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MEDICAL INNOVATIONS DURING AN ERA NANOTECHNOLOGY

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The development of medicine in the era of nanotechnology has been reviewed. The hallmark of this time is a broad use of rare and rare-earth metals. The molecular processes of nanotechnologies are similar to those of the origin of life. The genetic code of protobionts contained information about the maintenance of metal-ligand homeostasis and the composition and functions of cell walls and membranes under conditions existing 3,5-4 billion of years ago. Biological evolution resulted in origination of mechanisms:

1) a struggle in the form of antioxidant systems against the toxic effect of O_2;

2) harsh Ca^{2+} homeostasis in the form of I-containing Se-protein hormones.

Interdisciplinary medical bioinorganics is the basis for study of mechanisms of pathological processes. There has been formulated the law of substitution and its consequences for the explanation of the interaction of metals in metabolism. It is possible to predict new understanding of an etiology, pathogenesis and treatments of diseases.

1. The Era of Nanotechnology.

One of the creators of quantum electrodynamics *Richard P. Feynman* in 1959 regarding the supercompact encoding of a tremendous volume of information in biological systems turned out to be of great importance for the advancement of biology (as well as medicine). In his speech«There's Plenty of Room at the Bottom. An invitation to enter a new Field of Physics» at an annual American Physical Society meeting R. Feynman forecasted the Era of Nanotechnology in terms of manipulation of matter at the level of single atoms.

Humankind has passed through several periods in its progress – the Stone Era (> 4 thousand years Before the Common Era), the Copper Era(4-3 thousand years B.C.E.), the Bronze Era(before 13/11 centuries B.C.E.), and the Iron Era (before 1959 C.E.). One can easily note that the criterion for the determination of the epochs is the type of material (metal) that was used for making tools and weapons.

In this system of coordinates, the EraofNanotechnology differs from the Iron Era by its widespread use of rare and rare-earth metals. The elements that have hardly ever been used before are in extensive use. Computers work on alloys of Si, Ge, As, mobile phones and heterolasers – Ga, Al, As, In, P, the aviation and car industry – Ti, Al, Li, Ce, atomic power – U, Pu, Th, etc. The influence of these elements on the metabolism of organisms and the environment has not been studied enough.

2. The similarity of studying molecular nanotechnology and the origin of Life.

The spontaneous mechanism of adsorption of primary organic molecules on crystals in the prologue of life and the origin of self-replicating molecular machines in nanotechnologies, in particular as applied to the incipiency of enantiomorph ism, are the same. The application of nanotechnology to the research of the origin of life, and vice versa, can assure success in the creation of manageable synthetic life [1].

Chemical evolution, before biological, had occurred on the basis of chemical reactions, remaining in force to the present time. Biological evolution, followed the origin of protobionts, for various taxon's occurred in parallel response to *changes in environmental conditions.*

At the time of the origin of life, genetic information was inscribed under the conditions that existed 3,5-4 billion years ago. Among them the main ones were *an absence of oxygen in the atmosphere* and *the salt composition of the primary World Ocean*. It was different from the modern one (pH ~ 0,3 vs. 7,6-8,4 now, the total salinity ~2,5 % vs. 3,4-3,7 % now, a significant predominance of Na^+ and Mg^{2+}). The content of metals has gradually changed upwards in terms of K^+ and Ca^{2+} proportion in the modern World Ocean. Apparently, during the process of adaptation of the metabolism of living organisms to environmental conditions, yet unknown mechanisms of information coding from the receptors and ionic pumps of membranes of protobionts were engaged.

On the assumption of Curie's principle («dissymmetry creates the phenomenon») the development of protobionts could have not occurred without membranes. The hallmark of Life, as the mode of existence of protein bodies, is the processes of interaction with the environment. The origin of the organisms of various domains and taxon's was determined by the nature and functioning of the substances of the membranes as the only exchange mechanism of energy, information and matter between the protobionts and the environment.

Consequently, the correct theory can only be the theory of the origin of life that supposes the formation of membranes in protobionts. This is the «protein» theory of A.I. Oparin [2].

