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"New search for truths – only this is the only science"

Dm.I. Mendeleev

THE THEORY OF AGING FROM THE VIEW OF NATURAL LAW

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The "reasonable" arguments in the science without the use of mathematical formulas (mathematical models), by figurative expression of Bertrand Russell, sometimes lead to false conclusions. Therefore, the desire to seek an explanation of biological phenomena by means of mathematical methods, used for a long time to describe the behavior of inanimate objects, physical and chemical processes, is justified. The more that biological processes are such only in their final forms, but they are based on the same physical and chemical interactions. In particular, aging is common phenomenon for the natura. The physics and chemistry of aging are considered as a spontaneous irreversible change of the object due to thermal motion of atoms and molecules, the light and other radiation, mechanical forces, gravity and magnetic fields, and other factors, causing the loses of initial characteristics and structural properties of the object. In this connection, when considering the aging the main focus is on the inevitable degradation that occurs regardless of the ideal environmental conditions – as a consequence of the occurrence and existence of the object. In this inevitable instability ones often see the tendency to thermodynamic equilibrium, i.e., transition to a more probable state with maximum entropy. As it be noted by Ilya Prigogine, the laws of nature provide only death. In other words, the destruction, disappearance, and any manifestation of volatility also can be seen as the main trend in the nature, characterized as a desire to increase of the entropy by the second law of thermodynamics.

At the first examination, aging and death in the living nature fits well into this scheme. Therefore, from point of view of natural sciences, the failure to confront the destruction often is basis for consideration of aging from the perspective of the second law of thermodynamics and the increasing of entropy, which is a measure of disorder of a system. However, the biological process of aging has not found a satisfactory explanation within the framework of the thermodynamics conception. In this regard it should be noted some points predetermine unproductive use of the concept of a thermodynamic system (TS) and the related definitions of open, closed and isolated TS to support aging in nature. For example, a red blood cell – a cell that has lost the nucleus – remains an open TS, though doomed to die within a few weeks. At the same time similar open TS – the cells of the somatic tissues – continue to live for years and decades, to the death of the whole organism. It is also important to note that the terrestrial biosphere as the totality of all living things on the Earth, in relation to the Cosmos, is not an open system – it receives from the space only solar energy in the form of heat, but uses exclusively own organic and biochemical substrates. Such closed TS differs from isolated TS unable to exchange any substance or energy. For all that, the biosphere, remaining the closed TS, there is billions of years old, while the completely open TS inside it as individual organisms together with cells inside them constantly grow old and die.

You can select a range of inconsistencies, which show that the physical representation of the thermodynamic system and entropy is not well suited to explain aging in the nature. For example, the physical science does not consider the events in thermodynamic systems from the perspective of age-depending changes, which is a defining feature of biological aging. On the contrary, for the typical thermodynamic systems cyclical transitions from one state to another quasi-static state are inherent, but it cannot be applied to age-related changes of biological objects. An inevitable of the thermodynamic processes is not considered as irreversibility, what, however, is characteristic of aging as a biological phenomenon. Finally, the idea of thermodynamic openness cannot be adequately projected at the biological matter, as this was demonstrated in the above example of biosphere and the objects present in it.

In this regard, it should be noted that the non-applicability of the second law of thermodynamics makes terrestrial biosphere similar to the Universe. It is known that theoretical physics refutes the initial withdrawal of the second law of thermodynamics concerning the inevitable heat death of the Universe. It turned out that here the second law of thermodynamics should not be applied in relation to the presence of gravity as the organizing principle that amends the thermodynamics trend. Therefore, referring to the position of the laws of physics to biological aging, we must remember that the same organizing power is present in the living nature. So, this power is provided by nucleic acids (primarily DNA), and while they are present within the object, its metabolism is not subject to the general law of entropy, and the fate of the object is not determined by the thermodynamics concept of open or closed system. Fatal destiny of erythrocyte lost with the nucleus this organizing principle, against the background of continued existence of somatic cells in the body, one of the evidence of this principle. Thus, the idea of aging and the inevitability of the death of the biological objects under the second law of thermodynamics, providing an increase in entropy, is superficial. It uses only insignificant resemblance of the phenomenon of biological aging and the thermodynamic processes in the nature.

