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Paradoxes of adaptation to oxygen deficiency

Selected fragments of the article

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Life, oxygen and breathing

According to the concepts that are currently considered more or less generally accepted or at least consensus in the scientific community, life on Earth originated approximately 4.1 – 3.7 billion years ago. It is assumed that the emergence of life was preceded by a long chemical evolution, which, in the absence of free oxygen and other active oxidants in the atmosphere, led to the accumulation of a significant amount of organic substances abiogenic in origin and to the emergence of the so-called "primordial prebiotic soup" ("primary broth"). At high temperatures in volcanic lakes rich in mineral salts (or, according to another hypothesis, under the action of ultraviolet rays and electrical discharges), the first simplest hydrocarbon polymers such as alkanes and their derivatives and then more complex organic substances such as carbohydrates, lipids, amino acids, formaldehyde, polycyclic aromatic hydrocarbons, purine and pyrimidine nitrogenous bases could have been formed (and gradually accumulated) from ammonia, methane, hydrogen, carbon dioxide, carbon monoxide and water.

For many years, an unsolvable problem in the theory of evolution was that a polypeptide molecule (that is, a polymer of amino acids) that was hypothetically formed as a result of abiogenic synthesis, even if its sequence by chance would happened to be functional and it would have enzymatic activity, could not replicate by itself without a DNA template. On the other hand, if we assume that the primary molecule in the origin of life was not a peptide, but DNA, then it could not be reproduced without a ready-made enzymatic complex of polymerases (which are proteins). It would be too incredible to assume that the already functionally active polymerase and the DNA molecule encoding it arose simultaneously and independently, and then met by themselves. Moreover, even the assumption that such a DNA molecule could be spontaneously synthesized randomly, the sequence of which would be coding for a protein with DNA polymerase activity, looks very implausible, not to mention the fact that a spontaneously assembled ribosome and the entire complex of proteins for transcriptions and translations would also be required. The way out of this seemingly insoluble situation was the hypothesis of the so-called RNA world, according to which the initial molecule that gave rise to life was an RNA-like molecule capable of combining the ability to replicate with enzymatic activity as a ribozyme. Such a molecule, being itself both a matrix and a polymerase, could begin to self-replicate, using organic compounds of the surrounding “primordial soup” both as ready-made building blocks and as an energy source for their assembly. In turn, the emergence of the first RNA-like molecule, too complex for “random” self-assembly, is explained by additional hypotheses such as the hypothesis of the world of polyaromatic hydrocarbons that preceded the RNA world, etc.

In any case, the emergence of a molecule that combines the properties of a template for self-replication and an enzyme with polymerase activity would already be quite enough to start evolution. Further, it is not so difficult to imagine, on the one hand, the entry of such an RNA or RNA-like molecule into an isolated space bounded by a lipid protomembrane (or its initial

appearance already in such a space), and, on the other hand, the emergence of a mechanism for the polymerization of amino acids in peptides on its matrix with their subsequent co-evolution and natural selection of RNA based on the ability to encode more and more functional protein molecules.

Since the primary replicators (whether before or after the appearance of the first prokaryotic cell) both as a building material and as a source of energy probably used organic molecules of the "primordial soup", it is logical to assume that this "soup" began to be depleted. This is especially important given the fact that organic molecules, as building blocks, could not pass from one proto-living system to another without loss, since they, apparently, were also a source of energy. In the modern biosphere, for example, in accordance with the Lindeman rule, in the food chain, only about 10% of the eaten biomass is absorbed to produce its own mass, the rest is spent on movement, maintaining homeostasis, energy for biochemical rearrangements, etc. If such a reconstruction of events is correct, already at the dawn of its origin, life should have faced the first very serious crisis: it could maintain its existence only due to the irreversible depletion of resources accumulated over millions of years of abiogenic synthesis. Thus, the newly emerged life, undermined the source of its own existence, which, at first glance, was bound to end in collapse: having eaten all the “primordial soup”, and then, perhaps, each other, the primary living organisms or even the proto-organisms must eventually die.

