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Dualism of the Aging Process (Analytical Review)

By Vladimir N. Shabalin

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Dualism of the Aging Process (Analytical Review)

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The article attempts to find the cause of this contradiction. The author puts forward a position on the dual function of the aging process in the development of living matter: on the one hand, aging causes degradation of the organism as a system, on the other, it ensures the structural improvement of its tissues at the molecular level. That is, aging, as the main mechanism of evolution, is aimed not at preserving the organism as a system, but at preserving its individual elements (information blocks) that are of interest for building new structures of living matter as a whole. An evolutionary ladder is formed from these information blocks, along which living matter rises to a higher level of its development. Aging is not decay or damage, but a mechanism for transferring one structure of living tissue to another - more perfect, with its preservation in the form of a potential phase for use by new cellular generations of the same organism or other organisms.

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I. State of The Problem

The problem of aging has attracted biologists, physicians, philosophers, demographers, and recently representatives of the exact sciences - physicists, chemists, mathematicians, as well as economists, cultural scientists and other specialists for centuries. At the same time, there is still no generally accepted theory of aging in gerontology. Despite the obvious changes in the body during aging, the concept of "aging" remains vague. The reason for this situation is that life is a complex system consisting of many interacting elements with feedback loops, hierarchical structure, nonlinear dynamics and emergent properties [1]. All these dynamic elements of life are united by the principle of self-organization. So far, this great immanent principle remains a profound mystery [2]. According to modern scientific concepts, self-organization is the basis of the evolutionary development of living matter- all living beings acquire forms and functions as a result of self-organization [3]. Biological self-organization is directed and reinforced by natural selection, during which the most stable, flexible modular systems capable of further adaptation are preserved [4].

Prigogine demonstrated the possibility of the emergence of new properties and order in self-organizing systems - dissipative structures that are stabilized by energy exchange with the environment [5, 6]. Self-organization creates emergence - a phenomenon when new properties or new behavior arise in a system that its individual components do not have [7, 8]. The role of aging in the process of evolutionary self-organization is that it ensures the preservation of emergent properties that arise during the life of an organism. The relationship between a person and the microworld, animal and plant worlds is a fragment of a single coordinated information-analytical biospheric process. A person feeds on living matter - builds his tissues from structures created by various biological species. A person lives in an organic fog - a molecular, cellular, viral and other environment formed and thrown into the biosphere by various organisms. All of this enters the human body through the food, water and air cycles and is processed: structural information is extracted, which is assimilated in its tissues, ensuring its continuous development [9]. The aging process occupies a leading place in this development, covering numerous biomechanisms that ensure the diversity of its manifestations.

II. Scientific Approaches to Studying the Problem of Aging

Historically, there have always been two directions in science – reductionism ("understand more and more about less") and holism ("see more, neglecting less"). Today, there is a hypertrophied predominance of the first direction, which includes studying the problem of aging. However, it should be taken into account that we are simply not able to understand the system at the level of analyzing only its components [10]. Nevertheless, all existing hypotheses of aging are based on monofactorial analysis. Thus, I. Mechnikov saw the cause of aging in endogenous intoxication, L. Szilard - in radiation damage to chromosomes, A. Bogomolets - in connective tissue disorders, F. Sineks – in DNA errors, D. Harman - in tissue damage by free radicals, L. Orgel - in the

Author: Scientific Research Institute of General Pathology and Pathophysiology, Moscow, Russia. e-mail: shabalin.v2011@yandex.ru

synthesis of abnormal proteins. Like these popular theories, all the others also associate aging with the accumulation of negative changes in molecules and cells in the body. It seems that a person (or an individual of another species) lives in order to make negative changes in the structure of living matter. However, this contradicts the fact that damage and destructive changes cannot ensure progress in the evolutionary development of life. These and other numerous theories and hypotheses try to define a universal factor of aging. The following are proposed as such factors: mitochondrial dysfunction, oxidative stress, senile inflammation, impaired intercellular communication, genomic instability, telomere depletion, impaired proteostasis, epigenetic changes, depletion of stem cells and other causes [11]. Of course, it is very tempting to look for the cause of aging in some one factor, then it would be easier to find a means that radically changes the duration and quality of life of the organism. But, alas, the aging process includes all the numerous components (physical, chemical, biological, social) that ensure the dynamics of the organism's development.

According to some authors [11], the evolutionary hypothesis considers aging as one of the mechanisms that remove individuals who have lost the ability to reproduce from the population. However, firstly, all individuals will leave the population due to death, and secondly, individuals who have lost the ability to reproduce continue to remain in the population for a long time. Apparently, there is a certain evolutionary sense in this.

