

## Cycles of Nitric Oxide (NO), Superoxide Radical Anion ( $\cdot\text{O}_2^-$ ) and Hydrogen Sulfur/Sulfur Dioxide ( $\text{H}_2\text{S}/\text{SO}_2$ ) in Mammals

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### Abstract

The article analyzes the Cyclicity Principle, together with the atomic principle of the structure of matter and the holographic principle. According to the developed concepts, the above principles make it possible to answer the question: how nature is unified, and how living organisms ensure the regulation and stabilization of nitric oxide (NO), superoxide anion-radical ( $\cdot\text{O}_2^-$ ) and hydrogen sulfide/sulfur dioxide ( $\text{H}_2\text{S}/\text{SO}_2$ ), involved in intra- and intercellular signaling in mammals.

**Keywords:** Atomic Principle of the Structure of Matter; Cyclic Principle; Holographic Principle; Hydrogen Sulfide/Sulfur Dioxide Cycle; Nitric Oxide Cycle; Regulation of the Content of Reactive Nitrogen and Oxygen Species; Superoxide Anion-Radical Cycle

### Introduction

Human health, life and its quality are determined by the state of the regulatory systems of cells, organs and the body as a whole. The words of Rudolf Virchow (1821-1902) are still relevant: «It is not life in abnormal conditions, not a violation as such that causes the disease. On the contrary, the disease begins with a failure of the regulatory apparatus». Analysis of the literature data and the results of our morphological and biochemical studies made it possible to identify the main mechanisms leading to the transition from normal physiological processes to the development of general pathological changes. Previously, we proposed a generalizing concept of the development of pathological processes, according to which a typical pathological process is based on nonspecific violations of cyclic regulatory processes, when the content of reactive nitrogen and oxygen forms simultaneously increases and  $\text{NO}_2$  and peroxy nitrites, capable of oxidizing unsaturated fatty acids that are part of cell membranes and subcellular structures; oxidize and damage DNA/RNA guanine bases; oxidize SH-groups

of amino acids and proteins, and also participate in the nitrosylation of tyrosine residues of proteins [13,29,55-70]. We will begin the analysis of the problem of gaseous signaling molecules in living organisms [14-21,23-29,31-42] from the emergence of the primary and secondary atmosphere of the Earth and the properties of those atoms that became the main components of cells and became part of NO,  $\cdot\text{O}_2^-$ ,  $\text{H}_2\text{S}/\text{SO}_2$  and CO.

### Primary and Secondary Atmosphere of Earth and Atoms Becoming the Main Components of Cells

According to modern concepts, most of the primary atmosphere of the Earth consisted of hydrogen ( $^1\text{H}_2$ ) and helium ( $^4\text{He}$ ). This atmosphere was formed from a protoplanetary cloud during the formation of the solar system as a result of the capture of the above substances / elements by the Earth's gravitational field [1]. Events that took place in the solar system 5 billion years ago can be observed using modern astrophysical methods in the Andromeda galaxy [2]. The secondary atmosphere of the Earth, which arose after volcanic eruptions, mainly contained hydrogen ( $\text{H}_2$ ), methane ( $\text{CH}_4$ ), ammonia ( $\text{NH}_3$ ), and interconnected hydrogen and oxygen atoms ( $\text{H}_2\text{O}$ ) [3-6]. Atoms that were part of the primary and secondary atmosphere of the Earth have become the main components of the cells of microorganisms, plants and

animals [7]. Figuratively speaking, nature created life from what was. It is now known that all living organisms are 96% composed of hydrogen, carbon, nitrogen and oxygen atoms, which were part of the primary and secondary atmosphere of the Earth in a free ( $\text{H}_2$ ) state or in a state bound to other atoms ( $\text{CH}_4$ ,  $\text{NH}_3$ ,  $\text{H}_2\text{O}$ ) [8]. The rest of the atoms, according to modern concepts, including metals and trace elements that can be found in living organisms, make up no more than 4%. They appeared, as some researchers suggest, from the bowels of the planet as a result of volcanic eruptions [1-8]. The question of how inorganic compounds and organic substances entered the composition of living organisms, realizing numerous regulatory mechanisms and systems at various structural and functional levels, is the subject of research for the entire set of biomedical disciplines [9-12]. Why this became possible, and why nature is the same at all structural and functional levels, remains one of the mysteries that physicists, chemists and biologists have been trying to solve over the past centuries [8, 14]. However, these questions, formulated in a different form, have worried almost all natural scientists in the world, at least for 2500 years. In this article, analyzing the problem of gas transmitters in mammals, we will try to give one of the possible answers to the questions posed.

