Biological Role of Trace Elements and Viral Pathologies

V. V. Ermakov*, and L. N. Jovanović**, **

*Vernadsky Institute of Geochemistry and Analytical Chemistry, Russian Academy of Sciences, Moscow, 119991 Russia
**ALFA BK University, Palmira Toljatija, 3, Belgrade, 11070 Serbia
*e-mail: vad-ermak@yandex.ru
**e-mail: ecologica.drustvo@gmail.com

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Abstract—The review presents summarized information on a new research avenue in biogeochemistry and geochemical ecology: relationships between the microcosm (viruses) and manifestations of animal and human pathologies. Some aspects of the biological action of selenium, zinc, copper and iodine, their influence on the manifestation and course of viral infections are considered. Attention is focused on the antioxidant, membrane-protective, boosting immunity, hormonal functions of trace elements, and on the antibacterial and antiviral properties of metallic copper and its compounds. The criteria currently applied in assessing the Se status of territories are compared with the incidence of COVID-19 and HIV in the population of the Russian Federation. In some cases, selenium deficiency in the environment is shown to be associated with a higher susceptibility to RNA viral infections. Emphasis is put on the necessity of improving the criteria for assessing the trace element status of territories and further studies in the geochemical ecology of viruses and their role in the biosphere.

Keywords: biological role, viral infections, geochemical ecology, iodine, copper, selenium, COVID-19

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INTRODUCTION

In the context of the discovery of bacteriophage as a new form of living matter, V.I. Vernadsky wrote: “Studies of bacteriophages uncovery new manifestations of life on in the biosphere. First, these studies definitely indicate that some organisms can be even smaller than bacteria and possess even greater geochemical energy” (Vernadsky, 1940), and “life reaches here again it possible limit”. V.I. Vernadsky stressed therein not only the importance of the discovery of ultramicroorganisms but also their ability to be involved in the biogeneric migration of matter.

Other parasitic substances of the world of living organisms turned out to be viruses. They were discovered by D.I. Ivanovsky in 1892, when he studied the pathologies of tobacco leaves: the tobacco mosaics. The pathologies were proved to be caused by a substance that could pass through the pores of filters and characterized by infectivity. Further studies have proved that this substance was not of bacterial nature and was smaller than bacteria (Ivanovsky, 1892). This was a newly discovered agent of disease, which was later named virus by Martinus Beijerinck (Beijerinck, 1898).

According to V.M. Zhdanov, viruses (regnum Virae) are obligate intracellular parasites that are widespread among vertebrate and invertebrate animals and among plants, protozoans, fungi, bacteria, and archaea. Viruses are devoid of metabolic conversion and receive energy owing to the metabolism of the host cell. In spite of their small size (20 to 400 nm), viruses are a life form in the proper sense of the word, they carry genetic material, are able to reproduce themselves, show variability (both genetic and phenotypical), and evolve through natural selection. Their variability is maintained by genom variations and as a result of recombination, genetic reassortment, under impacts of the environment, and in interactions with the host organisms and other viruses (Zhdanov et al., 2012). Some viruses of insects can regulate the sizes of the insect populations and are able to pass into a latent state (Ermakova and Tarasevich, 1968).

The biological microworld thus comprises not only “usual” organisms, such as bacteria, fungi, actinomycetes, and ultramicrobacteria (Archaea, Actinibacteria, Cytophaga, and Proteobacteria) but also the realm of viruses (Virae), which is widespread in the biosphere. The contents of ultramicroorganisms in soils are very high an may reach dozens to hundreds of million cells per 1 g of soil (Lysak et al., 2010).

In spite of the rocketing progress in virology, genetics, and molecular biology, the roles of viruses in the lives of organisms, ecology, evolution of the biosphere, and geochemical impacts are understood still inadequately poorly.

Nowadays the humankind more and more suffers from the adverse effects of accelerating technological
progress. These effects resulted in numerous ecological problems, such as acid rains, ozone holes, environmental pollution with harmful and hazardous chemical elements and toxic compounds, as well as the deficiency of vitally important trace elements in biogeochemical food chains, which gives rise to pandemic diseases and new viral pathologies, which have not been known previously. The latter include the acquired immune deficiency syndrome (AIDS), various types of viral hepatitis, Ebola and Coxsackie’s diseases, cattle rabbies, syndromes and diseases induced by the avian influenza virus (SARS-1) and coronavirus (SARS–2; COVID–19), and Kawasaki’s disease in children (Jovanović and Ermakov, 2020).

Mechanisms through which global biospheric changes are related to some diseases are still largely uncertain, and this makes it much more difficult to undertake adequate countermeasures and synthesize new medications to cure these diseases. At the same time, some progress has been achieved in this field over the past two decades.

This publication focuses on the still poorly explored field of geochemical ecology: interrelations between viral pathologies and microelementoses.

**SELENIUM**

Biological Role of Selenium

Extensive research shows that one of the chemical elements, more specifically, its deficiency in the food of humans, plays a crucially important role in the development of the currently most dangerous diseases. This element is selenium, Se (Ermakov and Kovalsky, 1974; Golubkina and Papazyan, 2006; Combs, 2015).

The history of studies of the biological role of Se comprises three periods of time. Before 1957, Se and its compounds were thought to be extremely toxic for living organisms. The reason for this was mass cattle poisoning in the Great Plains in the United States. The next phase of interest in Se was stimulated by the discovery, made by K. Schwarz and C. Foltz in 1957, that liver necrosis in rats and exudative diathesis in poult's can be prevented by low doses of Na selenite. This discovery triggered Se application in the therapy of the white-muscle disease in animals and other diseases (Schwarz and Foltz, 1957).