It should be noted that the listed and other theories and hypotheses try to determine a universal factor of aging. The following factors have been proposed: mitochondrial dysfunction, oxidative stress, senile inflammation, impaired intercellular communication, genome instability, telomere depletion, impaired proteostasis, epigenetic changes, stem cell depletion and other causes [12]. Of course, it is very tempting to look for the cause of aging in some one factor, then it would be easier to find a means that radically changes the duration and quality of life of the organism. But, alas, the aging process includes all the numerous components (physical, chemical, biological, social) that ensure the dynamics of the organism's development.

Most researchers divide the aging process into two main variants: aging is hereditarily programmed and aging is caused by external factors [13, 14, 15]. However, such a division contains an error, since it is impossible to consider these two main causes of aging in isolation from each other. During the life of an organism, they constantly act together and only their combination determines the nature of aging and life expectancy. The fundamental possibility of mutations in the cell's DNA is embedded in its program, but the specific type of mutation is determined by a mutagen - an external biological, chemical or physical factor.

Attempts are being made to find genes that ensure the lifespan of an organism [16]. But is there any gene that does not affect the lifespan of an organism? If such assumptions arise, then this is most likely the result of a far from complete study of the functions of the entire genetic apparatus. The influence of genetic factors on the lifespan of an organism can only be considered as a systemic function of the genome as a whole.

Playing along with people's unrealistic but passionate dreams of eternal youth, research is currently ongoing on rejuvenating the genome and slowing down the aging process [17]. The history of the search for the source of eternal youth begins in ancient times, as evidenced by the legacy we inherited from the fathers of ancient medicine, medieval alchemists, and experimenters of the New Age [18]. Alas, the thousand-year search for rejuvenation has not yet yielded even encouraging results.

The problem of aging appears completely different when moving from reduction analysis to systemic analysis. A systemic approach to the problem of aging can be implemented from the standpoint of interactomics, which studies the interactions between proteins and other molecules within a cell, between organisms, between biological systems and their environment. This allows us to consider the biosystem as a whole [19, 20, 21]. Interactomics shows that only the entire complex of inherited and acquired information concentrated in the organism resolves the issue of the possibility of developing all complex, highly dynamic interweaving of age-related changes throughout the entire period of the organism's existence. It is interactomics, by forming the logistics of the development of living nature, that helps to avoid mutual misunderstanding in the scientific community.

III. Aging and Pathology

Along with the problem of aging in the evolutionary movement of life, the problem of pathology remains far from clear. The division of the concepts of "health" and "disease" is considered conditional, and the medical norm, which includes a wide range of healthy and pathological conditions, is identical to the biological norm [22]. Pathological forms of aging, like physiological aging, play a dual role: on the one hand, they burden the vital activity of the organism, and on the other, they contribute to the emergence of specific structures that provide resistance to negative environmental factors. Even Lactantius noted in the 4th century: "All disasters - both of all mankind and of individuals, are not useless and lead mankind, albeit in a roundabout way, to the same one goal that is set for people - improvement" [23].

In the process of natural selection, the body's response to the ongoing action of pathogenic factors gradually acquires an expedient, adaptive character. Non-specific adaptation factors are replaced by specific ones based on adequate complication of structure and function. According to the morbid concept of organic progress, to complicate the internal structure of the organism, it is not enough to change only the external conditions of existence (this is a way of idioadaptation), a stable change in the internal conditions of existence (disease) is also necessary [24].

No organism ever exists in a state of purely physiological development, its vital activity is a pathophysiological transformation of its own tissues [25]. That is, evolution always invests in its “working tools” (organisms) in various proportions and variants both components of the development of living matter – physiological and pathological. This connection has existed inseparably throughout the history of the development of life and is preserved as one of the basic principles of the transformation of the structure of living matter. Pathology is a special way of collecting biological information, different from the physiological one. During the period of illness of the organism, molecules, crossing the physiologically permissible boundaries of conformation, form non-standard structures that provide it with special forms of adaptation (maladaptation). In the evolutionary process, maladaptation plays no less an important role than physiological adaptation. Disadaptation “breaks” the previous systems of the organism, formed in the process of phylogenetic and ontogenetic development, reduces the vital activity of organisms and therefore, as a momentary phenomenon, has a negative meaning, but in evolutionary terms it has a tremendous positive meaning [26]. That is, the disease is a “non-standard” vector of evolutionary development.

According to Weismann's postulate, all biological individuals are united by a common phenotype and a single program for its construction (genotype), transmitted by inheritance [27]. Individuals and species of living nature are not independent objects of evolution, but work in the unity of genetically determined methods of qualitative transformation and growth of information archives of living matter and cannot exist outside this unity. Only the closest integration of biological species and individuals, different in their genetically determined specificity, forms mutually complementary methods of analyzing the information content of the internal and external environment of organisms. Integration ensures the development of the systemic structure of the biosphere, the accumulation of potential and kinetic energy in it, which is the essence of the total "aging" of living matter.