### **Gas Transmitters in Intercellular and Intracellular Signaling Systems**

Compounds were formed with the participation of hydrogen, carbon, nitrogen, and oxygen atoms, which began to perform an energetic function under the conditions of the existence of unicellular organisms [9-12]. The same atoms laid the foundation for nitric oxide (NO), superoxide radical anion ( $\cdot\text{O}_2^-$ ), carbon monoxide (CO), as well as hydrogen sulfide ( $\text{H}_2\text{S}$ ), sulfur dioxide ( $\text{SO}_2$ ) and polysulfides ( $\text{H}_2\text{S}_n$ ), which began to function as intracellular mediators [13-37].

After the emergence of multicellular organisms, compounds  $\cdot\text{O}_2^-/\text{O}_2$ ,  $\text{NO}_3^-/\text{NO}_2^-$ ,  $\text{SO}_4^-/\text{SO}_3^-$ ,  $\text{CO}_2/\text{CO}$ , which were previously formed during respiration, were used as electron acceptors, or in intracellular signaling systems, were adapted for intercellular signaling. However, these processes and phenomena were unknown in science in the second half of the XX century. Before the discovery of these compounds in living organisms, the discovery of their endogenous production, these molecules were known as toxic substances. Therefore, we can say with good reason that the problem of gaseous intermediaries (gas transmitters) has become a new problem in the 21<sup>st</sup> century. It is in recent decades that scientists have come to realize the specific role of gas transmitters that perform a signaling function in cells [15-20]. These substances have been assigned to a new class of biologically active substances,

### **Chemical Nature of Gas Mediators / Transmitters**

Gas transmitters are small molecules that easily cross biological membranes and do not act through special receptors [41-

47]. These compounds are synthesized in the body using special enzymes and are labile (their half-life is measured in seconds). They do not accumulate in cells and subcellular structures, since they cannot be enclosed in vesicles, like neurotransmitters [43-51]. Sometimes they can be bound by metals of proteins and enzymes, as well as SH-groups that are part of amino acids, bio phenols, for example, tyrosine and its derivatives, free or part of proteins, etc. Gas transmitters have endocrine, paracrine, autocrine, and intracrine effects [52-54].

### **Cyclic Organization of Gas Transmitters: Cycles of Nitric Oxide (NO), Superoxide Anion-Radical ( $\cdot\text{O}_2^-$ ) and Hydrogen Sulfur/Sulfur Dioxide ( $\text{H}_2\text{S}/\text{SO}_2$ ) In Mammals**

Over the past decades, we have suggested that the cyclical organization NO and  $\cdot\text{O}_2^-$  in cells and in the whole organism may be a consequence of the existence of such a principle, the universality (or globality) of which is comparable to the principle of the atomic structure of matter [7,8,55]. This principle extends its influence to almost all structural and functional levels in animate and inanimate nature, subordinates the behavior of living subjects and inanimate objects, and, sets the rules for the functioning of all regulatory systems that contain elements of negative and positive feedback. Moreover, this principle explains the nature of positive and negative feedbacks in living organisms and nonliving systems. It also answers the question of why development is carried out in a spiral, and why spirals are one of the main structural elements in DNA, proteins, in nerve fibers (myelin sheaths), glial cells (glial wraps in the central nervous system), etc. This principle also explains the nature of the cyclical / periodic pattern in the functioning of regulatory systems at almost all structural and functional levels in living organisms [7,8,55-69]. In addition, this principle and the consequences arising from it are in good agreement with other concepts and theories of Russian and foreign scientists. Suffice it to recall L.A. Orbeli, who, analyzing physiological processes, noted: we have little regard for the fact that all processes are carried out cyclically, and each process has its own cyclicity. The position of R. Virchow is well known: "It is not life in abnormal conditions, not a violation as such that causes the disease. On the contrary, the disease begins with a failure of the regulatory apparatus."

