V. I. Dontsov

General system theory of aging

Special role of the immune system

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Аннотация

The monograph examines the general methodological problems of the aging, main mechanisms, as well as consideration of the fundamental possibilities and directions of influence on this process. A special place is occupied by the use of system analysis, consideration of integrative systems, and the special role of the immune system, namely, that part of it, which is not responsible for immune phenomena proper, but regulates the interaction of proliferation of various cell populations in the body.

Содержание

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The monograph examines the general methodological problems of the aging of biological systems, debunking myths and cliches circulating in this area; modeling of the general aging process, highlighting the causes of aging, the main mechanisms, and their biological content, as well as consideration of the fundamental possibilities and directions of influence on this process.

A special place is occupied by the use of system analysis and consideration of integrative systems that combine hierarchically complex systems into a single whole, and the special role of the immune system, namely, that part of it, which is not responsible for immune phenomena proper, but regulates the interaction of various cell populations in the body. A single look at aging allows you to determine the possibilities and directions of influence on this process, and the allocation of aging syndromes, similar to those in common diseases, allows you to influence aging with conventional therapeutic agents.

The book is intended for specialists in the field of general biology and medicine, system analysis, for gerontologists and specialists in anti-age medicine and biology of aging, as well as for graduate students, teachers, and students of higher educational institutions, theorists and experimental studies.

Introduction

According to WHO, the level of health and life expectancy of the population are among the central indicators of the level and quality of life in the country. However, the increase in life expectancy, which is universally observed in all civilized countries, poses a serious problem associated with a simultaneous decrease in the birth rate, this is a worldwide trend of aging of the population. The problem of aging is occupied by the most diverse areas of theoretical science and their practical sections. General biology considers the emergence and evolution of ontogenesis, the species life span, the ecology of species and the Earth's overall ecosystem.

Demography develops population gerontology, especially the aging of various population groups and the change in mortality in different historical epochs. Molecular biology, genetics, physiology, biochemistry, and histology have thoroughly studied all the features of the manifestation of aging at the level of molecules, genes, cells, tissues and organs, as well as changes in the systemic relationships of organs and tissues in the whole organism throughout life. Geriatrics studies in detail the course and treatment of diseases in the elderly.

However, it is philosophy, its methodological section – gnoseology, and the modern methodological scientific principle – system analysis that plays a leading role in questions about the essence of life and death, constant movement and self-renewal, and also in methodological questions about the essence and cause of the aging phenomenon and the fundamental possibility of overcoming it, about the future of man as a race with global interventions in the biological nature of man and in other generally significant, human-common problems.

Knowledge of philosophy and methodology eliminates the typical flaws characteristic of modern representatives of highly specialized science, first of all, of replacing the essence of aging with its mechanisms, which led to the unrestrained reproduction of the "theories" of aging.

Practical success is always based on new scientific knowledge and theoretical work, which is especially important for the science of aging. In recent years, quite a lot of fundamental work has appeared on molecular, genetic, cellular manifestations of aging, and ideas about the role of apoptosis, telomerase and other relatively new scientific data on cellular processes in aging processes are being exaggerated. At the same time, no clear idea of aging as a single process affecting the whole organism is formed. It is not clear how important the studied mechanisms of aging are for the aging of the whole organism, how they interact with each other and how important they are.

In this monograph, using the system analysis methodology, to consider the aging process as a whole as a phenomenon typical of all living things, as well as to highlight the most important aging processes and mechanisms for mammals and humans first of all.

We also present a new look at the main mechanisms of aging associated with the development of regulatory models of aging and specifying their manifestation – through the immune mechanisms, and the immune mechanisms here act in a specific form – as regulators of the proliferative activity of somatic cells, which is pronounced decreases with age, defining age-related atrophy of tissues – this is a new trend in immunobiology, in which domestic scientists are ahead in the world.

The monograph makes it possible in general to create a general idea of aging, its causes and main mechanisms, and to evaluate the possibilities and ways of influencing, having a clear idea about the points of application and the possible effectiveness of effects, which is always the main complexity of modern theories and practical impacts on aging.

Main Points

The presence of hundreds of theories of aging to date indicates not only and not so much the lack of a unified theory, general views, or lack of knowledge of the causes and essence of aging, but often a **methodological lack** of subject matter understanding.

The development of a **systems approach** – a new, whole world view, brought science out of a methodological crisis, while not discarding what has been achieved.

The **general cause** of aging can be expressed only in the language of high-level abstraction as an objective pattern of life, being, as a principle, but not as specific mechanism in the organism. The reduction of principles to mechanisms is the main methodological error in the sciences, including in gerontology.

System analysis reflects not the material structure of the object that morphological sciences study, but a **hierarchy of essential principles** reflecting the laws of functioning and communication within and between the structural levels of the object being considered, which acts as a complex hierarchical dynamic system.

The **common cause of aging** is known as part of ontogenesis, part of life itself, as a phenomenon of disruptions in the structure and function of the system accumulating with age, as movements from order to chaos. In general, it is a natural process in nature, since it proceeds with an increasein entropy – the accumulation of chaos in a systems.

Aging has been known since antiquity – as a reduction in vitality with age. The current general definition of **aging as a reduction in overall vitality with age**.

The **first mathematical model of aging** was created almost 200 years ago by B. Gompertz (1825) and still most accurately describes the age dynamics of human mortality and, apparently, of most other organisms. Mortality, as quantitative characterization of the inability to resist destruction, can be viewed as the reciprocal of vitality.

A simple assumption about the stochasticity of the aging process is enough: the viability over time decreases in proportion to itself at each time point in order to obtain the basic law of aging: **mortality increases with age by the exponent**. Such a nonspecific increase in the body's vulnerability to all influences with age is called aging itself:

$d X / d t = - k X$, k is a coefficient, X is viability, t is time.

Considering the mortality (μ) as an inverse viability value ($\mu = 1 / X$), the basic aging formula is obtained (B. Gompertz and W. Makekem):

$\mu = Ro \exp (k t) + A$, Ro is the initial mortality rate, k is the rate of increase in mortality, A is the coefficient characterizing the external influences to mortality.

The general mechanisms of such processes are clear – these are **principally probabilistic** regularities associated with the ultimate stability of any elements delimited from the external environment; then a complex organism consisting of such elementary units can only lose them over time. The nature of such "elementary units of life": non-renewing elements of the body (nerve cells, nephrons, alveoli, teeth, etc.).

Another approach to the quantitative assessment of aging, based on the same definition – reducing overall viability with age, is to consider the overall viability of the system as an integral of the viability of its parts, which, as applied to the organism, means that the overall viability of the body consists of maintaining vitality (functional resource) of its main organs and systems:

$X = k_1 x_1 + k_2 x_2 + \ldots + k_n x_n$, where k is the coefficient, $x1 \ldots n$ is the viability of organs and systems. The definition of individual aging as a **biological age** is based on this.

The common single cause of aging is manifested by the **Main types (common mechanisms) of aging**.

A fully formed organism has many non-updated elements at all its hierarchical levels: unique genes, non-dividing cells (for example, nerve cells, including autonomic control centers), non-regenerating structures of organs (alveoli, nephrons, etc.), organs themselves and etc. The loss of non-regenerating elements with age is probabilistic, and therefore in the simplest case, it is described by the same type of formula (Gompertz) as the loss of overall viability. It is the **1-st General Type of Aging**. The only possibility at present to combat this aging mechanism: replacement of lost structuring units – mechanical prostheses (e.g., dental care) and transplantation of organs and tissues. l

Age-accumulated of non-functional and toxic elements of different nature is **2-nd General Type of Aging**. Activation of the organism's "cleaning" systems is a well-known and widely used tactic to influence this aging mechanism.

Aging of self-renewing elements of the organism structure (skin, mucous, parenchymal organs, etc.) is determined by a decrease in the rate of their self-renewal by reducing growth factors is the **3-d Main type of aging – regulatory aging**. Optimal is the impact on the regulatory centers and the introduction of tissue growth factors.

Global mechanisms of aging are manifested in the form of a variety of particular mechanisms for different structural units of the body, depending on the specific conditions and their structure. The effect on them is **symptomatic**. However, according to the common mechanisms, private mechanisms are grouped into **aging syndromes**, common to all effects (and diseases). Effects on them is the most promising at the moment, as you can use conventional remedies.

We have proposed a **general model of growth an development and regulatory aging**, which consists in disinhibition in the vegetative regulatory center (hypothalamus?) of stimulating cells when inhibiting cells die, which determines growth and development, but if death also affects stimulating regulatory cells, then over time the development program is depleted – regulatory aging. This is essentially and very simple model that describes changes in viability (and mortality as a quantitative criterion of aging in general) during all periods of an organism's life.

Our formula is analogous to the formula of Gompertz-Makeham:

our formula: $m=R*1/(Ho*Exp(-k1*t) — So*Exp(-k2*t) + c) + A;$

Gompertz-Makeham formula: $m = Ro * Exp(k*t)$ + A.

The most important formal differences are:

1. The exponent component, reflecting the age dependent mortality rate, is the result of the interaction of 2 exponents, reflecting stimulatory and inhibitory effects. This allows to simulate the initial shape of the mortality rate charts (1—25 years), characterized by a complex U-shaped.

2. The exponent component is influenced (mainly in its final segment) by the coefficient "*c*", reflecting the presence of long-livers persons with a genetically reduced rate of aging. This allows to simulate the final shape of the mortality charts (80—110 years), characterized by a complex S-shaped.

Our it is not empirical, and is based on fundamental biological processes and connects the aging process with the processes of growth and development. Regulatory non-dividing cells of the hypothalamus that produce growth factors in blood can be real morphological substratum (the "*h*" and "*s*" cells) of the described mechanism; for peripheral mechanisms – a variety of growing and self-updating proliferating somatic cells, the growth of which is regulated by the level of growth-stimulating factors.

The systemic nature of aging also requires a **systematic approach to the diagnosis** of aging and its **effects**.

The book describes the feature requirements for the indicator of Biological age, the components of bioage and the computer system determining of bioage and related indicators, including automatic processing of bioage biomarkers using elements of artificial intelligence.

Another computer system described in the book makes it possible to study aging in detail by studying the dynamics of **population mortality** using the formula of Gompertz-Makeham and its derivatives.

