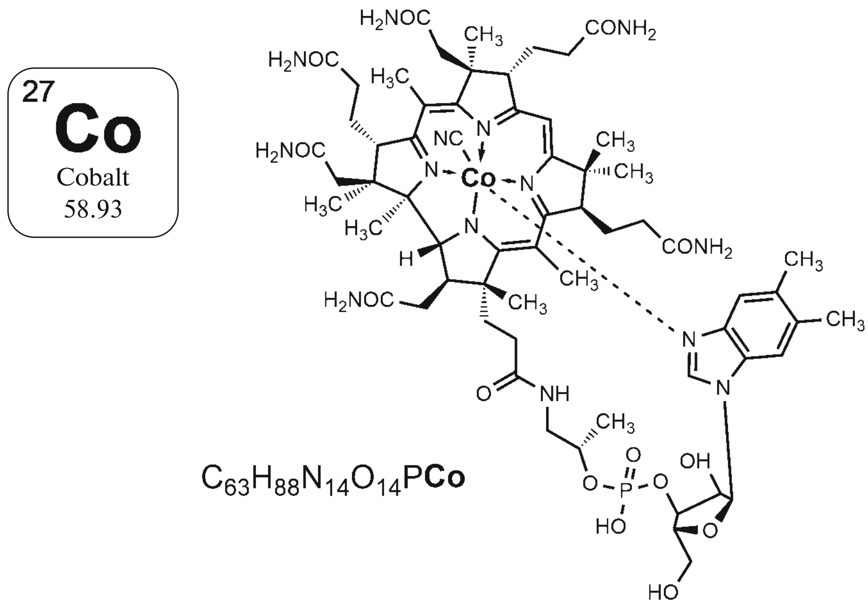


Fig. 5. Structure of vitamin B12 (adenosylcobalamin).

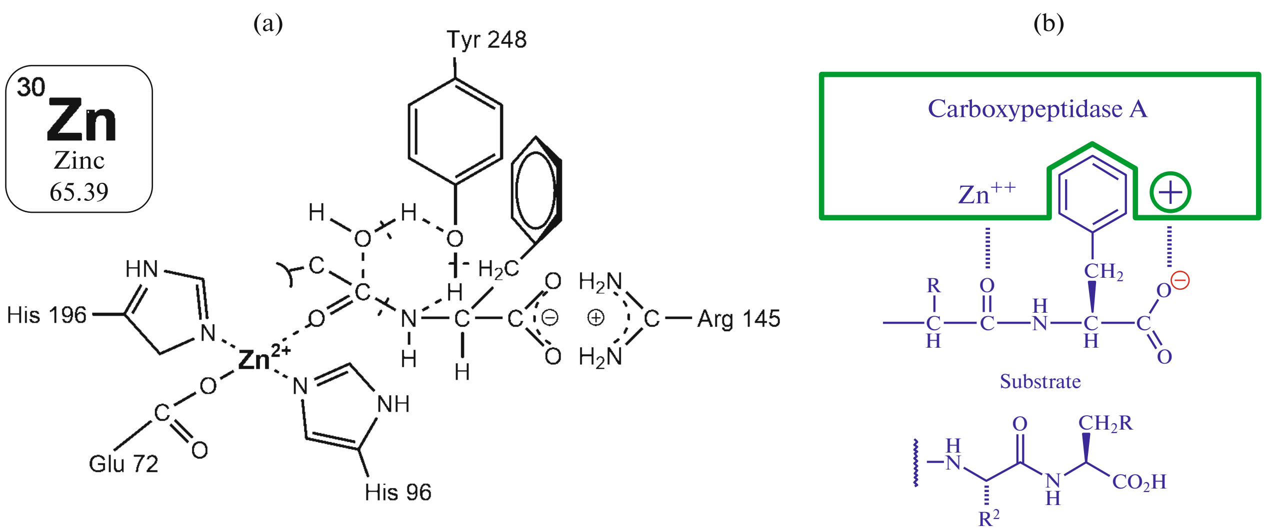
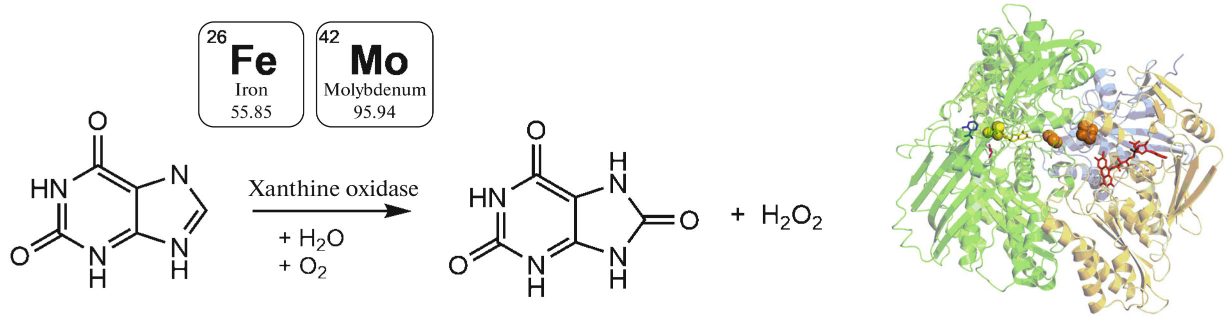