Thus, studying very specific substances (nitrates / nitrites and nitrogen oxides) [13], we came to the cyclic organization of their functioning [56-70], then found the same cyclic organization in the systems of other gas transmitters, analyzed the functioning of these compounds in health and development pathological processes [22,72]. These concepts, developed both for gas transmitters and for other processes and phenomena of animate and inanimate nature, are fundamentally new. They do not repeat other developments of foreign and Russian scientists. At the same time, they are in good agreement with practically all other known

experimental data and theoretical constructions. Let's give one more example. French mathematician, physicist and philosopher Henri Poincaré (1854-1912) created a new branch of mathematics - the qualitative theory of differential equations (1881-1882). He showed the existence of a huge class of phenomena that obey periodic laws. He also answered the question of how, without solving equations, one can obtain important information about the behavior of a family of solutions. "Any generalization," according to Poincaré, "to a certain extent presupposes belief in the unity and simplicity of nature. As far as unity is concerned, scientists usually do not encounter any difficulties. The question is, how is nature one? "How is nature united?" (A. Poincaré).

From our point of view, the atomic principle of the structure of matter, as well as the principle of cyclicity and the holographic principle proposed and substantiated as a global principle, answer the question of A. Poincaré: how is nature united? Let us recall that the holographic principle got its name from the Greek word *holos* - *all*, complete and *grapho* - *I write, I draw*. The result is: the optical equivalent of the object, the ideas of which were formulated by the Hungarian physicist Denis (Denesh) Gabor (1900-1979) in 1948 with the improvement of the electron microscope [56-60]. A. Poincaré realized that behind the numerous periodic processes that he described and analyzed using a system of differential equations, there are global laws. However, he could not know about the existence of the principles of cyclicity and the principle of holography. There, after posing the question and formulating the problem, A. Poincaré left its solution to future generations of researchers. The principle of cyclicity in combination with the holographic principle means that cyclic properties (or properties of a spiral in space, and periodicity in time) should be repeated at all structural and functional levels. In the same way, like the atomic principle of the structure of matter, it should also manifest itself at all structural and functional levels, because these principles are universal or global. Thus, the above three principles: the atomic principle of the structure of matter, the principle of cyclicity and the holographic principle, structure and combine the phenomena of animate and inanimate nature. It is these three principles, from our point of view, that make nature one, including inorganic compounds and organic substances into a single system. The cyclic organization of gas transmitters in mammals is one of the manifestations of this unity. To say that this is philosophy and not biochemistry, biophysics or physiology, from our point of view, is inappropriate. Good, deep and concrete science always has a direct connection with the philosophy of natural science. In the same way, like the philosophy of natural science, finds its embodiment and manifestation in specific sciences. Scientists from different countries have always strived to achieve the unity of the

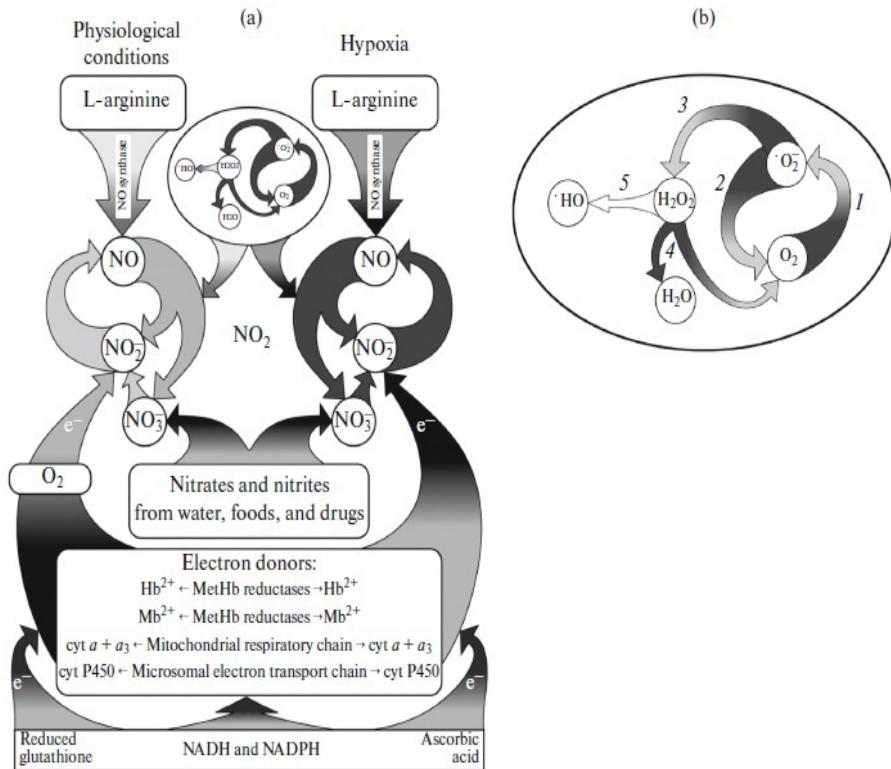
philosophy of natural science and specific sciences. Deep concrete science always has a direct connection with the philosophy of natural science.