The way out of this alleged first global crisis of life was the emergence of autotrophy, that is, the ability to synthesize organic compounds from inorganic ones, moreover, due to energy not associated with the oxidation of organic matter. There are two fundamentally possible types of such synthesis, which differ in the source of energy: chemosynthesis and photosynthesis. In the case of chemosynthesis, a living organism (in this case, a bacterial or archaean cell) synthesizes organic substances from carbon dioxide and water due to the oxidation energy of inorganic substances, such as ferrous salts, ammonia, hydrogen, hydrogen sulfide, thiosulfates, sulfites, sulfides and molecular sulfur. In the case of photosynthesis, the source of energy for the synthesis of organic substances from carbon dioxide and water is sunlight. At the same time, there are various forms of photosynthesis, including anoxygenic ones, that is, not associated with the formation of molecular oxygen, but oxygenic photosynthesis turned out to be the most effective in the end. However, oxygenic photosynthesis turned out to be the cause of the second global crisis faced by life – the so-called oxygen catastrophe.

The fact is that molecular oxygen, which we now perceive as a necessary source of life, was a strong poison for early life forms. Life arose and initially developed in a reductive environment. In the history of the development of life, oxygenic photosynthesis arose quite early. For a very long time, molecular oxygen formed in the process of oxygenic photosynthesis was successfully absorbed, oxidizing ferrous compounds and other reduced substances. However, in the end, the reductive resources of the atmosphere and the upper layers of the lithosphere were exhausted, and there was a sharp by geological standards increase in the concentration of oxygen. The appearance and progressive accumulation in the Earth's atmosphere of an aggressive oxidizing agent capable of oxidizing all the organic substances became most likely a real disaster for the anaerobic biosphere existing at that time. Here, by the way, an analogy with our modern technogenic civilization is quite appropriate: in both cases, life, having mastered a new source of energy for itself, carries out explosive development, simultaneously poisoning the environment with waste products of its vital activity and not at all caring about the consequences. It is only when faced with the catastrophe it has caused that it is forced to adapt to the new conditions that it itself has created as by-products of its development. In this sense, the opposition of "artificial", "dead" and "aggressive" human technogenic civilization to "nature", allegedly staying in eternal harmony and balance, is completely far-fetched: the unreasonableness of mankind in this case is completely natural and literally copies the behavior of any other kind of living beings. On the contrary, it is precisely rational behavior that

proceeds from the foresight of consequences that have not yet occurred and an attempt to prevent them, could, with certain reservations, be recognized as “unnatural” behavior, that is, different from the general principle of behavior of all other forms of life.

However, as we already know very well, the poisoning of the atmosphere with oxygen, which, among other things, also led to geological and climatic consequences that were colossal in scale, did not lead life to self-destruction. On the contrary, under the new prevailing conditions, completely new forms of life and fundamentally new metabolic pathways arose. Aerobic respiration turned out to be much more efficient and it set the main path for further evolution. The apparent self-evidence of this metabolic pathway makes it difficult to assess the degree of evolutionary adaptability of life. Drawing again an analogy with the modern development of technogenic civilization, the emergence of aerobic respiration can be likened to how some forms of life have adapted to breathe the emissions of chemical enterprises or assimilate the energy of radiation from radioactive waste.

It should be noted that in recent decades previously seemed generally accepted and undoubted concept of an oxygen catastrophe began to be questioned by some of scientists. Critics of this concept, in particular Heinrich Holland and Timothy W. Lyons, find arguments in favor of an alternative hypothesis, which consists in the idea that a sharp catastrophic jump that is the Great Oxygen Event, that changed the reducing atmosphere to an oxidizing one in a short period of time did not occur in the history of the Earth. In their opinion, the changes occurred slowly and gradually, without any sharp qualitative change, and were determined not so much by a change in the activity of photosynthetic organisms, but by a decrease in volcanic activity, which regularly supplied reduced compounds to the atmosphere that bound the free oxygen produced by photosynthetics. Nevertheless, even if we accept this version and assume that the transformation of the Earth's atmosphere from reducing to oxidizing occurred slowly, was not accompanied by a catastrophe, and gave to life enough time to adapt to smoothly changing conditions, this somewhat reduces the drama of our narrative, but does not violate it general logic. Albeit slowly and gradually, but autotrophs changed the composition of the atmosphere and were forced themselves, and also forced the overwhelming majority of other living creatures of that time either to die out or to adapt to existence in a new aggressively toxic oxidizing environment [1].