As you can see, the laws of thermodynamics cannot explain the aging and death of individual biological objects against endless reproduction of life, carried out in the biosphere by the same entities. The law of aging should simultaneously explain the endless life within the biosphere. Only in this way the problem marked by one of the greatest physicists of the 20th century the Nobel Prize winner Richard Feynman can be solved. The essence of his thesis is that the absence in biology of the law, which would claimed the necessarily ending of life of every individual, allows the possibility for immortality, i.e., a kind of biological perpetual motion machine, banned by the physics law. Just biosphere gives us an example of the same perpetual motion, as opposed to those objects which are included in it.

To sum up the above, it can be noted that aging, both in the living and inanimate nature, has something common and can be characterized as a destruction of the system, which is not capable of self-preservation of the structure. Although the nature abhors constancy, it is important to note that not all the changes and destruction occurring in it can be attributed to aging. For example, the Universe and the biosphere can be seen as the systems for which conception of aging cannot be applied. We emphasize that non susceptibility of aging does not mean eternal existence, but only indicates a lack of communication between the age and the possible destruction of the system. The main difference aging from other processes, including degradation which occurs in nature, is dependence on age. This most important feature is not interesting for thermodynamics, the laws of which some scientists try ineffectually to exploit to explaining aging in nature. Therefore, considering the living objects, which probability of death depends on the time of their existence, we should pay attention to certain physics laws that can become the basis of constructing a general theory of aging.

Within this theory, the aging of objects can be represented as the decay of the system, that consists of timeless elements in its structure.

This condition, unifying all aging objects of animate and inanimate nature, indicates a limit of structural organization – the elementary units, that are not subject to aging. This view is not usual for the biomedical approach, however, this absolutely follows from a mathematical law and the formula proposed by Benjamin Gompertz in the 19th century for description of the actual mortality charts. His mathematical model of aging is considering an increase in the probability of dying as a result of the uniform and age-independent loss of vitality (life power). It is important to emphasize that the Gompertz formula similar to the equations of a number of physical processes. However, in contrast to known formulas of physics, these symbols show only mathematical relationship, but not actually calculated values. Nevertheless, Gompertz formula reflects a very real plot showing the probability of death, defined as the ratio of deaths to the number of surviving within a certain age. B. Gompertz first noticed that this dependence can be expressed by an exponential function, and offered the coefficients for it:

$$h(t) = h_0 e^{kt}, \quad (1)$$

where $h_{(0,t)}$ is the probability of death in the initial and final period of life, k – option Gompertz' function reflecting the loss of vitality, e – base of natural logarithm, t – time.

The most interesting and, say, the mysterious in this formula is a coefficient k – a factor reflecting the regular loss of vitality. During the creation of this law was not known microscopic structure of the tissues and organs and, in particular, the universal role of cells shown later in the theory of the cell pathology by R. Virchow. However, even without this it is clear that a loss of the vitality should be understood as the loss of material substrates – the elementary structures that provide certain vital functions. Thus, if we replace the value of h, which reflects the probability of death in the formula (1), by the amount of vitality – N, then the formula will acquire the form:

$$N(t) = N_0 e^{-kt}, \quad (2)$$

and the exponent will have a decreasing character, similar to an curve of radioactive decay. Incidentally formula (2) also completely coincides with the equation of the radioactive decay. However, the law of the radioactive decay derived from actual observations of the physical process, where the first was the size of the experimentally established decay factor – k, that later made it possible to determine the age of the object. Experimental gerontology does not tie the coefficient k to real events and structures, it is determined not by experience, and calculated from the curve of the mortality. Therefore, the value of ***N*** is conditional and has no real content. It is necessary to find an ageless unit in the structure of the object – a kind of vitality, losing equally in proportion to their volume and available to quantify, that the law of aging has acquired the precision of physical law. So, the formula (2) becomes a real law of biological aging, where ***N*** and ***k*** will have the status of values that are bound to a specific structure of a living object.

Modern medical and biological sciences and gerontology in particular, consider this search as the search for cause of the cell aging, which is often associated with the accumulation irreversible damage inside the cell or permanent loss of the constituent elements. The question is what constitutes the elementary structure, with which life potential is wasting regularly? Thus, the thesis of the ultimate irreducibility of material objects, introduced in physics by Max Planck, suddenly acquires fundamental methodological sense when considering the biological aging. The search for cause of aging in nature leads us to the limit of the comprehension of the whole as a set of elementary components – the limit up to which you can go in explaining the properties of an object.