The use of mortality rate unless the external mortality component (*"m-A"*) graphs and the mortality rate increment (*"d (m)"*) graphs reflect the actual biological aging and show that the linear form of the graph (on a logarithmic scale) from the period of the end of growth and development remains the same, and decline in the rate of aging of centenarians.

The superposition of curves, reflecting the actual aging rate, shows that the **aging is the same in history until 1950** for a number of countries, however, **since the middle of the 20th century, the indicators of biological aging are constantly decreasing**. Also increases maximum lifespan and reduces the coefficient *k* of Gompertz chart.

The effect of reducing the aging rate ("*d (m)*") for middle ages is accompanied by the **phenomenon of inversion of the overall mortality** rate ("*m*") for ages of long-livers: the natural "*m*" decrease, observed for all countries in earlier historical periods, is replaced by an increase in modern times. However, in the "*d (m)*" charts, it can be seen that the decrease in the aging rate of the long-livers is preserved throughout all historical periods. The latter means that the phenomenon of mortality inversion is associated with the external influences on mortality, and not with a change in the aging rate at this time.

Ways to restore regulatory programs – the most promising direction for the impact on aging.

The problem of recovery and correction of regulatory programs of the brain is central to age biology, since many body functions (sexual, immune, metabolic rate, total hormones and the balance of different types of hormones, nervous trophism, growth program, etc.) undergo drastic changes throughout life precisely because of the programmed changes in the regulatory centers, primarily at the level of the hypothalamus.

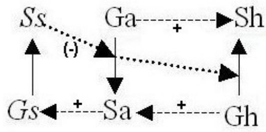
The methods of brain embryonic tissue transplantation developed in recent years make it possible to begin work on the restoration of depleted regulatory programs in old animals.

The results indicate the fundamental possibility of restoring development programs lost or exhausted with age, as well as, possibly, imposing new programs (for example, during interspecific transplants) in order to influence the aging process in the right direction. An alternative to surgical intervention are the methods of pharmacological or physiotherapeutic activation of the corresponding nuclei of the hypothalamus, as well as the creation of new regulatory centers and pacemakers, including the use of psychotherapeutic techniques, hypnosis, etc.

The **regulation of cellular growth** at different levels of hierarchical structures of the body is essential for the integrity of the body.

The works of M. Eigen and P. Schuster show how different types of structures (cells) could be combined with their own regulation systems. According to the authors' definition, a **hypercycle is a principle of natural self-organization**, causing integration and a coordinated evolution of a system of functionally related self-replicating units, uniting it into a single whole. The basis of the hypercycle theory is proof of the inevitability of the formation in the process of evolution of functional links of a higher order between self-replicating units — systems of a lower order that are part of a single hypercycle system. With such a union, a self-regulating system of a higher order is formed, which preserves the constancy of the interrelationships within the incoming systems.

The 3 elements (regulated population, helper and suppressor populations) form an elementary self-regulating unit of 3 cell populations – CELL HYPERCYCL: the population of somatic cells is regulated by stimulating (h) and inhibiting (s) regulatory populations.



Despite the simplicity of the description and great biological significance, the “cell hypercycle” is not given worthy attention in the literature, but the concept of a cell hypercycle means:

– a new mechanism in evolution during the formation of multicellular organisms, which made possible the very existence of multi-cell as a whole;

– a fundamentally new level of regulation of cell growth in the body (the level of cell populations), and, therefore, a new system in the body;

– the presence of self-organization processes at this level;

– the basis for the formation of higher levels of regulation (neuro-humoral) and their indirect effect on cell growth;

– the basis for the formation of a special cellular system for regulating the growth of somatic cells in the organism – a new system in the organism (Dontsov, 1986, 1987, 1989, 1990, 2009, 2011, 2017a, b), which in turn is the basis for the formation of special systems – including including the immune system – a new theory of the formation of immunity (Dontsov, 1989, 1990, 2011, 2017a, b),

– as well as a new “immune theory of aging” as a depletion of the immunity system due to changes in regulatory systems (Dontsov, 1989, 1990, 2011a, b).

Thus, the self-organization of growing cell populations into a single mutually coordinated system is the central and initial moment of the formation of a cell regulation system at the level of interaction of different types of cell systems in the body..

Further development of the cell hypercycle in phylogenesis should have taken place according to general evolutionary laws – the following biological phenomena can theoretically be predicted and experimentally observed:

– increase the number of regulated units,

– specialization of cell populations (the selection of somatic and regulatory populations);

– specialization of regulatory populations, leading, for example, to the phenomenon of “memory” in the regeneration of organs and tissues, transferred by T-lymphocytes.

– the emergence of functional regulation (the emergence of mechanisms Go/G1 transition and its regulation separately from the G1/S transition),

– add-on regulation systems of the whole organism (for the regulation of growth and development).

In general, such a system is represented by a number of differentiated functional types of cells (skin, mucous membranes, liver, kidneys, etc.), which perform primarily their own type of functions. They are usually at rest, but when cells of a certain tissue are activated, they become G1 ready for cell division.

The somatic cells entering the cell cycle (G1) are regulated by both nonspecific and specific for this tissue regulating cells of the stimulating and inhibiting type, integrating various growing cells into a single system.

Already specialized cell regulators – the Cells Regulators of Proliferation (CRP System), which themselves begin to activate and divide, react to this state, and also secrete growth factors for functional cell types, stimulating them to grow and divide.

In the course of growth and division of functional cell types, regulatory feedback cells are activated and their ratio to stimulating cell types determines the growth kinetics of functional tissue types. At the initial stages, nonspecific regulatory cells are activated, at later stages, specific CRP, which determine the effects of specific "memory" detected during repeated regeneration.

The **participation of lymphocytes in the processes**

of regeneration and normal tissue growth was emphasized by a number of authors, and from the very beginning the immune system was assigned the role of integrative, preserving the whole organism. Immunomodulators have long been proposed as stimulators of regeneration processes, as well as the idea that regeneration and the immune system are interrelated (Babeva et al., 1982, 1987; Giełdanowski, 1983; Romanova, 1984), and all organs influence a single mechanism on the growth of all other organs (Romanova, 1984), which requires a special system of such interactions.

The lymphocyte transfer of “regenerative information” by lymphocytes from animals with liver regeneration was able to induce the proliferation and growth of liver cells during the syngeneic transfer to intact animals (Babaeva, 1995; Babaeva et al., 1979, 1982, 1987, 2007).

The transfer of a hyperplastic reaction by lymphocytes is possible, apparently, for any tissue and for any processes, for example, with isoproterenol-induced hypertrophy of the salivary glands of rodents (Dontsov, 1985, 1986), with functional hyperplasia of the heart (Svet-Moldavsky et al., 1974) and other processes, as well as in hypo-plastic reactions and pathological osteopetrosis.

The growth processes of the whole organism are also associated with the immune system. It has long been known that general growth retardation (dwarfism of mice) can be eliminated by transferring lymphocytes from healthy animals, and T-lymphocytes have receptors for the somatotropic hormone and somatostatin, the number of receptors is higher during the growth of animals, and the effect of the hormone appears only in the presence of thymus; somatotropic hormone stimulates the production of thymocyte in dogs and restores the formation of autologous rosettes with thymocytes in hypothyroid rats, while somatostatin inhibits lymphocyte proliferation (Martunenko, Shostak, 1982 Payan et al., 1984).

Based on the idea of the important regulatory role of T-lymphocytes in the cellular growth of somatic tissues, it can be assumed that the system of regulatory T-lymphocytes should arise very early in phylogenesis and be sufficiently complex to manage the various processes of tissue growth, as well as their integration into a single growing system in the process of ontogeny. Based on all the above facts, we have assumed that the function of regulating the cell growth of different somatic cells is phylogenetically more ancient and more important. Actually, this is the evolutionary force that forms the complex system of T-lymphocyte regulators of the proliferation of any cells, including T and B-effectors of immunity, which are phylogenetically later and simpler. In this case, **the immune system is only a part of a more complex and general system for regulating the cellular growth** – the CRP system (Dontsov, 1989, 1990, 2011, 2011).

In particular, we have isolated and characterized such T-growth regulators of various somatic cells of the body, studied their kinetics, peculiarities of the phenotype, the reaction to some pharmacological agents, the selection of regulatory factors specific to somatic cells, etc. (Dontsov, 1990—2019).

Thus, it can be assumed that with aging, the function of T-lymphocytes of the CRP system decreases dramatically as a result of changes in the organism`s regulatory systems. We found a number of such data experimentally and showed the possibility of reactivation and rapid restoration of cell growth potential when exposed to the CRP-system cells (Dontsov, 1990, 2011).

The proposed **new immune theory of aging**, therefore, has not only theoretical interest but also allows you to use the full potential of immunopharmacology to counteract one of the most important mechanisms of aging — the reduction of cellular self-renewal in mammals and humans with age.

We have shown the possibility of restoring the cell tissue growth potential that decreases with age under the influence of Transfer Factor, which gives the right to speak about the likelihood of TF influence on other manifestations of aging. It has been shown that TF is able to reduce biological age, assessed by a variety of parameters, in humans; and correct age-related immunodeficiency with increasing potential of cell growth.

Chapter 1. Methodology and principles of studying the aging phenomenon

1.1. The main methodological errors, myths, and cliches in the general analysis of the problem of aging

The most famous and common is, apparently, a statement from which often popular, and often scientific, lectures on aging often begin.

They say that the general theory of aging does not exist, there are several hundreds of theories of aging, but none of them is true, that you need to create a "correct" theory of aging, which will indicate the unknown cause of aging and abolish aging, leading not only to eternal youth but also to immortality.

In fact, everything here is not true exactly the opposite: the theory of aging exist, it is one, it includes all existing "theories" as special cases – the mechanisms of aging, it is impossible to abolish aging as a general phenomenon of life, but also of Being as a whole, but' eternal youth 'does not mean immortality.

The common cause of aging is known as part of ontogenesis, part of life itself, as a phenomenon of disruptions in the structure and function of the system accumulating with age, as movements from order to chaos (Comfort, 1967; Galimov, 2006; Giaimo, 2014; Gibbs, 1928; Gompertz, 1825; Gladyshev, 2012; Hayflick, 2007; Dontsov, 1990, 1998; Dontsov, Krutko, 2009, 2012, 2016; Krut'ko et al, 2018; Nicolis, 1989).