The third phase began with the discovery of the Se-bearing enzyme glutathione peroxidase, which regulates the antioxidant state of an organism, and outlining of large territories with Se deficiencies in the environments, forage, and human food (Ermakov and Jovanović, 2010; Golubkina et al., 2017). Nevertheless, biochemical functions of Se in animals and humans had not been understood until 1973. In 1973, J. Rotruck with colleagues (Rotruck et al., 1973) in the United States and a team of researchers headed by L. Flohe (Flohe et al., 1973) in Germany demonstrated that Se is incorporated into the molecule of the previously known enzyme glutathione peroxidase (GPx), which protects (similar to catalase) erythrocyte membranes from oxidation by decomposing hydrogen peroxide.

Selenium deficiencies in natural environments was almost simultaneously discovered in the 1960s in New Zealand, Australia, United States, and Transbaikalia in the Soviet Union (Ermakov and Jovanovic, 2010a). More than thirty animal and human pathologies, including cardiovascular and tumorous ones, are thought to be related to Se deficiency in the environment, forage, and food (Ermakov et al., 2018).

Interest in the biological importance of Se does not wane until nowadays. The physiological and biochemical functions of this trace element have been identified, but the invention of new efficient and nonhazardous medications is a slow process, although multitudes of pharmaceuticals have already been tested and approved.

Currently, the presence of a whole family of selenium-containing glutathione peroxidases has been discovered, which can also act against various organic hydroperoxides in a wide variety of animal cells. About thirty selenoproteins have been discovered that play fairly important roles in the biochemistry of the cell (Turner and Finch, 1991).

Selenoproteins other than Se-glutathione peroxidases are deiodinases, a number of thioredoxin reductases, selenophosphate synthetase 2, selenoprotein P, W, T, M, and R, as well as a number of other active selenoproteins, whose functions are still not fully understood. Selenium can also be involved in the bases of modified nitrogen bases of tRNA (as 2-seleno-5-methylamino methyl uridine) (Arthur, 2000; Patching and Gardiner, 1999; Behne and Retiakopoulos, 2001) (Fig. 1).

Selenium is necessary for the living cell to enable its growth (Levander and Beck, 1999). For example, cultures of immune and nerve cells can grow in serum-free media only if Se, insulin, and transferrin are added. The principally important biological functions of Se are antioxidative, membrane-protecting, immune-regulating, endocrinous, and antimutagenic.

Importance of Selenium for the Prevention and Treatment of Viral Diseases

It is interesting to gain an insight into relations between Se deficiency and the etiology of viral diseases (Guseinov and Safarov, 2007). For example, it was determined that nonvirulent RNA B3-type Coxsackie virus (CVB3/0) can be transformed into virulent one in mice held on Se-deficient diet as a result of irreversible mutation related to a change in the genome structure (Beck et al., 1995; Levander and Beck, 1999). This seems to be directly related to myopathy: endemic Keshan disease that occurs in some areas in China and Russia and is related to Se deficiency in the environment (Ermakov and Jovanović, 2010a).
Certain microelemental interactions were identified in the host–parasite and host–microorganisms systems. It is known that the organisms of humans and animals accumulates necessary concentrations of trace elements, such as Fe, Mn, Cu, and Zn, with certain compounds (including proteins) and utilizes them in fighting pathogens. The pool of trace elements thus affects the resistibility to infection. The status of Se may affect the host–pathogen relations, but pathogens themselves possess mechanisms enabling them to counteract this ability of their hosts. Both microorganisms and parasites (helmints) are highly resistant to

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**Fig. 1.** Effect of Se deficiency on human health.
the effects of particularly high (and hence, toxic) concentrations of metal ions (Gabrashanska et al., 2016). The secondary protective mechanism is based on the production of reactive oxygen and nitrogen by immune cells of the host, which can damage tissues and organs of the host. Furthermore, gas transmitters of nitrogen oxide (oxidant) and carbon oxide are involved in other metabolic processes related to the immune response.

An important role of Se in the origin and development of AIDS has been proved by several researchers. At first, it has been noted that AIDS is widespread in geographic areas whose soils are poor in Se. In Africa, HIV infection in areas with low Se concentrations in the soils became pandemic, and more than one-forth of the human population of these areas suffer from AIDS (Guseinov and Safarov, 2007).

Areas with low Se concentrations are characterized by higher AIDS death rates. Also, AIDS, Kaposi’s sarcoma, and other cancerous tumors were proved to be more frequent in areas with Se-deficient soils, and this seems to pertain not only to Africa but also to worldwide AIDS incidence (Taylor, 1997; Taylor et al., 2000).

Selenium deficiency significantly affects the survival ratio of HIV-infected patients. This was first reported by a research team headed by M.K. Baum at the University of Miami in the United States. They have found out that HIV-1-infected patients with a Se deficiency die from HIV-related causes twenty times more frequently than patients with adequate levels of Se concentration. Among all substances studied by this research team, Se showed the strongest hampering effect on the AIDS death rate. The authors hypothesized that interrelations between a Se deficiency and AIDS mortality is explained by the role played by Se as an antioxidant and/or by its effect on the regulation of gene activity in response to HIV infection (Urban and Jarstrand, 1986; Turner and Finch, 1991; Taylor et al., 1997a; Zhao et al., 2000).

E. Taylor suggested that an important role in HIV may be played by selenoproteins, namely, glutathione peroxidase. He also suggested that a new virus-related mechanism may operate, according to which HIV causes a decrease in Se concentration in the organism and accelerates the disease progress, whereas a normal level of Se concentration may suppress the reproduction of the virus and thus weakens the disease (Taylor et al., 1997b). To prove that part of the HIV-1 genome does code the selenoenzyme glutathione peroxidase in mammals, E. Taylor and his colleagues later cloned this hypothetical HIV-1 gene to inject into kidney cells of a dog and into the MCP7 cells (Taylor, 1997; Taylor et al., 1997a). In both instances, the cells that acquired the HIV-1 gene strongly intensified the production of the selenoenzyme glutathione peroxidase. This convincingly proves that HIV-1 (and likely also HIV-2, Coxsackie B virus, and hepatitis B and C viruses) are able to produce glutathione peroxidase for their functions. In view of these data, it would have been logical to expect that these infections shall be at a minimum in areas with high Se concentrations. However, this is not the case, and numerous instances of the opposite effects were documented: a high dietary Se consumption results in a higher resistance of the organism to all of the aforementioned viruses (Clark et al., 1986; Combs and Gray, 1998).