Fig. 6. Example of the action of an enzyme that composition includes zinc ions: (a) active site of carboxypeptidase A; (b) an example of carboxypeptidase A action.

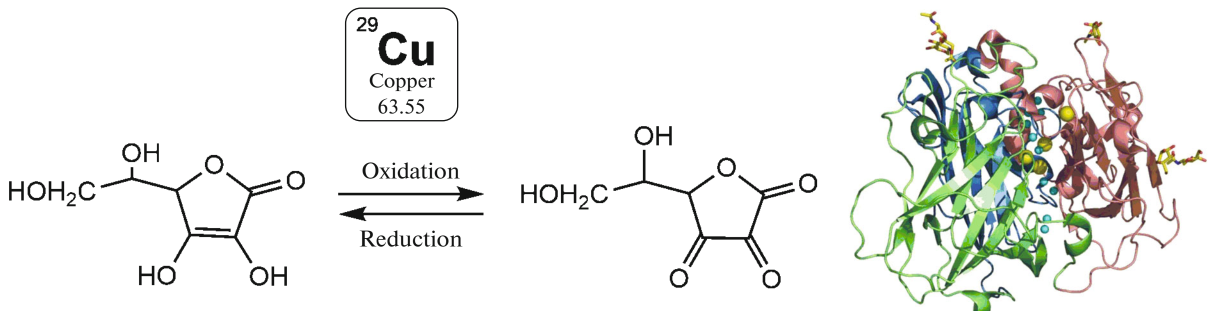
to the arsenal of various drugs [6–10]. The most common include, e.g., nitrofuran-derived antibacterial drugs (*Furacilin*, *Furadonin,* and *Furazplidone*); vasodilators and dihydropyridine-type antihypertensive agents (*nicardipine, nifedipine,* and *felodipine*); tranquilizers derivatives of 1,4-benzodiazepines (*diazepam, oxazepam, nitrazepam, phenazepam,* and *elenium*); and phenothiazine neuroleptics (*aminazine*, *propazine, and levomepromazine*) (Fig. 10) [6–10]. The heterocyclic skeleton is prominent in antibiotics of *penicillin* group discovered by the renowned English bacteriologist A. Fleming or semisynthetic penicillin or cephalosporin analogs (Fig. 11) [6–10].

Incorporating the fluorine atom in bio-active compounds assumes even greater importance [11, 12]. Natural fluorine-containing organic compounds are almost entirely missing from the organic world. At the same time, at least 20% of all pharmaceutical drugs developed across the globe contain atoms of fluorine, which enhances permeability through cell membranes and, generally, increases their activity. The modern "armory" of antibacterial drugs is inconceivable with-