In general, it is a natural process in nature, since it proceeds with an increase in entropy; in a particular form, this is known as the second law of thermodynamics – the accumulation of chaos in a discrete system.

But the reason is a principle, not a mechanism; it cannot be canceled (like most fundamental reasons); one can only oppose another principle (self-renewal and development).

The desired "eternal youth" would not lead to immortality, since aging is an increase in the probability of death with age, and eternal youth is only the constant (and not zero) probability of death throughout life. Such a situation would only lead to a different principle of extinction of the "ever young" population with a relatively small increase in Average life expectancy (ALE), but with a very large of psycho-social problems.

Indeed, during aging, when the probability of death increases with age by an order of magnitude, the main extinction of the population is drastically shifted to older ages, whereas with "eternal youth" the probability of death is constant throughout life and the average life expectancy (50% survival rate) sharply shifted to the left, which is typical of all systems with a constant stochastic loss of elements, for example, for the radioactive decay of elements.

From demographic data on mortality in developed countries, it is known that life expectancy in them now reaches 80—

85 years or more, that is, the population is guaranteed life expectancy, which is considered by the population as personally expected, “guaranteed” duration of their own lives, about 85—90% of “Maximum” (90—100 years).

On the other hand, the “forever young” ALE would not reach even 15% of the maximum possible life span, and the absolute values of the ALE are not important here since the fundamental mortality curve depends on the principle itself – the immutability of mortality with age ((*Figure 1*)).

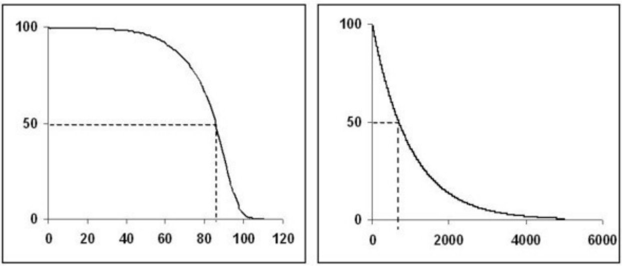


Figure 1. *The probability of mortality of the population for an aging (left) and ageless (right) population. Horizontal – time (years), vertical – the percentage of survivors persons. Average life expectancy is indicated by the vertical dotted line on the horizontal time axis. The probability of mortality of the population: ageless population, for 20-year-olds 0.001% per year.*

Among other myths, it should be mentioned first of all the idea that there is a Maximum life expectancy (MLE) equal to 100-120-140-170 years, etc. (depending on the personal preferences of the authors), and it can be achieved, it is enough just to study the experience and "device" of long-livers.

However, the available fixed maximum life spans are the Record life span (RLS) the exception is that the "tails" of the curves of the normal distribution of signs are impossible for any large part of the population to achieve. Such "tails" are typical for any statistical distribution and can only be oriented on the life expectancy policy. In addition, the MLE, in general, cannot exist as a definite digit: the extinction of a population is a probabilistic law (a curve, not a digit) and there is always some probability of living longer than a given limit. You can only talk about what percentage of the remaining population (and accordingly what percentage of the extinct population) is considered as the basis of the "MLE", which should rather be interpreted as SLE (the species limit of life).

At the same time, a sharp increase in mortality with age leads to the fact that the differences between the life span of the remaining 1%, 0.1%, 0.01% and so on, the populations differ not even by years, but by months, therefore the MLE it is quite adequate to consider the life span of the life span for the remaining 1% or even 5—10% of the population

The notion that mortality is determined only by a specific cause, and by removing specific causes we remove the mortality itself, indefinitely extending the life span – the typical "myth of doctors." This gave rise in the middle of the last century to numerous movements for general improvement. A number of longitudinal studies, however, showed that mortality in such groups, usually focused on the prevention of cardiovascular diseases, as the main cause of death, decreases very slightly, although the mortality from cardiovascular diseases itself is quite pronounced – there is a redistribution of mortality: "Compensatory phenomenon of mortality", with increased mortality from other causes. For a gerontologist biologist, however, it is quite obvious that mortality is the result primarily of a decrease in viability, and causes of mortality are secondary: mortality does not add up as the sum of causes, but decomposes according to them, while the specific causes of death and internal super-strong effects for the body.

The concepts of the relationship between aging and evolutionary processes are widespread (Flatt, Schmidt, 2009; Giaimo, 2014; Hughes, 2010; Kirkwood, Melov, 2011). The myth that aging is evolutionarily important: like the death of old for "opening the road to the young" is a typical myth of non-specialists in the field of evolutionary theory and ecology. It has long been known, however, that in real life with very high mortality to old age, almost no wild animal survives. On the other hand, in many cases, age experience (birds, mammals) or sizes that increase constantly with age (fish) reduce (!), and do not increase, actual mortality under natural conditions. In addition, evolution can only affect the reproductive period, and the older ages are simply “not visible” to it. Evolutionary influences are important in a certain form – evolutionary found mechanisms of maximum adaptation are not required for the period of aging, and if they are important for the maturity period but have “off” or mismatch mechanisms with age and other unfavorable moments, these features will appear in old age as regulatory mechanisms aging (typically – climax).

A whole group of myths is connected with the possibilities of absolute regeneration of all structures of the body or, on the contrary, with the programmed aging and death, which leads to ideas about biological “hours of death” (Kirkwood, Melov, 2011; Afanas’ev, 2010; Olovnikov, 2005; Rando, Chang, 2012; Walker, 2011). This is usually associated with cellular self-renewal: with the fact that cells, on the one hand, have a life limit within them (Hayflick phenomenon), on the other hand, many cells are immortal in culture, and on the third side, only stem cells are immortal and only update all body tissues. In fact, everything here is not true. It has long been shown that the Hayflick phenomenon is a purely cultural phenomenon and only for a limited cell type, with which the author himself had long agreed, preferring now stochastic ideas about the nature of aging (Hayflick, 2007). Cells in culture change over time, mutate and undergo selection, so over time, it is a different culture (this is well known to practitioners who initially work with one type of cells for a long time – the results obtained on cultures of the "same" cells with different groups of scientists are contradictory).

It is known that self-renewal of cells, such as the liver, is primarily due to the liver cells themselves, and not stem cells – this is clearly seen when regenerating it in an experiment, when almost all hepatic cells can enter during the first regenerative mitosis during the day; only when such regeneration is blocked, stem cells begin to be activated in significant quantities – the so-called "oval liver cells" (Strick-Marchand et al., 2008). Stem cells are not immortal – silent stem cells eventually die for purely probabilistic reasons and mechanisms; stem cells that emerged into division form populations that are also depleted over time, some are replaced by other populations. Whether dividing stem cells can go to rest and replenish the silent pool of stem cells, and not only differentiate into more specific, highly differentiated tissue cells, remains little understood. With aging, rather, the active effects of an old organism on the stem and other cells are revealed, which can be seen in systems of syngeneic transfer between young and old animals (Albright, Makinodan, 1976; Gorskaya, 2011).

The notion that there is an "aging program" is another widespread myth (Kirkwood, Melov, 2011; Olovnikov, 2005; Rando, Chang, 2012). It is enough, however, to indicate that they ignore (or rather, do not understand or even do not know) stochastic processes, which naturally direct any systems to decay, and which do not require any special “program” for this. It is easy to understand on the basis of a mechanical analogue: a mechanical machine is created according to the drawings – “according to the program”, but when it starts to be used, the program is completed and its aging goes not according to the program, but according to the stochastic mechanism, due to the law of increasing entropy.

Thus, it is quite clearly seen that the basis of all the myths about aging is the lack of knowledge of scientific methodology and the inability to apply theoretical methods on the one hand, while inflating particulars on the other. As a result of the extreme specialization of the sciences, there are almost no scientists with a broad view – there are narrow specialists who do not see the big picture. On the other hand, there is the issuance of their own desires for scientific truth, as well as abstract reasoning for experimentally verified facts.

In questions about the cause of aging, the main mistake is a lack of understanding of the epistemological (theory of knowledge) fundamentals: the **reason** is not a specific **mechanism**, but a **principle**, another level of problem analysis. For the reason they give out various particular mechanisms, which leads to the “theories” of aging that grow beyond any measure and which do not “see” each other and any other mechanisms of aging.

The lack of systematic thinking does not allow us to see the problem of aging in general, and the lack of consideration of the hierarchy of the structure of the system does not allow us to see a qualitative difference in the manifestations of aging for different levels of organization of living systems.

Modern scientific analysis of the aging process should be carried out at a high level of abstraction, describing aging as a general phenomenon of the world, pointing out the most common mechanisms of aging and discovering fundamental ways of influencing them; should allow a general mathematical idea, the conclusions of which should not contradict the well-established experimental data on aging, in particular, the probability distribution of age-related mortality, and also clearly indicate the main physicochemical and biological mechanisms of aging.

Only for a man the question of prolonging life and preserving the personality, and especially the question of aging as a phenomenon of life, has become urgent. This, in particular, means that a person currently does not obey the laws of biological evolution and opens up to him purely human tasks and prospects for further development, based on the peculiarities of a human being – his intellect and psyche.

The real victory over aging means not the frozen "eternal youth", but its further development in the physical and spiritual sense, controlled by the person himself.

For the level of all mankind – the taking under control of the biological nature of man and its further controlled development on the basis of a fundamentally new, that only man has – his mind and psyche.

1.2. History of views on the aging process

Aging of living organisms is difficult to study in the framework of a single discipline; therefore, this complex process is studied in various fields of science: biochemistry, molecular biology, genetics, demography, mathematics, medicine, and sociology (Anisimov, 2008; Atwood, Bowen, 2011; Burnet, 1970; Comfort, 1988; Babaeva, Zuev, 2007; Chebotarev, 1984; Chernilevsky, 2008; Dean, 1988; Gladyshev, 2012; Bogomolets, 1938; Gavrilov, Gavrilov, 1986; Davydovsky, 1966; Dilman, 1981; Dogel, 1922; Freitas, de Maga-lhães, 2011; Frolkis V.V., Muradjan, Fuente et al., 2011; Giaimo, 2014; Gompertz, 1825; Gorskaya et al., 2011; Harrison et al., 1982; Hayflick, 2007; Hughes, 2010; Jarygun, 2003; Khavinson, Konovalov, 2008; Khalyavkin A.V., Jashin, 2004; Kirkwood, Melov, 2011; Kishkun, 2008; 1967; Korshelt, 1925; Mechnikov, 1908, Nesterenko, 1984; Oliveira et al., 2010; Olovnikov, 2005; Rando, Chang, 2012; Semenkov et al.., 2005; Streler, 1964; 1992; Shabalin, 2005; Shmalgausen, 1926; Sohal, Orr, 2012; van Leeuwen et al., 2010; Veisman, 1914; Vojtenko, Poljuhov, 1986; Walford, 1969; Walker, 2011; Zavadsky, 1923).