The next big and important event in the history of the development of life on Earth, which is relevant to the topic of this article, was the emergence of the first eukaryotic cell. It is now generally accepted that all unicellular and multicellular eukaryotes now existing and ever existing are descendants of one common ancestor. According to modern concepts [2, 3], eukaryotes originate from archaea close to the recently discovered Lokiarchaeota in deep-sea thermal springs, and the relationship of eukaryotes to the living Lokiarchaeota is closer than the relationship of Lokiarchaeota to other types of archaea, even to related groups within the TACK supertype, which includes besides Lokiarchaeota also types Thaumarchaeota, Aigarchaeota, Crenarchaeota and Korarchaeota. A distinctive feature of lokiarchae, in addition to their genetic relationship with eukaryotes, is the presence in them of the actin gene, which suggests that they have the ability to phagocytosis, or at least the possibility of acquiring one. Apparently, it was this ability that allowed the earliest eukaryotic cells or even their immediate prokaryotic ancestors, which did not have the ability for aerobic respiration, to phagocytize bacteria (probably from the group of alpha-proteobacteria), which already possessed this ability. However, instead of digesting the phagocytosed alpha-proteobacterium, the host cell (an early eukaryote, or archaea – the immediate ancestor of eukaryotes) entered into symbiosis with it. The development of this symbiosis led to the fact that the symbiotic alpha-proteobacterium gradually lost the signs of a separate independent organism, to the point that a significant part of its genome (although not the entire genome) passed into the nucleus of the host cell. More and more deep functional specialization in the process of aerobic respiration has turned the once independent bacterial cell, together with the membrane of the

phagocytic vacuole of the host cell covering it, into the organelle of cellular respiration of the eukaryotic cell – the mitochondrion. On the other hand, the genome contained in the nucleus of a eukaryotic cell included both the original “lokiarchael” base and the genes that passed into the nucleus from the bacterium that turned into a mitochondrion.

It should be noted that, although most prokaryotic and eukaryotic organisms have not only adapted to exist in an oxidizing oxygen atmosphere, but are no longer able to exist without molecular oxygen in the environment, nevertheless, oxygen has remained an aggressive oxidizing agent, with the damaging effects of which the cell existing in an aerobic environment is forced to constantly fight. This applies even to the molecular oxygen of the atmosphere, but even more so to the so-called reactive oxygen species that arise in the process of cellular respiration. About 98% of the oxygen consumed by mitochondria during respiration undergoes four-electron reduction with the formation of two water molecules as a result of the coordinated work of all elements of the respiratory electron transport chain. However, in addition to the main oxidase pathway of oxygen metabolism, there is a side oxygenase pathway, which involves about 2% of the consumed oxygen [4]. In this case, oxygen undergoes one- (to $O_2^{\cdot-}$), two- (to H_2O_2) or three- (to water and $O^{\cdot-}$) electron reduction with the formation of highly reactive products: the so-called reactive oxygen species (ROS).

It is worth noting that the set of ROS has significant overlap with the set of free radicals, to the point that these terms are often used as synonyms, which is not entirely true, since not all ROS are actually free radicals, as well as not all free radicals arising in the cell are ROS. For example, superoxidanion radical ($O_2^{\cdot-}$), hydroxyl radical ($OH^{\cdot}$) and hydroperoxyl radical ($HO_2^{\cdot}$) are both free radicals and ROS, hydrogen peroxide (H_2O_2) and singlet oxygen belong to the class of ROS, but are not free radicals, and various alkyls are free radicals not being ROS and not even containing an oxygen atom at all [5]. However, ROS and free radicals are often combined into a general category both in terms of their origin in the cell and in terms of their functional significance. There are many sources of ROS and free radicals in the cell, however, one of the main or even their main source is regular "failures" in the work of the mitochondrial respiratory chain, which occur even under completely normal physiological conditions, but sharply increase in violation of normal functioning of the respiratory chain under the influence of a variety of stress factors.