Comparison of data on HIV incidence in Russia (Corona Virus, 2020) with those on the Se status of the areas (Ermakov, 2001) and average Se concentrations in the grain (Golubkina et al., 2017) and blood serum of persons in these areas (Golubkina et al., 2017; Golubkina and Papazyan, 2006) has not reveal any significant correlations between them. For example, the correlation coefficients for twenty administrative units of Russia between HIV incidence (percentage of the disease incidence of the total human population of the administrative unit), a score estimate of the Se status, and the average Se concentration in the grain turned out to be low: $r = -0.340$ and $-0.288$, respectively. No correlation has been identified between the incidence and the average Se concentration in the blood serum ($r = -0.01$).

AIDS-infected adults and children are characterized by a strong Se deficiency in the blood serum and a decrease in the number of T helpers and/or CD4 cells, and these lymphocytes are known to be the principal target of HIV. A decrease in the level of Se concentration reportedly (Foster, 2002) leads to a decrease in the number of CD4 cells, which in turn results in a decrease in Se concentration in the blood serum.

Similar to HIV, some other viruses reportedly (Foster, 2002) decrease the Se concentration, and their genome also contains the gene of the human enzyme glutathione peroxidase, which enables the virus to unlimitedly reproduce itself and thus deplete glutathione in the host organism, with this enzyme being an inhibitor of reverse transcriptase, an enzyme necessary for the replication of the virus. This group of viruses includes HIV-1 and HIV-2, as well as the Coxsackie B virus and hepatitis B and C viruses (Beck et al., 1995; Taylor, 1997; Levander and Beck, 1999; Foster, 2002; Guseinov and Safarov, 2007).

A biological role of Se was emphasized in studies of viral infections by COVID-19 (Mehri and Marjan, 2013). For instance, researchers at the Surrey University, China, have identified a statistically strong correlation between Se concentration in the ration and the percentages of recovery and fatal cases in patients with COVID-19. The provinces with high Se concentrations in the soils are characterized by lower fatality from COVID-19 compared to areas with Se-deficient soils (Zhang and Liu, 2020; Zhang et al., 2020) (Fig. 2).

Selenium deficiency in the ration of COVID-19 patients is favorable for mutations, replication, and virulence of RNA viruses. Selenium compounds are helpful in recovering the antioxidant ability of the
host, decrease in its apoptosis and damage of endothelial cells, and in the aggregation of its thrombocytes. Furthermore, a low Se status seems to be quite widespread in patients with a risk of a severe form of COVID-19, particularly in senior persons (Hiffler and Rakotoambinina, 2020).

Ecological Reasons for a Selenium Deficiency

It is widely known that air is most strongly polluted by industrial facilities and processes: combustion of hydrocarbons (and hence, ash production) for producing energy accompanied by exhausts from various engines (including cars, trucks, planes, motorbikes, etc.). A decrease in Se concentration in blood serum was found in humans living in large industrially developed population centers and the personnel at facilities of the chemical industry (Golubkina et al., 2017).

The three major reasons for selenium deficiency in soils are as follows. Acid rains caused by high sulfur and nitrogen concentrations in the air change the ability of the soils to bind chemically active elements. A change in the pH balance makes some chemical elements more biologically available (these are mostly toxic elements), whereas others (such as Se, Zn, and Mg) become less biologically available. The acidification of soils and natural waters may increase the incidence of cancer, AIDS, and CODID-19.

In general, the level of Se concentration in a biogeochemical food chain is related to the incidence of endemic Se-deficiency pathologies. A notable role in decreasing the ecological status of Se in the biosphere is played by industrial technologies. In particular, the intense application of phosphorus-bearing fertilizers and exhaustive cropping decrease the uptake of this trace element by plants (Ermakov, 2012; Golubkina et al., 2017). A Se-deficient state is aggravated by excess As and heavy metals (which are Se antagonists), which are brought to the landscapes when deposits of base metals are developed and when other industrial processes operate (Ermakov and Jovanovic, 2010a; Bigaliev, 2018; Radosavljević et al., 2018). As a soil becomes more acidic, its quality changes, and this increases the mobility of the ions of heavy metals and aluminum. This, in turn, increases the leaching rates of heavy metals from the soil and their uptake by the networks of plant roots. The intensity of the uptake of heavy metals by plants depends not only on concentrations of the metals in the soil but also on interactions between these ions with the ions of other metals. An increase in soil acidity increases the mobility and activates the migration of trace elements in the soils and acidifies the natural waters (Moiseenko, 2009).

These processes result in the degradation of the nutritional benefits of, first, the agricultures and them the foodstuff, which leads to that the food chains contain progressively less biologically important elements.

Environmental degradation and protein and vitamin deficiencies in the human food rations, as well as a deficiency in major and trace elements in the food-stuff, result in a decrease in the Se status and a simultaneous general weakening of the immune resistance (Keen and Gershwin, 1990).

The role of food supplements in preventing diseases and their curing is obvious. Reportedly (Montagnier, 1999), AIDS is characterized by a systematic redox misbalance and a decrease in the level of glutathione concentration in the blood of the patients, which even further strengthens the oxidation stress. This researcher believes that antioxidants are valuable for suppressing the replication of the virus and the apoptosis of AIDS patients.

Selenium-deficient states are corrected and immunity is strengthened by applying various selenium-bearing compounds in pharmaceuticals with multivitamins and nutritional supplements (Fig. 3). The most efficient one is Na selenite, although it is obviously toxic (Galochkin and Galochkina, 2011). Sodium selenite can oxidize SH groups in the disulfide isomerase of the virus protein, which disables the virus from passing through healthy cell membranes (Kieliszek and Lipinski, 2020). The therapy of virus-induced pathologies also utilizes other antioxidants (vitamin E, quercetin, rosemary acid, and luteolin) in combinations with antiviral, antibacterial, and immunomodulatory remedies (Krylova et al., 2016; Magagnoli et al., 2020; Zhang, lie, 2020; Zhang et al., 2020; Yao et al., 2020).