#### **Cycles of Nitrogen Oxide (NO), Superoxide Anion-Radical ( $\cdot\text{O}_2^-$ ) and Hydrogen Sulfur / Sulfur Dioxide ( $\text{H}_2\text{S}/\text{SO}_2$ )**

The concept of the nitric oxide cycle (Figure 1a) was substantiated more than 25 years ago [57-69]. Its substantiation became possible due to the detection of nitrite reductase activity of heme-containing proteins in mammals [70]. After 20 years, the nitrite reductase activity of hemoglobin in the deoxy-form was confirmed in the works of researchers from the United States [71]. Subsequently, this concept has repeatedly found its development and application for various normal and pathological processes [29,37-52,72]. The essence of this concept is that  $\text{NO}_2^-$ , ions formed from L-arginine can again, with the participation of nitrite reductase systems, including Hb, Mb, cyt *a* +  $\alpha_3$  and cyt *P-450*, close the chain: in to L-arginine  $\rightarrow$  NO  $\rightarrow$   $\text{NO}_2^-/\text{NO}_3^-$  into cycle. Oxygen, binding with heme, inhibits the nitrite reductase activity of these proteins [70]. Thus, at various functional states associated with insufficient oxygen supply to the body, the nitrite reductase component of the nitric oxide cycle will be activated (Figure 1a) [56-61]. However, such activation can be observed until the depletion of L-arginine occurs [66], which is included in the Krebs cycle at the level  $\alpha$ -ketoglutarate complex and serves as one of the sources of formation of succinate (or succinic acid). During relatively prolonged hypoxia / ischemia, as is known, succinate is actively used as an oxidation substrate for the formation of ATP and membrane potential in mitochondria. Therefore, researchers can sometimes observe a decrease in NO formation during prolonged experimental hypoxia / ischemia.

#### **Cycle of Superoxide Anion-Radical**

Analysis of the literature data and the results of our own research allowed us to put forward a hypothesis that, in addition to the nitric oxide cycle, there should also be a cycle of superoxide anion radical (Figure 1b) [59]. Oscillations in the concentrations of reactive oxygen species in biological systems, obtained by a number of authors, testified in favor of the existence of such a cycle. Since all cyclic processes always involve periodic oscillations, one could expect that the previously considered reaction products associated with the neutral  $\text{O}_2$  molecule and its active forms - superoxide, peroxide, as well as enzymes for activating molecular oxygen ( $\text{Fe}^{2+}$  and  $\text{Cu}^{2+}$  -containing proteins), superoxide dismutase and catalase can be closed in a cycle. The analysis of numerous literature data allowed us to propose a scheme for the cyclic organization of reactive oxygen species, which we called the superoxide anion radical cycle (Figure 1b). [59].