First paradox: hypoxia causes oxidative stress

There are very many professional scientific papers that begin with the words “it is known that one of the key factors of cell damage during hypoxia is the oxidative stress”. This statement is actually quite true, but it is so familiar to specialists that it is unlikely that many of them appreciated the full degree of its paradox. Rather, the paradoxical nature of this fact will be appreciated by a naive dilettante who has encountered this formulation for the first time. In fact, there is something to be surprised and something to think about. Hypoxia, in simple words, is oxygen deficiency, lack of oxygen. It can be caused by a variety of reasons, for example, by a decrease in the percentage of oxygen in the surrounding air even at normal pressure (such hypoxia is called normobaric), or, conversely, by general decrease of pressure (such hypoxia is called hypobaric, it is with it that a person faces when treating with barotherapy or getting into high altitude conditions), or, with a normal oxygen content in the atmosphere, hypoxia can be caused by a malfunction of the lungs or blockage of the arteries that deliver oxygenated blood to a specific organ or part of the organ (in this case, they talk about ischemia, however, the effect of hypoxia is superimposed here, at least, with the factor lack of sugar in the tissues, that is, hypoglycemia). So, in any case, hypoxia is a deficitof oxygen. Oxygen in the body, including in the cell, is the main and universal oxidizing agent. So how can one of the key damaging factors of oxidant deficiency be the development of oxidative stress? Is

there a clear logical contradiction here? Moreover, hyperoxygenation – a state of excess oxygen, diametrically opposed to hypoxia – at the same time, like hypoxia, causes oxidative stress.

In order to explain this paradox, it is first necessary to understand the terminology. The term "oxidative stress" is extremely widely used in the scientific literature, however, in our opinion, it is very unfortunate (although we were forced to use it ourselves). First, the so-called "oxidative stress" is not really stress. The term "stress" is commonly understood as the totality of the body's nonspecific reactions to the influence of various factors of the external or internal environment, and by no means these influencing factors themselves. Therefore, "oxidative stress" being not a reaction of the body but the factor itself, in fact is not a stress, but a stressor, that is, a stress-causing influence. But this term has a much more significant drawback. The term "oxidative stress" means two completely different and independent, although often (but not always!) coincident phenomena: 1) a significant sharp increase in the production and content of ROS and free radicals, and 2) a significant violation of redox balance with its shift towards the state of oxidation. The use of the same term in relation to two different phenomena leads to confusion both in concepts and, as a result, in a real understanding of the ongoing processes.

It is interesting to note how rapidly science has accumulated knowledge about the molecular mechanisms of adaptation to oxygen deficiency. Currently, thousands or maybe tens of thousands of scientific studies have been published on this topic, and the idea of the molecular intracellular mechanisms of regulation and adaptation to hypoxia in all the complexity of these mechanisms seems self-evident. However, until the mid-1950s, all studies of adaptation to oxygen starvation essentially boiled down to the regulation of pulmonary respiration, blood circulation intensity, and oxygen-binding blood capacity (erythrocyte count, hemoglobin content). In 1927, John Scott Haldane suggested (it was only a tentative guess!) that adaptive processes play an important role in adaptation to hypoxia, developing not only at the level of regulation of blood circulation and hematopoiesis, but also at the tissue level [6]. However, only in 1956, Professor Zoya Ivanovna Barbashova was able to confirm and prove this assumption with convincing experimental data [7-9]. In her article "**Tissue processes during acclimatization to oxygen starvation**", published in 1956, she wrote: "*Recently, the idea has been more and more asserted that the mechanism of acclimatization to a reduced partial pressure of oxygen in the inhaled air is not limited to those functional and morphological changes in the body, which are aimed at keeping the partial pressure of oxygen (pO_2) in the blood from falling too sharply. It has been repeatedly shown that an increase in erythropoiesis and the associated increase in the oxygen capacity of the blood, an increase in pulmonary ventilation and an increase in the minute volume of blood circulation cannot fully explain the body's adaptation to hypoxia*" [7]. Further in the same work, she writes that the search for other mechanisms has not yet yielded definite results. Thus, the idea put forward by Bohr [10] and actively supported by Haldane [11] about the active secretion of oxygen by the lung tissue under conditions of a decrease in pO_2 in the inhaled air (!) did not find experimental confirmation in the studies of numerous authors [7]. Further, she mentions the results of her expedition of 1939 year to the Hissor Range [12], during of which it was found that the oxygen capacity of the blood of mountain sheep of the Hissor breed is lower than that of lowland sheep, and its value does not change when rising from the valley to heights of more than 3500 m, while in lowland sheep it increases. Z.I. Barbashova concludes that "*the struggle of the body for oxygen under hypoxic conditions is carried out not only in the general systems of the body, but is also transferred to the tissues themselves. An increase in pulmonary ventilation, blood circulation and morphological changes in red blood with a significant depletion of oxygen in the environment cannot fully compensate for the influence of adverse conditions, and the oxygen tension in the capillary blood drops. Then the struggle for oxygen is transferred to the tissues, and the tissue factors of the acclimatization process come into play*" [7]. From here, she moves on to studies at the level of enzyme activity and shows that in acclimatized white mice and rats, the properties of cytochrome