Coacervate droplets of a polypeptide nature gradually accumulated polymers of nucleotides, porphyrins, carbohydrates, steroids, fatty acids, pyridoxine, and molecules of other classes of organic substances. Presumably, their total number for implementation of vital functions must have been at least 29 [3]. Initially many processes in

these droplets could have proceeded with the help of the catalytic properties of rocks and clays (aluminosilicates), in particular, in the form of Lewis and Brønsted centers for spontaneous synthesis of polypeptides [4] and FeS-catalysts – «mackinawite» ([Fe >> Ni)S]), «greigite» ($NiS_2[Fe_4S_4]S_2Fe$), etc.

First protobionts were chemosynthetics. Later on, the catalytic properties were multiply intensified in enzymes of a protein nature. Inside of the protobionts, a *metal-ligand homeostasis* (MLH) must have come into existence and been sustained. It can be vividly represented by the well-known symbol of Chinese natural philosophy «yin – yang» – the unity of opposites. But instead of darkness and light in this case the «mineral and organic» parts of the living matter are the subject. Both parts are of equal value for life, despite of a multiple quantitative predominance of organic matter mainly comprised of the following atoms C, N, O, H, P, S.

The ligands for metal ions, such as tetrapyrrole (porphyrinic) structures, had a material significance. The chelates with Mg^{2+} (chlorophylls) turned out to be able to capture the energy of photons and transform it into chemical energy in the form of $NADPH_2$ and ATP. The oxygen release into the atmosphere was an indirect result of photosynthesis. The porphyrinic chelates with ions of transition 3d metals (Fe, Cu, Co, V*)* in the form of he mog lob in, cytochromes, hemocyanin, cyanocobalamin and others turned out able to participate in the electron transfer in the processes of oxidation-reduction. The composition of the membranes initially included the substances of *a carbohydrate and lipid nature* which, are inherent in plants and bacteria now as well. Chemical specificity of various large taxon's and domains in the process of biological evolution has been maintained by the substances of the membranes of cells [5]. This information was encoded in DNA. After the formation of O_2, the connective tissue based on collagen and membranes of a *protein* nature in animals were formed. The information from DNA is decoded thanks to the functioning of cell walls and membranes [6].

Within the space of 3 billion years the evolution processes occurred under the constant pressure of two environmental factors: an increase in the content of O_2 and an increasing concentration of Ca^{2+}in the Ocean water. The intracellular structures in the form of a multicomponent antioxidative system (AOS) for protection against the poisoning activity of O_2 came into existence. The high-powered system for MLH maintenance, especially concerning the cytotoxic Ca^{2+} ion, came into existence as well. For some unknown reason, this second system functions in the participation of *I*-containing *Se*-proteins. Presumably, these elements constitute a semi conductive heterostructure that is necessary for the functioning of the Ca^{2+} homeostasis system.

3. Biology and Life are Chemistry [7, 8].

In the modern meaning, chemistry is considered an integrated science, consolidating the *historically developed subdisciplines (inorganic, organic, physical chemistry). This division* is artificial because they are methodically and thematically connected to each other. Studying the matter from only one perspective invariably results in incomprehensive understanding of the studied phenomenon [9].

In 1950, a new interdisciplinary scientific field came into existence. It is called «Biological Inorganic Chemistry» (BIC). It is between chemistry, biology, physics, pharmacy, and the science of material. The quintessence of BIC consists in «the application of notions of coordination chemistry to biological problems» [10]. The influence of one or another metal on metabolism depends not only on the functional groups and properties of ligands that are important for the stability constant (K_{st}) of coordinated bonds (donor-acceptor bonds) (complexes, chelates). The primary metal ions coming from the medium interact too with other metals.

It has been found that the stability constants of the complexes of the metals from one period with one and the same ligand (ethylenediamine) increase from left to right [11]. For this reason, the framework law was named by us as the ***law of substitution*** *of left members of each period by right members of the period in the complexes with the same ligands*. Taking into account the cybernetic principle of feedback, the law of substitution has two consequences. **The first one**: *right members of the period can be substituted by left ones in the case of their superfluous entry into the organism*. **The second one**: *an uncontrolled abundance of some element causes a deficiency of the elements metabolically interacting with it* [12].