General questions of the biology of aging and the specific manifestations of aging in various organisms in evolution are considered, for example, in reviews (Dean, 1988; Flatt, Schmidt, 2009; Freitas, de Magalhães, 2011; Hayflick, 2007; Hughes, 2010; Kirkwood, Melov, 2011; Masoro, Austad, 2011; Sohal, Orr, 2012; Vern et al, 2011; Walford, 1969).

The method of theoretical consideration of the issue is earlier than the experimental one, and no less important, and in some cases even the only possible way to obtain information on the most general laws, causes and essence of the phenomenon.

Gerontology studies the age dynamics of the vitality of the human body, the manifestations of aging at all hierarchical levels – from molecules and cells to organ systems and the whole organism, factors affecting viability, statistical patterns that characterize age-related changes in mortality in populations and in certain groups of the population, having certain differences related to gender, profession, ethnic characteristics, etc., as well as diagnostic methods for the aging of the whole organism and its parts and possible of life and would impact on aging with a view to slowing down and appeals.

The basis of modern scientific views on the essence of life and being in general is the doctrine of development, change, evolution, progress of all things, which, however, was known in ancient times: "Everything is in motion, everything flows, there is no rest and rest" (Heraclitus Ephesus, 480 y.).

One of the oldest explanations of the main cause of aging as a phenomenon inherent in living organisms was the study of the "life force" (Aristotle's "entelechy"), which tends only to be wasted over time for any born organism, the beginnings of life and death. These ideas served as the basis for the development of the whole complex of theories of “wear” of the body – from Mop (1888) and Gertvig (1914), who considered that “the body wears like a machine”, to modern theories of wear their specific material substratum of this “wear” – unique genes, etc..

With the development of modern narrowly specialized science, the criticism of general notions as “idealistic” was replaced by crude materialism, which often reduces the reason, manifested as a general, to its particular specific manifestations.

Not surprisingly, as a result, all theories of aging, based on particular propositions, failed and are recognized only as a description of the mechanisms of aging, but not its root causes. It is impossible not to see the continuity between the term “life force” and the terms “vitality”, which are essential for medicine, biology and gerontology. Similarly, the dual “entelechy” corresponds to the antagonism of catabolism and anabolism, or the opposite of the systemic process of destructive aging and the opposing complex of adaptations and increase in the vitality of the organism.

Interestingly, it is the general idea of the spontaneous loss of “life-ability” that is currently the cornerstone of all scientific gerontology. This idea was, in particular, the basis of the famous B. Gomperz formula (1825), which most accurately describes the mortality of man and, apparently, of most other organisms. Gompertz also noted the similarity of curves of changes in mortality and entropy, and Perks (1932) directly wrote that "the inability to resist destruction has the same nature as energy dissipation" (that is, aging is equivalent to an increase in entropy, which serves as a measure of the disorder of any system).

The well-known biologist of aging, A. Comfort, in his famous, classic classical "Biology of Aging" (1967), explicitly states that the mysterious "entelechy" and "vitality" at the modern level of understanding can be reduced to a fairly specific, though not the real substrate – "at the present time it seems quite probable that the information contained in the cells is that" biological energy", the existence of which was previously assumed and which was thought to be wasted with age".

The fact that entropy for any closed system only increases in time has long been known as the most general law of Being.

Life opposes the flow of entropy, organizing a counter-flow of order, however, effective opposition is possible only if all levels of the system are updated at all levels. For this reason, life as a whole does not age but develops, but by changing all forms – organisms. The organism, being by its nature a "complete" morpho-functional object, can only grow old immediately after cessation of growth and development. This pattern was grasped by many, having formed a number of theories of aging as "continuation of development", "end of growth and development", "consequences of cell differentiation", "restriction growth", "special type of growth restriction", etc. However, these theories lacked methodo-logical completeness – generality, which is due to the lack of an adequate language for describing general processes in general.

In biology, the whole problem of aging is closely related to a number of areas, among which traditionally stands out the theory of reversibility of life processes, which arose on the basis of the study of dedifferentiation and regeneration.

It is about the opposite (in the morphological sense) movement of the processes of development, or reduction. The experiments of L.Vudroff on the reduction of the hydra during the fasting and its new development after the fasting indirectly confirmed the possibility of directional influence on ontogenesis. The zoologist E. Schults wrote about the limitless ability of living matter to reduce and rejuvenate. In studies on the reduction of the body in experiments on planarians and other multicellular animals (1904—1908), E. Schulz believed that this would lead to the reverse development of the organism. However, in later studies of Shaksel, Driesch, Hakslee and others, it was shown that this is not quite the case.

A large series of works on rejuvenation was performed on multicellular animals with good ability to regenerate lost parts of the body. Thus, in the experiments of Korshelt (1925), periodic cutting off of a part of the body in planarians led to the regeneration of lost parts and to a 20-fold prolongation of life (from division to division). Even greater progress was achieved in experiments on unicellular animals. For example, Hartmann (1928), by means of 130 periodic amputations of the body of an amoeba, restrained her from division and thus prolonged life (without division) 65 times.

Many researchers have shown that a number of metabolic disorders and the functions of organs and systems in an aging organism are reversible, which opened the way for research on biostimulation as a separate direction in gerontology. Some preparations of cell and tissue therapy, as well as cytotoxic sera belonging to the group of biological stimulants, have high activity and the ability to slow down the aging process. In order to activate the elements of the connective tissue and the immune system, academician A.A. Bogomolets developed and introduced into the practice of medicine anti-reticular cytotoxic serum in 1938, which is successfully used to slow the aging process. Academician V.P. Filatov proposed a method for obtaining tissue therapy preparations or nonspecific biostimulants from animal and plant tissues.

Closely related to the work on biostimulation research on the effect of stress on aging. Whole theories have been developed that treat aging as "chronic stress." However, it seems to be of greater importance here to study the mechanisms of adaptation, when stress is only one of the stages of adaptation in general. In the creation of complete theories of adaptation, an important role belongs to domestic scientists. Thus, the studies of L.Kh.Garkavi, E.K. Kvakina and M.A. Ukolova (1975, 2002), recognized in the USSR as a discovery, showed the possibility of long-term support, not activation of stress, but biostimulation. It is accompanied not only by recovery from many chronic diseases but also by obvious signs of rejuvenation. The mechanisms of these influences, the authors see in the restructuring of the body's reactivity, and especially in improving immunity.

The important role of the immune system in aging was paid attention to for a long time, in particular, the great Russian immunologist and aging biologist I.I. Mechnikov, however, all attempts to create immune theories of aging and even to find out the specific mechanisms of the influence of immunity on aging until recent years were not consistent. This is all the more strange since the experiment has long been known that it is immunologic drugs that are the most effective geroprotectors and biostimulants, and changes in the organs of immunity (thymus) are the most demonstrative during aging.

Currently, however, Russian scientists have shown fundamentally new mechanisms of influence of immunotropic cells in the body. Studies of A.G. Babayeva awarded recognition as a discovery, showed that T-lymphocytes can directly influence the processes of cell growth and the differentiation of various cells. This was the basis for us to put forward a new immune theory of aging, which directly links involution with the age of the immune system and a sharp decline in cellular self-renewal in tissues with dividing cells (skin, mucous, parenchymal organs). These studies also give hope to use a wide class of immuno-pharmacological agents for the prevention and treatment of aging, which has been empirically proposed for a long time as many bio-activators that simultaneously increase the level of the body's immune defense.

In the last 20—30 years, a great number of researchers worked in the field of gerontology – specialists from very different fields, including physicists, chemists, and others.

Studies by academician N.M. Emanuel marked the beginning of the development of antioxidants for the prevention of aging and bio-stimulation. A modern, extensive complex of creams and other skin care products practically does not do without substances of this group, as well as programs for the prevention of age-related diseases.

Modern anti-aging creams also include liposomes – the result of modern research on the theory and practice of artificial membranes, as well as hyaluronic acid and collagen – the result of traditional research on the aging of connective tissue of a large group of domestic and foreign scientists.

Modern studies on biorhythmology and methods of restoring and harmonizing biorhythms are undoubtedly related to the most ancient practices of acupuncture therapy in China. Modern electroacupuncture methods have proven their effectiveness ("longevity point", etc.) and are waiting for wider use for the purposes of biostimulation and prolonging life.

Unfortunately, a large number of works claiming to discover the "fundamental causes and mechanisms" of aging, now have a purely historical interest. In many cases, these works only confused the essence of the issue, as they were based on particular issues, strengthening them to the general.

So, in fact, all theories that take the main role in aging chemical changes – the "spoilage" of proteins, DNA, colloids, etc. under the influence of cross-links, oxygen, etc., do not take into account the main feature of the living – self-renewal of the organism and cells and cannot explain the accumulation such changes over time.

Similarly, they did not give much either to practice or the theory of gerontologic and general conclusions not related to examining the organism in all its complexity: Rubner's theory, which asserted that the amount of energy processed throughout one kilogram of body weight of different animals equally; theories about the "life hours" and the spending of the "life element" – the enzyme (I.I. Schmalhausen), the gene (L. Scillard), germplasm, differentiated cells and other material non-aging substrate; theories about the origin of aging in evolution as an adaptive mechanism (including the Weismann theory), ignoring the obvious fact of the overwhelming death of wild animals at a young age; general theories about the relationship of aging and development, reducing aging to a specific aging program, including the "death genes" or the programmed number of divisions for each cell (Hayflick's theory), etc.; Carrel's observations, pointing to the "immortality" of dividing cells and not taking into account the principle difference between population cellular phenomena and processes in the whole organism; Minot's ideas, which associate cell differentiation with their death, but ignoring intracellular self-renewal, allowing non-fissile neurocytes to live throughout the whole organism and regulatetorus influences that sharply suppress potential-dividing cells, as well as many other ancient and modern theories. In general, it can be seen that research on the study of specific mechanisms of aging, very extensive and diverse, in most cases quite successfully led to the creation of various methods and means of biostimulation and prevention of individual manifestations of aging.