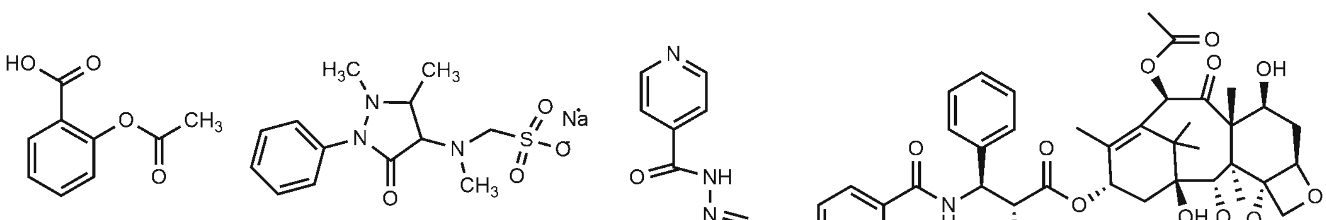
Xanthine Uric acid Xanthine oxidase 250 000

Fig. 7. Action of xanthine oxidase, which is a multicenter enzyme, comprising six atoms of iron and two atoms of molybdenum.



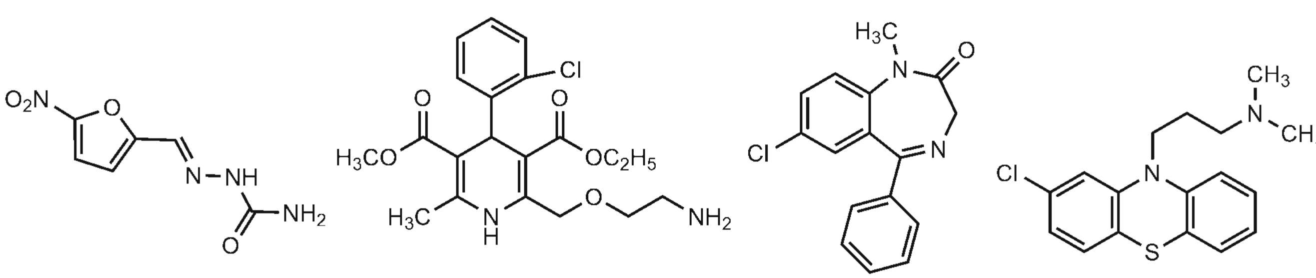
Ascorbic acid Dehydroascorbic acid L-ascorbate oxidase 150 000

Fig. 8. Action of ascorbic acid oxidase, which is a multicenter enzyme, comprising six copper atoms.



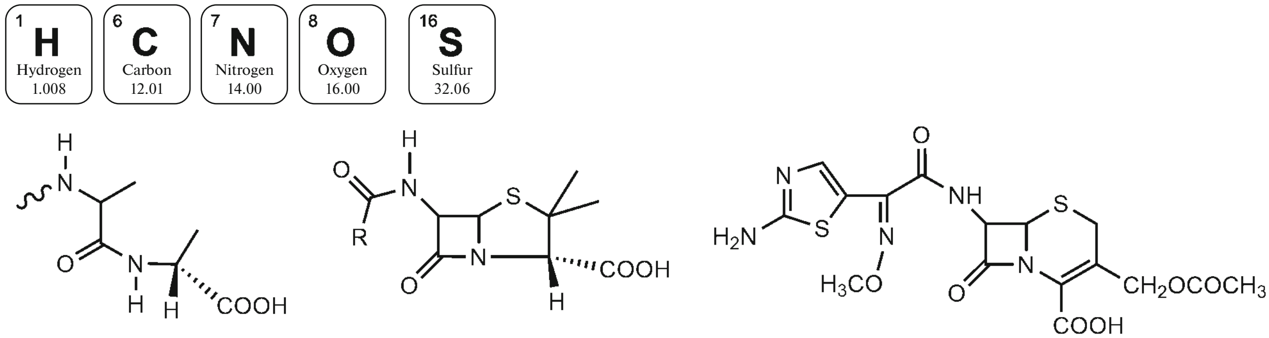
Aspirin *Analgin* *Ftivazid* Taxol

Fig. 9. Structure of selected pharmaceutical drugs.