IV. Proteins as the Main Creators and Keepers of Somatic Information

Proteins account for about 50% of the mass of a living cell. Each nuclear cell produces protein molecules, providing proteostasis - dynamic regulation of a balanced proteome. One part of the created protein molecules is used for intracellular reparative processes, the other part (secretome) is released into general circulation. More than 10,000–13,000 types of different proteins are expressed in human cells [28].

The protein molecule does not have a static form; as a result of metabolism and the action of environmental factors on the organism, it is in the process of continuous conformational transformations. Conformation (folding) of protein molecules is the initiating factor of the evolutionary transformation of living matter. In order to understand the general dynamics of biological processes at the level of the microworld of the organism, it should be taken into account that the total number of protein molecules in the human organism (presumably about 11^{15}) multiplied by the potential folding capabilities provides the broadest potential for finding the most effective tissue structures of living organisms in the process of evolutionary development [29, 30, 31, 32].

A protein molecule is not only a building block of life, but a complex information mechanism that constantly collects information, adapts, changes and transmits the accumulated "knowledge" to the structures of its own organism and the biosphere, ensuring the continuity of life in its diversity [33, 34]. Stable or transient protein-protein interactions form the basis of regulation and control within the cell through the transmission of internal and external signals [35]. Proteins, their associations and aggregations are essential for many processes that play a key role in various biological phenomena, from intercellular signaling to the development of diseases [36, 37, 38]. Figuratively speaking, protein molecules are the strings on which the main melody of life is played.

The quinary structure of the protein deserves special attention when analyzing the mechanisms of aging. It is the fifth level of protein complexity in addition to the primary, secondary, tertiary and quaternary structures [39, 40, 41]. In order to perform their functions, proteins often need to find a specific analogue with which (for archiving information) they will bind for a relatively long time. In the very crowded cytosol, in which proteins engage in a vast and complex network of attractive and repulsive interactions, such a search becomes a difficult task because it involves sampling a huge space of possible partners, of which very few will be productive. The solution to this problem requires that proteins spend as little time as possible on each encounter, so that they can explore a large number of surfaces, while simultaneously making this interaction

as intimate as possible, so that if they do encounter the right partner, they make firm contact. In this sense, the quinary structure is the result of a number of adaptations present on the surface of proteins that allow proteins to navigate the complex cellular environment [42]. It can be assumed that during the aging process, the molecule, as a result of collecting information, enters the fifth stage of folding - it is folded into an archival cocoon (a concentrate of basic information) - the result of the molecule's vital activity. In the final phase, the molecule can be metabolized by its own organism, or thrown into the biosphere in the form of an "information quantum" that is used by other organisms. Such transformations of protein molecules that are part of the cell structure, as they accumulate, determine the aging of the cell.

New structural information is transferred by the secretom of protein to the genome of somatic cells, where the issue of its preservation at the genetic level and transmission to daughter cells is decided [43, 44, 45].

Thus, it is difficult to imagine the enormous amount of work that a protein molecule performs throughout its life. But this work is the basis of evolution. The property of a protein molecule to change its structural form exceptionally quickly, breaking some chemical bonds and creating others in response to changes in the chemical composition of the environment, allows it to “calculate” thousands of thousands of different structural variants and select the most effective ones for building the most perfect forms of living matter. The selected variants are supplied with strong chemical bonds and are stored in the “archive blocks” of the structure of organic molecules. When the “archives” are filled, the molecule loses its functional (analytical) capabilities, the process of its conformation stops and (as one of the options) its disintegration begins. However, the blocks (oligopeptides) and amino acids of disintegrating protein molecules retain specific structures created by the organism, which transmit the corresponding information to new molecules formed inside the organism or, when they enter the biosphere, to the molecules of other organisms. Thus, the aging process is not an age-related degradation of the organism, but a “cocooning” of information collected by it during life.

V. Genome Transformations during the Aging Process

The existing classification of biological variability types contains many contradictions, which often serves as a source of mutual misunderstanding between biologists. There is still no generally accepted definition of mutation that would separate it from other types of variability [46, 47, 48, 49]. In particular, epigenetic changes also do not have a clear definition; they are often classified as processes close to mutations, and the term "epimutations" is used [50]. To avoid these contradictions, it may be appropriate to classify all changes in the information encrypted in the DNA structure as mutations [51].

The stage-by-stage development of an organism (zygote, embryo, fetus, newborn, stages of youth, maturity, old age and old age) occurs in "steps" of genome mutation and protein folding [52, 53]. In addition to the genetic information passed down from generation to generation, each organism is born with a small number of new genetic changes (de novo mutations) that occurred either during gamete formation or at the postzygotic stage. As the organism develops, new mutations continue to arise throughout postnatal and adult life in both somatic and germ cells [54]. With each age stage of the organism, its genome and somatic cell proteins collect information from external and internal signals, transform it, and create structural archives in the tissues of the organism. These archives occupy corresponding volumes in the structure of cells, thereby reducing their functional activity, which is generally expressed in their aging.