COVID-19 in Russia and the Selenium Status

Relationships between the viral pandemic disease and the Se status were estimated using information on

![Fig. 2. Correlation between the frequency of recovery from COVID-19 in 17 towns outside Hubei, China, as of February 18, 2020, and the Se status of the town populations (Se concentrations in hair), which was analyzed using weighted linear regression (mean value ± SD = 35.5 ± 11.1, \( R^2 = 0.72 \), F-test \( P < 0.0001 \)). Each data point represents the degree of recovery (the number of recovered patients divided by the number of confirmed cases, in %) (a). The size of the marker is proportional to the number of cases. The gray field is 95% Di; the continuous line is selected values; circles are the degree of recovery (b) (Zhang et al., 2020).]
the COVID-19 incidence in Russia over the period of time starting on September 5, 2020 (Corona Virus, 2020) through January 29, 2021 (Corona Virus, 2021). The scored estimation of the ecological status of various areas in Russia was carried out in compliance with a routine that had been worked out previously (Ermakov, 2001), with regard to Se concentrations in the herbaceous plants (cuts), surface- and groundwaters, annual precipitation, and the incidence of white-muscle disease in the farm livestock. The scores varied between the areas from 9 to 40 units. In addition, COVID-19 incidence was compared to the average Se concentration in the blood serum of humans in Russia, according to data available at that time (Golubkina et al., 2017; Golubkina and Papazyan, 2006).

The number sequences characterized 52 administrative units of Russia. The results obtained on relationships between COVID-19 incidence as of September 5, 2021, were processed with MS-Excel 2013 and revealed a weak negative correlation between the pathologies incidence and the Se status of the areas. The correlation coefficient between the COVID-19 incidence in Russia and the Se status was $-0.362$. Therewith no correlation was identified between the COVID-19 incidence and Se concentration in blood serum ($r = +0.049$).

Comparison of the incidence in 52 administrative units of Russia as of January 29, 2021 (Corona Virus, 2021), and the Se status of the territories led us to reveal a fairly strong negative correlation ($r = -0.726$). However, the COVID-19 incidence (incidence per 1000 persons in Russia) and the average Se concentration in the blood serum showed a weak correlation ($r = -0.344$) (Fig. 4). The correlation between the incidence and Se concentration in the grain is also weak ($r = -0.165$) (Golubkina et al., 2017).

The absence of correlation between the incidence of virus pathology and Se concentration in the blood serum is likely explained by that Se concentration in the blood of humans and animals varies depending on the food status of the microelement. The status of Se, an integral parameter reflecting the level of Se concentration in the environment, is more conservative. It corresponds to a greater part of daily Se consumption,
which depends on Se concentration in the environment (local agricultural foodstuff and water). In this situation, the status of Se is affected by its uncontrolled introduction into the human organism with foodstuff brought from other areas and states. Nevertheless, the variations in the Se status are smaller than the concentration of this microelement in the blood.

It should be mentioned that Se status can broadly vary within administrative units. Territories with relatively normal Se concentrations may include local areas with either very low or elevated concentrations of this element in the biogeochemical food chains. This situation is typical of Krasnoyarsk krai, Chelyabinsk oblast, Khabarovsk krai, Karelia, and Tuva (Ermakov and Kovalsky, 1974; Ermakov and Jovanovic, 2010; Golubkina et al., 2017).

The likely reasons for the difference between our estimates of relations between viral pathologies and the Se status in 2020 and 2021 are the character of the spread of this disease and the increase in the incidence in 2021.

It is pertinent to mention that relations between the incidence and Se status are better to estimate using the known biogeochemical indicator of the concentration of the microelement in the hair-covering of animals and humans. This indicator was employed by Chinese researchers (Zhang et al., 2020), and the biomaterial was obtained immediately from diseased patients. Note that in the diagnosis of Se-microelementosis in farm animals this method has proved successful (Ermakov and Usenko, 2004). However, the application of this approach for the identification of Se insufficiency in human organisms is limited by the scarcity of the data.

**ZINC**

**Biological Role of Zinc**

Zinc is a vitally important microelement of all living organisms (Rish, 2003; Chasapsis et al., 2012; Ermakov et al., 2018). This chemical element is not only found in all plants, animals, and humans but is
also involved in the operation of vitally important functions (Fig. 5). Mammals moderately maintain their Zn pool by regulating its intestinal absorption and interactions with glutathione and with metallothioneins. It is excess Zn in the cytosol of the cells in foodstuff that induces the synthesis of metallothioneins and ensures the relative homeostasis (Gibson and Ferguson, 1998).

Whereas toxic effects of Zn in living organisms are very rare, a deficiency in this microelement is fairly
Zinc deficiency may result from the insufficient consumption of foodstuffs containing this trace element or an insufficient intestinal absorption. Most types of Zn-rich foodstuffs are of animal origin. Food fibers and phytates, which are contained in such alimentary items as cereals and legumes, bind with Zn and thus hamper its absorption (Ruel et al., 1997). Children with Zn-deficiency symptoms are subject to a higher risk of growth retardation, diarrhea, and such respiratory diseases as acute infections of the lower respiratory tracts (Black, 2003). Results of some studies suggest that administering Zn-bearing remedies may suppress the incidence and severity of bronchiolitis and pneumonia in children (Aggarwal et al., 2007).