Considering the vital functions of organisms, we can go to the smallest level of biological molecules and of simple organic compounds. There is no doubt that the knowledge of this level is important for the understanding of living matter. However, knowledge about the functioning of the cells at the level of ultrastructure and macromolecules accumulated over the past century has not brought us an understanding of the mechanism of aging. Here it is useful to cite what has been told in 1915: "There is no methods that could detect and prove the aging of cells ... now is absolutely unbelievable that we can determine the aging process with the help of some reactions or physical-chemical tests" [5]. What has been said a hundred years ago, without cuts, fits into the current level of knowledge. You can spend the next hundred years, to further penetrate the cell structure and metabolism, trying to look at the nanolevel trigger mechanism of aging. But, rather, it is an occasion to reflect on the above-mentioned limit, up to which it is expedient to go. Otherwise modern gerontology can become like helpless Achilles, which, according to the famous paradox of Zeno, made it impossible to catch up with the sluggish turtle in result of substituting the concept of number as a property of the distance, the other concept, where the number appears only as an element of the search for the infinitesimal. So, gerontology is likely to remain in captivity of imaginary infinity in an effort to understand a particular phenomenon of nature, where everything is determined by finite quantities.

It should be noted that the answer to the question about the nature of the minimal value, which the body loses in the aging process, is partly contained in the mathematical law. To do this, the law must be projected on the certain knowledge that was acquired by biomedical science over the past century, i.e. it is need to look at the medical-biological phenomenon from the point of mathematical model. It is clear that this model does not disclose the fact and does not indicate the nature of the value – the life power that is lost evenly. However, there is an important and undisputed requirement: the loss of the structure, which carries the life power, should not depend on the age of the object and must be proportional to the magnitude of vitality. That is what the coefficient ***k*** represents in the formulas (1) and (2). Fundamental medical and biological importance of this factor is that it sets the boundary between what grow old in the body and what do not grow old.

So, with the medico-biological point of view, there is no doubt that the body grows old and organs and tissues grow old and there is certain morphological confirmation for this view. With regard to the aging of cells, it is still not found a structural equivalent for this phenomenon, although gerontology does not doubt the existence of cell aging. Previously, we came to the conclusion based on the medical and biological data that discussion of the aging of multicellular organism does not need a support on the thesis about the aging of cell, that is confirmed by nothing. So, aging was determined as the age-independent elimination of cells in the tissues [1-3]. Now we want to draw attention to the fact that despite the richness of gerontology articles with serious mathematical apparatus, an attention has not been paid on an unacceptable contradiction that idea of aging cells contributes to the structure of the mathematical law. With this we want to draw attention to the numerous facts indicating that during the age process the number of cells in the body decreases.

Of course, the body can lose some organs or parts of organs and tissues as a result of accidental injury, illness, etc. However, these losses are random, they are not connected with the process of aging, have no regular nature and is not peculiar to the aging organisms, not to mention the fact that loss of some bodies is not compatible with life. Therefore, these losses are not contrary to the Gompertz ‘law. If we talk about the loss of cells, this phenomenon has been noted as an integral element of aging else at the beginning of the last century. On this issue, there is an extensive, partly classified data. For example, the well-known monograph even indicates what percentage of cells is eliminated in a particular tissue or organ in the aging process [5]. In modern publications the fact of the age-related elimination of cells is given as common occurrence that can be evidenced by the following quote. "Reducing the number of cellular elements can affect the activity of an organ, tissue ... In addition, along with the dead cellular elements, many cells are in different stages of degeneration, on the stages from a period of normal metabolism and functions to their complete extinction. Thus, reducing the number of cells in the old is one of the factors that affect the function of organs, systems "[8].

Thus, recognizing the fact of the loss of the cells with age, gerontology overlooked that according to mathematical law, the regularly disappearing structure cannot grow old. In other words, the loss of cells in the tissues as a phenomenon associated with the aging of cells cannot exist within a mathematical law. The fact that in this case age-independent loss of vitality (as it required by the mathematical law) will not be! The loss of vitality will increase with age, and instead of ***k***-factor must be entered another exponential equation, reflecting the loss of vitality, such as, for example:

$$K_{(t)} = k + K_{(0)} \exp(tk) , \qquad (3)$$

where ***t*** indicates the time, ***K (t, 0)*** – rate of vitality during time of aging , that is caused by loss of cells due to aging of organism, ***k-*** factor reflecting the loss of the life power due to the aging of cells without their elimination.