A systematic study conducted on different mammal species showed that the frequency of somatic mutations is the main factor of aging [55]. Again, objective results of the study of age-related DNA changes are interpreted only as damage [56, 57, 58, 59, 60]. At the same time, when analyzing the role of mutations in the aging process, it should be taken into account that in many cases, the so-called DNA damage itself does not affect the functionality and performance of the cell [61]. Moreover, as some researchers note, disturbances in the genetic apparatus of the cell during aging can lead to the activation of genes that have been “silent” throughout life [62]. Of course, such changes cannot be attributed to damage. It is also interesting that mutations that were previously considered unnecessary can become useful and increase the survival of a given organism and its descendants [63].

The direct causes of DNA damage include a whole range of biochemical transformations: deamination of amino acids [64], glycation of proteins [65], shortening of telomeres [66] and many other reasons. Starting with L. Orgel [67], subsequently almost all modern researchers believe that with aging, the accumulation of DNA damage increases [68, 69], that after each cell division, degradation of genetic information contained in the chromosome occurs [70, 71]. According to the error theory, age-related mutations in cellular DNA entail the synthesis of altered RNA, and this in turn leads to the synthesis of altered proteins. Altered proteins induce the synthesis of "incorrect" ribonucleic acids - a vicious circle arises. However, all these and other numerous mechanisms involved in age-related transformations of tissue structures are more likely to be regarded as adaptive mechanisms than as negative factors. Why should all mutations be

considered as damages that cause cell dysfunction? Malicious DNA - in the physiological development of the aging process? No, these are not malicious DNA, but transformed genetic structures that carry new information collected during their life cycle.

VI. Epigenetic Modifications in Cell Aging

Recent studies have shown that epigenetic modifications play a key role in cellular aging [72]. DNA plasticity is partly due to epigenetic changes that affect cell function and can be transmitted to future generations [73]. DNA in the body is constantly disturbed by DNA-manipulating proteins [74]. Protein-DNA interactions provide feedback between genotypes and phenotypes [75, 76, 77]. These interactions indicate the exchange of information between genetic and somatic structures. The mechanisms of epigenetic variability represent a very diverse group of phenomena [78]. Age-related epigenetic changes include DNA methylation, histone modification, chromatin remodeling, regulation of non-coding RNAs and other modulating actions [79, 80]. Among the listed epigenetic factors of evolutionary transformation of the genome, DNA methylation is the most studied act. DNA methylation is considered to be a mechanism for implementing programmed aging [81]. DNA methylation activity can change and regulate gene expression depending on age [82]. Global DNA methylation levels increase during the first few years of life and then decrease starting in late adulthood [83]. Such dynamics of methylation activity indicate a physiological role of this process. It is important to note that epigenetic modifications are reversible: DNA methyltransferases, demethylases and associated proteins dynamically demethylate DNA [84, 85]. That is, it can be assumed that the cell is undergoing a process of rechecking and in-depth processing of information collected by the cell.

The role of gene regulatory networks in the aging process is performed by epigenetic regulators responsible for the reorganization and strengthening of certain chromatin structures [86]. During aging, chromatin becomes less active and compacted, and the connections between DNA and chromatin proteins also become stronger [87, 88]. These changes may indicate the archiving of information and the formation of protection of information structures from enzymatic destruction.

VII. Participation of Extracellular Nucleic Acids in the Formation of Biological Memory

Information probing in the body, along with proteins, is also carried out by extracellular (circulating) nucleic acids (cir-nNA). They are present in blood plasma, cerebrospinal fluid, saliva and other body fluids [89]. Extracellular DNA can penetrate cells with subsequent incorporation into their genome [90]. The presence of cir-nNA in the circulating fluids of the body indicates the existence of a special pathway for the transfer of genetic information between cells of various tissues of the body and participation in their transformation [91].

Thus, the body is constantly actively working to correct DNA changes, select useful information and eliminate living matter that is unpromising for further development. Mutations form new structures of body tissues that carry new functions and determine the limits of evolutionary trajectories [92]. As a result of the continuous collection of information by organic molecules coming from the external or internal environment and its delivery to the genome of somatic cells, mutations occur - a change in the genome that is passed on to the descendants of a given cell. The most significant mutations of somatic cells in the process of evolution can be transmitted to the genome of germ cells and change the gene pool of a biological species [93]. Figuratively speaking, life is a game of parts of a system with its environment. In such a game, a living system remembers successful decisions made in previous rounds and uses them to search for more perfect decisions in subsequent rounds.