oxidase in the brain, kidney, heart, and muscle tissues change, and the enzyme becomes more effective at low partial voltages of O_2 [7]. It is worth evaluating the scale of this breakthrough in science: from the discussion of absolutely fantastic hypotheses about the possibility of adaptation to oxygen deficiency through the active secretion of oxygen by the body's own tissues – to studies of the enzymatic activity of cytochrome oxidase, opening up an era for studying the molecular intracellular mechanisms of regulation and adaptation to hypoxia.

So what actually happens, according to modern scientific concepts, under conditions of insufficient oxygen supply to the cell (regardless of the reason, whether it is depressurization of the aircraft at high altitude or a blood clot in the vessel that prevents the delivery of oxygen to the tissue)? In this case, of course, the redox balance of the cell is shifted not towards oxidation, but towards reduction. The main factor supporting and, at the same time, reflecting the redox balance is the ratio of oxidized and reduced forms of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). Since oxidized NAD exists in the form of NAD^+, and reduced NAD exists in the form of $NADH + H^+$, a shift in the redox balance in the case of lack of oxygen can already correlate with an increase in the content of H^+ ions, that is, with an increase in acidity (acidosis, a decrease in pH). However, to explain the correlation between the state of hypoxia and the development of acidosis, it is much more important that under conditions of oxygen deficiency, the pyruvic acid (pyruvate) formed as a result of glycolysis is not utilized in the Krebs cycle, but is reduced to lactic acid (lactate), which accumulates, significantly increasing acidity. Another factor constituting the redox balance is the degree of unsaturation of lipids, that is, the ratio of simple (single), double and triple bonds in their molecules, as well as the ratio of thiol groups (-SH) and disulfide bridges (-S-S-) both in cysteine amino acid residues in the composition of proteins and peptides and in antioxidant molecules, regulating this ratio (glutathione, glutaredoxin and thioredoxin).

Let us pay attention once again: under conditions of insufficient oxygen supply to the cell, the redox balance, of course, shifts towards the state of reduction. But, at the same time, the lack of oxygen disrupts the normal functioning of the respiratory chain in the mitochondria. As a result of an increase in the frequency of failures in its work, the percentage of formation of products of the side oxygenase pathway, that is, just ROS, including free radicals and peroxides, sharply increases. Free radicals already have a very high oxidative activity, but in a reduced environment it increases even more. As a result, under conditions of a general shift in the redox balance of the cell towards the state of reduction (what a paradox!), chain reactions of free radical oxidation already begin to proceed intensively, causing damage to all major classes of organic molecules, including lipids, carbohydrates, proteins and nucleic acids.

What happens under conditions of restoration of the normal supply of oxygen to the cell, that is reoxygenation? If oxygen deficiency in its duration and intensity was relatively moderate, then there is a gradual restoration of the normal functioning of the respiratory chain, the formation of free radicals and ROS gradually decreases to a normal level, and the excess that has already arisen during hypoxia and the early stages of reoxygenation is gradually coped with antioxidant systems, the activity of which noticeably increases during this period. If oxygen deficiency (hypoxia) was too deep or too long, and the disruption of the respiratory chain became irreversible, then the influx of oxygen only enhances the production of ROS and the intensity of free radical oxidation reactions, which can lead the cell to death by apoptosis or even by necrosis.

Stress, training, adaptation and pathology

Here we come quite close to the topic of our own research. We studied the effect of the phenomenon, which in modern literature is called hypoxic preconditioning. Preconditioning in this case is called preliminary training for conditions of oxygen deficiency. It is well known that an

organism, which has successfully endured moderate (i.e., not causing irreversible damage), but at the same time quite strong effects associated with a lack of oxygen, subsequently tolerates more severe effects much more easily. which for an inexperienced, untrained organism would either be fatal or would lead to irreversible pathological consequences.