**Fig. 1.** Cycle of nitric oxide (a) and superoxide radical anion (b).

In the nitric oxide cycle, one can distinguish the NO-synthase component ("L-arginine - NO"), which synthesizes NO in the presence of oxygen, and the nitrite reductase component, the activity of which sharply increases under conditions of oxygen deficiency (hypoxia / ischemia). The formation of NO with the participation of the NO-synthase component is carried out as a result of the oxidation of the guanidine nitrogen of L-arginine.  $\text{NO}_2^-$  ions, formed from L-arginine, can again, with the participation of nitrite reductase systems, including Hb, Mb, cyt a + a<sub>3</sub>, and cyt P-450, close the chain of L-arginine → NO →  $\text{NO}_2^-$  /  $\text{NO}_3^-$  into a cycle. Oxygen, binding to heme, inhibits the nitrite reductase activity of these proteins. During hypoxia and functional stress, when heme-containing proteins are converted into deoxy-form,  $\text{NO}_2^-$  ions begin to actively reduce, accepting electrons from these heme-containing proteins. An important role in the reduction of  $\text{NO}_2^-$  ions to NO is also played by electron donor systems that reduce Hb, Mb, cyt a + a<sub>3</sub>, and cyt P-450. In addition to these electron transport systems (chains), ascorbic acid and reduced glutathione can play an important role in the reduction of  $\text{NO}_2^-$  ions. In the cycle of superoxide radical anion occur: 1 - reduction of oxygen ( $\text{O}_2$ ) and the formation of superoxide anion radical ( $\cdot\text{O}_2^-$ ); 2 and 3 - superoxide dismutation reactions catalyzed by superoxide dismutase; 4 - decomposition of hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) into water ( $\text{H}_2\text{O}$ ) and molecular oxygen ( $\text{O}_2$ ), carried out by the enzyme catalase; 5 - hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) 5 - hydrogen peroxide -  $\text{H}_2\text{O}_2$  - also decomposes to form two molecules of the OH-radical. The cyclic organization of reactive nitrogen and oxygen forms ensures the conversion of these reactive, highly reactive compounds into less active substances. When the cycles of nitric oxide and superoxide anion-radical are disrupted, even more active molecules of nitrogen dioxide and peroxynitrites appear, again decaying into NO<sub>2</sub> and OH-radicals, which damage the main components of living organisms.

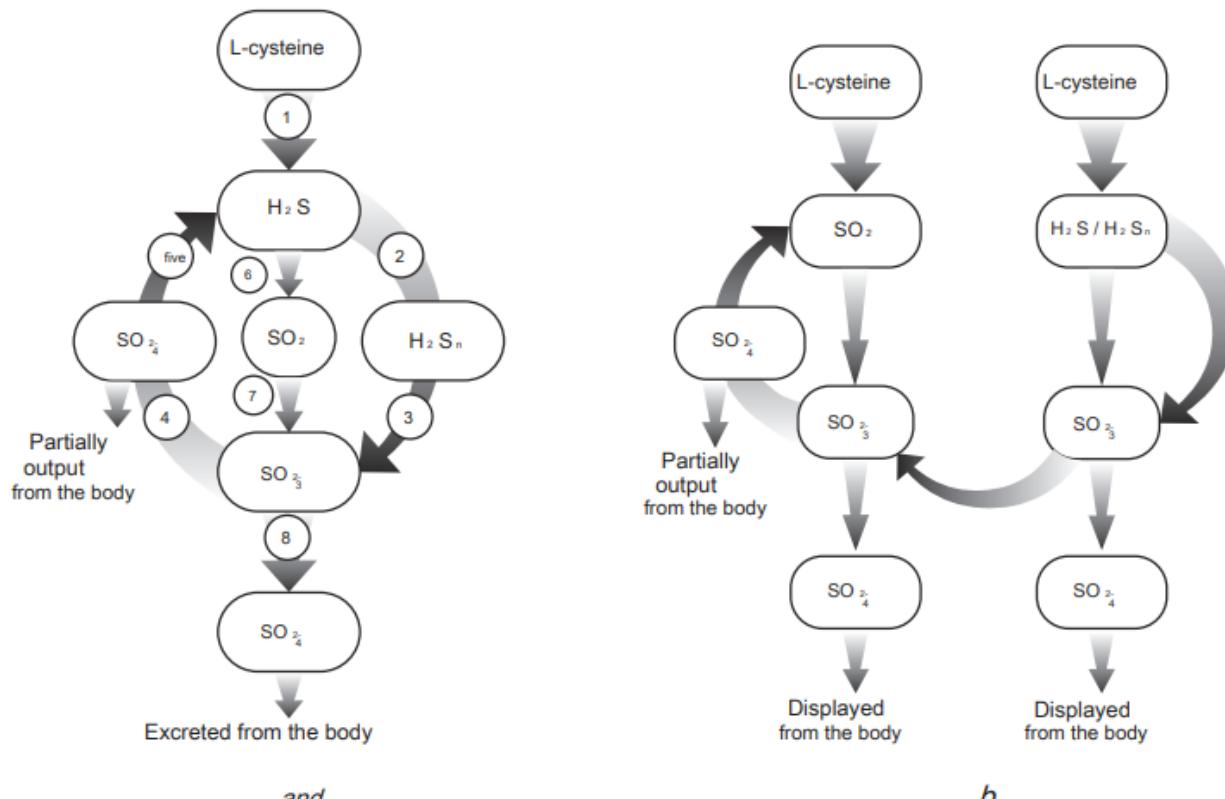
## Hydrogen Sulfur / Sulfur Dioxide Cycle ( $\text{H}_2\text{S}$ / $\text{SO}_2$ )