VIII. DNA Repair System

Of particular importance is the notion that the rate of aging is determined by the relationship between damaging factors on the one hand and tissue repair factors on the other. Cells have several mechanisms for repairing and overcoming DNA damage. The main and most universal mechanism used by mammalian cells to remove altered bases or nucleotides in DNA is known as base excision repair (BER). BER involves several enzymes, including DNA-glycosylases, AP-endonucleases, DNA-polymerases, DNA-ligases, and accessory proteins, which act sequentially on the same damaged DNA site. Instead of associating into a single stable multisubunit complex, these enzymes pass repair intermediates between themselves in a highly coordinated manner [94, 95, 96]. If the DNA damage is repaired, the cell cycle continues. Otherwise, molecular mechanisms are activated: either senescence or apoptosis [97]. Senescent (old) cells are metabolically active, but do not divide. They do not respond to growth factors and are resistant to apoptosis. These cells have a specific morphology - they are large, flattened, with a large nucleus, strongly vacuolated, their metabolism is preserved, but the gene expression profile changes significantly [98]. The structure of such cells indicates their high information saturation. In all likelihood, the preserved metabolism of senescent cells is completely aimed at internal processing of the collected

information, which forces the aging cell to disconnect from external functions.

With increased levels of DNA damage, proteostasis defense mechanisms, such as autophagy, are activated and become physiologically significant [99]. However, it should be taken into account that autophagy is an important element of the physiological clearance of the body and, naturally, it should be activated as the amount of metabolites in the body increases during aging. Autophagy can also be attributed not only to the mechanisms of reparation, but also to the mechanisms of processing information archives and transferring molecular structures to a higher functional level. The importance of an effective DNA "reparation" system for achieving longevity was noted in studies on supercentenarians (110 years) and semi-supercentenarians (105 years). Using whole-genome sequencing and comparison with young people from the same geographic regions, the authors were able to identify increased activity of DNA repair genes in older people, as well as a lower level of mutations compared to their young peers [100]. Apparently, in long-livers the program for processing DNA information blocks is aimed at longer and possibly higher quality processing.

IX. Phenomenon of Apoptosis in the Process of Aging

The significance of apoptosis in aging deserves special attention. It is believed that the presence of harmful DNA initiates signaling cascades that lead to cell cycle arrest or apoptosis [101]. Apoptosis is also associated with the "Hayflick limit" [102, 103]. It should be noted that apoptosis has its own rather complex mechanisms of implementation, in particular, senolytics are involved in them - small molecules that inhibit proteins of anti-apoptotic pathways, which triggers apoptosis [104]. The dualism of apoptosis is that, on the one hand, it causes physiological death of the cell, and on the other hand, it does not allow its enzymatic destruction. This ensures the preservation of the information collected by the cell. In the process of apoptosis, the aging cell itself stops its active life processes without any negative consequences for the body. Apoptosis does not simply remove cells from the body that have fulfilled their physiological functions, it allows the cell to fully implement its life program - to collect certain information, process it, archive it with strong chemical bonds and release it into the biosphere for transmission to other organisms. Thus, apoptosis can be considered a normal process that not only plays an important role in the development of the body, but is also the most important mechanism regulating the existence of almost all living beings on Earth.

X. The Role of the Extracellular Matrix in the Aging Process

When analyzing the aging process, it is also necessary to take into account that the entire mass of cells in a single organism is united by the extracellular matrix. Its basis is connective tissue, which, in addition to the function of the body's framework, carries out the binding and communication of cells with each other in the body. It is believed that stochastic non-enzymatic modifications of the extracellular matrix trigger cellular and other types of aging, affect the integrity of organ barriers and cause tissue fibrosis [105]. It is believed that during the aging process, extracellular matrix molecules are damaged as a result of many modifications, including glycation, cross-linking and accumulation, which leads to an increase in matrix rigidity [106]. At the same time, another version is also valid: the genetic aging program triggers modifications of the extracellular matrix, using the matrix rigidity as a factor in the stable storage of collected information.

XI. The Importance of Some Metabolic Formations in the Aging Process

Many theories base the aging process on the effect on tissues of individual physicochemical structures formed in the body during metabolism. For example, the free radical theory proposed by D. Harman in 1956 [107] states that aging occurs due to the accumulation of damage in cells caused by free radicals. This theory served as the basis for a huge number of studies [108, 109, 110]. At the same time, a number of studies note a different role of free radicals in the body. In particular, it has been experimentally shown that in the rodent Heterocephalusglaber (naked mole rat), which is distinguished by an exceptionally long lifespan, the levels of reactive oxygen species and oxidative damage are significantly higher than in the mouse (Musmusculus), which lives a much shorter life [111]. It is known that reactive oxygen species play a critical role in the functioning of the immune system, intercellular communications and stress reactions [112]. It has been shown that free radicals can not only cause molecular damage in cells, but also act as modulators of physiological processes [113]. The presented data indicate that free radicals have a physiological function and only their excess production due to one or another pathology causes negative effects.