In modern scientific literature, writing about hypoxic preconditioning, it is customary to refer to the articles of the second half of the 80s – early 90s of the XX century, in which this phenomenon was discovered and described on the model of short (training) sessions of ischemia first of the heart [13], and then the brain [14-17], preceding more severe and prolonged (testing) ischemia of the same organs. Meanwhile, the term "preconditioning" was used even before [18], and already in the first half of the 1960s it was shown that pre-exposure (that is, in the terminology that was established later, preconditioning) with short sessions of anoxia increases the resistance of rats to the subsequent longer anoxia [19]. Generally speaking, the idea that a pre-trained organism will better tolerate conditions of oxygen deficiency than an untrained organism is so simple that it is quite difficult to estimate when and by whom it was first discovered. Apparently, at the level of practical experience, this phenomenon has been known to mankind since the time when man first began to climb mountains back in prehistoric times. As for the scientific study of this topic, this effect was studied and described, for example, by the famous Soviet biochemist, Academician Georgy Efimovich Vladimirov and, simultaneously and independently of him, by the another famous Soviet physiologist Academician Nikolai Nikolaevich Sirotinin back in the late 30s years of the XX century [20-21]. It is possible, and even likely, that this phenomenon has been studied before, but this issue already belongs to the field of the history of science and goes far beyond the scope of this review. The works of the late 30s were about a fairly long acclimatization to a high-mountain climate, and the works carried out on the anoxic model in the 60s and on the ischemic models in the 80s and 90s were about training sessions of short, intermittent influences, which were originally called preconditioning. However, in principle, apparently, we are talking about the same phenomenon: the induction of hypoxic (including ischemic) tolerance as a result of preliminary training. Considering that the term "preconditioning" is currently used in a much broader sense than originally (in addition to ischemic preconditioning, the scientific literature writes about hypoxic [22], chemical [23], metabolic [24-25], etc. preconditioning, including chronic), the complex scientific term "preconditioning" in most cases can be replaced without loss of meaning by a simple words "preliminary training".

It should be noted that any training is associated with the development of stress reactions that increase the organism's resistance to subsequent adverse effects. The general principle of training (or preconditioning) in a rather vivid and aphoristic form worthy of mention was formulated at one time by a person not connected with science itself – by philosopher Friedrich Wilhelm Nietzsche. In the original German language, his aphorism reads as follows: "*Aus der Kriegsschule des Lebens. — Was mich nicht umbringt, macht mich stärker*". However, the English-language formulation is more correct (not in the sense of the accuracy of the translation, but in the sense of expressing the real essence of the phenomenon): "*what does not destroy me, makes me stronger*". Note that the German word "*umbringt*" is translated here not by the literal "*kill*", but as "*destroy*". This is an important clarification. Indeed, the endured excessive stress effect, which, although it did not kill, but crippled, that is, caused significant and irreversible disturbances in the structure and function of the cell or the organism as a whole, hardly thereby "made it stronger", that is, increased its survival rate, adaptability and reproductive potential. On the other hand, an insufficiently strong stress effect, which is tolerated by the organism too easily, does not change it and respectively does not leave a lasting stable mark in its structure and functions – not only pathological, but also adaptive, that is, it does not create any sustainable training effect. The whole point of the matter here is in maintaining the subtlest balance.

The fact is that a sufficiently stable adaptive response, which significantly increases the organism's resistance to subsequent adverse effects, can be triggered only by such level of stress that removes the organism (or an individual cell) out from a stable, “normal” functional state. In other words, any sustainable adaptation is possible only in response to an action, which containing a certain element of damage and disruption of structure and function. And, conversely, the development of any pathology caused by a damaging effect is almost always accompanied by an attempt of the organism to adapt, i.e. by launching quite adaptive reactions and processes, the capabilities of which, however, are in this case insufficient to full compensation of the damage. There is no adaptation without an element of pathology, and as long as the organism is alive and resisting, there is no pathology without adaptation. With respect to this thesis, mention should be made of works of Professors and doctors Gustavo Zubieta-Castillo (Sr.), Gustavo R. Zubieta-Calleja (Jr.), Luis Zubieta-Calleja, Natalia Zubieta-DeUrioste and Poul-Erik Paulev in which it was shown that symptoms of chronic mountain sickness (such as increased hematocrit) represents not "loss of adaptation" but the adaptation to some diseases in the specific hypoxic environment [26-28]. Also in this regard, it is worth noting our own researches on the effects of acute severe hypobaric hypoxia in a pressure chamber, in which the pathological processes were inextricably linked with the induction of the molecular adaptation mechanisms such as increased expression of endogenous antioxidants [29-35] as well as the works of Dr. Ekaterina Iosifovna Tyulkova with coauthors, which showed an inseparable relationship between pathological and adaptive effects of prenatal hypoxia [36].