However, all the claims of researchers of this type to the creation of general theories of aging turned out to be completely untenable. This is not surprising since it is not methodologically correct to reduce the general laws and principles (namely, at this level, the analysis of the essence and cause of aging should be carried out) to separate mechanisms and manifestations – to particular aspects of the complex and diverse phenomenon of aging. The extreme specialization of modern scientists, which has led to just such a result, in recent years has finally been realized that it has stimulated the development of general methods of analysis – the theory of systems, self-organization, cybernetics, synergetics, etc. allow you to see the features of a common single natural theory of aging, to the creation of which all scientists aspired. The rapid development of statistics and demography somewhat overshadowed by the biology of aging, the achievements obtained by specialists in life expectancy biology. Thus, data from radiobiology, largely based on an analysis of the survival rate of irradiated animals, showed the possibility of accelerating natural aging – this is practically the only method that makes it possible to simulate accelerated aging adequate to the natural one. An analysis of historical mortality data allowed us to detect the phenomenon of the historical stability of the age-related component of mortality with a sharp decrease in the background or "external medium" component of mortality, which indicates the possibility of a sharp decrease in mortality due to socio-preventive measures, but denies the possibility of influencing in this way essentially, on the essential, internal processes of aging for the body (Dontsov, 2019).

Comparison of the age-related component of mortality for different regions of the World showed that although for each region they are historically stable, they differ for different regions.

It was mathematics that long ago resolved the dispute about the Maximum life span, as biologists believed, the "ultimate survival age" for organisms, replacing the absolute limit with the probabilistic survival law, as well as radically changing the notion of hereditary longevity, the ability to increase the Maximum life span with disease does not match the essence of aging, etc.

1.3. Methodology of knowledge: three stages, three paradigms

The presence of hundreds of theories of aging to date indicates not only and not so much the lack of a unified theory, general views, or lack of knowledge of the causes and essence of aging, but often a methodological lack of understanding of the subject matter. Although many gerontologists understood the importance of general biological laws (Bogomolets, 1938; Comfort, 1967; Dilman, 1981; Dogel, 1922; Frolkis V.V., Muradjan, 1992; Korshelt, 1925; Streler, 1964; Shmalgausen, 1926; Nagorny A.V., Nikitin V.N., Bulankin, 1963; Vojtenko, Poljuhov, 1986; Zavadsky, 1923), the main attention was drawn to the study of specific mechanisms of aging, issued as a reason. Science in historical development has gone through three stages, and each is characterized by its own general paradigm.

The **first** stage is determinism, which has received its maximum expression, apparently, in Laplace. According to his extreme ideas, know-ledge of the initial conditions uniquely determines everything that follows: knowledge of the initial coordinates and momentum of all particles at the Beginning of the World uniquely determines its picture to the present moment and the future of the World. The main disadvantage of this methodical approach is the mechanism: everything is predetermined by initial conditions, there is no freedom, in fact, there is no place for life, feeling, intelligence, free will and the whole diversity of the real World.

The subsequent development of science has changed this view of the opposite. The **stochastic** vision of the World, most pronounced in probability theory and quantum mechanics, was based on the recognition of a physical law stating that it is impossible to simultaneously and accurately determine the coordinate and momentum – the uncertainty principle in quantum physics. However, the proliferation of global stochasticity as a method from the micro level to the level of complex objects led to another extreme – the general unpredictability of phenomena, which also does not correspond to the state of things.

The development of a **systems approach** brought science out of a methodological crisis, while not discarding what has been achieved. Already one enumeration of its characteristic features, shown below, shows the enormous potential possibilities of a systematic approach – a new, whole world view (Checkland, 1986; Wolfram, 2002, etc.).

1.4. Features of the system approach as a modern universal scientific method of problem analysis

1.4.1. Using a systematic approach to analyze of aging process

Already a short review of the system analysis requirements for the aging phenomenon makes it possible to see a number of crucially important points for analyzing the problem.

The principle of **unity of the whole** requires that a certain integral self-sufficient system be put in the basis of consideration. This means that the full consideration of aging is possible only for the level of the whole organism. Indeed, at the level of populations, the very concept of aging is blurred, as at the level of cells and molecules, when you can get a variety of cultural phenomena and interpret them in an arbitrary way. The importance of the principle of integrity, unity of the organism as a system is also clearly seen in the first experience of heart transplantation: in a couple of years the transplanted young heart was not much different from the old one: aging was directed by the whole organism, and the young part could not preserve its youth in the old organism. The same applies to the transfer of young stem cells to the old organism and vice versa: old cells retain their potencies and can manifest them in a young organism, while young cells reduce their abilities in the old organism (Albright., Makinodan,1976; Gorskaya et al., 2011) – the determining role of the microenvironment and external influences on the state of cells.

Considering the **reality of universal interrelationships** is all the more important since aging is a long-lasting process. At the same time, small changes and "side" for the main consideration of the reaction are decisive. So, besides the reactions directed by enzymes studied in biochemistry, all possible physicochemical processes in biological systems actually take place, which forms the basis of the aging processes in the form of "contamination" with secondary metabolites. Similarly, the universality of interrelations means a really huge number of influences on a real-life system and determines its fundamental vulnerability: the mortality of a particular system cannot be zero and even an "eternally young" organism will not be immortal – the stochastic mechanism of mortality. The same, when applied to specific internal structures, reveals the stochastic mechanism of system aging.

The idea that **parts of a whole are not separate entities**, but units of division of a fundamentally different type (entity-in-relationship) allows us to apply analysis methods at the abstract level and consider the real structure by considering the essential relationships of structural parts, which also applies to weakly structured systems (for example, metabolism for living organisms).

The most important position on the transition from the analysis of equilibrium states to the analysis of **nonequilibrium, irreversible states** (super) complex systems allows us to understand the fundamental unidirectionality of the aging phenomenon, to look for the presence of fundamentally irreducible phenomena that determine movement in one direction only.

The position of the system analysis that there is no entity, meaning and structure of an object outside of **evolution**, requires to consider the entire period of ontogenesis as a single whole, and not aging as a process that is separated from the development of the whole organism, needs to look for an association of aging with processes of growth and development of the body. In addition, the evolution of the living provides a vivid example of the evolution of the forms of aging and the possibilities of influencing it, as well as the dependence of such forms and influences on the specific structure of the living system of one or another level of complexity.

The principle of the consideration **hierarchy** actually reflects the different level of the real structure of the object, the presence of separate organs and systems with a special structure and function, which determines its particular mechanisms of aging for molecules, cells, organs, systems of the body and the whole organism with its common regulatory systems.

Finally, it is important to understand the essence of the phenomenon, which is considered as an ideal law that determines the appearance of the phenomenon, its functioning and evolution in the hierarchy of interrelationships of the whole.

This idea makes it possible to move away from considering the many specific mechanisms of aging to its cause, as an **ideal principle** and the essence of aging, and also to understand how the general principle is implemented by specific mechanisms. This is one of the stumbling blocks in modern gerontology, in which many open mechanisms of aging are given for a reason, which has already spawned hundreds of "theories" of aging.

The sticking point remains the question of the cause and nature of the phenomenon of aging, also solved by system analysis.

1.4.2. General methodology about the cause of phenomena

When one speaks of a single natural theory of aging, it is quite clear that it must answer a number of central questions:

– the time of appearance of aging in evolution;

– whether aging is a general law of nature or a private mechanism for the existence of individual forms of the living;

– what are the essence and the fundamental, common cause of aging;

– what are the general laws and particular types and mechanisms of the manifestation of aging;

– what are the fundamental features of human aging;

– what are the general perspectives and ways to overcome aging as a natural phenomenon;

– what are the specific approaches to the effects on the main types and mechanisms of aging;

– the importance of aging in general, the general way to overcome it, and the peculiarities of this task in humans.

One of the central issues in the consideration of aging as a global phenomenon is the question of the primary cause and the deep, fundamental nature of aging.

Regarding the general methodology for the consideration of the issue, it should be said that it was known in ancient times – Platon developed it in the most complete form. The leading contemporary philosopher-methodologist A.F. Losev formulates the most important provisions for us as follows: "Current experience gives us an idea only of flowing and scattered bodies and events, in which neither beginning nor end is seen and whose meaning remains vague due to its fluidity, very often incomprehensible and blind… And since the scientific understanding of a thing requires the final disclosure of its meaning, then the theory of ideas arises as ultimately developed communities.". A full-fledged scientific analysis is characterized as follows: "To understand and correct components is necessary through the whole… The idea is the ultimate community, has a structure and is meaningfully filled, respectively has it's own specific (own) … already purely ideal objectivity and reality… this limiting community manifests itself in its particular, in a semantic way, never moving beyond its limits… The essence (of something) is interpreted as a principle of structure…".

Thus, it is clear that the essence, the cause of aging can be expressed only in the language of high-level abstraction as an objective pattern of life, being, as a principle, but not at all as a process, much less as a specific special mechanism in the body. The reduction of principles to mechanisms is the main methodological error in the natural sciences, including in gerontology. It is quite clear that when defining the term "aging", the definition of the principle of aging as a phenomenon turns out to be necessary and sufficient, which has been known and understood for a long time: aging is a decrease in viability with age, or an increase in the probability of death with time, or, more, in general terms, it can be said that aging is an increase in the degree of chaos at all structural levels of the organism, which is manifested by a general decrease in the body's resistance to all factors and is recorded as an increase in the probability of death from all causes of aging.

The definition reveals the very essence of the phenomenon of aging, which acts as a global, fundamental cause of aging because the cause of the accumulation of chaos (entropy) in closed systems has long been known: it is a law of nature, known in particular as the second law of thermo-dynamics. Now the interpretation of this law has significantly expanded and deepened in connection with its extension to information processes.

In biology and mathematics, the most interesting are modern trends: theories of self-organization, theories of open systems, describing the generation of information, its relationship with chaos, the role of energy in this process, etc.