The initial substrate for the synthesis of all three mediators ( $\text{H}_2\text{S}/\text{H}_2\text{S}_n/\text{SO}_2$ ) (Fig.2) is sulfur-containing amino acids, primarily L-cysteine. Polysulfides are formed from hydrogen sulfide ( $\text{H}_2\text{S}$ ), and sulfur dioxide ( $\text{SO}_2$ ) is sulfite anhydride (sulfurous acid), which is formed during the oxidation of  $\text{H}_2\text{S}$ . The end product of the oxidation (degradation) of  $\text{H}_2\text{S}$ , like the oxidation of sulfur dioxide, is sulfate, which is excreted in the urine. It is known that the intestinal microflora synthesizes hydrogen sulfide from sulfate, reducing it. It is characteristic that an enzyme that oxidizes  $\text{H}_2\text{S}$  in mitochondria in animals, sulfide quinone oxidoreductase,

SQR, was also found in plants and bacteria [73]. The reduction of sulfate ( $\text{SO}_4$ ) to  $\text{H}_2\text{S}$  is possible in mammals with the participation of intestinal microflora. Thus, the cycle of hydrogen sulfide in the whole body of mammals exists (Figure 2). Our assumption about the reduction of  $\text{SO}_4$  to  $\text{H}_2\text{S}$  in mammalian cells is hypothetical. If such a reaction occurs, then we can say that the hydrogen sulfide cycle exists not only in the whole organism of mammals, but also in their cells. The cycles presented above are, from our point of view, a manifestation of the global principle of cyclicity [56,58,60]. At the same time, the geochemical cycles of nitrogen, carbon, sulfur and water are known as the natural cycles. Together

with the cycles we are analyzing, they are a manifestation of the principle of holography, when the cyclic properties of the general are manifested in the cyclic properties and regularities

of the particular, which lies at other structural and functional levels of animate and inanimate nature. Thus, through these three principles, the philosophy of natural science manifests itself in



**Fig. 2.** Cycle of hydrogen sulfide (a) and its SO<sub>2</sub><sup>-</sup> and H<sub>2</sub>S / H<sub>2</sub>S<sub>n</sub> compounds (b), which can be activated at various functional states.