XII. The Role of Cross-Links in the Aging Process

The theory of aging from "cross-links" suggests that the aging of living organisms is caused by the random formation of "cross-links" of bridges between protein molecules and DNA. Covalent binding of

proteins to the DNA chain leads to the formation of DNA-protein cross-links (DPCs). The authors of this theory consider DPCs to be one of the most harmful types of DNA damage, leading to blocking of DNA replication and transcription [114]. At the same time, there is a different understanding of the significance of compaction of aging tissues. It has been shown that DNA damage and endogenous products with carbonyl functional groups can form DPCs in genomic DNA under normal physiological conditions [115]. Genetic mutations can increase or decrease the energy of intermolecular binding [116], which determines the formation of cross-links. The variety and quantity of substances causing "cross-links" in the body are so great that there is no question whether this is enough for aging, but one is only surprised why aging proceeds so slowly [117, 118]. But it is no less surprising why cross-links are excluded by most researchers from the sphere of physiological processes of aging in general. The accelerated process of cross-link formation, for example, in diabetes mellitus, cardiopathology and other diseases can be considered as a factor of adaptation [119]. Is it not more likely to assume that the aging process itself causes the formation of cross-links as a mechanism that increases the protection of accumulated new genetic and somatic information? It is natural to assume that in order to preserve archival information, cellular elements require a compaction of the molecular structure and an increase in the strength of intermolecular bonds, which is what cross-links provide.

XIII. Autoimmune Aging. in Recent Years

The attention of researchers of the mechanisms of aging of the body has been attracted by the so-called autoimmune aging. In 2000, a group of Italian immunologists proposed a theory of aging called "inflammaging" - senile inflammation [120]. According to this theory, aging is the result of chronic low-level inflammation without signs of infection (sterile inflammation). In the process of "inflammaging", many cells, including cells of the immune system, predominantly produce proinflammatory cytokines [121, 122, 123]. It is characteristic that most researchers attribute inflammaging to a purely negative process, linking this condition with an increased risk of developing various age-related pathologies, including infections, cardiovascular, neurodegenerative and autoimmune diseases, cancer and other types of pathology [124, 125, 126, 127]. Inflammagingis defined as a systemic proinflammatory state caused by an imbalance between proinflammatory and anti-inflammatory mechanisms, which in turn leads to increased cytokine production. This imbalance causes a long-term state of low-grade inflammation and is even considered a biomarker of accelerated aging [128, 129]. Inflammaging is also suggested to cause damage to the extracellular matrix through multiple modifications including glycation, cross-linking, and accumulation, leading to fibroaging [130].

However, there are also opposing opinions. Many researchers consider inflammaging to be an adaptive process [131]. This version is supported by studies conducted on centenarians, which found that high levels of inflammatory biomarkers contribute to longevity [132, 133]. In elderly people, including those over 100 years old, high levels of autoantibodies were found, but the occurrence of autoimmune conditions was not observed [134, 135, 136]. The positive status of inflammagingis supported by the fact that autoantibodies are an important factor in maintaining homeostasis. In particular, they are able to bind to apoptotic cells, accelerating their elimination [137, 138]. Epidemiological studies have not provided sufficient evidence as to whether inflammation is primary in the initiation of chronic non-communicable diseases, or inflammation develops as a protective effect in response to the underlying pathological condition [139]. Therefore, in a logical analysis of the causes of age-related increase in autoimmune activity, it is entirely acceptable to interpret this phenomenon as an enhanced adaptive clearance, developing in response to an age-related increase in proteins and cells in the body that have fulfilled their physiological purpose and require removal from the body or processing for further use by the body itself. We also believe that inflammagingcan be attributed to a special type of systemic processing of information collected by the body in the process of life.

XIV. The Importance of the Aging Process in the Evolutionary Development of Human Intelligence

All of the above may indicate that the collection, processing and storage of information in the process of evolutionary development of living matter, where aging played a key role, led to the creation of the human brain - a carrier of thinking matter, capable of performing abstract analysis of the environment, encoding the collected information and transforming it into technical tools and technologies. Currently, a significant number of studies are devoted to the proteomics of the aging brain [140, 141, 142, 143]. Most researchers have identified the accumulation of potentially toxic protein aggregates and their spread throughout various areas of the brain as the main causes of aging. It is believed that the aging brain contains a large number of many types of misfolded proteins [144, 145]. In particular, it has been established that peptides and proteins have an innate tendency to pass from their natural functional

state into poorly soluble amyloid aggregates. At the same time, the ability of amyloids to encode and reproduce biological information has been noted [146]. Therefore, it would be incorrect to interpret amyloid structures as incorrectly folded proteins, since their rigid structure is one of the forms of stable storage of biological memory. During aging, the pigment lipofuscin also accumulates in brain tissues, which is considered one of the causes of neurodegeneration [147, 148, 149]. However, the question arises: why do incorrectly folded proteins appear in the brain during physiological aging, why does lipofuscin cause neurodegeneration? The opposite assumption is also acceptable - many brain proteins (including amyloids and lipofuscin) have a specific folding aimed at preserving the structure of the carriers of accumulated biological information.