The applicability of the second law of thermodynamics to living systems is related to the fact that they are only partially open systems: in any modern complex organism, there are structures that are not updated inside the organism – cells, molecules, organelles, organs, etc. Thus, the fundamental reason for the aging of any complex systems is the discreteness of the forms of existence of modern organisms on Earth – separation from the external environment, which puts a limit on the capacity for the internal evolution of an organism while preserving its quality as a separate system. In general, this is known as the inevitability of the accumulation of chaos in any partially open system limited from the external environment with time.

The self-renewability of a living system within itself is not a sufficient factor in counteracting aging in general, since it is possible to counteract the second law of thermodynamics only due to external influences on the system and these influences essentially lead to evolution, and not to stabilize any system.

1.4.3. Aging Hierarchy

The most important approach to the analysis in a systemic examination is to take into account the hierarchy of the structures of real complex systems. At the same time, system analysis requires consideration of principles characteristic of each hierarchical level.

Such a hierarchy of consideration in system analysis reflects not the material structure of the object that morphological sciences study, but a hierarchy of essential principles reflecting the laws of functioning and communication within and between the structural levels of the object being considered, which acts as a complex hierarchical dynamic system.

The following table gives an idea of the hierarchy of aging in terms of a systematic approach (*Table 1*).

Level	Level entity	Importance of aging problem	Impact accessibility
Cause of aging	Essential description, principle	Defines a fundamental opportunity to affect aging.	Not available in essence: the general, ideal essence of the cause of phenomena
Types of aging	General description of the cause as an evolution of the system	Defines a finite number of different types of changes with aging.	Impact acts as a description of common pathways and effects on aging.
Synd-romes of aging	General description of interrelated groups of mechanisms	Defines mutually-recognized change groups during aging.	Impact is described as complex groups of interrelated methods.
Mec-hani-sms of aging	Specific manifestation s of aging mechanisms	Defines an infinite variety of specific mechanisms of aging of molecules, cells, organs, and tissues.	It is described as a separate method of influence on a separate mechanism of aging.

Table 1. The hierarchy of consideration of aging in terms of a systematic approach

Three hierarchical levels of aging description are fundamentally ideal and are available only for theoretical analysis.

The last level is structural and its study is possible only when it is filled with biological content. With this consideration, it can be seen that the primary cause, as a principle, is manifested by several of the most common patterns – the types of aging inherent in all living systems. These types, in turn, form a number of interrelated groups of symptoms – aging syndromes, which already include specific manifestations of aging at the level of specific mechanisms that implement aging depending on specific conditions.

The systematic consideration of aging is also manifested in the fact that in each specific manifestation, the mechanism of aging, you can see all four levels mentioned above: a reflection of the ideal cause in specific conditions; relation to a greater extent to a certain type of aging; regular relationship at the level of mechanisms with other symptoms (*syndromes*); and, finally, the actual concrete actual manifestation of aging for the phenomenon under study in a specific case for a specific structure. Naturally, the more specific and narrow the phenomenon we study, the more specific, but more narrowly, the cause of aging manifests itself.

For the whole organism, aging as a whole can be sufficiently fully characterized only with the use of all four hierarchical levels of its presentation. An important and traditional is the structural consideration of the body or its individual elements.

Here again, the system approach allows revealing the moments obscured by usual consideration.

The dynamic view of the phenomenon under consideration indicates that living systems exist only as a stream, where continuity is preserved, but not always the entire real material structure. Processes in a living system occur at different time levels. So, at the metabolic level, these are (micro) seconds of biochemical reactions during which specific molecules exist; for cells, these are hours and days during which they are divided (cell cycle); for the whole organism, these are years, decades and even centuries.

Each level can have representation at a higher level with some of its structural elements (non-updated genes – at the cell level, non-dividing cells – at the suborgan level, etc.), then these lower-level elements become important for higher-level aging.

Each level is updated at the expense of a higher level, which reduces the absolute significance of the lowest level for aging higher (for example, cell growth and division sharply reduce the importance of aging or damage at the molecular level).

Each level is qualitatively different in structure and principles of organization and functioning.

All levels constitute a single whole, its change, in the final analysis, is only important as the aging of the organism is the aging of the whole.

Thus, consideration of the system analysis requirements for the aging phenomenon makes it possible to see the fundamentally important points of the problem analysis.

The most important is the ability to solve a number of central problems in gerontology in general, which allows to determine the common cause of aging systems and biological systems in particular, the main mechanisms for the manifestation of the common cause of aging, as well as the ways of manifestation of these common mechanisms of aging.

It is possible to identify the main properties of the biological system, which lead directly to its aging, to evaluate ways of influencing the aging of the organism and individual organs, systems, tissues and cells, as well as to clearly understand the prospects for such effects, their points of application and possible efficiency, as well as the fundamental The limited nature of these or other effects, the limits of their application and the ability to influence the aging of the whole organism.

The use of systems analysis puts gerontology as a science of aging on a clear methodological basis, leads it away from many circulating myths that are now replacing the general picture of aging and clear scientific views on it in gerontology.

System analysis in the first place allows you to move from the infinite consideration of particular views and mechanisms of aging to the consideration of the laws and principles that act during the aging of living systems, which just determines both the fundamentally possible main mechanisms of aging and the possible effects on it as well as the ultimate perspectives of such opportunities.

Thus, the use of the provisions of system analysis allows us to understand much in the problem of aging already at the level of abstract analysis.

1.5. Essential modeling – the basis of understanding the phenomenon of aging

The creation of theoretical models of the process under study is the most important element of knowledge, therefore this issue is given central attention in any modern field of science.

Gerontology in this regard is experiencing a crisis related to the fact that the old principles of creating conceptual models of aging, essentially reducing to the absolutization of certain observable phenomena and particular mechanisms of aging, have collapsed. All the so-called theories of aging, which now number hundreds already, have proved to be untenable in explaining the fundamental basis of aging and in many respects are only of historical interest.

On the other hand, a number of purely mathematical approaches to the modeling of aging does not meet with interest and recognition among biologists, since even with the most superficial study one can see biologically unjustified and in fact incorrect initial prerequisites of the models.

So, for example, fashionable environmental and evolutionary mathematical theories of aging, based on the idea of "expediency of aging" as a mechanism for the accelerated renewal of the species, ignore the obvious fact of high natural mortality in the wild when old animals are virtually absent in the population and almost all animals die young.

At the same time, there is an urgent need for a clear general view of the phenomenon of aging in general, using models that allow one to quantitatively and meaningfully interpret the aging of organisms. At present, one of the most important tasks of gerontology is the rather detailed development of essential models of aging, reflecting the very essence of this common to all living phenomenon and being biologically based and biologically meaningful.

Essential models must meet the following requirements:

– a clear understanding of the biological content of each element being modeled;

– a clear understanding of the biological significance of the results obtained in the simulation;

– a clear idea of the place of the model in the system hierarchy of aging processes (which part of the more general process is described);

– consideration of external factors that fundamentally affect the process being modeled.

Chapter 2. Theoretical approaches to the study of aging phenomenon

2.1. Essential definition and cause of aging

The **essence** of anything in philosophy is interpreted as the **principle** of structure. Thus, the essence or the essential, the main reason for aging can be expressed only in the language of high-level abstraction as an objective pattern of life, General Being, as a principle, but not at all as a process, much less as a specific special mechanism in the body. Such an essential definition of a global phenomenon, Aging has been known since antiquity – as a reduction in vitality with age. The current general definition of aging as a reduction in overall vitality with age actually does not differ from this in any way.

This definition is necessary and sufficient for a quantitative description of aging and clarification of the causes and main mechanisms of the aging process of organisms and its systems.

In its most general form, viability is the maintenance of structure and function – that is, the preservation of the identity (information) of a complex system (organism) over time.

The spontaneous direction of information change with time is closely connected in the global sense with the most general law of Being – the law of increasing entropy. Entropy and information are related, as is well known, by the following *formula* (1):

$$E = A * Ln W + B, (1)$$

where E is entropy, W is the probability of an event, A and B are coefficients.

That is, the "natural" probability of the direction of (bio) chemical (and any!) events in time leads to the achievement of chaos as the most probable event (no longer changing), which is known as the 2-nd law of thermodynamics. The mechanism of such a path (the global mechanism of entropy) is a random process.

It is known that resist chaos can only be an external flow of energy. This flow of energy is a metabolism that forms the very basis of life as a biological form of existence of matter.

2.2. Chaos and order processes, entropy and energy

Entropy and external energy are two opposing forces, responsible both for destruction and for self-organization and change of separate, both simple and most complex systems, including organisms. Most fully these processes are considered in this section of science, as thermodynamics. Its application is possible in the study of idealized equilibrium systems, as well as in the study of real quasi-isolated or quasi-closed systems and quasi-equilibrium processes. In addition, it may be applicable when studying the processes occurring in complex open systems. It is important to understand that in reality, in any system, all possible processes actually take place, which are real and should be considered when it comes to very long periods of time and very complex systems. System analysis, as a modern scientific methodology, is precisely capable of doing this.

The processes of chaos, together with the arrival of external energy, form the whole multitude of nonlinear, developing, dynamic self-organizing systems of the most diverse nature – physical, chemical, and biological. Even B. Gomperts (1825) noted the similarity of the curves of changes in mortality and entropy. It has long been clear that the inability to resist destruction has the same nature as energy dissipation (that is, aging is equivalent to an increase in entropy, which serves as a measure of the disorder of any system), and the well-known biologist of aging A. Comfort directly writes that "Entelechy" and "vitality" are information contained in a cell, which is "biological energy".

The relationship of order and chaos can be represented in the form of a general scheme, reflected in *Figure 2*.

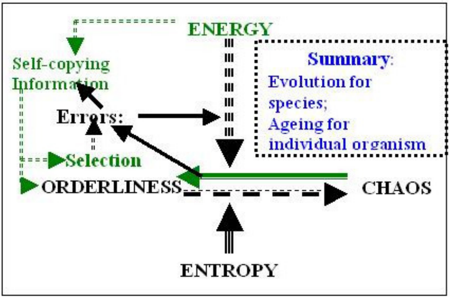


Figure 2. The relationship between the processes of order and chaos.