Furacilin Normodipine Diazepam *Aminazine*

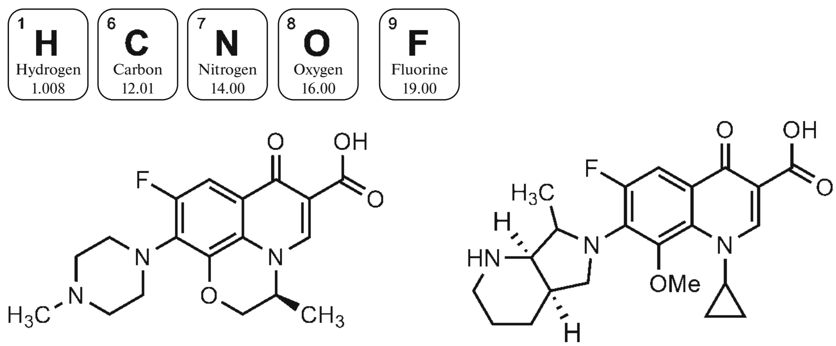
Fig. 10. Structure of selected pharmaceutical drugs, containing heterocyclic units.



Side of peptide chain terminus, linking to transpeptidase

Cefotaxime

Fig. 11. Key structures of beta-lactam antibiotics.



Levofloxacin

Moxifloxacin

Fig. 12. Structures of essential fluoroquinolones.

out *levofloxacin, moxifloxacin,* and other derivatives of fluoroquinolone family (Fig. 12) [12].

Recently we have seen the development of a new direction that has received the name of inorganic medicinal chemistry [13]. In addition to metals essential for life, many other elements and their compounds take center stage.

The application of metal-containing medicines and medical devices offers unique opportunities to tackle pathological conditions that failed to respond to the existing classical organic-based drug therapies. The most common include compounds with platinum, gold, lithium, tin, gadolinium, and lanthanum incorporated into clinical practice in the 20th century [14]. Just to name one, the first antibacterial drug *Salvarsan* (organoarsenic compound) was created by Nobel Laureate P. Ehrlich, the prominent German scientist, one of the founders of chemotherapy, in 1907.

A significant contribution to the development of inorganic medicinal chemistry was made by the outstanding Russian chemist A.N. Nesmeyanov, Academician of the USSR Academy of Sciences, who, among other things, in 1971 was the first to introduce into medical practice the nationally developed drug *Ferroceronum* based on the organometallic compound ferrocene for treating patients with iron deficiency anemia [15].

In clinical practice, lithium carbonate-based antidepressants have come into the common use to stay (e.g., *Sedalit* and its analogs), while barium sulfate has been used as an X-ray contrast agent for diagnostic procedures. There are the well-known gastroprotectants and medications for the treatment of gastrointestinal tract diseases that are based on bismuth compounds (*De-Nol* and *Desmol*).

Application of gold compound–based medications is currently known under the name *chrysotherapy.* Rheumatoid arthritis therapy actively involves medications, such as *Crysanolum* (calcium aurothiopropanal sulfonate), *Miochrysin* (sodium aurothiomalate), and *auranofin* (triethylphosphinegold compound with thioglucose).