Zinc plays an important role in processes related to immune resistance and blocking bacterial and viral pathologies (Keen and Gershwin, 1990; Tang et al., 1996). This trace element is thought to diminish susceptibility to acute infections in the lower respiratory tract at lung inflammation or damage (Bao and Knowell, 2006). Beneficial consequences of Zn medicines were found in South Asia, where no less than 70 g Zn per week were prescribed to children. Other experiments have shown that Zn is able to hamper the spread of pneumonia (Haider et al., 2006). However, a review of experimental data on administering Zn pharmaceuticals in curing acute infections of the lower respiratory tract, including pneumonia, have demonstrated the ambiguity of the therapeutic effect (Turner et al., 2000; Takkuoche, 2002; Brooks et al., 2005).

It is known that Zn is involved in practically all phases of the transmission of genetic information, is an indispensable component of more than twenty DNA- and RNA-polymerases, and is able to function as an in vitro nonenzymatic polymerase. Zinc is also contained in more than 200 proteins with so-called Zn fingers, which regulate genetic processes and mostly serve as transcription activation factors. Operating as such, Zn fingers recognize certain DNA sequences and thus ensure binding of specific regulatory proteins with them. Zinc is also a component of the aminoacyl-tRNA-synthetases and EF-1 translation factor (Dardenne and Jean-Marie, 1994; Rink and Kirchner, 2000; Rish, 2003).

The necessity of Zn for the immune system has been known for decades. Zinc deficiency is often associated with an immunodeficiency disorder (Rink and Kirchner, 2000). It is conventional to distinguish between Zn effects on the cell cycle and proliferation and the specific influence of this element on cells of the immune system (Dardenne and Jean-Marie, 1994). It has been proved that the amount of T cells diminishes because of thymic atrophy as a consequence of suppression of the synthesis of thymulin, a thymus hormone that is active in its Zn-bound state (Fig. 6).

Thymulin participates in the differentiation of T cells. Zink less obviously affects the system of B lymphocytes. The amount of monocytes/microphages in dendritic cells increases at a Zn deficiency, because a deficiency in this element is favorable for the differentiation of myeloid cells in monocytes/microphages and in maturation dendritic cells. Thereby the differentiation of neurons does not depend on Zn deficiency (Render et al., 2015).

A principally important clinical indication of an acute Zn deficiency in humans is growth retardation. This deficiency also leads to immune system dysfunctions, allergies, losses of smell and taste, loss of hair, white spots beneath nails, skin integument diseases, and sleep disorder (Fig. 6). The consequences of a marginal or weak Zn deficiency are not as obvious and can be easily treated. A decrease in the growth rate and weakened resistance to infections are often the only indications of a mild Zn deficiency in humans.

Toxicity symptoms manifest themselves at elevated Zn consumption (4–8 g), which can damage the immune system. Moreover, it has been demonstrated that a long-lasting effect of high Zn does results in disorders of the metabolic system and the metabolism of other microelements: a Zn deficiency in an organism is commonly associated with a Cu deficiency (Chan et al., 1998).

The interaction of Zn induced by a high Fe consumption is enhanced with an increase in the consumption of ascorbic acid. An adverse effect of Zn on Fe uptake was observed at Fe : Zn = 2 : 1. The absorption of Fe diminishes at a deficiency of vitamin C and phytate excess in the ration. This antagonism may also
Indirect evidence also indicates that Zn\(^{2+}\) may suppress SARS-CoV-2. This effect may explain the efficiency of antiviral activity by inhibiting the RNA polymerase of SARS-CoV-2. Experiments have demonstrated that Zn\(^{2+}\) shows an antiviral activity by inhibiting the replication of RNA viruses (Te Velthuis et al., 2010). Much interest is provoked by a combination of Zn compounds and flavonoids (quercetin), which seems to enhance the antioxidant action of the medicines at pathologies induced by both bacteria and viruses. However, some conclusions in this context are ambiguous (Magagnoli et al., 2020).

It is necessary to mention that Zn and Fe occur in the organisms of mammals in practically equal concentrations. Moreover, Zn consumption must not exceed 100 mg/day. The consumption of large Fe amounts may result in nausea, diarrhea, vertigo, sleepiness, and hallucinations (Mehri and Marjan, 2013).

The major sources of Fe are red meat, poultry, fish, cereals, eggs, and seeds. Green leaf vegetables and fruits contain little Zn because of the high water concentrations (Ermakov et al., 2018).

The carcinogenic activity of heavy metals that substitute Zn in transcription factors is reportedly explained by the generation of DNA-damaging free radicals. Currently artificial transcription factors are under construction, which contain Zn fingers able to identify known DNA sequences (TATA box and binding site for p53) or synthetic oligonucleotides 18—27 nucleotide residues in length. The building of artificial transcription factors that enable specifically regulate the expressions of certain genes opens the possibilities of principally new approaches in molecular genetic studies and the treatment of a wide circle of disorders, including cancer (Rish, 2003; Chasapis et al., 2012).

**Zinc and Viruses**

Zinc modulates antiviral and antibacterial immunity and affects inflammatory responses in the organisms of humans and animals. In spite of the absence of data of extensive clinical studies, information is currently available that a modulation of the Zn status can be important at COVID-19. For example, in vitro experiments have demonstrated that Zn\(^{2+}\) shows an antiviral activity by inhibiting the RNA polymerase of SARS-CoV-2. This effect may explain the efficiency of chloroquine, which is known to be a Zn ionophore. Indirect evidence also indicates that Zn\(^{2+}\) may suppress the activity of the angiotensin converting enzyme 2 (ACE2), which is a receptor for the SARS-CoV-2 virus (Rish, 2003; Chasapis et al., 2012). The enhancement of antiviral immune responses activated by Zn may result from the intensification of the synthesis of some interferon components. Thereby Zn, which is characterized by antiinflammatory activity, sometimes suppresses the development of bacterial infections. Because of its immunity-stimulating properties, Zn is used as a dietary supplement recommended at SARS.