In general, the processes of disintegration of any system are guided by the law of increasing entropy in the course of naturally occurring processes, which leads to an increase in chaos and a decrease in order in the system. The only way to resist the processes of entropy accumulation is external energy. External energy is necessary to obtain an order from chaos, but it operates under specific conditions, according to a specific plan, based on information from biological systems (development based on the organism's genetics), and by self-copying of existing biomolecules and biostructures.

The order (structure) of the system spontaneously (according to the law of increasing entropy) turns into chaos. This is opposed by the external energy, based on information (internal to the biological system) restoring the order (structure) of the system (by self-copying). Entropia also distorts this process, leading to errors. Errors of the (self) recovery of the system are controlled by selection: external and internal (by the immune system, etc.). The result is a constant dynamic process that ensures not only the constant preservation of the system, but its dynamic equilibrium and, if necessary, evolution.

Entropy counteracts this process through errors that inevitably manifest themselves at all and at all levels of system organization. Errors are confronted by selection (natural selection for the species and the immune and other mechanisms inside the body), however, the selection is also subject to inevitable errors and provides only material for the evolution of the system (organism).

In practice, it is impossible to achieve infinite evolution and complication within the organism, as is the case for species and the entire biosphere. In addition, due to the very existence of the organism as a separate system, the organism is fundamentally mortal, and selection and evolution do not have enough time and necessity (as well as opportunities) to form an ageless organism in which all errors are fully compensated inside it and full evolution and further infinite development occur. In fact, the inevitable accumulation of errors, cessation of development and reduction of orderliness in general, which is the aging of living organisms. The most important general point is that the very existence of the system is not stationarity and immutability, but a dynamic process that is in equilibrium with the external environment.

The decrease in the general metabolism known with age, the decrease in the reactivity and stability of the organism can be interpreted unambiguously as a decrease in the "openness" of the system, its renewability, and connection with the external environment. At the biochemical level, an increase in entropy is also manifested in a decrease in the orderliness of the network of metabolism, a decrease in the level of exchange of macromolecules (DNA repair in the first place), the accumulation of "errors" (including mutations), a decrease in "active protoplasm", etc.

A reduction in "active protoplasm" can be clearly measured as the degree of sclerosis and calcium accumulation in tissues, as a decrease in tissue respiration and the level of protein and DNA synthesis, as well as by the content of total and intracellular water and by the level of bound water – the degree of hydration of molecules, etc.

Thus, it can be seen that the general concepts of entropy as a very abstract indicator directly result in a whole series of manifestations, the meaning of which age changes can be clearly understood only taking into account the theoretical concepts of the essence, meaning and general cause of the aging phenomenon.

Repair of both inanimate and living systems is possible and really happens in a unique way – by replacing old structures with new ones. In organisms, all levels of their organization are updated: at the molecular level (metabolism); at the intracellular level, subcellular structures; at the level of cell populations – cell division; at the level of supra-cellular populations (nephrons, alveoli, etc.); at the level of regeneration of organs and tissues (regeneration itself – axolotl tail, etc.).

The higher the level of structure and organization, the less the possibility of full recovery. There are completely non-renewable (except for metabolism) organisms, for example, Drosophila, which, being postmitotic organisms, do not have dividing cells, their lifespan is determined and very small, aging as a process is expressed and occurs entirely in stochastic whose type is random cell death and supra-cellular structures. In contrast, there are fully renewed organisms: the hydra has no non-renewable cells, their aging is not pronounced, and the life expectancy is not determined.

2.3. The basic formula and the basic law of aging

The first mathematical model of aging was created almost 200 years ago by B. Gompertz (1825) and still most accurately describes the age dynamics of human mortality and, apparently, of most other organisms. As a specialist in life insurance, Gompertz theoretically derived the practically necessary formula for increasing his mortality rate with age, which until now has been the most common quantitative description of aging itself.

Mortality, as "quantitative characterization of the inability to resist destruction," can now be viewed as the reciprocal of vitality – the ability to withstand the totality of destructive processes.

A simple assumption about the stochasticity of the aging process is enough: the viability over time decreases in proportion to itself at each time point (*formula 2*) in order to obtain the basic law of aging: mortality increases with age by the exponent (*formula 3*). Such a nonspecific increase in the body's vulnerability to all influences with age is called aging itself.

$$d X / d t = - k X, (2)$$

where k is a coefficient, X is viability, t is time.

Considering the mortality (μ) as an inverse viability value ($\mu = 1 / X$), the basic *formula (3)* is obtained from *formula (2)* aging (B. Gompertz and W. Makekem) – with age, the overall mortality increases exponentially:

$$\mu = Ro \exp(\alpha t) + A, (3)$$

where *Ro* is the initial mortality rate, α is the rate of increase in mortality, *A* is the coefficient characterizing the contribution of external influences to mortality, the effect of which weakly depends on age.

The approach to writing formula is now theoretically clear: it is an elementary differential equation that describes, for example, radioactive decay in physics and other simple probabilistic processes. The essence of the phenomenon lies in the fact that at each moment in time the state change does not depend on the prehistory, but only on the present state of the system.

The general mechanisms of such processes are also clear – these are principally probabilistic regularities associated with the ultimate stability of any elements delimited from the external environment; then a complex organism consisting of such elementary units can only lose them over time. The main issue is then the nature of such "elementary units of life."

Gomperz himself noted the similarity of the curves of changes in mortality and entropy, and V. Perks (1932) directly wrote that "the inability to resist destruction has the same nature as energy dissipation" (that is, aging is equivalent to an increase in entropy, which serves as a measure of disorder any system); A. Comfort (1967) writes that viability can be reduced to a rather specific, though not material, substrate – information in cells, which is "just biological energy".

Thus, the meaningful interpretation of the concept of "viability" was reduced from the very beginning, and is reduced now, not so much to the material content, but to the energy and information content – to the "entelechy" of the ancients.

For a population of animals or a human cohort, by definition:

$$\mu = dN(t) / N(t),$$

where $N(t)$ is the number of members of an endangered population at time t. By integrating the Gompertz-Makema equation, one can obtain a direct formula for calculating the number of survivors of a certain age (*formula 4*):

$$N(t) = N_o exp((-A\, t - R_o/\alpha\, (exp(\alpha\, t) - 1)) \quad (4)$$

The qualitative view of the survival, mortality and survival curves corresponding to the formulas presented above corresponds to the real survival curves of various human populations, as well as a number of other species. However, the Gompertz-Makema formula describes only the middle part of the mortality intensity curve, whereas the initial part of the curve (growth and development processes – up to 20—25 years) and the final part (older than 80—90 years, individuals with hereditary longevity) cannot be taken into account in this way.

The full mortality curve, which takes into account the period of growth and development and hereditary longevity, can be obtained from the systemic stochastic-regulatory theory of aging discussed below and proposed by us earlier (Dontsov, 1990, 2012, 2017).

The general reason for allowing entropy to work in any system is the principle delimitation of this system from the external one, which does not allow it to fully renew itself and puts a limit to its existence as a separate system.

Similarly, the global cause of aging is the discreteness of the existence of life in the form of individual forms – living organisms, their fundamental limitations (limits of adaptation of all homeostasis mechanisms) in comparison with the almost infinite variety of influences on each particular organism of the rest of the World. The quantitative and qualitative infinity of the effects of the World on a discrete organism can only partially be compensated by homeostasis, which leads to the accumulation of uncompensated damage – the most common mechanism of aging.

Self-renewal of an organism at all its levels is not a sufficient anti-aging factor since the self-renewal process itself is not absolute and has the same random mechanisms.

Some obvious and experimentally and demographically confirmed conclusions are interesting, however, sometimes paradoxically sounding. So from the above, it is obvious that the greatest absolute decrease in viability can be observed at an early age, which we can see from the curves of changes in the ontogenesis of the absolute value of many physiological functions. This means that prevention of aging should begin at the earliest ages. At the same time, in old age, even small absolute changes in viability lead to pronounced changes in mortality, so at older ages, it is convenient to study the effects of adaptogens and biostimulants, although a small vital resource may not lead to a significant increase in life expectancy.

The mathematical analysis of the theories of aging, based on the modeling of its essence – the age-related decline in overall viability, turned out to be surprisingly fruitful and suitable both for objectives of theoretical research and for practical research in population gerontology. At the same time, the common cause of aging is manifested by some general mechanisms that should be modeled and evaluated for their contribution to the overall aging of the system.

Another approach to the quantitative assessment of aging, based on the same definition – reducing overall viability with age, is to consider the overall viability of the system as an integral of the viability of its parts, which, as applied to the body, means that the overall viability of the body consists of maintaining vitality (functional resource) of its main organs and systems (*formula* 5).

$$X = k_1 x_1 + k_2 x_2 + \ldots + k_n x_n \quad (5)$$

where *k* is the coefficient, *x1* … *n* is the viability of organs and systems.

The definition of individual aging as a biological age is based on this.

2.4. Basic global mechanisms: types of aging

2.4.1. The main common mechanisms are types of aging

System analysis allows us to consider aging from several global points of view, thereby revealing the fundamental, general, global mechanisms or types of aging, as a reflection of fundamentally unidirectional common processes of aging.

Although the specific mechanisms of aging for different types of tissues and organisms can be quite different, all of them can be grouped into 2 groups that are essentially homogeneous according to the global mechanism, resulting from the global cause of aging – the law of increasing entropy in some incompletely open systems, and also from counteraction by biological systems – processes of regulation of growth and development of a biosystem.

Existing theories of aging focus on several hundred specific mechanisms of aging. However, attentive analysis of these mechanisms and essential modeling of the aging process ((Dontsov, 1990; 2011; 2017; Gompertz, 1825; Hayflick, 2007; Murphy, Partridge, 2008; Vern et al., 2009: van Leeuwen et al., 2010; Walker, 2011; Kirkwood, Melov, 2011; Masoro, Austad, 2011; Rando, Chang, 2012), as well as consideration of the aging phenomenon given in previous publications, allow us to group these mechanisms into a small number of classes – general aging mechanisms and in general can only be theoretically reduced to stochastic and regulatory types of aging, while for biological systems the stochastic type appears as a probabilistic death of non-renewable elements, as well as a "contamination" of the system by external intoxes ikantami and internal metabolites.