These consequences manifest themselves in the case of uncontrolled superfluous entry of metals with drugs or during smoking or with food into the organism. These side effects also arise in the case of extracting the necessary metals from the active centers of the enzymes or other metabolic reactions by the substances with *active ligand groups* (pharmaceuticals, antigens of pathogenic bacteria, fungi and viruses or auto antigens, in particular, in the case of collagen diseases).

Nutritional experts established some other rules of behavior of elements in a living system («rules of Mertz»). They allowed the discussion of the nutritional issues at the symposium «Between a rock and a hard place». For each essential trace element, there are two ranges of intake associated with adverse health effects: intakes that are too low and can lead to nutritional deficit and intakes that are too high and can lead to toxicity (13). In such a way, all elements can be toxic [14].

4. The most important mineral elements in Life.

Ca was called «the main inorganic messenger», and Zn – «the main inorganic hormone» [15]. 3d transition metals, particularly Fe and Cu, are functionally important for processes associated with O_2 and the structure of connective tissue. Other elements also play an important role in certain pro-

cesses of metabolism depending on the properties of the complexes [16]. The final influence of the individual metals on the disease depends on their actual interaction with each other [17, 18].

In physiological conditions theme talion sa re mainly the central atoms (CA) incomplexes (orchelates). CA determine a geometrical structure of the complex and its Entatic State, i.e. an electron structure adapted to its function. Inthe case of a change in the valence of the CA, e.g. in the case of its oxidation, the ion radius decreases along with the change of Entatic Stateand function of the complex.

Because oft he unique variety off unctions of Ca (structural, neuromuscular, enzymatic, and signa ling) the role of the system of concentration maintenance of Ca^{2+} at a low level took on a key significance for all processes of a life activity [19-22]. Violation of MLH is the beginning of pathological processes [22]. Now it is possible to predict new understanding of an etiology and pathogenesis of diseases and aging.

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LEVEL OF MONOCYTIC CHEMOATTRACTANT PROETEIN, TRANSFORMING GROWTH FACTOR β_1, AND FIBROBLAST GROWTH FACTOR IN BLOOD SERUM OF PATIENTS WITH DIABETIC NEPHROPATHY

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The objective of this work is to study a character of monocytic chemoattractant protein (MCP-1), transforming growth factor β_1 (TGF-β_1), and fibroblast growth factor (FGF) among patients with diabetic nephrpathy (DN).

Methods and materials. Two groups of patients with sugar diabetes of type 2 with different stages of DN, according to classification I.I. Dedov and M.V. Shestakova, 2000, were included into the investigation. Group 1 ($n = 50$) – with albuminuria, average level of microalbuminuria among patients of this group equaled 149,8 ± 5,2 mg/day. Group 2 ($n = 35$) – with proteinuria, daily proteinuria did not exceed 1,1 ± 0,3 g/day. Duration of SD of type 2 oscillated from 1 to 15 years among the studied. Average age equaled 41,0 ± 6,5 years. Blood samples of 20 healthy donors were used as a control. Serum concentration of MCP-1, TGF-β_1, FGF was defined by the method of immunoferment analysis. Statistical processing of the received data was made with programme complex Statistica 8,0 for Windows.

Results and discussions. Defining contents of MCP-1 under DN has shown its increase 1,7 ± 0,2 times ($p < 0,05$) in proteinuric stage of DN, compared to the control (109,2 ± 4,1 pg/ml) and 1,3 ± 0,3 times ($p < 0,05$) – compared to the same index of albuminuric stage. Defining contents of FGF among patients with DN with albuminuric stage has established its reliable increase 1,5 ± 0,2 times ($p < 0,05$), compared to the control group (2,9 ± 1,1 pg/ml). The highest level of FGF,6,6 ± 2,4 pg/ml, was registered in blood serum of patients with proteinuric stage of DN. We have registered an increase in serum concentration of TGF-$\beta_1$among patients with SD of type 2 with a progressing nephropathy. Thus, under proteinuric stage of DN level of TGF-$\beta_1$equaled 122,4 ± 3,5 pg/ml and was reliably higher than un-