In the context of the current pandemic induced by the COVID-19 coronavirus, Zn and Se are tested (in combinations with other pharmaceuticals, such as chloroquine and hydroxychloroquine) by some countries as a remedy against pathologies related to this disease. Scientists emphasize that a combination of Zn and a Zn-bearing transport molecule facilitates Zn penetration into cells and efficiently suppresses the replication of RNA viruses (Te Velthuis et al., 2010). Much interest is provoked by a combination of Zn compounds and flavonoids (quercetin), which seems to enhance the antioxidant action of the medicines at pathologies induced by both bacteria and viruses. However, some conclusions in this context are ambiguous (Magagnoli et al., 2020).

**COPPER**

Biological Role of Copper

A Cu deficiency modifies the activities of several enzymes and thus induces significant disorders in the metabolic processes, for example, the exchange of lipids (a decrease in the concentrations of sphingomyelin and acetal phosphatidates in the white matter of the brain and spinal cord and disorders in the myelination of the central nervous system), chromoproteides (decrease in the hemoglobin concentration, partly in relation to a retardation in erythrocyte maturation and a decrease in their lifetime), synthesis of elastin and collagen (damages of the connective tissues and ruptures of the aorta and heart vessels), distortions in the purine exchange (which may result in an increase in the activity of xanthine oxidase, synthesis of uric acid, and urate oxidase activity), and inhibition of the oxidation of most substrates of the tricarboxylic acid cycle (citrate, malate, \(\alpha\)-ketoglutarate, pyruvate, and others) (Kovalsky, 1977; Ermakov et al., 2018).

The depression of the function of oxidizing enzymes at a Cu deficiency brings about disorders in many metabolic processes. The animal organism becomes involved in the vicious circle of interrelated reactions, and this results in the endemic diseases of ataxia in sheep (first of all, newborn lamb), cattle, and buffalo. Thereby voids develop in the brain and spinal cord because of the weakening of the synthesis of sphingomyelin and acetal phosphatidates, as well as because of the depression of oxidation processes and lower oxidation of the sulfhydryl groups of neurokera- tin into disulfide ones, which opens access to the proteolytic enzymes of tissues.

The newborn lambs are thereby affected by severe irreversible morphological changes in the nervous system: the cerebral hemispheres are strained, the cerebral gyri are smoothed off, the white matter of the brain swells up, and voids develop in it. Brain vessels become damaged: the permeability of the vascular walls is distorted, and vascular stasis and dystonia develop. This can also lead to the development of voids and brain edema, which affects the tissue respiration. Coupled injuries impact the motorial and sensitive pathways. Histological examinations of the
peripheral nervous system have discovered dystrophic and neurobiological changes in spinal ganglions, peripheral nerve stems, and their branches in muscles. Disorders in Cu metabolism and oxidative processes in tissues of the nervous system and pathological-morphological changes in them are reflected in the clinical symptoms of ataxia: the hindquarters of the lambs are unstable at standing, their movements are discoordinated at walking, and they are affected by convulsions and paralysis (Gireev, 1968).

Copper homeostasis is regulated by a complicated system of Cu chaperone proteins. Copper deficiency is the pre-eminent disordering of the synthesis of oxidizing enzymes. Because of this, the pathologic process involves many metabolic process, and the whole organism is impacted by the disease. The epidemic disease affects 1–27% (46% at a maximum) of the sheep stock, and the mortality amounts to 70–80% of the diseased animals. However, introduction of Cu salts into the animal organisms is able to prevent the further progress of the disease (Anke et al., 1996).

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At the same time, some pathologies in animals are caused by Cu excess in the forage and environment (Bath, 1979). These are various forms of so-called copper hepatitis (enzootic hepatitis). At a Cu excess, this element is accumulated in the liver with the subsequent sudden erythrocytosis and a sudden increase in the bilirubin concentration. The disease is of chronic nature and is characterized by a high sudden mortality rate, pancreatitis, anemia, hemoglobinina, megoglobinuria, methemoglobinina, and deep kidney pigmentation. The Cu concentration in the nonsurviving animals is as high as 700 μg/g. An effective prophylactic remedy is Mo salts (Rish, 2001; Harr et al., 2002). Copper compounds in high concentrations are also toxic for some aquatic organisms, both plants and animals (Moiseenko, 2009).

The reasons for copper toxicity at its excess in the ration are liver functional disorders, neurodegenerative changes, and other pathological conditions. It can occur at distortions in Cu homeostasis. The ability of initiating oxidation damage is reportedly related to Cu-induced cellular toxicity. The toxicity of Cu is thought to be associated with disorders in the lipid exchange, expression of genes, the aggregation of alpha-synuclein, activation of acid sphingomyelinase and release of ceramide, and changes in the spatial distribution of Cu in hepatocytes and the proteins of the nerve glia (Gaetke et al., 2014).

Copper significantly competitively affects Fe and Mo metabolism. Along with Zn, Cu is involved in the superoxide dismutase enzyme and thus participates in blocking excess highly toxic oxygen radicals, which are formed at metabolism of various products. Superoxide dismutase (SOD, EC 1.15.1.1) affiliates with the group of antioxidative enzymes. It catalyzes superoxide dismutation into oxygen and hydrogen peroxide and also precludes the oxidation of some biologically active substances (Ermakov et al., 2016). The identification of SOD activity in the blood of animals and humans is important when several pathologies are encountered. Thereby an important role in the SOD activity is played by Cu and Zn.

Antimicrobial and Antiviral Properties of Copper

Antimicrobial properties of Cu have been known to the humankind since high antiquity. Copper sulfate
turned out to be an efficient fungicide and was used in the preservation treatment of wood for construction purposes. Copperware was also found out to show bactericide properties. Copper drinking cups were manufactured and utilized in ancient India, and copperware is still customarily widely utilized in this country. Most water piping in the United States is made up of copper and copper alloys. Copper started to be widely applied in the construction industry with the beginning of the industrial revolution in the late 19th century. The metal is widely applied in the fitting and decoration of interiors. In the 20th century, this metal gradually gave way first to stainless steel and quenched glass and then also to plastics.