Thus, if there is one common cause of aging, there are 2 types of aging and 3 main, fundamental mechanisms of aging.

2.4.2. Stochastic dependent death non-elements of the system

A fully formed organism has many non-updated elements at all its hierarchical levels: unique genes, non-dividing cells (for example, nerve cells, including autonomic control centers), non-regenerating structures of organs (alveoli, nephrons, etc.), organs themselves and etc.

The loss of these elements with age is probabilistic, and therefore in the simplest case, it is described by the same type of formula as the loss of overall viability:

$$dX / dt = -k * X,$$

where X is the number of non-updated elements of the body.

Graphs of total aging (mortality) for Gompertz and mortality associated with a decrease in viability due to the loss of non-renewable elements, therefore, should coincide and is exponent.

It is known that the loss of alveoli, nephrons with age, reaches 50%, and that of nerve cells in the hypothalamic regulatory centers – 80% (which links this mechanism with the regulatory mechanism of aging). In nature, the stochastic mechanism of aging is fully realized in postmitotic animals (for example, in Drosophila), in which there are practically only non-updated structural units.

The death of elements is the extreme expression of the mechanism mentioned, which, in general terms, leads to changes in the elements of any system. With age, individual structures in the body can not only die, but also change due to accumulating micro- and macro- damage, or change the structure and function of adaptation.

Due to the non-ideal selection mechanisms and self-renewal of such structures in the body, these structures accumulate with age (increase in the number of old, incapacitated cells in all organs and tissues, degeneration, accumulation of mutations in the genome, decrease in the number and quality of sperm cells, accumulation of sclerotic elements in tissues, etc.); the functions of such structures are usually reduced. The accumulation of damaged elements is probabilistic in nature; therefore, the decrease in the number of normal, intact elements with age is described by the same type of formula as the Gompertz formula for loss of general viability.

The main role in the elimination of damage is played by the mechanism of cell division, therefore the deterioration of this process manifests itself morphologically in the form of a wide variety of tissue changes – changes in the forms and sizes of subunits, atrophy, hypertrophy of functional tissue, replacement with nonfunctional connective tissue elements, etc. This is the basis of an increase in morphological (and functional) diversity at the tissue level observed with age and a decrease in their functions. This mechanism underlies such a typical aging phenomenon as atrophy of tissues consisting of constantly self-renewing cells (for example, skin).

2.4.3. Stochastic dependent cumulative mechanism of aging

The most common mechanism for confronting entropy is the flow of energy from the outside, which is carried out for all living organisms through the processes of nutrition and respiration – metabolism. These processes cannot be perfect, therefore inevitably there should be "production waste" – unworkable ballast molecules and harmful toxic substances, the removal of which from the body in principle cannot be 100% ideal process, as a result of which "pollution" inevitably accumulates in the body.

Harmful elements contained in food, in inhaled air, in information flows (exotoxins) also contribute to this process.

The result is age-accumulated pollution, by which it is generally necessary to understand the interfering, non-functional and toxic elements of different nature.

Examples of this mechanism can serve in the general case: toxins and heavy metals associated with tissues; scars from old wounds and inflammatory processes; chronic infections; cholesterol plaques on vessels; not functioning protein complexes in cells, lipofuscin in nerve cells, osteochondrosis phenomena; effects of mental injury, etc.

The change with age of the flow of matter and energy through the organisms can be estimated from the level of metabolism. It is known that basal metabolism decreases with the age of about 10%.

Apparently, this mechanism is not leading, it is possible, however, that it can make a significant contribution in the later stages of life.

This is known, for example, for beetles – the accumulation of “contaminations” in the yellow body is critical for them at the end of life.

In humans, it is known to use enterosorbents in order to counteract this mechanism, which leads to an increase in real life expectancy of 5—7 years. Apparently, this is the real contribution of this mechanism to human aging.

Most importantly, the use of agents that oppose this mechanism seems to be for nerve cells, which in old age turn out to be filled with lymphuscin up to 70% of their volume. Centrofenoxin, which reduces its quantity, at the same time has a pronounced psychostimulating effect.

2.4.4. Regulatory aging

Growth and development are integral parts of life. The main mechanism of programmed regulation at the stage of organism formation is known: usually, a decrease in the function of suppressor cells leads to disinhibition of stimulating cells producing a regulatory factor. Nervous regulatory cells are concentrated primarily in the autonomic regulatory centers of the hypothalamus, in the nuclei of which the death of up to 80% of these cells is observed with age. The disinhibition of stimulating cells gives a constant growing gradient of a regulating factor with a maximum when the inhibitory population is completely disabled. Such a gradient, for example, of sex hormones (the final factors that realize the regulation for a given function) leads to the inclusion of puberty. If we assume that regulatory cells wear out with age, die in a random, probabilistic manner and do not resume, then it is easy to see that the age dynamics of these cells and the final regulatory factor can produce complex dynamics responsible for growth and development and for the subsequent period of aging.

We have proposed a general model of such regulation, which consists in disinhibition of stimulating cells when inhibiting death, which determines growth and development, but if death also affects stimulating regulatory cells, then over time the development program is depleted – regulatory aging develops

(Dontsov, 1990, 2011, 2017). Interestingly, this is essentially the only and very simple model that describes changes in viability (and mortality as a quantitative criterion of aging in general) during all periods of an organism's life. The latter suggests that regulatory mechanisms may play a crucial role in the aging process of the organism as a whole; while the remaining 3 common mechanisms of aging contribute to the last years of life and against the background of already developed pronounced regulatory changes.

Given the fact that the body has enough long-lived non-dividing nerve cells in other parts of the brain, we can speak about the fundamental possibility of a sharp slowdown in aging by replacing (transplant) quickly dying regulatory cells by long-lived or young, by reducing their death, pharmacologic stimulation, hypnosis, etc. Known since antiquity techniques of yoga, associated with psychopathy and activation of the lower-back parts of the brain.

Typical mechanisms of regulatory changes associated with aging in humans are — the end of growth (growth hormone) and development (sex hormones, menopause), immunity involution (epiphys hormones), changes in the insular system (latent diabetes of the elderly), etc., however, the main question remains — what is the main regulatory mechanism closely related to aging.

The most important mechanism to resist aging is, as noted above, cell division, which alone is capable of fully resisting all four common mechanisms of aging; its slowdown is critical for the manifestation of aging of self-renewing tissues, which are in the majority of mammals.

Therefore, the reduction of growth factors for self-renewing cells and the power of other regulatory systems of cell growth (including depletion and change in stem cell activity) is, in our opinion, the most important mechanism for the realization of aging in many species and in humans as well.

We have therefore developed an immuno-regulatory theory of aging (here "theory" is understood in the narrow sense as an important mechanism of aging), showing that age-related immune deficiency (as a result of central regulatory changes) affects the regulation of cellular growth of somatic tissues, being the most important mechanism for the aging of mammals in general and humans in particular (Dontsov, 1990, 2011, 2017).

In addition, regulatory mechanisms are important in connection with the end of growth and development programs, with which climax processes and associated osteoporosis are associated.

Replacement therapy with sex hormones, which was widely used at one time in developed countries, sharply reduced the severity of osteoporosis in women, alleviating the symptoms of menopause.

However, the side effects caused by the increased incidence of tumors led to the need to drastically limit such therapy.

This indicates that the body is aging as an integral system and influences individual mechanisms has either a small effect or even leads to pathology. Indeed, an increase in cell growth against the background of reduced immunity will only lead to an increase in the frequency of tumors.

2.4.5. The relationship of the main mechanisms of aging

The main mechanisms of aging, being the general directions for the implementation of a common single cause of aging, are already manifested by private mechanisms of aging, which can be grouped together according to similar mechanisms, representing general aging syndromes. The development of the syndrome itself in the body occurs according to general laws, regardless of the cause that caused them, therefore the syndromes that develop with aging are a convenient point of application of the effects of anti-aging agents.

Different mechanisms of aging are interconnected not only vertically, which realizes the common cause of aging depending on the specific conditions of its manifestation in various organs and tissues, but also horizontally – among themselves.

So, all three main mechanisms of aging are related to each other, affecting each other in one degree or another.

Consideration of the biological meaning of the main mechanisms of aging leads to the obvious conclusion that the data of the mechanisms inevitably interact with each other in the whole organism – they influence each other, interpenetrate each other:

– "pollution" reduces the stability of the elements, increasing the likelihood of their damage and death, reduces the efficiency of functioning, including the elements of regulation in the neuro-vegetative centers;

– the death of elements reduces the cleaning efficiency (including from damaged elements) and the number of regulatory elements;

– regulation that stimulates proliferation and renewal is, in fact, the main mechanism resisting pollution ("diluting" with rapidly growing new bioplasm), death and damage (adaptive influences). At the same time, impaired regulation is critical for overall adaptability and resistance of the body during aging.

Note that in the final analysis, the most important is the stochastic mechanism of aging, which implements the main aging process – the damage and death of the main structural units of the body.

This scheme can be mathematically calculated and opens up possibilities for modeling and forecasting external influences on the main aging processes in an experiment.

Chapter 3. Modeling the phenomenon and mechanisms of aging

3.1. Mechanical model of system aging

3.1.1. An example of a mechanical model of aging systems

Aging is a common property of both living and non-living systems and is the wear, degradation, reduction of the order, structure, and function of a complex system. The aging phenomenon is easily amenable to theoretical analysis using modern scientific methodology – the theory of systems (Checkland, 1986; Nicolis, 1989; Prigogine, 1960, etc.).

The basic patterns and the very cause of aging are clearly seen in the example of a mechanical model, for which it suffices to take an auto-car as a specific example of a mechanical system. In this case, it is quite clear that the general reason for the system's self-change from order to chaos is known; it is one – the natural direction of change sets the law of increasing entropy for naturally occurring reactions in nature for any systems.

This is the reason, as well as the main mechanism – the stochastic aging of the system.

Many different natural influences on such a mechanical system in a random way (guided by the law of increasing entropy) lead to the same thing – a decrease in its stability, order, an increase in chaos, that is, an aging system.

It is also easy to see on this model that the aging mechanisms of even such a simple system are multiple and probabilistic in nature: mechanical (tires, brakes), physical (metal fatigue), physical and chemical (burning out candles), chemical (rusting), biological (fungus), socio-psychological, etc.

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