This assumption can be confirmed by the fact that the current state of views on mental aging is characterized by a refusal to understand it exclusively as a time of “losses and losses.” It is being replaced by ideas about the complexity, inconsistency, and nonlinearity of changes occurring in life support systems, including the psyche [150]. It should be taken into account that during normal aging, the death of nerve cells is limited to certain areas of the nervous system and is insignificant [151]. The functional stability of the brain during aging is confirmed by data that the higher the initial level of intelligence, the less its decline in old age. Moreover, people with a high level of intelligence may experience an increase rather than a decline in old age [152]. It has also been noted that the accumulated knowledge of older people has a positive effect on current working memory [153].

Among the most common age-related symptoms is, first of all, a slowdown in the rate of activity (latency) of the brain. This is clearly visible when trying to retrieve information from memory storage systems. The reason for this is apparently that the main structural changes in brain tissue in old age include: a decrease in the number and length of dendrites, the loss of many dendritic spines, a decrease in the number of axons and their myelin sheaths, and a significant loss of synapses [154]. The rate of formation of new axons that form connections with neurons also decreases, which slows down the recall of information stored in them to the areas of the brain that use it. It is important that the memory archives of the aging brain remain intact. This is evidenced by the ability, with certain intellectual efforts, to recall facts that seemed to have disappeared from memory forever [155]. That is, aging causes changes mainly in the brain tissues that provide connections to memory archives, but not the loss of the archives themselves. It has also been established that with age, the number of connections between brain areas within the corresponding functional module (and not between modules) increases [156, 157]. Presumably, this may indicate an increase in the level of the brain's focus in old age on in-depth processing of information within archival modules. Indirect evidence of this is a certain paradox: the cognitive activity of the aging brain (processing of new information) decreases [158, 159], and the level of constant potential and energy expenditure in the deep structures of the brain of elderly people increase compared to normal values [160, 161]. Such an increase in energy expenditure can be considered as a result of age-related enhancement of the function of "intracerebral creativity" aimed at the final correction and systematization of archived information embedded in the structure of brain tissue.

Apparently, the human brain in old age gradually reduces the quality of its systemic organization, but in fact until the end of life it continues to preserve and improve the structural organization in local areas of archiving biological information. This information in the process of global biospheric metabolism forms the basis for further improvement of the structure and function of intellectual matter. It should be noted that specific knowledge archived in the brain of an individual is not transmitted genetically, but it can be assumed that a more advanced "genetic platform" formed on the basis of this knowledge is transmitted, and by standing on it, new generations of humanity receive higher cognitive and creative capabilities in the process of mastering continuously more complex biospheric information.

It is important to emphasize that at the stage of the modern development of thinking matter, that is, the human brain, people of older age groups are of priority interest for evolution - they are the carriers of the largest volume of carefully developed information structure of intellectual matter. This assumption is supported by the fact that the number of people over 60 years old is growing rapidly. Their total number in 2020 has already reached 1 billion people. If the current trend continues, by 2030 the number of this group will reach 1.4 billion, and by 2050 - 2.1 billion [162]. Evolutionary interest in the elderly is also confirmed by the dynamics of changes in the number of long-livers on the planet. If in 1950 the share of people aged 90 and older was 0.05% of the planet's population, then by 2020 it reached 0.27% - an increase of almost six times [163]. According to the forecast of the UN Department of Economic and Social Affairs, by 2050 0.79% of the planet's inhabitants will be over ninety years old, and by 2100 – 2.14% [164]. That is, in relation to 2020, in 2050 there will be an increase in the number of long-livers by almost 3 times, and by 2100 – almost 8 times. At the same time, the total population of the Earth by the end of the century will grow only 1.2 times [165]. Such age-related changes may indicate that the human brain is becoming the main interest of evolution, and the elderly are the most important biological object – carriers of the largest volume of carefully developed structure of intellectual matter.