It is currently known that Cu compounds and nanoparticles are efficient in fighting bacteria and viruses. For example, experiments by Ph.J. Kuhn in 1983 have demonstrated that Cu is able to decontaminate the surfaces of various Cu-bearing articles (Kuhn, 1983). Together with her students, this researcher carried out experiments on tamponing door knobs and handles, as well as other items made up of various materials. After the experiments, the cotton tampons were placed into Petri dishes, and then (in a few days) microflora in them was studied. The copper surfaces turned out to be much cleaner than the steel and plastic ones. Based on the results of the experiments, these researchers recommended not to rid of copper items or substitute them for analogous ones made of other materials.

The efficiency of Cu and its alloys as antimicrobial coatings have been estimated by the invasion of aurococcus Staphylococcus aureus. Again, the aluminum and steel surfaces were coated with a micrometer-thick Cu layer (applied by means of plasma, electric-arc, or cold sputter coating). Upon the sterilization of the prepared platelets, suspension with aurococcus from infected patients was applied to these platelets (after the sterilization of the prepared platelets). Aliquots of washoffs from the platelets (made in 2 h) were then placed into a Petri dish, and the staphylococcus colonies were led to grow (Champagne and Heifritch, 2013). The technique of cold sputtering has proved to be mostly antimicrobial because of the high activities of the sputtered particles at their collisions, which resulted in a high density of dislocation and intense ion diffusion (Fig. 7).

A.A. Rakhmetova (2011) has found out that the antimicrobial action of Cu nanoparticles depends on their content: when used in a concentration of 1 to 10 μg/L, Cu nanoparticles of sample 1 have shown a bactericidal action, they acted bacteriostatically when in a concentration of 0.5 μg/L, and no antimicrobial effect was identified when the concentration was 0.1 μg/L.

The spectrum of Cu action on microorganisms is very wide. Results of independent experiments conducted at laboratories of the United States Environmental Protection Agency in compliance with approved EPA protocols have proved that more than 99.9% bacteria die on copper, brass, and bronze surfaces within 2 h. These bacteria are:

- aurococcus (Staphylococcus aureus),
- aerobacter (Enterobacter aerogenes),
- coliform bacillus (Escherichia coli),
- blue pus bacillus (Pseudomonas aeruginosa),
- listeria monocytogene (Listeria monocytogenes),
- vancomycin-tolerant enterococcus (Enterococcus faecalis (VRE)),
- vancomycin- and methicillin-resistant aurococcus (meticillin-resistant Staphylococcus aureus (MRSA)),
- Clostridium difficile,
- salmonella (bacillus Gartner, Salmonella enteritidis)
- tubercle bacillus (Tubercle bacillus),
- acinetobacter Baumannii (Acinetobacter baumannii).

Moreover, Cu has been demonstrated to be able to kill adenovirus, Candida fungus (Candida albicans), black mold (Aspergillus niger), grippe A virus, and poliovirus. No other materials, even silver-bearing, are equally efficient. According to other researchers, Cu nanoparticles more obviously than Fe nanoparticles can inhibit of the growth of clinical isolates of aurococcus. The degree of inhibition also depends on the dozes of the ultrafine powders and on the incubation time (Babushkina et al., 2010; Molteni et al., 2010; Lemire et al., 2013; Warnes, 2014).
The surfaces of antimicrobial brass and bronze were characterized by a long-lasting antibacterial effect, which did not weaken within 2 h and killed the overwhelming majority of the bacteria even after wet and/or dry wiping and subsequent recontamination.

Although the mechanism by which Cu kills bacteria is complicated, its effect is simple. The effect of copper surfaces on bacteria is thought to involve two successive phases. First, a copper surface interacts with the outer membrane of the organism and thus damages the membrane of the pathogen. During the second phase, the microorganism cell looses water and nutrients through these holes in its membrane. A certain role in the inactivation of the microorganisms is therewith played by the transmembrane potential of the cell (Wobus et al., 2006; Griffith, 2012).

Decades after the first viral pandemic diseases spread, scientists estimated in much detail the role of Cu in deactivation of various viruses, including coronavirus 229E (a precursor of COVID-19) and COVID-19 itself (Warnes et al., 2015). A research team headed by William Keevil has proposed to apply Cu to fight coronavirus, with copper objects applied as widely as possible in public places. It is expedient to use this metal in manufacturing door knobs and handles, stair railings, and hand-rails in buses, trains, and other public transport. Thereby COVID-19 is deactivated in copper surfaces within a few hours by Cu ions, which attack the lipid membrane of the virus, invade it, and destroy its nucleic acids (Warnes et al., 2015).

Along with copper materials, nanocopper is nowadays progressively more widely used as an antiviral remedy (Frolov, 2020). A research team headed by G. Frolov at the National University of Science and Technology MISiS have synthesized the new Cu-based medicine spirtozol for the surface treatment of individual protective equipment, clothes, and various surfaces. This healthcare products is suspension of Cu nanoparticles (1 to 3 nm) in ethanol solution of the antiseptic cetyl pyridinium chloride. At disinfection treatment in wet air, Cu is transformed on the surface into positively charged ions of Cu hydroxide, which ensures the desired protection of the treated items against viruses and other pathogens. In this situation, Cu hydroxide ions are “soft” electrophilic agent, which enters a chemical reaction with sulfur-bearing structures of the virus and modifies the pH of the medium (acidifies it). This damages the envelope of any organism, including a virion. However, this medication in high concentrations is also hazardous for the cells of the host organism and may leads to irritation of its skin integuments. Healthcare products based on copper ions and copper compounds were proposed for usage as severe external disinfectants when applied together with the antiseptic cetyl pyridinium chloride (Frolov, 2020).