Thus, the age-dependent loss of cells (the same should be if the cells grow old) requires the formula (3) at consideration of the mathematical law, but this makes not possible to use a mathematical law with the form proposed by Gompertz for the study of mortality of aging populations. However, for this purpose Gompertz' law has been used successfully for many decades, without the need for any fundamental amendments and without alternatives. We conclude that the real loss of vitality occurs according to the formula of Gompertz – regardless of age. Therefore, if we observe elimination of cells in the body associated with aging, then this elimination should be age-independent. This is the only way to "reconcile" the fact of the age-associated loss of cells in the body with the formula (2), not inventing new mathematical laws of aging.

Thus, theoretically, based on the analysis of the known fact within the mathematical law of aging, one may conclude that the cell elimination of the organism tissue is not dependent on the age. This conclusion is the result of the mathematical law of aging, indicating the impossibility of cell loss in the body due to their aging. In other words, if the cell aging takes place, it should not lead to their elimination from the body, despite of medical and biological view where the cells aging, culminating in their death, can be considered as a quite common event, if to mean the outcome that is inevitable for organisms formed by the same cells. Here we are faced with an unusual situation for Medicine and Biology where 'reasonable' explanation must give way to the mathematical arguments.

However, gerontology continues to exploit the thesis of aging of cells as the cause of the aging of the whole organism, not trying to analyze the fact that really observed aging is associated with a loss of cells in many tissues and organs. Initially, we came to the resolution of this contradiction with medical and biological position, suggesting the concept of stochastic (age-independent) elimination of cells in tissues by a mechanism of apoptosis [1-3]. At the same time, not knowing how the loss of cells occurs in the body, we noted that there is age-independent process in the endothelium of the cornea. In other words, the first was seen medical-biological mechanism of age-independent cell elimination, that was promoted by studing of the cornea in the aging process and, in particular, the impact of age-related changes of the cell number on the functional state of the tissue. This study led to the conclusion that aging of an organism is not the result of the aging of cells, and is the result of the aging of tissues. The very same aging of the tissue is the result of a regular age-independent elimination of cells, leading to a reduction in the functional abilities of the tissue.

This explanation of the cause of aging of multicellular organisms, built on ignoring of the cell aging, quite expected invokes the non-acceptance not only among gerontologists, but also within general medical and biological society. This is due to the fact that the idea of aging cells, although has no tangible evidence, but over the past century has got the strong position in biology and medicine. It is constantly used not only in the discussion of subjects of gerontology, apoptosis or cellular pathology, it can be found in any other context. The move away from this stereotype requires not so much facts as revising the mentality of physicians and biologists that formed under the influence of the dogma for decades. Indeed, we should talk about dogma – a kind of symbol of faith, nothing confirmed, but it became necessary not only for understanding of the aging. As medieval phlogiston thesis of the aging of the cell become to biomedical science is not only a convenient abstraction, but an instrument of struggle against dissent, rejecting other visions. Thus, the idea of aging cells as an apodictic thesis, which does not require any proof because of the clearness, became the dominating in medicine and biology.

All this led to the need to discuss the concept proposed here as a physical theory is not only due to the fact that the living organisms are part of nature, (from the Greek, φύσις – Physics, nature), but also from the view of strictness of the evidence, when priority is given to mathematical understanding, rather than a "reasonable" arguments. In this context, mathematical refutation of the aging of cells in a multicellular organism, seen through the contradiction between the mathematical law and well-known fact of the reducing of the cells in the body with age, can be accepted as an important theoretical proof on the ways to overcome the stereotype of thinking. It is important also because the concept of cell aging is refuted by mathematics – in the framework of the mathematical model of aging recognized by gerontology. Thus, the mathematical model of aging provides only age-independent loss of vitality. It can be any structure – as being within the cells, and so it can be cells themselves. If we assume the aging of the cells, the non-growing old structure should be inside the cells and constantly disappear due to age, but the cells should not to disappear, although grow old.

As can be seen, the mathematical understanding of aging is such that any aging structure in the body can lose its vitality (life power), but cannot die as a result of aging. So, with the help of mathematical approach it is possible to estimate the meaning of the thesis that defines aging as a decay of a complex system consisting of timeless elements. This position is well known in physics especially as the example of radioactive elements and it has particular importance in gerontology. So we have gotten a mathematical justification of the thesis expressed earlier that the aging of the tissues takes place without an aging of cells and it is the decay of the tissue system. Here it should be emphasized again unfounded approach to the study of aging from the perspective of the laws of thermodynamics. This specificity of aging unites it with such physical process as radioactive decay, where the concept of TS also does not apply.