At the same time, a natural question arises: why does evolution need an older age group of the population after the possibility of transmitting genetic information sexually ceases? The fact is that the genetic (vertical) way of transmitting biological information in the evolutionary process is not the only one. At present, the problem of the so-called "horizontal genetic drift" is being discussed more and more actively [166, 167]. In general, the most powerful flow of biological information is carried out by the non-genetic (somatic) way - through food, water and air circulation in the biosphere. In this case, the vertical (genetic) way transmits systematized, clearly structured information (this is its advantage), but information collected by one organism (this is its weakness). The horizontal (somatic) way transmits more diverse information collected by different organisms (this is its advantage), but the information is scattered, not structured (this is its weakness). The combination of these two complementary forms of information transfer optimally determines evolutionary progress [168].

Thus, it can be noted that the process of development of the human brain is fundamentally unlimited, since development is the main way of existence of the individual. According to the law of cephalization (derived by D.D. Dan and D. Le Conte in the 1950s), the human brain continues to preserve and improve its structural and functional organization until the end of life. This law was supported and introduced into scientific circulation by V.I. Vernadsky [19]. Analysis of modern achievements of the evolution of life allowed V.I. Vernadsky [170] to raise the problem of the Noosphere, the sphere of reason, as the main goal of the development of life. The formation of the Noosphere means that thinking matter in the further evolutionary search for the optimal (ideal) version of its structure must move from a polysystemic (individualized) form of organization to a single system - the Integrated Biospheric Reason.

XV. Conclusion

Based on the analytical review of the dynamics of living matter, we can present the main provisions of the role of aging in the development of human life and the biosphere. All living things on our planet are united by a single metabolic process in which the waste products of some organisms serve as a food substrate for others. Metabolism is an interconnected and balanced process of assimilation (anabolism) and dissimilation (catabolism). That is, life is both creation and destruction, the birth of the new and the death of the old. But this is not the labor of Sisyphean, but a purposeful process of self-improvement. Anabolism does not repeat the structure of organic molecules that have undergone catabolic destruction, but creates more perfect molecular structures filled with new information from their fragments. The processing of constantly changing information in the biosphere is carried out by a "global revision" of its structural state: viruses invade bacterial cells, bacteria and fungi attack more organized representatives of life, which, in turn, metabolize the tissues of lower life forms. At the same time, each biological species, each organism, each organ, cell and molecule have their own specific functional programs and methods of transforming the forms of biological material. The harmonious activity of all this diversity forms the basic principle of a single information-analytical process of biospheric self-organization, ensuring the evolutionary development of life. In the process of this interaction, organic molecules are increasingly filled with potential energy and proportionally reduce kinetic energy, i.e. functional activity. This is the starting point of the aging process. The aging process forms structural information archives. From generation to generation, the information saturation of these archives increases.

Evolution is a fundamental mechanism of development of the material world, which formed a living substance from inert matter and endowed it with intelligence. The question arises: is it possible that this universe allows a systemic senseless destruction of the elements of its brainchild (living organisms) in the process of aging? If aging is not of great importance in the development of living matter, then why did evolution preserve this process in the life of an organism? The contradiction of the aging is that, on the one hand, in the process of aging, the organism degrades as a system, but, on the other hand, there is a structural improvement of its tissues at the molecular level. That is, aging ensures processes aimed not at preserving the organism as a system, but at preserving its individual elements (information blocks) that are of interest for the construction of new structures of living matter as a whole. An evolutionary ladder is formed from these information blocks, along which living matter rises to a higher level of its development. Aging is not decay or damage, but a mechanism for converting one structure of living tissue into another, more perfect one, while preserving it as a potential phase for use by new cellular generations of the same organism or by other organisms.

Living organisms are formed only from "semi-finished products" (atoms and molecules), which have previously been part of other living structures and acquired a certain volume and quality of structural information (biological memory). The death of an organism is the moment of its merging with the primordial basis of being. Dying, the organism passes on to newly emerging organisms a material substrate with an "improved" structure and the corresponding information, ensuring an integral increase in the quality of the biosphere. The biosphere is a huge "melting pot": just as an organism processes its aging elements - cells, so the biosphere processes its aging elements -

organisms. Aging and death of an organism is the process of transition of a fragment of living matter from an isolated (individualized) phase of development to the phase of integral development of the biosphere. The global nature of the aging problem is that it is not only an individual and not only a biological species that ages, but the entire biosphere as a whole. Thus, aging is a universal type of internal movement of living matter.

The task of modern science, given the established moral categories of humanity, is to maximize the lifespan of an individual. This task aligns with the "ultimate goal" of evolution, as it allows for the fullest realization of the program assigned to a specific organism in the search for more advanced life structures. It follows that aging cannot be stopped and should not be pursued, as stopping aging means halting development. At the same time, intellectual intervention in the aging process (in the interest of the individual) should focus on the prevention and correction of its pathological forms, without interfering with the process of physiological forms of tissue variability in the organism. This understanding of aging will define effective research directions in the field of gerontology and prevent researchers from straying onto the path of misconceptions.

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