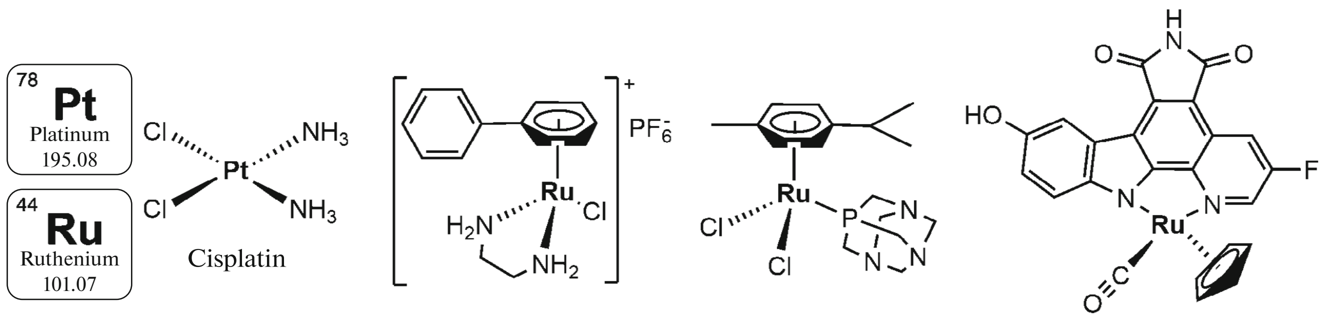
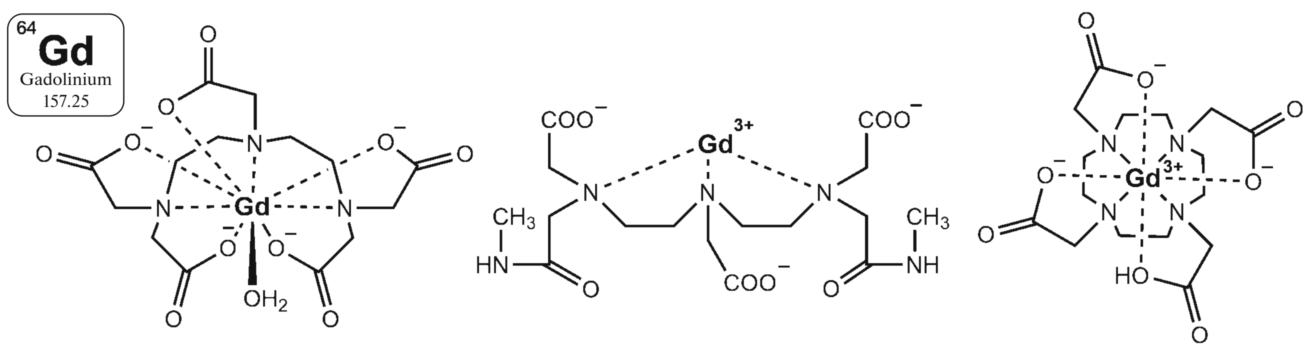


Fig. 13. Cisplatin and the ruthenium complexes used in medicine.



Gadopentetic acid Gadodiamide Gadoteric acid

Fig. 14. Gadolinium-based contrast reagents for MRI.

Platinum compounds have been effectively used in cancer treatment since the moment of the discovery by the American biophycisist B. Rosenberg of the antiproliferative action of *Cisplatin* and the introduction of the latter in clinical practice in 1965 and 1978, respectively, including Cisplastin analogs, such as *oxaliplatin, carboplatin, loboplatin,* and *heptaplatin*. Clinical trials are under way for a number of ruthenium complexes that have exhibited high antitumor activity (Fig. 13).

Gadolinium complexes play a special part in diagnostic procedures, inasmuch as gadolinium complex–based agents (*gadopentetic acid, gadodiamide*, and *gadoteric acid*) are widely used in magnetic resonance imaging (MRI) (Fig. 14). Contrast MRI images enhanced by gadolinium complexes allow diagnosis of abnormalities not visible when other visualization techniques are employed.

Isotopes of elements in medicine. Nuclear medicine is the most important and most rapidly developing field of research [16]. Dozens of chemical elements and radioactive isotopes have been finding increased use in the diagnostics and treatment of various medical conditions, and their number continues to grow (Fig. 15) [16].

Radioactive isotopes differ in the nature of emitted radiation (alpha- and beta-decay and "hard" gamma rays); their half-lives vary broadly (ranging from minutes and hours to many years); and, indeed, each of the nuclear medicine techniques is highly specific. Thus, positron emission tomography (PET) employs positron-emitting isotopes, such as carbon-11 ($T_{1/2}$ = 20.4 min); nitrogen-13 ($T_{1/2}$ = 9.96 min); oxygen-15 ($T_{1/2}$ = 2.03 min); and fluorine-18 ($T_{1/2}$ = 109.8 min).

PET scanning with fluorodeoxyglucose as a radiotracer (Fig. 16a) is widely applied in clinical oncology. The technique is based on an intensive uptake of glucose by rapidly growing tumor cells, which allows recording the sites of tracer accumulation using the PET scanner. Radiopharmaceuticals based on metastable 99-technetium allows detection of functional abnormalities in cardiac muscle activity (Fig. 16b). A gallium-68–based preparation is effective for prostate cancer visualization (Fig. 16c); it forms complexes with a specific peptide. The PSMA (prostate-specific membrane antigen) PET technique with gallium-68 allows classification of prostate cancer at any stage of the disease.