Iodine

Biological Importance of Iodine

Upon coming with food into the gastrointestinal system, iodine compounds are reduced to iodides and are absorbed mostly in the small intestine. The absorbed iodine is spread by blood throughout the organism, and its excess is deposited in lipids. It is mostly (up to 60%) absorbed by the thyroid gland and is then used to synthesize hormones. In the thyroid gland, blood iodides release free metalloid iodine under the effect of the enzyme iodidase. The molecular iodine is bound with the aminoacid tyrosine to form mono- and diiodotyrosine, from which thyroid hormones are synthesized: triiodothyronine (T<sub>3</sub>) and tetraiodothyronine (T<sub>4</sub>). These hormones are brought to blood to be bound in it with the globulins and albumines of the plasma. Iodine-bearing thyroid hormones stimulate the synthesis of many enzymes, increase their activity, and are thus involved in regulation of the metabolic activity and various physiological processes and functions (Rish, 2001; Ermakov et al., 2018).

Iodine participates in the development and differentiation of tissues, enhances oxygen absorption by tissues, and increases its utilization coefficient. This element activates heat production, synthesis of proteins in cells, and increases the activity and concentrations of cyclic 3,5-adenosine monophosphate in cells. Iodine stimulates trophic and immune processes, erythropoiesis, leucopoiesis, the secretory activity of the digestive and lacteal glands, the synthesis of milk fat, the activity of the generative organ, and fetation (Rish, 2003).

An iodine deficiency in the organisms of mammals is thought to be responsible for iodine-deficiency pathologies. One of the most widespread of them is endemic hypothyroidism. Nevertheless, the endocrinous function of iodine is interrelated with selenium (see above). Because of this, both of the trace elements are interrelated in metabolic and pathophysiological processes. Pathologies triggered by excess iodine are rare and are mostly allergic reactions, such as erubesence, breathlessness, etc. (Andryukov et al., 2015).

It is known that iodine was applied in the course of prophylaxis and therapy during the pandemic of COVID-19. The unique bactericide properties of iodine have been known for a long time (Kelly, 1961). Treatment with Mandla paint (tretman) in the course of 1957 Asian flu pandemic prevented the development of the disease. The percentage of diseased persons in the group to which no tretman was administered amounted to 14%, and that in the group treated with this medicine was 2.8%. Moreover, treatment with iodine even when flu was already in progress significantly decreased (after 3 days) the disease incidence compared to that in the control group, with the effect manifesting itself in 2 days after tretman was first administered (Menon, 1957).
Pathophysiological studies demonstrate that iodine can support the congenital immune system in fighting bacterial and viral infections (Fischer et al., 2011; Derscheid et al., 2014). In 2013, it has been demonstrated that iodine treatment of newborn lambs infected by respiratory syncytial virus (RSV) resulted in smaller damages of the lungs and smaller expression of RSV antigen in the lungs. It has also been demonstrated that administering iodine to three-week old lambs makes their RSV infection less severe (Derscheid et al., 2014). Finally, epidemiological data show that the current COVID-19 pandemic in the Japanese, who are known to consume much iodine, resulted in a very low COVID-19 mortality rate compared to other nations, in spite of the facts that the population of Japan is the world’s oldest and that the national isolation policy was so far relatively soft (WHO, 2019).

The aforementioned pathophysiological, clinical, and epidemiological data suggest that iodine may be a crucially important trace element for the optimal functioning of the immune system and can be efficient in fighting the COVID-19 pandemic, both clinically and preventively. Its prevention can be readily reached thanks to the very limited adverse side reactions and because of the fast uptake of the medicines when administered per orally. Also, it is worth mentioning in this context that one-third of the world’s population currently suffers from iodine deficiency (Verheesen and Traksel, 2020).

**CONCLUSIONS**

This publication presents a review of one of the phases of the current state of the biosphere: its anthropogenic modification and progressively more aggravating ecological problems. In spite of the undeniable advances in genetics, molecular biology, and virology, the humankind is impacted by unpredictable diseases: severe viral pathologies.

From the ecological standpoint, these problems once again highlight the unity and complicatedness of relations between discrete groups of living organisms and life cofactors. The COVID-19 viral pandemic is viewed by scientists as one of the stages of the variability of RNA-bearing viruses as a consequence of a combination of the anthropogenically affected evolution of the environment and disturbances in the links established between various organisms. Following ecological genetics, ecological virology starts developing. This is science that centers on interrelations between the host and virus. Mechanisms underlying these interactions are complicated and still poorly understood. However, the role of geochemical factors, as well as other features of the habitats of organisms, is thereby particularly important.

Relations between viral infections and biogeochemical factors once again confirms the validity of one of the concepts of geochemical ecology: the law of a minimum. On the one hand, the geochemical factor (in this situation, this is the status of necessary chemical elements) highlights life interrelations between organisms at a deficiency of elements. On the other hand, this also pertains to situations with an excess in trace elements in a biogeochemical food chain. For example, a Se deficiency makes humans more vulnerable to RNA-viral infections, with more severe disease outcomes. However, excess Se in the habitat leads to toxicosis in human and animal organisms and weakens their immunity.

Such relations are typical not only of Se but also of other vitally important trace elements, such as Zn, Cu, I, and Co. However, toxic properties of metals can be utilized in designing antibacterial and antiviral technologies, as was demonstrated at interaction of viruses and bacteria with the surface of copper items, nanoparticles of the metal, and its solute species.

The aforementioned facts of the participation of trace elements in strengthening immunity, as in the prevention of cancer and some other hazardous viral diseases (hepatitis, Ebola hemorrhagic fever, and COVID-19), highlight still other aspects of the biological role of trace elements. Similar to Se, Zn, Cu, and I are utilized in the prophylaxis of cardiovascular diseases and are involved in regulating the reproductive function and the functioning of the thyroid gland, as well as in preventing cataract and other diseases. This brings forth the key role played by vitally important trace elements in maintaining the health of human populations.

However, although much is known already on relations between deficiencies in trace elements and viral infections, this issue calls for further deeper virological, biochemical, and epidemiological studies. Nowadays the beneficial effects of trace-element food supplements can be viewed as therapeutic.

Moreover, current complicated geochemical states and conditions make it necessary to evaluate the criterion integral statuses of trace elements.

**CONFLICT OF INTEREST**

The authors declare that they have no conflicts of interest.

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