Moreover, the division of the reaction into pathological and adaptive components occurs exclusively in the mind of the observer, not in the material world. In reality, in response to any significant impact, damage and compensatory effects almost always go together, and they are inseparable (*indivisè et inseperabiliter*). Moreover, adaptation and pathology are not two different (even simultaneously occurring, but opposing) processes that involve different molecular mechanisms. It is always the same process that involves the same molecules, the same intracellular signaling systems, the same metabolic pathways. For example, caspases, protease proteins widely known as important initiator and effector molecules of apoptosis, are activated at the same time in any elementary act of learning. Let us pay attention to this: learning is a form of adaptation, adaptation is a consequence of the development of a stress reaction. That is, at the cellular level, learning (memorization) and death are actually realized through the same signaling pathways, through the same molecular mechanisms, the only question is the observance of the measure. Another characteristic example is the well-known and rather well-studied regulatory protein p53, which, depending on the intensity of stress and the redox status of the cell, can both start the cell death program and, conversely, stop the cell cycle to repair damaged DNA molecules.

It is interesting that science (in this case, molecular biology) in its development repeats the same path that religious thought traveled millennia earlier. More recently, the concept of the regulation of cell death was noticeably reminiscent of the worldview of dualistic religions such as Zoroastrianism or Manichaeism. In that old concept, the “evil dark army” of “death factors” was symmetrically opposed by the “good light army” of “survival factors” approximately equal in size and strength. Now scientific thought has come to the idea, which in Christianity is defined as the principle of the non-substance of evil. In fact, there are no factors, molecules and mechanisms that are “evil” in their nature. There is no also a symmetrical opposition of “life factors” to “death factors”. There is only a violation of the measure and an imbalance in the function of normal, natural and necessary for life molecules, which, being in the wrong amount, proportion and place or at the wrong time, acquire pathological properties and qualities. That is, nothing is “evil” by its nature, but can become such only by virtue of a violation of measure, balance and the correct order of things, that is, having fallen out of its “lawful” place in an ordered Being. However, even in this case, “evil” remains limited and conditional, and the locally emerging chaos only serves order, if to look at things from a higher level. So what appears to be a “death factor” at the level of an individual cell is

often necessary for normal functioning and survival of the organism as a whole. For example, almost all so-called proapoptotic factors, which at the level of the study of an individual cell are drawn in black as “death factors”, at the level of the organism turn out to be important oncoprotectors, that is, the most important “survival factors” (in this regard, apoptosis specialists and oncologists even have a different language of description). The death of an insufficiently adapted organism contributes to the improvement of the gene pool of a population and a species, and even the death of species and entire biocenoses is a normal and even necessary phenomenon in the process of the evolution of life as a whole.

It is worth mentioning another important feature of the training. Any stress effect, on the one hand, causes some disturbances in the state of the body, and, on the other hand, triggers the body's response aimed at correcting or compensating for these disorders. This adaptive compensatory response of the body always carries two components – specific to the particular stressor and nonspecific to a this factor. It is the second, non-specific component (the so-called general adaptation syndrome) that is called, according to the definition of the outstanding physiologist Hans Hugo Bruno Selye, in the proper sense, stress or stress response [37-38].

In practice, this means that training with sessions of moderate oxygen deficiency (for example, in a hypobaric chamber or by climbing to a certain height in the mountains) increases the body's resistance not only to subsequent significantly more severe conditions of oxygen deficiency, but also to many other stress factors, ranging from severe emotional and painful effects and ending with radiation. Conversely, chemical preconditioning or even moderate emotional stress (for example, immobilization, that is, associated with depriving of the ability to move freely) can effectively protect the body from subsequent severe ischemia. Thus, an important feature of the formation of a general adaptation syndrome consists precisely in its non-specificity to a particular form of exposure, that is in its generalized nature: in the fact that not only adaptation to one specific environmental factor occurs but the defenses of the organism as a whole increase to a potentially damaging effect of any nature.

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