Undoubtedly, new horizons have been opened by advancements in alpha-therapy with the use of actinium-225, the advantage of which lies in the decay with emission of four alpha-particles.

Diagnostics	9 **F** Fluorine 19.00	26 **Fe** Iron 55.85	29 **Cu** Copper 63.55	31 **Ga** Gallium 69.72	32 **Ge** Germanium 72.59	37 **Rb** Rubidium 85.47	39 **Y** Yttrium 88.91	40 **Zr** Zirconium 91.22	43 **Tc** Technetium 98.91	49 **In** Indium 114.82	53 **I** Iodine 126.90	54 **Xe** Xenon 131.29	56 **Ba** Barium 137.33	64 **Gd** Gadolinium 157.25
Radiotherapy	27 **Co** Cobalt 58.93	38 **Sr** Strontium 87.62	55 **Cs** Cesium 132.91	83 **Bi** Bismuth 208.98	85 **At** Astatine (210)	88 **Ra** Radium (226)	62 **Sm** Samarium 150.36	67 **Ho** Holmium 164.93	71 **Lu** Lutetium 174.97	89 **Ac** Actinium (227)				

Fig. 15. Elements employed in radiodiagnosis and nuclear medicine.

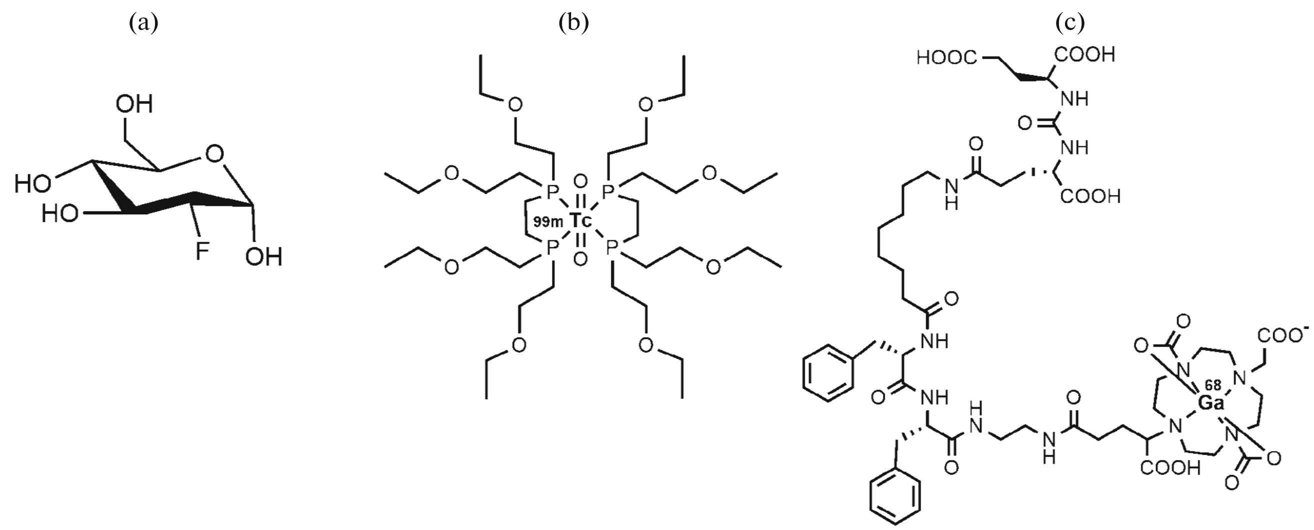


Fig. 16. Examples of radioactive substances used in medicine: (a) fluorodeoxyglucose (radioactive indicator ^{18}F); (b) metastable 99-technetium-based agent; (c) 68-gallium-based agent.