The initial substrate for the synthesis of all S-mediators is sulfur-containing amino acids, primarily L-cysteine. Hydrogen sulfide (H<sub>2</sub>S) is synthesized from L-cysteine (stage 1). Currently, 3 enzymes are known that are involved in the synthesis of H<sub>2</sub>S at this stage: in various mammalian cells: cystathione-β-synthase (CBS), Cystathione-γ-Lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3-MST). CBS synthesizes H<sub>2</sub>S primarily in nerve cells. CSE synthesizes H<sub>2</sub>S in blood vessel smooth muscle cells, and 3-MST synthesizes H<sub>2</sub>S in endothelial cells. Polysulfides (H<sub>2</sub>S<sub>n</sub>) are formed from hydrogen sulfide (H<sub>2</sub>S) (stage 2), and sulfur dioxide (SO<sub>2</sub>) is formed by the oxidation of H<sub>2</sub>S or L-cysteine (stage 6). The synthesis of SO<sub>2</sub> from L-cysteine occurs under the influence of the enzymes cysteine dioxygenase and aspartate aminotransferase (stage 7). Further, as H<sub>2</sub>S, so SO<sub>2</sub> is converted to sulfate (SO<sub>4</sub><sup>2-</sup>). An intermediate stage of this transformation for both H<sub>2</sub>S and SO<sub>2</sub> is sulfite (SO<sub>3</sub><sup>2-</sup>). However, H<sub>2</sub>S is initially oxidized to persulfide (RSSH) or polysulfide (H<sub>2</sub>S<sub>n</sub>) (stage 2) under the influence of sulfide quinone oxidoreductase (SQR), which is oxidized by persulfide oxygenase (ETEH1) to sulfite (stage 3). Sulfur dioxide (SO<sub>2</sub>) can be directly hydrogenated to sulfuric acid (H<sub>2</sub>SO<sub>3</sub>) to form sulfite ions (SO<sub>3</sub><sup>2-</sup>) (step 8). The latter is oxidized by sulfite oxidase to sulfate (SO<sub>4</sub><sup>2-</sup>) (stage 4), which, entering the intestine, is reduced to H<sub>2</sub>S (stage 5) and excreted in the urine. The end product of H<sub>2</sub>S oxidation, as well as sulfur dioxide (SO<sub>2</sub>) oxidation, is sulfate (SO<sub>4</sub><sup>2-</sup>), which either enters the intestines and is partially excreted from the body, or is excreted with urine. It is known that the intestinal microflora reduces SO<sub>4</sub><sup>2-</sup> with the formation of H<sub>2</sub>S. It is characteristic that the SQR enzyme, which oxidizes H<sub>2</sub>S in animal mitochondria, is also found in plants and bacteria. The reduction of sulfate (SO<sub>4</sub><sup>2-</sup>) to H<sub>2</sub>S is possible in mammals with the participation of intestinal microflora. Thus, the cycle of hydrogen sulfide in the whole body of mammals exists. Our hypothesis on the reduction of SO<sub>4</sub><sup>2-</sup> to H<sub>2</sub>S in mammalian cells is hypothetical. If such a reaction occurs, then we can say that the H<sub>2</sub>S cycle exists not only in the whole organism of mammals, but also in their cells.

### Is There A Cycle of Carbon Oxide (CO)?

This question remains open. However, based on the fact that along with other cycles in nature - nitrogen, sulfur, etc. (circulation of substances in nature), and the presence of the principle of

holography in addition to the principle of cyclicity [56,60], it can be expected that in the future the carbon monoxide (CO) cycle will take its rightful place among other fundamental cyclic processes.

## Conclusion

For several centuries, scientists and doctors have tried to identify specific changes in cells, subcellular structures and membranes in each pathological process and disease. However, it turned out that in many pathological processes, first of all, universal nonspecific changes in cells, plasma membranes and membranes of subcellular structures are observed. This made it possible to speak about the existence of typical nonspecific disorders of various cellular and subcellular structures. The concept we are developing about the cyclical organization of gas transmitters (NO,  $\cdot\text{O}_2$ ,  $\text{H}_2\text{S}/\text{SO}_2$ ) in the norm and its violation during the development of pathological processes makes it possible to understand the mechanisms of development of a typical pathological process, which is the common denominator of almost all pathological processes. For at least half a century, almost all scientists, including physicists, chemists and biologists working in the field of free radical processes in biology and medicine, have been trying to solve the riddle: how living systems provide regulation and stabilization of reactive oxygen, nitrogen, and also other free radicals. Our proposed concept for the cyclic organization of gas transmitters (NO,  $\cdot\text{O}_2$  and  $\text{H}_2\text{S}/\text{SO}_2$ ) may be one of the answers to the question posed more than half a century ago. In addition, the principles of cyclicity, the holographic principle, together with the principle of the atomic structure of matter, can give an answer to the question of A. Poincaré: "how is nature united?"

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