It should be noted that the thesis about aging as a decay of tissue system has been applied in conjunction with the proposed biomedical justification of the process [1]. However, in subsequent publications [2, 3] this feature is not used because of the obvious hint of known physical process, which, as it seemed, did not have sufficient ground. Now we come to the conclusion that the observed phenomenon of the age-independent elimination of cells in the tissue system must acquire same terminological meaning as the concept of decay. In this way it emphasizes that, although the process of aging of multicellular organisms is based on biological mechanism, its natural essence, i.e., physics, determined by universal mathematical algorithm that characterizes the processes of disintegration of compound systems, representing a combination of aging and timeless elements.

This understanding of the body as a system, losing non-aging elements, were incorporated in the Gompertz ‘formula, which interestingly coincides with the formula of radioactive decay. Unfortunately, the subsequent progress of medicine and biology, that led to the knowledge of the body at the level, which was not accessible at the beginning of the 19th century, created a temptation that the disclosure of the cause of aging lies solely in search for another unknown structure, but not in the understanding of the relationship between the already known structures. Now we can look at the aging of living objects like the physical process, the fundamental mechanism of which is described in a strict mathematical form that does not allow arbitrary interpretation of facts. One of these facts is a loss of cells in organs and tissues during aging, that refutes the thesis of the aging of cells.

As noted earlier, the original opinion on the age-independent elimination of the cells, i.e. view of the absence of their aging, arose on the basis of a few observations, not subjected to statistical analysis. The original idea was based mainly on medical and biological arguments. Now we are able to reinforce it, as well as demonstrate the medical and biological meaning of the mathematical reasoning, using the results of observations of a particular tissue system in the aging process. Below summarizes the cell density of 153 corneas obtained from the Eye bank (110 donors of different ages from 18 to 72 years). The number of cells (density per square mm.) is determined automatically by analyzing multi-endothelial microscope. The objects were divided into 5 age groups by decade, with a view to a more detailed (by-step) assessment of age-related changes. The data obtained are presented in Table 1.

Based on the data, the graph of the reducing of cellular density in the aging process will be as follows (Figure 1). As you can see, the exponent of tissue decay, which the corneal endothelium shows, close to the well known classic graph of radioactive decay. It is also important to note that the presented curve of the aging of the tissue is fundamentally different from standard curves that characterize the aging of population (Figure 2), which well known in gerontology [6].

Number of groop	Age groop	Density of endothelial cells in 1mm² (M±m)	Number of observations (n)
1	18-29 лет	3610±530	8
2	30-39 лет	3410±370	17
3	40-49 лет	2945±320	33
4	50-59 лет	2785±340	49
5	60-72 года	2660±280	46

Table 1. The changes of the cell density of the posterior corneal epithelium depending on age

Comparing these two graphs allows you to make sure that aging of the tissue system, which shows the corneal endothelium, is not the result of the aging of its cells (otherwise would have occurred graph as Figure 2), and their age-independent elimination can be described as the decay of tissue system, by analogy with known physical process.

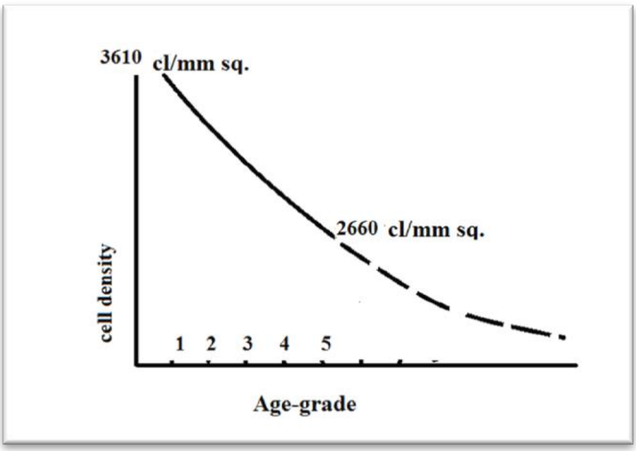

Fig. 1. The graph of the cell density changes in the tissue system (corneal endothelium) with age.

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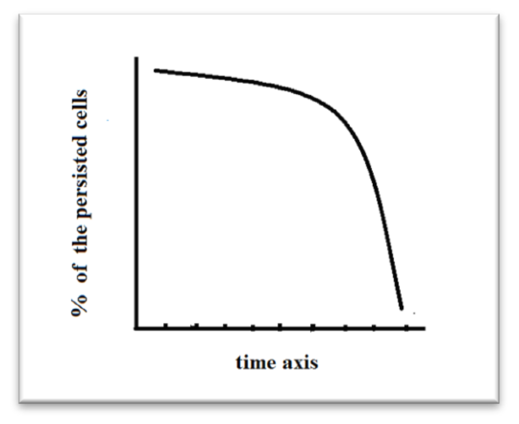

Fig. 2. Typical curve of the elimination in the aging populations (see the monograph of A. Comfort [6]).