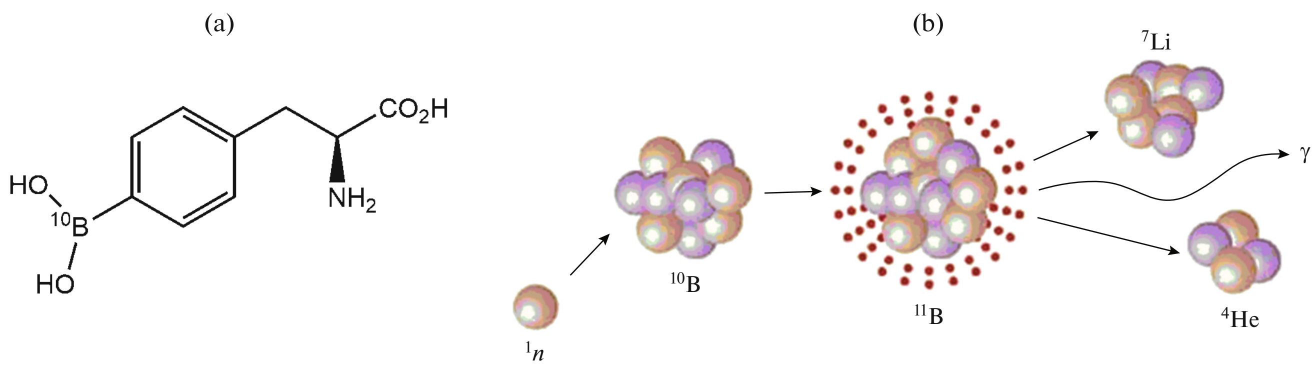


Fig. 17. Illustration of boron neutron capture therapy: (a) structure of borono-L-phenylalanine, which is ^{10}B-containing agent; (b) a scheme of neutron capture by boron compounds, leading to gamma ray emission and tumor destruction.

Nuclear medicine has embraced boron neutron capture therapy based on the unique ability of boron-10 to capture neutrons (Fig. 17).

Obviously, a broad range of elements (metals, non-metals, radioisotopes, etc.) has found application in medicine. A high value is placed even on inert gases, which have been known to possess a narcotic effect. Based on the strength of action, the narcotic effect diminishes in the series xenon-54—crypton-36—argon-18—neon-10—helium-2. In addition, helium mixed with oxygen is a medical treatment for patients with bronchial asthma and other diseases of the respiratory system.

Polymers in medicine. In our everyday lives, we have become increasingly encompassed by articles made of polymer materials. They have found their way into medicine and are used to manufacture prostheses of bones and teeth, artificial valves and vessels, and other medical items and materials [17]. Particularly important are biodegradable polymers employed in the production of absorbable surgical sutures and other medical materials. The majority among them belong to organic polymers, such as polyvinylpyrrolidone, carboxyl-containing copolymers, poly(vinyl sulfate), dextran sulfate, and polyvinyl pyridine-n-oxide [18].

Polymer complexes with iodine are known to exhibit high bactericidal activity. They are applied in aqueous solutions, gels, films, and sutures. *Iodinolum* (poly(vinyl alcohol)—iodine complex solution) is used in both human and veterinary medicine, while iodine complexes of polyvinylpyrrolidone serve effectively as antiseptics.

Particular reference should be made to silicon-containing substances, considering the affinity of silicon to carbon and their biocompatibility with tissues. Plastic surgery employs polymers based on organosilicon compounds (oligo- and polyorganosiloxanes) as implants, shunts, and catheters and liquid silicones as anticoagulants.

CONCLUSIONS

The role of all (more than 80) chemical elements and their compounds in modern clinical practice can hardly be overstated. It has been quite some time since medicine was limited to extracts from natural organic compounds constructed from organogenic elements characteristic of medicine in the ancient world or use of their pure forms.

Medicinal chemistry, a novel interdisciplinary field of science, has evolved in recent decades. Its firm standing and intensive development is determined by the active commercial distribution of chemically derived small molecule drugs across the global pharmaceutical market.

The modern armory of pharmaceutical drugs largely includes synthetic or semi-synthetic preparations of both organic and inorganic nature. The boundaries between organic and inorganic medicinal chemistry have been fading away, while an increasing diversity of chemical elements and their compounds have been mainstreamed in medical diagnostics and therapy.

Currently, the scientific community is facing new challenges associated with the occurrence of resistance to antibiotics and the emergence of novel viruses and mutation of known ones. This further necessitates more emphasis to be directed toward the development of organic synthesis and medicinal chemistry and consolidation of efforts on the part of chemists, biologists, and pharmacologists within interdisciplinary programs to provide adequate responses through joint efforts.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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