From the presented in Figure 1. graph shows that the dotted curve goes into the imaginary space that is far beyond the actual human life. This is understandable if we consider the specific figures. So, the factor (***k***) of the decay of the tissue system, which is fluxion of a function whose exponent is in Figure 1, can be represented by the standard formula of the differential:

$$\boldsymbol{k} = \boldsymbol{dN / N\, dt}, \qquad (4)$$

where ***k*** is decay factor (in this case it means likelihood of the elimination of the cells over a period of one year and is taken with a minus, considering the decrease in cell number), ***N*** is number of cells (in our case – density). The formula for calculating the coefficient ***k*** can be obtained from the formula (2):

$$\boldsymbol{k} = \ln \boldsymbol{N_t / N_0}\ \boldsymbol{/t}. \qquad (5)$$

Table 1 and Figure 1 shows that during a period (***t***) of from 20 to 70 years the cell density is decreased from 3610 (N_0) to 2660 (N_t). Substituting these data into the formula (5) we obtain an approximate value: ***k*** ≈ - 0,006.

Thus, the mathematical quantity, symbolizing the loss of vitality in the Gompertz' equation, appears as a biological constant characterizing the loss of cells in the tissue system. The elimination of the cells of the corneal endothelium became known in ophthalmology due to specular microscopy in 70-80th of the last century, even the percentage of cell density loss can be found in the literature as equal to

0.6% per year [4]. Presented as a probability - 0.6 / 100, this value is the same as the coefficient of decay (***k)*** found above. However, before this value was mentioned only as a statistical fact, and its mathematical relation to function of Gompertz has not been realized.

Knowing the constant ***k***, and the starting number of the cells in the tissue system (N_0) and the finite number, i.e. minimal number (N_t), below which the tissue system cannot function in the interests of the body, can determine the time (***t)***, which is designed for the function of the tissue system in the body. This leads to the formula (2), but is easier to use logistic formula, based on the known initial and final parameters as well as the loss ratio, then:

$$N_t = N_0 (1 - k)^t, \qquad (6)$$

wherefrom

$$t = \log_{(1-k)} N_t / N_0 . \qquad (7)$$

N_t value can be obtained as the minimal density of cells providing safety of barrier function, which is associated with the transparency of the cornea. This border, according to experts, is close to the level of 500 cells / mm ^{2} [7]. Then, on the basis of the data presented above, where the density in the younger age group is 3610 cells / mm^2, the time, for which the number of cells will be enough with an annual loss determined by coefficient ***k*** , will be:

$$N_t / N_0 = 500/3610 \approx 0{,}13$$

$$1 - k = 0{,}994$$

$$t = \log_{0{,}994} 0{,}13 \approx 339{,}0$$

Thus, the logarithm points out on a period 339 years, i.e. exponent in Figure 1 falls to 500 cells / mm^2 in a time which is many times higher than the real life. This explains the nature of the exponent in Fig.1. However, in the human population there are individual values for the younger age group 1000 cells / mm^2 or less. With this reserve, the entire exponent can meet in the segment up to 100 years, and the chances of preserving the functionality of the system to tissue aging are reduced, which sometimes manifests itself as a kind of age-related pathology named endothelial dystrophy.

There is no doubt that each tissue system has its own reserve of life, which accounts for the uneven aging of various organs and tissues. It is especially important to know the reserve (N_t / N_0) for tissue systems that determine the vital functions, in particular, the contractile function of the heart. This will allow a realistic assessment of the maximum life expectancy and explain the reason for the so-called "sudden" death. When this ratio is found, "sudden" death will cease to be sudden and unpredictable, which seemed endothelial dystrophy, while the limiting level of ($\boldsymbol{N_t}$) has been found for this tissue system. The ability to determine the maximum duration of human life, as it can now be done in relation to the viability of the cornea, stops speculation on topic of immortality or longevity records. It can hope that this paper as the first attempt to study a new mathematical concept of aging, will draw attention of the exact sciences to this subject, whereby biomedical science will be able to overcome the dogmatic view of the aging of the cells, which is a brake for gerontology.

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